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Asymmetric Hydrogenation of Olefins using Chiral Crabtree-type Catalysts – Scope and Limitations

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Pher G. Andersson*

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Introduction

1.1 Motivation and Scope

The asymmetric hydrogenation of alkenes using transition metal catalysts continues to be a growing field and a fundamental tool for organic synthetic chemists. In contrast to, for example, carbonyl reductions, the enantioselective addition of two hydrogen atoms to a carbon–carbon double bond relies almost exclusively on transition-metal-based catalysts. Moreover, the reaction frequently exhibits excellent chemo-, regio- and enantioselectivities. For the asymmetric hydrogenation of alkenes having coordinating functional groups such as amides and carboxylic acids in close proximity to the double bond, Rh(I) and Ru(II) species bearing diphosphine ligands (P,P ligands) are the catalysts of choice.¹ As a complement, for non-functionalized olefins carrying no neighboring coordinating group, chiral mimics of Crabtree's catalyst, $[\text{Ir}(\text{cod})(\text{Py})(\text{PCy}_3)][\text{PF}_6]$, have been developed into versatile reagents that can reduce both di-, tri-, and tetrasubstituted alkenes with high enantioselectivity.² A broad range of interesting alkene substrates have properties that lie in between these two extremes of functionalized and non-functionalized alkenes. Compounds such as α,β -unsaturated esters, enols and vinyl phosphonates, can be reduced selectively with several, fundamentally different, catalytic systems although chiral analogues of Crabtree's catalyst have proven superior to other catalyst types in many cases. Figure 1 summarizes the classification of alkene substrates in this review but is only a rough classification useful for the discussion and understanding. A specific alkene may chelate to metal centers in some cases but not in others.

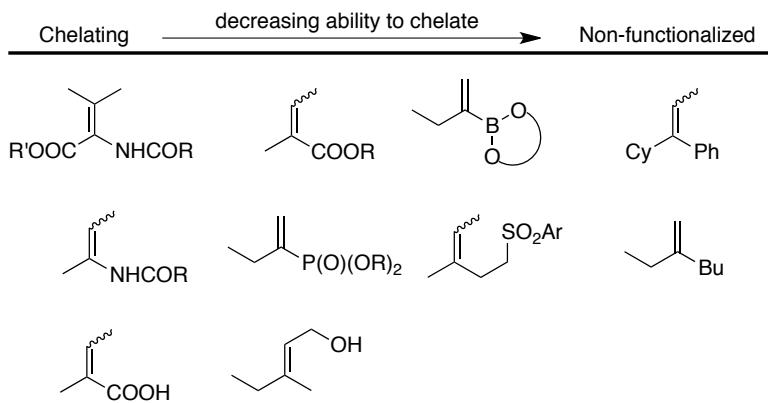


Figure 1 Alkene substrates for the asymmetric hydrogenation can be categorized as chelating (containing adjacent coordinating functional groups), intermediate, or non-functionalized (containing no heteroatoms).

In this comprehensive review, we describe the development of chiral analogues of Crabtree's catalyst for the asymmetric hydrogenation of alkenes with particular emphasis on the developments made during the past five years. The field has seen substantial expansion, especially in the substrate scope for this type of catalysts and the applications of the reaction. Although several surveys of the field have been published,^{2a,b,2d,e,3} a recent comprehensive review is lacking. Many of the recent developments in this field concern the use of N,P-ligated iridium catalysts to hydrogenate weakly functionalized alkenes, giving chiral products with great potential in chemical synthesis. Our aim is to provide a clear overview of the catalysts suitable for a particular application with a given alkene, and to define the areas that need further studies. In addition to reviewing recent advances, we also want to clarify the scope and limitations of the N,P-ligated iridium system and, where relevant, compare it to other available catalytic systems.

The mechanistic understanding of asymmetric hydrogenation catalyzed by $[\text{Ir}(\text{cod})(\text{N},\text{P}^*)]\text{[BAr}_\text{F}\text{]}$ ($\text{cod} = 1,5\text{-cyclooctadiene}$, $\text{BAr}_\text{F} = \text{tetrakis}(3,5\text{-bis(trifluoromethyl)phenyl})\text{borate}$) complexes has been significantly expanded by several computational works and will also be considered, along with the possibility to predict the stereochemical outcome.

We will focus exclusively on the enantioselective reduction of carbon–carbon double bonds using hydrogen gas, thus excluding carbonyl and imine reductions as well as the asymmetric hydrogenation of heteroaromatic substrates, a topic that has been recently and comprehensively reviewed.⁴

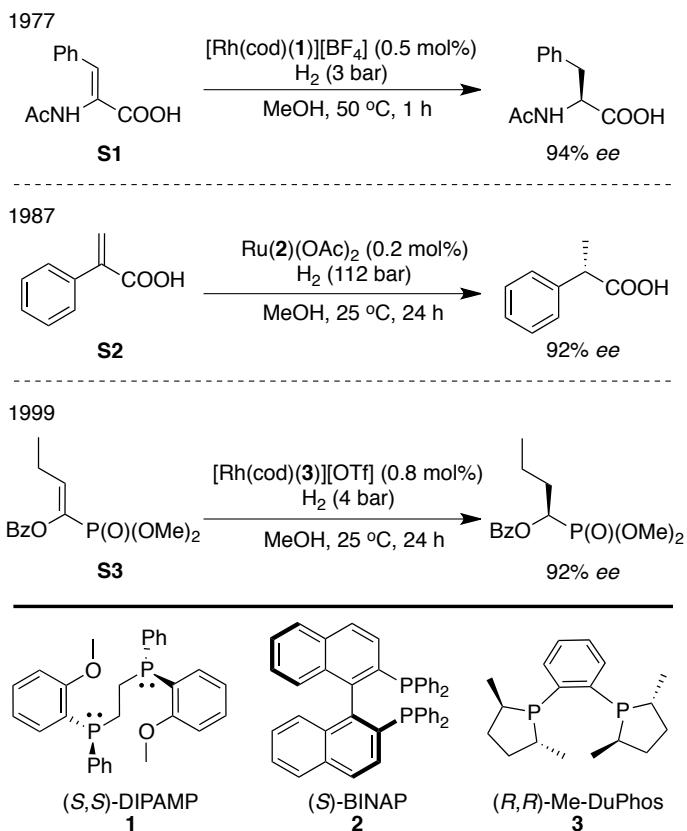
1.2 A Note on Conversion and Yield

Metal-catalyzed asymmetric hydrogenation is a uniquely mild chemical transformation in that few, if any, byproducts are formed in the reaction. It has therefore become standard practice in screening experiments to only report the alkene conversion (conversion = $100 * \text{product} / (\text{starting material} + \text{product})$), except where the reactions do not proceed cleanly. Since the conversion attained in specific catalytic reactions depend on parameters such as pre-catalyst loading, reaction time and temperature, and given that most authors develop systems that generate complete or at least high conversion, we will not discuss alkene conversion except when it is of special relevance. Instead, focus will be on the reaction conditions required to produce an efficient catalytic system. The reader should assume that the reactions proceed cleanly and in high conversion unless otherwise stated. Yields will be stated when relevant; this will primarily be in cases where asymmetric hydrogenation is used in a longer synthesis or when the reaction does not proceed cleanly.

1.3 Early Developments, Reduction of Functionalized Alkenes

The birth of asymmetric hydrogenation is usually associated with the introduction of the first chiral bidentate ligand DIOP, (2,3-O-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)-butane), and its use in the rhodium-catalyzed hydrogenation of dehydroamino acids. Using tartrate-derived (–)-DIOP, Dang and Kagan reduced several dehydroamino acids in >50% enantioselectivity at the beginning of the 1970s.⁵ In 1975, Knowles concluded that asymmetric hydrogenation finally approached Nature's capability in terms of stereospecificity.⁶ The hydrogenations of a range of α -acetamidoacrylic acids such as **S1** using Rh-DIPAMP (Scheme 1) occurred with enantioselectivities above 90% ee.⁷ The catalytic asymmetric synthesis of the

anti-Parkinson's drug L-DOPA using this methodology became a commercial process.⁸



Scheme 1 Asymmetric hydrogenation of functionalized alkenes using P,P-ligated Rh- and Ru-catalysts.

More than ten years later, Noyori and co-workers published the asymmetric hydrogenation of allylic and homoallylic alcohols using Ru(BINAP)(OAc)₂.⁹ This catalyst, based on BINAP¹⁰ **2**, proved uniquely versatile, and was also used in the first asymmetric hydrogenation of α,β -unsaturated carboxylic acids (Scheme 1), presented in the same year.¹¹

The DuPhos ligand **3**, developed by Burk and co-workers in 1990,¹² was unique in the sense that it could be easily modified and tuned to fit a specific substrate class. A new class of alkenes, enol esters, could be reduced in very high enantioselectivities using Rh catalysts ligated by DuPhos variants.¹³

Other novel substrate classes that could be reduced using DuPhos systems were α -enol benzoate- and α -acetamido phosphonates¹⁴ (Scheme 1) and β -acylamino acrylates.¹⁵

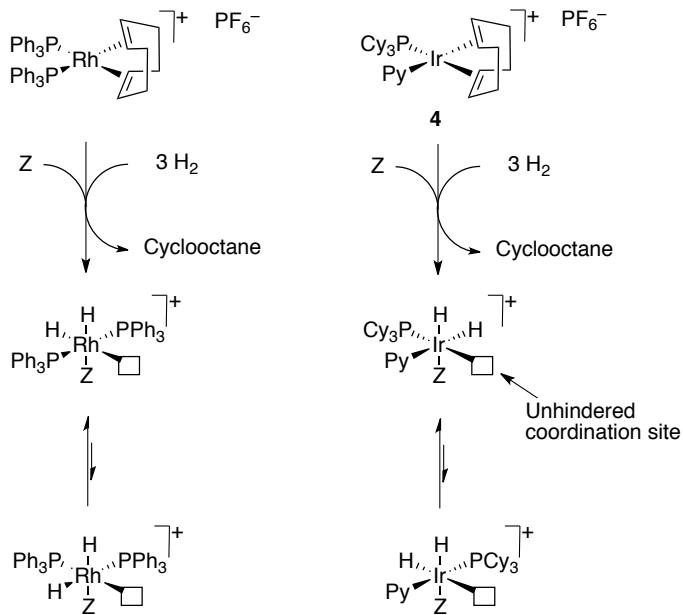
Asymmetric hydrogenation using Rh- and Ru-P,P systems has developed significantly over the last 40 years and allowed the enantioselective synthesis of a range of chiral synthetic intermediates with different functionalities. The asymmetric hydrogenation of alkenes by complexes of both types $[\text{Rh}(\text{diene})(\text{P},\text{P})][\text{X}]$ and $\text{Ru}(\text{P},\text{P})(\text{OOCR})_2$ rely on coordination of additional functional groups to the metal to obtain high stereoselectivity.¹⁶ Typically, the coordination of the alkene is accompanied by that of an acetamide, acetate or alcohol to form a chelate, which locks the alkene in position and limits the set of available conformations. Additionally, these catalysts are usually applied in alcohol solvents that stabilize the metal complex against decomposition and allow proton transfer; thus, non-chelating alkenes compete less favorably with the solvent for metal coordination sites and are reduced at a lower rate. Attempts to use the P,P-ligated systems for the hydrogenation of weakly or non-functionalized alkenes have frequently proven unsuccessful.¹⁷

1.4 The Iridium-N,P Catalytic Hydrogenation System

During the 1970s, Crabtree and co-workers studied the properties of metal complexes of the type $[\text{M}(\text{cod})\text{L}_2][\text{X}]$ ($\text{M} = \text{Rh}$ or Ir , $\text{L} = \text{phosphine ligand}$, $\text{X} = \text{Cl}$, BF_4 or PF_6), which had previously been reported by Schrock and Osborn,¹⁸ to form active hydrogenation catalysts when exposed to H_2 . The Ir-complexes were less active than their rhodium counterparts in the alkene hydrogenation and, in coordinating solvents, the Ir complexes formed the stable solvate complexes $[\text{Ir}(\text{H})_2(\text{S})_2\text{L}_2][\text{X}]$ ($\text{S} = \text{solvent}$) upon exposure to H_2 .¹⁹ When Crabtree and co-workers exchanged the coordinating solvents with polar, non-coordinating solvents such as CH_2Cl_2 , more active catalytic systems were obtained, especially in the iridium case.²⁰

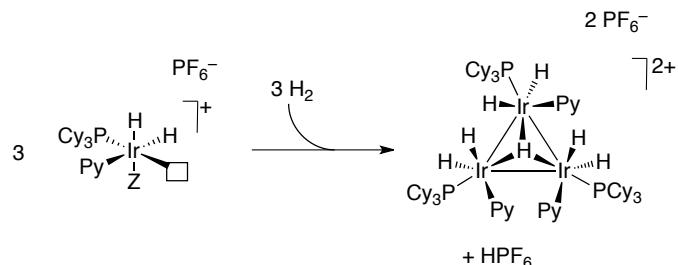
Ligand-screening experiments that aimed to produce Ir catalysts with improved properties demonstrated that the mixed-ligand complex $[\text{Ir}(\text{cod})(\text{Py})\text{PCy}_3]\text{[PF}_6]$ **4** ($\text{Py} = \text{pyridine}$, $\text{PCy}_3 = \text{tricyclohexylphosphine}$)

formed a catalyst which was both faster than the corresponding diphosphine-catalyst, and was able to reduce tri- and tetrasubstituted non-functionalized alkenes efficiently.^{20a} The high activity of complex **4** was attributed partially to the small size of the pyridine ligand. However, a *cis* conformation of the pyridine and PCy₃ ligands could be observed in some cases;²¹ it is thus possible that the activation of **4** with dihydrogen forms cations of the type [Ir(H)₂(Py)PCy₃Z]⁺ (Z = solvent, alkene or H₂), which would exhibit unusually open alkene coordination sites (Scheme 2). This is in contrast to the corresponding diphosphine complexes in which, upon activation with dihydrogen, the two bulky phosphines are arranged *trans* to each other.²²



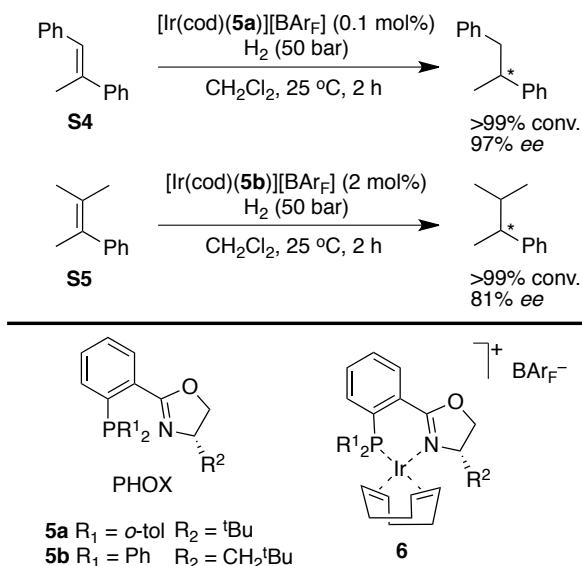
Scheme 2 Activation of **4** by H₂ may generate an iridium complex with an unhindered coordination site.

Compound **4**, commonly referred to as Crabtree's catalyst, also proved to be unusually air-stable, both as a solid and in solution. However cases where the coordination of the alkene to the metal was poor, the active catalyst decomposed into an inactive trinuclear iridium-hydride cluster (Scheme 3).²³ Thus, high loadings of pre-catalyst were required for high product yields.



Scheme 3 Complex **4** decomposes under H₂ when no alkene is coordinated to the metal. (Z = solvent or H₂)

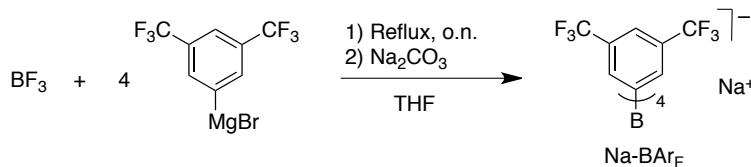
In 1997, Pfaltz and co-workers prepared the first chiral mimic of Crabtree's catalyst, $[\text{Ir}(\text{cod})(\text{N},\text{P}^*)]\text{[PF}_6]$, using a phosphinooxazoline **5** (PHOX)²⁴ as a chiral N,P-chelating species.²⁵ The complex was exceptionally enantioselective in the asymmetric hydrogenation of non-functionalized tri- and tetrasubstituted alkenes such as **S4** and **S5** (Scheme 4).²⁶ It did, as in the achiral version, decompose during the reaction, and full conversion could not be obtained with less than 3 mol% catalyst.²⁷ Based on the conclusion by Crabtree et al. that the catalyst was deactivated due to poor alkene coordination, the extremely weakly coordinating counterion BAr_F^- was tested as a replacement for PF_6^- , forming complexes of the type $[\text{Ir}(\text{cod})(\text{PHOX})]\text{[BAr}_\text{F}]$ such as **6** (Scheme 4). Indeed, both BAr_F^- and other, similar counterions gave catalysts that achieved higher turnover frequencies and stabilities, and consequently the catalyst loading could be decreased to below 1 mol% while maintaining high enantioselectivity (Scheme 4).^{26,28} Additionally, the catalyst became more stable to humidity and more soluble in non-polar solvents.



Scheme 4 The PHOX ligands **5** were the first chiral N,P-ligands to be used in complexes of the type $[\text{Ir}(\text{cod})(\text{N,P})][\text{BAr}_F]$ such as **6**, as catalysts for the asymmetric hydrogenation of non-functionalized tri- and tetrasubstituted alkenes.

These benefits of using BAr_F^- , which is prepared by quadruple alkylation of BF_3 with (3,5-bis(trifluoromethyl)phenyl)magnesium bromide²⁹ (Scheme 5), have made it the standard counterion for these catalytic systems.

Following the groundbreaking initial discoveries by Pfaltz, hundreds of chiral nitrogen–phosphorus, nitrogen–carbene and other ligands have been incorporated in iridium complexes and tested as asymmetric hydrogenation catalysts.^{2e,3a,3d} As a result, highly selective catalysts have been prepared for a wide range of sterically and electronically different alkene substrates.^{3c}



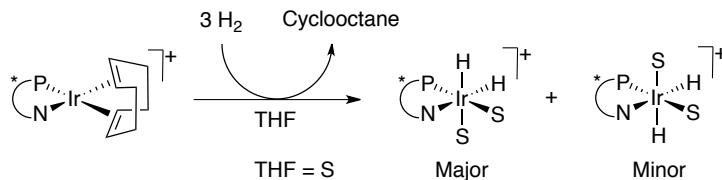
Scheme 5 Preparation of NaBAr_F .

1.5 Mechanistic Aspects

This section aims to describe the fundamental mechanics of catalytic hydrogenation using $[\text{Ir}(\text{cod})(\text{N},\text{P})][\text{BAr}_\text{F}]$ complexes. The implications of the mechanism on selectivity are discussed in Section 8.

As noted by Crabtree, oxidative addition of H_2 and subsequent alkene coordination, for cations of the type $[\text{Ir}(\text{cod})\text{LL}']^+$, are feasible,³⁰ and the reaction is especially rapid for Crabtree's catalyst.²¹ Crabtree and co-workers proposed $[\text{Ir}(\text{H})_2\text{LL}'(\text{alkene})\text{Z}]^+$ where Z = solvent or alkene or H_2 , as the catalyst resting state.^{22b} Additionally, they suggested that the migratory insertion was the rate-determining step in the catalytic cycle, and that the high (+3) oxidation state of the complex contributed to the exceptional stability of these catalysts towards oxidation.^{22b} Despite thorough studies of the $[\text{Ir}(\text{cod})\text{LL}'][\text{PF}_6]$ systems, mechanistic details proved hard to elucidate, due mainly to the high catalytic activity of the systems.

Meuwly, Pfaltz, and co-workers performed the first studies on the addition of dihydrogen to a chiral version of Crabtree's catalyst, $[\text{Ir}(\text{cod})(\text{N},\text{P})][\text{BAr}_\text{F}]$, using a bidentate PHOX ligand.³¹ ^1H NMR revealed that in THF, at 0 °C and under an atmosphere of H_2 , cyclooctadiene was quickly hydrogenated to form complexes of the type $[\text{Ir}(\text{H})_2(\text{N},\text{P})(\text{THF})_2]^+$. As shown in Scheme 6, the hydrides arranged themselves *trans* to the oxazoline nitrogen and to one of the solvent molecules. In dichloromethane, a complex mixture of hydridic metal complexes was observed, but DFT calculation indicated that similar structures were favorable in the two solvents.

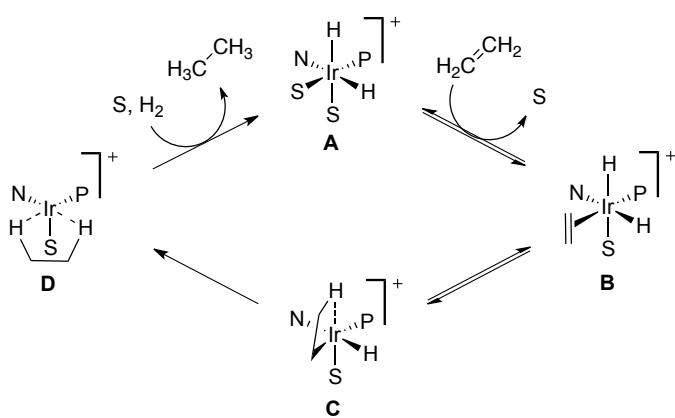


Scheme 6 Activation of $[\text{Ir}(\text{cod})(\text{N},\text{P})][\text{BAr}_\text{F}]$ by H_2 in THF generates a pair of isomers of $[\text{Ir}(\text{H})_2(\text{N},\text{P})(\text{THF})_2][\text{BAr}_\text{F}]$. The $[\text{BAr}_\text{F}]^-$ counterion has been omitted for clarity.

The simplest catalytic hydrogenation cycle starting from $[\text{Ir}(\text{H})_2(\text{N},\text{P})\text{S}_2]^+$ would be the substitution of the solvent by an alkene to form $[\text{Ir}(\text{H})_2(\text{N},\text{P})(\text{alkene})\text{Z}]^+$, where Z = solvent or H_2 , followed by migratory insertion and reductive elimination to release the product alkane. Such a reaction pathway, analogous to alkene hydrogenation by $[\text{Rh}(\text{diene})(\text{P},\text{P})]^+$,³² was indicated by Dieteker and Chen.³³ They studied gas-phase reactions of $[\text{Ir}(\text{cod})(\text{PHOX})][\text{BAr}_F]$, H_2 , and styrene using ESI-MS/MS and found that, when the hydrogenation product cation $[\text{Ir}(\text{PHOX})(\text{PhEt})]^+$ was isolated and collided with argon, $[\text{Ir}(\text{PHOX})(\text{styrene})]^+$ was the major species, thus showing that the reaction was reversible in the gas phase.

The observation of cations with masses corresponding to $[\text{IrH}_2(\text{PHOX})(\text{styrene})]^+$ and $[\text{IrH}_4(\text{PHOX})(\text{styrene})]^+$ implied that both oxidation states +3 and +5 were possible for iridium. However, collisions of $[\text{Ir}(\text{PHOX})(\text{styrene})]^+$ with D_2 only gave additional masses corresponding to d_1 - $[\text{Ir}(\text{PHOX})(\text{styrene})]^+$ and d_2 - $[\text{Ir}(\text{PHOX})(\text{styrene})]^+$. As only mono- and di-deuterated complexes could be detected, a mechanism involving more than two hydrides (such as Ir(V)) was deemed unlikely and an Ir(I)/Ir(III) catalytic cycle was proposed.

A similar, dihydridic, catalytic cycle was proposed for complexes such as $[\text{Ir}(\text{cod})(\text{IMes})(\text{P}(^7\text{Bu})_3)][\text{BAr}_F]$, (IMes = 1,3-bis(2,4,6-trimethylphenyl)-imidazol-2-ylidene) i.e. an achiral analogue of Crabtree's catalyst.³⁴ *Para*-hydrogen induced polarization (PHIP) ^1H NMR experiments indicated that a dihydride mechanism was operating, but other mechanisms could not be ruled out.³⁵ Roseblade and Pfaltz also considered a related mechanism,³⁶ starting from the oxidative addition product $[\text{Ir}(\text{H})_2(\text{N},\text{P})\text{S}_2]^+$ (Complex **A**, Scheme 7). They proposed that complex **A** underwent substitution by an alkene *trans* to the phosphorus, resulting in complex **B**. Alkene coordination to form **B** is usually facile; the rate of hydrogenation of a trisubstituted alkene catalyzed by $[\text{Ir}(\text{cod})(\text{PHOX})][\text{BAr}_F]$ has proven to be close to zero-order in alkene.²⁷ Hydride migration to the alkene then gives the σ -alkyl intermediate **C**, which subsequently undergoes reductive elimination to form **D**. Oxidation by a new molecule of H_2 and solvent coordination regenerate **A**.

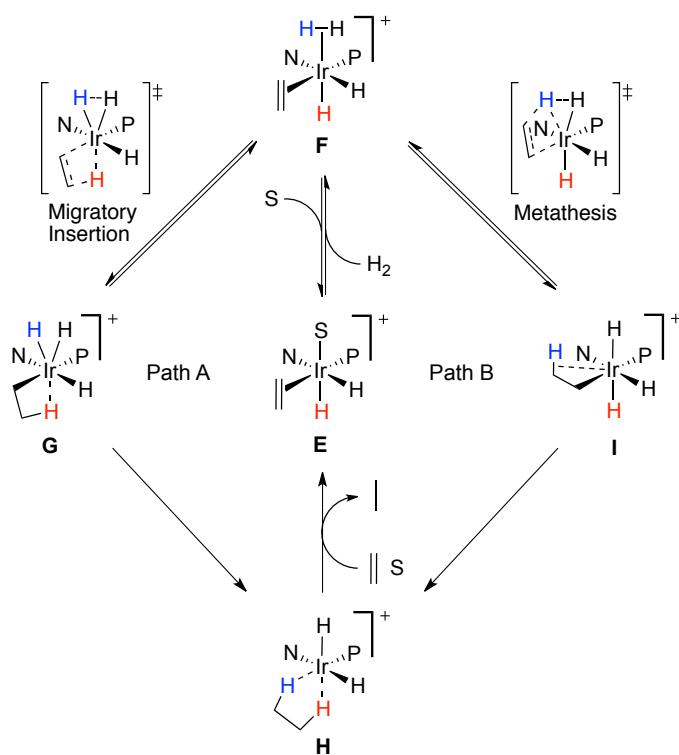


Scheme 7 Alkene hydrogenation via an Ir(I)/Ir(III) dihydride catalytic cycle. The BAr_F^- counterion has been omitted. S = solvent.

DFT studies starting from complexes of the type $[\text{Ir}(\text{H})_2(\text{N},\text{P})(\text{alkene})\text{S}]^+$ (S = solvent, alkene = ethane; Complex **B**, Scheme 7) with a truncated N,P ligand ($\text{N},\text{P} = \text{MeN}=\text{CH}-\text{CH}=\text{CH}-\text{PMe}_2$) prompted Brandt and co-workers to suggest an alternative mechanism.³⁷ Calculations indicated that both migratory insertion and reductive elimination, as shown in Scheme 7, had high energy barriers. However, when the coordinated CH_2Cl_2 was exchanged for an η^2 -coordinated H_2 molecule to give $[\text{Ir}(\text{H})_2(\text{H}_2)(\text{N},\text{P})(\text{alkene})]^+$ (Complex **F**, Scheme 8). Starting from **F**, both migratory insertion and reductive elimination are more feasible. Additionally, the migratory insertion occurred simultaneously with the oxidative addition of the coordinated dihydrogen molecule to form **G** (Scheme 8, Path A). The Ir(V) species **G** then undergoes reductive elimination to form **H** which, by coordination of another alkene and a solvent molecule, reforms **E** (the suggested catalyst resting state). The migratory insertion (step **F** \rightarrow **G**) was calculated to have the only significant energy barrier and was proposed to be the rate-determining step. However, kinetic studies have shown that the reaction is first-order in hydrogen pressure. This result was later confirmed for pressures up to 50 bar.²⁸ In order to reconcile these results, the authors noted that the substitution of CH_2Cl_2 by H_2 (Scheme 8, **E** \rightarrow **F**) could be the rate determining step if it were endergonic. Although DFT calculations indicated that it was thermodynamically neutral under standard conditions, the reaction could be endergonic under the reaction conditions,

where the concentration of CH_2Cl_2 is higher than that of H_2 . It is also possible, however, that the reaction rate can be limited by H_2 diffusion, at least in cases where the alkene hydrogenation is fast, as reported by Blackmond and co-workers.³⁸ They demonstrated that it was more important to control the rate of mass-transfer (i.e. convection) than the gas pressure over the solution, since the former had greater impact on the concentration of H_2 in solution.

The effect of hydrogen pressure on asymmetric hydrogenation using $[\text{Ir}(\text{cod})(\text{N},\text{C})]\text{[BAr}_F]$ pre-catalysts ($\text{C} = \text{N-heterocyclic carbene}$) has been studied. For some alkene substrates, no pressure-dependence was observed, whereas for others, pressure had significantly influenced both the reaction rate and enantioselectivity.³⁹



Scheme 8 Hydrogenation of an alkene starting from an $\eta^2\text{-H}_2$ complex (**F**) and going through an Ir(III)/Ir(V) catalytic cycle. The reaction has been suggested to go through either a concerted migratory insertion–oxidative

addition (Path A) or a hydrogen metathesis (Path B). The BAr_F^- counterion has been omitted for clarity. S = solvent.

Burgess, Hall and co-workers performed DFT calculations on the mechanism of Ir-catalyzed asymmetric olefin hydrogenation using their N,C-ligated system.⁴⁰ Their lowest energy pathway (Scheme 8, Path B) was similar to the one proposed by Brandt et al. Starting from complex **F**, they calculated that the first hydrogen was transferred to the alkene from the coordinated dihydrogen molecule via metathesis. The Ir(V) σ -alkyl complex **I** thus formed then underwent reductive elimination to yield **H**.

Calculations performed for an experimentally reported $[\text{Ir}(\text{cod})(\text{N},\text{P})]^+$ catalyst system, beginning from complex cations of the type $[\text{Ir}(\text{H})_2(\text{N},\text{P})(\text{alkene})\text{X}]^+$, revealed that the lowest energy barriers were available when X = H₂ and the system followed an Ir(III)/(V) pathway (Scheme 8).⁴¹ It also indicated that the migratory insertion (Path A) was lower in energy than the metathesis (Path B) for this type of catalyst. This was true for calculations of gas-phase species and for species in a solvent field. The Ir(I)/(III) pathways, calculated for X = CH₂Cl₂ or an empty coordination site, were more than 10 kcal/mol higher in energy. Analogous results have been obtained in studies on a $[\text{Ir}(\text{H})_2(\text{N},\text{P})(\text{alkene})\text{X}]^+$ system with a different ligand.⁴²

To conclude the mechanistic discussions, although much relevant experimental data is lacking, several DFT studies have indicated that the hydrogenation of non-functionalized alkenes by chiral mimics of Crabtree's catalyst proceeds via an Ir(III)/Ir(V) tetrahydride mechanism. It is likely, as noted by several authors, that the mechanism can depend on the substrate and the hydrogen concentration. For instance, chelating substrates can easily be envisioned to disfavor the formation of the Ir-dihydride-dihydrogen complex (**F**, Scheme 8) and instead form a dihydride complex with a chelating alkene (i.e. complexes **B** and **C**, Scheme 7, with S replaced by a coordinating functional group from the alkene).

2 Aryl and Alkyl Substituted Alkenes

2.1 Trisubstituted Alkenes

Aryl/alkyl trisubstituted alkenes (Figure 2) have become the benchmark substrates for assessing the efficiency of new catalytic systems in the hydrogenation of minimally functionalized olefins. In general, the asymmetric reduction of 1,2-diarylalkenes (such as *trans* α-methylstilbene **S4**), proceeds with higher enantioselectivities than monoarylated alkenes (i.e. *E*-2-(4-methoxyphenyl)-2-butene **S6**), for which only a limited number of catalysts provides high levels of enantioselectivity.^{2d,e,3a,3c,d,36,43} On the other hand, the geometry of the double bond also affects the catalytic outcome, and hydrogenation of *E*-olefins affords higher enantioselectivities than that of *Z*-olefins. The lower enantioselectivities achieved in the hydrogenation of *Z*-isomers can sometimes be attributed to an *Z/E* isomerization process to form the more stable *E*-alkene, which frequently gives the opposite enantiomer of the hydrogenated product.^{2d,e,3a,3c,d,36,43} The fact that the sense of enantioselectivity is controlled by the olefin geometry can be used to gain access to both enantiomers of the hydrogenated product with the same catalyst, provided that isomerization can be suppressed. However, this also presents a limitation since mixtures of *Z/E* isomers have to be avoided to achieve high enantioselectivities. *Z*-2-(4-methoxyphenyl)-2-butene **S7** and dihydronaphthalenes (i.e. 7-methoxy-4-methyl-1,2-dihydronaphthalene **S8**) are frequently used to study the ligand scope in the hydrogenation of *Z*-alkenes. Dihydronaphthalenes have recently received much attention because the corresponding chiral tetraline motif is found in numerous natural products.⁴⁴

Trialkyl substituted alkenes (substrates with no aromatic groups attached to the alkene) haven't been studied in detail. The reasons for limited information is probably due to the difficulty in developing methods for ee-determination and the lack of an aryl group that could direct the reaction via π-stacking interaction between the substrate and the chiral catalyst. Nevertheless, this substrate class has been hydrogenated using Ir-N,P

catalysts with high efficiency (ee's up to 95% in the hydrogenation of 1-methoxy-4-(3-methyl-pent-3-enyl)-benzene **S9**).⁴⁵

Recently, the substrate scope has been extended to 1,1-diaryl or 1,1,2-triaryl substituted substrates (i.e. 1-(1,2-diphenyl-vinyl)-3,5-dimethyl-benzene **S10**) and cyclic dienes (i.e. 1,5-dimethyl-cyclohexa-1,4-diene **S11**). The former substrate class provides an easy entry point to diarylmethine stereogenic centers, which are present in several important drugs and natural products.⁴⁶

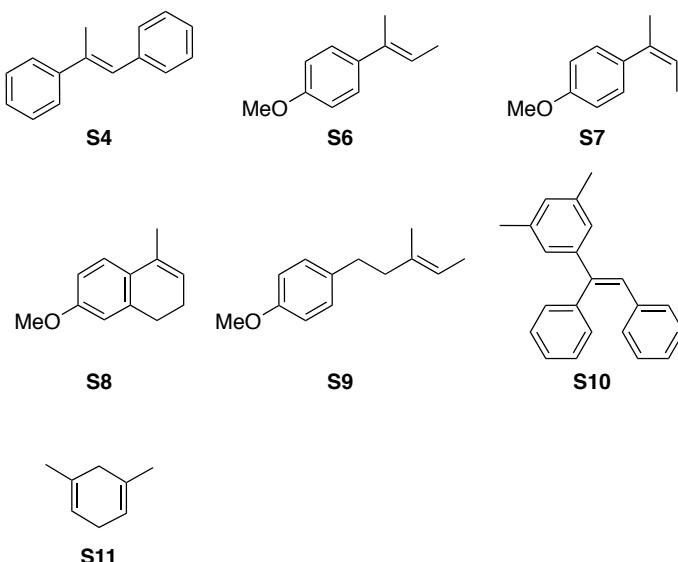
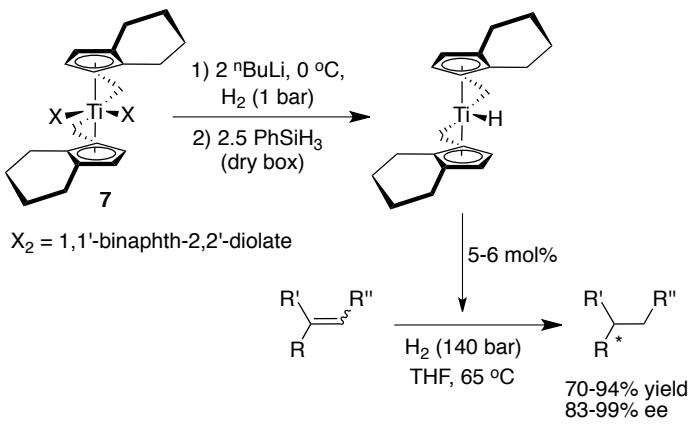


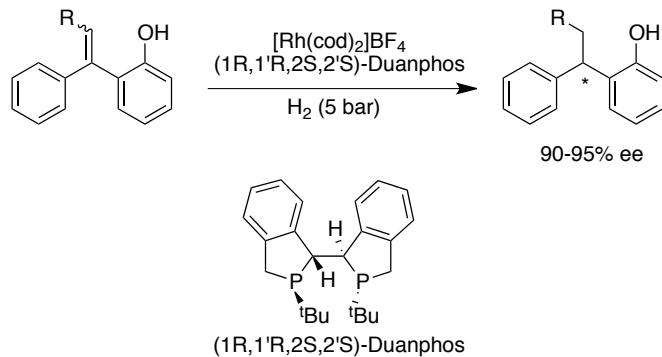
Figure 2 Representative aryl-alkyl, alkyl-alkyl and aryl-aryl trisubstituted alkenes.

The first successful application in the asymmetric reduction of minimally functionalized olefins was reported by Buchwald and co-workers in 1993.⁴⁷ A chiral titanocene catalyst precursor, **7**, provided high enantioselectivities (ee's ranging from 83% - >99%; Table 1, entry 1) in the hydrogenation of a limited range of *E*- and *Z*-trisubstituted olefins (Scheme 9). However, high pressure (140 bar of H₂), high temperature (65 °C) and long reaction times (several days) were required to achieve full alkene conversions. Moreover, the catalyst is highly unstable and the use of a dry-box is required for its preparation.



Scheme 9 Asymmetric hydrogenation of trisubstituted olefins using chiral titanocene complex 7.

The application of Rh- and Ru-catalyst precursors with phosphorus ligands for the asymmetric reduction of minimally functionalized trisubstituted olefins has not been accomplished with good enantioselectivities.⁴⁸ Nevertheless, $[\text{Rh}(\text{cod})(1R,1'R,2S,2'S\text{-Duanphos})]\text{BF}_4$ has been successfully applied in the asymmetric hydrogenation of trisubstituted olefins in various *E/Z*-mixtures (Scheme 10).⁴⁹ However, the presence of a directing hydroxyl group at the *ortho* position of a phenyl substituent in the substrate is required and the authors found that coordination of the phenol to Rh plays a crucial role in the enantiodiscrimination process. Thus, the hydrogenation of methyl ether analogues led to lower activities and enantioselectivities (ee's < 20%).



Scheme 10 Asymmetric hydrogenation of trisubstituted olefins containing a directing hydroxyl group using Rh-Duanphos catalysts.

As mentioned in Section 1.4, a breakthrough in the hydrogenation of minimally functionalized olefins came in 1997 when Pfaltz' and co-workers used phosphine-oxazoline ligands PHOX **5**^{26-27,50} (Figure 3; R¹= Ph, o-Tol and R²= ^tPr, ^tBu, CH₂^tBu) to design [Ir(cod)(PHOX)][BAr_F]⁻, a chiral analogue of Crabtree's catalyst.³⁰ These catalysts, in comparison to titanocene complex **7**, required lower pressures (50 bar of H₂), temperatures (rt) and reaction times (full conversions in 2 hours). They have been successfully used for the asymmetric hydrogenation of a limited range of alkenes (mainly trisubstituted E-1,2-diaryl olefins including those bearing a furyl and a thiophenyl heterocyclic substituents with ee's up to 98%; Table 1, entry 2).^{26-27,43,45,51} These catalysts, afforded lower levels of enantioselectivity in the hydrogenation of more demanding Z-olefins (42% ee in the hydrogenation of **S7**; Table 1, entry 2). The authors found that enantioselectivity is affected by the ligand parameters and the best enantioselectivities were obtained with the ligand that combines a *tert*-butyl on the oxazoline and a bis(o-tolyl)phosphanyl group (ligand **5a**, Table 1, entry 2).

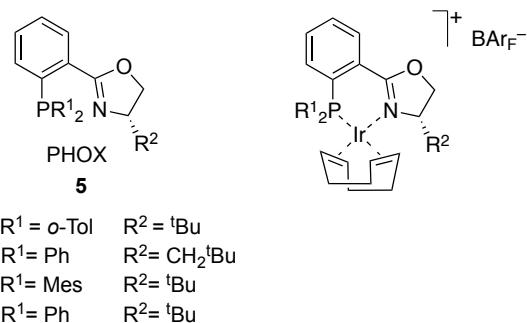


Figure 3 Phosphine-oxazoline PHOX ligands **5** and the corresponding Ir-precatalyst.

Since Pfaltz' discovery of the utility of [Ir(cod)**5**][BAr_F]⁻ the composition of the ligands has been extended by replacing the phosphine moiety with other phosphorus-donor group analogues (i.e. phosphinite, carbene and phosphite) and the oxazoline moiety with different N-donor groups (such as

pyridine, thiazole and oxazole). The structure of the chiral ligand's backbone has also been modified. Recently, the use of iridium catalysts containing P,S and P,O heterodonor ligands have been presented. All these modifications has led to the discovery of new ligands that have considerably broadened the scope of Ir-catalyzed asymmetric hydrogenation of minimally functionalized trisubstituted olefins. The enantioselective reduction of aryl/heteroaryl-alkyl olefins, triarylsupstituted olefins and pure alkyl olefins can be efficiently achieved.

In the following sections, we compile the most representative catalytic data reported in the Ir-catalyzed asymmetric hydrogenation of minimally functionalized trisubstituted olefins arranged according to the type of ligands. We also discuss their application to the synthesis of complex molecules.

2.1.1 Phosphorus/Carbene-Oxazoline Ligands

Several successful phosphorus/carbene-oxazoline compounds have been developed for the Ir-catalyzed asymmetric hydrogenation (Figure 4). Most of them are phosphine-oxazoline, N-phosphine-oxazoline and phosphinite-oxazoline ligands and to a lesser extent phosphite/phosphoroamidite-oxazoline and carbene-based ligands.

Phosphine-Oxazoline Ligands

A modification in the oxazoline moiety of the PHOX ligands, with the development of phosphine-benzoxazine analogues **8** (Figure 4, R = ^tBu, ⁱPr) was reported in 2001.⁵² As observed with the PHOX ligands, the presence of bulky *tert*-butyl groups at the oxazine ring led to the highest enantioselectivities. However, these ligands provided lower enantioselectivities (ee's up to 90% for substrate **S4**) than the PHOX ligands **5**.

Ligands **9** have been applied in the Ir-catalyzed hydrogenation of several trisubstituted aryl-alkyl alkenes (Figure 4, R¹ = Ph, o-Tol, R² = Me, ^tBu, 1-adamantyl, CPh₃)⁵³ and enantioselectivities shown to depend strongly on both the ligand parameters and the substrate type. Thus, while the best

enantioselectivities for *Z*-isomer **S7** were obtained with a *tert*-butyl group at the oxazoline and a diphenylphosphanyl group (ligand **9a**; Table 1, entry 3), for stilbene derivatives the presence of a *bis*(*o*-tolyl)phosphanyl group is needed for ee's to be high (ligand **9b**; Table 1, entry 3). These ligands proved to be superior to the PHOX ligands in the hydrogenation of *Z*-alkenes (i.e. 75% ee for substrate **S7**; Table 1, entries 2 vs 3), while ee's for the hydrogenation of *E*-alkenes were lower (ee's up to 94% for *trans*- α -methylstilbene **S4**; Table 1, entries 2 vs 3). A further modification of ligands **9** by introduction of the *ortho*-phenylene tether backbone motif of the PHOX ligands gave rise to new ligands **10** (Figure 4, R¹= Ph, Cy, and R²= ^tBu, 1-Ad, CHPh₂, 3,5-^tBu₂-Ph) that proved to be excellent in the hydrogenation of *trans*- α -methylstilbene derivatives (ee's up to 99%).⁵⁴ Again the presence of bulky substituents at both oxazoline and phosphine moieties (ligand **10a**) led to the highest enantioselectivities (Table 1, entry 4).

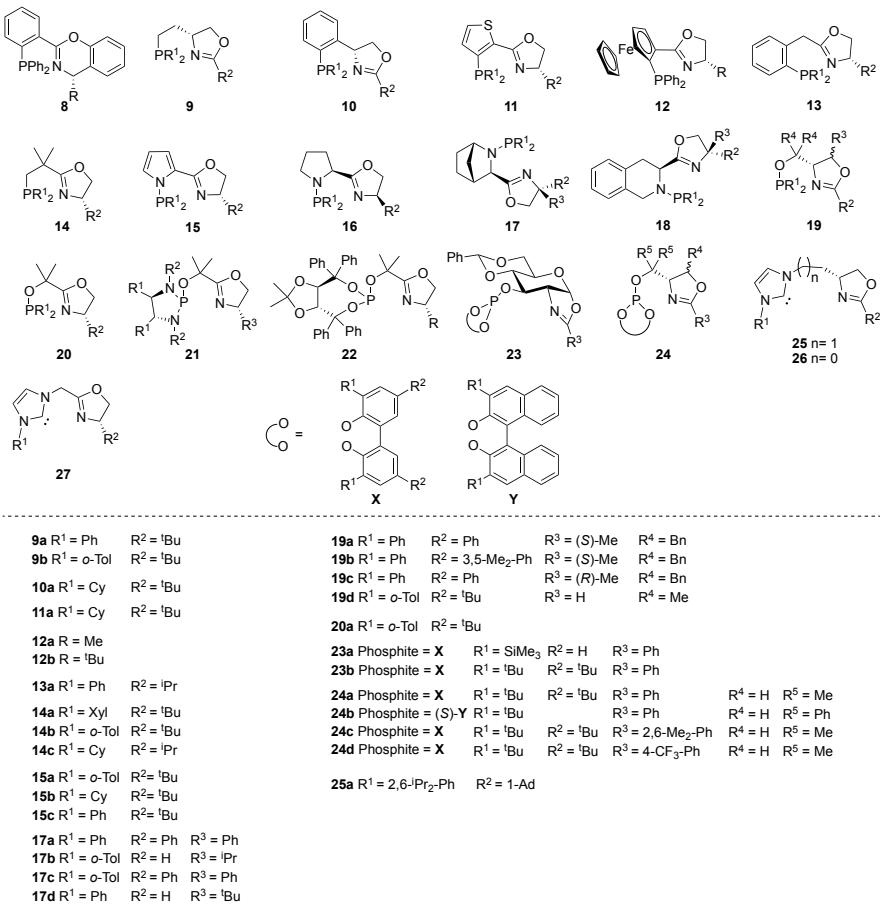


Figure 4 Phosphorus/carbene-oxazoline ligand families developed for the Ir-catalyzed asymmetric hydrogenation of aryl/alkyl trisubstituted olefins.

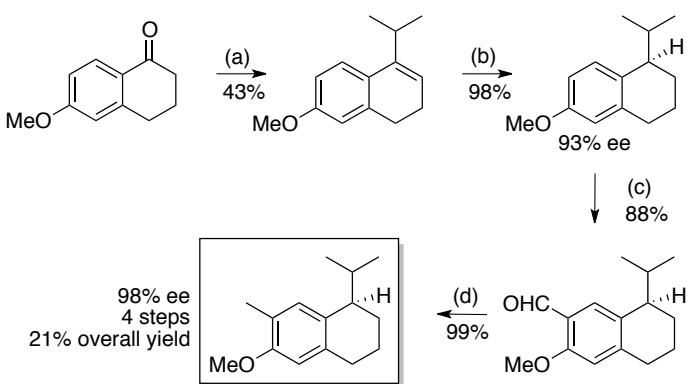
In 2003, the application of ligands **11** (Figure 4, $R^1 = \text{Ph}$, $o\text{-Tol}$, Cy , $R^2 = {^i\text{Pr}}$, ${^t\text{Bu}}$) in which the phenyl ring of the PHOX has been replaced by thiophene, was reported for the Ir-catalyzed hydrogenation of *trans*- α -methylstilbene (ee's up to 99%).⁵⁵ For ligands **10**, the best enantioselectivity was obtained with the ligand bearing a *tert*-butyl group at the oxazoline and a *biscyclohexylphosphanyl* group (ligand **11a**; Table 1, entry 5).

Another modification of the PHOX ligand in which a ferrocenyl group has been introduced instead of the phenyl ring (ligands **12**; Figure 4, $R = \text{Me}$, ${^i\text{Pr}}$, ${^t\text{Bu}}$, Ph , Bn) has been presented.⁵⁶ Interestingly, the best enantioselectivities were obtained with the ligand that contains a small methyl

substituent at the oxazoline moiety. These ligands proved to be superior to the PHOX ligands in the hydrogenation of the 4-methyl-1,2-dihydronaphthalene **S8** (89% ee) in which the alkene has *Z*-configuration, while ee's for the hydrogenation of *E*-alkenes were lower (ee's up to 89% for *trans*- α -methylstilbene **S4**).

In 2008, based on the PHOX ligands, new phosphine-oxazoline ligands **13** were developed. In these ligands, the flat *ortho*-phenylene tether is replaced by a benzylic group (Figure 4; R¹ = Ph, *o*-Tol, *p*-Tol, R² = Me, ⁱPr, ^tBu).⁵⁷ These ligands were successfully applied in the Ir-catalyzed asymmetric hydrogenation of a range of *E*- and *Z*-stilbene derivatives (ee's up to 97% and 90%, respectively; Table 1, entry 6). The best enantioselectivities were achieved with the ligand that contains an isopropyl oxazoline substituent and a diphenylphosphanyl group (ligand **13a**; Table 1, entry 6).

Ligands **14**, where the *ortho*-phenylene tether of the PHOX-ligand has been replaced by a branched alkyl chain, (Figure 4, R¹= Ph, *o*-Tol, Xyl, R²= ⁱPr, ^tBu, Bn) provided higher enantioselectivities in the hydrogenation of trisubstituted *E*- and *Z*-aryl/alkyl alkenes than the PHOX ligands (ee's up to 98% for *E*-isomers and 96% for *Z*-isomers).⁴⁴ Enantioselectivities were again best with ligand **14a** bearing bulky substituents at both oxazoline and phosphine moieties (Table 1, entry 7). The potential utility of these new ligands was demonstrated in the synthesis of (*R*)-7-demethyl-2-methoxycalamenene, an antitumor natural product (Scheme 11).



Scheme 11 Total synthesis of (*R*)-7-demethyl-2-methoxycalamenene.

N-Phosphine-Oxazoline Ligands

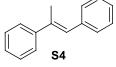
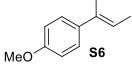
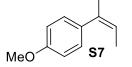
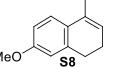
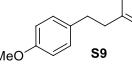
In 2001, a modified version of the PHOX ligands featuring a pyrrole group as linker to the phosphorus was presented.⁵⁸ These new ligands **15** proved to be highly efficient in the hydrogenation of trisubstituted alkenes (Figure 4, $\text{R}^1 = \text{Ph}$, *o*-Tol, Cy; $\text{R}^2 = ^i\text{Pr}$, ^tBu). Enantiomeric excesses surpassed those previously obtained with the PHOX ligands (i.e. ee's up to 99% for *E*-stilbenes and up to 92% for 4-methyl-1,2-dihydronaphthalenes; Table 1, entry 8). The best enantioselectivities were obtained with ligands bearing a *tert*-butyl group in the oxazoline moiety and either *ortho*-tolyl or cyclohexenyl P-substituents (ligands **15a** and **15b**, respectively).

The proline-derived N-phosphine-oxazoline ligands **16** (Figure 4, $\text{R}^1 = \text{Ph}$, *o*-Tol, $\text{R}^2 = ^i\text{Pr}$, ^tBu) provided lower enantioselectivities than the previous pyrrole-based ligands **15** (ee's up to 94% for *E*-stilbenes and up to 64% for 4-methyl-1,2-dihydronaphthalenes).⁵⁹ Again, the highest enantioselectivities were achieved with ligands bearing a bulky *tert*-butyl oxazoline moiety.

Andersson and co-workers developed ligands **17** and **18** for the Ir-catalyzed hydrogenation of alkenes (Figure 4, **17**; $\text{R}^1 = \text{Ph}$, *o*-Tol, Cy, $\text{R}^2 = \text{H}$, ^tBu , Ph, $\text{R}^3 = \text{H}$, Ph and **18**; $\text{R}^1 = \text{Ph}$, $\text{R}^2 = \text{H}$, ^iPr , Ph, $\text{R}^3 = \text{H}$, ^iPr , Ph).⁶⁰

Ligands **17**, containing a chiral rigid bicyclic backbone, provided much higher enantioselectivities than ligands **18**, with a more flexible backbone. The authors found that ligand **17a** with phenyl substituents at R¹, R² and R³ positions provided the best enantioselectivities (ee's up to 99% for *E*-isomers and 95% for 4-methyl-1,2-dihydronaphthalene **S8**; Table 1, entry 9).^{60a} It should be noted that Ir-**17a** catalyst also provided enantioselectivities up to 80% in the hydrogenation of triarylsubstituted olefins (Table 1, entry 9).⁶¹ These catalysts also afforded, for the first time, high enantioselectivities in the hydrogenation of enol phosphinates,⁶² vinyl silanes,⁶³ fluorinated olefins⁶⁴ and vinyl boronates⁶⁵ (*vide infra*).

Table 1 Enantioselectivities achieved using selected ligands in the asymmetric hydrogenation of the most representative, weakly functionalized, trisubstituted olefins.

entry	[M]/L							Ref.
1	Ti (7)	>99	95	-	93	-	-	47
2	Ir- 5a	97	61	42	-	87	-	26,45
3	Ir- 9a	88 (94) ^a	80	75	-	-	-	53
4	Ir- 10a	99	-	-	-	-	-	54
5	Ir- 11a	99	-	-	-	-	-	55
6	Ir- 13a	97	-	-	-	-	-	57
7	Ir- 14a	98	90	96	96	-	-	44
8	Ir- 15a	99	56 (75) ^b	59 (70) ^b	92	-	-	58
9	Ir- 17a	98	99	-	95	-	80 ^c	60a,61
10	Ir- 19a	99	99	89	71	-	-	66
11	Ir- 19b	99	92	92	74	-	-	66
12	Ir- 19c	97	98	88	85	-	-	66
13	Ir- 23a	>99	99	78	-	-	-	72
14	Ir- 23b	99	97	95	98	-	>99	72
15	Ir- 24a	99	>99	92	96	-	-	73a
16	Ir- 25a	98	96	79	-	-	-	39

17	Ir-28a	96	-	-	-	-	-	75
18	Ir-31a	97	87	90	-	-	-	77
19	Ir-32a	>99	>99	98	92 (99) ^d	95	-	79a-b,45
20	Ir-38	95	-	-	92	-	-	84
21	Ir-40a	94	81 (90) ^e	88	91	-	-	86
22	Ir-41a	93 (98) ^f	94	-	-	-	>99 ^c	61,87
23	Ir-42a	>99	96	-	94	-	94 ^c	61,89
24	Ir-45a	98	99	90	99	-	-	92
25	Ir-58a	99	99	94	86	-	99	102
26	Ir-61a	98	-	-	-	-	-	103a
27	Ir-61b	99	-	-	-	-	-	103a

^a Using ligand **9b**. ^b Using ligand **15b**. ^c With substrate 1-(1,2-diphenyl-vinyl)-4-methyl-

benzene. ^d Using ligand bearing bulky 2,4,6-tri-Me-Ph as R²-substituent. ^e Using ligand

40b. ^f Using ligand **41b**.

Phosphinite-Oxazoline Ligands

Two families of phosphinite-oxazoline ligands have been developed for Ir-catalyzed asymmetric hydrogenation. Phosphinite-oxazolines **19** (Figure 4, R¹ = Ph, o-Tol, Cy, R² = ^tBu, Ph, ferrocenyl, 2-Naph; R³ = H, Me, 3,5-Me₂-Ph and R⁴ = Me, ⁱPr, ^tBu, Bn) constitute one of the most effective ligands for this transformation⁶⁶ and the presence of a second stereocenter in the oxazoline moiety (R³= Me) affects enantioselectivity.^{66b} Enantioselectivities up to 99% for a range of *E*-isomers and up to 92% for *Z*-isomers were achieved. In general, the best enantioselectivities were achieved with ligands containing a methyl substituent at R³, a benzyl substituent at R⁴ and a phenyl at R¹. However, the appropriate substituent at the oxazoline and the configuration of the R³ substituent depends on the substrate to be reduced. Thus, for *E*-trisubstituted olefins ee's are best with ligands **19a** (Figure 4; Table 1, entry 10) and **19b** (Table 1, entry 11), while for *Z*-olefins **S7** and **S8** the highest enantioselectivities were achieved using ligands **19b** and **19c**, respectively (Table 1, entries 11-12). These ligands not only provided excellent enantioselectivities in the hydrogenation of a broad range of both *E*- and *Z*-trisubstituted olefins but also in the reduction of α,β -unsaturated esters⁶⁶ and a limited range of more challenging terminal olefins (*vide infra*).⁶⁷ It should be

noted that these catalysts work efficiently in propylene carbonate as an environmental friendly solvent and this allowed the Ir-catalysts to be reused while still maintaining the excellent enantioselectivities.⁶⁸

The second family of phosphinite-oxazoline ligands **20** (Figure 4, R¹ = Ph, o-Tol, R² = ^tPr, ^tBu) is based on ligands **19** in which the alkyl chain is bonded to carbon 2 instead of carbon 4 of the oxazoline moiety, which shifts the chirality from the alkyl chain to the oxazoline substituent.⁶⁹ The scope of these ligands is narrower in comparison with the phosphinite-oxazoline ligands **19** but they are complementary. Ligands **20** provided high enantioselectivities for allylic alcohols (ee's up to 97%) and alkenes bearing heteroaromatic substituents (ee's up to 99%), for which the privileged ligands **19** provided moderate enantioselectivities (*vide infra*).

Phosphoroamidite/Phosphite-Oxazoline Ligands

Despite the advantage of phosphite/phosphoroamidite ligands in asymmetric catalysis,⁷⁰ only a few of these ligand-types have been applied in Ir-catalyzed asymmetric hydrogenation. The first reports were based on the use of chiral 1,2-bis-sulfonylamines and TADDOL to synthesize chiral phosphoroamidite-oxazolines **21** and phosphite-oxazolines **22**, respectively (Figure 4, **21**; R¹ = Ph, p-Tol, Cy, 3,5-Xyl-(CH₂)₄, R² = SO₂-R, 3-OMe-Ph, 4-OMe-Ph, 4-^tBu-Ph, 4-Ph-Ph, 2-Naph, R³ = ^tBu, Ph and **22**; R = Ph, ^tBu).⁷¹ However, their substrate range limitation was higher and enantioselectivities and activities lower than their related phosphinite/phosphine-oxazoline ligands (i.e. **14**, **19** and **20**). They also required higher catalyst loadings (4 mol %) and higher pressures (100 bar) to achieve full conversions.

The first successful application of phosphite-oxazoline ligands for this process was reported in 2008. Pyranoside phosphite-oxazoline ligands **23** (Figure 4, R³= Me, ^tBu, ^tPr, Ph and Bn), derived from D-glucosamine, provided excellent enantioselectivities in the hydrogenation of a wide range of *E*- and *Z*- trisubstituted olefins, including 4-methyl-1,2-dihydronaphthalenes and triarylsubstituted alkenes (Table 1, entries 13 and 14).⁷² The best enantioselectivities were obtained with ligands that contain a phenyl oxazoline substituent and either an *ortho* disubstituted trimethylsilyl biphenyl phosphite

moiety (for *E*-isomers, ee's up to 99%; ligand **23a**, entry 13) or a tetra *tert*-butyl biphenyl phosphite moiety (for *Z*-isomers and triarylsubstituted alkenes, ee's up to 98% and >99%, respectively; ligand **23b**, entry 14). The effectiveness of this ligand family extends to the use of more challenging 1,1-disubstituted olefins and also to the use of olefins containing a neighboring polar group (*vide infra*). DFT calculations on this system agree with an Ir(III/V) catalytic cycle with migratory insertion of a hydride as the selectivity-determining step (*vide supra*).

Biaryl phosphite-oxazoline ligands **24** (Figure 4, R³= Ph, 4-Me-Ph, 4-CF₃-Ph; R⁴= H, Me and R⁵= H, Me), which are based on previous phosphinite-oxazoline ligands **19**, have been successfully applied in the hydrogenation of a range of *E*- and *Z*-trisubstituted olefins.⁷³ The results indicated that introducing a biaryl-phosphite moiety in the ligand design was highly advantageous in terms of catalytic activity and substrate versatility. Therefore, these ligands provided higher enantioselectivities and activities for a wider range of range of alkenes, including *E*- and *Z*-trisubstituted olefins (ee's up to >99% for *E*-isomers and up to 96% for *Z*-isomers; Table 1, entry 15), 1,1-disubstituted alkenes and alkenes containing a neighboring polar group (*vide infra*). The highest enantioselectivities for trisubstituted olefins were achieved with ligand **24a** (Figure 4), which contains bulky *tert*-butyl groups at the R¹ and R² positions of the biaryl phosphite moiety, a phenyl group at the oxazoline (R³), a hydrogen at R⁴ and methyl substituents at the R⁵ positions (entry 15).

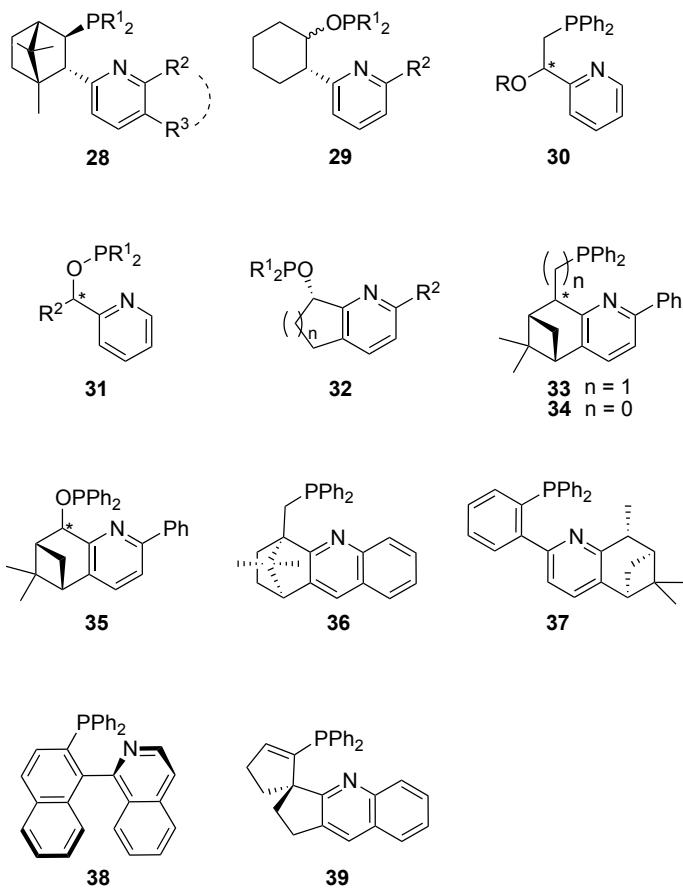
Carbene-Oxazoline Ligands

Ligands **25** (Figure 4, R¹= ^tBu, CHPh₂, Cy, 1-Ad, 2,4,6-Me₃-Ph, 2,6-ⁱPr₂-Ph and R²= 1-Ad, ^tBu, Bn, Ph), in which the phosphine group of ligands **9** has been replaced by a carbene moiety, were evaluated as ligands for Ir-catalyzed asymmetric hydrogenation in 2003.³⁹ The ligands were successfully applied in the reduction of a range of *E*-trisubstituted (ee's up to 98%; Table 1, entry 16) and *Z*-trisubstituted olefins (ee's up to 79%; Table 1, entry 16). This ligand library has also provided excellent enantioselectivities with substrates containing neighboring polar groups, which has been used in the synthesis of

valuable chiral intermediates (*vide infra*). The results, which are comparable to those obtained with ligands **9**, indicated that the presence of a sterically hindered 1-adamanthyl group in the oxazoline and an *ortho*-disubstituted aryl group in the carbene moiety is necessary to achieve the highest levels of enantioselectivity (ligand **25a**, entry 16). In certain cases the carbene group also allowed a decrease in hydrogen pressure to 1 bar (i.e. in the reduction of Z-2-(4-methoxyphenyl)-2-butene **S7**). These excellent results prompted the development of other carbene-based ligands (ligands **26** and **27**).⁷⁴ Ligands **26** (Figure 4; R¹= ⁱPr and R²= ^tBu) and **27** (Figure 4; R¹= Me, ⁱPr, ^tBu, 2,4,6-Me₃-Ph, Neopentyl and R²= ^tBu, Ph, 1-Ad, 2,6-Me₂-Ph) were designed by replacing the P-moiety in **19** and **5** respectively but afforded lower levels of enantioselectivity.

2.1.2 Phosphorus-Pyridine Ligands

In order to mimic the coordination sphere of Crabtree's catalyst, Knochel's group prepared a new kind of chiral N,P-ligand that incorporates a pyridine moiety as a N-donor. They developed phosphine-pyridine ligands **28** (Figure 5; R¹= Ph, Cy; R²= H, Ph; R³= H; R²-R³= CH-CH=CH-CH), synthesized from readily available D-(+)-camphor, for the hydrogenation of trisubstituted olefins and obtained moderate-to-high enantioselectivities in the reduction of *E*-stilbenes (ee's up to 96%; Table 1, entry 17).⁷⁵ The best enantioselectivities were achieved with the ligand that contains a diphenylphosphanyl group and a quinoline moiety (ligand **28a**, entry 17).



28a R¹ = Ph R²-R³ = CH=CH-CH=CH

31a R¹ = tBu R² = tBu

31b R¹ = o-Tol R² = tBu

32a n = 1 R¹ = o-Tol R² = Ph

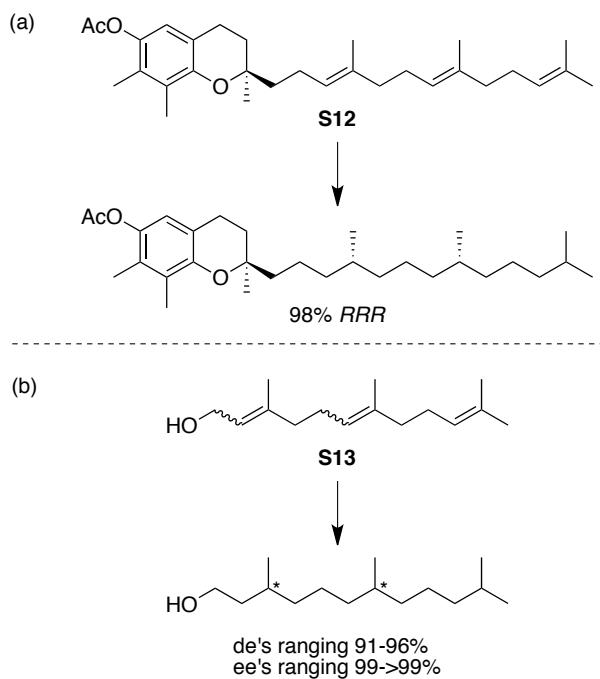
32b n = 1 R¹ = tBu R² = Ph

Figure 5 Phosphorus-pyridine ligands developed for the Ir-catalyzed asymmetric hydrogenation of trisubstituted olefins.

Phosphinite-pyridine ligands **29** (Figure 5, R¹= Ph, o-Tol; R²= H, Me, iPr) are related to **28** but the camphor moiety is replaced by a cyclohexanol group.⁷⁶ This modification led to lower enantioselectivities in the reduction of *E*-stilbenes (ee's up to 93%), indicating the importance of the bulky camphor component for high enantioselectivity.

Phosphine-pyridine ligands **30** (Figure 5)⁷⁷ contain several silyl ether substituents ($R = Si(^tBu)Me_2, Si(^iPr)_3, Si(^tBu)Ph_2$) at the alkyl chain bridge and were prepared with the aim to increase the rigidity and to provide a similar steric environment as the one in PHOX ligands **5**. Despite this, the catalytic performance of $[Ir(cod)\mathbf{30}][BAr_F]$ was inferior to that of the PHOX ligands. In the same report the phosphinite version of **30** (ligands **31**; Figure 5, $R^1 = Ph, o\text{-Tol}, Cy, ^tBu$ and $R^2 = Me, ^tBu, Ph, CPh_3$) was also tested.⁷⁷ The presence of a phosphinite moiety had a positive effect in terms of catalytic performance; i.e. the enantiomeric excess in the hydrogenation of *trans*- α -methylstilbene **S4** increased from 88% to 97%. The best enantioselectivities were obtained with ligand **31a** that contains *tert*-butyl substituents at both the phosphinite (R^1) and the alkyl backbone (R^2) moieties (Table 1, entry 18). Later, a series of phosphinite-pyridine ligands, related to **31** but with a (–)-menthol moiety at the R^2 position, were prepared. However these ligands were less enantioselective (ee's up to 80% in the reduction of *trans*- α -methylstilbene **S4**).⁷⁸

A second generation of phosphinite-pyridine ligands **32** (Figure 5; $R^1 = Ph, o\text{-Tol}, Cy, ^tBu ; R^2 = H, Ph, Me ; R^3 = H, Me$), has also been developed with the aim of increasing the rigidity in the alkyl bridge moiety.⁷⁹ This ligand family gave excellent enantioselectivities for a wide range of olefins (ee's up to >99%; Table 1, entry 19) including purely alkyl trisubstituted ones.^{79a-c} In general, the enantioselectivity was highest with a phenyl substituent at the R^2 position and bulky substituents at the phosphinite moiety (ligand **32a** and ligand **32b**). To obtain excellent enantiocontrol in the reduction of 7-methoxy-4-methyl-1,2-dihydronaphthalene **S8**, the introduction of a large aryl substituent (i.e. 2,4,6-tri-Me-Ph) at R^2 is necessary (Table 1, entry 19).^{79b} The utility of the catalytic system was demonstrated in the hydrogenation of γ -tocotrienyl acetate to obtain γ -tocopherol, a principal component of vitamin E,⁸⁰ resulting in enantioselectivity >98% for the *RRR* enantiomer (Scheme 12a).⁴⁵ Another synthetic application of Ir-**32a** can be found in the diastereo- and enantioselective hydrogenation of farnesol stereoisomers (Scheme 12b). By changing the double bond's geometry these catalysts give access to the four stereoisomers of the product in high selectivity (diastereo- and enantioselectivity).^{2d} See Chapter 5 for a detailed discussion on the asymmetric hydrogenation of allylic alcohols.



Scheme 12 Hydrogenation of: (a) γ -tocotrienyl acetate **S12** and (b) farnesol isomers **S13** using Ir-**32** catalysts.

The phosphine- and phosphinite-pyridine ligands **33** and **35** (Figure 5) were prepared to increase the rigidity of ligands **30** and **31** by introducing an enantiomerically pure bicyclic moiety.⁸¹ These ligands, derived from readily available α -pinene, showed high enantioselectivities (ee's up to 97%) but poor activities. A modification of ligand **33** in which the phosphine group is attached directly to the pinene moiety to form a five-membered chelate ring, yielded ligand **34** (Figure 5).⁸² Ligand **34** proved to be more effective in the reduction of enol phosphonates (ee's up to 90%, *vide infra*) rather than aryl/alkyl trisubstituted olefins (ee' up to 37%). Chelucci and coworkers increased the range of phosphine-pyridine ligands derived from α -pinene with the synthesis of compounds **36** and **37** (Figure 5).⁸³ However, these ligands provided lower enantioselectivities than ligand **33** (ee's up to 94% in the reduction of *trans*- α -methylstilbene **S4**).

In 2007, the phosphine-quinoline ligand **38** (Figure 5), with axial chirality, was applied in the Ir-catalyzed hydrogenation of minimally functionalized trisubstituted olefins with promising results (ee's up to 95% for both *E*- and *Z*-isomers; Table 1, entry 20).⁸⁴ The concept of axial chirality was also used in the spiro phosphine-quinoline ligand **39** (Figure 5).⁸⁵ This ligand showed low enantioselectivities in the Ir-hydrogenation of *trans*- α -methylstilbene **S4** (ee's up to 48% ee).

2.1.3 Phosphorus/Carbene-Other-Nitrogen-Donor Ligands

Although most of the ligands developed for the Ir-catalyzed asymmetric hydrogenation of minimally functionalized olefins contain either an oxazoline or a pyridine, other nitrogen donor groups have been successfully used in this process. The first application of other types of ligands in Ir-hydrogenation was reported with phosphine-imidazoline ligands **40** (Figure 6, R¹ = Ph, o-Tol; R² = ⁱPr, ^tBu; R³ = ⁱPr, ^tBu, Cy, Ph, Bn, *p*-Tol).⁸⁶ One advantage of the imidazoline moiety over the oxazoline is the possibility to introduce a new substituent R³ at the nitrogen that could serve as a linker to attach the ligand to a solid support. Enantioselectivities up to 94% were achieved for a range of standard *E*- and *Z*-aryl/alkyl trisubstituted olefins using [Ir(cod)**40a**][BAr_F] as precatalyst (Table 1, entry 21). In several cases, higher enantiomeric excesses were obtained than with analogous phosphine-oxazoline PHOX ligands (i.e. enantioselectivities for *Z*-2-(4-methoxyphenyl)-2-butene **S7** increased from 42% to 88% ee). The best enantioselectivities were achieved with ligands containing bulky substituents at both R¹ and R² positions, while the substituent at R³ had to be optimized for each substrate (i.e. ligands **40a** and **40b**, Table 1, entry 21). Zwitterionic versions of these iridium complexes were prepared by introducing an anionic moiety at the R³ position of the imidazole group.⁵¹ However, the presence of the anionic derivatization has a negative influence on the asymmetric induction of the iridium complex.

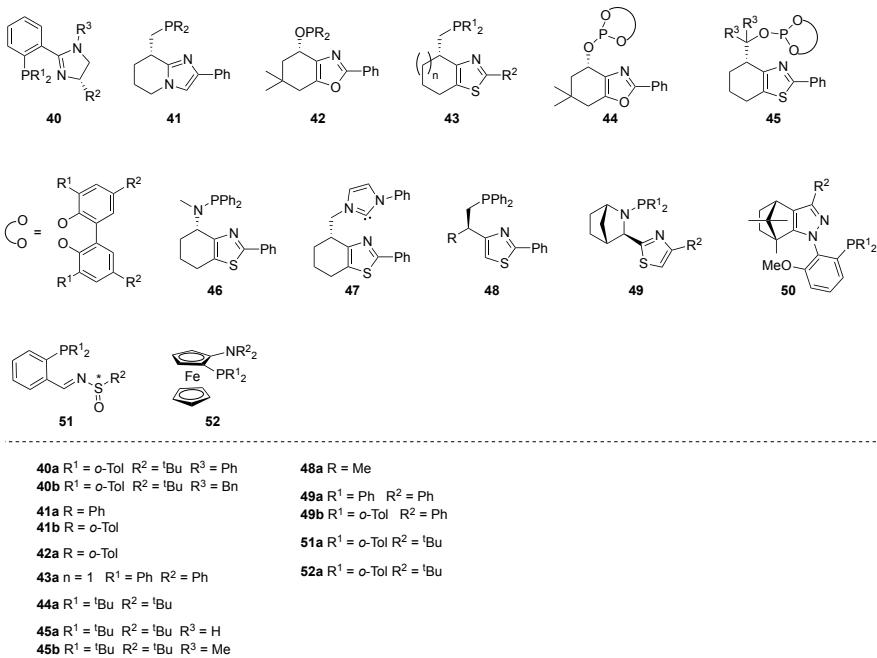


Figure 6 Phosphorus/carbene-other nitrogen donor ligands applied in the Ir-catalyzed asymmetric hydrogenation of aryl/alkyl trisubstituted olefins.

Phosphine-imidazole ligands **41** (Figure 6; R = Ph, o-Tol, 3,5-diMe-Ph) have been used for the Ir-catalyzed hydrogenation of unfunctionalized olefins and gave high enantioselectivities for *E*-aryl/alkyl trisubstituted olefins (ee's up to 98%; Table 1, entry 22)^{61,87} and cyclic dienes (ee's up to >99% for the *trans* isomer),⁸⁸ but was only moderate in the reduction of *Z*-olefins (ee's up to 72%).⁸⁷ In general, enantioselectivities were best for ligand **41a**, containing a bisphenylphosphanyl group (Table 1, entry 22). However, the highest enantioselectivity in the reduction of *trans*- α -methylstilbene **S4** was achieved with ligand **41b** containing a *bis*(o-tolyl)phosphanyl group (Table 1, entry 22). Phosphinite-oxazoles **42** (Figure 6; R = Ph, o-Tol, 3,5-diMe-Ph)⁸⁹ and phosphine-thiazoles **43** (Figure 6, R¹ = Ph, o-Tol; R² = H, Ph), related to ligands **41**, have also been evaluated.⁹⁰ Both families of ligands have proven valuable in hydrogenation of minimally functionalized olefins, including those containing a neighboring polar group (*vide infra*). These ligands provided excellent enantioselectivities in the hydrogenation of both *E*- and *Z*-aryl/alkyl

trisubstituted olefins (ee's up to >99% for *E*-substrates and up to 94% for *Z*-substrates; Table 1, entry 23).⁸⁹⁻⁹⁰ Ligands **43** have also proved to be optimal for the hydrogenation of cyclic alkenes,⁹¹ dienes (ee's up to 97% for the *trans* product in the hydrogenation of **S11**)⁸⁸ and 1,1-diaryl trisubstituted olefins (ee's up to >99%).⁶¹ Interestingly, while oxazole ligands gave the highest enantioselectivities with bulky *ortho*-tolyl substituents at the phosphinite group (ligand **42a**), thiazole ligands performed best with a diphenylphosphanyl group (ligand **43a**). The authors found that the results could be explained by using a simple quadrant model (See section 8 for a detailed discussion).

Later, several modifications of these ligands were developed, including the replacement of the phosphine/phosphinite moieties by N-phosphine, carbene and phosphite groups as well as modification in the ligand backbone. In this respect, biaryl phosphite containing ligands **44** and **45** (Figure 6, R³= Me or H), related to the successful ligands **42** and **43**, have also provided excellent enantioselectivities for both *E*- and *Z*-trisubstituted olefins (Table 1, entry 24).⁹² The introduction of a biaryl phosphite moiety increases the substrate scope (i.e. ee's increased up to 99% in the reduction of 4-methyl-1,2-dihydronaphthalene). In general phosphite-thiazole ligands **45** provided higher enantioselectivities than related phosphite-oxazole ligands **44**. For ligands **45** the best enantioselectivities were achieved using ligand **45a** (Figure 6), containing bulky *tert*-butyl groups at the *ortho* and *para* positions of the biphenyl phosphite moiety and hydrogens at the R³ positions. Related N-phosphine-thiazole ligand **46** has been successfully applied in the hydrogenation of 1,1-diarylsubstituted olefins, providing comparably excellent enantioselectivities (ee's up to >99%) to that of phosphine-thiazole ligands **43**.⁶¹ However, the replacement of the phosphine group in ligands **43** by a carbene moiety (Figure 6, ligand **47**) led to lower enantioselectivities (ee's up to 90%).⁹³ Ligands **48**, in which the rigid cyclic backbone in ligands **43** were eliminated, were less successful (Figure 6, R= Me, Bn, allyl).⁹⁴ Recently, the N-phosphine-thiazole ligands **49** (Figure 6, R¹ = Ph, o-Tol; R² = Me, ^tBu, Ph) with a more rigid bicyclic ligand backbone were prepared and evaluated.⁹⁵ High enantioselectivities were achieved in the reduction of *E*-trisubstituted olefins (ee's up to 97%) but enantioselectivities for *Z*-olefins decreased to 83%.

Other ligands in this class, **50**,⁹⁶ **51**,⁹⁷ and **52**⁹⁸ (Figure 6) have also been tested in the hydrogenation of *trans*- α -methylstilbene and other alkenes, but did not produce very high ee's.

2.1.4 Other Ligands

The Ir-catalyzed asymmetric hydrogenation of minimally functionalized olefins has been dominated by the use of chiral bidentate N,P-ligands. In 2009, a new concept was reported for the development of chiral versions of Crabtree's catalyst in which the chirality is introduced by using only a chiral ferrocene monodentate ligand **53** (Figure 7).⁹⁹ The use of $[\text{Ir}(\text{cod})(\mathbf{53})(\text{Py})][\text{BAr}_\text{F}]$ catalyst precursor proved to be active in the hydrogenation of several trisubstituted olefins, but enantioselectivities were poor (ee's up to 12%).

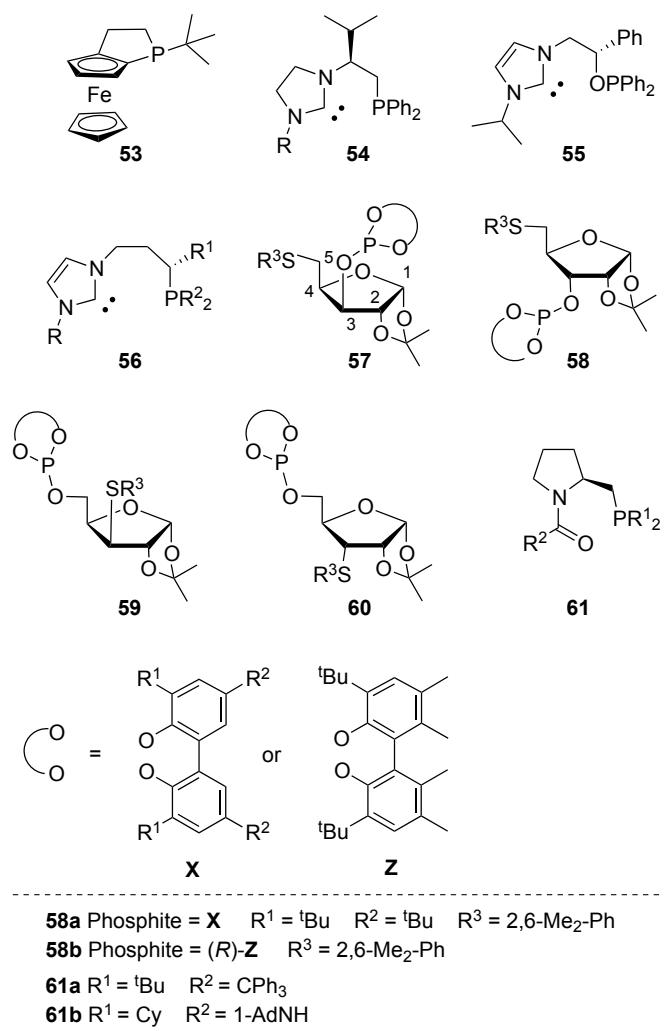


Figure 7 Other ligands applied in the asymmetric Ir-catalyzed hydrogenation of trisubstituted olefins.

Since most of the research in the design of new chiral ligands for Ir-catalyzed asymmetric hydrogenation has been focused on developing chiral mimics of Crabtree's catalyst, the possibility of changing the nature of the N-donor atom in these heterodonor ligands hasn't been considered to a large extent. In 2006, the application of phosphine/phosphinite carbene ligands **54** and **55** (Figure 7; R= Me, ⁱPr, Mes) in the Ir-catalyzed hydrogenation of both *E*- and *Z*-aryl/alkyl trisubstituted olefins was reported to give low activities and

enantioselectivities (ee's up to 63%).¹⁰⁰ Later phosphine-carbene ligands **56** (Figure 7; R¹= Me, Et, iPr; R²= 2,4,6-Me₃-Ph, 2,6-iPr₂-Ph) that formed a larger chelate ring-size upon coordination to Ir, provided higher activities, but enantioselectivities were still moderate.¹⁰¹

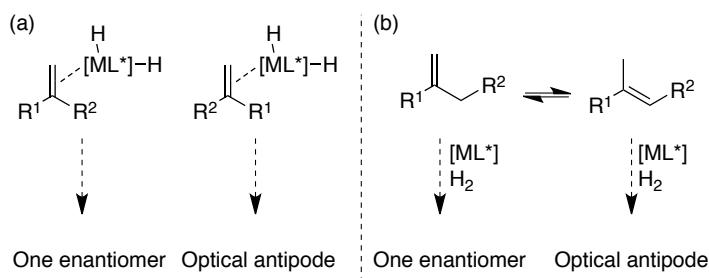
A breakthrough in the development of chiral non-N-containing ligands for this transformation came with the development of a highly modular phosphite-thioether ligand library (ligands **57-60**; Figure 7, R³= Me, iPr, tBu, Ph, 2,6-Me₂-Ph), which provides excellent activities and enantioselectivities for a wide range of *E*- and *Z*- trisubstituted olefins, including the more challenging 4-methyl-1,2-dihydronaphthalenes and 1,1-diaryl trisubstituted olefins (ee's up to 99%; Table 1, entry 25). These ligands consist of four main ligand backbones produced by systematically varying the position of the thioether group at either C-3 or C-5 of the furanoside backbone and the configuration of C-3. The introduction of a thioether moiety in the ligand design may be beneficial because: (i) the S atoms become a stereogenic center when coordinated to the metal, which moves the chirality closer to the metal, and (ii) the thioether group is more stable than the oxazoline moiety. The best results were obtained with ribofuranoside ligands **58** containing a bulky 2,6-Me₂-Ph thioether group in the C-5 position and either a tetra *tert*-butyl biphenyl phosphite moiety (ligand **58a**, Figure 7) or an *R*-enantiopure 5,5',6,6'-tetramethyl-3,3'-di-*tert*-butyl-1,1'-biphenyl-2,2'-diol (ligand **58b**) in the C-3 position of the furanoside backbone.¹⁰²

Proline-based chiral P,O ligands **61** (Figure 7, R¹= Ph, tBu, Cy, o-Tol and R²= tBu, 1-Ad, CPh₃, 1Ad-NH, MesNH, CPh₃NH) have also been used in Ir-catalyzed asymmetric hydrogenation.¹⁰³ Phosphines bearing either a bulky amide (ligand **61a**; Table 1, entry 26) or urea groups (ligand **61b**; Table 1, entry 27) at the pyrrolidine N-atom, formed efficient Ir-catalysts for the asymmetric hydrogenation of several minimally functionalized olefins (ee's up to 99% in the hydrogenation of *trans* α -methylstilbene **S4**).

2.2 1,1-Disubstituted Alkenes

Disubstituted terminal alkenes are a challenging substrate class when compared to the more widely investigated trisubstituted olefins. There are two

reasons for this. The first is that in the absence of a third substituent on the double bond, the catalyst has to distinguish solely between the two alkyl/aryl-substituents R¹ and R² for enantiodiscrimination (Scheme 13a). This is a more demanding task compared to distinguishing between hydrogen and an alkyl- or aryl-group as in the case of the trisubstituted alkenes. The second is that the terminal double bond can isomerize to form the more stable internal alkene, which usually leads to the predominant formation of the other enantiomer of the hydrogenated product (Scheme 13b). Efficient catalytic systems for the asymmetric reduction of 1,1-disubstituted aryl-alkyl alkenes have been elusive until very recently. Next, we discuss the progress made in the asymmetric hydrogenation of minimally functionalized terminal olefins, beginning with the latest development in design, from the initial discovery of lanthanide catalytic precursors, through to the use of transition metal-diphosphine/iminophosphorane precursors, to the successful Ir-N,P catalytic systems.



Scheme 13 Proposed reasons for the low enantioselectivities associated with the hydrogenation of terminal olefins.

The early approaches to tackle the asymmetric hydrogenation of disubstituted alkenes involved the use of chiral *biscyclopentadienyl* Sm-complexes¹⁰⁴ or Ru-diphosphine catalysts.¹⁰⁵ In the first case, enantioselectivities up to 96% in the reduction of 2-phenyl-but-1-ene **S14** (Table 2, entry 1) were achieved using [Sm(**62**)(CH(TMS)₂)] catalyst precursor (Figure 8). However, due to the low temperatures ($-78\text{ }^{\circ}\text{C}$) required to achieve the highest levels of enantioselectivity and the low modularity of the catalytic system,¹⁰⁴ the interest of using this type of complexes has

diminished. In the second case, enantioselectivities up to 89% were reported in the hydrogenation of a range of 2-phenyl-2-but-1-enes (Table 2, entries 2, 8, 10 and 22) using $[\text{RuCl}_2(\mathbf{3})]_n \cdot \text{DMF}$ (Figure 8).^{17c} It should be noted that the use of other diphosphine ligands (i.e. Et-DuPhos or BINAP) were not effective.^{17c}

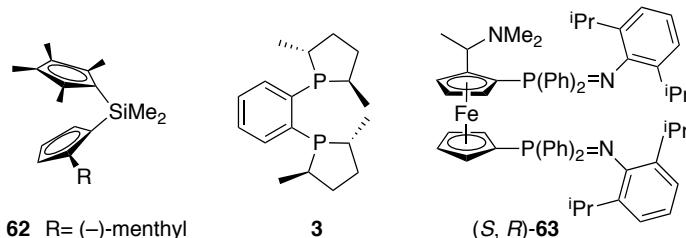
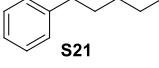
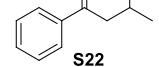
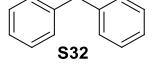
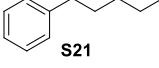
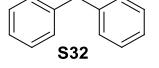
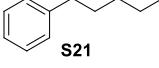
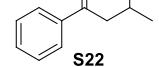
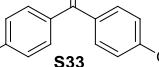
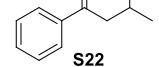
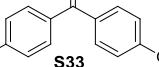


Figure 8 Ligands **62**, **3** and **63** applied in the asymmetric hydrogenation of 1,1-disubstituted aryl/alkyl olefins.

An important discovery in this area was made by Pfaltz and co-workers when they successfully applied Ir-N,P catalytic systems for the hydrogenation of minimally functionalized trisubstituted olefins to terminal olefins.^{2b,2d,e,3c,d} A complete screening of Ir-complexes containing highly modular phosphine-oxazoline ligands **5** (Figure 3) and phosphinite-oxazoline ligands **19** (Figure 4) in the reduction of a range of 2-phenyl-2-but-1-enes indicated that the ligand parameters have an important effect on enantioselectivity.⁶⁶⁻⁶⁷ The enantioselectivities (ee's up to 94%, Table 2, entries 9, 11, 15, 23, 41 and 42) were best with the Ir-catalytic system containing the basic cyclohexyl phosphinite-oxazoline derived from threonine **19a** (Figure 4). These results surpass the enantioselectivities obtained using Ru-**3** catalytic system (i.e. Table 2, entries 9 and 11 vs 8 and 10, respectively). Interestingly, the selectivity is highly pressure dependent in the Ir-catalyzed reduction of these terminal alkenes. Hydrogenation at atmospheric pressure of H_2 gave significantly higher ee's than at higher pressures (ee increases from 58% to 94% when pressure is decreased from 50 bar to 1 bar).^{66b}

Table 2 Enantioselectivities achieved using selected ligands in the asymmetric hydrogenation of 1,1'-disubstituted aryl-alkyl alkenes

Entry	Substrate	[M]/L	% ee	Ref.	Entry	Substrate	[M]/L	% ee	Ref.
1		Sm(62)	96	104	33		Ir-23a	93	72b
2		Ru-3	86	17c	34		Ir-24b	90	73b
3		Ir-42a	41	89	35		Ir-49a	44	95
4		Ir-49a	2	95	36		Ir-23a	83	72b
5		Ir-23a	99	72b	37		Ir-24b	97	73b
6		Ir-24b	99	73b	38		Ir-23a	84	72b
7		Ir-45a	94	92	39		Ir-24b	97	73b
8		Ru-3	87	17c	40		Ir-45a	94	92
9		Ir-19a	91	67	41		Ir-19a	46	67
10		Ru-3	81	17c	42		Ir-19a	82 ^a	68a
11		Ir-19a	88	67	43		Rh-63	94	108
12		Ir-23a	99	72b	44		Ir-24b	25	73b
13		Ir-24b	96	73b	45		Ir-24b	87 ^a	73b
14		Ir-45a	94	92	46		Ir-24b	99	73b
15		Ir-19a	94	67	47		Ir-23a	99	72b
16		Ir-25a	89	39	48		Ir-24b	>99	73b
17		Ir-42a	97	89	49		Ir-45a	96	92
18		Rh-63	97	108	50		Ir-58a	99	102
19		Ir-23a	98	72b	51		Ir-23a	99	72b
20		Ir-24b	>99	73b	52		Ir-24b	99	73b
21		Ir-45a	97	92	53		Ir-45a	99	92
22		Ru-3	86	17c	54		Ir-58a	60	102
23		Ir-19a	94	67	55		Ir-23a	90	72b
24					56		Ir-24b	96	73b
25		Ir-23a	97	72b	57		Ir-45a	90	92
26		Ir-24b	>99	73b	58		Ir-23a	70	72b
					59		Ir-24c	>99	73b
					60		Ir-58a	43	102

27		Ir-58a	98	102					
28		Ir-23a	90	72b	61		Ir-23a	68	72b
29		Ir-24b	94	73b	62		Ir-24c	99	73b
30		Ir-58a	62	102					
31		Ir-23a	93	72b	63		Ir-23a	65	72b
32		Ir-24b	93	73b	64		Ir-24d	65	73b

^a Using PC as solvent

Later, Börner's group disclosed that Ir-19a catalyst is efficient when using propylene carbonate (PC) as an environmentally friendly alternative solvent to dichloromethane.^{68a} Although reaction rates are lower in PC than in dichloromethane, the isomerization of the terminal double bond to the more stable internal alkene is also slower in PC than in dichloromethane. For example, the isomerization of 4-methylene-1,2,3,4-tetrahydronaphthalene **S26** to 4-methyl-1,2-dihydronaphthalene is approximately three times slower in PC than in dichloromethane. Due to the suppressed isomerization, enantioselectivities increased from 46% to 82% in the reduction of **S26** when using PC (Table 2, entries 41 vs 42). Another advantage of using PC as the solvent is that it allows catalysts to be repeatedly recycled by a simple two-phase extraction with an apolar solvent (typically hexane). Catalyst Ir-19a could be reused up to five times with no significant losses in enantioselectivity, although the reaction time increased.^{68a} This is probably due to the iridium catalyst partially passing into the hexane phase and/or the formation of inactive triiridium hydride clusters.^{23b,30}

The catalyst precursors [Ir(cod)**25**][BAr_F], containing N-heterocyclic carbene-oxazoline ligands **25** (Figure 4) have been applied in the reduction of 2-(4-methoxyphenyl)-1-butene **S17** (Table 2, entry 16).³⁹ Enantioselectivities up to 89%, comparable to those obtained using the Ru-3 catalytic system, were obtained using Ir-precursor containing ligand **25a** (Figure 4). Interestingly, the Ir-**25a** catalytic system was also successfully applied in the asymmetric reduction of unfunctionalized 1,1-disubstituted dienes with enantioselectivities up to 87% and good diastereoselectivities (Figure 9).¹⁰⁶

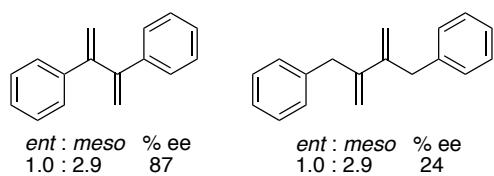


Figure 9 Asymmetric hydrogenation of 1,1-disubstituted dienes using Ir-**25a** catalyst.

The Ir-catalytic system containing phosphinite-oxazole **42a** (Figure 6) has been used to hydrogenate 2-(4-methoxyphenyl)-1-butene **S17** with enantioselectivities up to 97% (Table 2, entry 17).⁸⁹ However, enantioselectivities were only moderate for other terminal 2-arylbut-1-enes (i.e. Table 2, entry 3).¹⁰⁷ The application of a series of *N*-phosphine-thiazole ligands **49** (Figure 6) in the hydrogenation of some terminal aryl-alkyl olefins with moderate success was also reported (Table 2, entries 4, 24 and 35).⁹⁵ The best enantioselectivity (up to 86%) was obtained in the reduction of **S20** (Table 2, entry 24) using a ligand bearing phenyl substituents at both thiazole and *N*-phosphine moieties (ligand **49a**; Figure 6).

(Iminophosphoranyl)ferrocene ligands **64** (Figure 8) have been successfully applied in the Rh-catalyzed hydrogenation of **S13** (ee's up to 97%, Table 2, entry 18) and **S26** (ee's up to 94%, Table 1, entry 43).¹⁰⁸ Despite this success, no new substrates have been applied and the potential of this catalyst system needs to be further investigated.

Despite all these important contributions, the asymmetric hydrogenation of terminal alkenes using Ir-*N,P* catalyst systems still experienced a limited substrate scope. In 2008 it was shown that the presence of biaryl-phosphite moieties in the ligand design is highly advantageous for the Ir-catalyzed reduction of minimally functionalized olefins.⁷²⁻⁷³ Three families of phosphite-nitrogen ligands were successfully applied in the reduction of a broad range of 1,1-disubstituted alkenes (ligands **23**, **24** in Figure 4 and ligands **45** in Figure 6). The use of biaryl phosphite moieties in the ligand design is a common feature of these ligand libraries where the availability of biaryl alcohols and the robustness of the phosphite towards oxidation are the key factors for the high modularity and stability of

the ligands. The first family was the previously mentioned phosphite-oxazoline ligands **23** derived from D-glucosamine (Figure 4).^{72a} By carefully selecting the ligand parameters (substituents at the oxazoline moiety and substituents/configuration at the biaryl phosphite moiety) enantioselectivities ranging from 83 to 99% were obtained using ligand **23a** (Figure 4).^{72b} The results obtained when reducing several 1,1-disubstituted aryl/heteroaryl-alkyl substrates indicated that enantioselectivity is affected by the nature of the substrate alkyl chain (ee's ranging from 83% to 99%, Table 2, entries 5, 12, 19, 25, 28, 31, 33, 36, 38, 47, 51 and 55). One possible explanation for this is the competition between direct hydrogenation versus isomerization for the different substrates. This is supported by the fact that the hydrogenation of substrate **S20** bearing a *tert*-butyl group, for which isomerization cannot occur, provides high levels of enantioselectivity (ee's up to 97%; Table 2, entry 25), while the lowest enantioselectivity of the series (ee's up to 84%; Table 2, entries 36 and 38) is found for substrates **S24** and **S25**, which form the most stable isomerized tetrasubstituted olefins.

The second family, related to ligands **19**, proved to be superior to the glucosamine-based phosphite-oxazoline ligands **23**.⁷³ [Ir(cod)(**24**)][BAr_F] (Figure 4) appeared as a privileged catalytic system for the hydrogenation of several types of aryl-alkyl, heteroaryl-alkyl and aryl-aryl 1,1-disubstituted olefins, including those bearing a neighboring polar group (*vide infra*).^{73b} However, all these examples required the presence of an aromatic substituent conjugated to the alkene and there are no reported examples of purely alkyl-substituted terminal olefins. In contrast to trisubstituted olefins, enantioselectivities were best with the ligand containing an S-binaphthyl phosphite moiety and phenyl substituents at the alkyl backbone chain (ligand **24b**; Figure 4). Several *para*-substituted 2-phenylbut-2-enes and several α -alkylstyrenes bearing increasing sterically demanding alkyl substituents were hydrogenated with excellent enantioselectivities (90-99% ee) (Table 2, entries 6, 13, 20, 26, 29, 32, 34, 37 and 39). Ir-**24b** catalytic system was also used in combination with PC as the solvent. As observed by Börner and co-workers using Ir-**19a**, enantioselectivity in the reduction of **S26** was improved (Table 2, entries 44 vs 45) and catalysts were recycled up to five times with no significant losses in enantioselectivity. A range of heteroaryl-alkyl substrates

containing a furyl, pyridyl and thiophenyl groups could be hydrogenated efficiently at 1 bar of hydrogen using the Ir-**24b** catalytic system (ee's ranging 96->99%, Table 2, entries 46, 48, 52 and 56). By suitable tuning of the ligand components, the Ir-**24c** (Figure 4) and Ir-**24d** (Figure 4) catalysts were also efficient in the hydrogenation of 1,1-diaryl substrates, which provides a facile alternative for the preparation of diarylalkanes that are present in several drugs and research materials (Table 2, entries 59, 62 and 64).

The third family was designed to study how effective the biaryl phosphite moiety will be when combined with other *N*-donor groups than oxazolines. Two types of *N*-donor group were studied, oxazole (Figure 6, ligands **44**) and thiazole (Figure 6, ligands **45**).⁹² Phosphite-thiazole ligand **45a** (Figure 6) provided similar levels of enantioselectivity as those obtained with glucosamine-based Ir-**23a** catalytic system (Table 2, entries 7, 14, 21, 40, 49, 53 and 57).

The previously mentioned phosphite-thioether ligands **57-60** (Figure 7) were screened in the hydrogenation of several aryl/alkyl disubstituted substrates, including those containing a heteroaryl group. Again, furanoside ligand **58a** provided the highest enantioselectivities (ee's up to 99%; Table 2, entries 27, 30, 50, and 60).^{102a,b} For this substrate class the enantioselectivity is dependent on the alkyl substituent and this can, possibly, be attributed to the presence of an isomerization process under hydrogenation conditions. Enantioselectivities were best in the asymmetric reduction of aryl and heteroaryl/*tert*-butyl substrates **S20** and **S28**. Conveniently, both enantiomers of the hydrogenation product can be obtained in high enantioselectivity, by simply changing the configuration of the biaryl phosphite moiety.

While chiral versions of Crabtree's catalyst have proved very useful for the asymmetric hydrogenation of unfunctionalized 1,1-disubstituted alkenes, a complementary reactivity can be found in the previously described Rh-Duanphos catalytic system (Scheme 10). Here the hydrogenation of 1,1-diaryl substrates bearing a directing hydroxyl group at the *ortho* position of one of the aryl groups gives ee's up to >99% while the corresponding alkenes devoid of the hydroxyl moiety gives essentially racemic mixtures.⁴⁹

2.3 Tetrasubstituted Aryl/Alkyl Alkenes

Despite the advances during the last five years in the hydrogenation of minimally functionalized olefins and with the development of new ligand libraries that allowed a considerably increased range of substrates to be hydrogenated, the enantioselective reduction of tetrasubstituted olefins remain a challenge. The range of such substrates that can be efficiently hydrogenated is still narrow.

Buchwald and co-workers reported the first successful example on the asymmetric hydrogenation of tetrasubstituted alkenes. In this study, a chiral zirconocene complex **64** (Figure 10), which is the Zr analogue of the previously mentioned titanocene complex **7**, was used.¹⁰⁹ The hydride-zirconocene catalyst afforded high enantioselectivities (ee's over 90%) for a range of tetrasubstituted acyclic olefins and dihydronaphthalenes (Table 3, entries 1, 12, 15, 19 and 21). However, as observed for the titanium analogue **7**, the potential utility is hampered by the high catalyst loadings, long reaction times and high pressures required.

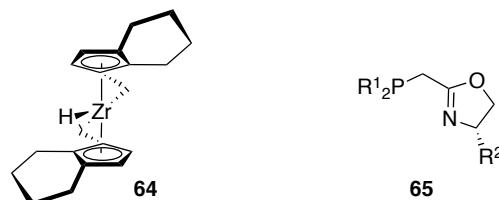


Figure 10 Zirconocene complex **64** and phosphine-oxazoline ligands **65** applied in the asymmetric hydrogenation of tetrasubstituted olefins.

Ir-PHOX catalytic systems (Figure 3) have also been applied in the hydrogenation of the tetrasubstituted olefin 1-(1,2-dimethyl-propenyl)-4-methoxy-benzene **S5**, providing promising results (ee's up to 81% and full conversion after 2 hours, Scheme 4) at a lower catalyst loading and pressure than what was required when using Zr-**64** (Table 3, entry 2).^{26-27,50} The requirements of the ligand to achieve high enantioselectivities for tetrasubstituted olefins are different from those needed for the reduction of trisubstituted ones. For tetrasubstituted alkenes, enantioselectivities are best with the less bulky ligand **5b** that contains a CH_2^tBu group on the oxazoline

and a bisphenylphosphanyl group (Figure 3). The Ir-PHOX ligands have been successfully applied in the hydrogenation of tricyclic ring olefins **S34** (Table 3, entry 10).¹¹⁰ These results opened up the asymmetric reduction of this substrate class to the use of other Ir-N,P catalysts and some of the ligands used in the reduction of trisubstituted olefins have also been tested. In this context, the previously mentioned phosphine-benzoxazine ligands **8** (Figure 4) provided low conversions (up to 63%) and enantioselectivities (up to 31%) in the hydrogenation of 1-(1,2-dimethyl-propenyl)-4-methoxy-benzene **S5** (Table 3, entry 3) and 1-isopropylidene-6-methoxy-1,2,3,4-tetrahydro-naphthalene.⁵²

The proline based N-phosphine-oxazoline ligands **16** (Figure 4), which provided higher enantioselectivities in the hydrogenation of trisubstituted olefins than PHOX ligands, have been tested in the hydrogenation of tetrasubstituted substrate **S5**.⁵⁹ However for this substrate low activities and enantioselectivities were obtained (ee's up to 16%; Table 3, entry 4).

The use of phosphinite-ligands **19** (Figure 4) provided similarly high levels of enantioselectivity as the PHOX-based catalytic system did in the hydrogenation of tetrasubstituted olefins (ee's up to 82%; Table 3, entry 5).¹¹⁰ As observed in the hydrogenation of disubstituted olefins and, in contrast to the hydrogenation of trisubstituted olefins, the ligand that provided the highest enantioselectivity with tetrasubstituted olefin **S5** contains cyclohexyl substitutents at the phosphinite moiety (ligand **19a**; Figure 4).

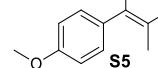
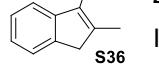
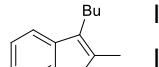
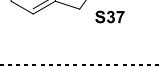
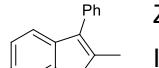
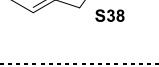
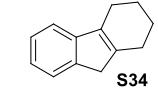
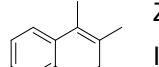
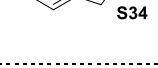
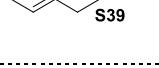
Phosphinite-oxazoline ligands **20** (Figure 4) have also been evaluated and provided low levels of enantioselectivity in the reduction of standard tetrasubstituted substrate **S5** (ee's up to 14%; Table 3, entry 6).¹¹⁰ However, **20a** provided excellent enantioselectivities (ee's up to 95%) for a limited range of tetrasubstituted dihydronaphthalenes (Table 3, entries 13 and 17).

The phosphinite-pyridine ligands **31** and **32** (Figure 5) have been screened for the Ir-catalyzed asymmetric hydrogenation of tetrasubstituted alkenes and Ir-**31** afforded higher enantioselectivities than Ir-**32** (Table 3, entries 7 vs 8).^{77,79a} Enantioselectivities up to 81%, comparable to that obtained for the PHOX ligands, were achieved using the phosphinite-pyridine ligand **31a** (Figure 5) in the reduction of substrate **S5**.

Phosphinite-oxazole ligands **42** (Figure 6) were evaluated in the hydrogenation of standard substrate **S5** but enantioselectivities and activities were low (ee's up to 15%).⁸⁹

An important discovery was the use of simple and readily available phosphine-oxazoline ligands **65** (Figure 10; R¹= Ph, Cy, ^tBu, o-Tol and R²= Ph, ⁱPr, ^tBu, CH₂^tBu, Bn), which form five membered chelate rings.¹¹⁰ This ligand family provided excellent enantioselectivities for the hydrogenation of the standard tetrasubstituted substrate **S5**, but also provided high enantioselectivities for a broad range of tetrasubstituted dihydronaphthalenes, including tricyclic ring olefins (Table 3, entries 9, 11, 14, 16, 18, 20, 22 and 23). Although, small changes at both the substituents of the ligands and that of the substrate affected the catalytic performance, it was found that ligand **65a** (Figure 10, R¹= Ph and R²= ⁱPr), containing an isopropyl oxazoline substituent and a bisphenylphosphanyl group, provided the highest enantioselectivities for a broad range of tetrasubstituted dihydronaphthalenes.

Table 3 Enantioselectivities achieved using selected ligands in the asymmetric hydrogenation of tetrasubstituted alkenes.

Entry	Substrate	[M]/L	% ee	Ref.	Entry	Substrate	[M]/L	% ee	Ref.
1		Zr	96 ^a	109	15		Zr (64)	93	109
2		(64)	81	26	16		Ir- 65a	94	110
3		Ir- 5b	31	52					
		Ir- 8							
4		Ir- 16	16	59	17		Ir- 20a	95	110
5		Ir- 19a	82	110	18		Ir- 65a	94	110
6		Ir- 20a	14	110					
7		Ir- 31a	81	77	19		Zr (64)	78	109
8		Ir- 32a	64	79a	20		Ir- 65a	96	110
9		Ir- 65a	97	110					
10		Ir- 5b	94	110	21		Zr (64)	92	109
11		Ir- 65a	96	110	22		Ir- 65a	73	110

12		Zr	52	109	23		Ir-65a	91	110
13	(64)		94	110					
14	Ir-20a		93	110					
	Ir-65a								

^a Using *p*-fluoro derivative instead of OMe in **S5**.

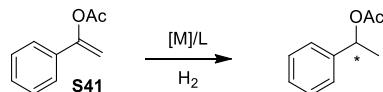
3 Enols

Traditionally, the asymmetric hydrogenation of enols has been the subject of interest as an alternative method to the asymmetric hydrogenation of ketones in the preparation of chiral alcohols. However, the hydrogenation of enol derivatives can give chiral products besides alcohols that are difficult to access from ketone reduction such as chiral cyclic ethers and phosphines. Moreover the great diversity of protecting groups that can be introduced in the enol substrate can be used after hydrogenation as an alcohol protective group that can be deprotected at a later step in the synthesis of a more complex molecule.

3.1 Enol Esters and Enol Carbamates

Enol esters are the most widely used enol type substrate in asymmetric hydrogenation.¹¹¹ The asymmetric hydrogenation of this substrate class readily gives access to chiral alcohols after hydrolysis of the ester group. The hydrogenation of this substrate class is dominated by Rh- and Ru-catalysts modified with chiral phosphorus ligands due to the coordinative ability of the ester group to the metal center (enol esters are structurally and electronically similar to enamides) (Table 4).¹¹¹⁻¹¹² There are very few examples of chiral analogues to Crabtree's catalyst that have been applied to this substrate class. For example, the hydrogenation of 1-phenylvinyl acetate **S41** using phosphine-thiazoline ligands **43** (Figure 6) was ineffective (no conversion; Table 4, entry 5) but the use of Ir-17 catalysts (Figure 4) afforded exclusively the desired acetate but in the racemic form (Table 4, entry 3).^{62b} Phosphinite-oxazole ligands **42** (Figure 6) however led to the formation of the decomposition product ethyl benzene (Table 4, entry 4).

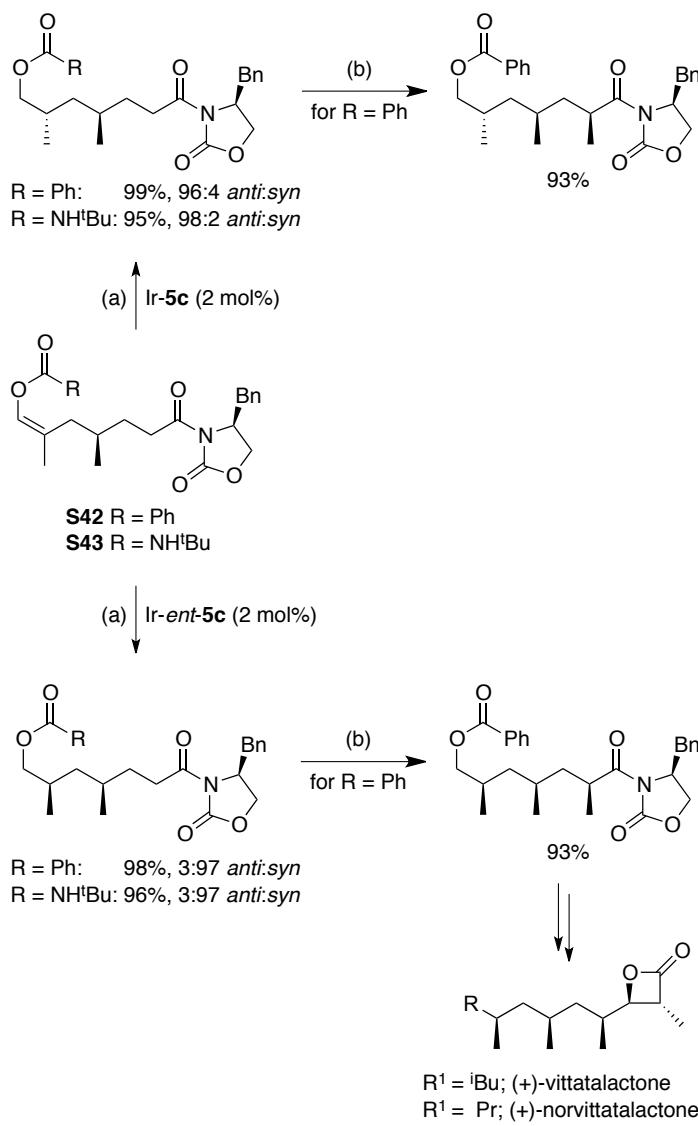
Table 4 Selected results for the asymmetric hydrogenation of model enol ester 1-phenylvinyl acetate **S41**



Entry	[M]/L	% Conv	% ee	Ref.
1	Rh-ZhangPhos	100	97	112b
2	Rh-Cy-SMS-Phos	100	97	112a
3	Ir-17	100	0	62b
4	Ir-42	100 ^a	-	62b
5	Ir-43	0	-	62b

^a Ethyl benzene was the major product

Recently, Schneider and co-workers have successfully applied Ir-phosphine/phosphinite-oxazoline catalysts in the diastereoselective hydrogenation of enol benzoate **S42** (Scheme 14, step (a)).¹¹³ It should be noted that various chiral Rh-catalysts have failed to hydrogenate this substrate. After screening several Ir-N,P systems the best results were obtained with the Ir-PHOX catalytic systems (Figure 3) affording significant diastereoselectivities. They also found that the steric bulk within the P-aryl group exerted a decisive effect on both the activity and selectivity. The best activities and selectivities were achieved using ligand **5c** containing bulky mesityl groups at the phosphine moiety (Figure 3).¹¹³ Enol benzoate **S42** was hydrogenated to the *anti* product in 99% yield and 96:4 dr, whereas the epimeric *syn* product was achieved in 98% yield and 97:3 dr using the enantiomeric **5c** ligand (Scheme 14, step (a)). The hydrogenated products were used to prepare biologically relevant trideoxypropionate building blocks in the optically pure form by a simple auxiliary-controlled enolate methylation (Scheme 14, step (b)). Trideoxypropionate has further been applied in the total synthesis of the pheromones (+)-vittatalactone and (+)-norvittatalactone of the striped cucumber beetle *Acalymma vittatum*.¹¹³⁻¹¹⁴



Scheme 14 Hydrogenation of **S42** and **S43** using Ir-PHOX catalysts, followed by α -methylation to form trideoxypropionates and their application in the total synthesis of pheromones.

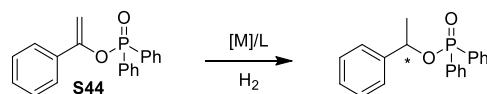
The coordinating ability of the carbamate acyl group to the metal closely resembles the enamide instead of the acyl group of an enol ester, which has slightly weaker coordinating ability.¹¹⁵ Thus enol carbamates have appeared

as an alternative to enol esters and for this substrate class Rh-phosphoroamidite catalysts have afforded excellent enantioselectivities (ee's up to 98%).¹¹⁵⁻¹¹⁶ However, Ir-PHOX catalysts (Figure 3) were efficient in the diastereoselective hydrogenation of the enol carbamate **S43**, analogue to enol ester **S42**, for which several Rh/P catalysts failed.¹¹³ As with enol ester **S42**, the use of the bulky PHOX ligand **5c** (Figure 3) and its enantiomer (*ent*-**5c**) afforded both diastereoisomers in high yields and diastereomeric ratios (Scheme 14).¹¹³

3.2 Enol Phosphinates and Enol Phosphonates

Although the phosphinate and the phosphonate group are coordinative groups, there is only one report on the use of Rh-catalysts for the hydrogenation of enol phosphinates/phosphonates. Moderate enantioselectivities were achieved in the hydrogenation of enol phosphinates using a cationic Rh-catalyst modified with (*R*)-1-[*(S*)-1',2'-bis(diphenylphosphino)ferrocenyl]ethanol ligand ((*R*)-(S)-BPPFOH) (ee's up to 78%; Table 5, entry 1).¹¹⁷ The presence of triethylamine was necessary for high activities, which underlines the acid-sensitive nature of these substrates. Enol phosphinates and in some cases enol phosphonates can be reduced effectively using chiral analogues of Crabtree's catalysts. A screening of several ligands developed in the Andersson group disclosed that N-phosphine-oxazoline ligand **17b** (Figure 4) is effective for the hydrogenation of terminal enol phosphinates (Table 5, entries 2 vs 3 and 4).^{62b} Excellent enantioselectivities were achieved for a wide range of aryl and alkyl enol phosphinates (Figure 11). The authors took advantage of Berens work¹¹⁸ to demonstrate that this methodology can be used to prepare chiral phosphines by replacing the phosphityl group with diphenylphosphine. In the same study they found that the Ir-**17b** catalyst can also be used in the hydrogenation of enol phosphonates albeit with lower enantioselectivities (i.e. ee's dropped from 95% to 65% by replacing the phosphinate group with a phosphonate moiety). It should be noted that for the more acid-sensitive substrates (i.e. substrate **S47**, Figure 11) the use of small amounts of poly(4-vinylpyridine) resin was necessary to avoid substrate hydrogenolysis.^{62b}

Table 5 Selected results for the asymmetric hydrogenation of model enol phosphinate 1-phenylvinyl diphenylphosphinate **S44**



Entry	[M]/L	% Conv	% ee	Ref.
1	Rh-(R)-(S)-BPPFOH	100	78	117
2	Ir-17b	100	95	62b
3	Ir-43	0	-	62b
4	Ir-42	47	63%	62b
5	Ir-44a	100	82%	92

It was also found that Ir-17b catalyst was able to efficiently reduce trisubstituted aryl-alkyl and ester-functionalized enol phosphinates.^{62a} Excellent enantioselectivities (up to >99%) and full conversion was observed for a range of substrates, including purely alkyl trisubstituted enol phosphinates (Figure 11). This latter finding is particularly valuable because the hydrogenation products, after deprotection, gives access to chiral alkyl alcohols that are usually difficult to obtain in high enantioselectivity from ketone hydrogenations.

Replacing the phosphinite moiety in ligands **42** by a biaryl phosphite group (ligand **44a**; Figure 6) has a positive effect on enantioselectivity (Table 5, entry 4 vs 5).⁹² High enantioselectivities (up to 92%) were obtained in the hydrogenation of several di- and trisubstituted enol phosphinates using this catalytic system however the enantioselectivities achieved do not surpass the values achieved with Ir-17b catalytic system.

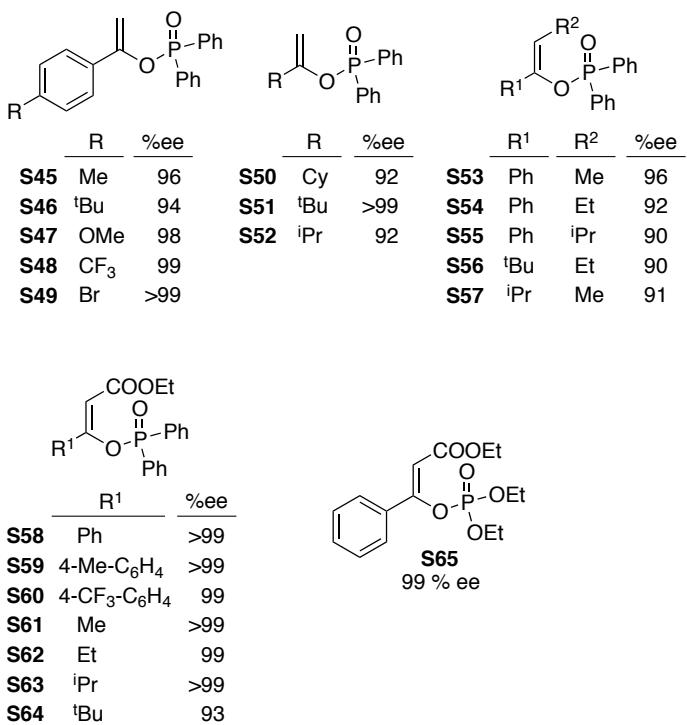


Figure 11 Representative enol phosphinates (**S45-S64**) and enol phosphonate (**S65**) efficiently reduced using Ir-**17b** catalytic system

3.3 Enol Ethers

In this section, simple enols, α -alkyloxy and α -alkyloxy α,β -unsaturated carbonyls will be discussed along with a few examples of enol ethers that are also allylic alcohols.

Asymmetric hydrogenation of enol ethers directly provides chiral ethers, which is advantageous to access building blocks used to prepare bioactive compounds such as Eriprotabid, Tesaglitazar and Aleglitazar¹¹⁹ that are of interest to the agrochemical and pharmaceutical industries.¹²⁰ However, enol ethers are sensitive to acid and since homogeneous hydrogenations tend to form protons, the addition of base is required.

Among the variety of enol ethers, α -aryloxy and α -alkoxy α,β -unsaturated carboxylic acids have been the most popular for asymmetric hydrogenation since the resulting optically active α -oxy-functionalized

carboxylic acids are important building blocks.¹²⁰⁻¹²¹ A feature of this α -aryloxy and α -alkoxy α,β -unsaturated carboxylic acids is that the carboxylate coordinates to the metal center, thus favoring the potential use of classical Rh- and Ru-diphosphine catalysts. In this context, a range of 3-methyl-2-aryloxyacrylic acids and 3-aryl-2-ethoxyacrylic acids have been successfully hydrogenated in excellent enantioselectivities using both Rh- and Ru-catalysts in the presence of base (Figure 12).¹²² However, none of the Rh- and Ru-catalysts have been reported to give high enantioselectivity in the asymmetric hydrogenation of both α -aryloxy and α -alkoxy α,β -unsaturated carboxylic acids.

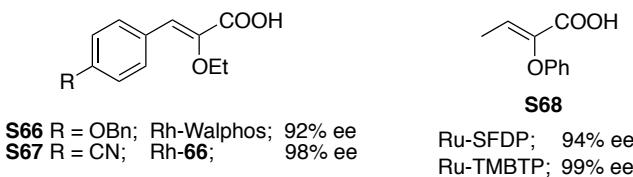


Figure 12 Representative enantioselectivities in the hydrogenation of 3-methyl-2-aryloxyacrylic acids and 3-aryl-2-ethoxyacrylic acids achieved using Rh- and Ru-catalytic systems. **66** = [(R_C,R_C), (S_{Fc},S_{Fc}), (S_P,S_P)]-1,1'-Bis[2-(1-N,N-Dimethylaminoethyl)-1-ferrocenyl]phenyl phosphino ferrocene.

Zhou and coworkers have recently shown that chiral Crabtree's analogues are extremely effective in the hydrogenation of both α -aryloxy and α -alkoxy α,β -unsaturated carboxylic acids.¹²³ The authors found that by using chiral spiro phosphino-oxazoline ligands **67** (Figure 13, R¹= Ph, 3,5-Me₂-Ph, 3,5-tBu₂-Ph and R²= Bn, Ph, Me and H), the hydrogenation proceeded smoothly to produce various α -aryloxy and α -alkoxy-substituted carboxylic acids with excellent enantioselectivities (ee's up to >99%) and reactivities (TON up to 10 000) under mild conditions (Figure 13). The results indicated that for aryloxy enol ethers **S69-S76** enantioselectivities were best using ligand **67a**, containing bulky aryl phosphine substituents and a benzyl moiety in the oxazoline (Figure 13, R¹=3,5-tBu₂-Ph and R²= Bn), while for alkoxy enol ethers **S77-S84** enantioselectivities were best with ligand **67b** with a methyl oxazoline substituent (Figure 13, R¹=3,5-tBu₂-Ph and R²= Me). It should be

noted that the hydrogenation of α -benzyloxy-substituted α,β -unsaturated acids provided an efficient alternative for the synthesis of chiral α -hydroxy acids after an easy deprotection. A mechanism involving a catalytic cycle between Ir^I and Ir^{III} was proposed on the basis of the coordination model of the unsaturated acids with the iridium metal center. The rationale for the catalytic cycle, with an olefin dihydride complex as the key intermediate, was supported by deuterium-labeling studies.

R ³	R ⁴	%ee	
S69	Me	Ph	99
S70	Me	4-Me-C ₆ H ₄	99
S71	Me	4-MeO-C ₆ H ₄	99
S72	Ph	Ph	99
S73	Ph	4-MeO-C ₆ H ₄	99
S74	4-OMe-Ph	Ph	99
S75	4-CF ₃ -Ph	Ph	99
S76	Furan-2-yl	Ph	99
S77	Ph	Me	99
S78	4-MeO-C ₆ H ₄	Me	99
S79	4-CF ₃ -C ₆ H ₄	Me	99
S80	Me	Me	99
S81	Et	Me	95
S82	Ph	Bn	99
S83	4-MeO-C ₆ H ₄	Bn	99
S84	4-CF ₃ -C ₆ H ₄	Bn	99

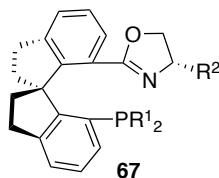


Figure 13 Representative enantioselectivities achieved in the hydrogenation of α -aryloxy substituted carboxylic acids (**S69-S76**) and α -alkoxy substituted carboxylic acids (**S77-S84**) using Ir-**67** catalytic system.

Another important class of enol ethers is the non-coordinating alkylated ones (those without the carboxylic group). For this substrate class, very few Rh- and Ru-catalysts have been applied and moderate enantioselectivities were observed. The Ru-BINAP catalytic system afforded enantioselectivities ranging from 64% to 91% for a small range of cyclic alkyl enol ethers (Figure 14).¹²⁴ Due to the lack of a coordinating group, Crabtree's analogues should be appropriate for this substrate class. The first report on the use of Ir/N,P

catalysts for this purpose was done by Pflatz and coworkers.^{2d} They disclosed that Ir-**19a** catalyst (Figure 4) was able to hydrogenate 2-phenyl-1,4-benzopyran **S88** with complete conversion and 98% ee (Figure 14).

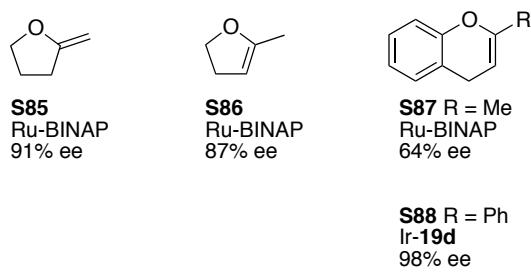
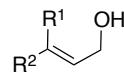
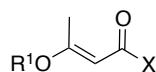
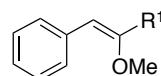
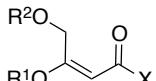


Figure 14 Representative enantioselectivities for the hydrogenation of cyclic alkyl enol ethers using Ru-BINAP and Ir-**19** catalysts.

Complexes of the type $[\text{Ir}(\text{cod})(\text{N},\text{P}^*)][\text{BAr}_F]$ have been shown to generate protons under hydrogenation conditions and sometimes decompose substrates such as alkyl enol ethers before they can be hydrogenated.¹²⁵ Iridium precursor with carbene-oxazoline ligand **25a** (Figure 4) is less prone to generate protons (i.e. less acidic) than similar N,P-ligated complexes and gave the chiral product without significant acid-mediated decomposition (Figure 15, ee's up to 98%).¹²⁶



R ¹	X	%ee	R ¹	R ²	%ee		
S89	Me	OEt	78	S93	Me	OMe	96
S90	Et	OEt	66	S94	Me	OEt	98
S91	Me	NMe(OMe)	90	S95	Bu	OMe	93
S92	Me	OtBu	88	S96	OMe	iPr	91



R ¹	R ²	X	%ee	R ¹	%ee		
S97	Me	Ac	NMe(OMe)	74	S101	CO ₂ tBu	9
S98	Me	TBDPS	NMe(OMe)	94	S77	CO ₂ H	23
S99	Me	TBDPS	OMe	75	S102	CH ₂ OH	61
S100	Bn	TBDPS	NMe(OMe)	90	S103	CH ₂ OTBDP	52

Figure 15 Representative enantioselectivities for the hydrogenation of alkyl enol ethers using Ir-25a catalyst.

3.4 Silyl Enol Ethers

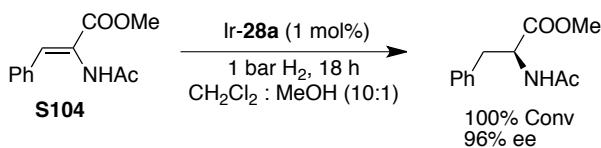
Silyl enol ethers are non-coordinative substrates of varying sensitivity towards acid-degradation. Silyl enol ethers have been hydrogenated using Rh-catalysts, though in the absence of an additional coordinating functionality the enantioselectivities were extremely low (ee's up to 10%).¹²⁷ Attempts to hydrogenate silyl enol ethers using analogues of Crabtree's catalyst containing ligands **17** (Figure 4), **42** and **43** (Figure 6) have been made, but for alkyl enol ethers, complex mixtures were obtained.^{62b} Thus, although no data has yet been reported, the use of Ir-catalysts modified with carbene-oxazoline ligands would be more appropriate in the asymmetric hydrogenation of silyl enol ethers.

4 Enamides and Enamines

Traditionally, the asymmetric hydrogenation of enamines and enamides has been the subject of interest as an alternative method to the asymmetric

hydrogenation of imines for the preparation of chiral amines that can be used as resolving reagents, chiral auxiliaries, and intermediates for the synthesis of a variety of biologically active molecules.¹²⁸

The hydrogenation of enamides is dominated by Rh- and Ru-catalysts modified with chiral phosphorus ligands primarily because of the coordinative ability of the amide group to the metal center.^{128a} However, Knochel's group has demonstrated that chiral Crabtree's catalyst analogues can be used successfully in the asymmetric hydrogenation of enamides.⁷⁵ They found that [Ir(cod)(**28a**)][BAr_F] catalytic precursor (Figure 5) can hydrogenate (Z)-methyl 2-acetylamino-3-phenylacrylate **S104** in high enantiomeric excess (up to 96.5%; Scheme 15) under mild reaction conditions (1 bar H₂). Despite this early success in the synthesis of chiral amino acids, the use of other Ir-complexes has not yet been reported.



Scheme 15 Asymmetric hydrogenation of enamide **S104** using Ir-**28** catalysts

In contrast with the hydrogenation of enamides, there are very few examples of successful enantioselective hydrogenation of *N,N*-dialkyl enamines, which provides a direct approach to chiral tertiary amines. Enamines are electron-rich and moisture sensitive, thus they make poor substrates,^{128a} but the low coordinative ability of the enamines still makes them an attractive class of alkenes for the enantioselective hydrogenation using Crabtree's analogues. Despite this, to the best of our knowledge, only two reports have been published.¹²⁹

In 2008, *N*-phosphine-oxazoline ligand **17b** (Figure 4) was identified as a suitable ligand for the hydrogenation of enamines (Table 6, entries 2-3 and 5-7).^{129a} Moderate-to-high enantioselectivities (ee's up to 84%) were achieved in the asymmetric reduction of terminal 1-amino-1-aryl alkenes with no β -substituents (Table 6, entries 2-3, 5-9, 10, 12, 14, 16). Interestingly, complete

conversion to the tertiary amine product was observed at room temperature using 50 bar H₂, but enantioselectivities were highly substrate dependent. The results indicate that enantioselectivities decreased considerably when the amino group was cyclic (i.e. ee's reduced from 84% to 33% by replacing the diethylamine group by a pyrrolidino group; Table 6, entries 2 vs 12) and for *exo*-cyclic enamines (i.e. Table 6, entry 14).

In 2009, phosphine-oxazolines **5** and **14** (Figures 3 and 4), phosphinite-oxazoline **19** (Figure 4) and phosphinite-pyridine **32** (Figure 5) were reported to be useful ligands in the asymmetric hydrogenation of several terminal 1-aryl-enamines as well as several *endo*-cyclic and *E*-acyclic enamines.^{129b} The best results were achieved with 1-amino-1-aryl alkenes bearing an aryl (ee's up to 91%; Table 6, entries 15, 18 and 20) or a benzyl (ee's up to 92.5%; Table 6, entries 23 and 25) substituent on the nitrogen atom, which were hydrogenated with good enantiomeric excesses using phosphine-oxazoline ligand **5d** (Figure 3) and the phosphinite-oxazoline ligand **19a** (Figure 4), respectively. Enantioselectivities in the hydrogenation of *endo*-cyclic and *E*-acyclic enamines were lower (ee's ranging 67-87%; Table 6, entries 26-29).

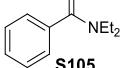
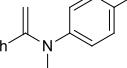
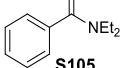
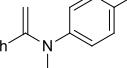
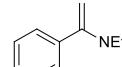
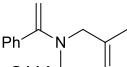
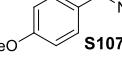
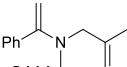
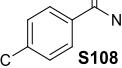
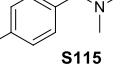
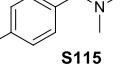
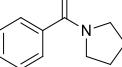
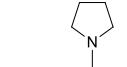
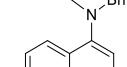
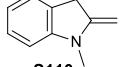
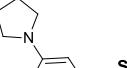
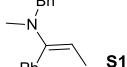
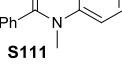
Entry	Substrate	[M]/L	%	Ref	ee	Entry	Substrate	[M]/L	%	Ref.	ee
1		Ir-5d	18	129b		18		Ir-5d	90	129b	
2		Ir-17a	84	129a		19		Ir-19a	20	129b	
3		Ir-17b	54	129a							
4		Ir-19a	54	129b							
5		Ir-41a	0	129a							
6		Ir-43a	14	129a							
7		Ir-49a	0	129a							
8		Ir-17b	87	129a		22		Ir-5d	56	129b	
9		Ir-17b	64	129a		23		Ir-19a	92.5	129b	
10		Ir-17b	77	129a		24		Ir-5d	27	129b	
11		Ir-5d	44	129b		25		Ir-19a	76	129b	
12		Ir-17b	33	129a		26		Ir-19a	87	129b	
13		Ir-19a	8	129b		27		Ir-32a	71	129b	
14		Ir-17b	20	129b		28		Ir-14c	69	129b	
15		Ir-5d	91	129b		29		Ir-14c	67	129b	
16		Ir-17b	79	129a							
17		Ir-19a	13	129b							

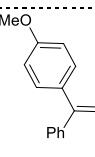
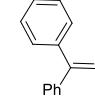
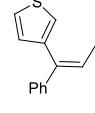
Table 6 Selected results for the asymmetric hydrogenation of enamines.

5 Allylic and Homoallylic Alcohols and Ethers

The asymmetric hydrogenation of allylic alcohols is of interest due to their abundance in natural sources such as essential oils, and their wide use as starting materials and/or major components in the food, fragrance and

pharmaceutical industries.¹³⁰ The hydrogenation of allylic alcohols has been traditionally dominated by Ru-complexes modified with chiral diphosphines.¹³¹ However, early reports on the use of chiral N,P-ligated Ir-catalysts with PHOX ligands **5** (Figure 3) indicated that this substrate class can be hydrogenated with high enantioselectivity.²⁶ *Trans*-2-methyl-3-phenyl-2-propen-1-ol **S120** was hydrogenated in excellent enantioselectivities (ee's up to 96%; Table 7, entry 1). Thus, the commercially available substrate **S120** has since been used as a benchmark to test new Ir-catalysts (Table 7). The best enantioselectivities have been achieved using ligands **12a**⁵⁶ (Figure 4) and **43a**⁹⁰ (Figure 6) (ee's up to 99%, Table 7, entries 3 and 16).

Table 7 Selected results for the asymmetric hydrogenation of allylic alcohols

Entry	Substrate	[M]/L	%	Ref	Entry	Substrate	[M]/L	%	Ref.
		ee					ee		
1		Ir-5a	96	26	25		Ir-48a	97	61
2		Ir-9b	67	53	26		Ir-35	90	94
3		Ir-12a	98	56					
4		Ir-13a	90	57					
5		Ir-14b	96	44					
6		Ir-15c	95	58	27		Ir-41b	92	61
7		Ir-19d	97	66a					
8		Ir-23a	92	72a					
9		Ir-24a	93	73a					
10		Ir-28a	69	75	28		Ir-41b	92	61
11		Ir-31b	96	77					
12		Ir-32a	97	79a					
13		Ir-34	42	82	29		Ir-41b	90	61
14		Ir-38	95	84					
15		Ir-42a	98	89					
16		Ir-43a	99	90					
17		Ir-45b	96	92					
18		Ir-48a	91	61	30		Ir-19d	91	79c
19		Ir-49a	93	94	31		Ir-32a	91	79c

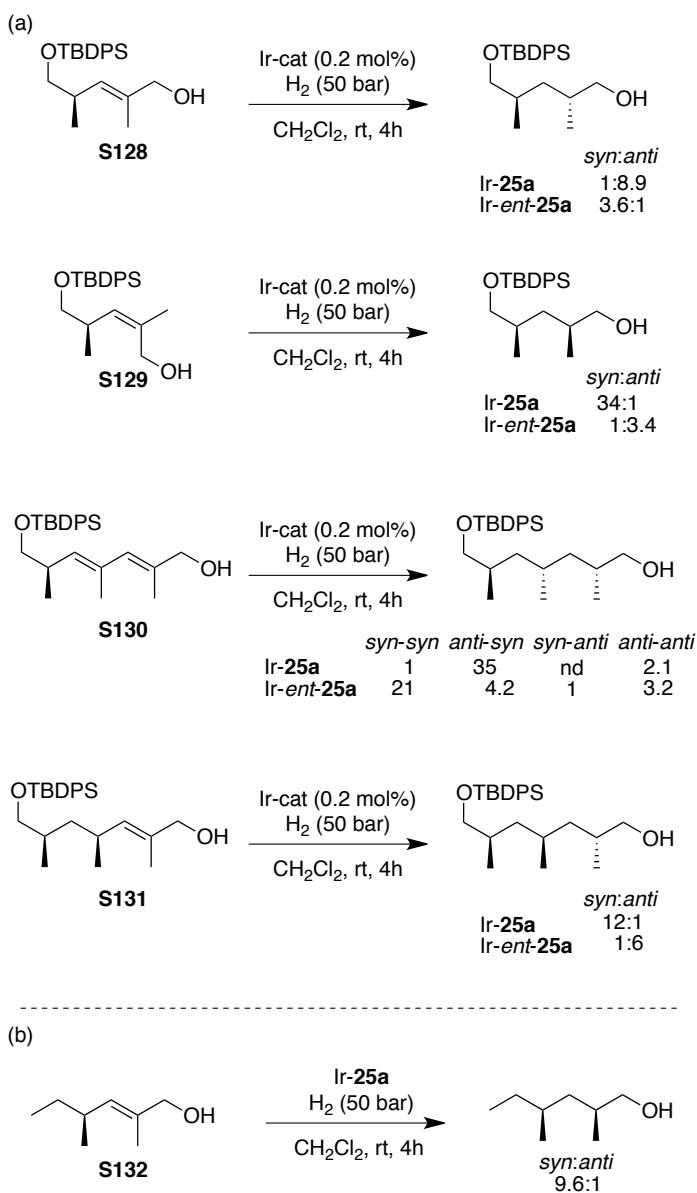
20	Ir-51a	70	97				
21	Ir-52a	49	98	32	S126		
22	Ir-53	20	99				
23	Ir-58b	90	102c	33		Ir-19a	88
24	Ir-61c ^g	81	103	34	S127	Ir-24b	95
				35		Ir-45b	90
						Ir-58b	83
							102c

^g R¹=^tBu; R²= NCy₂.

The substrate scope has recently been extended to include 1,1-aryl/alkyl-, 1,1-diaryl- and 1,3-dialkyl trisubstituted allylic alcohols and the challenging terminal allylic alcohols. For 1,1-aryl/alkyl and 1,1-diaryl trisubstituted olefins **S121-S124** the best enantioselectivities have been achieved using phosphine-thiazole **48a** (Figure 6) and phosphine-imidazole **41b** (Figure 6) ligands, respectively (Table 7, entries 25 and 27-29).^{61,94} For the alkyl allylic alcohol **S125** the use of phosphinite-oxazoline **19d** (Figure 4) and phosphinite-pyridine **32a** (Figure 5) ligands lead to high enantiomeric excess (ee's up to 91%; Table 7, entries 30-31).^{79c} This later finding was further exploited to hydrogenate all four stereoisomers of farnesol (Section 2.1.2, Scheme 12b).¹³² For terminal allylic alcohols, the Ir-catalyzed asymmetric hydrogenation has achieved ee's up to 88% in the hydrogenation of **S126** using phosphinite-oxazoline **19a** (Figure 4) ligand (Table 7, entry 32).⁶⁷ Introducing a phosphite moiety in the ligand design is advantageous, achieving enantioselectivities up to 95% in the reduction of **S127** (Table 7, entry 33).^{73b}

Diastereoselective hydrogenation of allylic alcohols can be efficiently used to construct α,ω -functionalized 1,3-dimethyl and 1,3,5-trimethyl fragments (Scheme 16a).¹³³ This finding constitutes an alternative to the diastereoselective hydrogenations of chiral homoallylic alcohols achieved largely using Rh- and Ir-diphosphine catalysts, which takes advantage of the chelating ability of the homoallylic substrate to achieve high diastereoselectivities.¹³⁴ They showed that the chiral Crabtree analogue containing carbene-oxazoline ligand **25a** (Figure 4) efficiently hydrogenated substrates **S128-S131** to achieve the α,ω -difunctionalized 2,4-dimethylpentane and 2,4,6-trimethylheptane in high diastereoselectivity.

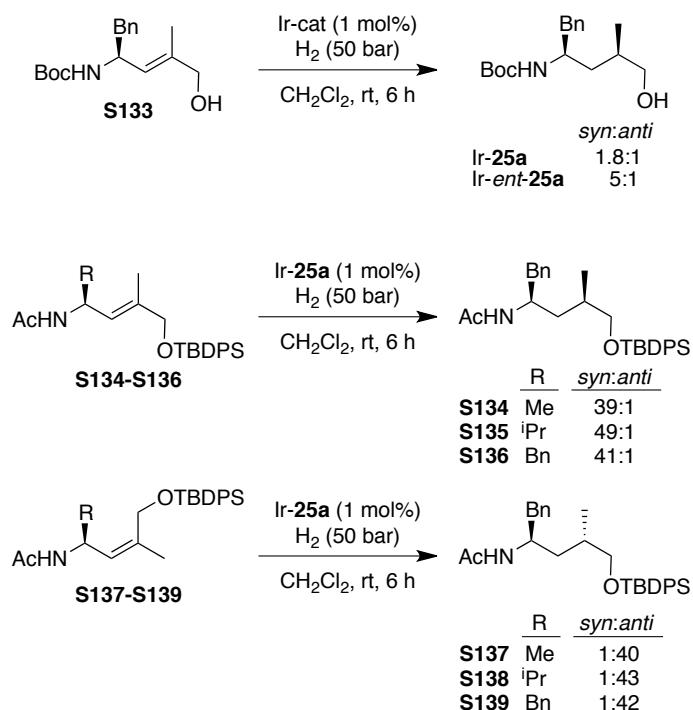
Interestingly, catalyst Ir-*ent*-**25a** gave appreciable selectivity for the opposite diastereoisomer, which illustrates that catalyst control is operative in these reactions. However, the geometry of the allylic alcohol is significant for optimizing the selectivity of the process. Thus, while for the reduction of *E*-allylic alcohol **S128**, the Ir-**25a** catalyst favored the *anti* product (*syn/anti*= 1:8.9), the use of *Z*-allylic alcohol **S129** favors the *syn* product (*syn/anti*= 34:1) using Ir-**25a** (Scheme 16a).^{133a,135} The potential application of this methodology has been demonstrated with the preparation of (*S,R,R,S,R,S*)-4,6,8,10,16,18-hexamethyldocosane, a putative sex pheromone from an Australian beetle, for which the diastereoselective hydrogenation of **S129** is the key step.^{133b} Additionally, the same authors proved that α -monofunctionalized 1,3-dimethyl chiral fragments can be achieved albeit with lower stereocontrol compared with the α,ω -difunctionalized (Scheme 16b).¹³⁶



Scheme 16 Hydrogenation of allylic alcohols **S128-S132**.

Recently this methodology has been used for the preparation of α -methyl- γ -aminoacid derivatives from *N*-acetyl protected allylic alcohols (*syn/anti* up to >19:1; Scheme 17).¹³⁷ The stereoselectivity can be improved further by

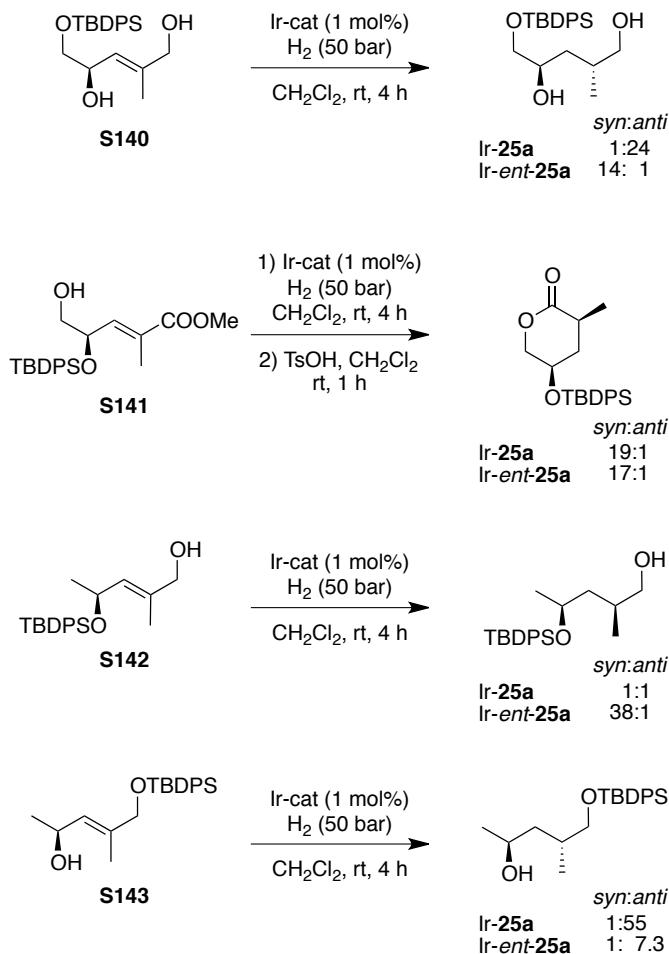
protecting the alcohol using a *tert*-butyldiphenylsilyl protecting group (*syn/anti* up to 49:1).



Scheme 17 Hydrogenation of *N*- or *O*-protected amino alcohol derivatives **S133-S139**.

Diastereoselective reduction of allylic alcohols can also be used as an efficient alternative for the preparation of 1,3-hydroxymethyl fragments.¹³⁸ The hydrogenation of the allylic alcohol **S140** is catalyst controlled, which allows the preparation of both *syn* and *anti* stereoisomers with high stereocontrol (Scheme 18). This behavior is in contrast to the one observed for the hydrogenation of the related homoallylic alcohol **S141**, which proceeds via substrate control and therefore only one isomer is preferentially formed (Scheme 18). Alkenes derived from lactic acid (substrates **S142** and **S143**, Scheme 18) were also explored and it was discovered that while the hydrogenation of **S142** proceeds via catalyst control, the reduction of **S143**, in which the protecting group was changed from a secondary alcohol to a primary one, proceeds via substrate control.¹³⁸ The latter has been attributed

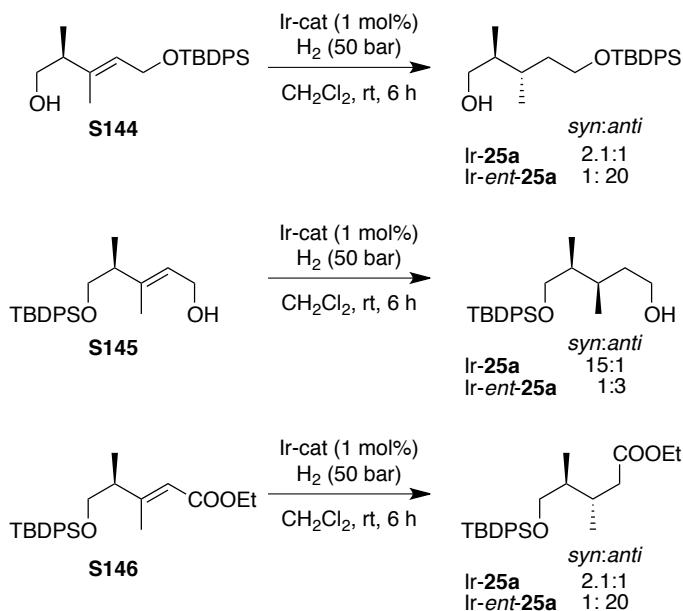
to the coordination of the allylic alcohol to iridium, which can occur via direct oxygen coordination to iridium or via hydrogen bonding from an Ir-hydride to the allylic alcohol oxygen. The authors illustrated the potential utility of this methodology in the total syntheses of (–)-dihydromyoporone¹³⁸ and (–)-spongidepsin.¹³⁹



Scheme 18 Hydrogenation of allylic and homoallylic alcohols **S140-S143**.

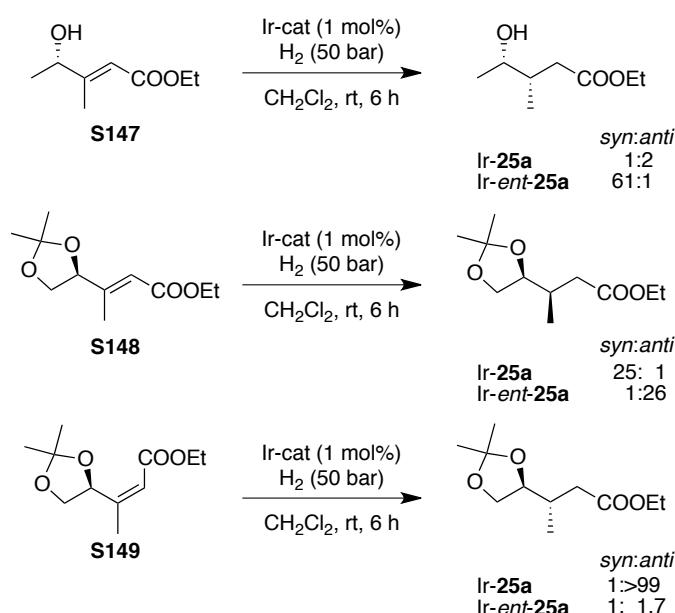
Chiral Crabtree-type catalysts have recently been used to prepare 1,2-dimethyl fragments very efficiently from chiral allylic and homoallylic alcohols (Scheme 19). In all the cases studied the hydrogenation proceeds via catalyst control rather than substrate control, which allows the formation of both

diastereoisomers.¹⁴⁰ The substrate however, also has an important effect on the stereoselectivities. Thus, while coordination effects are significant for homoallylic alcohols (i.e. substrate **S144**) the steric factors are important for the homoallylic silyl ethers (i.e. substrate **S145**). This methodology was used in the total synthesis of the neurotoxin (+)-kalkitoxin as well as in the total synthesis of (–)-lasitol, a substance isolated from *Lasius meridionalis* ants.¹⁴⁰



Scheme 19 Hydrogenation of allylic and homoallylic alcohols **S144-S146**

Similarly, chiral aldol-type 1,2-hydroxymethyl fragments were efficiently synthesized from trisubstituted allylic alcohols using chiral analogues of Crabtree's catalyst giving both the *syn*- and *anti*-isomers (Scheme 20).¹⁴¹ This methodology is in contrast to those developed using terminal allylic alcohols with metal-diphosphine catalysts that proceeds under substrate control.¹⁴² It is interesting to note that the best *syn*-selectivity was achieved using allylic alcohol **S147** (Scheme 20). Glucitol derivatives **S148-S149**, which gives access to α,ω -difunctional fragments, could also be selectively reduced (Scheme 20).



Scheme 20 Hydrogenation of allylic alcohol derivatives **S147-S149**.

6 α,β -Unsaturated Carbonyls

6.1 α,β -Unsaturated Carboxylic Acids

Asymmetric hydrogenation of α,β -unsaturated carboxylic acids using $[\text{Ru}(\text{BINAP})(\text{OAc})_2]$ (Scheme 1) was described by Noyori in 1987¹¹ and has been developed to include a variety of di- and trisubstituted examples (Figure 16).^{122a,b,143} The reaction has also proven to give high enantioselectivities using rhodium-diphosphine or phosphoramidite catalysts although with a somewhat limited substrate scope.^{122c,d,144}

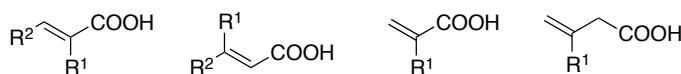


Figure 16 Typical substrates for the Rh and Ru catalyzed hydrogenation.

During the past few years, chiral analogues of Crabtree's catalyst have also been used to enantioselectively reduce α,β -unsaturated carboxylic acids.

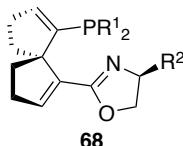
α -Substituted cinnamic acids, which have served as the benchmark substrates for the ruthenium-catalyzed reaction have also been extensively studied with $[\text{Ir}(\text{cod})(\text{N},\text{P})]\text{BAr}_\text{F}$ complexes. Unlike hydrogenation of weakly-functionalized olefins, the asymmetric hydrogenation of α,β -unsaturated carboxylic acids is usually performed in methanol and is hence similar to the traditional P,P-ligated rhodium catalytic systems. Analogous to the ruthenium and rhodium case, coordination of the carboxylate ion to form a chelate with iridium has been suggested.

Using their spirocyclic ligand **67a** (Figure 13, $\text{R}^1=3,5\text{-tBu}_2\text{-Ph}$ and $\text{R}^2=\text{Bn}$), Zhou and co-workers could reduce several α -alkyl substituted cinnamic acids (**S150** and **S151**) in excellent enantioselectivity (Table 8, entries 1 and 2).¹⁴⁵ The reaction featured high catalytic activity under mild conditions but addition of base was crucial for high catalytic activity. A slightly modified ligand **67c** (Figure 13, $\text{R}^1=3,5\text{-tBu}_2\text{-Ph}$ and $\text{R}^2=^i\text{Pr}$) was used when targeting alkyl-alkyl substituted alkenes (i.e. substrates **S152-S153**; Table 8, entries 3 and 4).

Table 8 Representative results from the asymmetric hydrogenation of α,β -disubstituted α,β -unsaturated carboxylic acids using spirocyclic ligands **67** and **68**.

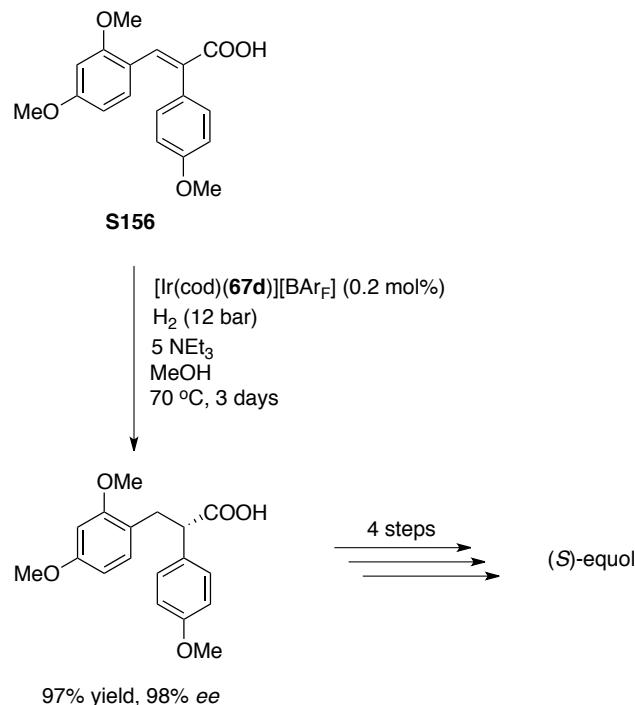
Entry	R ¹	R ²	Ir-cat. (mol%)	L	Base	ee (%)	Ref.	[Ir(cod)(L)][BAr _F]
								H ₂ (6-30 bar) rt, MeOH
1	S150	Me	Ph	0.25	67a	0.5 NEt ₃	>99	145
2	S151	iPr	Ph	0.25	67a	0.5 NEt ₃	99	145
3	S152	Me	Et	0.25	67c	0.5 Cs ₂ CO ₃	98	145
4	S153	nPr	Me	0.25	67c	0.5 Cs ₂ CO ₃	98	145
5	S154	Ph	Me	1.0	68a	1.0 NEt ₃	94	146
6 ^a	S155	Ph	Ph	1.0	68a	1.0 NEt ₃	94	146
7 ^b	S155	Ph	Ph	0.25	67d	0.5 Cs ₂ CO ₃	95	146

^a Reaction performed at 50 °C. ^b Reaction performed at 45 °C.



Another spirocyclic phosphine-oxazoline ligand, **68a** (Table 8, R¹= o-tol, R²= Ph), was utilized in the asymmetric hydrogenation of α -aryl substituted unsaturated carboxylates **S154** and **S155**.¹⁴⁶ Under somewhat forceful conditions, enantioselectivities >90% ee were obtained for a series of substrates (Table 8, entries 5 and 6). Ligand **67d** (Figure 13, R¹=3,5-tBu₂-Ph and R²= H), which contains an unsubstituted oxazoline ring, was the best ligand from this family in the reduction of these bulky alkene substrates (Table 8, entry 7).¹⁴⁷ The reaction could be performed under one atmosphere of H₂ and enantioselectivities over 90% were consistently obtained. Synthesis of the isoflavane derivative (*S*)-equol using this methodology as the enantiodetermining step resulted in conversion of **S156** in 97% yield and 98%

ee (Scheme 21). By increasing the reaction time and temperature a substrate to catalyst ratio of 5000:1 could be used.

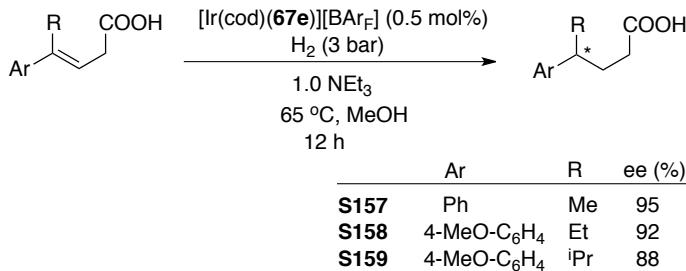


Scheme 21 The enantiodetermining step in the preparation of (S)-equol from **S156** is catalyzed by $[\text{Ir}(\text{cod})(\mathbf{67d})][\text{BAr}_F]$.

As mentioned in section 3.3, Zhou and co-workers also performed asymmetric hydrogenations of a variety α -aryloxy and α -alkyloxy crotonic and cinnamic acids using Ir-catalysts based on ligand **67** (Figure 13).¹⁴⁵ The catalytic system tolerated the variation of the ether-group but more importantly, the β -substituent could be changed from Ph to Me to H while retaining good enantioselectivity.¹²³

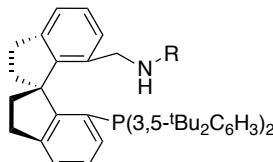
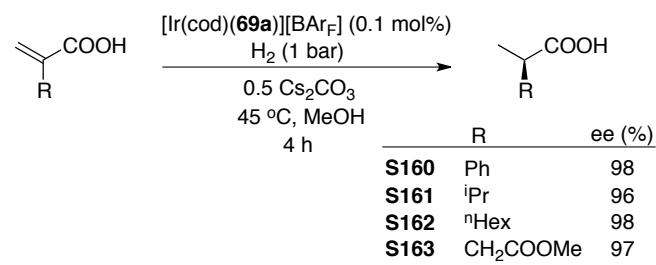
The successful asymmetric hydrogenations of crotonic- and cinnamic-acid derivatives using iridium catalysts based on the spirocyclic oxazoline backbones prompted further expansion of the substrate scope. At 65 °C, *E*-4-methyl-4-phenyl-3-butenoic acid **S157** could be effectively reduced by $[\text{Ir}(\text{cod})(\mathbf{67})][\text{BAr}_F]$ in 60 % ee provided that one equivalent of triethylamine or

a similar amine base was present.¹⁴⁸ Enantioselectivities above 90% ee could be obtained by changing the phosphine substituents to 3,5-dimethylphenyl. Furthermore, when the benzyl substituent on the oxazoline was changed to α -methylnaphthyl (ligand **67e**, Figure 13, $R^1=3,5\text{-Me}_2\text{Ph}$ and $R^2=\text{CH}_2\text{-1-naphthyl}$) ee's around 95% were obtained. With $[\text{Ir}(\text{cod})(\mathbf{67e})][\text{BAr}_F]$, a series of 4,4-disubstituted 3-butenoic acids could be hydrogenated with good enantioselectivities (Scheme 22).



Scheme 22 Asymmetric hydrogenation of some β,β -disubstituted- α,β -unsaturated acids **S157-S159**.

Another type of α,β -unsaturated carboxylic acids, α -substituted acrylic acids, were reduced slowly and in modest enantioselectivity using $[\text{Ir}(\text{cod})(\mathbf{67})][\text{BAr}_F]$, under reaction conditions similar to those described above. Spirocyclic ligands where the oxazoline N-donor had been replaced by a primary or secondary amine consistently gave enantioselectivities >90% ee.¹⁴⁹ Ligands **69a** and **69b** both exhibited high selectivity but the former was significantly faster and thus used for further studies of both alkyl- (**S161-S163**) and aryl-substituted (**S160**) derivatives (Scheme 23). Using 0.1 mol% of $[\text{Ir}(\text{cod})(\mathbf{69a})][\text{BAr}_F]$ under an atmosphere of hydrogen for 4 h produced quantitative yields and excellent enantioselectivities for a range of aryl- and alkyl-substituted substrates.

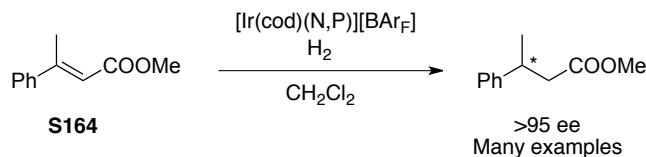


69a R = H
69b R = Me

Scheme 23 Asymmetric hydrogenation of some α -substituted acrylic acids using phosphine-primary amine catalyst Ir-**69a**.

6.2 α,β -Unsaturated Esters

While (deprotonated) carboxylic acids are excellent coordinating functional groups, α,β -unsaturated esters are less so. The α - and especially *trans*- β -methyl cinnamate esters such as **S164** (Scheme 24) are typical test substrates for the asymmetric hydrogenation using $[\text{Ir}(\text{cod})(\text{N},\text{P})][\text{BAr}_\text{F}]$ complexes in CH_2Cl_2 . The hydrogenation product has been obtained in >95% ee using several ligands (Scheme 24).^{43,71c,77,90,94-95,98,103a}



Scheme 24 *trans*- β -Methyl cinnamate ester **S164** has been hydrogenated in excellent enantioselectivity by a large number of N,P-ligated Ir-complexes.

Besides **S164**, β,β -disubstituted acrylate esters haven't been extensively explored. However recently, chiral mimics of Crabtree's catalyst have proven useful for the asymmetric hydrogenation of these alkenes. Both the *E*- and *Z*- isomer of the challenging methyl/phenethyl derivatives **S165**

and **S166** (Table 9, entries 1 and 2) could be reduced in good enantioselectivity using the successful pyridine-phosphinite ligands **32a** and **32b** (Figure 5).^{79a}

As described in section 3.3, the asymmetric hydrogenation of unsaturated esters that also contain vinylic ethers was successful using ligand **25a** (Figure 4).^{126a}

Ligand **13a** (Figure 4) was used to obtain enantioselectivities over 90% for several β,β -substituted α,β -unsaturated esters.⁵⁷ Both the β -methyl (**S167**) and β -ethyl (**S168**) derivative could be highly selectively reduced (Table 9, entries 3 and 4), but more significantly, the Z-alkene **S169** could be reduced in 92% enantioselectivity (entry 5).

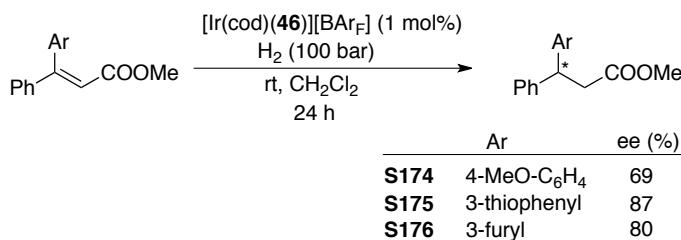
Recently, a comprehensive screening of α,β -unsaturated esters in the Ir-catalyzed asymmetric hydrogenation was performed in order to thoroughly establish the substrate scope.¹⁵⁰ Previously developed bicyclic ligands **17b** (Figure 4) and **49b** (Figure 6), which gave excellent enantioselectivity in the asymmetric hydrogenation of both *E*- and *Z*- β -methyl cinnamate esters were used.^{60a,95} A range of structurally different substrates (**S170-S173**) were reduced with excellent enantioselectivity (Table 9, entries 6–9).¹⁵⁰

Table 9 Representative results from the asymmetric hydrogenation of β,β -disubstituted acrylate esters.

Entry	R	R ¹	R ²	L	ee (%)	Ref.	Chemical reaction scheme:
							H ₂ rt, CH ₂ Cl ₂
1	S165	Me	CH ₂ Bn	Et	32a	89	79a
2	S166	CH ₂ Bn	Me	Et	32b	93	79a
3	S167	Me	4-MeO-C ₆ H ₄	Et	13a	98	57
4	S168	Et	4-MeO-C ₆ H ₄	Et	13a	98	57
5	S169	4-MeO-C ₆ H ₄	Me	Et	13a	92	57
6	S170	iPr	Ph	Et	17b	>99 (<i>S</i>)	150
7	S171	Ph	iPr	Et	49b	>99 (<i>R</i>)	150
8	S172	Me	CH ₂ Ph	Et	17b	93 (+)	150
9	S173	CH ₂ Ph	Me	Et	49b	85 (-)	150

For all cases, when changing between the *E*- and *Z*- isomers, products with the opposite absolute configuration were obtained when using catalysts with the same configuration (Table 9, **S170** vs. **S171** and **S172** vs. **S173**).

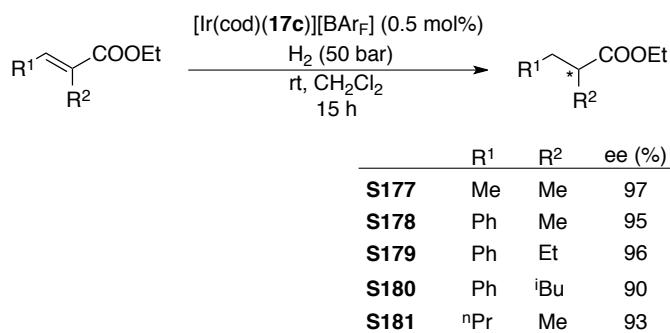
β,β -Diaryl methyl acrylates (β -aryl cinnamate esters) have been reduced using N,P-ligated iridium complexes, albeit less enantioselectively. With 1 mol% $[\text{Ir}(\text{cod})(\mathbf{46})]\text{[BAr}_F]$ under 100 bar H_2 , three sterically demanding alkenes (**S174-S176**) could be hydrogenated in moderate enantioselectivity (Scheme 25).⁶¹



Scheme 25 Asymmetric hydrogenation of some β -aryl cinnamate esters using $[\text{Ir}(\text{cod})(\mathbf{46})]\text{[BAr}_F]$.

The *trans*- α -methyl cinnamates have also been used as substrates for asymmetric hydrogenation with chiral analogues of Crabtree's catalyst but generally results in lower enantioselectivities than their β -substituted counterparts.^{60a,71c,95,103a}

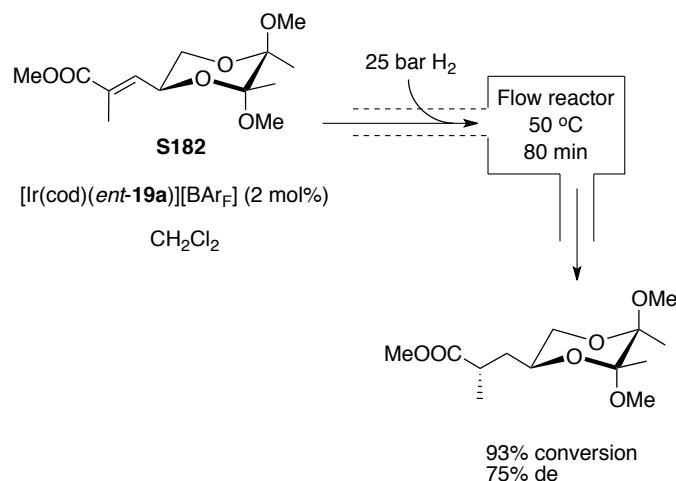
During attempts to identify suitable ligands for the asymmetric hydrogenation of α,β -substituted ethyl acrylates, bicyclic oxazoline **17c** (Figure 4) was identified as an especially selective ligand.¹⁵⁰ Using 0.5 mol% $[\text{Ir}(\text{cod})(\mathbf{17c})]\text{[BAr}_F]$, both alkyl and aryl-substituted alkenes could be reduced in excellent enantioselectivity (Scheme 26).



Scheme 26 Asymmetric hydrogenation of α,β -substituted ethyl acrylates **S177-S181**.

In addition to varying the alkene substituents, a comparison of different tiglate and α -methyl cinnamate esters was also done. It was found that the alcohol part of the ester only had a minor influence on the enantioselectivity (Et, Bn, iPr and (+)-1-phenylethyl esters all gave similar enantioselectivities).

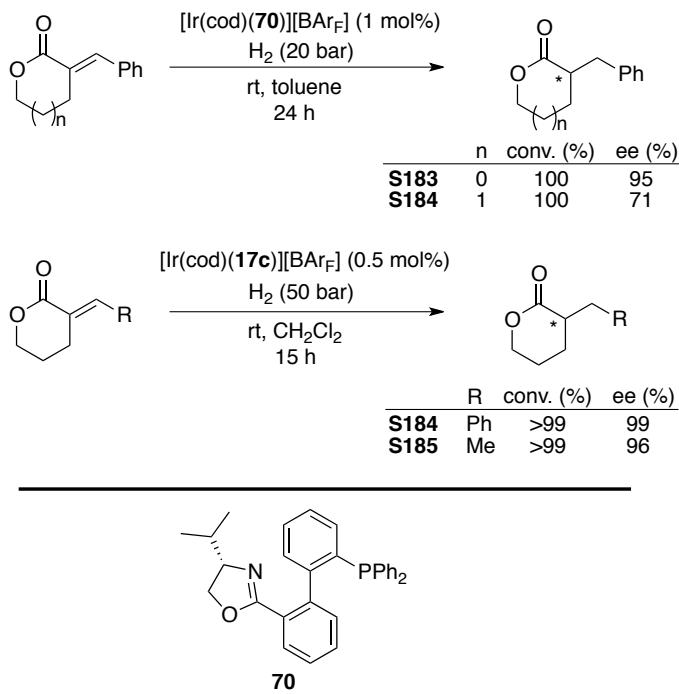
Newton, Ley and co-workers performed the diastereoselective hydrogenation of the α,β -unsaturated ester **S182** by feeding it together with 2 mol% [Ir(cod)(*ent*-**19a**)][BAr_F] (Figure 4) and CH₂Cl₂ into a flow-reactor.¹⁵¹ Hydrogen was added by a “tube-in-tube” diffusion system. By heating the flow to 50 °C for 80 min, the product could be obtained in 75% diastereomeric excess (Scheme 27). Modifications of the setup allowed a decrease the catalyst loading however, although several catalysts were tested, the diastereomeric excess could not be significantly improved.



Scheme 27 Diastereoselective hydrogenation of **S182** performed in a flow reactor setup.

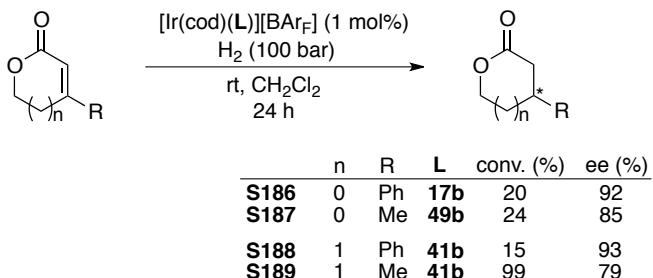
Ir-catalyzed asymmetric hydrogenation of five- and six-membered α,β -unsaturated lactones with exocyclic double bonds has also been performed.¹⁵² [Ir(cod)(**70**)][BAr_F], under 20 bar H₂ in toluene, reduced the unsaturated five-membered lactone **S183** in 95% ee and the unsaturated six-membered lactone **S184** in 71% ee (Scheme 28).

Ir-**17c** (Figure 4), which formed an excellent catalyst for the enantioselective reduction of α,β -substituted acyclic esters, also reduced the six-membered phenyl- and methyl-substituted alkenes **S184** and **S185**, giving the saturated lactones in excellent ee (Scheme 28).¹⁵⁰



Scheme 28 Asymmetric hydrogenation of some α,β -unsaturated lactones with exocyclic alkenes, **S183-S185**.

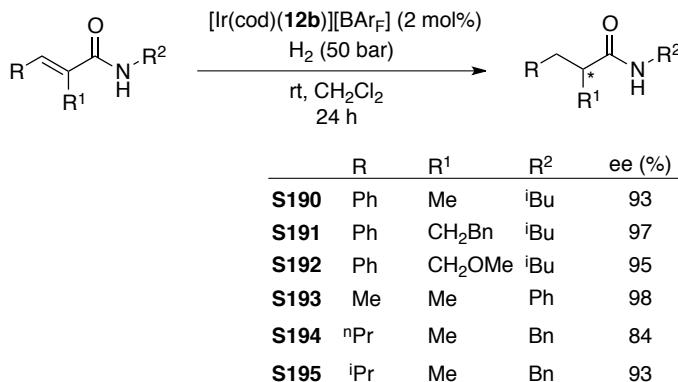
While the asymmetric hydrogenation of exocyclic alkenes in α,β -unsaturated lactones yields products with an $\alpha\text{-CH}_2\text{R}$ substituent, the reduction of α,β -unsaturated lactones with a β -substituted internal alkene gives more useful products. Unfortunately, the reduction of such alkenes has been shown to proceed only slowly.¹⁵³ Five-membered methyl- and phenyl-substituted alkenes **S186** and **S187** were reduced in good enantioselectivity but only to 20% conversion after 24h under 100 bar H_2 using catalysts based on bicyclic ligands **17b** (Figure 4) and **49b** (Figure 6) (Scheme 29). For the six-membered variants, phosphine-imidazole ligand **41b** (Figure 6) gave similar selectivity and conversion for the phenyl-derivative **S188** while the methyl-substituted alkene **S189** was completely reduced.¹⁵³



Scheme 29 Asymmetric hydrogenation of α,β -unsaturated lactones with endocyclic alkenes, **S186-S189**.

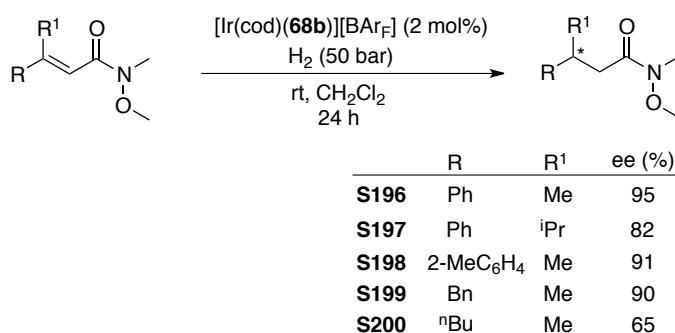
6.3 α,β -Unsaturated Amides

A few examples of asymmetric hydrogenation of acrylic amides, catalyzed by chiral analogues of Crabtree's catalyst, have also appeared. Ferrocene-based PHOX-mimic **12b** (Figure 4) was found to be the best ligand for the asymmetric hydrogenation of α,β -disubstituted acrylamides (Scheme 30).¹⁵⁴ While the α -substituent was either methyl or methylene throughout, the β -substituent could be either aryl (**S190-S192**) or alkyl (**S193-S195**). Changing the amide N-substituents moderately affected the enantioselectivity (this was also observed for the α,β -disubstituted esters where the alcohol part only had a minor influence on the enantioselectivity). It was however shown, that for the *trans*- α -methyl, β -phenyl derivatives such as **S190**, primary amides gave higher enantioselectivity than their secondary counterparts, and *i*Bu was the N-substituent that gave the highest ee.



Scheme 30 Representative results from the asymmetric hydrogenation of α,β -disubstituted acrylamides using $[\text{Ir}(\text{cod})(\mathbf{12b})]\text{[BAr}_\text{F}\text{]}$.

Recently, asymmetric hydrogenations of β,β -disubstituted acrylic Weinreb amides was presented.¹⁵⁵ Using $[\text{Ir}(\text{cod})(\mathbf{68b})]\text{[BAr}_\text{F}\text{]}$ (ligand **68b**; see Table 8, $R^1 = \text{Ph}$, $R^2 = \text{Bn}$) under 50 bar H_2 , high enantioselectivity could be obtained for several alkenes (Scheme 31). Although high enantioselectivities were maintained as long as the *trans*-substituent remained a bulky or aryl group ($R = \text{Ph}$, Bn , $^\text{t}\text{Bu}$), aliphatic *trans*-substituents such as in **S200** gave significantly lower selectivity ($R = ^\text{n}\text{Bu}$).



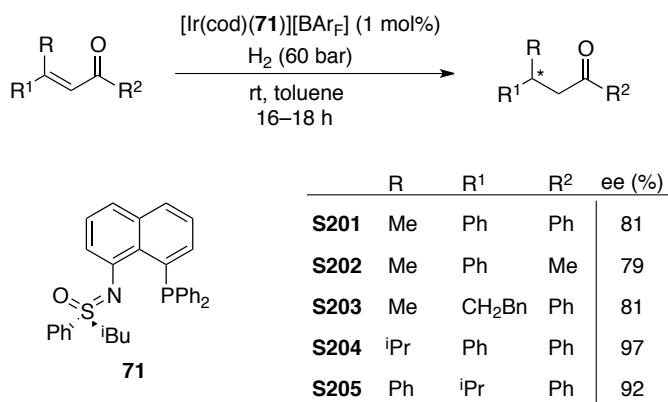
Scheme 31 Asymmetric hydrogenation of β,β -disubstituted acrylamides.

6.4 α,β -Unsaturated Ketones

The asymmetric hydrogenation of α,β -unsaturated ketones has been the subject of several studies. While the selective hydrogenation of the carbonyl function is best realized using the P,P-ligated Noyori-type catalytic systems,¹⁵⁶ Takaya and co-workers showed that $[\text{Ir}(\text{cod})(\text{BINAP})]\text{[BF}_4\text{]}$ could be chemoselective towards either the carbonyl- or alkene-function of *E*-4-phenyl-3-butene-2-one depending on the addition of auxiliary aminophosphine ligands.¹⁵⁷ Alkene-selective asymmetric hydrogenation of enones has been achieved using various systems; P,P-ligated Ru-^{124,158} Rh-¹⁵⁹ and Pd-catalysts¹⁶⁰ have proven to be efficient. Organocatalytic transfer-hydrogenation¹⁶¹ and auxiliary assisted heterogeneous systems¹⁶² have also

shown to be advantageous. The majority of the above-mentioned catalytic systems are highly enantioselective for cyclic substrates but not as useful for the reduction of linear alkenes, and here, chiral mimics of Crabtree's catalyst have proved valuable.

Iridium complex $[\text{Ir}(\text{cod})(\mathbf{71})]\text{[BAr}_F]$, based on sulphoximine-phosphine ligand **71**, was found to give trace amounts of carbonyl reduction in the asymmetric hydrogenation of acyclic β,β -disubstituted enones.¹⁶³ Thus, using $[(\mathbf{71})]\text{[BAr}_F]$ under 60 bar H_2 in toluene, the saturated ketone products could be obtained in good yield and enantioselectivity after 16–18 hours (Scheme 32). No change in selectivity was observed when the ketone substituent (R^2) was replaced from a phenyl (**S201**) to a methyl (**S202**). Both the *E*- and *Z*-isomers of the phenyl/iso-propyl derivative (**S204** and **S205**) gave excellent enantioselectivity but different absolute configurations of the product.



Scheme 32 Representative results from the asymmetric hydrogenation of β,β -disubstituted α,β -unsaturated ketones using $[\text{Ir}(\text{cod})(\mathbf{71})]\text{[BAr}_F]$.

$[\text{Ir}(\text{cod})(\mathbf{71})]\text{[BAr}_F]$ was also tested for the asymmetric hydrogenation of the α,β -disubstituted enone *E*-3-methyl-4-phenyl-3-buten-2-one but the product was obtained in 55% ee.¹⁶⁴ Instead, the PHOX ligand **5d**, (Figure 3) proved to be highly selective for this reaction and gave the saturated ketone as the only product. Interestingly, when β,β -disubstituted enones were reduced by the same complex, significant amounts of the saturated alcohol were obtained.¹⁶³ Using $[\text{Ir}(\text{cod})(\mathbf{5d})]\text{[BAr}_F]$, both aryl- and alkyl-substituted alkenes could be reduced in 3 hours and using only 2 bar H_2 (Table 10,

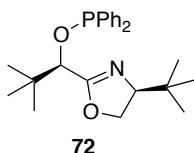
entries 1–6). Good-to-excellent enantioselectivity was observed for all substrates tested including one 1,1-disubstituted alkene (**S210**, entry 6) giving 86% ee.

While $[\text{Ir}(\text{cod})(\mathbf{71})]\text{[BAr}_\text{F}\text{]}$ achieved slightly higher enantioselectivities with toluene as solvent, $[\text{Ir}(\text{cod})(\mathbf{5d})]\text{[BAr}_\text{F}\text{]}$ was used for the reduction of **S207** and **S206** with dichloromethane and close to identical results were observed (Table 10, entries 7 and 8).¹⁶⁵

Recently, a catalytic system featuring phosphinite-oxazoline ligand **72**, developed by Kazmaier and co-workers, was shown to give excellent enantioselectivities (>99% ee) in the hydrogenation of two α,β -disubstituted enones (Table 10, entries 9 and 10).¹⁶⁶

Table 10 Representative results from the asymmetric hydrogenation of α,β -disubstituted enones.

Entry	R	R ¹	R ²	Ligand	Solvent	ee (%)	Ref.	
1	S206	Ph	Me	Ph	5d	toluene	99 (<i>S</i>)	164
2	S207	Ph	Me	Me	5d	toluene	98 (<i>S</i>)	164
4	S208	Ph	Ph	Ph	5d	toluene	99 (<i>R</i>)	164
5	S209	Et	Me	Ph	5d	toluene	87 (<i>S</i>)	164
6	S210	H	Bn	Ph	5d	toluene	86 (<i>S</i>)	164
7	S207	Ph	Me	Me	5d	CH ₂ Cl ₂	98	165
8	S206	Ph	Me	Ph	5d	CH ₂ Cl ₂	97	165
9	S207	Ph	Me	Me	72	CH ₂ Cl ₂	>99	166
10	S211	Ph	Et	Me	72	CH ₂ Cl ₂	>99	166



The exocyclic enones **S212** and **S213** are popular substrates for N,P-ligated Ir-catalyzed hydrogenation systems and have been reduced effectively and in high enantioselectivity by several catalytic systems.^{152,164-166}

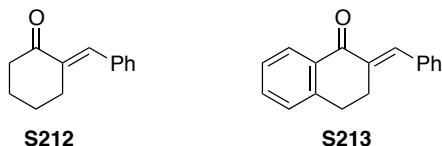
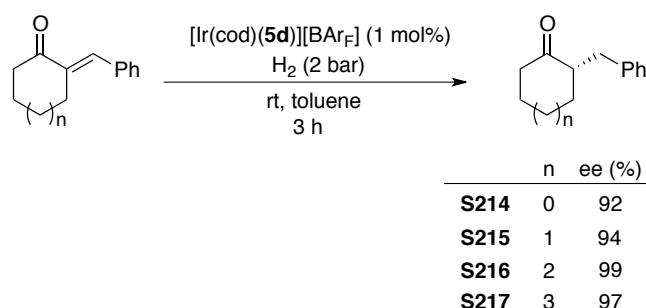


Figure 17 α,β-Disubstituted enones **S212** and **S213** are reduced in high enantioselectivity by several complexes of the type [Ir(cod)(N,P)][BAr_F].

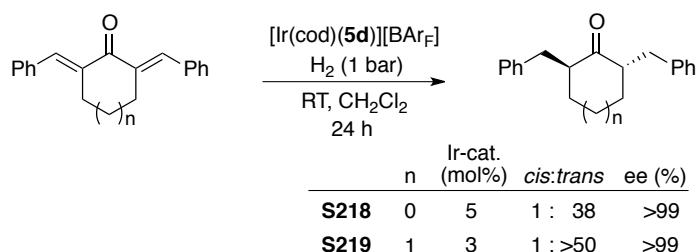
During the studies of linear alkenes, [Ir(cod)(**8d**)][BAr_F] was also applied to the asymmetric hydrogenation of cyclic substrates and the catalytic system was shown to reduce the five-, six-, seven-, and eight-membered

cyclic enones with exocyclic double bonds (**S214-S217**) in excellent enantioselectivity (Scheme 33).¹⁶⁴



Scheme 33 Asymmetric hydrogenation of cyclic enones **S214-S217** using $[\text{Ir}(\text{cod})(\mathbf{5d})][\text{BAr}_\text{F}]$.

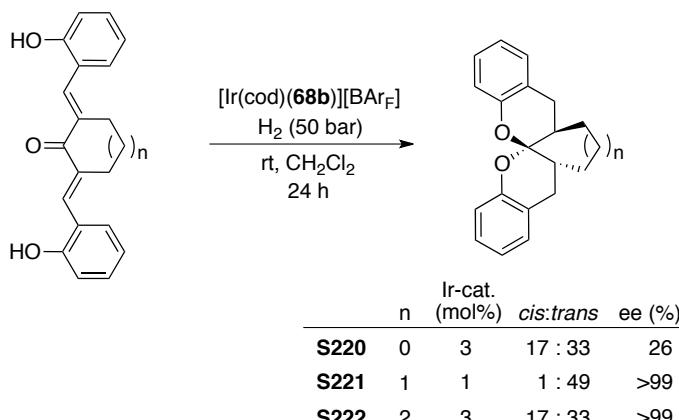
Very high diastereo- and enantioselectivities were also observed for the reduction of enones **S218** and **S219** using $[\text{Ir}(\text{cod})(\mathbf{5d})][\text{BAr}_\text{F}]$ (Scheme 34).¹⁶⁵



Scheme 34 Asymmetric hydrogenation of **S218** and **S219** using $[\text{Ir}(\text{cod})(\mathbf{5d})][\text{BAr}_\text{F}]$.

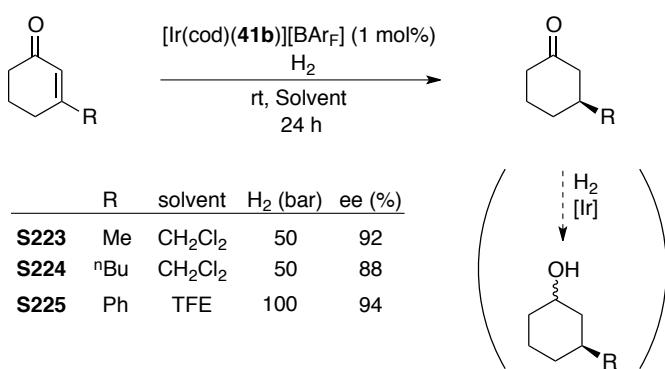
The results obtained in the hydrogenation of **S218** and **S219**, and especially the high distereoselectivities achieved, inspired the asymmetric hydrogenation of cyclic enones bearing 2-hydroxy groups **S220-S222** (Scheme 35).¹⁶⁷ *In situ* cyclization of the product ketones, possibly due to the acidity of the catalytic system, gave spiroketals which were isolated in good yields. Using ligand **68b** (Table 8, R¹= Ph, R²= Bn), the five-membered cyclic ketone **S220** was reduced in very low enantioselectivity while the six-membered ketone **S221** gave product spiroketals in excellent enantio- and

diastereoselectivity. The seven-membered ketone **S222** was also reduced in excellent ee but with a poor *cis:trans* ratio (Scheme 35).



Scheme 35 Representative results from the asymmetric hydrogenation of enones with tandem spiroketalization.

As in the case of lactones, cyclic enones containing internal alkenes are reduced considerably slower and only one successful N,P-ligated iridium catalytic system has thus far been presented. $[\text{Ir}(\text{cod})(\mathbf{41b})][\text{BAr}_F]$ (Figure 6), which also worked well in the reduction of the corresponding lactones (*vide supra*), was efficient in the asymmetric hydrogenation of three β -substituted cyclohex-2-enones.¹⁵³ Both the methyl- (**S223**) and butyl-derivative (**S224**) could be completely reduced in good enantioselectivity in CH_2Cl_2 however the reaction time and hydrogen pressure had to be carefully controlled since a prolonged reaction time led to a reduction of the product ketone to the saturated alcohol (Scheme 36). While the carbonyl reduction did not begin until the alkene had been consumed for $\text{R} = \text{Me}$ and ^7Bu , the phenyl derivative (**S225**) produced a mixture of saturated alcohols and ketone when performed in CH_2Cl_2 . Although the degree of carbonyl reduction could be controlled by adjusting the H_2 pressure, an alternative was to perform the reaction in 2,2,2-trifluoroethanol (TFE). Reduction of 3-phenyl-cyclohex-2-enone in this solvent under 100 bar H_2 gave the product (ketone) cleanly and in 94% ee (Scheme 36).



Scheme 36 The asymmetric hydrogenation of cyclic enones with $[\text{Ir}(\text{cod})(\mathbf{41b})][\text{BAr}_F]$. The reaction conditions have to be controlled to avoid reduction of the product carbonyl.

The enantioselectivities in CH_2Cl_2 and TFE were comparable but slightly better in TFE for $\text{R} = \text{Ph}$ and Me and somewhat better in CH_2Cl_2 for $\text{R} = ^n\text{Bu}$. N,P-ligated iridium species can be a source of significant acidity,¹²⁵ and it is possible that the alcoholic solvent acts as a buffer, preventing the carbonyl reduction either by removing formed protons or hydrogen bonding to the C=O thus inhibiting bonding of Lewis acidic iridium species.

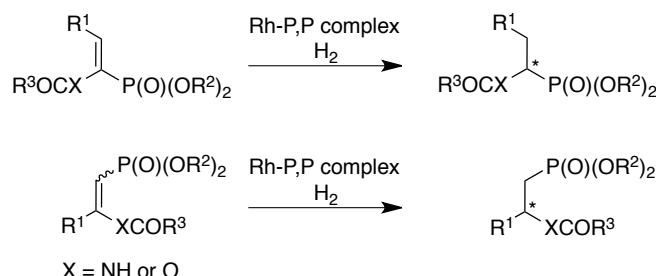
7 Alkenes Bearing Other Heteroatoms

Stereogenic centers bearing heteroatoms other than nitrogen or oxygen have also been prepared by asymmetric hydrogenation. With the exception of phosphorus as vinyl phosphonates, relatively few reports exist. The asymmetric hydrogenation of trisubstituted vinyl silanes has been performed exclusively using iridium N,P-catalysts,⁶³ and the hydrogenation of thio-enol ethers has only been reported using Rh-diphosphine catalytic system.¹⁶⁸ Vinyl fluorides and boronates have been enantioselectively reduced using different metal-ligand complexes and will be discussed.

7.1 Phosphorus

Vinyl phosphonates have frequently been used as substrates for asymmetric hydrogenation using rhodium-catalyzed systems. The majority of the reports focus on alkenes that, in addition to the phosphonate, also carry coordinating

functional groups such as enamido- or enol ester-functionalities in the α or β positions (Scheme 37).^{14,169} The products of these reactions are valuable as they are easily manipulated into α or β amino- or hydroxy- phosphonic acids which, as amino acid isosters, have various effects in biological systems.



Scheme 37 Asymmetric hydrogenation of α -enolbenzo- and α -acetamido-phosphonates are frequently performed with P,P-ligated rhodium catalysts.

Less functionalized vinyl phosphonates lack good coordinating groups like acetamides or enol esters. However, they still have the potential to coordinate through the $\text{P}(\text{O})(\text{OR})_2$ function and is an interesting class of substrates for metal-catalyzed hydrogenation. 1-Aryl-ethenylphosphonates have been used as substrates for asymmetric hydrogenation using ruthenium-diphosphine catalysts.¹⁷⁰ For rhodium just one example of ee's above 90% has been reported using a BoPhoz type ligand.¹⁷¹ With N,P-ligated Ir-catalysts, 94, 92 and 93% ee for the phenyl- and two naphthyl-derivatives **S226**, **S227** and **S228** (Table 11, entries 1, 3 and 4) was obtained using $[\text{Ir}(\text{cod})(\text{5a})][\text{BAr}_F]$ (PHOX-ligand **5a**; Figure 3).¹⁷² Under similar conditions, the phenyl-substituted product from **S226** could be obtained in >99 % ee using $[\text{Ir}(\text{cod})(\text{46})][\text{BAr}_F]$ (Figure 6).¹⁷³ In addition to phosphonate esters, the corresponding diphenylphosphine oxides **S229-S234** were evaluated in asymmetric hydrogenation reactions using $[\text{Ir}(\text{cod})(\text{46})][\text{BAr}_F]$. Aromatic (**S229-S231**) and aliphatic (**S232-S234**) 1,1-disubstituted diphenylvinylphosphine oxides could be reduced, often in >99 % ee, using this catalytic system (Table 11, entries 5-10).¹⁷³ Hence, it seems that replacement of the $\text{P}(\text{O})(\text{OEt})_2$ -group with the bulkier $\text{P}(\text{O})\text{Ph}_2$ is advantageous for the hydrogenation with chiral mimics of Crabtree's catalyst.

Table 11 Representative results from the asymmetric hydrogenation of 1-substituted ethenylphosphonates using [Ir(cod)(L)][BAr_F].

Entry	R	R ¹	L	[Ir(cod)(L)][BAr _F] (1 mol%)					Ref.
				temp (°C)	H ₂ (bar)	time (h)	ee (%)		
1	S226	Ph	OEt	5a	40	5	6	94	172
2	S226	Ph	OEt	46	rt	50	15	>99	173
3	S227	1-naphthyl	OEt	5a	40	5	6	92	172
4	S228	2-naphthyl	OEt	5a	40	5	6	93	172
5	S229	Ph	Ph	46	rt	50	15	>99	173
6	S230	4-F-C ₆ H ₄	Ph	46	rt	50	15	93	173
7	S231	4-MeO-C ₆ H ₄	Ph	46	rt	50	15	>99	173
8	S232	^t Bu	Ph	46	rt	50	15	90	173
9	S233	CH ₂ Bn	Ph	46	rt	50	15	>99	173
10	S234	CH ₂ CH ₂ OH	Ph	46	rt	100	15	>99	173

For the asymmetric hydrogenation of trisubstituted vinylphosphonates, a few catalytic systems utilizing rhodium-diphosphine and rhodium-phosphoramidite complexes have proved to be suitable. In 1999, [Rh(cod)(DIOP)][BF₄] was used to reduce *E*-β-methylphosphonato crotonate in 42% ee by stirring the reaction under an atmosphere of hydrogen for 78 hours without solvent.¹⁷⁴ The investigators reasoned that the poor enantioselectivity was due to lack of good coordinating functional groups. However, an in-depth study of this reaction was not undertaken. In a study of several substituted (*E*)-carboxymethyl vinylphosphonates, a range of diphosphine ligands were tested together with [Rh(cod)₂][BF₄] in the asymmetric hydrogenation.¹⁷⁵ Ligands from the Josiphos family were the most effective, reducing both alkyl and aryl substituted alkenes highly selectively. A high (5 mol%) catalyst loading was needed to ensure full conversion of the alkenes in 24 hours. In another report, *E*-(2-aryl-1-propene)phosphonates were reduced in excellent enantioselectivity by a rhodium-phosphoramidite catalyst.¹⁷⁶

The $[\text{Ir}(\text{cod})(\text{N},\text{P})][\text{BAr}_F]$ catalytic system has also proved useful in this reaction; iridium complexes derived from ligand **46** (Figure 6), that reduced 1,1-disubstituted vinyl phosphonates, also gave high enantioselectivities in the reduction of two (*E*)-carboxyethyl vinylphosphonates **S235** and **S236** (Table 12, entries 1–2).¹⁷³ Interestingly, the *Z*-isomer of the phenyl-substituted derivative (**S237**) was reduced faster than the *E*-isomer (**S235**), and in higher enantioselectivity but yielded the product with the same absolute configuration. This effect has sometimes been observed in the rhodium-catalyzed asymmetric hydrogenation of functionalized vinylphosphonates,¹⁷⁷ and can be attributed to substrate chelation. To our knowledge, this effect hasn't been observed previously in the Ir-catalyzed hydrogenation of alkenes. By contrast, in the hydrogenation of β,β -disubstituted- α,β -unsaturated vinyl phosphonates with a rhodium-phosphoramidite catalyst, both the *E*- and the *Z*-alkene gave excellent enantioselectivity, but the two isomers gave opposite enantiomers of the product.¹⁷⁶ Together these results illustrate the intermediate nature of the weakly functionalized vinyl phosphonates and the fact that, in some cases chelation takes place while in other cases it does not.

The phosphite-oxazole ligand **44a** (Figure 6) has also been used to obtain high enantioselectivity in the reduction of two trisubstituted vinylphosphonates with *Z*-configuration (Table 12, entries 4 and 5).⁹²

Table 12 Asymmetric hydrogenation of some trisubstituted vinyl phosphonates.

Entry	<i>Z/E</i>	<i>R</i> ¹	<i>R</i> ²	<i>R</i> ³	Ir-cat. (mol%)	<i>L</i>	ee (%)	Ref.	Chemical reaction scheme:
1	S235 <i>E</i>	COOEt	Ph	OEt	1	46	90	173	
2	S236 <i>E</i>	COOEt	Bn	OEt	1	46	>99	173	
3	S237 <i>Z</i>	COOEt	Ph	OEt	1	46	>99	173	
4	S238 <i>Z</i>	COOEt	Ph	Ph	0.2	44a	92	92	
5	S239 <i>Z</i>	Me	Ph	Ph	0.2	44a	91	92	

7.2 Boron

Asymmetric hydrogenation of trisubstituted vinylboronates was first performed in 2004.¹⁷⁸ In a screening using *E*-1,2-*bis*(Bpin)styrene **S240** (Bpin = 4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl) as substrate, rhodium was superior to iridium together with the P,P-ligands that were evaluated. Walphos type ligands were the most selective and the highest enantiomeric excess (93%) was obtained when the reaction was performed in toluene using 2 mol% Rh. Interestingly, a 2:1 ratio of ligand-to-metal gave the highest selectivity, while a 1:1 or lower, ligand-to-metal ratio gave reversed, and poor, enantioselectivity. 1,2-*Bis*(boronates) having aliphatic substituents could also be reduced in high enantioselectivity using a slightly modified ligand, but again, relatively high loadings of rhodium and the ligand were required.

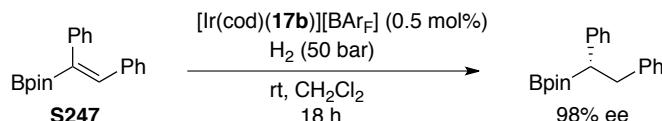
Chiral mimics of Crabtree's catalyst have proven useful in this reaction and, in the first study, hydrogenation of *E*-1,2-*bis*(Bpin)styrenes was attempted using different ligands.⁶⁵ When the reaction was performed under 1 bar of H₂, using 0.5 mol% [Ir(cod)(**49a**)][BAr_F] as pre-catalyst (**49a**; Figure 6), 1,2-di(Bpin)-1-phenyl-ethane was obtained in 96% ee from **S240** and the *para*-methoxy derivative in 88% ee from **S242** (Table 13, entries 1 and 5). Using **17d** (Figure 4) as the chiral ligand in the asymmetric hydrogenation of these alkenes gave close to racemic product mixtures and a higher hydrogen pressure resulted in significantly lower selectivity.⁶⁵ For the *n*-butyl derivative (**S243**, entry 6), the highest enantioselectivity obtained was 48% when [Ir(cod)(**18d**)][BAr_F] was used as pre-catalyst.

Recently, ligands **23b** (Figure 4) and **32b** (Figure 5), were applied in the iridium catalyzed asymmetric hydrogenation of 1,2-*bis*(boronates). While [Ir(cod)(**23b**)][BAr_F] gave excellent results for two *E*-1,2-*bis*(Bpin)styrenes (Table 13, entries 2 and 4),^{72b} [Ir(cod)(**32b**)][BAr_F] could reduce the phenyl-derivative (**S240**, entry 3) as well as the bulky cyclohexyl (**S245**, entry 8) and *tert*-butyl (**S246**, entry 9) derivatives highly selectively.¹⁷⁹ The *n*-hexyl derivative **S244** was reduced in 72% ee by this complex (entry 7).

Table 13 Representative results from the asymmetric hydrogenation of vinyl-1,2-*bis*(boronates) using complexes of the type [Ir(cod)(N,P)][BAr_F].

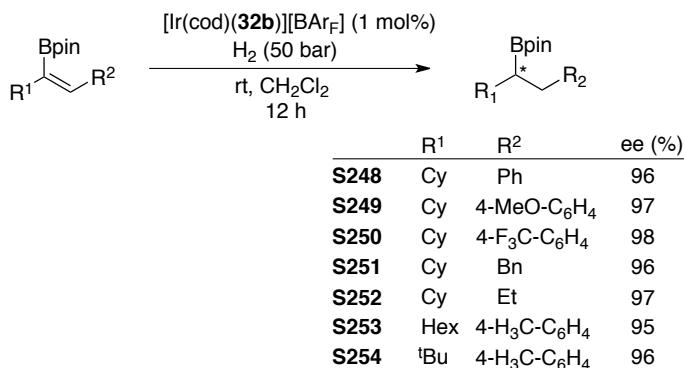
Entry	R	Ir-cat. (mol%)	L	H ₂ (bar)	time (h)	ee (%)	Ref.		
1	S240	Ph	0.5	49a	1	18	96	65	
2	S240	Ph	1	23b	50	2	>99	72b	
3	S240	Ph	1	32b	50	12	98	179	
4	S241	4-F-H ₄ C ₆	1	23b	50	2	92	72b	
5	S242	4-OMe-H ₄ C ₆	0.5	49a	1	18	88	65	
6	S243	nBu	0.5	17d	1	18	48	65	
7	S244	Hex	1	32b	50	12	72	179	
8	S245	Cy	1	32b	50	12	95	179	
9	S246	tBu	1	32b	50	12	85	179	

In addition to 1,2-*bis*(boronates), several trisubstituted alkenes containing only one boronic ester have been subjected to Ir-catalyzed asymmetric hydrogenation with good results. For instance, the sterically demanding *cis*-stilbene boronate **S247** could be reduced using 0.5 mol% $[\text{Ir}(\text{cod})(\mathbf{17b})]\text{[BAr}_F]$ (ligand **17b**; Figure 4) under 50 bar H_2 (Scheme 38).⁶⁵



Scheme 38 Asymmetric reduction of **S247** using $[\text{Ir}(\text{cod})(\mathbf{18b})]\text{[BAr}_F]$.

Recently, a range of chiral boronic esters were prepared by asymmetric hydrogenation of trisubstituted vinyl boronates using the Ir-complex of ligand **32b** (Figure 5), that was also used for *bis*(boronates).¹⁷⁹ Under 50 bar H_2 in CH_2Cl_2 , alkenes with various aliphatic and aromatic groups (**S248-S254**) could be reduced in very high enantioselectivities (Scheme 39). In all cases the substituent on the prochiral carbon atom (R^1) was a relatively bulky aliphatic group, indicating that this is a prerequisite for high enantiomeric excess.

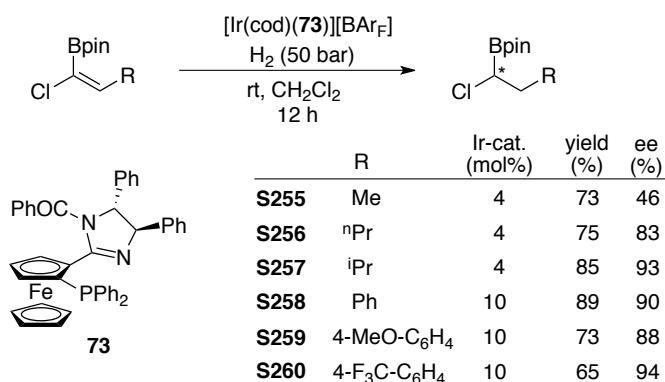


Scheme 39 Asymmetric hydrogenation of trisubstituted vinyl boronates using $[\text{Ir}(\text{cod})(\mathbf{32b})]\text{[BAr}_F]$.

1-Chloro-1-alkenyl boronates can also be reduced selectively using N,P-ligated Ir-complexes.¹⁸⁰ $[\text{Ir}(\text{cod})(\mathbf{73})]\text{[BAr}_F]$ and H_2 reduced several alkyl-

(**S255–S257**) and aryl-substituted (**S258–S260**) derivatives with high enantioselectivity and without significant de-chlorination, although a high (4–14 mol%) catalyst loading was required (Scheme 40). Several P,P-ligated rhodium complexes, as well as one ruthenium complex, was also tested in this reaction. The ruthenium complex gave the dechlorination product almost exclusively, while the rhodium-catalysts were both slow and unselective compared to the chiral analogues of Crabtree's catalyst.

These results demonstrate the high catalytic activity and the uniquely high tolerance of chiral Crabtree mimics to functional groups, even directly on the double bond, in asymmetric hydrogenation.



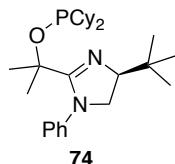
Scheme 40 Asymmetric hydrogenation of 1-chloro-1-alkenyl boronates.

The rhodium-Walphos system for the hydrogenation of 1,2-bis(boronates) also proved useful for the reduction of 1,1-disubstituted vinyl boronates. Several 1-alkyl-1-(Bpin)-ethenes could be hydrogenated in high enantioselectivity but the reduction required high catalyst loadings and low reaction temperature. It was selective for long chain and cyclic aliphatics as well as for homoallylic ethers and esters.¹⁸¹ Prior to this work, hydrogenation of 1-phenylethenyl boronic esters was achieved using 3 mol% [Rh(cod)(BINAP)][BF₄] as the catalyst precursor.¹⁸² The best selectivity (80 % ee) was obtained using simple 1,3,2-dioxaborolane as the boronate function and stirring the reaction at –20 °C for 7 days. With the pinacol ester as the boronate function and at room temperature, the reaction required only 24 hours to complete however the enantioselectivity was poor.

Iridium catalysts have also proven very useful in the hydrogenation of this type of prochiral alkenes. The phenyl- and hexyl-substituted vinyl pinacolboronates **S261** and **S262** were hydrogenated using the iridium complex of ligand **17d** (Figure 4) as catalyst. Good enantioselectivity was obtained for the phenyl derivative (Table 14, entry 1) but low selectivity was observed for the *n*-hexyl derivative (entry 3).⁶⁵ As in the case of trisubstituted vinyl(bis)boronates, significantly lower catalyst loading was required when using chiral versions of Crabtree's catalyst as compared to the rhodium-P,P-systems.

Table 14 Asymmetric hydrogenation of 1,1-disubstituted vinyl boronates.

Entry	R	[Ir(cod)(L)][BAr _F] (0.5 mol%)						Ref.
		L	temp (°C)	H ₂ (bar)	time (h)	ee (%)		
1	S261 Ph	17d	rt	50	18	89	65	
2	S261 Ph	74	-20	2	4	4	179	
3	S262 <i>n</i> Hex	17d	rt	50	18	18	65	
4	S262 <i>n</i> Hex	74	-20	2	4	96	179	
5	S263 Cy	74	-20	2	4	33	179	
6	S264 CH ₂ Bn	74	-20	2	4	94	179	
7	S265 Bn	74	-20	2	4	94	179	
8	S266 CH ₂ OTBDMS	74	-20	2	4	88	179	



[Ir(cod)(**74**)][BAr_F] could be used as precatalyst to obtain excellent enantioselectivity in the asymmetric hydrogenation of several 1-substituted 1-(Bpin)-ethenes after optimization of the catalytic system for the *n*-hexyl substituted alkene **S262** (Table 14, entries 4, 6, 7 and 8).¹⁷⁹ At -20 °C and under 2 bar of hydrogen, the reactions were complete after 4 hours using 0.5

mol% catalyst. Surprisingly, with R = Ph (**S261**), an essentially racemic mixture of products was obtained. Also the cyclohexyl derivative **S263** (entry 5) gave low enantioselectivity, indicating that this catalytic system is most efficient for alkenes in which the substituents are linked by a CH₂-function.

7.3 Fluorine

The enantioselective reduction of vinyl fluorides, another challenging alkene type, has been briefly evaluated. A few examples involving fluorinated olefins carrying coordinating functional groups exist. Both the *E*- and *Z*-isomer of the α,β-unsaturated carboxylic acid **S267** where R = ⁿPr could be reduced in 88–90% ee by Ru-BINAP.¹⁸³ The reaction proceeded smoothly at 50 °C in methanol, p(H₂) = 5–50 bar, for these two substrates but the scope of the reaction was not extended. For the *Z*-phenyl derivative enantioselectivity dropped significantly to 56%.

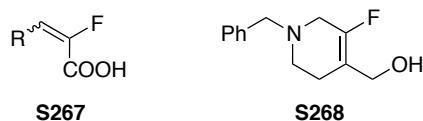


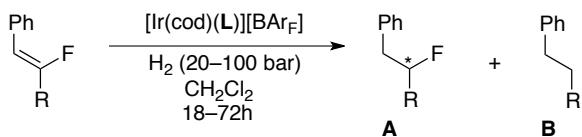
Figure 18 Vinyl fluorides **S267** and **S268**, carrying coordinating functional groups have been subjected to asymmetric hydrogenation using P,P-ligated ruthenium and rhodium complexes.

The tetrasubstituted vinyl fluoride **S268**, which is also an allylic alcohol, has been hydrogenated to its chiral product with *cis*-configuration in very high enantioselectivity.¹⁸⁴ Several chiral diphosphine ligands were screened with the metal precursors [Ir(cod)₂][BF₄] and [Rh(nbd)₂][BF₄] in CH₂Cl₂ and MeOH but the major product was the defluorinated compound in most cases. An N,P-ligand (PHOX), was also tested as ligand to iridium in dichloromethane but here as well, defluorination was a problem. Some rhodium catalysts and a P,P-ligated ruthenium complex exhibited significantly less defluorination and were studied further. Optimization of the reaction conditions eventually yielded the product in 99% ee (with a lower percentage of defluorination) using a rhodium-Walphos system.¹⁸⁴

Chiral mimics of Crabtree's catalyst have been used to prepare fluorine-bearing stereogenic centers by asymmetric hydrogenation of trisubstituted vinyl fluorides.⁶⁴ While significant amounts of defluorinated products were obtained using phosphine-oxazole and phosphine-thiazole ligands (**42** and **43**, Figure 6), azaphosphine P-donors (N-PAr₂), in general, appeared to give less defluorination. Thus, a thiazole N-donor ligand carrying an azadiarylphosphine, **46** (Figure 6), was prepared with the aim of obtaining low defluorination and high enantioselectivity. Indeed, when using [Ir(cod)(**46**)][BAr_F] a low percentage of defluorination and excellent ee's for the two alkenes **S269** and **S271** were obtained (Table 15, entries 1a and 2a).⁶⁴

In a subsequent study, imidazole-phosphine ligand **41a** (Figure 6) was prepared as a more basic ligand than the corresponding oxazoles and thiazoles.⁸⁷ Although there was a slight improvement in both selectivity and enantioselectivity, the effect was not very pronounced, suggesting that defluorination is affected by factors besides ligand acidity. [Ir(cod)(**41a**)][BAr_F] was tested in the asymmetric hydrogenation of a set of vinyl fluorides (**S269-S274**) with varying results (Table 15). As expected, Z-alkenes (i.e. sterically *trans* alkenes) **S269** and **S271** were reduced faster and more selectively than the *E*-isomers **S270** and **S272**. Less electron-poor alkenes **S269-S272** (R = CH₂OH and CH₂OAc) were also reduced faster than the very electron-deficient α,β-unsaturated esters **S273** and **S274**.⁸⁷

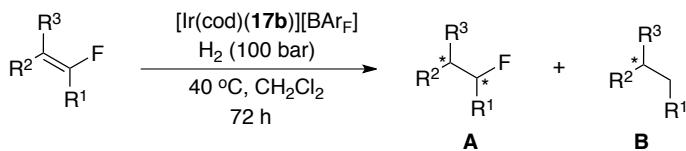
Table 15 Asymmetric hydrogenation of trisubstituted vinyl fluorides.



Entry	R	Z/E	temp (°C)	Ir-cat. (mol%)	L	A : B	ee (%)	Ref.	
1	S269	CH ₂ OAc	Z	25	0.5	46	95 : 5	>99	64
				25	1	41a	84 : 16	85	87
				25	1	41a	50 : 50	17	87
2	S271	CH ₂ OH	Z	25	0.5	46	100 : 0	99	64
				25	1	41a	92 : 8	80	87
				25	1	41a	43 : 57	52	87
3	S273	COOEt	Z	40	1	41a	66 : 34	46	87
				E ^a	40	41a	83 : 17	72	87

^a 10:1 E:Z

In addition to trisubstituted alkenes, a few tetrasubstituted vinyl fluorides could also be reduced using chiral mimics of Crabtree's catalyst. This is surprising, given that electron-poor alkenes are usually reduced more slowly using these catalytic systems. Using the bicyclic N-linked oxazoline ligand **17b** (Figure 4), three tetrasubstituted alkenes **S275–S277** could be reduced in ee's between 57 and 90% (Scheme 41).



	R ¹	R ²	R ³	Ir-cat. (mol%)	A : B	ee (%)
S275	COOEt	Me	Ph	0.5	100 : 0	57
S276	COOEt	Ph	Me	0.5	100 : 0	74
S277	CH ₂ OH	Ph	Me	1	71 : 29	90

Scheme 41 Asymmetric hydrogenation of tetrasubstituted vinyl fluorides.

7.4 Silicon

The hydrogenation of vinyl silanes, another challenging alkene type, hasn't been the focus of extensive study even though organosilanes are important organic intermediates and a number of innovative new organosilicon drugs

are in development.¹⁸⁵ To the best of our knowledge there is only one example in which a Rh-catalyst was used in the diastereoisomeric hydrogenation of vinylsilanes that also contain a hydroxyl group.¹⁸⁶

Chiral analogues of Crabtree's catalyst containing *N*-phosphine-oxazoline **17a** (Figure 4) and phosphine-thiazoline **43a** (Figure 6) hydrogenates (*E*)-trimethyl(2-phenylprop-1-en-1-yl)silane **S278** in high enantioselectivities (96% and 98% ee, respectively; Table 16, entries 1-2).⁶³ The hydrogenation of substrates containing the TMS group directly attached to the prochiral carbon led, however, to low-to-moderate enantioselectivities (i.e. substrates **S279-S281**; Table 16, entries 5-8). The hydrogenation of alkyl-substituted substrate **S282** also gave low enantioselectivity (Table 16, entry 9).

Recently, Ir-complexes with phosphite-containing ligands have proved to yield silicon-containing hydrogenation products effectively (ee's up to 98%; Table 16, entries 3 and 4).^{72b,92} As previously mentioned the application of phosphite-containing ligands has also opened the possibility to hydrogenate terminal olefins containing a neighboring trimethylsilyl group (substrate **S283**; Table 16, entries 10-12).^{72b,73b,92}

Table 16 Enantioselectivities achieved using chiral analogues of Crabtree's catalyst in the asymmetric hydrogenation of trimethylsilyl containing substrates **S278-S283**.

Entry	Substrate	L	ee (%)	Ref.
1		17a	96	63
2		43a	98	63
3		23a	97	72b
4		45a	98	92
5		17a	26	63
6		43a	28	63
7		43a	58	63
8		43a	48	63
9		43a	55	63
10		23a	96	72b
11		24a	96	73b
12		45a	93	92

8 Prediction of the Stereochemical Outcome

While the number of available ligands for the $[\text{Ir}(\text{cod})(\text{N},\text{P}^*)][\text{BAr}_\text{F}]$ catalytic system has grown, most of the published ligands give high enantioselectivity only for a narrow type of alkene.^{2c,3a} It appears as though the strict steric and geometric demands enforced by the ligands to obtain high enantioselectivity, also to a degree, prevent their generality. Thus, to reduce a specific alkene as part of a synthesis, one will likely have to screen a large array of different ligands to find the best one and, because of this, the incentive to provide easy, modular ligand syntheses is strong.

The Andersson group has developed two series of ligands that perform well in the asymmetric hydrogenation of a large set of prochiral trisubstituted alkenes.^{3c,d} The first is comprised of a variable ligand backbone that contains an oxazole, thiazole or imidazole N-donor, and a phosphine or phosphinite P-donor (Class **1**, Figure 19, bottom).^{87,89-90} The second system, based on a 2-aza-norbornane scaffold, consists of an oxazoline N-donor and an azaphosphinite P-donor (Class **2**, Figure 19, bottom).^{62a,65,129a,187} This system has been further modified to contain a thiazole N-donor.⁹⁵ A general structure of the successful N,P-ligands developed by several groups, with the individual elements highlighted, is shown in the upper part of Figure 19.

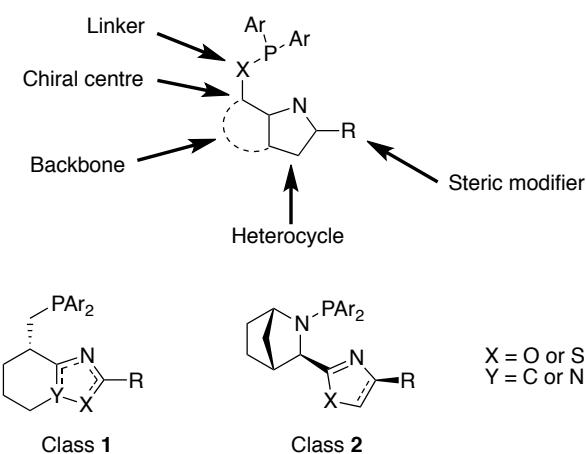


Figure 19 Top: General structure of many successful ligands for asymmetric hydrogenation, and Bottom: the two major ligand classes developed by Andersson and co-workers.

Computational^{37,40} and to some extent also experimental³¹ studies strongly indicate that a complex iridium cation $[\text{Ir}(\text{H})_2\text{Z}(\text{N},\text{P}^*)]^+$ (Figure 20a, center; N,P^* = chiral N,P-ligand, Z = solvent or H_2) is formed upon activation of the $[\text{Ir}(\text{cod})(\text{N},\text{P}^*)]^+$ precatalyst with hydrogen (see also section 1.4). The primary steric environment experienced by the incoming alkene, which will coordinate *trans* to phosphorus, is derived from the group R, which points out towards the alkene coordination site. Thus ligands from classes **1** and **2** produce differently shaped coordination pockets. This is illustrated in Figure 20a and

emphasized in 20b, where the complex is viewed along the Ir–P bond i.e. as it would be presented to an approaching alkene. For Class **1** ligands, the phenyl group on the thiazole ring will point out of the page and down. For Class **2** on the other hand, the isopropyl group on the oxazoline moiety will point out of the page and up. The situation can be represented as in Figure 20c, with a simple quadrant model.

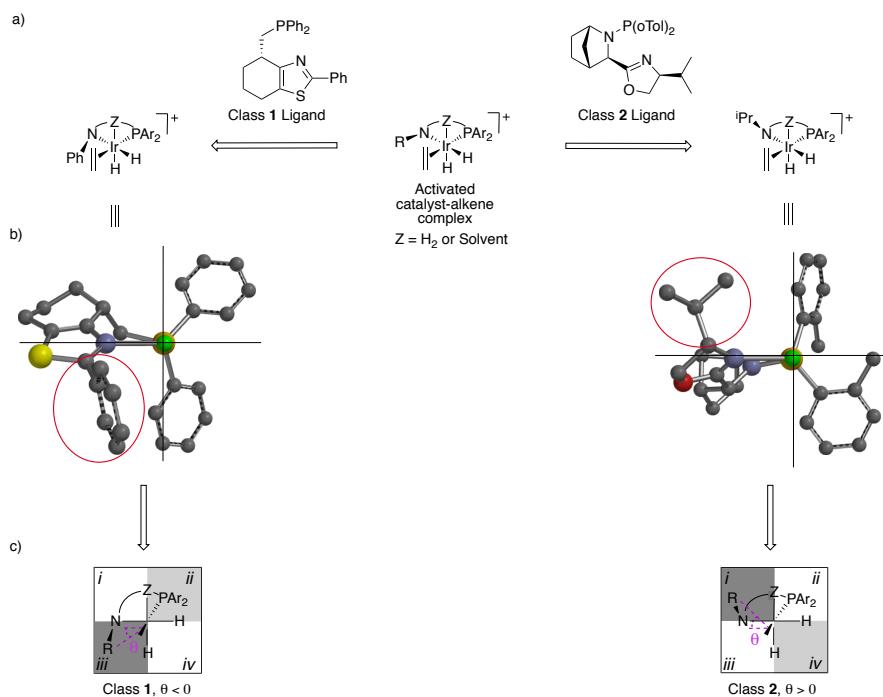


Figure 20 View of the steric environment experienced by an alkene approaching a $[\text{Ir}(\text{H})_2\text{Z}(\text{N},\text{P}^*)]^+$ complex. Z = Solvent or H_2 .

In Figure 20c, the situation is again viewed from the perspective of the incoming alkene. The dark-gray quadrants (*iii* for Class **1** and *i* for Class **2**) represent areas that are occupied by the R groups and the light-gray areas (*ii* for Class **1** and *iv* for Class **2**) are somewhat encumbered by one of the aryl groups on the phosphorus. The other quadrants do not have any significant parts of the ligand pointing towards the incoming alkene and are thus considered to be open, relative to the other quadrants.

For any N,P-ligated complex of this kind, the position of the steric bulk can be determined by measuring the angle (θ) between the N–Ir–P plane and the

center of the R-group, as shown in Figure 20c.⁴¹ The angle is negative for ligands in Class **1** and positive for those in Class **2**, indicating that the quadrant accommodating the R group will be in the lower and upper corner respectively, for catalysts bearing these ligands. The quadrant system can be used to predict the absolute configuration of the products obtained in the asymmetric hydrogenation of trisubstituted alkenes by chiral N,P-ligated iridium catalysts. Since a trisubstituted alkene only has one hydrogen substituent, it will be oriented towards the most crowded quadrant of the chiral pocket in order to minimize steric interactions. This determines which face of the olefin coordinates to Ir and, as the H atoms are added to the coordinated face, catalysts bearing Class **1** and Class **2** ligands give products of opposite absolute configuration upon alkene reduction.

This selectivity model has proven to correctly determine the absolute configuration for a wide range of substrates, including non-functionalized tri- and disubstituted alkenes, α,β -unsaturated esters and various cyclic alkenes. Figure 21 depicts the stereochemical outcome of the hydrogenations of a) cyclic alkenes ($X = \text{NTs}$ or O, $R = \text{aryl}$ or alkyl) and b) β,β -disubstituted α,β -unsaturated esters and acids ($R = \text{aryl}$ or alkyl, $R' = \text{H}$ or alkyl). Isomeric cyclic 2,3-alkenes and 3,4-alkenes are reduced to alkanes of opposite absolute configuration because they coordinate on opposite olefin faces (Figure 21a).^{91,153} Similarly, *E* and *Z* isomeric pairs of β,β -disubstituted unsaturated esters or acids are hydrogenated to products of opposite absolute configuration (Figure 21b).¹⁵⁰

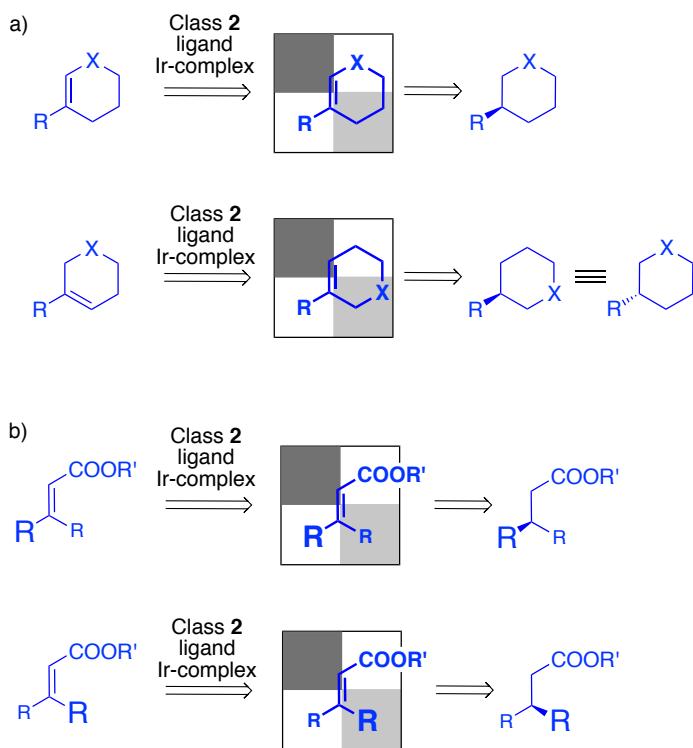


Figure 21 Prediction of the absolute configuration of the product alkanes from hydrogenation of isomeric alkenes using the quadrant-based selectivity model.

Interestingly, although the stereochemical outcome in the hydrogenation of β,β -disubstituted unsaturated esters can be predicted in this fashion, reductions of α,β -disubstituted unsaturated esters gives products of the opposite absolute configuration to what is suggested by the model.¹⁵⁰ A possible explanation for the failure of the model in this instance can be found in the strong polarization of the double bond in this type of substrates. The transfer of an iridium-bound hydride to a coordinated alkene is accompanied by a tilting of the alkene toward the Ir–H bond. This is feasible for β,β -disubstituted unsaturated esters, as depicted in Figure 22a, because the same configuration that allows a hydride to be transferred to the olefin terminus bearing the partial positive charge is the one that tilts the olefin away from the bulk of the ligand R group. Conversely, inserting a α,β -disubstituted

unsaturated ester into the quadrant model results in the situation shown in Figure 22b; here, addition to the β -C is hampered by steric interactions caused by the olefin tilting toward the ligand bulk whereas addition to the α -C is electronically disfavoured. Since the quadrant model relies on steric effects, the failure of the model for α,β -disubstituted substrates indicates that electronic factors dominate.

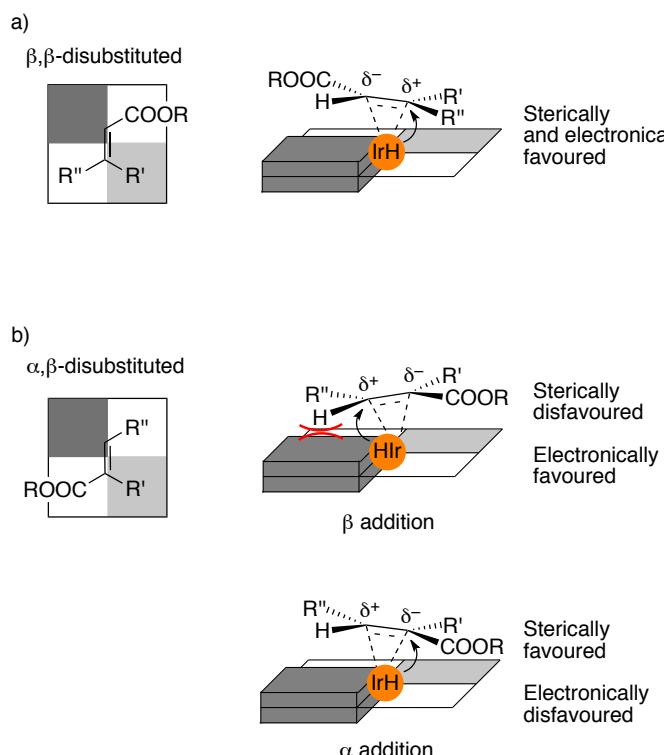


Figure 22 a) Hydride transfer to β,β -disubstituted α,β -unsaturated esters is both sterically and electronically favoured. b) Hydride transfer to α,β -disubstituted α,β -unsaturated esters is either sterically or electronically disfavoured.

The angle θ can also be used to correctly predict the stereochemical outcome of alkene hydrogenation by many other chiral analogues of Crabtree's catalyst.⁴¹ For instance, an Ir center bearing the ligand *ent*-9a⁵³ (Figure 4) has a calculated θ angle of -34.2° , and thus hydrogenates *E*-2-

phenyl-2-butene to (*S*)-2-phenylbutane as the major product (96% ee); whereas it reduces *Z*-2-phenyl-2-butene mainly to (*R*)-2-phenylbutane (87% ee). Correspondingly, when an iridium catalyst bearing the PHOX ligand **5a**^{69,188} (Figure 3, R¹= *o*-Tol and R²= ^tBu) for which θ was calculated to be +31.5°, is used, the product composition is inverted, with *E*-2-phenyl-2-butene producing mainly the (*R*) product (81% ee) and the *Z* alkene giving mainly the (*S*) product (63% ee). The calculated θ-angle, together with the quadrant model, can thus serve as a tool to readily predict the stereochemical outcome of hydrogenation reactions (Figure 23).

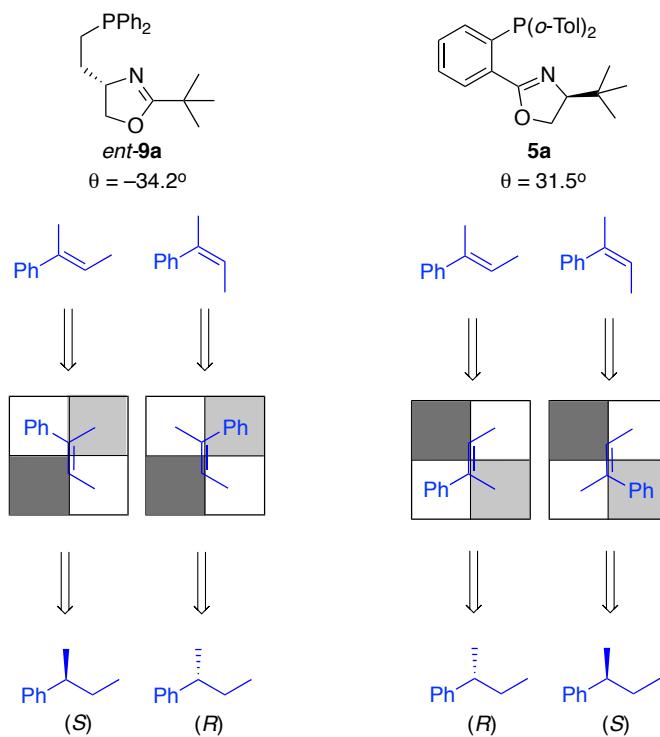


Figure 23 The angle θ (See Figure 20) correctly predicts the absolute configuration of the products of olefin hydrogenation by a wide range of N,P-ligated iridium complexes.

9 Conclusion and Perspective

Both the array of viable ligands for, and the substrate scope of, Ir-catalyzed asymmetric hydrogenation has expanded continuously over the past ten years. N,P-ligated iridium complexes are now not only the state-of-the-art method for the enantioselective reduction of tri-, tetra-, and 1,1-disubstituted non-functionalized alkenes, but also for several other substrates such as allylic alcohols, α,β -unsaturated esters and carboxylic acids, vinyl boronates and vinyl phosphonates. Ir-catalyzed asymmetric hydrogenation have shown great potential in the alkene classes of vinyl fluorides, enol ethers and enamines however effective and general reduction methods are still lacking.

The use of Ir-catalyzed asymmetric hydrogenation in total synthesis and in industry is still limited by the fact that very few, if any, easily prepared ligands have proven effective for a wide range of alkene substrates. As the enantioselectivity obtained using a particular ligand is often strongly substrate-dependent, ligand development should continue to move towards modular ligands prepared by simple and inexpensive, yet flexible, synthetic routes. Furthermore, although low (<0.5 mol%) catalyst loadings are frequently used for non-functionalized substrates, increased substrate functionalization typically lowers the turnover frequency (and thus, in practice, the catalyst loading) of Crabtree-type catalysts. Thus, effective methods for catalyst immobilization and/or re-use are highly desirable.

Although both supercritical CO₂ and propylene carbonate have proven to be useful solvents for Ir-catalyzed asymmetric hydrogenation, no solvent system has yet produced reduction results to rival those obtained in the environmentally unfriendly dichloromethane.

Finally, although a considerable degree of knowledge about the reaction mechanism has been acquired, primarily through quantum chemical calculations, experimental data is still limited.

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References

- (1) (a) Genêt, J.-P. In *Modern reduction methods*; Andersson, P. G., Munslow, I. J., Eds.; Wiley-VCH: Weinheim, **2008** (b) Chi, Y.; Tang, W.; Zhang, X. In *Modern rhodium-catalyzed organic reactions*; Evans, P. A., Ed.; Wiley-VCH: Weinheim, **2005** (c) Kitamura, M.; Noyori, R. In *Ruthenium in Organic Synthesis*; Murahashi, S.-I., Ed.; Wiley-VCH: Weinheim, **2004**.
- (2) (a) Woodmansee, D. H.; Pfaltz, A. *Chem. Commun.* **2011**, 47, 7912 (b) Pàmies, O.; Andersson, P. G.; Diéguez, M. *Chem. Eur. J.* **2010**, 16, 14232 (c) Diesen, J. S.; Andersson, P. G. In *Modern reduction methods*; Andersson, P. G., Munslow, I. J., Eds.; Wiley-VCH: Weinheim, **2008** (d) Roseblade, S. J.; Pfaltz, A. *Acc. Chem. Res.* **2007**, 40, 1402 (e) Cui, X.; Burgess, K. *Chem. Rev.* **2005**, 105, 3272.
- (3) (a) Woodmansee, D.; Pfaltz, A. In *Iridium Catalysis*; Andersson, P. G., Ed.; Springer: Berlin, **2011**; Vol. 34 (b) Ager, D. In *Science of Synthesis, Stereoselective Synthesis*; de Vries, J. G., Molander, G. A., Evans, P. A., Eds.; Georg Thieme Verlag: Stuttgart, **2011**; Vol. 1 (c) Church, T. L.; Andersson, P. G. *Coord. Chem. Rev.* **2008**, 252, 513 (d) Källström, K.; Munslow, I.; Andersson, P. G. *Chem. Eur. J.* **2006**, 12, 3194.
- (4) (a) Wang, D.-S.; Chen, Q.-A.; Lu, S.-M.; Zhou, Y.-G. *Chem. Rev.* **2011**, 112, 2557 (b) Zhou, Y.-G. *Acc. Chem. Res.* **2007**, 40, 1357 (c) Kuwano, R. *Heterocycles* **2008**, 76, 909 (d) Glorius, F. *Org. Biomol. Chem.* **2005**, 3, 4171.
- (5) Dang, T. P.; Kagan, H. B. *J. Chem. Soc. D* **1971**, 481.
- (6) Knowles, W. S.; Sabacky, M. J.; Vineyard, B. D.; Weinkauf, D. J. *J. Am. Chem. Soc.* **1975**, 97, 2567.
- (7) Vineyard, B. D.; Knowles, W. S.; Sabacky, M. J.; Bachman, G. L.; Weinkauf, D. J. *J. Am. Chem. Soc.* **1977**, 99, 5946.
- (8) Knowles, W. S. *J. Chem. Educ.* **1986**, 63, 222.
- (9) Takaya, H.; Ohta, T.; Sayo, N.; Kumabayashi, H.; Akutagawa, S.; Inoue, S.; Kasahara, I.; Noyori, R. *J. Am. Chem. Soc.* **1987**, 109, 1596.

- (10) Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 7932.
- (11) Ohta, T.; Takaya, H.; Kitamura, M.; Nagai, K.; Noyori, R. *J. Org. Chem.* **1987**, *52*, 3174.
- (12) Burk, M. J.; Feaster, J. E.; Harlow, R. L. *Organometallics* **1990**, *9*, 2653.
- (13) Burk, M. J. *J. Am. Chem. Soc.* **1991**, *113*, 8518.
- (14) Burk, M. J.; Stammers, T. A.; Straub, J. A. *Org. Lett.* **1999**, *1*, 387.
- (15) Zhu, G.; Chen, Z.; Zhang, X. *J. Org. Chem.* **1999**, *64*, 6907.
- (16) (a) Kitamura, M.; Tsukamoto, M.; Bessho, Y.; Yoshimura, M.; Kobs, U.; Widhalm, M.; Noyori, R. *J. Am. Chem. Soc.* **2002**, *124*, 6649 (b) Halpern, J. *Science* **1982**, *217*, 401 (c) Brown, J. M. *Chem. Soc. Rev.* **1993**, *22*, 25.
- (17) (a) Ohta, T.; Ikegami, H.; Miyake, T.; Takaya, H. *J. Organomet. Chem.* **1995**, *502*, 169 (b) Inagaki, K.; Ohta, T.; Nozaki, K.; Takaya, H. *J. Organomet. Chem.* **1997**, *531*, 159 (c) Forman, G. S.; Ohkuma, T.; Hems, W. P.; Noyori, R. *Tetrahedron Lett.* **2000**, *41*, 9471.
- (18) (a) Osborn, J. A.; Schrock, R. R. *J. Am. Chem. Soc.* **1971**, *93*, 3089
(b) Schrock, R. R.; Osborn, J. A. *J. Am. Chem. Soc.* **1976**, *98*, 2134.
- (19) Shapley, J. R.; Schrock, R. R.; Osborn, J. A. *J. Am. Chem. Soc.* **1969**, *91*, 2816.
- (20) (a) Crabtree, R. H.; Felkin, H.; Morris, G. E. *J. Organomet. Chem.* **1977**, *141*, 205 (b) Crabtree, R. H.; Gautier, A.; Giordano, G.; Khan, T. *J. Organomet. Chem.* **1977**, *141*, 113.
- (21) Crabtree, R. H.; Felkin, H.; Fillebeen-Khan, T.; Morris, G. E. *J. Organomet. Chem.* **1979**, *168*, 183.
- (22) (a) Meakin, P.; Jesson, J. P.; Tolman, C. A. *J. Am. Chem. Soc.* **1972**, *94*, 3240 (b) Crabtree, R. H.; Demou, P. C.; Eden, D.; Mihelcic, J. M.; Parnell, C. A.; Quirk, J. M.; Morris, G. E. *J. Am. Chem. Soc.* **1982**, *104*, 6994 (c) Halpern, J.; Okamoto, T.; Zakhariev, A. *J. Mol. Catal.* **1977**, *2*, 65.
- (23) (a) Chodosh, D. F.; Crabtree, R. H.; Felkin, H.; Morris, G. E. *J. Organomet. Chem.* **1978**, *161*, C67 (b) Smidt, S. P.; Pfaltz, A.;

Martínez-Viviente, E.; Pregosin, P. S.; Albinati, A. *Organometallics* **2003**, *22*, 1000.

- (24) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336.
- (25) Schnider, P.; Koch, G.; Prétôt, R.; Wang, G.; Bohnen, F. M.; Krüger, C.; Pfaltz, A. *Chem. Eur. J.* **1997**, *3*, 887.
- (26) Lightfoot, A.; Schnider, P.; Pfaltz, A. *Angew. Chem. Int. Ed.* **1998**, *37*, 2897.
- (27) Blackmond, D. G.; Lightfoot, A.; Pfaltz, A.; Rosner, T.; Schnider, P.; Zimmermann, N. *Chirality* **2000**, *12*, 442.
- (28) Smidt, S. P.; Zimmermann, N.; Studer, M.; Pfaltz, A. *Chem. Eur. J.* **2004**, *10*, 4685.
- (29) Nishida, H.; Takada, N.; Yoshimura, M.; Sonoda, T.; Kobayashi, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2600.
- (30) Crabtree, R. *Acc. Chem. Res.* **1979**, *12*, 331.
- (31) Mazet, C.; Smidt, S. P.; Meuwly, M.; Pfaltz, A. *J. Am. Chem. Soc.* **2004**, *126*, 14176.
- (32) Gridnev, I. D.; Imamoto, T. *Acc. Chem. Res.* **2004**, *37*, 633.
- (33) Dietiker, R.; Chen, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 5513.
- (34) Vazquez-Serrano, L. D.; Owens, B. T.; Buriak, J. M. *Inorg. Chim. Acta* **2006**, *359*, 2786.
- (35) Vazquez-Serrano, L. D.; Owens, B. T.; Buriak, J. M. *Chem. Commun.* **2002**, 2518.
- (36) Roseblade, S. J.; Pfaltz, A. *C. R. Chim.* **2007**, *10*, 178.
- (37) Brandt, P.; Hedberg, C.; Andersson, P. G. *Chem. Eur. J.* **2003**, *9*, 339.
- (38) Sun, Y.; Landau, R. N.; Wang, J.; LeBlond, C.; Blackmond, D. G. *J. Am. Chem. Soc.* **1996**, *118*, 1348.
- (39) Perry, M. C.; Cui, X.; Powell, M. T.; Hou, D.-R.; Reibenspies, J. H.; Burgess, K. *J. Am. Chem. Soc.* **2003**, *125*, 113.
- (40) Fan, Y.; Cui, X.; Burgess, K.; Hall, M. B. *J. Am. Chem. Soc.* **2004**, *126*, 16688.
- (41) Church, T. L.; Rasmussen, T.; Andersson, P. G. *Organometallics* **2010**, *29*, 6769.
- (42) Hopmann, K. H.; Bayer, A. *Organometallics* **2011**, *30*, 2483.

- (43) Pfaltz, A.; Blankenstein, J.; Hilgraf, R.; Hörmann, E.; McIntyre, S.; Menges, F.; Schönleber, M.; Smidt, S. P.; Wüstenberg, B.; Zimmermann, N. *Adv. Synth. Catal.* **2003**, *345*, 33.
- (44) Schrems, M. G.; Pfaltz, A. *Chem. Commun.* **2009**, 6210.
- (45) Bell, S.; Wüstenberg, B.; Kaiser, S.; Menges, F.; Netscher, T.; Pfaltz, A. *Science* **2006**, *311*, 642.
- (46) (a) Rovner, E. S.; Wein, A. J. *Eur. Urol.* **2002**, *41*, 6 (b) Wefer, J.; Truss, M. C.; Jonas, U. *World J. Urol.* **2001**, *19*, 312 (c) Hills, C. J.; Winter, S. A.; Balfour, J. A. *Drugs* **1998**, *55*, 813 (d) McRae, A. L.; Brady, K. T. *Expert Opin. Pharmacother.* **2001**, *2*, 883.
- (47) Broene, R. D.; Buchwald, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 12569.
- (48) (a) Noyori, R. *Science* **1990**, *248*, 1194 (b) Takaya, H.; Otha, T.; Noyori, R. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, **1993** (c) Ojima, I.; Clos, N.; Bastos, C. *Tetrahedron* **1989**, *45*, 6901 (d) Tanaka, M.; Ogata, I. *J. Chem. Soc. Chem. Commun.* **1975**, 735a.
- (49) Wang, X.; Guram, A.; Caille, S.; Hu, J.; Preston, J. P.; Ronk, M.; Walker, S. *Org. Lett.* **2011**, *13*, 1881.
- (50) Zimmerman, N. *Dissertation* **2001**, University of Basel.
- (51) Franzke, A.; Pfaltz, A. *Chem. Eur. J.* **2011**, *17*, 4131.
- (52) Bernardinelli, G. H.; Kündig, E. P.; Meier, P.; Pfaltz, A.; Radkowski, K.; Zimmerman, N.; Neuburger-Zehnder, M. *Helv. Chim. Acta* **2001**, *84*, 3233.
- (53) Hou, D.-R.; Reibenspies, J.; Colacot, T. J.; Burgess, K. *Chem. Eur. J.* **2001**, *7*, 5391.
- (54) Liu, D.; Tang, W.; Zhang, X. *Org. Lett.* **2004**, *6*, 513.
- (55) Cozzi, P. G.; Menges, F.; Kaiser, S. *Synlett* **2003**, 833.
- (56) Li, X.; Li, Q.; Wu, X.; Gao, Y.; Xu, D.; Kong, L. *Tetrahedron: Asymmetry* **2007**, *18*, 629.
- (57) Lu, W.-J.; Chen, Y.-W.; Hou, X.-L. *Adv. Synth. Catal.* **2010**, *352*, 103.
- (58) Cozzi, Pier G.; Zimmerman, N.; Hilgraf, R.; Schaffner, S.; Pfaltz, A. *Adv. Synth. Catal.* **2001**, *343*, 450.
- (59) Xu, G.; Gilbertson, S. R. *Tetrahedron Lett.* **2003**, *44*, 953.

opotse 25/10/2013 05:56
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- (60) (a) Trifonova, A.; Diesen, J. S.; Andersson, P. G. *Chem. Eur. J.* **2006**, 12, 2318 (b) Chakka, S. K.; Peters, B. K.; Andersson, P. G.; Maguire, G. E. M.; Kruger, H. G.; Govender, T. *Tetrahedron: Asymmetry* **2010**, 21, 2295.
- (61) Tolstoy, P.; Engman, M.; Paptchikhine, A.; Bergquist, J.; Church, T. L.; Leung, A. W. M.; Andersson, P. G. *J. Am. Chem. Soc.* **2009**, 131, 8855.
- (62) (a) Cheruku, P.; Diesen, J.; Andersson, P. G. *J. Am. Chem. Soc.* **2008**, 130, 5595 (b) Cheruku, P.; Gohil, S.; Andersson, P. G. *Org. Lett.* **2007**, 9, 1659.
- (63) Källström, K.; Munslow, I. J.; Hedberg, C.; Andersson, P. G. *Adv. Synth. Catal.* **2006**, 348, 2575.
- (64) Engman, M.; Diesen, J. S.; Paptchikhine, A.; Andersson, P. G. *J. Am. Chem. Soc.* **2007**, 129, 4536.
- (65) Paptchikhine, A.; Cheruku, P.; Engman, M.; Andersson, P. G. *Chem. Commun.* **2009**, 5996.
- (66) (a) Blankenstein, J.; Pfaltz, A. *Angew. Chem. Int. Ed.* **2001**, 40, 4445
(b) Menges, F.; Pfaltz, A. *Adv. Synth. Catal.* **2002**, 344, 40.
- (67) McIntyre, S.; Hörmann, E.; Menges, F.; Smidt, S. P.; Pfaltz, A. *Adv. Synth. Catal.* **2005**, 347, 282.
- (68) (a) Bayardon, J.; Holz, J.; Schäffner, B.; Andrushko, V.; Verevkin, S.; Preetz, A.; Börner, A. *Angew. Chem. Int. Ed.* **2007**, 46, 5971 (b) Verevkin, S. P.; Emel'yanenko, V. N.; Bayardon, J.; Schäffner, B.; Baumann, W.; Börner, A. *Ind. Eng. Chem. Res.* **2011**, 51, 126.
- (69) Smidt, S. P.; Menges, F.; Pfaltz, A. *Org. Lett.* **2004**, 6, 2023.
- (70) (a) Feringa, B. L. *Acc. Chem. Res.* **2000**, 33, 346 (b) van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Claver, C.; Pàmies, O.; Diéguez, M. *Chem. Rev.* **2010**, 111, 2077 (c) Diéguez, M.; Pàmies, O. *Acc. Chem. Res.* **2009**, 43, 312.
- (71) (a) Hilgraf, R.; Pfaltz, A. *Synlett* **1999**, 1814 (b) Hilgraf, R.; Pfaltz, A. *Adv. Synth. Catal.* **2005**, 347, 61 (c) Schönleber, M.; Hilgraf, R.; Pfaltz, A. *Adv. Synth. Catal.* **2008**, 350, 2033.
- (72) (a) Diéguez, M.; Mazuela, J.; Pàmies, O.; Verendel, J. J.; Andersson, P. G. *J. Am. Chem. Soc.* **2008**, 130, 7208 (b) Mazuela, J.; Norrby, P.-

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O.; Andersson, P. G.; Pàmies, O.; Diéguez, M. *J. Am. Chem. Soc.* **2011**, *133*, 13634.

- (73) (a) Diéguez, M.; Mazuela, J.; Pàmies, O.; Verendel, J. J.; Andersson, P. G. *Chem. Commun.* **2008**, 3888 (b) Mazuela, J.; Verendel, J. J.; Coll, M.; Schäffner, B.; Börner, A.; Andersson, P. G.; Pàmies, O.; Diéguez, M. *J. Am. Chem. Soc.* **2009**, *131*, 12344.
- (74) Nanchen, S.; Pfaltz, A. *Chem. Eur. J.* **2006**, *12*, 4550.
- (75) Bunlaksananusorn, T.; Polborn, K.; Knochel, P. *Angew. Chem. Int. Ed.* **2003**, *42*, 3941.
- (76) Liu, Q.-B.; Zhou, Y.-G. *Tetrahedron Lett.* **2007**, *48*, 2101.
- (77) Drury, W. J.; Zimmermann, N.; Keenan, M.; Hayashi, M.; Kaiser, S.; Goddard, R.; Pfaltz, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 70.
- (78) Zalubovskis, R.; Hörmann, E.; Pfaltz, A.; Moberg, C. *ARKIVOC* **2008**, *14*, 58.
- (79) (a) Kaiser, S.; Smidt, S. P.; Pfaltz, A. *Angew. Chem. Int. Ed.* **2006**, *45*, 5194 (b) Woodmansee, D. H.; Muller, M.-A.; Neuburger, M.; Pfaltz, A. *Chem. Sci.* **2010**, *1*, 72 (c) Wang, A.; Fraga, R. P. A.; Hörmann, E.; Pfaltz, A. *Chem. Asian. J.* **2011**, *6*, 599 (d) Liu, Q.-B.; Yu, C.-B.; Zhou, Y.-G. *Tetrahedron Lett.* **2006**, *47*, 4733.
- (80) Netscher, T. *CHIMIA* **1996**, *50*, 563.
- (81) Verendel, J. J.; Andersson, P. G. *Dalton Trans.* **2007**, 5603.
- (82) Meng, X.; Li, X.; Xu, D. *Tetrahedron: Asymmetry* **2009**, *20*, 1402.
- (83) Chelucci, G.; Marchetti, M.; Malkov, A. V.; Friscourt, F.; Swarbrick, M. E.; Kočovský, P. *Tetrahedron* **2011**, *67*, 5421.
- (84) Li, X.; Kong, L.; Gao, Y.; Wang, X. *Tetrahedron Lett.* **2007**, *48*, 3915.
- (85) Han, Z.; Wang, Z.; Zhang, X.; Ding, K. *Tetrahedron: Asymmetry* **2010**, *21*, 1529.
- (86) Menges, F.; Neuburger, M.; Pfaltz, A. *Org. Lett.* **2002**, *4*, 4713.
- (87) Kaukoranta, P.; Engman, M.; Hedberg, C.; Bergquist, J.; Andersson, P. G. *Adv. Synth. Catal.* **2008**, *350*, 1168.
- (88) Paptchikhine, A.; Itto, K.; Andersson, P. G. *Chem. Commun.* **2011**, *47*, 3989.
- (89) Källström, K.; Hedberg, C.; Brandt, P.; Bayer, A.; Andersson, P. G. *J. Am. Chem. Soc.* **2004**, *126*, 14308.

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- (90) Hedberg, C.; Källström, K.; Brandt, P.; Hansen, L. K.; Andersson, P. G. *J. Am. Chem. Soc.* **2006**, *128*, 2995.
- (91) Verendel, J. J.; Zhou, T.; Li, J.-Q.; Paptchikhine, A.; Lebedev, O.; Andersson, P. G. *J. Am. Chem. Soc.* **2010**, *132*, 8880.
- (92) Mazuela, J.; Paptchikhine, A.; Pàmies, O.; Andersson, P. G.; Diéguez, M. *Chem. Eur. J.* **2010**, *16*, 4567.
- (93) Källström, K.; Andersson, P. G. *Tetrahedron Lett.* **2006**, *47*, 7477.
- (94) Cheruku, P.; Paptchikhine, A.; Ali, M.; Neudörfl, J.-M.; Andersson, P. G. *Org. Biomol. Chem.* **2008**, *6*, 366.
- (95) Li, J.-Q.; Paptchikhine, A.; Govender, T.; Andersson, P. G. *Tetrahedron: Asymmetry* **2010**, *21*, 1328.
- (96) Ilaldinov, I.; Fatkulina, D.; Bucharov, S.; Jackstell, R.; Spannenberg, A.; Beller, M.; Kadyrov, R. *Tetrahedron: Asymmetry* **2011**, *22*, 1936.
- (97) Schenkel, L. B.; Ellman, J. A. *J. Org. Chem.* **2004**, *69*, 1800.
- (98) Metallinos, C.; Van Belle, L. *J. Organomet. Chem.* **2011**, *696*, 141.
- (99) Gschwend, B.; Pugin, B.; Bertogg, A.; Pfaltz, A. *Chem. Eur. J.* **2009**, *15*, 12993.
- (100) Nanchen, S.; Pfaltz, A. *Helv. Chim. Acta* **2006**, *89*, 1559.
- (101) Passays, J.; Ayad, T.; Ratovelomanana-Vidal, V.; Gaumont, A.-C.; Jubault, P.; Leclerc, E. *Tetrahedron: Asymmetry* **2011**, *22*, 562.
- (102) (a) Coll, M.; Pàmies, O.; Diéguez, M. *Chem. Commun.* **2011**, *47*, 9215
(b) Coll, M. *Dissertation* **2011**, Universitat Rovira i Virgili (c) Coll, M.; Pàmies, O.; Diéguez, M. *Adv. Synth. Catal.* **2013**, *355*, 143.
- (103) (a) Rageot, D.; Woodmansee, D. H.; Pugin, B.; Pfaltz, A. *Angew. Chem. Int. Ed.* **2011**, *50*, 9598 (b) Rageot, D.; Pfaltz, A. *Helv. Chim. Acta* **2012**, *95*, 2176.
- (104) Conticello, V. P.; Brard, L.; Giardello, M. A.; Tsuji, Y.; Sabat, M.; Stern, C. L.; Marks, T. J. *J. Am. Chem. Soc.* **1992**, *114*, 2761.
- (105) Giardello, M. A.; Conticello, V. P.; Brard, L.; Gagne, M. R.; Marks, T. J. *J. Am. Chem. Soc.* **1994**, *116*, 10241.
- (106) (a) Cui, X.; Burgess, K. *J. Am. Chem. Soc.* **2003**, *125*, 14212 (b) Cui, X.; Ogle, J. W.; Burgess, K. *Chem. Commun.* **2005**, 672.
- (107) Verendel, J. J.; Andersson, P. G. Unpublished Work.
- (108) Co, T. T.; Kim, T.-J. *Chem. Commun.* **2006**, 3537.

- (109) Troutman, M. V.; Appella, D. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 4916.
- (110) Schrems, M. G.; Neumann, E.; Pfaltz, A. *Angew. Chem. Int. Ed.* **2007**, *46*, 8274.
- (111) (a) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029 (b) Burk, M. J. *Acc. Chem. Res.* **2000**, *33*, 363.
- (112) (a) Zupančič, B.; Mohar, B.; Stephan, M. *Org. Lett.* **2010**, *12*, 3022 (b) Zhang, X.; Huang, K.; Hou, G.; Cao, B.; Zhang, X. *Angew. Chem. Int. Ed.* **2010**, *49*, 6421 (c) Reetz, M. T.; Goossen, L. J.; Meiswinkel, A.; Paetzold, J.; Jensen, J. F. *Org. Lett.* **2003**, *5*, 3099 (d) Qiu, L.; Wu, J.; Chan, S.; Au-Yeung, T. T.-L.; Ji, J.-X.; Guo, R.; Pai, C.-C.; Zhou, Z.; Li, X.; Fan, Q.-H.; Chan, A. S. C. *PNAS* **2004**, *101*, 5815.
- (113) Weise, C. F.; Pischl, M. C.; Pfaltz, A.; Schneider, C. *J. Org. Chem.* **2011**, *77*, 1477.
- (114) Morris, B. D.; Smyth, R. R.; Foster, S. P.; Hoffmann, M. P.; Roelofs, W. L.; Franke, S.; Francke, W. *J. Nat. Prod.* **2004**, *68*, 26.
- (115) Minnaard, A. J.; Feringa, B. L.; Lefort, L.; de Vries, J. G. *Acc. Chem. Res.* **2007**, *40*, 1267.
- (116) (a) Jiang, X.-b.; van den Berg, M.; Minnaard, A. J.; Feringa, B. L.; de Vries, J. G. *Tetrahedron: Asymmetry* **2004**, *15*, 2223 (b) Enthaler, S.; Erre, G.; Junge, K.; Michalik, D.; Spannenberg, A.; Marras, F.; Gladiali, S.; Beller, M. *Tetrahedron: Asymmetry* **2007**, *18*, 1288.
- (117) Hayashi, T.; Kanehira, K.; Kumada, M. *Tetrahedron Lett.* **1981**, *22*, 4417.
- (118) Berens, U., EP1582527A1, **2005**, CAN143:347296.
- (119) (a) Willson, T. M.; Brown, P. J.; Sternbach, D. D.; Henke, B. R. *J. Med. Chem.* **2000**, *43*, 527 (b) Liu, K. G.; Smith, J. S.; Ayscue, A. H.; Henke, B. R.; Lambert, M. H.; Leesnitzer, L. M.; Plunket, K. D.; Willson, T. M.; Sternbach, D. D. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2385 (c) Henke, B. R. *J. Med. Chem.* **2004**, *47*, 4118 (d) Aubert, J.; Clary, L.; Mauvais, P.; Rivier, M.; Thoreau, E.; Boiteau, J.-G., WO2005108352A1, **2005**, CAN143:477743 (e) Shrestha, S.; Bhattachari, B. R.; Cho, H.; Choi, J.-K.; Cho, H. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2728.

- (120) (a) Coppola, G. M.; Schuster, H. F. In *α -Hydroxy Acids in Enantioselective Syntheses*; Wiley-VCH Verlag GmbH & Co. KGaA, **2003** (b) Blaser, H.-U.; Schmidt, E. In *Asymmetric Catalysis on Industrial Scale*; Wiley-VCH Verlag GmbH & Co. KGaA, **2004**.
- (121) Hanessian, S. *Total Synthesis of Natural Products: The Chiron Approach*; Pergamon Press: New York, **1983**.
- (122) (a) Maligres, P. E.; Krska, S. W.; Humphrey, G. R. *Org. Lett.* **2004**, 6, 3147 (b) Cheng, X.; Xie, J.-H.; Li, S.; Zhou, Q.-L. *Adv. Synth. Catal.* **2006**, 348, 1271 (c) Houpis, I. N.; Patterson, L. E.; Alt, C. A.; Rizzo, J. R.; Zhang, T. Y.; Haurez, M. *Org. Lett.* **2005**, 7, 1947 (d) Chen, W.; McCormack, P. J.; Mohammed, K.; Mbafor, W.; Roberts, S. M.; Whittall, J. *Angew. Chem. Int. Ed.* **2007**, 46, 4141.
- (123) Li, S.; Zhu, S.-F.; Xie, J.-H.; Song, S.; Zhang, C.-M.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2010**, 132, 1172.
- (124) Ohta, T.; Miyake, T.; Seido, N.; Kumobayashi, H.; Takaya, H. *J. Org. Chem.* **1995**, 60, 357.
- (125) Zhu, Y.; Fan, Y.; Burgess, K. *J. Am. Chem. Soc.* **2010**, 132, 6249.
- (126) (a) Zhu, Y.; Burgess, K. *Adv. Synth. Catal.* **2008**, 350, 979 (b) Zhu, Y.; Burgess, K. *RSC Adv.* **2012**, 2, 4728.
- (127) (a) Kuwano, R.; Okuda, S.; Ito, Y. *J. Org. Chem.* **1998**, 63, 3499 (b) Tanaka, M.; Watanabe, Y.; Mitsudo, T.; Yasunori, Y.; Takegami, Y. *Chem. Lett.* **1974**, 3, 137.
- (128) (a) Xie, J.-H.; Zhu, S.-F.; Zhou, Q.-L. *Chem. Rev.* **2010**, 111, 1713 (b) Church, T. L.; Andersson, P. G. In *Chiral amine synthesis: Methods, Developments and Applications*; Nugent, T. C., Ed.; Wiley-VCH: Weinheim, **2010**.
- (129) (a) Cheruku, P.; Church, T. L.; Trifonova, A.; Wartmann, T.; Andersson, P. G. *Tetrahedron Lett.* **2008**, 49, 7290 (b) Baeza, A.; Pfaltz, A. *Chem. Eur. J.* **2009**, 15, 2266.
- (130) (a) Leleti, R. R.; Hu, B.; Prashad, M.; Repič, O. *Tetrahedron Lett.* **2007**, 48, 8505 (b) Reddy, L. R.; Hu, B.; Prashad, M.; Prasad, K. *Angew. Chem. Int. Ed.* **2009**, 48, 172 (c) Bonrath, W.; Eckhardt, J.-F.; Eggersdorfer, M. L.; Hinze, R.; Hoelderich, W. F., WO2008098774A1, **2008**, CAN149:290163.

opotse 25/10/2013 06:27

Deleted: -a.

- (131) Takaya, H.; Ohta, T.; Inoue, S.; Tokunaga, M.; Kitamura, M.; R., N. *Org. Synth. Coll. Vol.* **1998**, 9, 169.
- (132) Wang, A.; Wüstenberg, B.; Pfaltz, A. *Angew. Chem. Int. Ed.* **2008**, 47, 2298.
- (133) (a) Zhou, J.; Burgess, K. *Angew. Chem. Int. Ed.* **2007**, 46, 1129 (b) Zhou, J.; Zhu, Y.; Burgess, K. *Org. Lett.* **2007**, 9, 1391.
- (134) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, 93, 1307.
- (135) Interestingly, switching from alcohol to ester also reverses the catalyst selectivity.
- (136) Zhu, Y.; Burgess, K. *Acc. Chem. Res.* **2012**, 45, 1623.
- (137) Zhu, Y.; Khumsubdee, S.; Schaefer, A.; Burgess, K. *J. Org. Chem.* **2011**, 76, 7449.
- (138) Zhu, Y.; Burgess, K. *J. Am. Chem. Soc.* **2008**, 130, 8894.
- (139) Zhu, Y.; Loudet, A.; Burgess, K. *Org. Lett.* **2010**, 12, 4392.
- (140) Zhao, J.; Burgess, K. *J. Am. Chem. Soc.* **2009**, 131, 13236.
- (141) Zhao, J.; Burgess, K. *Org. Lett.* **2009**, 11, 2053.
- (142) Brown, J. M. *Angew. Chem. Int. Ed. Engl.* **1987**, 26, 190.
- (143) (a) Pai, C.-C.; Lin, C.-W.; Lin, C.-C.; Chen, C.-C.; Chan, A. S. C.; Wong, W. T. *J. Am. Chem. Soc.* **2000**, 122, 11513 (b) Scrivanti, A.; Bovo, S.; Ciappa, A.; Matteoli, U. *Tetrahedron Lett.* **2006**, 47, 9261 (c) Uemura, T.; Zhang, X.; Matsumura, K.; Sayo, N.; Kumobayashi, H.; Ohta, T.; Nozaki, K.; Takaya, H. *J. Org. Chem.* **1996**, 61, 5510 (d) Cheng, X.; Zhang, Q.; Xie, J.-H.; Wang, L.-X.; Zhou, Q.-L. *Angew. Chem. Int. Ed.* **2005**, 44, 1118.
- (144) (a) Brown, J. M.; Parker, D. *J. Org. Chem.* **1982**, 47, 2722 (b) Hoen, R.; Boogers, J. A. F.; Bernsmann, H.; Minnaard, A. J.; Meetsma, A.; Tiemersma-Wegman, T. D.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L. *Angew. Chem. Int. Ed.* **2005**, 44, 4209.
- (145) Li, S.; Zhu, S.-F.; Zhang, C.-M.; Song, S.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2008**, 130, 8584.
- (146) Zhang, Y.; Han, Z.; Li, F.; Ding, K.; Zhang, A. *Chem. Commun.* **2010**, 46, 156.
- (147) Yang, S.; Zhu, S.-F.; Zhang, C.-M.; Song, S.; Yu, Y.-B.; Li, S.; Zhou, Q.-L. *Tetrahedron* **2012**, 68, 5172.

- (148) Song, S.; Zhu, S.-F.; Yang, S.; Li, S.; Zhou, Q.-L. *Angew. Chem. Int. Ed.* **2012**, *51*, 2708.
- (149) Zhu, S.-F.; Yu, Y.-B.; Li, S.; Wang, L.-X.; Zhou, Q.-L. *Angew. Chem. Int. Ed.* **2012**, *51*, 8872.
- (150) Li, J.-Q.; Quan, X.; Andersson, P. G. *Chem. Eur. J.* **2012**, *18*, 10609.
- (151) Newton, S.; Ley, S. V.; Arcé, E. C.; Grainger, D. M. *Adv. Synth. Catal.* **2012**, *354*, 1805.
- (152) Tian, F.; Yao, D.; Liu, Y.; Xie, F.; Zhang, W. *Adv. Synth. Catal.* **2010**, *352*, 1841.
- (153) Verendel, J. J.; Li, J.-Q.; Quan, X.; Peters, B.; Zhou, T.; Gautun, O. R.; Govender, T.; Andersson, P. G. *Chem. Eur. J.* **2012**, *18*, 6507.
- (154) Lu, W.-J.; Hou, X.-L. *Adv. Synth. Catal.* **2009**, *351*, 1224.
- (155) (a) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815 (b) Shang, J.; Han, Z.; Li, Y.; Wang, Z.; Ding, K. *Chem. Commun.* **2012**, *48*, 5172.
- (156) (a) Ohkuma, T.; Ooka, H.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 10417 (b) Ohkuma, T.; Koizumi, M.; Doucet, H.; Pham, T.; Kozawa, M.; Murata, K.; Katayama, E.; Yokozawa, T.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1998**, *120*, 13529 (c) Burk, M. J.; Hems, W.; Herzberg, D.; Malan, C.; Zanotti-Gerosa, A. *Org. Lett.* **2000**, *2*, 4173.
- (157) Mashima, K.; Akutagawa, T.; Zhang, X.; Takaya, H.; Taketomi, T.; Kumobayashi, H.; Akutagawa, S. *J. Organomet. Chem.* **1992**, *428*, 213.
- (158) Fehr, M. J.; Consiglio, G.; Scalzone, M.; Schmid, R. *J. Org. Chem.* **1999**, *64*, 5768.
- (159) Ohshima, T.; Tadaoka, H.; Hori, K.; Sayo, N.; Mashima, K. *Chem. Eur. J.* **2008**, *14*, 2060.
- (160) Tsuchiya, Y.; Hamashima, Y.; Sodeoka, M. *Org. Lett.* **2006**, *8*, 4851.
- (161) (a) Martin, N. J. A.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 13368 (b) Tuttle, J. B.; Ouellet, S. G.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 12662.
- (162) (a) Thorey, C.; Bouquillon, S.; Helimi, A.; Hénin, F.; Muzart, J. *Eur. J. Org. Chem.* **2002**, *2002*, 2151 (b) Fogassy, G.; Tungler, A.; Lévai, A.;

- Tóth, G. *J. Mol. Catal. A: Chem.* **2002**, *179*, 101 (c) McIntosh, A. I.; Watson, D. J.; Burton, J. W.; Lambert, R. M. *J. Am. Chem. Soc.* **2006**, *128*, 7329.
- (163) Lu, S.-M.; Bolm, C. *Chem. Eur. J.* **2008**, *14*, 7513.
- (164) Lu, S.-M.; Bolm, C. *Angew. Chem. Int. Ed.* **2008**, *47*, 8920.
- (165) Lu, W.-J.; Chen, Y.-W.; Hou, X.-L. *Angew. Chem. Int. Ed.* **2008**, *47*, 10133.
- (166) Maurer, F.; Huch, V.; Ullrich, A.; Kazmaier, U. *J. Org. Chem.* **2012**, *77*, 5139.
- (167) Wang, X.; Han, Z.; Wang, Z.; Ding, K. *Angew. Chem. Int. Ed.* **2012**, *51*, 936.
- (168) (a) Meindertsma, A. F.; Pollard, M. M.; Feringa, B. L.; de Vries, J. G.; Minnaard, A. J. *Tetrahedron: Asymmetry* **2007**, *18*, 2849 (b) Zhang, W.; Zhang, X. *J. Org. Chem.* **2006**, *72*, 1020.
- (169) (a) Chávez, M. Á.; Vargas, S.; Suárez, A.; Álvarez, E.; Pizzano, A. *Adv. Synth. Catal.* **2011**, *353*, 2775 (b) Qiu, M.; Hu, X.-P.; Huang, J.-D.; Wang, D.-Y.; Deng, J.; Yu, S.-B.; Duan, Z.-C.; Zheng, Z. *Adv. Synth. Catal.* **2008**, *350*, 2683 (c) Gridnev, I. D.; Yasutake, M.; Imamoto, T.; Beletskaya, I. P. *PNAS* **2004**, *101*, 5385 (d) Wang, D.-Y.; Hu, X.-P.; Huang, J.-D.; Deng, J.; Yu, S.-B.; Duan, Z.-C.; Xu, X.-F.; Zheng, Z. *Angew. Chem. Int. Ed.* **2007**, *46*, 7810 (e) Rubio, M.; Vargas, S.; Suárez, A.; Álvarez, E.; Pizzano, A. *Chem. Eur. J.* **2007**, *13*, 1821 (f) Rubio, M.; Suarez, A.; Alvarez, E.; Pizzano, A. *Chem. Commun.* **2005**, 628 (g) Grassert, I.; Schmidt, U.; Ziegler, S.; Fischer, C.; Oehme, G. *Tetrahedron: Asymmetry* **1998**, *9*, 4193.
- (170) (a) Beghetto, V.; Matteoli, U.; Scrivanti, A. *Chem. Commun.* **2000**, 155 (b) Henry, J. C.; Lavergne, D.; Ratovelomanana-Vidal, V.; Genêt, J. P.; Beletskaya, I. P.; Dolgina, T. M. *Tetrahedron Lett.* **1998**, *39*, 3473 (c) Goulioukina, N. S.; Dolgina, T. y. M.; Beletskaya, I. P.; Henry, J.-C.; Lavergne, D.; Ratovelomanana-Vidal, V.; Genêt, J.-P. *Tetrahedron: Asymmetry* **2001**, *12*, 319.
- (171) Wang, D.-Y.; Hu, X.-P.; Deng, J.; Yu, S.-B.; Duan, Z.-C.; Zheng, Z. *J. Org. Chem.* **2009**, *74*, 4408.

- (172) Goulioukina, N. S.; Dolgina, T. y. M.; Bondarenko, G. N.; Beletskaya, I. P.; Ilyin, M. M.; Davankov, V. A.; Pfaltz, A. *Tetrahedron: Asymmetry* **2003**, *14*, 1397.
- (173) Cheruku, P.; Paptchikhine, A.; Church, T. L.; Andersson, P. G. *J. Am. Chem. Soc.* **2009**, *131*, 8285.
- (174) Kadyrov, R.; Selke, R.; Giernoth, R.; Bargon, J. *Synthesis* **1999**, *1056*.
- (175) Huang, Y.; Berthiol, F.; Stegink, B.; Pollard, M. M.; Minnaard, A. J. *Adv. Synth. Catal.* **2009**, *351*, 1423.
- (176) Duan, Z.-C.; Hu, X.-P.; Wang, D.-Y.; Huang, J.-D.; Yu, S.-B.; Deng, J.; Zheng, Z. *Adv. Synth. Catal.* **2008**, *350*, 1979.
- (177) (a) Kadyrov, R.; Holz, J.; Schäffner, B.; Zayas, O.; Almena, J.; Börner, A. *Tetrahedron: Asymmetry* **2008**, *19*, 1189 (b) Doherty, S.; Knight, J. G.; Bell, A. L.; El-Menabawey, S.; Vogels, C. M.; Decken, A.; Westcott, S. A. *Tetrahedron: Asymmetry* **2009**, *20*, 1437.
- (178) Morgan, J. B.; Morken, J. P. *J. Am. Chem. Soc.* **2004**, *126*, 15338.
- (179) Ganić, A.; Pfaltz, A. *Chem. Eur. J.* **2012**, *18*, 6724.
- (180) Gazić Smilović, I.; Casas-Arcé, E.; Roseblade, S. J.; Nettekoven, U.; Zanotti-Gerosa, A.; Kovačević, M.; Časar, Z. *Angew. Chem. Int. Ed.* **2012**, *51*, 1014.
- (181) Moran, W. J.; Morken, J. P. *Org. Lett.* **2006**, *8*, 2413.
- (182) Ueda, M.; Saitoh, A.; Miyaura, N. *J. Organomet. Chem.* **2002**, *642*, 145.
- (183) Saburi, M.; Shao, L.; Sakurai, T.; Uchida, Y. *Tetrahedron Lett.* **1992**, *33*, 7877.
- (184) Krska, S. W.; Mitten, J. V.; Dormer, P. G.; Mowrey, D.; Machrouhi, F.; Sun, Y.; Nelson, T. D. *Tetrahedron* **2009**, *65*, 8987.
- (185) (a) Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063 (b) Jones, G. R.; Landais, Y. *Tetrahedron* **1996**, *52*, 7599 (c) Bains, W.; Tacke, R. *Curr. Opin. Drug Discovery Dev.* **2003**, *6*, 526.
- (186) Lautens, M.; Zhang, C.; Crudden, C. M. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 232.
- (187) Trifonova, A.; Diesen, J. S.; Chapman, C. J.; Andersson, P. G. *Org. Lett.* **2004**, *6*, 3825.
- (188) Smidt, S. P.; Menges, F.; Pfaltz, A. *Org. Lett.* **2004**, *6*, 3653.

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