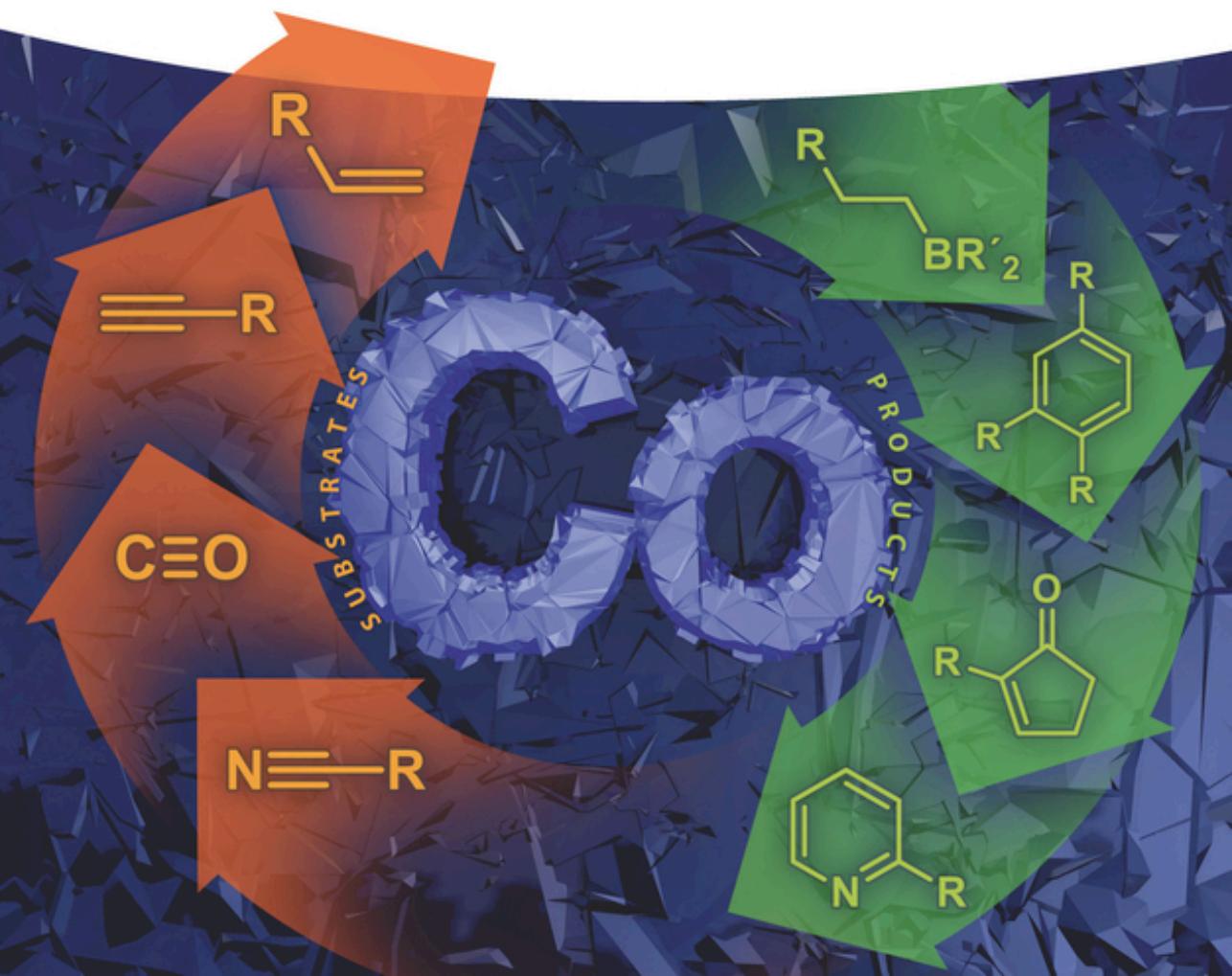


Edited by Marko Hapke and Gerhard Hilt

# Cobalt Catalysis in Organic Synthesis

Methods and Reactions





## **Cobalt Catalysis in Organic Synthesis**



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Methods and Reactions

*Edited by Marko Hapke and Gerhard Hilt*

**WILEY-VCH**

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## Preface

Catalysis promoted by transition metal complexes has revolutionized the art and practice of chemical synthesis. Approximately 85% of all chemical products are made using at least one catalytic transformation, and one estimate suggests that catalytic processes account for approximately 20% of the GDP of the United States (<https://catl.sites.acs.org/>). Why is this so? Catalytic reactions accelerate product formation, enable or enhance selectivity, and ultimately minimize waste and energy consumption and hence carbon dioxide footprint. While the catalyst landscape has principally been dominated by precious and terrestrially rare second- and third-row transition metals, there is increased emphasis on catalysts based on more Earth-abundant elements. Among these is cobalt.

It is interesting to ponder why precious metals have found wider use than more Earth-abundant alternatives. The answer is simple – they work! The predictable redox chemistry, resistance to deleterious autoxidation reactions, and availability of reliable synthetic precursors have enabled a broad spectrum of chemists to explore precious metals in catalytic reactions directed toward organic synthesis. Impressive advances as palladium-catalyzed cross-couplings, platinum-catalyzed hydrosilylations, ruthenium-promoted olefin metathesis, and rhodium- and ruthenium-catalyzed asymmetric hydrogenations have all been conducted on industrial scale and in many cases on advanced intermediates and densely functionalized molecules. Discovering cobalt catalysts that meet or surpass these criteria is certainly a tall order. Challenges range from realization of synthetic precursors to understanding fundamental reaction chemistry to optimized ligands for 3d transition metals [1].

This volume edited by *Hapke* and *Hilt* explores the evolving role of cobalt, a relatively Earth-abundant first-row transition metal, in catalytic reactions directed toward organic synthesis. Over the course of 11 distinct chapters each authored by leaders in the field, a contemporary view of the role of cobalt over a diverse range of catalytic transformations is presented. Importantly, each chapter blends advances in both the fundamental and the applied. Chapter 1, authored by the editors begins with an important historical overview of the element and its role in catalysis. Readers are reminded that while catalysis with cobalt and other Earth-abundant transition metals are at the forefront of modern sustainability research, application of cobalt in catalysis directed toward organic synthesis dates back nearly a century. *Roelen's* use of  $\text{Co}_2(\text{CO})_8$  in alkene hydroformylation [2] was a seminal example highlighting the impact of organometallic

cobalt catalysts on selective organic transformations and later demonstrated the utility of mechanistic understanding on improving overall catalyst performance. Interestingly, *Richard Heck* was instrumental in elucidating the mechanism of this reaction [3] and was one of the first organometallic transformations so thoroughly studied.

The following chapters are research monographs focused on a specific topic and groupings of chapters highlighting related areas of catalysis. Chapter 2 is authored by *Junge* and *Beller* and describes the explosive growth of cobalt catalysis in various classes of hydrogenation reactions. Particular emphasis is placed on complexes with multidentate ligands, as these contain many first-row metals likely because deleterious ligand dissociation pathways are suppressed. This chapter, like many others in the book, ends with a convenient infographic highlighting the various types of catalysts covered and the types of reactions each promotes. *Kim* and *Dong* in Chapter 3 cover related transformations on the hydrofunctionalization of C=C bonds. Again beginning with *Roelen*'s alkene hydroformylation chemistry, the chapter tracks the evolution of cobalt-catalyzed hydroacylation, hydrocyanation, hydrocarboxylation, and related reactions. It is remarkable to notice the impact cobalt catalysts have had on expanding the scope and range of organic methods, particularly in the synthesis of small rings and in enantioselective reactions.

The selective functionalization of carbon–hydrogen bonds is one of the most active areas in modern catalysis research. The potential impact of these methods is apparent – the selective conversion of ubiquitous C–H bonds to functional groups would transform the way synthetic chemists view and approach the reactivity of organic molecules. Not surprisingly, organometallic and coordination complexes of cobalt have been widely studied for these transformations. In a comprehensive monograph on a rather large body of research, *Yoshikai* in Chapter 4 highlights the long-standing impact of cobalt catalysis on C–H functionalization research. As with other chapters, the concluding infographic on the different transformations and catalyst types helps guide readers.

Metal-catalyzed cross-coupling, recognized with prestigious honors such as the 2010 Nobel Prize in Chemistry (for C–C bond formation; <https://www.nobelprize.org/prizes/chemistry/2010/summary/>) and the 2019 Wolf Prize (for C–N bond formation; <https://www.wolffund.org.il/index.php?dir=site&page=winners&name=&prize=3016&year=2019&field=3002>), is one of the most widely used metal-catalyzed reactions, particularly in the pharmaceutical industry. Attempts to promote these reactions with first-row metals date to the 1940s and the work of *Kharasch* [4]; these have since evolved into a vibrant field of research. Chapter 5, authored by *Dorval* and *Gosmini*, accounts both the latest developments and the historical contexts of cobalt-catalyzed cross-coupling. While impressive advances have been made, considerable improvements need to be realized for these reactions to reach the broad utility reported with palladium and nickel.

Three later chapters of the volume are devoted to the interaction and catalytic chemistry of  $\pi$ -systems with cobalt. Chapter 6 is principally focused on ionic and radical chemistry of  $\pi$ -bonded ligands, while Chapter 7 describes various cobalt-catalyzed cycloaddition reactions. Chapter 8 by *Lindsay* and

Kerr describes the rich cobalt chemistry associated with the *Pauson–Khand* reaction. In Chapter 9, editor *Hapke* and *Gläsel* describes cobalt-catalyzed [2+2+2] cycloaddition chemistry, a field with deep historical routes but one that continues to have modern advances and opportunities. In Chapter 10, *Pellisier* focuses on asymmetric catalysis with cobalt, another rich and growing field. The final chapter nicely rounds out the book and focuses on the bioorganometallic chemistry, including vitamin B12 and related cobalt compounds.

In summary, the volume covers the breadth of modern catalysis research involving cobalt. One pervasive theme throughout is the interplay of fundamental structure, reactivity, and organometallic chemistry with advances and applications in catalysis and organic methods. Although catalysis with cobalt has been studied for decades and impressive advances have been made, there are tremendous opportunities for the future. Cobalt and other Earth-abundant metals have yet to enjoy the same widespread adoption as their precious metal counterparts. Many challenges associated with catalyst handling, reaction scope, functional group tolerance, and air-sensitivity remain. It is apparent, however, that the journey is worth the effort as cobalt, time and again, has exhibited unique reaction chemistry distinct from the precious metals and inspires continued exploration both in the fundamental and applied. This book is a valuable resource for students and researchers alike and will likely serve to inspire new directions in cobalt catalysis research.

August 2019

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## Preface

Cobalt is a late member of the first-row transition metals and has only in recent years become an important catalyst metal in homogeneous catalysis and synthesis. This is quite surprising regarding the role of cobalt in the earliest developments of homogeneous catalysts on an industrial scale in the 1930s, with the hydroformylation chemistry developed at Oxo Chemie by Otto Roelen. It is even more surprising that, to date, no single monograph has been devoted solely to the catalysis and organic synthesis mediated by cobalt complexes and compounds, while all surrounding metals and group congeners like iron, nickel, ruthenium, rhodium, and iridium have been recognised this way.

The aim of the presented volume is to fill this gap and collect renowned authors and practitioners in the field of cobalt chemistry to outline the basics, increasing importance and contemporary developments in this field. The 11 chapters are headlining the various most valuable and applied classes of transformations involving cobalt complexes, including details on mechanistic aspects, elemental reaction steps, and organometallic chemistry. The application of cobalt catalysis ranges from basic transformations to evaluate the scope and limitations of the reactions up to the utilisation, e.g. in the synthesis of natural products and other complex organic molecules. In selected chapters also practical preparation procedures of some cobalt complexes have been included to illustrate the feasibility and experimental handling of cobalt catalysts in some detail.

As editors, we would like to give some additional comments. The extraordinarily large field of heterogeneous cobalt catalysis in academia and industry is not covered in this volume. However, this field has been reviewed in the literature thoroughly for an even longer time than is the case for homogeneous catalysis. The actual developments of energy conversion and storage including cobalt-containing materials is currently a very hot topic, with new results being constantly compiled and reviewed extensively in reports and commentaries. We have therefore decided to leave this topic out of the volume. As a more formal note, we would like to announce that only the names of the principal investigators are mentioned in the chapter texts, well aware that the actual work has been conducted by the co-workers and other authors of the cited papers.

We hope that the content of the book will provide valuable information to the readers and inspire researchers from academia and industry alike to include cobalt catalysts in their future research to solve synthetic challenges and take opportunity of the unique and fascinating properties of cobalt.

Linz and Oldenburg  
September 2019

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## 1

## Introduction to Cobalt Chemistry and Catalysis

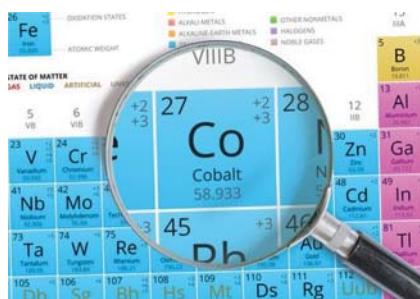
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### 1.1 Introduction



Cobalt (Co) is the first and lightest element among the group 9 transition metals, further members being rhodium (Rh), iridium (Ir), and meitnerium (Mt). In contrast to their significance in organic synthesis and catalysis, cobalt is by far the most abundant element of the group in the geosphere, compared with rhodium and iridium as its heavier congeners ( $\text{Co:Rh:Ir} = \text{c. } 10^4 : 5 : 1$ ) [1]. While rhodium and iridium complexes have been at the forefront of organotransition metal chemistry with relation to organic syntheses, steadily enabling novel and often unprecedented transformations of simple starting materials to complex products or opening the gate to novel fields of catalysis as has happened with C–H functionalisation reactions, cobalt stood back for a long time. Expression for the different significance of the three transition metals is also found in the literature, as monographs for either rhodium and iridium as catalyst metals for organic

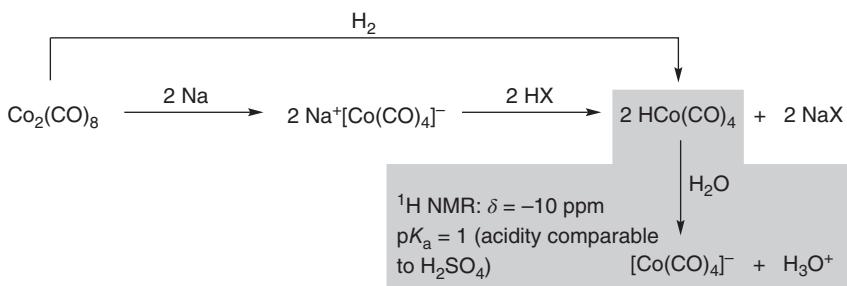
synthesis have already been published [2, 3]. However, some direct comparisons of the application of group 9 metals for organic synthesis and catalysis can be found in the literature [4]. Next to its membership in the first row of the transition metals, relative abundance, and biorelevance, it is also considered a sustainable metal, among other elements in this nowadays particularly important field [5].

Cobalt (the name is derived from the German word “Kobold” meaning goblin, due to the behaviour and confusion with silver–copper ores in medieval mining) has been isolated for the first time in 1735 by the Swedish chemist *Georg Brand*, who also recognised its elemental character. It is an essential trace element for humans and animals, and its main purpose is the constitution of vitamin B<sub>12</sub> (cobalamin), which has an important role for the regeneration of erythrocytes. Cobalamines are organometallic compounds with cobalt–carbon bonds, possessing cobalt in the oxidation states +1 to +3, and provide the only known cobalt-containing natural products.

Beside the importance for the human physiology, cobalt has evolved from an unwanted and downright abhorred element during silver and copper mining to a metal of strategic industrial importance and in recent years also a rising young star in homogeneous catalysis. How does this chemical version of “rags to riches” come into play? One modern reason is the importance of cobalt as metal used in high-performance alloys (e.g. stellite), permanent magnets, rechargeable batteries, cell phones, and many more technical applications [6]. Requirements of our modern society with respect to the production of chemicals and materials also heavily rely on the late, rare, and rather expensive platinum group metals (PGM). The implementation of sustainability and efficiency thus leading the way to explore the earth-abundant metals for both homogeneous and heterogeneous catalytic purposes [7, 8].

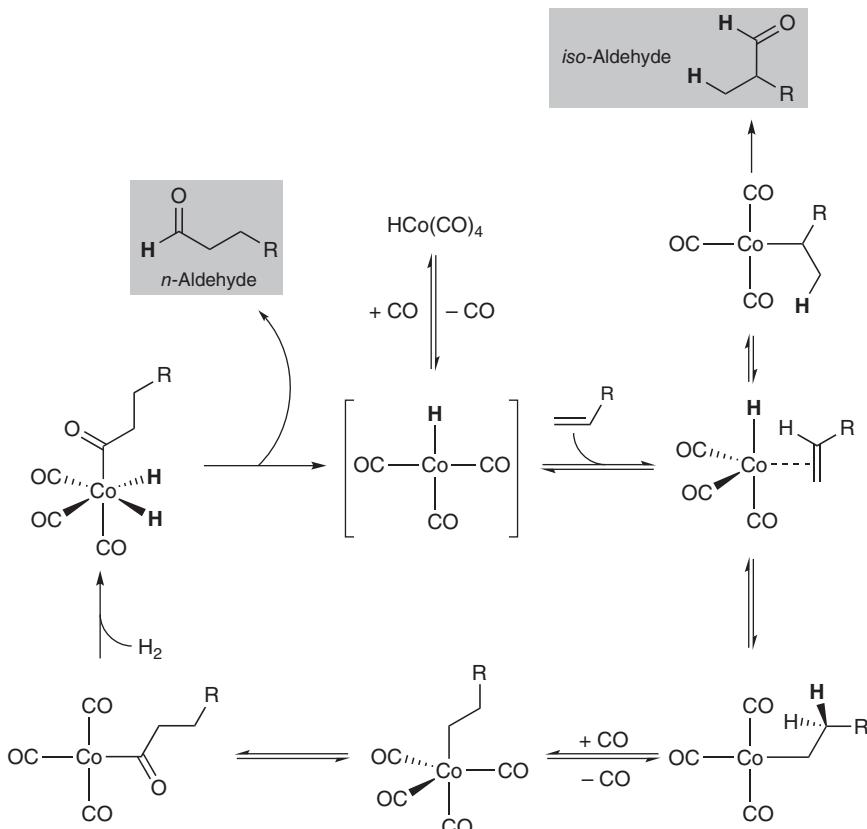
From a chemical and catalytical point of view, cobalt already inherits the role of a major player in the awakening of homogeneous organometallic catalysis in the first half of the twentieth century [9]. *Otto Roelen* at Ruhrchemie (now Oxea) in Oberhausen discovered the “oxo synthesis” in 1938, today named hydroformylation reaction, and introduced HCo(CO)<sub>4</sub> as catalyst for this reaction. Still today beside rhodium as metal with higher reactivity cobalt complexes are used as catalysts. Basis for this reaction was work from *Walter Hieber* on the synthesis of carbonyl metallates via the so-called “Hieber base reaction”, affording H<sub>2</sub>Fe(CO)<sub>4</sub> by the reaction of Fe(CO)<sub>5</sub> with NaOH. Because for cobalt no mononuclear binary carbonyl compound is known, therefore the related compound HCo(CO)<sub>4</sub> was generated from the prominent carbonyl complex Co<sub>2</sub>(CO)<sub>8</sub> by reductive splitting with sodium metal and protonation or even directly by oxidative splitting by molecular hydrogen itself (Scheme 1.1). The resulting cobalt carbonyl hydride is a proton donor, able to protonate water with an acidity comparable to sulfuric acid.

The mechanism of the hydroformylation process using HCo(CO)<sub>4</sub> and related compounds HCo(CO)<sub>3</sub>L (L = phosphine) has been studied in great detail, first proposed by *Breslow* and *Heck* [10]. Scheme 1.2 displays the now generally accepted mechanistic pathway for the cobalt-catalysed process [11]. Starting from the hydridic HCo(CO)<sub>4</sub>, reversible dissociation of a CO ligand followed by reversible olefin coordination led to migratory insertion, which would pave the way to either the *n*-aldehyde or *iso*-aldehyde, depending on the course of the



**Scheme 1.1** Synthesis of cobalt carbonyl hydride (the reaction with H<sub>2</sub> can be reversible).

insertion. Following the reaction cycle, alkyl migration led to formation of an acylcobalt species, which after oxidative addition of hydrogen was reductively eliminated as the *n*-aldehyde. This catalytic cycle combines all the significant elementary steps of homogeneous catalysis with metal complexes and provides a taste on the complexity for studying such reaction mechanisms in detail. Interest



**Scheme 1.2** Mechanism of the classical cobalt-catalysed hydroformylation reaction of terminal olefins.

and detailed studies in these first molecularly defined catalysts for the purpose of synthesising structurally advanced organic molecules has since filled the knowledge of organometallic chemistry.

## 1.2 Organometallic Cobalt Chemistry, Reactions, and Connections to Catalysis

Cobalt is a d<sup>9</sup>-metal and the by far mostly frequently occurring oxidation states in its compounds are −1, 0, +1, +2, and +3. The latter oxidation states also play the major role in stoichiometric/catalytic reactions, while complexes with the oxidation states −1 and 0 are found in some prominent complexes and starting materials. The preference of formal +1/+3 oxidation states in many catalytic transformations is in close relation to the catalytic behaviour of the heavier congeners, rhodium and iridium. In general, the largest number of contemporary catalytic processes include a catalyst generation step, in which, e.g. Co(II) salts are introduced, together with an appropriate ligand and a reducing agent or other additives to lower the oxidation state to +1, from which the species enters the catalytic cycle. On the other hand, a large number of organometallic compounds based on the unsubstituted cyclopentadienyl (Cp), related substituted cyclopentadienyl (Cp'), or pentamethylcyclopentadienyl (Cp\*) ligands are reported and well known, beside numerous isolated complexes with P- and N-donor atom-containing ligands. However, the coordination and organometallic chemistry of cobalt is a wide and multifaceted field and has been involved in ground-breaking research in either area [12].

Cobalt is also a widely used catalyst metal for heterogeneously catalysed processes. Especially the famous *Fischer–Tropsch* process is still relying on cobalt as the principal catalyst metal, as it was already from the initial reports on this large-scale industrial process [13]. Further modern applications in heterogeneous catalysis are often related to the conversion of small molecules in steam-reforming or partial oxidation processes (ethanol, methane) towards the formation of syngas, together with other applications for the allocation of clean energy. A highly current topic is therefore, e.g. the use of cobalt in heterogeneously catalysed electrochemical water splitting [14] or the reduction of CO<sub>2</sub> on cobalt-containing surfaces [15]. Analysis of the chemistry and catalytic performance of cobalt on surfaces is still a topic of ongoing investigations [16].

### 1.2.1 Cobalt Compounds and Complexes of Oxidation States +3 to −1

Cobalt is an electron-rich transition metal, like its latter group congeners; however, it is a first-row transition metal, which inherits also significant differences. Due to its electron richness, it belongs to the so-called “base metals”, including the neighbouring first-row transition metals manganese, iron, nickel, and copper. The abundance of low oxidation states (0, −1) is, however, quite unique for cobalt and also rather known for the compounds of neighboring iron than for

the heavier metals of group 9. Comparable especially to rhodium catalysis is the oxidation state +3 as usually highest occurring state during catalytic reactions.

### 1.2.1.1 Co(III) Compounds

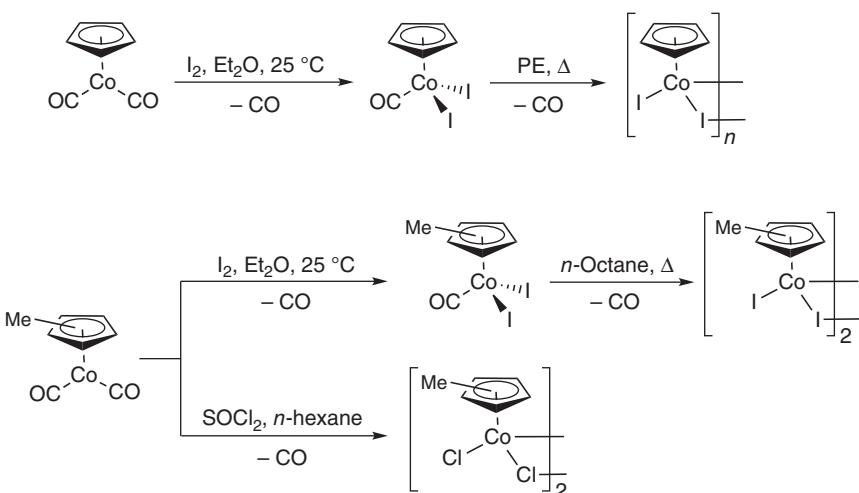
Isolated cobalt complexes in the oxidation state +3 are most often found in coordination compounds, because the  $d^6$  configuration is highly stable with ligands possessing a strong ligand field. There is only a limited number of Co(III) compounds commercially available and from the halides, only the binary  $\text{CoF}_3$  is known, which is an oxidant and can be used as fluorinating agent. This is in stark contrast to rhodium and iridium, where the oxidation state +3 is well known in compounds and all binary halides  $\text{MX}_3$  ( $\text{X} = \text{F}, \text{Cl}, \text{Br}, \text{I}$ ) are available for these metals.  $\text{RhCl}_3$  and  $\text{IrCl}_3$  and their hydrated versions are usually the starting materials for synthesising numerous precursor compounds and precatalysts for catalytic purposes, while  $\text{CoCl}_3$  is an unstable compound [17].

Cobalt(III) complexes played an important role in the development of the theory of coordination compounds by *Alfred Werner*, concerning the complexes of  $\text{CoCl}_3$  with different equivalents of ammonia,  $\text{NH}_3$ . The complexes  $[\text{Co}(\text{NH}_3)_4\text{Cl}_2]\text{Cl}$  exist in the form of two stereoisomers (*cis*- and *trans*-isomers of the octahedral polyhedron), allowing to address the stereochemistry of coordination compounds. The Co(III) complexes are kinetically inert, octahedral complexes with the configuration  $t_{sg}^6$ . Due to the inertness, indirect methods of synthesis are common, meaning to use Co(II) salts as starting compounds, coordination with desired ligands, and subsequent oxidation by, e.g. oxygen, to furnish the desired Co(III) complexes.

There are more organometallic Co(III) compounds known, owing to the strong ligand field of many groups used as organometallic ligands. As an example, cobaltocene,  $\text{Cp}_2\text{Co}$  is a rather unstable, 19-electron Co(II) complex, which can act as efficient one-electron reducing agent, yielding the stable cobaltocenium Co(III) cation ( $\text{Cp}_2\text{Co}^+$ ), being isoelectronic with ferrocene. While for ferrocene an extremely rich and diverse chemistry has been developed, e.g. as ligand backbone for phosphine ligands, such application of the cobaltocenium cation is lacking and started to develop only recently [18]. In addition, the synthesis of half-sandwich  $\text{CpCo(III)}$  complexes is well known and shares common features with  $\text{Cp}^*\text{Co}$  complexes. This is best exemplified by the reaction of the  $\text{CpCo(CO)}_2$  and  $\text{Cp}^*\text{Co(CO)}_2$  with elemental halides, furnishing the corresponding Co(III) complexes, which has been reported already during the time when the Cp–metal chemistry was still in its infancy (Scheme 1.3) [19, 20]. Especially  $\text{Cp}^*\text{CoI}_2(\text{CO})$  has become a precursor for a wide range of precatalyst compounds. The chemistry and catalytic applications of  $\text{CpCo(III)}$  and  $\text{Cp}^*\text{Co(III)}$  complexes as well as some structurally related  $\text{Cp}'\text{Co(III)}$  complexes has been compiled very recently [21].

### 1.2.1.2 Co(II) Compounds

Compared with its higher homologs, rhodium and iridium, the oxidation state +2 is one out of the two most important, while for the other two elements, it has only minor importance. All halides of this oxidation state are known and commercially available, stable compounds, being the starting material for a



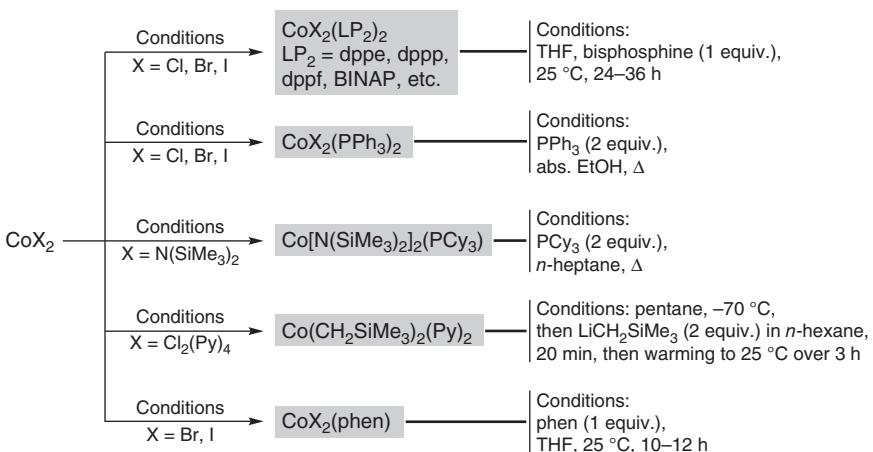
**Scheme 1.3** Synthesis of  $\text{CpCo}$ - and  $\text{Cp}^*\text{Co}$ -halides as synthetically useful precursors and precatalysts.

large number of complexes, e.g. as the hydrate  $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ . The configuration of  $\text{Co(II)}$  ions as being  $d^7$  does not favour a particular ligand arrangement for such paramagnetic complexes. Examples of coordination geometries comprise linear (e.g.  $[\text{Co}\{\text{N}(\text{SiMe}_3)_2\}_2]$ ), tetrahedral (e.g.  $[\text{CoCl}_4]^{2-}$ ,  $[\text{Co}(\text{N}_3)_4]^{2-}$ ,  $[\text{CoCl}_3(\text{NCMe})]^-$ ), square-based pyramidal (e.g.  $[\text{Co}(\text{CN})_5]^{3-}$ ), and dodecahedral (e.g.  $[\text{Co}(\text{NO}_3)_4]^{2-}$ ) forms, among many others, depending on the ligand properties [17].

$\text{Co(II)}$  salts used as precatalysts in catalytic reactions are usually reduced by less noble metals, such as zinc or manganese to  $\text{Co(I)}$ , which upon complexation to an appropriate ligand acts as catalytically active species. The salts can be introduced separately as halide salts and free ligand or as the isolated complex. The synthesis conditions of some typical  $\text{Co(II)}$  complexes are compiled in Scheme 1.4 [22]. A useful and very recently reported alternative to complexes of the type  $[\text{Co}(\text{R})_2(\text{Py})_2]$  is the compound  $[\text{Co}(\text{R})_2(\text{TMEDA})_2]$  ( $\text{R} = \text{CH}_2\text{SiMe}_3$ ,  $\text{CH}_2\text{CMe}_3$ ,  $\text{CH}_2\text{CMe}_2\text{Ph}$ ), allowed facile substitution of the “dummy” ligand for  $N$ -heterocyclic carbene (NHC) ligands or bidentate phosphines [23].

The reduction depends on conditions like the applied  $\text{Co(II)}$  salt, solvents, reductants involved, and even additives like *Lewis* acids, being able to remove a remaining halide from the metal centre [24]. In cross-coupling reactions utilising cobalt(II) precatalysts, the reduction to  $\text{Co(I)}$  or even  $\text{Co(0)}$  can also be achieved by an excess of the organometallic coupling reagent, often *Grignard* reagents [25].

Recently, novel  $\text{Co(II)}$  precursor compounds for catalytic applications came to the forefront and opened the door also for the synthesis of complexes being comparable to known precursor molecules with the latter homologs, e.g.  $[\text{M}(\text{COD})\text{Cl}]_2$  ( $\text{M} = \text{Rh}$ ,  $\text{Ir}$ ) or  $[\text{Rh}(\text{COD})_2](\text{BF}_4)$ . Chirik introduced  $(\text{Py})_2\text{Co}(\text{CH}_2\text{SiMe}_3)_2$  as precursor for the coordination to bisphosphines and subsequent asymmetric hydrogenation reactions, providing evidence for the

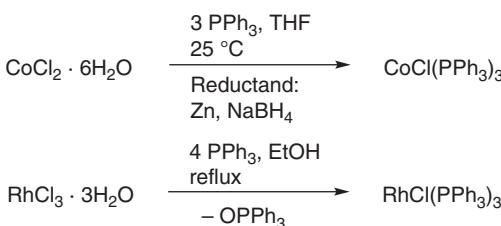


**Scheme 1.4** Synthesis of Co(II) complexes from simple Co(II) salts.

superiority of the cobalt precursor  $(\text{Py})_2\text{Co}(\text{CH}_2\text{SiMe}_3)_2$  compared with simple Co(II) salts [26].

### 1.2.1.3 Co(I) Compounds

There are significantly less Co(I) complexes known and commercially available compared with the Co(+2) and Co(+3) oxidation state. Most complexes are generated *in situ* or require strict handling under inert conditions. A common source is the *Wilkinson* complex,  $\text{RhCl}(\text{PPh}_3)_3$  and analogue of cobalt,  $\text{CoCl}(\text{PPh}_3)_3$ , which is used as synthetic precursor for the assembly of Co(I) complexes as well as precatalyst itself. Comparing the synthesis of these complexes nicely points out the differences between the metals (Scheme 1.5) [27, 28]. Synthesis of the bromide and iodide complexes,  $\text{CoX}(\text{PPh}_3)_3$  ( $\text{M} = \text{Br}, \text{I}$ ), can be obtained on an identical route compared with  $\text{CoCl}(\text{PPh}_3)_3$  [29]. The iridium analogue  $\text{IrCl}(\text{PPh}_3)_3$  is even more difficult to obtain and is not a suitable hydrogenation catalyst due to strong bonding of hydrogen [30]. In addition, it very readily undergoes *ortho*-metallation of a phosphine phenyl ring.



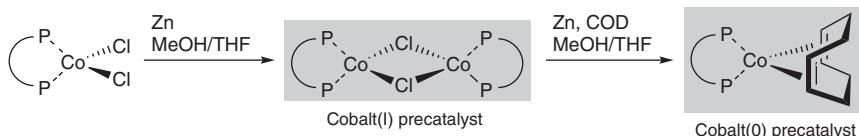
**Scheme 1.5** Synthesis of complexes of type  $\text{MCl}(\text{PPh}_3)_3$  ( $\text{M} = \text{Co, Rh}$ ).

While the *Wilkinson* complex is the classical catalyst for hydrogenation of multiple bonds, the cobalt analogue has been used much less in general

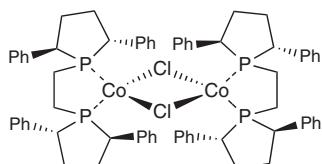
and reported reactions comprise more cyclisations and only few examples of hydrogenation [31].

As Rh(I) and Ir(I) complexes, suitable as metal sources for catalytic purposes, a number of either dinuclear, often halide-bridged olefin complexes, or mononuclear cationic complexes are readily available. This is in stark contrast to the lightest group member, which did not possess such a range of precursors. Only recently several examples for comparable complexes were reported. *Chirik* investigated the synthesis and reduction of  $\text{CoCl}_2$ (bisphosphine) by zinc and independently synthesised chlorido-bridged dinuclear Co(I) complexes, which can then also further be reduced to Co(0) complexes (Scheme 1.6) [32]. The analogue process for dinuclear Rh(I) complexes was systematically investigated by *Heller*, demonstrating the so far operationally more simple procedure for rhodium, which is possible by simply mixing the stable precursors  $[\text{RhCl}(\text{COD})_2]$  or  $[\text{RhCl}(\text{C}_2\text{H}_4)_2]$  with 2 equiv. of the diphosphine (Scheme 1.6) [33]. This methodology is very variably applicable to broad range of chiral ligands.

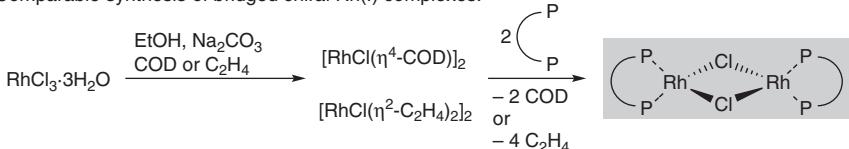
Synthesis of bridged chiral Co(I) complexes:



Example for a chiral dinuclear cobalt(I) complexes:



Comparable synthesis of bridged chiral Rh(I) complexes:



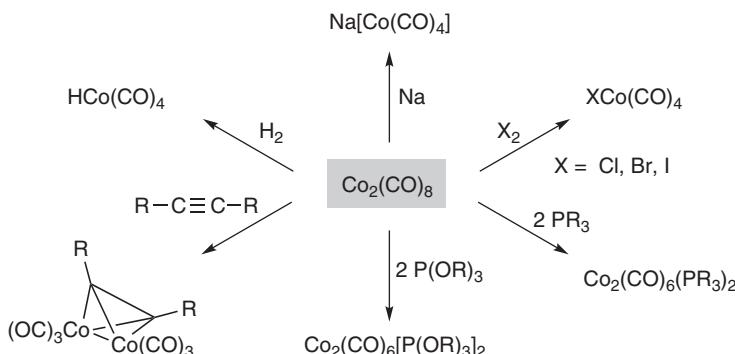
**Scheme 1.6** Synthesis of dinuclear halide-bridged Co(I)(diphosphine) complexes and the synthesis of related Rh(I) complexes for comparison.

Another rather large class of compounds are  $\text{CpCo}(\text{I})$  complexes with different neutral ligands, often simply derived from  $\text{CpCo}(\text{CO})_2$  by ligand exchange or reaction of the metallated Cp either with Co(II) halides under reductive conditions or from Co(I) halide complexes and subsequent ligand exchange [34]. The generation from cobaltocene by reductive removal of one Cp ligand in the presence of the corresponding ligand is also a possibility, *vide infra*.

#### 1.2.1.4 Co(0) Compounds

The most important Co(0) compound for synthetic and catalytic purposes is certainly the binary carbon monoxide-containing compound  $\text{Co}_2(\text{CO})_8$ , an

18-electron metal complex.  $\text{Co}_2(\text{CO})_8$  is not only synthesised by reaction of  $\text{Co}(\text{OAc})_2$  with hydrogen and CO at 150–200 °C and high pressure but can also be obtained from elemental cobalt and CO and is commercially available. It decomposes at increasing temperature to yield higher cobalt clusters compounds while releasing CO. The CO ligands can easily be exchanged for other donor ligands, and reactions with halides, hydrogen, or alkali metals can lead to either formal cationic or anionic  $[\text{Co}(\text{CO})_4]$  fragments, in both cases stabilised by the electronic moderation of the CO ligands (Scheme 1.7). These fragments are useful reagents for further synthetic transformations. Monodentate and bidentate phosphines as well as phosphite ligands can easily be introduced by ligand exchange, just to name the most prominent examples. The complexation of alkynes plays a significant role in the mechanism of the *Pauson–Khand* reaction, the *Nicholas* reaction or [2+2+2] cycloaddition reactions as well as one of the few protection groups for alkynes (see the corresponding chapters 6, 8 and 9 in this book).

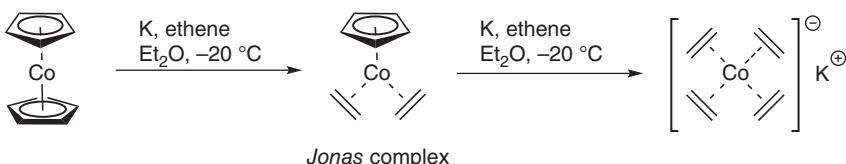


**Scheme 1.7**  $\text{Co}_2(\text{CO})_8$  as precursor for cobalt-carbonyl compounds.

Another 17-electron  $\text{Co}(0)$  compound, which has been used in catalytic applications like C–H activation and reductive C–C coupling [35], is the complex  $\text{Co}(\text{PMe}_3)_4$ , which can be prepared from  $\text{Co}(\text{II})$  halides in the presence of  $\text{PMe}_3$  by reduction with sodium amalgam [36]. The electron richness of this complex makes application in C–H functionalisation reactions a self-evident possibility.

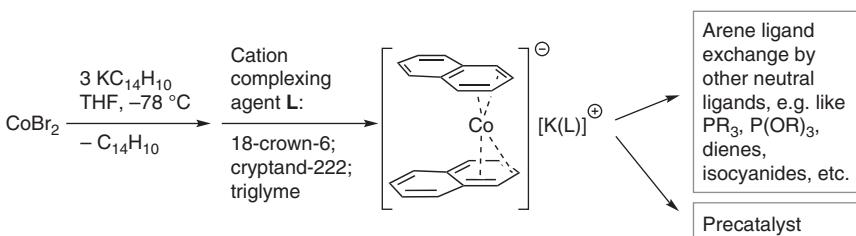
### 1.2.1.5 $\text{Co}(-\text{I})$ Compounds

As mentioned earlier, a formal anionic carbonyl cobaltate  $[\text{Co}(\text{CO})_4]^-$  can be simply generated by reaction of  $\text{Co}_2(\text{CO})_8$  with an alkali metal. The compounds are rather strong nucleophiles and therefore alkylation reactions are possible. An elegant reaction pathway was described by *Jonas*, who reduced cobaltocene in the presence of olefins (ethene, COD) with alkali metals by reductive removal of the Cp ligands (Scheme 1.8) [37]. Driving force of the reaction is the formation of the 18-electron complex from the 19-electron cobaltocene. The procedure is quite general and can be applied also to other olefins as general entry to  $\text{CpCo}(\text{I})$ -olefin and -diene complexes [38, 4b]. The olefin ligands act as  $\pi$ -acceptor ligands, thus reasonably stabilising the metallate.



**Scheme 1.8** Synthesis of the *Jonas* complex and subsequently the binary olefin cobaltate complex.

Other anionic cobaltates have been prepared by the inclusion of arene ligands by reduction in the presence of alkali metals (Scheme 1.9) [39]. The synthesis using naphthalene or anthracene yielded the bis(naphthalene)cobaltate ( $-I$ ) or bis(anthracene)cobaltate ( $-I$ ) as potassium salt, which can easily be transformed into metallates containing other neutral ligands, like dienes, phosphanes, phosphites, isocyanides beside the arenes, or exclusively containing the other ligands [40]. Such complexes are promising for the use in hydrogenation reactions, as was demonstrated recently by *Wolf* and *Jacobi von Wangelin* [41].

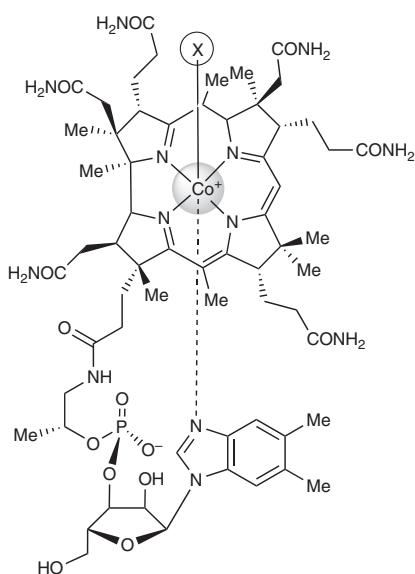


**Scheme 1.9** Preparation of anionic bis(naphthalene) Co( $-I$ ) complexes and subsequent reaction possibilities.

### 1.2.2 Bioorganometallic Cobalt Compounds

Cobalt is one of the few transition metals with a biorelevant organometallic chemistry. This is quite surprising, because it is the least abundant of the first-row (3d) transition metals in the Earth's upper crust and in sea water [42]. The coenzyme B<sub>12</sub>, part of the cobalamins, which feature corrin as the organic framework, and the studies of derivatives including vitamin B<sub>12</sub> have earned a lot of reputation for contributing significant knowledge not only to the organometallic chemistry of cobalt but moreover to bioorganometallic chemistry in general, natural product synthesis, and structure analytics [43]. The last aspect was spectacularly illustrated by awarding the Nobel Prize for chemistry to *Dorothy Crowfoot Hodgkin* for her X-ray crystallographic investigation of vitamin B<sub>12</sub>, beside other structurally complex molecules. Scheme 1.10 represents a structural overview on the cobalamins and the coordination environment of the cobalt centre during redox events.

The Co—CH<sub>3</sub> bond in methylcobalamin is unusually stable against hydrolysis in aqueous media; however, it can be homolytically split by formation of a methyl radical under enzymatic control. Electron donation and therefore reduction



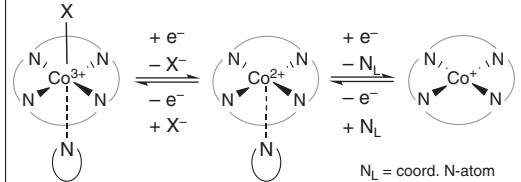
Functional groups bound to cobalt:

(X) = CH<sub>3</sub>: methylcobalamin

(X) = CN: cyanocobalamin  
(vitamin B<sub>12</sub>)

(X) = OH: hydroxycobalamin  
(vitamin B<sub>12a</sub>)

Oxidation and reduction at the cobalt centre:



Scheme 1.10 Cobalamins, vitamin B<sub>12</sub>, and the role of cobalt as metal centre.

of the cobalt from Co(III) to Co(I) is accompanied by removal of the axial ligands, thus resulting in a square planar Co(I) complex. A natural process is the methylation step in the synthesis of the amino acid methionine, where a generated methyl cation is transferred to the homocysteine moiety of the substrate, thus leaving the Co(I) as an electron-rich supernucleophilic  $d^8$ -configured metal centre. Two electrons occupy and fill up the antibonding  $d_{z^2}$  orbital, thus leading to an orbital with high affinity towards electrophiles, allowing for such electronically configured metals typical reactions like the oxidative addition of organic compounds R–X. This property allows the abstraction of a methyl cation from methyltetrahydrofolate, closing the catalytic cycle of the methylation process. Cobalamines are subject to a number of studies on their modification and application in catalytic organic transformations [44].

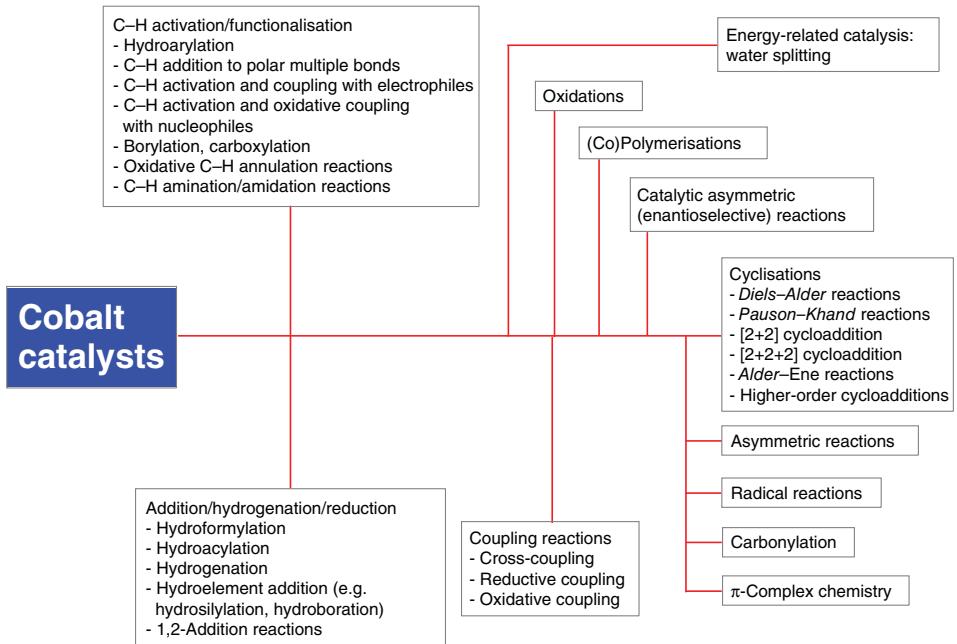
### 1.3 Applications in Organic Synthesis and Catalytic Transformations

Cobalt has become one of the rising stars in base metal catalysis for synthetic purposes, which have emerged over the recent decade. Interestingly, even when reviewed in 2011, no large-scale applications in the synthesis of pharmaceuticals were mentioned so far [45]. It can be foreseen that this situation might change in the future, following the recent developments in the area of cobalt-mediated reactions. As comparison with the other base metals provides, cobalt together with iron and nickel clearly dominate among the other 3d metals, when it comes to versatility of the reactions being mediated or catalysed [5]. In many cases even stereo- and enantioselective variants of achiral reactions have already been developed and implemented, although there is certainly room for improvement for future inquiries [46].

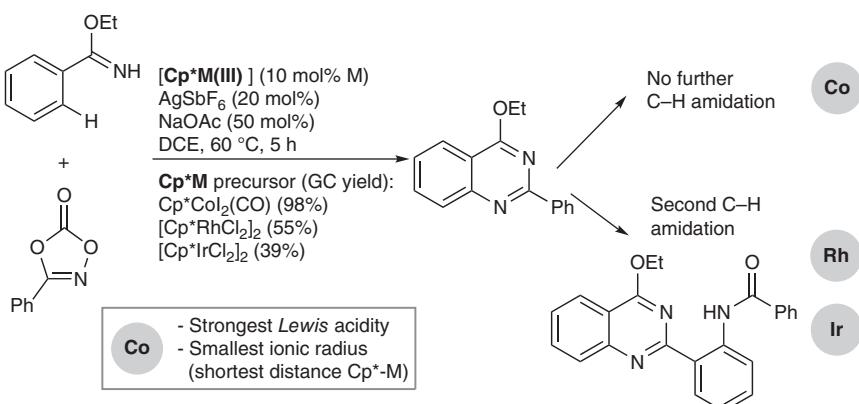
Scheme 1.11 illustrates an overview on different reactions that are either mediated by non-catalytic amounts of cobalt complexes or that are catalysed by cobalt complexes.

In the following just few aspects of the behaviour of cobalt catalysts in organic synthesis will be exemplarily discussed, as much more details can be found in the following chapters of this book.

The field of C–H activation/functionalisation reactions of cobalt complexes has flourished tremendously in recent years and although only relatively few complexes are applied, the substrate scope has extended very rapidly. This particular class of reactions can also serve as an example for the possibilities of the first-row transition metals to offer different oxidation states for catalysis compared with the heavier congeners [47]. Such comparative investigations have corroborated the differences between the group 9 transition metals, exemplified by catalytic C–H functionalisation of aryl imines and aryl amides with dioxazolones catalysed by  $\text{Cp}^*\text{M}$  derivatives as reported by *Chang* and *Glorius* independently (Scheme 1.12) [48, 49]. The latter investigation provided the insight that the strong *Lewis* acidity and smallest ionic radius of the Co(III) centre played a pivotal role in the reactivity of the  $\text{Cp}^*\text{M}$  fragment for accomplishing



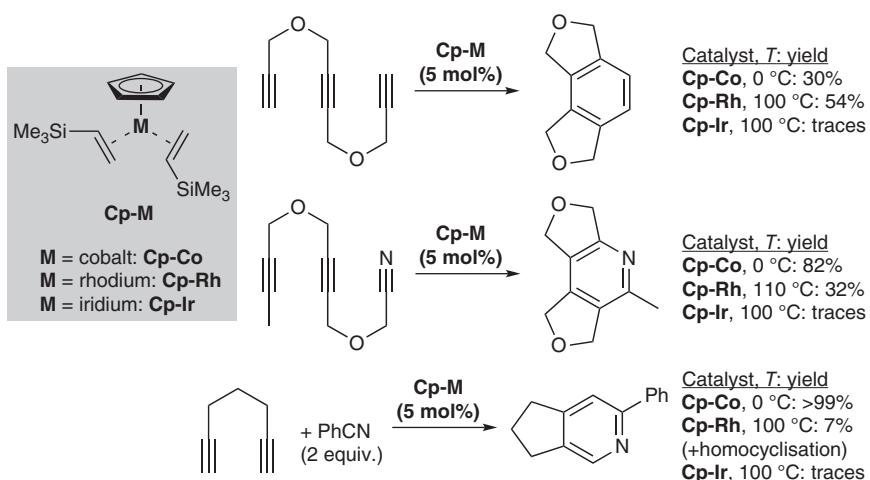
Scheme 1.11 Cobalt-mediated and cobalt-catalysed reactions for synthetic purposes.



Scheme 1.12 C–H functionalisation with group 9 metal complexes.

a complete and smooth reaction without changes in the formal oxidation state of the cobalt atom. While the *Lewis* acidity promoted the intramolecular cyclisation of the primary amidation product to yield the desired quinazoline derivative, the small ionic radius and shorter distance to the sterically cantilevered  $\text{Cp}^*$  group preventing the second undesired amidation step due to steric hindrance, thus yielding a single product. The results are comparable when  $[\text{Cp}^*\text{CoCl}_2]$  is used instead of  $[\text{Cp}^*\text{CoI}_2(\text{CO})]$ , as the investigation by Chang showed [48]. A detailed overview on shifts in selectivity and reactivity for the group 9 metal catalysts revealed the significant differences, especially between cobalt and rhodium complexes [50]. Unusual activation of other inert bonds (C–H, C–O) with 3d neighbour metal complexes and cobalt have also seen startling results in recent years, potentially allowing to rethink conventional approaches for C–C and other bond formations [51].

Reactions with substrates containing  $\pi$  bonds is a “home game” for cobalt complexes, which is illustrated throughout the literature [52]. Reactivity differences between the group 9 metals were exemplarily also illustrated for different reactions [4a], in particular for cyclotrimerisation reactions, where all three group 9 metals have found large applications [4b]. Especially for the cyclisation of diynes/nitriles, cyanodiynes, and triynes, when structurally identical complexes except for the central metal atom were applied, significant differences were accounted for (Scheme 1.13) [53]. The synthesis of the complexes **Cp-M** already demonstrated the different approaches to obtain the respective complexes with **Cp-Co** on one hand and **Cp-Rh** and **Cp-Ir** following identical protocols with the introduction of the  $\text{Cp}$ -ligand on the final stage on the other hand. In addition, the latter two complexes were rather stable and could in contrast to **Cp-Co** be handled in air, at least for short periods of time. The reactivity screening corroborated also the differences; in all investigated cases the precatalyst **Cp-Ir** was virtually inactive. Cyclisation of a terminally unsubstituted triyne gave 30% yield for **Cp-Co** even at 0 °C (higher temperatures led to increased decomposition), while **Cp-Rh** required 100 °C to promote the reaction, although with higher yields (Scheme 1.13, top). This changed when reacting cyanodiynes, again

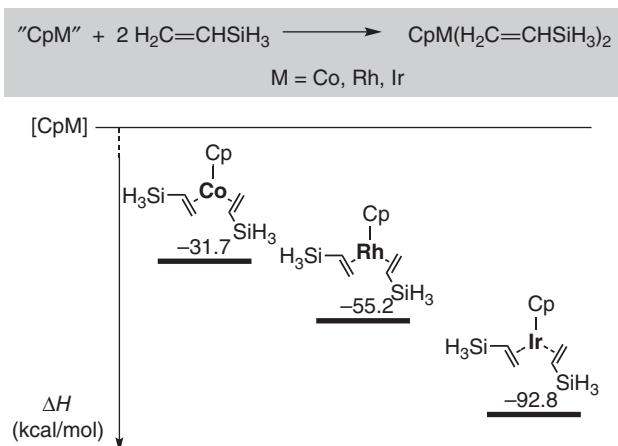


**Scheme 1.13** Cyclotrimerisation with structurally identical group 9 metal-cyclopentadienyl complexes and different substrates.

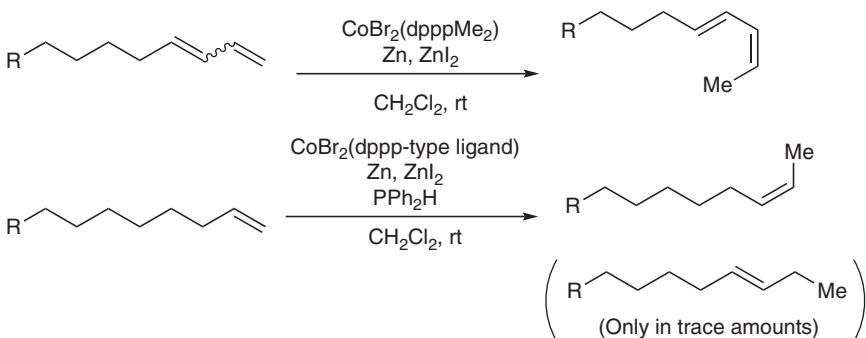
a reaction in completely intramolecular fashion. Here, **Cp-Co** gave excellent 82% pyridine, while **Cp-Rh** only furnished 32% (Scheme 1.13, middle). This even changed more dramatically in the case of the reaction of 1,6-heptadiyne with benzonitrile, yielding quantitative amounts of the pyridine product with **Cp-Co** and only 7% with **Cp-Rh** (Scheme 1.13, bottom). Here, however, larger quantities of aromatic homocyclisation product from the diyne were observed with **Cp-Rh**, providing evidence for the preference for carbocyclisation for the rhodium catalyst.

Further reactivity differences for **Cp-M** were encountered in hydrogenation and hydroformylation reactions, with the inclination of the cobalt complex for isomerisation of the double and not exclusively hydrogenation. Assessment of the reactivity of the complexes of the type **Cp-M** from computational calculations indicated the increasing stability of the olefin complexes when going to the heavier congeners (Scheme 1.14).

The previously mentioned isomerisation of double bonds has found increasing attention during the last decade due to the growing importance of selectively shifting this synthetically highly important functionality within a molecule. Cobalt complexes have also been utilised for the migrational transposition of double bonds along a carbon chain. Besides the isomerisation of a terminal 1,3-diene subunit towards a stereodefined 2 $Z$ ,4 $E$ -product also a transposition of a terminal alkene towards a 2 $Z$ -alkene could be realised by *Hilt* (Scheme 1.15) [54]. Crucial for the latter reaction was the application of diphenylphosphine ( $\text{PPh}_2\text{H}$ ) as ligand, and it is worth to mention that the chain walking of the double bond, e.g. towards the corresponding 3-alkenes and so on was only observed in trace amounts. Nevertheless, later on *Hilt* could show that the corresponding nickel-catalysed reactions were associated with a significantly higher reactivity and a broader substrate scope [54d–f].



**Scheme 1.14** Energetics of olefin coordination to CpM (M = Co, Rh, Ir) fragments. Source: Weding et al. 2011 [53]. Reproduced with permission of John Wiley and Sons.



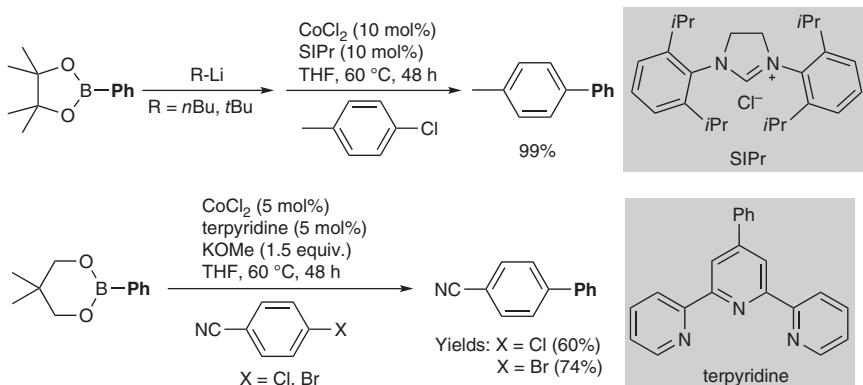
**Scheme 1.15** Cobalt-catalysed migrational transposition of double bonds.

To exemplarily delineate a forth field of catalytic applications, which interestingly has only seen cobalt to flourish in contrast to its heavier group congeners, is through cross-coupling reactions. This is certainly a big difference to the neighbouring group 10, where the heavier congener to nickel, palladium, is the archetype metal in cross-coupling catalysts [55]. On the other hand, neighbouring 3d element iron has seen a significant amount of application in cross-coupling reactions, including puzzling of the available reaction mechanisms [56]. Due to its very low toxicity and abundance, iron-catalysed cross-coupling reactions are of remarkable interest for manufacturing pharmaceuticals [57].

Cobalt-catalysed cross-coupling reactions have in principle a long history; however, mostly single reports on successful coupling reactions were recorded for a long time [25]. Especially during the last two decades, many useful protocols for introducing cobalt salts as catalysts for most cross-coupling reactions have been published. While for palladium-catalysed reactions the whole range of phosphorus-based ligands are usually applied, the picture is more differentiated

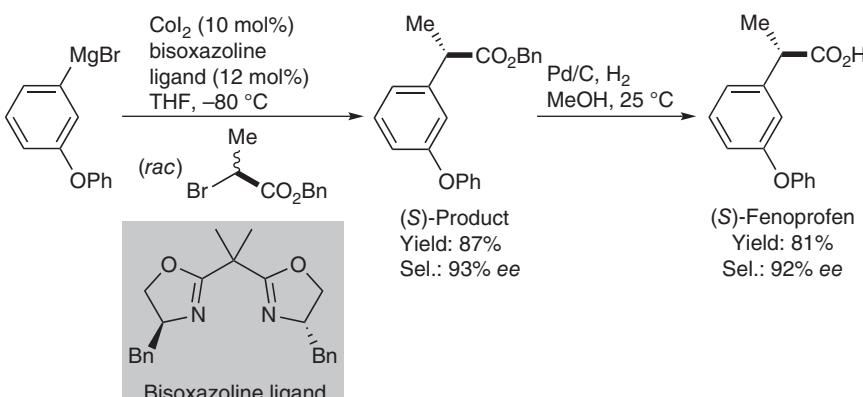
for cobalt complexes. The most versatile methodology with a very diverse array of nucleophiles has been established by the *Suzuki–Miyaura* reaction. Especially the direct application of the rather stable boronic acids, available with a huge structural diversity, is advantageous for this coupling protocol.

Initial experimental insight into the transmetallation in cobalt-catalysed *Suzuki–Miyaura* coupling through investigations by *Chirik*, utilising a Co(I)-PNP (bis(diisopropylphosphinomethyl)pyridine) pincer complex and aryl triflate and heteroarylboronic acid esters, showed that a cross-coupling with neutral boron nucleophiles is possible, when the cobalt centre carried a alkoxide anion [58]. However, so far no reliable successful *Suzuki–Miyaura* coupling with the free boronic acids has been established. Exemplary coupling reactions demonstrating the usefulness of cobalt catalysis in the coupling of aryl groups are shown in Scheme 1.15. *Bedford* applied NHC ligands like SIPr together with  $\text{CoCl}_2$  in a 1 : 1 ratio and a preformed anionic boron nucleophile for the successful coupling with halides, especially aryl chlorides, in good to excellent yields (Scheme 1.16) [59]. Possibly, the cobalt atom is reduced to  $\text{Co}(0)$  during the reaction. The cross-coupling with neopentyl glycolatophenyl boronates in the presence of a Co-terpyridine complex and a base allowed the coupling of arylchlorides and arylbromides as well as heteroarylhalides with often good to very good yields (Scheme 1.16) [60]. Regarding the importance of the *Suzuki–Miyaura* for pharmaceutical ingredients and fine chemicals synthesis and production [61], the cobalt-catalysed version is still in its infancy.



**Scheme 1.16** Cobalt-catalysed *Suzuki–Miyaura* coupling reactions for the preparation of biaryl.

The field of (asymmetric) cross-coupling reactions is dominated by nickel catalysis, especially with reaction partners possessing a  $\text{sp}^3$ -hybridised carbon atom, where the coupling is taking place [62]. Particularly interesting is the possibility to use ethers and esters as electrophiles for such reactions. Therefore, nickel complexes adopt an outstanding role as catalysts in this particular field of research [63]. However, quite recently the first asymmetric *Kumada* coupling catalysed by a cobalt complex has been published by *Zhong*

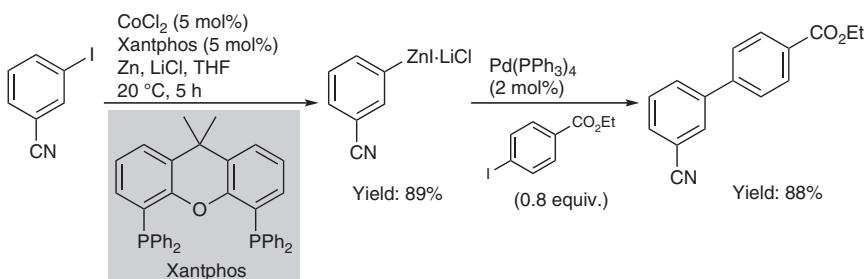


**Scheme 1.17** Asymmetric cobalt-catalysed *Kumada* cross-coupling reaction with alkyl bromides.

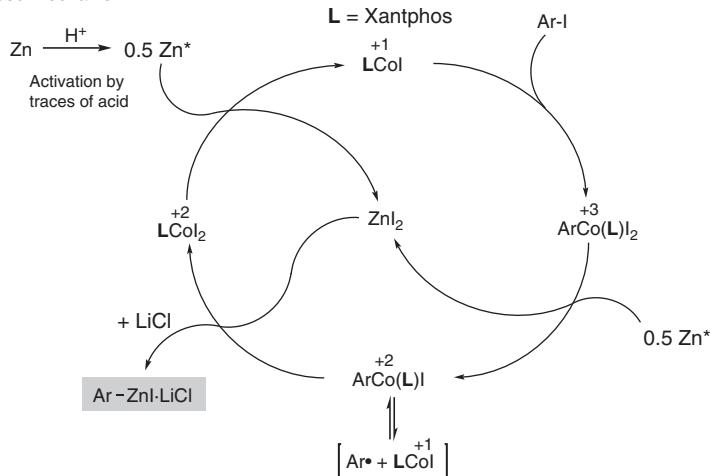
and *Bian* (Scheme 1.17) [64]. Again nitrogen-based chiral  $C_2$ -symmetrical bisoxazoline ligands were most successful for the formation of an efficient catalytic system. The investigation towards different cobalt sources showed the strong dependence from the counterion, with  $\text{CoI}_2$  being the preferable metal source. The observation of a strong influence of the cobalt source on *in situ*-generated catalysts is frequently observed, and screening of cobalt salts is therefore routine during the development of catalytic systems. The investigated reactions were performed at temperatures as low as  $-80\text{ }^\circ\text{C}$ , providing evidence for the extraordinary reactivity of the cobalt catalyst and accessing a rather unusual parameter space for cross-coupling reactions. In addition, at such low temperatures, *Grignard* reagents are quite tolerant for the presence of functional groups in the molecule, significantly broadening the scope of application of the methodology.

Finally, to demonstrate the unusual properties and catalytic possibilities of cobalt complexes, the metalation of an aryl iodide catalysed by a  $\text{Co(I)}$ -Xantphos complex is presented (Scheme 1.18). The metalation is followed by a cross-coupling reaction, e.g. with another aryl halide mediated by  $\text{Pd}(\text{PPh}_3)_4$  in a one-pot reaction without interference of the cobalt catalyst [65]. The reaction allows the preparation of arylzinc compounds from aryl iodides, bromides, and chlorides, and the added  $\text{LiCl}$  facilitates the reaction and later on complexes the organozinc reagent. The involved species presumably comprise  $\text{Co(I)}$  and  $\text{Co(III)}$  oxidation states, starting from  $\text{Co(II)}$  by one-electron reduction using the elemental zinc. The proposed reaction mechanism is illustrated in Scheme 1.18. Identical conditions were developed to prepare aryl- and heteroaryllindium compounds from indium metal [66]. Interestingly, however, the applied most efficient cobalt catalyst was a  $\text{Co(I)}$ -bathophenanthroline complex, although the likely mechanism followed the one proposed in Scheme 1.18.

The broad scope and exciting reactions catalysed by cobalt are illustrated significantly in more depth in the following chapters of this book.



Proposed mechanism:



**Scheme 1.18** Application of a catalysed zincation of an aryl iodide and subsequent palladium-catalysed *Negishi* coupling reactions, including the illustrated assumed mechanism of the cobalt–Xantphos-catalysed metalation reaction.

## 1.4 Conclusion and Outlook

Over recent years, cobalt complexes have seen a significant increase in application for modern and challenging reactions, which have so far often been the domain of its heavier, and more expensive group homologs, rhodium and iridium. This is interesting as the catalytic application of cobalt complexes in homogeneous catalysis has been long known, evidenced by the discovery of the so-called oxo-process (hydroformylation of alkenes) in the 1930s. Cobalt complexes are available in a large range of oxidation states, ranging from  $-1$  to  $+3$ , allowing rather simple change of oxidation states in catalytic reactions as well as the possibility to prepare compounds in the respective oxidation states. Current efforts are directed often to prepare novel cobalt complexes with diverse ligand structures and properties and to screen their potential towards the mediation of reactions, so far not or not typically catalysed or mediated by cobalt.

## Abbreviations

Ac	acetyl
Ar	aryl
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
COD	1,5-cyclooctadiene
Cp	cyclopentadienyl
Cp'	substituted cyclopentadienyl
Cp*	pentamethylcyclopentadienyl
DCE	1,2-dichloroethane
dppb	1,4-bis(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1'-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane
ee	enantiomeric excess
equiv.	equivalent
Et	ethyl
GC	gas chromatography
Me	methyl
NHC	<i>N</i> -heterocyclic carbene
NMR	nuclear magnetic resonance
phen	1,10-phenanthroline
PE	petrol ether
Ph	phenyl
PGM	platinum group metals
iPr	isopropyl
Py	pyridine
rac	racemic
sel.	selectivity
T	temperature
Tf	triflate
THF	tetrahydrofuran
TMEDA	<i>N,N,N',N'</i> -tetramethylethylenediamine
triglyme	1,2-bis(2-methoxyethoxy)ethane

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## 2

# Homogeneous Cobalt-Catalysed Hydrogenation Reactions

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## 2.1 Introduction

Catalytic reductions are regarded as one of the most frequently used methodologies in organic synthesis, which have attracted long-lasting interests in academia and industry [1]. In general, saturated compounds are formed in an atom-efficient and straightforward manner by the addition of hydrogen to the corresponding unsaturated substrates. Specifically, alkanes, alcohols, and amines are produced via hydrogenation of C=C, C=O, and C=N bonds. With the aid of catalysts, high efficiency and selectivity can be obtained in the presence of a suitable reductant. In this regard, the activation of reagents and the control of the selectivity by appropriate catalysis, especially by transition metal catalysis are essential. Until to date, most catalytic hydrogenations were developed using precious metals such as Ru, Rh, Ir, Pt, and Pd. Due to economic and ecologic constrains, the application of non-precious metals such as Fe, Mn, Ni, and Co took centre stage of catalysis [2]. While rhodium and iridium as its 4d and 5d congeners, respectively, had profound impact on the development of hydrogenation methodologies, the 3d metal cobalt has been studied to a much lesser extent. On the other hand, it is much less expensive and abundantly available due to its production as a by-product of copper and nickel mining. Furthermore, cobalt is an essential trace mineral and is found in nature as vitamin B<sub>12</sub> or coenzyme B<sub>12</sub> [3].

In this chapter, we summarised the use of cobalt-based homogeneous catalysts in hydrogenations of C—C multiple bond, carbonyl compounds, and CO<sub>2</sub> as well as C—X multiple bonds. In addition, few examples of asymmetric reductions of functionalised olefins, ketones, and imines were highlighted.

## 2.2 Hydrogenation of C—C Multiple Bonds (Alkenes, Alkynes)

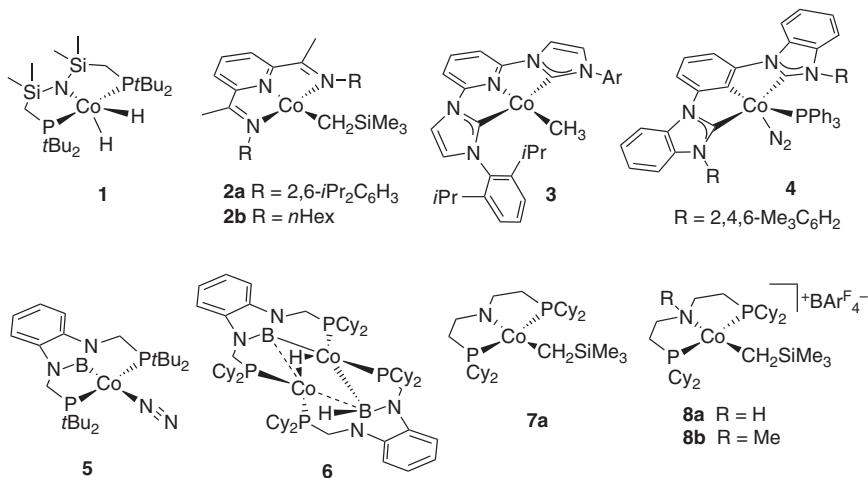
The first cobalt-catalysed hydrogenations of activated olefins were developed in the early 1960, when simple inorganic salts such as K<sub>3</sub>[Co(CN)<sub>5</sub>] [4] or



**Scheme 2.1** Activation of hydrogen by  $\text{K}_3[\text{Co}(\text{CN})_5]$  (Eq. (1)) or  $\text{Co}_2(\text{CO})_8$  (Eq. (2)).

organometallic compounds like  $\text{Co}_2(\text{CO})_8$  [5] were tested. Based on the even earlier findings of *Iguchi*, who observed the activation of hydrogen by aqueous potassium pentacyanocobaltate(II) leading to  $[\text{Co}(\text{CN})_5\text{H}]^{3-}$  (Scheme 2.1, Eq. (1)) [6], *Kwiatek* reported the catalytic hydrogenation of various dienes, aromatic olefins, or  $\alpha,\beta$ -unsaturated organic acids with  $\text{K}_3[\text{Co}(\text{CN})_5]$  at room temperature and atmospheric hydrogen pressure in aqueous solution [4a]. Few years later, *Murakami* and *Kang* applied an *in situ*-generated cyanocobaltate complex for the hydrogenation of unsaturated acids, where the regiochemistry was controlled by the variation of the  $\text{CN}^-/\text{Co}$  ratio. Regarding the mechanism a coordination of the substrate to the cobalt complex ion via functional groups was discussed [4b]. Although the transformation was realised under mild reaction conditions, this system was limited to aqueous solutions where catalyst deactivation took place during time and several substrates did not react because of low solubility [7]. Applying the lithium salt of the pentacyanocobaltate(II) species allowed hydrogenation of cyclopentadiene or butadiene in ethanol but a low substrate concentration was required to prevent possible formation of  $\pi$ -allyl complexes [4d]. Therefore, new approaches such as working in aqueous micellar solution [4e] or under phase transfer reaction conditions [4f] were developed enlarging the general applicability of  $\text{K}_3[\text{Co}(\text{CN})_5\text{H}]$  to water insoluble alkenes.

Also  $\text{Co}_2(\text{CO})_8$ , which was known as suitable catalyst for *Pauson–Khand* reactions (Chapter 3) and hydroformylations, had been studied for the hydrogenation of unsaturated compounds due to its ability to form  $\text{HCo}(\text{CO})_4$  (Scheme 2.1, Eq. (2)) [8]. *Orchin* reported that conjugated dienes [9] and phenyl-substituted ethylenes [10] were readily hydrogenated with stoichiometric amounts of  $\text{HCo}(\text{CO})_4$ , leading to the saturated hydrocarbons.  $\alpha,\beta$ -Unsaturated aldehydes, ketones, and esters underwent hydroformylation as well as hydrogenation under the same conditions [11]. If catalytic amounts of  $\text{Co}_2(\text{CO})_8$  were used for the hydrogenation of substituted cinnamaldehyde under hydroformylation conditions ( $\text{CO:H}_2 = 1 : 1$ ), the saturated aldehyde as well as the saturated alcohol were formed in a ratio of  $4 : 1$  [12]. Combinations of  $\text{Co}_2(\text{CO})_8$  with (di)phosphine, phosphinite, or amine ligands improved the selectivity towards the C–C double bond reduction in  $\alpha,\beta$ -unsaturated aldehydes and ketones [13]. The best results were obtained for  $\text{Co}_2(\text{CO})_8$ /diisopropylamine leading to 96% yield of saturated aldehyde [12b]. Furthermore,  $\text{Co}_2(\text{CO})_8$  has been reported for the hydrogenation of unsaturated fatty acid esters, but an appreciable degree of C–C double bond hydrogenation was only achieved under relatively harsh conditions ( $180^\circ\text{C}$ , 200 bar) [14]. Also non-activated alkenes, alkynes, and arenes were hydrogenated with cobalt carbonyl complexes, such as  $\text{HCo}(\text{CO})_4$  and  $[\text{Co}(\text{H})(\text{CO})(\text{PR}_3)_3]$  ( $\text{R} = n\text{Bu, Ph}$ ) [15]. Thus, the cobalt species  $[\text{RCo}(\text{CO})_2\text{L}_2]$  ( $\text{R} = \text{Me or MeC(O)}$ ,  $\text{L} = \text{P(OMe)}_3$ ) were very active for the hydrogenation of terminal olefins giving a turnover frequency (TOF) of  $450 \text{ h}^{-1}$  for 1-hexene [16]. Additionally,



**Figure 2.1** Cobalt PNP pincer complexes applied in olefin hydrogenation.

carbonyl-free cobalt complexes bearing P-ligands such as  $[\text{Co}(\text{H})(\text{N}_2)(\text{PPh}_3)_3]$  [17] and  $[\eta^3\text{-C}_3\text{H}_5\text{Co}(\text{P}\{\text{OR}\}_3)_3]$  [18] catalysed the hydrogenation of aromatic hydrocarbons, olefins, or  $\alpha,\beta$ -unsaturated ketones at room temperature.

A more recent approach to stabilise low spin Co(I) species was the use of pincer ligands, which were able to accept an electron from the metal centre. Although, the group of Caulton described the cobalt pincer complex **1**, which was able to reduce ethene in stoichiometric mode (Figure 2.1) [19], the first real catalytic applications with this class of complexes were published by Budzelaar for olefin hydrogenation [20]. Here, the diimine pyridine complexes ( $\text{NNN}^{\text{dip}}$ ) $\text{CoCH}_2\text{SiMe}_3$  (**2a**) and ( $\text{NNN}^{\text{hex}}$ ) $\text{CoCH}_2\text{SiMe}_3$  (**2b**), which were known as suitable polymerisation catalysts [21], have been successfully tested in the hydrogenation of mono- and disubstituted olefins. In the reaction mechanism the formation of a hydride ( $\text{NNN}$ ) $\text{CoH}$  complex was postulated followed by insertion of the olefin into the Co—H bond. Upon addition of hydrogen, the trimethylsilylalkyl group was hydrogenated to the tetramethylsilane and the cobalt hydride species was generated.

In the following, several pincer-based cobalt systems were described for the olefin hydrogenation. Specifically, Chirik explored cobalt complex ( $i\text{PrCNC}$ ) $\text{CoCH}_3$  (**3**) for the reduction of tri- and tetra-substituted non-activated alkenes, such as *trans*-methyl stilbene, 1-methyl-1-cyclohexene, and 2,3-dimethyl-2-butene under very mild conditions [22]. In this particular cobalt catalyst, the imine donors were replaced by *N*-heterocyclic carbenes, resulting in a significant improvement of reactivity. The catalytic activity of ( ${}^{\text{Mes}}\text{CCC}$ ) $\text{Co}^{\text{I}}(\text{N}_2)(\text{PPh}_3)$  (**4**) was tested in the reaction of styrene at room temperature [23]. The applicability of this method has been evaluated with more hindered alkenes, tolerating functionalities such as hydroxyl groups, ketones, anhydrides, and aldehydes (Table 2.1). The selectivity towards terminal alkenes over internal alkenes was achieved tuning the reaction conditions. An additional application of ( ${}^{\text{Mes}}\text{CCC}$ ) $\text{Co}^{\text{I}}(\text{N}_2)(\text{PPh}_3)$  (**4**) was found in the semihydrogenation

**Table 2.1** Hydrogenation of selected alkenes using cobalt catalyst **4**.<sup>a)</sup>

Entry	Substrate	Product	Conv. (%)	t (h)
1			>99	3
2			>99	2
3			>99	22
4			>99	2
5 <sup>b)</sup>			>99	2

a) Conversion was monitored by  $^1\text{H}$  NMR.

b) Alkane product obtained after heating to 60 °C for 19 hours.

of alkynes, which were realised at low temperatures (30 °C) for a broad range of substrates with high selectivity to *trans*-alkenes [24].

Also the Co(PBP) pincer complex **5** reduced 1-octene and styrene under very mild conditions (2 mol% **5**, three minutes, rt, 1 bar  $\text{H}_2$ ) and with a TOF = 1 000 h<sup>-1</sup>, while the reduction of internal alkenes was achieved with the bimetallic derivative **6** bearing cyclohexyl substituents on the chelating phosphorus atoms [25]. A comparison of the catalytic efficiency of the monomeric **5** and the dimeric complexes **6** showed a lower activity for the latter one.

The aliphatic cobalt PNP pincer complexes **7a** and **8a** reported by *Hanson's* group were able to hydrogenate alkenes, too (Table 2.2) [26]. At room temperature using 2 mol% **8a** or a combination of 2 mol% **7a** and  $\text{H}[\text{BAr}^{\text{F}}_4](\text{Et}_2\text{O})_2$  and 1 bar of  $\text{H}_2$  aromatic and aliphatic alkenes were reduced within 24–40 hours giving yields between 80% and 100%. In order to study the functional group tolerance, more challenging substrates were tested such as 4-pentenoic acid, furnishing pentanoic acid. Based on the fact that the N-methylated species **8b** was also active for styrene reduction, a possible involvement of the N–H group in the catalytic mechanism was excluded [27].

*Wolf and Jacobi von Wangelin* presented a new concept where the low-valent cobalt species were stabilised by the  $\pi$ -coordination of hydrocarbons (Figure 2.2) [28a]. Applying 1 mol% of potassium bis(anthracene)cobaltate (**9**), excellent

**Table 2.2** Catalytic olefin hydrogenation with **7a**<sup>a)</sup> and **9**<sup>b)</sup>

Entry	Substrate	t (h)	Yield for <b>7a</b> (%)	t (h)	Yield for <b>9</b> (%)
1		24	100	3	95
2		24	99	3	98
3		24	100	3	100
4		24	100	24	100 <sup>c)</sup>
5		24	100	24	92 <sup>d)</sup>
6		24	100	24	100 <sup>c)</sup>
7 <sup>e)</sup>		40	80	24	63 <sup>d)</sup>

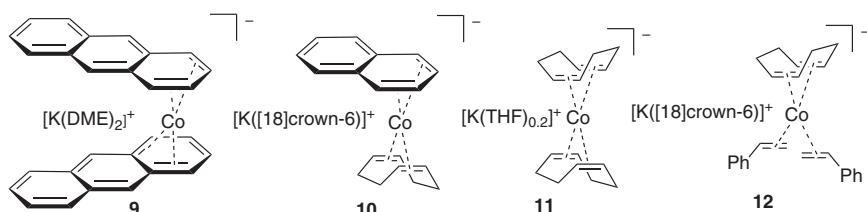
a) Conditions: 0.5 mmol substrate in THF, 1 bar H<sub>2</sub>, 25 °C, 2 mol% catalyst **7a**, 2 mol% [HBAr<sup>F</sup><sub>4</sub>](Et<sub>2</sub>O)<sub>2</sub>. The yield (in parentheses) was determined by GC analysis.

b) 0.5 mmol substrate in toluene, 1 mol% **9**, 20 °C, 2 bar H<sub>2</sub>.

c) 2 bar H<sub>2</sub>, 60 °C, 24 hours.

d) 5 mol% **9**, 10 bar H<sub>2</sub>, 60 °C, 24 hours.

e) Hydrogenation of the exocyclic double bond.

**Figure 2.2** Alkene and arene cobaltate complexes **9–12** for the hydrogenation of alkenes.

yields were obtained for  $\alpha$ -,  $\beta$ -, and ring-substituted styrenes at 2 bar H<sub>2</sub> pressure, while conversion of terminal, internal and di- as well as trisubstituted alkenes and alkynes required a higher catalyst loading (5 mol% **9**, 10 bar H<sub>2</sub>, 60 °C). In an extended study structurally related alkene and arene cobaltates **10–12** were applied as competent catalysts for the alkene hydrogenation under mild conditions (2 bar H<sub>2</sub>, 20 °C, 24 hours) [28b]. Based on spectroscopic experiments and the observation that complex **12** released ethylbenzene under H<sub>2</sub> atmosphere, they concluded that the olefin hydrogenation reaction was initiated by the substitution of one labile arene ligand by the  $\pi$ -acceptor substrate.

**Table 2.3** Asymmetric hydrogenation of selected olefins using cobalt catalysts **13a–b<sup>a)</sup>** or **14<sup>b)</sup>**

Entry	X	R	Yield (%)	ee (%)
1	H	iPr	87	<b>13a:</b> 90 ( <i>R</i> )
2			85	<b>13b:</b> 90 ( <i>S</i> )
3	H	tBu	5	<b>13a:</b> 98 ( <i>R</i> )
4 <sup>c)</sup>			99	<b>14:</b> 91 ( <i>R</i> )
5	4-NMe <sub>2</sub>	iPr	>98	<b>13a:</b> 96 ( <i>R</i> )
6	4-MeO	iPr	>98	<b>13a:</b> 94 ( <i>R</i> )
7 <sup>c)</sup>	4-MeO	Et	>99	<b>14:</b> 91 ( <i>R</i> )
8	4-F	iPr	>98	<b>13a:</b> 78 ( <i>R</i> )
9	2-Cl	Ph	99	<b>14:</b> 90 ( <i>S</i> )
10	2-Cl	3-CF <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	>99	<b>14:</b> 99 ( <i>S</i> )
11	2-Cl	3-MeO-C <sub>6</sub> H <sub>4</sub>	>99	<b>14:</b> 95 ( <i>S</i> )

a) Conditions: substrate (0.1 mmol), 5 mol% **13a** or **13b**, benzene (1 mL), 24 hours.

b) Conditions: substrate (0.5 mmol), 5 mol% **14**, 15 mol% NaBHEt<sub>3</sub>, toluene (1 mL), three hours.

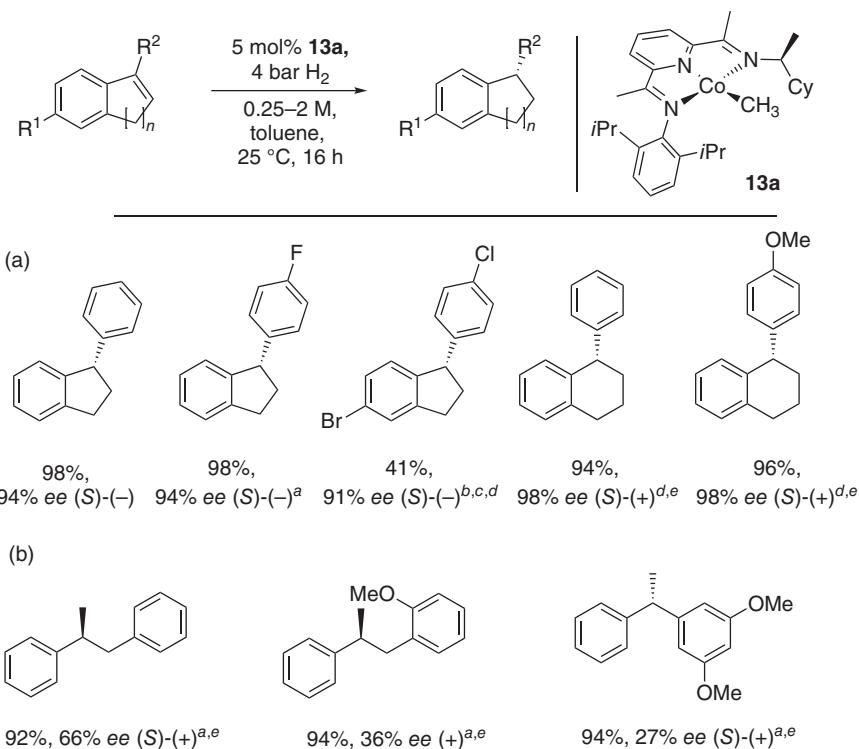
c) One hour. Yields determined by GC.

A comparison of both systems **7a** and **9** displayed comparable activity in the olefin reduction (Table 2.2), while **9** did not need additives for activation.

A stereoselective hydrogenation of prochiral alkenes catalysed by cobalt pincer-based complexes was achieved by suitable modification of the ligand architecture. Here, the cobalt pincer complexes **13a–b** contained one imine moiety substituted with a large aryl ring and another one bearing a chiral amine group [29]. Studying the organometallic chemistry of this complex, it was noticed that the cyclometalation of the chiral element (alkyl imine moiety) was competitive with the formation of the cobalt hydride, which had a detrimental effect on the catalytic activity [30]. In general, the highest selectivities and conversions were achieved with less hindered alkenes and electron-rich styrenes (Table 2.3). The arylated alkenes were hydrogenated with ee's (enantiomeric excess) of 80–98%, and the more crowded olefins showed the highest selectivities, albeit with lower conversion. Notably, the values of ee obtained with the catalyst **13a** were among the highest ee's, which were reported in the literature for the hydrogenation of alkenes.

A similar strategy for the development of chiral cobalt pincer catalysts for the enantioselective hydrogenation of alkenes was applied by *Lu*, when the iminopyridine ligand backbone was modified with the oxazoline moiety [31]. The bench-stable cobalt pincer complex **14** was successfully applied for the asymmetric reduction of 1,1-diarylethenes after activation with NaBH<sub>3</sub>Et and showed a unique *ortho*-chloride effect with high enantioselectivities up to 99% *ee* (Table 2.3, entries 9–11). Additionally,  $\alpha$ -alkylstyrenes were efficiently reduced within one hour using cobalt catalyst **14** (Table 2.3, entries 4 and 7).

Furthermore, *Chirik* explored the catalytic activity of **13a** for asymmetric hydrogenation of functionalised cyclic olefins and 1,1-disubstituted alkenes (Scheme 2.2) [32]. Cobalt pincer complex **13a** displayed excellent performance for reduction of 1,1-diaryl ethenes and related alkenes, although with decreased enantioselectivities (27–66% *ee*). The stereocontrol in the bis(imino)pyridine cobalt catalyst **13a** was further investigated in the asymmetric hydrogenation of isomeric exo- and endocyclic alkenes.

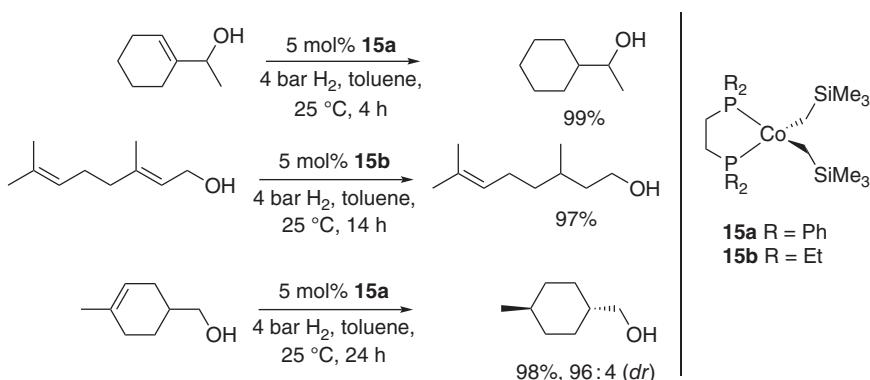


**Scheme 2.2** Selected examples of asymmetric hydrogenation of functionalised cyclic olefins (a) and 1,1-disubstituted alkenes (b) using cobalt catalysts **13a**. Conditions: 0.25 M, toluene (4 mL), substrate (0.1 mmol), 4 bar H<sub>2</sub>, 5 mol%, **13a**, 25 °C, 16 hours. <sup>a</sup> 1 bar H<sub>2</sub>. <sup>b</sup> Yields determined by NMR. <sup>c</sup> 1 M reaction. <sup>d</sup> 48 hours. <sup>e</sup> 2 M reaction.

While cobalt-mediated examples for the asymmetric hydrogenation of functionalised olefins were known, their substrate scope was limited and

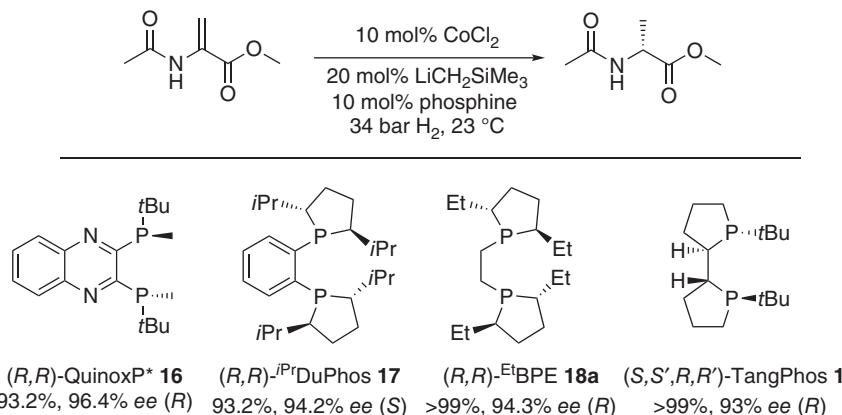
the yields and selectivities were often not synthetically viable. Thus, a series of reports based on the bis(dimethylglyoxime)cobalt(II),  $\text{Co}(\text{DMG})_2$  system was published by Ogho [33]. He applied  $\text{Co}(\text{DMG})_2$  as a model for coenzyme  $\text{B}_{12}$  [34] and studied the influence of chiral additives in the asymmetric reduction of various substituted olefinic compounds affording up to 49% *ee* for  $\alpha$ -phenylacrylophenone. Furthermore, the combination of various cobalt precursors with chiral phosphorous-containing ligands [35], bidentate nitrogen-based ligands [36], or chiral amino acids [37] were investigated for the asymmetric hydrogenation of functionalised olefins leading only to moderate chiral inductions. For example, Nindakova obtained 42% *ee* for *N*-acetamidocinnamate applying an *in situ* catalyst of  $\text{CoCl}_2$  and (–)-DIOP that was activated by  $\text{NaBH}_4$  in the presence of 30 bar of  $\text{H}_2$  [35d].

A real breakthrough in the cobalt-catalysed asymmetric hydrogenation of functionalised alkenes was achieved by Chirik [38]. Based on the observation that an improved hydrogenation performance was obtained with more electron-rich ligands, bis(phosphine) cobalt(II) dialkyl complexes, such as (dppe) $\text{Co}(\text{CH}_2\text{SiMe}_3)_2$  (**15a**) and (depe) $\text{Co}(\text{CH}_2\text{SiMe}_3)_2$  (**15b**), were synthesised and successfully applied in the reduction of germinal and 1,2-disubstituted alkenes at 4 bar of  $\text{H}_2$  (Scheme 2.3) [38b]. More hindered internal and endocyclic trisubstituted substrates were activated by an OH group leading to high diastereoselectivity.



**Scheme 2.3** Selected examples of hydrogenation of 1,2-disubstituted olefins and endocyclic trisubstituted alkenes using cobalt catalysts **15a–b**.

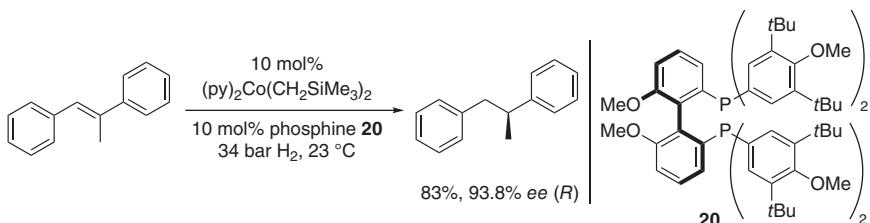
Logically, the coordination of chiral bis(phosphine) ligands to cobalt(II) precursors offered opportunities for a new class of catalysts that may expand the utility of asymmetric hydrogenation. The most selective and/or active ligand/cobalt salt combinations for the asymmetric hydrogenation of functionalised alkenes were identified via systematic high-throughput screening of commercially available P-ligands [38a]. For the model substrate methyl 2-acetamidoacrylate (MAA)  $\text{C}_2$ -symmetric phosphines forming a five-membered chelate ring were very efficient (Scheme 2.4). High yields and high levels of enantioselectivity for MAA were found for a combination of (*R,R*)-QuinoxP\* (**16**), (*R,R*)-*iPr*DuPhos



**Scheme 2.4** Selected phosphine/cobalt combinations providing high conversions and enantioselectivities.

(17), (R,R)-EtBPE (18a), or (S,S',R,R')-TangPhos (19) and  $\text{CoCl}_2$  and 2 equiv.  $\text{LiCH}_2\text{SiMe}_3$ .

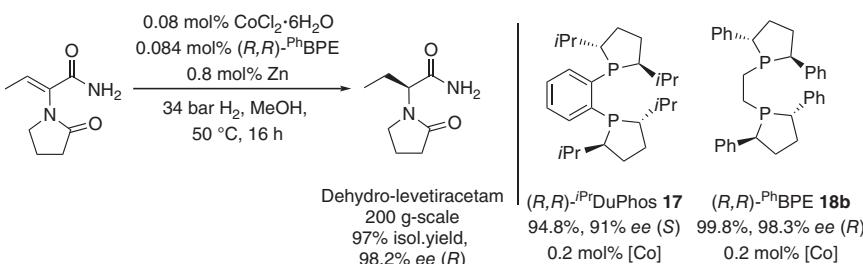
The versatility of the high-throughput screening approach and utility of various cobalt precursors was also demonstrated for the enantioselective hydrogenation of *E*-methylstilbene (Scheme 2.5). For this challenging substrate, the four-carbon-tethered Biphep derivative **20** was identified as an effective ligand for the cobalt-catalysed asymmetric hydrogenation producing 83% conversion and 93.8% *ee* after 20 hours at 23 °C.



**Scheme 2.5** Enantioselective hydrogenation of *E*-methylstilbene with an enantiopure cobalt diphosphine catalyst.

The major limitation of the previously described method is the use of a pyrophoric organolithium activator and the air sensitivity of the isolated catalyst  $\text{L}_2\text{Co}(\text{CH}_2\text{SiMe}_3)_2$ . These drawbacks were overcome with an improved procedure for the cobalt-catalysed, asymmetric hydrogenation of dehydro-levetiracetam developed by the same group [38d]. In a high-throughput approach, best results were obtained applying Zn dust as activator and the protic solvent methanol acting as potential stabilising ligands during the catalysis. Zn activation enabled high activity and enantioselectivity across a broad range of ligands and was also successfully assigned to the asymmetric hydrogenation of other dehydro  $\alpha$ -amino acid derivatives such as MAA. Among the many suitable ligands identified, (R,R)-*i*PrDuPhos (17) and (R,R)-*Ph*BPE (18b) displayed very good catalytic

performance for the enantioselective hydrogenation of dehydro-levetiracetam at 0.2 mol% catalyst loading (Scheme 2.6). By using optimised reaction conditions, a 200 g-scale reaction was carried out with 0.08 mol%  $(R,R)$ -<sup>Ph</sup>BPE (**18b**) yielding 97% of levetiracetam with 98.2% ee.



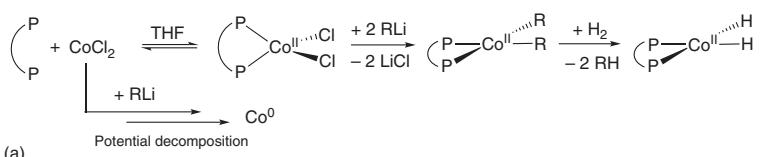
Scheme 2.6 Cobalt-catalysed asymmetric hydrogenation of dehydro-levetiracetam.

Two different activation modes for the cobalt-catalysed hydrogenation of dehydro- $\alpha$ -amino acid derivatives were discussed. In case of the alkyl lithium reagent, the proposed mechanism involved the formation of a Co(II) dihydride as the active species that promoted the 1,2-alkene insertion mode, which was underlined by density functional theory (DFT) calculations (Scheme 2.7a) [39]. The Zn–MeOH reduction was attributed to the enhanced activation where low oxidation state cobalt species with open coordination sites were generated due to the high  $\text{Cl}^-$  binding affinity of  $\text{Zn}^{2+}$  (Scheme 2.7b). Stoichiometric experiments showed dissolution of an isolated  $\text{P}_2\text{CoCl}_2$  complex in MeOH, forming the solvate complex  $[\text{Co}(\text{MeOH})_6]\text{Cl}_2$  and the free phosphine ligand as possible deactivation pathway. An excess of Zn in MeOH resulted in the isolation of a chloride-bridged Co(I)-dimer, while the phosphine ligand was inert to MeOH substitution. Hence, the catalyst deactivation by phosphine dissociation from Co(II) was suppressed by fast Zn reduction regenerating and preserving the chiral environment of the metal. Finally, a Co(0) complex was prepared by a prolonged treatment with Zn–MeOH by two sequential one-electron reductions in the presence of an ancillary ligand. Both types of low-valent cobalt species  $[\text{P}_2\text{CoCl}]_2$  and  $[\text{P}_2\text{Co}(\text{COD})]$  were active in the hydrogenation of dehydro-levetiracetam featuring the postulated mechanism.

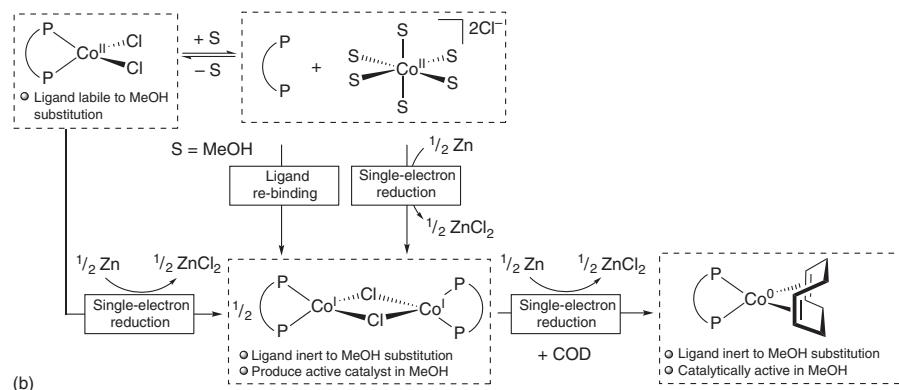
## 2.3 Hydrogenation of Carbonyl Compounds (Ketones, Aldehydes, Carboxylic Acid Derivatives, $\text{CO}_2$ )

### 2.3.1 Ketones and Aldehydes

The reduction of carbonyl compounds has been studied parallel to the investigations of olefin hydrogenation under hydroformylation conditions. Therefore, standard cobalt carbonyl compounds such as  $\text{Co}_2(\text{CO})_8$  or  $\text{HCo}(\text{CO})_4$  have been applied for these first cobalt-mediated hydrogenations of aldehydes and ketones



(a) Potential decomposition



**Scheme 2.7** Different activation modes for the cobalt-catalysed hydrogenation of alkenes. (a) Alkyl lithium reagent. (b) Zn-MeOH reduction.

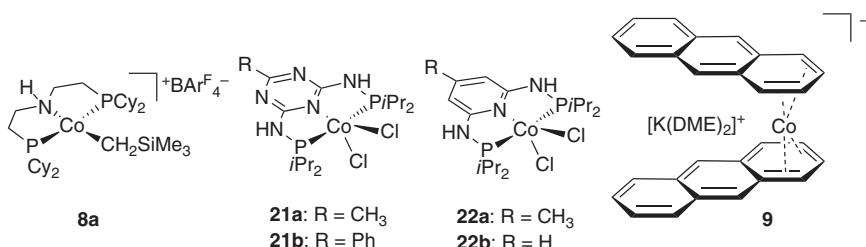


Figure 2.3 Cobalt-based catalysts for the hydrogenation of aldehydes and ketones.

[11a, 15a,c,d, 40]. Unfortunately, these catalysts were often used in stoichiometric amounts providing low product yields and low selectivity.

A breakthrough in the cobalt-catalysed hydrogenation of ketones and aldehydes was achieved with catalysts derived from cobalt pincer complexes and arene cobaltates (Figure 2.3). Pioneering work was done by *Hanson*, who demonstrated that the cobalt PNP pincer catalyst **8a** (generated *in situ* from **7a** and  $\text{H}[\text{BAr}^{\text{F}}_4](\text{Et}_2\text{O})_2$ ) was able to hydrogenate carbonyl compounds (Table 2.4) [26]. A broader number of ketones and aldehydes were reduced with **8a** under mild conditions (1 bar of  $\text{H}_2$ , 25–60 °C, 2 mol% **7a**,  $\text{H}[\text{BAr}^{\text{F}}_4](\text{Et}_2\text{O})_2$ , 24 hours). The reactions proceeded in nearly quantitative yield for both types of carbonyl compounds demonstrating tolerance of several functional groups. For example, in *N*-methyl-4-piperidone the amine moiety was not affected by the catalyst (Table 2.4, entry 14). When complex  $[(\text{PNMeP}^{\text{Cy}})\text{Co}^{\text{II}}(\text{CH}_2\text{SiMe}_3)][\text{BAr}^{\text{F}}_4]$  (**8b**) was tested in the hydrogenation of acetophenone, no activity at all was detected (Table 2.4, entry 2) [27]. Based on this observation a metal–ligand bifunctional pathway with participation of the N–H moiety in the ligand was assumed for the mechanism. Another family of cobalt pincer catalysts **21a–b** and **22a–b** for the hydrogenation of acetophenone was presented by *Kempe* (Figure 2.3) [41]. The precatalysts were activated via salt elimination adding of 2 equiv. of a base ( $\text{NaOtBu}$ ). A comparison between **21** and **22** showed a beneficial effect of the triazine ring for the catalytic efficiency (Table 2.4, entries 4–6). The most active cobalt PN<sub>5</sub>P complex **21a** (0.25–0.5 mol%) was able to hydrogenate a wider range of aryl–alkyl, diaryl, and aliphatic ketones under mild conditions with good tolerance for several functional groups. Thus, C=O bonds were selectively reduced in the presence of internal trisubstituted C=C bonds (Table 2.4, entry 18).

The heteroatom-free arene-cobaltate catalyst **9** was also described for the C=O hydrogenation by the group of *Wolf* and *Jacobi von Wangenheim* [28]. Here, a small selection of aromatic and aliphatic ketones was hydrogenated in good yields with 5 mol% of the catalyst, 10 bar  $\text{H}_2$  pressure at 60 °C, while no activation of the catalyst was required.

In the cobalt-catalysed enantioselective reduction of prochiral ketones, most reports focused on sodium borohydride as reducing agent, while the use of molecular hydrogen has been studied only on small scale [42]. Already in the 1970s the groups of *Oglio* [33, 43] and *Weber* [44] published a cobalt-dioxime-based system that catalysed the asymmetric hydrogenation of ketones. Although the substrate scope was limited to selected 1,2-dicarbonyl

**Table 2.4** Selected examples of ketone and aldehyde hydrogenations using cobalt catalysts **7a**,<sup>a)</sup> **9**,<sup>b)</sup> and **21a**.<sup>c)</sup>

Entry	Substrate	Product	<i>t</i> (h)	<i>T</i> (°C)	cat. (mol%)	Yield (%) <sup>d)</sup> (NMR) <sup>e)</sup> {GC} <sup>f)</sup>
						x mol% [Co] Solvent, <i>y</i> bar H <sub>2</sub> 25–60 °C, 24 h
1			24	25	2	<b>7a:</b> 89 (98)
2			24	25	2	<b>8b:</b> 0
3			24	20	0.25	<b>21a:</b> >99
4			24	20	2	<b>21b:</b> {30}
5			24	20	2	<b>22a:</b> {28}
6			24	20	2	<b>22b:</b> {23}
7			24	20	0.5	<b>21a:</b> >99
8			24	60	5	<b>9:</b> (88)
9			24	20	0.5	<b>21a:</b> {97}
10			24	20	3	<b>21a:</b> {95}
11			48	60	2	<b>7a:</b> 97 (99)

(Continued)

**Table 2.4** (Continued)

Entry	Substrate	Product	t (h)	T (°C)	cat. (mol%)	Yield (%) <sup>d</sup> (NMR) <sup>e</sup> {GC} <sup>f</sup>
12			24	60	5	<b>9</b> : (99)
13 <sup>g)</sup>			65	25	2	<b>7a</b> : {99}
14			65	60	2	<b>7a</b> : {66}
15			24	25	2	<b>7a</b> : 86 (92)
16			24	25	2	<b>7a</b> : 96 (>99)
17 <sup>h)</sup>			64	6	2	<b>7a</b> : 92 (>99)
18			24	20	0.5	<b>21a</b> : {>99}

a) Conditions: substrate (0.5 mmol), **7a** (2 mol%), H[Bar<sup>F</sup><sub>4</sub>](Et<sub>2</sub>O)<sub>2</sub> (2 mol%), THF (2 mL), H<sub>2</sub> (1 bar).b) Conditions: substrate (0.5 mmol), **9** (5 mol%), toluene (2 mL), H<sub>2</sub> (10 bar).c) Conditions: substrate (0.3 mmol), **21a** (0.25–3 mol%), 2-methyl-2-butanol (2 mL), NaOtBu (2 equiv.), H<sub>2</sub> (20 bar).

d) Isolated yields.

e) Yields determined by NMR spectroscopy.

f) Yields determined by GC analysis.

g) H<sub>2</sub> (4 bar).h) T = 60 °C, H<sub>2</sub> (4 bar).

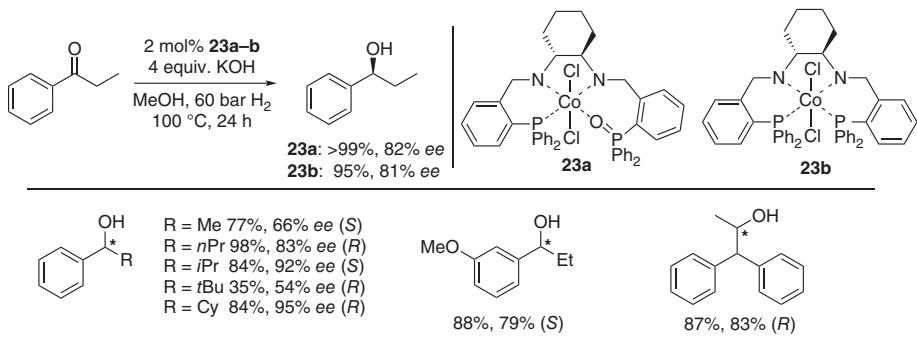
compounds, a relatively high chiral induction was achieved. Thus, benzil was reduced to benzoin with up to 79% *ee* with an optimised catalyst system generated from bis(dimethylglyoximato)cobalt(II) complex ( $\text{Co}(\text{DMG})_2$ ) and quinine as chiral ligand. Another *in situ* combination of cobalt carbonyl complexes with chiral phosphine ligands was less efficient [45]. Here, a small selection of alicyclic ketones was reduced with negligible enantiomeric excess (5% *ee*) for the corresponding alcohol.

A more general approach for the cobalt-catalysed asymmetric hydrogenation of ketones was demonstrated using the novel Co complexes **23a–b**, which were synthesised from the chiral tetradentate aminophosphine ligand (*R,R*)-PNNP and  $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$  (Scheme 2.8) [46]. Depending on the applied reaction conditions, well-defined complexes **23a** (20 hours reflux, air, MeCN) and **23b** (20 hours reflux,  $\text{N}_2$ , MeCN) were obtained and tested in the hydrogenation of propiophenone. Both complexes exhibited similar catalytic activity and enantioselectivity, while the formation of the same catalytic active species was conjectured under reaction conditions. Although the system was limited to aromatic ketones and required 4 equiv. of KOH for activation, it was quite efficient producing good yields and high enantioselectivities up to 95% *ee*.

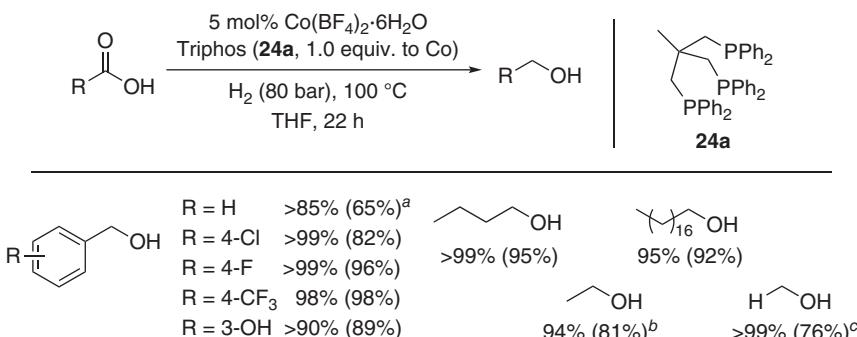
### 2.3.2 Carboxylic Acid Derivatives (Acids, Esters, Imides)

The reduction of carboxylic acids and their derivatives to alcohols is a straightforward and atom-efficient route for the pharmaceutical or fine-chemical industries and more recently for biomass conversion. The difficulty of the direct hydrogenation of carboxylic acids was attributed to the lower electrophilicity of carboxylic acid or carboxylate compared with the corresponding ester as well as their strong binding affinity to the catalyst. Hence, catalytic methods for the transformation of acid derivatives (esters, anhydrides, and amides) to alcohols have been studied more intensively than the direct route starting from the carboxylic acid [47, 48]. In 2015, a remarkable step forward was presented by Elsevier and *de Bruin* performing the hydrogenation of aromatic and aliphatic carboxylic acid with 2.5–10 mol%  $\text{Co}(\text{BF}_4)_2 \cdot 6\text{H}_2\text{O}$  and Triphos (**24a**) in tetrahydrofuran (THF) [49]. The described catalyst system operated at relatively low temperature (100 °C, 80 bar  $\text{H}_2$ ) with turnover number (TON) up to 8 000 (Scheme 2.9). Short-chain aliphatic acids were reduced more easily than long-chain ones, allowing a reduced catalyst loading and/or solvent-free conditions.

Inspired by this report, a cobalt-catalysed reductive alkylation was accomplished applying carboxylic acids as alkylating agents and  $\text{H}_2$  as reductant [50]. A  $\text{Co}(\text{acac})_3$ /Triphos (**24a**) mixture catalysed the hydrogenative *C*-alkylation of 2-methyl-1*H*-indole with both aromatic and aliphatic carboxylic acids affording the corresponding C3-alkylated indoles in good yields (Scheme 2.10). The catalytic performance was highly dependent on the presence of *Lewis* acidic Co-catalyst  $\text{Al}(\text{OTf})_3$  and showed no reactivity in the absence of this additive. Moreover, the *N*-protected indole also underwent a C3-alkylation process providing the *C*-alkylated indoles. Furthermore, this  $\text{Co}(\text{acac})_3$ /Triphos (**24a**)/ $\text{Al}(\text{OTf})_3$  catalytic system was extended to reductive C3-alkenylation of indoles using carboxylic acids.



**Scheme 2.8** Selected substrate scope for the asymmetric cobalt-catalysed hydrogenation of ketones in the presence of **23a**.



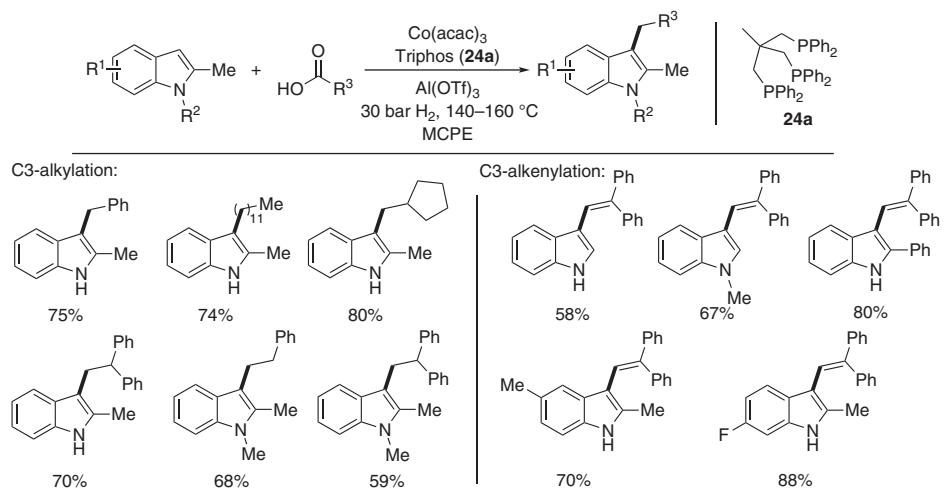
**Scheme 2.9** Selected substrate scope for the hydrogenation of carboxylic acids with  $\text{Co}(\text{BF}_4)_2 \cdot 6\text{H}_2\text{O}/\mathbf{24a}$ . Conditions: 0.15 M substrate, 5 mol%  $\text{Co}(\text{BF}_4)_2 \cdot 6\text{H}_2\text{O}$ , 5 mol% Triphos **24a**, THF, 80 bar  $\text{H}_2$ , 100 °C, 22 hours. Conversions are shown with CG yields, isolated yields in parentheses. <sup>a</sup> Four hours. <sup>b</sup> 0.25 mol%  $\text{Co}(\text{BF}_4)_2 \cdot 6\text{H}_2\text{O}$ , 0.25 mol% Triphos **24a**, neat. <sup>c</sup> 0.5 mol%  $\text{Co}(\text{BF}_4)_2 \cdot 6\text{H}_2\text{O}$ , 0.5 mol% Triphos **24a**.

Additionally, the  $\text{Co}(\text{BF}_4)_2 \cdot 6\text{H}_2\text{O}/\text{Triphos } \mathbf{24a}$  system smoothly transformed carboxylic acid esters to the corresponding alcohols, but a relatively high loading (5–10 mol%) was required while the scope was limited (Table 2.5, entries 1, 10, 15, and 18) [49]. A significant improvement in the efficiency of these reductions was achieved using cobalt pincer catalysts (Figure 2.4).

The first example of a cobalt-catalysed ester reduction was reported by *Milstein* using **25** [51]. At relatively high temperature (130 °C) in the presence of 25 mol% of base, the cobalt NHNP pincer complex **25** hydrogenated various primary, secondary, and tertiary aliphatic esters in good to high yields (Table 2.5, entries 9, 12, and 17).

Interestingly, aromatic and fluorinated esters were not reduced. The unexpected catalytic behaviour was explained by the hydrogenation of the enolate **B**, which was in an equilibrium with the aliphatic ester **A** under basic reaction conditions (Scheme 2.11a) [52]. According to the postulated mechanism, first the C=C double bond of the enolate **B** was reduced generating the salt of the hemiacetal **C**. Starting from **C** the aldehyde **D** and the alkoxide **E** were formed, which were hydrogenated to the corresponding alcohol **F** and the base. The mechanism, which was never reported before for esters hydrogenation, suggested selectivity for enolisable esters and explained, why aromatic carboxylic acid ester did not react.

Furthermore, the cationic cobalt pincer complex **8a** originally introduced by *Hanson* was used by *Jones* for the reduction of esters [53]. Next to slightly improved reaction parameters with respect to **25**, this catalyst reduced aliphatic as well as aromatic esters presenting a wider substrate scope (Table 2.5, entries 2, 5, 7, and 14). Noteworthy, **8a** worked without additives. When catalyst **8a** was tested in the hydrogenation of the unsaturated esters such as ethyl cinnamate, no selectivity in favour of carbonyl bond reduction was observed (Table 2.5, entry 14). In addition to aliphatic and aromatic esters, also biomass-derived  $\gamma$ -valerolactone was reduced on gram scale with a TON of 3 890 (Table 2.5, entry 11). Due to the fact that the *N*-methylated cobalt precatalyst **8b** showed



**Scheme 2.10**  $\text{Co}(\text{acac})_3/\text{Triphos (24a)}/\text{Al}(\text{OTf})_3$ -catalysed C3-alkylation and C3-alkenylation of indoles.

**Table 2.5** Selected examples for ester hydrogenation applying various cobalt complexes.<sup>a)</sup>

Entry	Ester	Alcohol	Catalyst (mol%)	<i>t</i> (h)/ <i>T</i> (°C)	Yield (%) <sup>b)</sup>	
					[Co]	100–130 °C, 50–80 bar H <sub>2</sub> , solvent
1			Co(BF <sub>4</sub> ) <sub>2</sub> /24a (10)	5/100	95	
2			8a (2)	20/120	15	
3			25 (4)	48/130	—	
4			26a (5)	6/100	96	
5			8a (2)	20/120	90	
6			26a (5)	6/120	99	
7			8a (2)	20/120	97	
8			8b (2)	20/120	91	
9			25 (4)	38/130	85	
10			Co(BF <sub>4</sub> ) <sub>2</sub> /24a (10)	22/100	63	
11 <sup>c)</sup>			8a (0.1)	5/120	92	
12			25 (4)	70/130	50	
13			26a (5)	24/120	94	

(Continued)

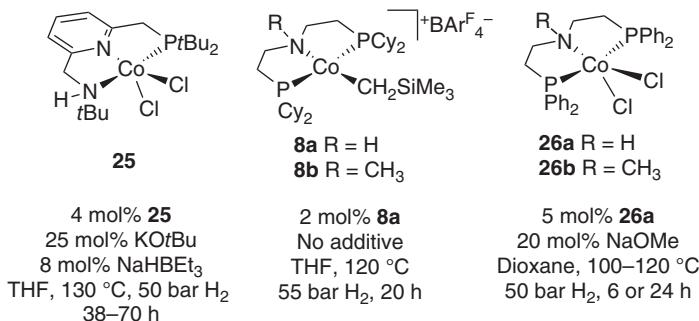
**Table 2.5** (Continued)

Entry	Ester	Alcohol	Catalyst (mol%)	t (h)/T (°C)	Yield (%) <sup>b</sup>
14			<b>8a</b> (2)	20/120	98
15			<b>Co(BF4)2/24a</b> (10)	22/100	90
16			<b>26a</b> (5)	6/120	55
17			<b>25</b> (4)	48/130	85
18			<b>Co(BF4)2/24a</b> (10)	22/100	72

a) Conditions for **Co(BF<sub>4</sub>)<sub>2</sub>/24a**: substrate (0.15 M), **Co(BF<sub>4</sub>)<sub>2</sub>/24a** 1 : 1 (10 mol%), MeOH, 22 hours, 100 °C, 80 bar H<sub>2</sub>. Conditions for **8a**: substrate (0.5 mmol), **8a** (2 mol%), THF (1 mL), 20 hours, 120 °C, 55 bar H<sub>2</sub>. Conditions for **25**: substrate (0.5 mmol), **25** (4 mol%), NaHBET<sub>3</sub> (8 mol%), KOtBu (25 mol%), THF (1 mL), 38–70 hours, 130 °C, 50 bar H<sub>2</sub>. Conditions for **26a**: substrate (0.5 mmol), **26a** (5 mol%), NaOMe (20 mol%), dioxane (2 mL), 6 or 24 hours, 120 °C, 50 bar H<sub>2</sub>.

b) Conversion and yield determined by GC analysis using internal standard.

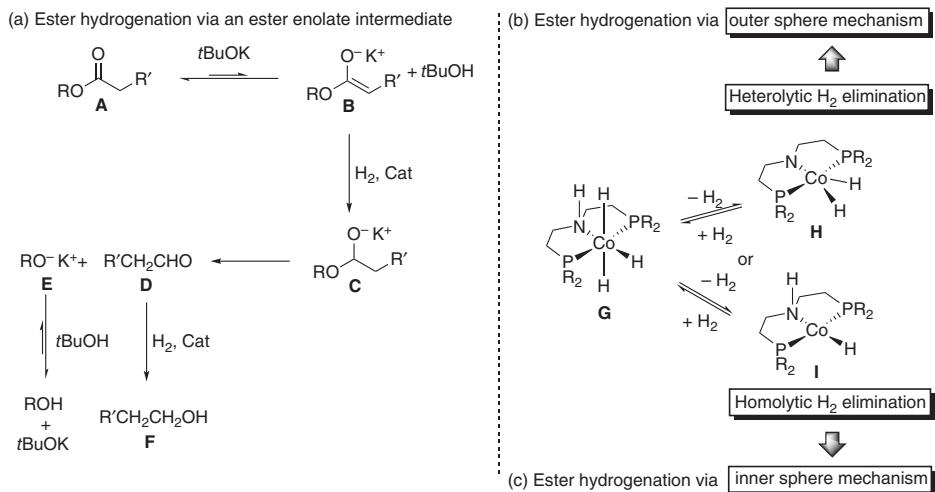
c) γ-Valerolactone (10 mmol, 1 g), no solvent. Isolated yield.



**Figure 2.4** Cobalt pincer complexes applied in esters hydrogenation.

similar catalytic performance in the ester hydrogenation compared with **8a** (Table 2.5, entries 7 and 8), a classic *Schrock–Osborn* (inner-sphere) mechanism was postulated (Scheme 2.11c) instead of metal–ligand cooperation (MLC) [54]. The most recent example for the hydrogenation of esters mediated by the aliphatic cobalt PNP pincer complex **26a** was reported by *Beller* [55]. The model substrate methyl benzoate was quantitatively reduced to benzylic alcohol at 100 °C, applying 5 mol% of catalyst loading in only six hours (Table 2.5, entry 4). The substrate scope included several aromatic, aliphatic, and cyclic carboxylic acid esters (Table 2.5, entries 6, 13, and 16). Advantageously, this catalytic system also presented selectivity in the hydrogenation of the C=O bond towards the C=C bond, e.g. methyl cyclohex-3-ene-1-carboxylate was reduced to the respective unsaturated alcohol (Table 2.5, entry 16). Due to the fact that the complex **26b** bearing a methyl substituent on the nitrogen of the pincer ligand was not active in the hydrogenation of methyl benzoate and methyl octanoate, a MLC mechanism was assumed (Scheme 2.11b) [56]. DFT computations were used starting from complex **G**, which was reported by *Arnold* [57]. The dehydrogenated complexes could be formed via heterolytic dehydrogenation across the N–H and the Co–H bond (**H**) and via homolytic dehydrogenation at the cobalt centre (**I**). Complex **H** was considered as the intermediate involved in an outer-sphere mechanism, while complex **I** was associated with an inner-sphere mechanism. Interestingly, due to the small differences in energy for the singlet state of **H** and the triplet state of **I** both heterolytic and homolytic H<sub>2</sub> elimination were thermodynamically possible and competitive. Therefore, depending on the reaction conditions, both mechanisms were possible.

Also, reduction of other carboxylic acid derivatives was studied. Thus, carboxylic acids anhydrides were catalytically hydrogenated with Co<sub>2</sub>(CO)<sub>8</sub>, giving the corresponding aldehydes and acids [58]. Moreover, the selective catalytic (mono)reduction of cyclic imides was explored. This transformation plays an important role in organic synthesis resulting in isoindolines or  $\gamma$ -lactams as heavily featured in pharmaceuticals and agrochemicals [59]. However, in case of phthalimides, such methods were often accompanied by concomitant arene ring hydrogenation, as well as over-reduction and even competitive C–N bond cleavage. Based on the noble metal congener Ru(acac)<sub>3</sub>/Triphos [60], the mixture of Co(BF<sub>4</sub>)<sub>2</sub> · 6H<sub>2</sub>O and Triphos (**24a**) was developed for the monoreduction of



**Scheme 2.11** Different plausible mechanisms for cobalt-catalysed ester hydrogenation.

cyclic imides (Scheme 2.12) [61]. In opposite to the ruthenium-based catalyst, this system did not require an acid Co-catalyst and performed the reductive alkoxylation reactions under milder conditions. Various symmetric and asymmetric substituted phthalimides as well as succinimides were converted to corresponding hydroxyl-substituted isoindolines and  $\gamma$ -lactams via selective reductive alkoxylation. Particularly interesting was the excellent regioselectivity, which was observed in case of some non-symmetric substrates.

### 2.3.3 Hydrogenation of Carbon Dioxide

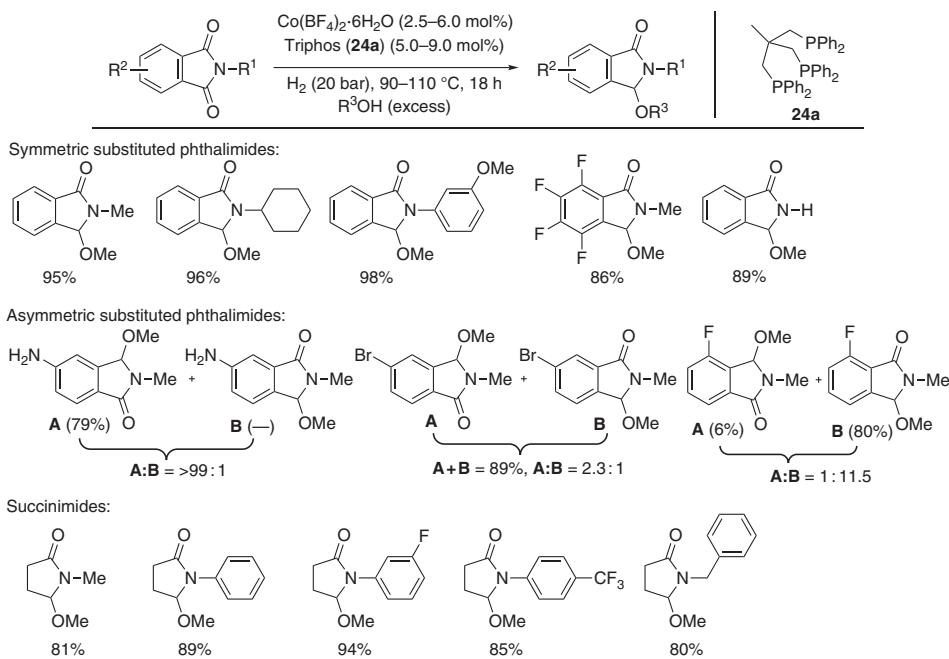
Recently, the utilisation of carbon dioxide ( $\text{CO}_2$ ) as renewable and non-toxic carbon resource attracted significant interest for energy storage technologies and the synthesis of value-added chemicals [62]. Depending on the catalyst and reaction conditions, the hydrogenation of  $\text{CO}_2$  can lead to the production of formic acid, methanol, and methane or under more drastic conditions to *Fischer–Tropsch* products.

Important research activities utilising precious metal catalysts for the synthesis of formates started in the 1990s [63]. In 2012, inspired by these works *Beller* accomplished the first hydrogenation of bicarbonates and  $\text{CO}_2$  under mild conditions ( $80^\circ\text{C}$ , 60 bar  $\text{H}_2$ ) with decent TON using a well-defined cobalt dihydride catalyst [64]. Surprisingly, only the combination of the  $\text{Co}(\text{BF}_4)_2 \cdot 6\text{H}_2\text{O}$  and the ligand Tetraphos (27a) led to catalytic turnover, while all other kinds of phosphine ligands exhibited no activity. As an example, the hydrogenation of sodium bicarbonate to sodium formate was achieved in high yield (94%) with TON = 645 (Table 2.6, entry 1). Increasing temperature ( $120^\circ\text{C}$ ) improved TON up to 3877 (Table 2.6, entry 2). Gratifyingly, the hydrogenation of  $\text{CO}_2$  in the presence of methanol or dimethylamine provided methyl formate and *N,N*-dimethylformamide (DMF) in similar yields and TONs (Table 2.6, entries 3 and 5).

In mechanistic investigations, the preformed monohydride complex  $[\text{Co}(\text{H})(27\text{a})]$  showed no catalytic activity in these hydrogenation reactions. However, three cobalt dihydrogen complexes, which were prepared from  $[\text{Co}(\text{H})(27\text{a})]$  by addition of triflic acid and stabilising anion sources (Scheme 2.13), exhibited desired reactivity. For example, complex  $[\text{Co}(\text{H}_2)(27\text{a})]^+\text{BPh}_4^-$  remained as active catalyst showing comparable efficiency (Table 2.6, entry 4).

$^1\text{H}$  NMR (nuclear magnetic resonance) studies indicated the formation of  $[\text{Co}(\text{H}_2)(27\text{a})]^+\text{BPh}_4^-$  ( $\delta_{\text{H}} = -11.05$  ppm). Based on these results, an *in situ*-generated dihydrogen cobalt(II)/Tetraphos (27a) complex was presumed to be the active species in this process.

The  $\text{CO}_2$ -to-formate hydrogenation was successfully achieved by a small family of cobalt precatalysts 28–30 [65]. Testing these complexes in the  $\text{CO}_2$  hydrogenation reaction, a high TON of 29 000 was obtained with the cationic dicarbonyl cobalt complex 29a in the presence of lithium triflate and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), which underlined the important role of *Lewis* acids as Co-catalysts (Table 2.7, entry 4). The catalytic performance of the cyclohexyl-substituted cobalt pincer species 29b showed only a slightly



**Scheme 2.12** Catalytic reductive alkoxylation of cyclic imides by cobalt/Triphos (**24a**) system.

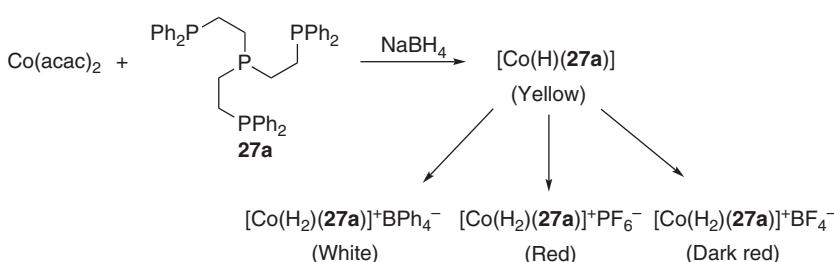
**Table 2.6** Cobalt-catalysed hydrogenation of sodium bicarbonate and CO<sub>2</sub>.<sup>a)</sup>

NaHCO <sub>3</sub> or CO <sub>2</sub> + H <sub>2</sub>		Co(BF <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O Tetraphos (27a) 80–120 °C 20 h	HCO <sub>2</sub> Na or HCO <sub>2</sub> Me or DMF		27a
Entry	Product	P <sub>H<sub>2</sub>CO<sub>2</sub></sub> (bar)	T (°C)	Yield (%)	TON
1	HCO <sub>2</sub> Na	60/0	80	94	645
2 <sup>b)</sup>	HCO <sub>2</sub> Na	60/0	120	71	3877
3	HCO <sub>2</sub> Me	60/30	100	83	427
4 <sup>c)</sup>	HCO <sub>2</sub> Me	60/30	100	80	392
5	DMF	60/30	100	73	1308

a) Co(BF<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O (28 × 10<sup>-6</sup> mol) and 27a (28 × 10<sup>-6</sup> mol), 20 hours; NEt<sub>3</sub> (2.0 mL) for HCO<sub>2</sub>Me; dimethylamine (0.05 mol) for DMF; HCO<sub>2</sub>Na: yield based on <sup>1</sup>H NMR signals of HCO<sub>2</sub>Na using THF as internal standard; HCO<sub>2</sub>Me and DMF: yield calculated by GC analysis based on Mol<sub>product</sub>/Mol<sub>base</sub>.

b) Catalyst loading: 3.49 × 10<sup>-6</sup> mol.

c) [Co(H<sub>2</sub>)(27a)]<sup>+</sup>BPh<sub>4</sub><sup>-</sup> was used as catalyst.



**Scheme 2.13** Preparation of cobalt mono- and dihydrogen complexes. Dihydride complexes were synthesised from the monohydride [Co(H)(27a)] by addition of triflic acid and a stabilising anion source.

reduced TON indicating the limited steric effect of the P-donor in the pincer ligand (Table 2.7, entry 5). Interestingly, the cationic cobalt PNP pincer complex with the NH-moiety **30** afforded a lower TON of 450 for the hydrogenation of CO<sub>2</sub> under optimised conditions (Table 2.7, entry 6), demonstrating that a bifunctional ligand was not advantageous for this type of cobalt pincer catalysts.

An elegant method for the catalytic application of CO<sub>2</sub> as C1 building block was reported by Milstein. More specifically, the direct *N*-formylation of amines was catalysed by the cobalt PNP pincer catalyst **31** applying CO<sub>2</sub> and H<sub>2</sub> as formylating agent (Scheme 2.14) [66]. A selection of primary and secondary amines was smoothly transferred to the corresponding formamides with 5 mol% **31**, at 150 °C reaction temperature over 36 hours.

**Table 2.7** CO<sub>2</sub>-to-formate hydrogenation using cobalt catalysts 28–30.<sup>a)</sup>

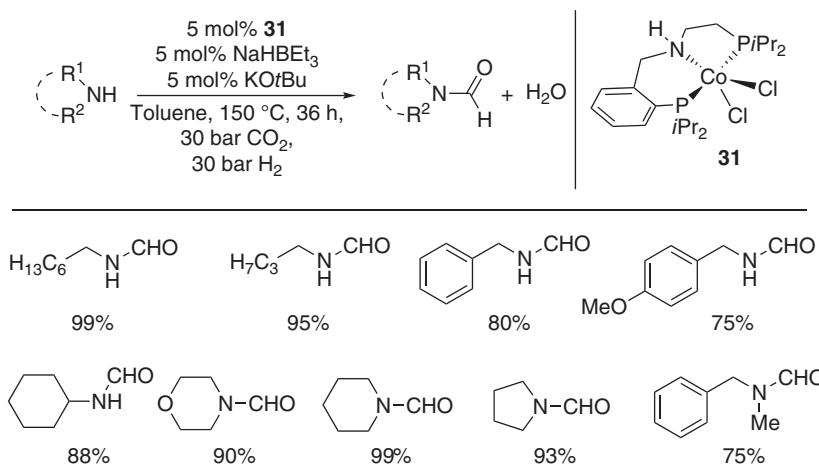
Entry	Catalyst	TON <sup>b)</sup>	Conv. <sup>c)</sup>
1	<b>28</b>	670	0.8
2	<b>29a</b>	10 000	13
3	<b>29a</b> /no LiOTf	460	0.6
4 <sup>d)</sup>	<b>29a</b>	29 000	—
5 <sup>d)</sup>	<b>29b</b>	24 000	—
6 <sup>d)</sup>	<b>30</b>	450	—

a) Conditions: 1000 psi (69 bar) of CO<sub>2</sub>/H<sub>2</sub> (1 : 1), 0.3 µmol of catalyst, 24 mmol DBU, 4.8 mmol LiOTf in 5 mL THF.

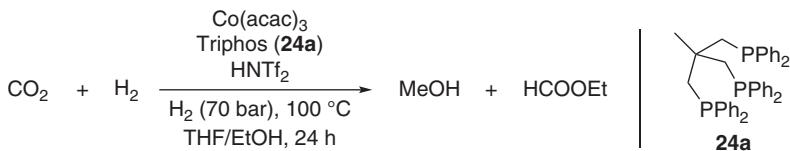
b) Average TON for three or more trials.

c) Reported conversions are based on a DBU/formate ratio of 1 : 1.

d) CO<sub>2</sub>, 500 psi = 34.5 bar H<sub>2</sub>, 0.3 µmol catalyst, 24 mmol DBU, 3.2 mmol LiOTf in 5 mL MeCN, 45 °C, 16 hours.

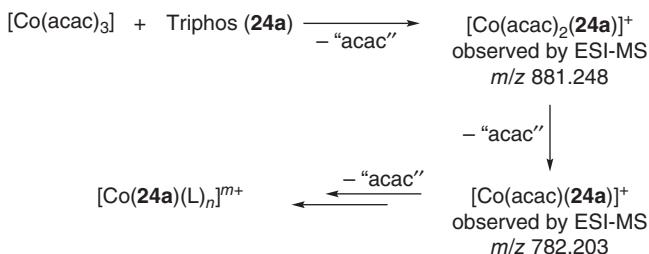
**Scheme 2.14** Selected examples for the N-formylation of amines using CO<sub>2</sub> and H<sub>2</sub> by cobalt PNP pincer complex 31.

The transformation of  $\text{CO}_2$  to methanol is of high concern for today's chemical industry and has also a wider potential for a so-called methanol economy [67]. So far, methanol was mainly produced from fossil fuels [68]. Hence, it was highly compelling to explore new, more sustainable strategies for its production [69]. In 2017, the first homogeneous cobalt-catalysed hydrogenation of  $\text{CO}_2$  to methanol was reported [70]. In this study,  $\text{Co}(\text{acac})_3/\text{Triphos (24a)}/\text{HNTf}_2$  was found to be the best combination to afford methanol with TON up to 50 under comparably mild conditions ( $100^\circ\text{C}$ , 70 bar  $\text{H}_2$ ) (Scheme 2.15). Again, the presence of the Co-catalyst ( $\text{HNTf}_2$ ) was crucial for the desired reactivity.



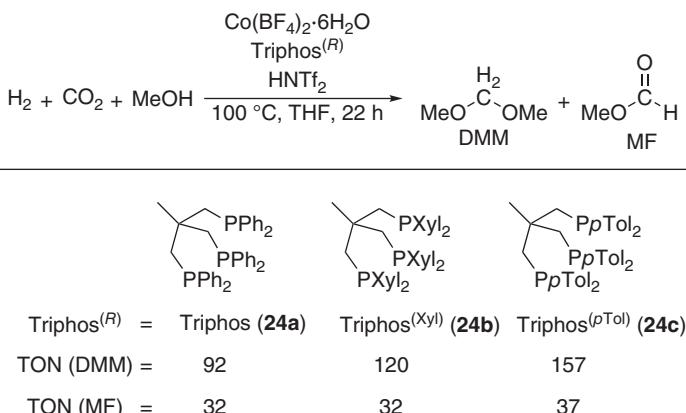
**Scheme 2.15**  $\text{Co}(\text{acac})_3/\text{Triphos (24a)}/\text{HNTf}_2$ -catalysed  $\text{CO}_2$  hydrogenation to methanol.

Mechanistic investigations of this process with NMR and mass spectroscopy showed that the initially formed cobalt–phosphine species was transformed into several catalytically active complexes. Furthermore, kinetic studies showed the presence of an induction period in the kinetic profile. Thus, the following reaction pathway was discussed (Scheme 2.16): First, the formation of active catalyst was initiated by the coordination of Triphos (24a) to  $\text{Co}(\text{acac})_3$  generating  $[\text{Co}(\text{acac})_2(24\text{a})]^+$ . After successive elimination of the remaining “acac” ligands, the active cationic cobalt–Triphos species was obtained, which was stabilised by  $\text{NTf}_2^-$ . The observed induction period of this catalysis was attributed to the slow removal of “acac” ligands.



**Scheme 2.16** Proposed pathway for the active catalyst formation from  $[\text{Co}(\text{acac})_3]/\text{Triphos (24a)}$ .

More recently, the selective formation of dimethoxymethane (DMM) ethers from  $\text{CO}_2$  and  $\text{H}_2$  mediated by a tailored cobalt/Triphos (24a) catalyst system was described by Klankermayer and Schieweck (Scheme 2.17) [71]. Noteworthy, the catalyst TON for the formation of DMM was enhanced by modifying the ligand skeleton. The unaltered Triphos ligand 24a in combination with  $\text{Co}(\text{BF}_4)_2$  resulted in a TON of 92 for the DMM formation, while with the sterically more



**Scheme 2.17** Cobalt-catalysed transformation of CO<sub>2</sub>/H<sub>2</sub> with modified Triphos ligands.

demanding and electron-richer derivatives even TONs of 120 (**24b**) and 157 (**24c**) were obtained, which reached comparable activity to the catalyst based on Ru/Triphos (**24a**) [72].

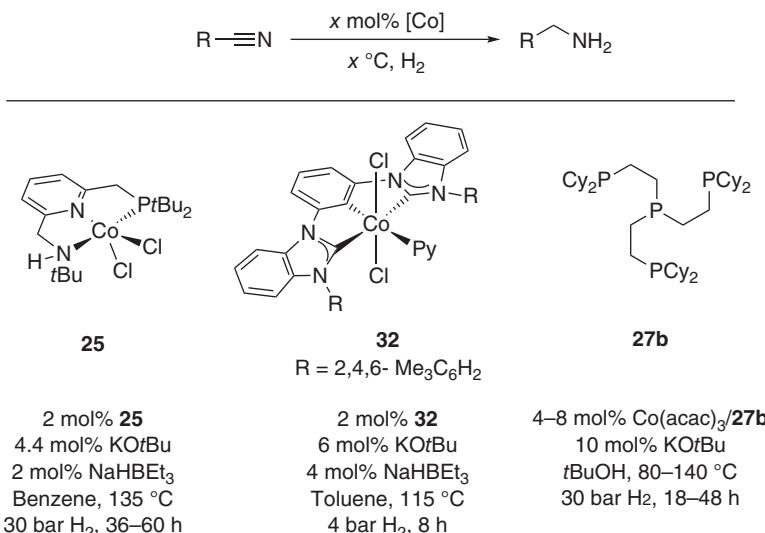
## 2.4 Hydrogenation of C—X Multiple Bonds (Imines, Nitriles)

### 2.4.1 Nitrile Hydrogenation

Among the known numerous protocols for the synthesis of primary amines, the catalytic hydrogenation of nitriles provided an atom-economic and practical procedure [73]. The challenging part of this reaction was the selective formation of the primary amines avoiding side products.

The group of *Milstein* described the first homogeneous cobalt-catalysed hydrogenation of nitriles to primary amines using again their Co<sup>II</sup>(NHNP) pincer complex (**25**) (Scheme 2.18) [74]. In the optimised system, 2 mol% of **25** were activated with 2 mol% of NaHB<sub>3</sub>E<sub>3</sub> and 4.4 mol% of NaOEt. At moderate conditions (135 °C, 30 bar H<sub>2</sub>, 36 hours) many (hetero)aromatic nitriles with both electron-donating and electron-withdrawing substituents as well as benzylic and aliphatic nitriles were hydrogenated to the desired primary amine in good to excellent yields (Table 2.8).

A significant improvement in the nitrile hydrogenation catalysed by cobalt pincer complexes was made by *Fout*, applying the bis(carbene) ligated cobalt pincer complex **32** [75]. This complex performed the reaction under milder conditions (4 bar H<sub>2</sub>, 115 °C, eight hours), but also in this case an activation with NaHB<sub>3</sub>E<sub>3</sub> was needed. The hydrogenation of a number of aliphatic and aromatic nitriles proceeded in good to excellent yields to the corresponding primary amines. Interestingly, acetonitrile and *t*-butylnitrile were hydrogenated for the first time by a first-row homogeneous catalyst (Table 2.8, entries 20 and 21). Mechanistic studies revealed the nature of the *Lewis*-acidic character of NaHB<sub>3</sub>E<sub>3</sub> that facilitated



**Scheme 2.18** Cobalt-based catalyst for the hydrogenation of nitriles.

a side-on coordination of the nitriles to the cobalt centre and allowed a transfer of H<sub>2</sub> through a Co(I/III) redox process.

Besides the cobalt pincer-based catalysts, recently, also the Co(acac)<sub>3</sub>/Tetraphos (**27b**)-catalysed hydrogenation of a broad range of (hetero)aromatic and aliphatic nitriles to primary amines was reported [76]. The activity of the catalytic system for the hydrogenation of benzonitrile was highly sensitive to the P-ligand structure. Among different Tetraphos (**27a–b**) and Triphos (**24a**) ligands, only ligand **27b** with cyclohexyl substituents at the phosphorous centre promoted the hydrogenation of benzonitrile to benzyl amine in quantitative yield. Various benzonitriles with electron-donating and electron-withdrawing groups as well as aliphatic substrates were successfully converted to the corresponding primary amines in high yields. Notably, the reducible amide group was tolerated under the standard conditions, providing exclusively the nitrile hydrogenation product in excellent yield (Table 2.8, entry 13). Moreover, dinitriles such as terephthalodinitrile were reduced in good yields to diamines (Table 2.8, entry 14).

The formations of primary and/or secondary imines as well as secondary amines were typical side reactions of the nitrile hydrogenation process. Depending on the applied reaction conditions and the catalyst selectivity, it was also possible to run the nitrile hydrogenation selectively to the secondary imine as main product.

The first example of a cobalt-catalysed selective hydrogenation of nitriles to secondary imines was demonstrated with cobalt–PN<sub>3</sub>P pincer complex **33** (Scheme 2.19) [77]. The switch in selectivity between secondary imine and primary amine was caused on the one hand by the reaction parameters. Using THF instead of toluene or benzene favoured the formation of the primary amine. Full conversion to the secondary imine was achieved at long reaction time

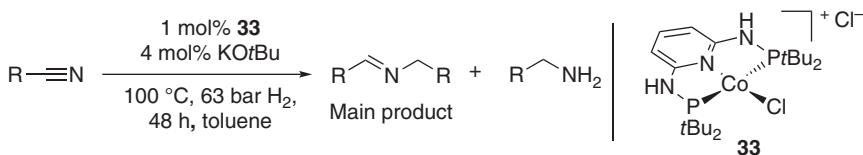
**Table 2.8** Selected examples for nitrile hydrogenation applying various cobalt complexes.<sup>a)</sup>

Entry	Nitrile	Amine	Catalyst (mol%)	x mol% [Co]	x °C, H <sub>2</sub>	R  NH <sub>2</sub>	t (h)/T (°C)	Yield (%) <sup>b),c)</sup>
				x				
1			<b>25</b> (2)				36/135	99
2			<b>32</b> (2)				8/115	(95)
3			Co(acac) <sub>3</sub> / <b>27b</b> (4)				18/80	99
4			<b>25</b> (2)				36/135	99 (85)
5			<b>32</b> (2)				8/115	(91)
6			Co(acac) <sub>3</sub> / <b>27b</b> (4)				18/100	97
7			<b>25</b> (2)				36/135	83
8			<b>32</b> (2)				8/115	(83)
9			Co(acac) <sub>3</sub> / <b>27b</b> (4)				18/100	96
10			<b>25</b> (2)				36/135	71
11			Co(acac) <sub>3</sub> / <b>27b</b> (4)				18/120	98
12			<b>32</b> (2)				8/115	(99)
13			Co(acac) <sub>3</sub> / <b>27b</b> (4)				18/100	(96)
14			Co(acac) <sub>3</sub> / <b>27b</b> (4)				18/120	(80)
15			<b>25</b> (2)				36/135	85
16			<b>32</b> (2)				8/115	(78)
17			Co(acac) <sub>3</sub> / <b>27b</b> (8)				24/140	71
18			<b>25</b> (2)				36/135	90
19			<b>32</b> (2)				8/115	(85)
20			Co(acac) <sub>3</sub> / <b>27b</b> (5)				24/140	99
21			<b>32</b> (2)				8/115	(39)
22			<b>32</b> (2)				8/115	(88)

a) Conditions for **25**: substrate (1 mmol), **25** (2 mol%), NaHB<sub>3</sub> (2 mol%), NaOEt (4.4 mol%), benzene (2 mL), 36 hours, 135 °C, 30 bar H<sub>2</sub>. Conditions for Co(acac)<sub>3</sub>/**27b**: substrate (0.25 mmol), Co(acac)<sub>3</sub>/**27b** 1 : 1.1 (4–5 mol%), KO*t*Bu (10 mol%), *t*BuOH (2 mL), 18–24 hours, 80–140 °C, 30 bar H<sub>2</sub>. Conditions for **32**: substrate (0.14 mmol), **32** (2 mol%), toluene (2 mL), 8 hours, 115 °C, 4 bar H<sub>2</sub>.

b) Yield determined by GC analysis using internal standard.

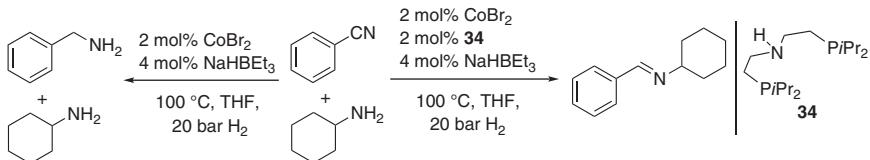
c) Isolated yield as ammonium salt in parentheses.



**Scheme 2.19** Cobalt-based catalyst for the partial hydrogenation of nitriles to secondary imine.

(48 hours) and 100 °C. On the other hand, the ligand structure played a crucial role on the catalyst performance. Notably, the related ruthenium– $\text{PN}_3\text{P}$  complex showed a significant enhanced reactivity for the dehydrogenation of amines to imines [78].

The important role of the ligand was also underlined with a cobalt-based “twin” catalyst system, where the selectivity of the nitrile hydrogenation was tuned by addition or omission of the pincer ligand  $\text{NH}(\text{CH}_2\text{CH}_2\text{PiPr}_2)_2$  (**34**) (Scheme 2.20) [79]. When the precursor  $\text{CoBr}_2$  was ligated with the pincer ligand **34** in the presence of base, a homogeneous catalyst was generated, which selectively transformed benzonitrile to secondary imine  $\text{PhCH}=\text{NCH}_2\text{Ph}$ . Here, the reaction of the intermediately formed imine  $\text{PhCH}=\text{NH}$  with the primary amine  $\text{PhCH}_2\text{NH}_2$  proceeded much faster than its hydrogenation to  $\text{PhCH}_2\text{NH}_2$ . Using an equimolar mixture of benzonitrile and cyclohexylamine with this homogeneous cobalt catalyst, hydrogenative coupling occurred producing the corresponding aldimine  $\text{PhCH}=\text{NCy}$ . In the absence of ligand **34** cobalt nanoparticles were formed from  $\text{CoBr}_2$  and  $\text{NaHBET}_3$ , which catalysed nitrile reduction to primary amines.

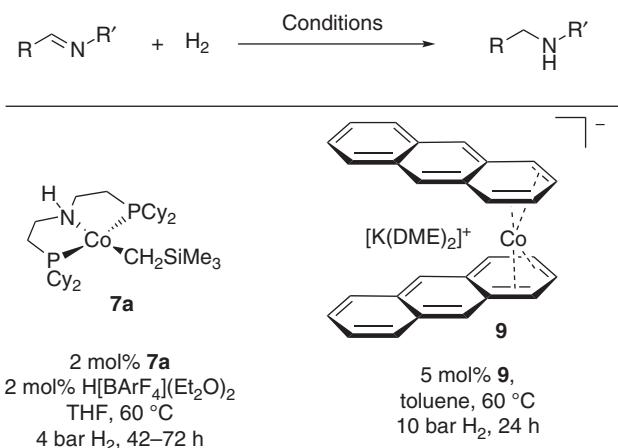


**Scheme 2.20** Cobalt-based “twin” catalyst for the hydrogenation of benzonitrile in the presence of cyclohexylamine.

## 2.4.2 Imine Hydrogenation

As discussed earlier, the first step of the nitrile reduction consisted of initial hydrogenation of nitrile to the corresponding primary imine, which was transferred to the desired primary amine in a second cycle. Until now, hydrogenation of imines was scarcely investigated with cobalt-based catalysts. *Hanson* provided three examples for reduction of secondary imines with catalyst **7a**, showing yields between 65% and 88% (Scheme 2.21) [26]. Also *Wolf* and *Jacobi von Wangelin* disclosed that their homoleptic arene cobalt complex **9** was able to hydrogenate imines towards amines [28].

Consequently, an enantioselective reduction of imines mediated by a cobalt catalyst was left relatively unexplored. In the 1980s one example for the catalytic reduction of methyl *N*-4-toluenesulfonyl-1-imino-1-phenylacetate was reported



Scheme 2.21 Cobalt-catalysed hydrogenation of secondary imines to amines.

using a mixture of  $\text{Co}(\text{DMG})_2$  and quinine [80]. The reaction proceeded smoothly at atmospheric hydrogen pressure to high product yield, but only with poor chiral induction (20% ee).

A better catalyst for the asymmetric hydrogenation of prochiral imines was generated from  $\text{Co}_2(\text{CO})_8$  and *R*-BINAP [81]. This combination was originally studied in the asymmetric *Pauson–Khand* reaction, where it provided high yield and ee for the synthesis of bicyclic cyclopentenones [82]. In the asymmetric hydrogenation a variety of imines derived from aniline and benzylamine derivatives was hydrogenated by a mixture of  $\text{Co}_2(\text{CO})_8$  and (*R*)-BINAP under optimised reaction conditions (THF, 3 bar  $\text{H}_2/\text{CO} = 1 : 3$ , 120 °C) (Table 2.9). Especially high enantioselectivities of up to 99% ee and excellent yields were obtained for imines with a *para*-methyl substituent on the aromatic ring in both types of substrates (Table 2.9, entries 2, 3, and 7).

#### 2.4.3 Hydrogenation of *N*-Heterocycles

Opposite to the reduction of polar functional groups such as nitrile, esters, or amides, the selective hydrogenation of *N*-heteroarenes to reduced *N*-heterocycles still constituted a challenging task owing to the resonance stabilisation. Therefore, the majority of known homogeneous transition metal-catalysed methods for such reduction processes was based on noble metal catalysts and often required additional Co-catalysts/additives for activation.

Inspired by the work of *Hanson* and his own background on iron pincer catalysis [83], *Jones* applied the isolated cobalt PNP system **8a** for the acceptorless, reversible (de)hydrogenation of *N*-heterocycles [84]. Notably, almost quantitative conversion was achieved with 5–10 mol% of catalyst **8a**, at 120 °C, 10–20 bar of hydrogen (Scheme 2.22). The role of the metal–ligand cooperativity was proven by experiments and DFT calculations. While the *N*-methylated cobalt complex **8b** completely inhibited the dehydrogenation of 1,2,3,4-tetrahydroquinaldine, the hydrogenation of quinaldine proceeded

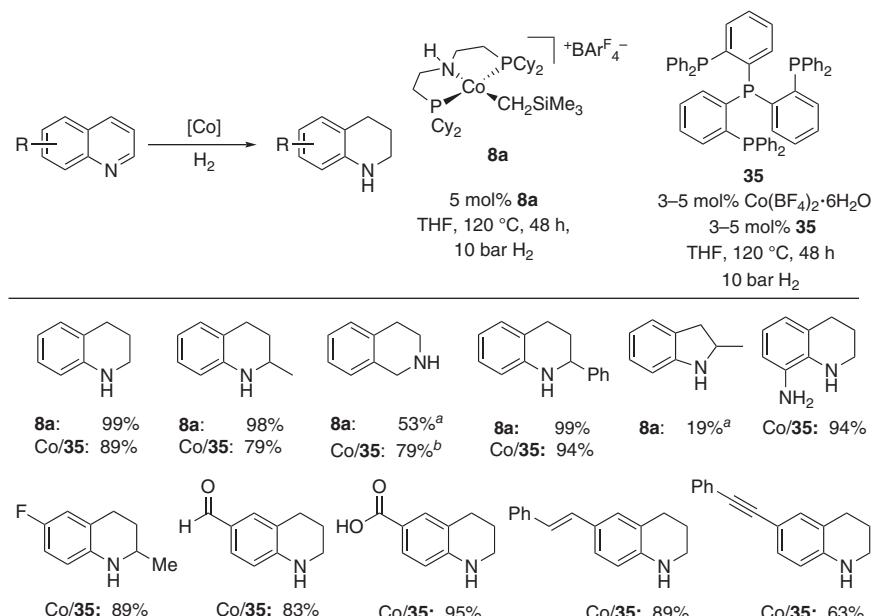
**Table 2.9** Asymmetric hydrogenation of imines from substituted anilines and benzylamines.<sup>a)</sup>

Entry	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	t (h)	Yield (%) <sup>b)</sup>	ee (%) <sup>c)</sup>
1	—	—	H	4-Cl	15	95	95
2	—	—	4-Me	4-Cl	15	94	99
3	—	—	4-Me	4-F	15	96	99
4	—	—	3-CF <sub>3</sub>	4-Me	15	93	72
5	4-Me	4-Cl	—	—	24	98	81
6	4-MeO	4-Cl	—	—	24	99	83
7	3-Cl	4-Me	—	—	24	95	91

a) Conditions: substrate (100 mg), Co<sub>2</sub>(CO)<sub>8</sub> (1 mol%), (R)-BINAP (2 mol%), dry THF (10 mL), 15 or 24 hours, 120 °C, 3 bar H<sub>2</sub>.

b) Isolated yield.

c) Determined by high-performance liquid chromatography (HPLC).



**Scheme 2.22** Hydrogenation of N-heterocycles applying **8a** and Co(BF<sub>4</sub>)<sub>2</sub> · 6H<sub>2</sub>O/**35**.<sup>a</sup> 10 mol% of **8a**, 20 atm H<sub>2</sub>. <sup>b</sup> 150 °C.

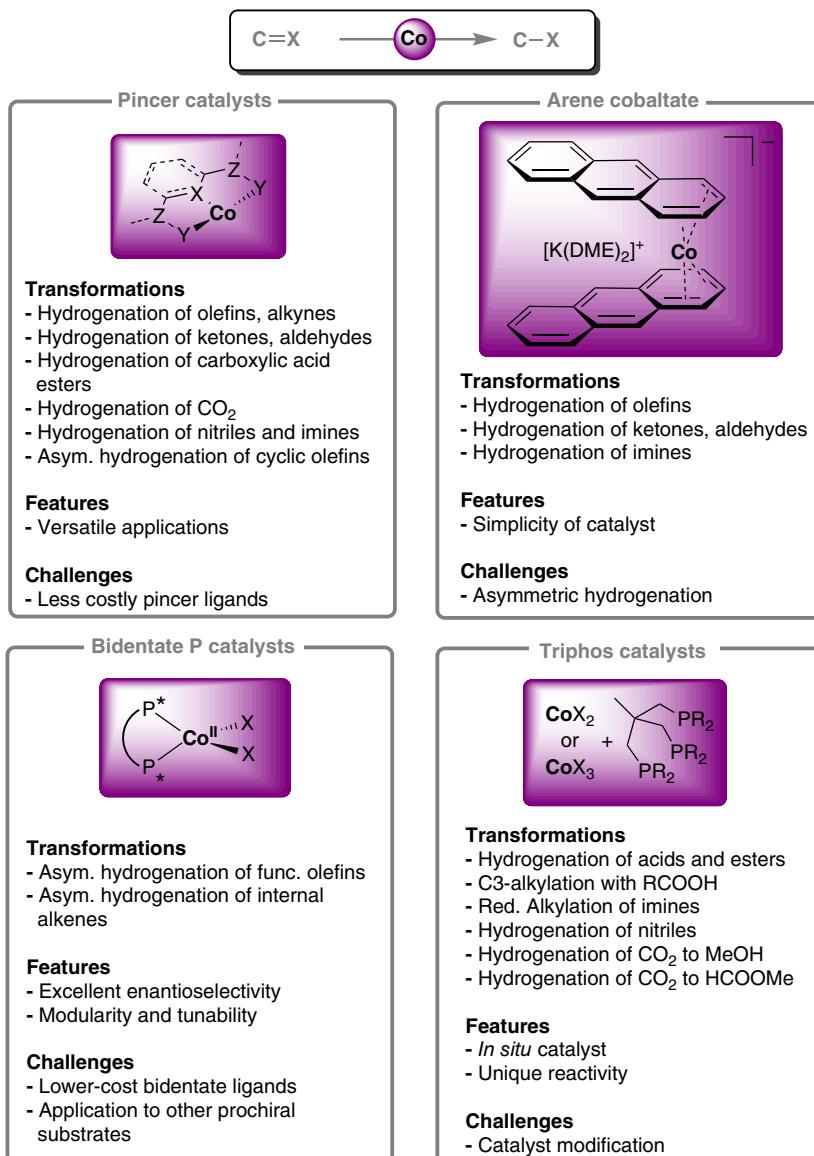
smoothly to the desired product. These findings suggest that cobalt catalyst **8a** acted in a cooperative fashion in the dehydrogenation part. In contrast for the mechanism of the hydrogenation reaction, no involvement of the NH moiety was postulated.

Another catalyst system composed of  $\text{Co}(\text{BF}_4)_2 \cdot 6\text{H}_2\text{O}$  and modified Tetraphos (**35**) was reported for the efficient and selective hydrogenation of quinoline (Scheme 2.22) [85]. Again, the structural feature of the P-ligand **35** was crucial for the desired reactivity, since other Triphos (**24a**) or Tetraphos (**27a–b**) derivatives did not catalyse this reaction. In this study, also the cationic complex  $[\text{Co}(\text{F})(\text{35})][\text{BF}_4]$  was prepared, which promoted the reaction analogous to the *in situ*-formed catalyst system in comparable efficiency. A variety of substituted *N*-heteroarenes was successfully hydrogenated to corresponding partially reduced *N*-heterocyclic compounds in moderate to excellent yields and good selectivity. Under the employed conditions, excellent functional group tolerance was noticed. For instance, other reducible functional groups (e.g. alkene, alkyne, F) remained stable.

## 2.5 Summary and Conclusions

Scheme 2.23 represents to most prominent type of cobalt catalyst, which were developed and applied for the catalytic hydrogenation of various substrates. Simple cobalt-based complexes, e.g. cobalt carbonyls, were among the first catalysts studied in homogeneous hydrogenation reactions. Despite the initial promising results, due to the success of noble metals, cobalt catalysts were somewhat neglected. Hence, for a long time they have been mainly applied in carbonylations such as the *Pauson–Khand* reaction as well as polymerisations. However, since the beginning of the new millennium, such catalysts raised increasing attention in the scientific community. Nowadays, a small selection of cobalt-based catalysts is available for different hydrogenations. Here, especially cobalt–pincer complexes, and *in situ* systems generated from  $\text{CoX}_2$  and Tri- or Tetraphos ligands should be highlighted, which excelled in versatile applications for nearly all kinds of substrates including chiral ones. Chiral bidentate phosphorous ligand-based cobalt catalysts allowed for the asymmetric reduction of dehydro-amino acid derivatives with excellent enantioselectivities, aiming at the range of selectivities found for noble metal catalysts.

Looking back at many of the original works in this area, it is not clear if molecularly defined cobalt complexes constituted the “real” active catalyst species or if alternatively, cobalt nanoparticles were formed, which were known as active hydrogenation catalysts under mild conditions, too. With today’s knowledge and improved analytical techniques, it seems worthwhile revisiting some of these early efforts. For a broader acceptance of cobalt catalysts in hydrogenation reactions in the future, apart from the pincer complexes, other more practical ligands systems have to be developed. With respect to catalysis, for real-world applications the efficiency of the catalysts must be improved by at least 2–3 orders of magnitude. From the point of basic research demanding reductions such as amide hydrogenation or dehydrogenative deoxygenations are desirable.



Scheme 2.23 Cobalt-catalysed hydrogenation: Current status and challenges.

## 2.6 Selected Experimental Procedures

### 2.6.1 Synthesis of Cobalt Complex $[(\text{PNHP}^{\text{Cy}})\text{Co}(\text{CH}_2\text{SiMe}_3)]\text{BAr}^{\text{F}}_4$ (8a)

As a representative example for a “modern” cobalt pincer complex, which was active in the hydrogenation of several classes of organic compounds, the preparation of **8a** is described in the following [26]:

(PNP<sup>Cy</sup>)Co(CH<sub>2</sub>SiMe<sub>3</sub>) (**7a**): in a small vial, bis[2-(dicyclohexylphosphino)ethyl]amine (PNHP<sup>Cy</sup>) (71.0 mg, 0.153 mmol) and (py)<sub>2</sub>Co(CH<sub>2</sub>SiMe<sub>3</sub>)<sub>2</sub> (61.0 mg, 0.156 mmol) were dissolved in toluene (2 mL). The solution was allowed to stand at room temperature for 20 minutes, during which time the colour changed from dark green to yellow-brown. The solvent was removed under vacuum, and the residue dissolved in diethylether (1 mL). Cooling to –20 °C overnight afforded yellow-brown crystals of **7a**. The supernatant was removed by pipette and the crystals were dried under vacuum. Yield: 78 mg (82%).

[(PNHP<sup>Cy</sup>)Co(CH<sub>2</sub>SiMe<sub>3</sub>)]BAr<sup>F</sup><sub>4</sub> (**8a**): In a small vial, complex **7a** (6.1 mg, 10 µmol) and H[BAr<sup>F</sup><sub>4</sub>] · (Et<sub>2</sub>O)<sub>2</sub> (10.1 mg, 10 µmol) were dissolved in diethyl ether (0.5 mL). The solution was layered carefully with pentane (1.0 mL) and the vial was sealed. Then the vial was cooled to –25 °C for three days, during which time yellow plates formed. The supernatant was removed by pipette, and then the crystals were washed with pentane (1 mL) and dried under vacuum. Yield: 12.5 mg (85%).

## Abbreviations

acac	acetylacetone
Ar	aryl
[BAr <sup>F</sup> <sub>4</sub> ] <sup>–</sup>	tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Biphep	(S)-(+) -2,2'-bis[di(3,5-di- <i>t</i> -butyl-4-methoxyphenyl)phosphino]-6,6'-dimethoxy-1,1'-biphenyl
Bn	benzyl
( <i>R,R</i> )-EtBPE	(+)-1,2-bis[(2 <i>R,5R</i> )-2,5-diethylphospholano]ethane
<i>n</i> Bu	<i>n</i> -butyl
<i>t</i> Bu	<i>tert</i> -butyl
<i>t</i> BuOH	<i>tert</i> -butanol
cat.	catalyst
Cy	cyclohexyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
depe	bis(diethylphosphino)ethane
DFT	density functional theory
dip	2,6-diisopropylphenyl
DIOP	O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
dme	dimethoxyethane
DMF	<i>N,N</i> -dimethylformamide
DMG	dimethylglyoxime
DMM	dimethoxymethane
dppe	1,2-bis(diphenylphosphino)ethane
( <i>R,R</i> )- <i>iPr</i> DuPhos	(+)-1,2-bis[(2 <i>R,5R</i> )-2,5-diisopropylphospholano]benzene
<i>ee</i>	enantiomeric excess
equiv.	equivalents

Et	ethyl
GC	gas chromatography
HNTf <sub>2</sub>	trifluoromethanesulfonimide
KOtBu	potassium <i>tert</i> -butoxide
L	ligand
MAA	methyl 2-acetamidoacrylate
Me	methyl
MeO	methoxy
MeOH	methanol
Mes	mesityl
min	minutes
MLC	metal–ligand cooperation
NaOtBu	sodium <i>tert</i> -butoxide
NMR	nuclear magnetic resonance
<i>o</i>	<i>ortho</i>
<i>p</i>	<i>para</i>
<i>nPen</i>	<i>n</i> -pentyl
Ph	phenyl
<i>iPr</i>	<i>iso</i> -propyl
py	pyridine
( <i>R,R</i> )-QuinoxP*	( <i>R,R</i> )-(–)-2,3-bis( <i>tert</i> -butylmethylphosphino)quinoxaline
R	rest
rt	room temperature
( <i>S,S',R,R'</i> )-TangPhos	( <i>S,S',2R,2R'</i> )-1,1'-di- <i>tert</i> -butyl-(2,2')-diphospholane
Tetraphos	tris(2-diphenylphosphinoethyl)phosphine
THF	tetrahydrofuran
TOF	turnover frequency
TON	turnover number
Triphos	1,1-tris(diphenylphosphinomethyl)ethane

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# 3

## Synthesis of C—C Bonds by Cobalt-Catalysed Hydrofunctionalisations

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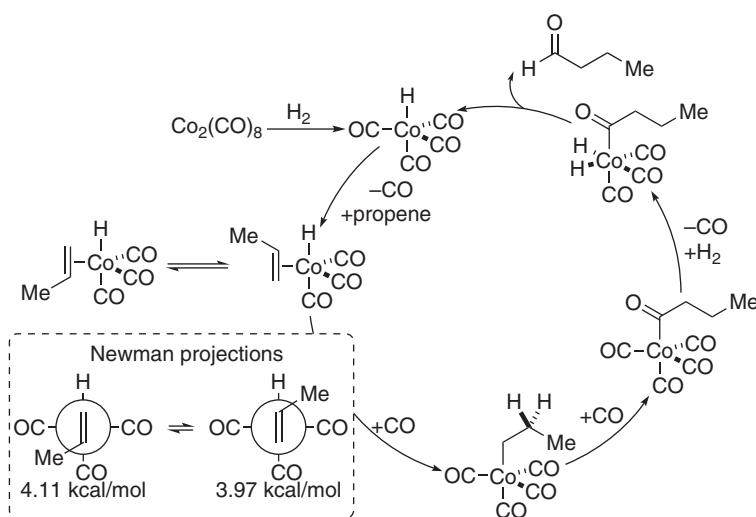
### 3.1 Introduction

Using alkenes for chemical synthesis is attractive due to their availability as commodity chemicals and petroleum feedstocks. In addition, there are also many synthetic methods available for constructing olefins from common reagents. Hydrofunctionalisation represents a powerful and atom-economic strategy for converting alkenes into valuable and chiral building blocks for organic synthesis. With hydrofunctionalisation of unsymmetrical alkenes, however, the selectivity of the site where the hydrogen and functional group add requires control. Within the literature on hydrofunctionalisations, a mixture of nomenclature is used (e.g. *Markovnikov* vs. *anti-Markovnikov*, branched vs. linear, or secondary vs. primary) to categorise the types of site selectivity observed. In this chapter, we highlight how different combinations of Co-catalysts and ligands can affect regioselectivity in C—C bond forming reactions. Several chiral ligands have also been promising for the control newly formed stereocentres.

### 3.2 Cobalt-Catalysed C—C Bond Formations via Hydrofunctionalisation

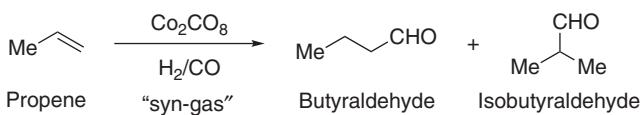
#### 3.2.1 Hydroformylation

Hydroformylation of feedstock olefins is the largest application of homogeneous catalysis in industry [1]. The atom-economic transformation generally uses synthesis gas ( $\text{CO}$  and  $\text{H}_2$ ) under high pressure and heat to form aldehydes. While olefins are valuable feedstock chemicals, the transformation to aldehydes allows for the creation of many bulk chemicals (alcohols, esters, acids, and amines) on a large and practical scale. Hydroformylation was first discovered in 1938 by *Otto Roelen* using Co-catalysis [2]. Mechanistic studies determined that the precursor  $\text{Co}_2(\text{CO})_8$  could be hydrogenated to the active catalyst  $\text{HCo}(\text{CO})_4$  (Scheme 3.1) [3].



Scheme 3.1 Proposed hydroformylation mechanism.

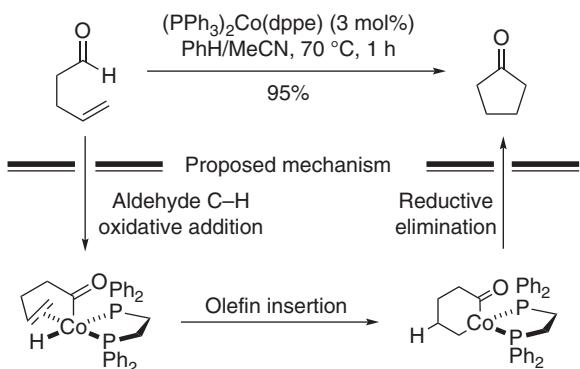
A fundamental challenge in all hydrofunctionalisation reactions is the control of site selectivity on the alkene partner. For example, the hydroformylation of simple olefins such as propene can provide both butyraldehyde and isobutyraldehyde (Scheme 3.2) [4]. Further studies showed that olefin insertion into metal hydride is favoured when Co can be placed in the sterically less hindered position, leading to higher percentages of linear aldehydes over branched aldehydes. The addition of bulky phosphine ligands could further enhance this selectivity [5]. Regardless, Rh-catalysis has emerged as a more effective catalyst for this transformation where turnover frequencies greater than 45 000 turnovers per hour could be achieved. Under Rh-catalysis, one can reduce the pressure of syngas used in hydroformylation [1, 6]. Given that both Co and Rh can catalyse hydroformylation, we often think of these metals as having related reactivity.



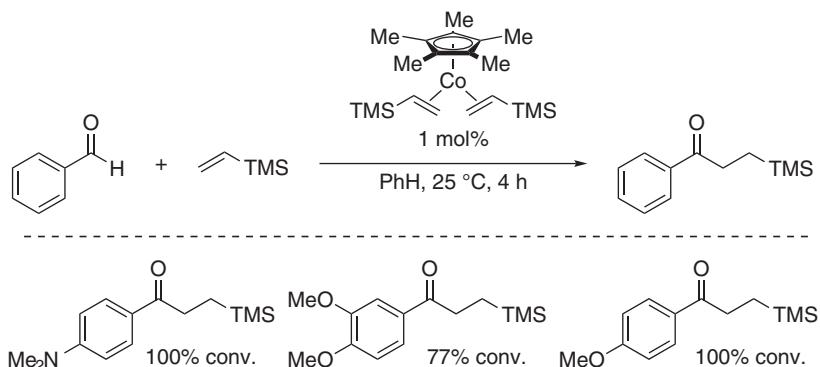
Scheme 3.2 Hydrofunctionalisation selectivity (linear vs. branched).

### 3.2.2 Hydroacylation

Early reports of cobalt-catalysed hydroacylation used low-valent cobalt complexes [7]. A rearrangement of 4-pentenal to cyclopentanone could be achieved in 95% yield (Scheme 3.3) [8]. While many mechanistic pathways are feasible, based on stoichiometric and mechanistic experiments, Vinogradov postulated a non-radical pathway. First,  $\text{Co}(0)$  can undergo a slow oxidative addition into the aldehyde C—H bond, followed by olefin insertion to form the six-membered cobaltacycle. Finally, reductive elimination occurs to forge the ketone C—C bond.

**Scheme 3.3** Intramolecular hydroacylation of 4-pentenal.

Intermolecular hydroacylation can also be achieved using a Co(I)-catalyst (Scheme 3.4) [9]. A variety of aromatic aldehydes could be coupled to vinyl silanes using mild room temperature conditions and low catalyst loadings (as low as 1 mol%). These two early examples demonstrate low-valent Co-complexes as effective catalysts for intra- and intermolecular hydroacylation reactions. Based on experimental evidence both groups report a well-accepted mechanism for metal-catalysed hydroacylation (namely, aldehyde C–H activation, olefin insertion, and reductive elimination).

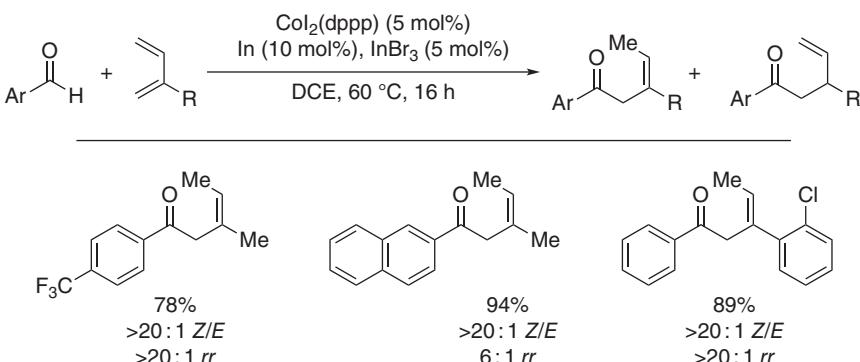
**Scheme 3.4** Intermolecular hydroacylation of vinyl silane with various benzaldehydes.

In Brookhart's system, the rate–turnover limiting step was determined to be reductive elimination [10]. At lower temperatures, a crystal structure of a Co-complex that had undergone aldehyde decarbonylation could be isolated. This product was presumed to arise by a deinsertion pathway, and this pathway explained the generation of ferrocene from ferrocenecarboxaldehyde. Additionally, branched aldehydes such as isobutyraldehyde could be coupled to vinyl silanes to form a mixture of isomeric ketones, an observation that further supports deinsertion and isomerisation pathways under Co-catalysis. In contrast, Vinogradov's intramolecular hydroacylation of 4-pentenal suggested that the

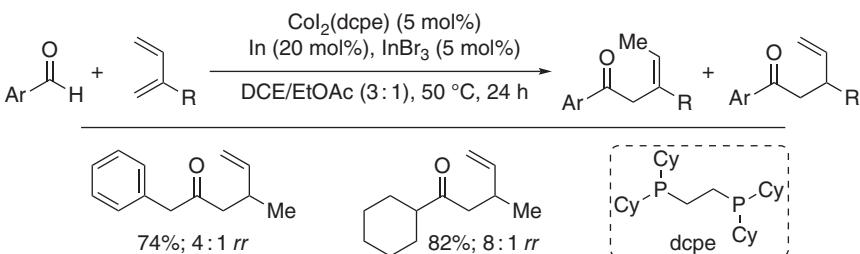
rate–turnover limiting step is most likely oxidative addition [8]. Additionally, a paramagnetic Co(0)/Co(II)-catalytic cycle was implicated when compared with Brookhart's example of a diamagnetic Co(I)/Co(III)-catalytic cycle.

While reactive and efficient, both low-valent Co-catalysts needed to be synthesised and stored under inert atmosphere. For rapid and modular Co-ligand evaluations, many catalysts employed in the hydroacylation of olefins in later studies are derived from the use of Co(II)-salts in combination with a reductant to access low-valent oxidation states [11]. This protocol allows for easier setup and more facile ligand evaluation. Additionally, cobalt catalysts are readily available as Co(II) and Co(III) salts due to their affordability and stability to air and moisture.

Our laboratory reported an intermolecular hydroacylation of 1,3-dienes that relies on a Co(II)-salt with reductant (Scheme 3.5) [12]. We found that a diarylphosphinopropane ligand (where Ar = 3,4-dimethoxyphenyl) in combination with indium as a reductant could afford 1,4-hydroacylation products to produce  $\beta,\gamma$ -unsaturated ketones. When switching to electronically rich aldehydes (aliphatic aldehydes) and by using a trialkylbisphosphine ligand, dcpe (1,2-bis(dicyclohexylphosphino)ethane),  $\gamma,\delta$ -unsaturated ketones are formed regioselectively by 1,2-hydroacylation (Scheme 3.6). In this case,  $\text{CoI}_2$  was much more reactive than the  $\text{CoBr}_2$  and  $\text{CoCl}_2$  catalysts. Additionally, the use of indium as a reductant and  $\text{InBr}_3$  as an additive were essential for



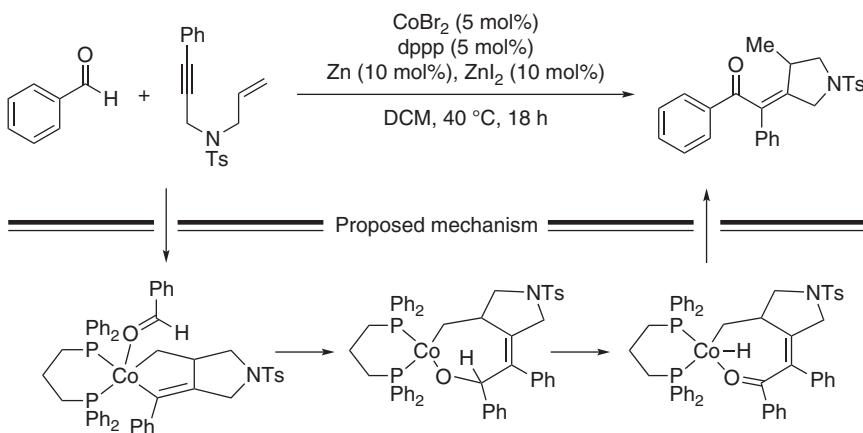
Scheme 3.5 Intermolecular 1,4-hydroacylation of 1,3-dienes with simple aldehydes.



Scheme 3.6 Change in regioselectivity with aliphatic aldehydes and ligand choice.

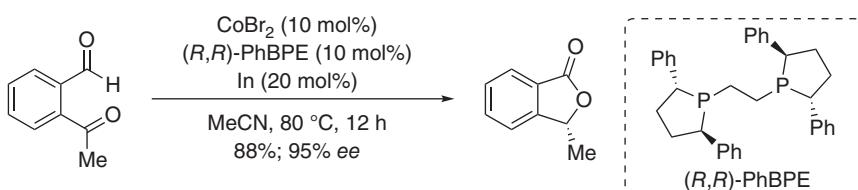
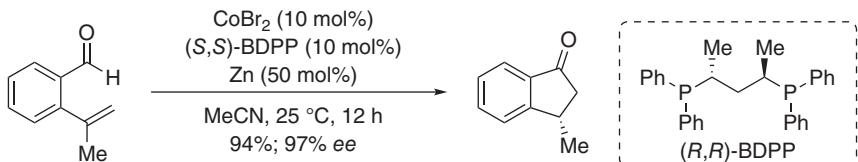
achieving high levels of reactivity and selectivity. The use of novel derivatives of 1,3-bis(diphenylphosphino)propane (dppp) where the aryl groups could be to subtly change the stereoelectronics of the ligand was key in achieving higher levels of reactivity and selectivity. Finally, we proposed that hydroacylation of 1,3-dienes might deviate from direct activation of the aldehyde C—H bond through oxidative addition but may proceed through an oxidative cyclisation pathway followed by  $\beta$ -hydride elimination and reductive elimination. While oxidative addition has been implicated in Co-catalysed hydroacylation, it is important to realise that first-row transition metals can readily undergo alternative mechanistic pathways such as oxidative cyclisation. These alternative pathways are distinct in mechanism in comparison to second-row transition metals such as Ru- or Rh-catalysis and can lead to alternative and complementary isomers.

As such, oxidative cyclisation of 1,6-enynes form a cobaltacycle that could couple with aldehydes to afford  $\alpha,\beta$ -unsaturated ketones with fully substituted olefins in high levels of efficiency and olefin stereoselectivity (Scheme 3.7) [13]. Cheng's group report demonstrates cobalt's affinity for olefins and alkynes and oxidative cyclisation to afford new types of  $\alpha,\beta$ -unsaturated ketones.

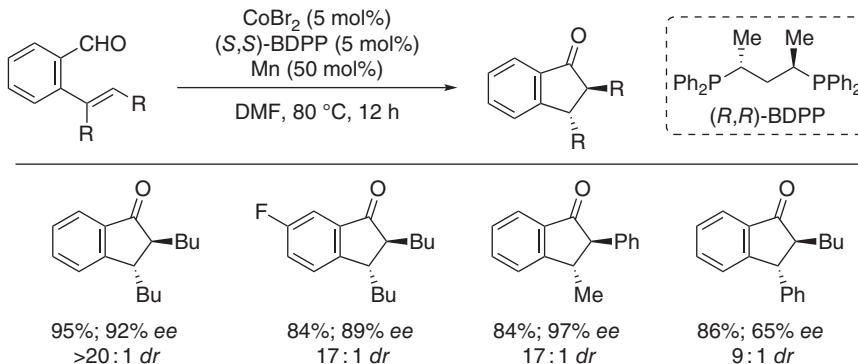


**Scheme 3.7** Intermolecular hydroacylation of 1,6-enynes by oxidative cyclisation mechanism.

However, the use of asymmetric catalysis in Co-catalysed hydroacylation was notably absent. *Yoshikai* demonstrated in an intramolecular setting that both 2-acylbenzaldehydes (Scheme 3.8) and 2-vinylbenzaldehydes (Scheme 3.9) could be turned into chiral lactones and indanones with high levels of stereoselectivities [14]. An important distinction to the use of metal reductants such as Mn, Fe, Zn, or In is the formation of *Lewis* acidic salts such as  $\text{MnBr}_2$ ,  $\text{FeBr}_2$ ,  $\text{ZnBr}_2$ , or  $\text{InBr}_3$ . These *Lewis* acids can coordinate to aldehydes to further activate aldehydes towards oxidative addition or oxidative cyclisation pathways. During the optimisation of the reaction, *Yoshikai* found that the identity of the *Lewis* acid had little to no impact on the outcome of the enantioselectivity but had an impact on reaction rates and efficiency.

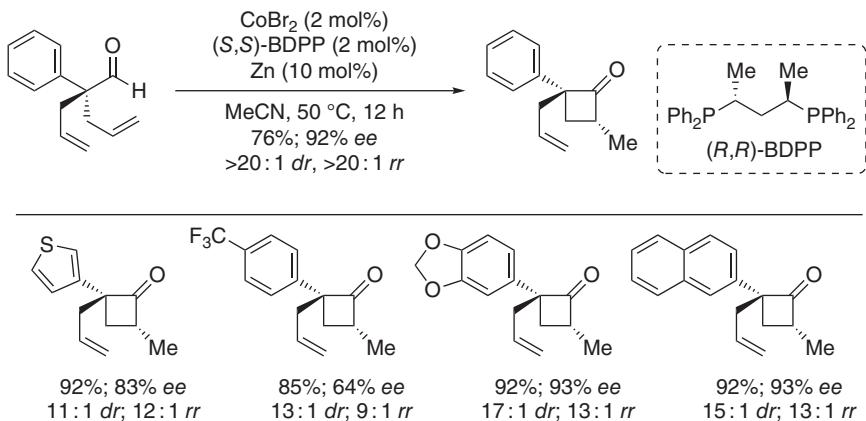
**Scheme 3.8** Enantioselective intramolecular hydroacylation of 2-acylbenzaldehydes.**Scheme 3.9** Enantioselective intramolecular hydroacylation of 2-vinylbenzaldehydes.

This important contribution set the stage for other challenging substrates in hydroacylation such as trisubstituted olefins (Scheme 3.10) [15]. In general, the hydrofunctionalisation of olefins becomes more challenging with transition metal catalysis where olefin insertion is hindered by bulky substituents. Remarkably, the hydroacylation of a trisubstituted olefin could be achieved to attain high levels of stereoselectivity. In these cases, a mixture of both *E*- and *Z*-olefins could be converted into the desired chiral ketone based on the choice of ligand enantiomer. Mechanistically, this result suggested reductive elimination as rate-limiting step, because the Co-catalyst could isomerise the starting material olefin to achieve catalyst-controlled selectivity, despite a mixture of olefin geometries at the onset.

**Scheme 3.10** Asymmetric hydroacylation of 2-vinylbenzaldehydes.

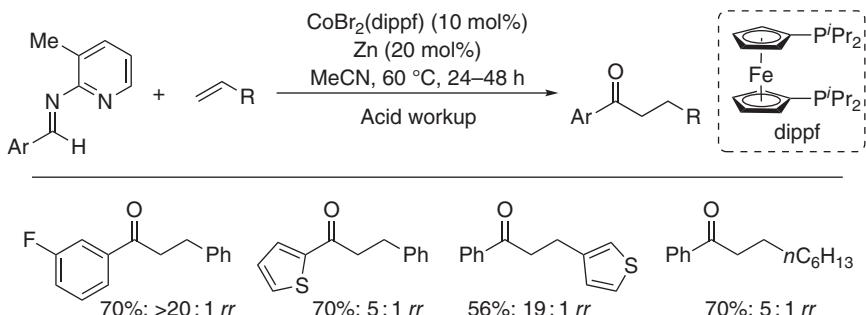
Asymmetric hydroacylation is an attractive way to access chiral ketones. While many of these transformations were first demonstrated with Rh-catalysis, related and complementary reactivity (or selectivity) can be achieved by switching to Co-catalysis. The majority of Co- and Rh-catalysed intramolecular

hydroacylations have been limited to making five-membered cyclic ketones. Our laboratory reported an intramolecular desymmetrisation of dienyl aldehydes with Co-catalysis that led to a strained four-membered cyclobutanone (Scheme 3.11) [16]. This result highlights the ability of cobalt to activate sterically hindered, tertiary aldehydes and make strained rings with high levels of efficiency and selectivity.



**Scheme 3.11** Asymmetric cyclisation to form strained cyclobutanones.

A major challenge in hydroacylation is the intermolecular coupling of olefins and aldehydes without the use of a directing group [17]. Employing a bisphosphine ligand with  $\text{CoBr}_2$  and Zn as a reductant, the intermolecular hydroacylation of aldimines could be achieved with high linear to branched ratio (Scheme 3.12). These aldimines derived from 2-aminopyridines are special as they act as a removable directing group (also known as a traceless or transient directing group) [18].

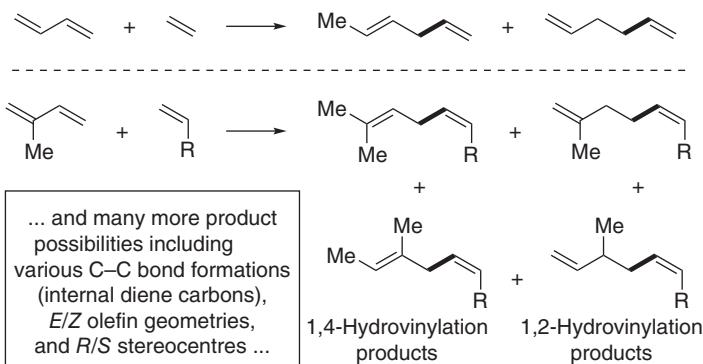


**Scheme 3.12** Intermolecular hydroacylation of simple olefins with removable directing group.

While Rh-catalysis dominates the area of hydroacylation, there are still many new modes of activation offered by Co-catalysis that can alter the selectivity and reactivity for new alternative aldehyde and olefin cross-coupling.

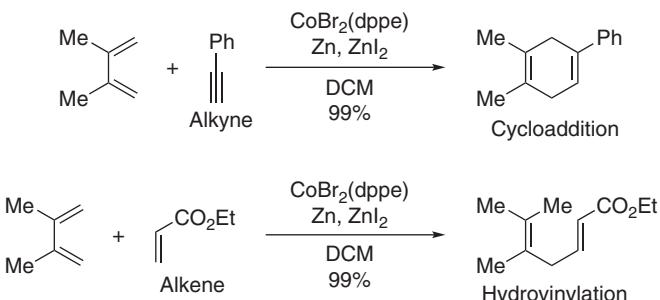
### 3.2.3 Hydrovinylation

Cobalt-catalysed hydrovinylation is a rich subset of hydrofunctionalisation that yields new C—C bonds. The coupling of dienes with olefins is commonly accomplished via a [4+2]-*Diels–Alder* cycloaddition reaction. However, *Hilt* showed the ability to selectively add a hydrogen and a vinyl group across a diene to form valuable acyclic products [19]. A major challenge and opportunity are the plethora of possible products (Scheme 3.13). The number of isomers increases when asymmetrical starting olefins are used. Additionally, hydrovinylation has the potential to turn feedstock chemicals derived from crude oils into valuable products, especially when the *E/Z*-olefin geometry and new stereocentres can be controlled.

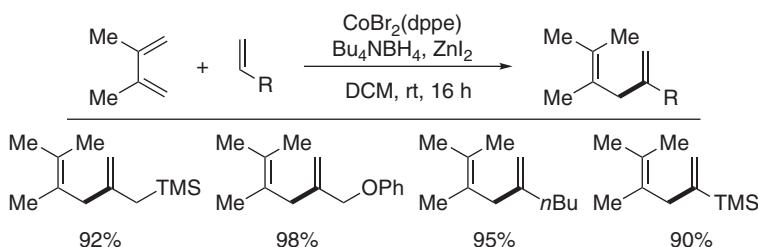


**Scheme 3.13** Challenges and opportunities in hydrovinylation reactions.

With the use of cobalt catalysis, the cycloaddition reactions of simple dienes and alkynes can be catalysed to form cyclohexadienes. However, when switching to alkenes, a hydrovinylation pathway is operative (Scheme 3.14). Mechanistically, if oxidative cyclisation is operative, the divergence in reactivity is due to the absence or presence of an accessible  $\beta$ -hydride. This result marked a significant breakthrough where the coupling of simple dienes and olefins yields 1,4-dienes (Scheme 3.15) [20].

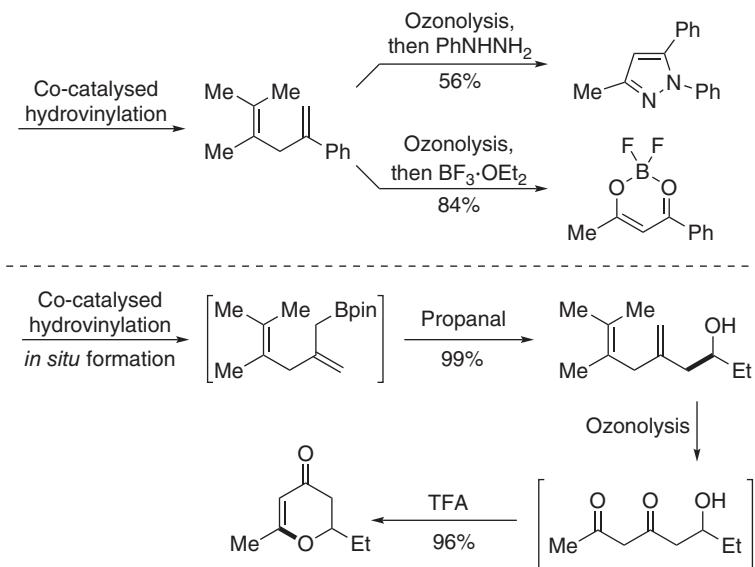


**Scheme 3.14** Substrate controlled switch in reactivity.



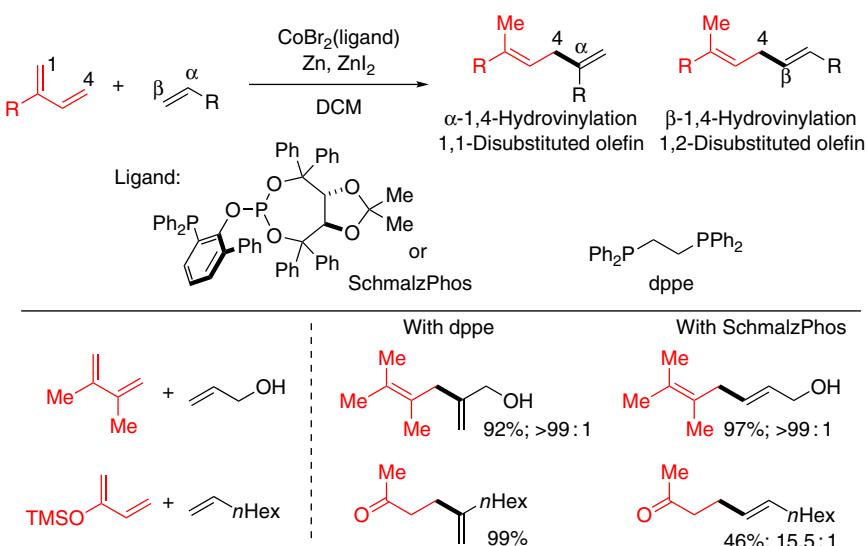
Scheme 3.15 Hydrovinylation of 2,3-dimethyl-1,3-butadiene with various alkenes.

These skipped dienes can be transformed into 1,3-diketones after ozonolysis [21]. Diketones are readily transformed to various functional groups and/or heterocycles including a protected  $\text{BF}_2$ -adduct [22]. If 2,3-dimethyl-1,3-butadiene is coupled with allyl silanes or allyl boranes, the resulting intermediates can be used as allylation reagents with aldehydes (Scheme 3.16) [23]. The selectivity of the 1,4-hydrovinylation reaction generally yields a single regiosomeric product. A switch in regioselectivity can be achieved by careful choice of the ligand.



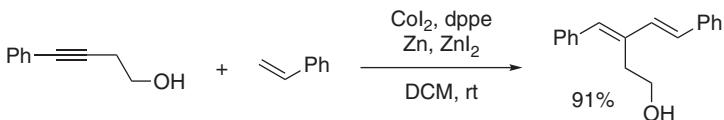
Scheme 3.16 Hydrovinylation products yield a variety of heterocycles.

Coupling of conjugated 1,3-dienes with alkenes can form either the linear or branched 1,4-hydrovinylation skipped diene products. The olefin geometry can afford either  $\alpha$ - or  $\beta$ -coupling (Scheme 3.17). The use of a simple 1,2-bis(diphenylphosphino)ethane (dppe) ligand affords 1,1-disubstituted alkenes ( $\alpha$ -coupling), while the use of SchmalzPhos affords 1,2-disubstituted alkenes ( $\beta$ -coupling) [24]. Non-symmetrical 2-substituted butadienes are challenging substrates due to the complexity of product possibilities. However, it was demonstrated that the ligand effect can control  $\alpha$ - vs.  $\beta$ -coupling, whereas the C1- vs. C4-coupling of the diene appears to be substrate-dependent.

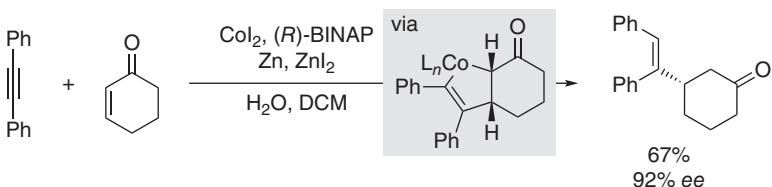


Scheme 3.17 Regioselective control of alkene addition by ligand control.

Alkenes can also undergo hydrovinylation with styrenes as the vinyl donor. Using the similar catalyst system where  $\text{CoI}_2$  is employed vs.  $\text{CoBr}_2$  (along with Zn reductant and  $\text{ZnI}_2$  additive) allows for the alkyne hydrovinylation of styrenes (Scheme 3.18) [25]. However, adding water (as a proton-source), alkyne, and alkene, the coupling is possible with good yield and selectivity, when the alkyne is the vinyl donor (Scheme 3.19) [26].



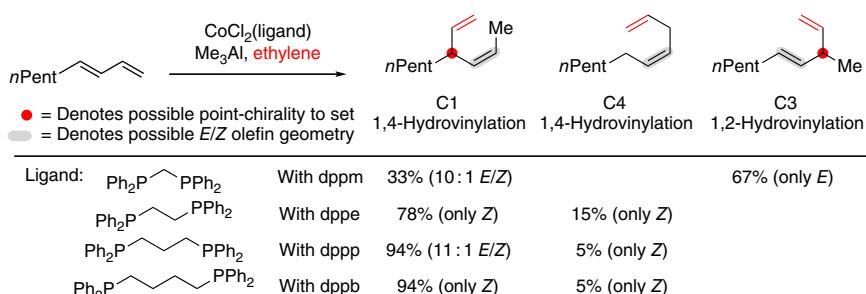
Scheme 3.18 Alkyne hydrovinylation with styrene.



Scheme 3.19 Alkyne hydrovinylation with enones.

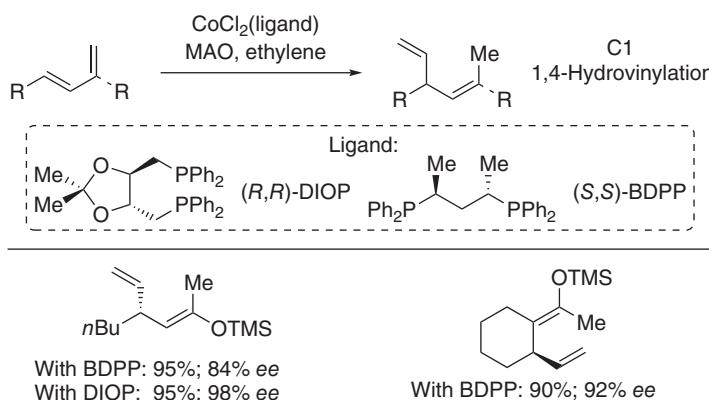
There have been additional breakthroughs in asymmetric variants [27]. *Vogt* demonstrated asymmetric branched selective hydrovinylation of styrenes, while *RajanBabu* used 1-substituted-1,3-butadienes. As in many Co-catalysed hydrovinylations, the ligand plays an important role in regiocontrol [28].

Bidentate ligands with various carbon-linker lengths change the outcome (Scheme 3.20). Small bite-angle ligand, dppm (1,1-bis(diphenylphosphino) methane) results in 1,2-hydrovinylation as the major product. Larger bite-angle ligands such as dppe and dppp leads to 1,4-hydrovinylation products where C1 C—C bond formation is the major product. And using 1,4-bis(diphenylphosphino)butane (dppb), resulted in better *E/Z* olefin geometries as well as C1- vs. C4-selectivity. In this case, organoaluminium reagents were used as the reducing agents to generate low-valent Co-catalysts. The authors note that Zn and ZnBr<sub>2</sub> were not effective when using a CoCl<sub>2</sub>.

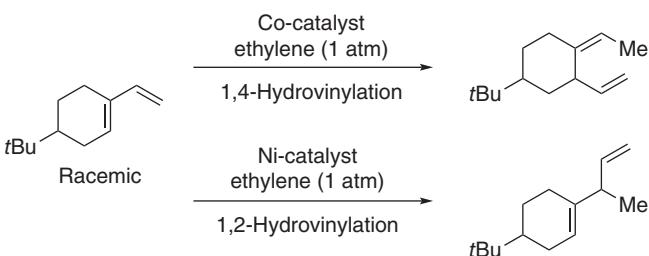


**Scheme 3.20** Ligand-controlled regioselective hydrovinylation of 1-substituted-1,3-butadienes.

RajanBabu synthesised a variety of chiral ligand bound Co-complexes, which have been shown to promote the 1,4-hydrovinylation with C1-coupling of ethylene with efficient yields and selectivities (Scheme 3.21) [28]. Furthermore, the asymmetric hydrovinylation of vinylcycloalkenes by Co-catalysis gave complementary product formation when compared with Ni-catalysis [29]. While Ni-catalysis affords branched 1,2-addition products, Co-catalysis affords 1,4-hydrovinylation products (Scheme 3.22). Thus, marked differences in regioselectivity are possible by tuning the metal. Although still under investigation, this difference may be due to a change in binding modes between 1,3-butadiene with

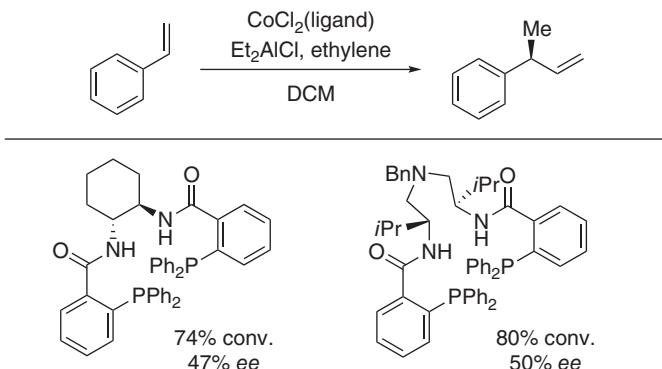


**Scheme 3.21** Enantioselective 1,4-hydrovinylation of unsymmetrical 1,3-butadienes.



**Scheme 3.22** Regioselective hydrovinylation of vinylcyclohexene by metal choice.

catalyst. This difference in binding could then lead to different regioselective outcomes. The asymmetric hydrovinylation of styrene by *Vogt* and *Schmalz* resulted in up to 50% *ee* (using a chiral *Trost*-ligand analogue at 30 bar of ethylene gas, Scheme 3.23) [30]. The low enantiocontrol is presumably due to styrene having fewer coordination sites when compared with dienes.



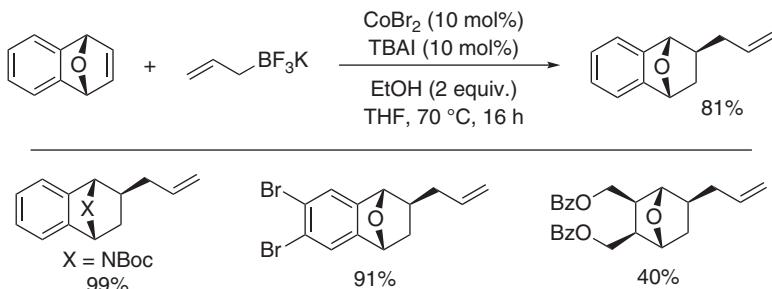
**Scheme 3.23** Enantioselective 1,4-hydrovinylation of unsymmetrical 1,3-butadienes.

The understanding of Co-catalysed reactivity has led to the development of tandem reactions by *Hilt* [31]. These sequences lead to new products and have been used in the synthesis of natural products or heterocycles [32]. The complexity of products obtained by hydrovinylation grows with the use of conjugated trienes. However, a diversity of products can be synthesised by choice of the coupling reagent and the Co-catalyst [33].

### 3.2.4 Hydroalkylation

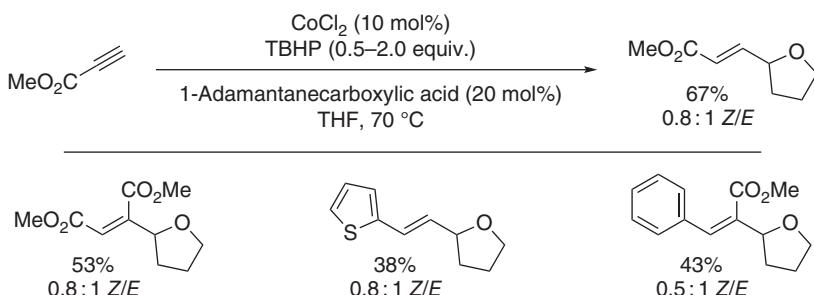
Allylation is a powerful way to form C—C bonds. Allylations into C—C  $\pi$ -systems such as  $\alpha,\beta$ -unsaturated carbonyls as well as allyl–allyl cross-coupling have been achieved using other transition metals [34]. *Zhao* published the first hydroallylation of heterobicyclic olefins by Co-catalysis [35]. This system does not require the use of a reductant to access low-valent Co-complexes. Instead, transmetalation occurs with an allylborate in the form of allyl-BF<sub>3</sub>K. By choice of additive or ligand, one can desymmetrise *meso*-heterobicycles. In the absence of a ligand,

direct hydroallylation is possible in good yields. In this case, addition of a protic solvent additive was necessary for protodemettalation giving rise to hydroallylation of the olefin (Scheme 3.24). With chiral bisphosphines as ligands, enantioselective ring-opening allylation is possible by  $\beta$ -oxygen elimination in good yields and enantioselectivities.



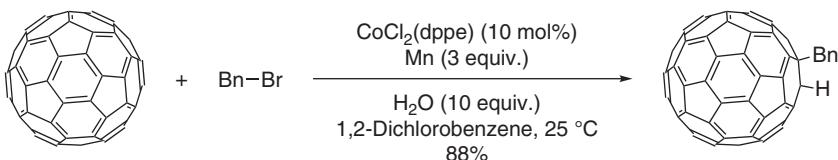
Scheme 3.24 Hydroallylation of heterobicyclic olefins.

The hydroalkylation of alkynes with tetrahydrofuran (THF) as the alkylation source was possible from by using a CoCl<sub>2</sub>-based catalyst (Scheme 3.25) [36]. As oxidant TBHP (*tert*-butyl hydroperoxide) was applied. Although the mechanism is still unclear, TBHP has been used to generate  $\alpha$ -oxycarbon-centred radical species from THF. Kang hypothesise a free radical process.



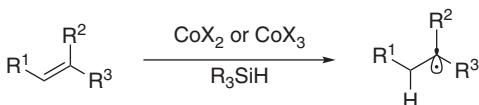
Scheme 3.25 Alkyne hydroalkylation of THF.

The functionalisation of olefins in fullerenes can provide a variety of potential molecular materials for biological and electronic devices (Scheme 3.26) [37]. Yamamoto described that the combination of Co(II)-salt and a reductant could activate benzyl bromides, allyl bromides, propargyl bromides, and  $\alpha$ -bromoesters for fullerene cross-coupling. The authors propose a radical-type mechanism where a Co(0)-complex could undergo halogen atom abstraction to form a stabilised radical. Radical–polar crossover could take place by a single-electron transfer (SET) between the Co(I)-complex and the radical fullerene intermediate that would form a fullerene anion. The anion can be protonated by water in the reaction and the Co(II)-catalyst is regenerated to turn over the catalytic cycle.

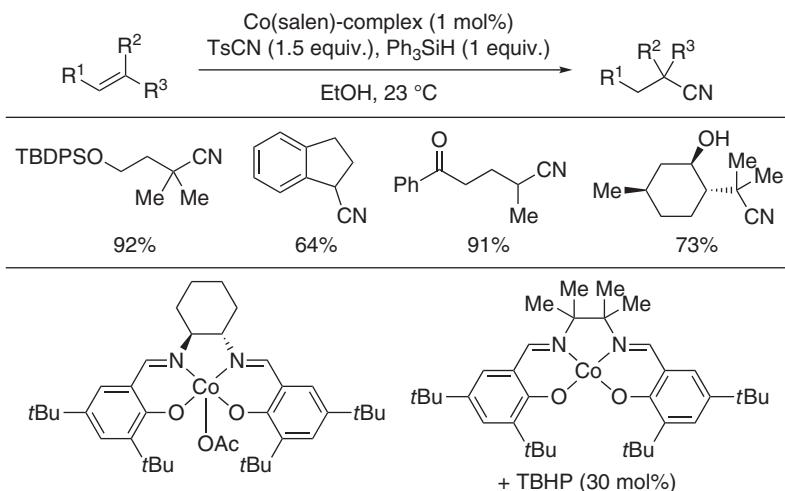
Scheme 3.26 Hydroalkylation of fullerene  $\text{C}_{60}$ .

### 3.2.5 Hydrocyanation

The hydrocyanation of olefins is an efficient way to transform olefins into nitrile compounds and represents a one-carbon homologation. The most atom-economical reagent for this coupling reaction is hydrogen cyanide (HCN). However, due to its toxicity, its use is avoided. Instead, the combination of Co(II)- and Co(III)-catalysts can be used in conjunction with silanes to form high-valent Co-hydrides. In contrast to low valent Co-catalysis, the insertion of trisubstituted olefins is facile. Mechanistically this highlights the non-canonical reactivity of Co–H vs. traditional mechanisms of metal hydrides. First-row metal hydrides derived from Mn, Fe and Co react as radical metal hydrides or as hydrogen atom transfer (HAT) reagents [38]. These metal hydride HAT catalysts prefer to add hydrogen to the less sterically hindered olefin position to form the most stable radical (Scheme 3.27). Radical stability leads to branched hydrofunctionalisation reactions. *Carriera* demonstrated that the use of TsCN, Co(salen)-complexes, and silane enables one to hydrocyanate electron-rich olefins (Scheme 3.28) [39].



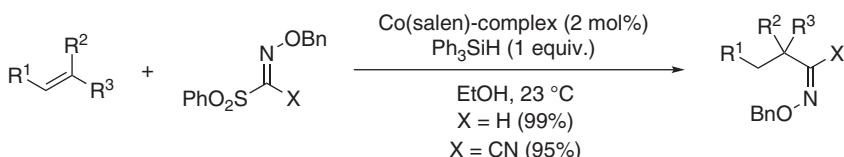
Scheme 3.27 Metal hydride HAT radical stability and selectivity.



Scheme 3.28 Hydrocyanation of olefins via Co(III)-hydride.

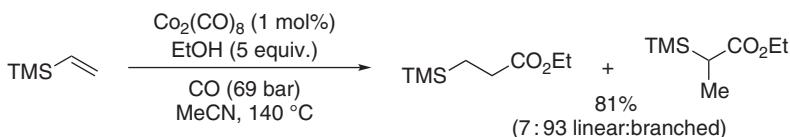
### 3.2.6 Hydrocarboxylation

Analogous to hydrocyanation with TsCN, *Carrierre* showed that a related carbonyl derivative could be used to hydrofunctionalise olefins (Scheme 3.29) [40]. In the proposed mechanism, a similar metal hydride HAT adds to the alkene to form a tertiary alkyl radical. The electron-rich radical can then add to the oxime ether followed by  $\beta$ -scission to release the  $\text{SO}_2\text{Ph}$  leaving group. Hydrolysis to the aldehyde constitutes an overall branched hydroformylation (complementary to linear hydroformylation). Additionally, the oximonitrile functional group can be transformed into amidoxime in two steps.



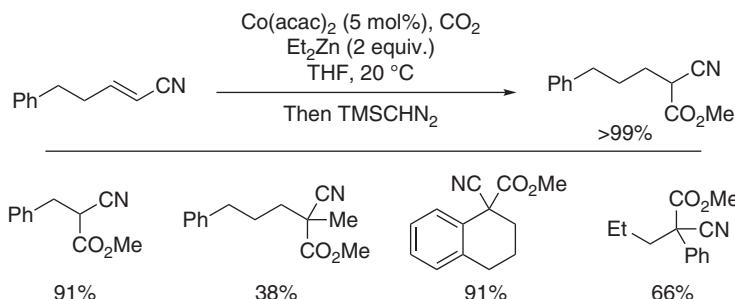
**Scheme 3.29** Hydrofunctionalisation of alkenes to form oximononitrile derivatives.

The use of cobalt carbonyl in the presence of high pressures of carbon monoxide gas and ethanol to form branched ethyl ester was independently described by *Alper* and *Sato* (Scheme 3.30) [41]. In contrast to Co, the use of  $\text{PdCl}_2(\text{PPh}_3)_2$  under analogous high CO pressure conditions yields the linear ester as the major product (95:5 linear:branched).

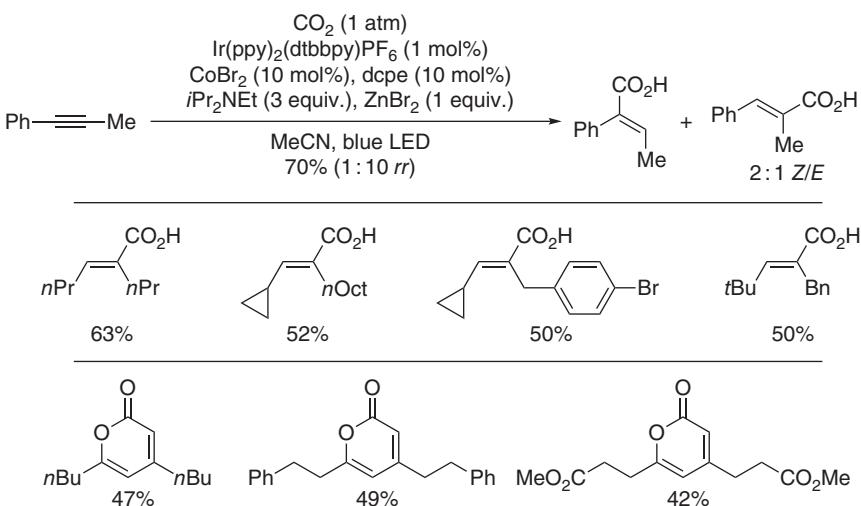


**Scheme 3.30** Hydroesterification of vinylsilane.

More broadly, *Yamada* demonstrated that hydrocarboxylation could be achieved from the combination of  $\text{Co}(\text{acac})_2$  as a catalyst with reductant (hydride source) and  $\text{CO}_2$  gas [42]. Treatment with  $\text{TMSCHN}_2$  allows for the isolation of the methyl ester (Scheme 3.31). Diethylzinc can be used as a



**Scheme 3.31** Hydroesterification of vinylnitriles.

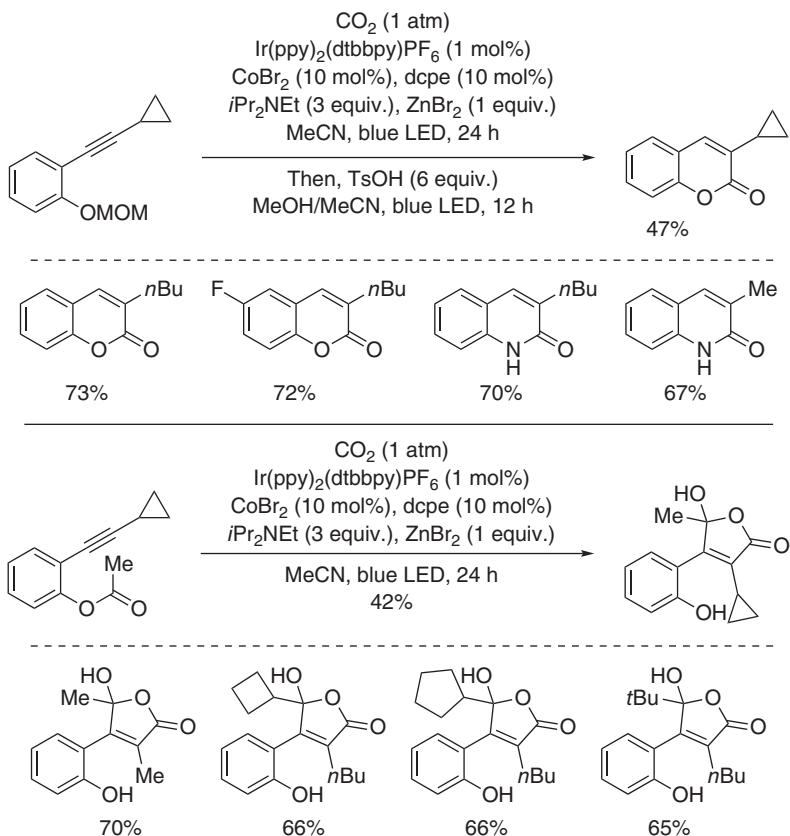


**Scheme 3.32** Hydrocarboxylation of internal alkyne and formal [2+2+2] cycloaddition products of terminal alkyne (below).

reductant and serves as a hydride source (via  $\beta$ -hydride elimination). Hydride addition into the *Michael*-acceptor leads to a Co-alkyl intermediate that can trap CO<sub>2</sub>. Transmetallation with ZnX<sub>2</sub> form a zinc-carboxylate. Workup of the zinc-carboxylate with TMSCHN<sub>2</sub> yields the methyl ester. Ensuing work demonstrated the same system where the *Michael*-acceptor could be modified to other synthetically useful esters and amides.

Recently the increase in light-driven metallaphotoredox catalysis has emerged as a powerful strategy for new bond formations and as a platform for cross-coupling reactions. An early observation was noted in the difference in reactivity between internal alkynes and terminal alkynes under the same conditions (Scheme 3.32) [43]. Wu's visible light-driven reaction catalyses a [2+2+2] cycloaddition reaction with CO<sub>2</sub> and terminal alkynes. Starting material remains and an alkyne trimer is the by-product. However, when switching to an internal alkyne, cycloaddition reactions were not observed. Instead direct hydrocarboxylation was observed. In addition, the use of a metal reductant was absent. Rather, diisopropylethylamine can be used as a reductant in the presence of an Ir-photocatalyst. Although the authors do not state the role of ZnBr<sub>2</sub> additive, without the zinc salt the yields were diminished as well as a significant amount of hydrogenated olefin by-products were observed.

With the use of visible light, the authors took advantage of *ortho*-substituted aryl alkynes to form heterocycles. Key to reactivity is the use of excited-state energy transfer from the Ir-photocatalyst to isomerise the olefin geometry. In a single-pot experiment, internal alkynes can undergo hydrocarboxylation, olefin-isomerisation, and then intramolecular cyclisation (Scheme 3.33).



Scheme 3.33 One-pot hydrocarboxylation/intramolecular cyclisation towards heterocycles.

### 3.3 Summary and Conclusions

Hydrofunctionalisation to make C—C bonds is a powerful method to turn abundant petroleum olefins into valuable molecular scaffolds. Early reports of hydrofunctionalisations tend to use low-valent Co-complexes that needed to be synthesised and stored under inert conditions. However, with the evolution of catalysis to be more general and modular, the *in situ* generation of active catalysts by using commercially available Co-catalyst precursors where ligands can be complexed *in situ* has facilitated catalyst discovery and optimisation. While Co(II)-salts are easily accessible, they are rarely implicated as the reactive catalysts. Studying the mechanism for Co-catalysed pathways remains a major challenge. In comparison to second- and third-row transition metal catalysis, Co can proceed by both single- and two-electron processes. While Co(I) is diamagnetic, traces of other oxidation states that are paramagnetic can make for more complicated nuclear magnetic resonance (NMR) mechanistic studies. Additionally, many of the examples showcased in the chapter have demonstrated

the power of low-valent Co-catalysis. In these cases, a reductant is required. In general, metal reductants (e.g. Zn, Mn, Fe and In) have been routinely used although organozinc, and organoaluminium reagents have been applied as well. Most of these metals are not fully soluble and, thus, the formation of heterogeneous mixtures makes it challenging to study kinetic profiles. It is still unclear whether these additives reduce Co(II) to Co(I) or Co(0), or if comproportionation/disproportionation play a role.

Hydrofunctionalisation of olefins by second- or third-row transition metals often progresses by olefin insertion into a M—H bond but other mechanisms can be considered. In many instances, complementary reactivity or selectivity is possible when using Co as compared with other transition metals. Additionally, the key Co—H species suggested in these pathways seems to differ in properties. In some cases, Co—H behaves as a metal hydride HAT reagent, while in other cases, Co—H participates in insertion or reductive elimination pathways. Understanding this dichotomy of reactivity will allow further control and scope in the use of Co-catalysis for (cross-)couplings with olefins.

## Abbreviations

Ac	acetyl
acac	acetylacetone
atm	atmosphere
Ar	aryl
Boc	<i>tert</i> -butyloxycarbonyl
Bn	benzyl
Bpin	pinacolato boryl
<i>n</i> Bu	<i>n</i> -butyl
OBz	benzoyl
°C	degrees Celsius
cm	centimetre
DCE	1,2-dichloroethane
dcpe	1,2-bis(dicyclohexylphosphino)ethane
DMF	dimethylformamide
dippf	1,1'-bis(diisopropylphosphino)ferrocene
dppb	1,4-bis(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphino)ethane
dppm	1,1-bis(diphenylphosphino)methane
dppp	1,3-bis(diphenylphosphino)propane
<i>dr</i>	diastereomeric ratio
<i>E</i>	<i>entgegen</i> (geometry)
<i>ee</i>	enantiomeric excess
EtOAc	ethyl acetate
Et	ethyl
equiv.	equivalent
h	hour
HAT	hydrogen atom transfer

<i>iPr</i>	isopropyl
$\text{Ir}(\text{ppy})_2(\text{dtbbpy})\text{PF}_6$	[4,4'-bis(1,1-dimethylethyl)-2,2'-bipyridine- <i>N1,N1'</i> ] bis[2-(2-pyridinyl- <i>N</i> )phenyl- <i>C</i> ]iridium(III) hexafluorophosphate
kcal	kilocalorie
kg	kilogram
LED	light emitting diode
M	metal
MAO	methylaluminoxane
Me	methyl
mol	mole
MOM	methoxymethyl
NMR	nuclear magnetic resonance
<i>n</i> Hex	<i>n</i> -hexyl
<i>n</i> Pent	<i>n</i> -pentyl
<i>n</i> Pr	<i>n</i> -propyl
<i>n</i> Oct	<i>n</i> -octyl
Ph	phenyl
( <i>R</i> )-BINAP	( <i>R</i> )-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
<i>rr</i>	regiometric ratio
( <i>R,R</i> )-DIOP	2,3- <i>O</i> -isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
( <i>R,R</i> )-PhBPE	1,2-bis((2 <i>R</i> ,5 <i>R</i> )-2,5-diphenylphospholano)ethane
rt	room temperature
salen	<i>N,N'</i> -bis(salicylidene)ethylenediamine
( <i>S,S</i> )-BDPP	(2 <i>S,4S</i> )-2,4-bis(diphenylphosphino)pentane
syngas	synthetic gas
TBAI	tetrabutylammonium iodide
TBHP	<i>tert</i> -butyl hydroperoxide
<i>t</i> Bu	<i>tert</i> -butyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMS	trimethylsilyl
Ts	tosyl
Z	<i>zusammen</i> (geometry)

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## 4

### Cobalt-Catalysed C–H Functionalisation

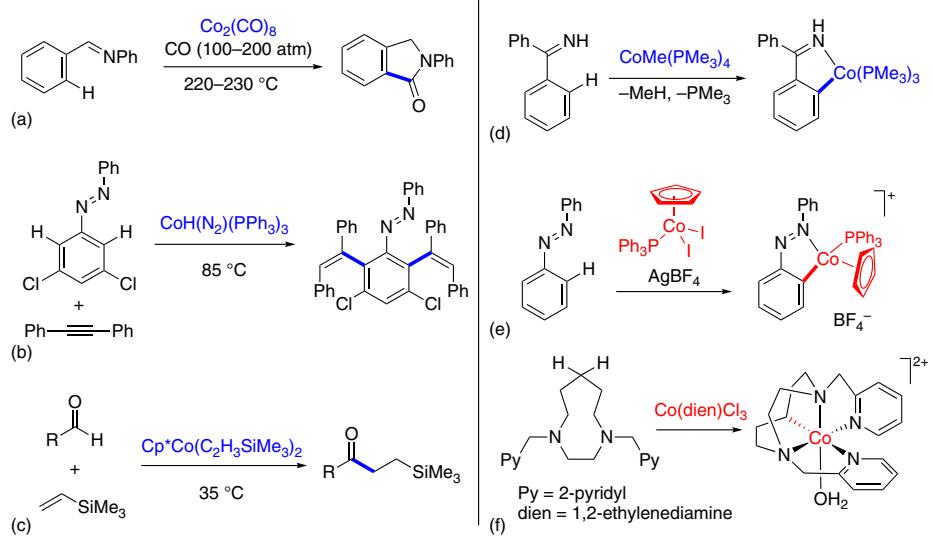
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#### 4.1 Introduction

Cobalt-catalysed C–H bond functionalisation dates back to 1955, when *Murahashi* reported carbonylation of a *Schiff* base using  $\text{Co}_2(\text{CO})_8$  under forcing conditions (Scheme 4.1a) [1]. This pioneering discovery, however, was followed by a long dormant period. Only limited examples of low-valent cobalt-catalysed C–H functionalisations, such as *ortho*-alkenylation of azobenzene derivatives with diphenylacetylene (Scheme 4.1b) [2] and intermolecular hydroacylation of vinylsilane (Scheme 4.1c) [3], among others [4], were reported before 2010. Meanwhile, stoichiometric cyclometallation reactions [5] were reported for monodentate chelating arenes with a  $\text{Co}^{\text{I}}$  complex  $[\text{CoMe}(\text{PMe}_3)_4]$  (Scheme 4.1d) [6] or a cyclopentadienyl ( $\text{Cp}$ )– $\text{Co}^{\text{III}}$  complex (Scheme 4.1e) [7] as well as for polydentate substrates with a simple  $\text{Co}^{\text{III}}$  salt (Scheme 4.1f) [8]. In retrospect, these precedents may be viewed as sign of significant potential of both low-valent and high-valent cobalt complexes for catalytic C–H functionalisation.

This chapter provides an overview of cobalt-catalysed C–H bond functionalisation reactions reported between 2010 and early 2018. The author intends to limit the contents to reactions involving inner-sphere C–H activation processes to generate organocobalt intermediates, while some examples may be mechanistically arguable. The reactions are primarily categorised according to the nature of the cobalt catalysts as well as the reaction conditions. Here, “low-valent” cobalt catalysis refers to reactions performed under reductive conditions or those involving well-defined  $\text{Co}^0$  or  $\text{Co}^{\text{I}}$  species responsible for C–H activation. On the other hand, “high-valent” cobalt catalysis refers to reactions involving well-defined  $\text{Co}^{\text{III}}$  species responsible for C–H activation or those employing  $\text{Co}^{\text{II}}$  or  $\text{Co}^{\text{III}}$  precatalysts under oxidative or non-reductive conditions. The coverage of certain reactions will be brief, considering overlap with other chapters in this book. A host of reviews and accounts have been published on this topic with or without specific focus on the type of the catalyst



**Scheme 4.1** (a–c) Early examples of cobalt-catalysed C–H functionalisation and (d–f) cobalt-mediated cyclometallation.

or reaction [9], and interested readers are advised to consult these authoritative articles for further information.

## 4.2 Low-valent Cobalt Catalysis

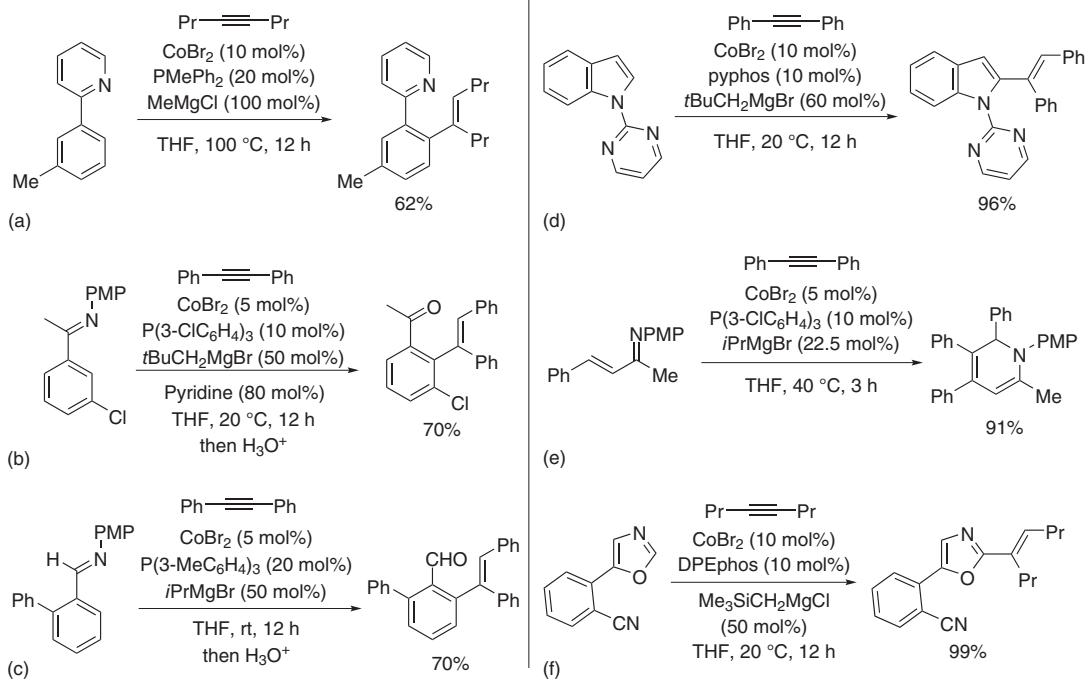
Rhodium(I)-phosphine and related low-valent rhodium complexes have proven to promote a broad range of chelation-assisted C—H bond functionalisation reactions [10]. They are also known to be engaged in remote C—H activation via 1,4-rhodium migration, typically when used together with arylboron reagents [11]. Rhodium(I)-diphosphine catalysts have been extensively used in intra- and intermolecular hydroacylation reactions, including enantioselective variants [12]. Low-valent rhodium and iridium complexes are known as privileged catalysts for C—H borylation, especially using aromatic substrates [13]. The efforts to emulate these group 9 transition metal-catalysed C—H activation manifolds using cobalt have not only established low-valent cobalt species as inexpensive alternative catalysts but also revealed their unique reactivities and selectivities, as discussed in the following sections.

### 4.2.1 C—H Functionalisation with *In Situ*-Reduced Cobalt Catalysts

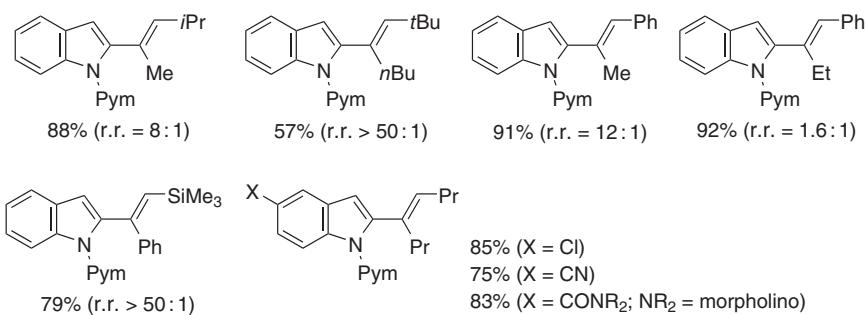
#### 4.2.1.1 Hydroarylation of Alkynes and Alkenes

In 2010, *Yoshikai* reported hydroarylation of an internal alkyne via chelation-assisted C—H activation of 2-arylpyridine using a low-valent cobalt catalyst generated *in situ* from a cobalt(II) salt, a phosphine ligand, and a *Grignard* reagent, affording the *ortho*-alkenylated product with *syn*-selectivity (Scheme 4.2a) [14]. The scope of aromatic substrates was then extended to aryl ketimines [15], aryl aldimines [16], and *N*-pyrimidylindoles [17] through optimisation of cobalt/ligand/*Grignard* reagent ternary catalytic systems (Scheme 4.2b–d). A [4+2] annulation of  $\alpha,\beta$ -unsaturated imine and alkyne via olefinic  $C(sp^2)$ —H alkenylation and  $6\pi$  electrocyclisation was also achieved (Scheme 4.2e) [18]. A cobalt-diphosphine catalytic system was developed for C2-alkenylation of azoles (Scheme 4.2f) [19]. These and related hydroarylation reactions typically require a larger amount of the *Grignard* reagent than required to reduce the Co<sup>II</sup> precatalyst to a Co<sup>0</sup> species. The reason for this requirement is not clear, while one may speculate the formation of an organocobalt ate species as the reactive species [15].

To provide a general idea about the regioselectivity trend and the functional group compatibility of *in situ*-reduced cobalt catalysts, a part of the substrate scope of alkyne hydroarylation using *N*-pyrimidylindole (Scheme 4.2d) [17] is shown in Scheme 4.3. The regioselectivity for unsymmetrical alkynes is controlled by steric parameters rather than electronic factors, with preferential C—C bond formation on the less hindered carbon of the alkyne. While the use of *Grignard* reagent as a reductant imposes limitations in tolerable functional groups, substituents such as chloro, cyano, and amide groups are compatible.

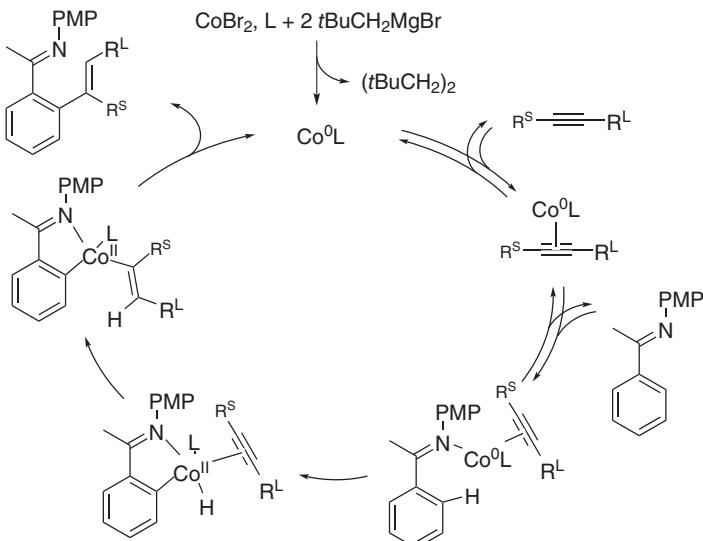


**Scheme 4.2** (a–f) Chelation-assisted hydroarylation of alkynes with *in situ*-generated low-valent cobalt catalysts (*PMP* = *p*-methoxyphenyl).



**Scheme 4.3** Products of alkyne hydroarylation with *N*-pyrimidylindole (Pym = 2-pyrimidyl).

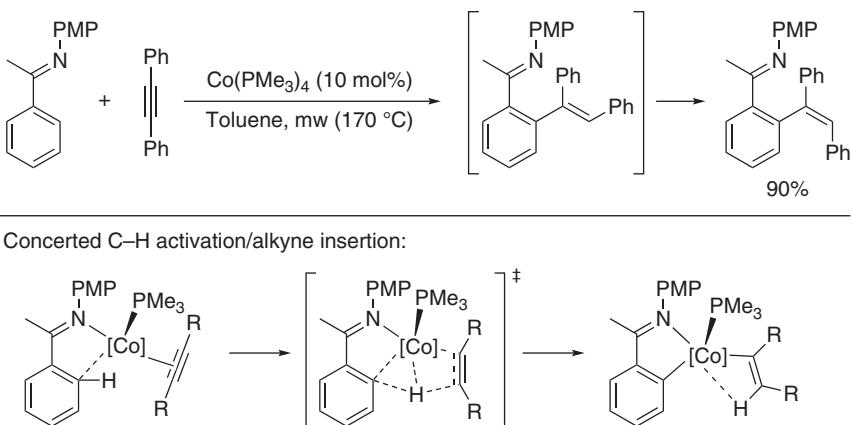
A catalytic cycle proposed for the imine-directed alkyne hydroarylation is shown in Scheme 4.4. The cobalt precatalyst is reduced by *Grignard* reagent to form an active low-valent cobalt species, which is assumed to have the oxidation state of Co<sup>0</sup>. The cobalt species undergoes reversible coordination of the alkyne and rate-determining chelation-assisted oxidative addition of the *ortho* C—H bond. Migratory insertion of the alkyne into the Co—H bond and subsequent C—C reductive elimination furnishes the hydroarylation product while regenerating the low-valent cobalt species. The preference of the cobalt centre to avoid steric repulsion during alkyne insertion is responsible for the observed regioselectivity.



**Scheme 4.4** Proposed catalytic cycle for ketimine-directed alkyne hydroarylation.

Petit demonstrated that a well-defined Co<sup>0</sup> complex  $[\text{Co}(\text{PMe}_3)_4]$  served as a viable catalyst for some of the previously mentioned alkyne hydroarylation reactions [20]. For example, the reaction of aryl ketimine was achieved with

microwave irradiation at 170 °C to afford the *anti*-hydroarylation product, which was formed by isomerisation of initially formed *syn*-hydroarylation product (Scheme 4.5). A density functional theory (DFT) study suggested that the C–H bond cleavage and the insertion of the alkyne take place in a concerted manner, through so-called ligand-to-ligand hydrogen transfer (LLHT) mechanism [21]. *Yoshikai's* *in situ*-generated cobalt catalysts might also operate by a similar concerted mechanism.

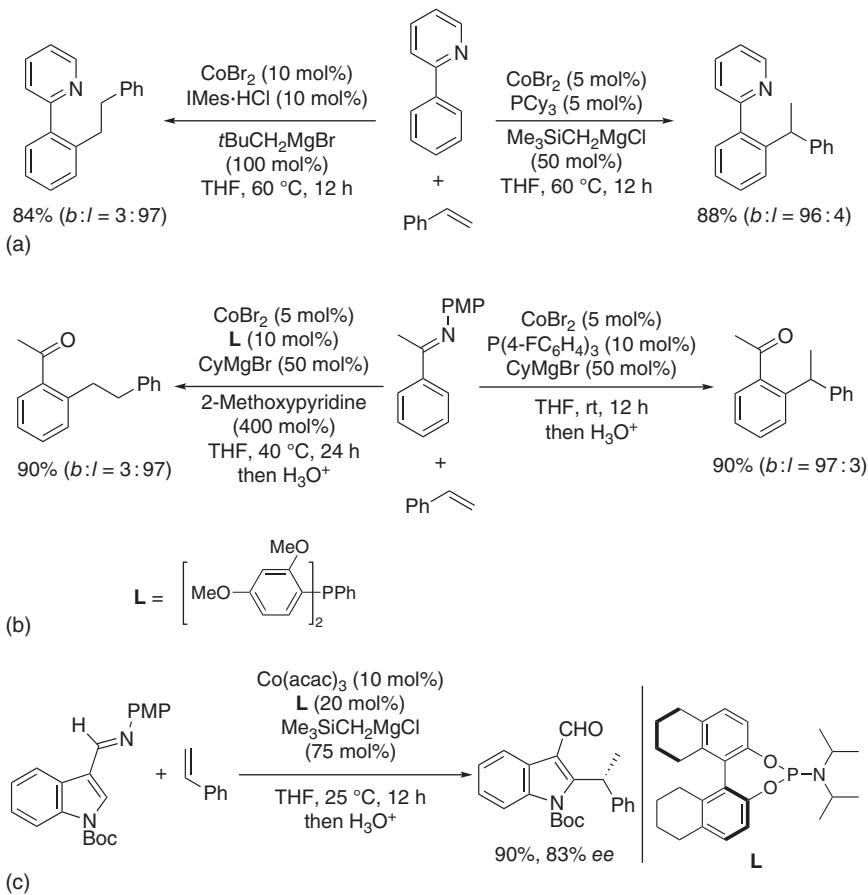


**Scheme 4.5** Ketimine-directed alkyne hydroarylation catalysed by  $\text{Co}(\text{PMe}_3)_4$ .

*Yoshikai* extended the low-valent cobalt catalysis to hydroarylation of styrenes. A regiodivergence was observed for the addition of 2-arylpyridine to styrene, where monophosphine such as  $\text{PCy}_3$  and bulky *N*-heterocyclic carbenes (NHC), such as 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene (IMes), displayed branched and linear selectivities, respectively (Scheme 4.6a) [22]. The scope of branched-selective hydroarylation was extended to aryl aldimines and ketimines using simple triarylphosphine as the supporting ligand [23]. Meanwhile, linear-selective hydroarylation of aryl ketimines was achieved by modification of the triarylphosphine structure with 2,4-dimethoxyphenyl groups (Scheme 4.6b) [24]. An enantioselective variant of the branched-selective reaction was also developed using a chiral phosphoramidite, while the substrate scope is limited to 3-iminoindole derivatives (Scheme 4.6c) [25].

A proposed catalytic cycle for the regiodivergent styrene hydroarylation is shown in Scheme 4.7. On the basis of deuterium-labelling experiments, the reaction is proposed to involve reversible C–H oxidative addition, reversible and competitive styrene insertion leading to branched or linear alkyl cobalt intermediates, and regioselectivity-determining C–C reductive elimination. The branched selectivity of the  $\text{Co-PCy}_3$  system was ascribed to favourable  $\eta^3$ -benzyl coordination, while the linear selectivity of the  $\text{Co-IMes}$  system was explained by the steric preference. These conjectures were supported by DFT studies, which also implied intrinsic preference of cobalt for branched selectivity [26].

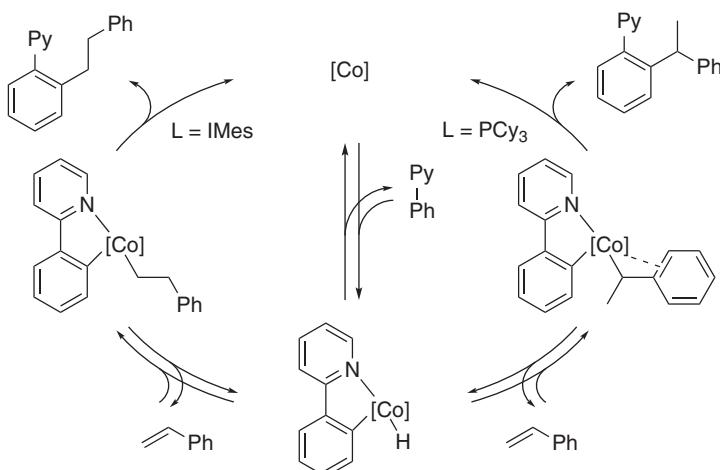
Hydroarylation reactions to simple alkenes other than styrenes were also developed. *Nakamura* reported the addition of secondary benzamide



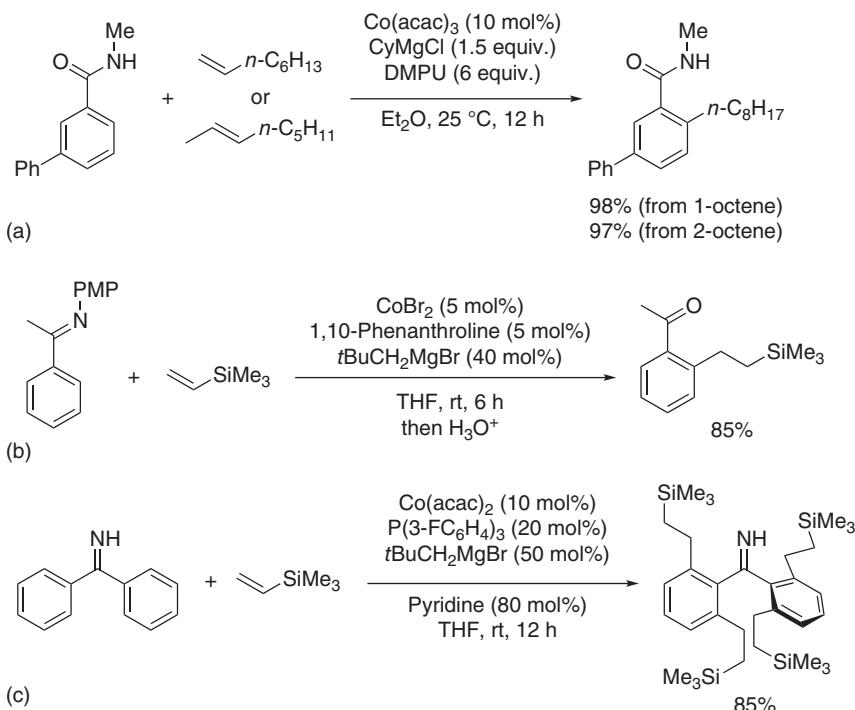
**Scheme 4.6** (a–c) Chelation-assisted hydroarylation of styrenes.

derivatives to alkenes using a catalyst generated from  $\text{Co}(\text{acac})_2$ ,  $\text{CyMgCl}$ , and  $N,N'$ -dimethylpropylene urea (DMPU) (Scheme 4.8a) [27]. Interestingly, both 1-octene and 2-octene afforded the same primary alkylation product, as the latter alkene likely underwent alkene isomerisation via insertion/ $\beta$ -hydride elimination. *Yoshikai* developed cobalt–phenanthroline catalysts for the addition of aryl  $N$ -aryl imines to vinylsilanes and alkyl olefins (Scheme 4.8b) [28]. Furthermore,  $N$ –H imine proved to serve as a more powerful directing group. For example, fourfold *ortho*-alkylation of benzophenone  $N$ –H imine with vinylsilane took place efficiently using a cobalt–triarylphosphine catalyst (Scheme 4.8c) [29].

Other examples of cobalt-catalysed alkene hydroarylation include intramolecular hydroarylation and tandem alkene isomerisation–hydroarylation. Cobalt–NHC catalysts promoted divergent cyclisation of 1-homoallyl-3-iminoindoles into five- or six-membered ring products depending on the steric nature of the NHC ligand (Scheme 4.9a) [30]. The reactions between 3-iminoindole and allyl-, homoallyl-, or bishomoallylbenzene under

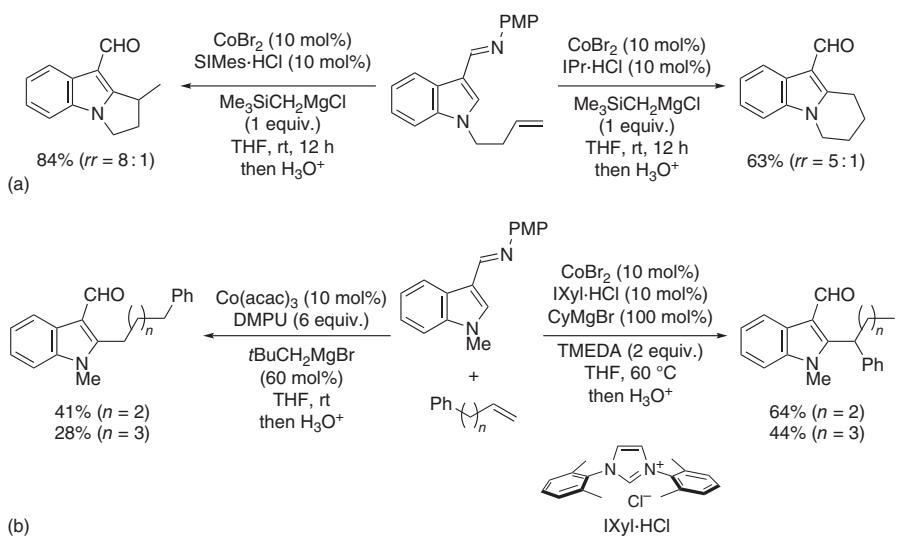


**Scheme 4.7** Proposed catalytic cycle for regiodivergent styrene hydroarylation.



**Scheme 4.8** Chelation-assisted hydroarylation of (a) alkyl-substituted olefins and (b, c) vinylsilane.

cobalt–NHC catalysis resulted in indolylation of the benzylic position, affording 1,1-diarylpropane products (Scheme 4.9b) [31]. This regioselectivity was in sharp contrast to the Co-DMPU catalytic system [27], which exclusively afforded the linear alkylation products.

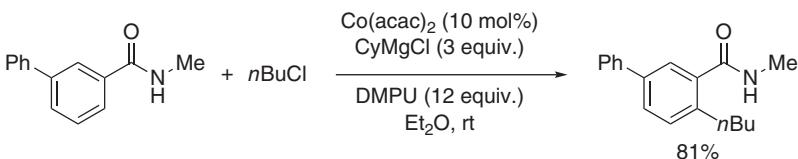


**Scheme 4.9** (a, b) Alkene hydroarylation using 3-iminoindoles.

*Petit* reported that  $\text{Co}(\text{PMe}_3)_4$  served as a catalyst for the inter- and intramolecular alkene hydroarylation using 3-iminoindoles [20c]. *Yoshikai* demonstrated that metallic magnesium can be used instead of *Grignard* reagent, as reductant for some of the previously mentioned hydroarylation reactions [32].

#### 4.2.1.2 C–H Functionalisation with Electrophiles

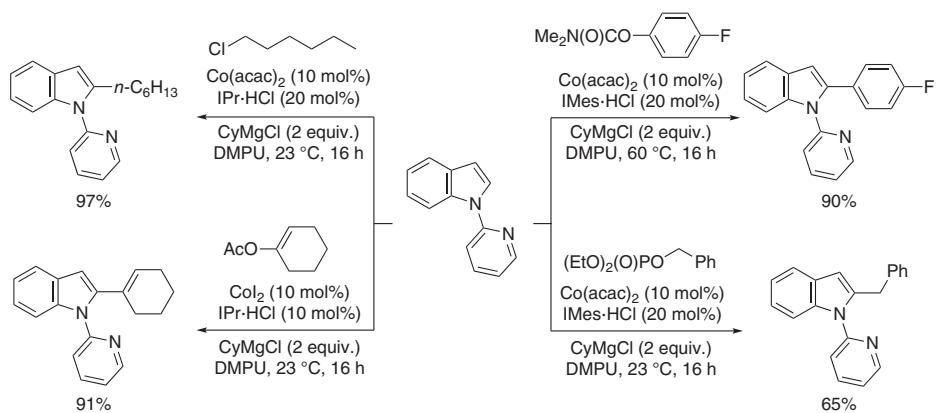
In 2011, *Nakamura* reported an *ortho*-alkylation of secondary benzamide with alkyl chloride in the presence of  $\text{Co}(\text{acac})_2$ , DMPU, and  $\text{CyMgCl}$ , where the *Grignard* reagent likely served as a reductant to reduce the  $\text{Co}^{\text{II}}$  precatalyst as well as a base to deprotonate the amide group and to remove the hydrogen atom in the *ortho*-position (Scheme 4.10) [33]. The reaction took place at a mild temperature using primary alkyl chlorides, while secondary chloride such as cyclohexyl chloride reacted sluggishly.



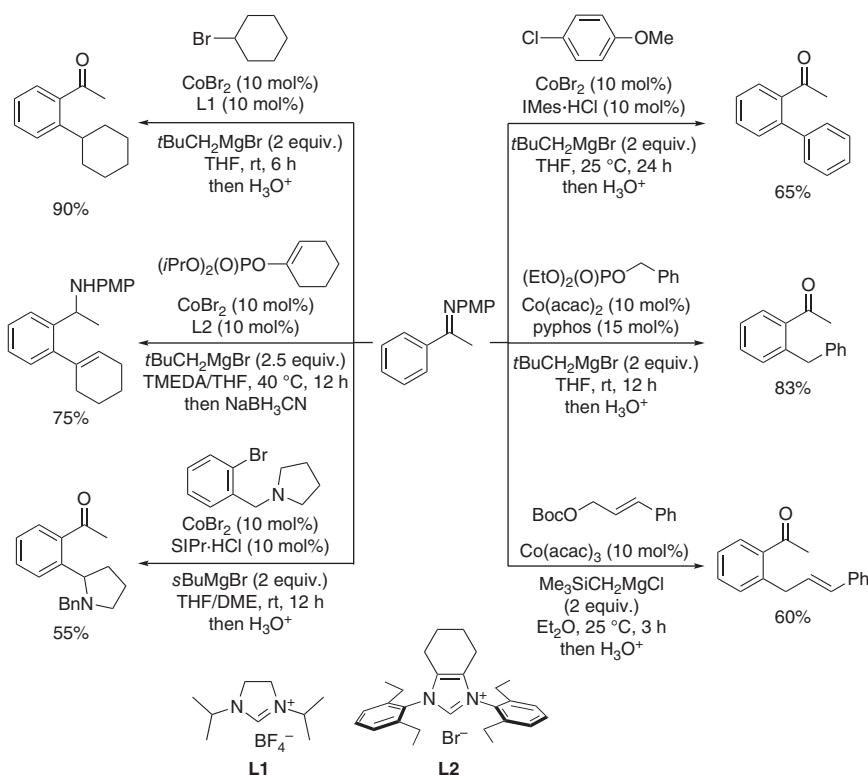
Scheme 4.10 *ortho*-Alkylation of benzamide with alkyl chloride.

The scope of low-valent cobalt-catalysed chelation-assisted C–H/electrophile coupling has been expanded significantly by cobalt–NHC catalytic systems developed by *Ackermann* and *Yoshikai*. *Ackermann*'s work has mainly revolved around functionalisation of 2-arylpyridines and *N*-pyr(i)mi)dylindoles with organic (pseudo)halides [34]. As illustrated in Scheme 4.11, catalytic systems comprised of  $\text{Co}^{\text{II}}$  salts, NHC precursors, and  $\text{CyMgCl}$  enabled a variety of C–C bond forming reactions such as arylation with aryl sulfamates, carbamates, and chlorides, benzylation with benzyl phosphates, alkylation with alkyl chlorides, and alkenylation with alkenyl acetate and related ketone-derived electrophiles. C–H arylation and alkylation have also been achieved for secondary benzamides, aryl tetrazoles, and 2-aryloxazoline derivatives [35].

*Yoshikai* mainly explored C–H/electrophile coupling of aryl ketimines and 2-arylpyridines (Scheme 4.12) [36]. Thus, cobalt–NHC catalytic systems were developed for arylation with aryl chlorides, alkylation with alkyl halides, and alkenylation with alkenyl phosphates, while *ortho*-benzylation with benzyl phosphates was achieved under cobalt–phosphine catalysis. Besides *N*-aryl ketimine, pivaloyl N–H imine also proved to serve as an excellent directing group for the *ortho*-alkylation, arylation, and alkenylation, where the N–H imine can be utilised as a cyano group surrogate [37]. The radical nature of these reactions (*vide infra*) enabled  $\text{C}(\text{sp}^2)\text{–C}(\text{sp}^3)$  coupling between aryl ketimine and *N*-(2-bromobenzyl)amine by a merger of *ortho* C–H activation and 1,5-hydrogen atom transfer processes. *Zeng* developed a ligand-free system for the *ortho*-allylation of 2-arylpyridines and aryl ketimines with allylic carbonates [38]. Besides organic halides and pseudohalides, *N*-aryl aldimines and aziridines were demonstrated to serve as electrophiles for the *ortho* C–H functionalisation of 2-arylpyridines under cobalt–NHC catalysis [39].



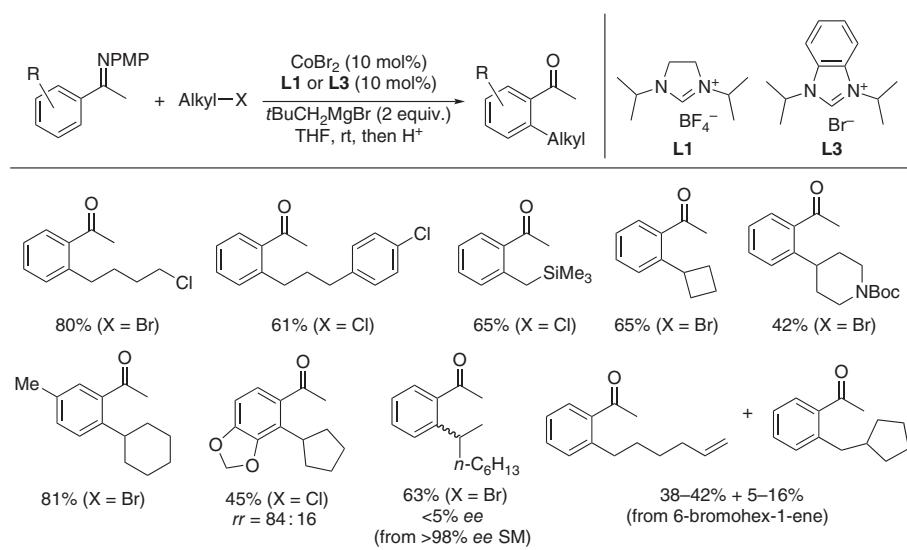
**Scheme 4.11** C–H functionalisations of *N*-pyridylindoles with electrophiles under Co–NHC catalysis.



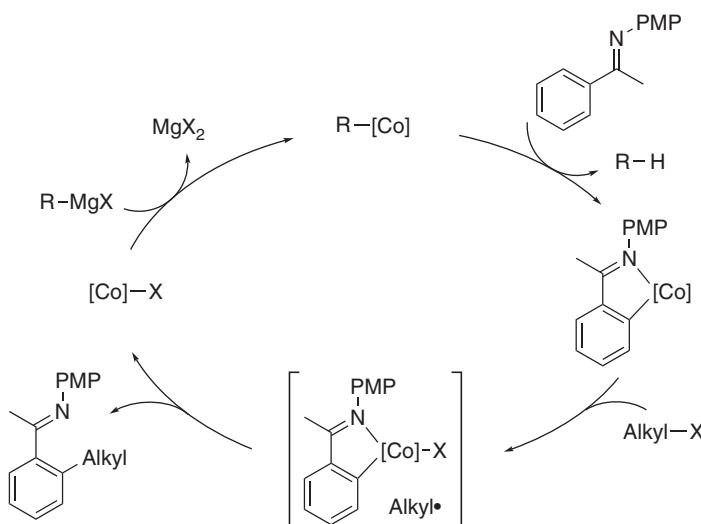
Scheme 4.12 C–H functionalisation of *N*-aryl ketimines with organic electrophiles.

To illustrate the typical nature of the Co–NHC catalytic systems in the C–H/electrophile coupling, examples of the *ortho*-alkylation of aryl ketimine are displayed in Scheme 4.13. The reaction is applicable to a range of primary and secondary alkyl chlorides/bromides while showing chemoselectivity towards C(sp<sup>3</sup>)–Br over C(sp<sup>3</sup>)–Cl bonds as well as towards C(sp<sup>3</sup>)–Cl over C(sp<sup>2</sup>)–Cl. Both steric effects and secondary directing effects operate to determine the positional selectivity of C–H activation. For example, an ether in the *meta*-position tends to favour C–H activation at its proximity, presumably due to attractive interaction between the ether oxygen and the cobalt catalyst. Involvement of an alkyl radical is indicated from the formation of a racemic product from enantiopure secondary alkyl bromide as well as the formation of a ring-closing alkylation product from 6-bromohex-1-ene.

Scheme 4.14 illustrates a proposed catalytic cycle for the ketimine-directed C–H alkylation. An alkyl cobalt species generated from the cobalt precatalyst and the *Grignard* reagent underwent cyclometallation of the aryl imine to form a cobaltacycle species. Single-electron transfer (SET) from cobalt to the alkyl halide generated an oxidised cobaltacycle and an alkyl radical, followed by C–C coupling, presumably via radical recombination and reductive elimination, to afford the alkylation product. Transmetallation between the thus-formed cobalt halide and the *Grignard* reagent regenerated the alkyl cobalt species. The SET



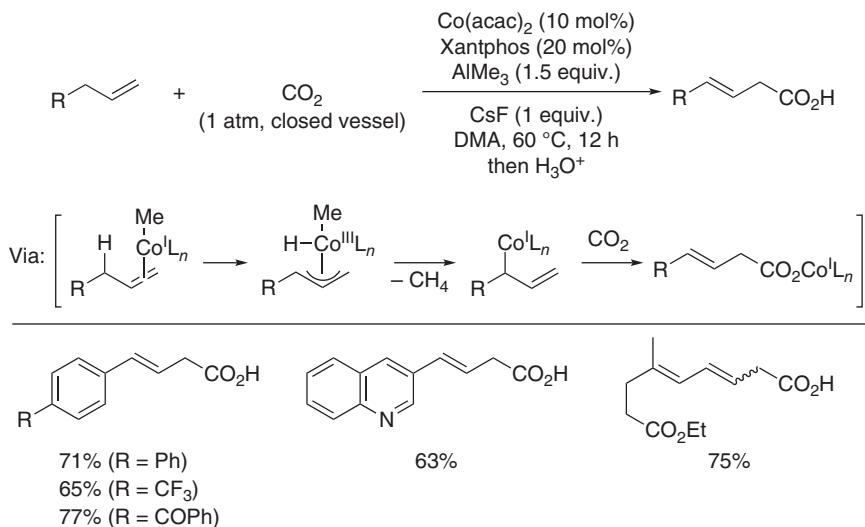
**Scheme 4.13** Examples of *ortho*-alkylation of aryl imines with alkyl halides.



**Scheme 4.14** Proposed catalytic cycle for imine-directed C–H alkylation with alkyl halide.

mechanism was also proposed to operate in some of other C–H/electrophile coupling reactions.

*Mita* and *Sato* reported a carboxylation of an allylic  $\text{C}(\text{sp}^3)-\text{H}$  bond with  $\text{CO}_2$  promoted by a combination of a cobalt(II) precatalyst, a diphosphine ligand, and  $\text{AlMe}_3$  (Scheme 4.15) [40]. The reaction of allyl arenes and 1,4-dienes resulted in carboxylation of the terminal position, affording cinnamic acid and related derivatives. The reaction was proposed to involve a methyl cobalt(I) species as a catalytically active species, and a sequence of allylic C–H oxidative addition,

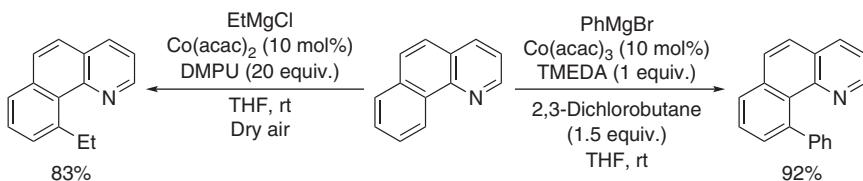


**Scheme 4.15** Allylic  $\text{C}(\text{sp}^3)-\text{H}$  carboxylation with  $\text{CO}_2$ .

reductive elimination of methane, and interception of allyl cobalt(I) species with CO<sub>2</sub>. The scope of this catalytic system was extended to direct addition of allyl arenes to ketones [41].

#### 4.2.1.3 C–H Functionalisation with Organometallic Reagents

Chelation-assisted C–H functionalisation using hard organometallic reagents such as organozinc, *Grignard*, and organoaluminium reagents has been extensively developed using iron catalysts [42]. Meanwhile, the same oxidative C–H functionalisation manifold was demonstrated with cobalt catalysis (Scheme 4.16). Wang and *Shi* developed *ortho*-arylation of 2-arylpyridines with aryl *Grignard* reagents using a catalytic system comprised of Co(acac)<sub>3</sub>, N,N,N',N'-tetramethylethylenediamine (TMEDA), and 2,3-dichlorobutane (DCB), where DCB serves as an oxidant [43]. The same catalytic system was also used for methylation of chelating ferrocenes with MeMgBr [44]. Nakamura reported an *ortho*-alkylation of 2-arylpyridines and secondary benzamides with alkyl *Grignard* reagents, where DMPU significantly promotes the oxidative coupling under dry air [45]. Also, *Xu* reported an *ortho*-methylation and ethylation of *N*-(8-quinolinyl)benzamide with the corresponding trialkyl aluminium reagent in the presence of DCB [46].



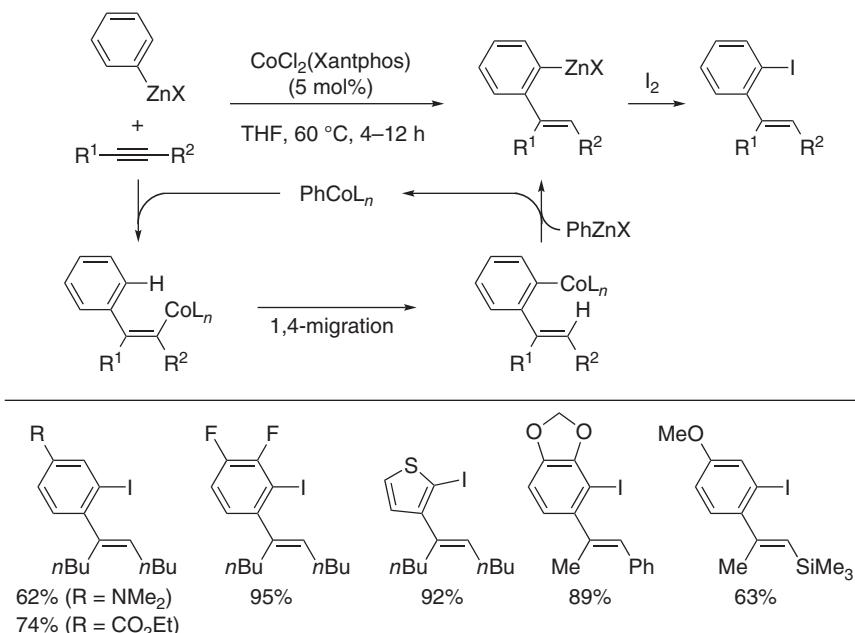
**Scheme 4.16** *ortho*-C–H functionalisation of benzo[*h*]quinoline with *Grignard* reagents.

#### 4.2.1.4 C–H Functionalisation via 1,4-Cobalt Migration

*Yoshikai* reported a cobalt-catalysed addition of aryl zinc reagents to alkynes to afford *ortho*-alkenylaryl zinc reagents (Scheme 4.17) [47]. This “migratory arylzincation” reaction likely involved alkyne insertion into an aryl cobalt species, vinyl-to-aryl 1,4-cobalt migration, and cobalt-to-zinc transmetallation. The reaction allowed simultaneous alkenylation of the aryl zinc reagent and functionalisation of the *ortho*-position and has found applications in the synthesis of various benzo[*b*]heterole derivatives [48]. 1,4-Cobalt migration was also reported for the addition of aryl zinc to norbornene [49] and utilised in intramolecular settings [50].

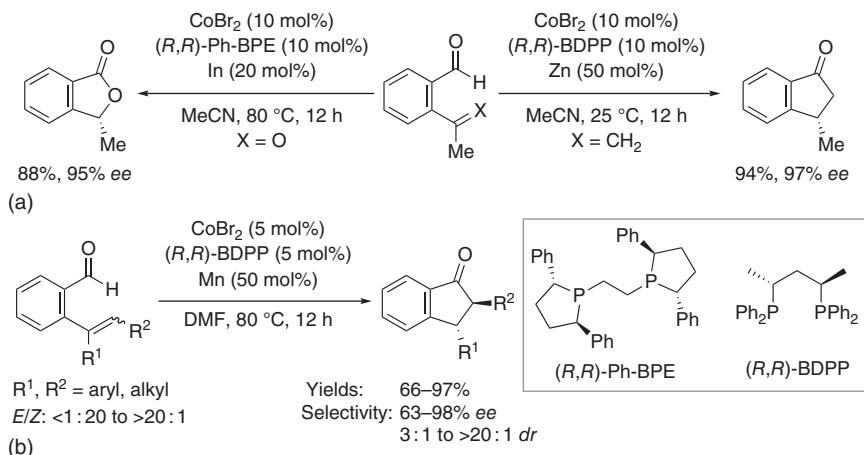
#### 4.2.1.5 Hydroacylation

While the use of cobalt catalysts for hydroacylation had been sporadic [3, 4], several examples of cobalt-catalysed inter- and intramolecular hydroacylation have been reported since 2014. *Dong* reported intermolecular hydroacylation of 1,3-diene using a low-valent cobalt–diphosphine catalyst generated by *in situ* reduction using indium powder [51]. Unlike the previously reported cobalt-catalysed hydroacylation, this reaction was proposed to proceed through



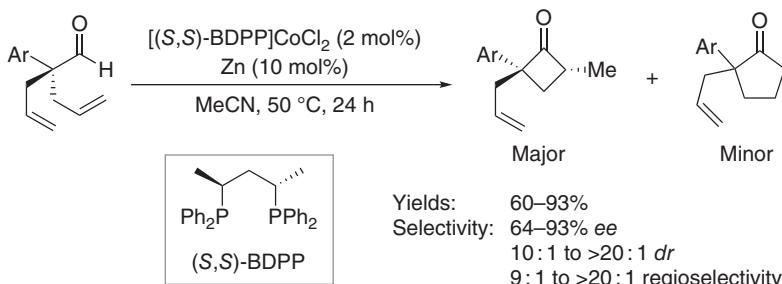
Scheme 4.17 Migratory arylzincation of alkynes via 1,4-cobalt migration.

oxidative cyclisation of aldehyde and a 1,3-diene onto Co<sup>I</sup> rather than insertion into the C–H bond of the aldehyde. Meanwhile, Yoshikai disclosed an enantioselective intramolecular hydroacylation of ketones and alkenes using cobalt–chiral diphosphine catalysts (Scheme 4.18) [52]. Notably, intramolecular hydroacylation of trisubstituted alkenes was achieved with high diastereo- and enantioselectivities starting from a mixture of *E*- and *Z*-alkenes.



Scheme 4.18 (a, b) Enantioselective intramolecular hydroacylation leading to chiral indanones and phthalides.

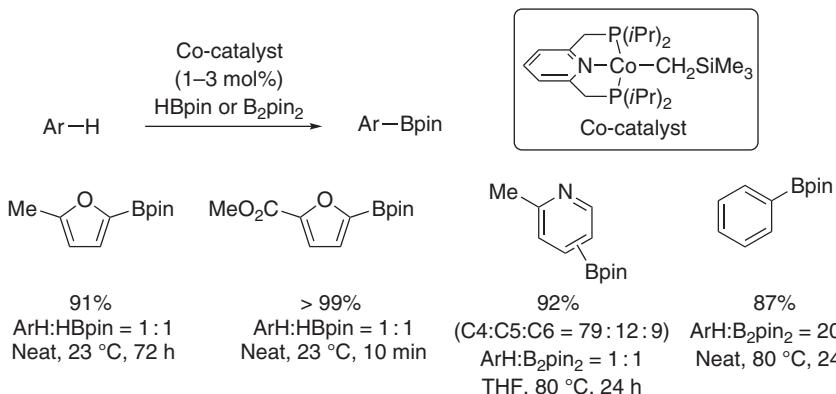
Dong reported a unique reactivity of a cobalt–chiral diphosphine catalyst in intramolecular hydroacylation of  $\alpha,\alpha$ -bisallyl-substituted aldehydes (Scheme 4.19) [53]. In contrast to rhodium-catalysed reactions of the same substrate, the cobalt catalysis promoted desymmetrisation, which resulted in strained cyclobutanone derivatives with high enantio-, diastereo-, and regioselectivities. Besides these intramolecular reactions, cobalt–achiral diphosphine catalysts were reported to promote intermolecular addition of *N*-3-picolin-2-yl aldimine to alkenes [54] and annulation of salicylaldehyde and alkyne [55].



Scheme 4.19 Enantioselective intramolecular hydroacylation leading to cyclobutanones.

#### 4.2.2 C–H Functionalisation with Pincer-Type Ligands and Related Well-Defined Cobalt Catalysts

Cobalt and iron complexes with pincer-type ligands have emerged as inexpensive and potentially superior alternatives to precious metal catalysts for important transformations such as hydrogenation, hydrosilylation, and hydroboration of unsaturated hydrocarbons [56]. Also, the C–H borylation represents a useful transformation [13], for which inexpensive alternatives to well-established iridium and rhodium catalysts have been awaited. In 2014, Chirik disclosed C–H borylation of heteroarenes and arenes catalysed by a 2,6-bis(phosphinomethyl)pyridine (PNP) pincer-ligated cobalt alkyl complex (Scheme 4.20) [57]. Electron-rich five-membered heteroarenes such as furan,



Scheme 4.20 C–H borylation of heteroarenes and arenes catalysed by a cobalt–PNP complex.

thiophene, and indole derivatives were borylated with HBpin under mild conditions, while pyridines and simple arenes underwent borylation with  $B_2\text{pin}_2$  under more forcing conditions. A cobalt(II)–PNP dichloride complex could be used as a precatalyst in combination with  $\text{NaBET}_3\text{H}$  as a reductant, and the electron-rich PNP ligand proved to show the highest activity among other pincer-type ligands [58].

*Chirik* performed detailed mechanistic studies on the Co–PNP-catalysed C–H borylation reactions of 2,6-lutidine [59] and benzofuran [60] to propose plausible catalytic cycles (Scheme 4.21). In the reaction of pyridine or benzene derivative, borylation of the pyridine C4-position of the pincer-type ligand was found to occur first. The main catalytic cycle involves oxidative addition of  $B_2\text{pin}_2$  to a cobalt(I) hydride species, reductive elimination of HBpin, oxidative addition of arene to cobalt(I) boryl species, and C–B reductive elimination. The C–H oxidative addition was identified as the turnover-limiting step (TLS), which was slowed by the electron-withdrawing C4-boryl group. This insight allowed development of an improved pincer-type ligand with the C4 position capped by a pyrrolidinyl group. The borylation of electron-rich five-membered heteroarene with HBpin also involved an analogous  $\text{Co}^{\text{I}}/\text{Co}^{\text{III}}$  catalytic cycle, while reductive elimination of  $\text{H}_2$  from cobalt(III) dihydride boryl was the TLS. *Chirik* also developed a ter-pyridine cobalt(II) diacetate as an air-stable precatalyst, which can be activated by LiOMe for C–H borylation [61].

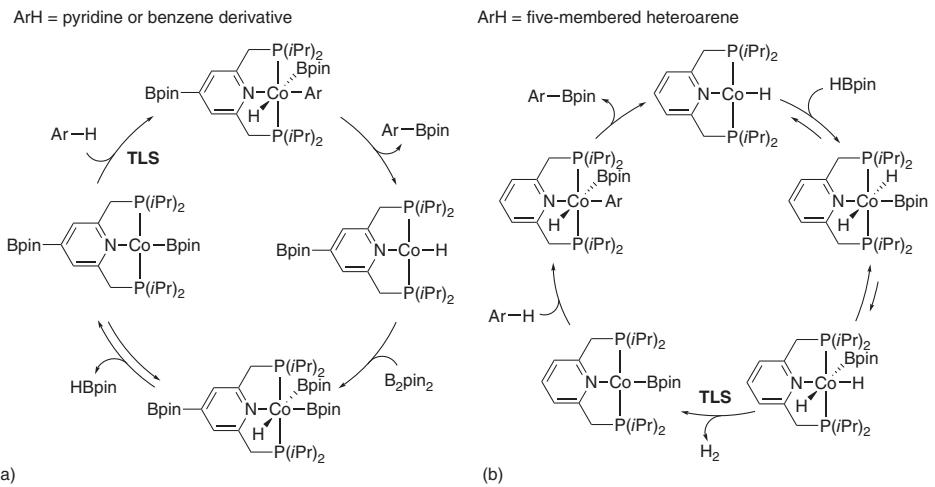
*Chirik* found unique site selectivity of cobalt–PNP-catalysed C–H borylation of fluorinated arenes (Scheme 4.22) [62]. While conventional iridium catalysts are known to borylate either the least hindered position or the proximity of certain directing groups such as Si–H moiety and amino group, the cobalt catalyst selectively borylates the *ortho*-position of the fluorine atom, which possesses the highest acidity among the aromatic C–H bonds. An air-stable cobalt(II) bis(pivalate) complex with a pincer-type ligand proved to serve as an effective precatalyst.

*Chirik* discovered that a cobalt  $\alpha$ -diimine complex promotes benzylic C–H borylation of toluene derivatives (Scheme 4.23) [63]. Mono-, di-, and even tri-borylated products could be obtained depending on the reaction conditions. Furthermore, branched alkyl arenes underwent C–H borylation at the homobenzylic position. The cobalt–diimine catalyst was also found to promote hydrogen isotope exchange on  $\text{C}(\text{sp}^3)\text{—H}$  bonds of alkyl arene derivatives [64].

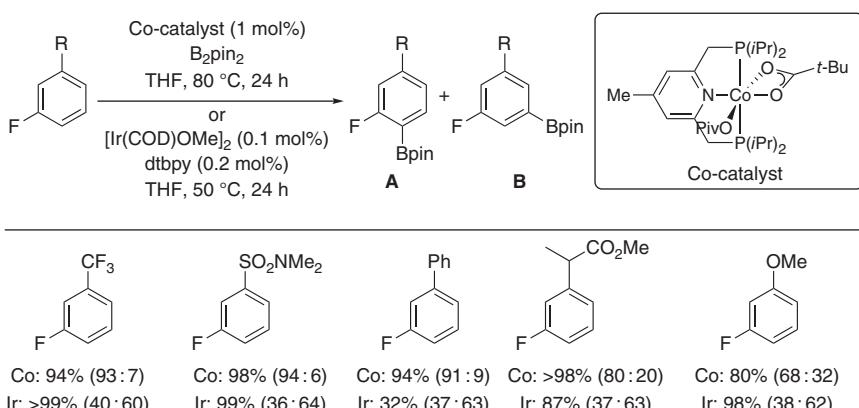
### 4.3 High-valent Cobalt Catalysis

#### 4.3.1 Chelation-Assisted C–H Functionalisation with $\text{Cp}^*\text{Co}^{\text{III}}$ Catalysts

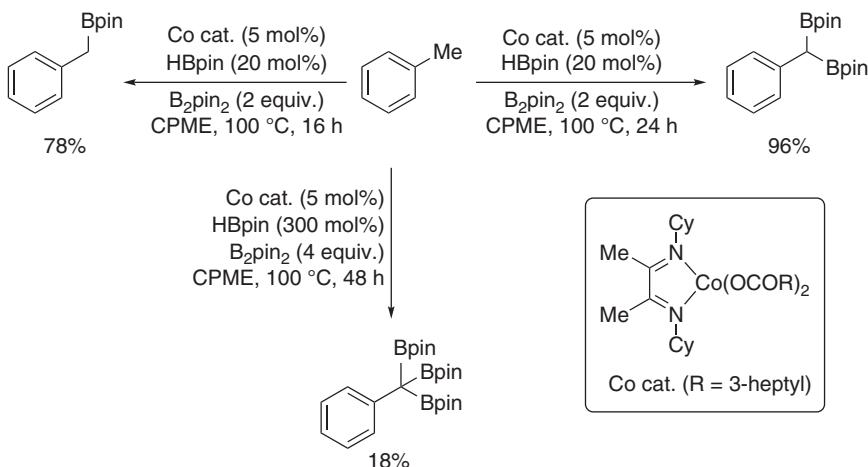
Since the initial report by *Matsunaga* and *Kanai* in 2013, (pentamethylcyclopentadienyl)cobalt(III) ( $\text{Cp}^*\text{Co}^{\text{III}}$ ) complexes have proven to catalyse a variety of chelation-assisted C–H functionalisation reactions, as overviewed in this section. These reactions are categorised according to the type of reactants used to functionalise the C–H bond, as illustrated in Scheme 4.24. While  $\text{Cp}^*\text{Co}^{\text{III}}$  is often reported as an inexpensive alternative catalyst for C–H functionalisations



**Scheme 4.21** Proposed catalytic cycles for cobalt–PNP-catalysed C–H borylations of (a) pyridine or benzene derivative and (b) five-membered heteroarene.



**Scheme 4.22** C—H borylation of fluorinated arenes. The ratio of the products **A** and **B** is shown in the parentheses.

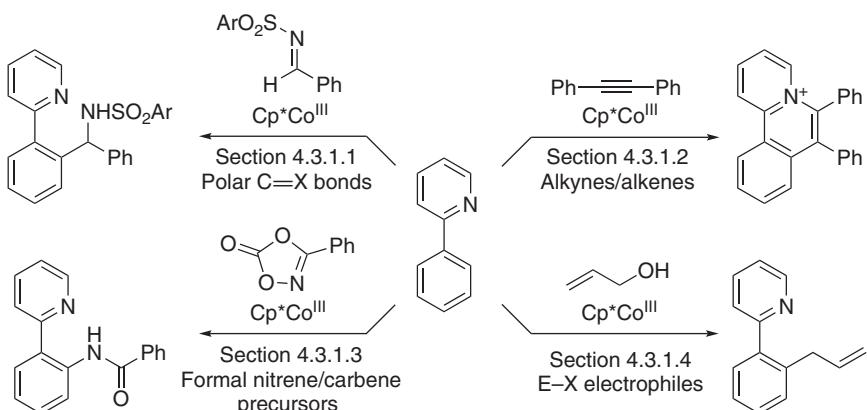


**Scheme 4.23** Benzyllic C(sp<sup>3</sup>)—H borylation of toluene (CPME = cyclopentyl methyl ether).

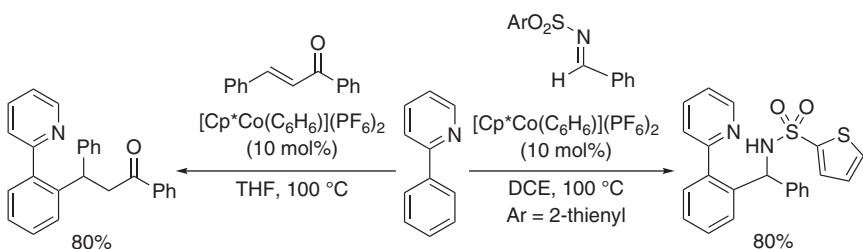
achieved earlier using analogous Cp<sup>\*</sup>Rh<sup>III</sup> (or Cp<sup>\*</sup>Ir<sup>III</sup>) catalysts [65], unique reactivity and selectivity of Cp<sup>\*</sup>Co<sup>III</sup> have also emerged [9g, 66], which are highlighted where appropriate.

#### 4.3.1.1 C—H Addition to Polar C=X Bonds

In 2013, Matsunaga and Kanai reported chelation-assisted addition of 2-arylpyridine to *N*-sulfonyl aldimine and  $\alpha,\beta$ -unsaturated carbonyl compound catalysed by a cationic Co<sup>III</sup> complex [Cp<sup>\*</sup>Co(C<sub>6</sub>H<sub>6</sub>)](PF<sub>6</sub>)<sub>2</sub> (Scheme 4.25) [67]. The reaction was not promoted using simple cobalt salts. While a neutral Co<sup>III</sup> complex [Cp<sup>\*</sup>CoCl<sub>2</sub>]<sub>2</sub> alone did not show catalytic activity, the addition of a silver salt, such as AgPF<sub>6</sub>, generated an active catalyst. The addition to an imine was also achieved using *N*-pyrimidylindole as the substrate, where the same Cp<sup>\*</sup>Co<sup>III</sup> catalyst was used in combination with KOAc [68].



**Scheme 4.24** Representative types of C–H functionalisations catalysed by  $\text{Cp}^*\text{Co}^{\text{III}}$ .

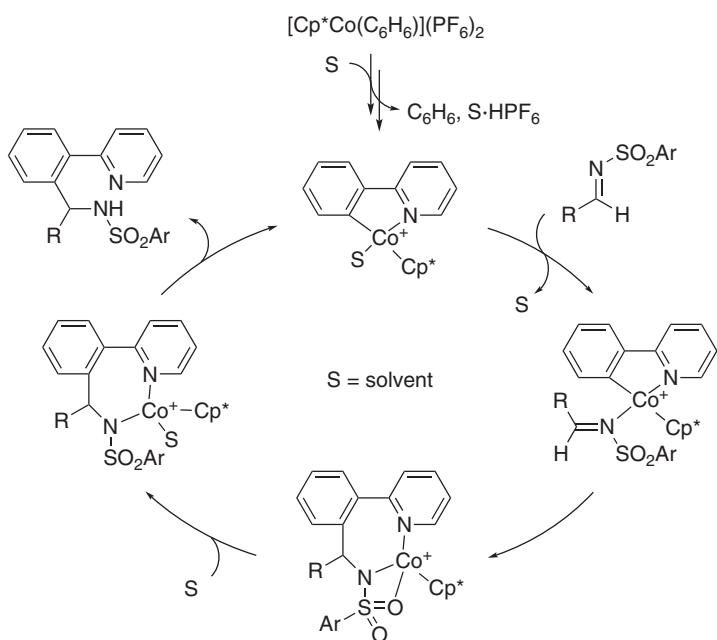


**Scheme 4.25** Pyridyl-directed addition of arene C–H bond to aldimines and enones.

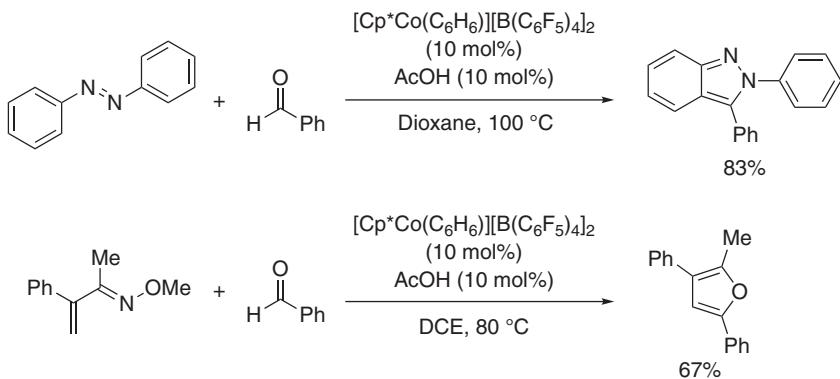
A proposed catalytic cycle for the addition of 2-phenylpyridine to aldimine is shown in Scheme 4.26. Upon dissociation of the labile benzene ligand, the  $\text{Cp}^*\text{Co}^{\text{III}}$  catalyst would initiate the reaction by chelation-assisted C–H activation of 2-phenylpyridine. The metallacycle intermediate then undergoes insertion of the aldimine, followed by protodemettalation by another molecule of 2-phenylpyridine (or other proton source) to liberate the product while regenerating the key metallacycle intermediate.

Hummel and Ellman reported a directed C–H functionalisation/cyclisation cascade between azobenzenes and aldehydes to form indazole derivatives (Scheme 4.27) [69]. The reaction was achieved efficiently using a cationic  $\text{Cp}^*\text{Co}^{\text{III}}$  complex bearing non-coordinating  $\text{B}(\text{C}_6\text{F}_5)_4$  anions and  $\text{AcOH}$ . The reaction is considered to proceed via chelation-assisted C–H addition to aldehyde followed by dehydrative cyclisation of the tertiary alcohol intermediate. The same catalytic system was also effective for the cyclisation of  $\alpha,\beta$ -unsaturated oxime ethers and aldehydes to furans. The identical type of cyclisation reaction between 2-arylpyridine and aldehyde into indolidine derivatives was also reported [70].

The scope of redox-neutral  $\text{Cp}^*\text{Co}^{\text{III}}$ -catalysed C–H addition to polar C=X and C=C bonds have been further expanded in terms of both C–H donors and acceptor electrophiles. Thus far, isocyanates [71], ketenimines [72], maleimides



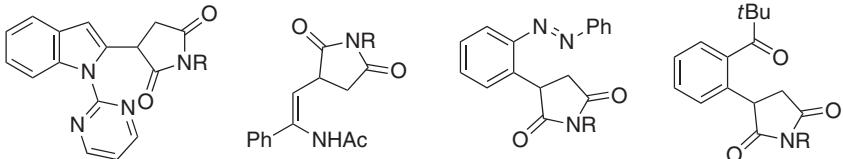
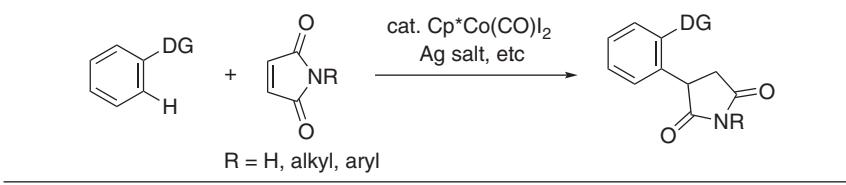
**Scheme 4.26** Proposed catalytic cycle for the addition of 2-phenylpyridine to aldimine.



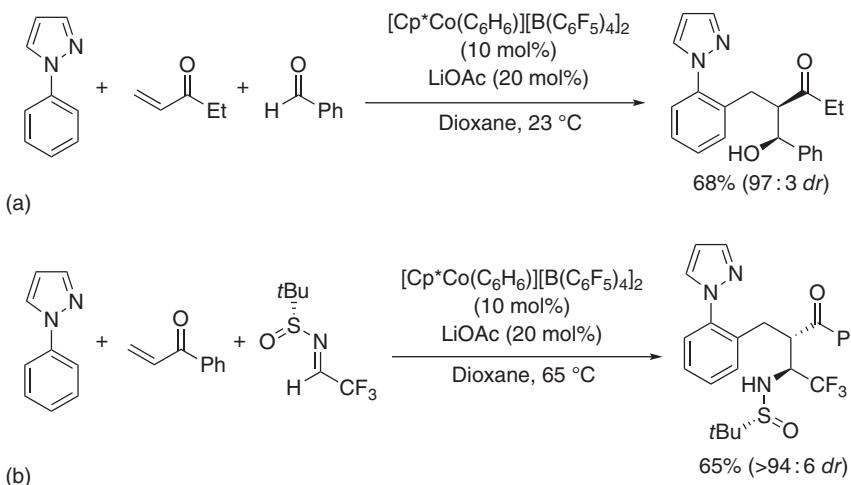
**Scheme 4.27** Synthesis of indazole and furan by C–H functionalisation/cyclisation cascade.

[73], glyoxylate [74], acrolein, and other *Michael* acceptors [75] have been shown to participate in the reaction with suitable C–H donor substrates. As for maleimides, a variety of C–H donors including *N*-pyrimidylindoles, enamides, azobenzenes, oxime ethers, and aryl ketones were reported to undergo efficient C–H addition to the activated C=C bond with the aid of a cationic Cp<sup>\*</sup>Co<sup>III</sup> catalyst generated from Cp<sup>\*</sup>Co(CO)<sub>2</sub> and a silver salt (Scheme 4.28).

*Ellman* reported a three-component coupling (TCC) of chelating arenes, α,β-unsaturated ketones, and aldehydes through a *Michael*/aldol cascade



**Scheme 4.28** Chelation-assisted C–H addition to maleimide.

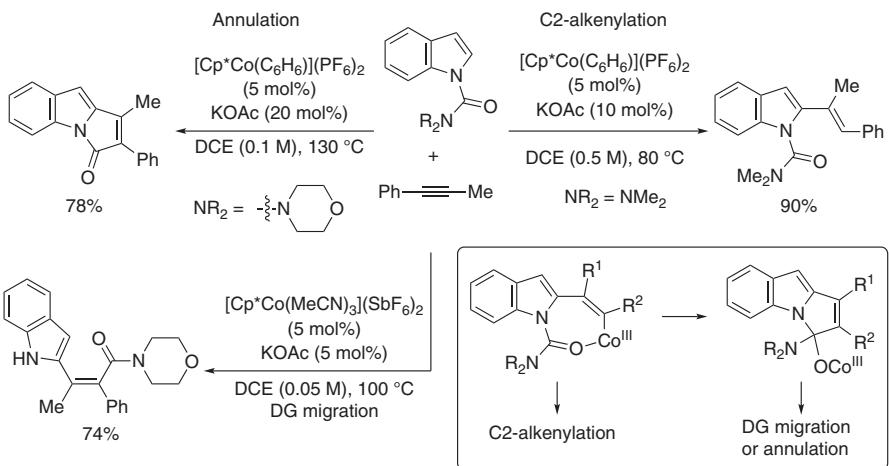


**Scheme 4.29** Three-component coupling of 1-arylpyrazole, enone, and (a) aldehyde or (b) aldimine.

catalysed by a cationic  $\text{Cp}^*\text{Co}^{\text{III}}$  catalyst (Scheme 4.29) [76]. For example, the reaction of 1-arylpyrazole proceeded using a near equimolar amount of enone and an excess amount of aldehyde at room temperature to afford the three-component product in good yield with high diastereoselectivity, accompanied by a minor amount of *Michael*-type adduct between arene and enone. Notably, an analogous  $\text{Cp}^*\text{Rh}^{\text{III}}$  catalyst predominantly promoted the *Michael* addition while affording only a trace amount of the TCC product. TCC using chiral *N*-sulfinyl imine instead of aldehyde was achieved with high diastereoselectivity.

#### 4.3.1.2 Reaction with Alkynes, Alkenes, and Allenes

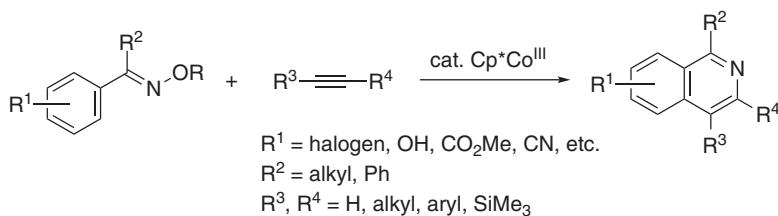
*Matsunaga* and *Kanai* reported a divergent coupling reactions between *N*-carbamoylindoles and internal alkynes catalysed by a cationic  $\text{Cp}^*\text{Co}^{\text{III}}$  complex (Scheme 4.30) [77]. Utilising an *N,N*-dimethylcarbamoyl group, high



Scheme 4.30 Divergent coupling reactions between *N*-carbamoylindole and alkyne.

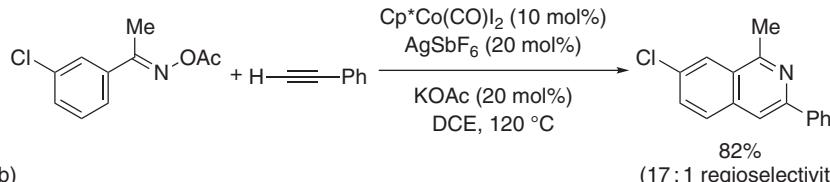
concentration, and lower temperature, the reaction afforded C2-alkenylated indoles in good yield with high regio- and stereoselectivity. A drastic reversal of chemoselectivity took place with the substrate bearing a morpholine group at lower concentration and higher temperature, resulting in deaminative annulation to afford a pyrroloindolone derivative. Particularly noteworthy is the latter reaction, which did not proceed using a  $\text{Cp}^*\text{Rh}^{\text{III}}$  catalyst. The C2-alkenylation was extended to *N*-carbamoylpyrroles, where  $\text{Cp}^*\text{Co}^{\text{III}}$  showed higher efficiency and selectivity than the  $\text{Cp}^*\text{Rh}^{\text{III}}$  species [78]. Upon further investigation, Matsunaga found that the annulation is preceded by migration of the carbamoyl directing group to form a tetrasubstituted alkenyl amide and developed suitable conditions to produce this kinetic product predominantly [79]. This intriguing chemodivergent system features an alkenyl cobalt species and its protodemettalation or intramolecular carbonyl addition, where the success of the latter process may be attributed to the higher nucleophilicity of the organocobalt species.

Sundararaju, Matsunaga/Kanai, and Ackermann independently reported annulation of aryl oxime derivatives and alkynes for the synthesis of isoquinolines (Scheme 4.31a) [80]. Sundararaju used non-protected oxime as the directing group, while Matsunaga/Kanai and Ackermann employed oxime acetate. Matsunaga and Kanai revealed noteworthy regioselectivity in the annulation of *meta*-substituted oximes. Thus, oxime derivatives bearing a *meta*-substituent such as chloro, bromo, iodo, ester, methyl, or  $\text{CF}_3$  group underwent C–H activation on the less hindered position with high selectivity (15 : 1 to >20 : 1) (see



Sundararaju	Matsunaga/Kanai	Ackermann
$\text{R} = \text{H}$	$\text{R} = \text{Ac}$	$\text{R} = \text{Ac}$
$\text{Cp}^*\text{Co}(\text{CO})_2$ (10 mol%)	$\text{Cp}^*\text{Co}(\text{CO})_2$ (10 mol%)	$\text{Cp}^*\text{Co}(\text{CO})_2$ (10 mol%)
$\text{NaOAc}$ (20 mol%)	$\text{AgSbF}_6$ (20 mol%)	$\text{AgSbF}_6$ (20 mol%)
TFE, 80 °C	KOAc (20 mol%)	$\text{NaOAc}$ (20 mol%)
	DCE, 80–120 °C	DCE, 120 °C

(a)

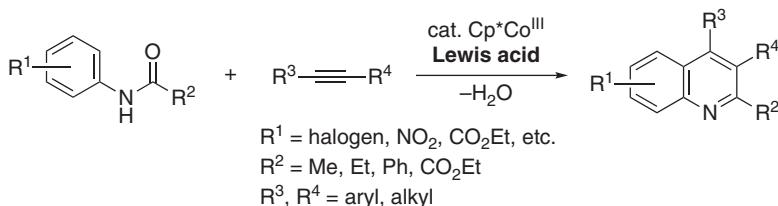


(b)

**Scheme 4.31** (a, b) Isoquinoline synthesis from oxime derivatives and alkynes.

Scheme 4.31b for example), while  $\text{Cp}^*\text{Rh}^{\text{III}}$  catalyst displayed rather poor regioselectivity. The high regioselectivity of  $\text{Cp}^*\text{Co}^{\text{III}}$  may be attributed to the shorter ionic radius of cobalt. Related redox-neutral annulative isoquinoline synthesis has also been achieved using *N*-hydroxybenzimidamide [81], *N*-Boc-hydrazone [82], *N*-sulfinylimines [83], unprotected hydrazone [84], 3-aryloxadizolones [85], and 3-aryloxadiazoles [86]. Isoquinoline synthesis via oxidative C–H activation/alkyne annulation of N–H imines and benzimidates was also reported [87].

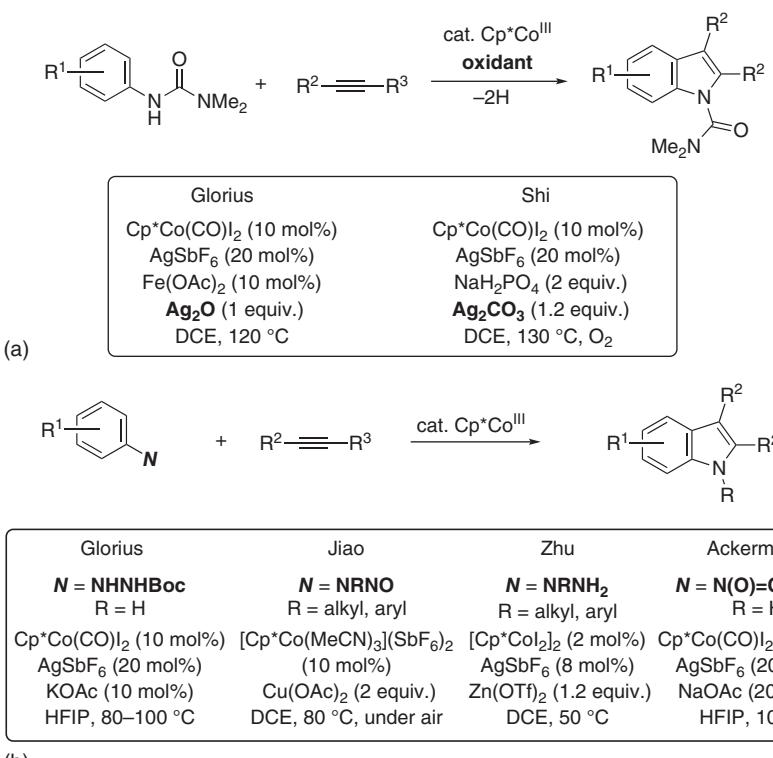
*Li*, *Glorius*, and *Zhang* independently developed dehydrative annulation between anilides and alkynes to afford quinoline derivatives (Scheme 4.32) [88]. While their catalytic systems are different in many details, they all feature the use of a stoichiometric or catalytic Lewis acid such as  $\text{AgNTf}_2$ ,  $\text{BF}_3\cdot\text{OEt}_2$ ,  $\text{B}(\text{C}_6\text{F}_5)_3$ , or  $\text{Zn}(\text{OTf})_2$  as a crucial additive. The reaction was proposed to proceed through cyclometallation, insertion of the alkyne into the aryl– $\text{Co}^{\text{III}}$  bond, intramolecular nucleophilic addition of alkenyl cobalt species to the carbonyl group, and dehydrative aromatisation, where the *Lewis* acid is assumed to facilitate the nucleophilic addition step. While mechanistically distinct, *Yi* and *Zhang* reported a quinoline synthesis from simple anilines via condensation with acetophenone and paraformaldehyde [89]. The same group also reported another quinoline synthesis starting from aniline, alkyne, and dimethylsulfoxide (DMSO) [90].



<i>Li</i>	<i>Glorius</i>	<i>Zhang</i>
$[\text{Cp}^*\text{CoCl}_2]_2$ (6 mol%)	$\text{Cp}^*\text{Co}(\text{CO})_2$ (10 mol%)	$\text{Cp}^*\text{Co}(\text{CO})_2$ (10 mol%)
$\text{AgNTf}_2$ (1 equiv.)	$\text{AgSbF}_6$ (20 mol%)	$\text{AgSbF}_6$ (20 mol%)
DCE, 130 °C	$\text{Fe}(\text{OAc})_2$ (10 mol%)	$\text{Li}_2\text{CO}_3$ (20 mol%)
Under air	$\text{BF}_3\cdot\text{OEt}_2$ or $\text{B}(\text{C}_6\text{F}_5)_3$ (50–80 mol%)	$\text{Zn}(\text{OTf})_2$ (20 mol%) TFE, 120 °C
	DCE, 135 °C	

**Scheme 4.32** Quinoline synthesis from anilides and alkynes.

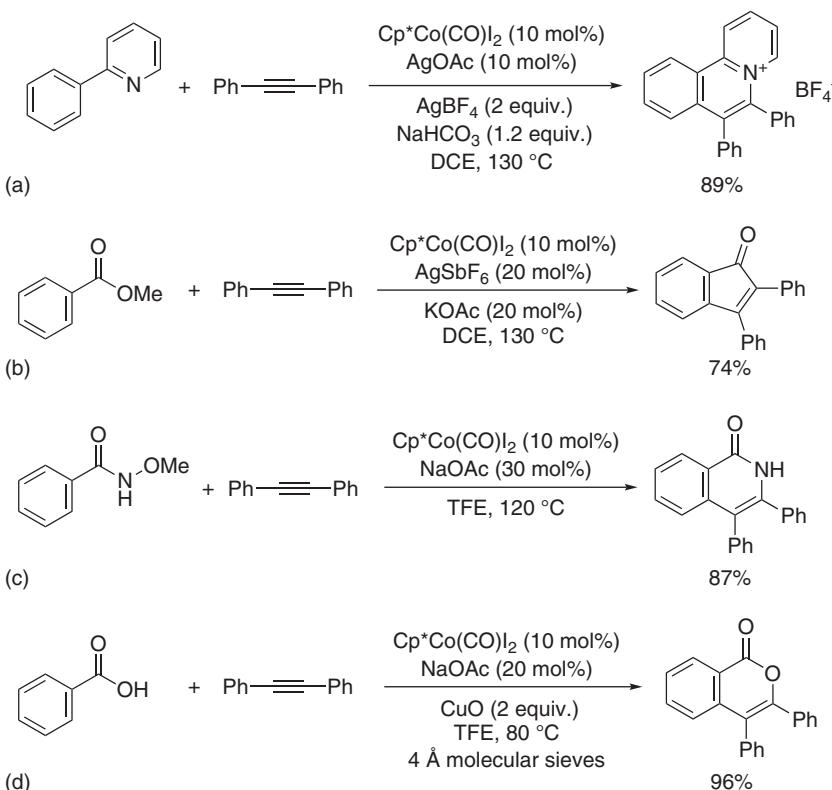
In the study of the annulation of anilides and alkynes, *Glorius* revealed a switch of the reaction outcome to indole formation by modification of the reaction conditions and the *N*-modifying substituent (Scheme 4.33a) [88b]. Thus, change of the acyl group to a carbamoyl group, along with the use of  $\text{Ag}_2\text{O}$  as oxidant, resulted in an exclusive formation of *N*-carbamoyl indole. The same transformation was independently reported by *Shi* using  $\text{Ag}_2\text{CO}_3$  as oxidant [91]. Meanwhile, a series of  $\text{Cp}^*\text{Co}^{\text{III}}$ -catalysed indole-forming annulation reactions were developed by capitalising on the oxidising directing group strategy (Scheme 4.33b) [92]. Thus, aniline derivatives with preinstalled oxidising moieties, that is, Boc-protected arylhydrazine [93], *N*-nitrosoaniline



**Scheme 4.33** (a, b) Indole synthesis from aniline derivatives and alkynes.

[94], arylhydrazine [95], and *N*-arylnitrones [96], were demonstrated to undergo annulation with alkynes to afford the corresponding NH indoles or *N*-substituted indoles.

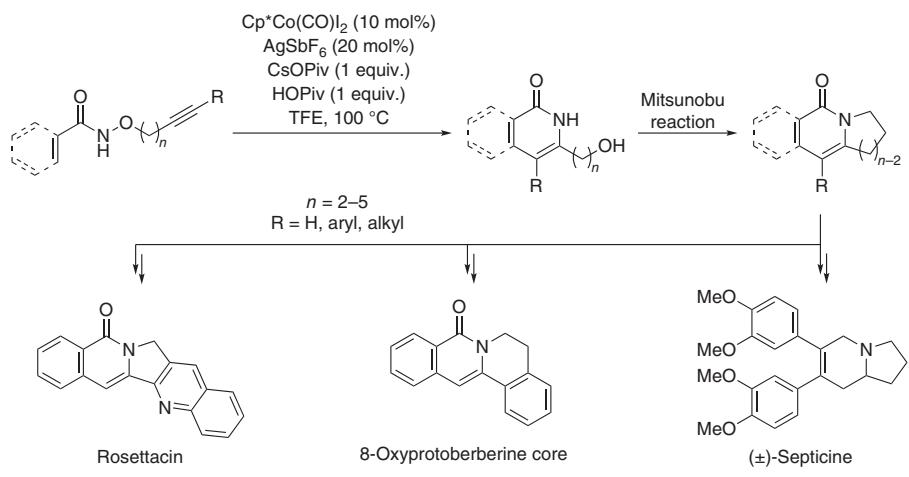
Besides the previously mentioned annulation reactions, a variety of  $\text{Cp}^*\text{Co}^{\text{III}}$ -catalysed chelation-assisted C–H activation/alkyne annulation reactions have been reported. *Cheng* developed an oxidative annulation of 2-arylpyridines, azobenzenes, and related  $\text{N}(\text{sp}^2)$ -appended arenes or alkenes with alkynes to afford the corresponding polycyclic quaternary ammonium salts (Scheme 4.34a) [97], which was followed by related reports by *Wang* [98] and *Li* [99]. *Zhang* and *Li* independently reported redox-neutral, dealkoxylative annulation of aromatic esters with alkynes to afford indenone derivatives (Scheme 4.34b) [100]. *Jeganmohan* reported isoquinolone synthesis from *N*-methoxybenzamides and alkynes, with the *N*–OMe group as the internal oxidant (Scheme 4.34c) [101]. *Sundararaju* extended this annulation reaction to 1,3-diynes, which enable regiocontrolled synthesis of bis-isoquinolones [102]. *Sundararaju* reported the synthesis of isocoumarins and pyrones via oxidative annulation of benzoic and acrylic acids with alkynes (Scheme 4.34d) [103]. Other examples include the synthesis of pyrroles via oxidative annulation of enamides and alkynes [104], and the synthesis of spirocyclic indenyl benzosultam via annulation of cyclic sulfonyl ketimines and alkynes [105].



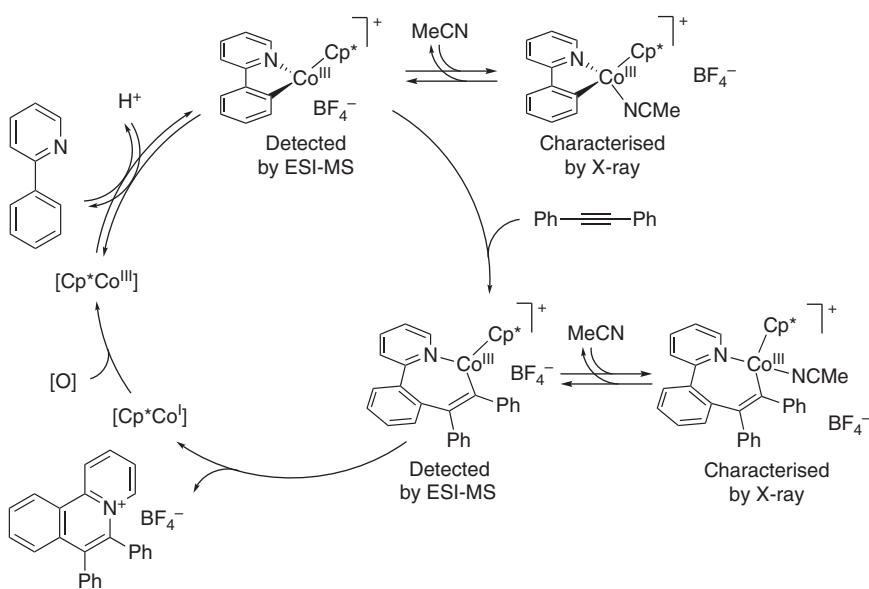
**Scheme 4.34** (a–d) Examples of annulative hetero- and carbocycle synthesis.

Glorius developed an intramolecular variant of a  $\text{Cp}^*\text{Co}^{\text{III}}$ -catalysed annulative C–H/alkyne coupling to demonstrate its utility in alkaloid synthesis (Scheme 4.35) [106]. Thus, *N*-alkoxybenzamides bearing tethered alkyne moieties underwent regioselective intramolecular annulation via N–O bond cleavage to afford isoquinolone and pyridone derivatives. Utilising the pendant hydroxyl group, the products could be readily transformed into a variety of aromathecin, protoberberine, and tylophora alkaloids.

The mechanism of the oxidative annulation of 2-arylpyridine and alkyne was studied in detail by Pérez-Temprano, which revealed a few key catalytic intermediates and the kinetic profile of the reaction (Scheme 4.36) [107]. A cationic cyclometallated complex of 2-phenylpyridine bearing an acetonitrile ligand was synthesised through C–I oxidative addition of 2-(2-iodophenyl)pyridine to a  $\text{Cp}^*\text{Co}^{\text{I}}$  complex, and its catalytic competence was demonstrated. Furthermore, a seven-membered metallacycle intermediate, formed upon alkyne insertion into the aryl– $\text{Co}^{\text{III}}$  bond, was also characterised. Thus, the reaction was proposed to proceed through cyclometallation with  $\text{Cp}^*\text{Co}^{\text{III}}$ , alkyne insertion into the aryl– $\text{Co}^{\text{III}}$  bond, C–N reductive elimination to form the product, and reoxidation of  $\text{Cp}^*\text{Co}^{\text{I}}$  to  $\text{Cp}^*\text{Co}^{\text{III}}$ .



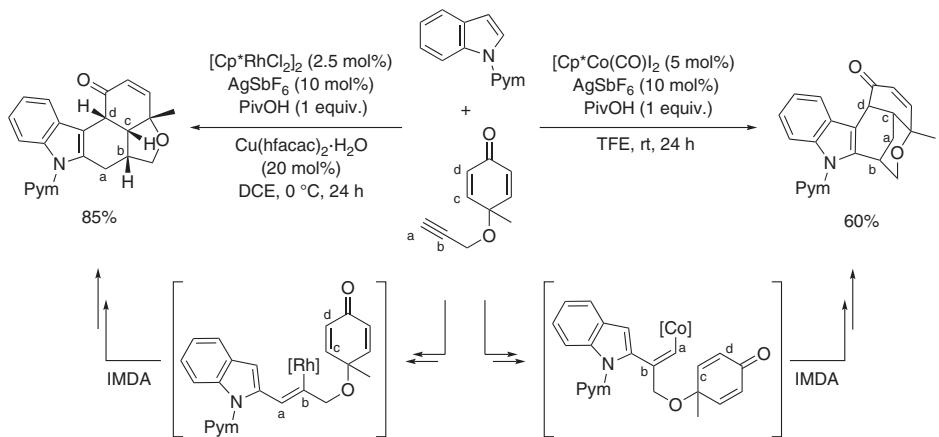
**Scheme 4.35** Intramolecular annulative synthesis of isoquinolones and pyridones towards alkaloid synthesis.



**Scheme 4.36** Plausible mechanism of oxidative annulation between 2-phenylpyridine and alkynes.

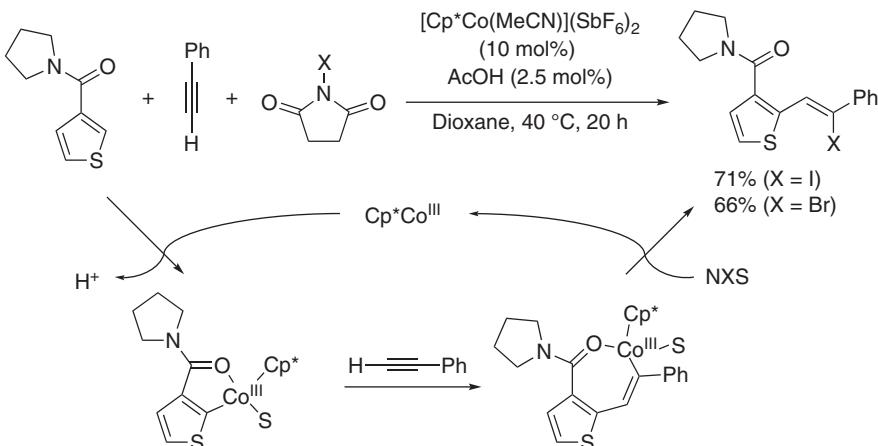
Besides C2-alkenylation of *N*-carbamoylindoles and -pyrroles with alkynes (Scheme 4.30), several examples of chelation-assisted C–H alkenylation with alkynes under  $Cp^*Co^{III}$  catalysis have been reported. *Yu* reported a linear-selective alkenylation of 2-arylpyridines with terminal alkynes [108]. *Sundararaju* reported a C(sp<sup>3</sup>)–H alkenylation of 8-methylquinoline with internal alkynes [109]. *Maji* reported an alkenylation of benzamides bearing a bulky *N*-*tert*-butyl group with internal alkynes [110]. *Li* found that the regioselectivity of C2-alkenylation of *N*-pyrimidylindole with a terminal alkyne depends on the alkyne substituent, and achieved branched-selective alkenylation using alkynyl silanes and propargyl alcohol derivatives [111]. *Sundararaju* reported a pyrazolyl-directed C–H alkenylation using various alkynes, where a seven-membered chelated alkynyl cobalt intermediate was characterised [112]. *Prabhu* reported a decarboxylative C–H alkenylation of benzamide derivatives with alkynyl carboxylic acids [113].

Alkenyl cobalt(III) species formed through cyclometallation and alkyne insertion have been intercepted in cascade transformations other than the heterocycle formations. *Sundararaju* reported  $Cp^*Co^{III}$ -catalysed coupling between quinoline *N*-oxides and alkynes via C–H alkenylation and oxygen atom transfer, affording  $\alpha$ -(8-quinolinyl)ketone derivatives [114]. *Li* reported C–H alkenylation/intramolecular *Diels–Alder* (IMDA) cascades between *N*-pyrimidylindole and 1,6-enyes containing terminal alkyne and 2,5-cyclohexadienone moieties (Scheme 4.37) [115]. Interestingly,  $Cp^*Co^{III}$  and  $Cp^*Rh^{III}$  catalysts displayed opposite regioselectivities of alkyne insertion, thus leading to distinct polycyclic products. *Ellman* achieved a TCC between a chelating arene, an alkyne or allene,



**Scheme 4.37** C–H Alkenylation/IMDA cascades with catalyst-controlled divergence.

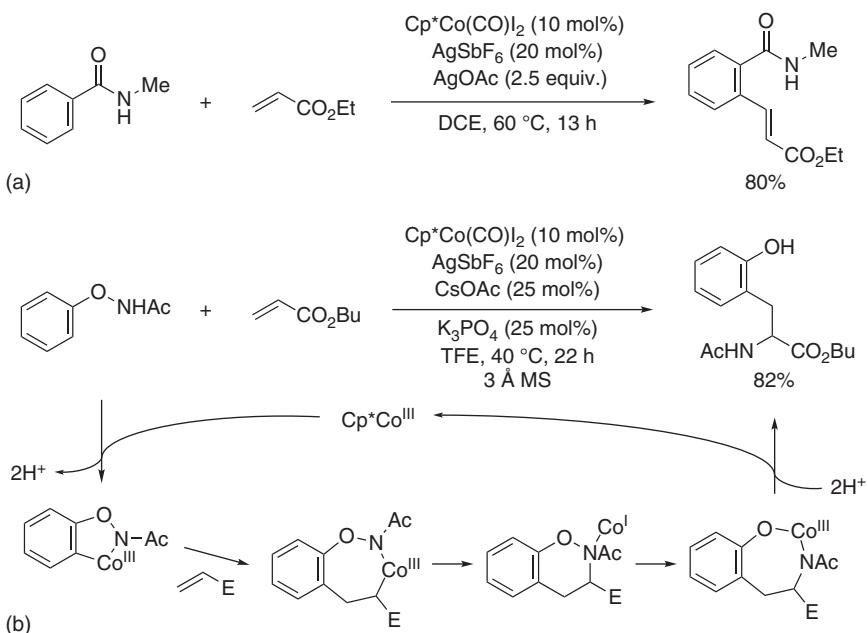
and a halogenating agent such as *N*-iodosuccinimide (NIS) to stereoselectively afford a functionalised alkenyl halide (Scheme 4.38) [116].



**Scheme 4.38** Three-component coupling of arene, alkyne, and *N*-halosuccinimide.

Since the initial report by *Matsunaga* and *Kanai* (Scheme 4.25), activated alkenes such as  $\alpha,\beta$ -unsaturated carbonyl compounds have been used as *Michaeli* acceptors in C–H activation/addition reactions using various C–H donor substrates (e.g. Scheme 4.28). Meanwhile, allylic alcohol derivatives have been utilised as electrophiles for  $\text{S}_{\text{N}}$ -type C–H allylation reactions (Section 3.1.4). Compared with these redox-neutral C–H functionalisation reactions, oxidative C–H/alkene coupling reactions under  $\text{Cp}^*\text{Co}^{\text{III}}$  catalysis are relatively sporadic. *Matsunaga* and *Kanai* reported oxidative C–H olefination of secondary benzamide with acrylate using  $\text{AgOAc}$  as an oxidant (Scheme 4.39a) [117]. *Glorius* reported the intermolecular carboamination of acrylate with phenoxyacetamide via C–H activation, C–N bond formation, and N–O cleavage (Scheme 4.39b) [118]. The reaction is proposed to proceed through C–H metallation, alkene insertion, C–N reductive elimination, O–N oxidative addition to  $\text{Co}^{\text{I}}$ , and protodemettallation. Interestingly, the use of a  $\text{Cp}^*\text{Rh}^{\text{III}}$  catalyst resulted in a Heck-type product due to facile  $\beta$ -hydride elimination. *Zhang* reported a spirocyclisation between imidate and maleimide that proceeds via C–H alkenylation and intramolecular *Michaeli* addition [119].

*Ackermann* achieved a regiodivergent C–H alkylation reactions of *N*-pyridylindoles with non-activated 1-alkenes by fine-tuning of reaction conditions (Scheme 4.40) [120]. Using a catalytic system comprised of  $\text{Cp}^*\text{Co}(\text{CO})\text{I}_2$  and  $\text{AgSbF}_6$ , the reaction exclusively afforded the linear alkylation product at  $120^\circ\text{C}$ . Strikingly, the addition of a hindered carboxylic acid, 1-Ad $\text{CO}_2\text{H}$ , to the system not only promoted the reaction at a lower temperature but also switched the regioselectivity, affording the branched adduct as the major product. Experimental and computational mechanistic studies suggested that the regiodivergence was ascribed to distinct mechanisms of protodemettallation



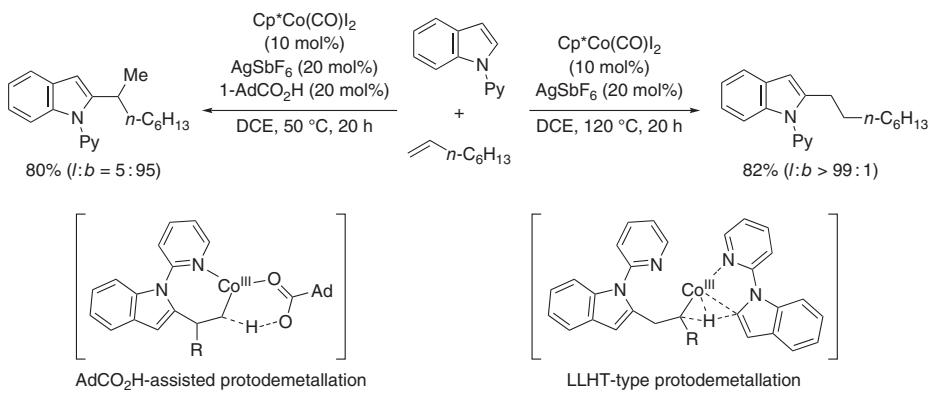
**Scheme 4.39** Chelation-assisted C–H functionalisation with acrylate assisted by (a) external or (b) internal oxidant.

of alkyl cobalt intermediates. The linear-selective reaction involves protodemettalation mediated by another molecule of *N*-pyridylindole, which coincides with C–H activation. On the other hand, the branched-selective reaction involves participation of the carboxylic acid in the protodemettalation step as well as in the C–H activation step.

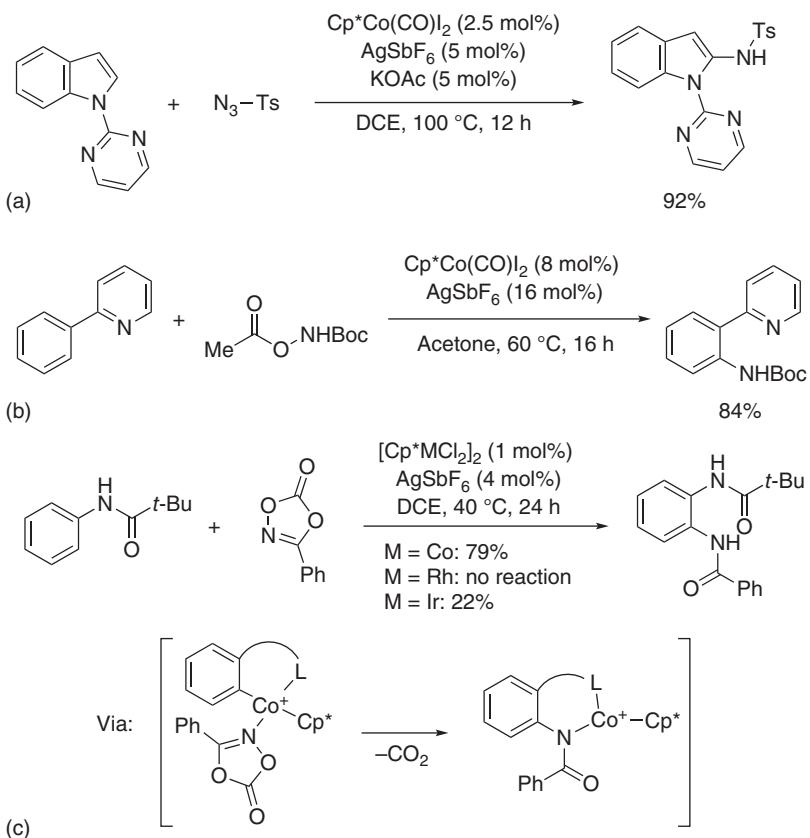
The use of allenes as coupling partners in  $\text{Cp}^*\text{Co}^{\text{III}}$ -catalysed C–H functionalisation remains sporadic. *Cheng* reported a [5+1] cycloaddition-type annulation between *ortho*-alkenylphenols and allenes to form 2*H*-chromene derivatives [121]. *Ackermann* reported a C–H alkenylation of *N*-pyrimidylindoles, 1-arylpyrazoles, and 2-arylpyridines with 1,1-disubstituted allenes [122]. *Cheng* reported [3+3] cycloaddition-type annulation between anilides and allenes to give dihydroquinoline derivatives [123].

#### 4.3.1.3 Reaction with Formal Nitrene or Carbene Precursors

In 2014, *Matsunaga* and *Kanai* reported  $\text{Cp}^*\text{Co}^{\text{III}}$ -catalysed C–H amidation of *N*-pyrimidylindole with tosyl azide (Scheme 4.41a), where generation of an active cationic catalyst from air-stable  $\text{Cp}^*\text{Co}(\text{CO})\text{I}_2$  and a silver Co-catalyst was demonstrated for the first time [124]. They also developed a phosphoramidation of the same indole substrate with phosphoryl azide [125]. Meanwhile, different types of amidating agents have been explored. *Chang* reported the amidation of 2-arylpyridines and related substrates with *tert*-butyl acetoxycarbamate (Scheme 4.41b) [126]. *Chang* and *Jiao* independently disclosed an amidation using dioxazolone as an amidating agent, which tolerated a broader scope of substrates including anilides, benzamides, 2-arylpyridines, and 6-arylpurines



**Scheme 4.40** Regiodivergent C2-alkylation of *N*-pyridylindole with 1-alkene.

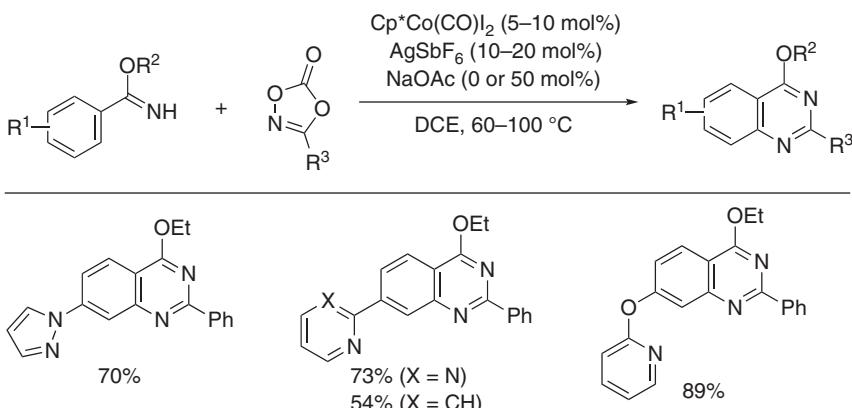


**Scheme 4.41** (a–c) C–H amidation using different amidating agents.

(Scheme 4.41c) [127]. Notably, the  $\text{Cp}^*\text{Co}^{\text{III}}$  catalyst displayed superior catalytic activity in the amidation of anilides compared with analogous Rh and Ir catalysts. The reaction was proposed to proceed through C–H metallation, coordination of dioxazolone to the cobaltacycle, amido insertion with concomitant decarboxylation, and protodemettalation of the amido–cobalt species.

The substrate scope of  $\text{Cp}^*\text{Co}^{\text{III}}$ -catalysed C–H amidation using dioxazolone has been extended to other aromatic and olefinic substrates such as 2-aryloxazolines [128], *N*-pyrimidylindoles [128, 129], enaminones [130], 2-pyridylferrocenes [131], acrylamides [132], 2-aryltriazoles [133], 4-aryltriazoles [134], and azobenzenes [135]. Furthermore, amidation of  $\text{C}(\text{sp}^3)\text{—H}$  bond was also achieved using quinoline [136] and thioamide [137] as directing groups.

*Li*, *Glorius*, and *Ackermann* independently reported quinazoline syntheses from benzimidate and dioxazolone via C–H amidation and subsequent dehydrative cyclisation (Scheme 4.42) [138]. *Li*'s work also demonstrated the quinazoline synthesis from *N*-sulfinylimines. *Glorius* demonstrated the superior catalytic activity of  $\text{Cp}^*\text{Co}^{\text{III}}$  compared with Rh and Ir congeners. Meanwhile, *Ackermann* extensively explored functional group compatibility of this

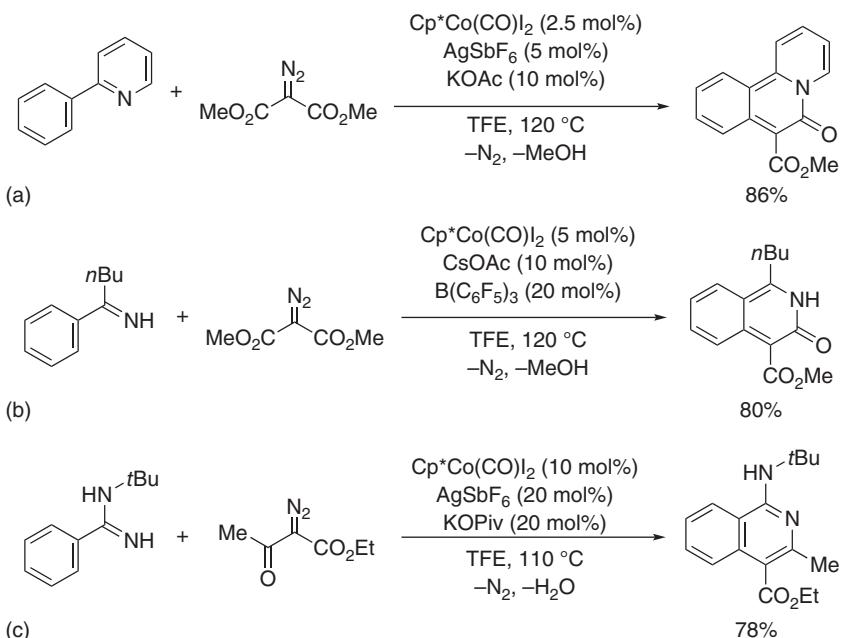


**Scheme 4.42** Quinazoline synthesis via C–H amidation of benzimidate.

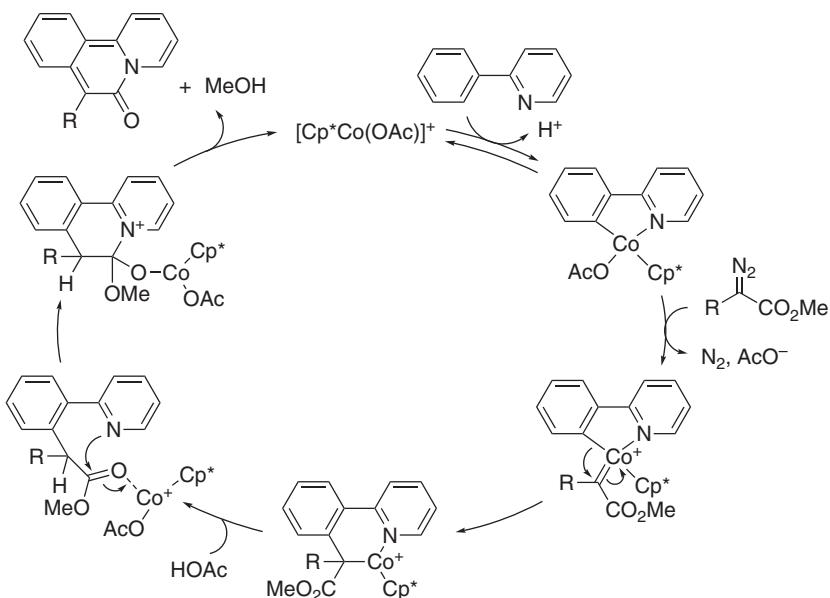
reaction to demonstrate its tolerance to a broad range of nitrogen-containing heterocycles, which potentially inhibit the desired reaction. Analogous C–H amidation/dehydrative cyclisation sequence was also utilised for the synthesis of thiadiazine 1-oxides [139] and pyridimidones [132] from NH-sulfoximines and acrylamides, respectively. In addition, *Li* reported an *ortho*-selective C–H amination/oxidative cyclisation reaction between benzimidates and anthranils cooperatively catalysed by  $\text{Cp}^*\text{Co}^{\text{III}}$  and  $\text{Cu}(\text{OAc})_2$  catalysts, which affords  $1H$ -indazole derivatives [140].

*Glorius* reported C–H functionalisation/cyclisation reactions between 2-arylpyridine derivatives and diazomalonate and related diazo compounds, affording novel nitrogen-containing  $\pi$ -conjugated systems (Scheme 4.43a) [141]. They extended this C–H functionalisation/cyclisation approach to N–H, *N*-alkyl, and *N*-aryl imines to achieve the synthesis of isoquinolin-3-ones, where the use of  $\text{B}(\text{C}_6\text{F}_5)_3$  as a *Lewis* acid Co-catalyst instead of a commonly utilised silver salt greatly accelerated the reaction (Scheme 4.43b) [142]. *Li* and *Ackermann* reported condensation of arylamidines and diazo ketoesters to give aminoisoquinolines (Scheme 4.43c) [143]. Besides these heterocycle syntheses, diazomalonates were used for simple C–H activation/embedding reactions of 1-arylpyrazoles [144], *N*-pyrimidylindoles [144], and 8-methylquinolines [145]. In addition, *Zeng* reported an oxindole synthesis from *N*-nitrosoaniline and diazo ketoester via C–H functionalisation and a *Wolf* rearrangement [146].

A proposed catalytic cycle for the condensation of 2-phenylpyridine and diazoester is shown in Scheme 4.44. The reaction was initiated by reversible C–H metallation of 2-phenylpyridine with a cationic  $\text{Cp}^*\text{Co}^{\text{III}}$  species. The cobaltacycle then reacted with diazoester to form a cobalt–carbene intermediate with concomitant loss of  $\text{N}_2$ . This was followed by migratory insertion of the carbene ligand, protodemettalation, and  $\text{Cp}^*\text{Co}^{\text{III}}$ -assisted intramolecular attack of the pyridyl nitrogen to the ester carbonyl. Finally, aromatisation occurred to give the polycyclic product and MeOH while regenerating the active catalyst.



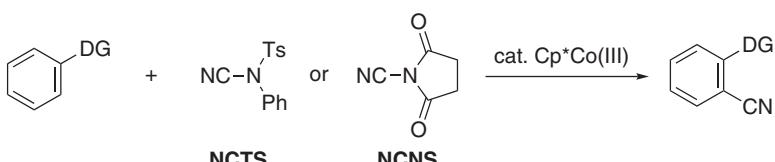
**Scheme 4.43** (a–c) Chelation-assisted C–H functionalisation/cyclisation using diazo compounds.



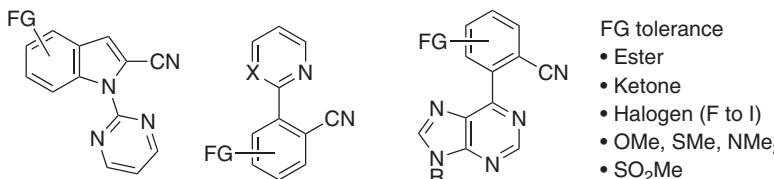
**Scheme 4.44** Proposed catalytic cycle for the annulation of 2-phenylpyridine with diazoester.

#### 4.3.1.4 Reaction with E–X-type Electrophiles

As summarised in the following text,  $\text{Cp}^*\text{Co}^{\text{III}}$  catalysis has proved to allow for chelation-assisted, formal  $S_N$ -type C–H functionalisation using a variety of electrophiles with leaving groups (E–X). In late 2014, *Glorius* and *Ackermann* independently reported C–H cyanation of 2-arylpyridines, *N*-pyrimidylindoles, and related (hetero)arenes with *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS) as a cyanating agent under similar cationic  $\text{Cp}^*\text{Co}^{\text{III}}$  catalytic systems (Scheme 4.45) [147]. Meanwhile, *Chang* demonstrated that *N*-cyanosuccinimide (NCNS) served as a viable reagent for C–H cyanation of 2-arylpyridine, 6-arylpurine and related arenes [148]. The key C–CN bond formation in these reactions was proposed to proceed through insertion of the C≡N bond into a cyclometallated cobalt intermediate and subsequent  $\beta$ -elimination.



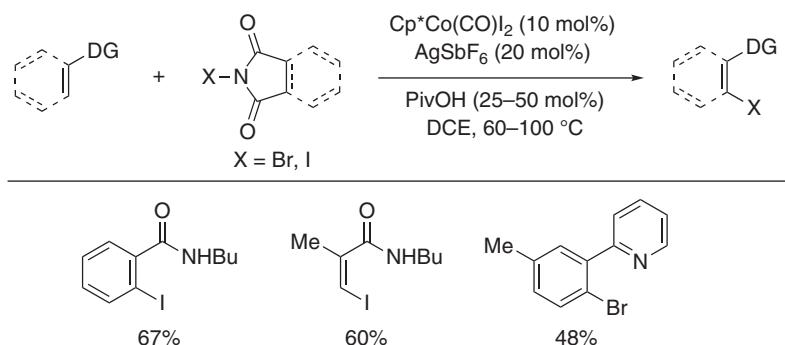
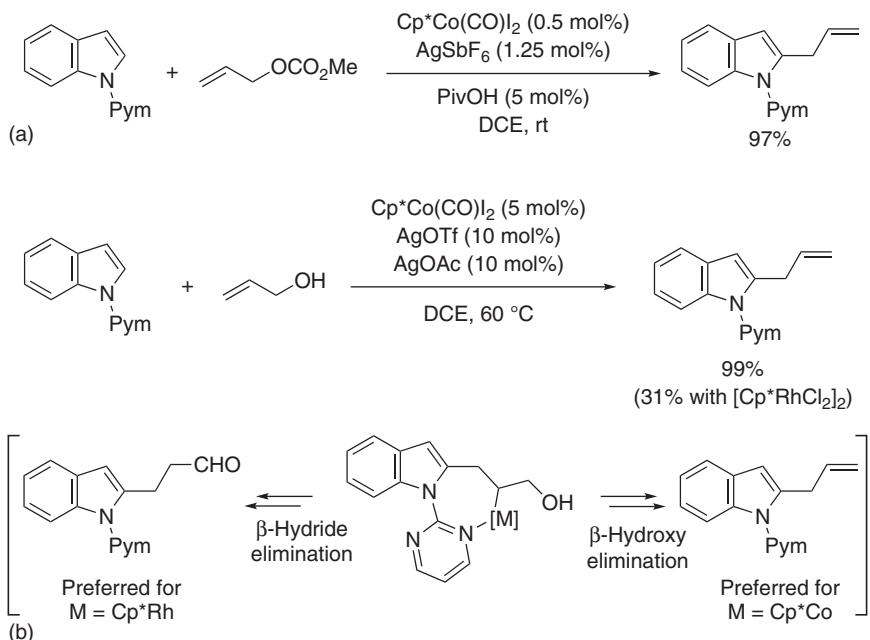
<i>Glorius</i>	<i>Ackermann</i>	<i>Chang</i>
<b>NCTS</b>	<b>NCTS</b>	<b>NCNS</b>
$\text{Cp}^*\text{Co}(\text{CO})_2$ (2.5–5 mol%)	$\text{Cp}^*\text{Co}(\text{CO})_2$ (2.5 mol%)	$\text{Cp}^*\text{Co}(\text{CO})_2$ (10 mol%)
$\text{AgSbF}_6$ (5–10 mol%)	$\text{AgSbF}_6$ (5 mol%)	$\text{AgNTf}_2$ (20 mol%)
$\text{NaOAc}$ (5–10 mol%)	$\text{KOAc}$ (5 mol%)	$\text{AgOAc}$ (20 mol%)
DCE, 110 °C	DCE, 120 °C	DCE, 120 °C



**Scheme 4.45** Chelation-assisted C–H cyanation with electrophilic cyanating agents.

*Glorius* also disclosed a C–H halogenation using electrophilic halogen sources such as NIS and *N*-bromophthalimide (NBP), which proved applicable to aromatic and olefinic substrates bearing pyridyl or amide directing group (Scheme 4.46) [147a]. The scope of the C–H iodination and bromination was later extended to 6-arylpurines [149].

*Glorius* was also the first to demonstrate the feasibility of  $\text{Cp}^*\text{Co}^{\text{III}}$ -catalysed C–H allylation using allyl carbonate as an allylating agent [147a]. Thus, C2-allylation of *N*-pyrimidylindole with allyl carbonate took place at room temperature with a low catalyst loading below 1 mol% (Scheme 4.47a). The reaction was proposed to involve insertion of the C=C bond into cyclometallated  $\text{Cp}^*\text{Co}^{\text{III}}$ -aryl species and subsequent  $\beta$ -oxygen elimination. *Glorius* extended the scope of C–H allylation to substituted allyl carbonates as well as to benzamide and acrylamide derivatives [150], while *Ackermann* developed

**Scheme 4.46** Chelation-assisted C–H halogenation.**Scheme 4.47** (a, b) Chelation-assisted C–H allylation with allylic alcohol derivatives.

pyrimidyl-directed allylation of indole, pyrrole, and arene using allyl acetate as the allylating agent [151]. Such C–H allylation was also achieved with enamides [73b], 1-arylpyrazoles [152], and aryl ketones [153] as the substrates. Matsunaga and Kanai reported a dehydrative allylation using unprotected allylic alcohols (Scheme 4.47b) [154]. This is particularly notable, not only for the favourable atom economy but also for the uniqueness of the cobalt catalyst, as the analogous  $\text{Cp}^*\text{Rh}^{III}$  catalyst showed only poor activity. The hard nature of the  $\text{Co}^{III}$  metal centre compared with the  $\text{Rh}^{III}$  ion is considered to facilitate  $\beta$ -hydroxy elimination rather than a competitive  $\beta$ -hydride elimination [155], thus enabling efficient allylation. Yoshino and Matsunaga extended the scope of the dehydrative allylation to 6-arylpurines and benzamides [156]. Sundararaju

also demonstrated the uniqueness of  $\text{Cp}^*\text{Co}^{\text{III}}$  in dehydrative allylation of quinoline *N*-oxide [157].

The alkene insertion/β-oxygen elimination process has also been utilised in  $\text{Cp}^*\text{Co}^{\text{III}}$ -catalysed C–H functionalisation reactions using electrophiles other than allyl alcohol derivatives. Such examples include C–H allylation of *N*-pyrimidylindoles and related substrates with vinyl oxiranes [158], dehydrative C–H naphthylation of *N*-pyrimidylindoles and 2-arylpyridines with 7-oxabenzonorbornadiene [158, 159], domino decarboxylative/dehydrative C–H/N–H allylation of benzimidates with vinylethylene carbonate [160], and dehydrative C–H allenylation of 1-arylpyrazoles with propargylic alcohols [161].

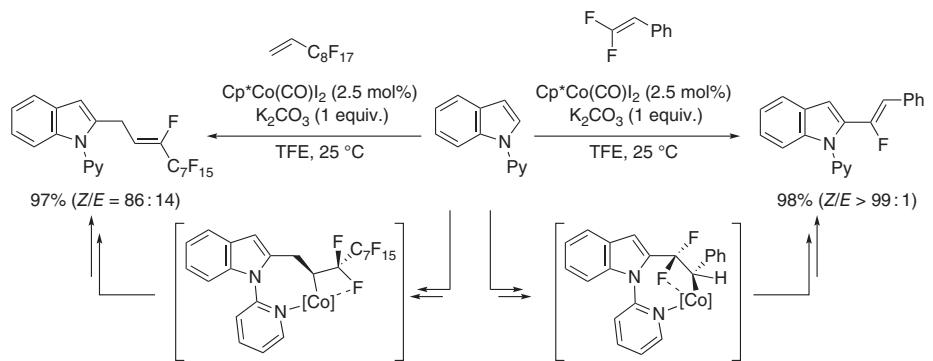
Fluorinated alkenes have been utilised as electrophiles for  $\text{Cp}^*\text{Co}^{\text{III}}$ -catalysed C–H functionalisation via C–F cleavage. *Li* reported an alkenylation of *N*-pyrimidylindole and related substrates with *gem*-difluorostyrenes [162], while *Ackermann* reported a catalytic system applicable to both allylation with fluoroalkyl-substituted olefins and alkenylation with *gem*-difluorostyrenes (Scheme 4.48) [163]. These reactions likely involved alkene insertion and stereoselective β-fluorine elimination as key steps. *Yoshino* and *Matsunaga* reported analogous transformations using 6-arylpurines [164].

*Ackermann* reported the use of vinylcyclopropane bearing a diester moiety for  $\text{Cp}^*\text{Co}^{\text{III}}$ -catalysed C–H functionalisation of *N*-pyridylindoles and related substrates via cyclopropane C–C cleavage (Scheme 4.49) [165]. Interestingly, the reaction selectively afforded the C–H allylation product with thermodynamically less stable *Z*-configuration, while a  $\text{Cp}^*\text{Rh}^{\text{III}}$  catalyst displayed preference for the *E*-product with only modest selectivity. Experimental and computational studies indicated that the diastereoselectivity was determined in the β-carbon elimination step, where the cobalt and rhodium catalysts were calculated to show opposite diastereoselectivity. For the cobalt catalyst, the transition state leading the *Z*-isomer, which was sterically tighter than the one leading to the *E*-isomer, was preferred, presumably due to shorter Co–C(alkyl) bonds.

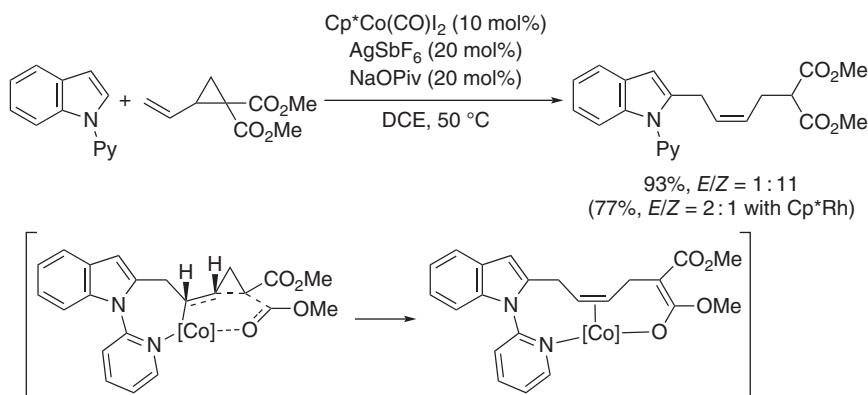
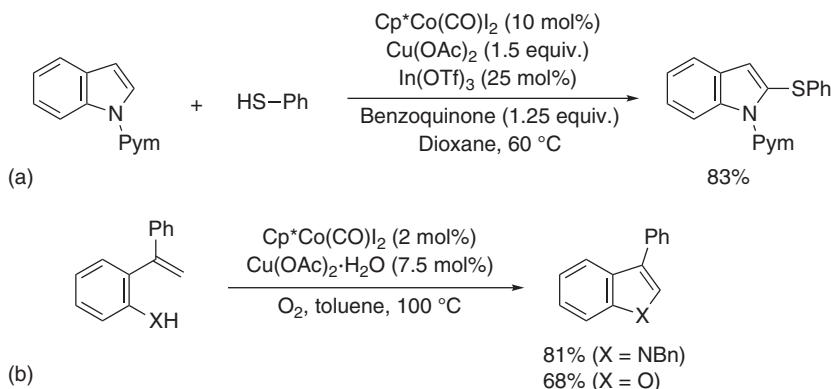
Several other C–H/electrophile coupling reactions have been developed using  $\text{Cp}^*\text{Co}^{\text{III}}$  catalysts. *Shi* reported C2-alkynylation of *N*-pyrimidylindoles with tri-isopropylsilyl (TIPS)-protected ethynylbenziodoxolone [166], while *Ackermann* achieved analogous alkynylation using TIPS-capped bromoalkyne [167]. *Yoshino* and *Matsunaga* developed a C–H trifluoromethylthiolation of 2-arylpyridines and 6-arylpurines using *N*-trifluoromethylthiodibenzenesulfonimide,  $\text{CF}_3\text{SN}(\text{SO}_2\text{Ph})_2$ , as the electrophile [168], while an alternative trifluoromethylthiolation method using  $\text{AgSCF}_3$  under oxidative conditions was reported by *Wang* [169].

#### 4.3.1.5 Miscellaneous

*Wang* reported coumarin syntheses via  $\text{Cp}^*\text{Co}^{\text{III}}$ -catalysed carbonylation of 2-alkenylphenols under oxidative conditions [170]. *Glorius* reported  $\text{Cp}^*\text{Co}^{\text{III}}$ -catalysed dehydrogenative cross-coupling between *N*-pyrimidylindoles and benzenethiols under oxidative conditions employing  $\text{Cu}(\text{OAc})_2$ , benzoquinone, and catalytic amounts of  $\text{In}(\text{OTf})_3$  (Scheme 4.50a) [171].  $\text{Cu}(\text{OAc})_2$  was proposed to generate a thiolate-transfer agent such as  $[\text{Cu}(\text{SPh})_2]^-$  *in situ* as well as to serve as an oxidant together with benzoquinone. The  $\text{In}(\text{OTf})_3$



**Scheme 4.48** C-H functionalisation with fluorinated alkenes via  $\beta$ -fluorine elimination.

**Scheme 4.49** C–H functionalisation with vinylcyclopropane via C–C cleavage.**Scheme 4.50** (a, b) Dehydrogenative cross-coupling for C–heteroatom bond formation.

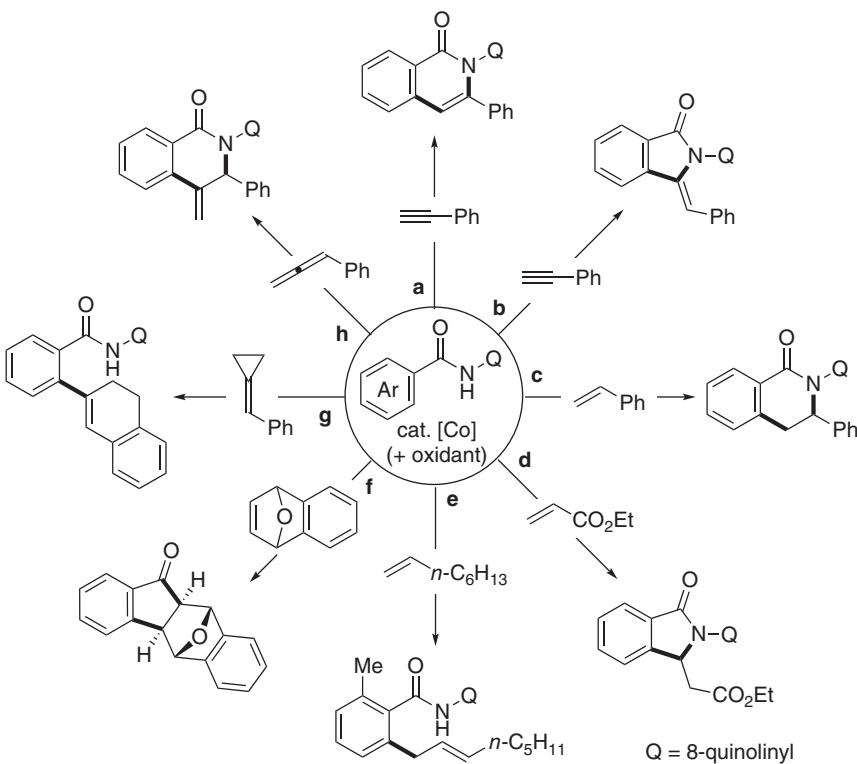
was assumed to abstract a halide ion from the precatalyst and also to facilitate thiolate transfer. Importantly, the reaction did not proceed at all using a  $\text{Cp}^*\text{Rh}^{\text{III}}$  catalyst, and the success of the  $\text{Cp}^*\text{Co}^{\text{III}}$  catalyst might be attributed to its hard nature preventing catalyst deactivation. As another example of dehydrogenative C–H/X–H coupling, *Anbarasan* reported an indole and benzofuran synthesis via cyclisation of *ortho*-vinylanilines and *ortho*-vinyl-substituted phenols under aerobic conditions (Scheme 4.50b) [172].

#### 4.3.2 Bidentate Chelation-Assisted C–H Functionalisation with $\text{Co}^{\text{III}}$ Catalysts

Since the pioneering work of *Daugulis* on palladium-catalysed arylation of  $\text{C}(\text{sp}^2)\text{—H}$  and  $\text{C}(\text{sp}^3)\text{—H}$  bonds assisted by 8-aminoquinoline-derived amide, the use of bidentate chelating functional groups for transition metal-catalysed C–H functionalisation has been extensively explored by *Daugulis*, *Chatani*, and many others [173]. Cobalt is no exception in this campaign, where simple and inexpensive cobalt salts rather than  $\text{Cp}^*\text{Co}^{\text{III}}$  complexes have proven to serve as effective (pre)catalysts [9i].

#### 4.3.2.1 Reaction with Alkynes, Alkenes, and Allenes

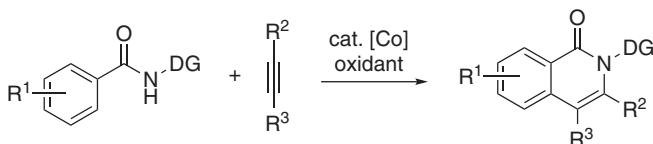
Since the initial report of *Daugulis* on a [4+2] cycloaddition-type annulation reaction between *N*-(8-quinolinyl)benzamide and alkyne [174], a wide variety of cobalt-catalysed, bidentate chelation-assisted C–H functionalisation reactions have been reported. Among several bidentate-chelating groups, the amide-bearing 8-quinolinyl group (Q) has been most extensively explored. Scheme 4.51 provides a quick summary on the breadth of C–H transformations of this substrate class using unsaturated hydrocarbons as reaction partners, and each of these transformations is discussed in the following text.



**Scheme 4.51** Summary of cobalt-catalysed, bidentate chelation-assisted C–H functionalisation with unsaturated hydrocarbons.

The [4+2] cycloaddition-type C–H/N–H/alkyne annulation (Scheme 4.51a) was first reported by *Daugulis* using *N*-(8-quinolinyl)benzamide (Scheme 4.52a) [174]. A catalytic system comprised of  $\text{Co}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ ,  $\text{NaOPiv}$ , and  $\text{Mn}(\text{OAc})_2$  afforded isoquinolone derivatives in trifluoroethanol under air. The reaction tolerated various functional groups and proved applicable to both internal and terminal alkynes. Annulation using 1,3-diyynes was also reported [175]. The reaction is proposed to proceed through amide-assisted C–H metallation with a  $\text{Co}^{\text{III}}$ -species generated by oxidation of  $\text{Co}(\text{OAc})_2$  with  $\text{Mn}(\text{OAc})_2$  and/or  $\text{O}_2$ , followed by alkyne insertion, C–N reductive elimination, and

catalyst reoxidation. Analogous C–H/N–H/alkyne annulation reactions were achieved using benzamide derivatives bearing 1-oxy-2-pyridyl (PyO) [176] or 2-pyridyl(methyl)amino [177] group, which allowed facile deprotection of the directing group to access unprotected isoquinolones. The reaction using PyO directing group is particularly notable, as O<sub>2</sub> can be used as the sole oxidant. More recently, electrochemical conditions have been developed for this reaction [178] and the annulation of *N*-(8-quinolinyl)benzamide and parent acetylene gas (1 atm) through anodic oxidation [179], thus eliminating the need for chemical or molecular oxidant. Related C–H/N–H/alkyne annulation reactions have been achieved using bidentate substrates bearing *N*-(8-quinolinyl)sulfonamide [180], *N*-(8-quinolinyl)phosphinamide [181], *N*-(2-pyridyl)hydrazone [182], and picolinamide [183] (Scheme 4.52b).



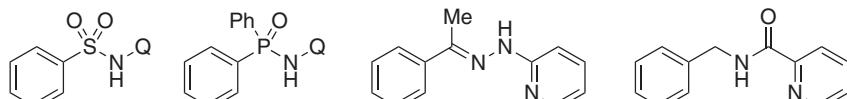
R<sup>1</sup> = halogen, CF<sub>3</sub>, NO<sub>2</sub>, etc.

Terminal alkynes (R<sup>3</sup> = H): R<sup>2</sup> = aryl, alkyl, silyl, CO<sub>2</sub>Et, etc.

Internal alkynes: R<sup>2</sup>, R<sup>3</sup> = aryl, alkyl

DG =  (Q)	DG =  (PyO)	DG =  (Zhai)
<i>Daugulis</i>	<i>Ackermann</i>	<i>Zhai</i>
Co(OAc) <sub>2</sub> ·4H <sub>2</sub> O (20 mol%) NaOPiv (2 equiv.) Mn(OAc) <sub>2</sub> (2 equiv.) CF <sub>3</sub> CH <sub>2</sub> OH, 80 °C, air	Co(OAc) <sub>2</sub> (10 mol%) PivOH (2 equiv.) CF <sub>3</sub> CH <sub>2</sub> OH, 60 °C O <sub>2</sub> (1 atm)	Co(OAc) <sub>2</sub> ·4H <sub>2</sub> O (20 mol%) Mn(OAc) <sub>2</sub> ·2H <sub>2</sub> O (2 equiv.) Na <sub>2</sub> CO <sub>3</sub> (2 equiv.) TBAI (2 equiv.) HFIP, 100 °C, air
<i>Lei</i>	<i>Ackermann</i>	
Co(acac) <sub>2</sub> (10 mol%) Divided cell: C(+)INi(−) NaOPiv (2 equiv.) Bu <sub>4</sub> NBF <sub>4</sub> (3 equiv.) CF <sub>3</sub> CH <sub>2</sub> OH, 70 °C Acetylene balloon	Co(OAc) <sub>2</sub> ·4H <sub>2</sub> O (10 mol%) Undivided cell: RVC(+) Pt(−) NaOPiv (2 equiv.) H <sub>2</sub> O/MeOH, 23 °C	

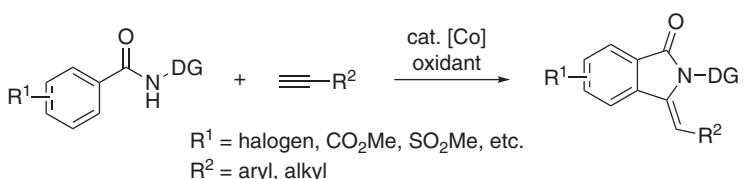
(a)



(b)

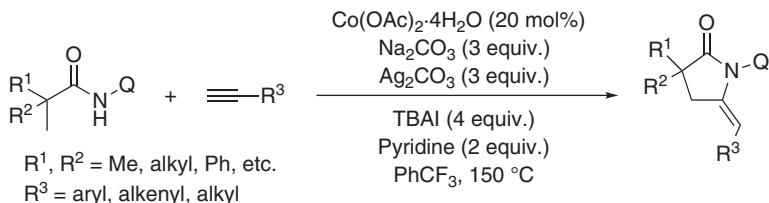
**Scheme 4.52** (a, b) Bidentate chelation-assisted [4+2] cycloaddition-type C–H/N–H/alkyne annulation.

The [4+1] cycloaddition-type annulation (Scheme 4.51b) was found as an alternative reaction pathway for the coupling between a bidentate benzamide and a terminal alkyne, leading to 3-alkylideneisoindolinone. *Niu* and *Song* employed a NHPyO directing group to achieve the [4+1] cycloaddition-type annulation with a catalytic system containing cobalt(II) oxalate as the precatalyst and AgOAc as the oxidant (Scheme 4.53a) [184]. A different catalytic system, which also contained a cobalt(II) salt and a silver-based oxidant, was developed by *Zhang* for the [4+1] annulation using a 8-quinolinylamino (NHQ) directing group [185]. *Zhang* also achieved the [4+1] annulation of tertiary alkyl carboxamides via C(sp<sup>3</sup>)-H activation (Scheme 4.53b). Later, *Niu* and *Song* reported [4+2] and [4+1] annulations between PyO-appended benzamide and alkynylcarboxylic acid via decarboxylation, leading to isoquinolone and 3-alkylideneisoindolinone, respectively [186].



<i>Niu, Song</i> DG = PyO $\text{CoC}_2\text{O}_4\cdot 4\text{H}_2\text{O}$ (5 mol%) $\text{Na}_2\text{C}_2\text{O}_4$ (1 equiv.) $\text{AgOAc}$ (2 equiv.) DMSO, 100 °C, air	<i>Zhang</i> DG = Q $\text{Co(OAc)}_2\cdot 4\text{H}_2\text{O}$ (20 mol%) $\text{Ag}_2\text{CO}_3$ (4 equiv.) TBAI (3 equiv.) $\text{PhCF}_3$ , 120 °C
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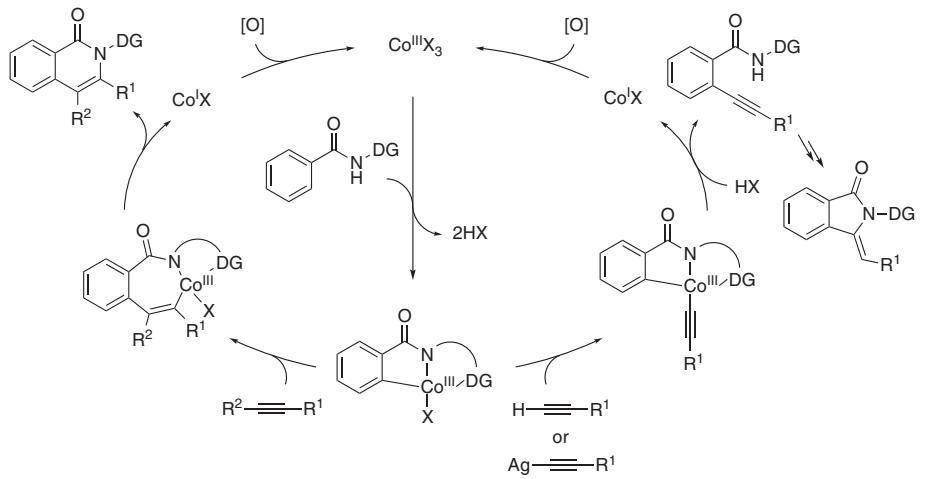
(a)



(b)

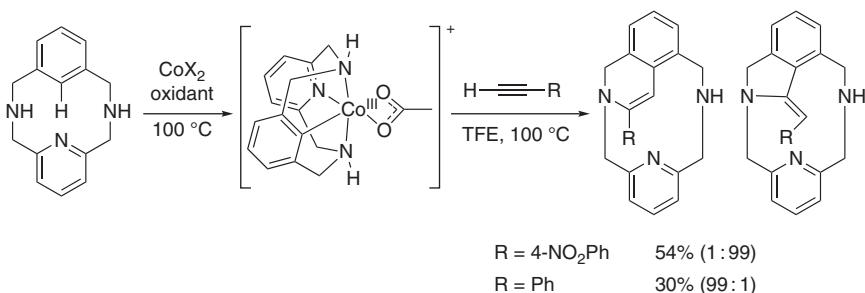
**Scheme 4.53** (a, b) Bidentate chelation-assisted [4+1] C–H/N–H/alkyne annulation (PyO = 1-oxy-2-pyridyl; Q = 8-quinolinyl).

Scheme 4.54 illustrates commonly proposed catalytic cycles for the [4+2] and [4+1] annulation reactions. Both the reactions were assumed to involve an active Co<sup>III</sup>-species and bidentate-assisted C–H metallation to afford a cyclometallated aryl cobalt(III) intermediate. Subsequent alkyne insertion and C–N reductive elimination furnished the [4+2] cycloaddition-type product, followed by reoxidation of Co<sup>I</sup> to Co<sup>III</sup>. On the other hand, the corresponding [4+1] annulation would have involved the reaction between the cyclometallated aryl cobalt(III) intermediate and terminal alkyne (or its silver acetylidyde) to generate a cobalt(III) acetylidyde species. Reductive elimination of this species and subsequent cyclisation then led to the formal [4+1] cycloaddition product.



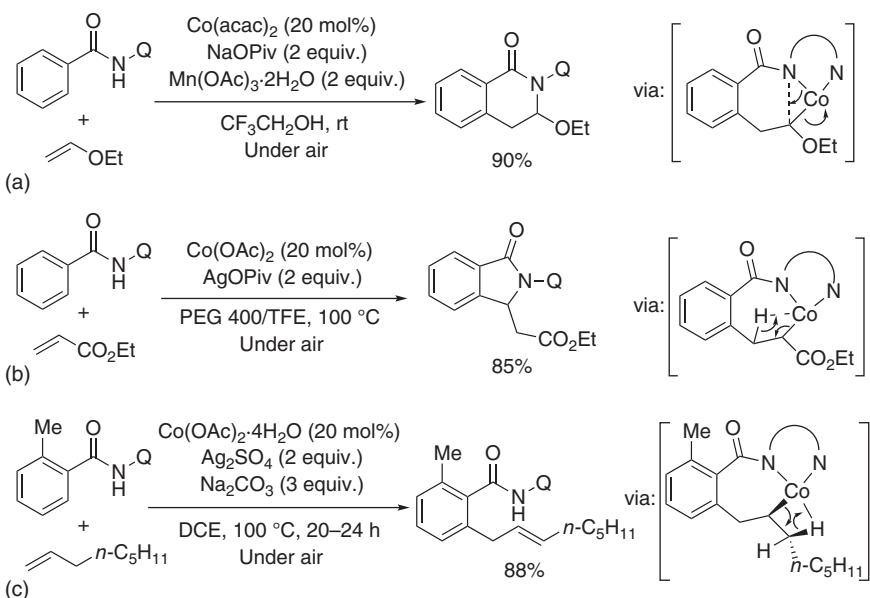
**Scheme 4.54** Commonly proposed catalytic cycles for formal [4+2] and [4+1] cycloaddition-type annulation reactions.

To gain insight into the dichotomy of [4+2] and [4+1] cycloaddition-type annulation reactions, *Ribas* studied the cobalt-mediated reaction of a tridentate macrocyclic arene substrate with alkynes (Scheme 4.55) [187]. Interestingly, the reaction of a well-defined cyclometallated aryl cobalt(III) complex was found to exhibit divergent reactivity depending on the nature of the alkyne. Contrary to the commonly perceived mechanisms (Scheme 4.54), both the annulation reactions using a terminal alkyne were suggested to proceed via aryl alkynyl cobalt(III) species, its reductive elimination, and cobalt-assisted intramolecular cyclisation. Using the same macrocyclic system, *Ribas* also studied the C–H functionalisation of the same macrocyclic substrate using ethyl diazoacetate and revealed the involvement of an aryl cobalt(III) C-enolate intermediate [188].



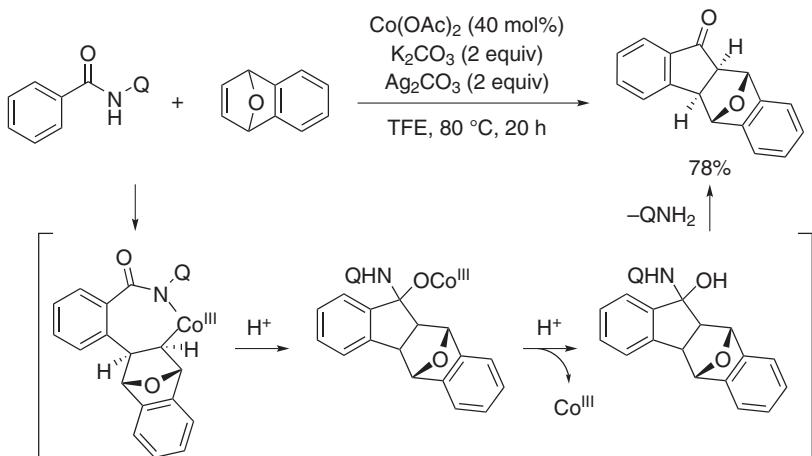
**Scheme 4.55** Reaction of cyclometallated aryl cobalt(III) complex with terminal alkynes.

The cobalt-catalysed reaction between *N*-(8-quinolinyl)benzamide and common alkenes has been found to afford different products depending on the substrates and the reaction conditions (Scheme 4.51c–e). *Daugulis* achieved oxidative [4+2] cycloaddition-type C–H/N–H/alkene annulation using air as oxidant and  $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$  as a co-catalyst, which proved applicable to various alkenes including ethylene; 1-alkenes, such as styrene, 1-hexene, allyl alcohol, and vinyl ethyl ether; and internal alkenes such as cyclopentene and cinnamyl alcohol (Scheme 4.56a) [189]. *Lei* achieved the annulation using ethylene (1 atm) under electrochemical conditions [179]. *Ackermann* reported oxidative coupling reaction using acrylates and related electron-deficient alkenes to afford isoindolinone derivatives, which likely involve C–H alkenylation via  $\beta$ -hydride elimination, followed by *Michael*-type cyclisation (Scheme 4.56b) [190] and analogous transformations were also achieved using maleimides as starting materials [191]. In addition, *Maiti*, *Jeganmohan*, and *Chatani* independently reported oxidative C–H allylation using alkyl-substituted olefins (Scheme 4.56c) [192]. Interestingly, *ortho*-substituted benzamide substrates underwent the allylation rather than more common alkenylation, presumably due to lower strain required in the corresponding  $\beta$ -hydride elimination step. Note that *Maiti* characterised a well-defined cyclometallated cobalt(III) complex and demonstrated its catalytic competence. *Maiti* further extended the scope of allylic-selective dehydrogenative *Heck*-type reaction to internal alkenes by employing a 1,5-chelating directing group [193].



**Scheme 4.56** (a–c) Bidentate chelation-assisted oxidative C–H functionalisation with alkenes ( $Q = 8\text{-quinolinyl}$ ).

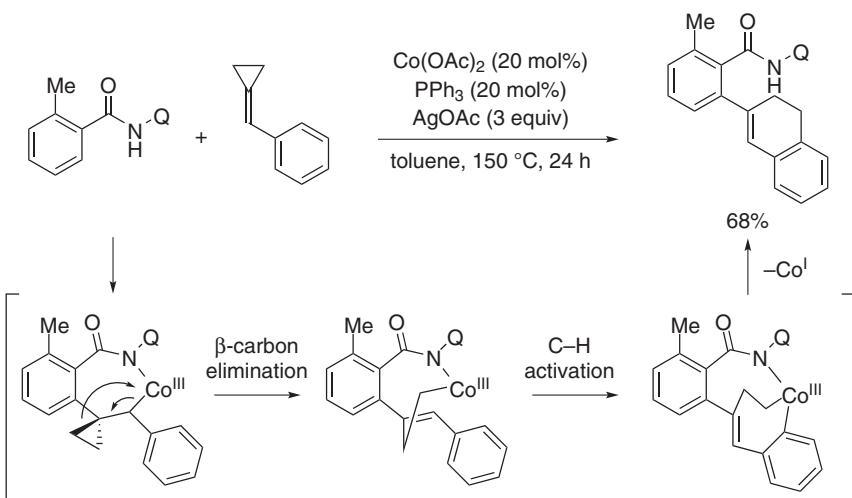
Cheng reported a cobalt-catalysed deaminative [3+2] cycloaddition-type annulation reaction between *N*-(8-quinolinyl)benzamide and strained bicyclic alkene (Scheme 4.57) [194]. The reaction was applicable to 7-oxabenzonorbornadiene, norbornene, and norbornadiene derivatives. The reaction was proposed to proceed through C–H metallation, insertion of the alkene, and intramolecular attack of the alkyl cobalt species to the amide carbonyl group, followed by



**Scheme 4.57** Deaminative [3+2] cycloaddition-type annulation with bicyclic alkene ( $Q = 8\text{-quinolinyl}$ ).

expulsion of 8-aminoquinoline. As the co-product, 8-aminoquinoline caused strong catalyst inhibition and hence necessitated a relatively high catalyst loading. Note that oxabicyclic alkenes were also used for the oxidative [4+2] cycloaddition-type annulation reaction assisted by the bidentate phosphinamide group [195].

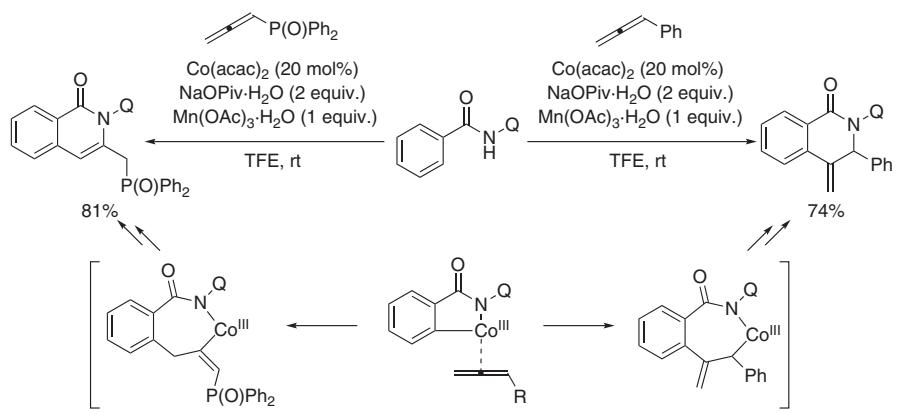
*Li* and *Kwong* disclosed a novel C–H functionalisation of *N*-(8-quinolinyl) benzamide with a benzylidenecyclopropane derivatives that involved C–C cleavage and C–H cleavage of the cyclopropane substrate, resulting in installation of a dihydronaphthalene moiety (Scheme 4.58). The reaction was proposed to proceed through amide-assisted C–H metallation, insertion of the alkylidene moiety, β-carbon elimination, intramolecular aryl C–H metallation, and C–C reductive elimination.



**Scheme 4.58** Bidentate chelation-assisted C–H functionalisation with alkylidenecyclopropane ( $\text{Q} = 8\text{-quinolinyl}$ ).

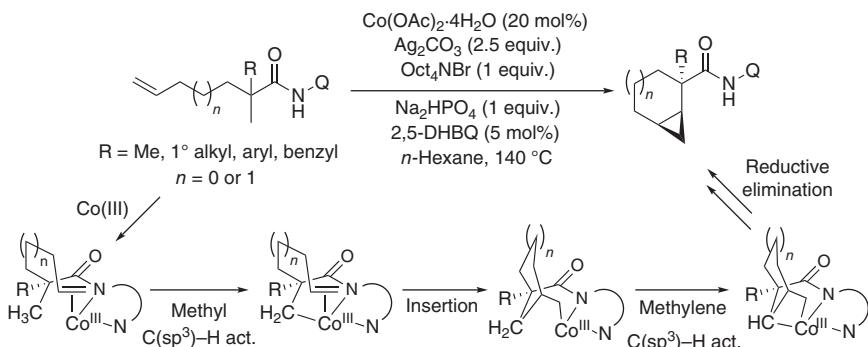
*Volla*, *Rao*, and *Cheng* independently reported [4+2] cycloaddition-type annulation reactions between *N*-(8-quinolinyl)benzamide and allenes, with regioselectivity depending on the allene substituents (Scheme 4.59) [196]. In *Volla*'s study, aryl-substituted allenes and 1,1-disubstituted allenes were found to react at the internal C=C bond to give 4-methylene-dihydroisoquinolone derivatives, while allenyl phosphonate and alkyl-substituted allenes underwent annulation at the less substituted C=C bond to afford isoquinolone products. Analogous [4+2] cycloaddition-type annulation reactions were also achieved using *N*-(8-quinolinyl)sulfonamide [197] and *N*-(8-quinolinyl)phosphinamide [198] as directing groups.

Besides the previously discussed intermolecular C–H functionalisations using unsaturated hydrocarbons, *Shi* reported a bidentate amide-assisted intramolecular C( $\text{sp}^3$ )–H functionalisation reaction of aliphatic carboxamides with alkenes (Scheme 4.60) [199]. Thus, tertiary alkyl carboxamides bearing a pendant alkene



**Scheme 4.59** Bidentate chelation-assisted [4+2] cycloaddition-type annulation with allenes (Q = 8-quinolinyl).

moiety underwent intramolecular cyclisation in the presence of a Co<sup>II</sup> precatalyst and a Ag-based oxidant to afford bicyclo[n.1.0]alkane derivatives ( $n = 3$  or 4). The reaction was proposed to proceed through complexation of the bidentate amide with Co<sup>III</sup>, C(sp<sup>3</sup>)–H activation of the methyl group, migratory insertion of the alkene moiety to form the cyclopentyl or cyclohexyl ring, second C(sp<sup>3</sup>)–H activation of the methylene group, and reductive elimination to form the cyclopropyl ring.

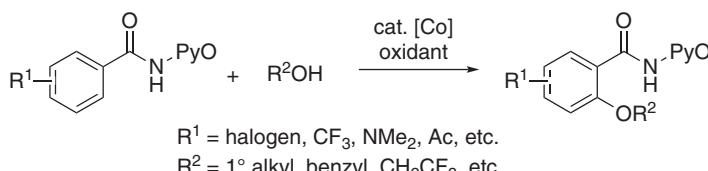


**Scheme 4.60** Formation of bicyclo[n.1.0] skeleton via intramolecular C(sp<sup>3</sup>)-H/olefin coupling (Q = 8-quinolinyl).

### 4.3.2.2 Dehydrogenative Cross-coupling Reactions

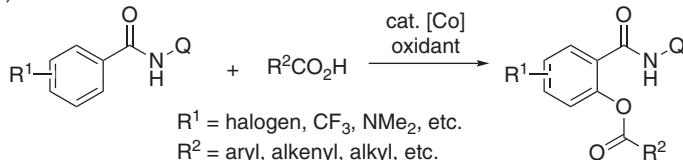
Bidentate chelation-assisted C–H activation has enabled cobalt-catalysed C–heteroatom bond formation via dehydrogenative cross-coupling. *Niu* and *Song* developed a C–H alkoxylation of *N*-(1-oxy-2-pyridyl)benzamides in alcoholic solvents using Ag<sub>2</sub>O as the oxidant (Scheme 4.61a) [200]. The reaction tolerated a variety of substituted aryl- and alkenyl amides as well as a series of primary alcohols. *Wei* and *Niu* studied the mechanism of this alkoxylation to suggest that the reaction involved SET between an alkoxy cobalt(III) species and the substrate, transfer of the alkoxy group, and rearomatisation by C–H cleavage [201]. They also demonstrated that Cp\*Co(CO)I<sub>2</sub> served as an alternative precatalyst. More recently, *Ackermann* achieved the same alkoxylation under electrochemical conditions, where anodic oxidation was suggested to take place during substrate activation and catalyst reoxidation [202]. *Zhang* and *Chatani* independently reported *ortho*-acyloxylation of *N*-(8-quinolinyl)benzamide with carboxylic acid using silver salts as oxidant (Scheme 4.61b) [203].

*Niu* and *Song* developed a C–H amination of *N*-(1-oxy-2-pyridyl)benzamides with secondary amines using AgNO<sub>3</sub> as the oxidant (Scheme 4.62a) [204]. The reaction proceeded well with morpholine and related six-membered cyclic secondary amines, while most of other cyclic and acyclic amines failed to participate in the reaction. *Zhang* reported analogous C–H amination using *N*-(8-quinolinyl)benzamides as the substrates [205]. More recently, these amination reactions have been achieved under milder conditions via electrochemical oxidation. *Ackermann* used NHPyO as directing group and



Niu, Song	Wei, Niu	Ackermann
$\text{Co(OAc)}_2 \cdot 4\text{H}_2\text{O}$ (20 mol%)	$\text{Cp}^*\text{Co}(\text{CO})\text{I}_2$ (20 mol%)	$\text{Co(OAc)}_2 \cdot 4\text{H}_2\text{O}$ (20 mol%)
$\text{Ag}_2\text{O}$ (1 equiv.)	$\text{Ag}_2\text{O}$ (2 equiv.)	Divided cell: $\text{RVC}(+) \parallel \text{Pt}(-)$
$\text{NaOAc}$ (2 equiv.)	$\text{NaOAc}$ (1 equiv.)	$\text{NaOPiv}$ (2 equiv.)
$\text{R}^2\text{OH}$ , 60 °C, air	$\text{R}^2\text{OH}$ , 70 °C, air	$\text{R}^2\text{OH}$ , rt

(a)



(b)

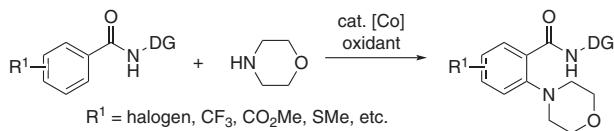
Zhang	Chatani
$\text{Co(OAc)}_2$ (20 mol%)	$\text{Co(acac)}_2$ (10 mol%)
$\text{Ag}_2\text{SO}_4$ (2.2 equiv.)	$\text{Ag}_2\text{CO}_3$ (1.3 equiv.)
$\text{Na}_2\text{CO}_3$ (1 equiv.)	DCE, 100 °C, air
DCE, 80 °C	

**Scheme 4.61** (a, b) Bidentate chelation-assisted C–H oxygenation ( $\text{PyO} = 1\text{-oxy-2-pyridyl}$ ;  $\text{Q} = 8\text{-quinolinyl}$ ).

performed the reaction in  $\gamma$ -valerolactone (GVL) as a renewable solvent [206], while *Lei* employed the NHQ directing group [207]. *Niu* and *Song* reported an *ortho*-selective C–H amination of *N*-(8-quinolinyl)benzamide with aniline derivatives, which led to triarylamine products (Scheme 4.62b) [208], and in addition, a cyclometallated Co<sup>III</sup> complex was isolated and characterised in a stoichiometric experiment.

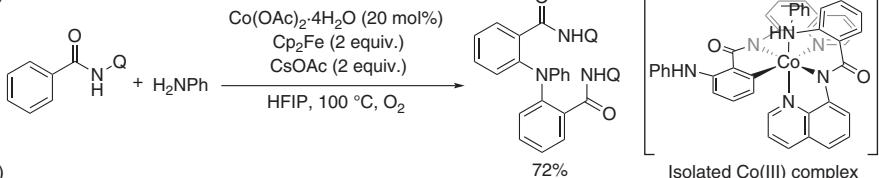
*Ge* reported C(sp<sup>3</sup>)–H amidation reactions of aliphatic amides assisted by a NHQ directing group (Scheme 4.63) [209]. With  $\text{Co(OAc)}_2$  as precatalyst and  $\text{Ag}_2\text{CO}_3$  as oxidant, a variety of tertiary and secondary alkyl carboxamides underwent intramolecular C(sp<sup>3</sup>)–H amidation of the sterically least hindered  $\beta$ -position or benzylic  $\beta$ -position to afford  $\beta$ -lactam products (Scheme 4.63a). The reaction was proposed to proceed through bidentate chelation of the amide substrate with Co<sup>III</sup> species, C(sp<sup>3</sup>)–H metallation, oxidation of the cobaltacycle, and C–N reductive elimination of the putative Co<sup>IV</sup> species. Silver-mediated oxidation would be crucial for facilitating reductive elimination as well as for reoxidation of Co<sup>II</sup> to Co<sup>III</sup>. Intermolecular C(sp<sup>3</sup>)–H amidation of tertiary carboxamides was also achieved using perfluoroalkyl carboxamides as amidating agents (Scheme 4.63b).

The cobalt-catalysed, bidentate amide-assisted C–H activation has been proven to enable C–C bond formation via dehydrogenative cross-coupling.



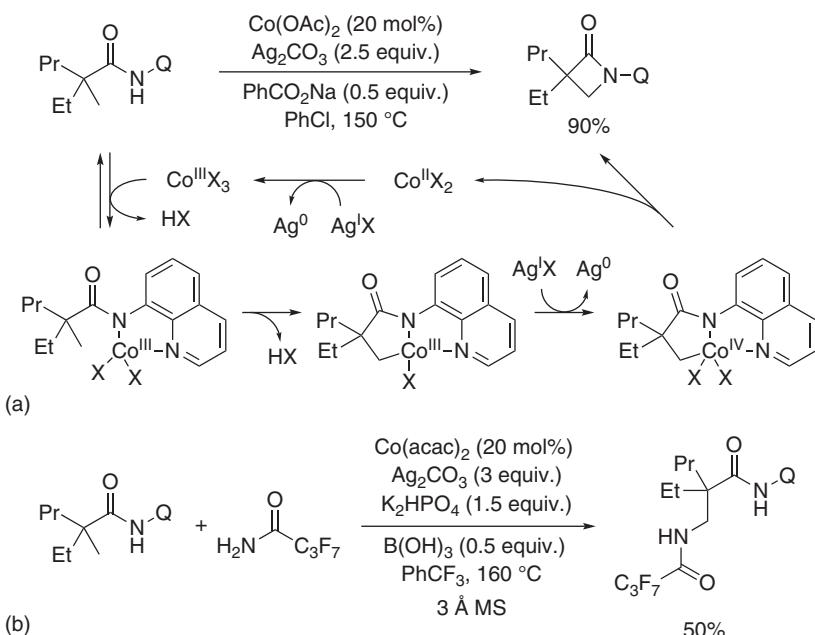
<i>Niu, Song</i>	<i>Zhang</i>	<i>Ackermann</i>	<i>Lei</i>
DG = PyO	DG = Q	DG = PyO	DG = Q
$\text{Co(OAc)}_2 \cdot 4\text{H}_2\text{O}$ (10 mol%)	$\text{Co}(\text{acac})_2$ (20 mol%)	$\text{Co}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ (10 mol%)	$\text{Co}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ (20 mol%)
$\text{AgNO}_3$ (2.5 equiv.)	$\text{Ag}_2\text{CO}_3$ (2 equiv.)	Undivided cell: $\text{RVC}(+)\text{IPt}(-)$	Divided cell: $\text{C}(+) \text{Ni}( - )$
$\text{NaOAc}$ (2 equiv.)	$\text{NaHCO}_3$ (2 equiv.)	$\text{KOAc}$ (3 equiv.)	$\text{NaOPiv}$ (1 equiv.)
$\text{KNO}_3$ (0.5 equiv.)	TFE, 130 °C	GVL, 40 °C	$\text{MeCN}$ , 65 °C
MeCN, 85 °C, air			

(a)



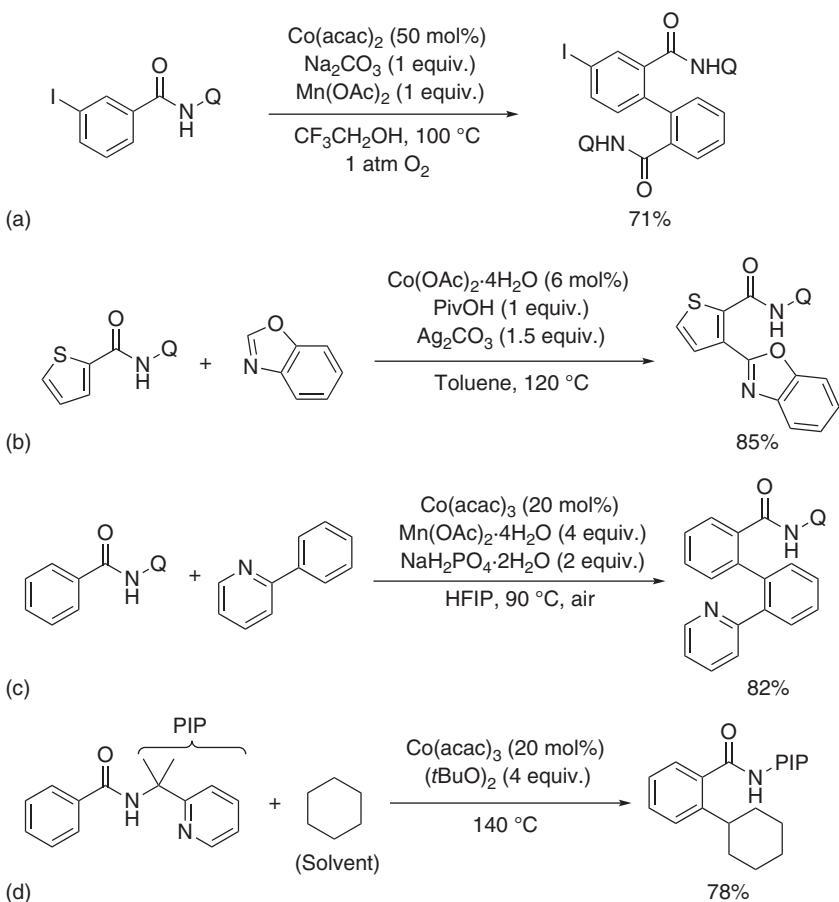
(b)

**Scheme 4.62** (a, b) Bidentate chelation-assisted C–H amination (PyO = 1-oxy-2-pyridyl; Q = 8-quinolinyl).



Scheme 4.63 (a, b) Bidentate chelation-assisted  $\text{C}(\text{sp}^3)\text{-H}$  amidation ( $\text{Q} = 8\text{-quinoliny}$ l).

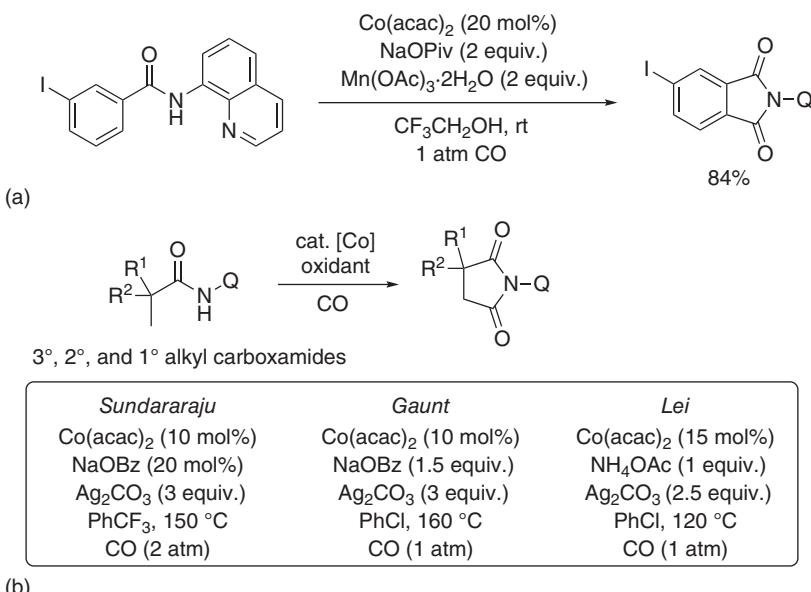
*Daugulis* reported the homocoupling of *N*-(8-quinoliny)benzamide using a semi-stoichiometric amount of  $\text{Co}(\text{acac})_2$  together with  $\text{Mn}(\text{OAc})_2/\text{O}_2$  as oxidant (Scheme 4.64a) [210]. *You* developed a heterobiaryl coupling between 8-quinolinylamide and azole-type heteroarenes using  $\text{Ag}_2\text{CO}_3$  as the oxidant (Scheme 4.64b) [211]. Using slight excess of azole (1.5 equiv.), the cross-coupling product was obtained with good chemoselectivity, along with small amount of homocoupling product of the amide substrate. The reaction was suggested to involve SET processes during the formation of cyclometallated arylcobalt(III) intermediate, which underwent metallation of azole and C–C reductive elimination. *Niu* and *Song* reported a chemoselective biaryl coupling between *N*-(8-quinoliny)benzamide and 2-arylpyridine (Scheme 4.64c) [212]. The reaction was proposed to involve sequential C–H metallation of 2-arylpyridine and *N*-(8-quinoliny)benzamide, leading to a key diaryl cobalt(IV) species. Besides these dehydrogenative cross-coupling arylations, also an arylation of *N*-(8-quinoliny)benzamide with arylboronic acids was achieved using stoichiometric  $\text{Co}^{\text{II}}$  salt [213]. *Lu* and *Li* reported a dehydrogenative *ortho*-alkylation of 2-pyridylisopropyl-(PIP)-protected benzamides with cycloalkane, toluene, dialkyl ether, and dialkyl sulfide derivatives using di-*tert*-butyl peroxide as the oxidant (Scheme 4.64d) [214]. The reaction was proposed to involve a coupling between cyclometallated  $\text{Co}^{\text{III}}$  species and an alkyl radical generated via hydrogen abstraction by a *tert*-butoxy radical. A similar study was also reported by *Liu* [215].



**Scheme 4.64** (a–d) Bidentate chelation-assisted dehydrogenative C—C bond formation ( $Q = 8\text{-quinolinyl}$ ).

#### 4.3.2.3 Carbonylation and Related Transformations

Grigorjeva and Daugulis reported a cobalt-catalysed  $\text{C}(\text{sp}^2)\text{—H}$  carbonylation/cyclisation reactions of  $N$ -(8-quinolinyl)benzamide under oxidative conditions and 1 atm CO, affording phthalimide derivatives (Scheme 4.65a) [216]. The reaction was compatible with various functional groups (e.g. halogen, nitro, and cyano) and was also applicable to analogous vinyl amides. Zhang demonstrated the successful use of azodicarboxylate as the carbonyl source for the same transformation [217]. Thereafter, Daugulis extended the scope of the  $\text{C}(\text{sp}^2)\text{—H}$  carbonylation/cyclisation towards  $N$ -(8-quinolinyl)sulfonamides [218]. Analogous  $\text{C}(\text{sp}^2)\text{—H}$  activation/cyclisation strategy using isocyanides was reported independently by Hao, Ji, and Sundararaju [219], while Sundararaju also demonstrated swapping of the  $N$ -(8-quinolinyl) group and the isocyanide ( $\text{RNC}$ )-derived NR group in a polar protic solvent [220]. Sundararaju, Gaunt, and Lei independently reported the use of 8-quinolinylamide-assisted  $\text{C}(\text{sp}^3)\text{—H}$  carbonylation employing silver salt as stoichiometric oxidant, affording

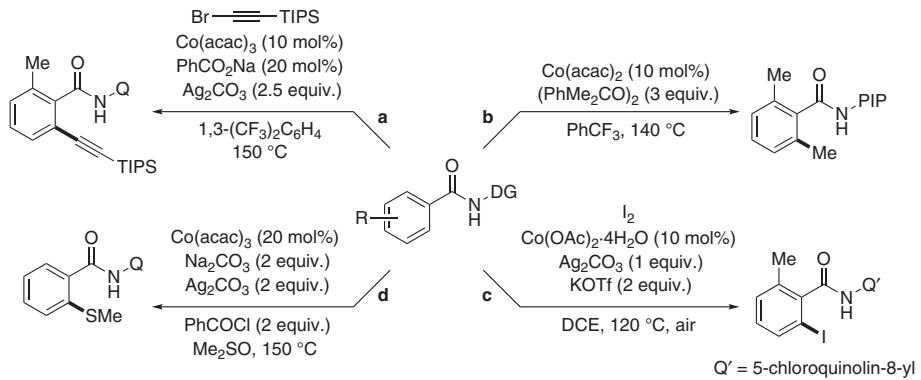


**Scheme 4.65** (a, b) Bidentate chelation-assisted C–H carbonylation (Q = 8-quinolinyl).

succinimide derivatives (Scheme 4.65b) [221]. The reaction worked particularly well with tertiary alkyl carboxamides, while certain secondary and primary alkyl carboxamides also underwent the desired carbonylation.

#### 4.3.2.4 Miscellaneous Transformations

Examples of different cobalt-catalysed C(sp<sup>2</sup>)–H transformations assisted by bidentate amide are illustrated in Scheme 4.66. *Balaraman* reported a C–H alkynylation of *N*-(8-quinolinyl)benzamide with TIPS-protected bromoacetylene (Scheme 4.66a), where the silver salt was assumed to play two major roles, that is, to generate alkynylsilver species for alkynyl group transfer and to reoxidise Co<sup>II</sup> to Co<sup>III</sup> to achieve the catalytic turnover [222]. Analogous *ortho*-alkynylation was achieved using benzylamines bearing *N*-picolinoyl chelating group [223]. *Li* and *Lu* reported the *ortho*-methylation of PIP-protected benzamides with cumoyl peroxide as a methylating agent (Scheme 4.66b) [224]. The reaction was proposed to involve the generation of an alkoxy radical (PhMe<sub>2</sub>CO<sup>·</sup>), which then transferred a methyl group to the cyclometallated Co<sup>III</sup> species with concomitant formation of acetophenone. *Chatani* reported a quinolinylamide-assisted C–H iodination with I<sub>2</sub>, where undesirable iodination of the quinolinyl group was prevented by blocking its 5-position with a Cl substituent (Scheme 4.66c) [225]. *Gui* reported an *ortho*-methylthiolation of *N*-(8-quinolinyl)benzamide using DMSO as a thiolating agent (Scheme 4.66d) [226]. Besides these amide-assisted reactions, nitration of *N*-(2-pyridyl)aniline with AgNO<sub>2</sub> was reported by *Das* [227].



**Scheme 4.66** Selection of C–H functionalisations assisted by bidentate amide ( $\text{Q} = 8$ -quinoliny).

### 4.3.3 Miscellaneous

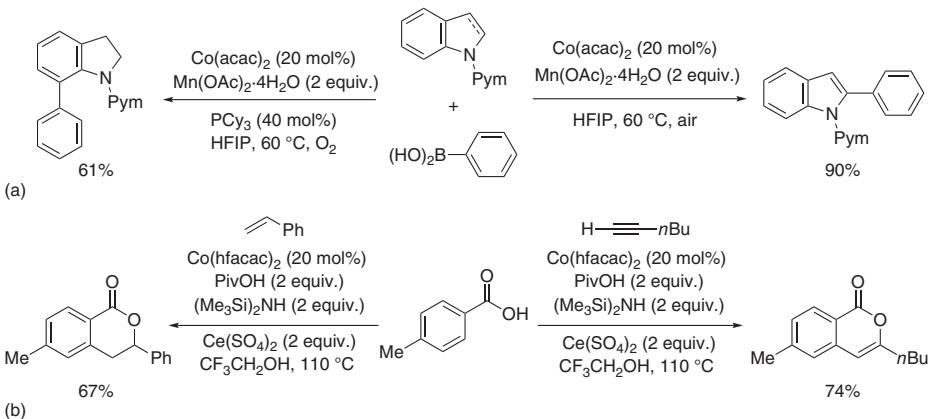
While relatively underdeveloped, high-valent cobalt-catalysed, chelation-assisted C–H functionalisation reactions that do not rely on either  $\text{Cp}^*\text{Co}^{\text{III}}$  catalyst or bidentate directing groups have been reported. Scheme 4.67 shows examples of such reactions under oxidative conditions. *Niu* and *Song* reported a C2-arylation of *N*-pyrimidylindoless with arylboronic acids using  $\text{Co}^{\text{II}}$  catalyst and  $\text{Mn}^{\text{II}}$  cooxidant under air [228], while a similar catalytic system was found to promote C7-arylation of *N*-pyrimidylindolines (Scheme 4.67a) [229]. *Daugulis* achieved an oxidative [4+2] annulation between simple benzoic acid derivatives and alkynes or styrenes (Scheme 4.67b) [230]. The reaction was achieved using  $\text{Co}(\text{hfacac})_2$  as a precatalyst,  $(\text{Me}_3\text{Si})_2\text{NH}$  as a base, and  $\text{Ce}(\text{SO}_4)_2/\text{O}_2$  as the oxidising system. Both terminal and internal alkynes participated in the [4+2] annulation to afford a variety of isochromenones, whereas the reaction using styrenes or 1,3-dienes produced isochromanones. A C2-nitration of Boc-protected indoless with  $t\text{BuNO}_2$  was also reported as an example of oxidative C–H functionalisation of monodentate substrates [231].

*Cheng* reported a cobalt-catalysed hydroarylation cyclisation of 1,6-enynes with aromatic ketones and esters involving *ortho* C–H activation (Scheme 4.68) [232]. The reaction was initiated by a low-valent  $\text{Co}^{\text{I}}$ -diphosphine species generated by reduction of a  $\text{Co}^{\text{II}}$  precatalyst, while a high-valent  $\text{Co}^{\text{III}}$  species is likely responsible for the *ortho* C–H activation. Thus, the reaction was considered to proceed through oxidative cyclisation of the enyne on  $\text{Co}^{\text{I}}$ , carbonyl-assisted cyclometalation with the resulting cobaltacycle intermediate, and C–C reductive elimination. The scope of the hydroarylation cyclisation was later extended to aromatic aldehydes [233].

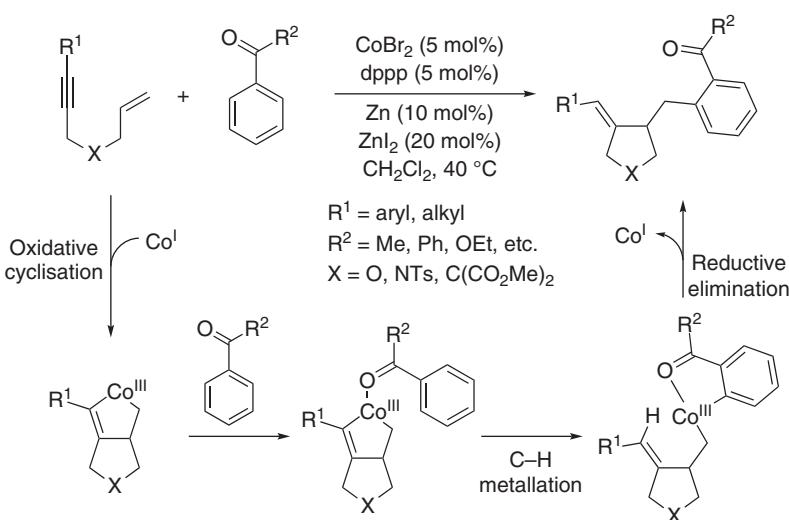
Besides chelating substrates, relatively acidic azole heterocycles have been utilised as substrates for high-valent cobalt-catalysed C–H functionalisations. *Chang* reported an oxidative amination with secondary amines (Scheme 4.69a) [234]. *Hirano* and *Miura* achieved installation of secondary alkyl groups through decomposition of tosylhydrazone (Scheme 4.69b) [235]. *Li* and *Lu* reported a decarboxylative acylation with  $\alpha$ -oxocarboxylic acids (Scheme 4.69c) [236] as well as cross-dehydrogenative alkylation with alkyl ethers (Scheme 4.69d) [237].

## 4.4 Summary and Outlook

Scheme 4.70 summarises the current scope of C–H bond functionalisation reactions promoted by different types of cobalt catalysts, their features in comparison with analogous precious metal catalysts, and some directions of future development. Low-valent cobalt catalysts generated *in situ* under reducing conditions promote chelation-assisted arene C–H functionalisations such as hydroarylation, C–H/C–X coupling, and C–H/C–M coupling. Also, cobalt-diphosphine catalysts have proven to promote 1,4-cobalt migration and hydroacylation. These *in situ*-generated catalysts are amenable to fine-tuning and display unique regio- and chemoselectivity and ability to engage in SET processes, while improved functional group compatibility, extension to  $\text{C}(\text{sp}^3)\text{–H}$

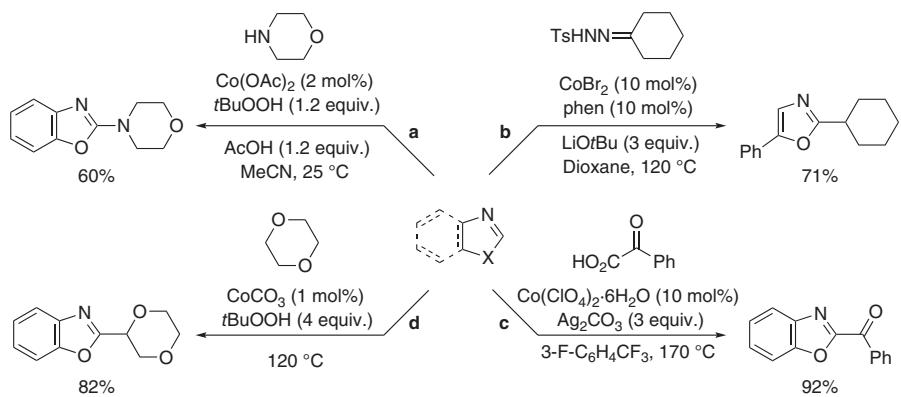


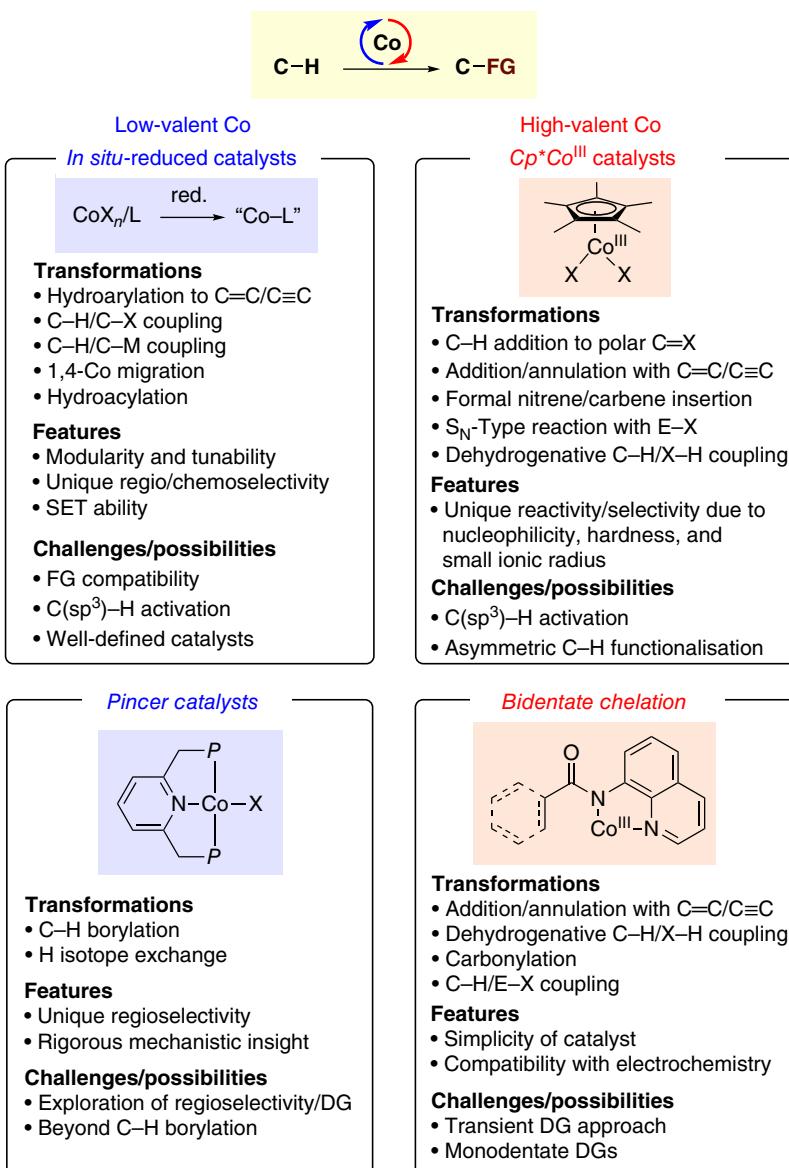
**Scheme 4.67** (a, b) Oxidative C–H functionalisation of mono-coordinating substrates.



**Scheme 4.68** Hydroarylation cyclisation of 1,6-ene via carbonyl-assisted C–H activation.

activation, and deeper mechanistic insight are desired. Well-defined pincer ligands are utilised in cobalt complexes and have emerged as catalysts for C–H borylation that display unique regioselectivity while enabling rigorous mechanistic investigation. Their practicality and scope would be further improved, while their catalytic activity towards other types of C–H functionalisation should deserve exploration. Cp<sup>\*</sup>Co<sup>III</sup>-based catalysts promote a diverse set of chelation-assisted arene C–H functionalisations such as C–H addition to polar C=X bond, addition/annulation reactions to alkynes and alkenes, C–H insertion with nitrene or carbene precursors, and S<sub>N</sub>-type reaction with various E–X-type electrophiles. They have not only proven to serve as cost-effective alternatives to Cp<sup>\*</sup>Rh<sup>III</sup> and Cp<sup>\*</sup>Ir<sup>III</sup> congeners but also displayed distinct reactivities and selectivities owing to higher nucleophilicity, harder nature, and shorter ionic radius. Activation of C(sp<sup>3</sup>)–H bonds with this class of catalysts remains underdeveloped. Exploration of more diverse catalyst architectures, including chiral ones, would be attractive for improved catalytic activities as well as for regio- and stereoselective C–H functionalisations [238]. The combination of bidentate directing groups and simple cobalt salts have enabled C(sp<sup>2</sup>)–H and C(sp<sup>3</sup>)–H functionalisations such as addition/annulation with unsaturated hydrocarbons, dehydrogenative C–C and C–heteroatom cross-coupling, and carbonylation. The successful integration of bidentate-assisted C–H activation and electrochemical oxidation represents a notable advance and a promising direction. The insight gained with static bidentate directing groups would stimulate exploration of transient directing groups [239] for cobalt-catalysed C–H functionalisation. Last but not least, the use of structurally simple cobalt catalysts and common monodentate functional groups also remains as a major challenge.



**Scheme 4.70** Cobalt-catalysed C–H functionalisation: current status and challenges.

## Abbreviations

acac	acetylacetoneato
act.	activation
$\text{B}_2\text{pin}_2$	bis(pinacolato)diboron
<i>n</i> Bu	<i>n</i> -butyl
<i>s</i> Bu	<i>sec</i> -butyl

<i>t</i> Bu	<i>tert</i> -butyl
COD	1,5-cyclooctadiene
Cp*	pentamethylcyclopentadienyl
Cy	cyclohexyl
CPME	cyclopentyl methyl ether
DCE	1,2-dichloroethane
DFT	density functional theory
DG	directing group
2,5-DHBQ	2,5-dihydroxy-1,4-benzoquinone
DMPU	<i>N,N'</i> -dimethylpropylene urea
DPEphos	bis[(2-diphenylphosphino)phenyl] ether
dtbpy	4,4'-di( <i>tert</i> -butyl)-2,2'-bipyridine
FG	functional group
HBpin	pinacoborane
hfacac	hexafluoroacetylacetone
HFIP	1,1,1,3,3,3-hexafluoro-2-propanol
IMes	1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene
IPr	1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene
LLHT	ligand-to-ligand hydrogen transfer
pin	pinacolyl
PMP	<i>p</i> -methoxyphenyl
<i>i</i> Pr	isopropyl
Py	2-pyridyl
Pym	2-pyrimidyl
pyphos	2-[2-(diphenylphosphino)ethyl]pyridine
RVC	reticulated vitreous carbon
SIMes	1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene
SIPr	1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene
TBAI	tetrabutylammonium iodide
TFE	2,2,2-trifluoroethanol
TMEDA	<i>N,N,N',N'</i> -tetramethylethylenediamine
Xantphos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

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## 5

# Low-valent Cobalt Complexes in C–X Coupling and Related Reactions

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## 5.1 Introduction

Over the last 40 years, the development of metal-catalysed cross-coupling reactions revolutionised the formation of carbon–carbon and carbon–heteroatom bonds. This tool of utmost relevance in organic synthesis has been awarded by a Nobel Prize in 2010 with palladium as catalyst metal [1]. Considering the scarcity and the high cost of this metal, organic chemists expended significant research efforts in developing efficient and sustainable procedures by using non-precious and earth-abundant metal catalysts [2, 3]. Among those, a particular attention has been granted to cobalt, which has already proven to be a quite efficient catalyst for cross-coupling reactions [4]. Indeed, cobalt catalysis allows the formation of carbon–carbon bonds of various hybridisation types as well as carbon–heteroatom bonds with organometallic species both in stoichiometric and catalytic amount.

## 5.2 Cobalt-Catalysed Coupling Reactions with Stoichiometric Organometallic Reagents

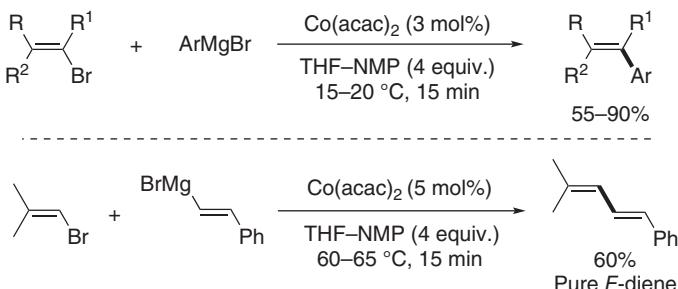
### 5.2.1 Cobalt-Catalysed Coupling Reactions with *Grignard* Reagents

Since *Kharasch* discovered that homocoupling of aromatic *Grignard* reagents could be catalysed by cobalt chloride in presence of an oxidant in the middle of the twentieth century [5], a large number of cobalt-catalysed coupling reactions have been discovered and optimised involving *Grignard* reagents. The methodology enabled the formation of bonds from the various types of carbon atom hybridisation. Numerous reviews or books can be consulted for further details [6].

### 5.2.1.1 $C_{sp^2}$ – $C_{sp^2}$ Bond Formation

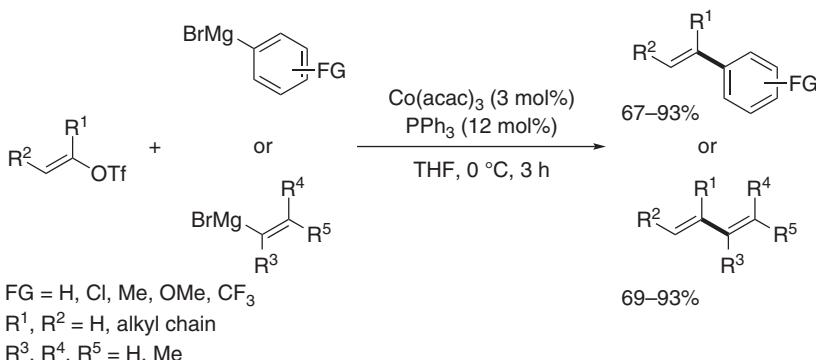
**Alkenylation** Since Kharasch first discovered the alkenylation of aromatic organomagnesium compounds catalysed by cobalt chloride in 1943 [7] and Uemura described the cobalt-catalysed coupling of alkenyl tellurides with aryl *Grignard* reagents in 1982 [8, 9], several significant improvements in  $C_{sp^2}$ – $C_{sp^2}$  bond formation have been made.

In 1998, Cahiez was the first to report great enhancements in yield, scope, and reaction time of the stereospecific cobalt-catalysed alkenylation of aromatic organomagnesium reagents by using *N*-methyl-2-pyrrolidone (NMP) as a co-solvent with tetrahydrofuran (THF) (Scheme 5.1, top) [10]. NMP was assumed to serve as a ligand to the cobalt species and to stabilise *Grignard* reagents, thanks to its *Lewis* basicity. With this catalytic system, Cahiez was also the first to describe an example of a stereospecific cobalt-catalysed cross-coupling between an alkenyl halide and an alkenyl *Grignard* reagent in moderate yield (Scheme 5.1, bottom).



**Scheme 5.1** Cobalt-catalysed alkenylation of aromatic (top) and alkenyl (bottom) organomagnesium reagents in the presence of NMP.

Ten years later, Hayashi reported the cobalt-catalysed coupling of alkenyl triflates with aromatic and alkenyl *Grignard* reagents (Scheme 5.2) [11]. The catalytic system involved was quite different from the one used by Cahiez.

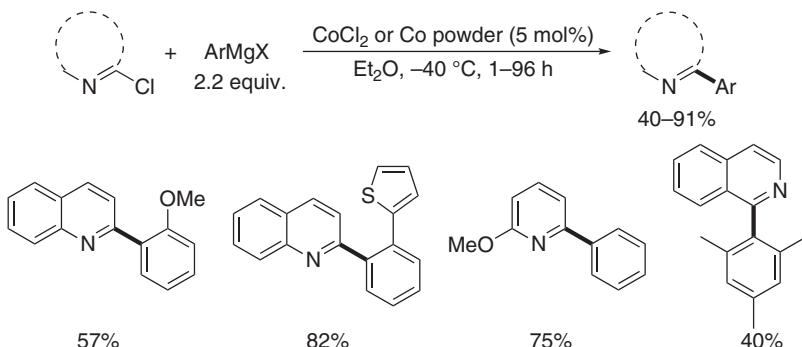


**Scheme 5.2** Cobalt-catalysed cross-coupling of alkenyl triflates with aryl or alkenyl *Grignard* reagents.

Here, the catalyst was generated *in situ* from a cobalt(III) salt and  $\text{PPh}_3$  as a ligand, replacing the NMP as a co-solvent for stabilisation of the cobalt catalyst, affording very good to excellent yields of the cross-coupling products.

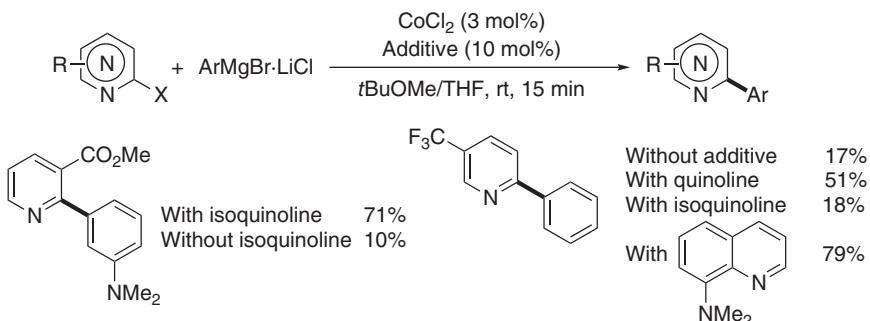
**Aryl-Aryl Cross-coupling** Since Uemura reported the cobalt-catalysed cross-coupling between diaryltellurides and aromatic *Grignard* reagents in 1983, major improvements have been made.

In 2003, Knochel and Cahiez described a method for cross-coupling *N*-heteroaryl chlorides and aryl- or heteroaryl magnesium halides in good to excellent yields catalysed either by cobalt(II) chloride or by cobalt powder (Scheme 5.3) [12].



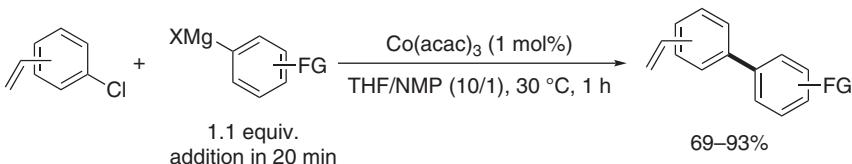
**Scheme 5.3** Cobalt-catalysed cross-coupling between *N*-heteroaryl chlorides and aryl- or heteroaryl magnesium halides.

However, the reaction time required to complete the reaction ranged from 1 to 96 hours, the latter being required for the successful reaction of less reactive substrates. Inspired by his work on iron catalysis [13], Knochel dramatically improved both yield and reaction rate of this transformation. Indeed, cross-coupling products were obtained within 15 minutes by using  $^t\text{BuOMe}$  as a co-solvent and quinoline, isoquinoline [14], or *N,N*-dimethylquinoline-8-amine [15] as a ligand in presence of an aromatic *Grignard* reagent prepared with LiCl salt (Scheme 5.4).



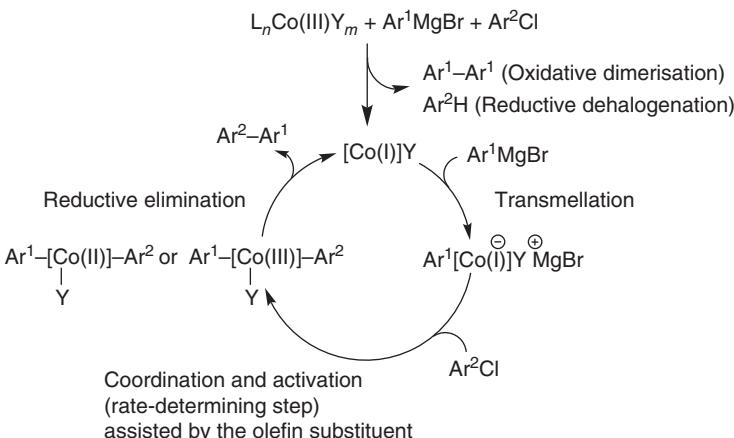
**Scheme 5.4** Improvements in cobalt-catalysed cross-coupling between *N*-heteroaromatic halides and aryl *Grignard* reagents.

Later, *Jacobi von Wangenheim* reported a highly efficient and chemoselective cobalt-catalysed biaryl cross-coupling reaction of unactivated chlorostyrenes with only 1.1 equiv. of aromatic *Grignard* reagents in the presence of only 1 mol%  $\text{Co}(\text{acac})_3$  and NMP as crucial co-solvent (Scheme 5.5) [16].



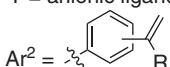
**Scheme 5.5** Cobalt-catalysed cross-coupling between chlorostyrenes and aryl *Grignard* reagents.

It is interesting to note that chlorostyrene derivatives were more reactive than most aryl bromides, which could be quite useful in organic synthesis. Thorough mechanistic and kinetic studies of the reaction have been achieved, showing, on one hand, that the vinyl substituent considerably facilitated the activation of C–Cl bonds by chelating the cobalt catalyst. On the other hand, comparison of the activity of cobalt(III), cobalt(–I), and cobalt(I) precatalysts provided insights of a catalytically active cobalt(I) species for this reaction. Those studies led the authors to propose the following reaction mechanism (Scheme 5.6):



L = THF, NMP

Y = anionic ligand such as halide, acac,  $\text{Ar}^1$

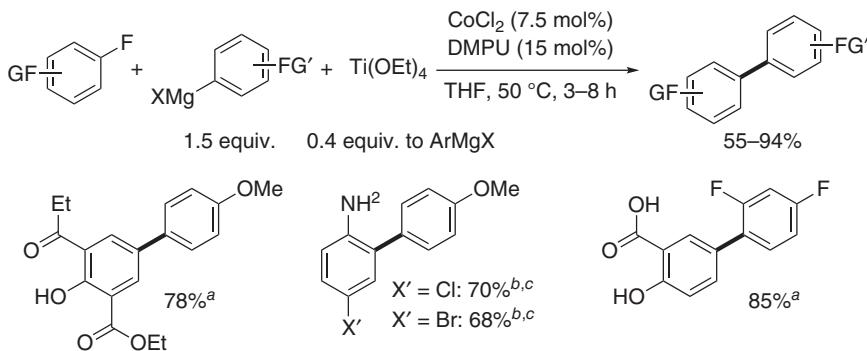


**Scheme 5.6** Proposed mechanism of the chemoselective cobalt-catalysed cross-coupling between chlorostyrenes and aryl *Grignard* reagents.

reduction of the cobalt(III) into the catalytically active cobalt(I) species through oxidative dimerization of the *Grignard* reagent or reductive dehalogenation of the aryl chloride. The active species could then transmetallate with the *Grignard* reagent, affording a cobaltate(I) complex. After the rate-determining olefin coordination and activation of the C—Cl bond of the chlorostyrene derivative by this cobaltate(I) species, through an oxidative addition or single-electron transfer, the diaryl complex formed underwent reductive elimination leading to the product and regenerating the cobalt(I) catalyst.

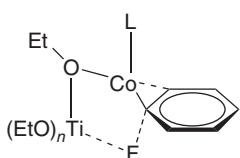
Although the methods described earlier are quite efficient, they are limited to specific substrates: *N*-heteroaryl halides bearing the halide atom on the carbon in  $\alpha$ -position to the ring nitrogen on one hand and derivatives of chlorostyrene on the other hand. In both cases, the cross-coupling was facilitated by a chelation effect occurring through the substrate.

Recently, inspired by his previous work [17, 18], *Duan* disclosed a cobalt-catalysed cross-coupling between aryl *Grignard* reagents and unactivated aryls by C—F bond activation [19]. Unlike the activation of C—F bond by Pd or Ni complexes, this method used neither phosphine nor *N*-heterocyclic carbene (NHC) ligands [20–25]. The procedure consisted in using a catalytic amount of  $\text{CoCl}_2$ , *N,N'*-dimethylpropylene urea (DMPU) as a ligand and a substoichiometric amount of  $\text{Ti}(\text{OEt})_4$  as an additive to avoid formation of side products and improved the overall yield of the reaction (Scheme 5.7). The authors assumed that  $\text{Ti}(\text{OEt})_4$  had two roles. On one hand, it might have formed a titanate complex  $[\text{ArTi}(\text{OEt})_4\text{-MgX}]$ , which had already been shown to modify the reactivity of *Grignard* reagents [26], leading to better chemoselectivity. On the other hand, the authors postulated the formation of the transition state described in Figure 5.1, which promoted the C—F bond cleavage in a synergistic process driven by the formation of the Ti—F bond [27, 28].



**Scheme 5.7** Cobalt-catalysed C—F activation biaryl couplings under phosphine or NHC-free conditions. <sup>a</sup> With 3.5 equiv. of  $\text{ArMgX}$  and 0.6 equiv. of  $\text{Ti}(\text{OEt})_4$ . <sup>b</sup> With 3.0 equiv. of  $\text{ArMgX}$  and 0.4 equiv. of  $\text{Ti}(\text{OEt})_4$ . <sup>c</sup> No diarylated products from C—Cl or C—Br observed.

Thus, it was possible to couple at the *ortho*-, *meta*-, and *para*-positions and various activated and unactivated aryls bearing a wide range of functional groups including ketone, ester, free alcohol, free amine, or free carboxylic acid, with many



**Figure 5.1** Postulated transition state for the Co/Ti cooperativity oxidative addition step.

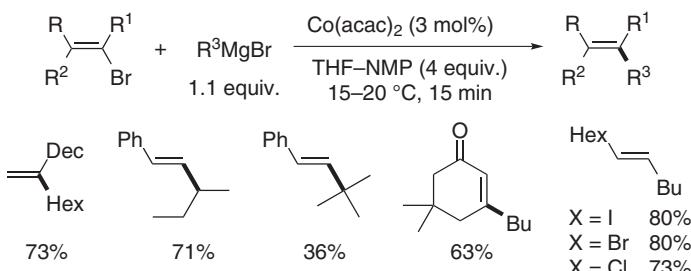
aryl *Grignard* reagents (Scheme 5.7). Furthermore, this method was selective to the C–F bond compared with C–Br and C–Cl bonds and between two C–F bonds led selectively to monoarylated product (Scheme 5.7).

In addition to halide or pseudo-halide compounds previously presented, cobalt can also activate other C–X bonds to perform arylation of aryl electrophiles. Indeed, Reeves developed the cross-coupling of sodium salts of arylsulfonic acids with aromatic organomagnesium reagents catalysed by only 1 mol% of  $\text{CoCl}_2(\text{PCy}_3)_2$  in excellent yields [29].

### 5.2.1.2 $\text{C}_{\text{sp}^2}$ – $\text{C}_{\text{sp}^3}$ Bond Formation

Since the pioneering work of Kharasch [30] who discovered the  $\beta$ -bromostyrene can couple with methylmagnesium iodide in presence of cobalt(II) chloride, and Hey [31], who reported the first cobalt-catalysed arylation of  $\text{C}_{\text{sp}^3}$  center, several improvements have been made to form  $\text{C}_{\text{sp}^2}$ – $\text{C}_{\text{sp}^3}$  bonds from both alkene and aryl moieties.

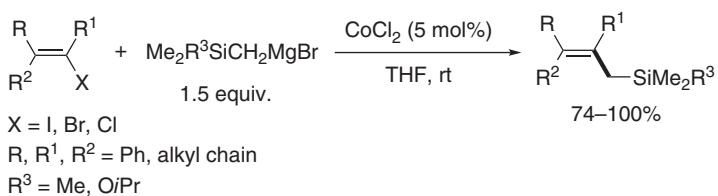
**Alkenylation** In 1998, Cahiez refined the work of Kharasch and succeeded in coupling various alkenyl halides with only 1.1 equiv. of alkyl *Grignard* reagents by using NMP as an essential co-solvent with THF (Scheme 5.8) [10].



**Scheme 5.8** Cobalt-catalysed coupling between alkenyl halides and aliphatic *Grignard* reagents.

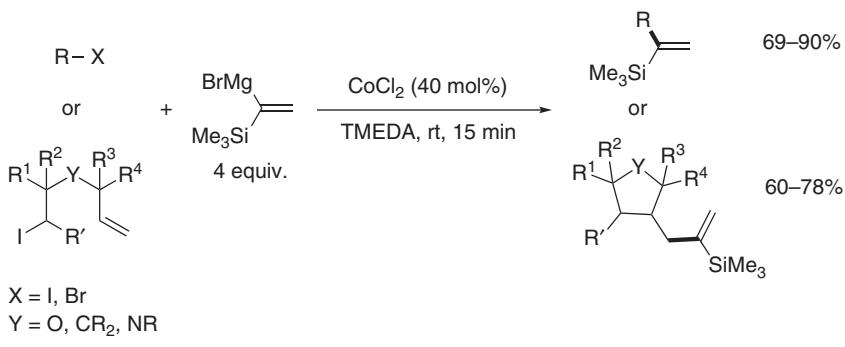
The reaction tolerated alkenyl iodides, bromides, and chlorides and afforded good yields with primary and secondary *Grignard* reagents, whereas tertiary *Grignard* reagents provided poorer yields (Scheme 5.8). The reaction was chemoselective, hence it tolerated ester and ketone groups. It is noteworthy that the reaction was also stereospecific since (*Z*)-substrate (respectively, (*E*)-substrate) gave (*Z*)-product (respectively, (*E*)-product) in similar yields and that dihalogenated substrates led to monosubstituted products.

In 2006, Oshima reported a coupling between alkenyl halides and silylated *Grignard* reagents using a ligand-less catalytic system: simple cobalt(II) chloride in THF [32]. The yields were good to excellent, except for  $\alpha,\beta$ -disubstituted alkenyl halides (only 25% yield) (Scheme 5.9).



**Scheme 5.9** Cobalt-catalysed cross-coupling between alkenyl halides and alkylsilylated *Grignard* reagents.

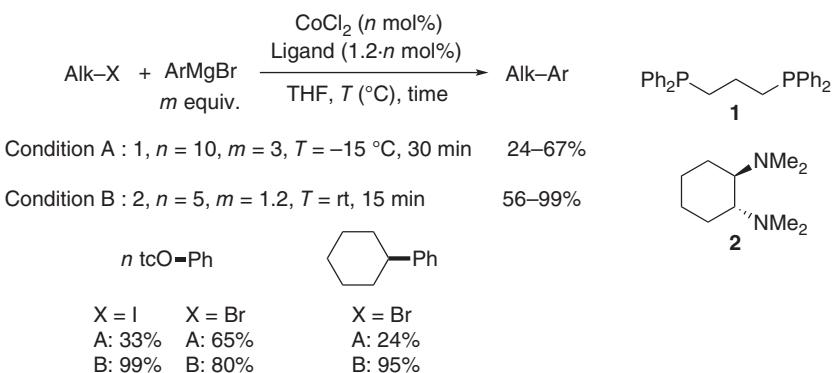
In the same year, the same authors firstly described the cobalt-catalysed cross-coupling reaction of primary and secondary alkyl halides and 1-(trimethylsilyl) ethenylmagnesium bromide in *N,N,N',N'*-tetramethylenediamine (TMEDA) as a solvent [33]. Although good to excellent yields were achieved, this method featured two major drawbacks: a quite important amount of catalyst was needed (40 mol%) and a large excess of the *Grignard* reagent (4 equiv.), which besides seems to be the only *Grignard* reagent able to react (Scheme 5.10).



**Scheme 5.10** Cobalt-mediated cross-coupling reaction of primary and secondary alkyl halides and 1-(trimethylsilyl)ethenylmagnesium bromide.

Nevertheless, it is a useful tool to synthesise heterocyclic compound, since  $\epsilon$ -unsaturated alkyl iodides can perform radical cyclisations, followed by a cross-coupling reaction in very good yields.

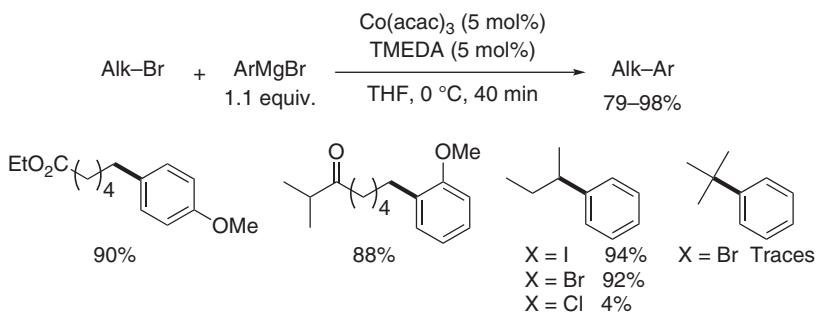
**Arylation** *Oshima* was the first in 2006 to improve the cross-coupling reaction observed by *Hey* [31] in 1969 between primary alkyl halides and aromatic *Grignard* reagents catalysed by  $\text{CoCl}_2(\text{dppp})$  [34]. However, a large excess of *Grignard* reagent was needed (3 equiv.), which led to moderate yields only for primary alkyl bromides. Indeed, primary alkyl iodides and secondary alkyl bromides reacted poorly, and no reactivity was observed with alkyl chlorides. Hindered *Grignard* reagents also did not perform the reactions (Scheme 5.11, condition A). *Oshima* finally found in the same year that impressively better results for this coupling were reached when *N,N,N',N'*-tetramethyl-1,2-cyclohexanediamine (**2**) was used as a ligand [35]. Its introduction as ligand broadened the scope of the reaction, since now also secondary alkyl bromides and iodides could be



**Scheme 5.11** Comparative results for cross-coupling between alkyl halides and aromatic Grignard reagents according to the conditions used.

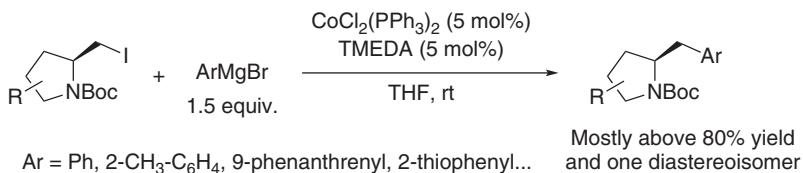
coupled successfully. In addition, it allowed decreasing the required excess of *Grignard* reagents to 1.2 equiv. only and the use of more hindered organomagnesium compounds (Scheme 5.11, condition B). Furthermore, with this ligand the reaction was chemoselective, allowing alkyl halides bearing ester as functional group to couple successfully.

Later, *Cahiez* reported some improvements to this reaction: first, by using the commercial and cheap TMEDA as a ligand to  $\text{Co}(\text{acac})_3$  instead of *N,N,N',N'*-tetramethyl-1,2-cyclohexanediamine [36]. Furthermore, whereas *Oshima*'s method led to lower yield with alkyl bromides than with alkyl iodides (Scheme 5.11), this catalytic system afforded similar yields (Scheme 5.12). Finally, the reaction was highly chemoselective since sensitive groups such as ester, amide, and ketone reacted smoothly (Scheme 5.12). However, alkyl chlorides and tertiary alkyl halides reacted only sluggishly.



**Scheme 5.12** Cobalt-catalysed cross-coupling between aliphatic bromides and aromatic Grignard reagents.

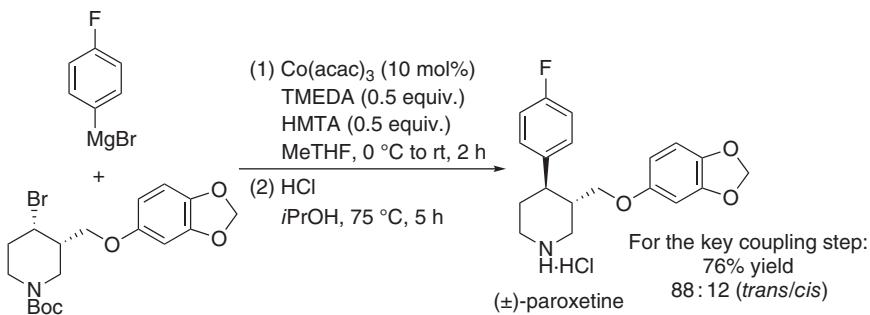
Both works of *Oshima* [34, 35] and *Cahiez* [36] inspired the recent invention of selective synthetic methods. *Wu* developed the synthesis of enantiopure pyrrolidine derivatives catalysed by  $\text{CoCl}_2(\text{PPh}_3)_2$  with TMEDA as an additive (Scheme 5.13) [37].



**Scheme 5.13** Synthesis of enantiopure arylated pyrrolidines through cobalt-catalysed cross-coupling reaction.

Inspired from *Oshima*'s catalytic system [35], *Cossy* first disclosed a direct cross-coupling with various aryl- and heteroaryl magnesium reagents and iodo-azetidines, -pyrrolidines, and -piperidines alike [38]. Then, *Cossy* and *Reymond* expanded *Cahiez*'s work [36] to the diastereoselective synthesis of *C*-aryl and *C*-vinyl glycosides [39] as well as *C*-furanosides illustrated by the total synthesis of (*-*)-isoaltholactone [40]. And finally, *Cossy* and *Guérinot* extended both methodologies, allowing the coupling reaction of *N*-protected 3- and 4-iodopiperidines with various *Grignard* reagents [41].

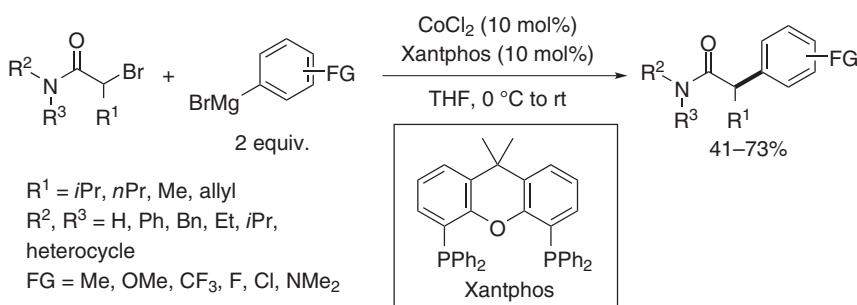
*Linclau* [42] refined *Cahiez*'s catalytic systems [36, 43] by using Co(acac)<sub>3</sub> with TMEDA and hexamethylenetetramine (HMTA) as cooperative ligands in 2-methyltetrahydrofuran (MeTHF) to perform the key stereoconvergent coupling step in a total synthesis of ( $\pm$ )-paroxetine on a gram scale (Scheme 5.14).



**Scheme 5.14** Key coupling step for the gram scale synthesis of ( $\pm$ )-paroxetine.

*Knochel* [44] was also inspired by *Cahiez*'s catalytic system [36] to diastereoselectively connect cyclic halohydrins with aryl *Grignard* reagents. Moderate to good yields and excellent diastereoisomeric ratios in favour of the most stable product were obtained with a simple catalytic system comprising of THF-soluble CoCl<sub>2</sub>·2LiCl and TMEDA. The authors were able to extend this reactivity to the diastereoselective cross-coupling of cyclo- and heterocycloalkyl iodides with aryl *Grignard* reagents by only changing TMEDA by neocuproine as a ligand [45].

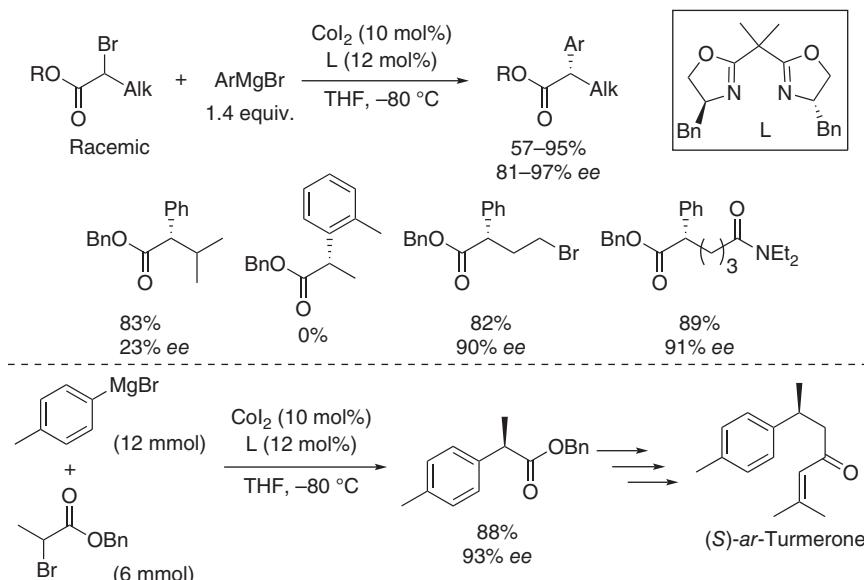
Very recently, *Guérinot* and *Cossy* developed a method using CoCl<sub>2</sub> as a catalyst and Xantphos as a ligand to couple arylmagnesium reagents with  $\alpha$ -bromoamides in moderate to good yields (Scheme 5.15) [46]. Concerning the scope of the *Grignard* reagent, the reaction displayed low sensitivity to electronic effects since both electron-donating and electron-withdrawing groups reacted



Scheme 5.15 Cobalt-catalysed cross-coupling of  $\alpha$ -bromo amides with *Grignard* reagents.

smoothly but did not tolerate *ortho*-substituents. As for the amide, only tertiary amides showed good reactivity, allowing the nitrogen to carry bulky substituents. The reaction was also efficient using vinyl *Grignard* reagents as nucleophiles.

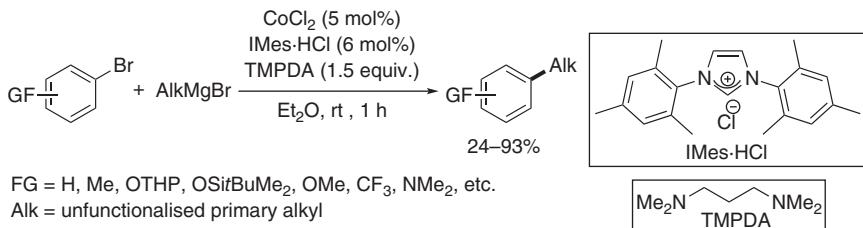
Finally, *Zhong* and *Bian* reported the first highly enantioselective cobalt-catalysed *Kumada* cross-coupling reaction between racemic  $\alpha$ -bromoesters and aryl *Grignard* reagents using cobalt(II) iodide and a bisoxazoline ligand [47]. Excellent yields and enantiomeric excesses were obtained from a broad range of both *Grignard* reagents and  $\alpha$ -bromoesters independently from the electronic nature of the substituents (Scheme 5.16). However, the reaction was quite sensitive to steric hindrance. Indeed,  $\alpha$ -bromoesters bearing secondary alkyl groups on the carbon in the  $\alpha$ -position of the ester moiety performed the cross-coupling in very good yields but with a dramatic drop of the enantiomeric



Scheme 5.16 Enantioselective *Kumada* cross-coupling of racemic  $\alpha$ -bromoesters with arylmagnesium compounds.

excess. Furthermore, *Grignard* reagents bearing *ortho*-substituents did not perform any cross-coupling reaction. Nevertheless, the reaction displayed high chemoselectivity since very good yields and enantioselectivities were achieved with a wide range of primary alkyl groups bearing bromine, chlorine, ester, or amide moieties (Scheme 5.16). Finally, the authors showed the utility and scalability of their method by synthesising the biologically active compound (*S*)-*ar*-turmerone on a large scale with high selectivity (Scheme 5.16).

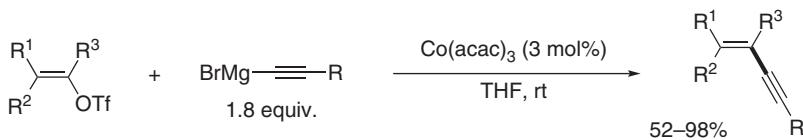
**Alkylation** In 2008, *Oshima* reported the cross-coupling reaction between aryl bromides and aliphatic *Grignard* reagents by using the NHC ligand coming from the deprotonation of 1,3-bis(2,4,6-trimethylphenyl)-imidazolium chloride (IMes-HCl), and *N,N,N',N'*-tetramethylpropylene-1,3-diamine (TMEDA) as additive [48]. Good to excellent yields were obtained but only primary alkyl and unfunctionalised *Grignard* reagents could be used, limiting the scope of the reaction (Scheme 5.17).



**Scheme 5.17** Cobalt-catalysed cross-coupling between aryl bromides and alkyl *Grignard* reagents.

### 5.2.1.3 C<sub>sp</sub>—C<sub>sp<sup>2</sup></sub> Bond Formation

Very few examples of C<sub>sp</sub>—C<sub>sp<sup>2</sup></sub> have been described so far. In 2007, *Hayashi* reported the coupling between alkynyl *Grignard* reagents and alkenyl triflates in presence of Co(acac)<sub>3</sub> leading to various conjugated enynes (Scheme 5.18) [49].



R, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> = mostly carbon chains without functionalisation

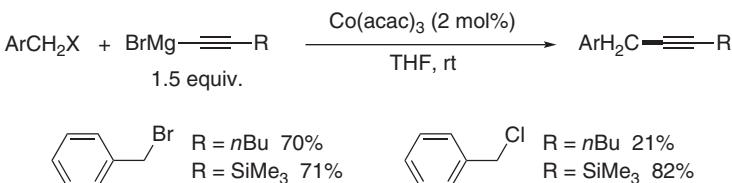
**Scheme 5.18** Cobalt-catalysed coupling between alkynyl *Grignard* reagents and alkenyl triflates.

### 5.2.1.4 C<sub>sp</sub>—C<sub>sp<sup>3</sup></sub> Bond Formation

Since the pioneering work of *Kharasch* [50], *Franzen* [51], and *Weedon* [52], only few improvements have been made in C<sub>sp</sub>—C<sub>sp<sup>3</sup></sub> bond formation.

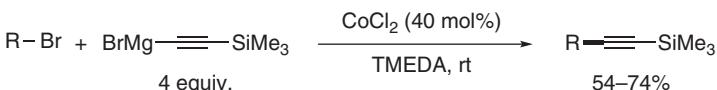
*Okamoto* developed the benzylation of alkynylmagnesium reagents catalysed by Co(acac)<sub>3</sub> without using any additional ligand [53]. Good yields were generally

obtained from trimethylsilylethynylmagnesium reagents with benzyl bromides and chlorides alike, whereas the reaction with 1-hexynyl *Grignard* reagent gave only good yields with benzyl bromides (Scheme 5.19). Unfortunately, this catalytic system was specific to benzylic halides, affording no coupling product with allyl or alkyl halides.



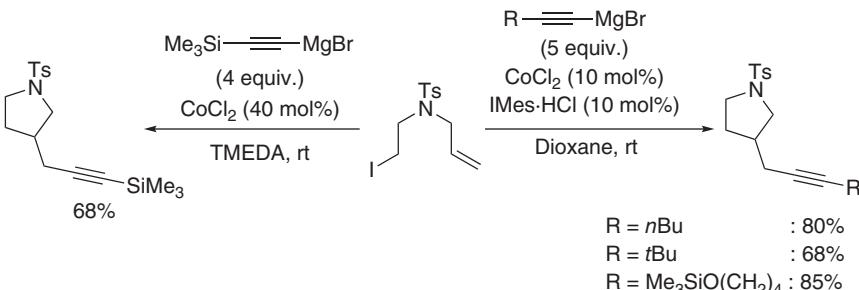
**Scheme 5.19** Cobalt-catalysed benzylation of alkynyl *Grignard* reagents.

The same year, *Oshima* reported the cobalt-mediated coupling of primary and secondary bromides with trimethylsilylethynylmagnesium bromide in TMEDA as a solvent [33]. A large excess of *Grignard* reagent (4 equiv.) was needed to achieve satisfying yields (Scheme 5.20).



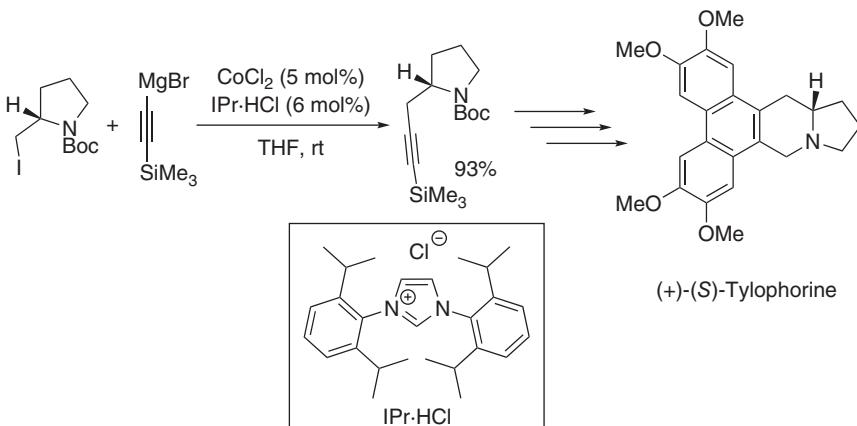
**Scheme 5.20** Cobalt-mediated coupling of primary and secondary bromides with trimethylsilylethynylmagnesium bromide.

The authors then expanded this methodology to 5,6-unsaturated alkyl iodides, which performed a tandem radical cyclisation and alkynylation to afford various heterocycle compounds bearing a triple bond. Coupling partners were on one hand trimethylsilylethynylmagnesium bromide (Scheme 5.21, left) [33] and on the other hand simple acetylenic *Grignard* reagents [54], which could be used by refining the catalytic system, combining cobalt chloride with the NHC ligand, supplied from the deprotonation of IMes·HCl salt, in dioxane (Scheme 5.21, right). However, a large excess of *Grignard* reagent was still needed (5 equiv.).



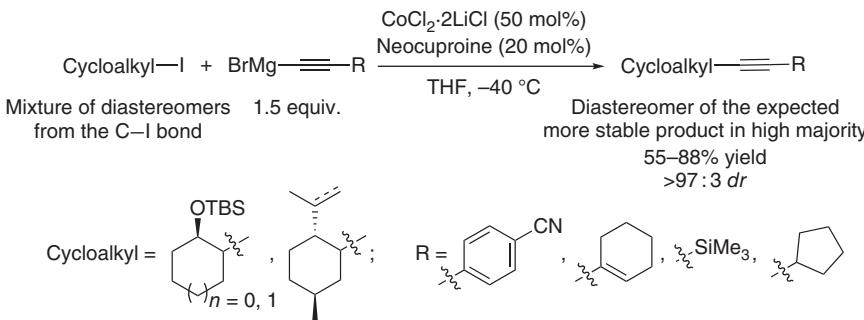
**Scheme 5.21** Cobalt-catalysed tandem radical cyclisation and alkynyl coupling reaction; left: with trimethylsilylethynylmagnesium bromide; right: with simple acetylenic *Grignard* reagents.

This procedure inspired Wu's method to enantioselectively synthesise (+)-(S)-tylophorine (Scheme 5.22) [38].



**Scheme 5.22** Cobalt-catalysed key coupling step for the synthesis of (+)-(S)-tylophorine.

Finally, in 2016, Knochel described the diastereoselective cobalt-mediated cross-coupling of cycloalkyl iodides with alkynyl *Grignard* reagents [45]. In the presence of  $\text{CoCl}_2 \cdot 2\text{LiCl}$  (50 mol%) and neocuproine (20 mol%) good yields and excellent diastereoselectivities, leading almost exclusively to the expected more stable product, were obtained (Scheme 5.23).

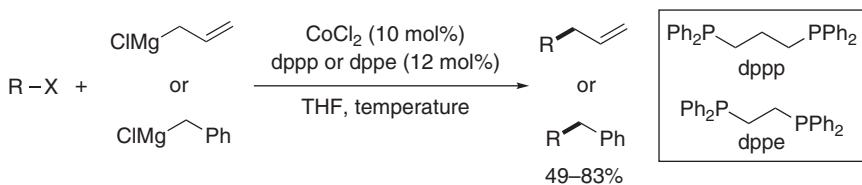


**Scheme 5.23** Diastereoselective cobalt-mediated cross-coupling of cycloalkyl iodides with alkynyl *Grignard* reagents.

### 5.2.1.5 $\text{C}_{\text{sp}}^3\text{—C}_{\text{sp}}^3$ Bond Formation

Besides its moderate cost and toxicity, cobalt has the particularity to not undergo  $\beta$ -hydrogen elimination of alkyl–cobalt intermediates, unlike alkyl–palladium or alkyl–nickel intermediates, which makes it a competent catalyst to couple  $\text{C}_{\text{sp}}^3$ -hybridised carbons [4]. Yet, the investigation of cobalt-catalysed  $\text{C}_{\text{sp}}^3\text{—C}_{\text{sp}}^3$  bond formation has only been reported quite recently. Indeed, it was only in 2002 when Oshima reported the coupling between unactivated alkyl halides and allylic *Grignard* reagents catalysed by  $\text{CoCl}_2$  and 1,3-bis(diphenylphosphino)propane

(dppp) or 1,2-bis(diphenylphosphino)ethane (dppe) as a ligand (Scheme 5.24) [55]. This catalytic system could also be applied to some benzylic *Grignard* reagents but in moderate to poor yields [56]. Although the temperature needed to perform the reaction was quite dependent on the substrate, a broad range of unfunctionalised alkyl iodides and bromides achieved good to very good yields. However, alkyl chlorides gave only poor results.

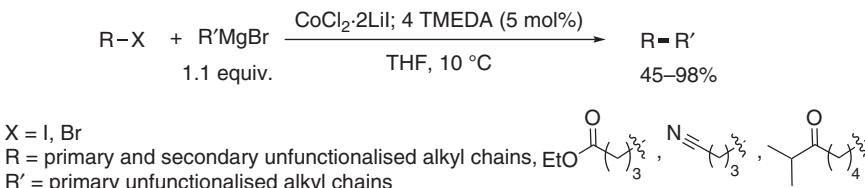


$R$  = primary, secondary, and tertiary unfunctionalised alkyl chains  
 $X$  = I, Br, Cl (poor yields)

**Scheme 5.24** Cobalt-catalysed cross-coupling between unactivated alkyl halides and allylic *Grignard* reagents.

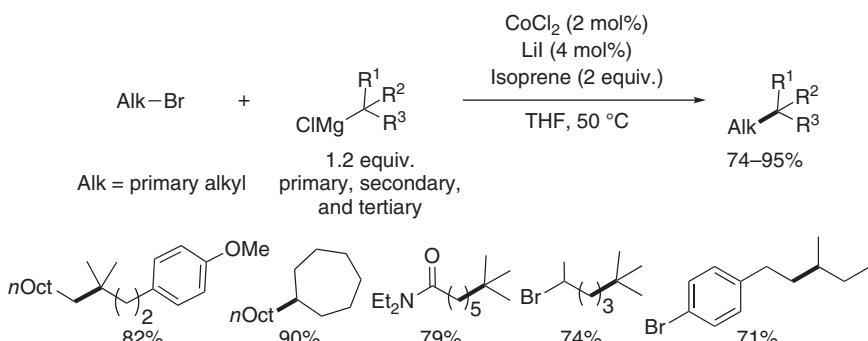
On the other hand, substituted allylic *Grignard* reagents gave a mixture of products with a majority of the branched products.

In 2008, Cahiez was the first to reveal a cobalt-catalysed cross-coupling not only limited to specific alkyl *Grignard* reagents like allyl or benzyl. Indeed, by using the ate complex  $\text{CoCl}_2 \cdot 2\text{LiI}$  and TMEDA as a ligand, he could successfully couple functionalised alkyl halides and aliphatic *Grignard* reagents (Scheme 5.25) [57]. Good yields were obtained from a broad range of primary and secondary alkyl bromides and iodides; however, alkyl chlorides were found not to react. It is also interesting to notice that the reaction was sensitive to steric effects. Indeed, tertiary alkyl halides as well as secondary and tertiary *Grignard* reagents were not performing the coupling. Nevertheless, the reaction was chemoselective since it tolerated, e.g. ester, nitrile, or keto groups in the substrate.



**Scheme 5.25** Cobalt-catalysed coupling between alkyl halides and aliphatic *Grignard* reagents.

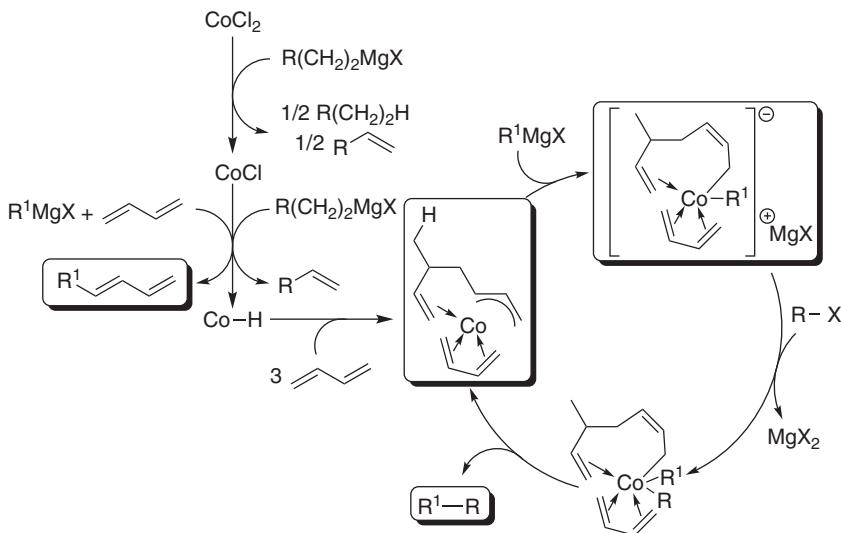
It was only in 2013 that Kambe reported the successful cobalt-catalysed cross-coupling of various alkyl halides with tertiary alkyl *Grignard* reagents [58, 59]. He also used the ate complex  $\text{CoCl}_2 \cdot 2\text{LiI}$ , but instead of using TMEDA as a ligand like Cahiez [57], isoprene was applied as additive to avoid reduction of the *Grignard* reagent (Scheme 5.26). A wide range of *Grignard* reagents were tolerated, from primary to secondary and tertiary, and also cyclic and acyclic



**Scheme 5.26** Cobalt-catalysed cross-coupling of alkylmagnesium reagents with multiple alkyl halides

groups. Likewise, a broad variety of alkyl halides were tolerated such as those bearing olefin, alkyne, amide, acetal, or ester groups. Moreover, it had been shown that the reaction was chemoselective. Indeed, in case of dibromoalkanes bearing primary and secondary alkylbromo moieties, the reaction was selectively performed at the primary site. Finally, site selectivity was also observed in favour of  $C_{sp^3}$ —Br bond in presence of a  $C_{sp^2}$ —Br bond.

With further mechanistic studies, the authors proposed the mechanism depicted in Scheme 5.27 for the reaction.

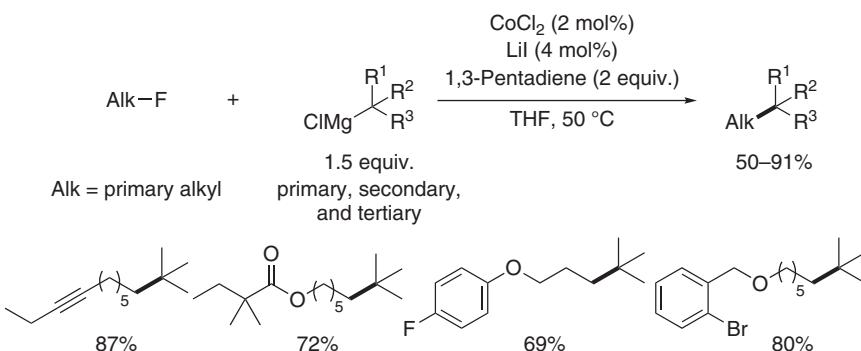


**Scheme 5.27** Mechanism proposed by Kambe for the cobalt-catalysed cross-coupling of alkyl halides with alkyl *Grignard* reagents. On the left, some mechanistic precisions from Koszinowski's work.

The Co-H intermediate species considered was consistent with *Grignard* reagents having no  $\beta$ -hydrogens not reacting. Very recently, *Koszinowski* validated the mechanism proposed of *Kambe* with a very precise and detailed

mass-spectrometry study, including the observation of the species framed in Scheme 5.27 [60]. It also allowed them to identify another way to form the Co–H precursor (Scheme 5.27, left).

During his investigations, *Kambe* discovered that alkyl fluorides showed some reactivity with the catalytic system developed according to the following order of reactivity  $I > OTs > Br > F \gg Cl$  [58]. The authors then extended their study, and only by using 1,3-pentadiene as additive instead of isoprene, they were able to perform couplings with alkyl fluoride [61]. The characteristics of the reaction were comparable to those of the previously developed method [60], and moderate to good yields were obtained from various substrates (Scheme 5.28).



**Scheme 5.28** Cobalt-catalysed cross-coupling reaction between alkyl fluorides and alkyl *Grignard* reagents.

Finally, the tolerance of alkyl fluorides under the conditions of several metal-catalysed cross-coupling reactions makes this method a useful synthetic tool for, e.g. the late-stage introduction of a quaternary carbon [61].

In addition to the activation of carbon–halogen bonds, *Oshima* described the cobalt-catalysed coupling reaction of allylic ether with both trimethylsilyl-methylmagnesium chloride and allylic *Grignard* reagents [62]. Good yields were generally obtained, but the reaction seems to operate regioselectively only with very few substrates, and it is interesting to notice that the regioselectivity of the reaction can be controlled by changing the nature of the catalyst (Scheme 5.29). He extended his method to allylic acetals, and depending on the amount of *Grignard* used, 1.5 or 3 equiv., it was possible to substitute one or both of the methoxy groups [62].



**Scheme 5.29** Cobalt-catalysed coupling reaction of (3-methoxy-1-propenyl)benzene and allylmagnesium bromide.

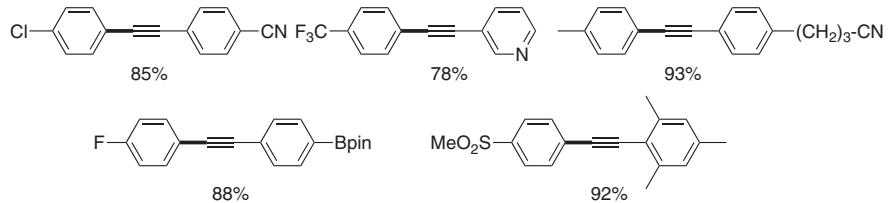
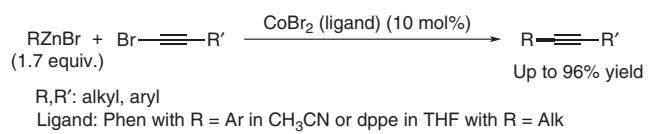
### 5.2.2 Cobalt-Catalysed Coupling Reactions with Organozinc Reagents

Although palladium and nickel complexes are by far the most employed metal catalysts for cross-coupling involving an organometallic species, other metallic salts such as Cu, Fe, and especially Co have recently seen increasing use in this field. Although the first cobalt-catalysed cross-coupling involving an organometallic species was reported with a *Grignard* reagent [30], the need to use other organometallic species was required especially when reactive functional substituents were present on the two partners. To overcome the difficulties associated with the use of *Grignard* reagents, an interesting alternative was the employment of organozinc species. Their accesses by traditional transmetallation from organomagnesium or organolithium compounds are still very common today, but other syntheses directly from the corresponding organic halides in the presence of a transition metal such as nickel [63] or cobalt salts [64] are also another currently investigated alternative. Thus, original chemical reactions allowed for the preparation of aromatic zinc species, especially using cobalt catalysis. These reactions require commercially available zinc dust and cobalt bromide along with acetonitrile as solvent in the case of aryl iodides and bromides bearing various electron-donating or electron-withdrawing groups in all positions (*ortho*, *meta*, *para*). Under these conditions often good to excellent yields could be obtained. With less reactive compounds such as aryl chlorides and triflates, pyridine and another additional ligand (2,2'-bipyridine) are usually necessary to stabilise the low-valent cobalt and to improve the overall performance [65]. In general, the direct reaction of organozinc species with electrophiles is quite inefficient without catalyst, therefore various transition metals can be exploited for their successful cross-coupling, such as Pd, Ni, Cu, and Co. In the case of arylzinc species formation using cobalt catalysis, the presence of cobalt(I) complexes produced in the medium was found to effectively catalyse some carbon–carbon or carbon–heteroatom bond forming reactions. However, with arylzinc species synthesised by other methods in different solvents, cross-coupling reactions were also possible adding cobalt salts to the medium.

Main utilisation of cobalt-catalysed cross-coupling reactions involve arylzinc species to create different  $C_{sp}—C_{sp^2}$ ,  $C_{sp^2}—C_{sp^2}$ , and  $C_{sp^2}—C_{sp^3}$  bonds.

#### 5.2.2.1 $C_{sp}—C_{sp^2}/C_{sp}—C_{sp^3}$ Bond Formation

In general, the reaction involving an alkyne moiety as electrophilic partner and an aryl halide as nucleophile has received much less attention than the reverse case when the alkyne derivative was used as nucleophile. The presence of a heteroatom substituent on the triple bond has a strong influence on the alkyne's reactivity, and moreover, palladium was the main catalyst. Although alkynylhalides are less reactive, they were more easily obtainable and therefore convenient reagents for cross-coupling processes. *Kharasch* reported that *Grignard* reagents reacted with haloalkynes under cobalt catalysis in low yields [50]. However, the cobalt-catalysed cross-coupling involving an arylzinc bromide was described just recently (Scheme 5.30) [66]. This reaction tolerated a large number of functional groups and yields ranged from modest to excellent.



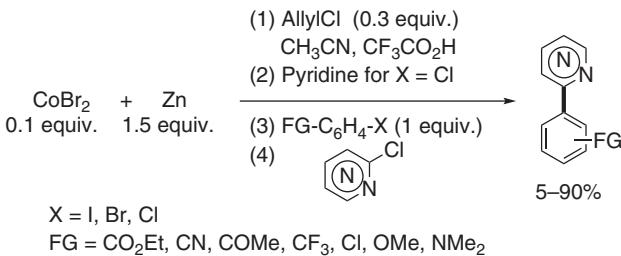
**Scheme 5.30** Cobalt-catalysed cross-coupling reactions of organozinc species with alkynylhalides.

Changing ligand and solvent (dppe in THF instead of 1,10-phenanthroline [phen] in MeCN), this cobalt-catalysed cross-coupling was extended to alkylzinc species allowing the access to unsymmetrical dialkylalkynes. However, in the case of arylzinc reagents, the same cobalt catalyst,  $\text{CoBr}_2(\text{phen})$ , could be used for both the synthesis of the organozinc species and after filtration also in the cross-coupling reaction. In this case, the steric hindrance of the alkyne partner had no influence and the alkyne was the limiting reagent.

### 5.2.2.2 $\text{C}_{\text{sp}^2}-\text{C}_{\text{sp}^2}$ Bond Formation

Although the  $\text{C}_{\text{sp}^2}-\text{C}_{\text{sp}^2}$  cross-couplings are difficult to realise without transition metal in general, the cobalt-catalysed bond formation involving an organozinc species is the most studied case.

Few years ago, *Gosmini* reported in satisfactory yields the first cobalt-catalysed cross-coupling of functionalised aryl halides with heteroaromatic halides such as 2-chloropyrimidines or 2-chloropyrazines via an intermediate arylzinc species [67]. Depending on the nature of substrates, this process allowed the synthesis of a wide range of aryldiazines in a more convenient *Barbier*-type fashion. With the more reactive 2-chloropyrazines, aryl iodides were necessary to conduct the reaction in a *Barbier* fashion whereas with less reactive 2-chloropyrazines, aryl bromides were sufficient (Scheme 5.31).

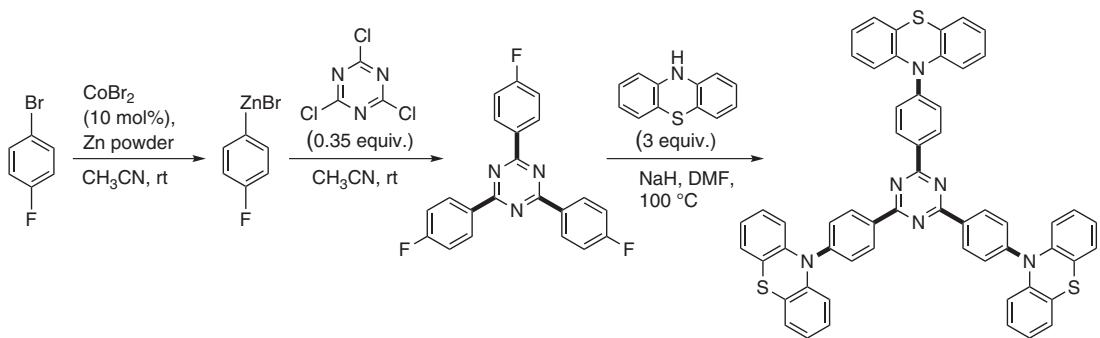


Scheme 5.31 Cobalt-catalysed synthesis of aryldiazines.

In the same way, a variety of functionalised aryl bromides were coupled with 2-chloro-4,6-dimethoxy-1,3,5-triazine in good yields by a one-step procedure via cobalt catalysis [68].

This process could be used to reduce substantially the cost for the synthesis of highly efficient thermally activated delayed fluorescent (TADF) emitters, thanks to the low cost of cobalt employed as catalyst in the synthesis. The corresponding TADF emitter synthesised from (4-fluorophenyl)zinc bromide and trichloro-1,3,5-triazine containing three phenothiazines as donor units and 2,4,6-triphenyl-1,3,5-triazine as the acceptor unit, was obtained in good yield (Scheme 5.32) [69].

This study was extended to the cross-coupling of various functionalised aryl bromides and 2-methylthio-4-chloropyrimidine [70]. The disubstituted pyrimidine was obtained in good yield by increasing the amount of  $\text{CoBr}_2$ . Then, an expedient route to cobalt-catalysed activation of the SMe bond of various methylthio-substituted *N*-heterocycles had been devised. Various symmetrical



**Scheme 5.32** Cobalt-catalysed synthesis of the TADF emitter.

and unsymmetrical 2,4-diarylpyrimidines were isolated in good yields first by reaction with the chlorine and in a second step with the SMe group of the 2-methylthio-4-chloropyrimidine. Different thioether derivatives such as 2-methylthiobenzo[*b*]thiazole could be successfully coupled in a *Barbier*-type procedure with benzylzinc species or in a two-step procedure with arylzinc species (Scheme 5.33).

More recently, *Knochel* reported the cross-coupling of various electron-rich or electron-deficient heteroarylzinc reagents with different *N*-heterocyclic chlorides and bromides as well as halogenated aromatic ketones using a catalytic system consisting of  $\text{CoCl}_2 \cdot 2\text{LiCl}$  and sodium formate as additive, being the key to the success for this transformation. The main effect of  $\text{HCO}_2\text{Na}$  was to considerably reduce the occurrence of side reactions (Scheme 5.34) [71].

Using this method, polyfunctional naphthyridines were prepared from halogenated naphthyridines and aryl- or benzylzinc reagents [72]. Some of them were highly fluorescent with tuneable emission from blue to yellow.

Recently, *Knochel* reported that organozinc pivalates ( $\text{RZnOPiv}$ ) showed a greatly improved air and moisture stability compared with classical organozinc reagents [73]. Consequently, he developed a robust and broadly applicable cobalt-catalysed cross-coupling between functionalised heteroarylzinc pivalates with unsaturated halides such as various electron-deficient aryl and heteroaryl halides or (*E*)- or (*Z*)-bromo- or iodoalkenes (Scheme 5.35) [74]. Interestingly, the yields were higher than with classical zinc species and the retention of configuration was possible with alkenyl compounds. This cobalt-catalysed cross-coupling was also briefly extended to bromoalkynes as coupling partners.

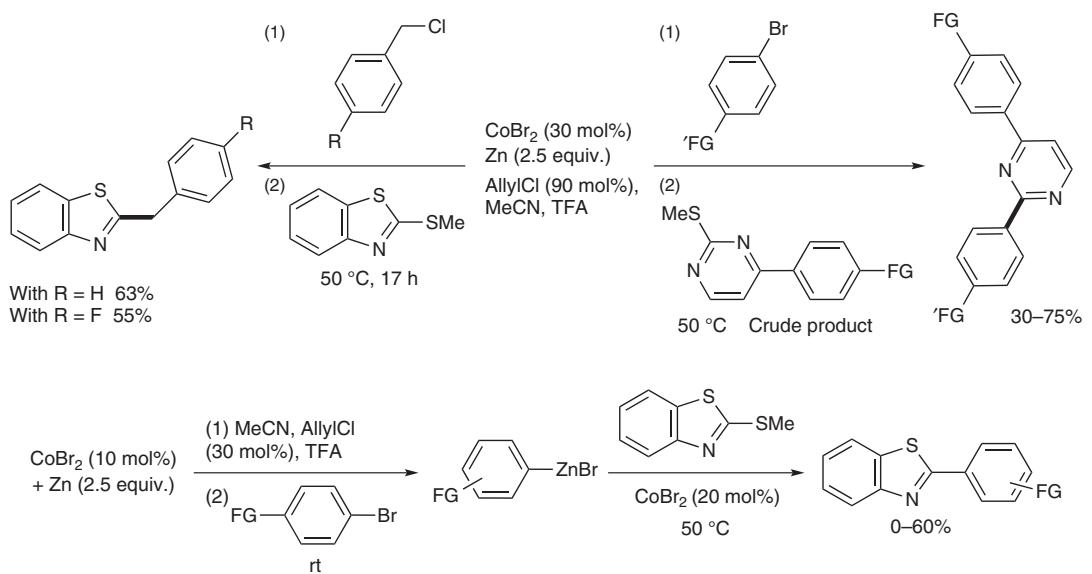
### 5.2.2.3 $\text{C}_{\text{sp}^2}-\text{C}_{\text{sp}^3}$ Bond Formation

Despite the advances of cobalt-catalysed cross-coupling reactions of  $\text{C}_{\text{sp}^2}$ - and  $\text{C}_{\text{sp}^3}$ -halide substrates using *Grignard* reagents, just a few *Negishi*-type cobalt-catalysed  $\text{C}_{\text{sp}^2}-\text{C}_{\text{sp}^3}$  bond connections by cross-coupling processes using organozinc species have been described.

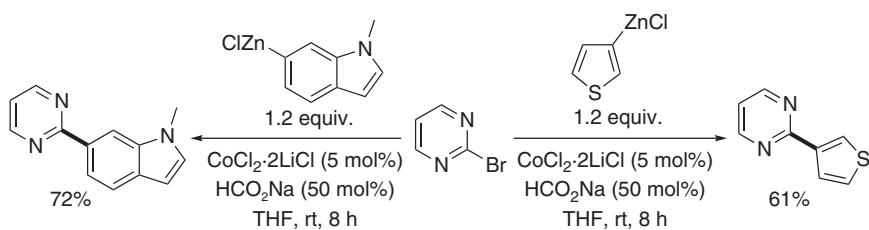
The first one was reported using arylzinc species and reactive alkyl chlorides such as benzyl chlorides in acetonitrile [75]. *Gosmini* showed that arylzinc reagents generated *in situ* via a cobalt-catalysed zinc insertion underwent cross-coupling in a one-pot procedure with benzyl chlorides. However, with the more reactive benzyl chlorides substituted in  $\alpha$ -position, the cross-coupling should be conducted in a two-step procedure to obtain good yields.

*Inoue* also reported the efficient cobalt-catalysed cross-coupling of various arylzinc species with the reactive ethylbromodifluoroacetate at room temperature using a diamine ligand like *N,N,N',N'*-tetramethyl-1,2-diaminocyclohexane (Scheme 5.36) [76].

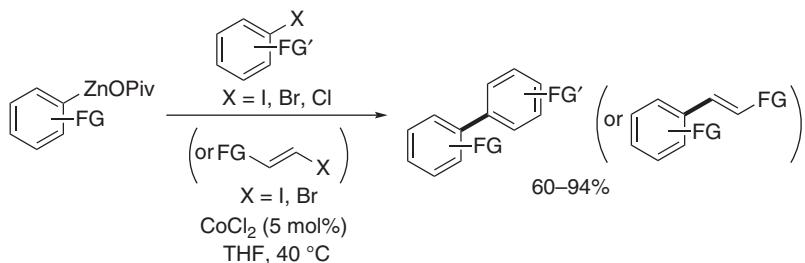
However, with less reactive alkyl halides (bromides or iodides), the use of more reactive diarylzinc species was required. Different diarylzinc reagents were prepared by a direct deprotonation using  $\text{TMP}_2\text{Zn} \cdot 2\text{MgCl}_2 \cdot 2\text{LiCl}$ . This reaction was also compatible with a range of functional groups (e.g.  $\text{COOR}$ ,  $\text{CN}$ ,  $\text{CF}_3$ ,  $\text{F}$ ) and led to the corresponding alkylated product in up to 88% yield using THF-soluble  $\text{CoCl}_2 \cdot 2\text{LiCl}$  and TMEDA as ligand (Scheme 5.37) [77].



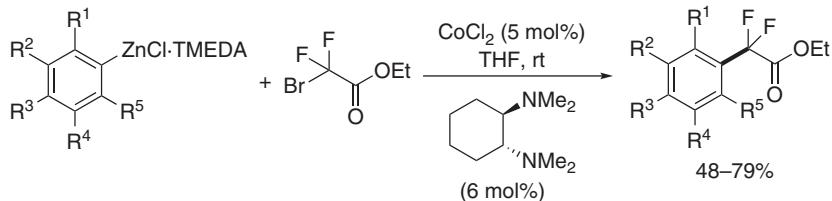
**Scheme 5.33** Cobalt-catalysed C—SMe bond activation of heteroaromatic thioethers.



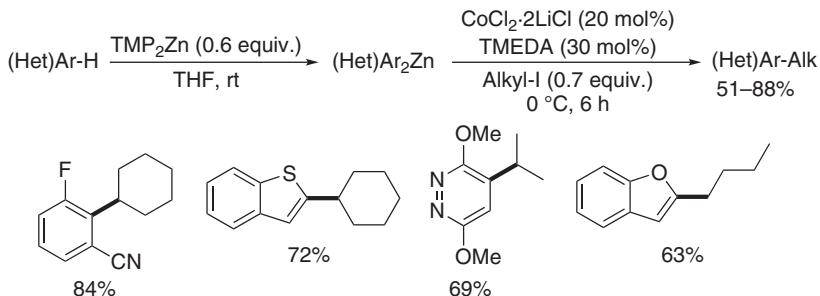
**Scheme 5.34** Cobalt-catalysed cross-coupling of heteroarylzinc reagents with 2-bromopyridine



**Scheme 5.35** Cobalt-catalysed cross-coupling between functionalised aryl- or heteroarylzinc pivalates with unsaturated halides.



**Scheme 5.36** Cobalt-catalysed cross-coupling of various arylzinc species with ethylbromodifluoroacetate.



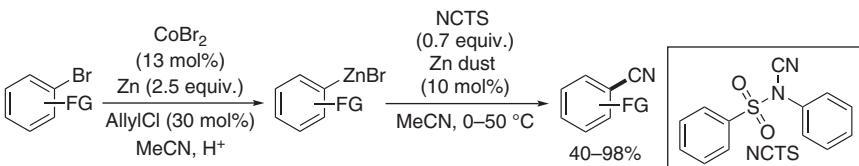
**Scheme 5.37** Cobalt-catalysed cross-coupling of diarylzinc species with alkyl halides.

This cross-coupling reaction involving an alkyl halide could be applied to the alkylation of heterocycles or coumarine [78].

A cobalt-catalysed, isoquinoline-promoted cross-coupling of various benzylzinc chlorides with a wide range of aryl or heteroaryl bromides was reported in good yields [78]. The association of methyl *tert*-butyl ether as co-solvent beside the THF and isoquinoline as additive minimised the formation of homo-coupling products.

#### 5.2.2.4 $C_{sp^2}$ —CN Bond Formation

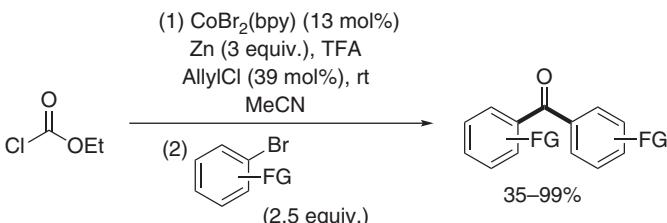
The formation of benzonitriles was performed by a cobalt-catalysed cyanation of arylzinc halides with *N*-cyano-*N*-phenyl-*p*-methylbenzenesulfonamide (NCTS) [79]. This electrophilic cyanation offers an excellent alternative to the drawbacks of the nucleophilic cyanation. The same catalyst (cobalt bromide) was used both for the synthesis of the organozinc species and the cross-coupling reaction (Scheme 5.38). However, in that case a catalytic amount of zinc dust after filtration of the formed organozinc reagent was necessary in the second step to de-coordinate the low-valent cobalt from the cyano group. This method allowed a convenient access to various functionalised benzonitriles and nicely complemented known methodologies using nucleophilic nitrile sources. The yields ranged from moderate to excellent.



**Scheme 5.38** Cobalt-catalysed electrophilic cyanation of arylzinc species with *N*-cyano-*N*-phenyl-*p*-methylbenzenesulfonamide.

#### 5.2.2.5 $C_{sp^2}$ —CO Bond Formation

Functionalised organozinc halides could be efficiently carbonylated under atmospheric pressure in THF/NMP in the presence of cobalt bromide and carbon monoxide leading to polyfunctionalised symmetrical ketones in moderate to good yields [80]. Although many functional groups were tolerated, the handling of toxic carbon monoxide gas was problematic. Then, *Gosmini* described the synthesis of symmetrical diaryl ketones by a cross-coupling reaction between various aryl bromides and ethyl chloroformate in moderate to excellent yields



**Scheme 5.39** Cobalt-catalysed formation of symmetrical diaryl ketones from arylzinc species and ethyl chloroformate.

(Scheme 5.39) [81]. Although the reaction was carried out in a one-pot procedure to increase the yields, an intermediate arylzinc species was involved. This was the first time a chloroformate had been used as a surrogate of carbon monoxide in the synthesis of diaryl ketones.

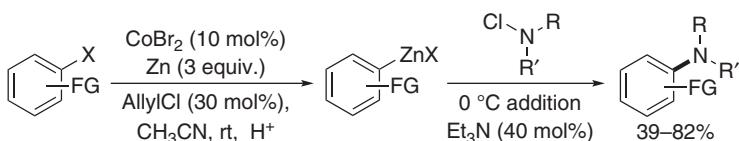
To obtain unsymmetrical ketones, organozinc species also reacted with acyl chloride in a two-step reaction [82] or with anhydride acid in a one-step reaction [83] in the presence of cobalt bromide. The same catalyst participated both in the formation of arylzinc species and the cross-coupling.

### 5.2.3 Carbon–Heteroatom Bond Formation

Few examples of carbon–heteroatom bonds formation were presented with cobalt catalysis and organozinc species.

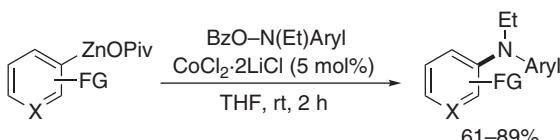
#### 5.2.3.1 C—N Bond Formation

Aromatic C—N bond-forming reactions are important for the synthesis of biologically active substructures and medicinal chemistry targets. The electrophilic amination with diorganozinc species was already reported in the presence of copper or nickel complexes [84]. Moreover, a few years ago, C—N bond formation was also performed without a catalyst by cross-coupling of aniline derivatives and 2-chloropyrimidines in the presence of an arylzinc species as base [85]. However, this approach was limited to 2-chloropyrimidines. Then, a complementary approach involving a variety of cobalt-catalysed arylzinc species formation and their subsequent amination reaction with *N*-chloroamines at room temperature, after filtration of the arylzinc species, was also devised without supplementary catalyst (Scheme 5.40) [86]. In this cross-coupling under mild conditions, triethylamine accelerated the reaction significantly and allowed the isolation of the products in higher yields. Both secondary and tertiary arylamines were obtained in moderate to excellent yields, except for diarylamines.



**Scheme 5.40** Cobalt-catalysed amination reactions using substituted *N*-chloroamines.

This restriction was circumvented using *N*-hydroxylamine benzoates. Then, more recently, cobalt-catalysed electrophilic amination of aryl and heteroarylzinc pivalates was published with this electrophilic amine to furnish the corresponding tertiary arylated or heteroarylated amines in good yields (Scheme 5.41)

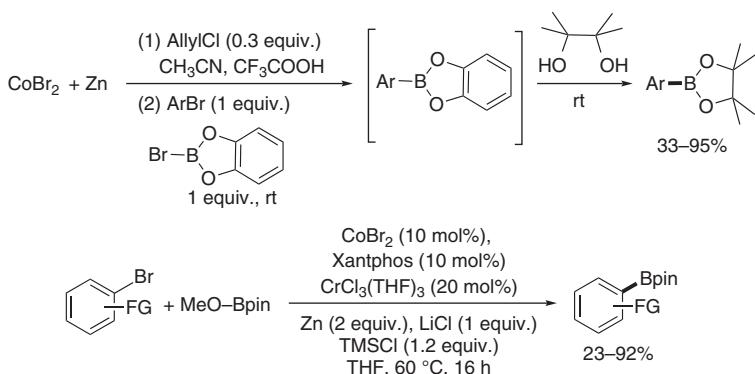


**Scheme 5.41** Cobalt-catalysed synthesis of diaryl- or aryl-heteroarylamines.

[87]. The application of *O*-benzoylhydroxyaniline allowed access to diaryl- or aryl–heteroaryl amines under very mild conditions, compared with the method using unstable *N*-chloroanilines.

### 5.2.3.2 C—B Bond Formation

Arylboronates, which could be isolated and stored, attracted great attention due to their versatile functional group tolerance. However, they were generally obtained from arylmagnesium or -lithium reagents, which limited the scope because of their incompatibility with sensitive functionalities. To avoid this drawback, alternative synthetic methodologies are highly recommended notably from arylzinc species. Therefore, cobalt-catalysed coupling reactions of arylzinc species with halogenocatecholborane [88] or MeOB(OR)<sub>2</sub> [89] were developed, respectively, without or with Xantphos as a ligand. Various functionalised arylboronates were obtained in moderate to excellent yields by one-step chemical procedure from corresponding bromides via an intermediate arylzinc species (Scheme 5.42). The authors suggested an aryl chromium species as a key intermediate in the borylation in presence of cobalt bromide and chromium. This arylchromium(II) species seem to trigger the borylation step.



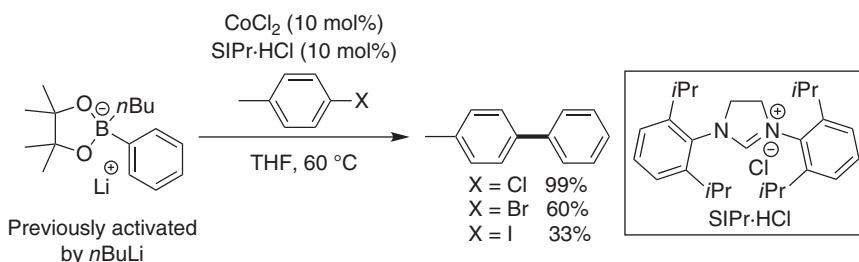
Scheme 5.42 Cobalt-catalysed synthesis of arylboronates.

### 5.2.4 Cobalt-Catalysed Coupling Reactions with Organoboron Reagents

Organoboron reagents are widely available, relatively air- and moisture-stable, and eco-friendly compounds, which allow mild reaction conditions to operate, making them convenient coupling partners compared with the significantly more reactive but also delicate to handle *Grignard* reagents or organozinc reagents. Therefore, very recently, significant efforts were dedicated to develop cobalt-catalysed *Suzuki–Miyaura*-type cross-coupling reactions.

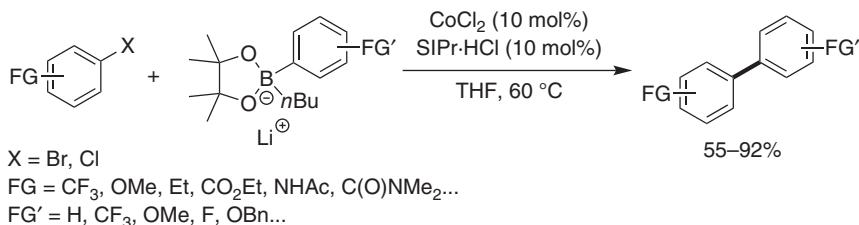
In 2017, *Bedford* released a report on quite successful cobalt-catalysed *Suzuki–Miyaura* coupling reactions between aryl chlorides and bromides and activated arylboronic esters [90]. To do so, he developed a catalytic system, which involved  $\text{CoCl}_2$  with 1,3-bis(2,6-diisopropylphenyl)-imidazolinium

chloride ( $\text{SiPr}\cdot\text{HCl}$ ) as ligand and arylboronic esters activated by  $n\text{BuLi}$  under an inert atmosphere. Investigating the scope of the reaction, he interestingly noticed that many aryl chlorides gave better results compared with their homologous aryl bromides and iodides (Scheme 5.43), which was in contrast with palladium-catalysed *Suzuki–Miyaura* cross-coupling reactions.



**Scheme 5.43** Comparison of the reactivity of various aryl halides.

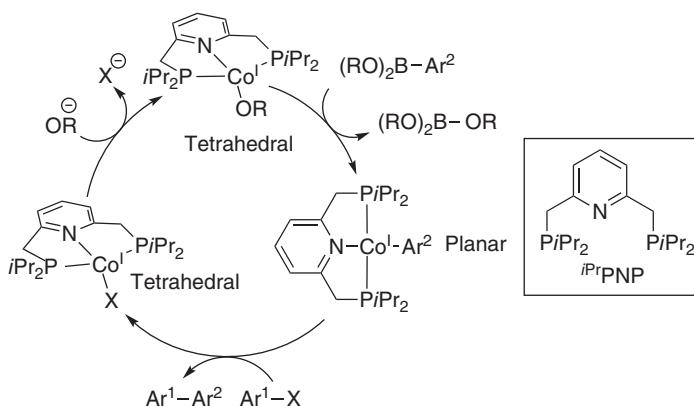
From the scope study, it could be concluded that a broad range of aryl halides react efficiently, allowing also moderate steric hindrance on those substrates. The reaction was quite chemoselective since ester, tertiary amine, amide, or trifluoromethyl groups were tolerated. However, nitro, cyano, aldehyde, and ketone groups gave low yields as well as heterocyclic halides due to the difficulty to isolate the cross-coupling product from the dimer product of the nucleophile (Scheme 5.44).



**Scheme 5.44** Cobalt-catalysed *Suzuki–Miyaura* coupling of aryl chlorides and bromides with activated arylboronic esters.

Finally, as for preliminary mechanistic studies, thanks to nuclear magnetic resonance (NMR) spectroscopy, the authors proved that the cobalt/NHC complex was reduced by the organoborate to a zero-valent cobalt complex [91]. Although, this transformation was quite efficient, the necessity of activating the organoboron species somehow cancelled the advantages of using mild reagents like organoboron instead of organomagnesium or organozinc reagents.

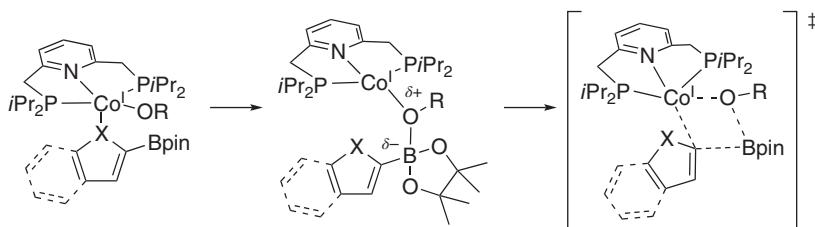
In 2016, Chirik, by investigating the elementary steps of the catalytic reaction (Scheme 5.45) through stoichiometric reactions, could draw several conclusions leading to the most favourable conditions to perform the first cobalt-catalysed *Suzuki–Miyaura*-type coupling with boronic esters [91].



**Scheme 5.45** Plausible catalytic cycle for cobalt-catalysed Suzuki–Miyaura coupling.

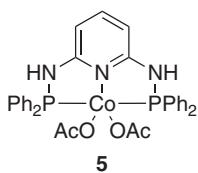
First, the authors showed the necessity of the flexible diisopropyl-substituted bis(methylphosphino)pyridine pincer ligand (*i*PrPNP) (Scheme 5.45) in order to be able to switch between both tetrahedral and planar configuration, as well as to favour the two-electron oxidative addition, needed to perform the catalytic reaction.

Moreover, implemented by kinetic studies, they displayed that the presence of a heteroatom with a lone pair on the organoboron derivative was crucial to achieve the coupling and hypothesised that an initial coordination of the lone pair to cobalt promoted the transmetallation step (Scheme 5.46).



**Scheme 5.46** Hypothesised coordination of the lone pair to promote transmetallation step.

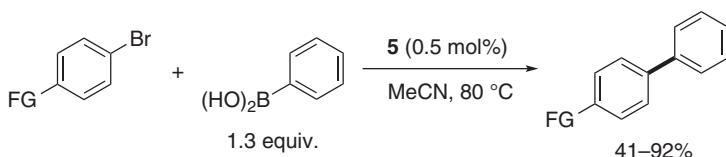
The authors then demonstrated that the use of NaOCH(Ph)Me as a base was optimal since it facilitated the salt metathesis from the (*i*PrPNP)CoCl catalyst precursor, leading to a comparably stable complex and showing good reactivity for the subsequent transmetallation step. Finally, the same group also made the observation that aryl triflates were better suited than aryl halides to perform the reaction and that heating to 60 °C was essential for catalytic turnover. Although, the scope of the reaction seemed quite limited and specific for both substrates, especially with the need of a lone pair on the neutral organoboron derivative, the authors presumed that modifications on the ligand could overcome some difficulties.



**Figure 5.2** Cobalt-pincer complex used as catalyst in the reaction studied.

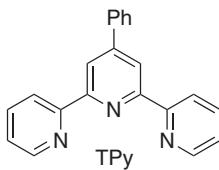
By using a comparable ligand approach, *Bhat* concurrently developed a cobalt-catalysed *Suzuki–Miyaura* cross-coupling with a  $\text{Co}(\text{OAc})_2/\text{PNP}$ -based pincer complex **5** (Figure 5.2) [92].

A large array of aryl halides could be cross-coupled with phenyl boronic acid. As a rule, electron-withdrawing groups accelerated the reactions, whereas electron-donating groups led to lower conversions (Scheme 5.47).



FG = CN, OMe, Me, OH, C(O)H, C(O)Me...

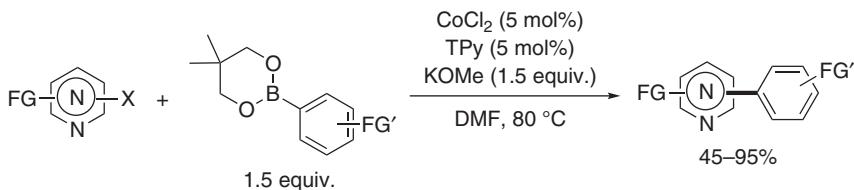
**Scheme 5.47** Cobalt-catalysed *Suzuki–Miyaura* cross-coupling catalysed by  $\text{Co}(\text{OAc})_2/\text{PNP}$ -based pincer complex **5**.



**Figure 5.3** Structure of the ligand 4'-phenyl-2,2':6',2''-terpyridine (TPy).

Finally, very recently, *Duong* reported a successful cobalt-catalysed *Suzuki–Miyaura* cross-coupling reaction between aryl- and heteroaryl halides and arylboronic esters [93]. The catalytic system involved  $\text{CoCl}_2$  as a catalyst and 4'-phenyl-2,2':6',2''-terpyridine (TPy) (Figure 5.3) as a ligand.

A broad range of *N*-heteroaryl halides and arylboronic esters reacted smoothly allowing moderate steric hindrance on both coupling partners (Scheme 5.48).



X = Br, Cl

FG = H, Cl, Br, Me, OMe, CF3, CO2Me...

FG' = H, OMe, CF3

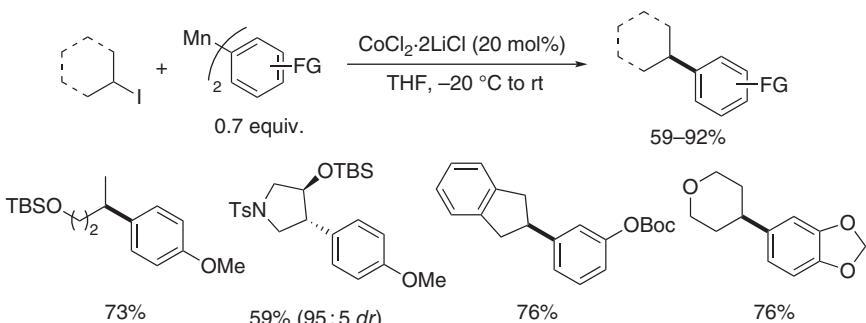
**Scheme 5.48** Cobalt-catalysed *Suzuki–Miyaura* coupling between various *N*-heteroaryl halides and boronic esters.

On the other hand, aryl halides were less reactive. Finally, thanks to a preliminary mechanistic study, the authors hypothesised on the reduction of cobalt(II) by the organoborate species formed *in situ*, and the resulting formation of a

catalytically active cobalt(I)-complex, following a similar catalytic cycle as the one proposed by Chirik [91].

### 5.3 Cobalt-Catalysed Coupling Reactions with Organomanganese Reagents

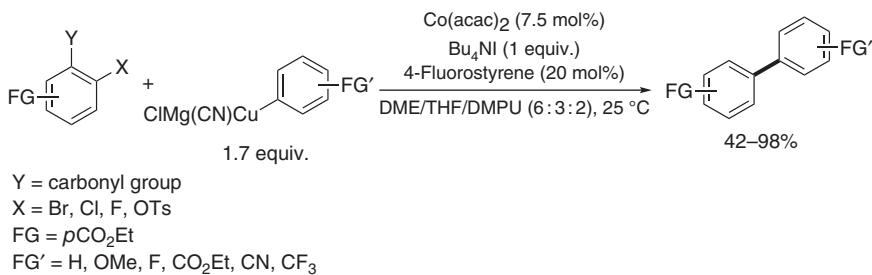
Recently, *Knochel* has reported on the cobalt-catalysed  $C_{sp^2}-C_{sp^3}$  cross-coupling reaction of diarylmanganese reagents with secondary alkyl iodides [94]. Although primary and tertiary alkyl iodides did not lead to good conversion and the use of alkyl bromides or chlorides was not mentioned, a large number of secondary iodides reacted smoothly with a broad range of diarylmanganese reagents bearing both electro-donating or -withdrawing groups (Scheme 5.49).



**Scheme 5.49** Cobalt-catalysed cross-coupling reaction between diarylmanganese reagents and secondary alkyl iodides.

### 5.4 Cobalt-Catalysed Coupling Reactions with Copper Reagents

*Knochel* reported a cobalt-catalysed cross-coupling of aryl- and heteroaryl copper reagents with aryl bromides and chlorides [95] on one hand and aryl fluorides and tosylates [96] on the other hand to form  $C_{sp^2}-C_{sp^2}$  bonds. For a complete conversion of the starting halide, both  $Bu_4NI$  (1 equiv.) and 4-fluorostyrene (20 mol%) were required as additives. Indeed, in previous works, *Knochel* showed the coordination of the double bond of the 4-fluorostyrene to the metal centre, removing electron density from it and therefore facilitated the reductive-elimination step of the cross-coupling sequence [97]. To perform the reaction faster, it was necessary to use a mixture of THF/DME/DMPU instead of pure THF as a solvent (15 minutes instead of 21 hours reaction time). However, for this reaction to perform, it seemed necessary, that aryl halides or pseudo-halides involved in the coupling reaction were decorated with a keto, ester, or aldehyde group in the *ortho*-position since *meta*- and *para*-substituted aryl halides led to lower yields (Scheme 5.50). This might be due to a chelation effect, which could enhance the reactivity and help performing the coupling.



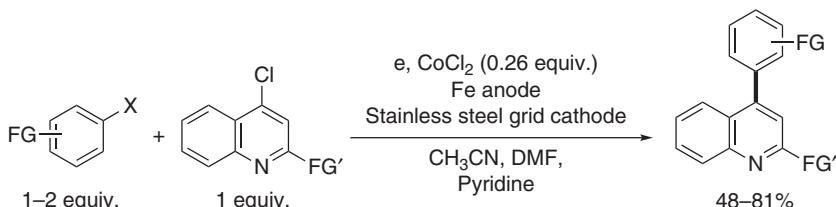
**Scheme 5.50** Cobalt-catalysed cross-coupling between aryl- and heteroaryl copper reagents and aryl halides and pseudo-halides.

## 5.5 Cobalt-Catalysed Reductive Cross-coupling Reactions

As previously reported, most approaches to form C—C bonds require the use of an organic halide or pseudo-halide in conjunction with reactive organometallic species such as organozinc or *Grignard* reagents, as demonstrated impressively for the cobalt catalysis. However, C—C bond formation reactions mediated by an organometallic catalyst instead of a stoichiometric component present a powerful alternative especially with catalytic organocobalt reagents. Actually, the preliminary preparation of organometallic compounds can be challenging, especially when the organic halide bears a reactive functional group. Hence, electrochemical and thereafter, chemical cobalt-catalysed processes have been developed to avoid the organometallic step preparation allowing the presence of sensitive functional groups. These reactions employ  $\text{C}_{\text{sp}}^2$ -bonded electrophiles such as aryl and vinyl groups and  $\text{C}_{\text{sp}}^3$ -bonded electrophiles such as alkyl, benzyl, and allyl compounds.

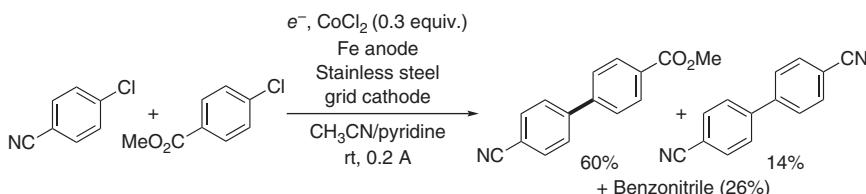
### 5.5.1 $\text{C}_{\text{sp}}^2$ — $\text{C}_{\text{sp}}^2$ Bond Formation

The first cobalt-catalysed reductive couplings were performed by electrosynthesis using the sacrificial anode process in order to synthesise biaryl compounds at the beginning of this century. Early on, various 4-phenylquinoline derivatives were synthesised in a one-compartment cell fitted with an iron anode, in good to high yield starting from different functionalised aryl halides (Scheme 5.51) [98].



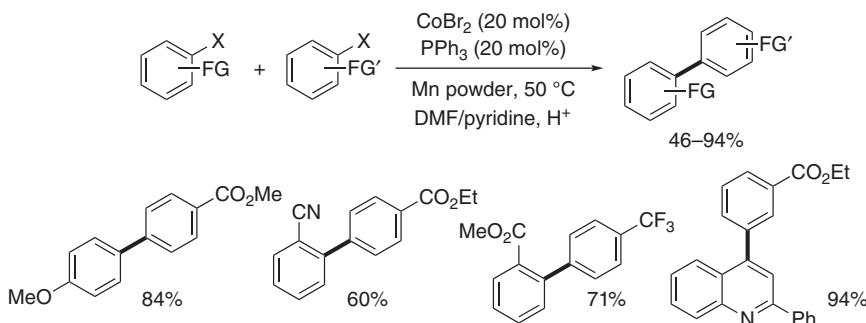
**Scheme 5.51** Synthesis of 4-phenylquinolines derivatives by electrosynthesis.

One year later, this reaction was extended to the synthesis of unsymmetrical biaryls by electro-reductive cobalt-catalysed cross-coupling of two different aryl halides in good to excellent yields (Scheme 5.52) [99]. This coupling reaction was compatible with various electron-donating or electron-withdrawing substituents in *ortho*-, *meta*-, and *para*-position from aryl iodides, bromides and chlorides, and even 3-bromothiophene. In this reaction, the more reactive aromatic halide was applied in excess.



**Scheme 5.52** Cobalt-catalysed synthesis of unsymmetrical biaryls by electrosynthesis.

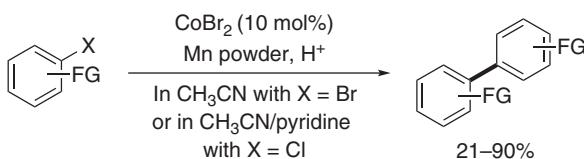
Although this transformation was efficient with aryl bromides, no reaction was observed with aryl pseudo-halides, and lower yields were obtained from aryl chlorides. Moreover, a large quantity of the catalyst was required to accomplish maximum yields. Therefore, an expedient chemical route to functionalised biaryl and heteroaryl–aryl compounds had been devised from halides to triflates with a very simple catalytic system, relying on the use of cobalt halide ligated by triphenylphosphine as a catalyst in a mixture of DMF/pyridine (Scheme 5.53). A broad range of biaryl compounds was synthesised in satisfactory to high yields under simple reaction conditions. Mechanistic studies showed that a radical pathway could be ruled out [100].



**Scheme 5.53** Cobalt-catalysed formation of unsymmetrical biaryls.

A versatile simplified process was issued to synthesise a broad spectrum of symmetrical biaryls bearing a wide variety of functional groups in satisfactory to high yields and was compared favourably with other transition metal-based catalysts (Scheme 5.54) [101].

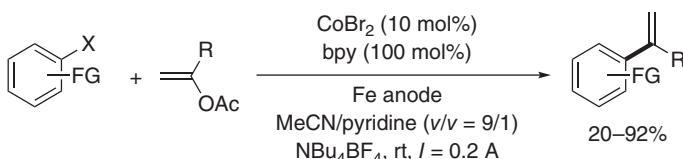
The cross-coupling with vinyl compounds was also reported first by cobalt-catalysed electrochemical vinylation of various functionalised aryl or heteroaryl halides ( $X = Br$  or  $Cl$ ) with different vinyl acetates in order to



$\text{FG} = \text{CO}_2\text{Et}, \text{MeCO}, \text{CN}, \text{CF}_3, \text{F}, \text{Cl}, \text{H}, \text{Me}, \text{MeO}, \text{NMe}_2$

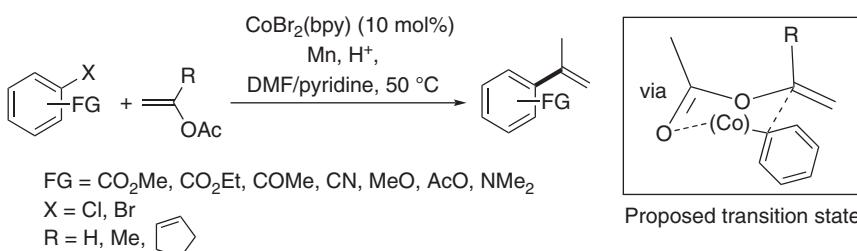
**Scheme 5.54** Cobalt-catalysed reductive cross-coupling of symmetrical biaryls.

form  $\alpha$ -substituted styrene derivatives. In this process a combination of  $\text{CoBr}_2$  and 2,2'-bipyridine appeared to be the most efficient catalyst. However, a stoichiometric amount of 2,2'-bipyridine and the use of a consumable iron anode was essential for the success of this reaction (Scheme 5.55) [102].



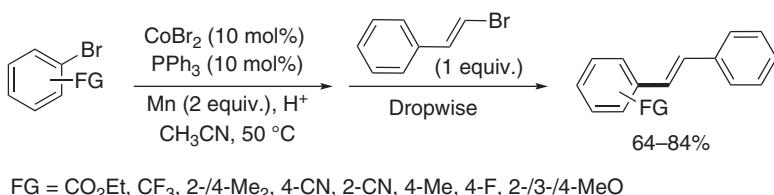
**Scheme 5.55** Cobalt-catalysed electrochemical vinylation of various heteroaryl halides with vinyl acetates.

Later, this reaction was performed by a pure chemical process. Instead of electricity, cobalt was reduced by elemental manganese in DMF/pyridine requiring only a catalytic amount of 2,2'-bipyridine (Scheme 5.56). Moderate to good yields of styrene derivatives were isolated from aryl bromides and chlorides bearing electron-donating or electron-withdrawing groups. With substituted vinyl acetate, the involvement of a cyclic six-membered transition state, in which the aryl group was well positioned to be added on the most substituted carbon atom of the double bond was proposed to explain the transfer of the aryl moiety onto the carbon attached to the acetate group [103].



**Scheme 5.56** Cobalt-catalysed chemical vinylation with vinyl acetates.

Similarly, a cobalt-catalysed vinylation of aromatic halides using very reactive  $\beta$ -halostyrenes had been developed in order to form functionalised stilbenes. In this procedure, the dropwise addition of  $\beta$ -halostyrenes ( $\text{X} = \text{Br}$  or  $\text{Cl}$ ) in the reaction mixture was crucial to limit its dimerisation. The total retention of the double bond was preserved (Scheme 5.57) [104].

**Scheme 5.57** Cobalt-catalysed chemical vinylation with halostyrenes.

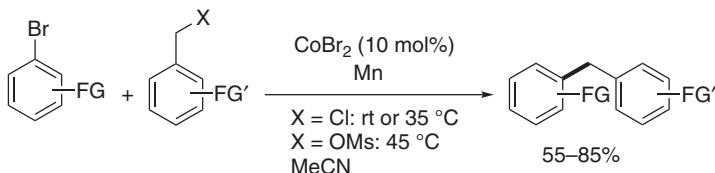
In all these C<sub>sp<sup>2</sup></sub>—C<sub>sp<sup>3</sup></sub> bond-forming processes, the absence of both organomanganese and free radical intermediates were proven by scavenging experiments and some density functional theory (DFT) studies.

### 5.5.2 C<sub>sp<sup>2</sup></sub>—C<sub>sp<sup>3</sup></sub> Bond Formation

The reductive cobalt-catalysed cross-coupling reactions involving two electrophiles such as C<sub>sp<sup>2</sup>-</sub> and C<sub>sp<sup>3</sup></sub>-hybridised carbons were reported with aryl and vinyl compounds and reactive alkyl compounds such as benzyl or allyl reagents.

### 5.5.3 Couplings with Benzylic Compounds

Diarylmethane motifs are ubiquitous in many pharmacologically active compounds, agrochemical and supramolecular sub-units. Approaches for their synthesis devoid of pre-formed organometallic reagents are of great interest for the preparative chemist. Thus recently, *Gosmini* reported the cobalt-catalysed cross-coupling involving various functionalised aryl bromides and benzyl chlorides (Scheme 5.58) [105]. Nevertheless, the availability, low toxicity, low price, and natural abundance of benzyl alcohols was a strong driving force to use these compounds in cross-coupling reactions. Consequently, *Weix* introduced the synthesis of various diarylmethanes, thanks to a Ni/Co catalysis approach, in which the Co-catalyst, the cobalt phthalocyanide, formed selectively benzyl radicals from benzyl mesylates [106]. Yet, this elegant method required both nickel and cobalt catalysts. To avoid the use of toxic nickel, a very simple cobalt-catalysed formation of functionalised diarylmethanes from benzyl mesylates and heteroaryl halides was also discovered. Yields were moderate to

**Scheme 5.58** Cobalt-catalysed formation of diarylmethanes from benzyl chlorides or mesylates.

excellent despite the position of the substituent in the coupling partner. This procedure could also be conducted with  $\alpha$ -substituted benzyl in a two-step manner and directly from the benzyl alcohol [107].

An efficient and simple cobalt-catalysed reductive cross-coupling involving benzyl chloride was also reported with styryl halides as coupling partners to afford 1,3-diarylpropenes in a stereoselective manner [108]. This reaction proceeded smoothly in the presence of the preformed  $\text{CoBr}_2(\text{PPh}_3)_2$  with NaI as an additive in acetonitrile with a broad scope of functionalised substrates and the retention of the double-bond configuration.

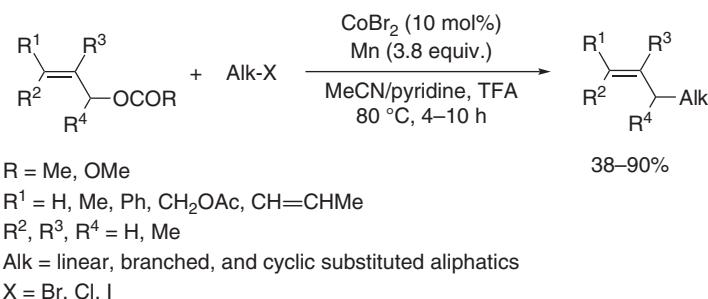
In these reactions involving a benzyl compound, the proposed mechanism suggested the reduction of  $\text{Co}^{\text{II}}$  in  $\text{Co}^{\text{I}}$  by manganese. The latter gave a  $\text{Co}^{\text{III}}$  intermediate by oxidative addition of aryl halide was reduced another time by manganese to a  $\text{Co}^{\text{II}}$  derivative that was able to react with the radical benzylic species yielding another  $\text{Co}^{\text{II}}$  species. Then, the coupling product was released by reductive elimination regenerating the active catalyst.

#### 5.5.4 Couplings with Allylic Acetates

The aryl–allyl skeleton is also a common structure of many natural products and can be synthesised by cobalt-catalysed reductive coupling between allyl carboxylates (carbonates or acetates) and aryl or heteroaryl halides. First of all, an electrochemical protocol was described in acetonitrile/pyridine solvent mixture in the presence of cobalt(II) bromide without ligand [109]. This reaction was performed in an undivided cell fitted with an iron anode at constant current ( $I = 0.2 \text{ A}$ ) at  $50^\circ\text{C}$ . Various aryl–allyl products were obtained in good yields. One year later, the transposition of this electrochemical allylation was developed by a pure chemical process using Zn as reducing metal in the case of aryl bromides in acetonitrile. In the case of less reactive aryl chlorides, the reaction was carried out in acetonitrile/pyridine with Mn as reducing metal in the presence of a stoichiometric amount of iron bromide at  $50^\circ\text{C}$  instead of room temperature. Good yields were obtained with electron-donating or electron-withdrawing substituents at the aromatic moiety and non-substituted acetates [110]. The complex reaction mechanism of the process was studied by electrochemical behaviour of cobalt complexes in the presence of the starting reagents [111].

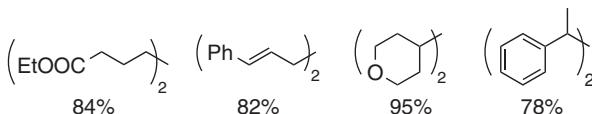
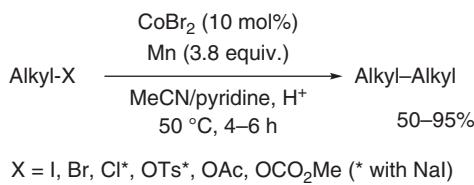
#### 5.5.5 $\text{C}_{\text{sp}^3}$ — $\text{C}_{\text{sp}^3}$ Carbon Bond Forming Reactions

A new and general method for the direct-catalysed reductive cross-coupling of allylic acetates and carbonates with alkyl halides also comprised a  $\text{CoBr}_2/\text{Mn}$  catalytic system without ligand (Scheme 5.59) [112]. This method was very straightforward and efficient for a large variety of primary, secondary, and even tertiary alkyl halides with substituted allylic compounds as coupling partners. Depending on the nature of the alkyl halide, allylic acetates or carbonates could be used affording the linear product as the major or the sole product in the case of substituted allyl acetates. From a mechanistic point of view, initial reduction of the  $\text{Co}^{\text{II}}$  precatalyst furnished a catalytically active low-valent cobalt species.

**Scheme 5.59** Cobalt-catalysed allylation of alkyl halides.

Subsequent oxidative addition to the allyl acetate formed an allyl cobalt intermediate that was again subjected to reduction by manganese dust. This allyl cobalt complex reacted with an alkyl halide to form an allyl–alkyl–cobalt complex through the formation of an alkyl radical. Then reductive elimination occurred to furnish the cross-coupling product along with the regeneration of the active species.

Although the dimerisation of alkene, alkyne, and aryl compounds has been well developed, the dimerisation of alkyl compounds has been investigated relatively poor. As a result, a novel protocol for cobalt-catalysed  $C_{sp^3}$ – $C_{sp^3}$  homo-coupling has been developed (Scheme 5.60) [113]. Good to excellent yields were obtained with a large variety of functionalised alkyl compounds (I, Br, Cl, OTs, OAc, OCOMe) in acetonitrile/pyridine at 50 °C without ligand. With unactivated alkyl compounds such as alkyl chlorides or tosylates, the addition of sodium iodide was required as reported in some nickel-catalysed reductive cross-couplings [114].

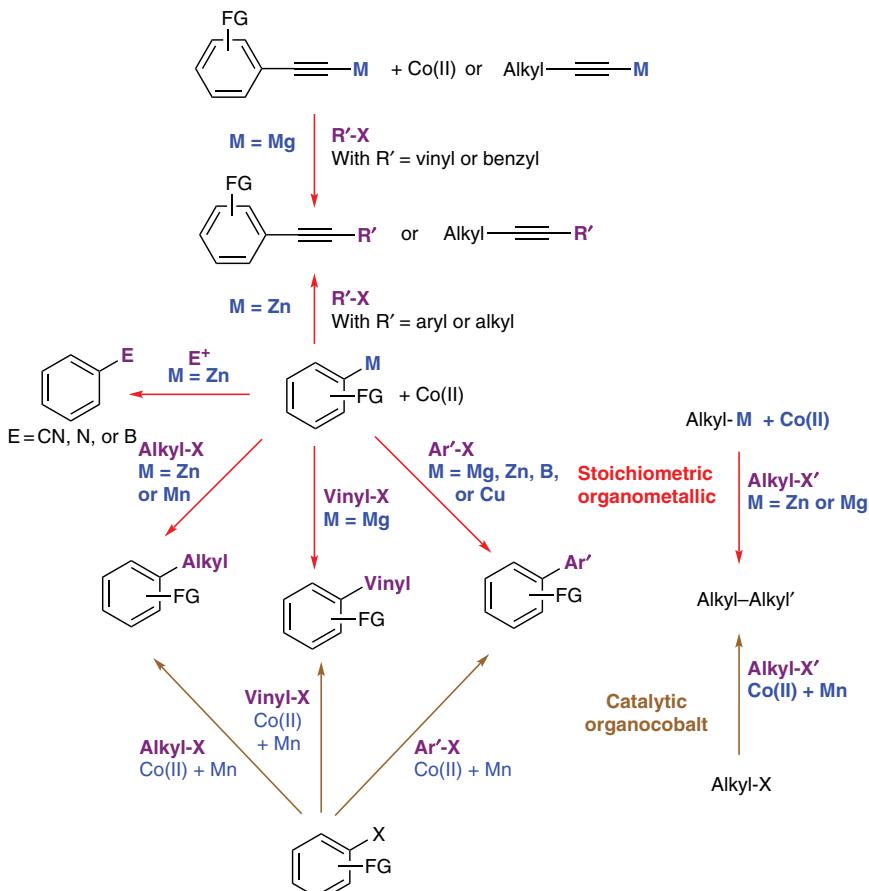
**Scheme 5.60** Cobalt-catalysed dimerisation of alkyl compounds.

As already reported with alkyl compounds, some experimental evidence existed to demonstrate that a radical intermediate was generated in the medium.

In conclusion, various efficient reductive cross-coupling reactions have been presented using the simple, inexpensive, and environment-friendly low-valent cobalt complexes as catalyst. These different cobalt-based catalytic systems were complementary and compare favourably to coupling methods including the conventional expensive palladium and toxic nickel catalysts.

## 5.6 Overview and Perspectives

This chapter deals with low-valent cobalt-catalysed cross-couplings involving stoichiometric or catalytic organometallic species. Mainly, metallated aromatic compounds such as *Grignard*, organozinc, organoboron, organocupper, and organomanganese reagents are involved in the cross-coupling reactions. More recently, alkyl compounds including challenging alkyl electrophiles bearing  $\beta$ -hydrogen atoms have emerged as promising candidates to complement and extend these reactions. Moreover, direct approaches for cobalt-catalysed cross-coupling that does not rely on the utilisation of a preformed organometallic were also develop mainly from corresponding halides as coupling partners.



In the future, other partners such as C–O electrophiles have recently shown to be powerful alternative to overcome drawbacks associated to halogenated wastes and should be developed. Similarly, efforts to activate new feedstocks such as amine derivatives should be made for cobalt-catalysed cross-couplings.

Furthermore, another challenge is to develop new reductive cross-coupling methods decreasing the amount of metal such as manganese using other reducing compounds or going back to electrosynthesis. Additional development will probably concern the extension of the existing and novel arsenal of couplings to enantioselective connections.

## 5.7 Abbreviations

Ac	acetyl
acac	acetylacetone
Alk	alkyl
Ar	aryl
Bn	benzyl
Boc	<i>tert</i> -butyloxycarbonyl
Bu	butyl
Cy	cyclohexyl
Dec	decyl
DME	1,2-dimethoxyethane
DMF	<i>N,N</i> -dimethylformamide
DMPU	<i>N,N'</i> -dimethylpropylene urea
dppe	1,2-bis(diphenylphosphino)ethane
dppp	1,3-bis(diphenylphosphino)propane
<i>dr</i>	diastereomeric ratio
<i>ee</i>	enantiomeric excess
equiv.	equivalent
Et	ethyl
FG	functional group
h	hour
Hex	hexyl
HMTA	hexamethylenetetramine
<i>i</i>	<i>iso</i>
IMes	1,3-bis(2,4,6-trimethylphenyl)-imidazolium
IPr	1,3-bis(2,6-diisopropylphenyl)-imidazolium
<i>m</i>	<i>meta</i>
Me	methyl
MeCN	acetonitrile
MeTHF	2-methyltetrahydrofuran
min	minute
<i>n</i>	normal
NHC	<i>N</i> -heterocyclic carbene
NMP	<i>N</i> -methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
<i>o</i>	<i>ortho</i>
Oct	octyl
<i>p</i>	<i>para</i>
Ph	phenyl

phen	1,10-phenanthroline
pin	pinacol
PNP	bis(methylphosphino)pyridine
Pr	propyl
rt	room temperature
SIPr	1,3-bis(2,6-diisopropylphenyl)-imidazolinium
T	temperature
t	tertiary
TBS	<i>tert</i> -butyldimethylsilyl
Tf	triflyl or trifluoromethanesulfonyl
THF	tetrahydrofuran
THP	tetrahydropyranyl
TMEDA	<i>N,N,N',N'</i> -tetramethylenediamine
TMPDA	<i>N,N,N',N'</i> -tetramethylpropylene-1,3-diamine
TMS	trimethylsilyl
TPy	4'-phenyl-2,2':6',2''-terpyridine
Ts	tosyl or <i>para</i> -toluenesulfonyl

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# 6

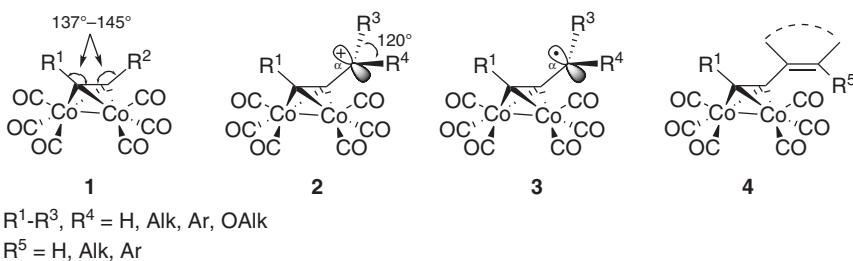
## Ionic and Radical Reactions of $\pi$ -Bonded Cobalt Complexes

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### 6.1 Introduction

In the last several decades, organometallic chemistry has drastically changed the landscape of organic chemistry by enabling conceptually novel reactions that could not have been carried out in a purely organic setting, by achieving the levels of stereocontrol that has been unheard of in non-metal environments, and by isolating and characterising reactive intermediates that have long been known to be transient in nature, and observable only spectrally at low temperatures [1]. Among the two main types of chemical bonding between an organic entity and a transition metal – sigma( $\sigma$ ) and pi( $\pi$ ) –, the latter is the focal point of this account [1, 2]. Chronologically, chemistry of  $\pi$ -complexes has advanced through three developmental phases, with *phase I* being entirely devoted to understanding the nature of bonding between unsaturated organic ligands and transition metals in various oxidation states, establishing the nature of electronic communication between the “matching” unsaturated ligands and d-orbitals in transition metals, and structurally characterising said complexes by the plethora of analytical methods, including X-ray crystallography [1]. This knowledge-accumulation period has paved way for exploiting a newly discovered ability of transition metals to go beyond the carbon atoms directly involved in  $\pi$ -bonding and electronically stabilising the reactive intermediates such as carbocations, or carbanions, located  $\alpha$  to the metal core (*phase II*) [1–3]. The ferrocenyl cation [4] is the case study, which became an archetype for an array of transition metal-stabilised carbocations, such as alkyne–cobalt, 1,3-diene–iron, arene–chromium, and alkyne–molybdenum complexes [1, 3, 5]. Subsequently, *phase II* enabled the commencement of the next stage (*phase III*), wherein the  $\pi$ -bonded transition metal cores were successfully exploited for achieving high regio-, chemo-, diastereo-, and enantioselectivities in C–C and C–X (O, N, P, S) bond formation reactions, both in inter- and intramolecular settings, [1, 3, 5] and also for applying the newly acquired synthetic arsenal for

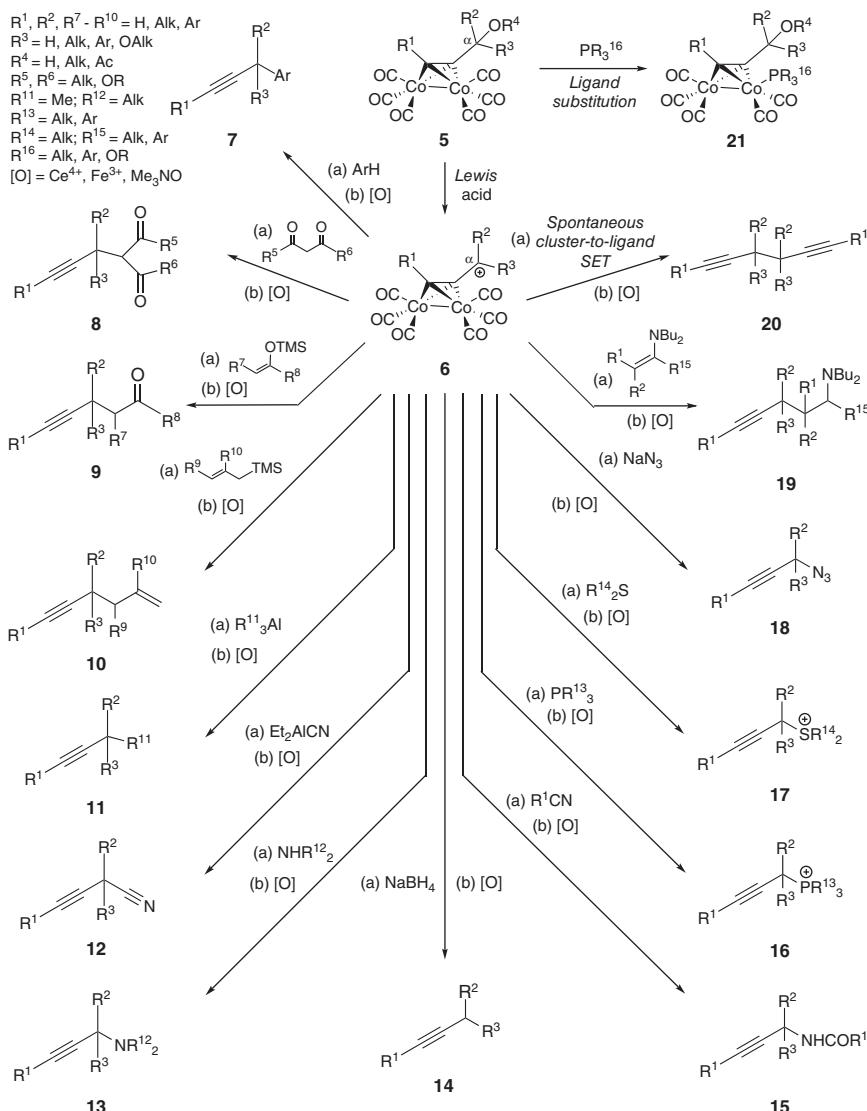


**Figure 6.1** Dinuclear,  $\pi$ -bonded cobalt–alkyne complexes and reactive intermediates.

targeted syntheses. This chapter focuses on electrophilic and radical reactions of pre-isolated, structurally characterised  $\pi$ -bonded dinuclear cobalt(0)-complexes with unsaturated ligands such as alkynes and their structural analogues of a higher level of unsaturation such as 1,3-enynes. The transient, *in situ*-generated  $\pi$ -complexes that are known intermediates in catalytic reactions promoted by cobalt derivatives, such as  $\text{CpCo}(\text{CO})_2$ , [6] will remain beyond the scope of discussion, as well as the Pauson–Khand reaction given the number of excellent reviews already reported, including chapter 8 in this book [7]. Chronologically, the first  $\text{Co}_2(\text{CO})_6$ -alkyne complex was synthesised by the interaction of acetylene with dicobaltoctacarbonyl, [8] thus opening the floodgate to the synthesis, structural, and spectral characterisation of functionally diverse cobalt–alkyne complexes (**1**, Figure 6.1) [3a, b, 5a, b, 9]. The notable bending of the otherwise linear acetylenic moiety is a reflection of  $\pi$ -bonding, [2] effectively transforming the carbon–carbon triple bond into a pseudo-double bond [3a, b, 9]. The first cobalt-complexed propargyl cation (**2**) was isolated in 1977 [10] with its structure being studied by nuclear magnetic resonance (NMR), [10, 11] and, due to its poor crystallinity, resolved by X-ray crystallography only 21 years later [12]. The triple bond preserves the bent geometry ( $135.5^\circ$ ,  $135.9^\circ$ ), the  $\alpha$  carbon atom maintains nearly ideal bond angles around the cationic centre ( $118.6\text{--}120.9^\circ$ ), and noticeably shifts towards one of the cobalt atoms (up to  $0.38\text{ \AA}$ ) supposedly to facilitate through-the-space electron transfer [12]. Among the configurational changes attendant with the generation of the positive charge  $\alpha$  to the metal core is a substantial deviation from the linearity around the coordination sites ( $\theta 55^\circ/43^\circ$  as opposed to  $\theta 4.8^\circ/4.4^\circ$ ) [12]. The stability of cobalt-complexed propargyl cations is truly remarkable, i.e. red to black solids can be kept at low temperatures for months without any noticeable deterioration [3a, b]. The second major species in this chapter will become cobalt-complexed propargyl radicals (**3**). Their systematic studies commenced in the early 1990s, [13] developed into a potent synthetic field, provided access to classes of organic compounds hardly accessible by alternative means, and allowed for achieving levels of stereo-, regio-, and chemoselectivity that are unprecedented for free propargyl radicals [14]. Cobalt-complexed 1,3-enynes **4** – albeit less studied – can serve as precursors to respective propargyl cations (**2**) and radicals (**3**), thus expanding the substrate base and substantially enhancing their synthetic potential [14, 15].

## 6.2 Cobalt-Alkyne Complexes: Electrophilic Reactions

Cobalt–alkyne complexes **5** can be converted to propargyl cations **6** most commonly by treating respective alcohols or ethers with a strong *Lewis acid* ( $\text{HBF}_4$ ,  $\text{HPF}_6$ ,  $\text{BF}_3$ ) (Scheme 6.1) [3a, b, 5a, b, 9a–c, 16]. The cation generation can take place in a variety of dry solvents, including alkanes, diethyl ether, or methylene chloride. In most cases, propargyl cations **2** are scarcely soluble in ether or pentane, allowing for the intermediate to precipitate and for an excess



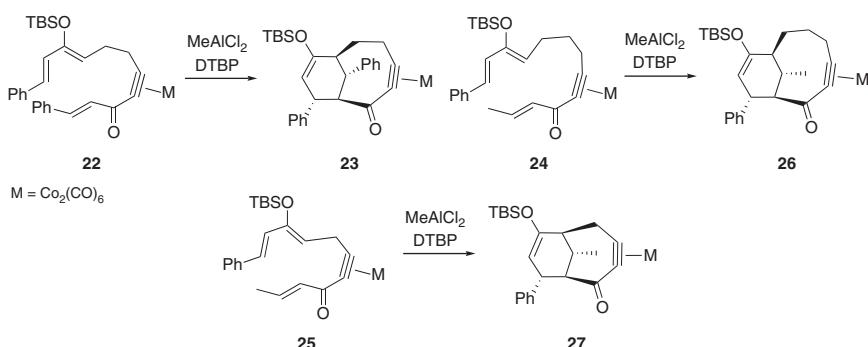
Scheme 6.1 Summary of chemical properties of cobalt-complexed propargyl cations.

of *Lewis* acid to be removed, thus greatly facilitating the isolation procedure. In those cases when reactions are carried out in methylene chloride, the cation precipitation does not occur and subsequent steps are carried out with *in situ*-generated species. Over the last several decades, cobalt-complexed propargyl cations **6** underwent an extensive, multidimensional exploration with nucleophiles attacking the electropositive carbon atom and forming a new covalent bond in  $\alpha$ -position to the metal core. With respect to nucleophilic substrates, the reactions provide a convenient propargylation method applicable to a wide variety of aromatics (**7**),  $\beta$ -diketones (**8**),  $\beta$ -keto esters (**8**), silyl enol ethers (**9**), allyl silanes (**10**), trialkyl aluminium compounds (**11**), and dialkyl aluminium nitriles (**12**) [16, 17]. Besides C-nucleophiles, propargyl cations **6** also readily react with amines (**13**), hydrides (**14**), alkyl nitriles (**15**), phosphines (**16**), sulfides (**17**), azides (**18**), and enamines (**19**) [17, 18] as well as undergo the spontaneous conversion to propargyl radicals [14] yielding head-to-head dimeric products (**20**, Scheme 6.1). Ligand substitution reactions allowed for the selective substitution of axial carbon monoxide ligands with phosphines and phosphites (**21**), [19] that in turn, due to the electron-donating nature of phosphorous ligands, facilitated the generation of the respective propargyl cations, as well as provided a novel mechanistic tool for controlling the stereoselectivity of ionic reactions due to an enhanced bulkiness of the metal core [20].

Intramolecular reactions were designed to exploit a bent geometry of the cobalt–alkyne moiety [2, 3a, b, 12] by bringing reacting termini into a closer vicinity, imposing additional conformational restraints, and lowering the energy of the tentative transition states, thus facilitating the desired chemical transformations [21–30]. Some representative examples are showcased in the following text in order to highlight the coordination-induced efficiency, as well as the topological and functional diversity of target molecules in turn indicative of a high degree of functional group tolerance in cobalt-assisted reactions. The most attractive feature of the intramolecular reactions is the ease at which the pending functionalities can be attached to the metal–alkyne core, and their structures – length of the carbon chain, degree of substitution, topology, functionality – can be varied based on the commercially available reagents.

### 6.2.1 Intramolecular Diels–Alder Reactions

A bent structure of a cobalt–alkyne core was exploited in intramolecular *Diels–Alder* reactions with a dienophile tethered – via a  $\text{Co}_2\text{C}_2$ -link – to 1,3-diene moieties (Scheme 6.2) [21]. The rationale was that the presence of a bulky  $\text{Co}_2\text{C}_2$ -core would impose conformational restraints upon a carbon tether and facilitate the formation of the targeted bridged compounds by bringing the reaction termini into a closer proximity to each other. For silyloxy-substituted diene **22**, the [4+2]-cycloaddition reaction is best catalysed with  $\text{MeAlCl}_2$  as *Lewis* acid affording bicyclo[5.3.1]undec-3-yn-2-one **23** in high yields. The compatibility of the acid catalyst with labile, hydrolysis-prone silyl enol ether moiety is achieved by carrying out the reaction in the presence of 2,6-di-*tert*-butylpyridine (DTBP), a proton scavenger. A two-way expansion of the substrate base included the lengthening and shortening of the tether by one

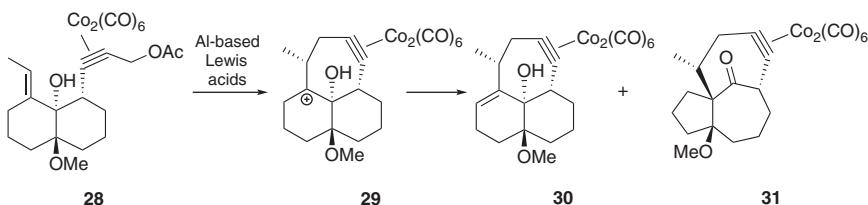


**Scheme 6.2** Intramolecular Diels–Alder reactions stereodirected by a metal core.

carbon (**24**, **25**; Scheme 6.2) [21]. The cycloaddition reactions occurred under an analogous albeit somewhat modified protocol, affording novel bridged assemblies, i.e. bicyclo[6.3.1]dodec-3-yn-2-one **26** and bicyclo[4.3.1]dec-3-yn-2-one **27**. Most remarkably, cycloaddition reactions followed a highly stereoselective pathway, producing single stereoisomers for which relative configurations were established by X-ray crystallography. Mechanistic studies allowed for concluding that the cycloadditions in question do not have a profile of a concerted process, but consecutive *Michael* addition reactions. Decomplexations were carried out with rather unconventional reagents ( $Et_3SiH$ ;  $NaH_2PO_2$ ) allowing for secondary transformations of the carbon–carbon triple bond such as hydrosilylation and hydrogenation (Scheme 6.2) [21].

### 6.2.2 Assembling Tricyclic Ring Systems

The skeletal rearrangements became a key step in assembling of ingenanes' carbon framework, a group of natural compounds of plant origin with a broad range of biological activities (Scheme 6.3). *Trans*-decalin was used as a molecular platform for bringing propargyl and unsaturated moieties in a close proximity to each other. In particular, propargyl acetate **28** was treated with a variety of aluminium-based species to first generate cation **29** *in situ* and then to study the chemoselectivity with a *Lewis* acid being the main determinant. For selective synthesis of  $\beta$ -deprotonation product **30**, dimethyl aluminium chloride proved to be optimal. A variety of other species, such as  $Me_2AlOTf$ ,  $MeAl(OTf)_2$ ,  $MeAl(OCOCF_3)_2$ , and  $MeAl(OCOCF_3)(O-2,6-Me_2-4-NO_2C_6H_2)$

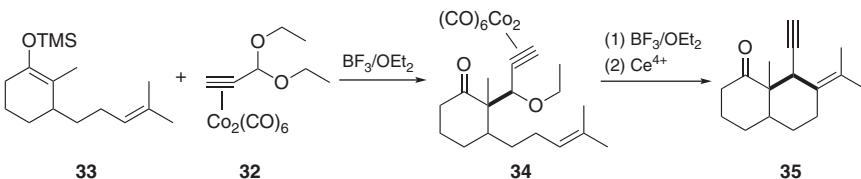


**Scheme 6.3** Skeletal rearrangements in tricyclic cobalt-complexed propargyl cations.

gave rise to a mixture of  $\beta$ -deprotonation product **30** and tricycle **31**, a product of pinacol-type rearrangement. The latter exhibited the highest chemoselectivity affording competing products in 21% and 77% yields, respectively [22a]. Intramolecular cyclisations were enabled by a bent geometry of a cobalt–alkyne unit as well as an ability of aluminium derivatives to generate cobalt-stabilised cationoid species *in situ* bypassing the cation isolation step. The methodology thus created has become an experimental knowledge base for developing the total synthesis of ingenol [22b].

### 6.2.3 Assembling Bicyclic Ring Systems: Decalines

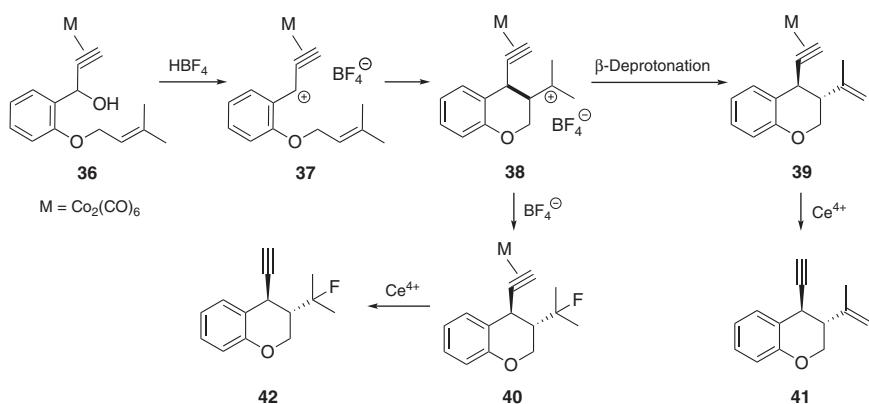
Cobalt-complexed propargyl acetals such as **32** are of special interest for serving as precursors to the respective cations given the opportunity for the sequential generation of the positive charge  $\alpha$  to the metal core, effecting first an intermolecular reaction, followed by an intramolecular cyclisation [23]. Substrate **33** is a bifunctional molecule containing the recipients of the electrophilic attacks tethered together via a relatively short carbon chain. Thus, an interaction of propargyl acetal **32** with  $\text{BF}_3$  generates an  $\alpha$  alkoxy-substituted propargyl cation that in turn reacts intermolecularly with a silyl enol ether moiety forming ketone **34**. Secondary generation of the positive charge in the propargylic position enables an intramolecular reaction upon the pending double bond, producing decaline derivative **35** upon release of organic product from the metal bondage (Scheme 6.4) [23]. The methodology greatly expands the synthetic versatility of propargyl cations since the ring sizes, functionalities, and topology of reaction components can be varied affording a range of polysubstituted bicyclic compounds.



Scheme 6.4 Tandem, one-pot cobalt-mediated assembling of the decalin ring.

### 6.2.4 Assembling Heterocyclic Ring Systems: Benzopyrans

Benzopyrans – bicyclic compounds widely abundant in nature – can be synthesised by an intramolecular cyclisation of the cobalt–alkyne complexes, such as **36**, which contain, as aromatic substituents, propargyl and alkenyl groups positioned *ortho* to each other (Scheme 6.5) [24]. A *Lewis* acid-initiated generation of the intermediate cation **37** is followed by an intramolecular addition across the pending trisubstituted double bond. The tertiary carbocation **38** thus formed undergoes either  $\beta$ -deprotonation, or a fluorine ion transfer, affording benzopyrans **39** and **40**, respectively. Cyclisations occur with a high stereoselectivity, forming exclusively the tetrahydropyran rings with *trans*-configuration. All three steps – complexation, cyclisation, decomplexation – can be carried



**Scheme 6.5** Synthesis of benzopyrans via electrophilic cyclisation reactions.

out in one pot, yielding benzopyrans **41** and **42** in comparable amounts. The variation of substituents around the periphery of the aromatic rings, as well as experimentation with *Lewis* acids ( $\text{HBF}_4$ ,  $\text{BF}_3$ ,  $\text{AlCl}_3$ ,  $\text{TiCl}_4$ ,  $\text{SnCl}_4$ ,  $\text{Bu}_2\text{BOTf}$ ) allowed to find conditions under which the  $\beta$ -deprotonation and halide ion transfer products were formed exclusively (Scheme 6.5) [24].

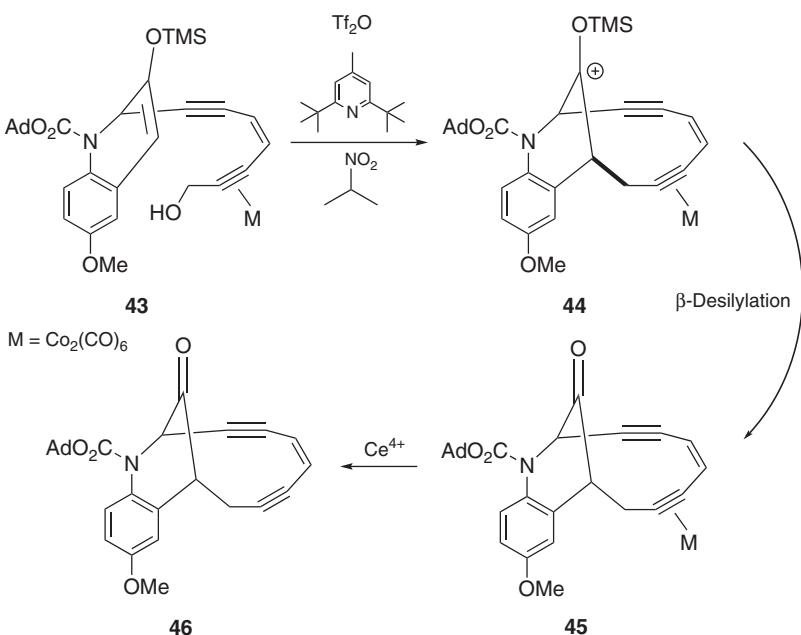
### 6.2.5 Synthesis of Enediynes

One of the main areas in which cobalt-complexed propargylations have successfully been used, as a key step, is towards the synthesis of enediyne antibiotics, a class of DNA-cleaving natural products [25]. Several representatives of enediynes – *dynemicin*, *calicheamicin*, *esperamicin* – have become household names being widely used in cancer clinical practice. Enediyne **43** is designed in such a way so that the reacting termini – cobalt-complexed primary propargyl alcohol and silyl enol ether – are brought into a closer proximity to each other, thus facilitating the key cyclisation step (Scheme 6.6) [25a]. Triflic anhydride stimulates the development of the positive charge located in  $\alpha$ -position to a metal core and capable of adding across the electron-rich double bond in enol ethers.

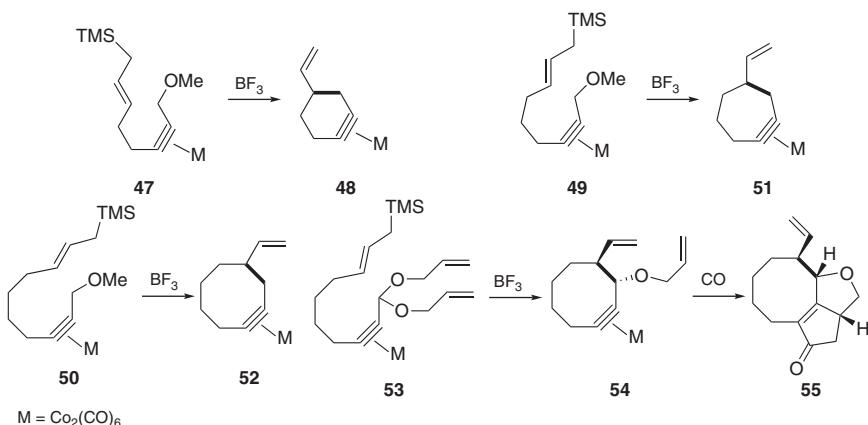
Bridged carbocation **44** undergoes facile  $\beta$ -desilylation reforming a keto group in cyclised product **45**. A successful cyclisation in the presence of acid-sensitive moieties – enediyne and silyl enol ether – is enabled by the presence of a pyridine derivative that was able to “neutralise” an unwanted acidity of triflic anhydride and preserve the integrity of highly labile molecular units (Scheme 6.6) [25a]. Decomplexation under oxidising conditions afforded enediyne **46** that represents the *dynemicin* core structure (Scheme 6.6) [25a]. Analogous methodology and topological design were applied in the synthesis of the *neocarcinostatin chromophore A* core structure [25b].

### 6.2.6 Assembling Strained Ring Systems

In a purely “organic” environment, introducing a carbon–carbon triple bond into a small-to-mid size carbocycle cannot be accomplished given the amount of ring

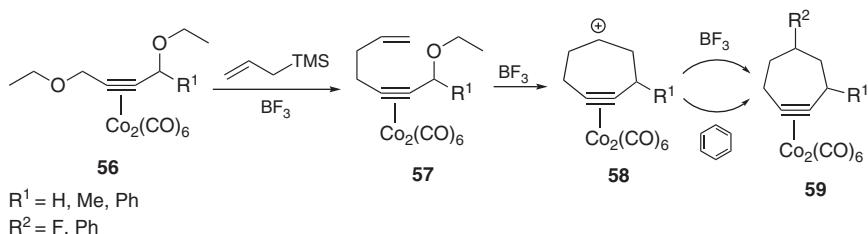
Scheme 6.6 Synthesis of the *dynemicin* core structure.

strain attendant with it. The departure from linearity in the cobalt-complexed acetylenes ( $135^\circ$ – $140^\circ$ ) [2, 3, 12] allows for relieving the angle strain and provides for sufficient stability so that the respected cobalt complexes can be isolated and characterised. In particular, a six-membered ring was assembled by using, as a key step, a *Lewis* acid-mediated interaction of methyl propargyl ether and allyl silane moieties incorporated into cobalt complex 47 (Scheme 6.7) [26]. Cyclohexyne 48 was formed due to the generation of the propargyl cationic species stabilised by a  $\text{Co}_2(\text{CO})_6$ -core and a subsequent intramolecular electrophilic attack upon the



Scheme 6.7 Cobalt–alkyne core-assisted syntheses of six to eight-membered carbocycles.

pending double bond. Sterically, the formation of the carbon–carbon bond (*bold-faced*) became possible due to the bent geometry of the coordinated triple bond bringing the reacting centres into a closer proximity to each other. Lengthening a carbon tether – by one (**49**) or two (**50**) carbon atoms – allowed for expanding the substrate base and accessing larger rings, i.e. cycloheptyne **51** and cyclooctyne **52**. The synthesis and characterisation of the relatively small cycloalkyne rings (C6–C8) is not only of significant theoretical importance; their synthetic utility arises from secondary reactions that could accompany the decomplexation step and structurally modify a triple bond, thus forming stable organic products. Such a synthetic possibility is demonstrated by carrying out the intramolecular cyclisation with cobalt-complexed propargyl acetal **53**, an  $\alpha,\alpha'$ -bifunctional molecule that allows for facile generation of the  $\alpha$ -alkoxy stabilised propargyl cation, an intramolecular cyclisation affording cyclooctyne **54**, and then, by exploiting a pending allyloxy group, effects a [2+2+1] *Pauson–Khand* reaction to form tricycle **55** in a high yield (Scheme 6.7) [26]. Cobalt-stabilised cycloheptynes can also be synthesised via [4+3] cycloaddition reaction by using  $\alpha,\alpha'$ -diethoxy ethers, such as **56**, as substrates (Scheme 6.8) [27]. An interaction with allyl silane is thought to occur, first, at the primary propargyl carbon, forming mono-ether **57**, which then undergoes an intramolecular cyclisation upon a pending allyl group generating a secondary cation **58**. The latter can either abstract a fluoride ion, forming fluorocycloheptyne (**59**;  $R^2 = F$ ), or alkylate an aromatic ring if benzene is used as a solvent (**59**;  $R^2 = Ph$ ).

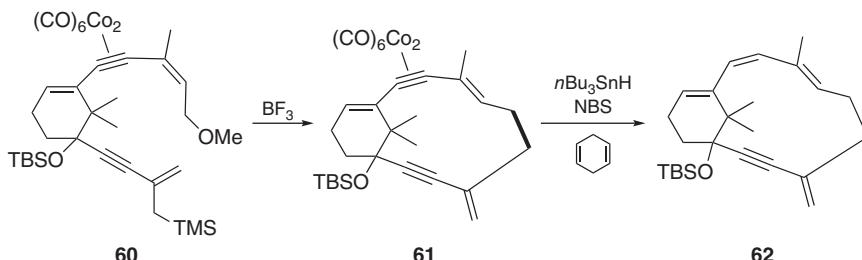


**Scheme 6.8** Metal core-assisted syntheses of cycloheptyne derivatives.

### 6.2.7 Assembling Natural Carbon Skeletons

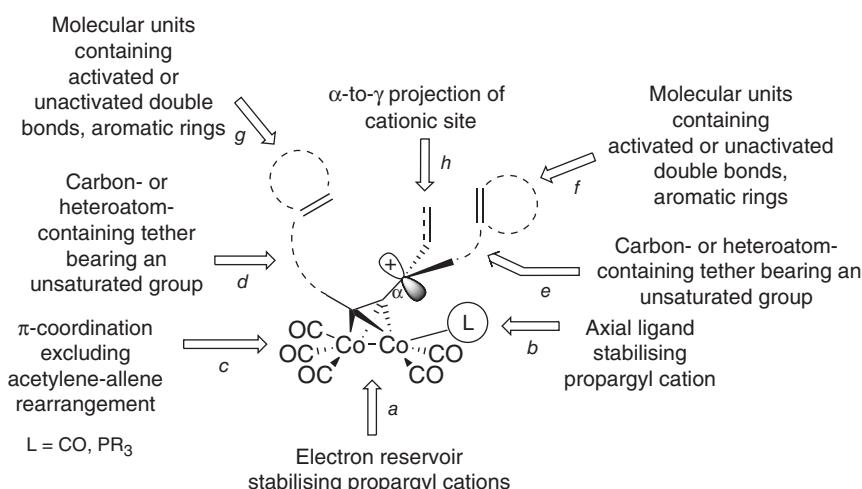
Intramolecular cyclisations of cobalt-complexed propargyl cations were also successfully used in the construction of bridged and fused molecules of natural origin, such as plant-derived taxoids [28] and marine-based toxins (*ciguatoxin*; *gambierotoxin*) [29]. In particular, two 1,3-eneyne moieties were incorporated into polyunsaturated substrate **60** with only one triple bond being blocked with the dicobalthexacarbonyl core (Scheme 6.9) [28]. Cyclisation mediated by  $BF_3$  or  $TfOH$  proceeded with methyl ether, as well as propargyl acetate or TBS ether, affording cyclised product **61**. The decomplexation step was carried out with quite an unconventional mixture of tributyltin hydride (TBTH), *N*-bromosuccinimide (NBS), and 1,4-cyclohexadiene. The rationale was that releasing a metal core might occur via radical mechanism, and the presence of a radical initiator could facilitate the process. The acetylenic group converts

to a *cis*-double bond with 1,4-cyclohexadiene acting as a source of hydrogen atoms. Organic product **62**, bicyclo[9.3.1]pentadecatriene, has a diterpenoid taxoid skeleton, indicating that the methodology can be applied for accessing functionally diverse representatives of the *taxane* family (Scheme 6.9) [28].



**Scheme 6.9** Assembling taxoid carbon framework.

Overall, the totality of the experimental data accumulated over the several decades by various research groups revealed a multitude of functions that topologically distinct parts of the cobalt–alkyne complexes can fulfil with each molecular unit, substantially improving the reaction characteristics, and thus outpacing those of uncomplexed acetylenic compounds (Figure 6.2). Given the oxidation state of the cobalt atoms and its nuclearity, tetrahedral  $\text{Co}_2\text{C}_2$  clusters exhibit an electron-rich behaviour that extends beyond the immediate confines of a  $\pi$ -bond and reaches the  $\alpha$  carbon atom in the propargyl ligand (*path a*). The stabilisation provided by metal core is further enhanced by axially located phosphines and phosphites, which facilitate the propargyl cation isolation and represent a mechanistic tool for controlling the stereoselectivity of the electrophilic reactions (*path b*). The formation of the  $\pi$ -bond between the metal cluster and carbon–carbon triple bond plays a critical role in inhibiting an



**Figure 6.2** Diverse functions fulfilled by select parts of cobalt–alkyne complexes.

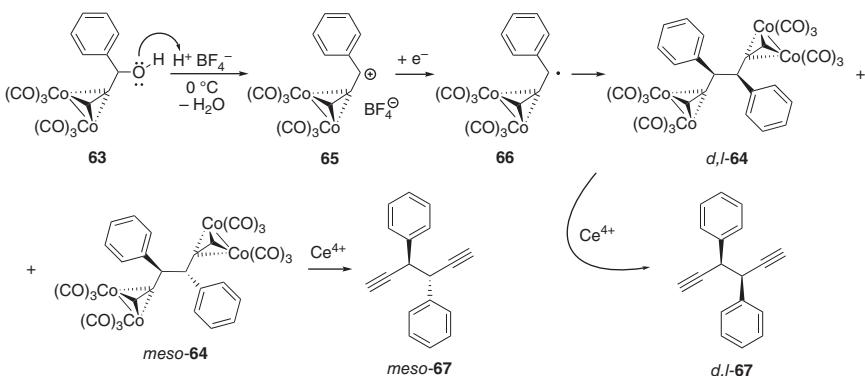
acetylene–allene rearrangement, which has long been the compromising, and unavoidable, feature in acetylene chemistry (*path c*). A terminal triple bond, as well as an  $\alpha$  carbon atom, were used as suitable sites for introducing tethers that would connect the metal core with a recipient of the electrophilic attack, thus creating topologically diverse substrates for intramolecular reactions (*paths d, e*). Unsaturated groups were represented by double bonds, silyl enol ethers, allyl silanes, and aromatic nuclei, with the all-carbon and heteroatom-containing tethers affording mono-, di-, tri-, tetra-, and bridged carbo- and heterocyclic compounds (*paths f, g*). In both locales, the unsaturated units can be replaced with a pending hydroxyl group with the length of the carbon link predetermining the ring size of the oxygen-containing heterocycles. Introducing a double bond provides a new avenue for enhancing the synthetic potential by projecting the cationic reaction site from the  $\alpha$  to  $\gamma$  carbon atom within the allylic triad (*path h*).

### 6.3 Cobalt–Alkyne Complexes: Radical Reactions

In the early 1990s, the chemistry of  $\pi$ -bonded organometallic radicals with an unpaired electron located  $\alpha$  to the metal core was in its infancy – from the development standpoint [14]. In the case of propargyl radicals, there has been objective reasons why the complexation with a cobalt core (**3**, Figure 6.1) could have improved the inferior reaction characteristics: (i) a compromising acetylene–allene rearrangement could be impeded due to a decrease in the bond order, and attendant with it, “freezing” of an electron cloud within the confines of the  $\text{Co}_2\text{C}_2$ -core; (ii) the linearity could have been avoided by bending a triple bond and acquiring a mechanistic tool for influencing the configuration of the stereocentres developing in the  $\alpha$ -position; and (iii) a small, selectivity-denying size of the acetylenic group could have been drastically increased due to a bulky  $\text{Co}_2(\text{CO})_6$ -group, thus providing a lever for controlling the path of converging propargyl radicals.

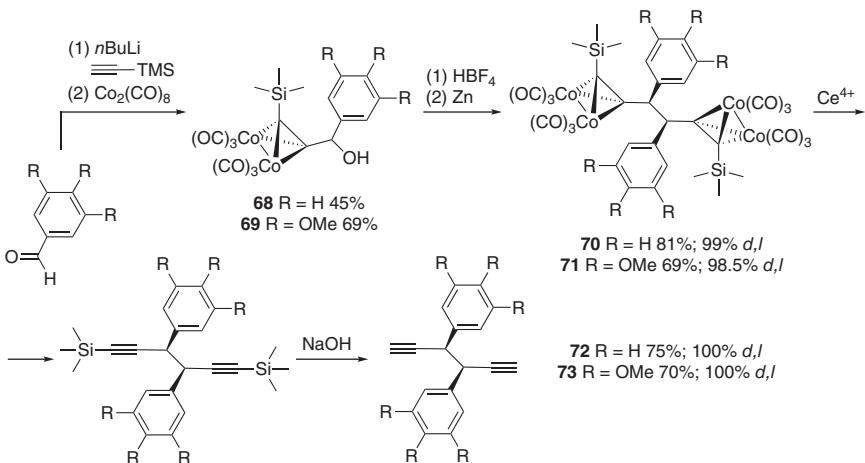
The standard protocol for radical dimerisation reactions includes an acidic treatment of the cobalt-complexed propargyl alcohols, precipitation of propargyl cations in a carefully selected solvent, or combination of solvents, and reduction with Zn, or  $\text{Cp}_2\text{Co}$ , usually in dichloromethane [31]. Chronologically, [31a] the first substrate studied was  $\alpha$ -phenyl alcohol **63**, which forms *d,l*- and *meso*-dimers **64** via cation **65** and transient radical **66** (Scheme 6.10). A low-temperature ( $-78$  to  $0$  °C) decomplexation with ceric ammonium nitrate is a standard protocol most commonly used for releasing organic products [3, 9, 14]. With parent alcohol **63**, organic products – *d,l*-**67** and *meso*-**67** – were isolated in a stereochemically pure form and high yields (78–80%). With *d,l*-isomers being the predominant structure, stereoselectivity varies from 84 : 16 (Zn) to 74 : 26 ( $\text{Cp}_2\text{Co}$ ) [31b].

A bent geometry of the cobalt-complexed propargyl cations [2] (**2**, Figure 6.1) provided a mechanistic tool for controlling the convergence of propargyl radicals and achieving a nearly exclusive formation of *d,l*-diastereomers. Given the results of model studies, the trimethylsilyl (TMS) group was chosen as a molecular unit that could induce an efficient 1,3-steric induction over the metal-complexed



Scheme 6.10 Dimerisation of cobalt-complexed propargyl radicals.

triple bond [32a]. Thus,  $\gamma$ -TMS propargyl alcohols (**68**, **69**) were synthesised by a condensation–complexation sequence, followed by treatment with  $\text{HBF}_4^-$  and reduction of cationic salts with zinc (Scheme 6.11). Radical dimers (**70**, **71**) were isolated in high yields and with an excellent diastereoselectivity (98.5–99% *d,l*). Decomplexation allowed for the release of organic dimers, which were then desilylated yielding isomerically pure *d,l*-**72** and *d,l*-**73**. Overall, the synthetic strategy employing a  $\text{Me}_3\text{Si}$ -auxiliary group involves five steps and yields – with 28–33% overall yields – individual *d,l*-diastereomers, which are otherwise hardly accessible [32a].

Scheme 6.11 The 1,3-steric induction by a removable  $\gamma$ -TMS substituent.

The concept of *preorganization of reactive termini* widely used in organic and bioorganic chemistry was exploited within the organometallic context by introducing a rigidity element into the carbon tether that imposed conformational restraints upon converging bis-propargyl radicals, which in turn resulted in higher yields and enhanced stereoselectivity (Table 6.1). With a phenyl group

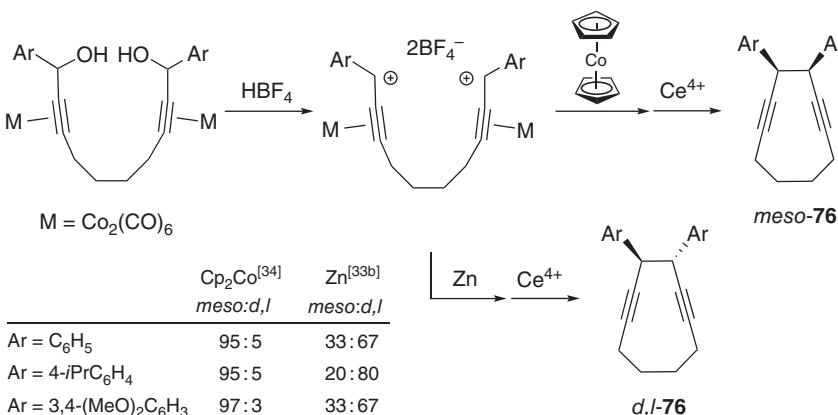
**Table 6.1** The impact of tether rigidity upon stereoselectivity of cyclisation.

**Diastereoselectivity**

Substrates	With rigid tether [33a]		With flexible tether [33b]	
	<i>d,l:meso</i>	<i>de</i>	<i>d,l:meso</i>	<i>de</i>
R <sup>1</sup> = R <sup>2</sup> = H	100 : 0	100	67 : 33	34
R <sup>1</sup> = iPr; R <sup>2</sup> = H	100 : 0	100	80 : 20	60
R <sup>1</sup> = R <sup>2</sup> = OMe	95 : 5	90	54 : 46	8

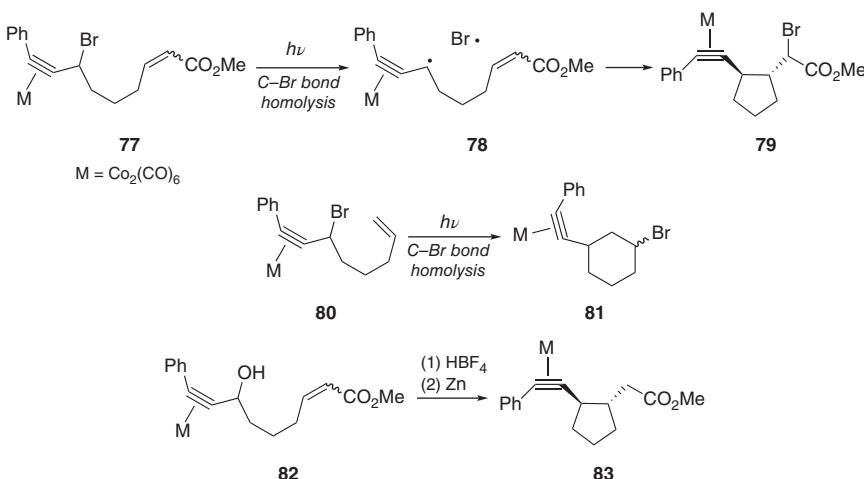
incorporated into a carbon link (74, R<sup>1</sup> = R<sup>2</sup> = H; Table 6.1), 1,5-cyclodecadiyne 75 was obtained in 85% yield, as a single *d,l*-diastereomer [33a]. For comparison, with a flexible carbon tether, the respective 1,5-cyclodecadiyne was obtained in 41% yield, as an inseparable diastereomeric mixture (*d,l:meso*, 67 : 33; Table 6.1, entry 1) [33b]. A rigid tether was proven efficient even with the most “problematic”, 3,4,5-trimethoxy derivative 74: cyclisation occurs nearly stereorandomly with a flexible tether (R<sup>1</sup> = R<sup>2</sup> = OMe: *d,l:meso*, 54 : 46; Table 6.1, entry 3) [33b] while reaching an excellent level of *d,l*-diastereoselectivity with a rigid carbon chain (R<sup>1</sup> = R<sup>2</sup> = OMe: *d,l:meso*, 95 : 5; Table 6.1, entry 3) [33a]. This mechanistic tool for controlling the stereoselectivity of the radical cyclisations – *de* = 90–100% [33a] vs. 8–34% [33b] – can be further expanded to include other configurationally rigid moieties, such as a double bond or cyclic acetal groups.

The stereoselectivity of the intramolecular cyclisation reactions underwent a remarkable reversal – from *d,l*- to *meso*- – when the reduction method was changed, i.e. from heterogeneous to homogeneous (Scheme 6.12) [34]. With zinc as a reducing agent, diastereomeric ratio of *meso*- and *d,l*-1,5-cyclodecadiynes 76 varies from 33 : 67 to 20 : 80 with the *d,l*-configuration being most favoured [33b]. When carrying out reductions with cobaltocene, Cp<sub>2</sub>Co, *meso*-diastereomers 76 are formed with an excellent stereoselectivity (94–95%) [34]. Since 2009, the method remains the only synthetic access to highly elusive *meso*-1,5-cyclodecadiynes (Scheme 6.12) [34]. The observed stereoselectivity reversal may be explained in terms of “sequestered” organometallic radicals, a term coined later on to explain disparities in intermolecular dimerisation reactions [31b].

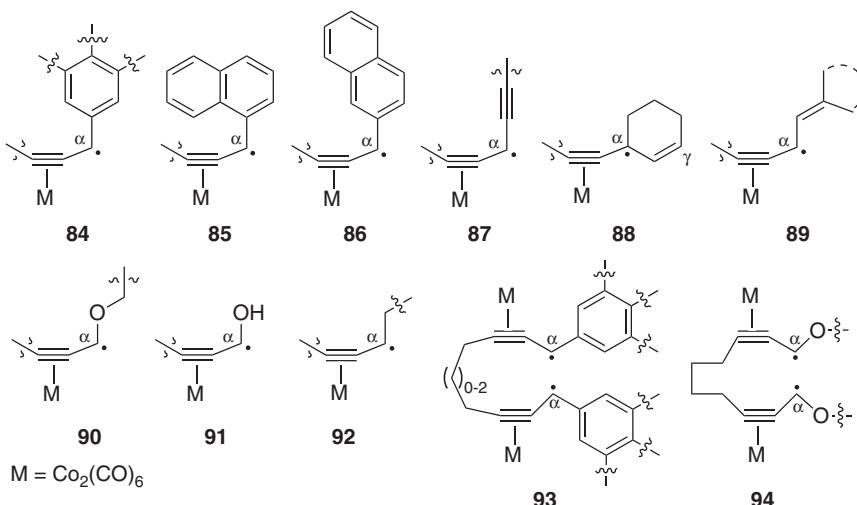


Scheme 6.12 Impact of reducing agent upon stereoselectivity of cyclisation.

Cyclisation reactions of cobalt-complexed propargyl radicals are not only limited to larger 1,5-alkadiynes ( $C_8$ , [35b]  $C_9$ , [35a]  $C_{10}$  [31, 33, 34]). Medium-sized rings ( $C_5$ ,  $C_6$ ) can also be assembled by tethering the cobalt–alkyne units with a suitable recipient of the radical attack [36]. The homolysis of the C–Br bond places an unpaired electron  $\alpha$  to the metal core, which can then add across the activated double bond forming either five- or six-membered rings (Scheme 6.13). In particular, photocyclisation of propargyl bromide 77 allowed for an *in situ* generation of transient radicals 78, which then undergo regio- and stereoselective cyclisation to *trans*-cyclopentane 79. With a pending terminal double bond (80), regioselectivity is fully reversed, although the formation of cyclohexane 81 lacks stereoselectivity. When propargyl alcohol 82 is treated with  $HBF_4$  and the intermediate cation reduced with zinc, the regio- and stereoselective formation of the five-membered ring (83) was observed



Scheme 6.13 Intramolecular cyclisations leading to five- and six-membered carbocycles.

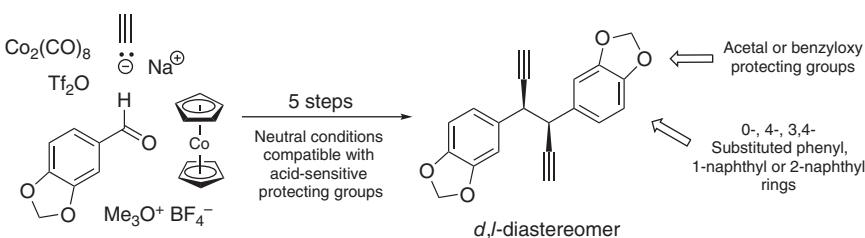


**Figure 6.3** Alternative types of cobalt-complexed radicals.

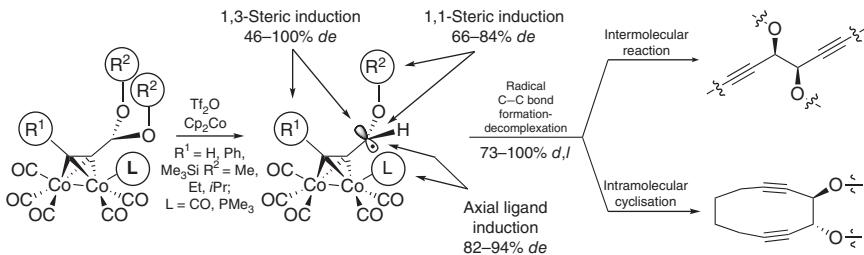
although the radical intermediate was stabilised not by a Br-atom transfer (**81**), but by an H-atom abstraction reaction [36].

Overall, structural, topological, and functional variations of the propargyl substrates and expansion of the substrate base (alcohols, acetals, methyl ethers, aldehydes) provided easy access to a wide array of transient radicals **84–92** as well as those containing dual radical centres and primed for intramolecular cyclisations (**93**, **94**; Figure 6.3). Consequently, stereo- and regioselective synthetic methods for polysubstituted 1,5-alkadiynes, [31, 32, 37a, b] 3,4-dialkoxy-1,5-(cyclo)alkadiynes, [37c] 3,4-dihydroxy-1,5-alkadiynes, [38] 1,1,2,2-tetraethynylethylenes, [37d] 1,1,2,2-tetraethynylethenes, [37d] and 3,7-diene-1,9-alkadiynes [37e] were developed, which in turn are ripe for being used in targeted synthesis of organic compounds of relevance to medicinal chemistry, materials science, and natural product syntheses.

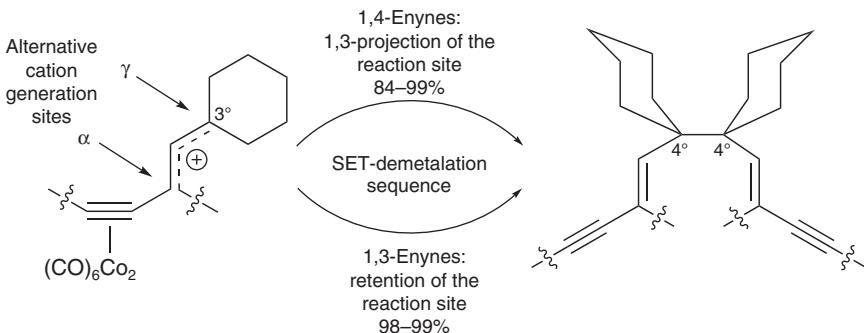
Some research highlights are summarised in Figures 6.4–6.9, in particular: (i) for the first time, propargyl cations were synthesised in the absence of strong acids, thus achieving a long sought after compatibility with acid-sensitive functionalities, such as an acetal moiety (Figure 6.4), [37f]; (ii) the first radical reaction of propargyl acetals in organic and organometallic chemistry was reported with cobalt-complexed propargyl acetals as a new type of substrate in cobaltocene-induced radical reactions (Figure 6.5), [37c]; (iii) a novel, highly efficient method for the syntheses of compounds with contiguous quaternary carbon atoms was developed by exploiting, as a structural vehicle, a 1,3-projection of the reaction site (Figure 6.6), [37e]; (iv) over the last four decades, the first radical reaction of 1,4-diynes was reported providing access to 1,1,2,2-tetraalkynyl ethenes (Figure 6.7), [37d]; (v) new paradigms for making propargyl radicals persistent were created, the persistency thresholds numerically defined, newly acquired dichotomy in allylic radicals ( $\alpha$ -persistent- $\gamma$ -transient) and trichotomy in pentadienyl radicals ( $\alpha$ -persistent- $\gamma$ -transient- $\epsilon$ -transient) were



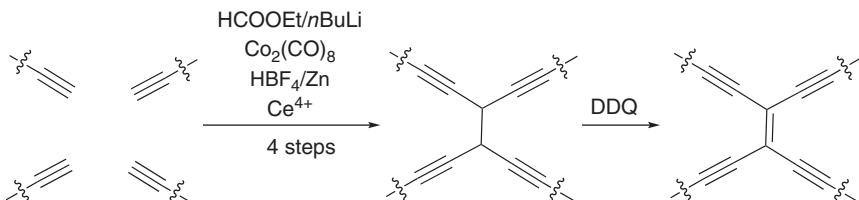
**Figure 6.4** Generation of cobalt-complexed propargyl cations in the absence of the strong acids. Source: Reprinted with permission from Melikyan et al. [37f]. Copyright 2012, American Chemical Society.



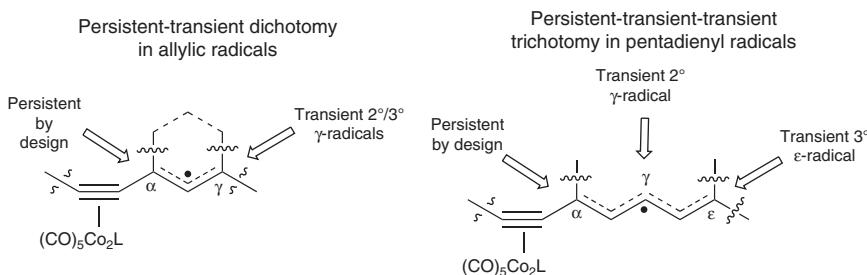
**Figure 6.5** Cobalt-complexed propargyl acetals as new substrates for radical coupling reactions. Source: Reprinted with permission from Melikyan et al. [37c]. Copyright 2014, American Chemical Society.



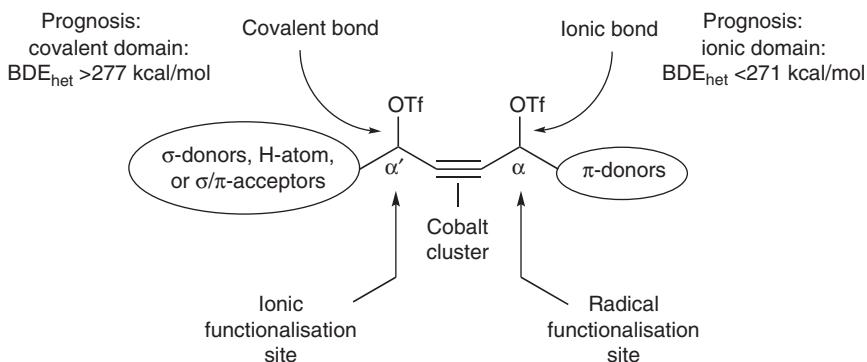
**Figure 6.6** A 1,3-projection of the reaction site and facile entry to compounds with contiguous quaternary carbon atoms. Source: Reprinted with permission from Melikyan et al. [37e]. Copyright 2015, American Chemical Society.



**Figure 6.7** A facile entry to 1,1,2,2-tetraalkynyl ethenes via cobalt-complexed propargyl radicals. Source: Reprinted with permission from Melikyan and Anker [37d]. Copyright 2015, American Chemical Society.



**Figure 6.8** Exploiting dichotomy and trichotomy of cobalt-complexed propargyl radicals.  
Source: Reprinted with permission from Melikyan et al. [37g]. Copyright 2016, American Chemical Society.



**Figure 6.9** Reducibility of a C-OTf bond as a function of the relative stabilities of propargyl cations.  
Source: Reprinted with permission from Melikyan et al. [37h]. Copyright 2016, American Chemical Society.

synthetically exploited in various molecular platforms (Figure 6.8), [37g]; and (vi) site-differentiation in propargyl polyethers was achieved based on the ionic nature of an  $\alpha$ -C-OTf bond and its reducibility with  $\text{Cp}_2\text{Co}$  (Figure 6.9) [37h].

In the course of the systematic studies on cobalt-associated propargyl radicals, new phenomena were discovered, novel concepts developed, and relevant terms suggested:

- (1) “*Unorthodox organometallic radical chemistry*” (2006): [39] The term refers to conceptually related reactions wherein the generation of radicals occurs via (i) spontaneous conversion of diamagnetic cobalt-complexed cations to propargyl radicals occurring within the wide temperature range, from 11 hours to 1 minute, [40a, b] and (ii) an accelerated tetrahydrofuran (THF)-mediated reaction that includes the cluster-to-cluster and cluster-to-ligand single electron transfer (SET) processes. [40c]
- (2) “*Sequestered*” organometallic radicals (2013): [31b] This concept was developed for explaining disparity in the diastereoselectivity of radical reactions with homogeneous and heterogeneous reducing agents. A high *d,l*-diastereoselectivity observed under homogeneous conditions was

attributed to the involvement of “non-free”, “sequestered” organometallic radicals associated with bulky reductant-derived, oxidised species.

- (3) “Chiralisation by metal complexation” (2015): [37d] This phenomenon was discovered while studying radical dimerisation reactions of cobalt-complexed  $\alpha$ -alkynyl propargyl radicals. It allows for chirality to be introduced into an achiral molecule without altering the carbon framework of the substrate, i.e. cleaving and forming new  $\sigma$ -bonds.
- (4) “Caged triple bond” (2015): [37d] This term refers to the novel method for protecting triple bond by introducing it, by design, into a constrained area of the molecule. The concept was first demonstrated for cobalt complexation reactions but might be applicable for other reagents capable of reacting with the acetylenic moiety.
- (5) “Background steric factor” (BSF) and “Threshold steric factor” (TSF) (2018): These terms were coined in the follow-up to the publication on persistent cobalt-complexed propargyl radicals [37g] and are being reported here for the first time. The former refers to the maximum molecular volume that the metal cluster must have so that a pre-calculated alteration in substituents, and their volumes, would cause a qualitative change in the ability of radicals to dimerise, i.e. converting transient species into persistent analogues (“threshold steric factor”). In a purely organic setting, replacing an H-atom (**95**) with a methyl group (**96**) does not change the level of radical persistency (Figure 6.10). With the secondary radical being complexed to a bulky cobalt cluster, the same change in volume ( $V_{\text{CH}_2} \sim 21 \text{ \AA}^3$ ) converts transient 2° radical (**97**) into persistent 3° species (**98**), which, by definition, are resistant to dimerisation. Thus, the “background steric factor” for cobalt-complexed propargyl radicals can be estimated as  $248 \text{ \AA}^3$ , while the “threshold steric factor” being around  $269 \text{ \AA}^3$ . Given the chemical context, said values must be empirically determined for each reaction based on the intended increase in bulkiness ( $\text{\AA}^3$ ) and the nature of the anticipated qualitative change.

Overall, systematic studies on cobalt-complexed propargyl radicals revealed a remarkable multitude of functions (9) that various parts of the cobalt–alkyne molecular assembly can fulfil, and distinct, non-overlapping roles that each part can play in determining the synthetic and stereochemical outcome of the radical process (Figure 6.11). A  $\pi$ -coordination to the triple bond eliminates one of the main obstacles to selective radical reactions in propargyl systems, i.e. acetylene–allene rearrangement (*path a*). Given the oxidation state of cobalt atoms, the metal core –  $\text{Co}_2(\text{CO})_6$  – can act as an electron reservoir donating electrons towards an  $\alpha$ -position and decisively contributing to an unprecedented

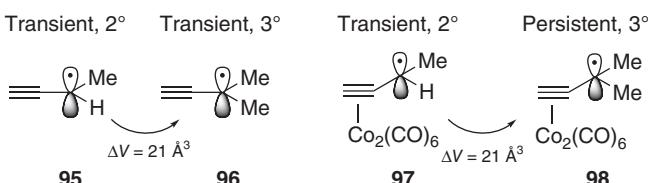
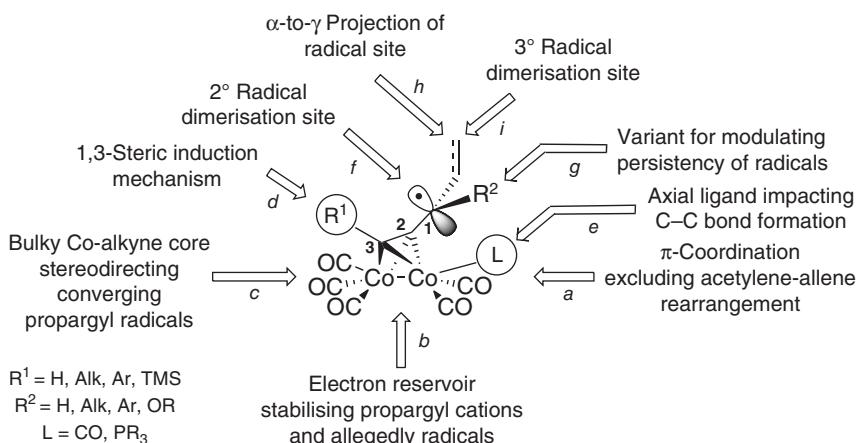


Figure 6.10 Cobalt-complexed propargyl radicals: from transiency to persistency.



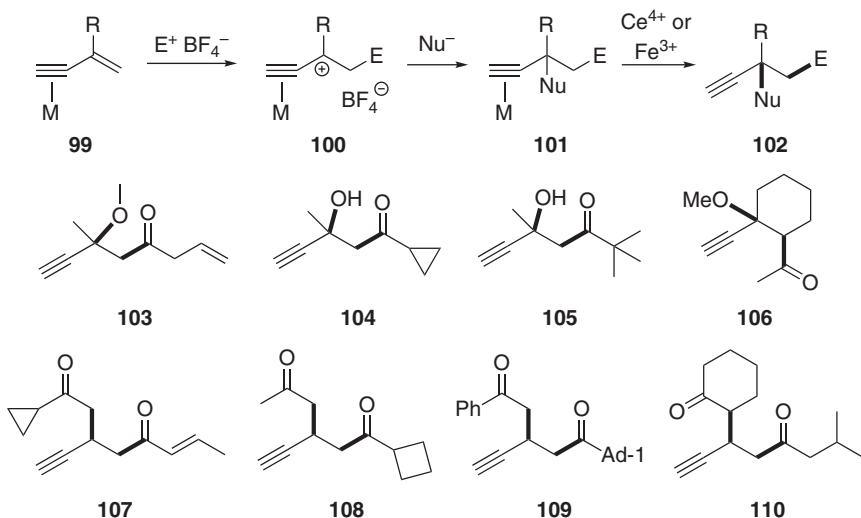
**Figure 6.11** Diverse functions fulfilled by select parts of cobalt–alkyne complexes. Source: Adapted with permission from Melikyan [14]. Copyright 2015, American Chemical Society.

stability of the cationic species (*path b*). A degree of stabilisation provided by said delocalisation to  $\alpha$ -positioned radicals is more difficult to assess due to a rapid dimerisation reaction and a lesser demand towards electrons because of a lower electrophilicity. Besides an electronic function affecting the stability of the intermediates, the cobalt core can also play a purely steric role, enhancing the stereochemical outcome of radical reactions by increasing the energy differences between the competing orientations of the converging radicals (*path c*). The case of a remote stereocontrol (1,3-steric induction; *d,l* up to 100%) was discovered with bulky groups ( $R^1 = \text{TMS}, t\text{Bu}$ ) being introduced to the acetylenic termini (*path d*). A comparable level of diastereocontrol (95–100% *d,l*) was achieved by exploiting an alternative mechanism for a remote stereocontrol, i.e. substitution of an axial CO with much bulkier, phosphorus-based ligands (*path e*). An  $\alpha$  carbon atom ( $C1, R^2 = H$ ) represents the main C–C bond formation site with its core function being to maintain the transiency of radicals even in the presence of the relatively large substituents, such as aryl or naphthyl groups (*path f*). An  $\alpha$  carbon atom exhibited an extreme sensitivity towards a degree of substitution (2° vs. 3°), effectively converting transient radicals (2°;  $R^2 = H$ ) to persistent ones (3°,  $R^2 = \text{Me}$ ). Such sensitivity (“background steric factor” phenomenon) is created by the bulky cobalt–alkyne cluster when even a subtle change in the volume ( $H$  vs.  $\text{Me}$ ) drastically impacts the ability of a radical to undergo dimerisation. Thus, within the metal–propargyl framework, the  $R^2$  substituent becomes a key variant for modulating the radical persistency (*path g*). A double bond introduced  $\alpha$  to the radical centre fulfilled the role of the conduit, projecting the reaction site –  $\alpha$ -to- $\gamma$  – towards the periphery of the conjugated system (*path h*). An ability to “travel” not only over one but two double bonds demonstrated, on a conceptual level, that the projections –  $\alpha$ -to- $\gamma$  and  $\alpha$ -to- $\epsilon$  – are possible in this type of radical processes with the highest carbon span still to be determined. Relocation of the radical site allows to effect dimerisation even at the tertiary  $\gamma$  carbon atoms (*path i*). The said projection revealed a newly acquired role for  $\gamma$

carbon atoms, i.e. to create a new reaction site –  $\gamma$  to a metal core – at the time when  $\alpha$ -positions are made persistent by the molecular design.

## 6.4 Cobalt-1,3-enyne Complexes: Electrophilic Reactions

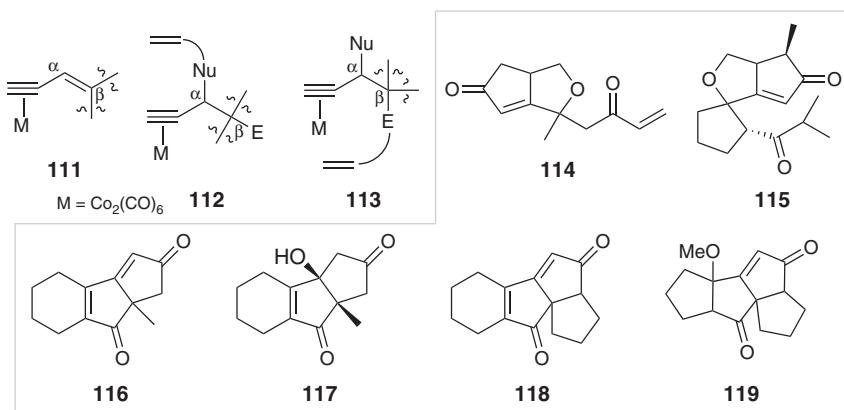
The ability of a  $\text{Co}_2(\text{CO})_6$ -group to recognise the carbon–carbon bond order makes 1,3-enynes ideal molecular systems for selective protection of the acetylenic moiety and subsequent functionalisation of the double bond [3a, 15, 16a]. In general, given the level of unsaturation, conjugated enynes can serve as a molecular scaffold for introducing six new  $\sigma$ -bonds in a series of addition steps [15]. An initial, two-step electrophilic addition ( $\text{Ad}_E$ ) sequence involves the complexation with dicobaltoctacarbonyl and interaction of enyne complex **99** with an electrophilic agent (Scheme 6.14). The formation of the propargyl cation **100** occurs in a highly regioselective manner given the ability of a  $\text{Co}_2(\text{CO})_6$  group to stabilise the positive charge developing in  $\alpha$ -position to the metal core [3, 9]. The use of non-nucleophilic anions, such as  $\text{BF}_4^-$ , allows for separation of the functionalisation steps in time and introducing nucleophiles of choice in  $\alpha$ -position to the metal core. Adducts **101** can be released of the metal bondage under oxidative conditions, usually with ceric ammonium nitrate at low temperatures ( $-78$  to  $+20^\circ\text{C}$ ). The novel carbon–carbon bonds (*boldfaced*) in  $\text{Ad}_E$  products **102** are positioned vicinally to each other and can be formed in a one-pot synthesis by bypassing an isolation of cation **100** [15, 41a]. A variety of electrophiles such as carbonium, acylium, nitronium, and sulfenium



Scheme 6.14 The two-step,  $\text{Ad}_E$  reactions of cobalt-complexed 1,3-enynes.

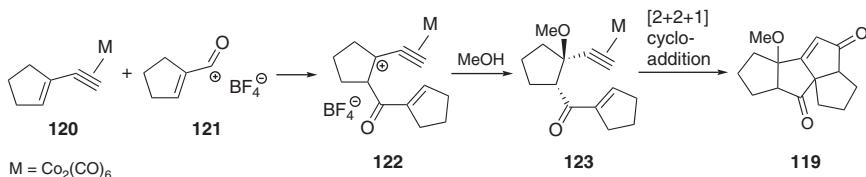
tetrafluoroborates are shown to add to the double bond without affecting the cobalt-protected acetylenic unit. The nucleophiles used for cation quenching can be grouped into heteroatom-containing such as water or methanol and carbon-based such as allyl silanes, aromatics, or silyl enol ethers. To demonstrate the remarkable structural diversity and richness in functionality, select structures are shown for both types of nucleophiles (**103–110**, Scheme 6.14) [41b, c]. With the relatively small, non-carbon nucleophiles, both secondary and tertiary ( $R = H, Me$ ) carbocations can be employed (**103–106**), while with silyl enol ethers, both cyclic and acyclic, only secondary intermediates exhibit relatively high yields (**107–110**). In two-step  $Ad_E$  reactions, benzhydryl cations, generated from respective chlorides and  $TiCl_4$ , can also serve as electrophiles, forming an ionic pair with  $Ti_2Cl_9^-$  as a new type of non-nucleophilic counterion, and being intercepted with allyl silanes [41d].

The synthetic potential of the two-step  $Ad_E$  reactions rose to a qualitatively higher level due to introducing a pending double bond and thus creating a structural precondition for subsequent *Pauson–Khand* reaction (Figure 6.12) [15, 42]. The topology of 1,3-enyne **111** allows for incorporation of a pending unsaturated unit in  $\alpha$ -(**112**) or  $\beta$ -(**113**) positions, implying that the double bond must be integrated into either nucleophilic (Nu) or electrophilic (E) agents, respectively. The various combinations of cyclic and acyclic substrates, acylating agents and nucleophiles provided access to fused and spiro, di-, tri-, and tetracyclic molecular assemblies of unique architecture, mostly in a stereoselective manner (**114–119**, Figure 6.12) [15, 42a–c]. In particular, with unsaturated alcohols, acting as nucleophiles, derivatives of 3-oxabicyclo-[3.3.0]octanone derivatives (**114**, **115**) were assembled, while an alternative approach utilising the unsaturated acylating agents, provided access to tri-(**116**, **117**) and tetracyclic- (**118**, **119**) carbon frameworks representing the ring systems in natural terpenes of a higher complexity [15, 42a–c]. The synthetic scheme for tetracycle **119** involves an interaction of cobalt-complexed cyclopentenyl acetylene **120** with acylium tetrafluoroborate **121**, yielding propargyl cation **122** (Scheme 6.15) [42d, e]. Quenching with MeOH occurs non-stereoselectively affording adduct



**Figure 6.12** The consecutive  $Ad_E$  and  $[2+2+1]$  cycloaddition reactions.

**123** as a diastereoisomeric mixture. Only one isomer is capable of undergoing a cyclisation reaction to tetracycle **119**, while the other could be equilibrated with  $\text{BF}_3$  to further maximise the yield and overall atom efficacy [42d, e].



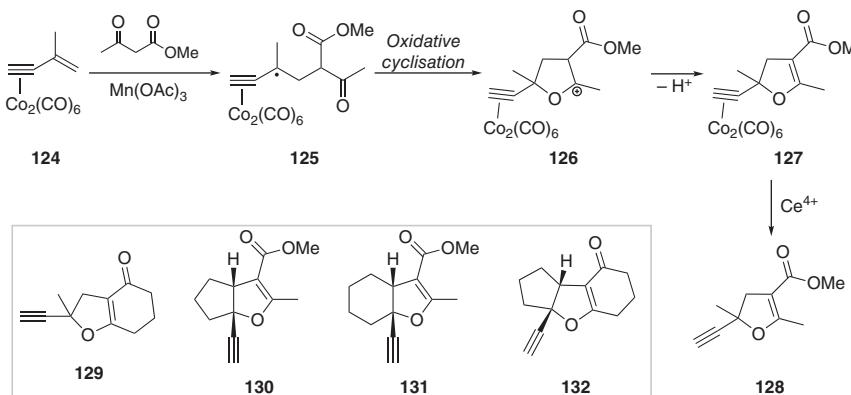
**Scheme 6.15** Assembling tetracyclic carbon framework via sequential  $\text{Ad}_{\text{E}}$  and cycloaddition reactions.

## 6.5 Cobalt-1,3-enyne Complexes: Radical Reactions

Radical reactions of cobalt-complexed 1,3-enynes remain a scarcely studied area with only one type of radical –  $\alpha,\alpha'$ -dioxocarbonyl – being cycloadded across the double bond [13, 43]. In the absence of the protecting group, radical reactions of 1,3-enynes lack chemoselectivity with both multiple bonds exhibiting a comparable affinity towards attacking electrophilic radicals [43b]. Methyl acetoacetate represents a typical radical precursor that can regioselectively add, upon oxidation with  $\text{Mn}(\text{OAc})_3$ , to the  $\beta$ -carbon atom in enyne **124** forming adduct-radical **125** (Scheme 6.16). Its oxidative cyclisation aided by trivalent manganese results in heterocyclic cation **126** with its formation being proven by trapping experiments [43a].  $\beta$ -Deprotonation to dihydrofuran **127** and subsequent cerium(IV)-induced decomplexation yields polysubstituted cycloaddition product **128**. The scope of the reaction was expanded to involve cyclic enynes and  $\beta$ -dicarbonyl compounds, thus gaining access to di- and tricyclic heterocycles **129–132** (Scheme 6.16) [13b, 43a]. The  $\text{Co}_2(\text{CO})_6$ -group plays multiple roles in enabling a highly selective three-step entry to fused [4.3.0] and [3.3.0] assemblies, in particular by protecting a triple bond against incoming radicals, inhibiting an acetylene–allene rearrangement, stabilising cationic/radical intermediates located  $\alpha$  to the metal core, and due to the steric effect, forming the cyclised products in a *cis*-stereoselective manner.

## 6.6 Prospects

In the past several decades, cobalt-assisted stoichiometric organic chemistry developed into a potent synthetic field, which produced a plethora of novel synthetic methodologies, provided access to an impressive array of topologically complex organic molecules, reached levels of efficiency – chemo-, regio-, stereo-, diastereo – that could rival, or outperform, those created in adjacent research fields, both organic and organometallic. Unsaturated organic compounds  $\pi$ -bonded to a cobalt carbonyl core substantially altered their electronic



**Scheme 6.16** Cobalt-complexed 1,3-enynes: radical cycloadditions mediated by trivalent manganese.

nature along with their spatial, kinetic, conformational, and thermodynamic characteristics. The totality of the experimental mass thus created, and the original approaches that have been developed, could become a useful guide for advancing, for developing ionic and radical chemistry of other  $\pi$ -bonded metal complexes.

While making predictions with respect to science can be risky, and compromising when not coming to fruition, nevertheless some “prophecies” are offered hereafter, hoping that at least some of them will be proven right by the future development of this field of study:

*Prospect #1:* Elaboration of a *catalytic version* for every reaction that has been developed with stoichiometric amounts of cobalt complexes; elaboration of the cobalt-catalysed reactions that would not require pre-isolation of  $\pi$ -bonded cobalt(0)-complexes, while maintaining the high efficiency and key parameters of the parent synthetic schemes.

*Prospect #2:* Development of the conceptually novel mechanistic tools for controlling the configuration in newly formed stereocentres in  $\alpha$ -position to the metal core as well as in more remote positions of  $\pi$ -bonded ligands.

*Prospect #3:* Transitioning from complete diastereoccontrol providing pure *d,l*- and *meso*-diastereomers in inter- and intramolecular reactions, to complete enantiocontrol, i.e. acquiring an ability for regulating an absolute configuration of the newly formed asymmetric carbons throughout the  $\pi$ -bonded unsaturated molecules.

*Prospect #4:* Discovery of the synthetic potential of cobalt–alkyne chemistry, both ionic and radical, by the scientific community, and widespread applications of original methods and methodologies for practical purposes in medicinal chemistry, materials science, natural product synthesis, and polymer chemistry.

*Prospect #5:* Application of mechanistic tools for controlling stereoselectivity in inter- and intramolecular cobalt–alkyne chemistry to other  $\pi$ -bonded

unsaturated units (dienes, arenes, diynes, enynes) and transition metals other than cobalt (Fe, Cr, Mo, W, Mn).

*Prospect #6:* In cobalt chemistry, probing new types of  $\pi$ -bonded unsaturated ligands such as fumarate [Co(0)], [44a] maleic anhydride [Co(0)], [44a] duroquinone [Co(I)], [44b, c] cyclobutadiene [Co(I)], [44d, e] acetylenes [Co(I)], [44e] arenes [Co(I)], [44f, g] allyl groups [Co(I)], [44g] *p*-benzoquinone [Co(I)], [44h] 1,3-cyclopentadiene [Co(I)], [44i] and 1,3-butadiene [Co(I)] [44j] with the synthetic objective being the development of electrophilic, radical, and anionic chemistry in the  $\alpha$ -position to the metal core.

*Prospect #7:* Elaboration of nucleophilic reactions of  $\pi$ -bonded cobalt complexes wherein the novel methodologies for placing a negative charge  $\alpha$  to the metal core will be explored, its interaction with transition metal orbitals adequately understood, methods for stabilising a negative charge uncovered, and an anionic chemistry developed.

Understandably, there will be important breakthroughs and developments, which could not have been predicted based on the current level of knowledge, simple expansions, or design by analogy, but which constitute the beauty of science and without which the scientific enterprise would lose much of its appeal and fascination.

## Abbreviations

Ac	acetyl
Ad <sub>E</sub>	addition electrophilic
Ar	aryl
Alk	alkyl
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DNA	deoxyribonucleic acid
DTBP	di- <i>tert</i> -butylpyridine
<i>i</i> Pr	isopropyl
<i>n</i> Bu	<i>n</i> -butyl
NBS	<i>N</i> -bromosuccinimide
NMR	nuclear magnetic resonance
SET	single electron transfer
TBS	tributylsilyl
TBTH	tributyltin hydride
THF	tetrahydrofuran
TMS	trimethylsilyl

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**7****Cobalt-Catalysed Cycloaddition Reactions***Gerhard Hilt*

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**7.1 Introduction**

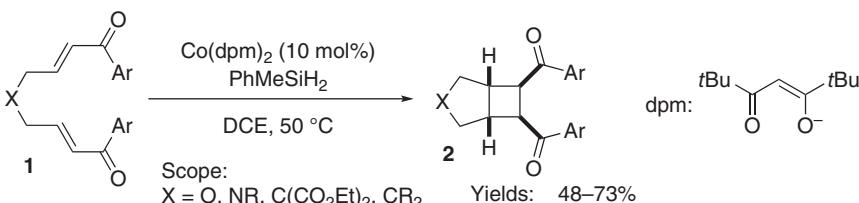
The synthesis of small- and medium-sized carbocyclic ring systems is an important subject in organic synthesis. The *Woodward–Hoffmann* rules are extremely useful to explain the reactivity of the starting materials – 1,3-dienes and alkenes/alkynes as dienophiles – the regioselectivities, and the stereochemical outcome of those reactions under thermal or photochemical conditions. When transition metals are involved, the reactions proceed most likely not in a concerted fashion and therefore, the *Woodward–Hoffmann* rules cannot explain the reactivities and selectivities observed in those stepwise reactions, where d-orbitals of the transition metal are involved.

In this chapter, the focus is set upon cobalt-catalysed cycloaddition reactions to form carbocyclic four- and six-membered ring systems as well as a limited number of cycloadditions for the formation of larger carbocyclic ring systems. The chapter covers the literature of the last 10 years in this field and will only refer to older literature when appropriate to illustrate the context, and older contributions have been reviewed several times [1–3]. For [2+1] cycloadditions, such as the (enantioselective) cyclopropanation, the [2+2+1] cycloadditions, such as the *Pauson–Khand* reaction, or [2+2+2] cyclotrimerisation of alkynes, see for the corresponding chapters in this book.

**7.2 Four-Membered Carbocyclic Ring Formation Reactions****7.2.1 [2+2] Cycloaddition of Two Alkenes**

The *Woodward–Hoffmann* rules imply strict guidelines for a [2+2] cycloaddition reaction of two alkenes in a thermal or photochemical reaction. A thermal [2+2] cycloaddition cannot be realised easily. Nevertheless, a stepwise, non-concerted transition metal-catalysed process is possible under thermal conditions but remains rare [4, 5].

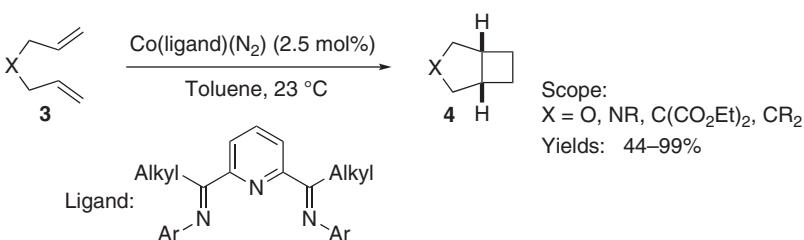
An intramolecular process was reported by *Krische* for the first examples of a diastereoselective [2+2] cycloaddition of bis-enones **1** for the formation of a *cis*-configured bicyclic cyclobutane derivatives of type **2** (Scheme 7.1) [6].



**Scheme 7.1** Intramolecular cobalt-catalysed [2+2] cycloaddition of enones.

The reaction was mostly restricted to  $\alpha,\beta$ -unsaturated ketones with arene substituents. Nevertheless, a derivative with a cyclopropyl-substituted ketone was also tested and the cyclopropyl moiety remained unchanged in the product, indicating that radical species were unlikely to be involved. Also, upon treatment with acid, a *cis-trans* isomerisation of the two carbonyl groups on the four-membered ring was observed. On the other hand, an electrochemical hydrodimerisation reaction of **1** led to a mixture of the *cis*- and *trans*-configured product in lower yield.

Later on, *Chirik* reported the application of cobalt complexes in the intramolecular [2+2] cycloaddition of bis-allyl ethers, amines, or other bis-allyl species of type **3** [7]. The process was realised with a preformed, low-valent cobalt complex at ambient temperatures to afford the generally *cis*-fused bicyclic products of type **4** (Scheme 7.2). Elaborated kinetic studies and deuterium-labelling experiments revealed important information of the reaction mechanism and explained the stereospecificity of the reaction.



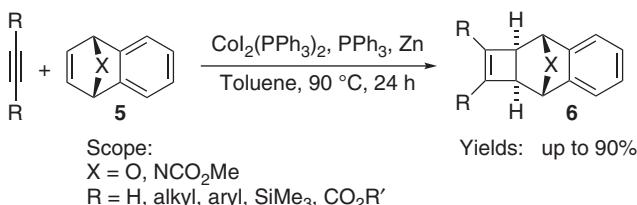
**Scheme 7.2** Intramolecular [2+2] cycloaddition of tethered terminal alkenes.

The starting materials **3** with geminal dimethyl-type subunits or bis-allyl ethers and amines were applied successfully in this reaction, generating the bicyclic products **4** in excellent yields of up to 99%. However, higher substituted double bond derivatives were not reported. Nevertheless, for 1,6-heptadiene (**3**, X = CH<sub>2</sub>), a respectable 44% yield of the bicyclic product was obtained after prolonged reaction time utilising a special aryl substituent on the ligand (Ar = 2,4,6-(C<sub>5</sub>H<sub>9</sub>)<sub>3</sub>C<sub>6</sub>H<sub>2</sub>). In electron spin resonance spectroscopy (EPR)

experiments a radical character of the catalyst was observed, which was reasoned to be a critical factor of the transformation. The ligand seemed to be redox active, forming a Co(I)-species with a delocalised radical in the ligand system. A switch from planar coordination in the resting state of the catalyst to a tetrahedral coordination for the active species enabled the electron transfer from the single occupied molecular orbital (SOMO) of the ligand to the metal centre, which is crucial for the [2+2] cycloaddition to proceed.

### 7.2.2 [2+2] Cycloaddition of an Alkene and an Alkyne

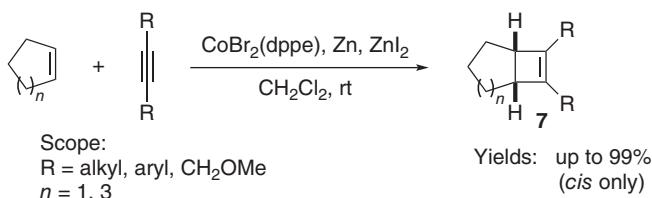
The [2+2] cycloaddition of an alkene and an alkyne would generate strained cyclobutene derivatives. For such reactions, a number of transition metal-catalysed processes have been described utilising various precious metal catalysts. The cobalt-catalysed [2+2] cycloaddition was reported by *Cheng* utilising terminal as well as internal alkynes for the reaction with strained tricyclic starting materials, such as **5** (Scheme 7.3) [8]. The reaction was catalysed by an *in situ*-generated catalyst comprising  $\text{CoI}_2(\text{PPh}_3)_2$ ,  $\text{PPh}_3$ , and zinc powder as reducing agent.



Scheme 7.3 [2+2] Cycloaddition of alkynes with strained tricyclic alkenes.

The products of type **6** were obtained exclusively as *exo*-isomers in moderate to good yields. The polycyclic products were generated from a small number of oxo- and azabenzenonorbornadiene derivatives but a broad variety of terminal and internal alkynes could be applied.

As an extension of this methodology, *Hilt* reported a simple cobalt catalyst system ( $\text{CoBr}_2(\text{dppe})/\text{Zn}/\text{ZnI}_2$ ) that accepted not only norbornyl derivatives as starting materials. In addition, also acenaphthylen and even cyclopentene and cycloheptene could be applied for the synthesis of cyclobutene derivatives such as **7** (Scheme 7.4). Remarkably, the reactions with cyclohexene as well as various

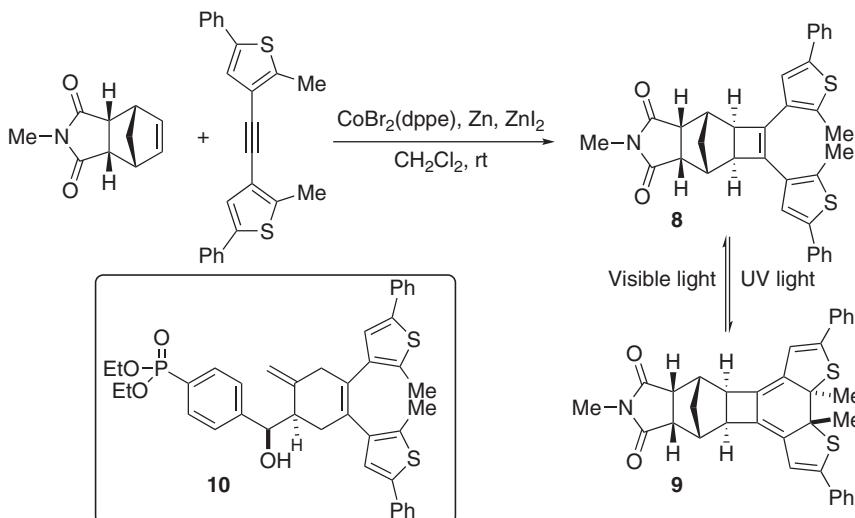


Scheme 7.4 [2+2] Cycloaddition of cyclic alkenes with internal alkynes.

substituted cyclopentene/cycloheptene derivatives were not successful, which limited the scope of the transformation significantly [9, 10].

However, only internal alkynes could be used because of the competing reaction pathway of cyclotrimerisation of terminal alkynes to the corresponding benzene derivative, which is predominant in these cases.

The cobalt-catalysed [2+2] cycloaddition was utilised by *König* for the synthesis of a photochemical switch (**8**) that was designed to have a linker group (imide group) attached for fixation on surfaces or polymers when the methyl group would be replaced with suitable functionalised side chains (Scheme 7.5) [11].



**Scheme 7.5** [2+2] Cycloaddition as key step for the synthesis of photochemical switches.

Unfortunately, the photochemical switch **8/9** proved to be not completely reversible so that long-time applications were not investigated. Nevertheless, the authors demonstrated that the products are in principle suitable for material science applications. Later on, the same authors demonstrated that a photochemical switch (**10**), which was derived from a cobalt-catalysed *Diels–Alder* reaction, could be bound to cellulose (by a linker system attached to the free OH group) or to silica gel (via the phosphonate group) and successfully switched by visible light and UV light [12].

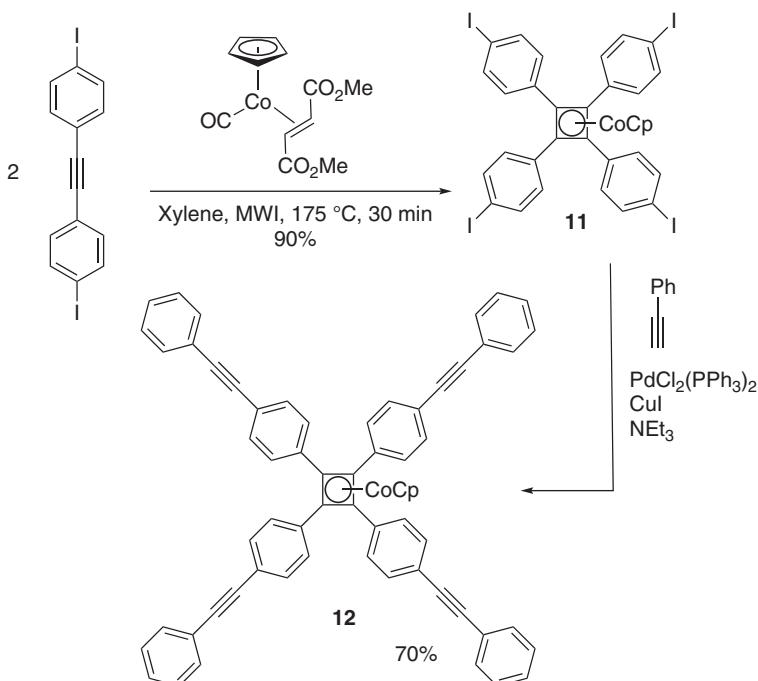
### 7.2.3 [2+2] Cycloaddition of Two Alkynes

The [2+2] cycloaddition of two alkynes would generate cyclobutadiene derivatives and based on the *anti*-aromatic character of this structure motif. Such species can only be stabilised in inert matrices at extremely low temperatures. However, when a transition metal fragment is coordinated to such a cyclobutadiene derivative, the metal fragment can stabilise those species, e.g. by formal

donation of two electrons to generate a “ $6\pi$ -aromatic” ligand, so that they can be isolated and characterised.

In this respect, the CpCo-fragment has been utilised to stabilise such unusual four-membered ring systems. The cobalt-catalysed [2+2] cycloaddition of two alkynes was realised by *Hamilton* and *Elias* in 2008 utilising diphenylacetylene as alkyne and the cyclopentadienyl cobalt fragment for their stabilisation [13, 14]. When a CO-containing cobalt precursor was used, also the formation of cyclopentadienone products was observed and the desired cyclobutadienyl complexes were obtained in up to 52% yield. The sterically hindered alkyne is important, because the coordination of a third alkyne is disfavoured, which would result in the [2+2+2] cycloaddition of three alkynes to produce benzene derivatives.

This reaction was improved by *Gandon* in 2012, when sterically hindered diaryl acetylenes (tolane derivatives) were reacted with the air-stable CpCo(CO)(fumaric ester) precursor for the generation of complexes such as **11** in up to 93% yield [15, 16]. The reaction could be applied to a wide variety of functionalised arene subunits in the 3- and 4-position, such as esters, boronic esters, and halide functionalities, so that follow-up reactions could be investigated to generate hitherto unprecedented structures, such as **12** (Scheme 7.6). However, when the steric hindrance was further increased, for example, with an additional methyl group in the 2-position of the phenyl ring, the reaction was completely inhibited. This observation indicated that the alkyne coordination



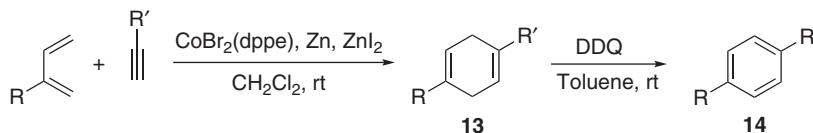
**Scheme 7.6** [2+2] Cycloaddition of tolane derivatives to CpCo(cyclobutadiene) complexes.

of two such starting materials was not possible anymore. Applications of these interesting structures in material science are yet to be explored.

## 7.3 Six-Membered Ring Formation Reactions

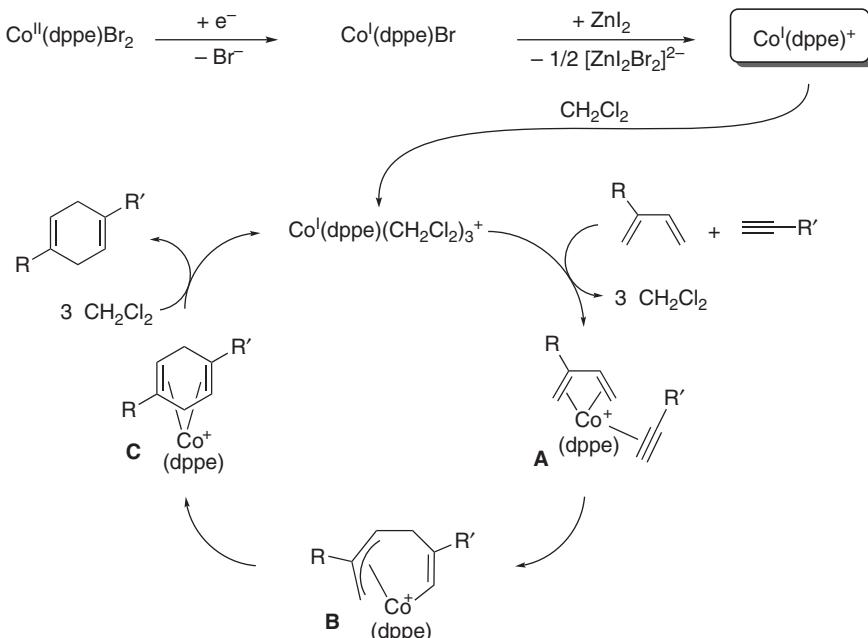
### 7.3.1 Cobalt-Catalysed Diels–Alder Reactions

Over the last decades, the *Hilt* group was dedicated towards the investigation of the cobalt-catalysed transformation of alkynes with 1,3-dienes. The transformations were conducted from a simple and air-stable cobalt(II) dihalide catalyst precursor, and the reactive species were generated *in situ* by addition of a *Lewis* acid as well as a reducing agent (Scheme 7.7). As a *Lewis* acid, zinc salts were applied most often but also other *Lewis* acids were applied successfully to abstract the halide anions from the cobalt centre. Noteworthy, in our hands Ag(I) did not result in a successful activation of the catalyst precursor but rather the formation



Proposed catalytic species:  $[\text{Co}^{\text{I}}(\text{dppe})]^+$

## Proposed reaction mechanism



**Scheme 7.7** General scheme and proposed mechanism of the cobalt-catalysed *Diels–Alder* reaction.

of a silver mirror on the glass wall of the flask was observed. For the reduction of the Co(II) precursor to the active Co(I) oxidation state of the catalyst, various reducing agents could be applied. While zinc powder proved to be very successful and cost efficient, also other metals could be applied as was shown by many other authors. The application of *n*-Bu<sub>4</sub>NBH<sub>4</sub> as reducing agent to generate cobalt(I) species was also possible, but this reducing agent should be used carefully. The formed by-product (BH<sub>3</sub>) was able to form *Lewis* acid adducts with the phosphine ligands and the coordination of phosphine ligands to the cobalt metal centre was a prerequisite for the *Diels–Alder* reaction to occur [17].

In general, the cobalt-catalysed *Diels–Alder* reaction of terminal alkynes with 1,3-dienes could be conducted at ambient temperatures under an inert atmosphere, best at molar concentrations of the starting materials – the concentrated, the better. Small amounts of water were tolerated but water as a co-solvent inhibited the reactions. The *Lewis* acid applied – mostly ZnI<sub>2</sub> – should be dried *in vacuo* overnight and stored under inert atmosphere. Thereafter, contact with moisture should be avoided or kept to a minimum.

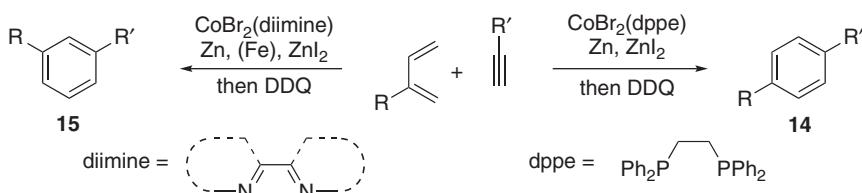
The primary product of the cobalt-catalysed *Diels–Alder* reactions are 1,4-cyclohexadiene derivatives (**13**, Scheme 7.7), which could be isolated in pure form. However, these materials were very air-sensitive resulting in the formation of the corresponding aromatic products. For the quantitative oxidation towards the arene products **14**, several oxidising agents were applied; the *Hilt* group used mostly the quinone 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) as efficient oxidising agent.

The proposed reaction mechanism (Scheme 7.7) consists of a stepwise activation to generate the active species [Co(dppe)]<sup>+</sup> that coordinates either to the solvent, which is replaced by the starting materials to afford intermediate A. A regioselective insertion towards **B** and ring closure within the ligand sphere of the cobalt catalyst generates intermediate C from which the desired product dissociates and concludes the catalytic cycle.

Concerning the mechanism of the reaction, gas phase ion-molecule reactions of isolated ions were conducted in a quadrupole ion trap attached to a mass spectrometer. Therein, cationic cobalt(II) complexes, such as [Co<sup>II</sup>Br(dppe)]<sup>+</sup>, proved to have a low affinity towards alkynes or 1,3-dienes, whereas cobalt(I) species, such as [Co<sup>I</sup>(dppe)]<sup>+</sup>, exhibited a very fast saturation with these starting materials (isoprene and phenylacetylene) in the gas phase [18, 19]. In normalised collision experiments the isolated fragment [Co<sup>I</sup>(dppe)(isoprene)(phenyl-acetylene)]<sup>+</sup> released mainly the *Diels–Alder* cycloadduct rather than the starting materials that indicated that the reaction took place in the ligand sphere already. Theoretical investigations conducted by *Frenking* in combination with EPR experiments underlined these findings, and the regioselectivity of the cobalt-catalysed *Diels–Alder* reaction could also be reproduced *in silico*. Furthermore, a prediction for untested ligands was made possible. Interestingly, the modifications of the ligands with electron-donating as well as electron-withdrawing substituents revealed that the regioselectivity of the cobalt-catalysed *Diels–Alder* reactions were affected by steric parameters rather than electronic effects. Also, it should be noted that the efficiency and chemoselectivity of the cobalt-catalysed

*Diels–Alder* reaction responded very sensitive on the bite-angle of the bidentate phosphine ligands.

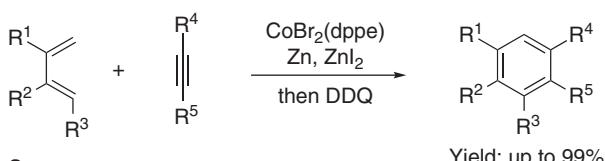
In contrast to the applicable *ortho/para*-rule in thermal *Diels–Alder* reactions, the regioselectivity of the cobalt-catalysed transformations was controlled by the ligand design. In 2006 *Hilt* reported cobalt catalysts with diimine-type ligand systems, which inverted the previously observed regioselectivity of cobalt catalysts with diphosphine-type ligands in *Diels–Alder* reactions (Scheme 7.8). With these catalyst systems, the 1,3-disubstituted arenes **15** could be generated efficiently, and in some cases the addition of catalytic amounts of iron dust improved the yield and regioselectivity of these *Diels–Alder* reactions.



Scheme 7.8 Ligand-dependent regiodiverse cobalt-catalysed *Diels–Alder* reactions.

One of the most important aspects of the cobalt-catalysed *Diels–Alder* reactions was the high functional group (FG) tolerance of the cobalt catalyst. Many different functional groups were incorporated and in several cases used directly for follow-up reactions. Although most of these reports of the *Hilt* group have been summarised in reviews in the past [2, 20, 21], a general overview towards the application of such functionalised building blocks will be given herein.

The alkyne can be acetylene itself, terminal alkyl-substituted alkynes as well as internal dialkyl-substituted alkynes [22]. Conjugated enynes and 1,3-diyne proved to be reactive as well and led to styrene or biphenyl derivatives. Functional groups in the aliphatic side chain, such as halides and tosylates in non-benzylic position of aliphatic side-chains are well accepted and could be used in follow-up reactions (Scheme 7.9). Cyclopropyl-substituted starting materials were accepted as well and ring-opened products were not detected [23].



Scope:

mono- and disubstituted 1,3-diene with:

R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> = H, alkyl, (hetero)aryl

Terminal and internal alkyne with:

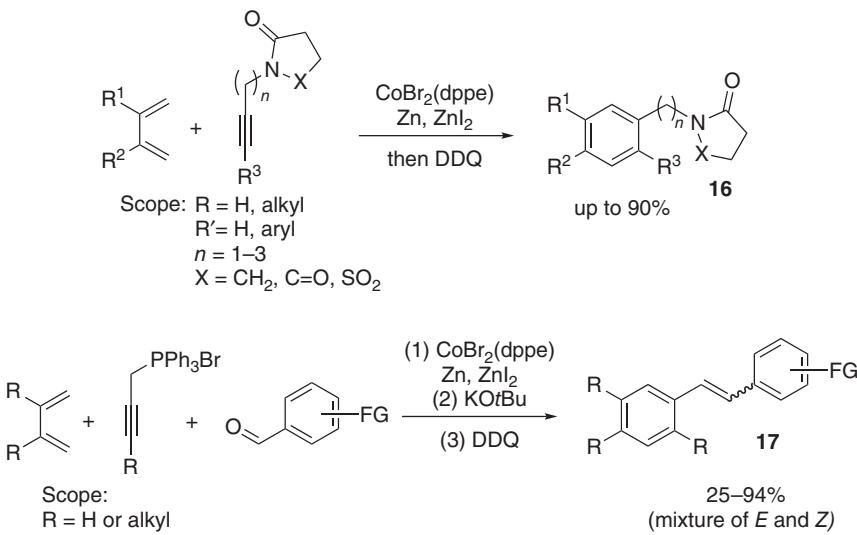
R<sup>4</sup> = H, alkyl, functionalised (hetero)aryl, Me<sub>3</sub>Si

R<sup>5</sup> = alkyl, functionalised (hetero)aryl, alkenyl, alkynyl

Scheme 7.9 Scope of the cobalt-catalysed *Diels–Alder* reactions with respect to aliphatic and aromatic substituents.

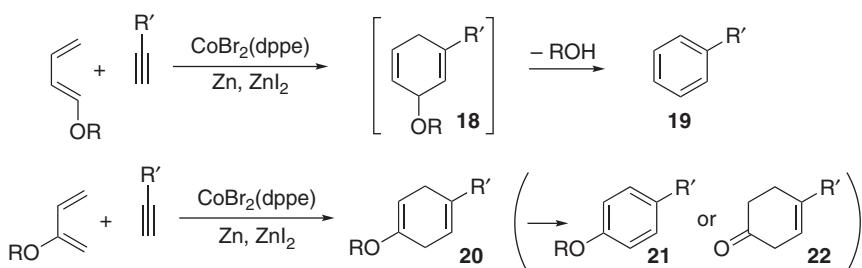
(Hetero)aryl substituents are also tolerated and many functional groups could be incorporated on the arene moieties. Worth mentioning are halide-substituted arene moieties ranging all the way from fluoro-, chloro-, bromo-, to iodoarenes [24–27].

Also, aromatic boronic esters, trimethylsilyl-substituted arenes and benzylic alcohols were applicable. Interestingly, over the DDQ oxidation of the dihydroaromatic intermediate, also the benzylic alcohol was oxidised to the corresponding aldehydes, allowing the synthesis of interesting multi-functionalised building blocks. Other nitrogen-containing functional groups within the alkynyl side chain, such as amides, sulfonamides, and imides could be applied successfully (Scheme 7.10) [28, 29]. The products of type **16** could be isolated in moderate to good yields, and follow-up reactions were particularly investigated when aryl substituents were introduced in position R<sup>3</sup> for the synthesis of nitrogen-containing large ring systems. However, neither amines (primary, secondary or tertiary) nor amides with a free NH-group were accepted, most likely because coordination to the catalyst inhibited an efficient turnover. Phosphonium salts were also applied in one-pot protocols in Wittig-type reactions to realise three-component reaction sequences for the synthesis of mostly diaryl-substituted alkenes, such as **17** [30, 31]. The scope of the reaction was scarcely investigated with respect to the substituents on the 1,3-diene or the phosphonium salt and as could be expected, very little limitations were found for functional groups (FG) on the aromatic aldehydes.



**Scheme 7.10** Nitrogen- and phosphorous-functionalised starting materials in cobalt-catalysed *Diels–Alder* reactions.

On the other hand, potentially also good ligating functional groups, such as the alkoxy-substituents on the alkyne (such as CH<sub>2</sub>OMe) or such directly attached to the 1,3-diene (Scheme 7.11) were tolerated. The alkoxy-substituents

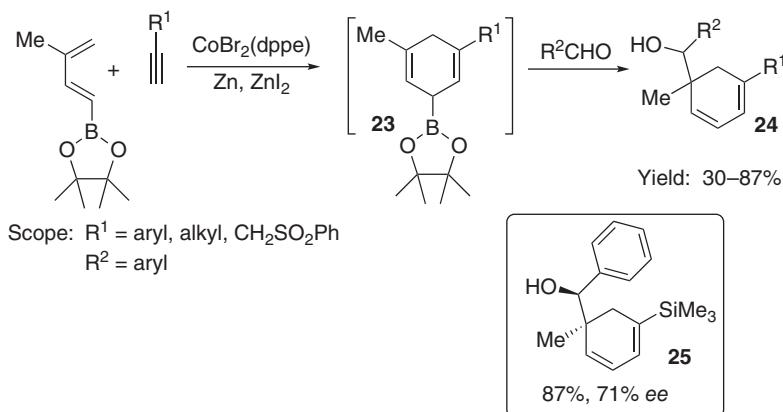


Scheme 7.11 Oxygen-functionalised 1,3-dienes in cobalt-catalysed *Diels–Alder* reactions.

on the 1,3-diene starting material are well accepted and two scenarios should be distinguished. For once, an alkoxy-substituent in the 1-position of the 1,3-diene resulted in the formation of the formal “*anti-Birch*” reduction product **18** [32]. This type of cycloadducts proved to be unstable and eliminated the alkoxy substituent immediately to form the defunctionalised arenes of type **19**. Secondly, when 2-alkoxy-functionalised 1,3-dienes were applied, the intermediate **20** – which corresponds formally to the “*Birch* reduction product” – could be isolated in good yields. Either oxidation to the arene (**21**) or mild hydrolysis to the non-conjugated cyclohexenone products of type **22** was reported.

Also, the higher homologues sulfur und selenium could be utilised in cobalt-catalysed *Diels–Alder* reactions. In these cases, alkynyl sulfides [33, 34] and alkynyl selenides [35] could be applied successfully, albeit higher catalyst loadings were needed for the latter two types of starting materials.

On the other hand, if an boronic ester functional group was located in the 1-position of the 1,3-diene, a similar elimination of a borane  $\text{HB}(\text{OR})_2$  was not observed and the dihydroaromatic intermediate **23** could be utilised in a chemoselective allylation reaction (Scheme 7.12) [36]. Accordingly, a sequential three-component reaction for the synthesis of more complex structures, such as **24** could be established. Enantio-enriched synthesis of these products were



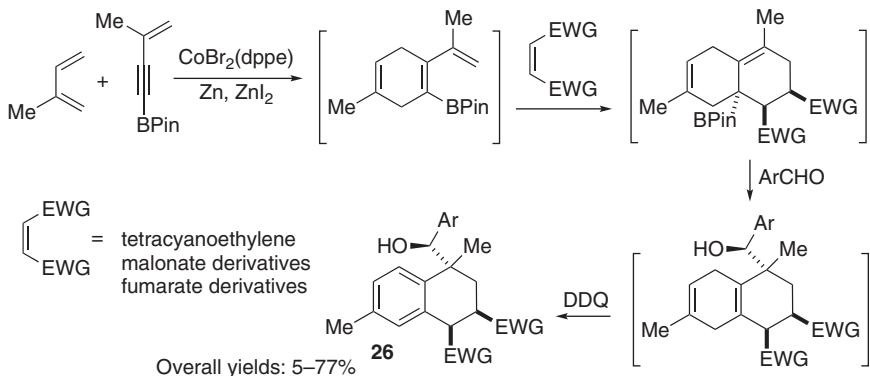
Scheme 7.12 Boronic ester-functionalised 1,3-dienes and alkynes in cobalt-catalysed *Diels–Alder* reactions and follow-up reaction sequences.

realised with chiral phosphine ligands, such as Norphos, so that the final product, such as **25**, could be isolated in 87% yield and up to 71% *ee*.

Unfortunately, these types of products are relatively unstable and tend to decompose in acidic as well as under basic conditions. Also, natural products with this substructure have not been reported in the literature, so that target-oriented syntheses were not performed.

The boronic ester functionality was also introduced in alkynyl position and these starting materials allowed a broader chemistry to be explored. For once, after the cobalt-catalysed *Diels–Alder* reaction and subsequent oxidation to the aryl boronic ester, traditional palladium-catalysed cross-coupling reactions were reported and a wide variety of phenanthrene and phenanthridine derivatives were synthesised in short reaction sequences [37, 38].

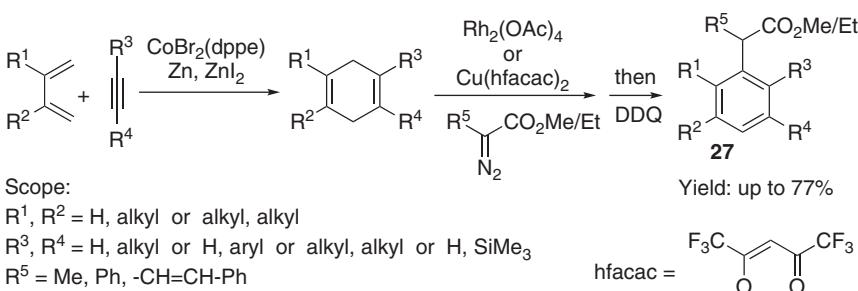
A sequential four-component reaction was realised when conjugated enyne boronic esters were applied. In these cases an allyl-boronic ester moiety was generated upon a sequence consisting of a cobalt-catalysed *Diels–Alder* reaction followed by a thermal *Diels–Alder* reaction with reactive dienophiles and finally the reaction with aromatic aldehydes generated the tetrahydronaphthalene products of type **26** in low to good overall yields (Scheme 7.13) [39].



**Scheme 7.13** Four-component reaction sequence towards substituted tetrahydronaphthalenes.

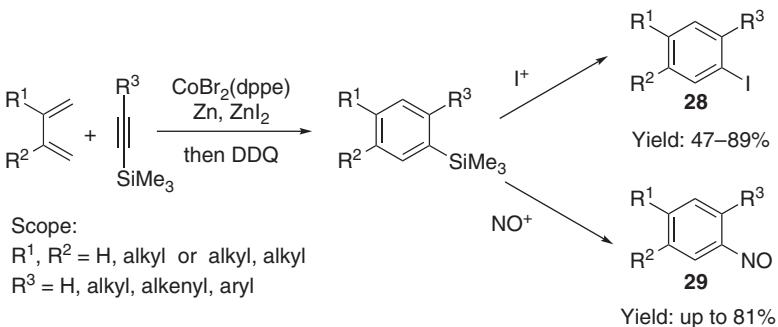
Also noteworthy are the follow-up modifications of the dihydroaromatic products after the *Diels–Alder* reactions. This could be realised by rhodium- and copper-catalysed regioselective CH-insertion reactions with diazo esters (Scheme 7.14). Thereby, tri-, tetra-, and even penta-substituted arenes of type **27** could be synthesised in good overall yields of up to 77% in a short reaction sequence. When unsymmetrical starting materials were used, the dihydroaromatic intermediate has two  $\text{CH}_2$  groups, which could react with the transition metal carbene complexes to undergo the insertion reaction. The reactions led with high regiocontrol to the insertion product, where the less hindered  $\text{CH}_2$  group reacted even if isoprene was used as 1,3-diene so that the methyl group shielded the attack of the carbene complex efficiently [40, 41].

Recent reports from the *Hilt* group described the use of the *Diels–Alder* products in *ipso*-substitution reactions, such as the formation of iodoarenes



Scheme 7.14 Carbene insertion reaction of dihydroaromatic intermediates.

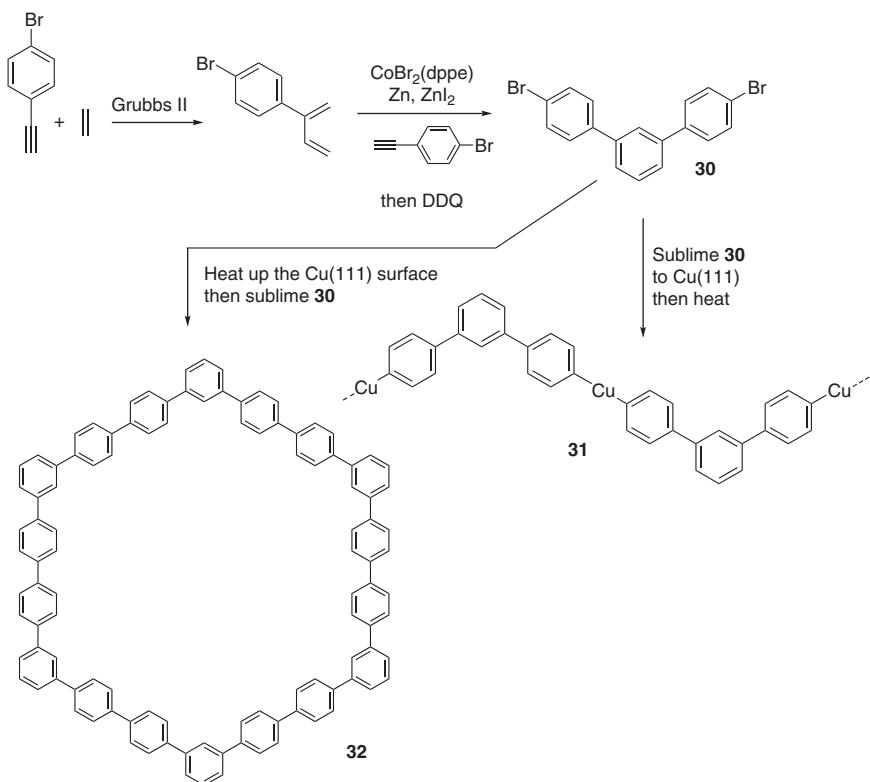
(28) or nitrosoarenes (29) from the corresponding trimethylsilyl-functionalised arenes (Scheme 7.15). In these cases, the silyl-functionalised alkynes were well accepted as starting materials, whereas 2-trimethylsilyl-functionalised 1,3-dienes gave very low conversions.

Scheme 7.15 *Ipso*-substitution of trimethylsilyl-functionalised arenes.

The iodonium ions were either generated by chemical methods from  $ZnI_2$  via oxidation with  $tBuOOH$  [42] or from KI via electrochemical oxidation at the anode [43]. The *ipso*-substitution reactions of the trimethylsilyl group with  $NOBF_4$  were very dependent from the substitution pattern and the electronic parameters of the substrate. The best results were obtained for electron-rich arenes, while some electron-deficient substrates gave only traces of conversion [44].

Applications in material science were realised by *Hilt* and *Gottfried* utilising the *meta*-selective cobalt-catalysed *Diels–Alder* reaction as starting point. The *Grubbs* enyne-metathesis reaction of materials such as 4-bromophenyl acetylene was utilised to generate a 2-aryl-substituted 1,3-diene, which was immediately reacted with 4-bromophenyl acetylene to afford the *meta*-terphenylene derivative **30** after oxidation with DDQ (Scheme 7.16).

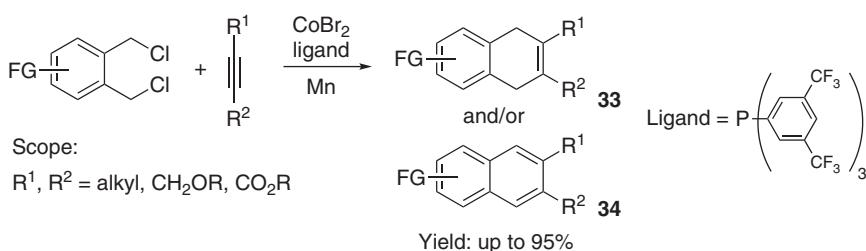
Sublimation on metal surfaces under high *in vacuo* conditions and heating of the metal surfaces, such as a Cu(111) surface, initiated a very traditional *Ullmann* coupling reaction. Under certain conditions a polymerisation towards a well-ordered zigzag-type Cu(II)-intermediate **31** could be observed on the metal



**Scheme 7.16** Synthesis of dibromo-functionalised terphenylenes for application in material sciences.

surface. On the other hand, when the metal surface was heated ahead of the sublimation of the starting material, the formation of large ring systems (32, also called honeycombenes) was observed [45]. Other macrocyclic ring sizes were also observed when  $\text{Ag}(111)$  was used. Those materials show interesting electronic features, because the electrons on the metal surface now behave like a “particle in a box” and show electron density pointing out of the surface with different energetic levels depending from the macrocyclic ring sizes [46]. Other application of similar dibrominated quarterphenylene derivatives led to the first observation of large ordered structures, such as Serpiński-triangles on a metal surface [47].

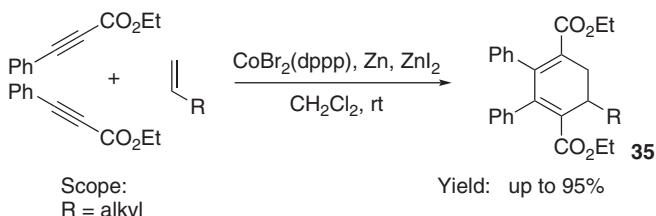
Another formal *Diels–Alder*-type cycloaddition was realised by Komeyama when 1,2-bis(chlormethyl)benzenes were reacted as surrogates for *ortho*-quinodimethanes in the cobalt-catalysed cycloaddition with alkynes (Scheme 7.17) [48]. Therefore, various (dihydro)naphthalene derivatives, such as 33/34, could be generated in moderate to good yields and a number of functional groups (FG) were tolerated on the arene starting material. The reaction was successfully conducted with internal alkynes including electron-donating as well as electron-withdrawing functional groups, and even cyclopropyl-modified alkynes were converted without ring-opening of the three-membered ring in good yields.



Scheme 7.17 *Ortho*-quinodimethanes in cobalt-catalysed *Diels–Alder* reactions.

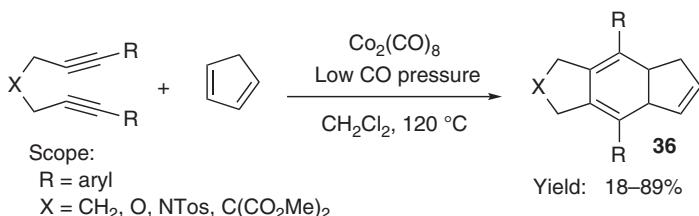
### 7.3.2 Cobalt-Catalysed [2+2+2] Cycloaddition Reactions Other than Cyclotrimerisation of Alkynes

The cyclotrimerisation of alkynes is a well-known process to form aromatic compounds. When one of the alkynes was substituted by an alkene, 1,3-cyclohexadiene derivatives were generated. For this rather unusual reaction, only a small number of contributions can be found in the literature. One example was reported by *Hilt*, where preferentially propiolate derivatives were reacted with terminal alkenes utilising a  $\text{CoBr}_2(\text{dppp})$  catalyst precursor to afford the cyclohexadienes in mostly moderate yields but good regioselectivity (Scheme 7.18) [49, 50].



Scheme 7.18 Intermolecular cobalt-catalysed [2+2+2] cycloaddition.

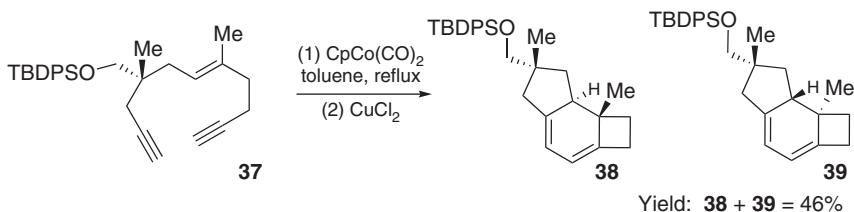
A partially intramolecular version of a [2+2+2] cycloaddition was reported by *Kim* when at low CO pressures the desired *Pauson–Khand* reaction – the insertion of CO to form a cyclopentenone product – was outrun by a [2+2+2] cycloaddition process. In this case the originally undesired product **36** was obtained in up to 89% yield (Scheme 7.19) [51].



Scheme 7.19 [2+2+2] Cycloaddition of diynes with alkenes.

In similar cases, the formation of 1,3-cyclohexadiene-type products **36** were also reported by *Gandon* when alkyl-linked diynes were reacted with enolethers to the corresponding 1,3-cyclohexadienyl cycloadducts with an additional alkoxy-substituent. However, under the forcing reaction conditions (microwave, 200 °C) an alcohol elimination occurred (similar to Scheme 7.11) to afford the corresponding bicyclic arene products in moderate to good yields. Interestingly, under certain circumstances, the authors were able to isolate and characterise some of the proposed CpCo-bonded dihydroaromatic intermediates [52].

An intramolecular version of this type of [2+2+2] cycloaddition was reported by *Aubert* and *Gandon* for the cyclisation of endiynes [53]. Lateron *Mulzer* utilised this method in the total synthesis of the tricyclic backbone of *pasteurestins A* and *B* [54]. The intramolecular [2+2+2] cycloaddition of the endiyne **37** was the key of the synthesis, and the tricyclic products **38** and **39** could be isolated in acceptable yields (Scheme 7.20). Unfortunately, the diastereoselectivity of the cycloaddition reaction was only moderately controlled by the remote stereogenic centre within the starting material.

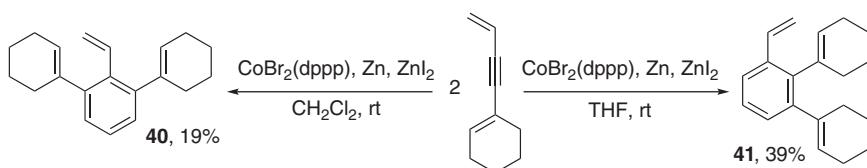


**Scheme 7.20** Application of a [2+2+2] cycloaddition towards 1,3-hexadienes in natural product synthesis.

Nevertheless, this application demonstrated that even complex molecules could be constructed by this methodology.

### 7.3.3 Cobalt-Catalysed Benzannulation Reactions

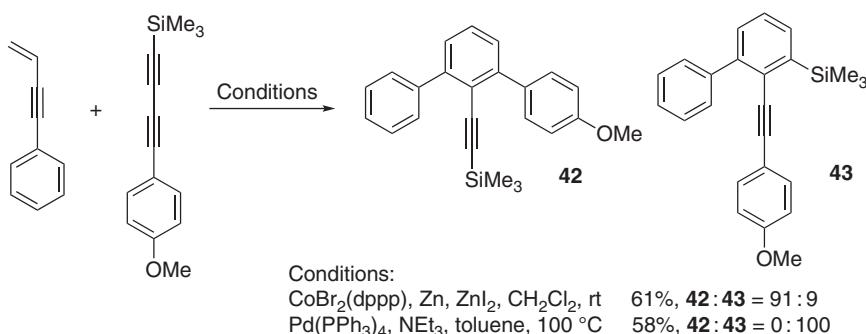
While the *Diels–Alder* reaction of alkynes and 1,3-dienes generates dihydroaromatic products, a direct access towards aromatic products can be realised in the benzannulation reaction. For this purpose two conjugated enynes are reacted to generate the desired arenes as two regioisomeric products. While palladium-catalysed reactions, mostly investigated by *Gevorgyan* [55], led to the symmetrical products, the cobalt-catalysed benzannulation generated either the symmetrical or the unsymmetrical isomer, depending from the solvent used. While in dichloromethane predominantly the symmetrical 2,6-disubstituted products of type **40** are formed (in up to 74% yield), in tetrahydrofuran (THF) the unprecedented benzannulation to the unsymmetrical 2,3-disubstituted arenes of type **41** was observed, albeit sometimes only in moderate yields (Scheme 7.21) [56, 57]. This distinct solvent effect is believed to rely on the stronger donor ability of THF in comparison to dichloromethane, and THF might occupy a ligand site in the regioselectivity-determining step when the starting materials



**Scheme 7.21** Solvent-dependent cobalt-catalysed benzannulation of conjugated enynes.

are coordinated to the cobalt catalyst and therefore alters the orientation of the enynes within the ligand sphere.

An expansion of this chemistry was realised by *Hilt* for the application of symmetrical as well as unsymmetrical 1,3-diyne in the benzannulation with conjugated enynes (Scheme 7.22) [58]. In the latter case, a chemoselective reaction could be observed when trimethylsilyl-functionalised 1,3-diyne were used. In these reactions the regioisomer **42** was formed predominantly and in comparison, the palladium-catalysed benzannulation led to the symmetrical regioisomer **43** in comparable yield and perfect regioselectivity.



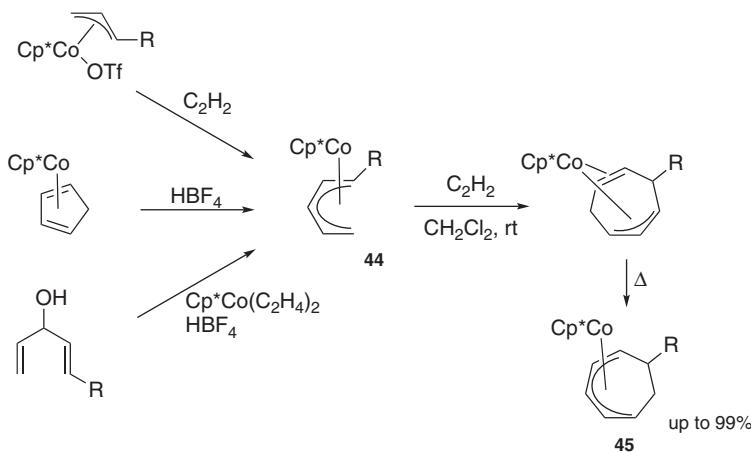
**Scheme 7.22** Comparison between cobalt- and palladium-catalysed benzannulation of conjugated enynes with 1,3-diyne.

Unfortunately, the cobalt-catalysed reactions are limited to unsubstituted enynes on the double bond and further substituents are not accepted. In contrast, additional substituents are well tolerated in the palladium-catalysed benzannulation.

## 7.4 Synthesis of Larger Carbocyclic Ring Systems

### 7.4.1 [3+2+2] and [5+2] Cycloaddition Reaction

This type of cycloaddition is based on the finding that pentamethylcyclopentadienyl cobalt(III) allyl complexes react stepwise with 2 equiv. of alkynes, as was reported by *Stryker* in 1998, to form seven-membered carbocyclic ring systems [59, 60]. The allyl cobalt complexes were generated either from simple allyl alcohol or from a 1,3-butadiene derivative and addition of TFOH (Scheme 7.23). The addition of the first alkyne led to the formation of a  $\eta^5$ -pentadienyl cobalt



**Scheme 7.23** Synthetic approaches towards  $\text{Cp}^*\text{Co}$  complexes with seven-membered ring ligands.

intermediate **44** that reacted readily with a second alkyne to result in a stabilised cobalt complex **45** of which a large number was isolated and characterised.

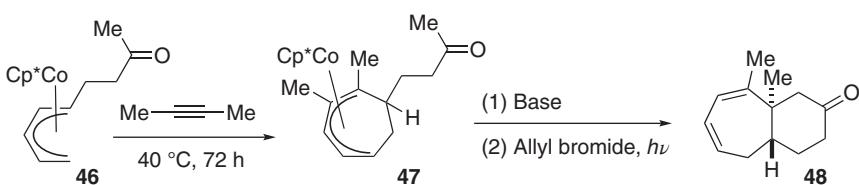
The authors also reported that  $\text{Cp}^*\text{Co}$  complexes with a substituted cyclopentadienyl ligand could be used as substrate for the formation of similar complexes of type **44** [61]. As an alternative approach, *Stryker* reported later on the access to acyclic  $\eta^5$ -pentadienyl cobalt intermediates from simple 1,4-alkandien-3-ols when reacted with  $\text{Cp}^*\text{Co}(\text{C}_2\text{H}_4)_2$  under acidic conditions. In general, these complexes reacted with acetylene, as well as terminal and electron-rich alkynes to form the desired seven-membered ring systems (**45**) in excellent yields [62].

The reaction mechanism of the [5+2] cycloaddition and the influence of the substituents upon the structures of the  $\eta^5$ -pentadienyl cobalt intermediates were also reported [63]. The rate-limiting step seemed to be the coordination of the alkyne to the cobalt fragment and all follow-up steps in this multi-step process revealed lower reaction barriers. Accordingly, substituent effects are relevant for the coordination of the alkyne and therefore rationalise the observed reactivities.

The usefulness of the reaction for applications in organic synthesis was realised when *Stryker* reported the liberation of the organic ligand from the  $\text{Cp}^*\text{Co}$  fragment by reaction with allyl bromide under photochemical conditions [64]. Eventually, *Stryker* also realised the application of more complex 1,3- as well as 1,4-pentadienols and applied this protocol in the synthesis of **48** in a multi-step reaction sequence (Scheme 7.24). The key step in the synthesis of **48** was the [5+2] cycloaddition of the functionalised pentadienyl complex **46** with 2-butyne to afford the intermediate **47**, which underwent cyclisation under basic conditions and decomplexation with allyl bromide.

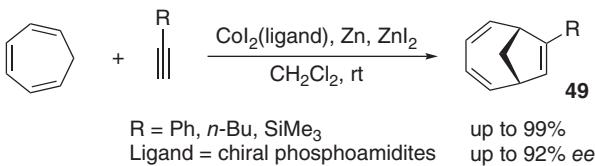
#### 7.4.2 [6+2] Cycloaddition Reaction

For the synthesis of larger ring systems, such as eight-membered rings, cobalt-catalysed reactions have been used as well. In this respect, *Buono*



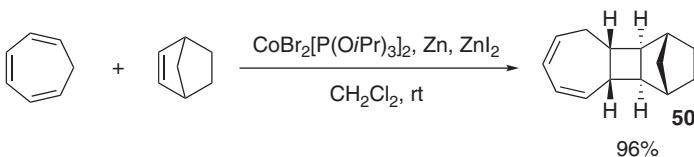
**Scheme 7.24** Synthesis of [5.4.0] bicyclic products starting from  $\text{Cp}^*\text{Co}$  pentadienyl complexes.

reported the reaction of cycloheptatriene with terminal alkynes leading to a [6+2] cycloaddition and the formation of bicyclic [4.2.1] nonatrienes [65]. In a similar fashion, *Buono* also described the reaction of cycloheptatriene with allenes to generate the corresponding [4.2.1] nonadienes with an additional exocyclic double bond [66]. Eventually, *Buono* was able to realise an asymmetric version of the cobalt-catalysed [6+2] cycloaddition utilising terminal alkynes. The highest enantioselectivities were obtained with chiral phosphoramidite ligands to generate the products of type **49** in good yields and enantioselectivities of up to 92% ee (Scheme 7.25) [67].



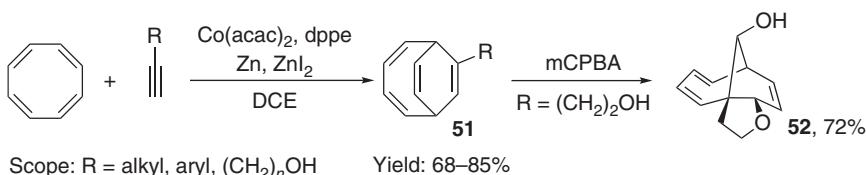
**Scheme 7.25** Synthesis of [4.2.1] bicyclic products by a cobalt-catalysed [6+2] cycloaddition.

The cobalt-catalysed [6+2] cycloaddition of cycloheptatriene with internal alkynes was later realised by *Hilt* utilising a cobalt catalyst system where phosphite ligands gave the best results (Scheme 7.26). Worth mentioning is the reaction of cycloheptatriene with terminal alkenes for the synthesis of [4.2.1] nonadiene derivatives as well as the reaction of cycloheptatriene with norbornene to give the tetracyclic product **50** in high yield [66].



**Scheme 7.26** Synthesis of a tetracyclic product utilising a cobalt–phosphite complex precursor.

Recently, the [6+2] cycloaddition reaction was expanded towards the application of cyclooctatriene for the cycloaddition with 1,3-diynes [68]. Also, applications of cyclooctatetraene that were originally reported by *Buono* [69] were reinvestigated by *Dzhemilev*. These cobalt-catalysed transformations of cyclooctatetraene with allenes [70] and particularly of interest with alkynes

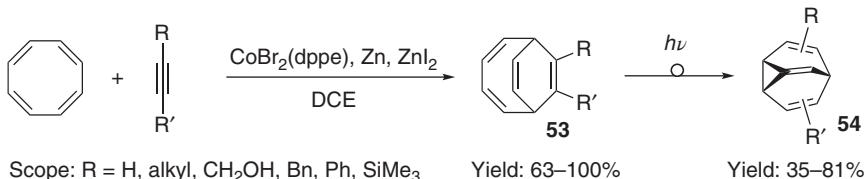


**Scheme 7.27** Cobalt-catalysed synthesis of [4.2.2] bicyclic products starting cyclooctatetraene.

(Scheme 7.27) [71], led to bicyclic structures, such as **51**, which were generated in moderate to good yields.

Interestingly, for these transformation the originally used  $\text{CoI}_2$  was successfully replaced by  $\text{Co}(\text{acac})_{2/3}$  as catalyst precursor and in combination with other reducing metals, such as magnesium and indium, no significant change of the yields was observed. Nevertheless, the reaction seemed to be limited to terminal alkynes with aromatic and aliphatic substituents bearing a small selection of functional groups. It should be noted that *Dzhemilev* investigated oxidative follow-up reactions (e.g. 3-chloroperbenzoic acid [mCPBA] as oxidising agent) of these bicyclic compounds and obtained a range of oxygenated bicyclic products with a rearranged skeleton, such as **52**.

The same cobalt-catalysed cycloaddition was later on reported by *Paštěka* and *Fallon* who extended the scope to a number of internal and terminal alkynes utilising almost identical reaction conditions (Scheme 7.28) [72]. When the products of type **53** were treated under photochemical conditions, the system rearranged to a range of bullvalene isomers **54** in moderate to good yields (35–81%).



**Scheme 7.28** Cobalt-catalysed synthesis of disubstituted [4.2.2] bicyclic products and transformation towards bullvalenes.

## 7.5 Conclusions

The stable oxidation states of cobalt cover a broad range and for cycloaddition processes the oxidation states 0 and +1 seem to be predominantly successful. These species can be stabilised by nitrogen as well as phosphine ligands. In addition, the structure of the ligands had a distinctive influence on the reactivity of the cobalt complexes. While redox-active pyridine-diimine-type ligands were successfully applied in [2+2] cycloadditions of two alkenes, [2+2] cycloadditions of strained alkenes and alkynes were mainly performed with cobalt(I) phosphine complexes. Finally, for the [2+2] cycloadditions of two

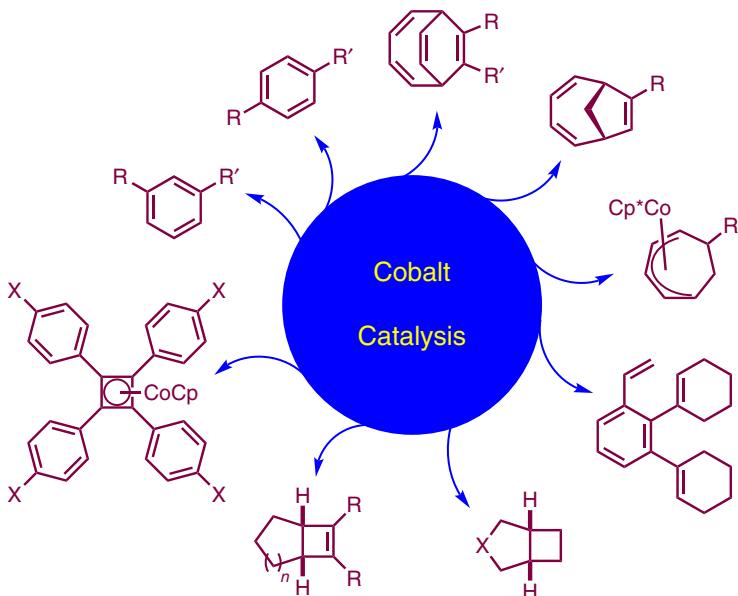
alkynes CpCo(I)-complexes are needed to stabilise the generated cyclobutadiene species.

For [4+2] cycloaddition processes, such as the *Diels–Alder* reaction, pyridine-imine as well as phosphine ligands were applied and very interesting effects on the regioselectivity of these cycloadditions could be observed, leading either to *meta*- or to *para*-substituted products, respectively. The high functional group tolerance of these cobalt catalysts made them perfect to investigate a broad range of applications towards functionalised arenes that are useful in various fields of modern research.

Cycloadditions beyond the formation of six-membered ring systems via the *Diels–Alder* reaction also [5+2], [6+2] cycloadditions and similar reactions have been realised in recent years. These make cobalt one of the most versatile metal for cycloaddition processes known up to date.

In various fields cobalt complexes exhibit complementary reactions patterns to established catalysts systems. This is not only true for cross-coupling reaction (Pd vs. Co) and for *Alder-ene* reactions (Ru vs. Co) but also for benzannulation reactions as was shown in this chapter. Accordingly, cobalt catalysts have expanded the arsenal of transformations for organic chemists considerably.

One of the main reasons for the success of cobalt catalysts seems to be the fact that rather small changes in the ligand decoration – either electronic or steric changes or bite angle of bidentate ligands – are highly important to differentiate between different possible reaction pathways. There is much more to be explored!



## Abbreviations

Ac	acetyl
Acac	acetylacetone
Ar	aryl
Cp	cyclopentadienyl
Cp*	pentamethylcyclopentadienyl
DCE	dichloroethane
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
dppe	1,2-bis(diphenylphosphino)ethane
dppp	1,3-bis(diphenylphosphino)propane
EPR	electron spin resonance spectroscopy
FG	functional group
$h\nu$	light irradiation
mCPBA	3-chloroperbenzoic acid
Me	methyl
MWI	microwave irradiation
Ph	phenyl
Pin	pinacol
rt	room temperature
SOMO	single occupied molecular orbital
TBDPS	<i>tert</i> -butyldiphenylsilyl
TfOH	trifluorosulfonic acid
THF	tetrahydrofuran
Tos	tosylate (4-methylphenylsulfonate)
UV	ultraviolet irradiation

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**8****Recent Advances in the Pauson–Khand Reaction***David M. Lindsay and William J. Kerr**WestCHEM, University of Strathclyde, Department of Pure and Applied Chemistry, 295 Cathedral Street, Glasgow, G1 1XL, Scotland (UK)***8.1 Introduction**

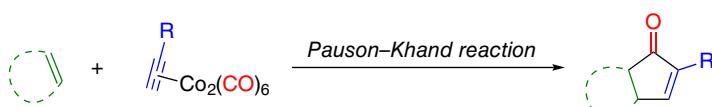
The *Pauson–Khand* reaction (PKR) is a formal [2+2+1] cycloaddition of an alkene, an alkyne, and CO to give substituted cyclopentenones [1]. As originally discovered by *Peter L. Pauson* and *Ihsan U. Khand* at the University of Strathclyde in 1971, this annulation process was mediated by cobalt (Scheme 8.1) [2].

Early variants of the reaction were conducted under purely thermal conditions, and low yields of cyclopentenone product would often result, admixed with a spectrum of organic and organometallic by-products. In the decades since its discovery, a range of promotional techniques have been developed, and, along with increased understanding of the reaction mechanism [3], this reaction has been transformed into a high yielding process of extremely broad scope, which has found numerous applications in synthetic chemistry.

The reaction continues to attract considerable interest, with studies encompassing methods of promotion, asymmetric and catalytic variants, and the reaction mechanism, in addition to numerous applications in total synthesis programmes and in preparative organic chemistry more generally. Within this chapter, developments in the PKR in these areas from 2013 to 2018 will be described. Given the remit of this book, only the cobalt-mediated processes will be discussed. Even with this restriction, due to the large number of studies published on this reaction, and the limited space for discussion, this review will not be comprehensive, but will instead focus on work that the authors feel highlights key advances in the area and those that have the potential to lead to new avenues of investigation in the future.

**8.2 Advances in the Pauson–Khand Reaction****8.2.1 New Methods to Promote the *Pauson–Khand* Reaction**

For several years following its discovery, the *PKR* was carried out under thermal conditions. However, from the late 1980s onwards, a range of methods were

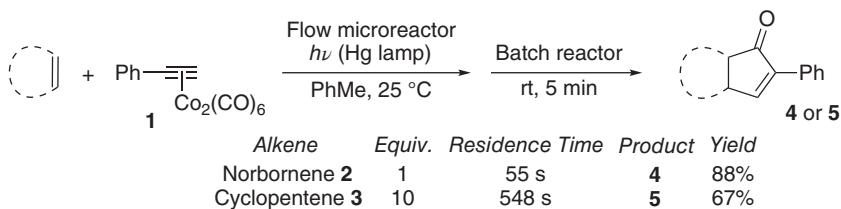


**Scheme 8.1** The Pauson–Khand reaction (PKR).

developed to promote the reaction, including techniques such as the use of ultrasound [4], dry state adsorption [5], and photochemical promotion [6] and additives such as amine *N*-oxides [7], alkyl sulfides [8], and primary amines [9]. During the current review period, there have been few notable additions to these established techniques or additives used to promote the PKR. Those that have been reported, however, are discussed in the following text.

#### 8.2.1.1 Flow Chemistry Applications of the Pauson–Khand Reaction

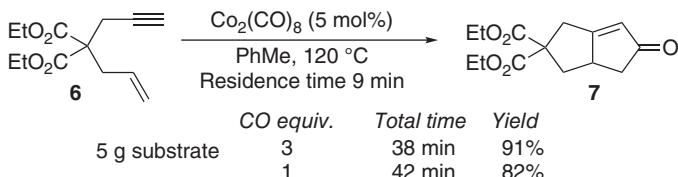
In 2013, *Yoshida* described a range of PKRs in a photochemical flow reactor [10]. These photochemically promoted PKRs in flow were shown to be considerably more effective than a control experiment in batch. However, in practice, following the end of the photochemically promoted reaction in the microreactor, the collected solution was stirred at room temperature for a further five minutes in a *Schlenk* flask (“batch reactor”). According to the authors, this is “in order to ensure that the reaction was complete”, although no comment is made by the authors on the extent of reaction following the flow portion of the process, so it is difficult to judge the necessity of this batch step. Nonetheless, the method was applied to a range of inter- and intramolecular PKRs. Notably, in intermolecular reactions with relatively unreactive alkene partners, very good yields were obtained in three cases when a somewhat modest excess (10 equiv.) of the alkene was employed. For example, as shown in Scheme 8.2, in the reaction of phenylacetylene-cobalt complex **1** with both norbornene **2** and the less reactive cyclopentene **3**, good yields of cyclopentenones **4** and **5** were obtained. Interestingly, the optimal solvent for the intramolecular reactions was different to that for the intermolecular processes (1,2-dimethoxyethane (DME) vs. toluene, respectively).



**Scheme 8.2** Photochemically promoted PKR in a flow microreactor.

More recently, *Blanco-Urgoiti* and *Pérez-Castells* reported a PKR in a plug flow reactor [11]. This report differed substantially from *Yoshida*'s work [10] in that the reaction was promoted thermally (usually 120 °C), and, most significantly, only a substoichiometric amount of Co<sub>2</sub>(CO)<sub>8</sub> was required (5 mol%), along with only

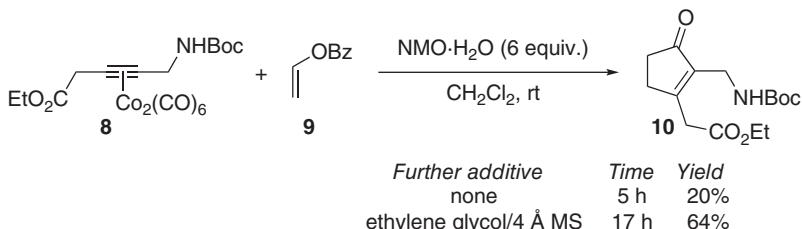
1.5 equiv. of CO (supplied at 5 bar). These conditions delivered excellent yields (78–99%) in a range of intramolecular PKRs. The reaction was scaled up to 5 g of substrate **6**, and excellent yields of product **7** could be obtained in ~40 minutes total time (Scheme 8.3). Good yields were also obtained in a small number of intermolecular examples, which all employed the highly reactive norbornene as the alkene component.



**Scheme 8.3** Catalytic intramolecular PKR performed in a plug flow reactor.

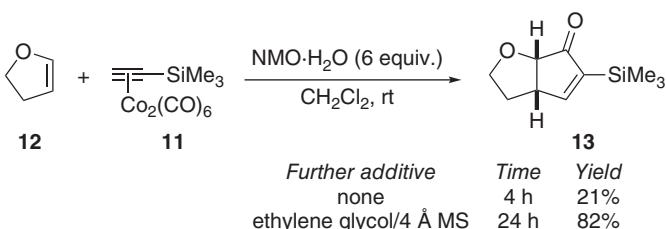
### 8.2.1.2 New Promoters

In 2017, *Verdaguer* and *Riera* studied the effect of ethylene glycol as an additive in the PKR [12]. Their studies were prompted by *Baran*'s observation, within a total synthesis programme directed towards the ( $\pm$ )-axinellamines A and B [13], of the dramatic enhancement of an intermolecular PKR by the addition of ethylene glycol, along with the more established promoters *N*-methylmorpholine *N*-oxide (NMO) [7] and 4 Å molecular sieves (MS) (4 Å MS) [14]. Following this, *Verdaguer* and *Riera* studied the NMO/ethylene glycol/4 Å MS combination in a range of intermolecular PKRs. Starting with the reactive alkene partner norbornene, the study then moved to medium ring *trans*-alkenes (see Section 8.2.2.3), followed by ethylene and ethylene equivalents (with terminal and internal alkynes), and, finally, the unreactive alkenes cyclopentene and 2,3-dihydrofuran. The optimal quantities of additive found to be required are relatively modest, at 317 mg of 4 Å MS and 1.7 mL of ethylene glycol per mmol of cobalt complex employed.



**Scheme 8.4** Ethylene equivalent PKR promoted by ethylene glycol and molecular sieves.

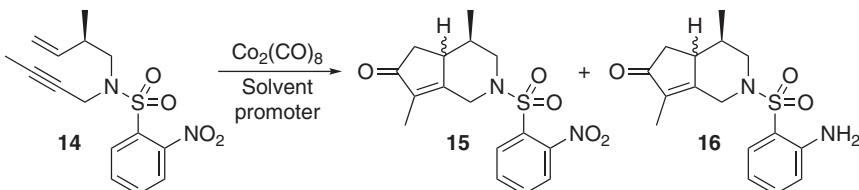
In most cases, an increase in yield was observed, compared with the conditions employing only NMO as the promoter. Of particular note is the very good yield obtained with functionalised internal alkyne **8** and ethylene equivalent vinyl benzoate **9** [15] to give cyclopentenone **10** (Scheme 8.4) and the dramatic enhancement of the PKR of trimethylsilylacetylene complex **11** with 2,3-dihydrofuran **12**, from 21% yield of **13** using only NMO·H<sub>2</sub>O, to 82% under the *N*-oxide/ethylene glycol/4 Å MS conditions (Scheme 8.5).



Scheme 8.5 PKR of 2,3-dihydrofuran promoted by ethylene glycol and molecular sieves.

There are, however, some issues with this study that make direct comparison of the various conditions difficult. In some cases, when comparing the *N*-oxide method to the *N*-oxide/ethylene glycol/4 Å MS conditions, a different quantity of *N*-oxide is used. For example, in the reaction of the *tert*-butyldimethylsilyl (TBS)-protected propargyl alcohol cobalt complex with *trans*-cyclooctene, 6 equiv. of NMO·H<sub>2</sub>O was used in the *N*-oxide-only “control” experiment vs. 10 equiv. of NMO·H<sub>2</sub>O when employed in conjunction with ethylene glycol and 4 Å MS. Additionally, only in the cyclopentene reactions did the authors evaluate the effect of the molecular sieves by comparing *N*-oxide/ethylene glycol/4 Å MS conditions with *N*-oxide/ethylene glycol conditions. In both examples studied, the *N*-oxide/ethylene glycol/4 Å MS conditions afforded higher yields, albeit with extended reaction times. More generally, in most cases, the *N*-oxide/ethylene glycol/4 Å MS reactions required a considerably longer reaction time to proceed to completion than the *N*-oxide only reactions. In some cases, the preparative chemist may wish to consider this in balance with the increased yield the combined conditions deliver. More positively, and also worthy of consideration for practitioners, the authors note that the ethylene glycol reactions afforded cleaner crude reaction mixtures that are easier to purify.

The second main development within the review period in this area of emerging promoters was a study on aromatic amines and nitro compounds by Kaneda [16]. The context for this study was the group’s earlier work examining alternatives to the tosyl unit for amine protection as part of a PKR within a total synthesis campaign [17]. Interestingly, PKRs of nosyl-protected enyne **14** gave mixtures of the expected product **15**, along with varying quantities of the corresponding aniline **16** (Scheme 8.6).



Scheme 8.6 PKR with a nitrosulfonyl enyne.

These observations prompted a screen of various aniline (Table 8.1) and nitrobenzene derivatives as additives in the Pauson–Khand cyclisation of model

**Table 8.1** Additive screening for the intramolecular PKR of enyne **17**.

 <b>17</b>	$\xrightarrow[\substack{\text{(2) Additive} \\ \text{60 }^\circ\text{C, 24 h}}]{\substack{\text{(1) Co}_2(\text{CO})_8 \\ \text{1,2-DCE, rt, 2 h}}}$	 <b>18</b>
Additive	Equiv.	Yield (%)
Aniline	1	82
Aniline	0.1	51
Aniline	3	81
Aniline	10	96
<i>N</i> -Methylaniline	1	62
<i>N,N</i> -Dimethylaniline	1	51

*N*-sulfonyl enyne **17**. Aniline was found to be superior to both *N*-methylaniline and *N,N*-dimethylaniline, with 1–10 equiv. of aniline delivering very good yields of cyclised product **18**.

Attention then turned to nitro-functionalised *N*-sulfonyl enynes **19**, the effect of aniline and nitrobenzene additives on both the yield of the *Pauson–Khand* cyclisation, and the fate of the nitro group in the substrate (Table 8.2). With aniline as the additive, 2-NO<sub>2</sub>-**19** was cyclised effectively, but with a 2 : 1 ratio in favour of reduction product 2-NH<sub>2</sub>-**21** to desired product 2-NO<sub>2</sub>-**20**. Interestingly, this reduction could be suppressed by switching to nitrobenzene as the additive, delivering a 21% yield of the desired product 2-NO<sub>2</sub>-**20**, with only 5% of the reduced product 2-NH<sub>2</sub>-**21**. Employing (at least) a 10-fold excess of both aniline and nitrobenzene additives allowed an increase of the nitro

**Table 8.2** Optimisation of the intramolecular PKR with nitrobenzene and aniline promoters.

 <b>19</b>	$\xrightarrow[\substack{\text{(2) Additive} \\ \text{60 }^\circ\text{C, 24 h}}]{\substack{\text{(1) Co}_2(\text{CO})_8 \\ \text{1,2-DCE, rt, 2 h}}}$	 <b>20</b>	 <b>21</b>	
Substrate	Additive	Equiv.	Yield of 20	Yield of 21
2-NO <sub>2</sub>	Aniline	1	16%	34%
2-NO <sub>2</sub>	Nitrobenzene	10	21%	5%
2-NO <sub>2</sub>	Aniline + nitrobenzene	10 + 10	50%	8%
3-NO <sub>2</sub>	Aniline + nitrobenzene	10 + 10	54%	Trace
4-NO <sub>2</sub>	Aniline + nitrobenzene	10 + 10	55%	Trace
2,4-(NO <sub>2</sub> ) <sub>2</sub>	Aniline + nitrobenzene	10 + 20	43%	Trace

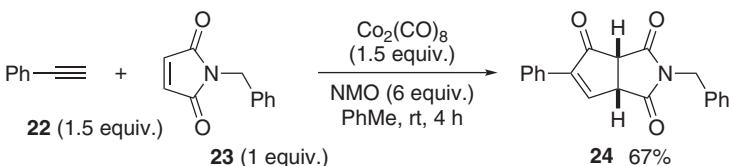
products 2-NO<sub>2</sub>-**20**, 3-NO<sub>2</sub>-**20**, and 4-NO<sub>2</sub>-**20**, and 2,4-(NO<sub>2</sub>)<sub>2</sub>-**20** to 43–55%, with minimal formation of the corresponding reduced products. The authors did not comment on the reduction of the nitro group or how this combination of additives operated, but there was clearly scope for further investigation of this methodology with respect to substrates containing other functional groups that have the potential to be vulnerable to the low-valent cobalt species that may be produced in such PKRs.

### 8.2.2 Novel Substrates

Over the years since the discovery of this annulation process, the *PKR* has been carried out with an array of terminal and internal alkynes and alkenes in both an inter- and intramolecular sense [1]. This section will describe the employment of new, unusual, or interesting substrates disclosed during the review period.

#### 8.2.2.1 Maleimides as Alkene Partners

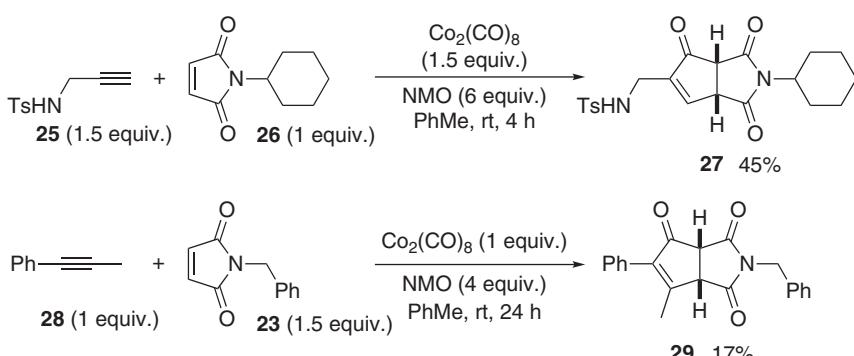
Electron-deficient and other conjugated alkenes have long been considered to be problematic in the *PKR*. In many of these cases, such as with styrenes, the cyclopentenone-forming reaction process is often derailed, and dienes result as the major products [18]. However, *Coombs* and *Brantley* have recently reported the use of *N*-substituted maleimides as alkene partners in the intermolecular *PKR* [19]. A brief screen of reaction parameters revealed that a relatively standard set of conditions (toluene as solvent, NMO as promoter) could deliver a good yield in the model reaction of the dicobalthexacarbonyl complex of phenylacetylene **22** (generated *in situ* and used in excess) with *N*-benzylmaleimide **23**, giving the interesting and highly functionalised bicyclic system **24** (Scheme 8.7).



**Scheme 8.7** Intermolecular PKR using maleimide as the alkene partner.

The reaction scope was then explored, and a total of 15 different examples were reported, including the products **27** and **29**, by reaction of *N*-cyclohexylmaleimide **26** with *N*-tosylpropargylamine **25** and *N*-benzylmaleimide **23** with 1-phenyl-1-propyne, **28**, respectively (Scheme 8.8).

Product **27** contains a dense array of functionality, with an allylic amine, an  $\alpha,\beta$ -unsaturated ketone, a 1,3-dicarbonyl system, and an imide all contained within and around the bicyclo[3.3.0]octane skeleton. Such scaffolds could certainly be of interest from a diversity-oriented synthesis perspective. Although product **29** was formed in a very low 17% yield, the challenging nature of this PKR must be recognised, with an internal alkyne reacting with an electron-poor maleimide. This yield was obtained using slightly amended reaction conditions, where the reaction time was extended, the quantity of NMO promoter used was

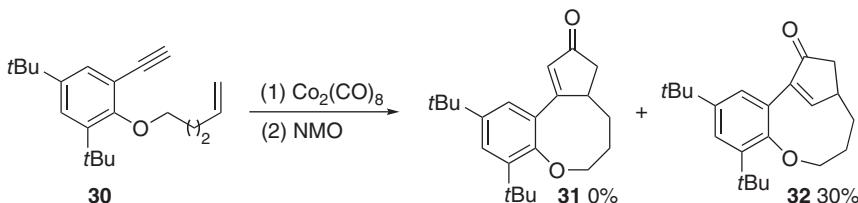


**Scheme 8.8** Scope of the PKR using maleimide as the alkene partner.

decreased slightly, and the alkyne, rather than the alkene, was employed as the limiting reagent. Under the original conditions, a slightly lower 13% yield was obtained. This second set of conditions also delivered an improved yield in some of the examples where a terminal alkyne was employed.

### 8.2.2.2 Novel Enyne Substrates

Lovely extensively studied the *PKR* of aryl-tethered enynes as a means to access cyclopentenones fused with medium ring systems. In earlier studies [20], the phenylacetylene derivative **30** did not give the expected 6,8,5-tricyclic system **31** in the *PKR*, but instead delivered 6,9,5-tricyclic head-to-tail product **32** (Scheme 8.9).



**Scheme 8.9** Formation of fused medium-sized ring products via the PKR.

Additionally, a bulky substituent in the position *ortho* to the alkene side chain on the aryl ring was required for the reactions to proceed in reasonable yields, a feature this group termed “steric buttressing”, with the proposal that these substituents were acting to reduce the number of unproductive conformations of the enyne and, thus, enhance the desired annulation process.

In an attempt to avoid the head-to-tail regioselectivity but retain cyclisation reactivity using the steric buttressing concept, more recent studies [21] have seen the same group employ benzylic alkynes within enynes of the type **33** (Table 8.3). A broad range of substrates were studied, with variation at the alkyne and terminal alkene substituents, as well as the inclusion of benzylic alcohol derivatives. In all cases, however, the alkene side chain length was such that the seven-membered benzoxepane products **34** were formed, as opposed to the

**Table 8.3** Steric buttressing in the intramolecular PKR.

Entry	Substrate	Product	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Conditions	Yield (%)
1	33a	34a	H	Ph	OH	A	31
2	33a	34a	H	Ph	OH	B	8
3	33b	34b	H	Ph	OTBS	A	50
4	33c	34c	tBu	Ph	H	A	56
5	33d	34d	tBu	Ph	OH	A	99
6	33e	34e	tBu	TMS	OH	B	70

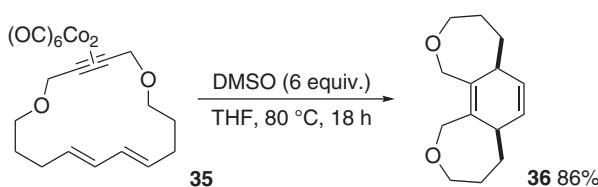
eight-membered ring products targeted in the earlier studies [20]. A few selected examples are presented in Table 8.3, to demonstrate the beneficial effect of steric buttressing in this system.

On model system **33a**, with no bulky substituents *ortho* to the alkene side chain, low yields of product **34a** were obtained under thermal (entry 1) and *N*-oxide (entry 2) conditions. The use of TBS-protected analogue **33b** improved the yield of **34b** to 50% (entry 3). Several byproducts were formed during the PKRs of the first buttressed systems ( $R^1 = t\text{Bu}$ ), and this led to removal of the benzylic alcohol functionality for part of the subsequent studies. Accordingly, substrate **33c** (entry 4) provided a 56% yield of the *Pauson–Khand* product **34c**. However, with internal alkynes **33d** and **33e**, the benzylic alcohol functionality was tolerated, and excellent yields of products **34d** and **34e** were observed (entries 5 and 6).

Following this, a range of 1,2-disubstituted alkenes were examined, with a focus on the diastereoselectivity of the process [21]. Overall, this work by *Lovely* represents an interesting extension of the steric buttressing concept and revealed a complex interplay of the various arene, alkyne, and alkene substituents in determining the success, or otherwise, of the PKR towards these medium-sized ring systems.

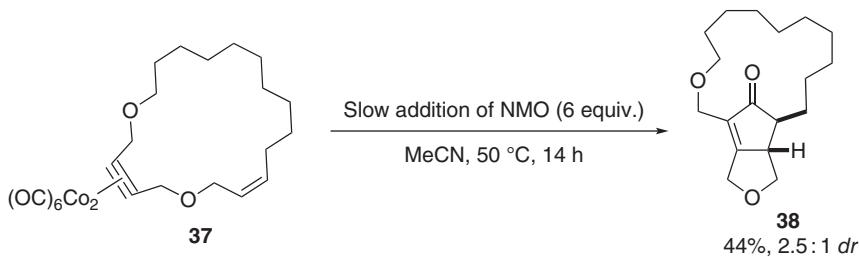
*Merlic* studied transannular *Diels–Alder* (TADA) reactions in a number of systems, including macrocyclic dicobalt-complexed dienynes [22]. For example, complexed diynne **35** underwent decomplexation of cobalt and subsequent TADA reaction to give tricyclic diene **36** in excellent yield (Scheme 8.10).

During this study, a variety of PKR promotion techniques were employed to decomplex the cobalt, triggering the TADA reaction. In addition to this, and more generally, cobalt-complexed dienynes often undergo the PKR as a side reaction when other transformations are sought [23]. However, in *Merlic*'s studies, no cyclopentenone products were observed. As a result, this group were inspired to



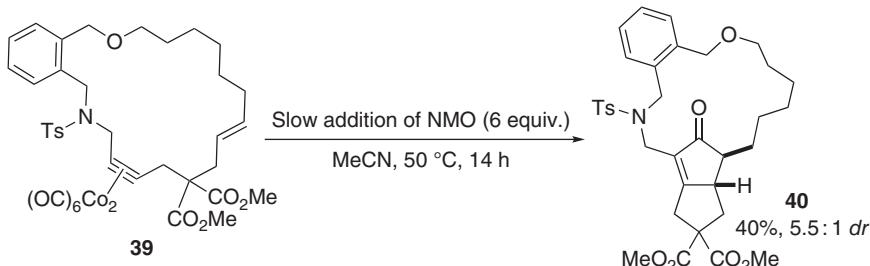
**Scheme 8.10** Transannular Diels–Alder reaction of a macrocyclic cobalt–alkyne diene complex.

alter the macrocycles of type **35** in an attempt to force these substrates towards a highly unusual transannular PKR, rather than a TADA process [24]. Several substrates were examined, unsuccessfully; however, these investigations, augmented by DFT studies, ultimately led to an understanding of the requirements for a successful transannular PKR. This work revealed that the two links between the alkene and alkyne complex needed to be asymmetric, with one short-chain and one long-chain length between the alkyne and the alkene. As a result of this, macrocycle **37** was designed and prepared and was found to undergo the transannular PKR in a moderate 44% yield, producing the interesting tricyclic product **38** (Scheme 8.11).



**Scheme 8.11** Transannular PKR of a macrocyclic ether tethered cobalt–enyne complex.

Phenylene-bridged amino ether **39**, containing a *gem*-diester unit, also successfully underwent the transannular PKR, giving product **40**, again in a moderate yield (Scheme 8.12) [24].



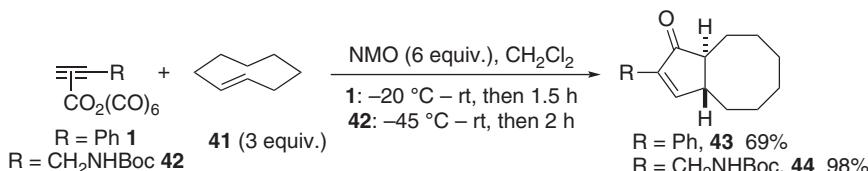
**Scheme 8.12** Transannular PKR of a phenylene-bridged macrocycle.

Developments in the area of transannular PKRs are clearly still in the early phase, but the insight gained from these studies provide the underpinning to enable further exploitation of this transformation to access a range of highly interesting polycyclic structures.

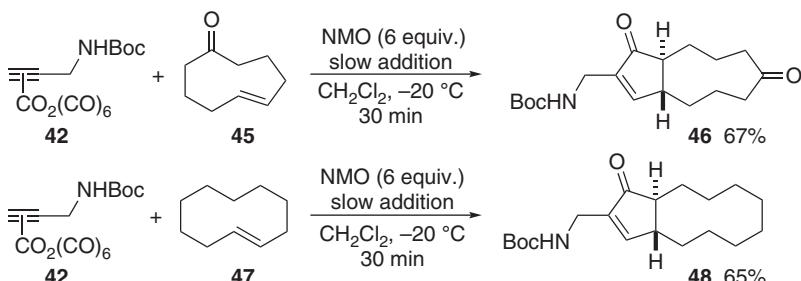
### 8.2.2.3 Strained Reaction Partners

Medium-sized ring alkenes are unreactive in the *PKR*; this is believed to be due to their lack of strain. However, it is perceived that the *E*-isomers of such alkenes should possess appreciably more potential for reactivity in the *PKR*. *Lledó* and *Riera* therefore undertook investigations into the *E*-isomers of medium-sized ring alkenes in the *PKR* [25]. Although *E*-cyclooctene **41** was unreactive under thermal conditions, the use of NMO as promoter allowed the reaction to be carried out under milder conditions, resulting in very good yields of bicyclic ketones with a range of alkyne complexes (Scheme 8.13). For example, use of phenylacetylene complex **1** led to bicyclic ketone **43** in a good 69% yield, while Boc-protected propargylamine complex **42** gave product **44** in an excellent 98% yield. Correspondingly, the *Z*-isomer of cyclooctene required a reaction time of two days and delivered only an 18% yield of product with phenylacetylene complex **1**. Although not demonstrated in this report, the *cis*-fused products could potentially be accessed by isomerisation of the products **43** and **44**, given that one of the ring junctions is  $\alpha$  to the carbonyl group and thus readily epimerised.

Under slightly modified conditions, *trans*-cyclonon-5-en-1-one **45** and *trans*-cyclododecene **47** were reacted with *N*-Boc propargylamine complex **42** to give bicyclic diketone **46** and bicyclic ketone **48**, respectively, in good yields (Scheme 8.14) [25]. Other cobalt alkyne complexes were also employed with these alkene partners, although yields were slightly lower.



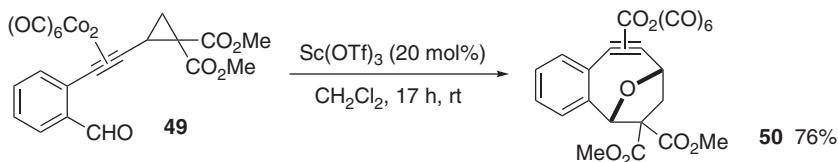
Scheme 8.13 PKRs using *E*-cyclooctene.



Scheme 8.14 Further PKRs using *E*-configured medium-sized ring alkenes.

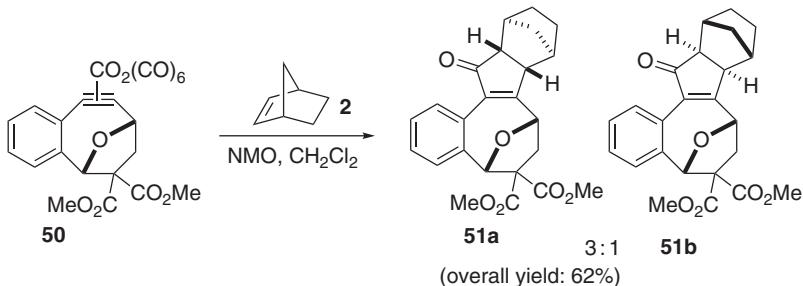
Such fused, small-/medium-sized ring structures are unusual and would be preparatively challenging to access via other routes. Therefore, there is considerable scope for further exploration of the PKR of medium-sized ring *E*-configured alkenes and the products thereof.

Strained cyclic alkyne reaction partners have also been studied recently. Wang reported an unusual, *Lewis* acid-mediated [3+2] intramolecular cross-cycloaddition of cyclopropylalkyne cobalt complexes, such as **49**, to give oxo-bridged benzocyclooctyne-cobalt complex **50** (Scheme 8.15) [26].



**Scheme 8.15** Access to strained cyclooctyne–cobalt complexes.

Wang then investigated the reactivity of products, such as **50**, and in the course of this study considered, quite naturally, the potential of such cobalt–alkyne complexes to undergo the PKR [26]. Reaction with norbornene **2**, promoted by NMO, delivered the cyclised products **51a/b** in a respectable 62% yield (Scheme 8.16). Interestingly, **51** was obtained as a 3 : 1 mixture of the two possible *exo*-diastereoisomers.

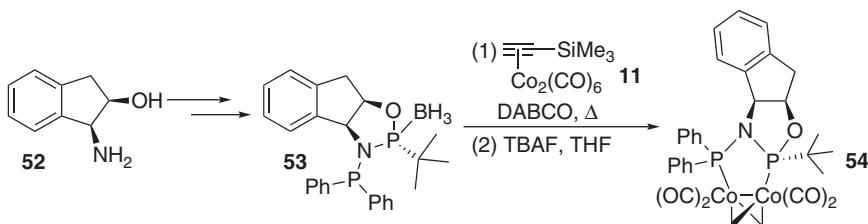


**Scheme 8.16** PKR of a strained cyclooctyne–cobalt complex.

### 8.3 Asymmetric Pauson–Khand Reaction

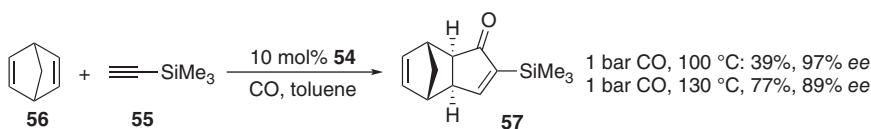
Over the past three decades, appreciable advances in asymmetric *Pauson–Khand* processes have been made [27]. This includes the use of chiral substrates, employment of chiral auxiliaries, generation of chiral complexes, and the development of chiral reagents and catalyst systems. During the current review period, there have been reduced levels of activity in the area of cobalt-mediated asymmetric PKRs, with only three studies examining new approaches to generating chiral cyclopentenone products. Interestingly, all three studies are based on the concept of a chiral chelating ligand bridging across the two cobalt atoms of the dicobalt alkyne cluster, and with all three focusing on the catalytic, asymmetric variant of the PKR. These studies are discussed in the following text.

*Verdaguer* and *Riera* have had some success in the stoichiometric PKR using cobalt complexes modified by coordination with chiral *P,S*-ligands [28]. Unfortunately, these ligands afforded low levels of enantioinduction when employed in a catalytic PKR, and the authors postulated that this was due to their hemilabile nature. In relation to this, a chiral diphosphine ligand appeared to be an attractive proposition, given the range of chiral variants available and the level of understanding surrounding these ubiquitous motifs. However, with chelates bearing two strongly donating atoms, the increased level of electron density bestowed by the ligand results in more tightly bound CO ligands, and, thus, overall lowered reactivity in the PKR, due to the required carbonyl dissociation in the first step [29]. As a result, for a successful chiral chelating ligand in the catalytic, asymmetric PKR, a balance needed to be sought whereby the ligand remained chelated to the cobalt cluster throughout the reaction but was not so strongly electron-donating that it inhibited the *Pauson–Khand* process. Noting the report by *Gimbert* [30], whereby a dicobalt-bisamidophosphinite chelate was able to catalyse the PKR with good levels of reactivity, *Verdaguer* and *Riera* looked for electronically related, chiral, bidentate motifs that would be applicable in the asymmetric, catalytic PKR. Bisphosphanes based on the aminoindanol scaffold **52** were prepared, leading to the diphenylphosphoryl derivative **53** shown in Scheme 8.17 [31].



**Scheme 8.17** A chiral phosphine cobalt–alkyne complex as a pre-catalyst for the asymmetric PKR.

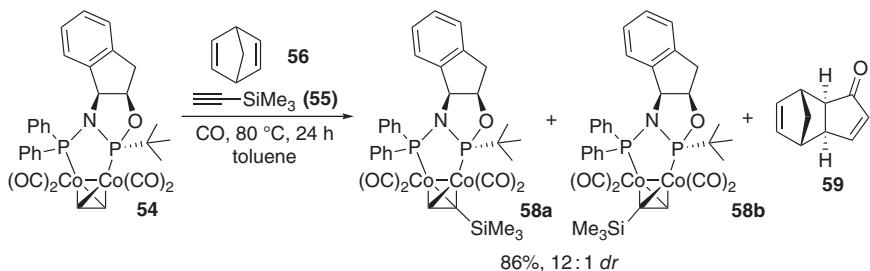
This ligand **53**, protected as the phosphine–borane complex, was reacted with the dicobalhexacarbonyl complex of trimethylsilyl acetylene **11**, followed by treatment with *tetra-n*-butylammonium fluoride (TBAF), to produce the bridged, chiral dicobalt acetylene complex **54** (Scheme 8.17), and this species was then tested in the asymmetric PKR (Scheme 8.18). Excellent enantioselectivities were obtained when using trimethylsilylacetylene **55** with norbornadiene **56** in toluene at 100 °C using a balloon of CO, delivering cyclopentenone **57** in 39% yield and 97% ee. In contrast, a 77% yield and a slightly lower 89% ee resulted with 1 bar of CO and a temperature of 130 °C in toluene. This temperature and solvent combination presumably implied a sealed reaction vessel and therefore the potential for a higher CO pressure than stated. Using this method, dimethylphenylsilylacetylene was also tolerated; however phenylacetylene and 1-hexyne delivered lower levels of enantioselectivity. A range of other solvents, temperatures, and chiral ligands (varying the diphenyl groups on the phosphine) were examined, but no combinations exceeded the yield or ee from



Scheme 8.18 Asymmetric PKRs using pre-catalyst 54.

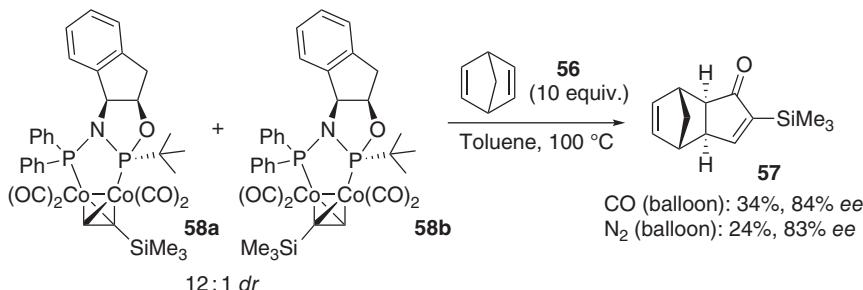
the conditions in Scheme 8.18. In general, there appeared to be a trade-off in yield and *ee* in this system, where one can be maximised only at the expense of the other.

Studying the system in more detail, complex 54 was reacted with trimethylsilyl acetylene 55 and norbornadiene 56 at the lower temperature of 80 °C. Cyclopentenone 59 was isolated in an undisclosed yield, but, more interestingly, complexes 58a and 58b were isolated in good yield (Scheme 8.19). Due to the tetrahedral nature of the C<sub>2</sub>Co<sub>2</sub> cluster, with a substituent introduced onto the alkyne these complexes now became diastereomeric, and in this case 58a and 58b were isolated in a 12 : 1 ratio.



Scheme 8.19 Formation of diastereomeric cobalt–alkyne complexes.

Interestingly, when the 12 : 1 58a/b mixture was then subjected to a stoichiometric PKR with norbornadiene 56, the product 57 was isolated in 34% yield and 84% *ee* on reaction under a CO atmosphere and in 24% yield and an almost identical 83% *ee* on reaction under a N<sub>2</sub> atmosphere (Scheme 8.20). These enantiomeric excesses correspond to an 11 : 1 ratio of enantiomers, almost exactly reflecting the initial diastereomeric ratio of the complex. The implication of this



Scheme 8.20 PKR of a diastereomeric mixture of cobalt–alkyne complexes.

study was that transfer of chirality from the cobalt–phosphane complex was completely maintained, and, thus, high diastereorecontrol in cobalt–alkyne complex formation during catalyst turnover is key to achieving a high enantioselectivity in this catalytic process. This important observation clearly has implications for the design criteria of future ligand series in this area.

*Verdaguer and Riera* continued their studies into bidentate chiral ligands in the catalytic asymmetric PKR by exploring the stereoselectivity of complex formation in more detail [32]. In this instance, the chiral ligand chosen was QuinoxP\* (60) [33], which was reacted with a range of cobalt–alkyne complexes **1**, **11**, and **61–63** (Table 8.4) to form the corresponding bis(phosphine) complexes **64–68**.

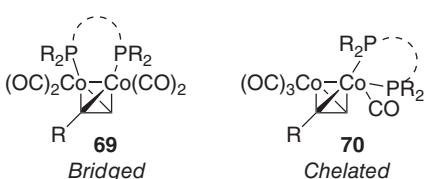
The data in Table 8.4 clearly shows a dependency of the alkyne substituent on the diastereoselectivity of QuinoxP\* **60** complex formation, with increasing steric bulk of the substituent appearing to lead to an increase in diastereoselectivity.

However, the mode of ligand coordination is a more complex issue, with the ligand able to bridge across both cobalt atoms (Figure 8.1, **69**), or to chelate to only one of the two cobalt atoms (Figure 8.1, **70**).

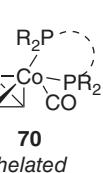
A detailed experimental and computational study was thus carried out, and these studies revealed that in all cases, the chelated complex mode **70** was shown to be favoured, both experimentally and computationally. This was in contrast to the previous ligand complex system **54** reported by *Verdaguer and Riera* [31], and presumably the smaller chelate bite angle of the ligand system in **54** favours bridging across the two cobalt centres. Returning to the case of QuinoxP\* **60**, the

**Table 8.4** Formation of a range of cobalt–alkyne QuinoxP\* complexes.

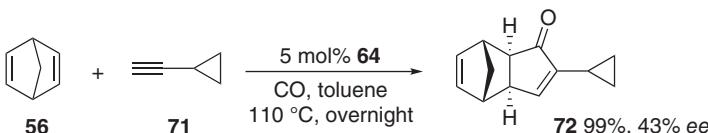
Entry	Starting complex	R	Product complex	Yield (%)	dr
1	<b>61</b>	H	<b>64</b>	36	—
2	<b>62</b>	nOct	<b>65</b>	45	1.3 : 1
3	<b>1</b>	Ph	<b>66</b>	70	4 : 1
4	<b>63</b>	CMe <sub>2</sub> OH	<b>67</b>	33	8 : 1
5	<b>11</b>	SiMe <sub>3</sub>	<b>68</b>	46	10 : 1



**Figure 8.1** Bridging vs. chelating modes of diphosphine complexation.



matter was further complicated by the choice of axial or equatorial coordination sites in each case and the potential for fluxional behaviour between these various configurations. Finally, the chiral complexes were evaluated in catalytic PKRs with norbornadiene **56**. Although yields were generally high, the enantioselectivities were low in all cases, with the reaction of cyclopropylacetylene **71** giving the best selectivity, resulting in the formation of product **72** in 43% *ee* using 5 mol% of the acetylene–hexacarbonyldicobalt–QuinoxP\* complex **64** (Scheme 8.21).



**Scheme 8.21** Asymmetric PKR using cyclopropylacetylene and QuinoxP\* complex **64**.

Nonetheless, the enhanced structural understanding of modified cobalt–alkyne complexes mean that these detailed structural studies should provide the foundations for further advances in catalytic, asymmetric *Pauson–Khand* processes.

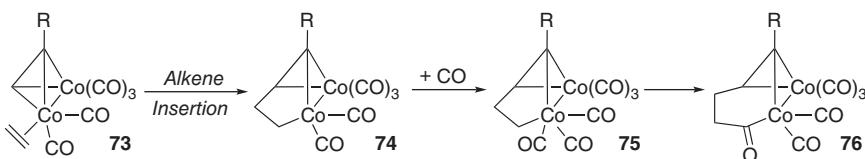
In a departure from the traditional dicobalt motif associated with the PKR, *Nordlander* studied chiral diphosphine derivatives of alkylidene nonacarbonyltricobalt clusters in the PKR [34]. A range of Josiphos and Walphos derivatives were complexed to the tricobalt cluster, and, again, structural studies were undertaken to establish the mode and position of coordination. The complexes were evaluated in a range of PKRs, with essentially racemic products observed in all cases, along with low yields. Clearly, further studies into the tricobalt motif are required before this can be considered as a viable option for asymmetric *Pauson–Khand* annulations.

## 8.4 Mechanistic and Theoretical Studies

A detailed mechanistic picture of the *PKR* continues to grow [3], and this review period has seen ongoing interest in the study of various aspects of the reaction pathway, both experimentally and computationally. Specifically, there have been a series of recent reports examining further detail of the reaction mechanism, and these areas will now be discussed in turn.

*Gimbert* used mass spectrometry techniques to investigate several aspects of the *PKR* mechanism. In 2014, the group reported an isotope labelling study using  $^{13}\text{CO}$ , in order to determine the origin of the carbonyl group present in the cyclopentenone product [35]. In terms of the proposed mechanism, the authors felt that intermediate **74**, the product of insertion from olefin complex **73** (Scheme 8.22), warranted investigation, and, in particular, they were curious about the feasibility of the following step, where a CO molecule returns to complex **74** to give **75**, which then undergoes CO insertion to give acyl complex **76**.

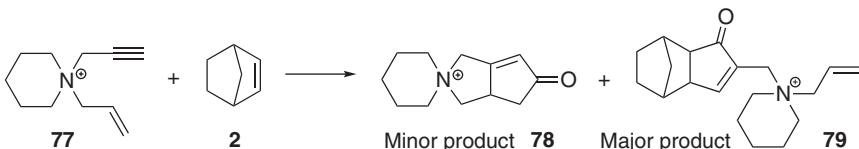
Mass spectrometry ion-molecule experiments were performed on a suitably charged complex, and no  $^{13}\text{C}$  incorporation was observed in the final product.



**Scheme 8.22** Alkene coordination and insertion followed by CO coordination and insertion portions of the proposed PKR mechanism.

From this, the authors infer that external CO does not return to complex 74 to give hexacarbonyl complex 75, which is part of the currently accepted mechanism. Supported by computational studies and kinetic modelling, the authors propose a series of alternative pathways involving internal CO transfer from the other cobalt atom, which is currently assumed to be a “spectator” in this process. The clear implication of this work is that a fundamental revision of one of the key steps in the proposed *Pauson–Khand* mechanism is required, and further studies in this area will aid in refining *Gimbert’s* hypotheses to arrive at a more definitive proposal.

More recently, *Gimbert’s* group have used gas phase studies involving electrospray ionisation in tandem with mass spectrometry to study the intermolecular PKR of various alkenes, as well as comparing the inter- vs. intramolecular PKRs [36]. When investigating norbornene, cyclopentene, and 1-hexene as alkene partners, the authors found that the gas phase reactivity matched the solution phase hierarchy. More interestingly, it was also found that a reactive alkene such as norbornene **2** could outcompete the alkene of an enyne, favouring an intermolecular reaction when an intramolecular pathway is possible. Specifically, and as shown in Scheme 8.23, the gas phase reaction of charged enyne **77** in the presence of norbornene **2** led to both intra- and intermolecular *Pauson–Khand* products, **78** and **79**, respectively, being observed by mass spectrometry; however, intermolecular product **79** was considerably more abundant.



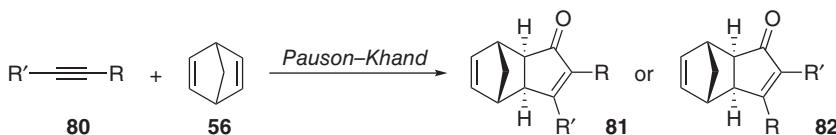
**Scheme 8.23** Gas phase competition experiment between intra- vs. intermolecular PKR pathways.

Clearly, general inferences around intra- vs. intermolecular reactions cannot be drawn from this example, and the ratio of the two processes will depend on the nature of the enyne and competing alkene, along with a host of other reaction parameters. However, this observation could serve as the impetus for a more extensive preparative study to establish more detailed reactivity guidelines.

Continuing with studies into the fundamental steps of the *Pauson–Khand* mechanism, *Uyeda* reported a framework that allows for investigation of some of the proposed intermediates in the reaction that are not readily observable

due to the exergonic nature of the process following alkene coordination [37]. These researchers have employed a dinickel naphthyridine–diimine complex as a surrogate for the hexacarbonyldicobalt cluster. Not only does this new moiety mediate the PKR of enynes, but also, in this system, a number of intermediates *en route* to the cyclopentenone product were stable and isolable. There are clearly some caveats to this work, in that the mechanism involving this dinickel cluster may not necessarily mirror the dicobalt variant; however, this work still provided an interesting insight into some of the PKR's proposed intermediates. Additionally, this new dinickel template has considerable potential for exploration in terms of both catalytic and asymmetric *Pauson–Khand*-type processes.

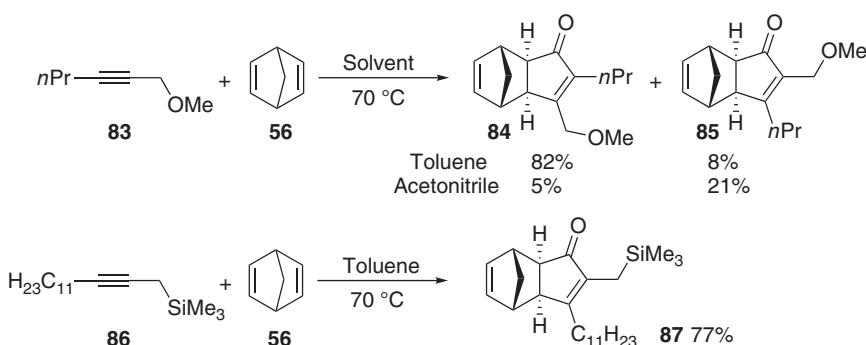
Moving away from studies on the fundamental mechanistic steps, and onto the nature of the reaction partners, *Riera* and *Helaja* reported a combined theoretical and experimental study on the relationship between polarisation of the alkyne component, and the regioselectivity of cyclopentenone formation in intermolecular PKRs [38]. In the case of terminal alkynes, the regiochemistry with respect to alkyne was well established, with the alkyne substituent found at the 2-position of the product cyclopentenone. In contrast, with non-terminal alkynes the parameters governing the regioselectivity are less clear. For example, unsymmetrical internal alkynes **80** can react (with norbornadiene **56**, for example) to give two regiosomeric cyclopentenones, **81** and **82** (Scheme 8.24).



**Scheme 8.24** Possible regiosomers in the *Pauson–Khand* reaction of internal alkynes.

*Riera* and *Helaja*'s study examined a range of internal alkynes containing inductively withdrawing (OR, NR<sub>2</sub>) groups in the propargyl position, along with inductively donating groups (SiR<sub>3</sub>, CR<sub>3</sub>) to evaluate the effect of alkyne polarisation on PKR regioselectivity [38]. The study found that the inductively withdrawing substrates tended to result in this group being placed at the 3-position in the final product, while inductively donating groups were found at the 2-position. This is summarised in Scheme 8.25, where 1-methoxy-2-hexyne **83** reacts with norbornadiene **56** to give **84** in 82% yield, with only 8% of regiosomer **85**. Of note, however, is the fact that in this case, regioselectivity could be reversed by employing acetonitrile as solvent, giving a 21% yield of **85** and a 5% yield of **84**, although this change had a significant impact upon the reaction yield. Even a 1 : 1 mixture of acetonitrile with toluene continued to favour this regioselectivity, although further dilution of acetonitrile in this solvent mixture led to a restoration of the original regioselectivity and reaction efficiency.

For the inductively donating 1-(trimethylsilyl)tetradec-2-yne **86**, regiosomer **87** was obtained as the sole product in 77% yield under standard thermal conditions in toluene. A similar regiochemical outcome was also observed with the analogue of **86** where the trimethylsilyl group was replaced by a *tert*-butyl group. In this case, the alkyne was not highly polarised but a completely regioselective



**Scheme 8.25** Electronically dependent regioselectivity in PKRs with internal alkynes.

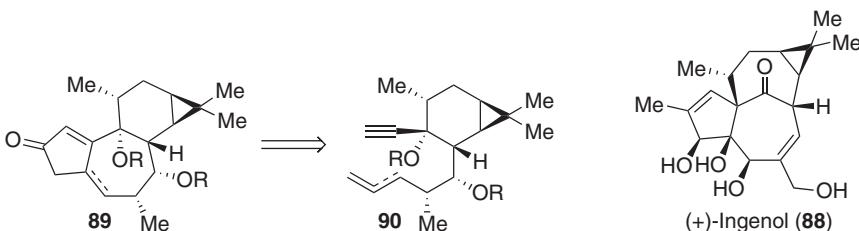
process was still observed. As with terminal alkynes, these observations showed that steric properties of the alkyne substrates also influenced the regiochemical outcome with internal alkynes. Overall, this study represents considerable progress in terms of understanding the factors that influence selectivity in the PKR of internal alkynes, as well as demonstrating that these substrates can be synthetically viable partners in terms of reaction yield.

## 8.5 Total Synthesis

The *PKR* has been employed, often, as the key step in an impressive array of synthetic routes towards desirable natural and unnatural targets [39]. In this section, notable and effective recent uses of the *PKR* within total synthesis programmes are discussed.

### 8.5.1 Synthesis of (+)-Ingenol

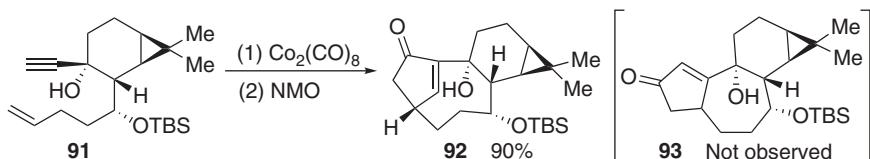
(+)-Ingenol **88** is a diterpene isolated from *Euphorbia ingens* [40]. This architecture has attracted the considerable attention of synthetic chemists due to the intriguing structure and biological activity of this natural product, with four total syntheses reported to date [41]. In Baran's full account of the synthesis of **88** [41]e, a *PKR* of enyne (or allene-yne) **90** was initially proposed, to deliver the tetracyclic system **89** (Scheme 8.26), which, following methyl addition to the cyclopentenone carbonyl, was designed to subsequently undergo a



**Scheme 8.26** Pauson–Khand disconnection in the retrosynthesis of (+)-Ingenol (**88**).

biosynthetically inspired vinylogous pinacol rearrangement to establish the carbon framework of **88**.

In the event, cobalt-mediated PKR of **91** delivered not the expected “head-to-head” intramolecular cyclisation product **93**, but the unusual head-to-tail product **92** (Scheme 8.27) in an excellent 90% yield.



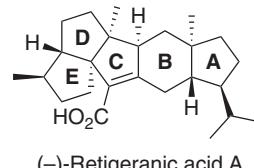
**Scheme 8.27** Attempted cobalt-mediated PKR towards (+)-Ingenol (**88**).

This head-to-tail regioselectivity has also been observed by *Lovely* (see Section 2.2.2) in the intramolecular PKR of sterically congested, phenylene-bridged enynes [20]. The issue was overcome in this instance by employing a rhodium-catalysed allenic PKR [41e, 42], which is outside the scope of this review. Nonetheless, the cobalt-mediated transformation here is of considerable interest, due to the high yield obtained in such a regioisomerically abnormal process.

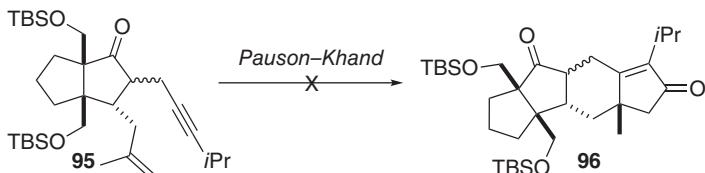
### 8.5.2 Towards Retigeranic Acid A

Retigeranic acid A **94** is a sesterterpenoid isolated from *Himalayan lichen* [43]. Among the challenges its structure poses to synthetic chemists are three quaternary stereogenic centres and a rare, *trans*-fused hydrindane ring system. As a result of its challenging structure (Figure 8.2), **94** and its stereoisomeric family members were the subject of four total syntheses in the 1980s [44].

*Lan, Gong, and Yang* planned to assemble the ABCD ring system of **94** via an intramolecular PKR of DC-containing enyne **95** (Scheme 8.28) [45]. However, under a range of typical conditions, product **96** was not observed.



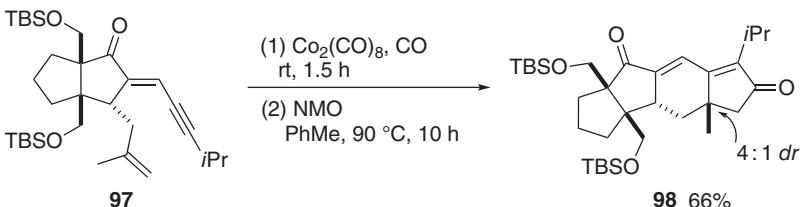
**Figure 8.2** Structure of (-)-Retigeranic acid A (**94**).



**Scheme 8.28** Attempted PKR towards Retigeranic acid A (**94**).

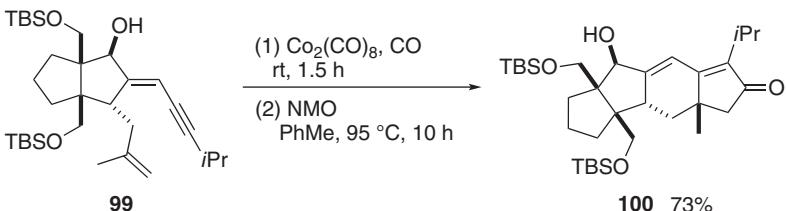
Second-generation substrate **97** was then prepared, with the alkyne side chain conformation restricted by the introduction of unsaturation. Following

this modification, the PKR proceeded under thermal conditions with *N*-oxide promotion, giving tetracyclic enone **98** in a good 66% yield, as a mixture of diastereomers favouring the desired methyl stereochemistry at the 6,5-ring junction (Scheme 8.29) [45].



**Scheme 8.29** Second-generation PKR towards Retigeranic acid A (94).

Following a computational assessment of the intermediates and transition states in the stereo-determining step, third-generation substrate **99** was designed and prepared. Pleasingly, PKR of **99** afforded enone **100** as a single diastereomer in an improved 73% yield (Scheme 8.30) [45].

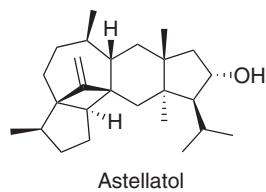


**Scheme 8.30** Third-generation PKR towards Retigeranic acid A (94).

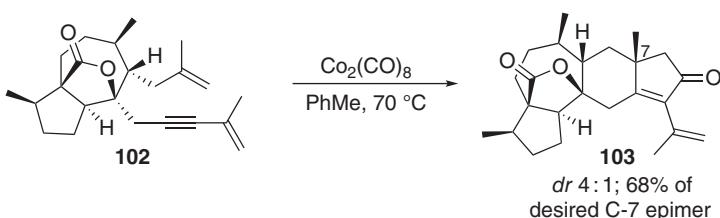
### 8.5.3 The Total Synthesis of Astellatol

Astellatol (**101**), like Retigeranic acid A (**94**), is a *trans*-hydrindane-containing sesterterpenoid (see Figure 8.3) [46], whose synthesis remained elusive until only recently, when reported by Xu [47].

Inspired by Yang's successful Pauson–Khand approach to the 6,5-hydrindane system [45], Xu reported a similar strategy, with enyne **102** undergoing a highly efficient thermal PKR to deliver advanced intermediate **103** with good yield and in good diastereoselectivity (Scheme 8.31) [47]. Notably, and in contrast to Yang's studies, no conformational locking of the alkyne side chain was required, simplifying the synthetic task following the cyclisation. On the other hand, Xu was unable to prepare the requisite *iso*-propyl-substituted alkyne precursor, and instead had to carry this moiety through the synthesis as the *iso*-propenyl unit, which would undergo a late-stage hydrogenation to obtain the desired *iso*-propyl substituent.



**Figure 8.3** Structure of (-)-Astellatol (**101**).

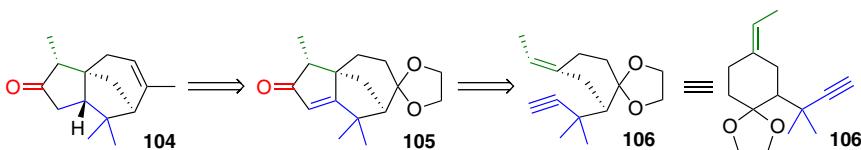


Scheme 8.31 Intramolecular PKR towards Astellatol (101).

#### 8.5.4 The Total Synthesis of 2-*epi*- $\alpha$ -Cedrene-3-one

2-*epi*- $\alpha$ -Cedrene-3-one **104** is a sesquiterpene isolated in 2000 from the essential oil of *Juniperus thurifera* [48]. Along with other members of the cedrene family, the interesting and preparatively challenging tricyclic framework of 2-*epi*- $\alpha$ -cedrene-3-one presents an inviting target for synthetic chemists.

Kerr recently disclosed a total synthesis of 2-*epi*- $\alpha$ -cedrene-3-one (**104**), employing a PKR as a key step [49]. Retrosynthetic analysis (Scheme 8.32) revealed that the key tricyclic core **105**, including the required ketone could be accessed via PKR of methylenecyclohexane derivative **106**.



Scheme 8.32 Retrosynthetic analysis of 2-*epi*- $\alpha$ -cedrene-3-one (104).

Enyne substrate **106** was readily prepared in six steps from commercially available materials. A catalytic variant of the PKR was envisaged, and the cyclisation was initially evaluated using 10 mol%  $\text{Co}_2(\text{CO})_8$  and the sulfide promoters tetramethylthiourea (TMTU) and tri-*n*-butylphosphine sulfide (*n*Bu<sub>3</sub>PS) along with 1 atm of CO (Table 8.5, entries 1 and 2, respectively), with only moderate yields of product **105** observed. The catalyst loading was increased to 20 mol% and, along with this, the reaction was performed in a sealed vessel under microwave irradiation (Table 8.5, entries 3–5). Using *n*BuSMe as promoter in toluene under microwave conditions (entry 5), 20 mol% of  $\text{Co}_2(\text{CO})_8$  delivered an excellent 85% yield of product **105**. Notably, no external source of CO was required as part of this reaction setup. In all cases, the *E*:*Z* ratio of the alkene in **106** was translated directly to the diastereomeric ratio of the methyl-bearing stereocentre in **105** [49, 50]. Following this, the natural product was then accessed from tricyclic cyclopentenone **105** in a further seven steps. The optimised PKR conditions reported here represent one of the most efficient catalytic protocols reported and have the potential to be adopted for more widespread use in total synthesis.

**Table 8.5** Optimisation of the PKR.

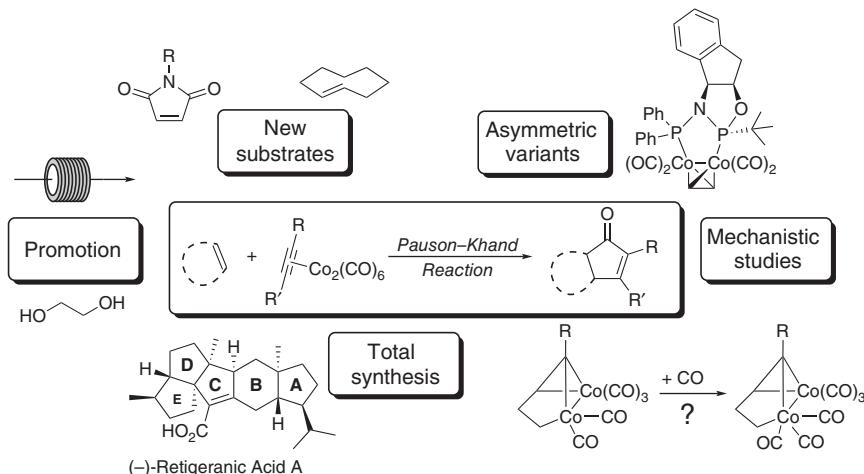
Entry	$\text{Co}_2(\text{CO})_8$ (mol%)	Conditions <sup>a)</sup>	Yield (%)
1	10	TMTU, 1 atm. CO, PhH, 80 °C, 6 h	20 <sup>b)</sup>
2	10	<i>nBu</i> <sub>3</sub> PS, 1 atm. CO, PhH, 80 °C, 18 h	48
3	20	CyNH <sub>2</sub> , PhMe, MWI, 100 °C, 10 min	69
4	20	<i>nBuSMe</i> , 1,2-DCE, MWI, 100 °C, 10 min	65
5	20	<i>nBuSMe</i> , PhMe, MWI, 100 °C, 10 min	85

a) MWI: microwave irradiation.

b) Conversion.

## 8.6 Summary and Conclusions

The breadth and depth of studies reported in the last five years in the *PKR* are a clear indication of utility of the transformation and the health of this research area (Scheme 8.33).

**Scheme 8.33** Overview of ongoing areas of study and recent advances in relation to the PKR.

Considerable advances have been made in all areas, including new techniques for promotion, the incorporation of previously challenging substrates, new asymmetric variants, increased mechanistic understanding, and applications in complex molecule synthesis.

The application of flow techniques to the PKR is still at the early stage, but this method already shows clear promise, and interest in this area is likely to grow further in the coming years. Likewise, the application of chemically benign and simple promoters such as ethylene glycol should also become more prominent.

In terms of substrate scope, electron-poor alkenes, such as maleimides, can now be used, as can strained and highly reactive *trans*-cycloalkenes. In terms of the alkyne component, internal alkynes can now be employed routinely in good yields, and with enhanced understanding of the effects leading to regioselectivity in relation to alkyne incorporation. One issue that remains to be resolved, however, is the understanding and control of regioselectivity in the reaction of unsymmetrical alkenes. This area may currently be one of the PKR's largest limiters, and advances in this area will broaden its scope even further.

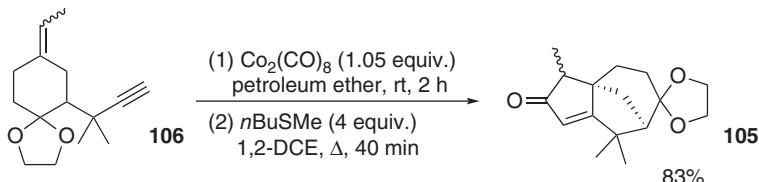
Advances continue to be made in the asymmetric variants of the reaction, with a range of chiral ligands complexed to cobalt now able to effect the reaction in substoichiometric, rather than stoichiometric, amounts.

Our mechanistic understanding of the transformation continues to grow, with recent studies challenging the validity of some of the most fundamentally accepted steps in the proposed mechanism. Continued progress in this area will undoubtedly lead to further enhanced practical methods.

In terms of total synthesis, the last five years have seen an appreciable number of applications of the PKR, with the transformation being applied in some cases at considerably advanced stages of total synthesis programmes. The examples in target-oriented synthesis also demonstrate catalytic applications, and the often exquisite levels of diastereoccontrol that can result in the PKRs of chiral substrates. The use of an intermolecular PKR in a total synthesis programme is also noteworthy (see Section 2.1.2) [13], since the overwhelming number of uses in total synthesis involves intramolecular variants. Given the continued activity in the area, we can expect to witness sustained advances in all aspects of the PKR in the coming years.

## 8.7 Practical Procedures for Stoichiometric and Substoichiometric Pauson–Khand Reactions

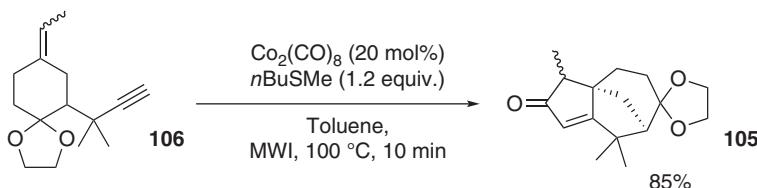
Using a stoichiometric amount of cobalt [49]:



To (*E*)/(*Z*)-8-ethylidene-6-[3-methylbut-1-yn-3-yl]-1,4-dioxaspiro[4.5]decane **106** (1.05 g, 4.47 mmol) in petroleum ether (90 mL) was added dicobalt octacarbonyl (1.61 g, 4.69 mmol) and the solution was stirred for two hours. The solvent

was then removed *in vacuo* and the brown residue filtered through a short pad of silica gel. This  $\text{Co}_2(\text{CO})_6$ -alkyne complex was taken up in 1,2-dichloroethane (DCE) (60 mL) and *n*BuSMe (2.25 mL, 18.5 mmol) added. This solution was then heated to reflux (83 °C) for 40 minutes before cooling to room temperature and the solvent removed *in vacuo*. Purification via column chromatography (20% diethyl ether:petroleum ether) delivered the cyclopentenone diastereomers **105** (0.97 g, 83% yield).

Using a substoichiometric amount of cobalt [49]:



(*E*)/(*Z*)-8-Ethylidene-6-[3-methylbut-1-yn-3-yl]-1,4-dioxaspiro[4.5]decane **106** (60 mg), toluene (3 mL), *n*BuSMe (38  $\mu$ L), and dicobalt octacarbonyl (18 mg) were added to a 10 mL CEM microwave vessel also containing a stirrer bar, the tube sealed immediately, and placed in the microwave reactor (CEM discovery apparatus). The reaction vessel was then heated by microwave irradiation to 100 °C for 10 minutes. On completion of the reaction, the crude mixture was purified via column chromatography (50% diethyl ether:petroleum ether) to yield product **105** (57 mg, 85% yield).

## Abbreviations

Boc	<i>tert</i> -butoxycarbonyl
<i>n</i> Bu	<i>n</i> -butyl
<i>t</i> Bu	<i>tert</i> -butyl
DABCO	1,4-diazabicyclo[2.2.2]octane
1,2-DCE	1,2-dichloroethane
1,2-DME	1,2-dimethoxyethane
Fmoc	fluorenylmethyloxycarbonyl
MS	molecular sieves
MWI	microwave irradiation
NMO	<i>N</i> -methylmorpholine <i>N</i> -oxide
<i>i</i> Pr	isopropyl
PKR	Pauson–Khand reaction
TADA	transannular Diels–Alder reaction
TBAF	tetra- <i>n</i> -butylammonium fluoride
TBS	<i>tert</i> -butyldimethylsilyl
TMTU	tetramethylthiourea

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## 9

### Cobalt-Catalysed [2+2+2] Cycloadditions

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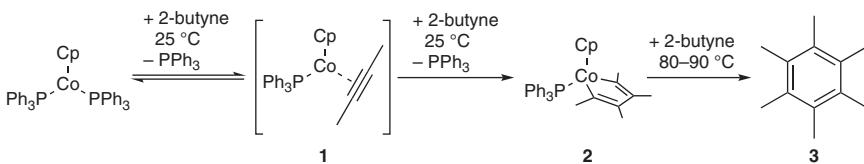
#### 9.1 Introduction

The assembly of large carbo- and heterocyclic molecules from structurally much simpler unsaturated precursor molecules has evolved since its initial steps in the earlier part of the last century into a matured synthetic methodology, which still is the source of significant developments in synthetic chemistry. While the *Diels–Alder* reaction is nowadays the most well-known and widely applied reaction in organic synthesis for the assembly of six-membered ring systems [1], including asymmetric catalytic variations, the transition metal-mediated [2+2+2] cycloaddition of C–C triple bonds only evolved over the last decades into a valuable tool in the synthetic chemist’s toolbox. Since *Reppe* reported his systematic studies on cyclotri- and -tetramerisation of alkynes using nickel complexes in the 1940s, many transition metals were found to catalyse cyclotrimerisation reactions including alkynes, nitriles, allenes, and heterocumulenes involving N, O, and S as heteroatoms. The topic has been quite thoroughly reviewed under different aspects in recent years, comprising detailed information on the applications in complex and asymmetric organic synthesis [2, 3]. The most often applied metals so far are ruthenium, the group 9 metals (Co, Rh, and Ir), and nickel, and their application as well as the utilisation of less well-known metal catalysts was also compiled recently [4]. The development and application of different transition metal-free cyclotrimerisations processes has been collected in an overview [5]. *Gandon* has described cobalt-mediated [2+2+2] cycloaddition reactions in a devoted book chapter in 2013, and we will focus on general aspects of cobalt catalysts and their most recent applications [6].

## 9.2 Reaction Mechanisms of Cobalt-Catalysed Cyclotrimerisations

The mechanistic picture of cobalt-catalysed [2+2+2] cycloaddition reactions for the assembly of benzenes or pyridines has been the subject to a number of experimental and especially in recent years also theoretical studies.

Initial experimental investigations by *Wakatsuki* applied  $\text{CpCo}(\text{PPh}_3)_2$  as starting complex, which has been used in early attempts for alkyne cyclotrimerisations [7]. The experiments produced a number of different isolable cobaltacyclopentadienes, being stable compounds in the presence of the phosphane. It was demonstrated that the structural nature of the alkyne plays a significant role for the stability of the cobaltacyclopentadienes.  $\text{CpCo}$ -alkyne complexes with acetylene are too unstable for direct identification or detection, and the unsubstituted cobaltacyclopentadiene can only be isolated as phosphane complex in low yield, together with a large number of by-products. Work by *Butenschön* also showed that the complexed acetylene molecules can undergo rearrangement to the corresponding vinylidene complexes [8]. Such initial intermediates of the catalytic cycle are much easier to isolate with substituted alkynes like 2-butyne, who provide a different reactivity (Scheme 9.1) [9]. Successive exchange of a phosphane from  $\text{CpCo}(\text{PPh}_3)_2$  led reversibly to intermediate complex **1** and then in the presence of more 2-butyne under oxidative cyclisation to cobaltacyclopentadiene **2**, from where the catalytic cycle can be closed with another 2-butyne molecule to yield the product hexamethylbenzene (**3**).



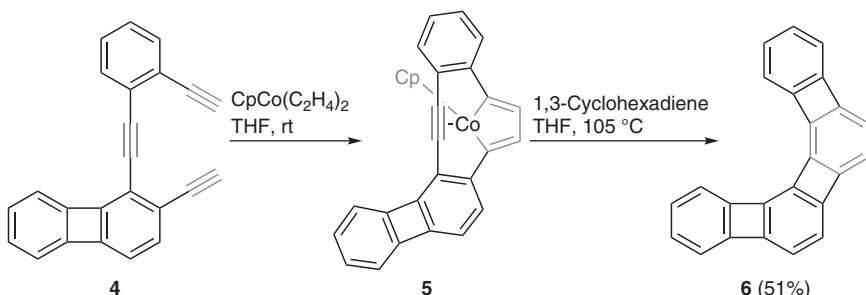
**Scheme 9.1** Intermediates in early studies on the cyclotrimerisation reaction.

Monoalkyne complexes of type **1** can be easily isolated in the case of more electron-deficient alkynes like diphenylacetylene or phenylmethoxycarbonylacetylene and subsequent reactions with other alkynes led to differently substituted cobaltacyclopentadienes. Reactions with unsymmetrical substituted alkynes led to the formation of regioisomers of cobaltacyclopentadienes, and it was shown that the  $\alpha$ -carbon atom of the metallacycle carries the sterically larger substituent, and this preference is based more on sterical and less electronic factors, being responsible for the often observed preferential formation of one regioisomer during the cyclisation reaction [7a]. Application of substituted alkynes allows the systematical isolation of stable complexes of the type  $\text{CpCo}(\text{PPh}_3)(\text{alkyne})$  [10] and  $\text{Cp}^{\text{R}}\text{Co}(\text{CO})(\text{alkyne})$  ( $\text{Cp}^{\text{R}} = \text{Cp}$  or subst.  $\text{Cp}$ ), the latter one accessible from  $\text{CpCo}(\text{CO})_2$  [11]. The general possibility of a cobalt-tetramethylcyclobutadiene intermediate in the cyclisation processes could be ruled out by a study by *Whitesides* using  $1,1,1-d_3$ -2-butyne as reaction

partner and analysing the resulting isotopomers of the hexamethylbenzene [12]. However, it corroborated the intermediacy of a metallacyclopentadiene. A more detailed examination revealed that the formation of a cyclobutadiene complex  $\text{CpCo}(\eta^4\text{-C}_4\text{R}_4)$  in general is a catalytical “dead end” and furthermore a possible significant deactivation pathway for catalytic cyclotrimerisations, although exceptions exist [13].

The neutral ligand dissociation and exchange with substrate molecules from the 18-electron  $\text{CpCoL}_2$  starting complex usually initiates the catalytic cycle; therefore, the structure of the 18-electron complex plays a significant role for the starting phase of the reaction. The exchange of ligands can in general follow an associative or dissociative pathway. Initial studies to such substitution processes of the group 9 metals including cobalt were conducted by *Basolo*, who investigated the exchange of CO for different phosphines or phosphites [14]. The dissociative pathway was corroborated spectroscopically for the reaction of  $\text{CpCo}(\text{PPh}_3)_2$  with  $\text{PMe}_3$ , showing a rapid exchange process even at low temperature, following a first-order kinetic [15]. Ligand substitution events at transition metal centres in combination with changes in the spin states of the complexes have increasingly come into the focus of experimental and theoretical investigations [16]. Especially for complexes of the type  $\text{CpM}(\text{CO})_2$  of the group 9 metals ( $\text{M} = \text{Co, Rh, Ir}$ ), a number of photochemical and spectroscopic investigations were conducted, targeting reactive species from ligand exchange processes by isolation at low temperature matrices or capture of subsequent reaction products for indirect detection. Out of a number of studies with  $\text{CpCo}$ -complexes, just a few recent should be mentioned in this regard [17]. *Poli* calculated the  $[\text{CpCoL}]$  ( $\text{L} = \text{CO, PH}_3, \text{H}_2\text{C}=\text{CH}_2$ ) species derived from the 18-electron  $\text{CpCoL}_2$  complexes to be significantly lower in energy in the triplet state compared with the singlet state [18]. Some of the most recent results were contributed by *Harris* using ultrafast time-resolved infrared spectroscopy, which allows the study of the dynamics of spin states, together with the interplay of theoretical calculation on the spin states [19]. A study of the same group with relation to cyclotrimerisation reactions showed that photogenerated  ${}^3[\text{CpCo}(\text{CO})]$  can  $\eta^2$ -coordinate to 1-hexene as well as 1-hexyne, after which a spin transition occurs into the corresponding  ${}^1[\text{CpCo}(\text{CO})]$  singlet species, in the case of 1-hexyne being the initial step before entering the catalytic cycle [20]. Such spin transitions play an important role in the theoretical description of cyclotrimerisation reaction, as it is shortly discussed later in this chapter.

The most descriptive experimental evidence for a cobaltacyclopentadiene preceding the final cyclotrimerisation step was contributed by *Vollhardt* [21]. They synthesised the 1,2-phenylene-bridged triyne **4** and reacted it either with the *Jonas* complex,  $\text{CpCo}(\text{H}_2\text{C}=\text{CH}_2)_2$ , or pentamethylcyclopentadienyl ( $\text{Cp}^*$ ) $\text{Co}(\text{H}_2\text{C}=\text{CH}_2)_2$ , to obtain a strained dibenzodehydro-[10]annulene (**5**, Scheme 9.2). The corresponding X-ray structure analysis showed the cobalta-cyclopentadiene fragment and the coordination of the remaining free alkyne bond. The bonding distances of the cobalt centre to the alkyne moiety are relatively large, explaining a weak cobalt–alkyne interaction and the absence of more such structurally unambiguously characterised complexes in the literature. Heating of the isolated intermediate **5** to 105 °C in a solvent mixture



**Scheme 9.2** Intermediates in the [2+2+2] cycloaddition reaction.

furnished the cyclisation product **6** in 51% yield with  $\text{CpCo}(\text{H}_2\text{C}=\text{CH}_2)_2$ . When  $\text{Cp}^*\text{Co}(\text{H}_2\text{C}=\text{CH}_2)_2$  was used as  $\text{Cp}^*\text{Co}$  fragment source, the thermal cyclisation occurred at 150 °C and furnishing the product only with 22% yield. Irradiation of the analogous cobaltacyclopentadiene yielded exclusively the  $\text{Cp}^*\text{Co}-\text{cyclobutadiene}$  complex. An overview on the mechanisms of the third alkyne to metallacyclopentadienes derived from the different transition metals including cobalt has appeared recently [22].

Over the last decade a number of theoretical studies have been published dealing with [2+2+2] cycloaddition reactions mediated by cobalt complexes [23]. The results have also been compiled in several reviews [3, 6]. *Gandon* and *Aubert* reported an investigation on the mechanism of the formation of cyclohexadienes from two alkynes and an alkene molecule by mediation of the  $\text{CpCo}$ -fragment, resembling significant parts of a related cycle for alkyne cyclotrimerisation [24]. The coordination to the cobaltacyclopentadiene intermediate by an ethene or ethyne molecule shows energetically only very little difference; therefore, both products can be observed as long as the alkene is not applied in a significant excess in the reaction to shift the product formation towards the cyclohexadiene.

A number of studies have been concerned with the cyclotrimerisation of alkynes, especially two detailed theoretical studies by *Dahy* and *Koga* have studied the transformation of the  $\text{CpCo}$ -bisacetylene complex as well as the reaction of the resulting cobaltacyclopentadiene with acetylene to the benzene product. The authors paid special attention to the existence of the singlet and triplet state of the involved 16-electron intermediates, leading to energetically different reaction pathways [25]. Another detailed study was initiated by *Gandon* and *Aubert*, investigating the possibility and conditions for different imaginable reaction pathways, depending, e.g. from the nature of the different neutral ligands present for coordination of the cobalt centre (Figure 9.1) [26]. The calculations resulted in the postulation of essentially two different pathways for the reaction, being dependent from the neutral ligands involved. The results are presented in an overview in Figure 9.1. Oxidative cyclisation of the bisacetylene complex **A** led to the cobaltacyclopentadiene **B**, which undergoes a spin change into  ${}^3\mathbf{B}$ . In the presence of ethyne (or substituted analogues) coordination to  ${}^3\mathbf{B}$  led to complex **C**, from which, after a metal-assisted concerted [4+2] cycloaddition, the  $\eta^4$ -arene complex **D** resulted. This complex then converses into the 20-electron  $\eta^6$ -arene complex  ${}^3\mathbf{D}$ , from which reductive elimination

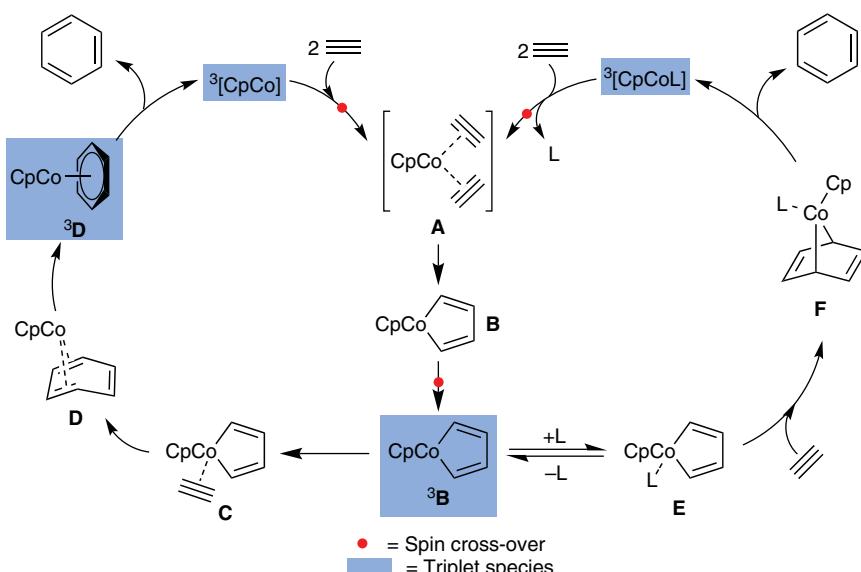


Figure 9.1 Different reaction pathways for the  $\text{CpCo}$ -catalysed cyclotrimerisation reaction.

delivers the product and the unsaturated triplet fragment  ${}^3[\text{CpCo}]$ , returning to the catalytic cycle by coordination of two alkynes. Such a 20-electron  $\eta^6$ -arene complex like  ${}^3\text{D}$  has been prepared and identified in the cyclisation of 2-butyne as alkyne and whose magnetic moment corresponds to the existence of two unpaired electrons [27].

In the presence of strongly coordinating neutral ligands like  $\text{PMe}_3$  or  $\text{CO}$ , the complex **E** resulted from  ${}^3\text{B}$  and subsequent [4+2] cycloaddition resulted in the formation of the 7-cobaltanorbornen complex **F**. Reductive elimination again led to the formation of the unsaturated triplet fragment  ${}^3[\text{CpCo}]$  and the arene product. Therefore, the individual reaction pathways depend from the ligands present in the reaction mixture; however, the outcome is the same [9].

The synthesis of pyridines from two alkynes and a nitrile has become a prominent preserve for  $\text{CpCo}$ -based catalysts. Experimental studies excluded cobaltaazacyclopentadienes from being an intermediate in the cyclisation; however, the reaction obviously proceeds by substitution of additionally coordinated neutral ligands like, e.g.  $\text{PPh}_3$  from the cobaltaazacyclopentadienes against the corresponding nitrile. Subsequently the pyridine ring is formed by reaction with the nitrile group. *Ingrosso* and *Lucherini* could show that the observed regioselectivities were dominated by steric factors [28]. Furthermore, they also proved the influence of the temperature on the reaction: at lower temperatures the formation of pyridines is preferred, while at higher temperature the formation of benzene derivatives has more impact.

The reaction of cobaltaazacyclopentadienes and different nitriles was analysed in detail by theoretical studies by *Dahy* and *Koga* [29]. This investigation illustrated evidence that especially the electronic influence of the substituent on the cyano group plays a significant role on the mechanistic proceeding of the reaction.

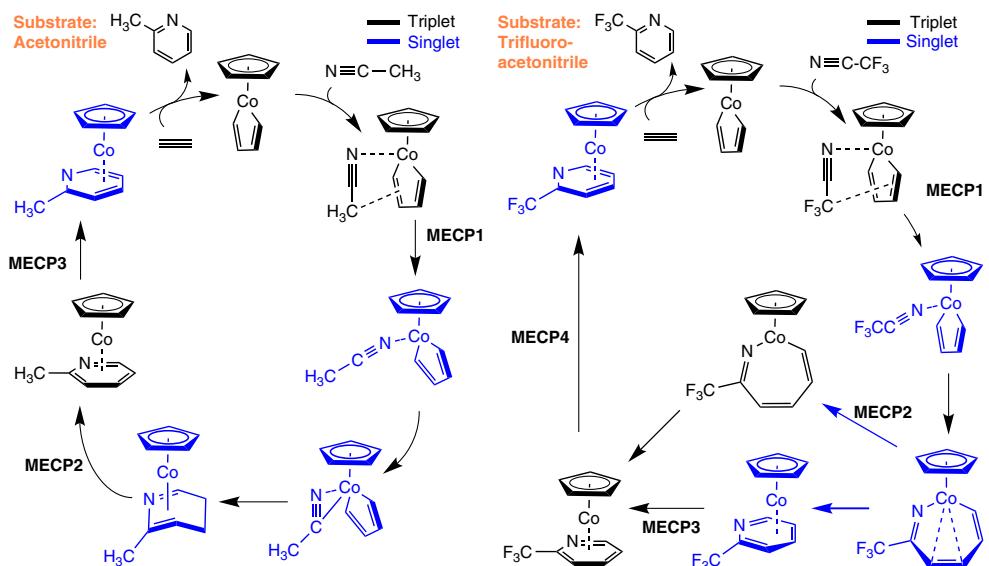
Different from alkynes, nitriles can either coordinate end-on with the nitrogen atom or side-on with the triple bond to the cobalt atom [30]. The analogies and differences for the cyclisation of different nitriles are shown in Figure 9.2. Again, a two-state reactivity (TSR) mechanism is preferred over a pure singlet state or triplet state reactivity mechanism. The reaction for acetonitrile (Figure 9.2, left) starts by coordination of the acetonitrile by the nitrogen lone pair to the Co(III) centre with its empty d orbital, being significantly more stable in the singlet state. Rearrangement of the nitrile to the side-on bound nitrile and subsequent [4+2] cycloaddition led to the pyridine product complex, which presumably exists in several stable isomers and an isomerisation via a triplet state delivers a singlet 2-methylpyridine complex, from which the CpCo fragment can return to the catalytic cycle after product decomplexation. The cyclisation using trifluoroacetonitrile (and also hydrogencyanide, Figure 9.2, right) initially resembles features for the catalytic cycle of the acetonitrile in terms of coordination to the cobalt centre. However, from the complex with end-on coordinated nitrile a [4+2] cycloaddition would be energetically less favourable. Therefore, a [2+2] cycloaddition followed by Co–C bond cleavage lead to the azacobaltacycloheptatriene, in which the cobalt coordinates an internal double bond. The reaction proceeds over the energetically more favourable triplet state, from which in a very exothermic reaction the C–N bond is formed. The formation of a CpCo-( $\eta^2$ -trifluoromethylpyridine) complex is followed by further coordinative slippage and final decomplexation of the product and return of the fragment to the catalytic cycle.

*Daly/Koga* and also *Lv* have also published another study on the reaction of cobaltacyclopentadienes with isocyanate and thioisocyanate, where also by a multi-state pathway, the formation of pyridin-2-ones and pyridin-2-thiones are preferred after the TSR mechanism [31].

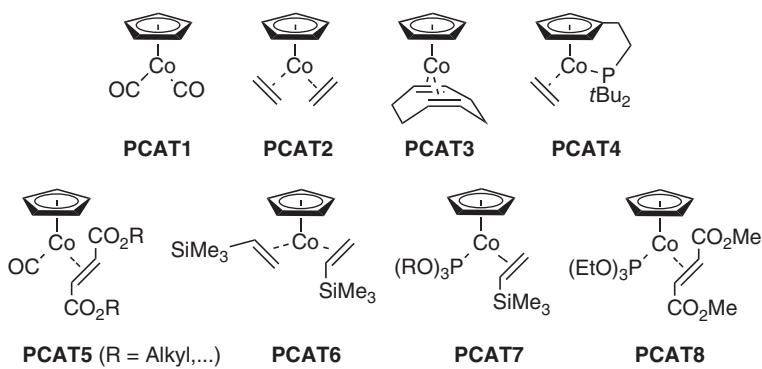
The influence of microwave irradiation on cyclotrimerisation reactions was investigated and although no “non-thermal” influence was accounted for [32], theoretical investigations by *Prieto* and *García* pointed towards an additional positive effect by stabilisation of triplet intermediates of the catalytic cycle by the microwave irradiation [33].

### 9.3 Cobalt-Based Catalysts and Catalytic Systems

Cobalt complexes are typically applied as precatalysts in form of isolated complexes or organometallic compounds in a low oxidation state (“single-site catalysts”) on one side or are applied as *in situ*-generated catalytic system, usually consisting of cobalt(II) salt and ligands as well as reductants and additives, on the other side. The last decade has seen the development and application of a number of novel catalyst systems in both categories, significantly improving the utilisation of cobalt-based catalysts for (co)cyclotrimerisation [4, 6]. The generally applied and recently reported CpCo-based precatalysts (PCATs) are displayed in Figure 9.3. CpCo(CO)<sub>2</sub> (**PCAT1**) is a commercially available compound and still the most often used precatalyst, although it requires large amounts of heat and frequently additional irradiation for activation and successful application



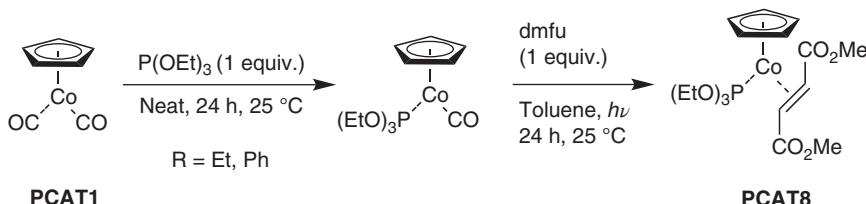
**Figure 9.2** Catalytic TSR mechanism for the cycloaddition of electronically different nitriles to cobaltacyclopentadienes, yielding substituted pyridines (MECP = Minimum Energy Crossing Point). Source: Dzik *et al.* 2016 [25c]. Reproduced with permission of John Wiley and Sons.



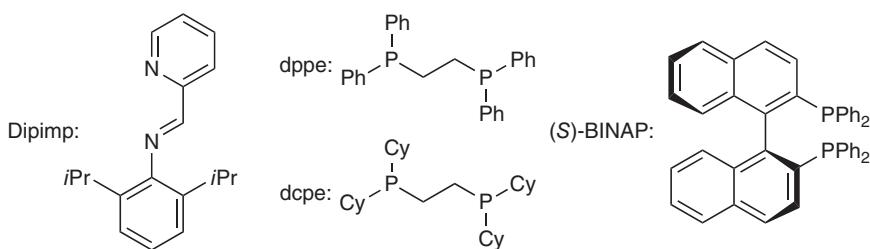
**Figure 9.3**  $\text{CpCo}(\text{I})$ -precatalysts regularly applied or recently reported for application in cyclotrimerisation reactions.

in cyclotrimerisations. The *Jonas'* olefin complexes **PCAT2** and **PCAT3** can be employed under mild conditions as well as under photochemical conditions at low temperatures [27]. A related complex **PCAT4** was reported by *Butenschön*, with a tethered phosphino group at the  $\text{Cp}$  ring, catalysing cyclotrimerisations of alkynes under aqueous conditions [34]. A substantial impetus for the development of novel precatalysts came by the substitution of one CO ligand by acetylene dicarboxylic esters, as reported by *Gandon* [35]. The resulting complexes **PCAT5** are air-stable compounds.

*Hapke* reported the synthesis of the trimethylvinylsilane complex **PCAT6**, which proved to be the most highly reactive  $\text{CpCo}$ -precatalyst for co-cycloadditions between diynes and nitriles [36]. This complex, however, has a somewhat challenging synthesis and is delicate to handle. Addition of a phosphite ligand delivers complexes of the type **PCAT7**, still retaining a remarkable activity, but much better to handle [37]. Further evolution of the ligand exchange approach finally led to air-stable and recyclable olefin–phosphite complexes of the type **PCAT8**, possessing dimethylfumarate (dmfu) as electron-deficient olefin ligand. Originally synthesised from **PCAT6**, a route starting from the commercially compound **PCAT1** was developed, leading to a flexible approach towards different derived complexes of type **PCAT8** [38]. The complete synthesis sequence is given in Scheme 9.3, yielding the currently commercially available complex [39].



**Scheme 9.3** Reaction pathway for the synthesis of modified, air-stable  $\text{CpCo}$ -precatalysts **PCAT8**.

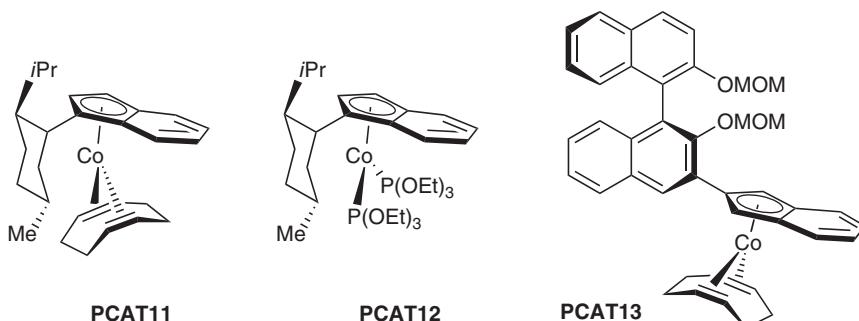


**Figure 9.4** Selected examples of frequently used ligands for *in situ*-generated cobalt-based catalytic systems applied for [2+2+2] cycloadditions.

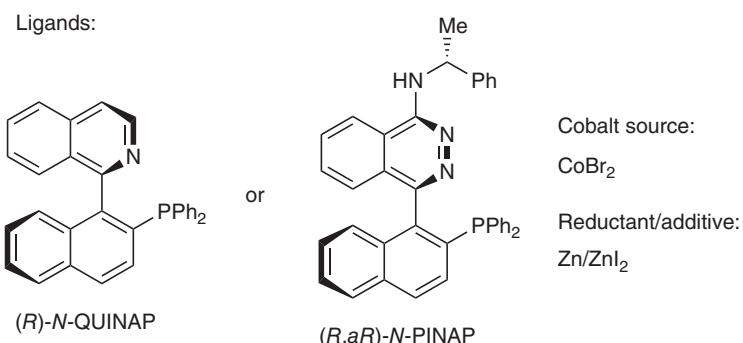
There exist only few isolated *non-Cp*-based precatalysts that are regularly used in [2+2+2] cycloaddition reactions. Among them commercially available dicobaltoctacarbonyl ( $\text{Co}_2(\text{CO})_8$ , **PCAT9**) is one of the most prominent candidates, and only recently renewed interest in cyclisations under unusual conditions was encountered (see later paragraphs). Also, recently the cobalt analogue of the *Wilkinson* catalyst,  $\text{CoCl}(\text{PPh}_3)_3$  (**PCAT10**), was investigated in detail towards its usefulness in cyclisation reactions. The compound is also commercially available and can also easily be made from  $\text{CoCl}_2$ ; however, the preparation as well as storage needs to be carefully executed [40].

Recently, different *in situ*-generated catalytic systems for carbocyclisation reactions have been reported, utilising, e.g. *N*-heterocyclic carbenes (NHCs), iminopyridines, or chelating phosphines like 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) as ligands together with cobalt(II) salts and a reductant (Figure 9.4). Even more recently, *in situ* catalysts for the assembly of cyanoalkynes to pyridines were found, applying bisphosphine ligands like 1,2-bis(diphenylphosphino)ethane (dppe) or the rather unusual dcpe for the transformation. Examples are discussed in the corresponding following paragraphs.

Compared with the heavier group congener rhodium with its wealth of different *in situ*-generated chiral catalytic systems [3g, 41], there are existing only few cobalt-based chiral catalysts, which can perform asymmetric cyclisation reactions (Figure 9.5). The chiral indenyl-complex **PCAT11** developed by Heller and



**Figure 9.5** Chiral indenyl-Co-precatalysts for asymmetric cyclotrimerisation reactions.



**Figure 9.6** Components of the stereoselective Co(I)-based catalytic system for asymmetric cyclotrimerisations.

*Gutnov* was the first chiral catalyst to assemble heterobiaryls from diynes and nitriles under photochemical conditions and even at reaction temperatures as low as  $-20^\circ\text{C}$  [42]. Photochemical ligand exchange led to bisphosphite complex **PCAT12** in excellent yield, which can also be activated under thermal conditions [43]. Incorporation of a chiral 3-binaphthyl group in the 2-position of the indenyl ligand like in **PCAT13** did not give a catalyst, which is capable of introducing chirality in cyclisation reactions.

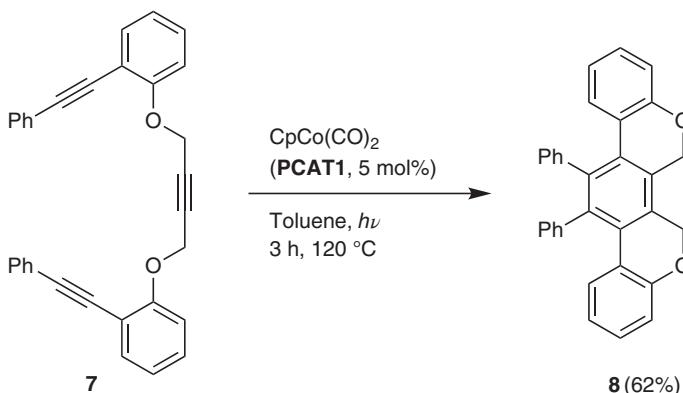
The development of *in situ*-generated chiral catalysts from cobalt salts and well-known chiral diphosphines like BINAP or  $\text{H}_8$ -BINAP and their derivatives, which have highly successfully been applied in Rh-catalysed [2+2+2] cycloadditions, did not yield any efficient stereoselective catalytic cyclisation system so far. Recently, *Hapke* reported the application of *P,N* ligands, like 1-(2-diphenylphosphino-1-naphthyl)isoquinoline (QUINAP) and e. g. (*S*)-(–)-4-[2-(diphenylphosphino)-1-naphthalenyl]-*N*-[(*R*)-1-phenylethyl]-1-phenylazinamine (PINAP), for the asymmetric cyclisation of triynes in combination with  $\text{CoBr}_2$  as cobalt source for the *in situ* catalyst generation (Figure 9.6) [44].

## 9.4 CpCo-Based Cyclisations

### 9.4.1 Carbocyclic Compounds

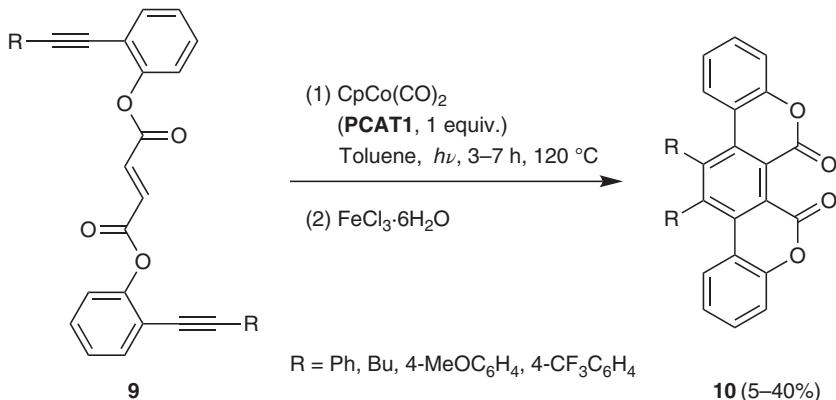
$\text{CpCo}(\text{I})$ -precursor complexes are the most widely and generally used class of complexes for the assembly of carbocycles from (di-/tri-/oligo-) alkynes. In contrast to *in situ*-generated catalysts, the use of an isolated complex provides a much more defined reaction environment and often minimises side reactions. As said before, the most frequently deployed precatalyst for [2+2+2] cycloaddition reactions is still  $\text{CpCo}(\text{CO})_2$  (**PCAT1**) due to its versatility and easy availability, however, in general requiring rather harsh reaction conditions. An exemplary catalytic transformation was reported by *Bessières* for the intramolecular cyclisation of triyne **7** to yield pentacyclic product **8** (Scheme 9.4) [45].

Opposite to the previously described synthesis of a bis-benzochromene, the use of yne-ene-ynes (**9**) as substrates requires the use of stoichiometric



**Scheme 9.4** Application of **PCAT1** for the formation of the bis-benzochromene **8** from triyne **7**.

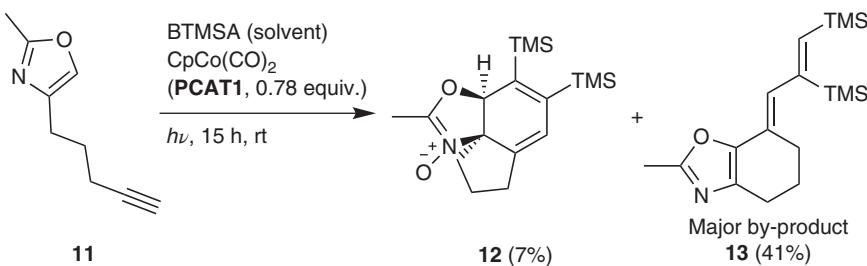
amounts of **PCAT1**, due to the formation of a cyclohexadiene intermediate, coordinating strongly to the  $\text{CpCo(I)}$ -centre, thus inhibiting participation in another catalytic cycle (Scheme 9.5). Therefore, subsequent oxidative removal of the  $\text{CpCo}$ -fragment from the organic product (**10**) by addition of iron(III) chloride was necessary.



**Scheme 9.5** Application of **PCAT1** for the cyclisation of yne-ene-yne (**9**).

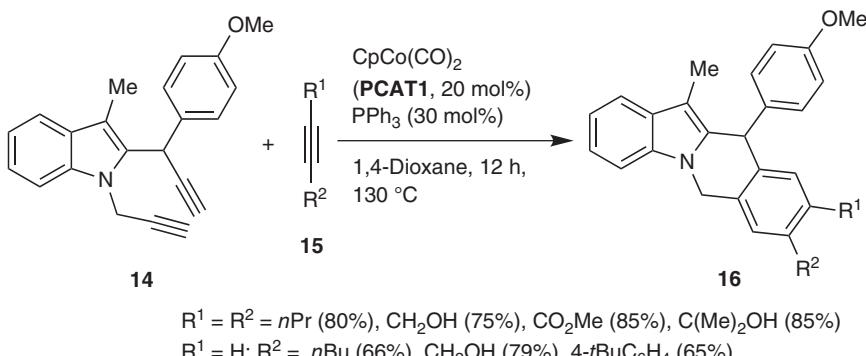
Further sophisticated building blocks containing heterocycles in the backbone could be obtained by cyclising alkyl-alkynyl oxazoles **11** with bistrimethylsilylacetylethane (BTMSA, Scheme 9.6). Unfortunately, unexpected high quantities of by-products were detected (exemplified by **13** in Scheme 9.6) in addition to low amounts of the cyclisation *N*-oxidation product **12**. Similar results were observed for thiazoles while applying an excess of 1.3 equiv.  $\text{CpCo}(\text{CO})_2$  (**PCAT1**), just 11% of the desired cyclisation product were isolated [46].

Ramana extended the application of **PCAT1** to the formation indolisoquinolines (**16**) as one of the most frequent structural motifs in alkaloids [47]. The cyclisation of the aminodiyne **14** and symmetrical alkynes (**15**) were performed under



**Scheme 9.6** Cyclisation of oxazole-functionalised alkynes **11** with BTMSA, which also acts as solvent.

relatively harsh conditions providing structurally diversified indolisoquinolines with good yields (Scheme 9.7). The deployment of terminal alkynes resulted in the exclusive formation of one regiosisomer, accordingly also the analogous reaction with 3,5-difluorobenzonitrile selectively led to an exclusively formed pyridine isomer.



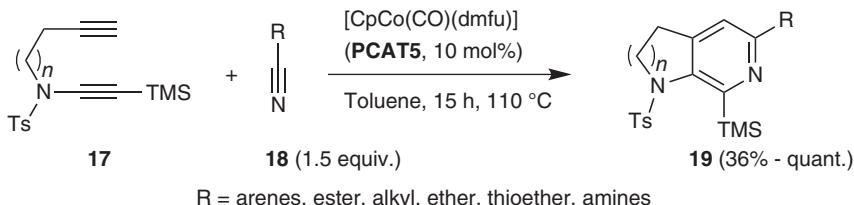
**Scheme 9.7** Utilisation of **PCAT1** for the synthesis of functionalised indolisoquinolines **16**.

*Lang* synthesised highly decorated multiferrocenyl-substituted benzenes by  $\text{CpCo}(\text{CO})_2$  (**PCAT 1**)-mediated cyclotrimerisation of ferrocenyl diynes with subsequent C–H activation [48]. Related multiferrocenyl benzenes and pyridines were built up analogously by *Suo*, extending the substrate scope to include nitriles [49].

#### 9.4.2 Heterocyclic Compounds

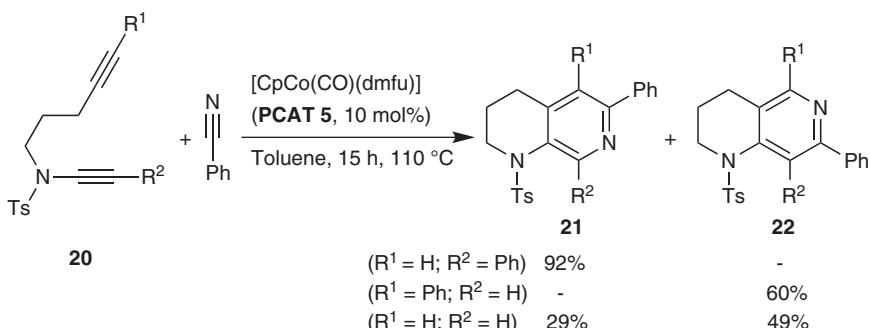
The application of  $\text{CpCo(I)}$ -complexes for the assembly of heterocyclic motifs from alkynes and nitriles is a rather well-established process. High regioselectivity is involved in this approach due to the coordination and preorganisation of the nitrile at the cobalt centre, allowing the construction of aminopyridines (**19**) and aminopyridones with high regioselectivity from yneamides (**17**) and nitriles (**18**) as substrates [50]. *Gandon* depicted the correlation between a rising steric demand of the nitrile substituent going together with a decreasing yield of

the cyclisation product, exemplified by the decrease in yields from quantitative conversion for the 2,4,6-trifluoro phenyl, 89% for the benzyl, 72% for the methyl substituent, finally decreasing to 36% yield for the *tert*-butyl-substituted nitrile (Scheme 9.8). Advantageous for this method is the large tolerance of functional groups the nitrile could contain, e.g. ether, thioether, tertiary amine, or ester moieties were successfully cyclised in contrast to alkyl halides, sulfones, acids, or bromoacetonitrile, the last one forming a cyanoyneamide.



**Scheme 9.8** Cyclisation of yneamines and nitriles to yield 3-aminopyridines.

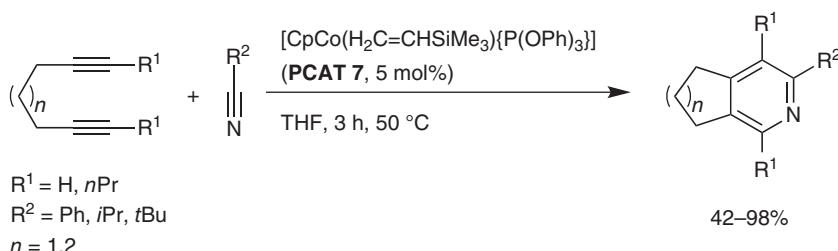
The  $[\text{CpCo}(\text{CO})(\text{dmfu})]$  (**PCAT5**) catalyst provides the possibility to form pyridines with various nitriles, and especially electron-poor nitriles are suitable substrates in opposite to the use of the *Jonas* complex (**PCAT2**), which often works sluggishly under these conditions (Scheme 9.9). To switch the regioselectivity towards the 4-aminopyridine (**22**), only the terminal alkyne of the alkynyl moiety of the diyneamine (**20**) can carry a substituent, selectively providing access to the 4-aminopyridines during the  $[2+2+2]$  cycloaddition. Terminal functionalisation of both alkynes resulted in the formation of an isomeric mixture of (**21**) and (**22**).



**Scheme 9.9** Regioselectivity in the synthesis of 3- or 4-aminopyridines (**21** and **22**) from diyneamides (**20**).

To mitigate reaction conditions and afford a more convenient handling as well as possibly enable the asymmetric catalysis with indenyl-cobalt-based derivatives, it appeared to be necessary to facilitate the activation step. Therefore, ligands with moderate coordination strength to the metal, like electron-rich olefins or phosphites, are deployed to substitute the strongly bound CO ligands,

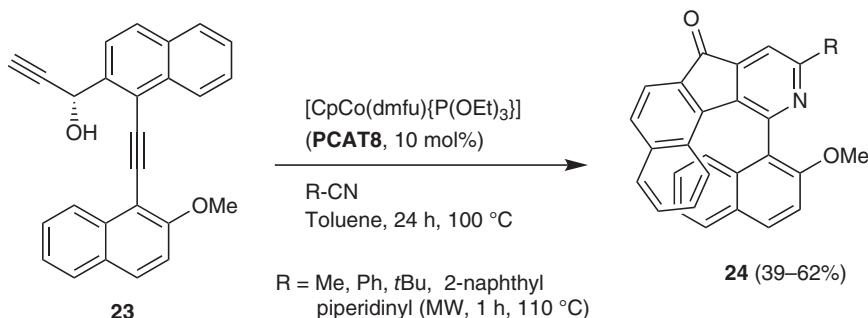
like done by *Hapke* with vinylsilanes and phosphites. (**PCAT6**, **PCAT7**) [37]. Exchange of an olefin for a phosphite raised the complex stability significantly; however, compared with other well-known olefin complexes like  $\text{CpCo}(\text{COD})$  (**PCAT3**), still a largely lower activation temperature was observed. The corresponding conditions for the exemplary investigation of complex **PCAT7** is shown in Scheme 9.10.



**Scheme 9.10** Deployment of  $\text{CpCo}(\text{olefin})(\text{phosphite})$ -complex **PCAT7** for the assembling of pyridines.

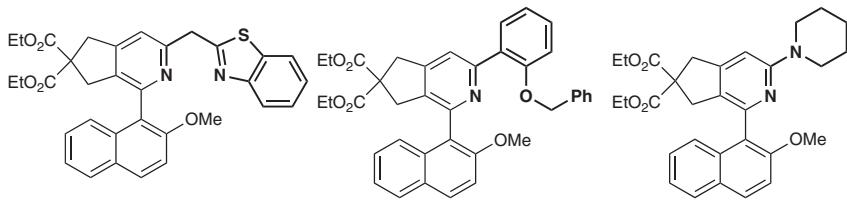
Taking the aforementioned initial results a step further, the combination of an electron-poor olefin like dmfu and a phosphite as ligand proved as an excellent choice with regard to the reactivity and stability [38]. The convenient synthetic protocol allows the versatile introduction of both, different olefins and phosphites (Scheme 9.3); however, **PCAT8** has proven so far as an excellent precatalyst for different synthetic applications. It was reusable at least three times, when the test reaction was executed under thermal conditions. The photochemical reaction procedure would isomerise the olefin, thus preventing reisolation of the precatalyst.

An exemplary recent application of complex (**PCAT8**) comprised the synthesis of sterically hindered naphthylpyridines (**24**) from diyne **23** applying the [2+2+2] cycloaddition with nitriles as a key step (Scheme 9.11) [51]. The cyclisation proceeded with moderate to good yield, including a somewhat surprising oxidation of the unprotected chiral alcohol to the conjugated ketone.



**Scheme 9.11** Application of **PCAT8** in the cyclisation of chiral diyne **23** with nitriles.

A comparative study towards the influence of the energy supply for cyclisation reactions of diynes/nitriles and triynes using **PCAT8** was undertaken by *Hapke*, providing evidence that the precatalyst can be activated under conventional thermal, microwave, and irradiation conditions [52]. The yields depended on the structure of the substrates; however, superior and most rapid achievable results were obtained by microwave heating, although irradiation at room temperature with longer reaction times gave good results as well (Scheme 9.12). In the same investigation the performance of catalyst **PCAT1** and **PCAT8** under microwave conditions were compared, thereby revealing a significantly higher reactivity for **PCAT8**. The cyclisation to compound **25** (Scheme 9.12), mediated with excellent 96% yield for **PCAT8**, only gave 72% yield under identical conditions for catalyst **PCAT1**. In some cases, utilising comparable substrates or even triynes, no reaction at all was observed for **PCAT1**, while **PCAT8** still catalyses the transformation.



### Conditions for the synthesis with PCAT8:

MW, toluene, 0.5 h, 140 °C: 54%  
 MW, toluene, 0.5 h, 160 °C: 59%

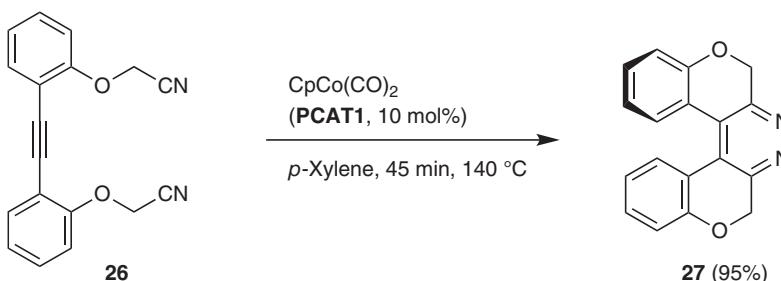
MW, toluene, 0.5 h, 140 °C: 44%  
 MW, toluene, 0.5 h, 160 °C: 22%

Toluene,  $\Delta$ , 22 h, 100 °C: 82%  
 Toluene, MW, 0.5 h, 160 °C: 96%

THE  $h_u$  22 h 25 °C: 82%

**Scheme 9.12** Comparison of various conditions, especially different methods of energy supply for activation of precatalyst PCAT8 in cyclisation reactions (former nitrile moiety with consolidated bonds)

The extension of the applicability of CpCo-mediated co-cyclotrimerisations for the assembling of two nitrogen atom-containing pyridazines **27** was demonstrated by Starý and Stará, deploying two nitrile groups and an alkyne moiety in ynedinitriles as cyclisation substrate (Scheme 9.13) [53]. The amount of CpCo(CO)<sub>2</sub> (**PCAT1**) as mediating complex strongly depends on the substitution pattern of the biarylacetylene-bridged dinitriles, ranging from 0.1 up to



**Scheme 9.13** CpCo(CO)<sub>2</sub>-mediated formation of pyridazine **27** from ynedinitrile **26**.

7 equiv. Sterically demanding substituted substrates required relatively harsh conditions, showing that phenoxyacetonitrile-derived substrate **26** gave the best yield with regard to the cyclotrimerisation. The usage of a flow reactor led to largely increased yields with simultaneously shorter transformation times for reluctantly reacting substrates.

The possibility to construct pyridazine cores by an intramolecular cyclisation of ynedinitriles was also applied by *Snyder*, thereby revealing that rhodium-based catalysts like *Wilkinson's* catalyst did not show any noticeable product formation, completely opposing the reactivity of different CpCo-based systems [54].

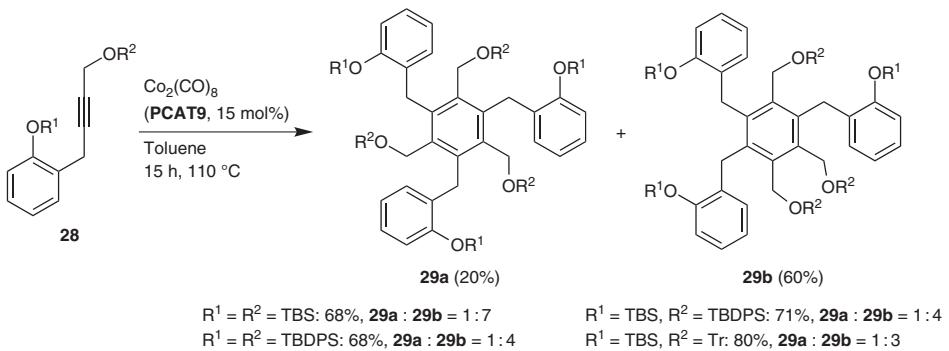
## 9.5 Non-CpCo-Based Cobalt-Catalysed Cyclisations

### 9.5.1 $\text{Co}_2(\text{CO})_8$ -Mediated Cyclisations of Carbocyclic Compounds

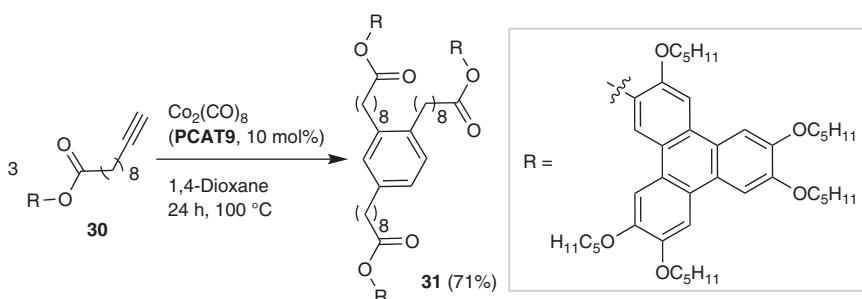
The cyclotrimerisation of alkynes is predestinated to form substituted  $C_3$ -symmetric benzenes due to the high efficiency and atom economy. *Martin* exemplarily reported the use of the reaction as a key step in the synthesis of new receptors for the tetramethylammonium ion recognition [55]. After accomplishing the substrate synthesis within four steps, applying *tert*-butyldiphenylsilyl (TBDPS)- and Tr-protecting groups for the alcohol functions, the [2+2+2] cycloaddition of **28** (Scheme 9.14) using  $\text{Co}_2(\text{CO})_8$  (**PCAT9**) as catalyst in toluene at 110 °C was investigated. Regioselectivity issues naturally play a role with such unsymmetrical substrates and the best results provided the symmetrical product (**29a**) with 20% yield and an overall yield of 80% for all obtained cyclisation products (**29a+29b**). Catalysts based on Ni, Pd, Rh, or Ir showed no conversion, including  $\text{CpCo}(\text{CO})_2$  (**PCAT1**), demonstrating the intricacy of this [2+2+2] cycloaddition and dependency on the nature of substrate, catalyst, and the optimal reaction parameter.

The ability to assemble polyfunctional benzenes led *Zhao* to deploy catalytic amounts of  $\text{Co}_2(\text{CO})_8$  (**PCAT9**) to build up triphenylene discotic liquid crystal trimers **31** starting from alkynylesters **30** (Scheme 9.15) [56]. The initially obtained isomers with a product ratio of 19 : 1 for the 1,2,4- and 1,3,5-isomer could not be separated; however, substrate modifications opened up the possibility to inhibit the formation of the symmetrical product. Thus increasing the sterical demand by shortening of the chain length to one methylene ether fragment between the alkyne and triphenylene function furnished the 1,2,4-isomers as single product, albeit with significantly lowered yield of 36%.

The catalyst **PCAT9** was furthermore applied for the synthesis of sterically highly decorated benzenes as reported by *Hupp*. Starting from diyne **33** and tetrayne **32** as cycloaddition substrates afforded catechol-functionalised organic polymers (**34**) in quantitative yields (Scheme 9.16) [57]. The potential chelate formation of the catechol moiety with the cobalt catalyst was prevented by use of an acid-cleavable protection group for the hydroxy groups, thus enabling the assembling of three-dimensional porous polymeric networks capable to coordinate various metals in a following step, leading to possible applications for gas storage or separation.



**Scheme 9.14**  $\text{Co}_2(\text{CO})_8$ -catalysed cyclotrimerisation of silyloxy-substituted alkynes to the benzene core of benzocyclotrimer analogues.



**Scheme 9.15** Utilisation of  $\text{Co}_2(\text{CO})_8$  (**PCAT9**) to catalyse the assembly of triphenylene discotic liquid crystal trimer, exemplified for compound **31**.

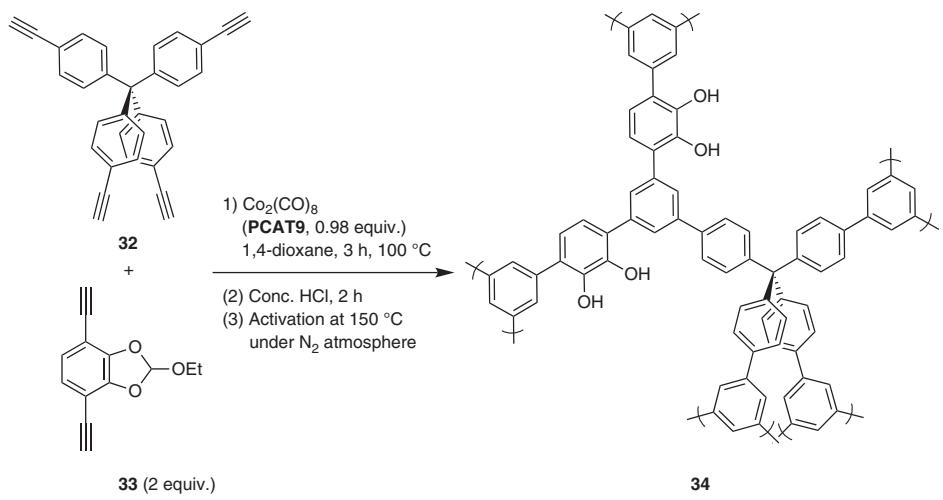
The assembling of sterically demanding fully substituted, fluorinated benzenes was attained by *Konno* through cyclotrimerisation of fluorinated and non-fluorinated alkynes, utilising for optimal conditions a large excess of the non-fluorinated alkyne (up to 6 equiv.), a large dilution and the stoichiometric use of  $\text{Co}_2(\text{CO})_8$  (**PCAT9**) to achieve a high conversion (Scheme 9.17) [58]. The method provides a wide range of tolerable substrates including electron-donating as well as electron-withdrawing substituents and different substitution pattern of the phenyl ring. Detrimental for obtaining good yields are the presence of substituents in *ortho*- or *meta*-position of the phenyl ring, nitro groups, or deployment of an unprotected propargylic alcohol.

The versatility of cobalt-mediated transformations was highlighted in the cyclotrimerisation of macrocycles as demonstrated in work by *Merlic* [59]. In this specific case the [2+2+2] cycloaddition competes with the transannular *Pauson–Khand* reaction of dienyne **35**. To control the structure of the product (**36**) and assure its general formation, the use of an understoichiometric amount of  $\text{Co}_2(\text{CO})_8$  (**PCAT9**) as well as the absence of *Pauson–Khand* promoting reagents like tetramethylthiourea are urgently necessary, therefore furnishing the macrocyclic ethers with good yields (Scheme 9.18).

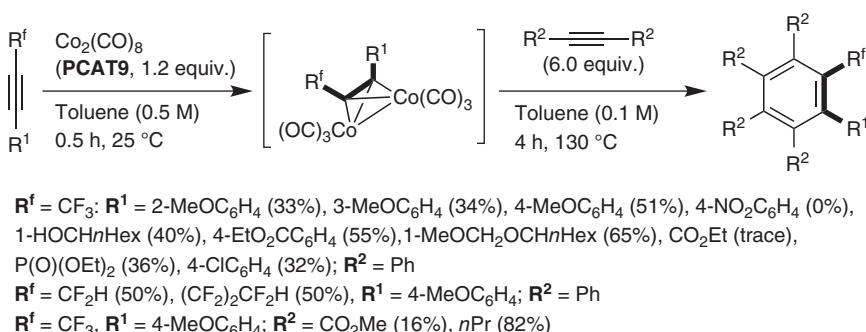
The efficient concept of building up symmetrical benzenes by cyclotrimerisations could enhance the arsenal of methods available for the assembling of completely substituted benzenes, frequently used in the material science as fluorescence emitters or as liquid crystals [60]. Starting from diarylacetylenic substrates a range of benzene core structures is accessible with good yields by utilising  $\text{Co}_2(\text{CO})_8$  (**PCAT9**) as catalyst. The bulky alkyne substituents usually require longer reaction times at high temperatures, ranging from one night to several days.

### 9.5.2 In Situ-Generated Catalysts and Precatalysts in Carbocyclisations of Alkynes

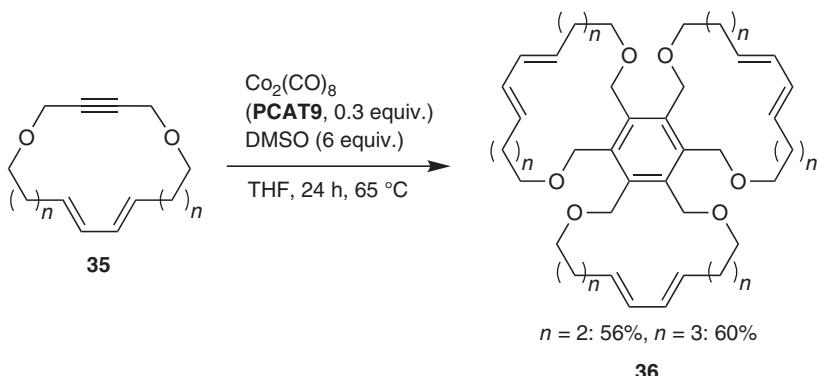
In contradiction to the already discussed isolated  $\text{CpCo(I)}$ -complexes or  $\text{Co}_2(\text{CO})_8$  (**PCAT9**) used to catalyse [2+2+2] cycloadditions, *in situ*-generated systems allow the much easier and diversified generation of catalyst systems from simple precursor molecules, including, e.g. commercially available ligands,



**Scheme 9.16** Synthesis of catechol-containing porous organic polymers by cyclotrimerisation.



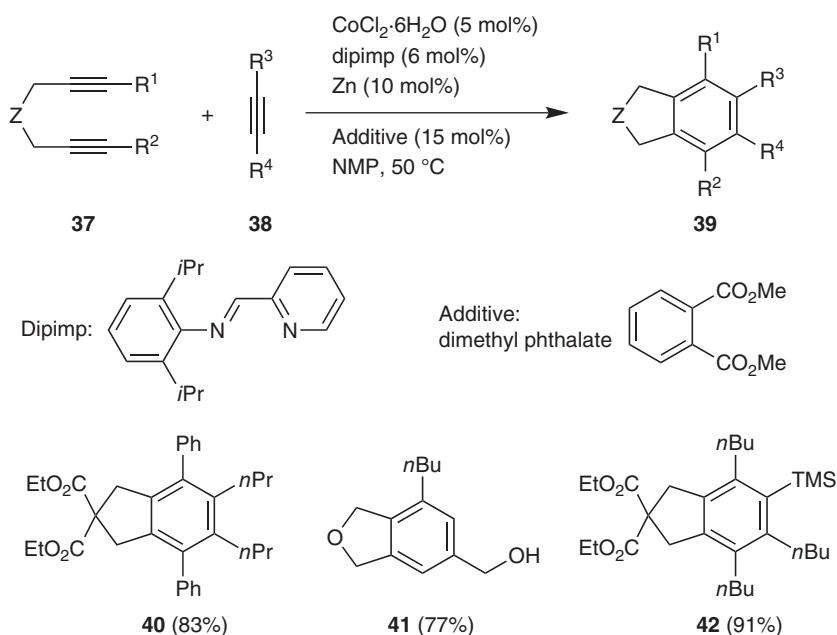
**Scheme 9.17** Cyclotrimerisation of fluorinated alkynes yielding fluorinated benzenes (**R<sup>f</sup>** is the fluorinated group).



**Scheme 9.18** Utilisation of Co<sub>2</sub>(CO)<sub>8</sub> (PCAT9) for the formation of macrocyclic ethers (36).

and allow even hydrated cobalt salts as metal source. The general drawback is the necessity of reduction of the cobalt(II) salt to generate the active catalyst and the sometimes less well-defined catalyst environment, which can also promote side reactions. There is a steady interest in the evolution of such systems especially also including the base metals like cobalt, as they allow easy modification of structural ligand parameters and adaption to different substrates and target structures.

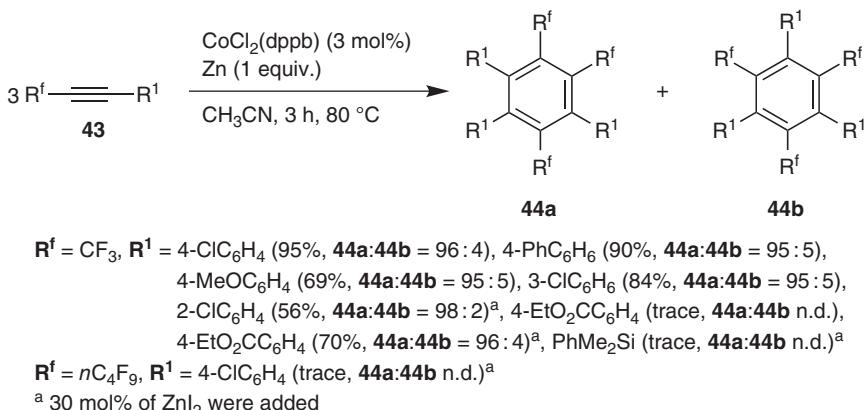
Challenges for these reactions are the replacement of terminal alkynes as substrates for internal counterparts (37) without the need of harsher conditions for the cyclisation or the application of possible additives, which, e.g. help to speed up various cyclotrimerisations to form fully substituted benzenes (39) at mild conditions (Scheme 9.19) [61]. The iminopyridine ligand dipimp was essential together with CoCl<sub>2</sub>·6H<sub>2</sub>O as metal source. The addition of dicarbonyl compounds, and especially dimethyl phthalate, turned out to be the most effective variation, enabling to lower the catalyst loading to 2 mol% while conceding only a marginally lower yield. The application scope covers many different substrates and some of their products are shown (Scheme 9.19, 40–42). When deploying unsymmetrical alkynes (38), it was demonstrated



**Scheme 9.19** Application of dimethyl phthalate as activator for the [2+2+2] cycloaddition of diynes **37** and alkynes **38**.

that the regioselectivity is rarely influenced by the use of dimethyl phthalate as an additive; however, the reaction time could be shortened from three days to three hours in the best case.

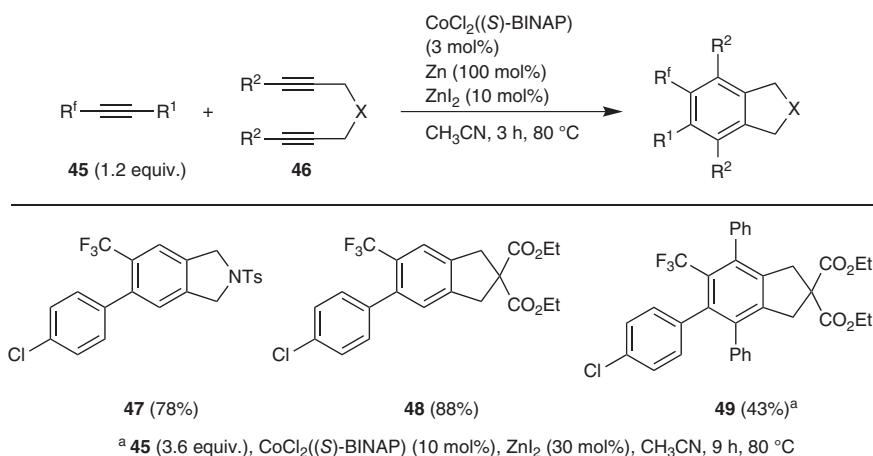
An enhanced procedure was developed by *Konno*, requiring less amounts of cobalt and simultaneously utilising the less sensitive cobalt(II) hexahydrate as metal source to convert fluorine-containing internal alkynes (**43**) (Scheme 9.20) [62]. The examination of suitable ligands provided evidence



**Scheme 9.20** Fully intermolecular [2+2+2] cycloaddition of internal, fluorine-containing alkynes (**43**,  $\text{R}^f$  is the fluorinated group).

that monodentate ligands like  $\text{PPh}_3$  did not increase significantly the yield in comparison to the uncomplexed metal. A further improvement was achieved by using bidentate phosphine ligands, leading to the conclusion that the length of the linking carbon chain tether is largely affecting the regioselectivity of the cyclisation products. The highest ratio of regioisomers (**44a**,**44b**) was obtained, when deploying 1,4-bis(diphenylphosphino)butane (dppb) or 1,3-bis(diphenylphosphino)propane (dppp) as ligands with a ratio of 96 : 4 for the 1,2,4-isomer (**44a**); however, deploying dppe or (*S*)-BINAP decreased the ratio to 84 : 16 and 92 : 8. The ligand 1,1'-bis(diphenylphosphino)ferrocene (dppf) was also found to deliver the same good regioselectivity but a lower overall yield. When investigating the substrate scope, it appeared that substitution of the alkyne-attached phenyl ring in *meta*- or *para*-position did rarely affect the regioselectivity and yield of the cyclotrimerisation reaction, in opposite to an *ortho*- or electron-withdrawing substitution that inhibited the formation of any cyclisation product. This inhibition could partly be overcome by adding 30 mol% of  $\text{ZnI}_2$  as additive to achieve up to 70% yield.

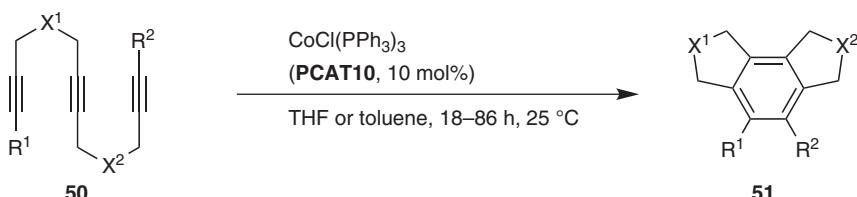
The capabilities of such systems are not only limited to fully intermolecular cyclotrimerisations of fluorine-containing alkynes, but also partly intramolecular cyclisations of diynes (**46**) with a fluorinated internal alkyne (**45**, Scheme 9.21) were mediated with moderate to good yields of **47**–**49**. The scope is, however, limited to the formation of five-membered rings in the backbone. Substrates like 1,7-octadiyne showed no conversion and even the use of internal diynes produced low yields or required a bigger excess of the fluoroalkyne (**45**) and a higher amount of  $\text{ZnI}_2$  to achieve moderate 43% isolated yield.



**Scheme 9.21** Partly intramolecular cyclisation of fluorine-containing alkynes (**45**,  $\text{R}^f$  is the fluorinated group).

In contrast to the *in situ*-generated systems and methodologies presented before, the cobalt analogue of the Wilkinson complex,  $\text{CoCl}(\text{PPh}_3)_3$  (**PCAT10**), is a molecularly well-defined compound, which has until recently only seen very limited use as catalyst in [2+2+2] cycloadditions. *Hapke* firstly evaluated

its capability as catalyst for intramolecular cyclotrimerisations of triynes (**50**, Scheme 9.22) [40]. While the catalyst is commercially available and in addition easy to prepare, its purity and stability against air need to be paid attention to. After all, it's an immediately applicable precatalyst without the requirement of further necessary modification or activation steps. A wide range of different triynes (**50**) was synthesised and successfully transformed into the corresponding benzenes (**51**) under mild conditions. The products were in general obtained in good to excellent yields. The reaction tolerated large aromatic moieties like phenanthryl or heteroaromatic substituents without significant loss of yield. Switching the tethering groups from ether to malonyl or enlargement of the newly formed saturated ring required higher reaction temperatures to achieve comparable good yields (Scheme 9.22).



$X^1 = X^2 = O$ :  $R^1 = R^2 = 1\text{-naphthyl}$  (92%); 2-MeO-1-naphthyl (0%); 9-phenanthryl (86%); 2-methylbenzoate (51%); quinolin-4-yl (94%)

$X^1 = X^2 = O$ ;  $R^1 = 1\text{-naphthyl}$ ,  $R^2 = Me$  (96%);  $R^1 = 1\text{-naphthyl}$ ,  $R^2 = 2\text{-MeO-1-naphthyl}$  (90%)

$X^1 = X^2 = C(CO_2Et)_2^a$ :  $R^1 = R^2 = 1\text{-naphthyl}$  (81%); 2-MeO-1-naphthyl (96%)

$X^1 = X^2 = C(CO_2Et)_2^a$ :  $R^1 = 2\text{-MeO-1-naphthyl}$ ,  $R^2 = Me$  (82%)

$X^1 = C(CO_2Et)_2^a$ ,  $X^2 = CH_2C(CO_2Et)_2^a$ :  $R^1 = 2\text{-MeO-1-naphthyl}$ ,  $R^2 = Ph$  (92%)

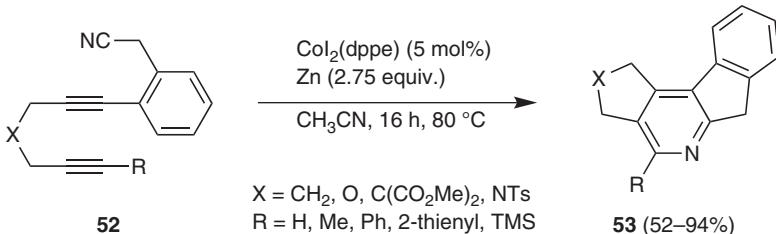
<sup>a</sup> Required a higher temperature of 60–95 °C

**Scheme 9.22** Application of  $\text{CoCl}(\text{PPh}_3)_3$  (PCAT10) as molecular defined catalyst for the cyclotrimerisation of substituted triynes **50**.

### 9.5.3 In Situ-Generated Catalysts in the Cyclisation of Alkynes to Heterocyclic Compounds

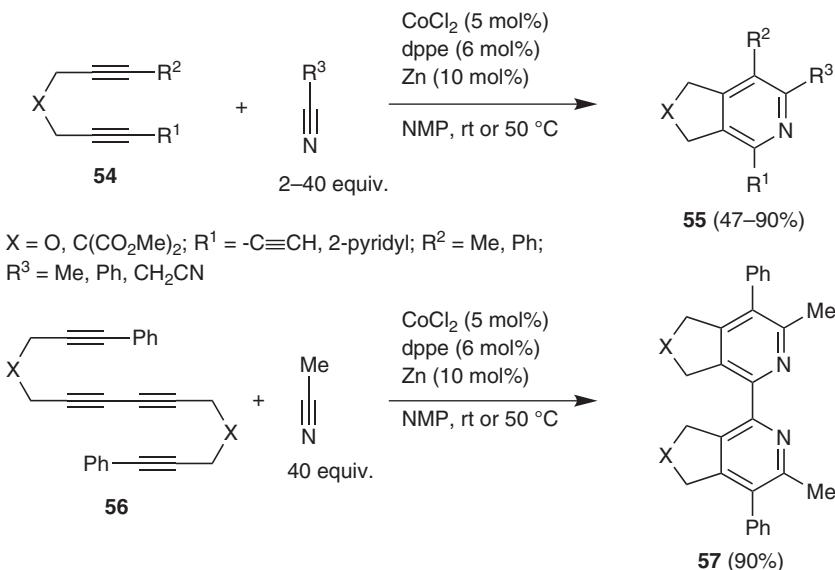
The limitation of *in situ*-based cobalt catalytic systems for the formation of carbocycles were partly overcome in recent years, enlarging the substrate scope to nitriles, thus enabling a new way of pyridine synthesis, which has previously been a pure domain of CpCo-based catalysts [63–65]. In this context the novel application of cobalt-based *in situ* catalytic systems for the formation of polymers containing a pyridine core should be mentioned [66]. The possibilities to synthesise substituted pyridines by an *in situ*-generated catalytic system were investigated in more detail by Cheng, who developed a methodology to assemble tetracyclic pyridines (**53**) via the cyclisation of cyanodiynes (**52**, Scheme 9.23) [63]. An interesting facet of this catalytic system was that only acetonitrile works as suitable solvent, which however is not incorporated into the newly formed pyridine ring under reaction conditions. This method is limited to cyanodiynes (**52**) as substrates and moderate to excellent yields were achieved for various examples. The substrate scope covered different types of bridges between the two alkyne moieties, e.g. ether, tosylamide, malonyl, or alkyl functions, and

tolerated substituents like alkyl, aryl, silyl, or thienyl groups. A crucial feature of the catalytic system seems to be the application of a ligand, which is able to form a five-membered chelate ring with the cobalt atom to successfully assemble the pyridine core.



**Scheme 9.23** Formation of pyridines (**53**) by fully intramolecular cyclisation of **52**, mediated by an *in situ*-generated catalytic system.

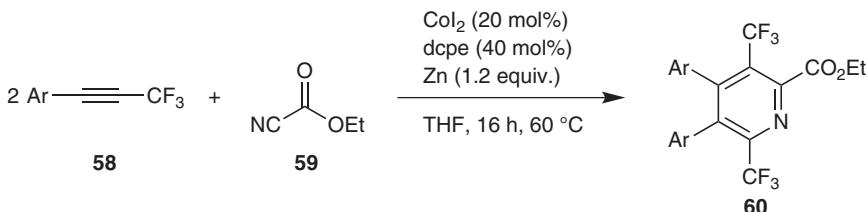
In addition to the complete intramolecular reaction described before, the partially intramolecular cyclisation of a diyne component (**54**) and a nitrile molecule is a likely logical extension and was first performed by *Okamoto* [64]. Again, the screening of ligands provided the insight that five-membered ring chelate-forming bisphosphine ligands are necessary for the successful performance of the reaction. Nevertheless, a large excess of up to 40 equiv. of the nitrile was required to obtain the synthesised pyridines (**55**) with moderate to excellent yields. In return, the catalytic system tolerated many functional groups like phenyl, pyridyl, and various alkyl substituents as well as ether- and malonyl-bridging in the diyne (Scheme 9.24). The pyridine **55** was formed



**Scheme 9.24** Utilisation of an *in situ*-generated catalytic system for the partly intramolecular cyclisation of alkynes and nitriles.

highly regioselective, in most cases with a ratio of higher than 99 : 1 to the corresponding regioisomer. The amount of the minor regioisomer could be promoted by applying electron-deficient nitriles like 2-cyanopyridine. *Okamoto* also demonstrated the possibility to assemble 2,2'-bipyridines (**57**) with this system by co-cyclisation of symmetrical tetrynes (**56**) with two nitriles (Scheme 9.24).

The permanent need for new fluorine-containing compounds itself and the development of new methods to obtain these inspired *Kawatsura* to exploit the advantages of assembling aromatic fluorinated carbo- and heterocycles from smaller building blocks by deploying the [2+2+2] cycloaddition reaction. Central elements of the strategy are the fully intermolecular cyclisation of aryl trifluoromethyl alkynes (**58**) and cyanoformate **59** to furnish substituted picolimates (**60**, Scheme 9.25) [65]. To obtain good conversions a higher catalyst loading is required to convert these electron-deficient substrates sufficiently. It is quite interesting to note that during ligand screening the relatively electron-rich 1,2-bis(dicyclohexylphosphino)ethane (dcpe) with a larger steric demand than previously investigated ligands was found to work much better in this case. Utilised in the polycyclotrimerisation of internal alkynes bearing bulkier alkyl substituents, lower reaction rates were observed as shown by *Okamoto* [66]. Increasing the amount of elemental zinc from 0.4 up to 1.2 equiv. could help further improve the yield. A possible explanation for the observed absolute regioselectivity (no other regioisomers than that pictured in Scheme 9.25 was found) of the cyclisation might be the electron-withdrawing effect of the alkyne carbon atom attached to the trifluoromethyl group, which led to a closer binding to the active cobalt centre and therefore pre-orientation of the alkyne for the cyclisation process.

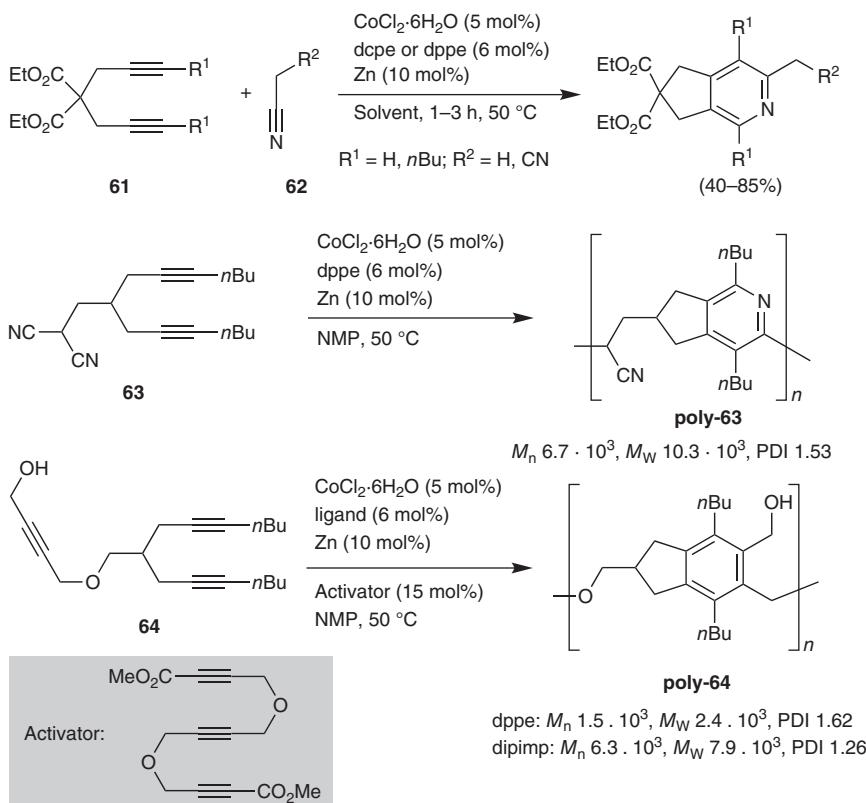


Ar = Ph (65%), 4-PhC<sub>6</sub>H<sub>4</sub> (87%), 4-tBuC<sub>6</sub>H<sub>4</sub> (94%), 4-FC<sub>6</sub>H<sub>4</sub> (85%), 4-ClC<sub>6</sub>H<sub>4</sub> (85%), 4-BrC<sub>6</sub>H<sub>4</sub> (98%), 4-CF<sub>3</sub>OC<sub>6</sub>H<sub>4</sub> (82%), 4-EtO<sub>2</sub>CC<sub>6</sub>H<sub>4</sub> (57%), 4-CF<sub>3</sub>C<sub>6</sub>H<sub>4</sub> (17%)

**Scheme 9.25** Construction of fluorinated picolimates (**60**) from trifluoromethylated arylalkynes (**58**) and cyanoformate (**59**).

The substrate scope encompasses various decorated arenes, while multiple substitutions in different positions are well tolerated, even with moderate electron-withdrawing groups. Sluggish conversions were observed for strong electron-withdrawing groups like nitro or trifluoromethyl functionalities and a decreased yield in the range of 65–85% was put in context to *ortho*-substitutions of the benzene ring. Noteworthy, the nitrile component was not used in excess and high yields were achieved due to the under mild conditions *in situ*-generated active catalytic species.

The abilities of *in situ*-generated catalytic systems based on cobalt were also exploited by the stepwise polymerisation of triynes **64** or diynedinitriles **63** via co-cyclotrimerisation, a so-called cycloaddition polymerisation process (Scheme 9.26) [67]. This reaction is related to the longer-known and well-studied 1,3-dipolar and [4+2] cycloaddition polymerisations, as well as the less familiar [2+2] cycloaddition polymerisation [68]. For the successful polymerisation in a linear step-growth fashion, it is necessary to achieve a selective cross-cycloaddition between the dyne and nitrile to avoid the undesired branched structures or the termination of the polymerisation process. Therefore, for the desired stepwise polymerisation process, the structure of the monomer and catalyst function need to inhibit the formation of carbocycles. Electron-rich diphosphine ligands like dcpe or dppe proved as the best choice during ligand screening, in opposition to nitrogen-containing ligands like dipimp, which worked great for pure carbocyclic polymer **poly-64** (Scheme 9.26), but no formation of the desired pyridine product were observed [66, 69]. Okamoto experienced that dcpe worked excellent for the unsubstituted screening substrates (**61,62**), but only sluggishly when using *n*-butyl-substituted dyne **61**,



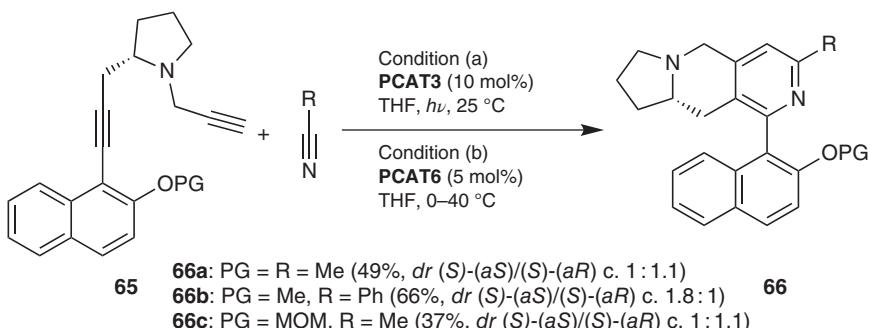
**Scheme 9.26** Step-growth fashioned cycloaddition polymerisation of dyne, triyne, and cyanodiyne monomers.

reconfirmed in the much lower molecular weight obtained by polymerisation of **63**. With the optimised reaction parameters, the polymerisation via the nitrile–diyne polycycloaddition proceeded smoothly and generated selectively the linear polymer (**poly-63**) with the pyridine core structure in a step-growth fashion.

## 9.6 Cobalt-Mediated Asymmetric [2+2+2] Cycloadditions

Cobalt complexes as chiral catalysts in asymmetric syntheses are covered in detail in Chapter 10 of this book and even more thoroughly in a very recently published monography [70]. [2+2+2] Cycloaddition reactions allow the preservation or introduction of the different chiral elements in organic compounds by designing and synthesising appropriate chiral or prochiral alkyne substrates [71]. However, the introduction of chirality by applying chiral Co(I) catalysts to achiral substrates is still a challenging task. For the cyclisation of chiral substrates, an achiral catalyst like **PCAT1** is regularly used, and the structural requirement for the chiral centre(s) is the stability against the usually rather high reaction temperatures [71a]. An example was reported by *Heller*, who assembled chiral pyridines by using acetylene or substituted alkynes and enantiopure nitriles under photochemical conditions using CpCo(COD) (**PCAT3**) as catalyst [72]. Later, a two-step approach towards chiral pyridyl alcohols using asymmetric cyanation of aldehyde followed by photochemically assisted cobalt-catalysed [2+2+2] cycloaddition with acetylene was outlined by *Heller* and *Hapke* [73].

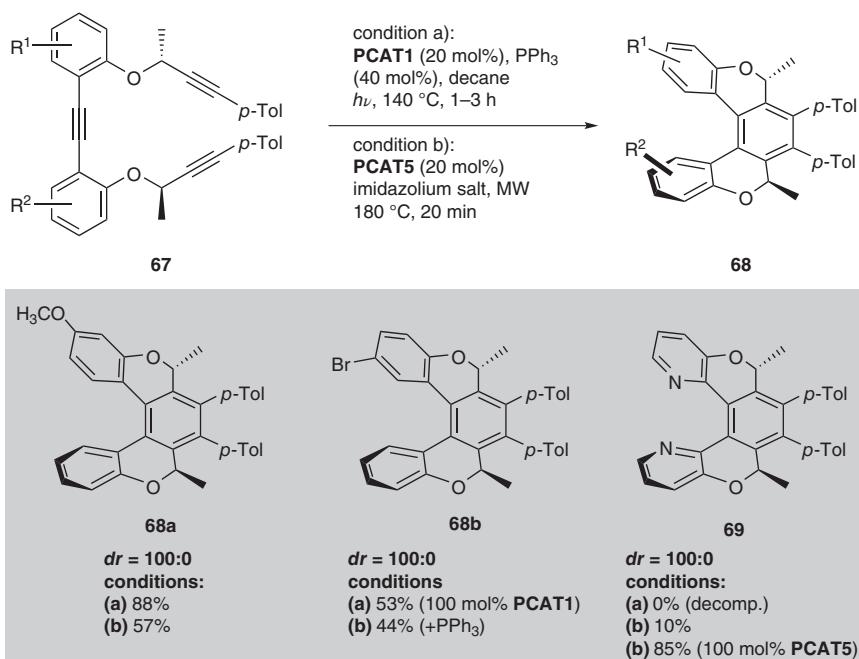
The convergent construction of a chiral biaryl platform (**66**) based on a proline backbone-derived chiral diyne (**65**) was realised by *Hapke*, applying Co(I) catalysis for the cyclisation step, which can be performed under thermal and photochemical conditions at mild temperatures using precatalysts **PCAT3** and **PCAT6** (Scheme 9.27). This approach finally led to diastereomeric atropisomers, which can usually be separated simply by column chromatography. The absolute configuration of the formed diastereoisomers (**66a–c**) was determined by X-ray analysis [74].



**Scheme 9.27** Synthesis of diastereomeric pyridine atropisomers.

Another example for the formation of a chiral pyridine was given by *Kotora*, utilising the co-cyclotrimerisation of 1,7-octadiyne and (*R*)-tetrahydrofuran-2-yl nitrile by usage of **CpCo(CO)<sub>2</sub>** (**PCAT1**) as catalyst to obtain the corresponding pyridine derivative with 28% yield [75].

While for the enantioselective synthesis of chiral helicenes by cyclotrimerisation, rhodium-based catalytic systems have been extensively investigated recently [76], the introduction of chiral centres in the cyclisation precursor molecules was the essential strategy in the assembly of chiral helical diastereomers (**68**) by CpCo-mediated reactions, demonstrated by extensive work from *Stará* and *Starý*. They synthesised chiral triynes (**67**) and cyclised them using **PCAT1** or **PCAT5**, which led to diastereomerically pure products (**68a–b**) in dependence from the substitution pattern of the terminal alkynes in a thermodynamically controlled fashion (Scheme 9.28) [77].

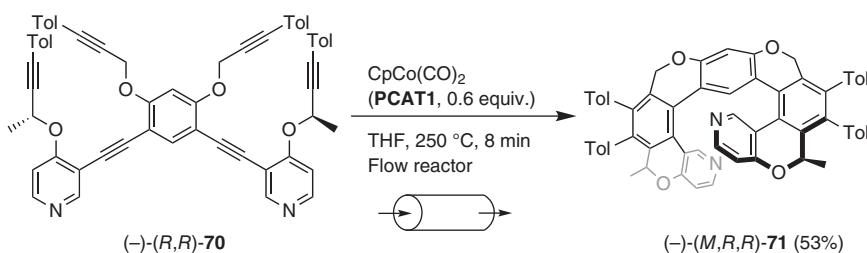


**Scheme 9.28** Synthesis of diastereomerically pure helicenes by CpCo-mediated cyclisation.

An adaptation of this method enabled a new access to pyridohelicines (**69**) in a diastereo- and enantioselective manner by chiral substrate-driven cyclisation of cyanodiynes in analogy to the previously mentioned procedure [78]. Noteworthy is the superior efficiency of **PCAT1** with respect to different Ni(0) and Rh(I) catalyst systems.

The related approach was also taken for the preparation of long oxahelicenes **71** (oxa[19]helicenes) by synthesising the corresponding required chiral oligoyne substrates **70**. The optimal cyclisation conditions were found to require the

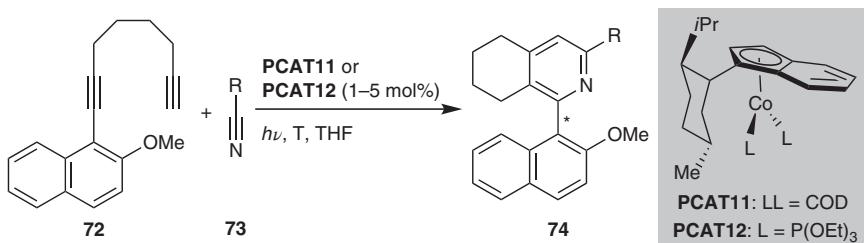
reaction to run in a plug flow reactor with tetrahydrofuran (THF) as solvent at 250 °C within short reaction times applying slightly substoichiometric to superstoichiometric catalysts loading of **PCAT1**, leading to yields up to 53% (Scheme 9.29) [79]. The plug flow reactor methodology has been rarely applied to such [2+2+2] cycloadditions, allowing significantly higher temperatures and pressures and thereby requiring much shorter resident times compared even with microwave (MW) methodologies. The mounted chiral methyl groups again allowed stereocontrol, leading to enantiomerically pure oligoyne precursors and a diastereoselective formation of the oxahelicene.



**Scheme 9.29** Exemplary synthesis of oxahelicene **(-)-(M,R,R)-71**.

An identical approach again using **(-)-(S)-3-butyn-2-ol** as chiral building block in the synthesis of the cyclisation precursor was included for the assembly of diastereo- and enantiopure bioxahelicene 2,2'-bipyridines [80]. In this synthetic endeavour the catalyst  $\text{CpCo}(\text{CO})(\text{dmfu})$  (**PCAT5**) was applied in selected reactions under microwave conditions with chlorobenzene as solvent at 150–160 °C, when nickel catalysis did not work. The rather drastic conditions are necessary due to the formation of the 2,2'-bipyridine core, which can act as inhibitor for the catalyst.

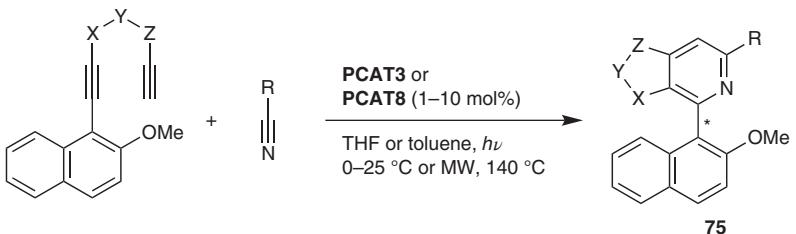
The first example for a photoactivable chiral menthylindenylcobalt(I)-complex (**PCAT11**) was reported by *Heller* and *Gutnov* [42]. The catalyst was exemplarily applied in the synthesis of chiral pyridines and biaryls, including gaseous acetylene as reaction partner [81]. The positioning of the chiral group at an indenyl ring turned out to be crucial for the selectivity of the catalyst [82]. *Hapke* extended the application of **PCAT11** to the assembly of a set of 1-naphthyltetrahydroisoquinolines (**74**) from diynes **72** and different nitriles (**73**), the latter containing alkyl and heteroalkyl groups as well as substituted aryl groups with, e.g. methoxy, chloro, and boryl substituents (Scheme 9.30) [83]. Exchange of the 1,5-cyclooctadiene (COD) ligand in **PCAT11** for phosphites gave complex **PCAT12**, which could be thermally and photochemically activated and showed some selectivity in the cyclisation of **72** and  $\text{PhCN}$  ( $\text{R} = \text{Ph}$ ). However, selectivity and yield were lower than in the photochemical process and higher reaction temperatures compromised the selectivity [43]. Synthesis and attempted application of a chiral 2-binaphthyl 2-indenyl-cobalt complex in the cyclotrimerisation process provided good yield but no selectivity and demonstrated the unique properties of precatalyst **PCAT11**.



For **PCAT11**: R = Me, 66%, 90% ee; tBu, 79%, 91% ee; 3,4,5-(MeO)<sub>3</sub>C<sub>6</sub>H<sub>2</sub>, 64%, 91% ee; 2,3,4-(MeO)<sub>3</sub>C<sub>6</sub>H<sub>2</sub>, 44%, 94% ee; 4-CF<sub>3</sub>C<sub>6</sub>H<sub>4</sub>, 59%, 86% ee; 4-BPinC<sub>6</sub>H<sub>4</sub>, 45%, 75% ee; 2-furanyl, 81%, 91% ee; 1-piperidinyl, 89%, 87% ee

**Scheme 9.30** Enantioselective synthesis of chiral 1-naphthyltetrahydroisoquinolines.

Structural analogues of 1-naphthyltetrahydroisoquinolines (**75**) containing five-membered substituted rings in the backbone were systematically synthesised using CpCo(I)-catalysts, and their barriers of rotation were investigated and determined by dynamic high-performance liquid chromatography (HPLC) on chiral phases (Scheme 9.31) [84]. The accurate substitution pattern led to configurationally stable biaryls with an annellated five-membered ring at the pyridine core, and this could be demonstrated by using chiral **PCAT11** for an exemplary asymmetric cyclisation under photochemical conditions. The barriers of activation for free rotation around the biaryl axis were determined to be larger than  $\Delta G^\ddagger > 115$  kJ/mol for the accordingly substituted biaryls.

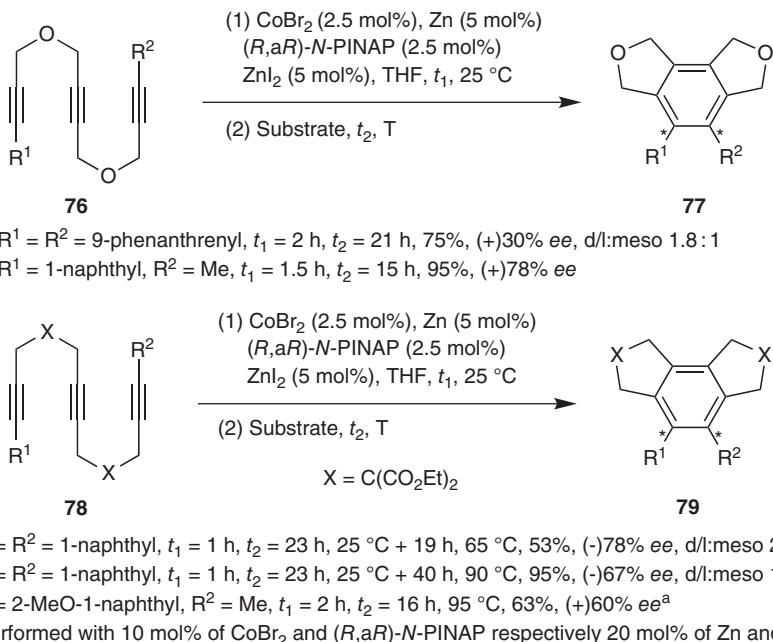


For **PCAT3** (irradiation): R = Me: X = Z = Si(Me)<sub>2</sub>, Y = O, 93%  
R = Ph: X = C=O, Y = Z = CH<sub>2</sub>, 70%                   X = Z = SiMe<sub>2</sub>, Y = O, 44%  
   X = Z = CH<sub>2</sub>, Y = NMes, 43%  
   X = CMe<sub>2</sub>, Y = NH, Z = CH<sub>2</sub>, 62%  
   X = CMe<sub>2</sub>, Y = NMe, Z = CH<sub>2</sub>, 62%

For **PCAT 8** (MW): R = Ph: X = CMe<sub>2</sub>, Y = NTs, Z = CH<sub>2</sub>, 71%  
   X = C = CH<sub>2</sub>, Y = Z = CH<sub>2</sub>, 56%

**Scheme 9.31** Synthesis of configurational stable heterobiaryls by Co(I)-catalysed co-cyclotrimerisation of substituted heptadiynes and derivatives with nitriles.

The field of chiral Co(I)-catalysed [2+2+2] cycloadditions has just recently been extended to involve *in situ*-generated systems, utilising  $\text{CoBr}_2$ , zinc, and zinc(II) iodide in combination with chiral *P*, *N* ligands for the intramolecular cyclisation of various triynes (**76**,**78**), furnishing bi- or triaryls (**77**,**79**) with good enantioselectivity up to 78% and good to excellent yields under mild conditions (Scheme 9.32) [44]. Substrates included ether- and malonyl-bridged triynes, terminally substituted by alkyl or aryl groups. The highest enantioselectivities were obtained by using (aS)-QUINAP and (*R,aR*)-*N*-PINAP, assuming that the formation of a six-membered chelate with the cobalt centre is essential to induce the chirality during the cyclisation process.

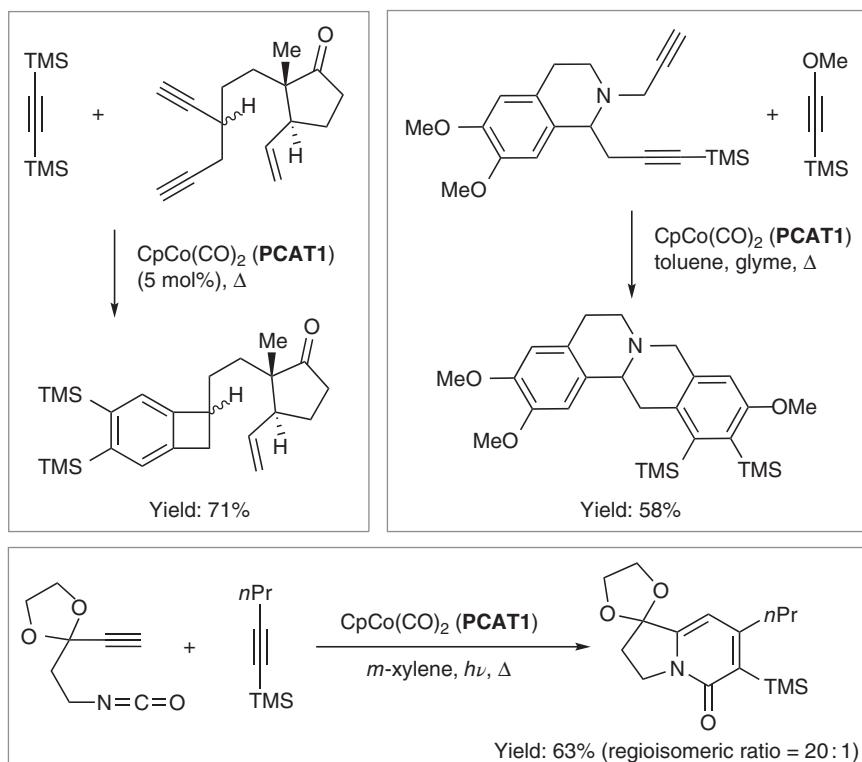


**Scheme 9.32** Chiral [2+2+2] cycloaddition of triynes applying an *in situ*-generated chiral Co(I) catalyst.

## 9.7 Cobalt-Mediated Cyclisations in Natural Product Synthesis

The special ability of the [2+2+2] cycloaddition to form a number of new bonds within one step and thereby assembling smaller synthons to a bigger core structure predestinates this reaction to be applied for the synthesis of natural products [85]. Due to the pre-eminence of cobalt as first-row transition

catalyst metal in the infancy of cyclotrimerisation reactions, a number of studies were published, where a cobalt-mediated key step was implemented [6]. The preeminent studies were undertaken by *Vollhardt*, who synthesised (+)-estrone including a conceptually novel cyclotrimerisation step, followed by several other exemplary elaborations of natural product building blocks (see Scheme 9.33 for examples) [86].

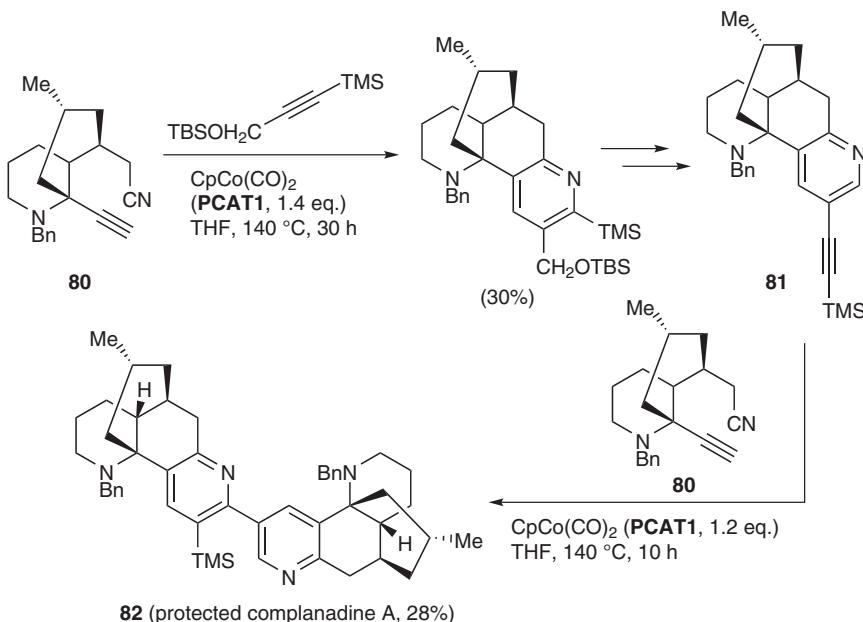


Scheme 9.33  $\text{CpCo}$ -mediated cyclotrimerisations in natural product syntheses.

Beside cobalt mainly nickel, rhodium, and ruthenium catalysts are applied in the synthesis of natural products by a cyclotrimerisation key step, especially  $\text{Cp}^*\text{Ru}$  catalysts nicely complement the scope of cobalt catalysts, e.g. when electron-deficient alkynes or haloalkynes are cyclisation partners. Compound **PCAT5** is capable of accepting bromoalkynes as substrates, while ruthenium catalysts furthermore also allow the successful conversion of chloro- and iodoalkyne moieties [87]. Another recent example of direct comparison between  $\text{Cp}^*\text{Ru}$ - and  $\text{CpCo}$ -catalysis was reported for the synthesis of the pyridine core of cyclothiazomycin, where the  $\text{Cp}^*\text{Ru}$ -complex successfully converted the thiazolcarbonitrile with the functionalised diyne [88]. However, cobalt-catalysed cyclotrimerisations have been applied in numerous constructions of natural products as central ingredient of the key step of the sequence [89]. In the following paragraph we discuss selected recent examples of

natural product synthesis, where a cobalt-mediated cyclotrimerisation plays an important role.

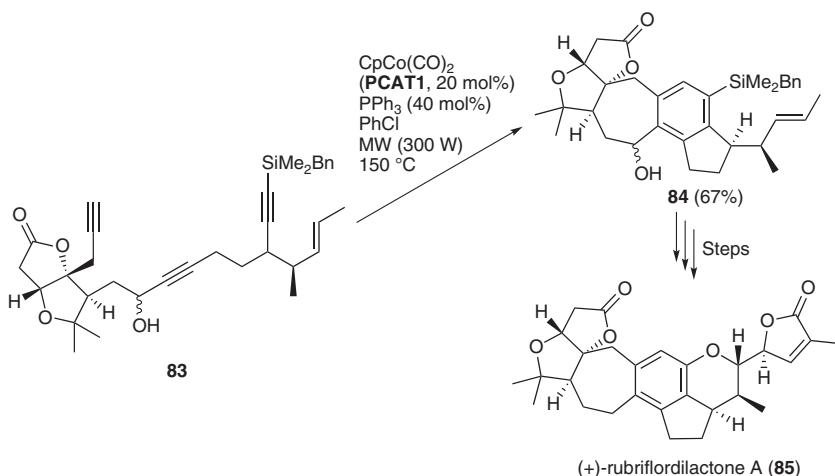
The cobalt-mediated twofold [2+2+2] cycloaddition in the preparation of (+)-complanadine A (**82**) resulted in the formation of a highly substituted 2,3'-bipyridine core, which was constructed from two nearly identical cyanoalkynes **80** and via the intermediate alkyne derivative **81** (Scheme 9.34) [90]. Siegel studied the process in remarkable detail including structurally modified cyclisation precursors and different solvents and additives for the cyclisation process [91]. During cyclisation process the formation of the 2,2'- and desired 2,3'-bipyridine core is happening concurrently; however, addition of *Lewis* basic additives and additional ligands like 4-dimethylaminopyridine (DMAP),  $\text{PPh}_3$  or  $\text{AsPh}_3$  allow the modification of the ratio towards the desired product. In all cases at least stoichiometric amounts of **PCAT1** are required as well as temperatures of  $140^\circ\text{C}$ .



**Scheme 9.34** CpCo-mediated cyclisations in the total synthesis of complanadine A.

Several groups published synthetic approaches towards the total or partial synthesis of rubriflordinilactones A (**85**) and B, assembling the benzene core either by palladium-catalysed cyclisation of a bromoenediye or cobalt-catalysed cyclisation of a functionalised triyne. Anderson studied initially with some simpler model substrates to reconnoitre the most promising route to the CDE rings of the rubriflordinilactones A and B [92]. Their results led to a total synthesis, which included the late-stage cyclisation of a triyne **83**, which already contains the A and B ring and afforded the CDE ring fragment by the [2+2+2] cycloaddition (Scheme 9.35) [93]. The newly formed central arene ring **84** is

annellated with a highly substituent-decorated five- and seven-membered ring, which is an unusual and very rare structural element to be generated by such a cyclotrimerisation process. The conditions of the cyclisation are also rather unusual, because chlorobenzene is used as solvent in the microwave-assisted cyclisation, requiring only 20 mol% catalyst, however, together with 2 equiv. of  $\text{PPh}_3$  ligand. The reaction yield of 67% is remarkable for such a process and the possibly competing intermolecular reaction was not observed.

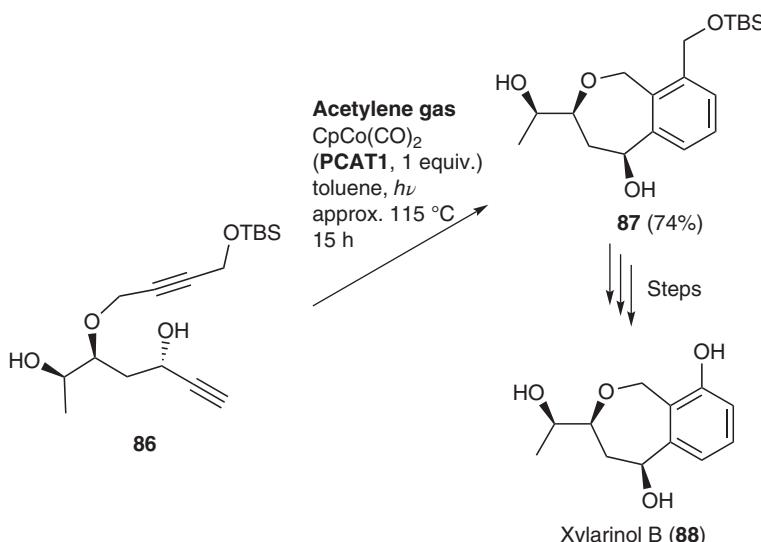


**Scheme 9.35**  $\text{CpCo}$ -catalysed cyclisation key step in the total synthesis of **(+)-rubriflordilactone A (85)**.

A related study on the synthesis of rubriflordilactone B (**85**) was undertaken by *Xie* and also featured a cyclotrimerisation process [94]. The cyclisation precursor was a terminal diyne and the cycloaddition was most successful with  $\text{RhCl}(\text{PPh}_3)_3$  (yield around 76%); however, no details on the outcome with other catalysts like cobalt complexes were reported.

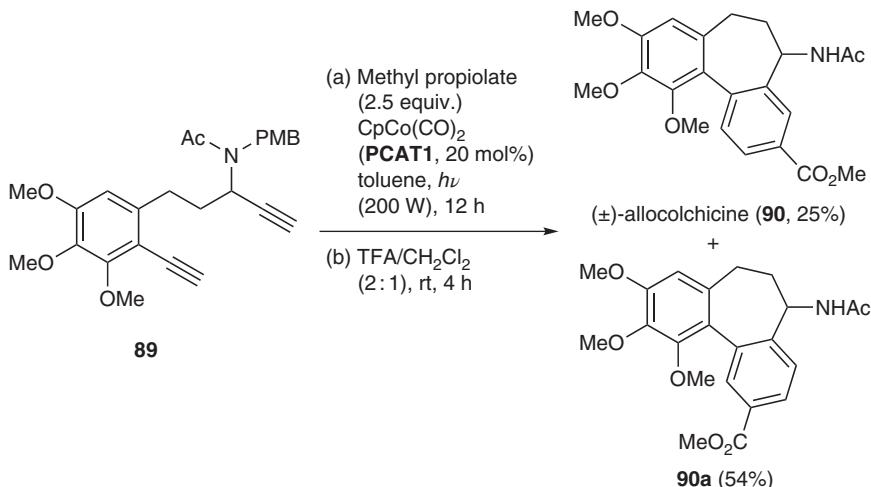
An interesting approach to assemble the aromatic core of xylarinol B (**88**) by incorporating acetylene as reaction partner was investigated by *Ramana* [95]. A common unusual feature to the synthesis of xylarinol B is the construction of an arene core **87** with annellated oxacycloheptane ring incorporating three stereocentres (Scheme 9.36). The required chiral diyne precursor **86** was synthesised starting from D-glucose as cheap chiral pool building block and was used for the studies of cyclisation conditions without protection of the OH groups. All studies using *Wilkinson* catalyst or  $\text{Cp}^*\text{RuCl}(\text{COD})$  as catalyst did not give any useful result. Switching to **PCAT1** the best conditions were found using irradiation at  $115^\circ\text{C}$  in a pressure tube under acetylene atmosphere with stoichiometric amounts of catalyst, affording impressive 74% yield; lowering the catalyst loading to 0.5 equiv.  $\text{CpCo}(\text{COD})$  (**PCAT3**) gave less than half of the amount of product (32%).

The synthesis of **(±)-allocolchicine 90** and certain derivatives has been devoted to a structural target, which has attracted several approaches using transition



**Scheme 9.36**  $\text{CpCo}$ -mediated cycloaddition of a chiral diyne and acetylene gas in the preparation of xylarinol B (**88**).

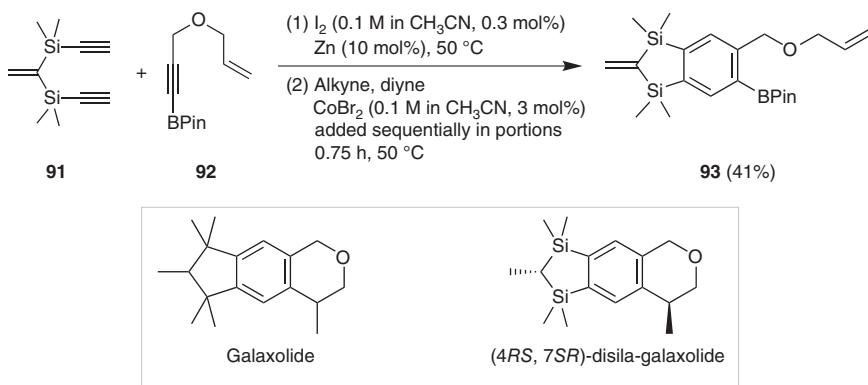
metal catalysis and also including cyclotrimerisation key step strategies. *Schmalz* synthesised derivatives of allocolchicine by application of cobalt-catalysed cyclotrimerisation, in a particular case also constructing a pyridine derivative by cyclisation of a cyanodiye [89e, 96]. The application of the cobalt-catalysed cyclisation in the total synthesis of  $(\pm)$ -allocolchicine and some respective analogues was very recently demonstrated by *Ramana* (Scheme 9.37) [97].



**Scheme 9.37** Synthesis of  $(\pm)$ -allocolchicine (**90**) from diyne **89** and methyl propiolate under photo-assisted cobalt catalysis and formation of the regioisomer **90a**.

The synthesis of diyne **89** was following standard routes of alkyne chemistry including *Sonogashira* coupling and *Ohira–Bestmann* alkynylation and the reaction with **PCAT1** was performed under photochemical conditions and at high temperatures with only 2.5 equiv. of methyl propiolate as electron-deficient alkyne component. The total yield was very good (79%), while unfortunately the undesired regioisomer **90a** was formed with roughly 2 : 1 excess. The cyclopropyl-derived diyne was cyclised with identical yield, but exclusively furnishing the corresponding derivative of **90a**, while the reaction was performed under heating to 150 °C in dioxane [97a].

Also structurally unusual cyclisation products of natural compounds analogues can be made by application of the cobalt-mediated [2+2+2] cycloaddition, as it is illustrated by the key step in the synthesis of galaxolide derivatives **93**, for possible use as odorants (Scheme 9.38) [98]. The multisubstituted benzene core is formed by reacting terminal diynes like **91** with an internal alkyne **92** by deploying solely  $\text{CoBr}_2$  as catalyst, achieving the desired product with a yield of 41%. Remarkable is the omission of any ligand in the catalytic step.



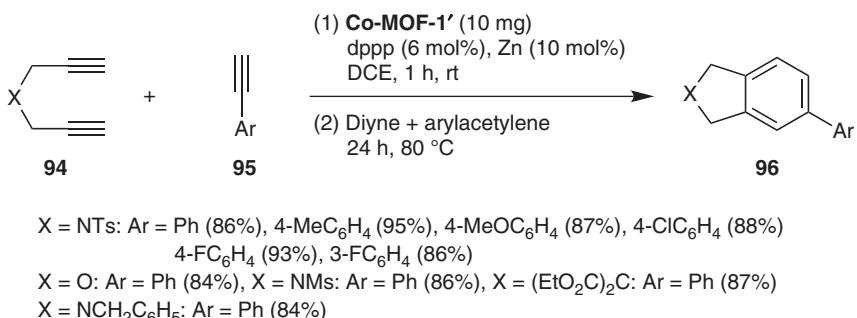
**Scheme 9.38** Co(I)-mediated [2+2+2] cycloaddition in the synthesis of disilagalaxolide derivatives **93**.

## 9.8 Novel Developments of Cobalt-Mediated Cycloaddition Catalysis

Several novel approaches for applying cobalt compounds in cyclisation reactions have been reported in recent years and will be shortly described in this subsection. The approaches comprise, e.g. the introduction of the cobalt catalyst centre within a defined environment into the reaction solution and the application of photosensitizers for the activation of cobalt catalysts in the cyclisation process.

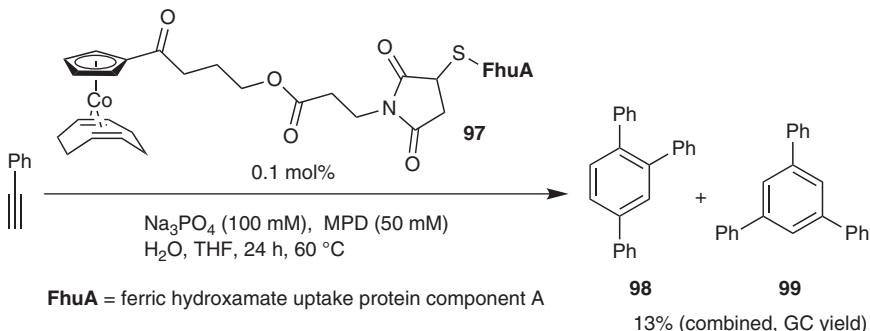
Heterogenisation of catalysts by tethering them to metal–organic frameworks (MOFs) is a more recent approach for combining homogeneous and heterogeneous catalysis, intending to add recyclability to the catalytic system as well as sustainability. Work on this approach for cobalt catalysts was conducted by *Du*, assembling different cobalt-based MOFs and

deploying them in [2+2+2] cycloadditions (Scheme 9.39) [99]. The synthesised  $[\text{Co}_2(\text{HCOO})_2(\text{CPT})_2](\text{NMF})_5(\text{H}_2\text{O})_2$  (**Co-MOF-1'**) was activated by a repeated solvent exchange with  $\text{CH}_2\text{Cl}_2$  and heating to 70 °C, when the activated, dissolved form of **Co-MOF1** was obtained. The material was applied in combination with dppp as ligand and zinc powder as reductant to convert different bridged diynes (**94**) and various substituted arylacetylenes (**95**) into the respective products (**96**). The formed carbocycles were obtained in excellent yields and the subsequent recovery experiments resulted in at least five more successful cyclisation experiments cycles without any recognisable loss of activity.



**Scheme 9.39** Application of cobalt-based MOF catalyst for [2+2+2] cycloaddition of diynes (**94**) and arylacetylenes (**95**).

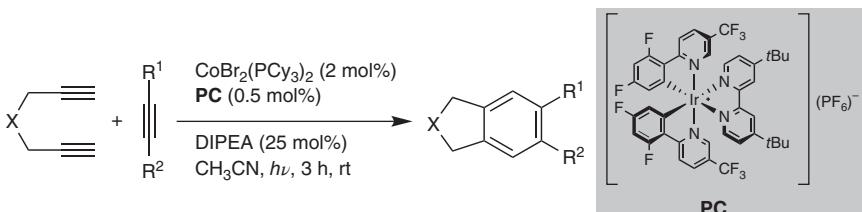
The attachment of Co(I)-based catalysts was extended to protein scaffolds by *Okuda* through anchoring a **PCAT3** analogous catalyst tethered at the Cp-ring to an engineered transmembrane protein [100]. The anchor consists of an ester and maleimide function whereby the latter one acts as cross-linking entity to the free thiol function of a cysteine unit. The natural aqueous environment of proteins is not suitable for the solvation of nonpolar organic substrates like phenylacetylene and leads to unsatisfactory conversion rates in the cyclotrimerisation (Scheme 9.40). This issue was overcome by the use of aqueous THF mixtures facilitating a conversion of up to 13% (gas chromatography, GC) when



**Scheme 9.40** Application of protein-attached CpCo-catalyst **97** for [2+2+2] cycloaddition of phenylacetylene.

deploying 0.1 mol% of catalyst **97**. The deployment of 5 mol% of the tethered catalyst without the attached protein leads to nearly full conversion after 21 days at 60 °C. Shortening the reaction duration to three or seven days results in a half, respectively, 82% conversion (GC). The attached protein shows no significant influence to the regioselectivity resulting in an approximately 7 : 1 ratio of the unsymmetrical (**98**) and symmetrical benzene (**99**), independent from the actually applied catalyst.

The possibilities of activating and controlling catalytic processes by visible light through introduction of a photocatalyst have become a significant topic only recently. *Rovis* introduced the well-established  $[\text{Ir}\{\text{dF}-(\text{CF}_3)\text{ppy}\}_2(\text{dtbbpy})]\text{PF}_6$  (**PC**) as photocatalyst for cobalt-catalysed cyclootrimerisation processes [101]. The invented system comprises the iridium-based photocatalyst (**PC**) and the precatalyst  $\text{CoBr}_2(\text{PCy}_3)_2$ , enabling temporal control of the cycloaddition reaction by switching of the light source, thus turning the reaction on or off (Scheme 9.41). The photocatalyst **PC** operates as reductant and provides access to all oxidation states of cobalt between 0 and +3 and is regenerated by *N,N*-diisopropylethylamine (DIPEA) as sacrificial reagent. The opportunities of this unique catalytic system enabled the use in material design, demonstrated exemplarily by the utilisation of this catalytic system for photolithographic patterning of diyne bearing polydimethylsiloxane.

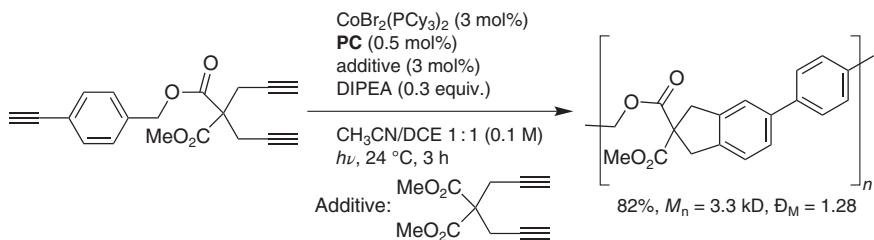


$X = (\text{MeO}_2\text{C})_2\text{C}$ ,  $R^1 = \text{H}$ ;  $R^2 = \text{Ph}$  (92%);  $X = \text{TsN}$ ,  $R^1 = \text{H}$ ,  $R^2 = \text{C}_6\text{H}_{13}$  (68%);  
 $X = \text{CH}_2$ ,  $R^1 = \text{H}$ ,  $R^2 = \text{C}_6\text{H}_{13}$  (60%, DCE was used as solvent)

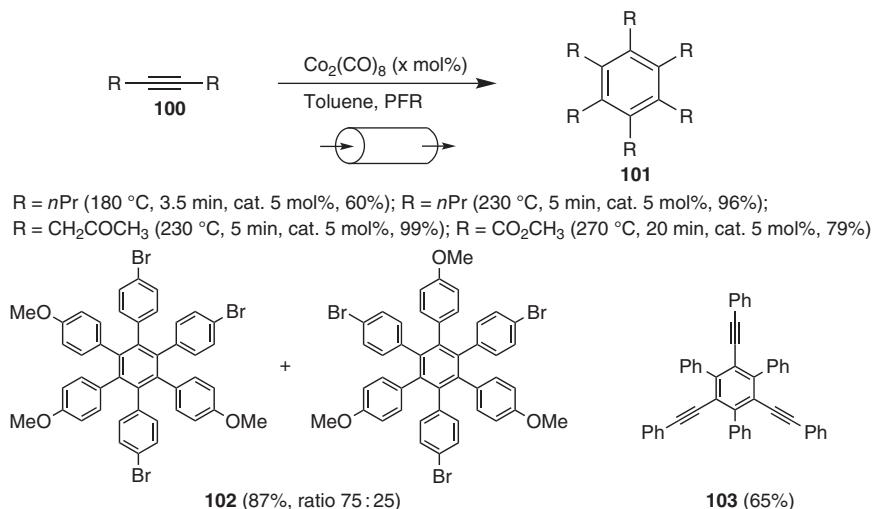
**Scheme 9.41** Visible light-controlled temporary resolved [2+2+2] cycloaddition.

Application of this novel catalytic system could be enlarged to an external regulated cobalt-catalysed cyclisation polymerisation [102]. *Rovis* adapted the catalytic system, which was first described by *Konno*, and curiously achieved a radical decrease of dispersity by addition of 3% of dipropargylmalonate (Scheme 9.42). Due to the presence of the photoredox catalyst, the stepwise growth of the polymer was directly controlled by the presence of light.

Another profound investigation for the utilisation of a plug flow reactor for alkyne cyclootrimerisation was undertaken by *Pérez-Castells*, including the deployment of  $\text{Co}_2(\text{CO})_8$  as still rather rarely applied catalyst to build up various benzenes (**101**) [103]. Notable results were achieved by using temperatures up to 230 °C to keep up with short reactor residence times of only a few minutes, resulting in nearly full conversion and good to excellent isolated yields, even when using internal alkynes (**100**) with big substituents as substrates (Scheme 9.43). Comparison experiments with batch reactions in refluxing



Scheme 9.42 Visible light-controlled cyclisation polymerisation.

Scheme 9.43 Cyclotrimerisation of internal alkynes using a plug flow reactor with  $\text{Co}_2(\text{CO})_8$  (CAT10) as catalyst.

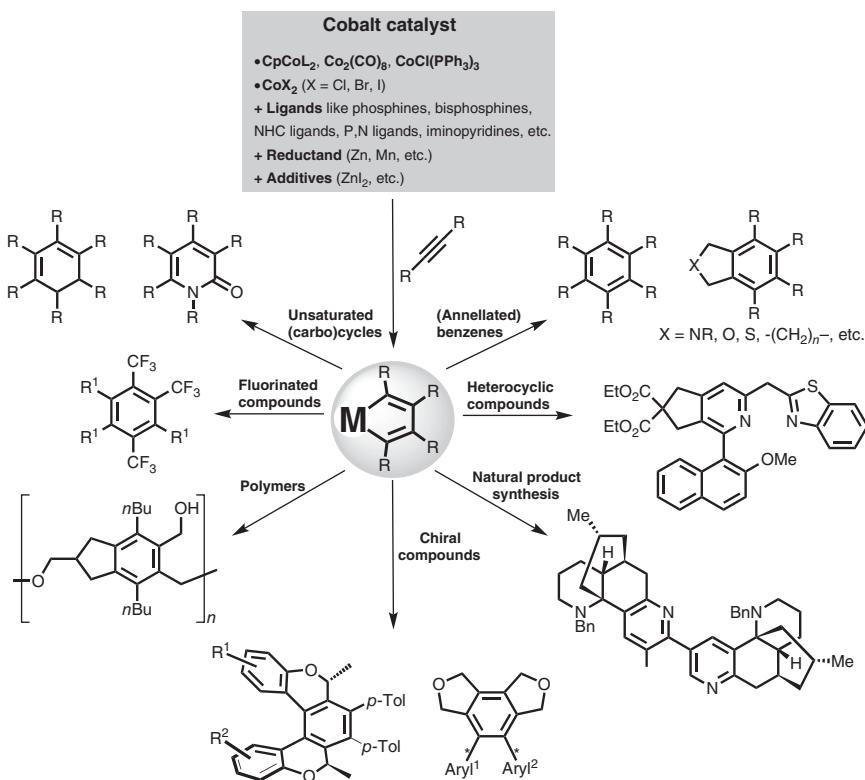
toluene showed either no or when using microwave heating of sealed samples only much less product formation. The variability of the presented method was furthermore demonstrated by broadening the substrate scope to differently substituted alkynes including the fully intermolecular cyclotrimerisation of three alkynes with acceptable high regioselectivity (**102**, ratio 75 : 25). The classical method to synthesise **102** utilises the same catalyst but required two weeks of heating in dioxane to  $110^\circ\text{C}$  to indicate noticeable progress of assembling **102**, however, with only 28% yield [104]. Additionally, product **103** could be assembled by the utilisation of three symmetrical phenyl substituted diynes with good yield [102].

Related to the aforementioned method is the transformation of 1,4-bis(phenylethyynyl)benzene, 4,4'-bis(phenylethyynyl)biphenyl, and 4-(phenylethyynyl)phenyl-acetylene in different combinations via  $\text{Co}_2(\text{CO})_8$  (PCAT10)-catalysed poly-cyclotrimerisations to partly cross-linked or hyperbranched polyphenylenes, exhibiting photoluminescence properties [105]. This approach used the classical thermal way of energy supply and required a reaction time of up to two weeks for the sufficient conversion into larger polymers.

## 9.9 Summary and Outlook

The application of cobalt catalysts in [2+2+2] cycloaddition reactions of alkynes, oligoynes, alkenes, and nitriles to afford substituted benzenes, heterocycles, cyclohexadienes, and a large array of derived derivatives has been an active field of research over the last centuries. During the last decade also the heavier group congeners had significant impact in this field of research, especially rhodium catalysts extended the field of application of cyclotrimerisations into asymmetric catalysis. However, cobalt catalysis is still often the first choice, when planning to include a cyclotrimerisation reaction in a synthetic sequence. Just again over the last decade, new catalysts and *in situ*-generated catalytic systems were developed, which allow application of cobalt complexes under milder conditions as well as CpCo-based catalysts, which can be applied under thermal as well as photochemical conditions, which is unique for cobalt. The invention of suitable *in situ*-based catalyst generation allows the more rapid screening of catalytic systems, conditions, and ligands, exemplified by the first chiral catalyst for asymmetric triyne cyclisation and photoswitchable catalysts. In addition, expanding the substrate scope also allowed access to novel products, exemplified in the application for natural product synthesis or preparation of natural product building blocks. The mechanistic understanding for the [2+2+2] cycloaddition reactions has been deepened especially by theoretical investigations.

The potential reservoir for cobalt, counted to the so-called “base metals”, is much larger compared with the precious metals of its own and the neighbouring groups in the periodic table. However, not only this fact but also the different chemical properties especially compared with rhodium and iridium makes the far less expensive cobalt a highly interesting alternative catalyst metal. Although applied widely in cyclotrimerisation reactions already, there is much more to discover in the future. From the standpoint of sustainable chemistry, e.g. lower catalyst loadings (meaning more active catalysts) would be desirable as well as catalytic systems, which would enable the recycling of the catalyst for reuse or at least easier separation. Improving or enabling to switch selectivity in [2+2+2] cycloaddition reactions of unsymmetrically substituted alkynes towards the 1,2,4- or 1,3,5-isomer is a topic that is still not generally solved, much less for the highly ordered coupling of three different alkynes. Including substrates like phosphalkynes as cyclotrimerisation substrates would certainly find interest not only from chemists interested in phosphorus chemistry. Also, in the field of asymmetric (co-)cyclotrimerisations with cobalt complexes first delectable results were observed, but that just opened the door for more general applications. The triggering of such cobalt-mediated cycloaddition reactions either by irradiation or heating or even both should quicken the appetite to investigate such rare opportunities in more detail. Even cobalts’ name heritage derives from the German word for “goblin”, in general understanding a scallywag, in the case on hand this one is rather a positive jack of all trades.



## 9.10 Selected Experimental Procedures

### 9.10.1 Synthesis of $[\text{CpCo}(\text{CO})(\text{trans}-\text{MeO}_2\text{CCH}=\text{CHCO}_2\text{Me})]$ (PCAT5)

A toluene solution (30 mL) of dmfu (216 mg, 1.5 mmol) and  $\text{CpCo}(\text{CO})_2$  (210  $\mu\text{L}$ , 1.5 mmol) was refluxed for three hours under visible light irradiation. The mixture was concentrated under reduced pressure and purified over silica gel using PE/EtOAc (7 : 3 v/v) as eluent, yielding 439 mg (quant.) of **PCAT5** as a red solid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta = 3.28$  (d,  $J = 10.3$  Hz, 1H), 3.61 (s, 3H), 3.71 (s, 3H), 3.86 (d,  $J = 10.3$  Hz, 1H), and 4.99 (s, 5H, Cp) ppm.  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta = 37.1$  (CH), 38.2 (CH), 51.4 (CH<sub>3</sub>), 51.5 (CH<sub>3</sub>), 87.2 (5 CH, Cp), 175.6 (C, C=O), 176.2 (C, C=O), and 199.2 (C, CO) ppm. IR (neat):  $\nu_{\text{max}} = 824, 1022, 1156, 1308, 1435, 1693$ , and  $2012\text{ cm}^{-1}$  [35].

### 9.10.2 Synthesis of $[\text{CpCo}(\text{CO})\{\text{P}(\text{OEt})_3\}]$ and $[\text{CpCo}(\text{trans}-\text{MeO}_2\text{CCH}=\text{CHCO}_2\text{Me})\{\text{P}(\text{OEt})_3\}]$ (PCAT8)

$[\text{CpCo}(\text{CO})\{\text{P}(\text{OEt})_3\}]$ : Commercially available  $[\text{CpCo}(\text{CO})_2]$  (**PCAT1**) (0.35 mL, 2.5 mmol) and triethylphosphite (0.42 mL, 2.5 mmol) are stirred at room

temperature for 24 hours, before heated to 60 °C for three hours. The solution is filtered over a small amount of neutral Al<sub>2</sub>O<sub>3</sub> (Brockman Type I), which is washed with THF (20 mL). After removal of the solvent, the deep red liquid is dried under vacuum (yield: 796 mg, quantitative). <sup>1</sup>H NMR (C<sub>6</sub>D<sub>6</sub>): δ = 1.08 (t, *J* = 7.1 Hz, CH<sub>3</sub>, 9H), 3.93 (quin, *J* = 7.4 Hz, CH<sub>2</sub>, 6H), and 4.78 (s, Cp, 5H) ppm. <sup>31</sup>P NMR (C<sub>6</sub>D<sub>6</sub>): δ = 173.7 (bs) ppm. <sup>13</sup>C NMR (C<sub>6</sub>D<sub>6</sub>): δ = 16.4 (d, *J* = 7.1 Hz, CH<sub>3</sub>), 60.6 (s, CH<sub>2</sub>), and 82.4 (d, *J* = 1.3 Hz, Cp) ppm. IR (neat): ν<sub>max</sub> = 936, 1028, 1388, 1934, 2023, 2899, 2931, and 2979 cm<sup>-1</sup> [38].

[CpCo(*trans*-MeO<sub>2</sub>CCH=CHCO<sub>2</sub>Me){P(OEt)<sub>3</sub>}] (**PCAT8**): dmfu (1.30 g, 9.0 mmol) is secured in a double-walled glass reactor and dissolved in anhydrous toluene (40 mL) under argon. Subsequently the previously prepared [CpCo(CO){P(OEt)<sub>3</sub>}] (3.0 g, 9.0 mmol) was weighted and added via syringe. A slight vacuum was put on the reactor and the vessel closed, and the red solution irradiated for 16 hours with a medium-pressure mercury vapour lamp<sup>1</sup>. The irradiation was shortly stopped and again a slight vacuum was applied to the reactor, sealed again, and the irradiation continued. This was repeated three more times every 8–11 hours. The red solution is irradiated with light under this reduced pressure for a total of 50 hours (smaller amounts of reactand requires less intermediate evacuation events). After the irradiation is finished, the solvent is removed in high vacuum via a cool trap. The residue is dissolved in THF and filtration is done over a column (15 cm length, 2.5 cm diameter) filled with neutral Al<sub>2</sub>O<sub>3</sub> (Brockman Type I). The product is eluted through the column with THF and the solvent removed under reduced pressure to complete dryness. The residue is then dissolved in *n*-pentane (c. 40 mL) and allowed to crystallise at –40 °C. Collection of the crystals by filtration and drying in high vacuum gave the product (1. Fraction 2.7 g, 69% yield). <sup>1</sup>H NMR (C<sub>6</sub>D<sub>6</sub>): δ = 1.04 (t, *J* = 7.1 Hz, CH<sub>3</sub>, 9H), 3.19 (t, *J* = 10.8 Hz, CH, 1H), 3.43 (s, CH<sub>3</sub>, 3H), 3.51 (s, CH<sub>3</sub>, 3H), 3.81 (m, CH<sub>2</sub>, 6H), 4.10 (dd, *J* = 3.7, 10.7 Hz, CH, 1H), and 4.67 (s, Cp, 5H) ppm. <sup>31</sup>P NMR (C<sub>6</sub>D<sub>6</sub>): δ = 160.8 (bs) ppm. <sup>13</sup>C NMR (C<sub>6</sub>D<sub>6</sub>): δ = 16.1 (s), 16.2 (s), 31.2 (d, *J* = 5.2 Hz), 35.4 (d, *J* = 7.8 Hz), 50.5 (s), 50.7 (s), 60.6 (d, *J* = 2.9 Hz), 85.2 (d, *J* = 2.9 Hz, Cp), 177.1 (s), and 178.4 (s) ppm. IR (neat): ν<sub>max</sub> = 924, 1016, 1156, 1435, 1689, 2011, and 2950 cm<sup>-1</sup> [38].

## Abbreviations

Ac	acetyl
Ar	aryl
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BPin	pinacolyl boryl
Bu	butyl
<i>t</i> Bu	<i>tert</i> -butyl
BTMSA	bis(trimethylsilyl)acetylene
COD	1,5-cyclooctadiene
Cp	cyclopentadienyl

<sup>1</sup> See supporting information of reference [84] for apparatus details of the photoreactor

Cp*	pentamethylcyclopentadienyl
Cy	cyclohexyl
dba	dibenzylideneacetone
DCE	1,2-dichloroethane
Dec	decyl
dcpe	1,3-bis(dicyclohexylphosphino)ethane
dF-(CF <sub>3</sub> )ppy	2-(2,4-difluorophenyl)-5-trifluoromethyl-pyridyl
DIPEA	N,N-diisopropylethylamine
dipimp	(E)-N-(2,6-diisopropylphenyl)-1-(pyridin-2-yl)methanimine
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
dmfu	dimethylfumarate
DMSO	dimethylsulfoxide
dppb	1,4-bis(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1'-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane
dtbbpy	4,4'-di- <i>tert</i> -butyl-2,2'-bipyridine
ee	enantiomeric excess
equiv.	equivalent
Et	ethyl
nHex	<i>n</i> -hexyl
GC	gas chromatography
HPLC	high-performance liquid chromatography
Me	methyl
MECP	Minimum Energy Crossing Point
mM	milli molar
MOF	metal–organic framework
MOM	methoxymethyl acetal
MPD	2-methyl-2,4-pentanediol
MW	microwave
NHC	<i>N</i> -heterocyclic carbene
NMP	<i>N</i> -methylpyrrolidone
PC	photo catalyst
PDI	polydispersity index
PFR	plug flow reactor
Ph	phenyl
iPr	isopropyl
nPr	<i>n</i> -propyl
quant.	quantitative
QUINAP	1-(2-diphenylphosphino-1-naphthyl)isoquinoline
rt	room temperature
TBDPS	<i>tert</i> -butyldiphenylsilyl
TBS	<i>tert</i> -butyldimethylsilyl
Tf	triflate
TFA	trifluoroacetic acid
THF	tetrahydrofuran

TMS	trimethylsilyl
p-Tol	para-tolyl
Tr	triphenylmethyl
Ts	tosyl

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## 10

### Enantioselective Cobalt-Catalysed Transformations

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#### 10.1 Introduction

The broad utility of synthetic chiral molecules has made asymmetric catalysis a prominent area of investigation [1]. Especially, the use of transition metals has become a powerful tool to perform reactions in a highly enantioselective fashion in the last few decades [2]. For a long time, efforts in this field have focused on the use of palladium, rhodium, copper, iridium, or ruthenium. However, by the very fact of the lower costs and toxicity of cobalt catalysts in comparison with other transition metals, ecological cobalt-mediated transformations have received a continuous ever-growing attention during the last three decades. Moreover, cobalt catalysts are known to exhibit an excellent tolerance to various functional groups, rendering the reaction scopes particularly wide, and cobalt presents a high affinity to carbon–carbon  $\pi$ -bonds, carbon–nitrogen  $\pi$ -bonds, and carbonyl groups. Related to their extraordinary ability to adopt unexpected reaction pathways, chiral cobalt catalysts have allowed an impressive variety of various asymmetric transformations to be achieved in high enantioselectivities. The goal of this book chapter is to highlight major developments in enantioselective cobalt-catalysed transformations, allowing the synthesis of many types of either acyclic or cyclic chiral compounds under relatively mild conditions. The field of (asymmetric) cobalt catalysis was previously reviewed by several authors [2j, 3–6]. Moreover, it must be noted that a *Synthesis* special topic dedicated to cobalt in organic synthesis was recently published including only one example of enantioselective transformations [7]. Moreover, Gladysz recently reported a specific review on hydrogen bonding motifs in structurally characterised salts of the tris(ethylenediamine) cobalt trication, but it included only structural information and no catalytic applications [8]. The book chapter is divided into two principal sections dealing successively with the synthesis of chiral acyclic compounds through enantioselective cobalt-catalysed transformations and enantioselective cobalt-catalysed cyclisation reactions. The first section deals with *Michael* and (nitro)-Aldol reactions, reduction reactions, ring-opening reactions, hydrovinylation and hydroboration reactions, cross-coupling reactions, and miscellaneous reactions, affording acyclic products, while the second

one includes [2+1] cycloadditions, different cycloadditions, cyclisations through domino reactions, and further other cyclisations, leading to cyclic chiral products.

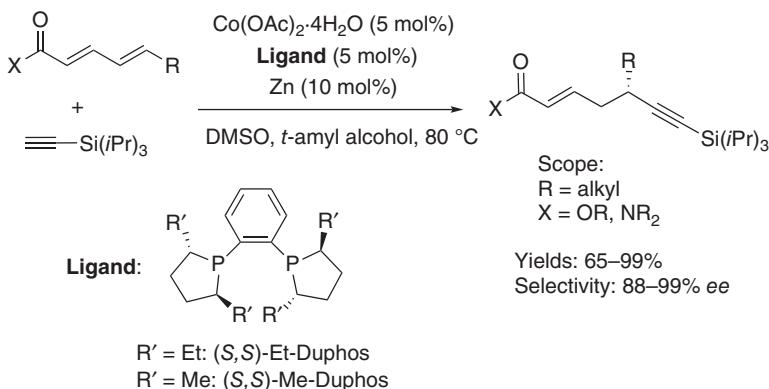
## 10.2 Synthesis of Chiral Acyclic Compounds Through Enantioselective Cobalt-Catalysed Reactions

### 10.2.1 Michael and (Nitro)-Aldol Reactions

#### 10.2.1.1 Michael Reactions

The *Michael* addition of nucleophiles to electron-poor alkenes, such as  $\alpha,\beta$ -unsaturated carbonyl compounds, constitutes a powerful tool in organic synthesis, since it allows carbon–carbon and carbon–heteroatom bond-forming reactions to be easily achieved [9]. Many asymmetric versions of these reactions have been developed, using a wide variety of conjugate acceptors, nucleophiles, and catalysts [10]. In the area of cobalt catalysis, the pioneering works were reported by *Brunner* in 1984, demonstrating that a catalytic system *in situ* generated from  $\text{Co}(\text{acac})_2$  and (+)-1,2-diphenylethylenediamine as chiral ligand was capable to promote the addition of methyl 1-oxo-2-indanecarboxylate to methyl vinyl ketone with a moderate enantioselectivity of 66% *ee* [11]. However, attempts to improve the enantioselectivity of the *Michael* addition of 1,3-dicarbonyl compounds by involving other chiral ligands, such as alkaloid or salicylaldimine derivatives [11b,c], proline-based ligands [12], or spirobiindane-containing ligands [13] remained unsuccessful for a long time. Indeed, it was only in 1998 that *Pfaltz* described enantioselectivities of up to 89% *ee* albeit combined with low yields (12–17%), using *tert*-butyl-substituted chiral bisoxazoline oxalamide ligands in the *Michael* addition of malonates to chalcone [14]. Later in 2006, *Zhou* designed two novel chiral  $C_2$ -symmetric spiro nitrogen-containing ligands including pyridine or quinolone units, such as 7,7'-bis(2-pyridinecarboxamido)-1,1'-spirobiindane and 7,7'-bis(2-quinolinecarboxamido)-1,1'-spirobiindane [13]. When combined with  $\text{Co}(\text{OAc})_2$  and applied to the enantioselective *Michael* addition of malonates to chalcones, the corresponding *Michael* products were obtained in good yields (70–78%) albeit with moderate enantioselectivities of 47–57% *ee*. In 2015, *Yamada* and *Tsubo* reported the enantioselective *Michael* addition of various dialkyl malonates to cyclic  $\alpha,\beta$ -unsaturated ketones promoted by a chiral cobalt(III) salen catalyst bearing a 1-chlorovinyl axial ligand [15], which afforded the corresponding *Michael* products in low to quantitative yields (21–98%) and moderate to good enantioselectivities (52–88% *ee*). The catalytic system tolerated five-membered, six-membered, and seven-membered  $\alpha,\beta$ -unsaturated ketones. Earlier in 2008, *Ganzmann* and *Gladysz* reported a low enantioselectivity of 33% *ee* combined with a yield of 78% in related *Michael* addition of dimethyl malonate to 2-cyclopenten-1-one promoted by a chiral octahedral tris(ethylenediamine) cobalt complex [16]. In 2014, another type of chiral cobalt catalysts, *in situ* generated from  $\text{Co}(\text{BF}_4)_2 \cdot 6\text{H}_2\text{O}$  and chiral  $N,N'$ -dioxide ligands, was applied by *Feng* to promote the enantioselective addition of cyclic  $\beta$ -ketoamides to

alkynes [17]. The corresponding chiral *Michael* products were obtained as mixtures of *Z*- and *E*-diastereomers (*Z/E* = 52 : 48 to 78 : 22) in high yields (80–99%) and moderate to excellent enantioselectivities (69–97% *ee*). Other types of nucleophiles have also been involved in enantioselective cobalt-catalysed *Michael* additions to  $\alpha,\beta$ -unsaturated carbonyl compounds. For example in 1997, *Feringa* and *de Vries* reported the conjugate addition of diethylzinc to chalcone promoted by a chiral cobalt complex generated from  $\text{Co}(\text{acac})_2$  and chiral amino alcohols [18]. The best enantioselectivity of 83% *ee* was achieved by using a ligand derived from (+)-camphor. In 2008, *Itoh* reported high enantioselectivities of up to 95% *ee* along with moderate to high yields (85–90%) for the asymmetric *Michael* addition of thiols to (*E*)-3-crotonoyloxazolidin-2-one by using a catalytic system based on the combination of  $\text{Co}(\text{ClO}_4)_2 \cdot 6(\text{H}_2\text{O})$  with (*S,S*)-*iPr*-Pybox [19]. More recently, *Nishimura* and *Hayashi* investigated the cobalt-catalysed asymmetric conjugate addition of (triisopropylsilyl)acetylene to  $\alpha,\beta$ -unsaturated ketones [20]. Using a bidentate diphenylphosphino(ethane) ligand, a range of chiral  $\beta$ -alkynylketones were obtained in moderate to high yields (53–93%) and good to high enantioselectivities (79–91% *ee*). The same authors also investigated the enantioselective addition of (triisopropylsilyl)acetylene to extended conjugate systems, such as  $\alpha,\beta,\gamma,\delta$ -unsaturated carbonyl compounds, in the presence of another biphosphine ligand such as (*S,S*)-Et-Duphos [20b]. As shown in Scheme 10.1, the addition of this terminal alkyne to aliphatic dienoates and dienamides occurred exclusively in the  $\delta$ -position, affording the corresponding 1,6-conjugate products in good to quantitative yields (65–99%) and high enantioselectivities of 88–99% *ee*.

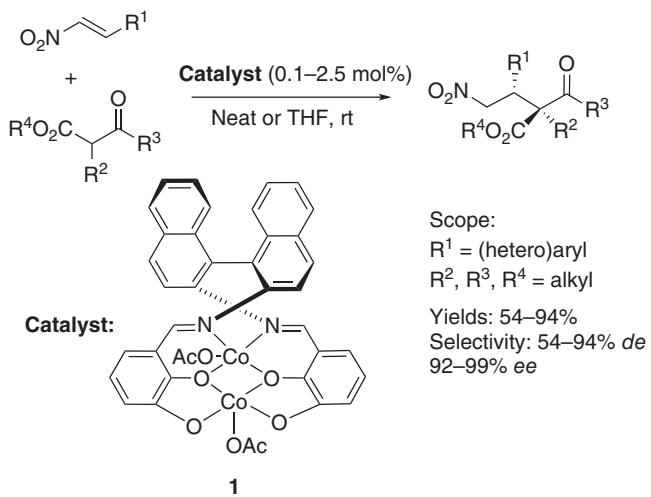


**Scheme 10.1** *Michael* addition of (triisopropylsilyl)acetylene to aliphatic dienoates and dienamides.

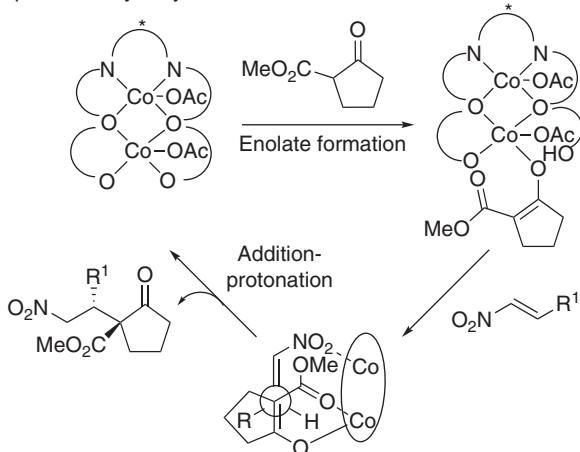
In 2014, *Belokon* reported enantioselectivities of 60–96% *ee* combined to good to quantitative yields (70–97%) and low to complete diastereoselectivities (34–99% *de*) in enantioselective *Michael* additions of a glycine *Schiff* base to activated olefins, such as  $\alpha,\beta$ -unsaturated esters,  $\alpha,\beta$ -unsaturated nitriles, and  $\alpha,\beta$ -unsaturated ketones, promoted by cationic chiral cobalt(III) complexes prepared from *Schiff* bases derived from chiral diamines and

salicylaldehydes [21]. In 2015, a novel cobalt complex derived from a chiral diamidine ligand was introduced by *Kitamura* to catalyse at 25 °C and at only 1 mol% of catalyst loading the asymmetric NaBH<sub>4</sub> conjugate reduction of C3-disubstituted 2-propenoates to give the corresponding chiral esters with both high to excellent yields (72–98%) and enantioselectivities (84–98% ee) [22].

Along with  $\alpha,\beta$ -unsaturated carbonyl compounds, nitroolefins have also been used as *Michael* acceptors in various enantioselective cobalt-catalysed conjugate additions. For example, in 2010, *Matsunaga* and *Shibasaki* reported the use of a chiral bis-Co(III) complex **1** (Scheme 10.2) to efficiently promote the addition of a range of cyclic as well as acyclic  $\beta$ -ketoesters to nitroalkenes, providing the corresponding nitro-*Michael* adducts in high to excellent yields (73–99%) with both



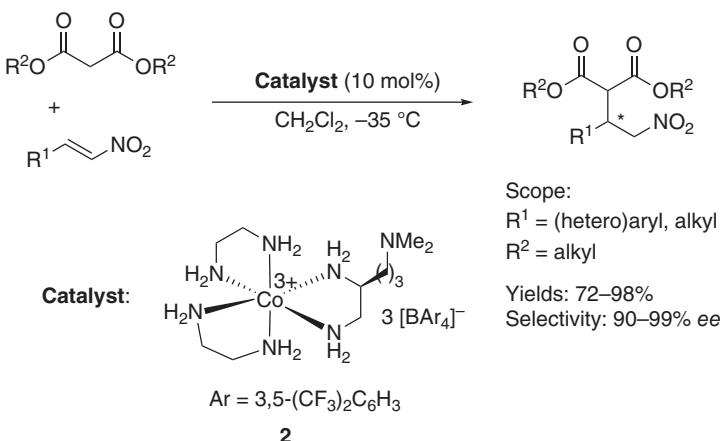
Proposed catalytic cycle:



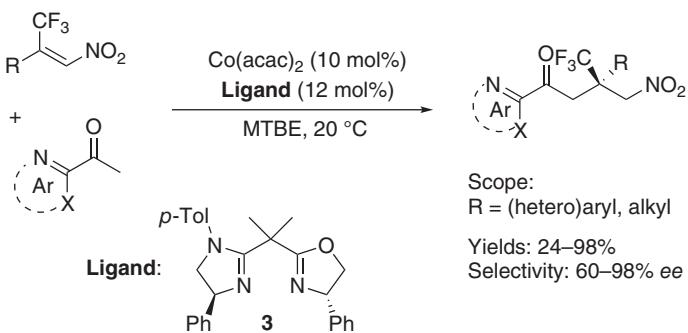
Scheme 10.2 *Michael* addition of  $\beta$ -ketoesters to nitroalkenes.

good to excellent diastereo- and enantioselectivities of up to 94% *de* and 99% *ee*, respectively [23]. An interesting feature of this catalytic system was that it was compatible with the absence of solvent and operated well with a catalyst loading as low as 0.1 mol%. Moreover, mechanistic studies and control experiments were carried out in order to confirm the intramolecular cooperative effect of the two cobalt centres. The postulated catalytic cycle of the reaction is depicted in Scheme 10.2. The authors assumed that the  $\beta$ -keto ester coordinated to the sterically less hindered outer Co-metal centre of the catalyst. One of Co-aryloxide (or Co-acetate) deprotonated the  $\alpha$ -proton of  $\beta$ -keto ester to generate a Co-enolate. The inner Co-metal centre acted as a *Lewis* acid to activate the nitroalkene in a similar manner as observed in the monomeric Co-salen system. 1,4-Addition via bimetallic transition state followed by protonation afforded the final products and regenerated the catalyst. In addition, these reaction conditions were also successfully applied to the enantioselective *Michael* addition of cyclic as well as acyclic  $\beta$ -ketoesters to alkynes, providing the corresponding chiral enones in remarkable results since a general diastereoselectivity of 94% *de* was obtained in all cases of substrates studied in combination with high yields of 83–96% and excellent enantioselectivities of 91–99% *ee* [24].

Later in 2014, *Feng* developed the enantioselective conjugate addition of cyclic  $\beta$ -ketoamides to nitroolefins promoted by cobalt catalysts *in situ* generated from  $\text{Co}(\text{BF}_4)_2 \cdot 6\text{H}_2\text{O}$  and chiral  $N,N'$ -dioxide ligands [17]. The reaction afforded the corresponding densely functionalised chiral *Michael* products bearing a quaternary carbon centre as mixtures of two diastereomers in moderate to quantitative yields (51–98%) combined with low to moderate diastereoselectivities (8–44% *de*). The major diastereomers were achieved in uniformly excellent enantioselectivities (93–97% *ee*), while the minor ones in lower enantioselectivities (55–90% *ee*). The same year, *Kezuka* reported that chiral cobalt(II) salen complexes were effective catalysts for the enantioselective *Michael* addition of *O*-alkylhydroxylamines to nitroolefins to afford the corresponding chiral *N*-alkylhydroxyl-1,2-nitroamines [25]. The corresponding chiral products were obtained in moderate to quantitative yields (58–99%) and moderate to high enantioselectivities (56–91% *ee*) starting from either alkyl- or (hetero)aryl-substituted nitroalkenes. Notably, this study represented the first example of a transition metal-catalysed asymmetric *Michael* addition of amines to nitroalkenes. In 2015, *Gladysz* investigated the use of another type of cobalt catalysts, such as *Werner* complexes based on the  $D_3$ -symmetric chiral trication  $[\text{Co}((S,S)\text{-dpn})_3]^{3+}$  ( $\text{dpn} = 1,2\text{-diphenylethylenediamine}$ ), in the enantioselective *Michael* addition of dimethyl malonate to nitroolefins [26]. The reaction led to the corresponding chiral nitroalkanes in uniformly excellent yields (93–98%) and high enantioselectivities (85–98% *ee*). This study illustrated the possibility associated with enantioselective second coordination sphere-promoted catalysis. As illustrated in Scheme 10.3, *Werner* cobalt complex **2**, incorporating a dimethylamino group, promoted the reaction of dialkyl malonates with aryl- as well as alkyl-substituted nitroalkenes to give the corresponding chiral nitroalkanes in moderate to quantitative yields (72–98%) and uniformly excellent enantioselectivities (90–99% *ee*), as shown in Scheme 10.3 [27].

Scheme 10.3 *Michael* addition of dialkyl malonates to nitroalkenes.

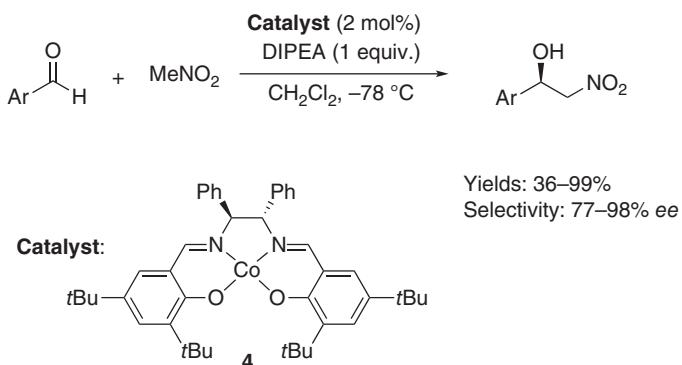
In 2017, *Song* and *Gong* reported the synthesis of novel imidazoline/oxazoline *N,N'*-didentate chiral ligands, such as **3**, derived from 2,2-dimethylmalonic acid that were further used to develop the first enantioselective cobalt-catalysed *Michael* addition of 2-acetyl azaarenes to  $\beta$ -CF<sub>3</sub>- $\beta$ -disubstituted nitroolefins (Scheme 10.4) [28]. The corresponding chiral products bearing a trifluoromethylated all-carbon quaternary centre were obtained in low to quantitative yields (24–98%) and moderate to excellent enantioselectivities (60–98% *ee*). As illustrated in Scheme 10.4, the reaction tolerated a wide variety of  $\beta$ -CF<sub>3</sub>- $\beta$ -(hetero) aryl-disubstituted nitroalkenes and a range of 2-acetyl azaarenes containing thiazole, *N*-methylimidazole (NMI), pyrazine, benzothiazole, quinoxaline, benzoxazole, pyrimidine, and quinolone groups.

Scheme 10.4 *Michael* addition of 2-acetyl azaarenes to  $\beta$ -CF<sub>3</sub>- $\beta$ -disubstituted nitroolefins.

### 10.2.1.2 (Nitro)-Aldol Reactions

Aldol reactions are among the most widely studied and applied transformations to simply achieve carbon–carbon bond formations. Among them, the *Henry* reaction or nitro-Aldol reaction is a convenient reaction not requiring any

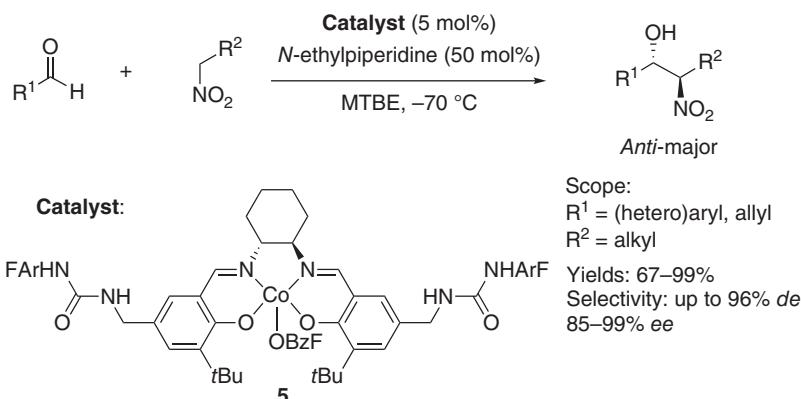
pretreatment to afford  $\beta$ -hydroxy-nitroalkanes from aldehydes and nitroalkanes. Since the first catalytic enantioselective version of this reaction reported in 1992 by *Shibasaki*, based on the use of heterobimetallic lanthanide 1,1'-bi-2-naphthol (BINOL) catalyst systems [29], various catalytic systems have been successfully developed. For example in 2004, *Yamada* found that chiral ketoiminato cobalt complexes efficiently catalysed the enantioselective *Henry* reaction of aldehydes in the presence of a tertiary amine such as diisopropylethylamine (DIPEA) [30]. The optimal catalyst provided low to quantitative yields (11–100%) and moderate to high enantioselectivities of 53–92% *ee*. The same authors obtained even better results for the reaction of aromatic aldehydes with nitromethane by using chiral cobalt salen complexes such as **4**. As shown in Scheme 10.5, a range of chiral  $\beta$ -nitroalcohols were obtained in moderate to quantitative yields and enantioselectivities of 77–98% *ee* [31].



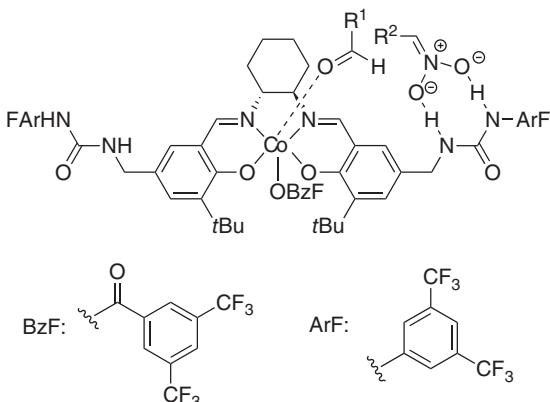
**Scheme 10.5** *Henry* reaction of aromatic aldehydes with nitromethane catalysed by cobalt(II) salen complexes.

In 2008, these reactions were also studied by *Hong* [32]. They employed a newly designed self-assembled chiral dinuclear cobalt(II) salen complex *in situ* generated from the reaction of the corresponding cobalt(II) salen complex with  $\text{Co}(\text{OAc})_2 \cdot 4(\text{H}_2\text{O})$  through hydrogen bonding. The reaction afforded the corresponding chiral alcohols in moderate to quantitative yields (65–99%) and good to high enantioselectivities of 81–96% *ee* in the presence of DIPEA. Later in 2012, the same authors developed a diastereo- and enantioselective nitro-Aldol reaction of aliphatic as well as aromatic aldehydes with various nitroalkanes to afford the corresponding *Henry* products bearing two stereocentres [33]. When the process was promoted by novel chiral (bisurea–salen) cobalt(III) catalyst **5**, it provided high *anti* selectivities of up to 96% *de* as well as excellent enantioselectivities of up to 99% *ee*, as shown in Scheme 10.6. The cooperative activation by H-bonds of urea and the *Lewis* acid cobalt centre is shown in Scheme 10.6.

In 2014, *Wang* reported the synthesis of novel  $C_2$ -symmetric salen ligands bearing morpholine functional group based on a BINOL framework to be investigated in enantioselective cobalt-catalysed *Henry* reaction of aldehydes



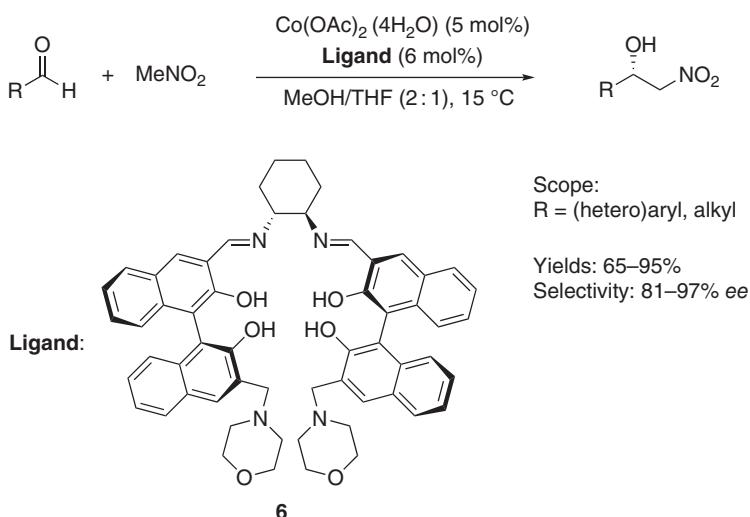
Cooperative activation by H-bonds of urea and cobalt center:



**Scheme 10.6** Henry reaction of aromatic and aliphatic aldehydes with nitroalkanes catalysed by a (bisurea–salen) cobalt(III) complex.

with nitromethane [34]. Among them, ligand **6** was selected as optimal one to promote the addition of nitromethane to a range of aromatic as well as aliphatic aldehydes, leading to the corresponding chiral *Henry* products in moderate to excellent yields (65–95%) and high enantioselectivities (81–97% *ee*), as shown in Scheme 10.7.

The *Henry* reaction of aromatic aldehydes with nitromethane was also investigated by *Xu* using related chiral cobalt salen catalysts in the presence of DIPEA as base, allowing a wide variety of chiral aromatic alcohols to be achieved in moderate to quantitative yields (48–99%) and moderate to excellent enantioselectivities (70–98% *ee*) [35]. In 2016, *Yashima* reported the synthesis of a novel double-helical bimetallic cobalt(II) salen complex stabilised by chiral amidinium–carboxylate salt bridges to catalyse the asymmetric *Henry* reaction of *o*-methoxybenzaldehyde with nitromethane [36]. In the presence of DIPEA as base, the corresponding *Henry* product was obtained in both high yield (91%) and enantioselectivity (89% *ee*).



**Scheme 10.7** Henry reaction of aldehydes with nitromethane catalysed by a BINOL-based cobalt salt.

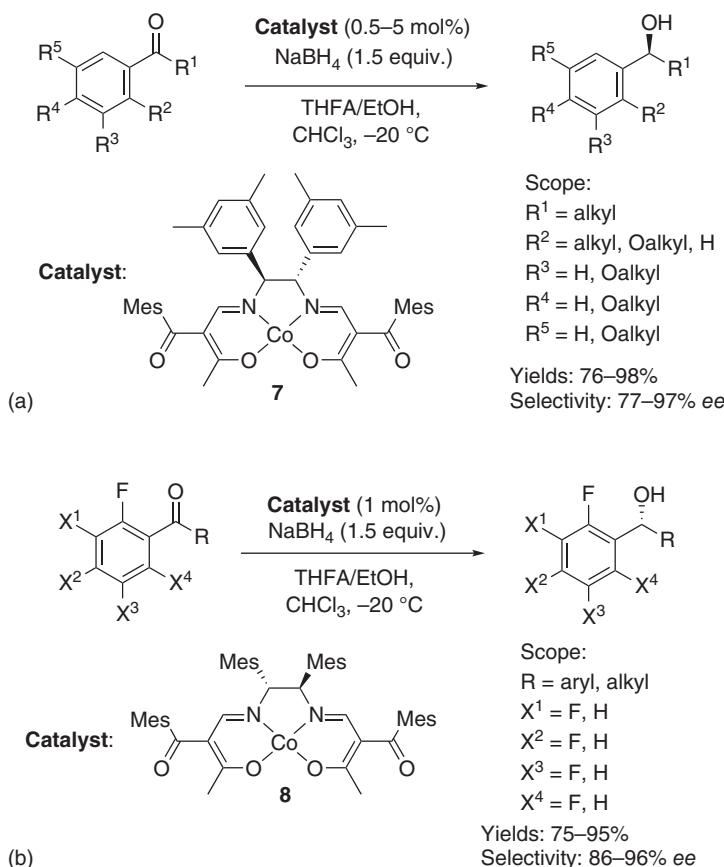
The direct catalytic asymmetric aldol reaction is a powerful and atom-economical method for synthesising chiral  $\beta$ -hydroxy carbonyl compounds. Many metals and also organocatalysts for reactions of aldehyde electrophiles have been developed in the past decade [37]. For example in 2011, *Reiser* reported the highly efficient use of simple L-proline as chiral ligand of cobalt to catalyse the enantioselective direct aldol reaction of a range of aromatic and aliphatic aldehydes with cyclic as well as acyclic ketones [38]. The authors found that the efficiency of these reactions was significantly higher compared with the analogous classical proline-catalysed processes as well as with other metal–proline complexes employed previously. This novel protocol presented the advantage of being very simple through mixing inexpensive  $\text{CoCl}_2$  and L-proline in methanol at room temperature. In general, the best results for the formation of a number of chiral alcohols were reached in the case of using cyclic ketones as the substrates with various aromatic and aliphatic aldehydes, providing moderate to high yields (50–93%), high diastereoselectivities of up to 96% *de*, and excellent enantioselectivities of up to 98% *ee*. The scope of the methodology was extended to acyclic unsymmetrical ketones that provided by reaction with aromatic aldehydes the corresponding chiral alcohols in moderate to high yields (64–92%), low to moderate diastereoselectivities (34–66% *de*) combined with moderate to high enantioselectivities of 50–91% *ee*. The same year, *Duan* reported the synthesis of a catalyst incorporating an L-proline moiety within a cobalto-helical triangle formed by assembling cobalt ions and two tridentate  $\text{N}_2\text{O}$  units containing amide groups within a central benzene ring at the *meta* sites [39]. Therefore, it included L-proline moieties as asymmetric catalytic sites and a helical-like cavity and was proved to work as an asymmetric catalyst to promote aldol reaction of *ortho*-, *meta*-, and *para*-nitrobenzaldehydes

with cyclohexanone with size-, diastereo- (0–83% *de*), and enantioselectivity (44–73% *ee*) combined with low to moderate yields (21–42%).

### 10.2.2 Reduction Reactions

#### 10.2.2.1 Reductions of Carbonyl Compounds and Derivatives

The reduction of carbonyl compounds is one of the simplest routes to chiral alcohols from ketones [40]. In 1995, the group of *Mukaiyama* reported the first enantioselective borohydride 1,2-reduction of ketones catalysed by chiral cobalt complexes [41]. The reduction of a range of aromatic ketones was successfully achieved by using  $\text{NaBH}_4$  in the presence of chiral ( $\beta$ -oxoaldiminato) cobalt(II) complex 7, leading to the corresponding alcohols in excellent yields and high enantioselectivities of up to 97% (Scheme 10.8a) [42]. In the same area, *Yamada* proposed a novel route to chiral *ortho*-fluorinated benzhydrols based on related enantioselective borohydride reduction of the corresponding *ortho*-fluorinated benzophenones [43]. In this case, the process was catalysed by an even more

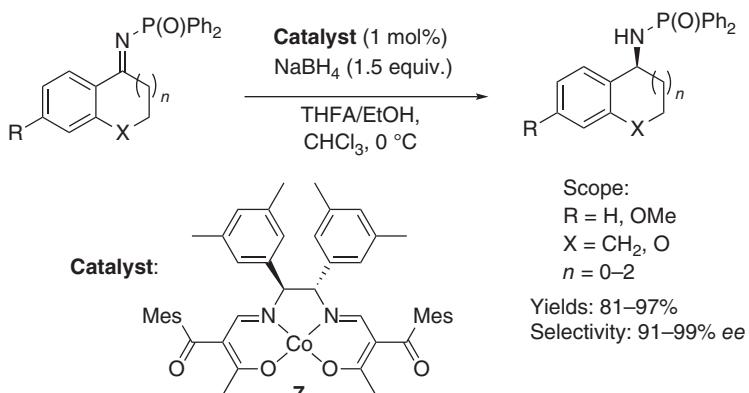


Scheme 10.8 Borohydride reductions of aromatic ketones.

sterically hindered chiral cobalt(II) complex **8**, providing high yields and enantioselectivities of up to 96% *ee* as shown in Scheme 10.8b.

Remarkable enantioselectivities of up to 99% *ee* were also reported by these authors in the enantioselective borohydride reduction of various 1,3-dicarbonyl compounds based on the use of other chiral ( $\beta$ -oxoaldiminato) cobalt(II) complexes [44]. Therefore, highly chemoselective, diastereoselective, and enantioselective reduction of various asymmetrical 1,2-dialkyl-3-aryl-1,3-diketones provided the corresponding *anti*-Aldol-type compounds in moderate yields (41–48%) and both excellent diastereo- and enantioselectivities (94–99% *de* and 95–98% *ee*, respectively) [45]. Another extension of this methodology was the enantioselective reduction of 2-alkyl-3-aryl-3-keto esters achieved through dynamic kinetic resolution, allowing a range of optically active *anti*-2-alkyl-3-hydroxy esters to be synthesised in high yields (82–93%) and high diastereoselectivities and enantioselectivities of up to 92% *de* and 95% *ee*, respectively [46]. Higher diastereoselectivities of 98–99% *de*, in combination with both excellent yields and enantioselectivities of 97–99% *ee*, were reached in the application of the same conditions to the reduction of 2-substituted-1,3-diaryl-1,3-propanediones into the corresponding chiral 2-substituted-1,3-diaryl-3-hydroxypropanones [47]. Furthermore, the same authors reported an *atropo*-enantioselective borohydride reduction of biaryl lactones also evolving through dynamic kinetic resolution to afford the corresponding chiral opened biaryl products [48]. When the reaction was catalysed by another chiral  $\beta$ -ketoinatocobalt(II) complex, the products were obtained in moderate to high yields (64–96%) and enantioselectivities (80–93% *ee*). In 2003, the same authors applied the identical type of catalysts to promote the enantioselective borohydride reduction of 2-substituted 3-ketoesters via dynamic kinetic resolution [49]. In addition to remarkable enantioselectivities of 97–99% *ee* and yields of 68–97%, a general excellent diastereoselectivity of 99% *de* was obtained for the produced *anti*-2-substituted-3-hydroxy esters. The same catalysts allowed the enantioselective borodeuteride reduction of *p*-methyl benzaldehyde to be achieved in quantitative yield and 77% *ee* [50] as well as that towards the reduction of 2-phenacylpyridine, providing the corresponding chiral amine in 94% yield and 92% *ee* [51]. This methodology was also applied to an efficient preparation of  $C_2$ -symmetrical chiral ferrocenyl diols through enantioselective borohydride reduction of the corresponding 1,1'-diacylferrocenes into the corresponding enantiopure  $C_2$ -symmetrical ferrocenyldiols in high yields (69–94%) and moderate to excellent *dl*:*meso* ratio (80 : 20 to 99 : 1) [52]. In another context, the enantioselective reduction of *N*- diarylphosphinyl imines was also investigated by these authors, providing the corresponding chiral amines in good yields (81–97%) and enantioselectivities of 77–99% *ee* when induced by closely related catalysts, such as **7**, employed at less than 1 mol% of catalyst loading (Scheme 10.9) [53].

Over the course of their studies on cobalt-catalysed enantioselective borohydride reductions of various ketones [54], the same authors have also demonstrated that tetralone derivatives could be reduced into the corresponding alcohols by treatment with  $\text{NaBH}_4$  in the presence of chiral cobalt catalyst **7** in

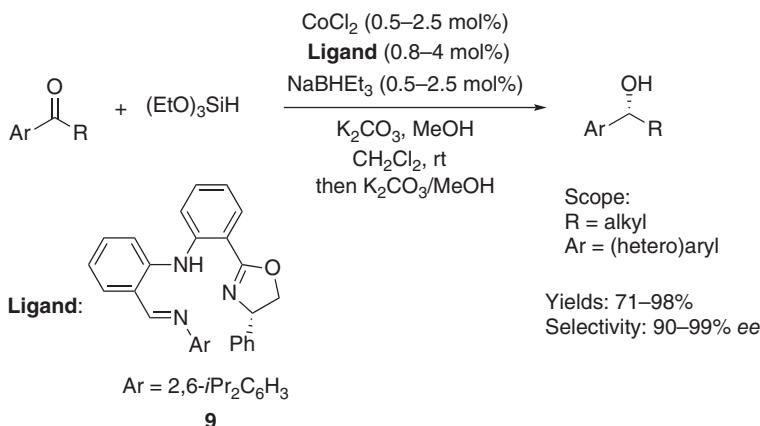


Scheme 10.9 Borohydride reduction of *N*-diphenylphosphinyl imines.

high yields and enantioselectivities of up to 91% *ee* under continuous-flow conditions [42d, 55]. Although the aryl carbonyl derivatives are suitable substrates to achieve a high enantioselectivity in borohydride reduction, the enantioselective reduction of aliphatic ketones still needed to be developed. In this context, the same authors have recently designed a novel *in situ*-generated cobalt(III) salen complex bearing a 1-chlorovinyl group [56]. This *in situ*-generated catalyst was found to provide moderate to high enantioselectivities of 61–90% *ee* in the enantioselective reduction of various aliphatic ketones including dialkyl ketones and 1-adamantyl ketones into the corresponding alcohols, along with moderate to excellent yields (16–97%). Very recently, the same authors demonstrated that the corresponding reusable and recyclable cobalt system was also efficient to induce chirality in comparable reactions [57]. In addition, it must be noted that *Kim* investigated the catalytic activity of novel chiral cobalt salen complexes immobilised on mesoporous MCM-41 by grafting in the enantioselective borohydride reduction of aromatic ketones [58]. These complexes were synthesised from 3-aminopropyltrimethoxysilane and 2,6-diformyl-4-*tert*-butylphenol through the multi-grafting method.

In another context, the asymmetric 1,2-hydrosilylation of carbon–heteroatom bonds catalysed by chiral transition metals complexes also constitutes an alternative to asymmetric hydrogenation owing the mild conditions and manipulative simplicity [59]. In the past two decades, a variety of transition metal chiral catalysts have been employed to promote these reactions; however, the asymmetric hydrosilylation of ketones mediated by cobalt has received relatively moderate attention, since the pioneering works reported by *Brunner* and *Amberger*, in 1991 [60]. In this work, *in situ*-generated chiral cobalt(I) pyridinyloxazoline complexes provided moderate enantioselectivities of up to 56% *ee* in the hydrosilylation of acetophenones with diphenylsilane. In 2010, *Nishiyama* achieved a breakthrough in this field since he disclosed a highly efficient cobalt(II) complex of a chiral bis(oxazolinylphenyl)amine, allowing enantioselectivities of up to 98% *ee* to be achieved [61]. In the same context, *Gade* designed a novel family of chiral C<sub>2</sub> symmetric tridentate monoanionic *N,N,N*-pincer ligands based on the

1,3-bis(2-pyridylimino)isoindoline framework, which were further investigated as cobalt ligands to induce chirality in hydrosilylation of several aryl methyl ketones with tertiary silanes such as  $(\text{EtO})_2\text{MeSiH}$  [62]. The corresponding alcohols were obtained in moderate to quantitative yields (58–100%) and low to high enantioselectivities (25–91% ee). In 2011, another asymmetric hydrosilylation of aryl alkyl ketones was developed by *Chan* [63]. This reaction employed  $\text{PhSiH}_3$  as the hydride donor, and a cobalt catalyst *in situ* generated from a chiral dipyridylphosphine such as (*S*)-Xyl-P-Phos and  $\text{Co}(\text{OAc})_2(\text{H}_2\text{O})_4$ , providing moderate to high enantioselectivities (51–94% ee) combined to low to quantitative yields (6–99%). Later in 2016, *Lu* and *Chen* reported enantioselectivities of up to 99% ee in the enantioselective hydrosilylation of simple aryl alkyl ketones promoted by a chiral cobalt catalyst *in situ* generated from  $\text{CoCl}_2$  and novel chiral iminophenyl oxazolinylphenylamine ligand **9** (Scheme 10.10) [64]. The reaction involved  $(\text{EtO})_3\text{SiH}$  as a reductant and  $\text{NaBHET}_3$  as an activating agent of the precatalyst. It led to a range of optically active aromatic alcohols in high to quantitative yields (71–98%) and uniformly excellent enantioselectivities (90–99% ee).



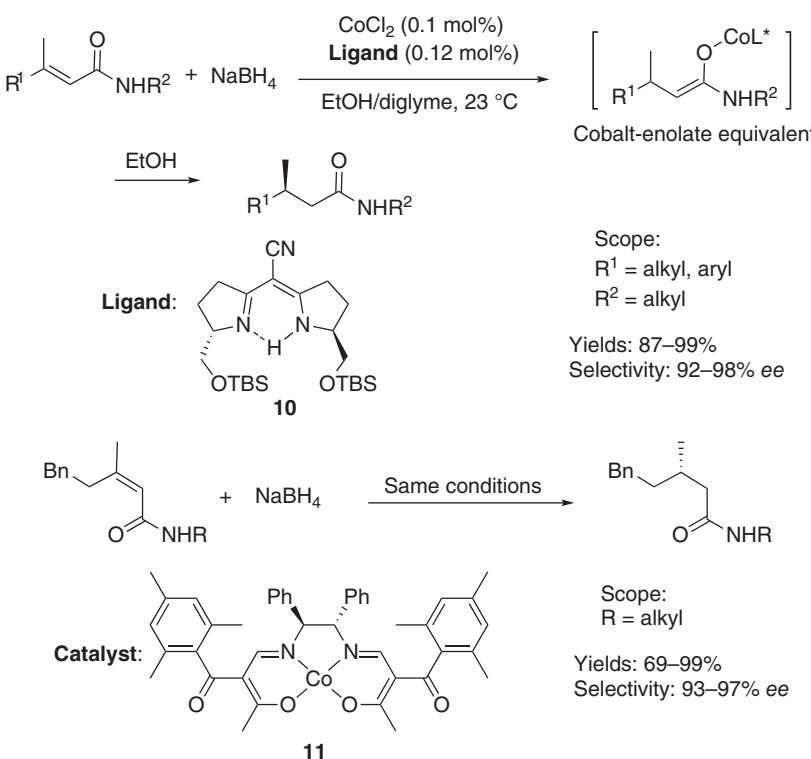
**Scheme 10.10** Hydrosilylation of aryl ketones.

On the other hand, chiral cobalt complexes have been rarely applied as catalysts in enantioselective metal-catalysed hydrogenations of ketones and, moreover, with only moderate enantioselectivities. For example, *Li* recently reported the synthesis of a novel cobalt complex containing a chiral PNPP-type ligand that was investigated to promote the hydrogenation of various aromatic ketones [65]. Employed at 100 °C in the presence of KOH as base, the reaction led to a range of chiral aromatic alcohols in low to quantitative yields (31–99%) and low to excellent enantioselectivities (35–92% ee).

### 10.2.2.2 Reductions of Alkenes

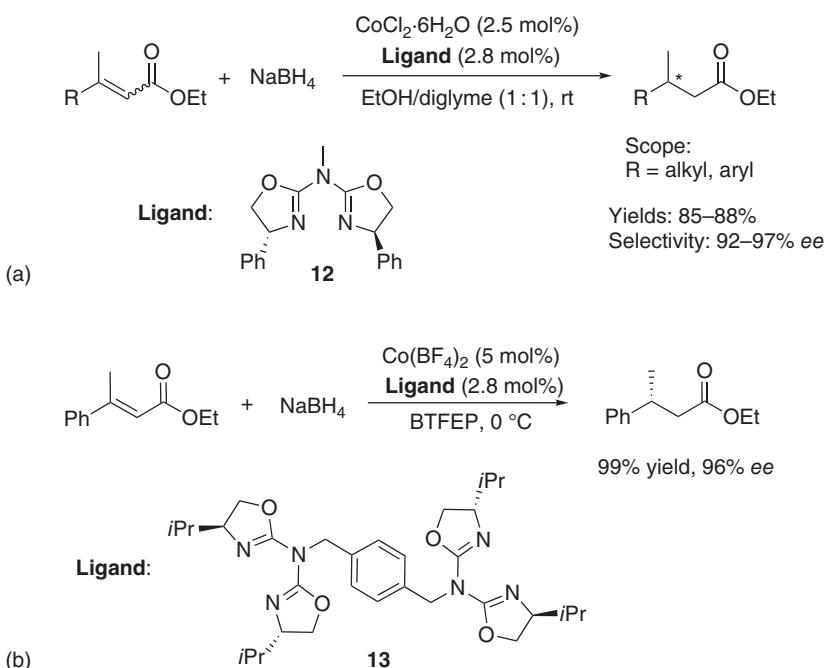
In 1989, *Pfaltz* reported an enantioselective conjugate reduction of (*E*)- $\alpha,\beta$ -unsaturated carboxylates with sodium borohydride promoted by a

chiral cobalt complex *in situ* generated from  $\text{CoCl}_2$  and ligand **10** [3]. The corresponding chiral esters were obtained in good to high yields (84–97%) and enantioselectivities (73–96% *ee*). Later, the same authors extended these reaction conditions to the highly enantioselective conjugate reduction of  $\alpha,\beta$ -unsaturated carboxamides with sodium borohydride promoted by chiral semicorrin cobalt catalysts (Scheme 10.11) [66]. Remarkably, enantioselectivities of up to 98% *ee* combined with quantitative yields were achieved for the corresponding formed amides, as shown in Scheme 10.11. Later, Yamada reinvestigated these reactions by using chiral  $\beta$ -ketoiminato cobalt(II) complexes [67], such as **11** (Scheme 10.11), which provided good to high yields (69–99%) and enantioselectivities of up to 97% *ee*.



Scheme 10.11 Conjugate additions of  $\text{NaBH}_4$  to  $\alpha,\beta$ -unsaturated carboxamides.

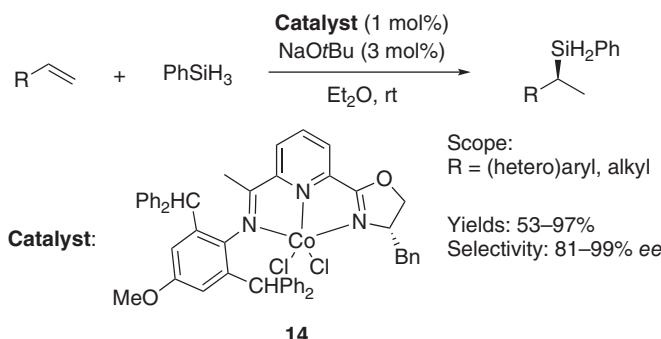
In 2005, Reiser introduced the use of readily available chiral azabis(oxazoline) ligands in enantioselective conjugate reduction of  $\alpha,\beta$ -unsaturated esters with sodium borohydride [68]. Several differently substituted chiral ligands were screened and the phenyl-substituted **12** was selected as the optimal one, allowing high to excellent enantioselectivities of 92–97% *ee* to be achieved in combination with high yields (85–89%) for the conjugate reduction of various aromatic as well as aliphatic  $\alpha,\beta$ -unsaturated esters into the corresponding esters



**Scheme 10.12** Conjugate additions of  $\text{NaBH}_4$  to  $\alpha,\beta$ -unsaturated esters.

(Scheme 10.12a) The scope of this methodology was extended to other *Michael* acceptors, such as  $\gamma$ -butyrolactones and  $\alpha,\beta$ -unsaturated amides, which afforded the corresponding saturated esters in good to high yields of 54–65% and 81–88%, respectively, in combination with enantioselectivities of up to 86% *ee* and 95% *ee*, respectively. Later in 2010, *Fraile* reported a study on the recycling possibilities for chiral azabis(oxazoline)-cobalt complexes as catalysts for the enantioselective conjugate addition of  $\text{NaBH}_4$  to ethyl (*E*)-3-phenylbut-2-enoate (Scheme 10.12b) [69]. The authors demonstrated that the best method for recycling was the use of liquid–liquid biphasic system. Thus, the utilisation of a cobalt complex of chiral ditopic azabis(oxazoline) **13** in 1,3-bis(2,2,2-trifluoroethoxy)propan-2-ol (BTFEP) as the solvent was shown to allow the conjugated reduction of substrate into the corresponding product with enantioselectivities of up to 96% *ee* to be achieved in association with an excellent yield of 99% (Scheme 10.12b).

In 2010, *Nishiyama* reported moderate to good enantioselectivities ( $\leq 75\%$  *ee*) in the cobalt-catalysed asymmetric conjugate hydrosilylation of enones with  $(\text{EtO})_2\text{MeSiH}$  by using chiral bis(oxazolinylphenyl)amine ligands, such as *Bopa-dpm* [61]. In 2017, *Lu* developed an enantioselective *Markovnikov*-type hydrosilylation of simple alkenes with  $\text{PhSiH}_3$  to provide the corresponding chiral dihydrosilanes [70]. The process was promoted by cobalt complex **14** derived from a chiral iminopyridine oxazoline ligand in the presence of  $\text{NaOtBu}$ . It was suitable to a wide range of both aryl and aliphatic alkenes with excellent functional group tolerance, allowing a variety of chiral dihydrosilanes to be synthesised with moderate to high yields (53–97%) and high enantioselectivities (81–99% *ee*), as illustrated in Scheme 10.13.



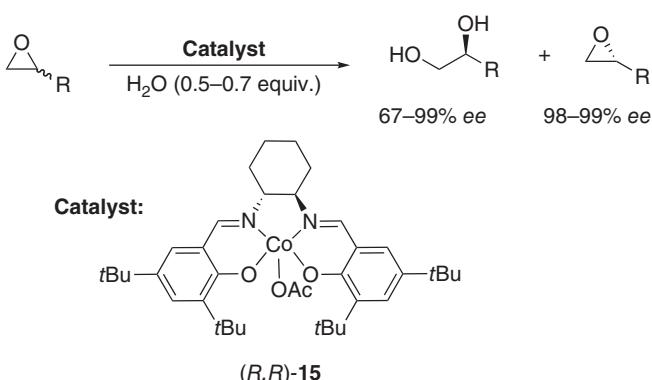
Scheme 10.13 Hydrosilylation of alkenes.

On the other hand, examples of enantioselective cobalt-catalysed hydrogenation of alkenes still remain rare. In 1981, *Ohgo* investigated the asymmetric hydrogenation of alkenes using dimethylglyoximatocobalt(II) complexes in the presence of quinine, which provided low to moderate optical yields (7–49% *ee*) [71], while enantioselectivities of up to 96% *ee* were reached by *Pfaltz* in the asymmetric hydrogenation of  $\alpha,\beta$ -unsaturated esters catalysed by *in situ*-generated chiral cobalt semicorrin complexes [3]. In 2012, *Chirik* employed enantiopure  $C_1$ -symmetric bis(imino)pyridine cobalt complexes for the asymmetric hydrogenation of geminal-disubstituted olefins [72]. Chiral  $C_1$ -symmetric bis(imino)pyridine cobalt chloride, methyl, hydride, and cyclometalated complexes were investigated as catalysts for the enantioselective hydrogenation of a range of styrenes, providing the hydrogenated products in low to excellent yields (5–98%) combined with moderate to excellent enantioselectivities of up to 98% *ee* [72]. Later, the same authors described the asymmetric hydrogenation of cyclic alkenes with the same type of catalysts [73]. High yields and enantioselectivities of up to 98% and 99% *ee*, respectively, were achieved in the reaction of substituted benzo-fused five- and six-membered alkenes to give the corresponding products. In 2016, *Lu* reported the first highly enantioselective hydrogenation of 1,1-diarylalkenes promoted by a combination of a metal and a chiral base ligand [74]. The reaction was catalysed by a chiral cobalt complex exhibiting a chiral oxazoline iminopyridine ligand in the presence of  $\text{NaBHET}_3$  as reductant. It led to the corresponding chiral 1,1-diarylethanes in good to quantitative yields (77–99%) and moderate to excellent enantioselectivities (58–99% *ee*). Moreover, there have been only few reports on the asymmetric hydrogenation of  $\beta$ -enamino esters especially using chiral cobalt catalysts. Among them, *Cabrera* and *Amezquita-Valencia* recently investigated these reactions in the presence of different ligands including (*R*)-BINAP and other chiral bisphosphines like (*R,R*)-DIOP, (*R,R*)-Me-DuPhos, and (*R*)-Prophos [75]. The authors demonstrated that a combination of  $\text{Co}_2(\text{CO})_8$  with (*R*)-BINAP was the optimal catalytic system for the asymmetric hydrogenation of a range of  $\beta$ -enamino esters since the corresponding chiral amino esters were obtained in high yields (82–93%) albeit with low enantioselectivities (4–43% *ee*).

### 10.2.3 Ring-Opening Reactions

#### 10.2.3.1 Hydrolytic Ring-Openings of Epoxides

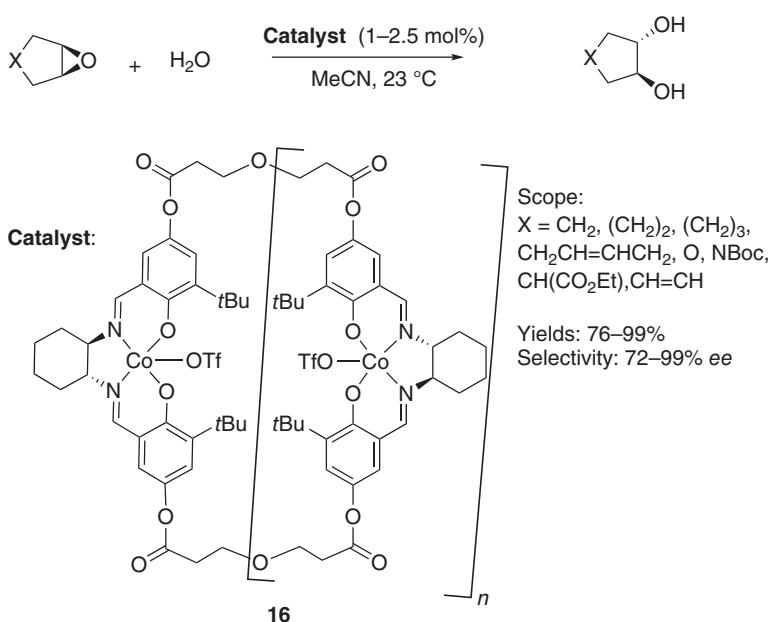
Catalytic kinetic resolutions [76] constitute useful tools in asymmetric catalysis, complementing other approaches to chiral products, such as asymmetric synthesis and classical resolution [77]. A wide number of reactions evolving through kinetic resolution have been developed with high efficiency, such as nucleophilic ring-opening reactions of racemic epoxides [78]. For example, the hydrolytic kinetic resolution constitutes a simple methodology for the synthesis of chiral epoxides and diols [79]. The process was reported by *Jacobsen* in 1997 to prepare terminal epoxides along with the corresponding diols in virtually enantiomerically pure form [80]. It employed water (0.5–0.7 equiv.) as the sole reagent, small amounts of solvent, and low catalytic loadings (0.2–2 mol%) of recyclable chiral cobalt(III) salen complexes. This methodology has been applied to the preparation of many building blocks for the synthesis of complex natural products and biologically active compounds [81]. The hydrolytic kinetic resolution based on the use of *Jacobsen's* chiral Co(III) salen complexes, such as catalyst **15**, has emerged as a general method for resolving a wide range of terminal racemic epoxides, such as alkyl-, halo alkyl-, aryl-, vinyl-, and alkynyl-epoxides, including epoxides exhibiting various functional groups, affording the corresponding chiral diols as well as recovered epoxides in enantioselectivities of up to 99% ee (Scheme 10.14) [82, 83]. It must be noted that examples of hydrolytic kinetic resolution of epoxides bearing two stereocentres still remain rare. Among them, a resolved epoxypentenol was generated in 48% yield and 98% ee and further employed as key intermediate in the total synthesis of (5S,7R)-kurzilactone [84]. In 2010, another example was reported by *Sudalai* who applied the same methodology to a series of benzyloxy- and azido-epoxides, affording a wide range of enantiopure *syn*- or *anti*-alkoxy- and azido-epoxides, which were applied to the synthesis of bioactive molecules, such as (S,S)-reboxetine and (+)-*epi*-cytoxazone [85]. In addition, efficient total syntheses of patulolide C, 11-epipatulolide C [86], and (+)-boronolide [87] have been independently described by *Sharma, Babu, Kumar, and Naidu*,



Scheme 10.14 Hydrolytic kinetic resolution of epoxides.

respectively, on the basis of this methodology. Several other biologically active products, such as cryptocarya diacetate [88], yene-polyol macrolide RK-397 [89], and macroviracin A [90] have also involved in their syntheses hydrolytic kinetic resolutions of epoxides bearing at least two stereocentres. In 2014, an hydrolytic kinetic resolution of a racemic azido epoxide using catalyst (*S,S*)-**15** was included by *Sudalai* in a concise enantioselective synthesis of (+)-L-733,060, a potent and selective nerokinin-1 substance P receptor antagonist [91]. More recently in 2017, the same authors reported a total synthesis of the naturally occurring and biologically active alkaloid 1,4-dideoxy-1,4-imino-D-arabinitol (DAB-1), and the key step of which was the hydrolytic kinetic resolution of another racemic azido epoxide promoted by the same catalyst [92]. Many other natural products and bioactive compounds have been synthesised according to these methodologies [93, 94].

Dinuclear cobalt salen catalysts have been demonstrated to exhibit an enhanced reactivity relative to conventional monomeric salen catalyst systems [95]. For example, a recyclable dimeric homochiral cobalt(III) salen complex that was developed by *Kureshy* [96], a chiral bimetallic cobalt(III) salen-calix[4]arene hybrid [97] and a chiral macrocyclic dinuclear cobalt salen complex [98], both developed by *Kleij*, and various dimeric chiral cobalt salen complexes activated by  $\text{InCl}_3$ ,  $\text{GaCl}_3$ , or  $\text{BF}_3$  and developed by *Kim* have allowed remarkable enantioselectivities of up to 98% *ee* for the corresponding diols and 99% *ee* for the recovered epoxides to be obtained [99]. Dinuclear chiral cobalt salen catalysts have also been demonstrated by *Kim* to be highly efficient and enantioselective in hydrolytic kinetic resolutions of various epoxides [100]. Excellent enantioselectivities of up to 99% *ee* for the recovered epoxides combined with enantioselectivities of up to >85% *ee* for the corresponding ring-opened products and very high catalytic activity could be reached. Furthermore, oligomeric cobalt salen catalyst systems exhibited extremely high reactivities and enantioselectivities in the hydrolytic kinetic resolution of a variety of terminal epoxides under neat conditions with low catalyst loadings (0.01 mol%) [83h,o, 101]. Therefore, the immobilisation of Co(III) salen complexes on various supports [102], such as polymers [103], gold colloids [104], mesoporous silica [105], or zeolite [106] was recently reported by several authors and its successful application to the hydrolytic kinetic resolution of epoxides, providing remarkable enantioselectivities of up to 99% *ee*. In addition, *Pozzi* have demonstrated that the hydrolytic kinetic resolution of epoxides was feasible under fluorous biphasic conditions with up to 99% *ee* [107]. On the other hand, ring-opening of epoxides can also be performed through dynamic kinetic resolution in a flow-through mode with up to 91% *ee* [108]. Moreover, *Jacobsen* reported the synthesis of novel cyclic oligomeric cobalt salen catalysts to be applied at remarkably low catalyst loadings (0.0003–0.04 mol%) to promote the hydrolytic kinetic resolution of terminal epoxides [109]. The hydrolysis of *meso*-epoxides derived from cyclic alkenes represents an attractive approach to chiral diols that are not accessible via asymmetric alkene dihydroxylation. In this context, the same authors showed that oligomeric cobalt salen complex **16** was a highly efficient catalyst in the hydrolytic desymmetrisation of a variety of cyclic *meso*-epoxides (Scheme 10.15) [109]. The corresponding chiral *trans*-1,2-diols were obtained in



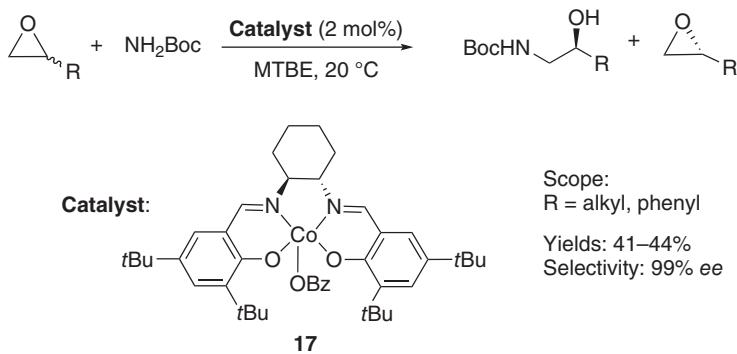
Scheme 10.15 Hydrolytic desymmetrisation of *meso*-epoxides.

good to quantitative yields (76–99%) and generally excellent enantioselectivities (96–99% *ee*). A lower enantioselectivity of 72% *ee* was observed in the case of a seven-membered substrate ( $X = (\text{CH}_2)_3$ ).

The synthesis of another type of recoverable oligomeric cobalt salen complexes was reported by Schulz in 2014 [110]. These chiral cobalt salen complexes were investigated as catalysts to promote the asymmetric hydrolytic ring-opening of epibromohydrin through dynamic kinetic resolution with complete conversion (99% conversion) and high enantioselectivity (92% *ee*). Later in 2016, the same authors reinvestigated this reaction by using a combination of chiral oligomeric cobalt- and manganese-based salen complexes as catalysts, which led to the chiral diol in both excellent yield (97%) and enantioselectivity (92% *ee*) [111]. In 2015, Thakur reported the synthesis of a chiral dinuclear cobalt salen complex incorporating  $\text{Y}(\text{OTf})_3$  to be investigated in the hydrolytic kinetic resolution of terminal epoxides [112]. This catalyst provided higher reactivity and enantioselectivity than its monomer analogue since a range of chiral terminal epoxides could be recovered with uniformly excellent enantioselectivities (97–99% *ee*) and good yields (42–46%). The same year, Sun described the synthesis of novel macroporous helical silica-supported cobalt salen complexes to be investigated in water in the same reactions [113]. Among them, a catalyst prepared from an (*S*)-amino alcohol-doped silica and a cobalt (*R,R*) –salen complex was found as optimal catalyst, allowing the recovering of chiral 1,2-epoxybutane ( $R = \text{Et}$ ) in good yield (46%) and high enantioselectivity (91% *ee*) along with the formation of the corresponding chiral diol in comparable yield (49%) and enantioselectivity (91% *ee*).

### 10.2.3.2 Ring-Openings of Epoxides by Nucleophiles Other than Water

Epoxides can also be resolved through ring-opening by nucleophiles other than water, such as amines [114], carbamates, imides, phenols [83b, 115], alcohols [116], azides [83b, 117], fluorides [118], carboxylic acids [119], or carbon nucleophiles [120], allowing the synthesis of various important chiral functionalised compounds to be achieved [121]. Among them, chiral  $\beta$ -amino alcohols are valuable intermediates in the synthesis of a variety of biologically active products and also play a very significant role in asymmetric catalysis [122]. Various efficient methods have been reported for their synthesis; among them is the asymmetric ring-opening aminolytic kinetic resolution of racemic terminal epoxides with alkyl/aryl amines by using different catalysts [123]. In particular, the use of carbamates as nucleophiles has provided excellent results in the ring-opening of epoxides through kinetic resolution. As an example, *Bartoli* have used chiral *Jacobsen's* cobalt(III) salen complex **17** to open terminal epoxides with  $\text{NH}_2\text{Boc}$ , leading to the corresponding Boc-protected 1,2-amino alcohols in good yields and with remarkable enantioselectivity of 99% *ee*, as shown in Scheme 10.16 [124]. Selectivity factors were found to be >500. This methodology was later extended to the enantioselective preparation of 5-substituted oxazolidinones, which are known to be valuable structural motifs of medicinally active drugs [125]. Later in 2009, *Kureshy* reported the use of highly efficient recyclable cobalt(III) salen complexes in ionic liquids in the cobalt-catalysed kinetic resolution of aryloxy/terminal epoxides using carbamates as nucleophiles, providing high regio- and enantioselectivities of 99% *ee* for both the formed amino alcohols and the recovered epoxides [126].

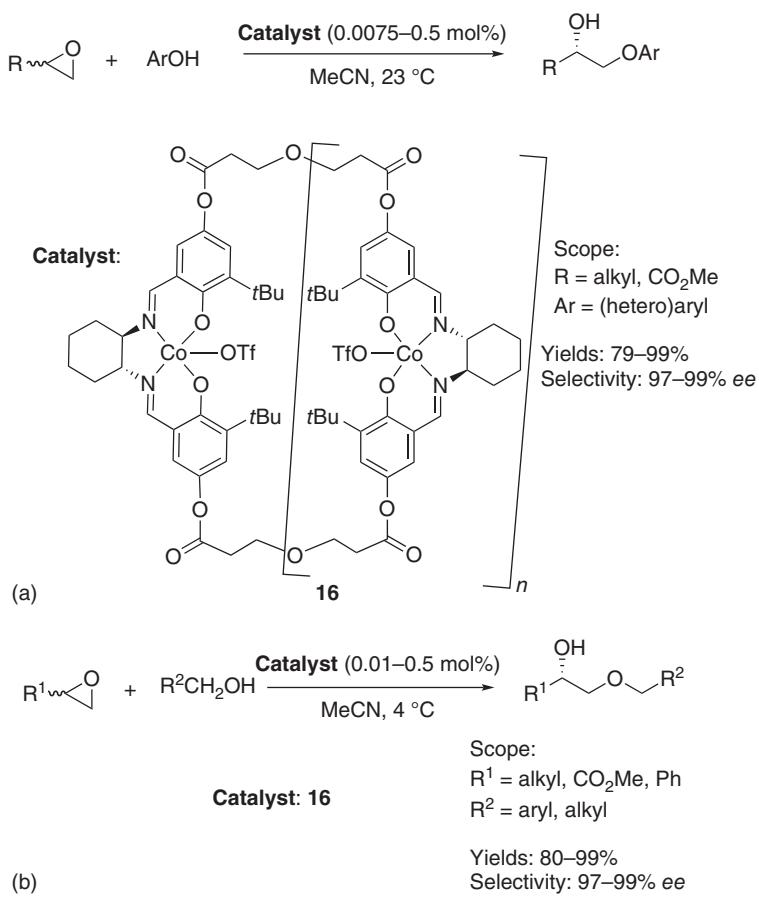


**Scheme 10.16** Kinetic resolution of epoxides through ring-opening with carbamates.

In 2014, an oligomeric cobalt salen complex was applied by *Jacobsen* to promote the carbamolytic desymmetrisation of several cyclic *meso*-epoxides through ring-opening reaction with phenyl carbamate [109]. Starting from five-membered substrates, the reaction provided the corresponding chiral ring-opened products in moderate yields (49–66%) with remarkable enantioselectivity (99% *ee*). In 2016, a mesoporous recyclable silica-supported cobalt salen complex was designed by *Islam* and *Bhaumik* [127]. It showed an excellent catalytic activity for the regio- and enantioselective asymmetric ring-opening

of terminal epoxides using aromatic as well as cyclic aliphatic amines, leading to the corresponding chiral *β*-amino alcohols in both excellent yields (92–98%) and enantioselectivities (87–99% ee). The scope of the process was extended to *meso*-epoxides, such as cyclohexene oxide, with high yields (87–97%) and good to excellent enantioselectivities (77–99% ee).

Cobalt(III) salen complexes were applied by *Sudalai* to the phenolic ring-opening of racemic azido and benzyloxy epoxides into the corresponding chiral *anti*-1-aryloxy-3-azido or benzyloxy-2-alcohols with both excellent yields of up to 98% and enantioselectivities of up to 99% ee [128]. The utility of this methodology was demonstrated in its application to a total synthesis of the  $\beta$ -blocker ICI-118,551. The efficiency of oligomeric chiral cobalt salen catalyst **16** was applied to the regioselective phenolytic ring-opening of terminal epoxides that afforded the corresponding chiral alcohols in high yields (79–97%) and enantioselectivities (97–99% ee) (Scheme 10.17a). Moreover, the regioselective ring-opening of terminal epoxides with aliphatic alcohols could be performed under comparable reaction conditions, providing the corresponding chiral



**Scheme 10.17** Ring-openings of epoxides with alcohols.

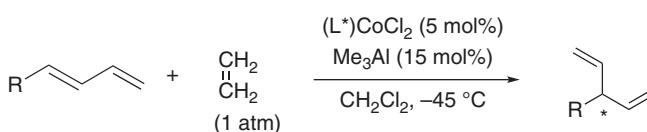
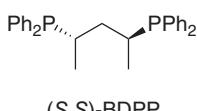
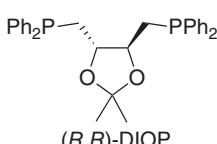
monoprotected 1,2-diols in high to quantitative yields (80–99%) and remarkable enantioselectivities (98–99% *ee*) (Scheme 10.17b).

In another area, chiral cobalt catalysts have also been applied to the enantioselective polymerisation of monosubstituted epoxides where chiral racemic monomers are kinetically resolved during polymerisation. This process provided two desirable products, such as enantiopure epoxides and stereoregular chiral polyethers. In 2008, *Coates* described the first highly enantioselective polymerisation catalyst to be used in the kinetic resolution of monosubstituted epoxides [129]. Indeed, a chiral bimetallic cobalt(III) catalyst was found to exhibit high levels of activity and enantioselectivity of up to 99% *ee* for a range of ring-opened isotactic chiral polyethers possessing alkyl, aryl, and ether substituents. The copolymerisation of monosubstituted epoxides with CO<sub>2</sub> constitutes a powerful method for the synthesis of polycarbonates [130]. In 2010, a highly enantioselective version of this process was developed by *Lu* [131]. In this study, the authors investigated the enantioselective copolymerisation of cyclohexene oxide with CO<sub>2</sub> catalysed by chiral dissymmetrical bulky cobalt(III)NO<sub>3</sub> salen complexes. This methodology allowed the synthesis of the corresponding optically active polycarbonate to be achieved with enantioselectivities of up to 96% *ee*. In 2014, the same authors reinvestigated this reaction by using a chiral dinuclear cobalt salen complex, which provided enantioselectivities of up to 98% *ee* [132].

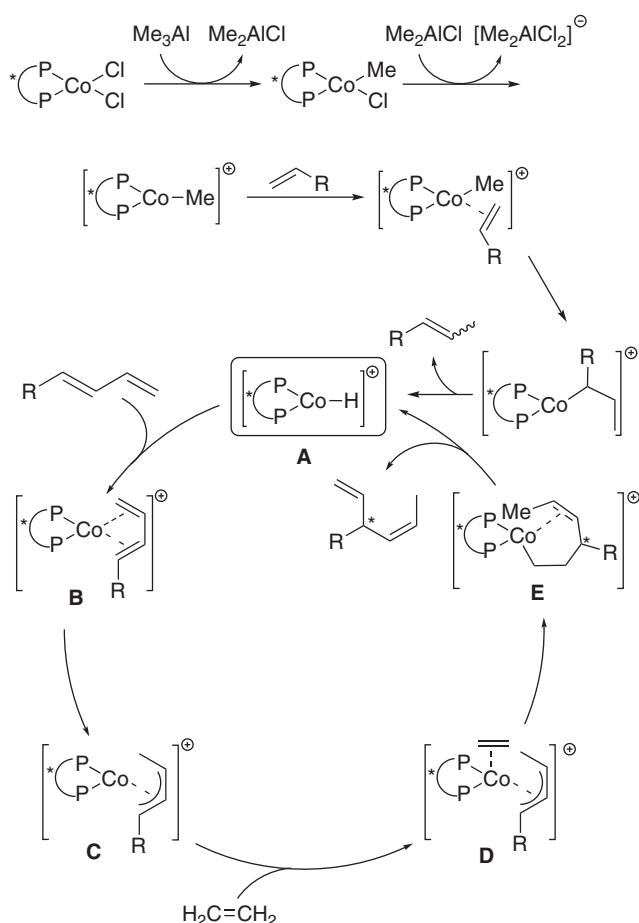
## 10.2.4 Hydrovinylation and Hydroboration Reactions

### 10.2.4.1 Hydrovinylations

Only moderate success has been reported in the first examples of cobalt-catalysed hydrovinylation reactions [133], and most of the time, these processes [134] were catalysed by nickel or palladium complexes, often limited to monodentate ligands [135]. Inspired by the work of *Hilt* reported in 2001, dealing with the cobalt-catalysed codimerisation of a range of 1,3-dienes with alkenes [136], *Vogt* investigated in 2009 the asymmetric cobalt-catalysed hydrovinylation of styrene with ethene, providing the corresponding chiral 3-phenyl-1-butene [137]. The activation of [CoX<sub>2</sub>(phosphine)] complexes by alkylating agents, such as Et<sub>2</sub>AlCl, afforded very active catalysts with unprecedented high selectivity for the formation of the expected codimer. The product was obtained with more than 99% selectivity without trace of double bond isomerisation while combined with a moderate enantioselectivity (50% *ee*) by using chiral bis(amido-phosphine) ligands. In 2010, *Sharma* and *RajanBabu* reported the very efficient and highly enantioselective hydrovinylation of a range of substituted unactivated linear 1,3-dienes with ethene, providing exclusively the corresponding chiral (*Z*)-1,4-adducts bearing a *Z*-internal alkene without any trace of the corresponding 1,2-regioisomers or any homo-dimerisation products [138]. Among chiral ligands investigated, (*R,R*)-DIOP and (*S,S*)-BDPP were found to give the best results with quantitative yields and remarkable enantioselectivities of up to 99% *ee*, as shown in Scheme 10.18. The authors proposed the mechanism depicted in Scheme 10.18 in which a [(L\*)Co(II)–H]<sup>+</sup> intermediate A was the catalytic species generated by metathesis of the Al–Me/Co–Cl bonds and migratory insertion of an alkene into Co–Me bond, followed by

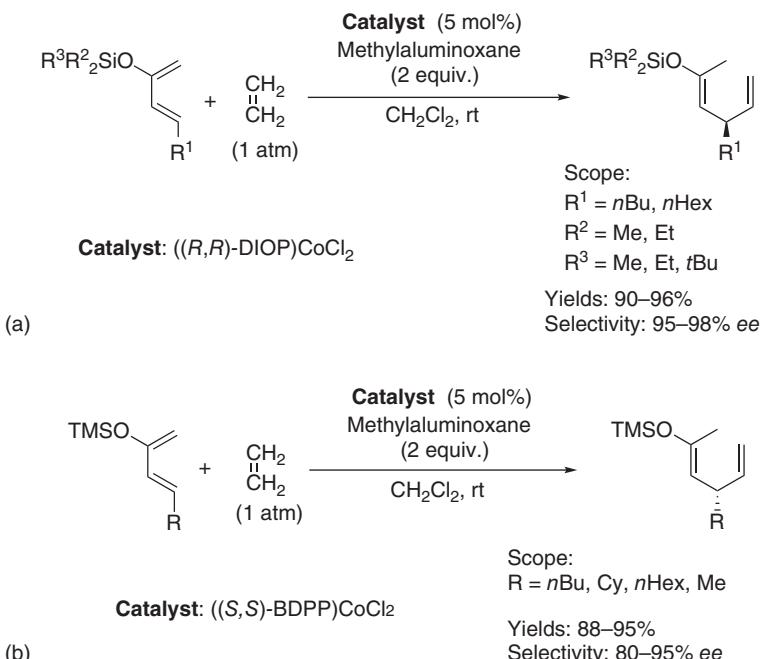
**Ligands ( $\text{L}^*$ ):**Scope:  
 $\text{R}$  = alkylYields: 40–99%  
Selectivity: 89–99% ee

Possible mechanism:

**Scheme 10.18** Hydrovinylation of substituted 1,3-dienes with ethene.

reductive elimination. Addition of the Co–H via an  $\eta^4$ -diene complex **B** yielded a *syn-anti*-(allyl)Co-species **C**, which then underwent coupling with ethene to give intermediate **E**. The reductive elimination of **E** regenerated the catalyst and afforded the final product.

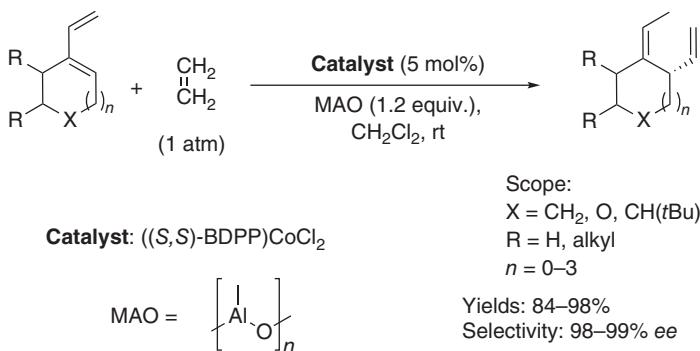
Later, the same authors also developed the same process in the presence of the cobalt catalyst derived from (*S,S*)-DIOP ligand, which afforded the corresponding chiral products in moderate to quantitative yields (40–98%) combined with uniformly very high enantioselectivities (95–96% *ee*) [139]. On the other hand, chiral trialkylsilyl enol ethers constitute versatile intermediates for the synthesis of optically active carbonyl compounds. Nevertheless, there are still few reports of broadly applicable catalytic methods for their synthesis. In 2015, RajanBabu reported a general procedure for highly chemoselective, regioselective, and enantioselective synthesis of trialkylsilyl enol ethers exhibiting a vinyl-bearing chiral centre at the  $\alpha$ -position [140]. The reactions were promoted by a cobalt catalyst derived from (*R,R*)-DIOP and 2 equiv. of methylalumininoxane (MAO). The reaction of various 1,3-siloxydienes with ethene led regioselectively to the corresponding branched 1,4-hydrovinylation chiral products in both remarkable yields (90–96%) and enantioselectivities (95–98% *ee*) (Scheme 10.19a). These reactions were also promoted by a cobalt catalyst derived from (*S,S*)-BDPP, providing the opposite enantiomers in comparable yields (88–95%) and good to excellent enantioselectivities (80–95% *ee*), as shown in Scheme 10.19b.



**Scheme 10.19** Hydrovinylations of 1,3-siloxydienes with ethene.

In 2016, Schmalz reported an efficient and practical protocol for the enantioselective cobalt-catalysed hydrovinylation of vinylarenes with ethene

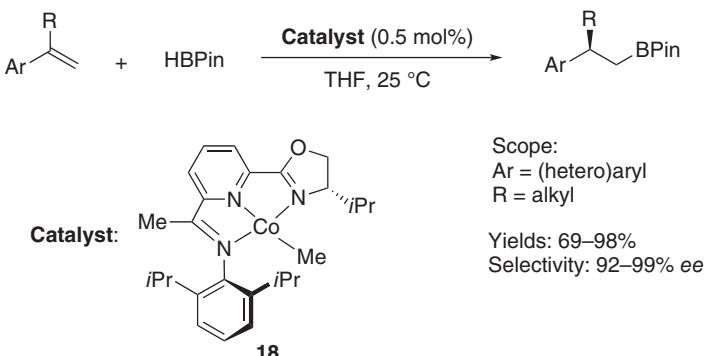
at low pressure (1.2 bar) [141]. The reactions were catalysed by a chiral cobalt catalyst *in situ* generated from  $\text{CoCl}_2$  and a TADDOL ( $\alpha,\alpha,\alpha',\alpha'$ -tetraphenyl-2,2-dimethyl-1,3-dioxolane-4,5-dimethanol)-derived phosphine–phosphite ligand in the presence of  $\text{Et}_2\text{AlCl}$ . It led regioselectively to a wide range of chiral branched products in high yields (76–99%) and moderate to excellent enantioselectivities (44–99% *ee*). Related reaction conditions were applied to the asymmetric hydrovinylation of  $\beta$ -alkyl-styrenes that regioselectively provided the corresponding 1,4-hydrovinylation chiral products in good to high yields (74–96%) and low to good enantioselectivities (16–84% *ee*). In both types of substrates, vinylarenes and  $\beta$ -alkyl-styrenes, an almost complete regioselectivity was observed ( $\geq 98 : 2$ ). In 2012, *RajanBabu* and *Page* applied (*S,S*)-BDPP-based cobalt complex to promote a remarkable asymmetric hydrovinylation of 1-vinylcycloalkenes with ethene that gave highly regioselectivity and enantioslectivity to the corresponding chiral 1-alkylidene-2-vinylcycloalkanes in the presence of MAO [142]. As shown in Scheme 10.20, these chiral products were produced in uniformly high yields (84–98%) with enantioselectivities of 98% *ee*. The ratios between the expected 1,4-hydrovinylation adducts and the undesired 1,2-hydrovinylation regioisomers ranged from 85 : 15 to 99.5 : 0.5.



**Scheme 10.20** Hydrovinylation of 1-vinylcycloalkenes with ethene.

#### 10.2.4.2 Hydroborations

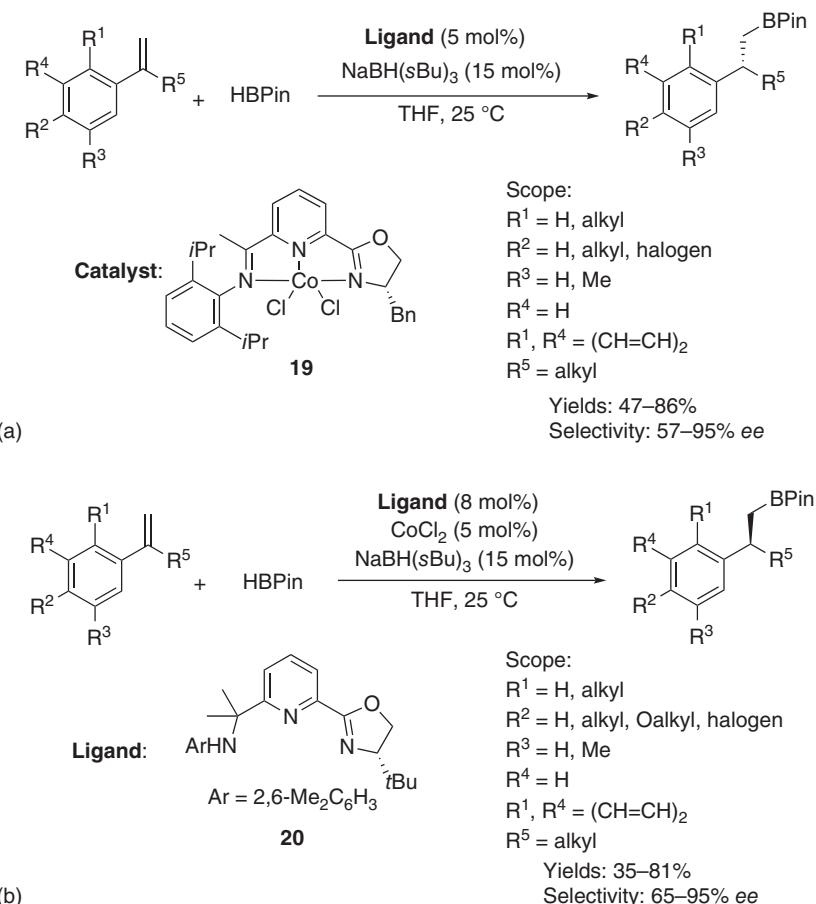
The catalytic asymmetric hydroboration of alkenes constitutes an efficient method for the synthesis of chiral alkylboronic acid derivatives [143]. Along with rhodium, iridium, copper, and iron catalysts, chiral cobalt complexes have been found to be even more active promoters for asymmetric hydroborations of 1,1-disubstituted alkenes. For example, *Huang* have reported excellent enantioselectivities of 92–99% *ee* when these reactions were catalysed with only 0.5 mol% of novel cobalt(II) complex with ligand **18**, derived from a chiral iminopyridine–oxazoline ligand (Scheme 10.21) [144]. Indeed, the asymmetric hydroboration of a wide range of 1,1-disubstituted aryl alkyl alkenes with  $\text{HBPin}$  afforded the corresponding chiral  $\alpha$ -alkyl- $\beta$ -pinacolatoboranes with exclusive *anti-Markovnikov* regioselectivity in moderate to high yields (69–98%) and uniformly excellent enantioselectivities (92–99% *ee*).



Scheme 10.21 Hydroboration of 1,1-disubstituted aryl alkyl alkenes.

Comparable reactions were also investigated by *Lu* in the presence of a related cobalt complex derived from another chiral iminopyridine–oxazoline ligand [145]. In this case, the process employed NaBH<sub>3</sub>Et as activating agent, providing a range of chiral  $\alpha$ -alkyl- $\beta$ -pinacolatoboranes with exclusive *anti-Markovnikov* regioselectivity in moderate to excellent yields (45–96%) and enantioselectivities (53–99% *ee*). Since no example of enantioselective hydroboration of vinylsilanes was previously reported, the same authors successfully applied the same catalyst to develop the first asymmetric hydroboration of  $\alpha$ -silyl alkenes [146]. The reaction of the latter with HBPin in the presence of NaBH<sub>3</sub>Et led regioselectively to the corresponding chiral *anti-Markovnikov* products in good yields (76–82%) and enantioselectivities (80–85% *ee*). Another closely related cobalt catalyst **19** was used by these authors for the asymmetric *anti-Markovnikov* hydroboration of challenging sterically hindered styrenes [147]. When this catalyst was employed in the presence of NaBH(sBu)<sub>3</sub>, the hydroboration with HBPin led to the corresponding products in moderate to high yields (47–86%) and enantioslectivities (57–95% *ee*) (Scheme 10.22a). Furthermore, the authors discovered that by using another cobalt catalyst, *in situ* generated from CoCl<sub>2</sub> and chiral oxazoline aminopyridine ligand **20** under the same reaction conditions, the process led to products exhibiting the opposite absolute configuration. These products were obtained in slightly lower yields (35–81%) and moderate to high enantioselectivities (65–95% *ee*) (Scheme 10.22b).

In 1995, the group of *Mukaiyama* reported the first enantioselective borohydride 1,2-reduction of ketones catalysed by chiral cobalt complexes [41]. Although aryl ketones and sterically hindered aliphatic ketones were successfully reduced to afford the corresponding alcohols with enantioselectivities of up to 99% *ee*, the chiral ligands used were limited in the semi-corrin structure for a long time. However in 2015, *Lu* demonstrated that a cobalt complex derived from a chiral iminopyridine oxazoline ligand could promote highly enantioselective hydroboration of aryl ketones with HBPin under mild conditions [148]. Indeed, the reduction of a range of aryl ketones with NaBH<sub>3</sub>Et as reductant led to the corresponding chiral alcohols in good to quantitative yields (71–99%) and moderate to excellent enantioselectivities (63–99% *ee*).



Scheme 10.22 Hydroborations of sterically hindered styrenes.

### 10.2.5 Cross-coupling Reactions

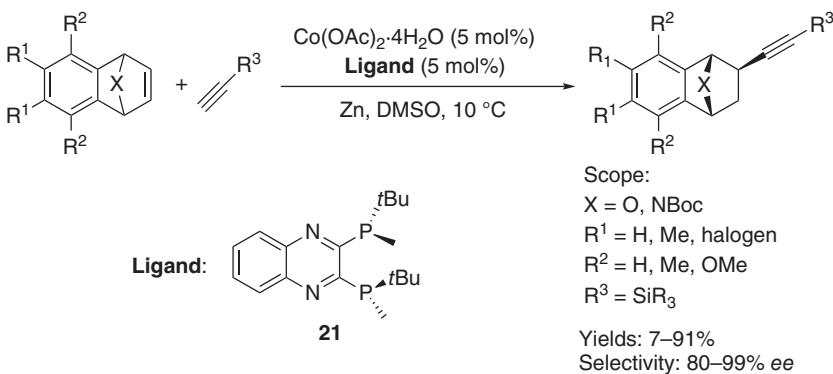
Metal-catalysed coupling reactions represent efficient tools for the elaboration of carbon–carbon bonds [149]. In particular, the asymmetric metal-catalysed reductive coupling of alkynes with various types of  $\pi$ -components, such as aldehydes, ketones, imines, and epoxides, constitutes a powerful methodology for the highly regio- and enantioselective synthesis of substituted alkenes. However, the asymmetric version of the reductive coupling of alkynes with alkenes still remains little explored. A rare example was reported in 2011 by Cheng with an enantioselective synthesis of  $\beta$ -substituted cyclic ketones through cobalt-catalysed asymmetric reductive coupling of alkynes with cyclic enones [150]. The process was promoted by a chiral cobalt complex *in situ* generated from  $\text{CoI}_2$  and (*R,R*)-BINAP, leading regioselectively in the presence of zinc as the reducing agent to the corresponding chiral  $\beta$ -alkenyl cyclic ketones in good yields (58–83%) and enantioselectivities of up to 96% *ee*, as shown in Scheme 10.23. The scope of the reaction was found to be wide with



Scheme 10.23 Reductive coupling of alkynes with cyclic enones.

comparable results for symmetrical as well as unsymmetrical alkynes, including electron-deficient ones, but it was not compatible for terminal alkynes.

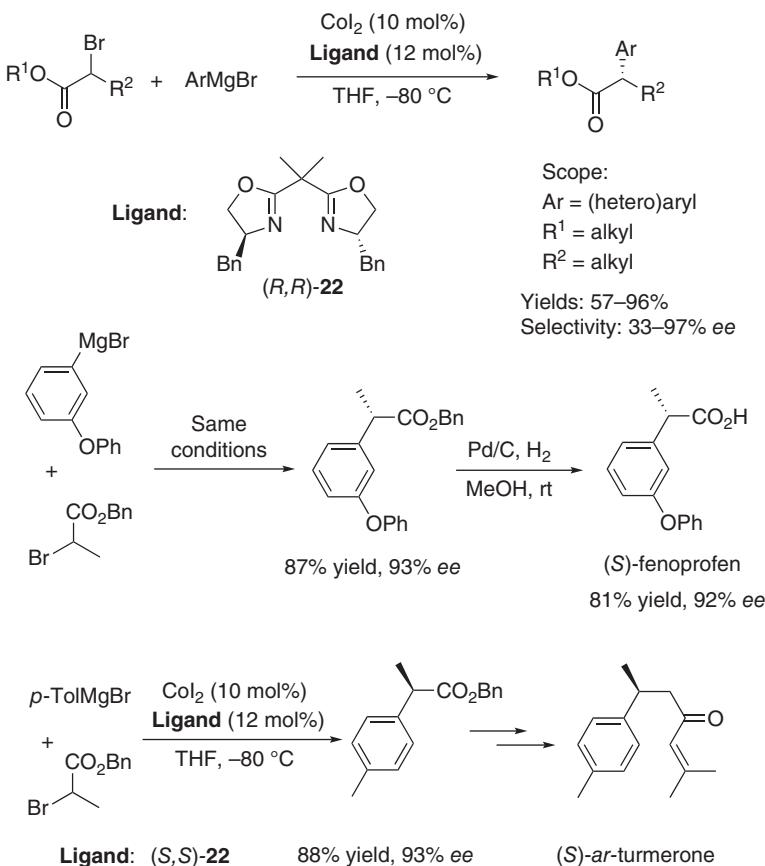
Later in 2012, *Hayashi* described the catalytic asymmetric addition of terminal alkynes, such as silylacetylenes, to oxa- and azabenzonorbornadienes, which afforded the corresponding chiral 1,2,3,4-tetrahydro-2-alkynyl-1,4-epoxy(aza)naphthalenes (Scheme 10.24) [151]. Among a series of chiral ligands, including (*S,S*)-Chiraphos, (*S,S*)-BDPP, (*R,R*)-BINAP, (*R,R*)-Dipamp, and (*S,S*)-Me-Duphos, ligand (*R,R*)-QuinoxP\* **21** was selected as the most efficient to provide excellent enantioselectivities of up to 99% ee, in combination with generally high yields of up to 91%, as shown in Scheme 10.24.



Scheme 10.24 Coupling of alkynes with oxa- and azabenzonorbornadienes.

Among other metal-catalysed coupling reactions is the catalytic cross-coupling reaction of *Grignard* reagents with organic electrophiles also called the *Kumada* coupling [143b]. In spite of recent improvements in this area based on the use of more active catalyst systems derived from nickel, palladium, cobalt, copper, and iron, very few enantioselective versions allowed chiral products to be achieved in useful levels of enantioselectivity. It is only in 2014 that the first highly enantioselective cobalt-catalysed *Kumada* cross-coupling reaction was reported by *Zhong* and *Bian* [152]. The process occurred between  $\alpha$ -bromo esters and aryl *Grignard* reagents in the presence of a combination of  $\text{CoI}_2$  and bisoxazoline **22**, affording a wide variety of chiral  $\alpha$ -arylalkanoic esters in moderate to excellent yields

(57–96%) and enantioselectivities (33–97% ee), as illustrated in Scheme 10.25. The synthetic utility of this novel procedure was shown by its application to the total synthesis of nonsteroidal anti-inflammatory drugs, such as (*S*)-fenoprofen and (*S*)-*ar*-turmerone, the latter by using (*S,S*)-22 as ligand.



**Scheme 10.25** Kumada cross-coupling reactions of  $\alpha$ -bromo esters with aryl Grignard reagents and synthesis of (*S*)-fenoprofen and (*S*)-*ar*-turmerone.

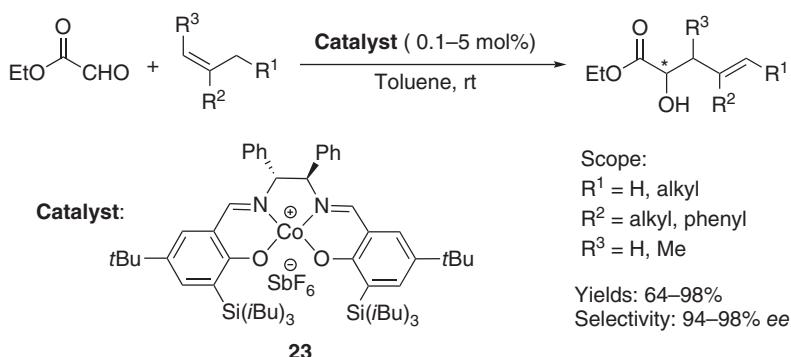
Later in 2016, this methodology was also applied by *Bian* to develop an efficient and concise synthesis of two naturally occurring and biologically active products, such as (*R*)-*ar*-curcumene and (*R*)-4,7-dimethyl-1-tetralone [153]. Indeed, the key step of the synthesis was the cobalt-catalysed Kumada cross-coupling of an  $\alpha$ -bromo ester with *p*-tolylmagnesium bromide performed in the presence of the same chiral ligand 22 under similar reaction conditions, leading to the corresponding chiral benzyl ester in both high yield (88%) and enantioselectivity (92% ee). The same year, *Zhong* described the synthesis of novel chiral cyclopropane-based bisoxazolines to be investigated as chiral ligands in these reactions, which were performed with good to high yields (79–93%) and moderate to good enantioselectivities (56–84% ee) [154]. To demonstrate

the utility of this methodology, the anti-inflammatory drug (*S*)-ibuprofen was prepared with 98% *ee*.

### 10.2.6 Miscellaneous Reactions

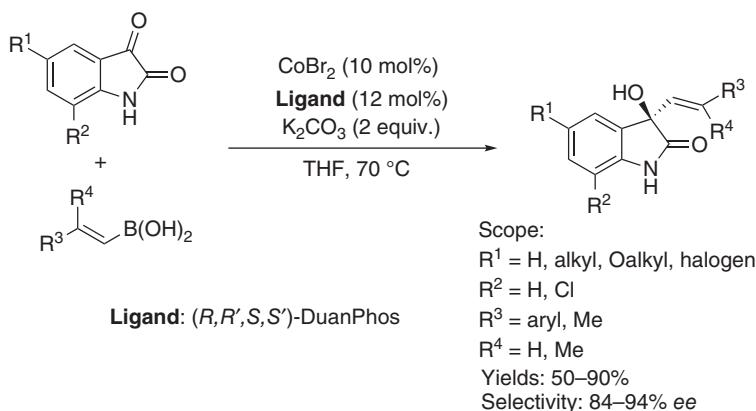
In 2003, a chiral cobalt(II) salen complex was applied by *Jurczak* to catalyse a rare high-pressure *Friedel–Crafts* alkylation between 2-methylfuran with alkyl glyoxylates to afford the corresponding chiral furfuryl alcohols in moderate yields (47–50%) and enantioselectivities ( $\leq 76\%$  *ee*) [155]. In another context, cobalt-catalysed kinetic resolutions of secondary alcohols with molecular oxygen have been developed by *Yamada* by employing other chiral cobalt(II) salen complexes [156]. This type of chiral cobalt catalysts were also applied by *Tokunaga* to the hydrolysis of *cis*-2-*tert*-butylcyclohexyl vinyl ether into the corresponding ketone evolving through kinetic resolution [157]. *North* reported the synthesis of novel  $C_1$ -symmetrical salen ligands, which were further investigated as chiral cobalt ligands in several asymmetric reactions under phase-transfer conditions including asymmetric alkylation of alanine derivative with benzylbromide that was achieved with both good enantioselectivity (80% *ee*) and yield (83%) [158]. Chiral fluorinated organic compounds represent important materials in the field of medicinal chemistry. Recently, several groups have shown that chiral catalysts of various metals, such as titanium, ruthenium, palladium, copper, nickel, or magnesium could promote highly enantioselective  $\alpha$ -fluorination of  $\beta$ -ketoesters. Despite these pioneering studies of enantioselective fluorinations, the development of a new catalyst system was still required. In this context, *Itoh* demonstrated the cobalt-catalysed asymmetric  $\alpha$ -fluorination of cyclic  $\beta$ -ketoesters with *N*-fluorobenzenesulfonimide, in 2010 [159]. This process was promoted by a chiral cobalt complex prepared from  $Co(acac)_2$  and *Jacobsen's* (*R,R*)-salen ligand, leading to the corresponding  $\alpha$ -fluorinated products in moderate yields (65–75%) and enantioselectivities of up to 90% *ee*. On the other hand, the enantioselective carbonyl-ene reaction promoted by a *Lewis* acid is a direct route to optically active homoallylic alcohols, not requiring any pretreatment of carbonyl compounds such as enolisation. In 2001, chiral cationic cobalt(III) salen complexes were investigated by *Yamada* as promoters for the enantioselective carbonyl-ene reaction of glyoxal derivatives with a variety of alkenes [160]. This reaction afforded the corresponding homoallylic alcohols in moderate to quantitative yields (60–99%) and high enantioselectivities of up to 96%. In 2007, *Rawal* reinvestigated this type of reactions by using a sterically hindered catalyst **23** [161]. This complex catalysed the reactions of various 1,1-disubstituted as well as trisubstituted alkenes with ethyl glyoxylate at catalyst loadings as low as 0.1 mol%, providing the corresponding homoallylic alcohols in moderate to quantitative yields (64–98%) combined with both high diastereoisomer (92% *de*) and enantioselectivities (94–98% *ee*), as shown in Scheme 10.26.

Other chiral cobalt salen complexes were also successfully applied to other types of transformations, such as asymmetric cyanosilylations [162]. Another type of chiral cobalt catalysts, such as those derived from chiral diphosphines, has allowed the first enantioselective cobalt-catalysed addition reaction of various phenylboronic acids to substituted aldehydes to be achieved by *Cheng*,



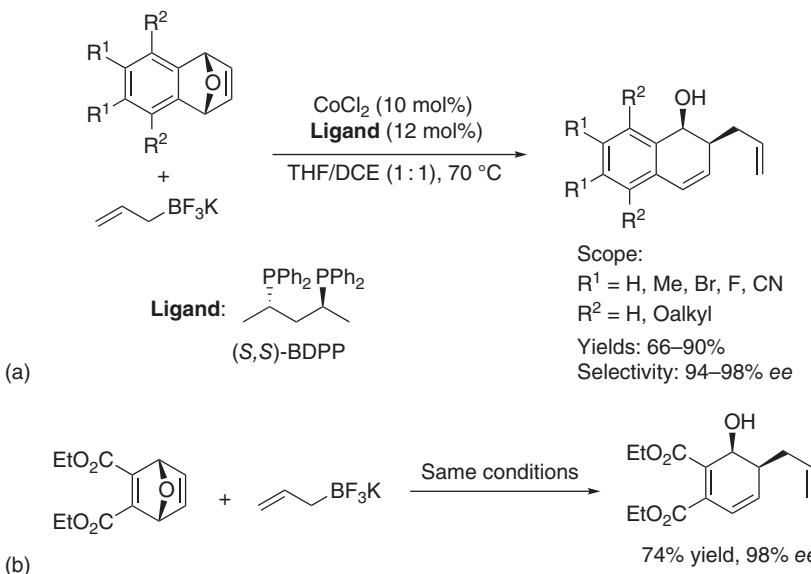
Scheme 10.26 Carbonyl-ene reaction of di- and trisubstituted alkenes with ethyl glyoxylate.

providing the corresponding biologically useful substituted diarylmethanols in both high yields (82–99%) and enantioselectivities (86–99% ee) [163]. Moreover, the use of (*S,S*)-BDPP ligand was later applied as cobalt ligand by *Zhao* to promote the first cobalt-catalysed enantioselective vinylation of activated carbonyl compounds such as  $\alpha$ -ketoesters [164]. Indeed, when the addition of vinyl boronic acids to  $\alpha$ -ketoesters was promoted by a combination of (*S,S*)-BDPP with  $\text{CoI}_2$  in the presence of  $\text{K}_2\text{CO}_3$  as base, it afforded the corresponding chiral tertiary allylic  $\alpha$ -hydroxy esters in low to moderate yields (30–75%) and good to high enantioselectivities (78–92% ee). Furthermore, (*R,R',S,S'*)-DuanPhos was used by the same authors in combination with  $\text{CoBr}_2$  as catalytic system to promote the first enantioselective cobalt-catalysed vinylation of isatins under the same reaction conditions [164]. As shown in Scheme 10.27, the addition of vinyl boronic acids to variously substituted isatins led to the corresponding tertiary alcohols in moderate to high yields (50–90%) and high enantioselectivities (84–94% ee). The scope of this methodology was also extended to the first asymmetric cobalt-catalysed vinylation of imines, affording a range of enantiopure cyclic allylic amines (98–99% ee) in moderate to good yields (52–85%) [164].



Scheme 10.27 Addition of vinyl boronic acids to isatins.

In 2015, the same authors also reported the first enantioselective cobalt-catalysed allylation of heterobicyclic alkenes, employing potassium allyltri-fluoroborate as allylating agent [165]. Among a series of chiral bisphosphines investigated as ligands, (*S,S*)-BDPP was found the optimal one when combined with  $\text{CoCl}_2$ . The reaction of various heterobicyclic alkenes with potassium allyltri-fluoroborate led to the corresponding ring-opened chiral products in moderate to quantitative yields (66–90%) and uniformly excellent enantioselectivities (94–98% *ee*) (Scheme 10.28a). The extension of the scope of the reaction to a less reactive non-benzofused substrate proved to be successful since the corresponding product was obtained in 74% yield and 98% *ee* (Scheme 10.28b).

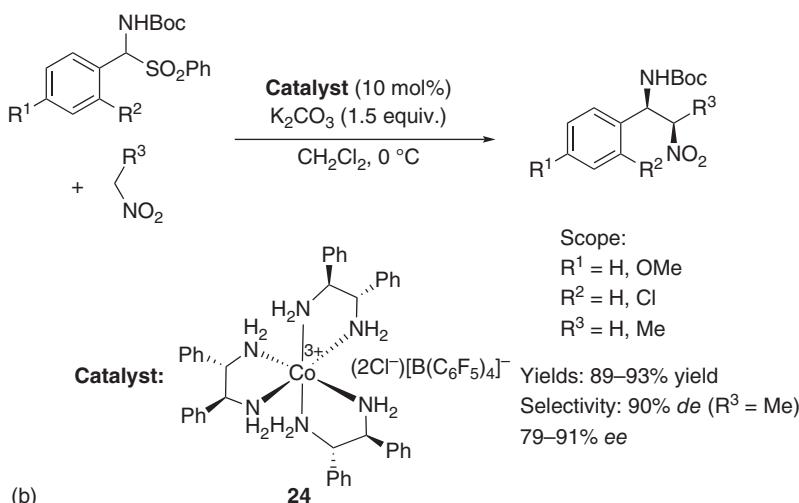
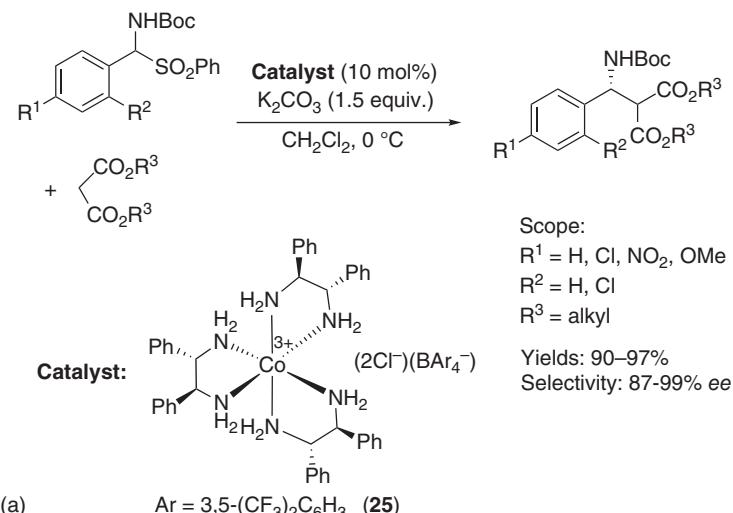


**Scheme 10.28** Allylations of heterobicyclic alkenes.

Chiral phosphoramidite cobalt complexes have also been successfully applied to promote different type of asymmetric transformations, including the first asymmetric version of the *Nicholas* reaction reported in 2008 by *Kann* [166]. Indeed the treatment of propargylic alcohols with the cobalt carbonyl complex derived from a chiral pyrrolidine-substituted phosphoramidite ligand, followed by reaction with various nucleophiles in the presence of a *Lewis* acid such as  $\text{BF}_3\cdot\text{OEt}_2$  afforded, after decomplexation by treatment with cerium ammonium nitrate, the corresponding *Nicholas* products in low to high yields (30–90%) and enantioselectivities (12–90% *ee*). This type of ligands was also used in 2015 by *Yoshikai* and *Lee* to promote a cobalt-catalysed enantioselective C2-alkylation of Boc-protected indoles with aryl alkenes, allowing chiral C2-alkylated indoles to be achieved in low to high yields (16–88%) and moderate to good enantioselectivities (68–87% *ee*) [167].

In 2016, *Gladysz* reported the use of *Werner* complex **24** based on chiral trication  $\Delta\text{-}[\text{Co}((S,S)\text{-dpen})_3]^{3+}$  (*dpen* = 1,2-diphenylethylenediamine) to promote

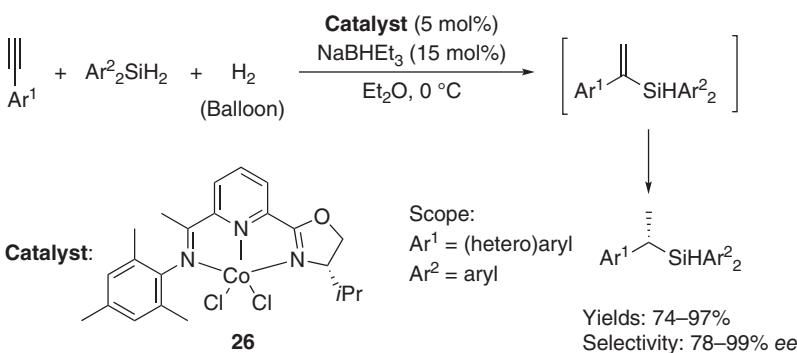
enantioselective  $\alpha$ -aminations of 1,3-dicarbonyl compounds and related substrates with di-*tert*-butyl azodicarboxylate, thus affording chiral tertiary amines in high to quantitative yields (88–98%) and moderate to excellent enantioselectivities (72–99% *ee*) [168]. Later in 2017, catalyst **24** and related Werner complex **25** were applied by the same authors to promote enantioselective nucleophilic additions to imines *in situ* generated from  $\alpha$ -amido sulfones [169]. Cobalt catalyst **25** promoted in the presence of  $K_2CO_3$  as base the addition of various dialkyl malonates to  $\alpha$ -amido sulfones to give the corresponding chiral products in both high yields (90–97%) and enantioselectivities (87–99% *ee*) (Scheme 10.29a). Furthermore, the addition of nitroalkanes to the same  $\alpha$ -amido



**Scheme 10.29** Additions of malonates and nitroalkanes to imines derived from  $\alpha$ -amido sulfones.

sulfones was catalysed under the same reaction conditions by Werner complex **24** to afford the corresponding chiral nitroalkanes in high yields (89–93%) and enantioselectivities (79–91% ee) (Scheme 10.29b).

Other types of cobalt catalysts, including chiral octahedral cobalt complexes, such as  $(-)$ -<sub>546</sub>-K[Co(edta) $\cdot$ 2H<sub>2</sub>O], were found capable to promote the highly enantioselective addition of diisopropylzinc to pyrimidine-5-carbaldehyde, affording the corresponding pyrimidyl alkanol in quantitative yield and enantioselectivity of up to 94% ee [170]. In 2010, the use of another type of cobalt complex bearing *Schiff* base ligands, allowed the kinetic resolution of  $\alpha$ -hydroxy ketones and  $\alpha$ -hydroxy esters to be achieved in high selectivity factors of up to 47 and 31.9, respectively [171]. In 2017, an asymmetric three-component domino hydrosilylation/hydrogenation reaction of terminal aryl alkynes with Ar<sub>2</sub>SiH<sub>2</sub> and H<sub>2</sub> was reported by Lu [172]. This one-pot process was promoted by chiral cobalt–pyridine–oxazoline catalyst **26** in the presence of NaBH<sub>Et</sub><sub>3</sub> as reductant, providing the corresponding chiral silanes in moderate to excellent yields (74–97%) and enantioselectivities (78–99% ee), as shown in Scheme 10.30.



**Scheme 10.30** Three-component domino hydrosilylation/hydrogenation reaction of terminal aryl alkynes.

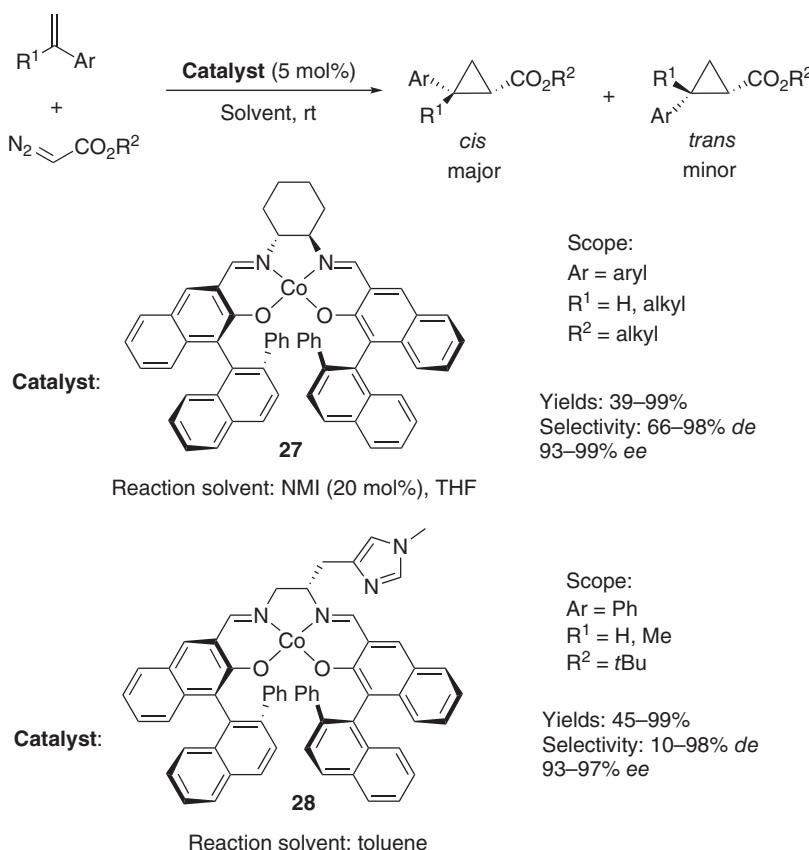
## 10.3 Enantioselective Cobalt-Catalysed Cyclisation Reactions

### 10.3.1 [2+1] Cycloadditions

Cycloaddition reactions constitute important tools for the assembly of complex molecular structures [6a, 173]. Among the metals used to catalyse cycloadditions, cobalt has been found effective to promote the formation of carbo- and heterocycles of different ring sizes enantioselectively. In particular, chemists have always been fascinated by the strained structure of the cyclopropane subunit [174]. Indeed, not only chiral cyclopropanes but also their heterocyclic counterparts, such as aziridines and epoxides, represent useful building blocks in synthesis as well as important synthetic targets. The interest towards synthetic methodologies for their preparation has increased over the last decade

[175–177], dictated either by the biological activities displayed by many naturally occurring products bearing a three-membered unit or by being useful precursors for accessing more complex interesting molecules [178]. The cyclopropanation of olefins based on the transition metal-catalysed decomposition of diazoalkanes is one of the most extensively studied transformations in organic chemistry [179]. One of the first successes in enantioselective intermolecular cobalt-catalysed cyclopropanation reactions was described by *Nakamura* in 1978 by using a chiral dioximatocobalt(II) complex derived from camphor, which allowed enantioselectivities of up to 88% *ee* to be achieved [180]. Later, *Katsuki* introduced novel chiral cobalt(III) salen complexes to induce *trans*-selective cyclopropanation reactions with enantioselectivities of 92–96% *ee* along with high yields of up to 87% and diastereoselectivities of up to 94% *de* [181]. In 1999, *Yamada* applied chiral 3-oxobutylideneaminatocobalt(II) complexes [182] to the same *trans*-selective reaction of monoaryl-substituted alkenes with *tert*-butyl diazoacetate [183]. The presence of a catalytic amount of NMI as additive was found to increase both the rate of the reaction and the enantioselectivity. The process was found, however, limited to aryl-substituted alkenes, leading to the corresponding chiral *trans*-cyclopropanes in uniformly high yields (85–99%), generally good *trans*-diastereoselectivities (64–82% *de*) combined with excellent enantioselectivities (92–96% *ee*). Later in 2005, *Gao* applied dinuclear cobalt(II) salen complexes to the cyclopropanation of styrene with ethyl diazoacetate, providing the corresponding *trans*-cyclopropane as the major product with a moderate diastereoselectivity of 48% *de*, a high yield of 92%, and good enantioselectivities of up to 94% *ee* [184]. In addition to cobalt salen complexes, cobalt(II) porphyrin complexes [185] have been proved by *Zhang* to be general and efficient catalysts for diastereo- and enantioselective *trans*-cyclopropanation of alkenes [186]. Indeed, cobalt(II)  $D_2$ -symmetric porphyrins derived from chiral cyclopropanecarboxamides were successfully investigated in the cyclopropanation of styrene with ethyl and *tert*-butyl diazoacetates, providing the corresponding *trans*-cycloadducts in high yields (up to 88%), diastereo- (up to 98% *de*) and enantioselectivities (up to 95% *ee*) [187]. In 2007, the scope of this methodology was extended to a broad range of styrene derivatives bearing various substituents on the phenyl ring, such as methoxy, methyl, *tert*-butyl, bromide, chloride, fluoride, acetate, and trifluoromethyl groups, providing the corresponding cyclopropanes in good yields, combined with diastereo- and enantioselectivities of up to 100% *de* and 98% *ee*, respectively [188]. Later in 2008, other chiral cobalt(II) bis(binaphthyl) porphyrin complexes were developed by *Gallo* to promote the cyclopropanation of mono- and disubstituted alkenes with ethyl diazoacetate, giving the corresponding *trans*-cyclopropanes in good yields albeit with low to moderate enantioselectivities (<71% *ee*) [189]. The same year, the synthesis of a novel type of highly modular and readily accessible pincer ligands, such as chiral bis(pyridylimino)isoindoles, was described by *Gade* to be investigated in cobalt-catalysed intermolecular cyclisations of aromatic alkenes with ethyl diazoacetate [190]. Their versatility as efficient stereodirecting ligands was demonstrated by the observation of high enantioselectivities of up to 94% *ee* for *trans*-cyclopropanes arising from the corresponding monosubstituted alkenes. Earlier, *Katsuki* succeeded in designing rare *cis*-selective catalysts

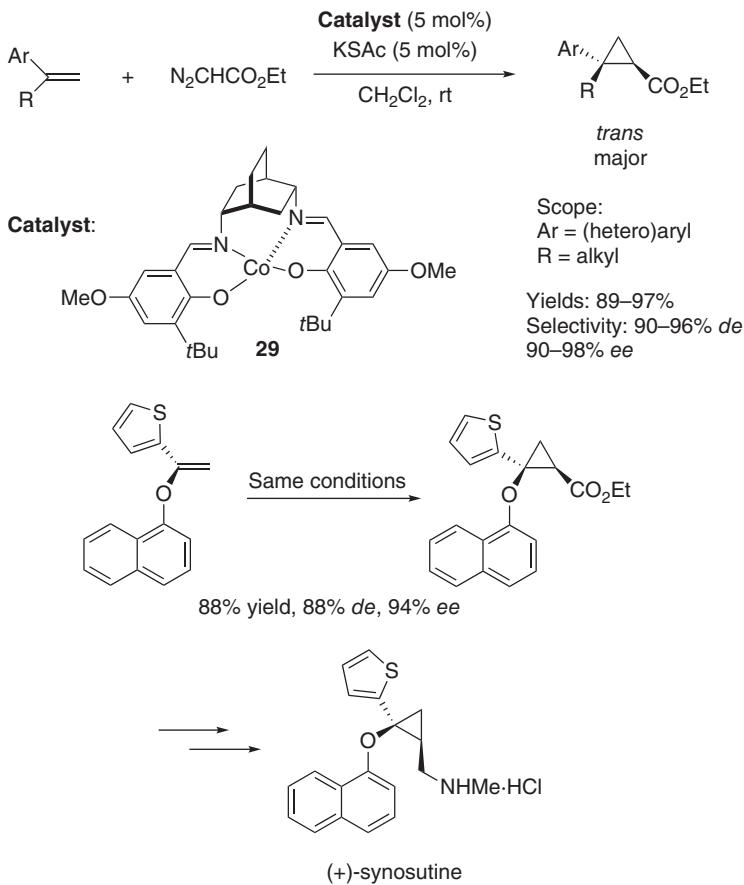
based on the salen scaffold, such as cobalt complex **27** [6c, 191]. The reaction of various aromatic mono- and disubstituted alkenes with ethyl and *tert*-butyl diazoacetates proceeded smoothly in the presence of NMI as additive, providing the corresponding *cis*-cyclopropanes in good to quantitative yields, good to excellent diastereoselectivities of up to 98% *de*, and excellent enantioselectivities of up to 99% *ee*. In 2007, the same authors investigated other cobalt(II) complexes having chiral pentadentate salen ligands bearing imidazole or pyridine moieties as the fifth coordinating group in the same cyclopropanation reaction [192]. Catalyst **28** bearing an imidazole was proved to be the optimal one to promote high *cis*-diastereoselectivity of 78–98% *de* in the reaction of monosubstituted aromatic alkenes with *tert*-butyl diazoacetate to give the corresponding *cis*-cyclopropanes, as shown in Scheme 10.31. Moreover, these products were obtained in excellent yields of 93% to quantitative, combined with enantioselectivities of 93–96% *ee*.



Scheme 10.31 *Cis*-selective cyclopropanation of aromatic alkenes.

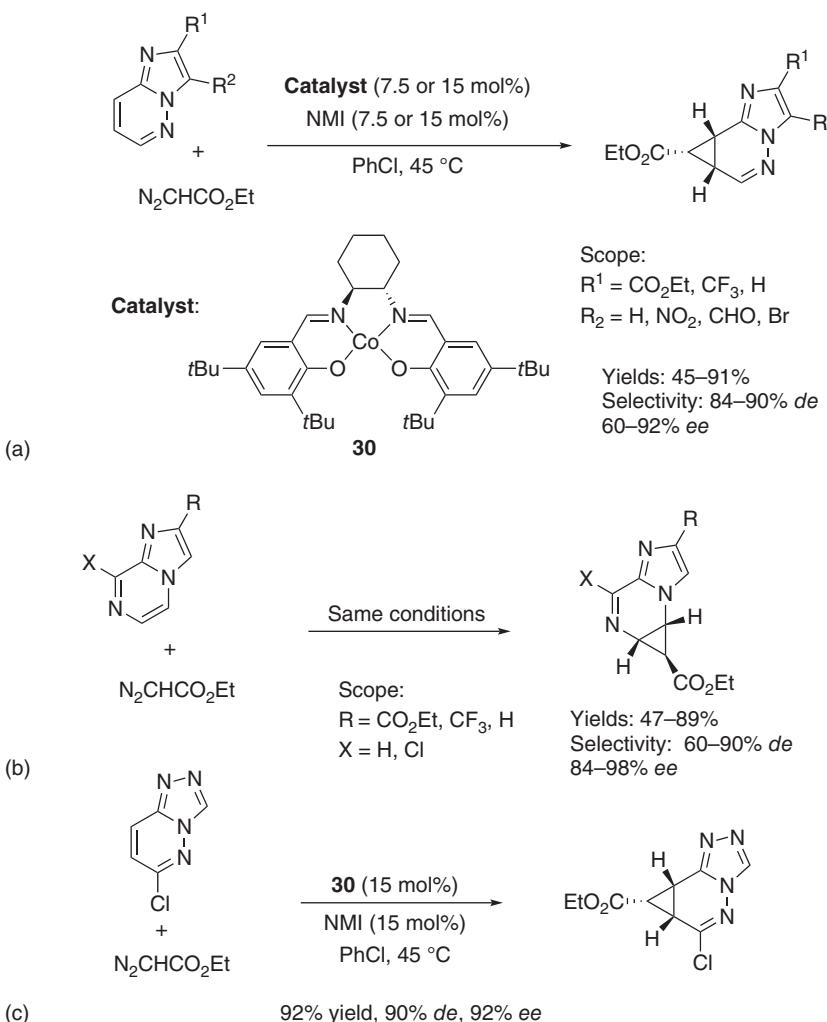
In 2007, *Zhang* investigated the asymmetric cyclopropanation of more challenging substrates, such as electron-deficient non-styrenic olefins, with

ethyl and *tert*-butyl diazoacetates using a cobalt(II) porphyrin catalyst [193]. Good to high yields (66–94%), high *trans*-diastereoselectivities of up to 98% *de*, and enantioselectivities of up to 95% *ee* were obtained for a range of formed *trans*-cyclopropanated products. In 2008, the same authors applied the same catalyst to the cyclopropanation of styrenes with  $\alpha$ -nitrodiazoacetates to give the corresponding chiral *cis*-cyclopropane  $\alpha$ -nitroesters in moderate to excellent yields (51–98%), good to almost complete *cis*-diastereoselectivities (80–98% *de*), and good to high enantioselectivities (82–95% *ee*) [194]. In 2014, novel  $C_2$ -symmetric cobalt(II) salen complex **29** was used by White and Shaw to promote the enantioselective cyclopropanation of a range of 1,1-disubstituted alkenes with ethyl diazoacetate (Scheme 10.32) [195]. The process afforded the corresponding chiral trisubstituted *trans*-cyclopropanes as almost single diastereomers (90–96% *de*) in uniformly high yields (89–97%) and enantioselectivities (90–98% *ee*). This methodology was applied as key step in a short and efficient synthesis of the dual serotonin–epinephrine reuptake inhibitor (+)-synosutine, as illustrated in Scheme 10.32.



**Scheme 10.32** *Trans*-selective cyclopropanations of 1,1-disubstituted alkenes and synthesis of (+)-synosutine.

In 2016, the dearomatisation of a series of electron-deficient nitrogen heterocycles was reported for the first time by *Chen* on the basis of enantioselective cobalt-catalysed cyclopropanations [196]. The reactions of different types of fused heteroaromatic substrates were promoted by cobalt(II) salen complex **30** in the presence of NMI as additive. For example, the reaction of various imidazopyrazine derivatives with ethyl diazoacetate led to the corresponding tricyclic chiral products exhibiting the *cis*-configuration as major diastereomers (84–90% *de*). These chiral polynitrogenated heterocycles were obtained in moderate to high yields (45–91%) and enantioselectivities (60–92% *ee*) (Scheme 10.33a). The scope of the process was extended to imidazopyridazines, which led by reaction with ethyl diazoacetate to the corresponding *cis*-heterocyclic cyclopropanes



Scheme 10.33 Cyclopropanations of heteroaromatic substrates.

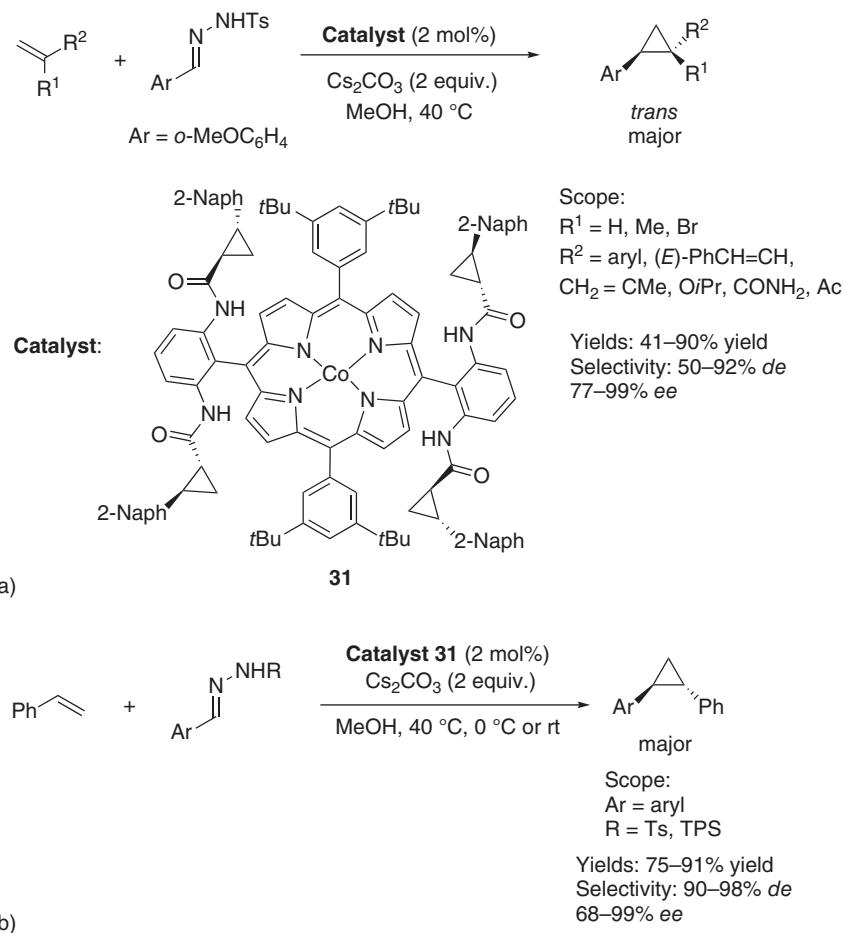
as major diastereomers in moderate yields (47–89%) and diastereoselectivities (60–90% *de*) along with high enantioselectivities (84–98% *ee*) (Scheme 10.33b). Other fused heteroaromatic substrates were compatible to the reaction conditions, such as 6-chloro-[1,2,4]triazolo[4,3-*b*]pyridazine, which provided the desired product in 92% yield, with both high *cis*-diastereoselectivity (90% *de*) and enantioselectivity (92% *ee*) (Scheme 10.33c).

In 2017, *Zhang* employed chiral amidoporphyrin cobalt complexes to develop the first asymmetric cyclopropanation of aromatic and aliphatic alkenes with  $\alpha$ -formyldiazoacetates to give the corresponding synthetically useful 1,1-cyclopropaneformylesters in moderate to quantitative yields (61–99%), good to excellent enantioselectivities (77–99% *ee*), and generally high *trans*-diastereoselectivities of up to 98% *de* [197]. Earlier in 2009, the same authors also reported the asymmetric cyclopropanation of aliphatic and aromatic alkenes with another unusual diazo reagent such as succinimidyl diazoacetate [198]. The reaction was catalysed by the same cobalt(II)  $D_2$ -symmetric chiral cyclopropyl porphyrin, providing a range of chiral cyclopropane succinimidyl esters in moderate to high yields (30–90%) and remarkable *trans*-diastereo- and enantioselectivities of 98% *de* and 89–98% *ee*, respectively. Always in the context of asymmetric cobalt-catalysed cyclopropanations of alkenes with unusual diazo reagents, these authors developed a closely related methodology for the *trans*-cyclopropanation of alkenes with  $\alpha$ -cyanodiazoacetates, such as *tert*-butyl  $\alpha$ -cyanodiazoacetate, providing the corresponding densely functionalised chiral cyclopropanes, possessing a myriad of potential synthetic and biological applications, with enantioselectivities of up to 99% *ee* and almost complete *trans*-diastereoselectivity of 98% *de* [199]. As another extension of this methodology, these authors developed the asymmetric cyclopropenation of terminal aromatic and related conjugated alkynes bearing varied steric and electronic properties with various acceptor/acceptor-substituted diazo compounds, such as  $\alpha$ -cyanodiazoacetates and  $\alpha$ -cyanodiazoacetamides, which provided the corresponding chiral trisubstituted cyclopropenes as single diastereomers in good to high yields (42–97%), and high enantiocontrol of the all-carbon quaternary stereogenic centres with enantioselectivities of 80–98% *ee* [200]. Under these reaction conditions, a remarkable degree of tolerance of this catalyst towards various functionalities, including CHO, OH, and NH<sub>2</sub> groups, was demonstrated. In addition, the same authors have successfully developed cobalt-catalysed asymmetric cyclopropanations of alkenes with a range of other unusual diazo compounds, such as diazosulfones, by using a chiral porphyrin ligand [201]. The corresponding chiral cyclopropyl sulfones were obtained in good to excellent yields of up to 99%, excellent *trans*-diastereoselectivities of 98% *de*, and general excellent enantioselectivities of 90–97% *ee*. There is still scarcity of approaches for the enantioselective generation of trifluoromethyl-substituted cyclopropanes that constitute important building blocks for drug discovery. In this context, *Carreira* have developed a novel enantioselective cobalt-catalysed route to these chiral products based on cyclopropanation of styrenes with *in situ*-generated trifluoromethyl diazomethane [202]. After screening another type of cobalt catalysts derived from (*S,S*)-1,2-cyclohexyldiamine and 2-dihydroxy-3-*O*-*iso*-butyl-5,6-dichlorobenzaldehyde, these authors

selected a novel catalyst bearing a combination of electron-donating and electron-withdrawing substituents on benzaldehydes as the optimal catalyst. The cyclopropanation of a range of styrenes with  $\text{CF}_3\text{CH}_2\text{NH}_3\text{Cl}$  as cyclopropanation reagent afforded the corresponding chiral *trans*-disubstituted cyclopropanes in moderate to high yields (49–95%), high diastereoselectivities of 84–98% *de*, and enantioselectivities of 84–94% *ee*. The scope of this methodology was extended to 1,1-disubstituted styrenes, which furnished the corresponding trisubstituted cyclopropanes in enantioselectivities of 87–97% *ee*, albeit in generally lower diastereoselectivities (34–80% *de*). Donor-substituted diazo reagents, *in situ* generated from sulfonyl hydrazones in the presence of a base such as  $\text{Cs}_2\text{CO}_3$ , were shown for the first time by Zhang to be suitable radical precursors for enantioselective cobalt-catalysed cyclopropanation of alkenes [203]. Chiral amidoporphyrin cobalt complex **31** was found efficient to activate N-tosyl hydrazone for asymmetric radical *trans*-cyclopropanation of a broad range of aromatic and aliphatic alkenes, affording the corresponding chiral cyclopropanes in moderate to high yields (41–90%), *trans*-diastereoselectivities (50–92% *de*), and enantioselectivities (77–99% *ee*) (Scheme 10.34a). This catalytic system was also applied to the reaction between various arylsulfonyl hydrazones and styrene, leading to the corresponding products in good to high yields (75–91%), uniformly excellent diastereoselectivities (90–98% *de*), and moderate to excellent enantioselectivities (68–99% *ee*) (Scheme 10.34b).

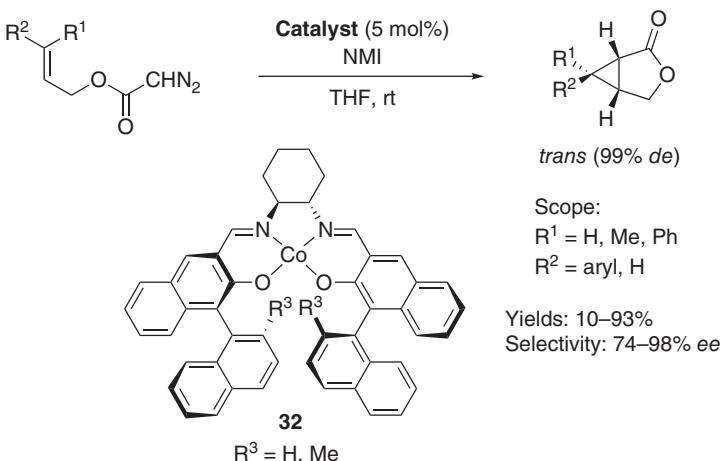
Intramolecular versions of enantioselective cobalt-catalysed cyclopropanation of alkenes have been recently developed by several groups. As an example, Katsumuki designed a series of novel chiral cobalt(II) salen catalysts that proved to be very efficient for the intramolecular cyclopropanation of various (*E*)-2-alkenyl  $\alpha$ -diazoacetates in the presence of NMI [204]. As shown in Scheme 10.35, the cyclopropanation of (*E*)-(aryl)allyl diazoacetates into the corresponding chiral bicyclic products proceeded in good to excellent enantioselectivities of up to 98% *ee* by using catalysts **32**, while lower enantioselectivities (74% *ee*) were obtained in the case of (*Z*)-(aryl)allyl diazoacetates.

Furthermore, a novel cobalt(II) catalyst derived from a chiral cyclopropanecarboxamide containing two contiguous stereocentres was designed by Zhang and subsequently investigated as promotor of an original asymmetric intramolecular cyclopropanation of a range of  $\alpha$ -acceptor-substituted allylic diazoacetates [205]. This highly efficient novel methodology allowed for the first time the transformation of  $\alpha$ -acceptor-substituted diazoacetates into enantioenriched 3-oxabicyclo[3.1.0]hexan-2-one derivatives bearing three contiguous stereocentres with multiple functionalities in good to excellent yields of 73–99% combined with excellent *trans*-diastereoselectivities of up to 98% *de* and moderate to high enantioselectivities of 73–99% *ee*. In 2014, a chiral amidoporphyrin cobalt complex was also proven by these authors to be an effective catalyst for the asymmetric intramolecular cyclopropanation of allyl  $\alpha$ -diazoacetates [206]. In the presence of 4-(*N,N'*-dimethylamino)pyridine (DMAP) as an additive, a series of allyl  $\alpha$ -diazoacetates were converted into the corresponding chiral [3.1.0]bicyclic products as single *trans*-diastereomers (98% *de*) in moderate to excellent yields (62–95%) and moderate to good enantioselectivities (63–86% *ee*).

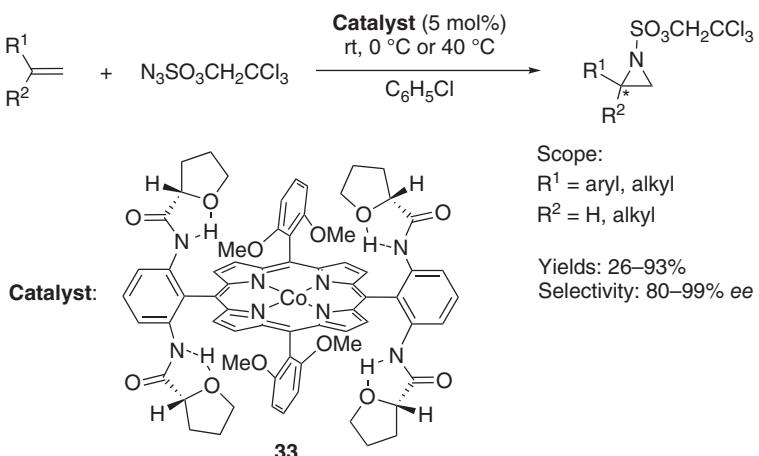


**Scheme 10.34** *Trans*-selective cyclopropanations of aromatic and aliphatic alkenes with sulfonyl hydrazones.

On the other hand, aziridines are among the most fascinating heterocyclic intermediates in organic synthesis [207], acting as precursors of many complex molecules including natural and biologically active products due to the high strain incorporated in their skeletons [208]. The last decade has witnessed tremendous activity in the area of discovering new methodologies for their synthesis and transformations [209, 210]. *Zhang* showed that cobalt was able to promote the asymmetric aziridination of olefins using diphenylphosphoryl azide as the nitrene source, affording the corresponding *N*-phosphorylated aziridines [211]. The reaction was performed in the presence of  $D_2$ -symmetric chiral porphyrins and was applied to a wide variety of styrenes, giving the corresponding enantioenriched aziridines in good yields combined with moderate enantioselectivities ( $\leq 71\% \text{ ee}$ ). Later in 2014, related chiral  $D_2$ -symmetric amidoporphyrin cobalt catalysts were applied by the same authors to promote the asymmetric aziridination of variously substituted styrenes with a phosphoryl

Scheme 10.35 *Trans*-selective intramolecular cyclopropanation of allylic  $\alpha$ -diazoacetates.

azide, leading to the corresponding chiral *N*-phosphorylaziridines in moderate to quantitative yields (64–99%) and low to good enantioselectivities (23–85% *ee*) [212]. Earlier in 2009, better enantioselectivities of up to 94% *ee* were reported by the same authors in the asymmetric aziridination of a range of aromatic as well as aliphatic monosubstituted alkenes with trichloroethoxysulfonyl azide by using cobalt(II) complexes with chiral rigid and polar porphyrin **33** [213]. The process provided the corresponding chiral aziridines in good to high yields (82–93%) and enantioselectivities (80–99% *ee*) in the case of monosubstituted aromatic alkenes as substrates, whereas monosubstituted aliphatic alkenes produced the corresponding aziridines in lower yields (26–42%) but with comparable high enantioselectivities (91–94% *ee*), as shown in Scheme 10.36. The scope of this methodology could be extended to aliphatic dienes, such



Scheme 10.36 Aziridination of alkenes with trichloroethoxysulfonyl azide.

as 2,3-dimethylbutadiene, which afforded the corresponding disubstituted aziridine in 53% yield and 87% *ee*. In 2017, a related chiral  $D_2$ -symmetric amido-porphyrin cobalt catalyst was applied by the same authors to develop the first enantioselective radical aziridination of allyl azidoformates [214]. The reaction led to the corresponding chiral aziridine/oxazolidinone-fused bicyclic products as single diastereomers (99% *de*) in excellent yields (90–99%) and moderate to excellent enantioselectivities (70–99% *ee*).

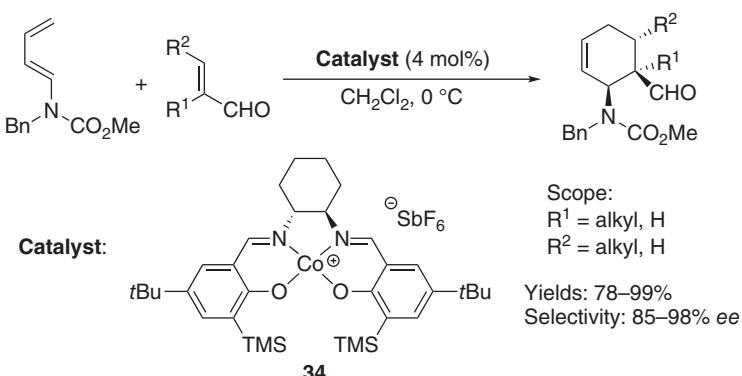
Along with aziridines, epoxides also constitute strained three-membered rings of wide importance as versatile synthetic intermediates in total synthesis of a number of important products [210, 215]. The epoxidation of alkenes is undoubtedly the most investigated and convenient approach to obtain epoxides [216] and especially its asymmetric version [217]. In 2015, *Belokon* described the use of a chiral positively charged cobalt complex to catalyse the asymmetric epoxidation of chalcones with  $H_2O_2$  under phase transfer conditions [218]. Indeed, treatment of a variety of chalcones with a 30% aqueous solution of  $H_2O_2$  in the presence of this cobalt catalyst and *tBuOK* as base yielded the corresponding chiral epoxides with moderate to complete conversions (50–99%) and moderate enantioselectivities (35–55% *ee*).

### 10.3.2 Miscellaneous Cycloadditions

#### 10.3.2.1 (Hetero)-Diels–Alder Cycloadditions

The *Diels–Alder* reaction is a versatile reaction for the stereospecific construction of six-membered rings. Its thermal uncatalysed versions sometimes required harsh reaction conditions to be achieved, and consequently a number of methods have been developed to overcome this obstacle, such as transition metal catalysis [219]. It must be noted that so far there are only few excellent works focussing on enantioselective cobalt-catalysed *Diels–Alder* cycloadditions. Among early examples, *Kanemasa* reported in 1998 the use of a cationic chiral aqua complex derived from a *trans*-chelating tridentate ligand, (*R,R*)-4,6-dibenzofurandyl-2,2'-bis-(4-phenyloxazoline) (DBFOX/Ph), and cobalt(II) perchlorate to promote the asymmetric *Diels–Alder* cycloaddition of cyclopentadiene with 3-acryloyl-2-oxazolidinone [220]. The corresponding cycloadduct was achieved in excellent yield of 97%, high *endo*-diastereoselectivity of 94% *de* and remarkable enantioselectivity of 99% *ee*. Later, *Rawal* designed highly efficient chiral cobalt(III) salen complexes, such as **34**, to promote the *Diels–Alder* cycloaddition between carbamate-substituted dienes and  $\alpha,\beta$ -unsaturated aldehydes (Scheme 10.37) [221]. The corresponding chiral *Diels–Alder* cycloadducts were obtained in both high yields (78–99%) and enantioselectivities (85–98% *ee*).

Many total syntheses of important natural products are based on asymmetric *Diels–Alder* reactions as key steps, among them that of antibiotic (–)-platencin. Indeed, this novel synthesis, reported by *Nicolaou* in 2009, included an enantioselective *Diels–Alder* cycloaddition of a functionalised diene with a dienophile catalysed by chiral cobalt(III) salen catalysts, which afforded the corresponding densely functionalised cycloadduct in both excellent yield (97%) and enantioselectivity (96% *ee*) [222]. Later in 2011, the same catalysts were

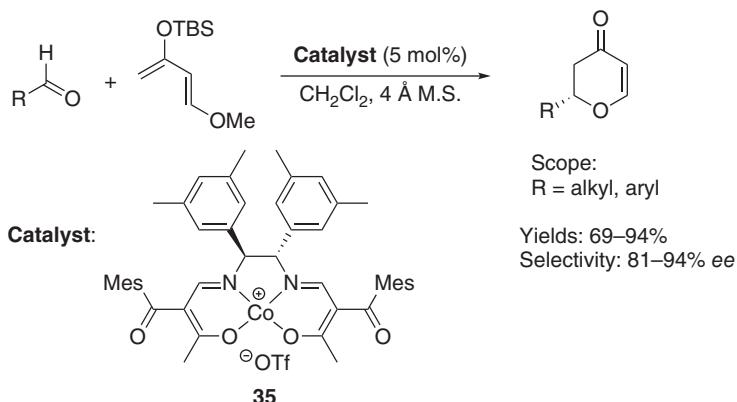


**Scheme 10.37** *Diels–Alder* reaction of a dienamine with  $\alpha,\beta$ -unsaturated aldehydes.

also employed by *Brimble* to promote an asymmetric *Diels–Alder* cycloaddition that afforded a chiral functionalised cyclohexene, which constituted a key intermediate in the asymmetric synthesis of a tetracyclic alkaloid methyllycaconitine analogue [223]. Furthermore, the asymmetric hetero-*Diels–Alder* reaction is one of the most efficient synthetic methodologies for the regio- and stereoselective construction of chiral six-membered heterocycles [224]. In 1998, *Wu* reported the enantioselective hetero-*Diels–Alder* cycloaddition of 1-(2-benzoyloxyethyl)-3-(*tert*-butyldimethylsilyl)oxy-1,3-butadiene with methyl glyoxylate catalysed by a chiral cobalt(II) salen catalyst, providing the corresponding cycloadduct in 75% yield with excellent *endo*:*exo* ratio of 99 : 1 albeit combined with a moderate enantioselectivity of 52% *ee* [225]. Later in 2004, the same catalyst was applied by *Jurczak* to induce the high-pressure (10–11 kbar) *Diels–Alder* cycloaddition between 1-methoxybuta-1,3-diene with *tert*-butyldimethylsilyloxyacetaldehyde to give the corresponding *cis*-cycloadduct in 52% yield with a *cis*-diastereoselectivity of 90% *de* and a high enantioselectivity of 94% *ee* [226]. Earlier, *Yamada* developed novel chiral cationic cobalt(III) triflate complexes, such as **35**, as effective catalysts for the enantioselective hetero-*Diels–Alder* cycloaddition of various aryl and alkyl aldehydes with 1-methoxy-[3-(*tert*-butyldimethylsilyl)oxy]-1,3-butadiene, leading to the corresponding chiral cycloadducts in good to high yields (69–94%) and high general enantioselectivities of 81–94% *ee* (Scheme 10.38) [227].

### 10.3.2.2 1,3-Dipolar Cycloadditions

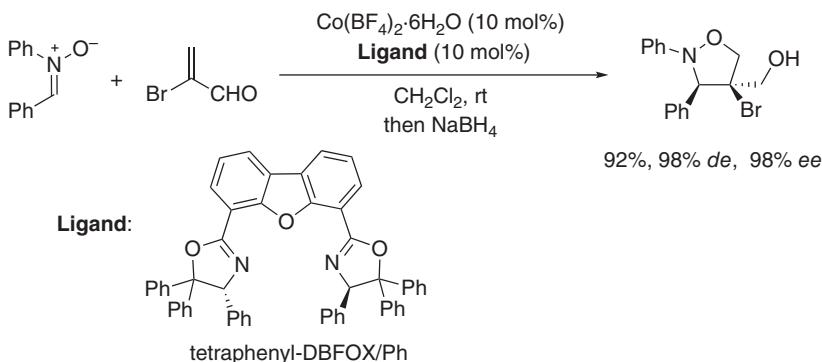
The 1,3-dipolar cycloaddition [228] of a dipolarophile with a 1,3-dipolar compound allows the synthesis of five-membered heterocycles [229, 230]. A variety of enantioselective versions of this reaction have successfully used chiral cationic cobalt(III) complexes as chiral catalysts [2j]. For example in the 2000s, *Yamada* reported the use of this type of catalysts to promote the enantioselective 1,3-dipolar cycloaddition reaction between  $\alpha,\beta$ -unsaturated aldehydes and nitrones with complete regioselectively, *endo*-selectively and good to high enantioselectivities of up to 92% *ee* [231]. Later, the same authors employed related cationic cobalt(III) catalysts to promote the enantioselective



**Scheme 10.38** Hetero-Diels–Alder reaction of 1-methoxy-[3-(tert-butyldimethylsilyl)oxy]-1,3-butadiene with aldehydes.

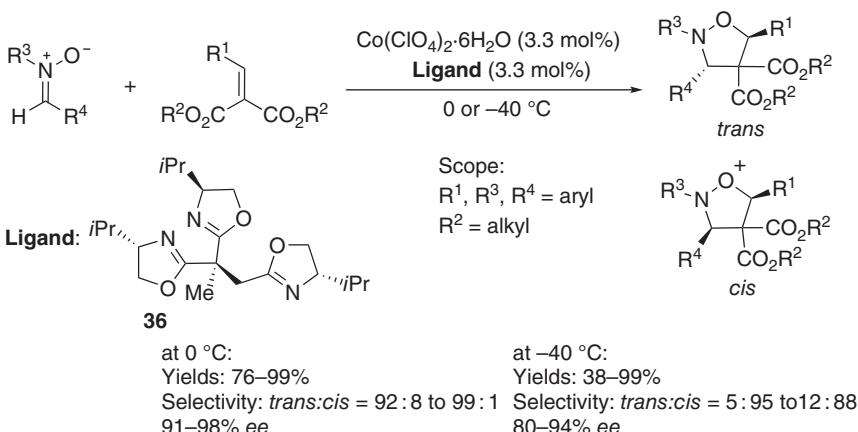
1,3-dipolar cycloaddition reaction of dihydrofuran with nitrones bearing an electron-withdrawing group, which led to the corresponding cycloadducts in moderate to good yields (40–87%) and low to excellent *endo*-selectivities (28–98% *de*) combined with low to moderate enantioselectivities (6–73% *ee*) [232]. In 2004, Kanemasa employed a substituted cationic chiral aqua complex derived from a *trans*-chelating tridentate ligand, tetraphenyl-substituted (*R,R*)-4,6-dibenzofurandiyl-2,2'-bis-(4-phenyloxazoline) (tetraphenyl-DBFOX/Ph), and  $\text{Co}(\text{BF}_4)_2$  to induce the enantioselective 1,3-dipolar cycloaddition of *N*-benzylideneaniline *N*-oxide with  $\alpha$ -bromoacrolein at room temperature [233]. As shown in Scheme 10.39, the corresponding cycloadduct was obtained in 92% yield with both remarkable diastereo- and enantioselectivities of 98% *de* and 98% *ee*, respectively.

The same year, Tang reported the first example of enantioselective cycloadditions between various nitrones and alkylidene malonates [234]. This reaction was promoted by a chiral cobalt catalyst *in situ* generated from  $\text{Co}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$  and chiral trioxazoline **36**, which provided the corresponding chiral isoxazolidines



**Scheme 10.39** 1,3-Dipolar cycloaddition of *N*-benzylideneaniline *N*-oxide with  $\alpha$ -bromoacrolein.

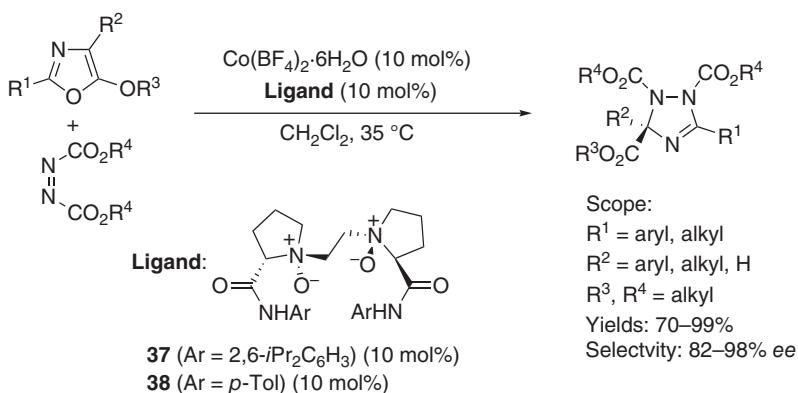
with both high enantioselectivities and high *exo*-diastereoselectivities of up to 98% *de* and 98% *ee*, respectively (Scheme 10.40). Surprisingly, the authors found that, by simply changing the temperature of the reaction, both *cis*- and *trans*-cycloadducts could be prepared with high enantioselectivity.



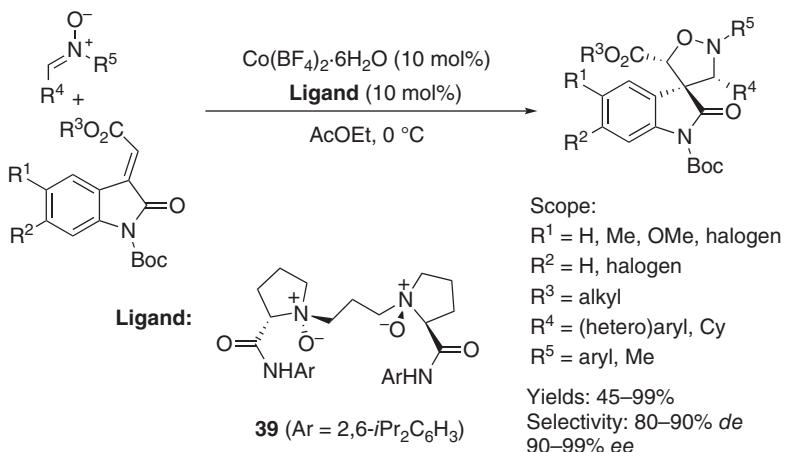
Scheme 10.40 1,3-Dipolar cycloaddition of nitrones with alkylidene malonates.

In 2012, *Cheng* reported an enantioselective cobalt-catalysed reductive [3+2] cycloaddition of various alkynes with cyclic  $\alpha,\beta$ -unsaturated ketones, leading to the corresponding chiral bicyclic tertiary alcohols with high regioselectivity [235]. When the reaction was induced by the chiral cobalt complex *in situ* generated from  $\text{CoI}_2$  and (*R,R,S,S*)-Duanphos ligand in the presence of Zn as a mild reducing agent, it allowed a range of chiral cycloadducts to be achieved in good yields (50–76%) and high enantioselectivities of up to 99% *ee*. In 2017, *Feng* and *Liu* developed highly efficient catalytic asymmetric formal 1,3-dipolar cycloadditions of 5-alkoxyoxazoles with azodicarboxylates performed in the presence of another type of chiral cobalt catalysts [236]. The latter were *in situ* generated from  $\text{Co}(\text{BF}_4)_2 \cdot 6\text{H}_2\text{O}$  and chiral  $N,N'$ -dioxides **37** or **38**. As shown in Scheme 10.41, both the two catalytic systems tolerated a range of variously substituted 5-alkoxyoxazoles, which led to the corresponding multisubstituted chiral 1,2,4-triazolines in good to quantitative yields (70–99%) and high enantioselectivities (82–98% *ee*).

Soon after, the same authors investigated the 1,3-dipolar cycloaddition of nitrones with methyleneindolinones by using a related chiral  $N,N'$ -dioxide ligand [237]. As illustrated in Scheme 10.42, the use of a combination of  $\text{Co}(\text{BF}_4)_2 \cdot 6(\text{H}_2\text{O})$  and ligand **39** as catalytic system allowed the [3+2] cycloaddition of a wide variety of nitrones with methyleneindolinones to give the corresponding chiral multisubstituted spiroisoxazolidines exhibiting three contiguous quaternary/tertiary stereocentres in almost all cases as single diastereomers (90% *de*) in moderate to excellent yields (45–99%) and uniformly excellent enantioselectivities (90–99% *ee*).



Scheme 10.41 1,3-Dipolar cycloaddition of 5-alkoxyoxazoles with azodicarboxylates.

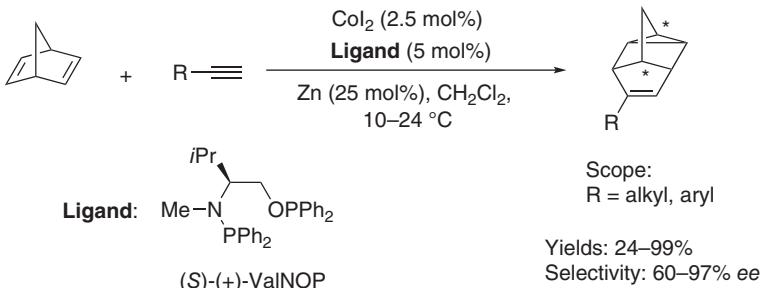


Scheme 10.42 1,3-Dipolar cycloaddition of nitrones with methyleneindolinones.

### 10.3.2.3 Other Cycloadditions

The transition metal-catalysed [2+2+2] cycloaddition of unsaturated motifs, such as alkynes and alkenes, constitutes the most atom-economical protocol for the construction of a six-membered ring system [6b, 238, 239]. In 1990, *Lautens* [240] and *Brunner* [241] independently reported the first highly enantioselective cobalt-catalysed [2+2+2] cycloadditions performed in the presence of chiral phosphines with enantioselectivities of up to 98% ee. These processes occurred between norbornadiene and acetylenic compounds, allowing the corresponding chiral monosubstituted deltacyclenes to be synthesised in high yields and enantioselectivities of up to 98% ee. The effective catalysts used by these authors were obtained upon reduction of  $\text{Co}(\text{acac})_3$  with  $\text{Et}_2\text{AlCl}$  in the presence of chiral ligands such as (*S,S*)-Chiraphos or (+)-Norphos, providing enantioselectivities of up to 91% ee and 98% ee, respectively. Later, *Buono* demonstrated that these reactions could be catalysed by a new catalytic system [ $\text{CoI}_2/\text{Zn}/\text{L}^*$ ] with chiral

organophosphorus bidentate ligands, such as *(S)*-*(+)*-ValNOP [242]. Therefore, a range of variously monofunctionalised deltacyclenes could be achieved from the corresponding acetylenic and propargylic compounds in moderate to excellent yields and high to excellent enantioselectivities of up to 97% *ee* (Scheme 10.43).

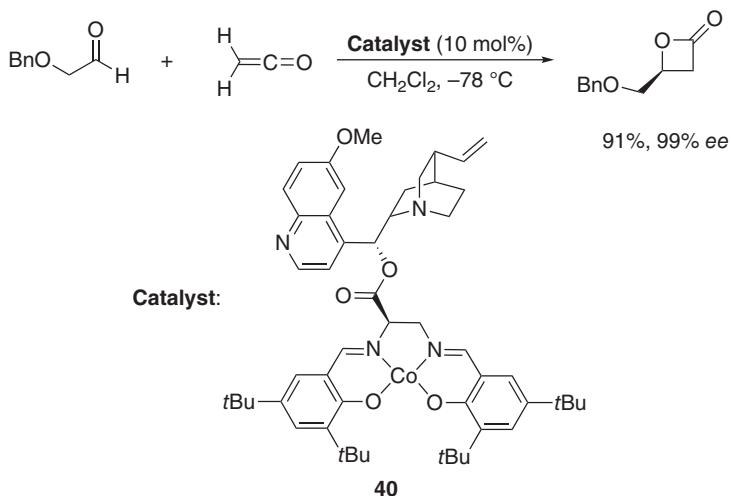


**Scheme 10.43** [2+2+2] Cycloaddition of norbornadiene with alkynes.

In 2004, *Heller* and *Gutnov* investigated enantioselective cobalt-catalysed [2+2+2] cycloaddition of alkynes with nitriles such as 2-substituted 1-naphthonitriles [243]. To promote the reaction of 2-substituted 1-naphthonitriles with 2 equiv. of alkynes, the authors employed tartrate- and menthol-derived chiral cyclopentadienyl or indenyl cobalt(I) complexes, which provided the corresponding 2-arylpyridines in low yields (3–11%) and moderate enantioslectivities of 40–64% *ee*. The procedure was further extended by *Hapke* and *Heller* into a novel route to axially chiral 1-aryl-5,6,7,8-tetrahydroisoquinolines on the basis of a cobalt-catalysed [2+2+2] cycloaddition occurring between 1-aryl-1,7-octadiynes and nitriles [244]. The process was catalysed by a planar chiral (1-neomenthylindenyl)cobalt(cod) complex under photochemical conditions, allowing the formation of various axially chiral 2-arylpyridines to be achieved in good yields and enantioselectivities of up to 94% *ee* from the reaction of the corresponding 1-naphthyldiynes with a range of differently functionalised nitriles. Recently in 2016, *Hapke* reported the synthesis of novel indenyl-based chiral cobalt complexes that were further investigated as catalysts in the asymmetric thermal and photochemical [2+2+2] cycloaddition of naphthyldiyne with nitriles to give the corresponding chiral heterobiaryl compounds [245]. For example, the photochemical cycloaddition of naphthyldiyne with benzonitrile allowed the corresponding product to be obtained in both high yield (86%) and enantioselectivity (93% *ee*). Moreover, the same authors described the first enantioselective cobalt-catalysed intramolecular [2+2+2] cycloaddition of triynes, which was catalysed by a cobalt complex of the (*R,R*)-*N*-PINAP ligand [246]. It led to variously substituted chiral tricyclic products in low to excellent yields (32–95%), low to moderate diastereoselectivities (10–46% *de*), and low to good enantioselectivities (7–78% *ee*).

Another type of cycloadditions, such as [2+2+1] cycloadditions [247], has been successfully developed in the presence of chiral cobalt catalysts. In 2000, *Hiroi* reported the first example of a catalytic asymmetric synthesis of 2-cyclopentenone systems using a cobalt catalyst derived from chiral phosphines [248]. Indeed, the intramolecular *Pauson–Khand* reaction of 1,6-enynes under

carbon monoxide atmosphere, using (*S*)-BINAP as most effective ligand of  $\text{Co}_2(\text{CO})_8$ , led to the corresponding 2-cyclopentenone derivatives in moderate to good yields and enantioselectivities of up to 90% *ee*. The scope of the reaction was extended to sulfonamides that provided under the same reaction conditions the corresponding bicyclic products in comparable results with enantioselectivities of up to 94% *ee*. In 2002, *Buchwald* and *Sturla* demonstrated that moderate enantioselectivities ( $\leq 75\%$  *ee*) were achieved in comparable reactions by using chiral aryl bisphosphite ligands [249]. In 2004, enantioselectivities of up to 91% *ee* combined with high yields of up to 95% were reported by *Consiglio* employing (*R*)-MeO-BIPHEP as chiral ligand of  $\text{Co}_2(\text{CO})_8$  in the cyclocarbonylation of 4,4-bis(carboethoxy)hex-6-en-1-yne [250]. In 2015, *Riera* and *Verdaguer* reported the synthesis of chiral cobalt complexes derived from novel P-stereogenic aminodiphosphane ligands to be investigated as promoters in enantioselective *Pauson–Khand* reaction of norbornadiene with terminal alkynes [251]. Useful levels of enantioselection (up to 97% *ee*) for the reaction between norbornadiene and trimethylsilylacetylene ( $\text{R} = \text{TMS}$ ) were achieved. In 1993, *Lautens* reported the first enantioselective cobalt-catalysed [4+2+2] cycloaddition of various 2-substituted buta-1,2-dienes with norbornadiene [252]. This transformation was performed in the presence of  $\text{Co}(\text{acac})_2$  combined with a chiral phosphine ligand as catalyst system and  $\text{Et}_2\text{AlCl}$  as reducing agent. Among chiral phosphines investigated, including (*R*)-*Prophos*, (*S,S*)-*Chiraphos*, or (*S,S*)-*Me-Duphos*, (*R*)-*Prophos* was selected as optimal ligand, allowing moderate enantioselectivities ( $\leq 79\%$  *ee*) to be obtained, combined with moderate yields ( $\leq 66\%$ ). In 2007, *Lin* reported another type of cycloadditions, such as the [2+2] cycloaddition between 2-benzoyloxyacetaldehyde and ketene, catalysed by chiral bifunctional cobalt(II) salen catalyst **40** incorporating a quinine moiety [253]. The corresponding  $\beta$ -lactone was generated with an excellent yield (91%) and a complete enantioselectivity (99% *ee*), as shown in Scheme 10.44.



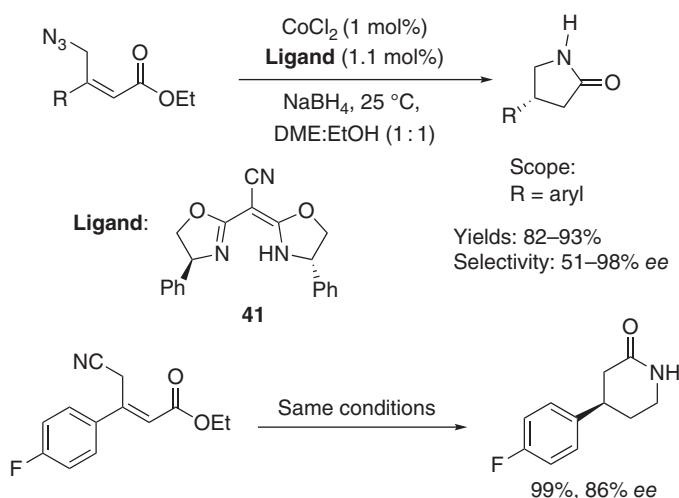
**Scheme 10.44** [2+2] Cycloaddition of 2-benzoyloxyacetaldehyde with ketene.

In addition, *Buono* described in 2008 the first enantioselective cobalt-catalysed [6+2] cycloaddition of cycloheptatriene with alkynes, providing the corresponding chiral [4.2.1]bicyclononatrienes in good yields (up to 89%) and moderate to high enantioselectivities (47–92% *ee*) by using chiral phosphoramidites based on 3,3'-disubstituted (*R*)-BINOL as ligands [254]. Later, these authors developed novel P-stereogenic triaminophosphines featuring an indoline or a 1,2,3,4-tetrahydroquinolidine pattern that were also investigated as chiral ligands in the same cobalt-catalysed [6+2] cycloaddition, albeit providing moderate enantioselectivities of up to 52% *ee* [255]. Finally, the kinetic resolution of racemic epoxides with carbon dioxide was performed by *Jing* in the presence of novel chiral oligomers of spiro-cobalt salen complexes, in 2016 [256]. The corresponding chiral cyclic carbonates were synthesised in moderate conversions (38–45%) and enantioselectivities (54–61% *ee*).

### 10.3.3 Cyclisations Through Domino Reactions

The use of one-pot domino reactions [257, 258] in organic synthesis is increasing constantly, since they allow the synthesis of a wide range of complex molecules, including natural products and biologically active compounds, in an economically favourable way by using processes that avoid the use of costly and time-consuming protection–deprotection processes, as well as purification procedures of intermediates [259]. In recent years, various types of enantioselective cobalt-catalysed domino reactions have been developed. Among them, an enantioselective cobalt-catalysed multicomponent reaction initiated by a *Diels–Alder* cycloaddition was developed by *Hilt*, in 2006 [260]. The process began with the *Diels–Alder* reaction of an 1-boron-functionalised 1,3-diene with an alkyne, giving the corresponding 1,4-cyclohexadiene borane intermediate, which subsequently underwent an allylboration reaction with an aldehyde to provide the final chiral multifunctionalised domino product in moderate to good yields (57–87%) and moderate enantioselectivities (71–78% *ee*). This product, exhibiting a stereogenic quaternary centre next to a stereogenic secondary alcohol functionality, was regio- and diastereoselectively obtained by using a combination of  $\text{CoBr}_2$  with (*S,S*)-Norphos. On the other hand in 2006, *Sudalai* and *Paraskar* developed a novel enantioselective cobalt-catalysed domino reductive cyclisation reaction of substituted  $\gamma$ -azido- $\alpha,\beta$ -unsaturated esters to afford the corresponding  $\gamma$ -lactams in high yields [261]. As shown in Scheme 10.45, the process was promoted by a combination of  $\text{CoCl}_2$  with chiral oxazoline **41** in the presence of  $\text{NaBH}_4$  as reducing agent. The chiral  $\gamma$ -lactams were obtained in good to high yields (82–93%) and moderate to excellent enantioselectivities of 51–98% *ee*. The utility of these reactions were demonstrated by their applications to the total syntheses of (*R*)-baclofen, (*R*)-rolipram, and (*R*)-4-fluorophenylpiperidinone, a key intermediate for (–)-paroxetine.

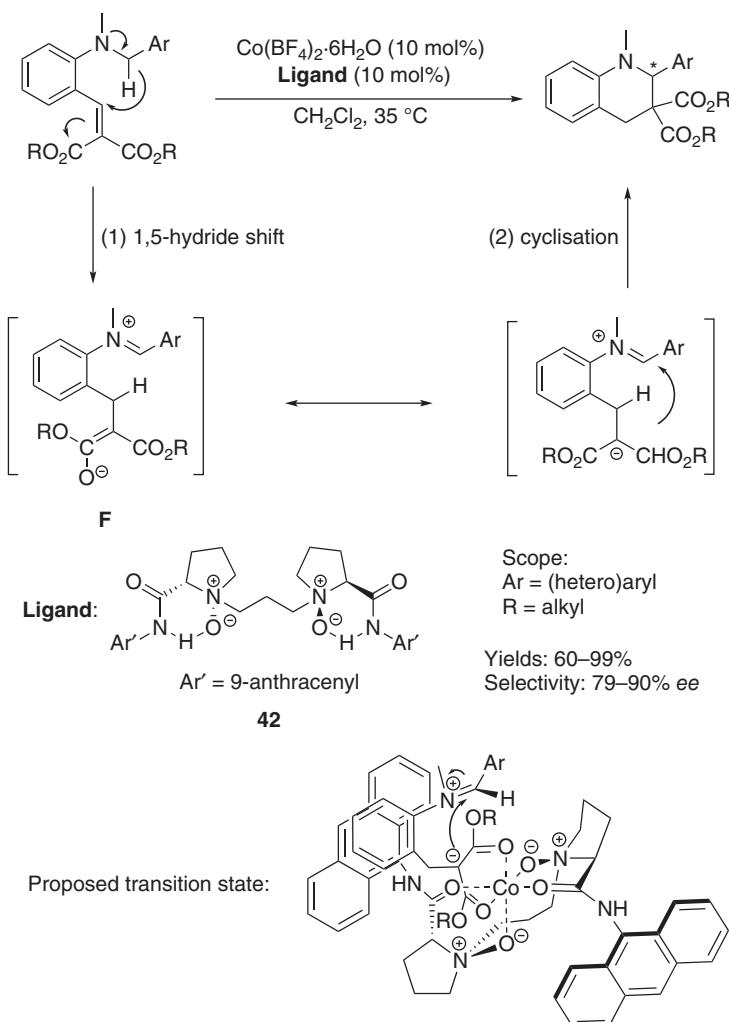
Chiral tetrahydroquinoline derivatives are widely used in organic synthesis and pharmaceutical chemistry due to their significant building blocks and intriguing biological activities. A straightforward approach to these products is a tandem hydride transfer/cyclisation process that undergoes a zwitterionic intermediate formed by a 1,5-hydride transfer. Therefore, a highly enantioselective synthesis



**Scheme 10.45** Domino reductive cyclisation reactions.

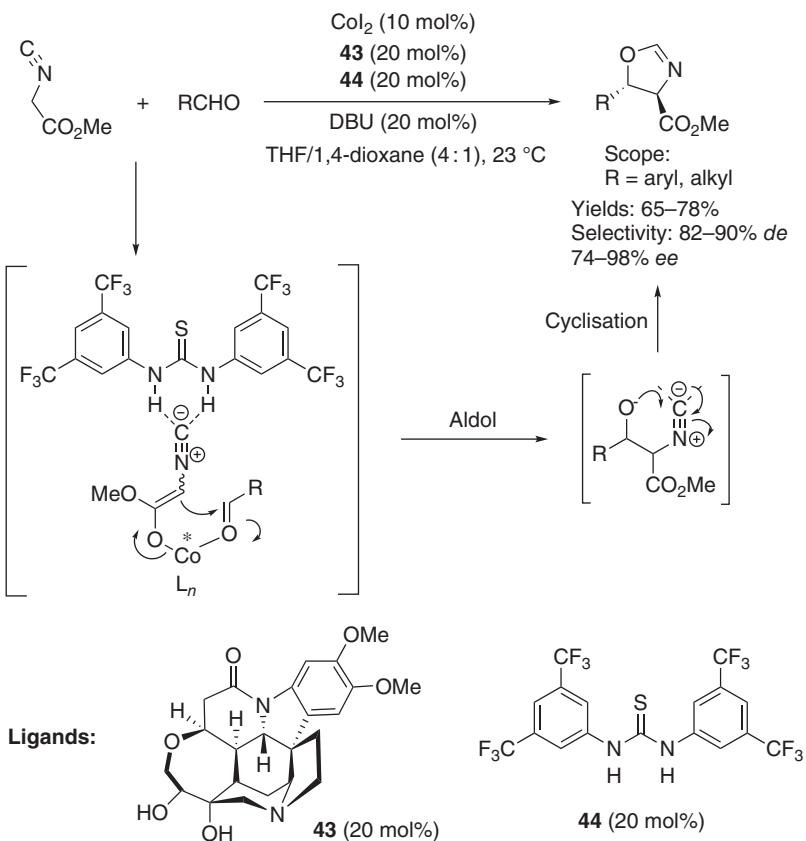
of tetrahydroquinolines was developed by *Feng* via cobalt(II)-catalysed domino 1,5-hydride transfer/cyclisation reaction [262]. As shown in Scheme 10.46, a chiral catalyst generated from L-proline-derived *N,N'*-dioxide **42** and  $\text{Co}(\text{BF}_4)_2 \cdot 6(\text{H}_2\text{O})$  was applied to the asymmetric intramolecular hydride transfer-initiated cyclisation reaction of a series of *o*-dialkylamino-substituted alkylidene malonate derivatives to provide the corresponding tetrahydroquinolines in moderate to quantitative yields (60–99%) and high enantioselectivities of up to 90% *ee*. The mechanism of the process involved the formation of zwitterionic intermediate **F** through intramolecular hydride transfer, which subsequently cyclised to give the final product (Scheme 10.46). A possible transition state model depicted in Scheme 10.46 was proposed by the authors to explain the absolute configuration of the products. In this model, the oxygens of *N,N'*-dioxide, amide oxygens, and the alkylidene malonate coordinated to cobalt(II) in a hexadentate manner. The carbanion preferred to attack the *Re* face rather than the *Si* face of the imine because the latter was strongly shielded by the nearby anthracenyl ring, which resulted in the *S*-configured product.

In another context, a number of enantioselective domino reactions initiated by a *Michael* addition have been promoted by chiral metal catalysts [259k, 263]. As an example, *Feng* have reported an efficient asymmetric synthesis of 4*H*-chromene derivatives through a domino *Michael*/cyclisation reaction of cyclohexane-1,3-diones with ethyl 2-cyano-3-arylacrylates [264]. The reaction was catalysed by a chiral cobalt complex *in situ* generated from  $\text{Co}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$  and chiral salen ligand **4** derived from (*R,R*)-1,2-diphenylethane-1,2-diamine and 3,5-di-*tert*-butylsalicylaldehyde. The corresponding chiral 2-amino-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene derivatives, having extensive biological and pharmacological activities, were produced with moderate to good yields ( $\leq 81\%$ ) combined with good to high enantioselectivities (up to 89% *ee*). In the last few years, a large number of multiple-catalyst systems for various organic transformations have been developed, including asymmetric



Scheme 10.46 Domino 1,5-hydride transfer/cyclisation reaction.

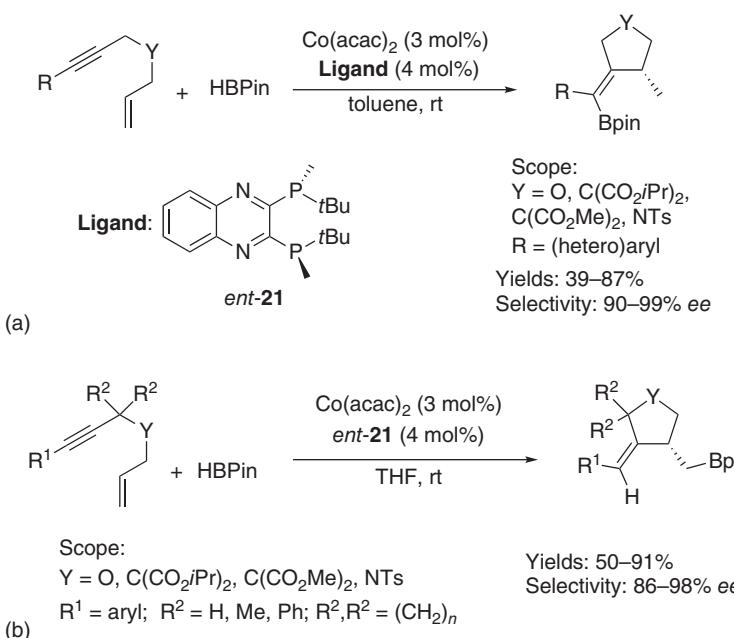
domino processes [265]. A recent example of enantioselective domino reaction catalysed by a combination of a chiral cobalt catalyst and an achiral organocatalyst was described by *Oh* and *Kim* in 2011 [266]. The process consisted in a domino Aldol/cyclisation reaction between aromatic as well as aliphatic aldehydes and methyl  $\alpha$ -isocyanate, to give the corresponding chiral *trans*-oxazolines. By using a chiral cobalt complex *in situ* generated from  $\text{CoI}_2$  and brucine amino diol **43** in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a base and with achiral thiourea **44**, a range of chiral oxazolines were achieved in good to high yields, *trans*-diastereo- and enantioselectivities of up to 90% *de* and 98% *ee*, respectively, as shown in Scheme 10.47. The key of the success in this process lied in the strong anion-binding interaction between the isocyanide and thiourea



Scheme 10.47 Domino Aldol/cyclisation reaction.

**44**, which potentially disturbed the intrinsic cobalt–isocyanide complexation (Scheme 10.47).

In 2017, Ge developed the first enantioselective cobalt-catalysed domino hydroboration/cyclisation reaction of 1,6-enynes with pinacolborane [267]. The cobalt catalyst was *in situ* generated from Co(acac)<sub>2</sub> and a chiral bisphosphine *ent*-**21**. A variety of oxygen-, nitrogen-, and carbon-tethered 1,6-enynes underwent the asymmetric reaction with HBPin, yielding the corresponding vinyl-substituted boronate esters containing chiral tetrahydrofuran (THF), pyrrolidine, and cyclopentane moieties with moderate to high yields (39–87%) and uniformly excellent enantioselectivities (90–99% *ee*) (Scheme 10.48a). On the other hand, the authors found that enynes containing *ortho*-substituted aryl groups ( $R^1 = o\text{-Tol}$ , 2-Naph) reacted with HBPin to provide the corresponding alkyl boronate esters in high yields (86–88%) and enantioselectivities (88–90% *ee*), as shown in Scheme 10.48. Furthermore, this *anti*-Markovnikov hydroboration/cyclisation process tolerated O-tethered 1,6-enynes bearing two substituents at the propargylic position as well as N- and C-tethered 1,6-enynes that afforded the corresponding products in moderate to high yields (50–91%) and high enantioselectivities (86–98% *ee*) (Scheme 10.48b)).

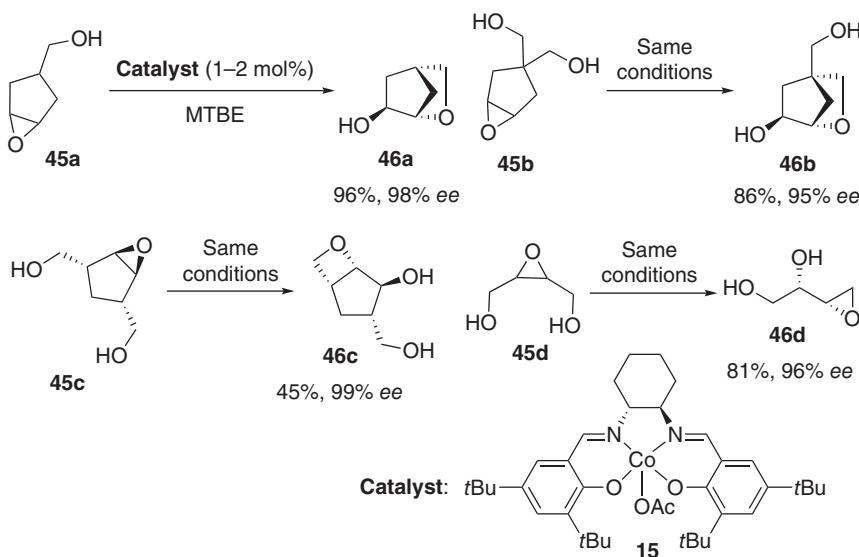


**Scheme 10.48** Domino hydroboration/cyclisation reactions of 1,6-enynes with pinacolborane. (a) Synthesis of vinyl boronate esters. (b) Synthesis of alkyl boronate esters.

### 10.3.4 Miscellaneous Cyclisations

Many types of other cyclisation reactions have been catalysed by chiral cobalt complexes, such as *Nazarov* reactions developed in 2010 by *Itoh* in the presence of cobalt complexes derived from chiral pybox-type ligands [268]. Indeed, the asymmetric *Nazarov* reaction of divinyl ketones using a chiral cobalt complex *in situ* generated from Co(ClO<sub>4</sub>)<sub>2</sub>·6(H<sub>2</sub>O) and (*S,S*)-*ip*-Pybox ligand led to the corresponding enantioenriched functionalised cyclopentenones in moderate enantioselectivities ( $\leq 63\%$  ee) combined with low to moderate yields (23–70%). Later in 2001, *Katsuki* and *Uchida* reported that chiral cationic cobalt(III) salen complexes could promote the asymmetric *Baeyer–Villiger* reaction of 3-substituted cyclobutanones using hydrogen peroxide as oxidant [269]. It afforded the corresponding chiral 3-aryl butyrolactones in good yields (75–85%) and enantioselectivities of 75–78% ee. In 2002, the same authors designed novel cobalt(III) salen complexes bearing a chiral ethane-1,2-diamine moiety [270]. These catalysts were investigated to promote the same *Baeyer–Villiger* oxidation of 3-aryl as well as 3-alkyl cyclobutanones into the corresponding chiral lactones in the presence of hydrogen peroxide. The use of cobalt complexes exhibiting a chiral binaphthalenediamine unit provided a moderate to good level of enantioselectivity (69–79% ee). Earlier in 1999, *Yokota* reported an asymmetric cyclisation of a *meso*-diepoxyde through hydration using chiral cobalt(III) salen complexes [271]. Therefore, the treatment of *meso*-1,2 : 4,5-dianhydro-3-*O*-methylxylitol with *Jacobsen's* cobalt (*R,R*)-salen catalyst led to the exclusive formation of the *D*-enantiomer of 1,4-anhydro-3-*O*-methylarabinitol in 78% yield and excellent

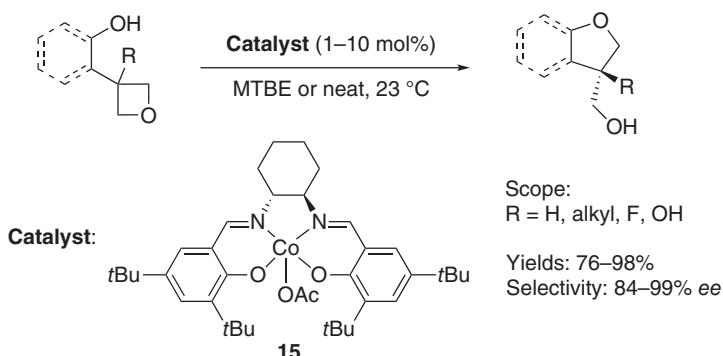
enantioselectivity of 99% *ee*. The same year, Jacobsen reported the use of chiral cobalt(III) salen complexes to induce intramolecular desymmetrisation of *meso*-epoxy alcohols into the corresponding almost enantiopure bicyclic products [272]. As depicted in Scheme 10.49, treatment of epoxy alcohol **45a** by chiral catalyst **15** under hydrolytic conditions led to bicyclic compound **46a** in 96% yield and excellent enantioselectivity of 98% *ee*. Similarly, *gem*-bishydroxymethylcyclopentene oxide **45b** cleanly cyclised under the same reaction conditions into the corresponding bicyclic ring system **46b** in 86% yield and 95% *ee*. Moreover, *meso*-epoxy diol **45c** underwent an exclusive 4-*exo* ring closure to afford enantiopure oxetane **46c** in 45% yield, while *meso*-epoxy diol **45d** underwent a cobalt-catalysed *Payne* rearrangement to provide 1,2-anhydrothreitol product **46d** in 81% yield and 96% *ee*.



Scheme 10.49 Intramolecular cyclisations of *meso*-epoxy alcohols.

In 2009, the same authors described an enantioselective intramolecular opening of 3-substituted oxetanes catalysed by chiral cobalt(III) salen complexes to afford the corresponding chiral functionalised THFs [273]. When oxetanes were activated by the same monomeric cobalt salen catalyst **15**, they provided the corresponding THFs in high yields (76–98%) and enantioselectivities of up to 99% *ee* (Scheme 10.50). The scope of the reaction of oxetanes with *O*-centred nucleophiles was examined with a variety of oxetanes bearing nucleophilic appendages. Thus, a series of substituted ethanol derivatives underwent ring-opening with good to excellent enantioselectivities of 84–99% *ee*.

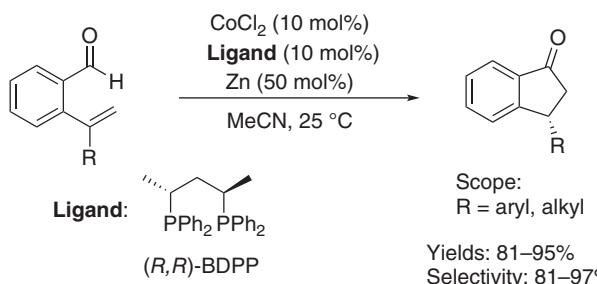
In 2007, Cheng reported a highly efficient cyclisation of *o*-iodobenzoates with aldehydes induced by cobalt-bisphosphine complexes [274]. An asymmetric version of this process was developed by using a cobalt complex derived from (*S,S*)-Dipamp ligand in the presence of zinc powder. Various aromatic aldehydes underwent cyclisation with methyl 2-iodobenzoate to give the corresponding



Scheme 10.50 Intramolecular opening of oxetanes.

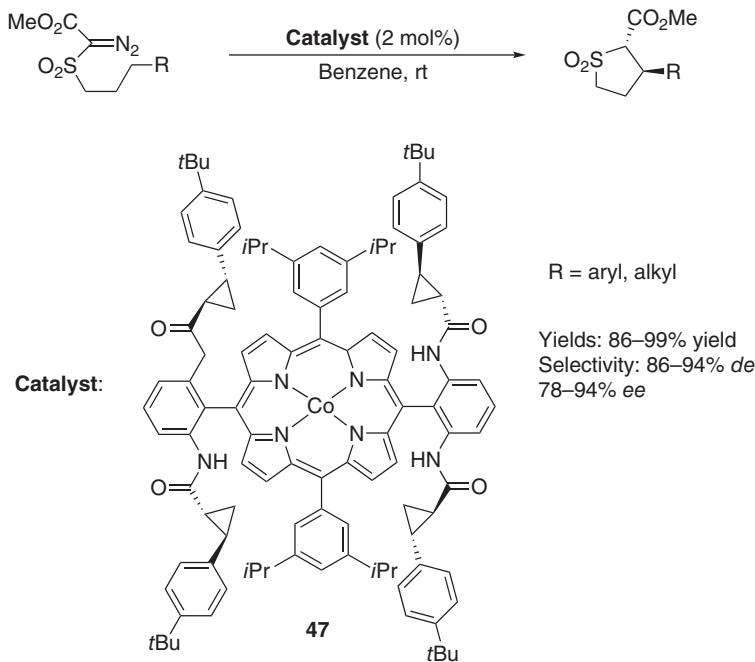
(*S*)-phthalides in good to high yields (80–89%) and enantioselectivities (70–98% *ee*). This methodology has opened a novel route to these important chiral five-membered lactones that are present in a large number of biologically active compounds and that are also key intermediates for the synthesis of natural products. In another area, the asymmetric halolactonisation of unsaturated carboxylic acids is a powerful methodology to not only build small to large lactone rings but also functionalise olefinic double bonds. In 2011, *Gao* investigated a range of chiral cobalt salen catalysts in the asymmetric iodolactonisation of 5-substituted-4-pentenoic acid derivatives [275]. Moderate enantioselectivities ( $\leq 74\% \text{ ee}$ ) were obtained for iodolactones arising from the corresponding (*E*)-5-substituted-4-pentenoic acid derivatives, whereas the (*Z*)-5-substituted-4-pentenoic acid derivatives led to the corresponding iodolactones in enantioselectivities lower than 12% *ee*. In addition, the kinetic resolution of racemic terminal epoxides based on a coupling with carbon dioxide to give the corresponding chiral five-membered cyclic carbonates has also been investigated in the presence of chiral cobalt complexes, providing moderate to high enantioselectivities of up to 92% *ee*, albeit often combined with moderate conversions [115e, k, 276–279].

The hydroacylation, consisting in the catalytic addition of an aldehyde C—H bond across an unsaturated bond, represents an atom-efficient synthetic approach to carbonyl compounds [280]. These reactions are generally catalysed by rhodium complexes; however, rare examples employing cobalt catalysts have been recently developed. Among them, *Yoshikai* and *Yang* have reported the enantioselective intramolecular hydroacylation of 2-alkenylbenzaldehydes promoted by a chiral cobalt catalyst *in situ* generated from  $\text{CoCl}_2$  and (*R,R*)-BDPP ligand (Scheme 10.51) [281]. Performed in the presence of zinc as reductant, the process led to differently substituted chiral indanones in both high yields (81–95%) and enantioselectivities (81–97% *ee*). In order to extend the scope of this catalytic system to substrates bearing trisubstituted alkenes, these authors found that the use of  $\text{CoBr}_2$  instead of  $\text{CoCl}_2$  as precatalyst and performing the reaction in *N,N*-dimethylformamide (DMF) at 80 °C instead of acetonitrile at 25 °C allowed the corresponding chiral 2,3-disubstituted indanones to be achieved in moderate to quantitative yields (66–99%) combined with moderate to excellent diastereo- (54–90% *de*) and enantioselectivities (63–97% *ee*) [282].



**Scheme 10.51** Intramolecular hydroacylation of 2-alkenylbenzaldehydes.

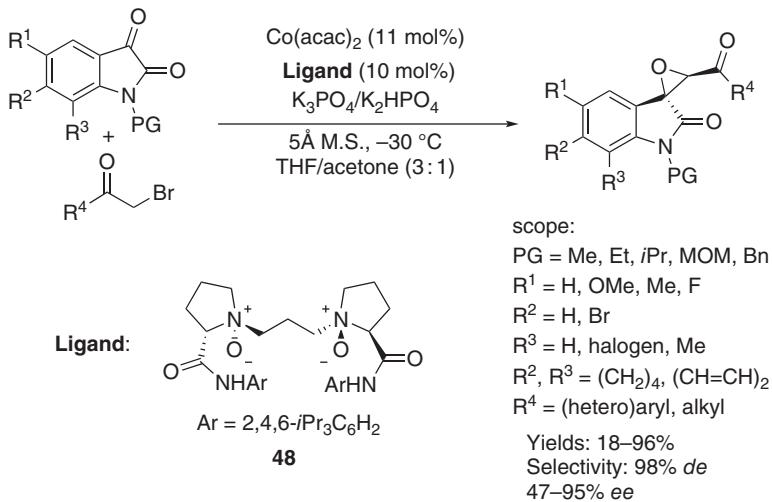
In 2015, cobalt-based metalloradical catalysis was, for the first time, successfully applied by *Zhang* to develop asymmetric intramolecular C–H alkylation of acceptor/acceptor-substituted diazo reagents, such as  $\alpha$ -methoxycarbonyl- $\alpha$ -diazosulfones [283]. Indeed, based on the design and synthesis of novel  $D_2$ -symmetric chiral amidoporphyrin as chiral ligand, the corresponding cobalt-based metalloradical system **47** was found capable to promote the radical intramolecular C–H alkylation of  $\alpha$ -methoxycarbonyl- $\alpha$ -diazosulfones having a broad range of electronic properties, which afforded the corresponding chiral *trans*-five-membered sulfolane derivatives in high yields (86–99%), diastereoselectivities (86–94% de), and enantioselectivities (78–94% ee), as shown in Scheme 10.52.



**Scheme 10.52** Radical intramolecular C–H alkylation of  $\alpha$ -methoxycarbonyl- $\alpha$ -diazosulfones.

Another cobalt–porphyrin catalyst was used by *De Bruin* to promote the asymmetric intramolecular ring-closing C–H bond amination of an azide into the corresponding chiral pyrrolidine albeit with low yield (22%) and modest

enantioselectivity (46% *ee*) [284]. In another area, asymmetric *Darzens* condensation of  $\alpha$ -haloamides with benzaldehyde was investigated by *North*, using a range of cobalt complexes of novel  $C_1$ -symmetrical salen ligands derived from amino acids, such as (*S*)-alanine, (*S*)-phenylalanine, (*R*)-phenylglycine, and (*S*)-valine [158a]. Even if the corresponding epoxides were obtained in good to excellent yields (72–97%) as mixtures of *cis*- and *trans*-diastereomers, low to moderate enantioselectivities ( $\leq 44\%$  *ee*) were obtained for both these two diastereomers. Earlier in 2007, the same authors investigated these reactions by using chiral cobalt(II) salen complexes derived from diaminocyclohexane, which provided comparable enantioselectivities ( $\leq 47\%$  *ee*) combined with moderate diastereoselectivities (14–42% *de*) and good to excellent yields (71–97%) [285]. Later in 2014, *Feng* reported enantioselective cobalt-catalysed *Darzens* reactions of *N*-protected isatins with phenacyl bromides in order to synthesise potentially bioactive spiroepoxyxindoles [286]. The optimal catalyst system for this process was constituted by a combination of  $\text{Co}(\text{acac})_2$  with chiral *N,N'*-dioxide ligand **48**. The reaction of a range of *N*-protected isatins with phenacyl bromides, performed in the presence of a mixture of  $\text{K}_3\text{PO}_4$  and  $\text{K}_2\text{HPO}_4$  as base, led to the corresponding chiral spiroepoxyxindoles as single diastereomers (98% *de*) in low to excellent yields (18–96%) and enantioselectivities (47–95% *ee*), as illustrated in Scheme 10.53.

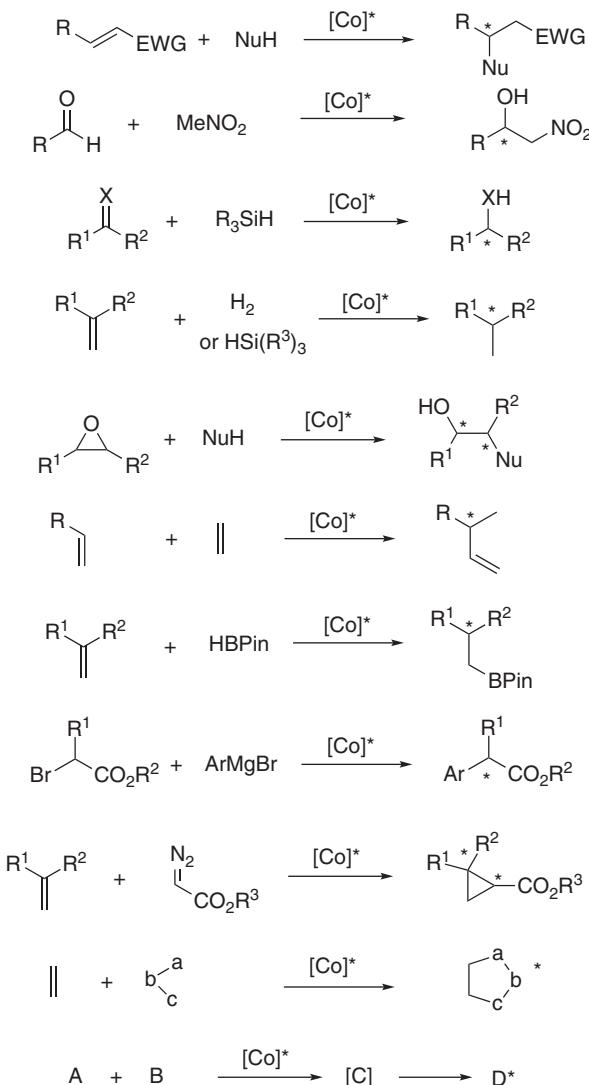


**Scheme 10.53** *Darzens* reaction of isatins with phenacyl bromides.

Finally in 2015, *Gong* demonstrated that the sodium salts of anionic chiral cobalt complexes were highly promising catalysts for the asymmetric *Povarov* reaction of 2-azadienes with various dienophiles [287]. For example, the enantioselective *Povarov* reaction between 2-azadienes and 2,3-dihydrofuran gave the corresponding chiral tetrahydroquinolines exhibiting three contiguous stereocentres in moderate to high yields (40–93%), uniformly excellent *endo*-diastereoselectivity (88–90% *de*), and low to high enantioselectivities (23–90% *ee*).

## 10.4 Conclusions

This chapter collects the major results in the field of enantioselective transformations promoted by chiral cobalt catalysts, illustrating the power of these special “green” catalysts to provide new reaction pathways. These complexes have become catalysts of first choice for many types of asymmetric reactions generally performed under mild reaction conditions, as summarised in Scheme 10.54.



**Scheme 10.54** Various enantioselective transformations catalysed with chiral cobalt complexes.

## Abbreviations

Acac	acetylacetone
Ar	aryl
BDPP	2,4-bis(diphenylphosphino)pentane
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-bi-2-naphthol
BIPHEP	2,2'-bis(diphenylphosphino)-1,1'-biphenyl
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
BOPA	bis(oxazolinylphenyl)amine
BTFEP	1,3-bis(2,2,2-trifluoroethoxy)propan-2-ol
<i>i</i> Bu	isobutyl
<i>s</i> Bu	<i>sec</i> -butyl
<i>t</i> Bu	<i>tert</i> -butyl
Bz	benzoyl
Chiraphos	2,3-bis(diphenylphosphine)butane
Cod	cyclooctadiene
Cy	cyclohexyl
DAB	1,4-dideoxy-1,4-imino-D-arabinitol
DBFOX	4,6-dibenzofurandiyI-2,2'-bis-(4-phenyloxazoline)
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
<i>de</i>	diastereomeric excess
DIOP	2,3- <i>O</i> -isopropylidene-2,3-dihydroxy-1,4-bis-(diphenylphosphino)butane
Dipamp	1,2-[(2-methoxyphenyl)phenylphosphino]ethane
DIPEA	diisopropylethylamine
DMAP	4-( <i>N,N'</i> -dimethylamino)pyridine
DME	dimethoxyethane
DMF	N,N-dimethylformamide
DMSO	dimethylsulfoxide
( <i>R,R,S,S</i> )-DUANPHOS	(1 <i>R</i> ,1' <i>R</i> ,2 <i>S</i> ,2' <i>S</i> )-2,2'-di- <i>tert</i> -butyl-2,3,2',3'-tetrahydro-1 <i>H</i> ,1 <i>H'</i> -(1,1')biisophospindolyl
DUPHOS	1,2-bis(phospholano)benzene
<i>ee</i>	enantiomeric excess
Et	ethyl
<i>n</i> Hex	<i>n</i> -hexyl
L	ligand
MAO	methylalumininoxane
Me	methyl
Mes	mesityl (2,4,6-trimethylphenyl)
MOM	methoxymethyl
M.S.	molecular sieves
MTBE	methyl <i>tert</i> -butyl ether
Naph	1-naphthyl
NMI	<i>N</i> -methylimidazole

Norphos	2,3-bis(diphenylphosphino)-bicyclo[2.2.1]hept-5-ene
PG	protecting group
Pin	pinacolato
PINAP	4-[2-(diphenylphosphino)-1-naphthalenyl]- <i>N</i> -[1-phenylethyl]-1-phthalazinamine
<i>iPr</i>	isopropyl
Prophos	1,2-bis(diphenylphosphino)propane
Pybox	pyridine-bisoxazoline
QUINOX	2-(4,5-dihydro-2-oxazolyl)quinoline
rt	room temperature
Salen	<i>N,N'</i> -ethylenebis(salicylideneiminato)
TADDOL	a,a,a',a'-tetraphenyl-2,2-dimethyl-1,3-dioxolane-4,5-dimethanol
<i>t</i> -Amyl	2-methylbutyl
TBS	<i>tert</i> -butyldimethylsilyl
Tf	trifluoromethanesulfonyl
THF	tetrahydropuran
THFA	tetrahydrofurfuryl alcohol
TMS	trimethylsilyl
Tol	tolyl
Ts	4-toluenesulfonyl (tosyl)
VALNOP	<i>N</i> -diphenylphosphino-2-(diphenylphosphino- xymethyl)pyrrolidine
Xyl-P-Phos	2,2',6,6'-tetramethoxy-4,4'-bis[di(3,5-dimethylphenyl) phosphino]-3,3'-bipyridine

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## 11

# Cobalt Radical Chemistry in Synthesis and Biomimetic Reactions (Including Vitamin B<sub>12</sub>)

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### 11.1 Introduction

In recent years, transition metal-mediated radical reactions have emerged as an increasingly viable tool for the facile functionalisation and assembly of organic molecules. In this context, cobalt deserves particular attention, seeing that it was designated as the “reversible carrier” of radicals by Nature herself. The best testimony to this is the fact that mammalian organisms are highly dependent on the radical chemistry of a cobalt complex – vitamin B<sub>12</sub> [1].

Since the elucidation of its structure in 1956 [2], numerous reactions inspired by the biological functions of vitamin B<sub>12</sub> have been developed [3]. Yet cobalt has much more to offer in the area of radical chemistry as various transformations, unprecedented in the natural world have been discovered and applied in drug development, total synthesis, and industry [4–6]. Moreover, environmentally benign cobalt catalysts are an attractive alternative to the noble metal complexes currently widely employed.

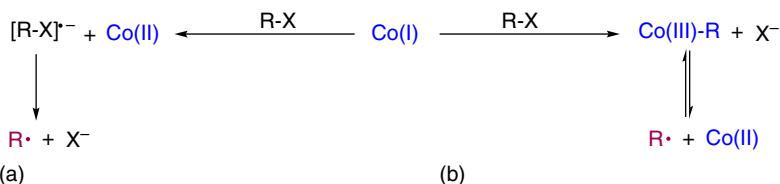
In this chapter, we will highlight advances in cobalt radical chemistry with a particular focus on the application of such reactions. This survey of the literature is accompanied by discussions concerning mechanistic aspects of the featured transformations, providing the reader with the basic tools to approach, design, and implement cobalt-mediated radical reactions in organic synthesis.

### 11.2 Cobalt-Mediated Reactions of Carbon-Centred Radicals

The radical chemistry of cobalt is heavily reliant on its redox properties, with complexes in the +1 and +2 oxidation states playing the most active roles.

Cobalt(I)-species are generally good reductants (with redox properties strongly dependent on the nature of ligands [7]) and also display “supernucleophilic” properties [3]. The former feature allows them to form carbon radicals via a

single-electron reduction of redox-active species (Scheme 11.1a). This mode of action is characteristic for complexes with monovalent organic and inorganic ligands (i.e.  $\text{CoX}_2$ ,  $\text{CoCl}(\text{PPh}_3)_3$ ). On the other hand, the “supernucleophilic” properties enable access to Co–C complexes from electrophilic species via nucleophilic substitution (Scheme 11.1b). Due to low dissociation energies of Co–C bonds (80–168 kJ/mol) [8], alkyl cobalt compounds are prone to homolytic scission via photo-, electro-, or thermolysis, which leads to carbon-centred radicals. This mechanism is characteristic for porphyrin-type and oxime cobalt complexes, including vitamin B<sub>12</sub> derivatives.



**Scheme 11.1** Most common mechanisms of the Co-mediated generation of carbon-centred radicals. (a) Single-electron transfer. (b) Nucleophilic substitution.

It is noteworthy that most Co(I)-species are easily oxidised under aerobic conditions, and as a consequence their prolonged storage and handling may be problematic. This issue is usually solved by utilising air-stable precatalysts with cobalt in the +2 or +3 oxidation state and addition of an external reductant to generate active Co(I)-species *in situ*.

A profound impact on cobalt radical chemistry has the persistent radical effect imposed by Co(II)-species [9]. This phenomenon suppresses the undesirably high reactivity of transient radicals, due to the existence of an equilibrium between an open-shell radical species and an alkyl cobalt(III) complex (Scheme 11.1b). This equilibrium can be altered in the presence of radical traps, whereby free radicals can engage in irreversible reactions. The importance of the persistent radical effect underscores the high selectivity of numerous vitamin B<sub>12</sub>-catalysed transformations [3, 9].

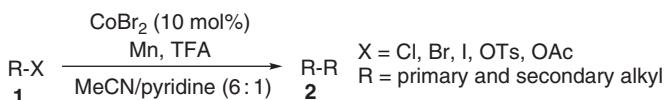
Although the aforementioned reactivity is common for the vast majority of Co-promoted radical reactions in this chapter, we will also discuss unique transformations relying on the other types of mechanisms.

### 11.2.1 Homocoupling Reactions

Radicals generated via cobalt-mediated pathways readily undergo dimerisation in the absence of coupling partners.

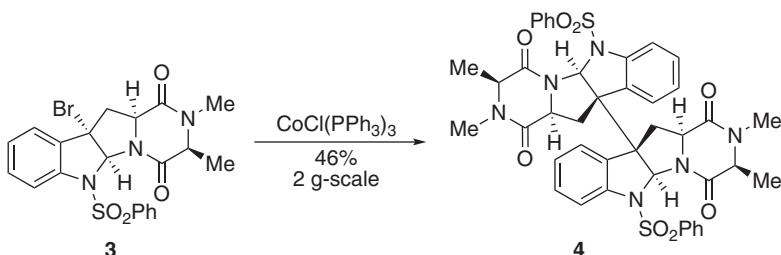
*Yamada* explored the reactivity of allylic bromides in Co(I)-catalysed homo-coupling reactions [10]. The use of Co(I)-catalyst – e.g.  $\text{CoCl}(\text{PPh}_3)_3$  – facilitated this type of reaction without the need for the addition of an external reducing agent. This procedure was applied to the synthesis of complex polyenes, most notably dimers of farnesyl and geranyl bromides. *Gosmini* extended the scope of the reaction by using primary and secondary alkyl halides, tosylates, and

acetates, in the presence of  $\text{CoBr}_2$  as the precatalyst and Mn as a reducing agent (Scheme 11.2) [11]. The addition of trifluoroacetic acid was crucial for *in situ* activation of the manganese powder. The reaction tolerated a broad range of functional groups such as: esters, nitriles, phthalimides, acetals, ketones, and aryl halides.



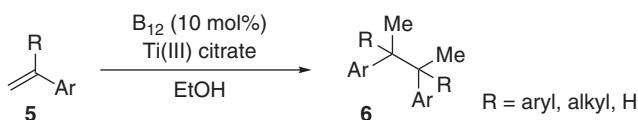
**Scheme 11.2** Cobalt-catalysed homocoupling reaction.

The most impressive applications of cobalt-catalysed radical homocouplings came from the works of *Baldwin* [12] and *Movassaghi* [13, 14] where this chemistry was applied to the bioinspired total syntheses of numerous terpenes and alkaloids. One remarkable example was represented by a highly diastereoselective key step in the gram scale synthesis of a fungal metabolite – (+)-11,11'-dideoxyverticillin A (Scheme 11.3) [14].



**Scheme 11.3** Application of cobalt catalysis in the homocoupling of (+)-11,11'-dideoxyverticillin A intermediate **3**.

The vitamin B<sub>12</sub>-catalysed homocoupling of benzyl halides was extensively studied by *Gryko* [15], *Hisaeda* [16], and *van der Donk* [17]. These studies indicated that microwave irradiation [15] or electrochemical reduction [16] could dramatically improve the efficiency of the reaction. In addition, vitamin B<sub>12</sub> (in the form of aquacobalamin) catalysed reductive dimerisation of styrene derivatives **5** (Scheme 11.4) [17]. Mechanistic studies by *van der Donk* suggested that the key steps of this reaction involve hydrocobalatation of the alkene, homolytic cleavage of the Co–C bond, and dimerisation of the resulting radical. The reaction displayed remarkable regioselectivity, furnishing only products functionalised at the more substituted end of the double bond.

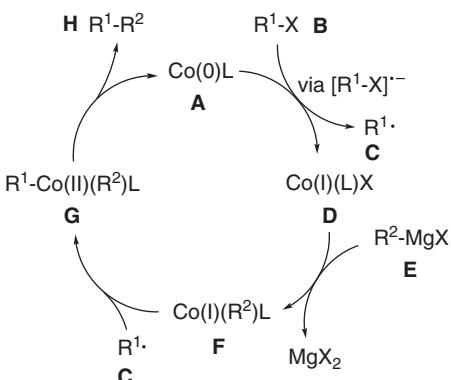


**Scheme 11.4** Vitamin B<sub>12</sub>-catalysed reductive dimerisation of styrene derivatives.

### 11.2.2 Cross-coupling Reactions

The pioneering work of *Kharasch* in the field of cobalt catalysis [18] set the stage for multiple radical cross-couplings, most notably for *Kumada*- and *Heck*-type reactions [19]. These cobalt-catalysed transformations are complementary to their palladium- or nickel-catalysed counterparts, as their radical nature obviates the lingering problem of  $\beta$ -hydrogen elimination. In this context, cobalt catalysis enables the use of challenging alkyl halides as electrophilic coupling partners to form  $C_{sp^3}-C$  bonds.

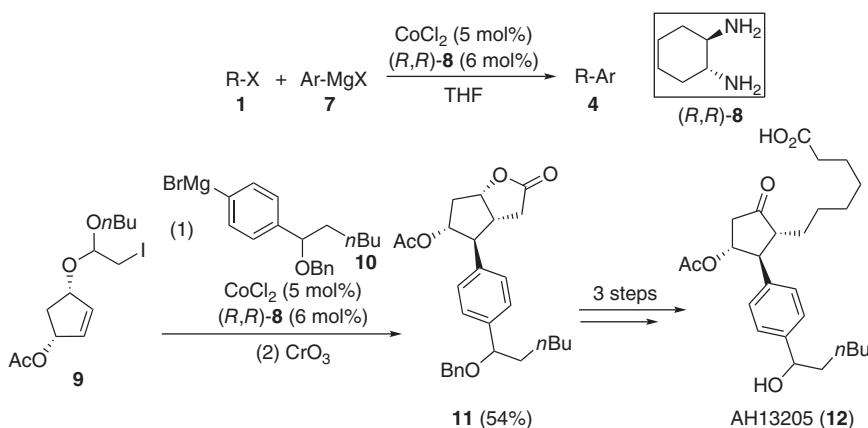
Based on mechanistic studies by *Oshima*, Co-catalysed *Kumada* reactions (coupling with *Grignard* reagents) are presumed to occur via the radical Co(II)/Co(0) catalytic cycle (Scheme 11.5) [20]. Co(0)-complex **A**, generated in the initial step from a precatalyst, reduces alkyl halide **B** via a single-electron transfer producing Co(I) complex **D**, which rapidly reacts with a *Grignard* reagent to furnish alkyl cobalt compound **F**. Subsequently, the alkyl radical **C** is trapped by intermediate **F** forming complex **G**, which undergoes reductive elimination furnishing product **H** and closing the catalytic cycle.



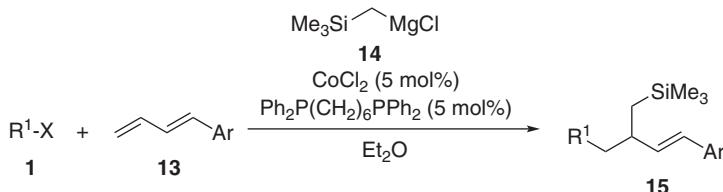
**Scheme 11.5** General mechanism of the Co-catalysed coupling of alkyl halides with *Grignard* reagents (L – usually diphosphine ligand).

A variety of primary and secondary alkyl halides undergo coupling reactions with aryl magnesium reagents in the presence of a simple catalytic system comprising of  $\text{CoCl}_2$  and diamine ( $R_2R'$ )-**8** (Scheme 11.6) [21]. The synthetic potential of this method was represented by a key step in the synthesis of prostaglandin AH13205 (**12**). Further studies by *Cahiez* showed that diamine **8** could be substituted with inexpensive tetramethylethylenediamine (TMEDA) [22]. By employing  $\text{Co}(\text{acac})_3/\text{TMEDA}$  as a catalytic system, the scope of the starting materials was expanded to vinyl and alkynyl *Grignard* reagents [23].

Additionally, *Grignard* reagents were viable promoters of Co-catalysed *Heck*-type couplings of alkyl halides with styrene derivatives [20, 24]. In these reactions *Grignard* reagents played the role of a reducing agent. Moreover, merging of the cobalt-catalysed *Kumada*- and *Heck*-type couplings resulted in the three-component reaction of alkyl halide **1**, alkyl magnesium reagent **14**, and 1,3-diene **13** (Scheme 11.7) [25].

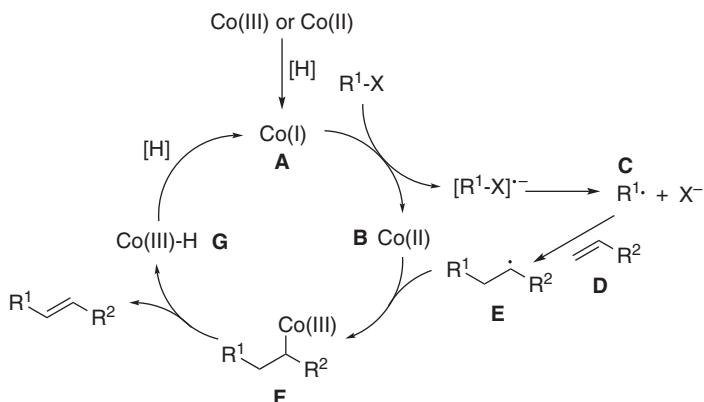


**Scheme 11.6** The Co-catalysed Kumada coupling and its application in the synthesis of prostaglandin AH13205 (12).



**Scheme 11.7** Co-catalysed three-component coupling reaction.

In contrast to the *Kumada* coupling, Co-catalysed Heck-type reactions are presumed to undergo the coupling via a Co(I)/Co(III) cycle (Scheme 11.8) [26, 27]. The catalytically active Co(I)-compound **A** reduces an alkyl halide via a single-electron transfer giving Co(II)-complex **B** and an alkyl radical **C**. The subsequent addition of alkyl radical **C** to alkene **D** furnishes radical **E**, which

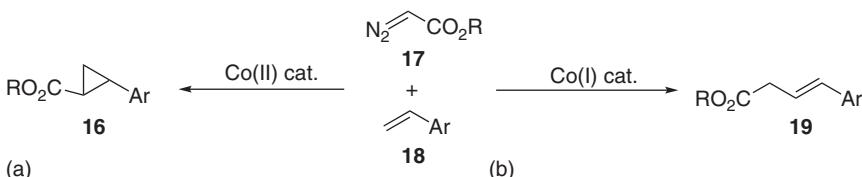


**Scheme 11.8** General mechanism of the cobalt-catalysed coupling of alkyl halides and alkenes (ligands on cobalt omitted for clarity).

is trapped by the “persistent” Co(II)-species **B** yielding Co(III)-alkyl complex **F**. The hydrogen β-elimination step produces an alkene and cobalt hydride **G**, which after reduction to Co(I) closes the catalytic cycle. In the absence of alkyl magnesium reagents, addition of a reducing agent (usually Zn or Mn) is necessary to maintain the catalytic cycle.

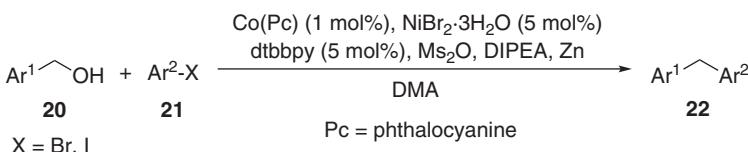
The radical mechanism of Co-mediated Heck-type couplings enabled their application to the functionalisation of both electron-rich and electron-poor alkenes. In this line, *Branchaud*'s pioneering work demonstrated that alkyl complexes of cobaloxime (cobalt dimethylglyoxime complex) undergo visible light-induced reaction with styrene derivatives leading to substituted olefins [27]. This reaction was found to be particularly useful in the alkenylation of glycosides. Furthermore, *Gosmini* reported a catalytic cross-coupling of benzyl chlorides with styryl bromides [28].

The immense effect of the cobalt oxidation state on the outcome of a reaction was reflected in the vitamin B<sub>12</sub>-catalysed reaction of styrene derivatives **18** with diazoacetates **17** (Scheme 11.9). *Zhang* showed that if a Co(II)-catalyst is utilised in this reaction, cyclopropanation of the double bond occurred, presumably via a carbenoid complex (Scheme 11.9a) [29]. On the other hand, *Gryko* demonstrated that Co(I)-complexes facilitate the radical pathway, furnishing functionalised styrene derivatives **19** (Scheme 11.9b) [30].



**Scheme 11.9** Influence of the cobalt oxidation state on the outcome of the reaction of styrene derivatives with diazoacetates. (a) Cyclopropanation and (b) The Heck coupling.

Cobalt-mediated cross-coupling reactions are not limited to the use of alkyl halides as electrophiles. Nucleophilic properties of Co(I)-complexes also enabled access to radicals derived from alkyl sulfonylates [26]. In this context, *Weix* reported the cross-coupling of benzyl mesylates (generated *in situ* from benzylic alcohols **20**) with aryl halides **21** catalysed by a Co/Ni dual metal catalytic system (Scheme 11.10) [31]. Due to their highly negative reduction potentials, benzyl mesylates reacted with Ni-catalysts slowly leading to mainly homocoupled products. This problem was eliminated by applying Co(II)-phthalocyanine as a Co-catalyst. The role of the cobalt catalyst was to generate a radical from benzyl



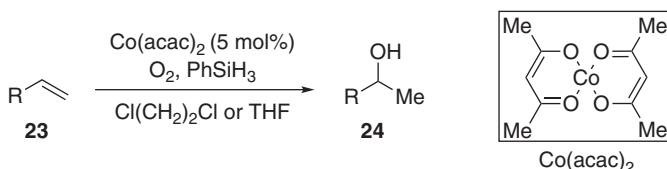
**Scheme 11.10** Coupling of benzyl mesylates and aryl halides enabled by a Co/Ni dual catalytic system.

mesylate (via nucleophilic substitution followed by homolysis of the Co—C bond), which was subsequently intercepted by the Ni-catalyst. This example showcased the potential of cobalt catalysts to access unexplored reactivities in dual catalytic systems.

In addition, cobalt compounds could also be applied to oxidative couplings of alkyl radicals with heteroarenes and alkynes [32–34]. These reactions usually required the use of an external oxidant such as O<sub>2</sub> or tBuOOH as well as elevated temperatures (120–200 °C).

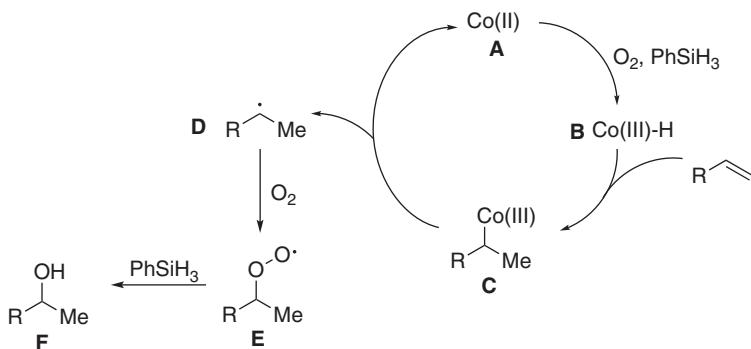
### 11.2.3 Additions to Alkenes and Alkynes

One of the most widely employed cobalt radical reactions is the *Mukaiyama* hydration (Scheme 11.11) [35, 36]. Due to its high chemoselectivity and mild conditions, this reaction has found numerous applications (i.e. in total synthesis of natural products garsubellin A [4] and indoxamycin B [37]). The *Mukaiyama* hydration falls into a broader category of cobalt-catalysed hydrofunctionalisations of alkenes. Common features of this class of reactions are similar mechanisms and excellent *Markovnikov* selectivity. Interestingly, although the aforementioned reaction is widely recognised as the progenitor of Co-mediated oxidative functionalisation of alkenes, *Pattenden* reported at roughly the same time conceptually similar work describing hydroalkylation of alkenes in the presence of cobaloxime derivatives [38].



Scheme 11.11 *Mukaiyama* hydration.

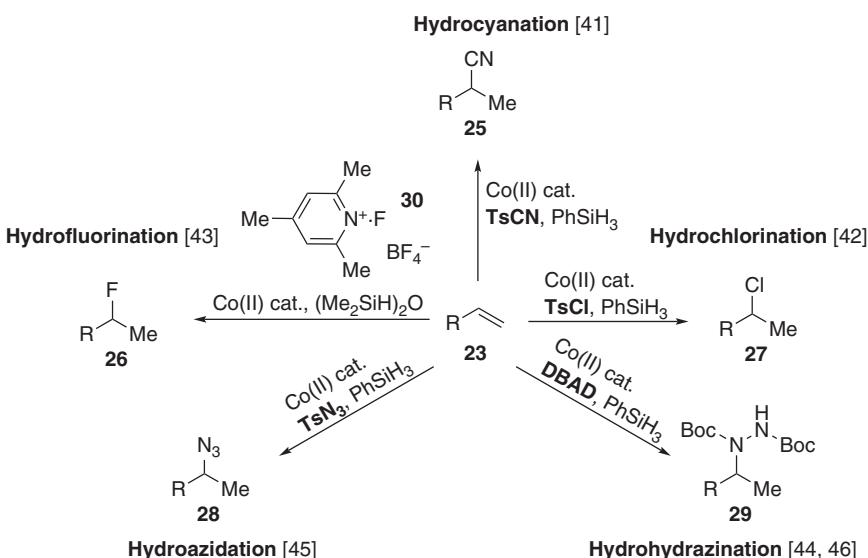
Mechanistic studies by *Nojima* supported the mechanism involving cobalt(III) hydride **B** as an intermediate (Scheme 11.12) [35, 39]. Hydride **B** reacts with an alkene in the hydrocobaltation step furnishing Co(III)-alkyl complex **C** with



Scheme 11.12 Mechanism of the *Mukaiyama* hydration.

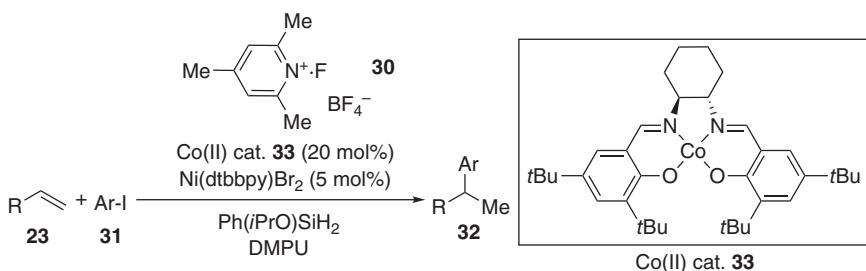
*Markovnikov* selectivity. Still, the nature of this step is disputable as different mechanistic studies support either concerted [39] or hydrogen atom transfer (HAT) mechanisms [40]. Subsequently, complex **C** undergoes homolytic cleavage to form alkyl radical **D** that is intercepted by a radical trap (in this case oxygen). The resulting peroxide radical **E** is reduced to alcohol **F** by a reductant ( $\text{PhSiH}_3$ ).

The replacement of oxygen with various radical traps led to numerous cobalt-catalysed hydrofunctionalisation reactions, namely, hydrocyanation [41], hydrochlorination [42], hydrofluorination [43], hydrohydrazination [44], and hydroazidation [45] (Scheme 11.13). Although most of these reactions could be catalysed by simple ionic Co(II)-compounds, *Carreira* found that in several cases the yield of a reaction dramatically increased when employing Co(III)- or Co(II)-complexes with salen ligands [41]. It is important to note that these reactions exhibited excellent chemoselectivity, tolerating unprotected hydroxyl groups, silyl ethers, amides, esters, ketones, acetals, halogens, nitro groups, and heterocyclic rings [41–45]. Moreover, when 1,3-dienes and 1,3-enynes were employed as substrates in hydrohydrazination reactions, 1,4-addition was favoured over 1,2-addition, leading to allylic amines [46].



Scheme 11.13 Co-catalysed hydrofunctionalisation reactions.

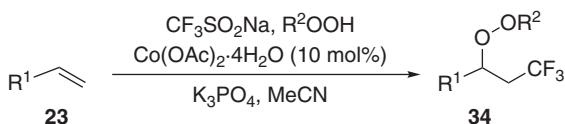
The importance of C—C bond forming reactions in organic synthesis had impelled researchers to explore the utility of the Co-catalysed hydrofunctionalisation for these types of transformations. As early as 1988, *Pattenden* showed that carbon radicals, generated by the homolytic scission of the Co—C bond in alkylcobaloxime complexes (derived from alkenes), could be trapped by *Michael* acceptors [38]. Later, *Carreira* developed catalytic C—C hydroalkylation reactions employing tosyl oximes as alkylating agents [47]. Recently, *Shenvi* reported hydroarylation of alkenes based on the Co/Ni dual catalytic system (Scheme 11.14) [48]. In this reaction  $\text{Ph}(i\text{-PrO})\text{SiH}_2$  proved to be a more



Scheme 11.14 Hydroarylation of alkenes employing Co/Ni dual catalytic system.

efficient reductant than the more generally employed  $\text{PhSiH}_3$ . Interestingly, fluoropyridinium salt **30**, usually employed as a fluorinating agent [43], served as an oxidant to facilitate the oxidation of Co(II) to Co(III) required to maintain the cobalt catalytic cycle. Moreover, the Co(II)-(salen) complex **33** was crucial for the reaction as  $\text{Co}(\text{acac})_2$  does not furnish the desired product **32**.

Co-catalysed additions to alkenes are not limited to hydrofunctionalisation reactions, as transformations allowing for installation of functional groups at both ends of the double bond are also possible. In this context, *Zhang* developed the Co-catalysed trifluoromethylation-peroxidation of double bonds (Scheme 11.15) [49]. In this reaction peroxide was installed with *Markovnikov* selectivity, while the  $\text{CF}_3$  group bounded to the less substituted end of the double bond. Moreover, *Jacobi von Wangenheim* reported a procedure for the bromo- and iodoalkylation of double and triple bonds [50]. Similarly to the reaction developed by *Zhang*, the trifluoromethyl group was introduced with *anti-Markovnikov* selectivity.

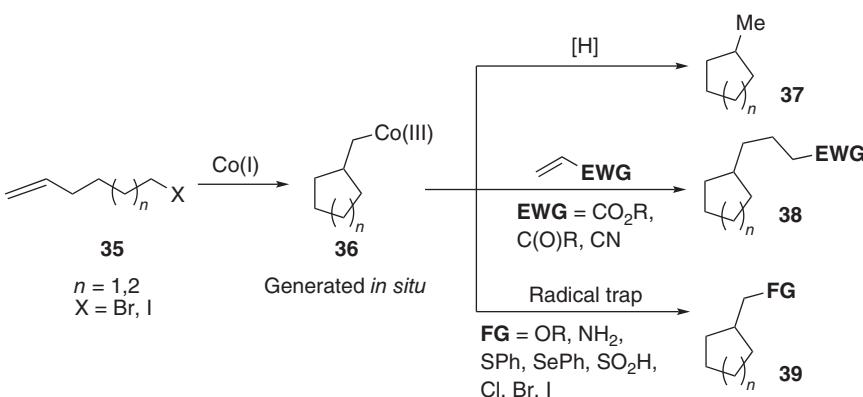


Scheme 11.15 Co-catalysed trifluoromethylation-peroxidation of alkenes.

#### 11.2.4 Cyclisation Reactions

Intramolecular reactions of radicals with multiple bonds, yielding cycloalkyl radical intermediates, are extremely fast and selective [51]. Application of the cobalt radical chemistry to these types of transformations enables multiple tandem cyclisation–functionalisation reactions.

Inspired by the mode of action of vitamin  $\text{B}_{12}$ , *Pattenden* studied the Co-mediated radical formation of five- and six-membered rings using cobaloxime and Co(salen) complexes as  $\text{B}_{12}$  mimics [52]. Under reductive conditions (electrochemical reduction,  $\text{Zn}$ ,  $\text{NaBH}_4$ ), bromo- and iodoalkenes **35** underwent cyclisations mediated by the “supernucleophilic” Co(I)-form (Scheme 11.16) [53]. On the other hand, when these reactions were carried out in the presence of radical traps or *Michael* acceptors, cyclisation–functionalisation

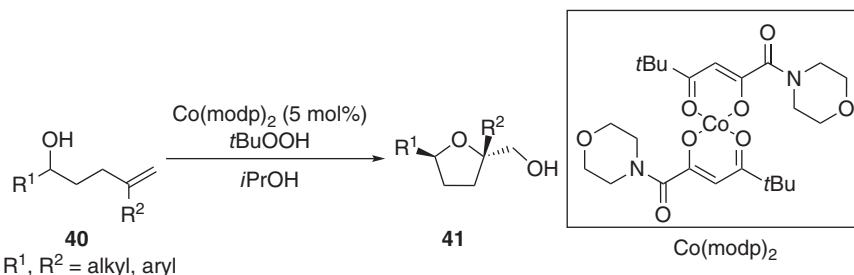


Scheme 11.16 Vitamin B<sub>12</sub>-model catalysed cyclofunctionalisation reactions.

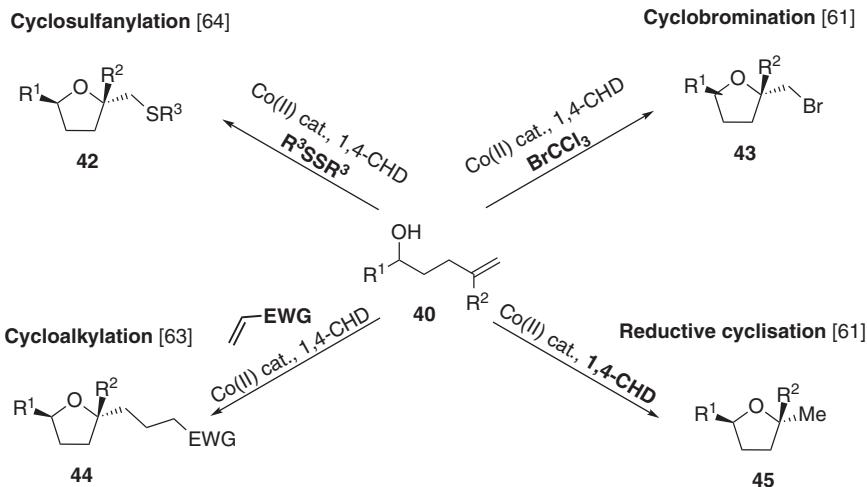
products were formed (Scheme 11.16) [54–56]. As typical for radical reactions, *exo*-trig cyclisation was generally favoured; however, in compliance with *Baldwin's rules*, 5-bromoalkenes furnished exclusively five-membered rings via a 5-*endo*-trig mechanism.

The aforementioned methods have found application in the synthesis of heterocycles. Co(salen) complexes have been used as catalysts in the synthesis of benzofurans and indoles from allyl-substituted 2-iodophenols and anilines, respectively [57]. The mild conditions required for this method allowed for its efficacy in the synthesis of functionalised  $\beta$ -lactams from *N*-allylcaramoyl chlorides using carbamoylcobalt(salophen) complexes [58, 59]. The same conditions were also suitable for the synthesis of  $\gamma$ - and  $\delta$ -lactams [58, 59].

Studies on the *Mukaiyama* hydration led to the discovery of an unexpected cyclisation of  $\gamma,\delta$ -unsaturated alcohols **40** to functionalised tetrahydrofurans (THFs) **41** (Scheme 11.17) [60]. The reaction could be performed using hydroperoxides (i.e. *t*BuOOH) or oxygen (including atmospheric O<sub>2</sub>) as oxidants [60, 61]. Similarly to the *Mukaiyama* hydration, the replacement of an oxidant with a radical trap led to numerous cyclisation/functionalisation reactions (Scheme 11.18) [61–64]. Interestingly, these reactions required the addition of an external reductant (usually 1,4-cyclohexadiene [1,4-CHD]), suggesting that in the absence of an oxidant, the reductive mechanism is favoured.

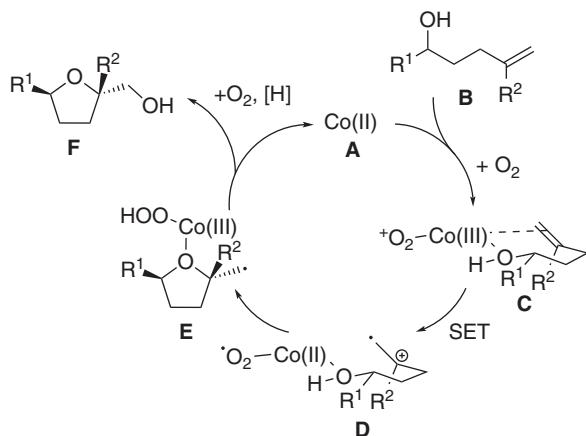


Scheme 11.17 The *Mukaiyama* cyclisation of  $\gamma,\delta$ -unsaturated alcohols **43**.



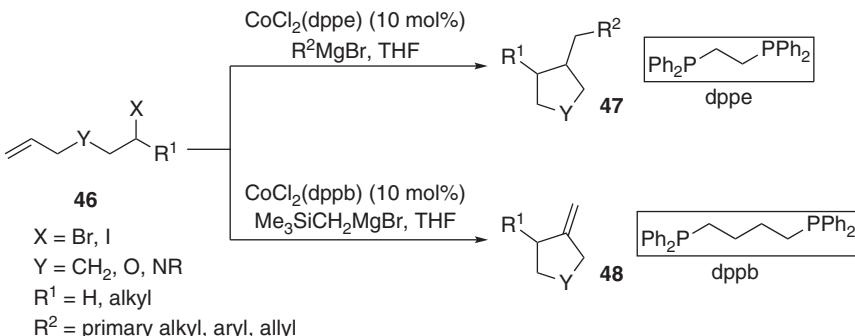
Scheme 11.18 Modifications of the Mukaiyama cyclisation.

Based on the mechanistic studies by Hartung [61, 65], it was proposed that the hydroxyl group is coordinated by a Co(III)-ion in intermediate complex **C** (Scheme 11.19). Subsequently, the double bond undergoes a single-electron oxidation by the cobalt superoxide complex, followed by intramolecular cyclisation. The reaction proceeded with an excellent 2,5-*trans*-selectivity, which was explained by the chair-like thermodynamically favoured folding of the alkenol chain in intermediates **C** and **D** directing substituents at C2 and C5 in *pseudo-equatorial* positions. Importantly, while the diastereoselectivity of the oxidative cyclisation (Scheme 11.17) was highest in polar solvents, the reductive cyclisation/functionalisation reactions (Scheme 11.18) provided the best results in terms of stereoselectivity in nonpolar solvents [61].



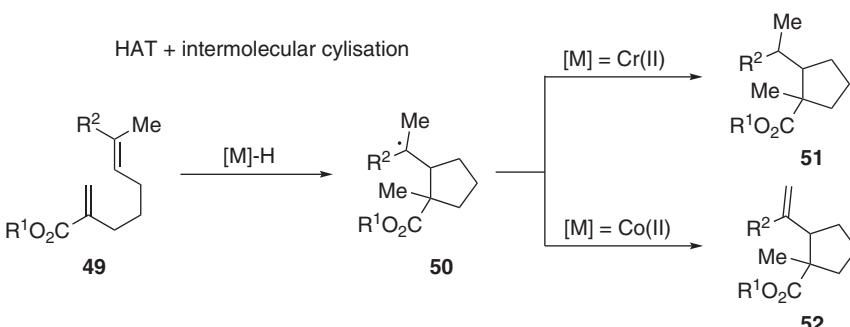
Scheme 11.19 Mechanism of the oxidative Mukaiyama cyclisation proposed by Hartung [65].

Merging the cobalt-catalysed cross-coupling chemistry with a radical ring-closure enabled tandem cyclisation–coupling reactions. In the case when the electrophilic coupling partner contained multiple bonds in its structure, alkyl radicals formed via the single-electron transfer process (Section 11.2.2; Schemes 11.5 and 11.8) preferentially underwent intermolecular ring-closure, followed by the coupling step. *Oshima* applied this concept in both *Kumada*-[66, 67] and *Heck*-type couplings (Scheme 11.20) [68]. Furthermore, the *Kumada*/cyclisation reaction was also suitable for the synthesis of functionalised lactones [67].



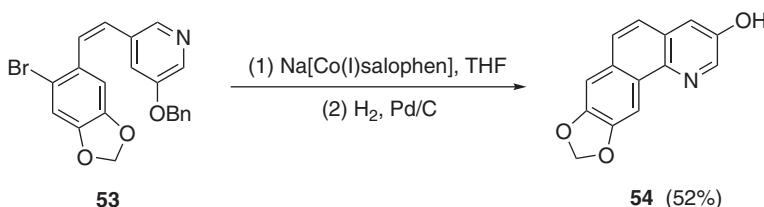
Scheme 11.20 Cobalt-catalysed tandem cyclisation/cross-coupling reactions.

*Norton* studied cobalt-catalysed reductive cyclisation [69] and cycloisomerisation [70] of dienes under H<sub>2</sub> atmosphere. Mechanistic studies supported the HAT mechanism involving a cobalt hydride as an intermediate (Scheme 11.21). Furthermore, the Co–H complex favoured the reaction with electron-deficient olefins. Interestingly, kinetic studies and experimental results showed that the outcome of the reaction could be altered by the choice of a catalyst. Chromium complexes forming relatively stable hydrides (i.e. CpCr(CO)<sub>3</sub>H, Cp = η<sup>5</sup>-cyclopentadienyl) promoted the reductive cyclisation to product 51. Conversely, cobaloxime complexes, due to their “persistent” radical nature, easily partook in the abstraction of the hydrogen radical, leading to cycloisomerised product 52.



Scheme 11.21 Cobalt vs. chromium in reductive cyclisation.

So far all of the discussed cyclisation reactions led to the formation of saturated cyclic compounds. Nevertheless, radical cobalt-mediated reactions could be also utilised for the synthesis of aromatic rings. In this context, *Harrowven* reported the total synthesis of an alkaloid – taddoquinoline (**54**) – in which the key cyclisation step was mediated by a Co(I)-salophen complex (Scheme 11.22) [71]. In this reaction, the cobalt complex not only generated an aryl radical but also coordinated to the nitrogen lone pair of the pyridine ring, promoting the radical cyclisation with excellent regioselectivity. In addition, *Chattopadhyay* showed that  $\alpha$ -pyridyldiazo compounds undergo the Co(II)porphyrin-catalysed radical addition either to alkynes or alkenes, affording indolizines and cyclopropanes, respectively [72].



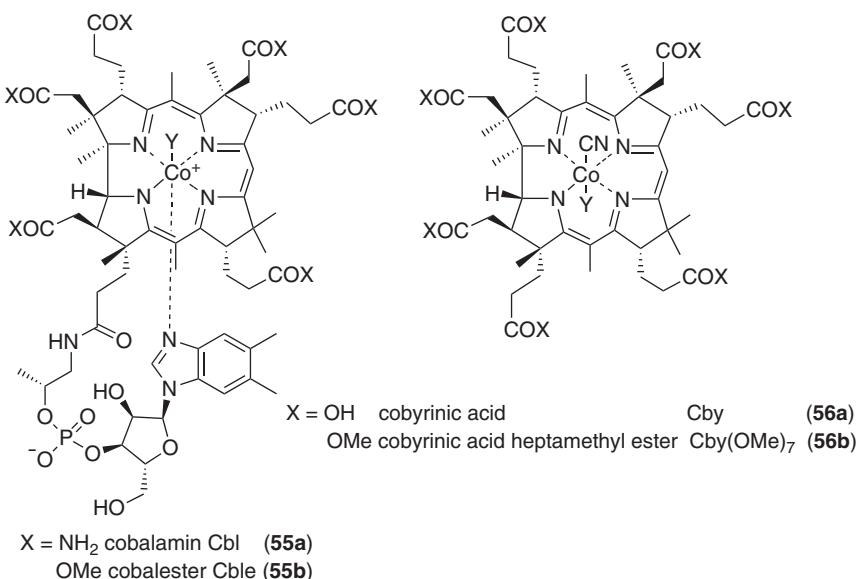
**Scheme 11.22** Cobalt-mediated cyclisation in the synthesis of taddoquinoline (**54**).

### 11.2.5 Dehalogenation

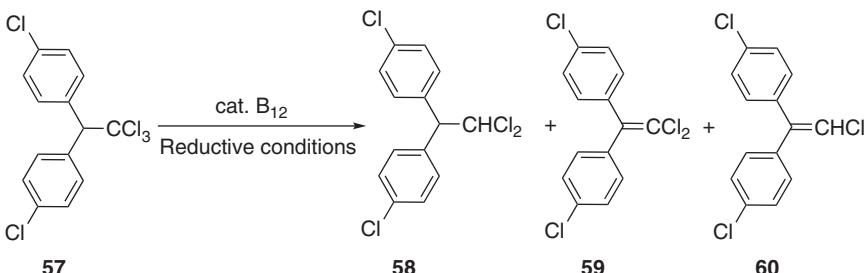
Dehalogenation is among the most comprehensively studied reactions catalysed by vitamin B<sub>12</sub> and its derivatives. Inspiration for this type of reactions came from the discovery of B<sub>12</sub>-dependent reductive dehalogenases in organohalide-respiring bacteria [73]. Due to its potential utility in the remediation of polyhalogenated pollutants, a great effort was made to harness this reactivity for synthetic organic chemistry [3].

Mechanistic studies on the vitamin B<sub>12</sub>-catalysed dehalogenation revealed that the reaction occurs via a nucleophilic substitution of the halogen atom by the “supernucleophilic” Co(I)-complex [74]. However, recent work suggested that in particular cases (i.e. dehalogenation of haloalkenes or -arenes), a single-electron transfer step may be involved [74, 75]. Due to the stability of Co in the +3 oxidation state in vitamin B<sub>12</sub> derivatives, reductive conditions are required to generate a catalytically active form of Co(I). As the high polarity of native vitamin B<sub>12</sub> (cobalamin, Cbl) (**55a**) renders it insoluble in most commonly used organic solvents (i.e. acetonitrile, THF, toluene), the amphiphilic cobalester (**55b**) and hydrophobic cobyrinic acid derivatives (Cby) **56** are frequently used as B<sub>12</sub>-models in organic media (Figure 11.1) [3, 76].

In view of the aforementioned reactivity of a wide variety of halogenated compounds with vitamin B<sub>12</sub>, *Schrauzer* applied this process for the degradation of toxic pesticides (mirex and keptone) [77]. In this line, *Hisaeda* extensively studied the dehalogenation of insecticide DDT (dichlorodiphenyltrichloroethane, **57**), infamous for its negative environmental impact (Scheme 11.23) [78]. These reactions could be realised using numerous reductive methods including chemical



**Figure 11.1** Structure of native vitamin B<sub>12</sub> (55a), amphiphilic cobalester (55b), and hydrophobic cobyrinic acid derivatives 56.

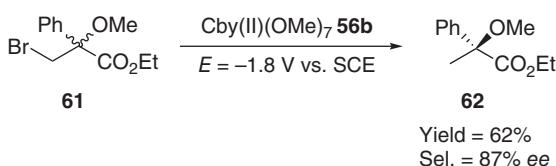


**Scheme 11.23** Vitamin B<sub>12</sub>-catalysed dehalogenation of toxic insecticide – DDT (57).

(i.e. Zn or  $\text{NaBH}_4$ ) [79], electrochemical [80], and photocatalytic [81]. In addition, heterogeneous catalysts obtained by immobilisation of vitamin B<sub>12</sub> derivatives on electrodes [81, 82], binding within hyperbranched polymers [80], or adsorption on nanomaterials [83] proved to be effective for such dehalogenation reactions.

The chiral structure of vitamin B<sub>12</sub> and derivatives opened a possibility for their application in asymmetric catalysis. Murakami studied the enantioselective debromination of  $\beta$ -bromoester **61** (Scheme 11.24) [84]. Using the hydrophobic catalyst **56b** in combination with electrochemical reduction, the reaction furnished the *S* isomer of product **62** with *ee* = 87%.

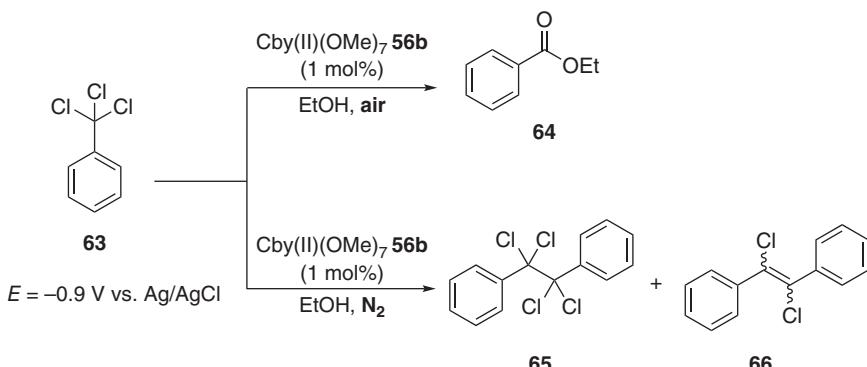
Most of the vitamin B<sub>12</sub>-catalysed dehalogenation reactions are based on the cleavage of C–Cl, C–Br, or C–I bonds. Defluorination reactions are much more challenging due to the higher dissociation energy of the C–F bond (ca. 485 kJ/mol). Nevertheless, native vitamin B<sub>12</sub> in the presence of Ti(III) citrate as a reductant catalysed radical defluorination of polyfluorinated



Scheme 11.24 Vitamin B<sub>12</sub>-catalysed asymmetric debromination.

sulfones [85]. Recently, Hisaeda reported defluorination of allylic fluorides via a S<sub>N</sub>2' mechanism, in which the Co(I)-form of the catalyst plays the role of a nucleophile [86].

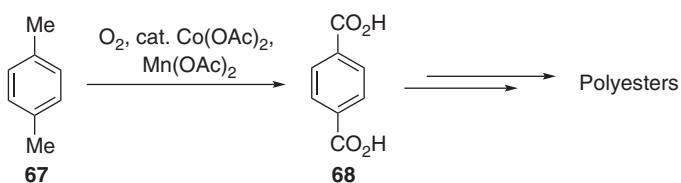
The reaction conditions had a significant impact on the outcome of the dehalogenation of trichlorotoluene (**63**) (Scheme 11.25) [87, 88]. When the reaction was performed in alcohols (i.e. MeOH, EtOH) under an atmosphere of air, benzoic acid esters **64** were obtained instead of the expected dehalogenated products **65** and **66**. Mechanistic studies revealed that in the presence of oxygen, an acyl chloride was formed as an intermediate, which subsequently reacted with the solvent. Similarly, when the reaction was performed in the presence of amines, corresponding amides were obtained.



Scheme 11.25 The influence of the reaction conditions on the outcome of a Co-catalysed dehalogenation reaction.

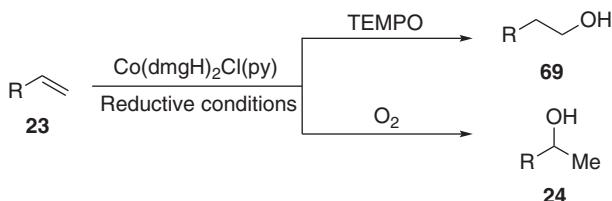
### 11.2.6 Oxidation

Cobalt-catalysed radical oxidation reactions are highly significant in the chemical industry as they have found applications in converting hydrocarbons – a petroleum-based feedstock – to products of commercial importance [89–91]. For example, cobalt–manganese catalysts are routinely used in process-scale oxidation of *p*-xylene (**67**) to terephthalic acid (**68**) – a substrate for polyesters production (i.e. PET – poly(ethylene terephthalate)) (Scheme 11.26) [89, 90]. In these processes, the cobalt catalyst is involved in the generation of a range of carbon- and oxygen-centred radicals by initiating chain decomposition of hydroperoxides, formed as intermediates in the reaction [90].



**Scheme 11.26** Application of cobalt catalysis in the industrial synthesis of terephthalic acid (68).

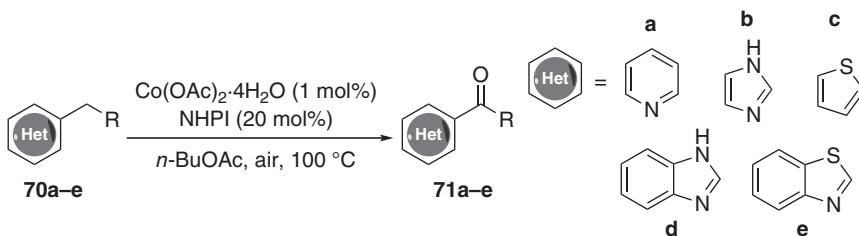
Reactions catalysed by vitamin B<sub>12</sub> models (cobaloximes and Co(salen) complexes) in the presence of molecular oxygen and O-centred radical traps (i.e. TEMPO – (2,2,6,6-tetramethylpiperidin-1-yl)oxyl) were studied by *Pattenden* and *Prandi* [92, 93]. Cobaloxime was shown to enable the selective oxidation of alkenes and polyenes [92]. In the presence of TEMPO as a radical trap, oxidation occurred with *anti-Markovnikov* selectivity, while under an oxygen atmosphere, oxidation was favoured at the more substituted end of the double bond (Scheme 11.27). The authors suggested that differences in the selectivity could be explained by the relative steric demands of the two oxidants.



**Scheme 11.27** Dependence of the Co-catalysed oxidation outcome on the oxidant.

Co-catalysed tandem cyclisation–oxidation reactions were applied to the synthesis of numerous biologically important scaffolds [93, 94]. *Prandi* utilised this chemistry in the functionalisation of glycosides and synthesis of carbocyclic analogues of sugars [93]. Co(acac)<sub>2</sub>, in the presence of *t*BuOOH as an oxidant, catalysed the synthesis of functionalised quinolin-2-(1*H*)-ones [94]. In this reaction, the cobalt catalyst played a dual role – generating an alkyl radical to initiate cyclisation and forming an oxygen-centred radical from hydroperoxide promoting the oxidation. It was proposed that the oxidation step follows the *Kornblum–DeLaMare* rearrangement mechanism.

The catalytic system Co(OAc)<sub>2</sub>/NHPI (*N*-hydroxyphthalimide) was employed in peroxide-free aerobic oxidation reactions [95, 96]. In these reactions, Co-catalyst mediates the formation of oxygen-centred radicals from NHPI, which subsequently form alkyl radicals via hydrogen atom abstraction. *Shia* applied this system in the tandem cyclisation/oxidation of 5,6-ynones leading to substituted cyclopentenes [95]. Moreover, the aforementioned catalyst also enabled benzylic C–H oxidation of pharmaceutically relevant molecules (Scheme 11.28) [96]. Challenging heterocyclic substrates, most notably imidazole, benzothiazole, and benzimidazole derivatives like **70a–e** were viable substrates in this reaction, allowing its application to the synthesis of phosphodiesterase 10A



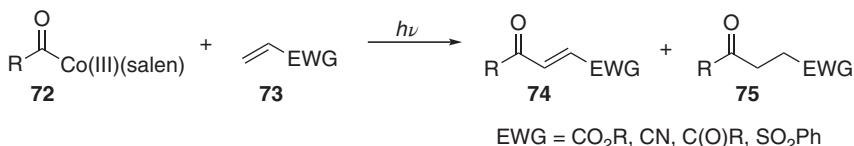
**Scheme 11.28** Benzyl C–H oxidation of pharmaceutically relevant molecules.

inhibitor – AMG 579. The oxidation proceeded with good yields regardless of the position of an alkyl chain on the heterocycle (excluding heteroatoms).

### 11.2.7 Acylation

All of the previously discussed reactions involved generation of alkyl radicals. Besides their reactivity towards alkyl electrophiles, “supernucleophilic” Co(I)-species also react with electrophilic acyl derivatives leading to acyl-cobalt(III) complexes. The tendency of the Co(III)–C bonds towards homolytic scission renders them a useful tool for generation of acyl radicals. Nucleophilic reactivity of these species enables their application as an acyl anion equivalent in organic synthesis [97].

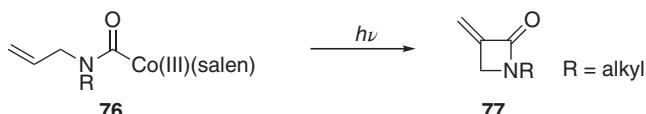
Pattenden studied the reactivity of acyl cobalt complex **72**, formed in the stoichiometric reaction of cobalt(II)-(salen) with acyl chlorides under reductive conditions (sodium amalgam) [59, 98]. These compounds proved to be air-stable, crystalline solids that facilitated their isolation. Photolytic dissociation of the Co–C bond in these complexes led to acyl radicals, which reacted with *Michael* acceptors **73** furnishing a mixture of products **74** and **75** (Scheme 11.29) [98]. On the other hand, acyl cobalt-(salen) complexes, formed from benzylacetyl or allylacetyl chlorides, in the presence of radical traps (TEMPO, phenyl disulfide, nitrogen oxide) gave exclusively alkyl derivatives [59]. In this case, the competing decarbonylation of acyl radicals predominated due to the formation of stabilised benzyl and allyl radicals.



**Scheme 11.29** Reaction of acyl cobalt(salen) complexes **72** with *Michael* acceptors **73**.

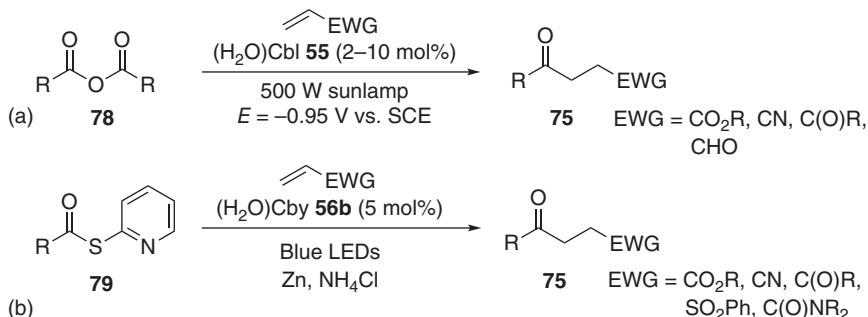
The scope of acyl cobalt-(salen) complexes was further expanded by alkoxy [59] and carbamoyl derivatives [58]. In the presence of radical traps (i.e. TEMPO) alkoxy derivatives furnished the corresponding oxyacyl derivatives, while in the absence of trapping agents, alkoxy carbonyl cobalt complexes bearing double bonds in their structure underwent cyclisation furnishing lactones [59]. Similarly

carbamoyl radicals generated from *N*-allylcarbamoylcobalt complexes **76** have found application in the synthesis of  $\beta$ -lactams **77** under photochemical conditions (Scheme 11.30) [58]. Remarkably, in this reaction a 4-*exo*-trig mechanism leading to a more strained four-membered ring was favoured. Despite being favoured by the *Baldwin's* rules, radical 4-*exo* cyclisations are scarce in the literature, due to their low reaction rates competing with intermolecular radical termination. Presumably, in the aforementioned example stabilising effect of “persistent” Co(II) complex facilitates intramolecular cyclisation.



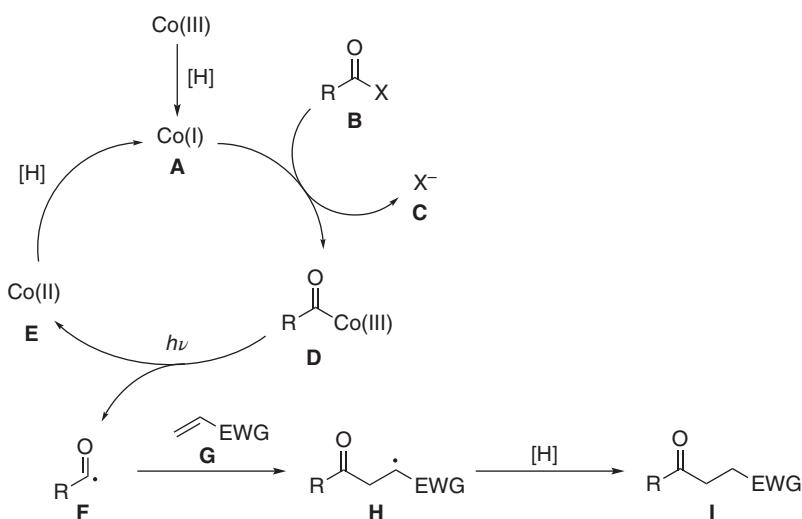
**Scheme 11.30** Application of carbamoyl cobalt(salen) complexes **76** in the synthesis of  $\beta$ -lactams **77**.

The main drawback of the discussed methods is the requirement of using the acylcobalt reagents in a stoichiometric amount. In order to overcome this limitation, Scheffold and Gryko investigated catalytic methods for the generation of acyl radicals using vitamin B<sub>12</sub> derivatives **55** and **56b** as catalysts and employed them in the acylation of *Michael* acceptors (Scheme 11.31) [99, 100]. Scheffold's method was based on the utilisation of carboxylic acid anhydrides **78** under electrochemical reduction conditions ( $E = -0.95$  V vs. SCE [saturated calomel electrode]) (Scheme 11.31a) [99], while Gryko's used 2-*S*-pyridyl thioesters **79** in the presence of Zn/NH<sub>4</sub>Cl as a reductant (Scheme 11.31b) [100]. Both methods tolerate a wide range of Michael acceptors; however, the Gryko's reaction is more general in respect to the acyl coupling partner, as 2-*S*-pyridyl thioesters **79** are air and moisture stable and can be readily prepared from carboxylic acids.



**Scheme 11.31** Cobalt-catalysed acylation of *Michael* acceptors.

Mechanistic studies show that in these reactions the Co(I)-form **A**, formed *in situ* under reductive conditions, reacts with the electrophilic acyl derivative **B** giving acylcobalt complex **D** (Scheme 11.32) [100]. Subsequently, acyl radical **F**, generated by photolytic cleavage of the Co—C bond, undergoes the *Giese*-type addition to *Michael* acceptors **G**.



**Scheme 11.32** Mechanism of cobalt-catalysed acylation of *Michael acceptors*.

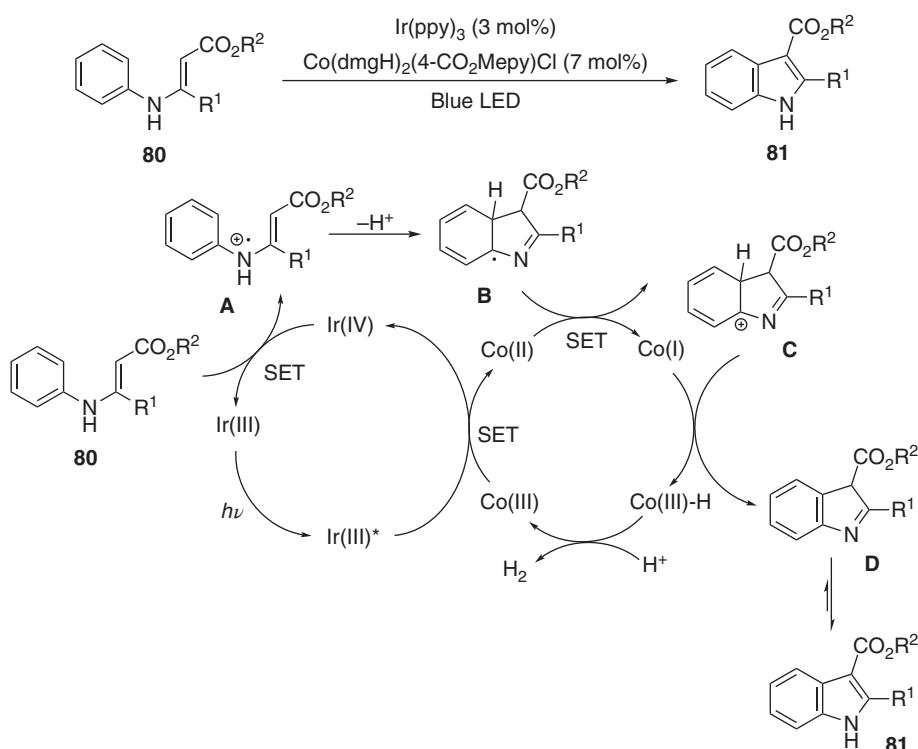
### 11.2.8 Applications of Cobalt Complexes in Photoredox Catalysis

The renaissance of photochemistry in recent years is associated with the rapid development of photoredox catalysis [101, 102]. The merging of light-mediated processes with cobalt radical chemistry has opened new avenues in organic synthesis. In this line, the use of cobaloxime complexes in combination with a photocatalyst enabled the realisation of stepwise two-electron transformations via two consecutive single-electron oxidations of a substrate.

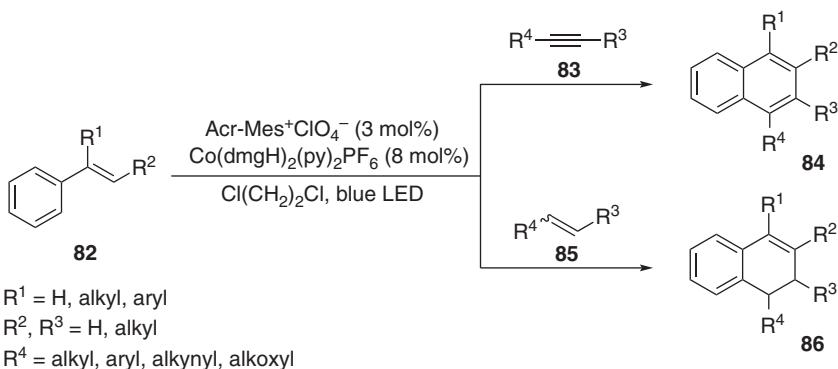
Mechanistic aspects of cobalt/photoredox dual catalysis can be discussed through examination of indole (**81**) synthesis via light-driven radical intramolecular cyclisation of substrate **80** (Scheme 11.33) [103]. The main role of the iridium photocatalyst is the single-electron oxidation of enamine **80** to a radical cation **A**, which subsequently undergoes cyclisation to intermediate **B**. Cobaloxime plays a triple role by (i) providing an oxidised form of the photocatalyst by the oxidative quenching of its excited state, (ii) oxidising radical **B** to cation **C**, and (iii) deprotonating intermediates **A** and **C**, which obviates the requirement of an external base. Moreover, the Co/photoredox dual catalytic reactions are usually accompanied by the evolution of hydrogen, which can serve as a reductant in this reaction.

*Lei* demonstrated that replacement of enamines with thiobenzanilides, in the aforementioned reaction, enabled the synthesis of benzothiazoles [104]. Moreover, the application of H<sub>2</sub> generated as a by-product was used in the *in situ* reduction of nitroarenes, without addition of a sacrificial oxidant or reductant [104].

Cobalt catalysts can also be used in conjunction with organic dyes. Combination of cobaloxime with *Fukuzumi's* 9-mesityl-10-methylacridinium (Acr-Mes<sup>+</sup>) salts facilitated the construction of aromatic rings via the formal [4+2] cycloaddition of styrene **82** to alkyne **83** or alkene **85** (Scheme 11.34) [105]. In these reactions a highly oxidative photoredox catalyst [Acr-Mes<sup>+</sup>; E<sub>1/2</sub>(PC<sup>\*</sup>/PC<sup>-</sup>) = +2.06 V vs. SCE] was required to generate a radical cation



Scheme 11.33 Proposed mechanism of Ir/Co-catalysed indole synthesis (ligands and charges of Co and Ir catalysts omitted for clarity).



Scheme 11.34 Cobalt/photoredox-catalysed formal [4+2] cyclisation.

from an unactivated double bond. As in the example depicted on Scheme 11.33, the cobaloxime catalytic cycle played a triple role and was accompanied by the evolution of H<sub>2</sub>. In addition, using benzylimines instead of styrenes led to functionalised 3,4-dihydroisoquinolines [106].

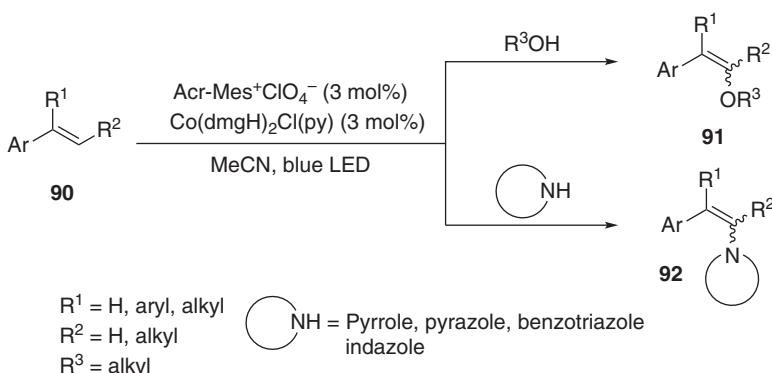
Besides the aforementioned cyclisations, cobaloxime/photoredox dual catalytic systems offer access to numerous intermolecular C—C and C—X bond-forming reactions. Merging two inexpensive catalysts – Eosin Y and

$\text{Co}(\text{dmgH})_2\text{Cl}_2$  – enabled the construction of a  $C_{\text{sp}}^3$ – $C_{\text{sp}}^2$  bond in the oxidative alkylation of indoles [107]. This reaction occurred with the excellent C-3 regioselectivity and tolerated unprotected indoles as well as a range of functionalities (i.e. ester, aryl halides). However, with respect to alkylating agents, it was limited to radical cations generated from *N*-aryl tetrahydroisoquinolines. Moreover, the triple catalytic system:  $\text{Acr-Mes}^+\text{ClO}_4^-/\text{Co}(\text{dmgBF}_2)_2/\text{Cu}(\text{OTf})_2$  promoted  $C_{\text{sp}}^3$ – $C_{\text{sp}}^3$  bond forming reactions of oxonium ions (generated *in situ* in radical fashion from substrate **87**) with 1,3-dicarbonyl compounds **88** (Scheme 11.35) [108]. In this reaction, the Cu-catalyst acted as a *Lewis* acid activating nucleophile, and it is noteworthy that several other *Lewis* acids including Fe salts were also effective in the reaction.



Scheme 11.35 Photoredox C–H alkylation of 1,3-dicarbonyl compounds **88**.

Late-stage selective introduction of small functional groups (i.e. OH,  $\text{NH}_2$ ) is of uttermost importance in the field of drug development. Recognising this issue, *Wu* and *Tung* reported cobaloxime/quinolinium-catalysed C–H amination and hydroxylation reactions of aromatic rings [109]. The challenging generation of an aryl radical cation required the highly oxidative 3-cyano-1-methylquinolinium dye [ $E_{1/2}(\text{PC}^*/\text{PC}^-) = +2.72 \text{ V vs. SCE}$ ], and as a consequence UV light irradiation was to promote the photocatalyst to an excited state. *Lei* further developed this strategy, reporting C–H alkyloxylation and amination of styrene derivatives **90** under visible light irradiation (Scheme 11.36) [110]. This reaction gave straightforward access to multiple enol ethers **91** and pyrrole derivatives **92**. Moreover, the introduction of a functional group occurred selectively at the terminal end of the double bond.

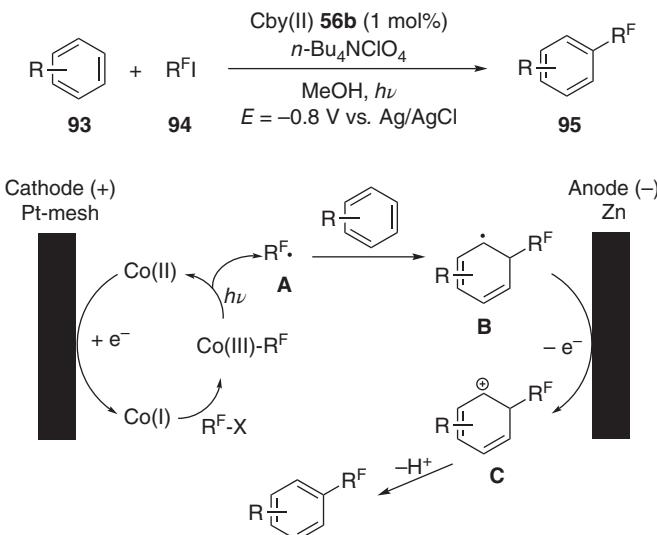


Scheme 11.36 Photoredox C–H alkyloxylation and amination of styrenes **90**.

### 11.2.9 Miscellaneous Reactions

In addition to the reaction types discussed in the previous sections, cobalt radical chemistry offers access to a number of less explored transformations.

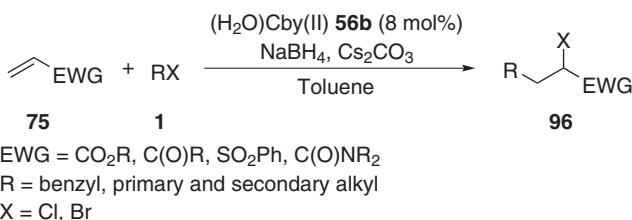
*Hisaeda* reported electrochemical trifluoromethylation and perfluoroalkylation of arenes catalysed by vitamin B<sub>12</sub> derivative **56b** (Scheme 11.37) [111]. This reaction used a paired electrode system, with the Co-catalyst being reduced to the active “supernucleophilic” form on the cathode (Pt-mesh). Although, the mechanism has not been fully elucidated, oxidation of radical intermediate **B** to cation **C** is likely to proceed on the anode (Zn) surface due to the absence of external oxidants. In addition, electron-rich heterocycles (*N*-substituted pyrroles and indoles) were suitable substrates. The activation of the Co—CF<sub>3</sub> bond was also investigated by *Soper*, who studied the photochemical properties of a trifluoromethylated Co(III)-complex with pincer ligands [112]. Photolytic cleavage of the Co—C bond in this complex allowed for trifluoromethylation of arenes and heteroarenes (pyrroles, furans, thiophenes).



**Scheme 11.37** Electrochemically enabled Co-catalysed prefluoroalkylation of arenes.

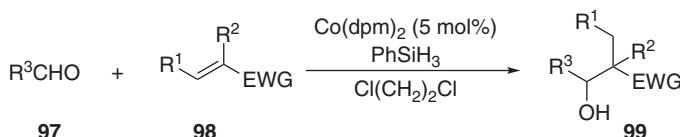
Although vitamin B<sub>12</sub> derivatives are well known for their reactivity in dehalogenation reactions (Section 2.5), they can also be applied in C—X bond formation reactions [113]. Heptamethyl cobyrinate (**56b**), under reductive conditions catalysed atom-transfer radical addition (ATRA) of alkyl halides **1** to *Michael* acceptors **75** (Scheme 11.38). Due to the fact that long reaction times favoured dehalogenation, the efficiency of ATRA was dramatically improved by employing microwave irradiation. This work displayed the ability of cobalt species to catalyse a reaction that for a long time has only been associated to work with other transition metals (i.e. Cu) [114].

Application of *Mukaiyama* hydration conditions (Section 2.3) to the reaction of aldehydes **97** with *Michael* acceptors **98** led to a remarkable example of the



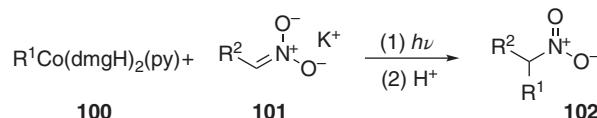
Scheme 11.38 Co-catalysed atom-transfer radical addition.

Co-mediated quaternary carbon centre formation [115]. The reaction between two electrophilic compounds led to the formation of  $\beta$ -hydroxy esters, nitriles, or ketones **99** (Scheme 11.39). Interestingly, in the case of amides, the reaction favoured the formation of *syn*-products, while other *Michael* acceptors produced statistical mixtures of diastereoisomers.



Scheme 11.39 Mukaiyama reaction of aldehydes **97** with *Michael* acceptors **98**.

In general, reactions of alkyl halides with alkanenitronates **101** led to O-alkylation with only a little amount of the C-alkylation product observed [116]. However, *Branchaud* reported that excellent regioselectivity in C-alkylation could be achieved in the reaction of alkanenitronates **101** with alkyl radicals generated from alkylcobaloxime complexes **100** (Scheme 11.40) [117]. The main drawback of this method is the lack of a catalytic protocol, due to incompatibility of the nitro group with the reductive conditions required to close the cobalt catalytic cycle. Further studies showed that the scope of the aforementioned reaction could be expanded by pyridinium, quinolinium, benzothiazolium, and benzimidazolium salts [118]. While alkylations of benzothiazolium and benzimidazolium substrates occurred exclusively at the C-2 position, reactions with pyridinium and quinolinium cations led to mixtures of *ortho*- and *para*-substituted products.



Scheme 11.40 Co-mediated regioselective C-alkylation of alkanenitronates **101**.

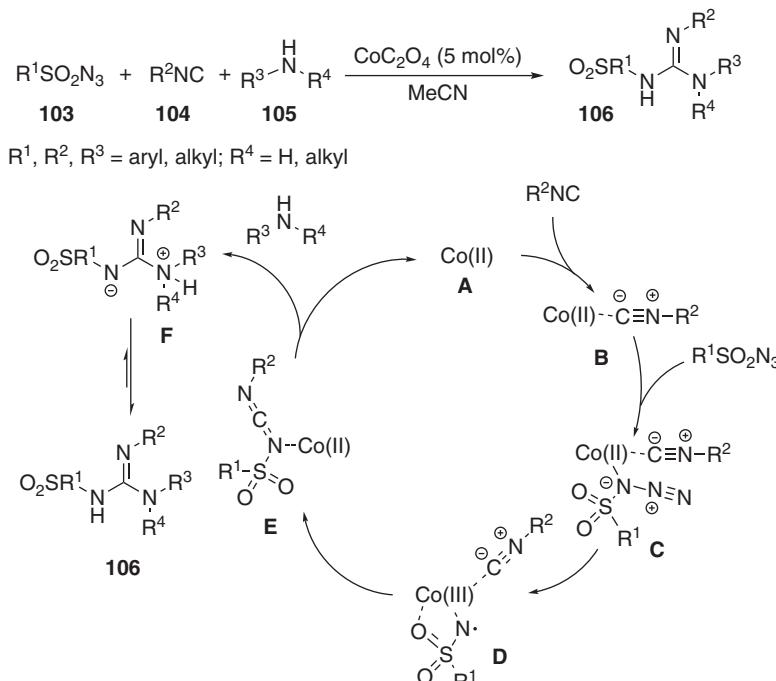
## 11.3 Cobalt-Mediated Reactions of Heteroatom-Centred Radicals

### 11.3.1 Nitrogen-Centred Radicals

Co(II)-complexes, especially of porphyrinoid type, are remarkably effective at activation of organic azides via the formation of metallonitrene radicals [119]. This section highlights applications of these reactive species in cobalt-promoted reactions.

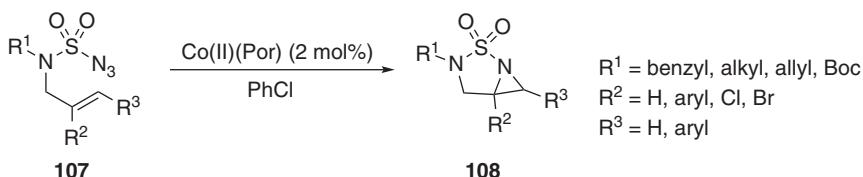
The simple cobalt salt – cobalt(II) oxalate – proved to be an effective catalyst in the three-component reaction of sulfonyl azides **103** and isonitriles **104** with amines **105**, leading to functionalised guanidines **106** (Scheme 11.41) [120]. Based on mechanistic and computational studies, authors suggested that the main catalytic role of the Co-catalyst may be attributed to promoting the dissociation of nitrogen from the azide to produce the Co(III)-nitrene radical intermediate **D**. Moreover, the high affinity of Co towards isocyanide ligands simplified the subsequent coupling of intermediate **D** with isocyanide. The resulting electrophilic carbodiimide **E** readily reacted with a nucleophilic amine furnishing guanidine **106**.

Co(II)-based metallonitrene catalysis has been successfully applied in numerous cyclisation reactions leading to *N*-heterocycles. Zhang reported a Co(porphyrin)-catalysed synthesis of [3.1.0]-bicyclic sulfamoyl aziridines **108** via the intramolecular aziridination of *N*-allylic sulfamoyl azides **107**



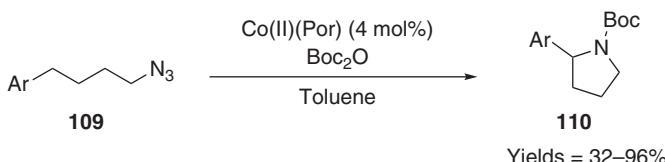
Scheme 11.41 Mechanism of the Co-catalysed three-component synthesis of guanidines **106**.

(Scheme 11.42) [121]. Moreover, the intermolecular reaction facilitated the formation of aziridines from sulfonyl azides and styrene derivatives [122]. Application of computational methods allowed for optimisation of the catalyst's structure [121, 122], and as a result, introduction of *ortho*-*N*-acylanilyl substituents at the *meso*-positions of the porphyrin ring led to an increase in the efficacy of the catalyst, due to stabilisation of the nitrene radical via intramolecular hydrogen bonding.



**Scheme 11.42** Synthesis of bicyclic compounds **108** via Co-catalysed intramolecular aziridination.

Furthermore, cobalt catalysts have found applications in the synthesis of five- and six-membered heterocycles via intramolecular C–H amination. *Zhang* presented a Co(porphyrin)-catalysed formation of six-membered heterocycles via amination of electron-deficient C–H bonds [119]. In this line, *de Bruin* synthesised *N*-acylated pyrrolidines **110** from 4-arylazides **109** (Scheme 11.43) [123]. The addition of an amine-trapping agent ( $\text{Boc}_2\text{O}$ ) proved to be crucial, as in its absence no conversion of starting material **109** was observed. This reaction served as a model for extensive studies on the catalytic properties of a series of Co(II)-corroles [124].

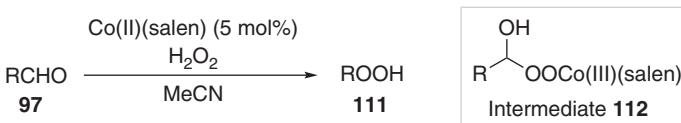


**Scheme 11.43** Co(porphyrin)-catalysed cyclisation of azides **109**.

### 11.3.2 Other Types of Radicals

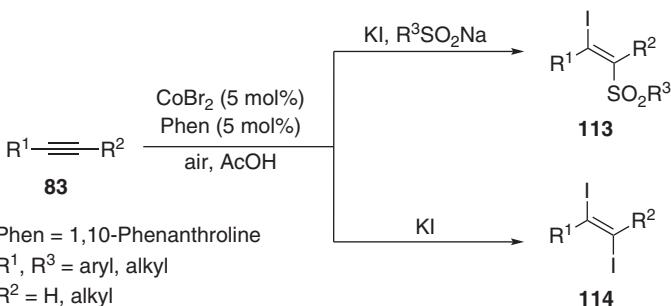
Although the application of Co-complexes for the generation of radicals different to those previously discussed still remain largely unexplored, however, several reports showed their utility in the formation of chalcogen-centred radicals.

Studies on Co(II)(salen) complexes with aryloxy ligands indicated their ability to significantly reduce the oxidation potential required to generate aryloxy radicals from the corresponding anions [125]. Moreover, Co(II)(salen) complexes reacted with  $\text{H}_2\text{O}_2$  furnishing Co(III) hydroperoxide and peroxide radicals. This reactivity has found application in the oxidative deformylation of aldehydes **97** leading to alkyl hydroperoxides **111** (Scheme 11.44) [126]. It was proposed that the deformylation step occurs via fragmentation of intermediate **112**, formed in the reaction of an aldehyde with a Co(III)-peroxide radical.



**Scheme 11.44** Deformylative oxidation of aldehydes via Co(III)-intermediate 112.

Inspired by the biological interactions of vitamin B<sub>12</sub> with glutathione [1, 127], Hisaeda studied the Co—S bond reactivity in complex **56b** with axial phenylthiolate ligands [128]. Similarly to Co(III)—C bonds in vitamin B<sub>12</sub> complexes, Co(III)—S bonds underwent homolytic dissociation under photocatalytic and thermolytic conditions. The reactivity of the B<sub>12</sub>—thiolate model complex could be utilised in the catalytic oxidation of arylthiols to the corresponding disulfides. Moreover, Co-complexes generated sulfur-centred radicals via single-electron transfer. The radical iodosulfonylation of alkynes yielding products **113** was enabled by Co(II)-mediated oxidation of a sulfinate anion to a S-centred radical (Scheme 11.45) [129]. In the absence of sulfonate salts, this reaction led to diiodination product **114**, the formation of which indicated the ability of Co(II) to oxidize an iodide anion to an iodine radical.



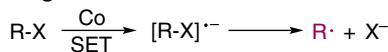
**Scheme 11.45** Co-catalysed iodosulfonylation and diiodination of alkynes.

## 11.4 Overview and Conclusion

Cobalt radical chemistry, without a doubt, offers many powerful tools for organic synthetic chemists. The astonishing array of possible transformations discussed in this chapter underscores its broad utility in the chemical science. In addition, cobalt complexes enable access to various radicals from a plethora of functionalities. In this context, Scheme 11.46 summarises the most general mechanistic pathways to access radicals from different starting materials discussed in this chapter.

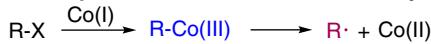
Despite advancements featured herein, there still remain opportunities for further exploration. Although, proven possible by Murakami [84], asymmetric versions of Co-catalysed radical reactions are yet to be developed. Furthermore, merger of cobalt reactivity with modern catalytic approaches (i.e. photocatalysis) will undoubtedly result in valuable tools for organic synthesis. Lastly, the role

## Single-electron transfer



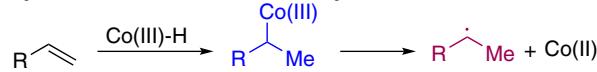
*Functional groups:* Alkyl, aryl, and vinylic halides, pseudohalides

## Nucleophilic substitution + Co-C homolysis



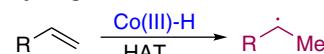
*Functional groups:* Alkyl halides, pseudohalides, diazoesters

### **Hydrocobaltation + Co–C homolysis**



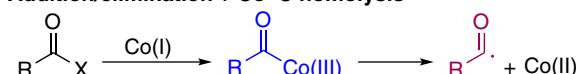
## *Functional groups: Alkenes*

## Hydrogen atom transfer



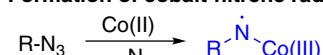
### *Functional groups: Alkenes*

### Addition/elimination + C<sub>9</sub>-C homolysis



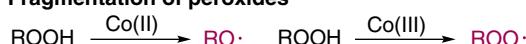
*Functional groups:* Acyl chlorides, anhydrides, thioesters

### **Formation of cobalt-nitrene radical complex**



### *Functional groups: Azides*

## Fragmentation of peroxides



### *Functional groups: Peroxides*

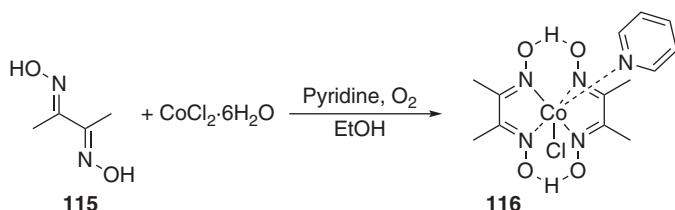
**Scheme 11.46** General reaction pathways for Co-mediated generation of radicals

of vitamin B<sub>12</sub> in numerous biological processes still remains to be elucidated, holding promise for discovery of new reactions.

We believe that further research in the area of cobalt radical chemistry will bring fascinating and important science in the years to come.

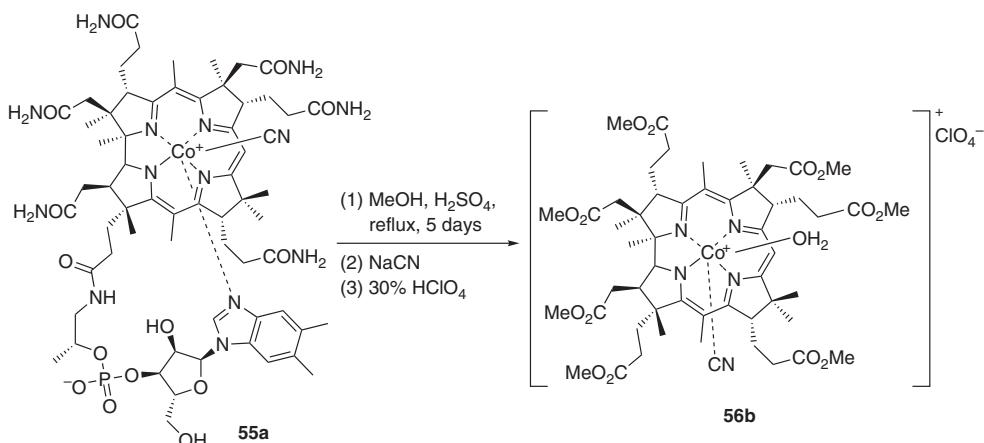
## 11.5 Experimental Section

### 11.5.1 Synthesis of Chloro(pyridine)cobaloxime Co(dmgH)<sub>2</sub>Cl(py) (116)



A solution of CoCl<sub>2</sub>·6H<sub>2</sub>O (5.0 g, 21 mmol, 1.0 equiv.) and dimethylglyoxime **115** (5.5 g, 47 mmol, 2.2 equiv.) in EtOH (200 mL, 95%) was heated to 60 °C, and pyridine (3.4 g, 43.0 mmol, 2.0 equiv.) was added. After five minutes, the resulting mixture was cooled down to room temperature and a stream of air was bubbled through the solution for 30 minutes. The mixture was left for one hour, during which time the product crystallised from solution. This precipitate was collected by filtration and washed successively with water (50 mL), ethanol (50 mL), and diethyl ether (50 mL) and dried *in vacuo* to afford 5.9 g of compound **116** as brown crystals (yield = 70%). The preparation of the cobaloxime complexes with bases other than pyridine and anions other than chlorine is described in the literature [130].

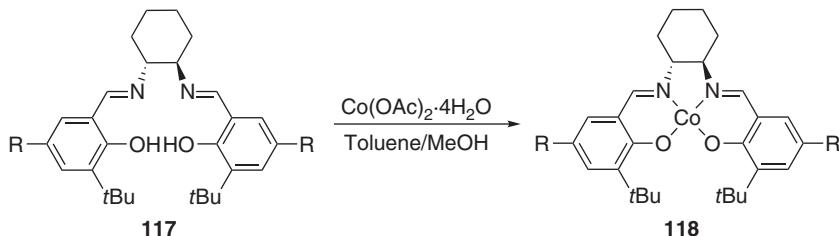
### 11.5.2 Synthesis of Aqua(cyano)heptamethyl Cobyrinate (**56b**) – Hydrophobic Vitamin B12 Model



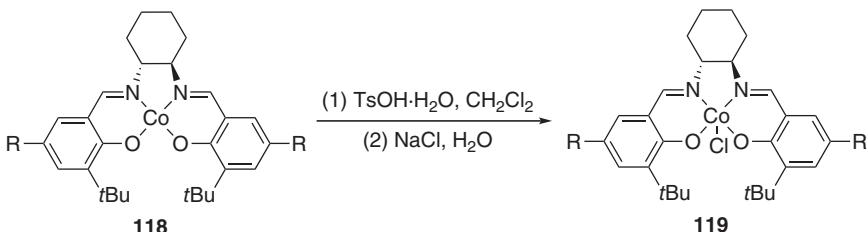
To a solution of vitamin B<sub>12</sub> (cyanocobalamin, **55a**; 3.0 g, 2.2 mmol) in degassed MeOH (380 mL), concentrated H<sub>2</sub>SO<sub>4</sub> (98% aq. solution; 12 mL) was added dropwise, and the resulting mixture was refluxed for five days. Subsequently, the reaction mixture was concentrated to 1/4 of its volume and diluted with water (200 mL). The resulting solution was carefully neutralised with solid NaHCO<sub>3</sub>, followed by the addition of few granulates of NaCN (the solution turned from red to deep purple). (*Caution: addition of NaCN to acidic solution would result in the formation of highly toxic HCN.*) The aqueous solution was then extracted with three portions of CH<sub>2</sub>Cl<sub>2</sub> (500 mL, then 2 × 200 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The crude product was purified by dry column vacuum chromatography (DCVC) [131] (Merck silica gel 60-H) (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, gradient from 100 : 0 to 98 : 2). (*A small amount of NaCN was placed on the top of the column to prevent dissociation of the axial CN ligands during chromatography.*) The column was then flushed with MeOH to remove all unreacted material that was subjected to the reaction procedure, worked-up, and purified as before. Two combined purified fractions were dissolved in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) and washed with 30% aqueous HClO<sub>4</sub> (30 mL)

(the solution turned from purple to red). The organic phase was washed with water (30 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated *in vacuo* to afford 1.5 g (1.3 mmol) of catalyst **56b** as a red powder (yield = 58%) [76, 100].

### 11.5.3 General Procedure for Synthesis of Co(II)(salen) and Co(III)(salen) Complexes



A round-bottomed flask was charged with a salen ligand (1.0 mmol, 1.0 equiv.) and purged with nitrogen. Degassed toluene (10 mL) was added to give a yellow solution.  $\text{Co}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$  dissolved in degassed MeOH (20 mL) was added, and the solution immediately turned dark red, and a red precipitate was observed usually within 10 minutes. The mixture was stirred for 20 minutes at room temperature, cooled to 0 °C, and stirred for 20 minutes. The red or orange Co(II)(salen) complex **118** was isolated by filtration and washed with cold MeOH ( $3 \times 10$  mL).



Co(II)(salen) complex **118** (1.0 mmol, 1.0 equiv.) was suspended in  $\text{CH}_2\text{Cl}_2$  (50 mL) and  $\text{TsOH}\cdot\text{H}_2\text{O}$  (1.0 mmol, 1.0 equiv.) was added. The resulting mixture was stirred for one hour, after which period the solution turned from red to dark green. The mixture was washed with brine ( $3 \times 30$  mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered through a pad of celites, and concentrated *in vacuo* to give a dark green or black solid. The solid was suspended in pentane (50 mL), filtered, and washed with pentane ( $5 \times 50$  mL) to give Co(III)(salen) complex **119**.

(Yields over two steps: R = H – 26%; R = Me – 54%; R = Et – 36%; R = *i*-Pr – 49%; R = *t*-Bu – 66%; R =  $\text{SiMe}_3$  – 53%).)

The synthesis of salen ligands is described in the literature [132].

## Abbreviations

1,4-CHD	1,4-cyclohexadiene
[H]	reductive conditions
acac	acetylacetone

Acr	acridine
Acr-Mes	9-mesityl-10-methylacridinium
ATRA	atom-transfer radical addition
Cbl	cobalamin
Cble	cobalester
Cby	cobyrinic acid
DCVC	dry column vacuum chromatography
DDT	1,1'-(2,2,2-trichloroethane-1,1-diyl)bis(4-chlorobenzene)
DBAD	di- <i>tert</i> -butyl azodicarboxylate
DIPEA	<i>N,N</i> -diisopropylethylamine
DMA	dimethylacetamide
dmgH	dimethylglyoxime
DMPU	<i>N,N'</i> -dimethylpropyleneurea
dpm	2,2,6,6-tetramethyl-3,5-heptanedionate
dppb	1,4-bis(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphine)ethylene
dtbbpy	4,4'-di- <i>tert</i> -butyl-2,2'-bipyridyl
EWG	electron-withdrawing group
HAT	hydrogen atom transfer
$h\nu$	visible light
LED	light-emitting diode
Ms	mesyl
modp	1-morpholinocarbamoyl-4,4-dimethyl-1,3-pentanedionate
NHPI	<i>N</i> -hydroxyphthalimide
PC	photocatalyst
PET	poly(ethylene terephthalate)
phen	1,10-phenanthroline
Por	porphyrin
ppy	2-phenylpyridine
py	pyridine
SCE	saturated calomel electrode
sel.	selectivity
SET	single-electron transfer
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMEDA	<i>N,N,N',N'</i> -tetramethylethylenediamine

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