

Edited by Paul T. Anastas

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Volume 7: Green Synthesis

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WILEY-VCH Verlag GmbH & Co. KGaA

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Handbook of Green Chemistry – Green Processes

Vol. 7: Green Synthesis

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Set III (3 volumes):

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Set (12 volumes):

ISBN: 978-3-527-31404-1

eBook ISBN: 978-3-527-62869-8

The cover picture contains images from Corbis
Digital Stock (Dictionary) and PhotoDisc, Inc./Getty
Images (Flak containing a blue liquid).

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Library of Congress Card No.: applied for

British Library Cataloguing-in-Publication Data

A catalogue record for this book is available from the British Library.

**Bibliographic information published by
the Deutsche Nationalbibliothek**

The Deutsche Nationalbibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data are available on the Internet at <http://dnb.d-nb.de>.

© 2012 Wiley-VCH Verlag & Co. KGaA,
Boschstr. 12, 69469 Weinheim, Germany

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Composition Thomson Digital, Noida, India

Printing and Binding betz-druck GmbH,
Darmstadt

Cover Design Adam Design, Weinheim

Printed in the Federal Republic of Germany

Printed on acid-free paper

ISBN: 978-3-527-32602-0

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Preface

Ever since the synthesis of urea by Friedrich Wöhler near two centuries ago, organic synthesis has become the foundation of modern medicines for human health, produced new agrochemicals to boost world food supply, created various synthetic fibers for daily usages, and bestowed a colorful enchantment through synthetic dyes. In spite of these great achievements, the general features of organic syntheses have been, by and large, unchanged over a century: e.g., non-renewable feedstock, batch reactor, and refluxing. In addition, classical organic syntheses often produce stoichiometric amount of waste, use organic solvents and sometimes dangerous reagents, require extensive protection-deprotection of functional groups, need pre-functionalized starting materials, and involve multi-step operations, which resulted in low efficiency in resource utilization and led to various concerns due to waste generations. While, in the past, the primary goal of organic syntheses is “to get the target product”, the sustainability of chemical synthesis becomes a more and more important issue. This volume of Green Syntheses illustrated some examples to address this issue ranging from starting materials, reaction design, choice of solvent, energy input, to reactor design. The chapter by Trost describes the general principle of greener synthesis; the chapter by Behr shows examples of using renewable feedstocks for making chemical products; the chapter by Horvath describes the use of alternative solvents for organic synthesis; the chapters by Zhu, Hoffman and Watts describe methods of reducing synthetic steps by running multi-component reactions, avoiding protecting groups, and in flow respectively; the chapters by Ackermann and Li show examples of direct conversion of C–H bonds; the chapters by Varma and Yoshida presents alternative energy input in chemical reactions through light and electricity; the chapters by Tao and Akiyama give examples of using enzymes and organo catalysts for synthetic purposes; and finally the chapter by Andraos uses computation methods to evaluate the relative efficiency of different synthetic routes. We hope that these examples will provide food-for-thought for further innovations in developing greener syntheses.

Montreal, April 2012

C-J Li

1

Atom Economy: a Challenge for Enhanced Synthetic Efficiency

Barry M. Trost

The design of structure for function is the major task for helping to solve problems ranging from material science to human health. The demands and expectations for extremely high levels of performance frequently increases the molecular complexity needed. Thus, a major goal must be to allow the synthesis of such complex molecular arrays in a time-effective manner. The strategic design for the synthesis of complex molecules derives from the available basic tools – the reactions, reagents, and catalysts. Although some might think we have a pretty full toolbox, the reality is that, in most likelihood, only a very small fraction of the true total number of reactions possible is known today. Hence a great unknown awaits us, and chipping away at those unknown processes presents a great opportunity for discovery that will undoubtedly change the practice of the science.

In undertaking a program of discovery for new processes, the characteristics that defines the requirements for these new reactions/reagents/catalysts must be appreciated. In 1983, selectivity was noted as key to evolving reasonable efficiency in the synthesis of complex molecules [1]. The issue of chemoselectivity, defined as discriminating reactivity among various bond types in a molecule without employing activating or blocking groups, was placed at the top of the list! There is no question that problems of chemoselectivity are the single biggest factor in creating synthetic inefficiencies. More than 25 years later, the primacy of this selectivity issue was still noted [2]. It is so pervasive in the science that it undoubtedly will remain the greatest challenge for a long time to come. The second issue is regioselectivity, which is defined as orientational control in the joining of a reagent with an unsymmetrical functional group. Controlling stereochemistry constitutes the third major challenge. There are two fundamentally different issues embodied within this topic – controlling relative stereochemistry or diastereoselectivity and absolute stereochemistry or enantioselectivity.

By and large, selectivity was equated with efficiency. However, just a little further thought makes us realize that we are missing one key aspect of efficiency by focusing only on selectivity, that is, by ignoring an obvious but neglected aspect, which is, simply put, how much of what you put into your pot ends up in your product? In 1991, this fundamental and critical issue was explicitly recognized and referred to as “atom economy” [3]. In 1992, the *E* factor was introduced, which also

provided a quantitative metric to evaluate the degree of atom economy [4]. Atom economy, which basically emphasizes maximal use of raw materials and minimization of waste, has become one of the 12 principles of Green Chemistry [5]. Making synthetic chemistry more “environmentally benign by design” has become a mantra.

The ideal reaction is one in which 100% of what is introduced into a reaction ends up as product and, if anything else is required, it is needed only catalytically. Thus, a bimolecular reaction should be a single addition and a unimolecular reaction should be an isomerization. Such processes are clearly known and heavily used, such as a Diels–Alder reaction and Claisen and Cope rearrangements. However, such processes constitute only a very small fraction of our toolbox. In the late 1980s, we began a deliberate program to invent processes that theoretically are 100% atom economic. I note this goal as theoretical since to achieve it fully requires the yield to be quantitative, which rarely occurs, but at least the possibility does exist. A reaction of the type $A + B \rightarrow C + D$ suffers from the fact that it theoretically cannot be 100% atom economic and also suffers from the issue of yields typically being less than quantitative. This overview reports the evolution of one of our programs for semi-rationally inventing atom economic processes based upon catalysis with ruthenium complexes.

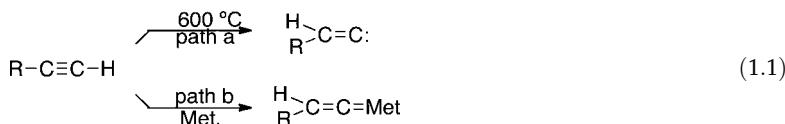
1.1

Vinylidenes

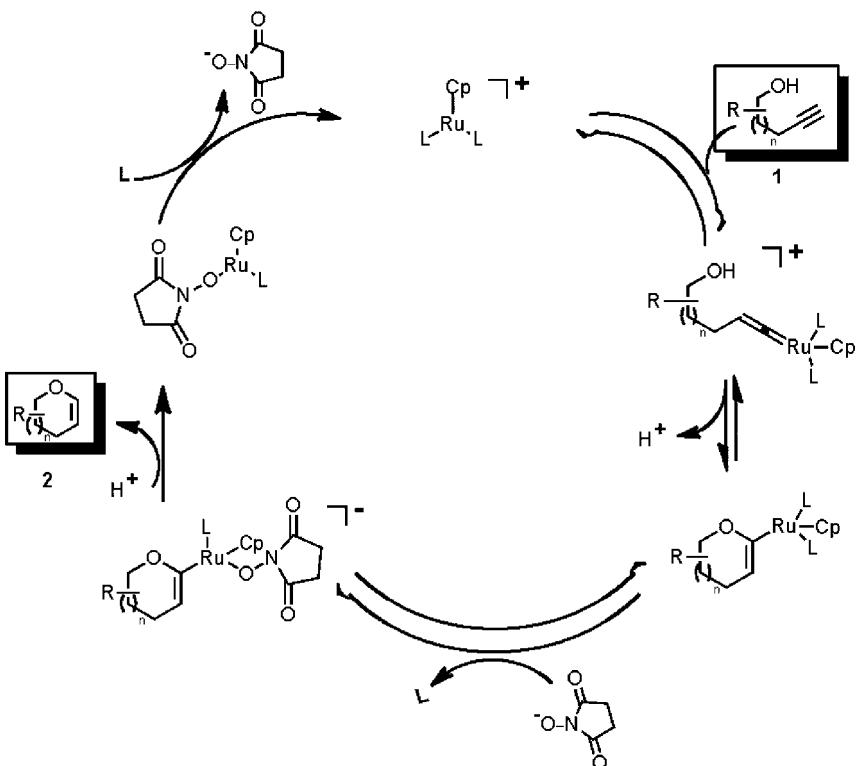
1.1.1

Cycloisomerization of Hydroxyalkynes

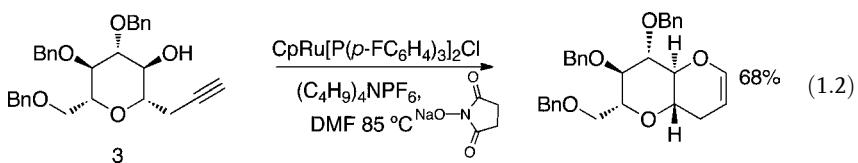
The formation of reactive intermediates provides possible opportunities for new reaction design. An attractive highly reactive intermediate, carbenes, which demonstrate numerous useful synthetic pathways, most notably by addition to alkenes and alkynes and also insertion into X–H bonds, where X is both carbon and heteroatoms, suffers from problems associated with their accessibility. Undoubtedly, the most useful class of precursor is the diazo compounds, whose safety problems restrict their use. For the specific case of vinylidenes, an attractive possibility is a terminal alkyne which is isomeric with a vinylidene. Although the thermolysis appears to effect this transformation (Equation 1.1, path a), the extraordinarily high temperatures required make the prospect of a transition metal-catalyzed version (Equation 1.1, path b) attractive. The early studies of Werner [6] using Rh and Bruce and co-workers [7] using Ru proved the facility with which such species would form; however, the studies focused on the formation and isolation of the vinylidene–metal complexes and their stoichiometric reactions.



Based on these studies and choosing to focus on Ru for practical considerations such as cost, we envisioned a possible catalytic cycle shown in Scheme 1.1, wherein an ω -alkynyl alcohol 1 would cycloisomerize to the dihydropyran. Although McDonald's group has pioneered the use of molybdenum- and tungsten-mediated processes, several issues related to chemoselectivity and the common need for stoichiometric amounts make the development of other catalysts for such processes desirable [8]. Using $CpRu(PAr_3)_2Cl$ -based complexes, less electron-rich arylphosphine ligands such as *m*- or *p*-fluorophenylphosphines promote such processes (Equation 1.2) [9].

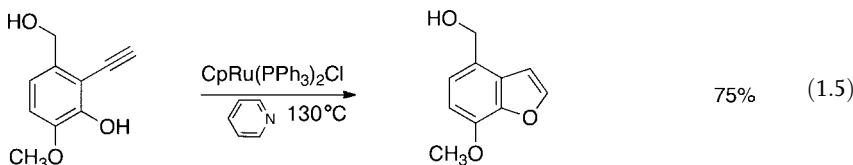
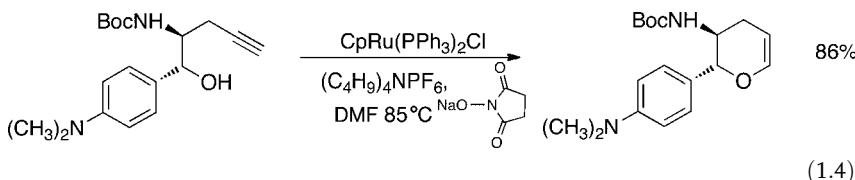
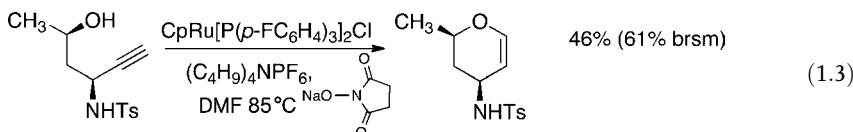


Scheme 1.1 Cycloisomerization of hydroxyalkenes.

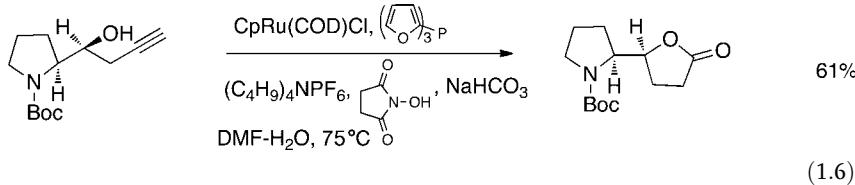


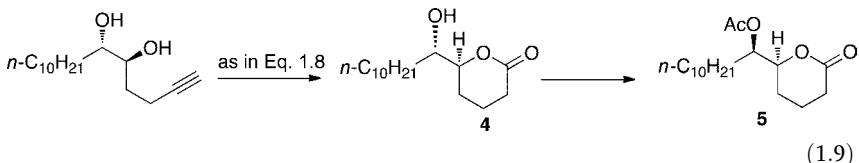
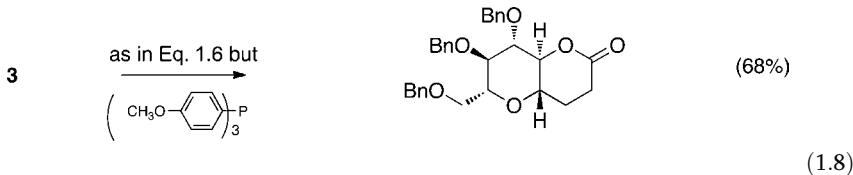
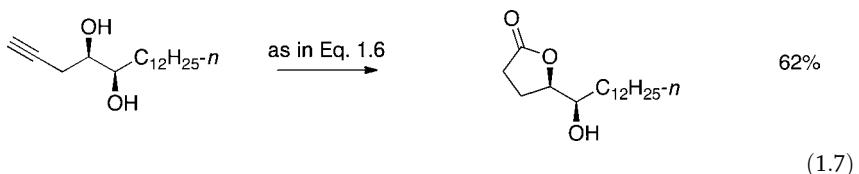
While the presence of propargylic hydroxy groups has proven problematic (see below), the presence of a propargylic *N*-tosylamido group is tolerated (Equation 1.3).

Interestingly, the presence of a bis-homopropargylic secondary amide does not lead to insertion into the N–H (as happens with a tungsten catalyst [8c]) competing with formation of the dihydropyran as shown in Equation 1.4 [10]. This reaction extends to the insertion into a phenolic OH to form benzofurans (Equation 1.5). In this case, the presence of an amine such as *n*-butylamine or pyridine appears to be required [11]. It should be noted that insertion into the benzylic OH to form the pyran system does not compete.

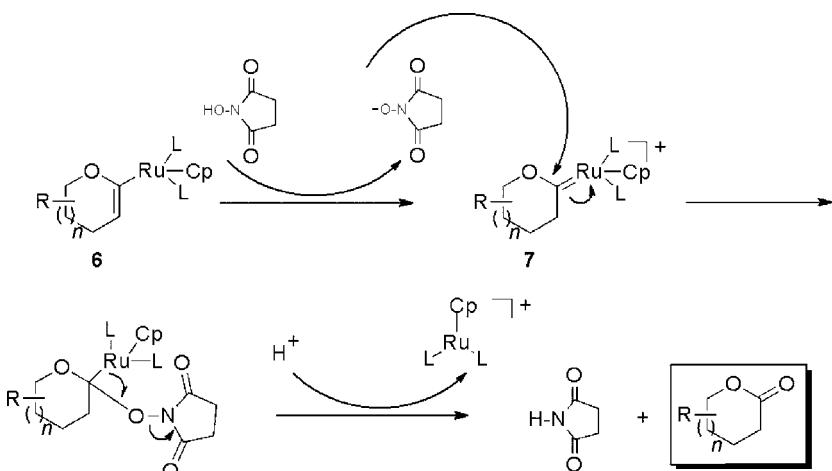


Interestingly, making the reaction less basic, increasing the amount of N-hydroxysuccinimide to 3 equiv., and changing the phosphine reorients the course of the reaction to an oxidative cyclization to form lactones. For example, γ -butyrolactones form fairly readily from homopropargylic alcohols (Equation 1.6) and even preferentially when the possibility for forming the thermodynamically more stable six-membered ring lactones could occur (Equation 1.7) [12]. The synthesis of the butyrolactones is optimized using trifurylphosphine as the ligand. Nevertheless, bis-homopropargyl alcohols also undergo oxidative cyclization. Thus, the homopropargyl alcohol 3 in Equation 1.2 under the conditions of Equation 1.6 except that the phosphine ligand is changed to tris(*p*-methoxyphenyl) phosphine gives the δ -lactone 4 in 65% yield (Equation 1.8) [9]. As expected, competing a six- versus a seven-membered ring leads exclusively to cyclization to form the six-membered ring (Equation 1.9).





After esterification of alcohol **4** with inversion of configuration, the oviposition attractant pheromone of the mosquito *sCulex pipiens fatigans* **5** is formed. The stereochemistry of this sequence originated from the asymmetric dihydroxylation of the *trans*-alkene. Although the oxidative cyclization is significantly less atom economic than the cycloisomerization, since it requires stoichiometric amounts of *N*-hydroxysuccinimide, the recyclability of the resultant succinimide mitigates this defect somewhat. This switch in pathway as a function of pH can be understood by the sequence depicted in Scheme 1.2. In particular, the initially formed vinyl Ru complex **6**, whose coordination with the anion derived from hydroxysuccinimide, thus facilitating protonation to the enol ether, preferentially protonates to form the carbene complex **7**. Now the electrophilic carbene carbon undergoes nucleophilic addition of this same anion, leading ultimately to fragmentation with generation of the lactone.

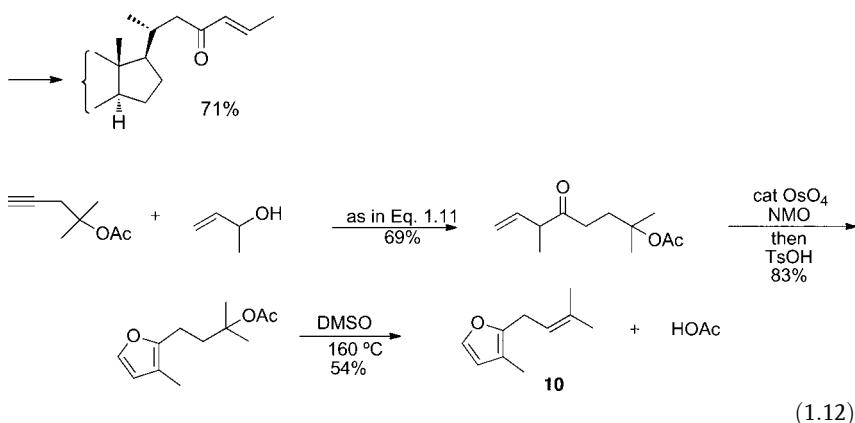
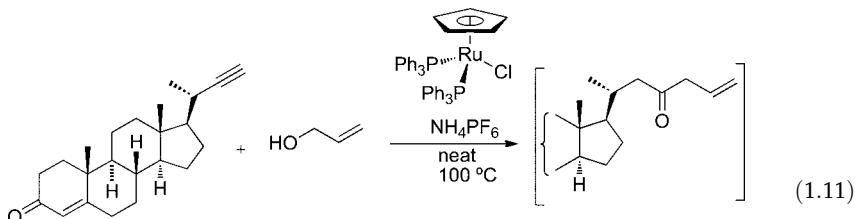
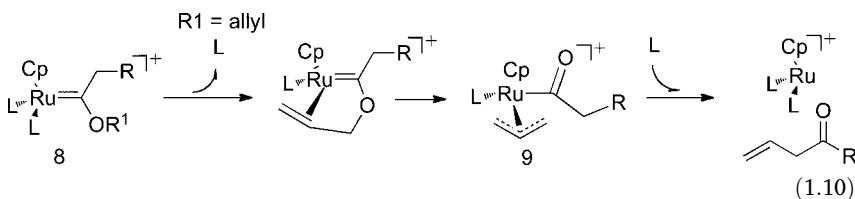


Scheme 1.2 Mechanistic rationale for oxidative cyclization.

1.1.2

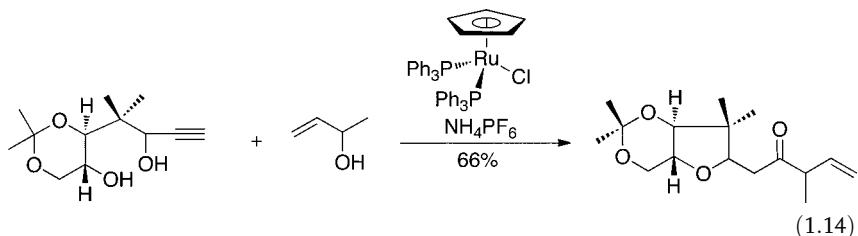
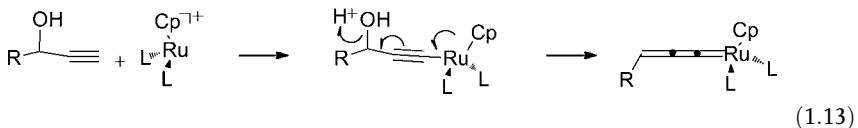
Reconstitutive Condensation

The intermolecular variant of the O–H insertion reaction gets stuck at the stage of the initial adduct **8**. We envisioned that if $R^1 = \text{allyl}$, coordination of the double bond to the metal would initiate a Claisen-type process to form the π -allylruthenium complex **9**, whose reductive elimination would form the allyl ketone starting from terminal alkynes and allyl alcohols (Equation 1.10). Gratifyingly, this prediction was fully realized as shown in Equation 1.11 [13]. A tertiary ester does not undergo elimination under these reaction conditions (Equation 1.12). Dihydroxylation of the double bond and subsequent acidification effect cyclodehydration to form furans in two overall “steps.” Subsequent elimination of the elements of acetic acid completes a synthesis of rosefuran **10**, one of the most prized fragrances [14].



With terminal alkynes bearing propargylic alcohols, formation of the vinylidene is complicated by the competitive formation of the allenylidene as shown in Equation 1.13.

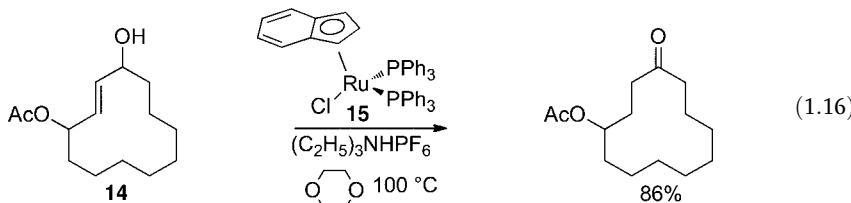
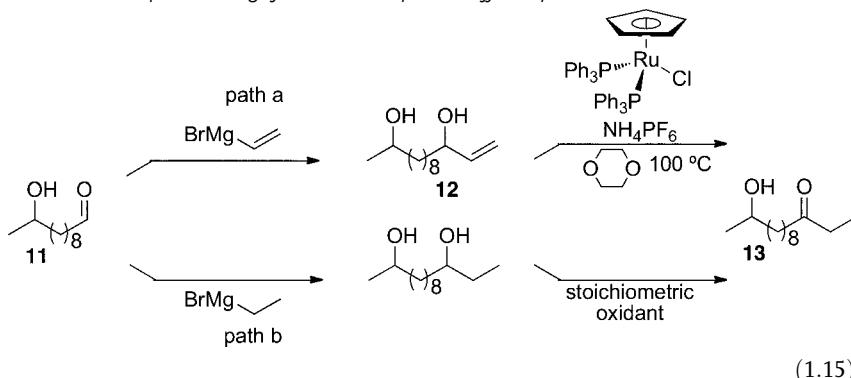
In the case of a substrate bearing a second hydroxyl group, the allenylidene can undergo nucleophilic attack at the γ -carbon to re-form a vinylidene [15]. In such an event, the newly formed vinylidene can then undergo the reconstitutive condensation shown in Equation 1.14 [16]. This reaction provides access to the spiroketal of calyculin A, a nanomolar inhibitor of serine/threonine phosphatases.



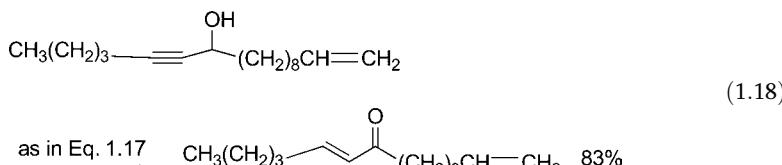
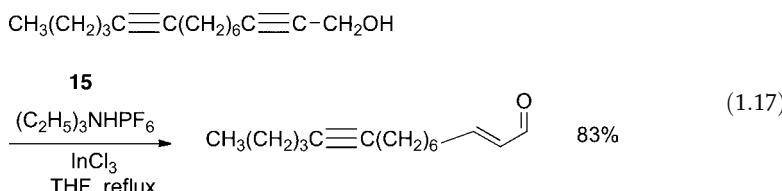
1.2 Redox Isomerization

1.2.1 Allyl Alcohols

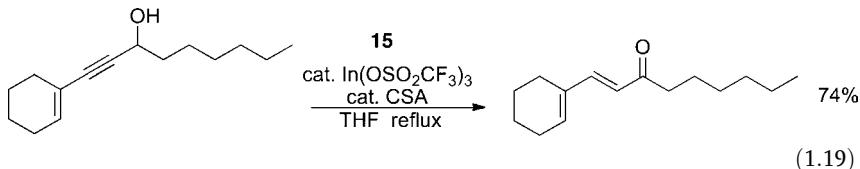
In the reconstitutive addition in which we used the allyl alcohol as both reactant and solvent, we noted that propanal was detected as a by-product. This observation led us to consider the use of CpRuL_2Cl as a catalyst for redox isomerization of allyl alcohols in general. Indeed, subjecting allyl alcohol **12** to the standard Ru catalyst effects chemoselective isomerization to the saturated ketone **13** (Equation 1.15) [17]. Normally starting from aldehyde **11**, the typical route to saturated ketone **13**, path b, involves a stoichiometric oxidant for one step. Furthermore, there is also a chemoselectivity issue in this example, thereby further enhancing the inefficiency by requiring a protecting group operation. By simply switching to an unsaturated organometallic for the first step, a stoichiometric oxidant is avoided, as is any need for protecting groups, thereby improving the overall atom economy. For more substituted double bonds, the (indenyl)Ru(PPh_3)₂Cl catalyst, which can slip from an η^5 to an η^3 complex, allows a decrease in steric hindrance in addition to being accompanied by the formation of a coordinatively unsaturated ruthenium which improves the reactivity. Thus, the 1,2-disubstituted alkene substrate **14** (Equation 1.16) undergoes redox isomerization within 3 h, whereas such substrates barely react at all with the $\text{CpRu}(\text{PPh}_3)_2\text{Cl}$ complex.



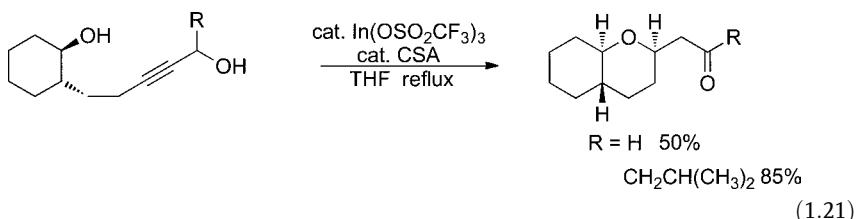
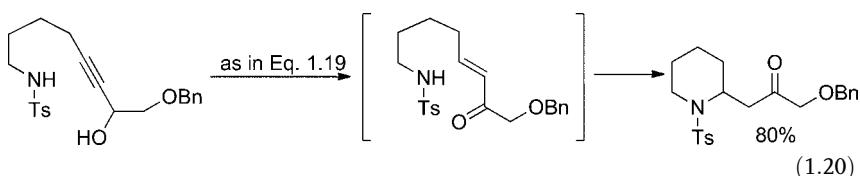
Application of this catalyst system to propargyl alcohols provides α,β -unsaturated aldehydes (Equation 1.17) and ketones (Equation 1.18) [18]. The ease of accessibility of the substrates by simple addition of terminal alkynes to aldehydes followed by this redox isomerization constitutes a highly chemoselective and atom economic strategy to these unsaturated carbonyl compounds. The chemoselectivity problems of the direct aldol condensation and the poor atom economy of olefination methods make this new strategy the most efficient and reliable approach to these units.



A significant improvement in the catalyst adds further utility to this strategy. Using 1–5 mol% of indenyl complex 15 along with indium triflate and camphorsulfonic acid (CSA) as cocatalysts, the redox isomerization in Equation 1.19 was completed in 20 min compared with 1.5 h under the indium chloride cocatalyst conditions.



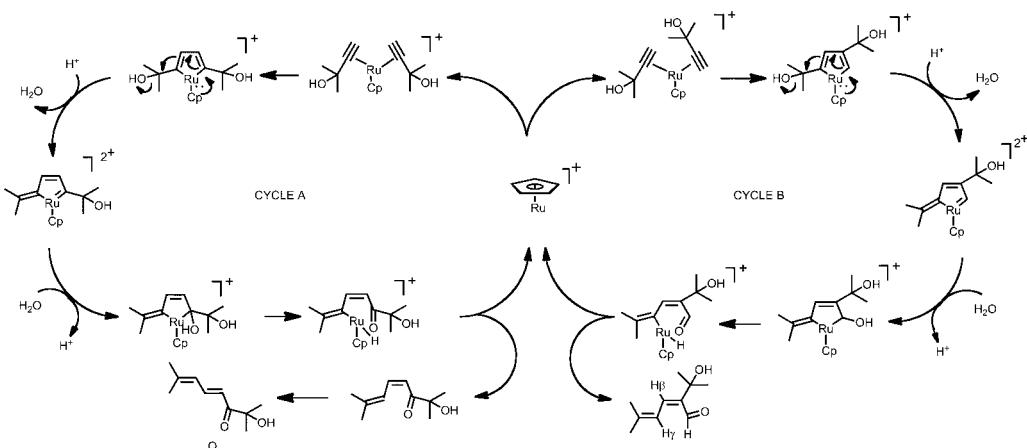
The formation of a good Michael acceptor in this process opens the avenue to the formation of cyclic compounds by the appropriate juxtaposition of a suitable Michael donor. For example, five- and six-membered ring *N*-heterocycles bearing a Boc or arylsulfonyl group on the nitrogen cyclize directly under the conditions of the redox isomerization, as shown for a piperidine in Equation 1.20 [19]. Similarly, a propargyl alcohol bearing a secondary hydroxyl group three or four carbons away directly form tetrahydrofurans or -pyrans as in Equation 1.21 [20]. Overall, each of these processes is simply an isomerization.



1.3 Ruthenacyclopentadiene Intermediates

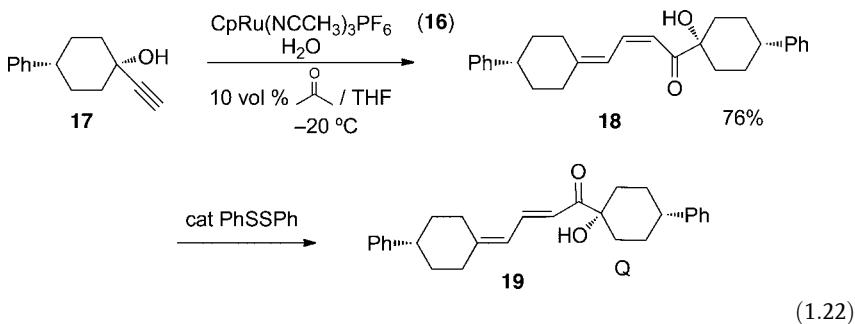
The strong forward donation–back donation of electrons (i.e., the Chatt model) between alkynes and ruthenium makes such a bond a very good ligand for Ru. Hence it is not surprising that reactions involving ruthenacyclopentadienes as intermediates, notably in the trimerization of alkynes to benzenes, occur readily. Intercepting the ruthenacyclopentadiene prior to its reaction with an additional alkyne, however, is rather rare. A unique juxtaposition of functionality occurs when a propargyl alcohol is the alkyne partner which allows such a diversion as shown in Scheme 1.3.

In this homocoupling, two orientations are possible, head-to-head as in cycle A and head-to-tail as in cycle B. Indeed, exposing the propargyl alcohol **17** to the trisacetonitrile complex **16** [21], whose ease of dissociation of this ligand makes it a functional equivalent of a highly coordinatively unsaturated ruthenium, effects coupling even



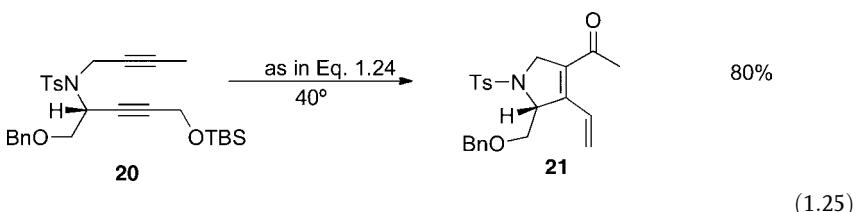
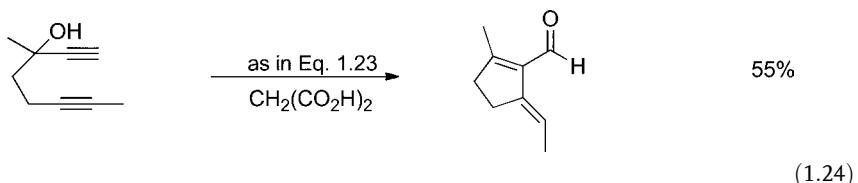
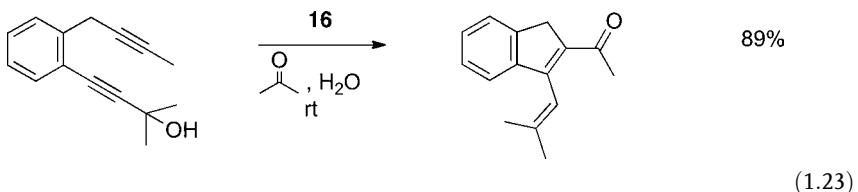
Scheme 1.3 Coupling of propargyl alcohols.

at -20°C (Equation 1.22) [22]. In agreement with the catalytic cycle A in Scheme 1.3, the disubstituted alkene double bond is the thermodynamically unstable *Z*-isomer **18**. Exposure to a catalytic amount of phenylthio radical from diphenyl disulfide quantitatively isomerizes the (*Z*)-alkene into the thermodynamically more stable *E*-isomer **19**. This highly atom economic process, which functions as a superior surrogate for an aldol condensation, (1) employs much more accessible starting materials such as the propargylic alcohol **17**, which is available in one step, (2) requires no protecting groups, and (3) provides equal access to the (*E*)- or (*Z*)-alkene **18**.

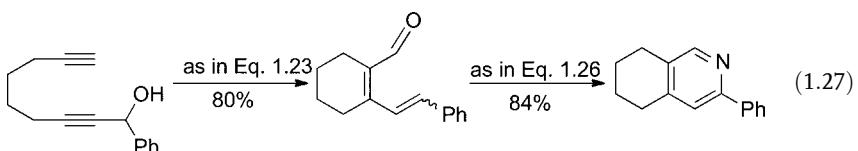
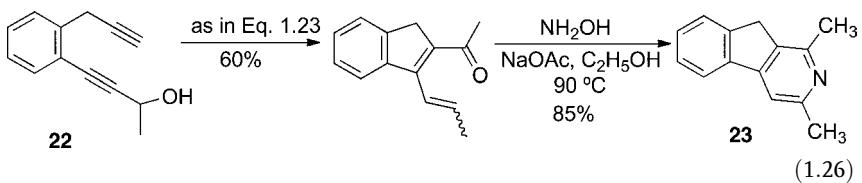


In principle only one propargylic alcohol is required as a reaction partner; the second alkyne need not be. However, such a prospect in an intermolecular fashion is clouded by the self-coupling of the propargylic alcohol. Tethering a simple alkyne to a propargylic alcohol as in Equation 1.23 should obviate this problem, as indeed it does [23]. The placement of the propargylic alcohol on the tether is also tolerated and generates a cross-conjugated system as in Equation 1.24. This process does not require a tertiary alcohol or a free alcohol. Thus, subjection of the silyl ether **20** to the same conditions with malonic acid as a cocatalyst but at 40°C gave the dihydropyrrole

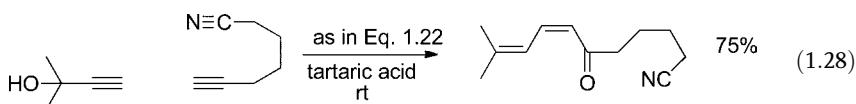
21 (Equation 1.25), which served as a synthetic intermediate for the synthesis of kainic acid, a neuroexcitatory amine acid.



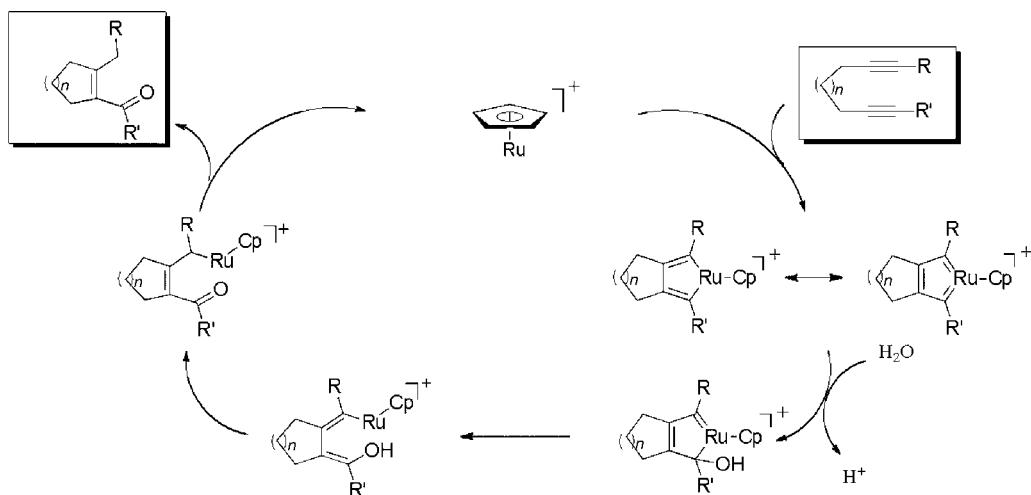
A most useful application of this process is the invention of a highly atom economic synthesis of pyridines, wherein the only stoichiometric by-product is water. Cycloisomerization of diyne **22** followed by reaction with hydroxylamine provides the tricyclic pyridine **23** with only water as the stoichiometric by-product (Equation 1.26) [24]. The Ru-catalyzed cycloisomerization of propargyl alcohols can also generate six membered rings, which then form tetrahydroisoquinolines as shown in Equation 1.27.



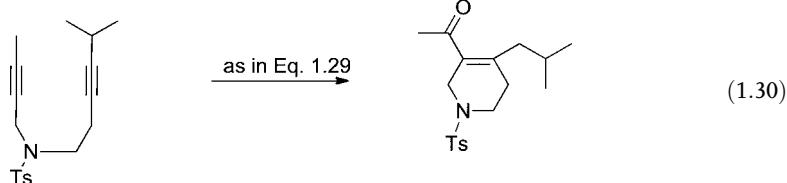
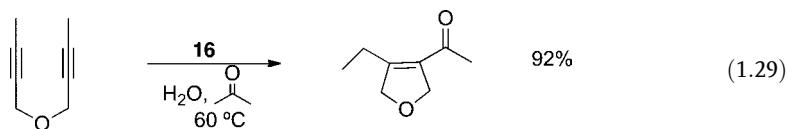
An intermolecular cross-coupling requires that the simple alkyne be a better binder to Ru than the propargyl alcohol. ω -Cyanoalkynes meet that requirement. Thus, 6-cyano-1-hexyne generates the crossed coupled product in 75% yield (Equation 1.28) [25].



The ability of water to attack the ruthenium–carbon double bond suggested that the ruthenacyclopentadiene might add water as depicted in Scheme 1.4. Remarkably, heating a tethered diyne in aqueous acetone to 60 °C in the presence of the trisacetonitrile complex **16** gave a nearly quantitative yield of the hydrated cyclization product as depicted in Equation 1.29 [26]. Unsymmetrical diynes showed exquisite regioselectivity wherein the water attacked the least sterically hindered alkyne carbon (Equation 1.30).

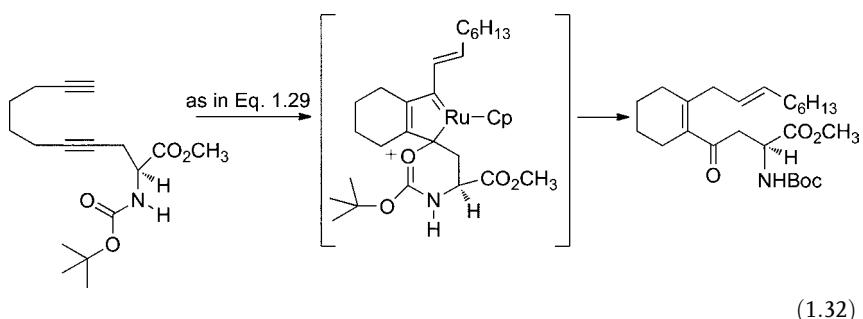
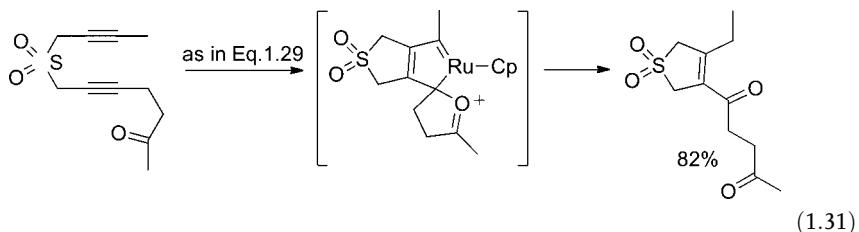


Scheme 1.4 Hydrative diyne cyclization.



In substrates bearing suitable functionality that could lead to internal nucleophilic attack by an oxygen, even a carbonyl oxygen, excellent regioselectivity may occur. Equation 1.31 illustrates an example of a ketone playing such a role [27]. Such an effect can even lead to hydration at the more hindered alkyne as shown in

Equation 1.32 [28]. Thus, nicely functionalized five- and six-membered carbocyclic and heterocyclic rings derive simply by an atom economic addition of water to a suitable diyne. The ease of accessing such diarynes makes this methodology particularly attractive.

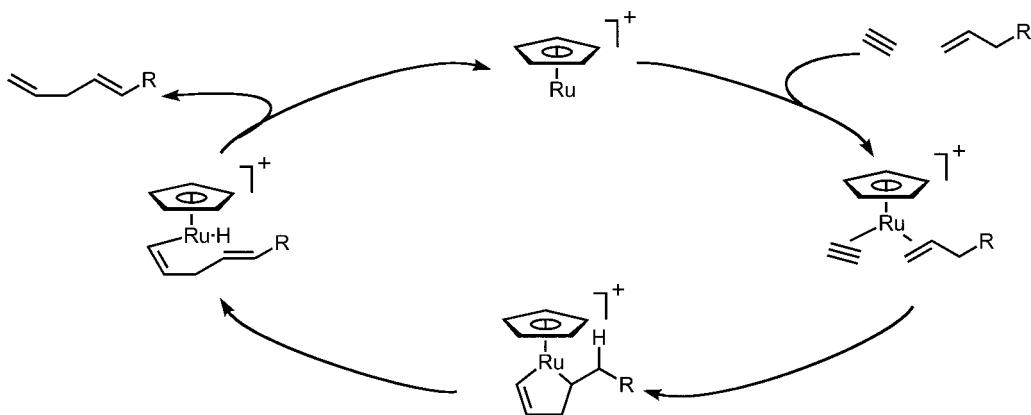


1.4 Ruthenacyclopentene Intermediates

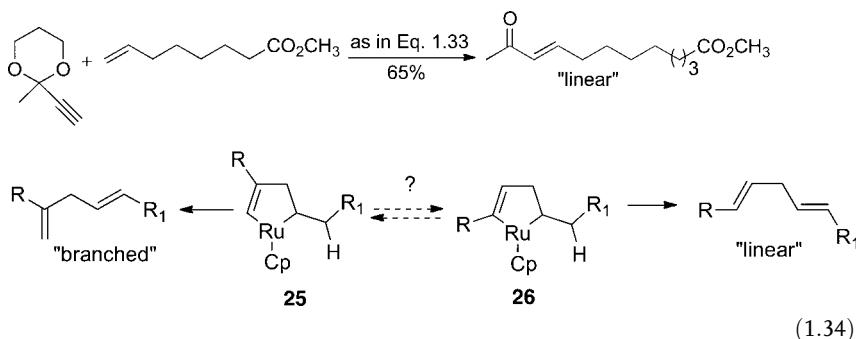
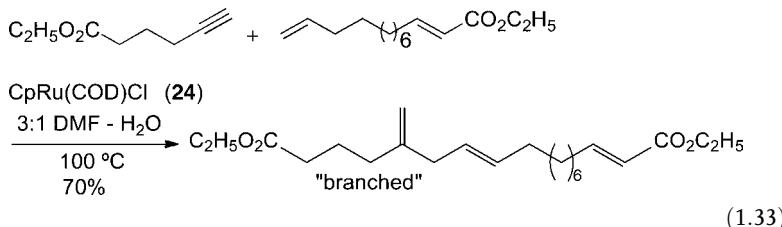
1.4.1 Intermolecular Alkene-Alkyne Coupling

Given the preferential complexation of an alkyne compared with an alkene to ruthenium, the notion that alkene–alkyne coupling (Scheme 1.5) would occur seemed remote. However, to the extent that formation of the ruthenacyclopentene occurs, it can become irreversible because there exists a low-energy pathway by which it can further react, namely β -hydrogen elimination. A final reductive elimination then completes a catalytic cycle wherein an alkene and an alkyne couple to form a 1,4-diene.

Using $\text{CpRu}(\text{cod})\text{Cl}$ (24) as a precursor of a highly coordinatively unsaturated ruthenium, we examined simple unhindered alkenes and alkynes such as that shown in Equation 1.33 to give the coupled 1,4-diene favoring C–C bond formation at the internal carbon, creating a “branched” product [29]. On the other hand, on making the propargylic position sterically demanding as shown in Equation 1.34, this regioselectivity reversed to generate the “linear” product. This can be understood by kinetic preference for the formation of ruthenacyclopentene 25 when steric hindrance is minimal; however, with a sterically bulky R group, ruthenacycle 26

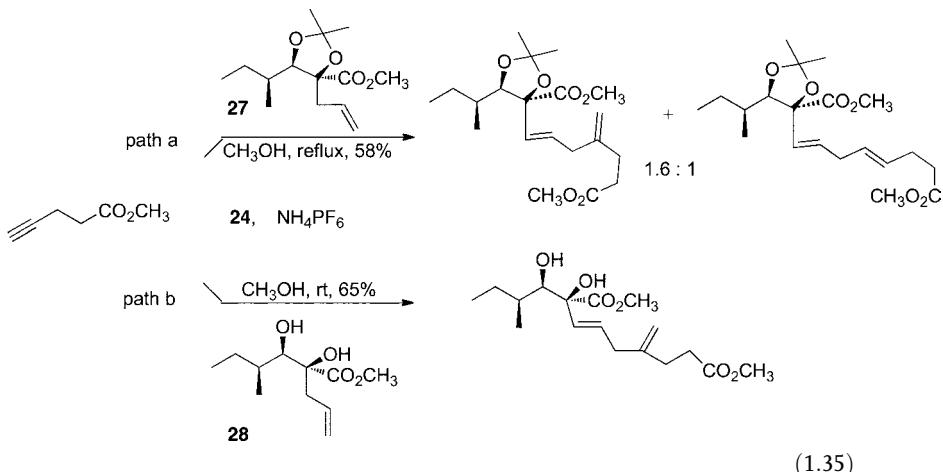
**Scheme 1.5** Alkene–alkyne coupling.

becomes favored due to minimizing steric strain in forming the C–C bond and then leading to the linear isomer.

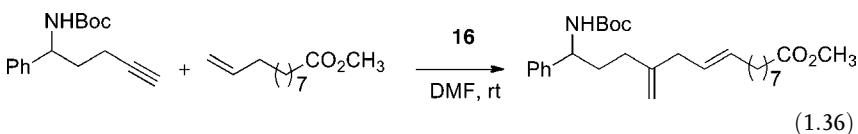


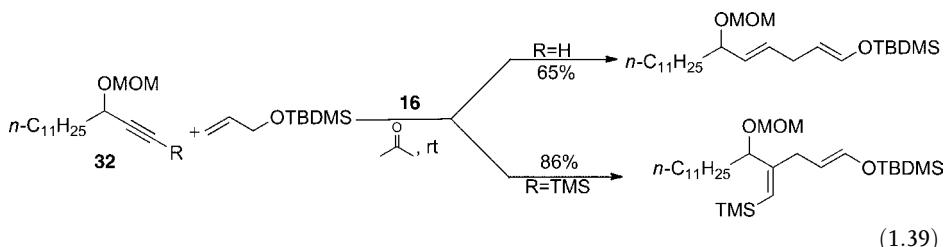
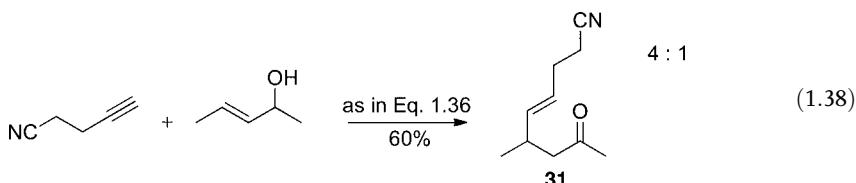
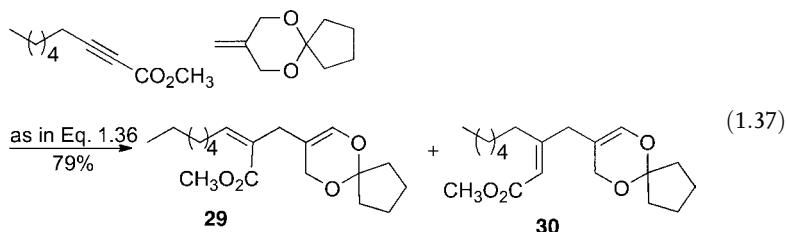
This issue of regioselectivity can be tuned by proper design of the substrate. Using an unhindered alkyne, *tert*-butyl 4-pentynoate, and acetonide 27, the reaction required heating and generated a 1.6:1 mixture of the branched and linear isomers (Equation 1.35) [30]. Using the free diol 28 not only allows the reaction to proceed at room temperature but also generates the branched product almost exclusively. Curiously, this alkene–alkyne coupling prefers the totally unprotected substrate – a reverse from the

normal expectation and thus enhancing the atom economy of the process because of its high chemoselectivity even in the presence of obviously potentially coordinating functionality such as hydroxyl groups.

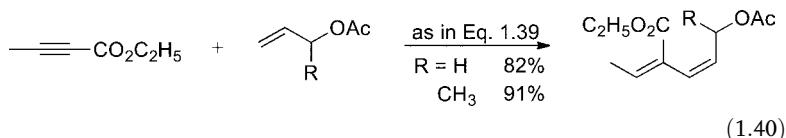


The tris(acetonitrile)Ru(II) complex **16** proved to be a more effective catalyst [31]. Alcohol solvents are incompatible with this more coordinatively unsaturated complex but water can be tolerated. Excellent solvents include methylene chloride, 1,2-dichloroethane, acetone, and dimethylformamide (DMF). Thus, the alkene–alkyne coupling in Equation 1.36 proceeds at room temperature in DMF. Good selectivity for branched products is typically observed [32], whereas typically only monosubstituted alkenes react, which imparts excellent chemoselectivity; however, it is a limitation of scope. With this more active catalyst, 1,1- and 1,2-disubstituted alkenes nicely participate (Equations 1.37 and 1.38). Interestingly, with propiolate acceptors, the predominant regioisomer is the α -isomer **29**. In the latter case, the direct product is the ketone **31** via tautomerization of the initial enol [33]. If the silyl ether is employed, the intermediate enol silyl ether may be isolated [34]. As typically observed with alkyne partners bearing propargylic alcohol functionality such as **32**, the linear product dominates as shown in Equation 1.39. Similar results are obtained with the amides of allylamine [35]. If R is a silyl group, the exclusive regioisomer formed occurs distal to the TMS group (i.e., proximal to the propargyl alcohol substituent). On the other hand, for less bulky groups such as simple internal alkynes, a regioselectivity favoring C–C bond formation distal to the hydroxyl group is observed [36].





In the reaction of allyl esters and ethers bearing monosubstituted alkenes with propargyl esters, (*Z,Z*)-1,3-dienes result – the only such cases observed (Equation 1.40) [37].

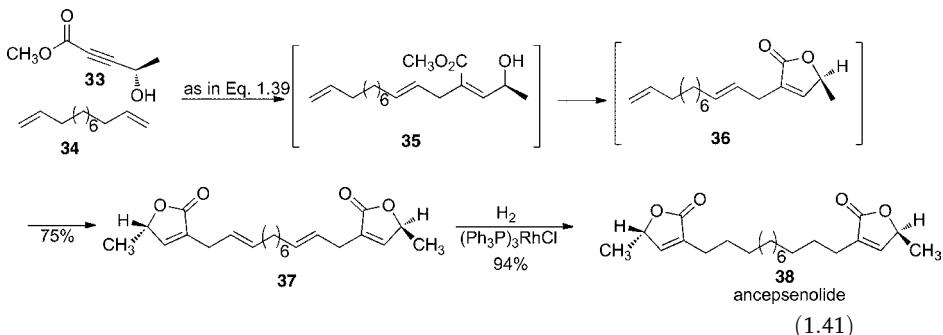


1.4.2

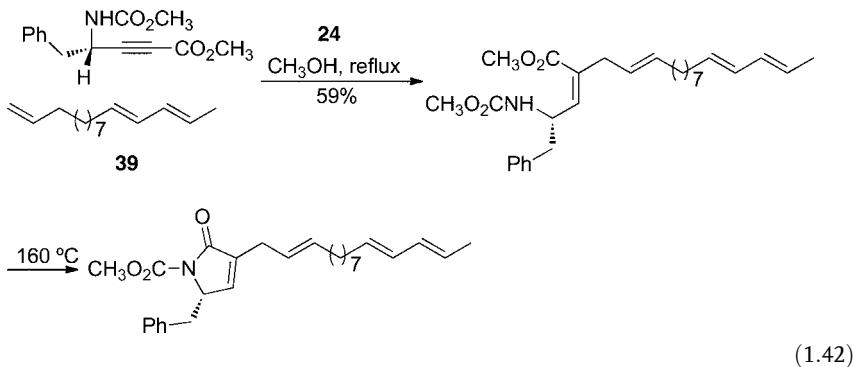
Butenolide Formation and Related Reactions

Using a γ -hydroxyalkynoate combines two effects – the unusual contra-electronic regioselectivity leading to α -attack and a cyclization evolving from the juxtaposition of the hydroxyl and ester functionalities. Thus, as shown in Equation 1.41, the initial adduct 35 between hydroxyalkynoate 33 and alkene 34 spontaneously lactonizes upon its formation to form butenolide 36. The presence of a second monosubstituted double bond proceeds equally facilely in like fashion such that the bis-annulated product 37 is directly formed [38]. Chemoselective addition of the less sterically

hindered double bond then provides (+)-ancepsenolide. This butenolide annulation of alkenes has proven valuable for the synthesis of numerous acetogenins [39].

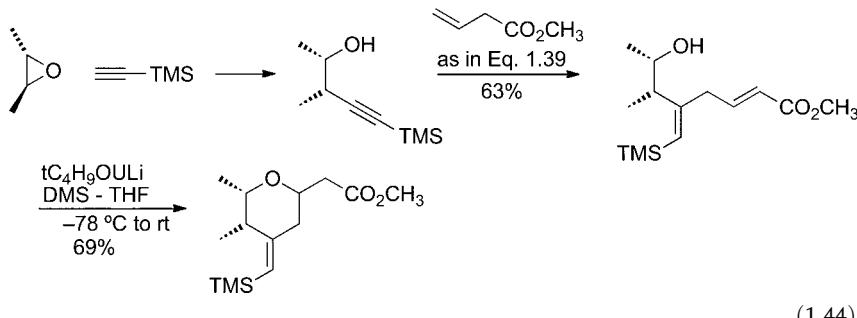
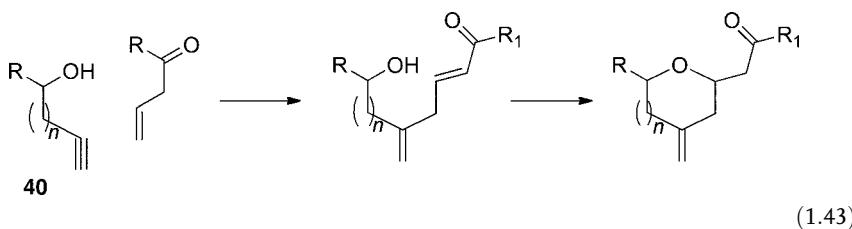


Replacing the hydroxyl group with an amido group provides access to the corresponding nitrogen heterocycles, the 3-pyrrolinones [40]. The example in Equation 1.42 highlights the chemoselectivity of the process since normally the diene moiety of substrate **39** is considered the more reactive functionality.

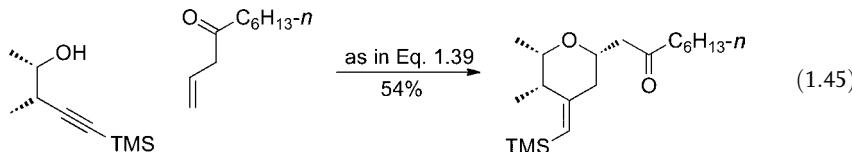


1.4.3 Pyran Formation

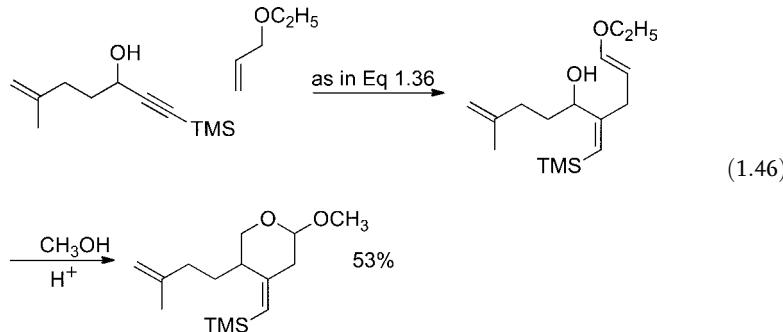
By decorating the alkyne with a suitably placed hydroxyl group and the alkene with an appropriately placed carbonyl group, an atom economic synthesis of oxygen heterocycles can emerge as shown in Equation 1.43. The alkene–alkyne coupling sets the stage for an intramolecular Michael addition to form the pyran. In principle, both five- (**40**, $n=0$) and six-membered (**40**, $n=1$) oxygen heterocycles can form. With specific natural product targets in mind, focus was placed on pyrans. Using an ester as the functional group for the alkene, the alkene–alkyne coupling proceeded to the simple adduct (Equation 1.44) [41]. The accessibility of the starting homopropargyl alcohol by the base-catalyzed addition of a terminal alkyne to an epoxide makes this ring forming strategy highly atom economic.



Replacing the ester by a ketone sufficiently enhances the reactivity of the Michael acceptor that the Michael addition occurs during the alkene–alkyne coupling to give the tetrahydropyran directly, as shown in Equation 1.45. This facile atom economic tandem process has already proven effective in streamlining syntheses to complex targets [42, 43].



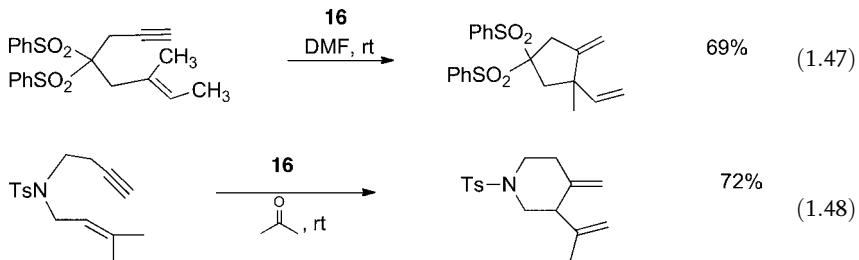
Replacing the β,γ -unsaturated carbonyl group by an alkoxy group offers a different cyclization process for tetrahydropyran formation, namely simple acetalizations as shown in Equation 1.46 [44].



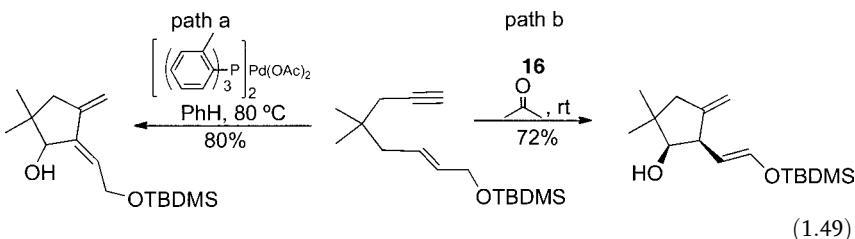
1.4.4

Intramolecular Alkene–Alkyne Coupling

The tethering of the alkene and alkyne expands the scope of alkene partners to include more hindered disubstituted alkenes and especially trisubstituted alkenes. Equations 1.47 and 1.48 show two differently arranged trisubstituted alkene partners as well as being able to form five- and six-membered rings [45, 46].



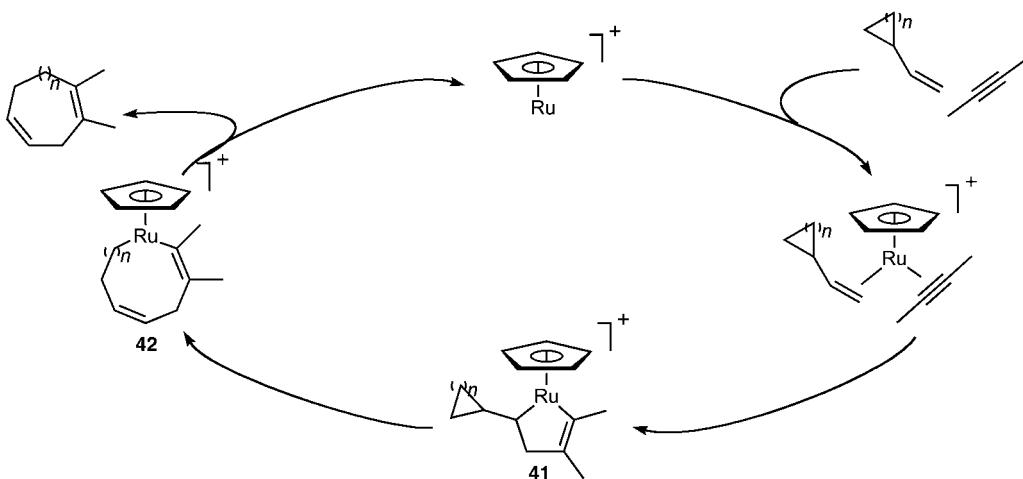
In previous work using Pd catalysts, cycloisomerizations involving substrates bearing siloxy groups at the allylic position generated 1,3-dienes preferentially (Equation 1.49, path a), in contrast to their normal behavior [47]. In the Ru-catalyzed version, the normal 1,4-diene is obtained (Equation 1.49, path b), which generates a very useful enol silyl ether with excellent chemo-, regio-, and diastereoselectivity [48].



1.4.5

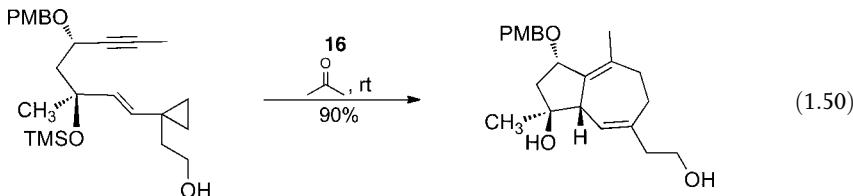
[5 + 2] Cycloaddition

When a small strained ring is attached to the alkene partner, the intermediate ruthenacyclopentene **41** can relieve ring strain by undergoing a cyclopropyl carbonyl to homoallyl ring opening to metallacyclooctatrienyl **42**, as depicted in Scheme 1.6. Reductive elimination from **42** then generates a seven-membered ring for $n = 1$. One could imagine that this same logic could apply to a vinylcyclobutane ($n = 2$) to give eight-membered rings.

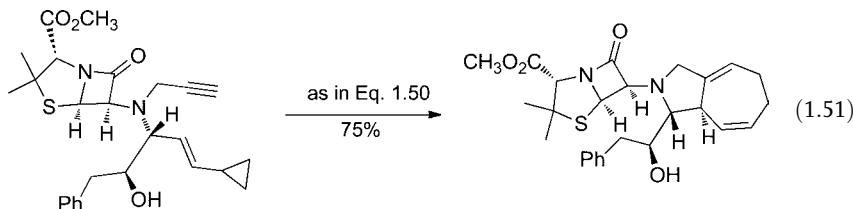


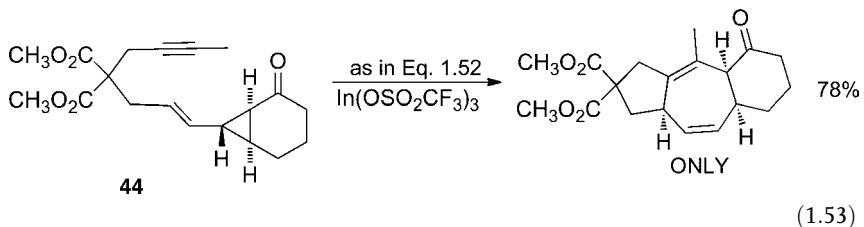
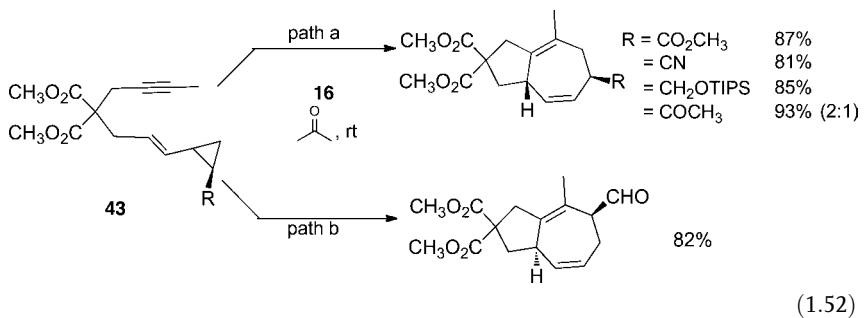
Scheme 1.6 Ru-catalyzed [5 + 2] cycloaddition.

With Ru catalysts, the reaction current works well in an intramolecular fashion as illustrated in Equation 1.50 [49]. As this example illustrates, excellent diastereoselectivity accompanies this process.

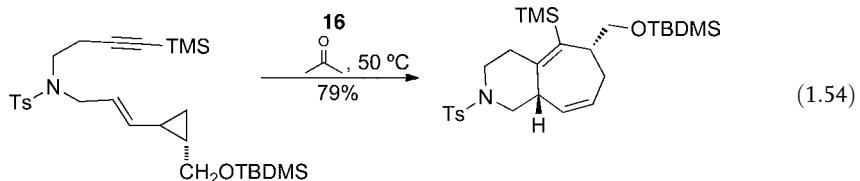


The extraordinary chemoselectivity of the process is illustrated in Equation 1.51, wherein a penicillin unit remains fully compatible. Again, the diastereoselectivity is excellent [50]. The effect of substituents on the regioselectivity proves most interesting. Using enyne **43** as the template, for all substituents examined, except for a carboxyaldehyde, the major to exclusive product was derived from opening of the less hindered bond following path a in Equation 1.52. In the case of an acetyl group, a 2:1 ratio of path a to path b was observed. Switching to a carboxaldehyde led exclusively to the product involving opening of the more substituted cyclopropyl bond as in path b. Stabilization by forming an Ru enolate accounts for the switch in regioselectivity. This effect can be enhanced by adding a Lewis acid cocatalyst. For example, the norcarane substrate **44** produces a 6:1 ratio of regioisomers, which improves to complete as shown in Equation 1.53 upon addition of indium triflate.





The factors controlling the regioselectivity appear to be more subtle than simple steric hindrance. For example, in the formation of a 6,7-bicycle, the opposite regioselectivity from that observed in path a in Equation 1.52 occurs, as illustrated in Equation 1.54 [49a]. The conformational constraints imposed in forming the six-membered ring may account for this anomaly.

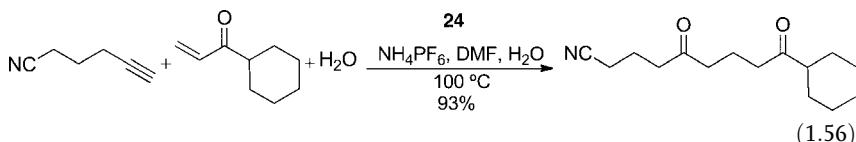
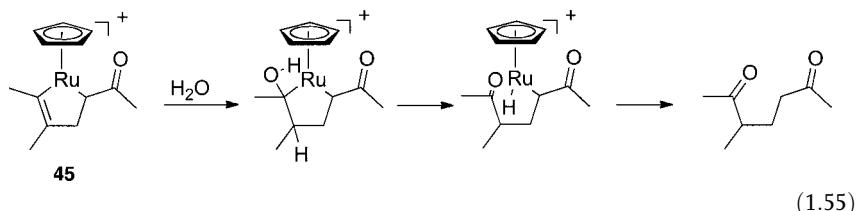


It should be noted that Rh complexes are very effective for such [5 + 2] cyclizations and, unlike Ru, extend to intermolecular processes [51]. Since they appear to be mechanistically completely distinct from each other, they will likely be complementary processes.

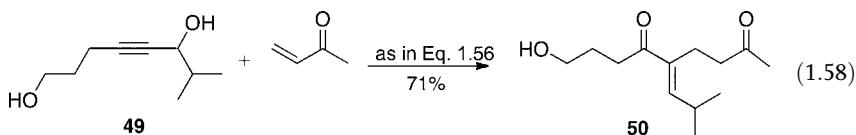
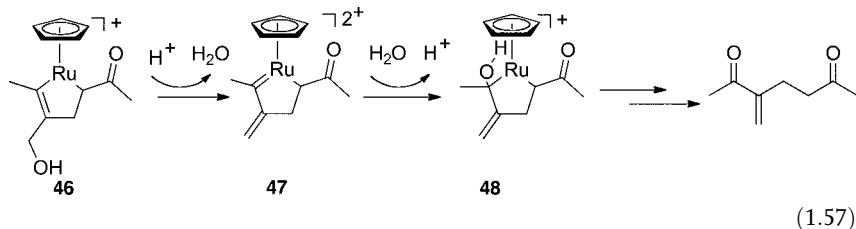
1.4.6

Vinyl Ketones as Alkyne Partners

What happens when β -hydrogen elimination in the ruthenacyclic intermediate **45** is precluded, as in the case when vinyl ketones are the alkene partners (Equation 1.55)? Given the extraordinary ability of Ru to interconvert easily among numerous oxidation states, one can imagine that the Ru can activate the double bond towards additions. For example, in the presence of water, protonation at the carbon β to Ru in the ruthenacyclopentene followed by nucleophilic addition of hydroxide can lead to 1,5-diketone formation. Indeed, terminal alkynes undergo smooth three-component coupling to form 1,5-diketones as shown in Equation 1.56 [52].

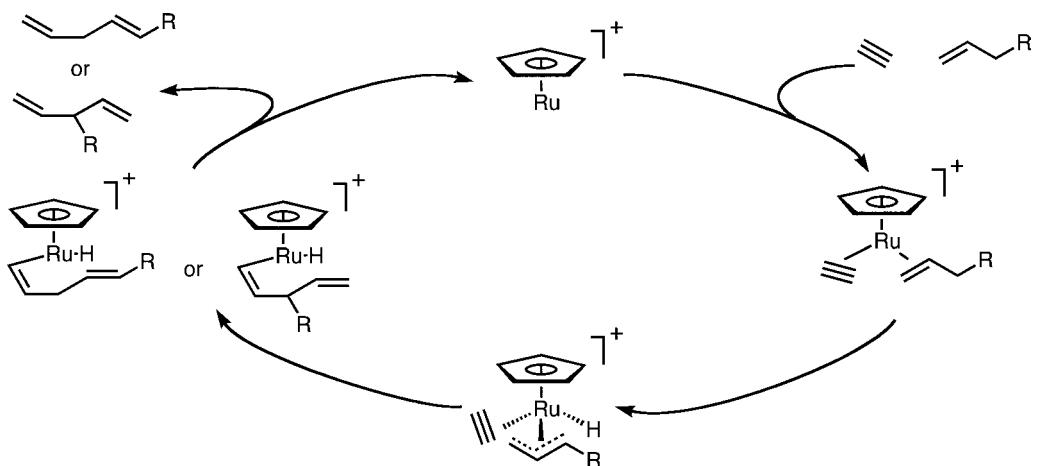


In the case that the alkyne partner contains a propargylic hydroxyl group, the flexibility of Ru to form higher oxidation states may allow ionization of this hydroxyl group followed by recombination as shown in Equation 1.57, ruthenacycle **46** to **47** to **48**. Indeed, the simple addition of propargyl alcohol **49** and methyl vinyl ketone produces the nicely functionalized 1,5-diketone **50** (Equation 1.58) [53]. Such functionality sets the stage well for further elaborations.



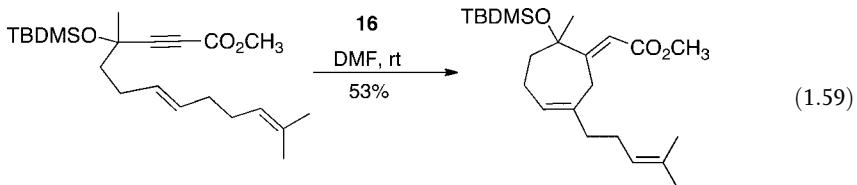
1.5 Allylic C–H Insertion

The ability of the tris-acetonitrile complex **16** to function as a highly reactive, coordinatively unsaturated ruthenium sets the stage for its functioning in a C–H insertion as a potential competing path. This possibility initially arose in intramolecular alkene–alkyne coupling involving sterically congested substrates. As shown in Scheme 1.7, such a pathway allows for addition to either allyl terminus. In an intramolecular process, such a regioselectivity outcome leads to seven-membered ring formation competing with five-membered ring formation. Indeed, alkyne

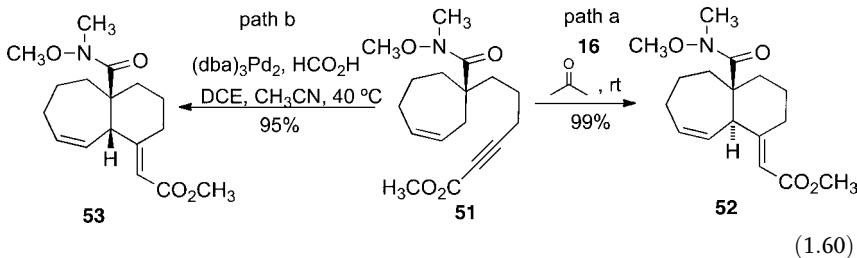


Scheme 1.7 Alkene–alkyne coupling initiated by C–H activation.

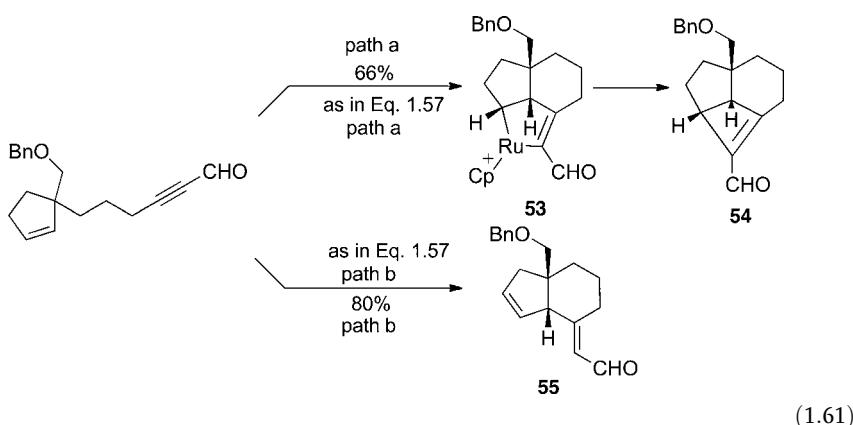
partners of the type shown in Equation 1.59 lead solely to such seven-membered rings [46, 54].



In the case of the cyclic substrate **51**, the intervention of a C–H insertion pathway reveals itself in terms of the diastereoselectivity, not regioselectivity. Thus, exposure of enyne **51** to the standard Ru catalyst at ambient temperature produced the *trans*-fused bicyclo[5.4.0]undecene **52** (Equation 1.60, path a) [55]. If a metallacycle mechanism was operative, coordination of the metal with both the alkene and alkyne must occur to form the *cis*-fused product. On the other hand, coordination of the Ru with the Lewis basic bridgehead substituent directs it to abstract an allylic C–H on the same face as the substituent, which then leads to the *trans*-fused product as observed. On the other hand, cycloisomerization using a Pd(0) precatalyst does indeed lead to the *Z*-fused bicyclic (Equation 1.60, path b).



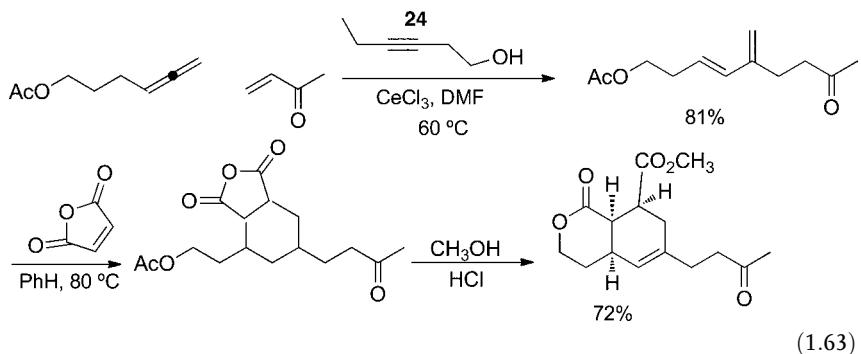
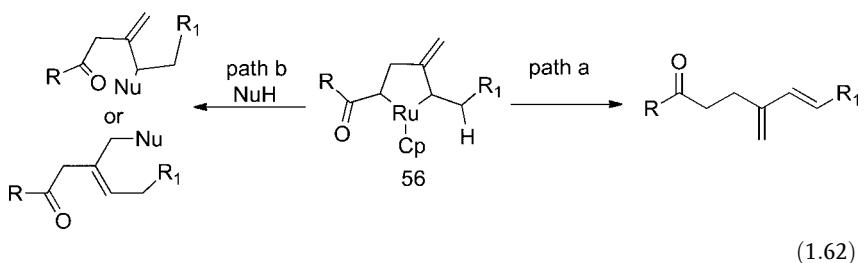
Whereas the pre-existing ring can be either six- or seven-membered with no change, a five-membered ring substrate follows a completely different pathway. The geometric restrictions make it difficult to form the π -allyl Ru complex. On the other hand, a metallacycle process can intervene. Being initiated by coordination to the alkene and alkyne, the *cis*-fused intermediate **53** will form. Since β -hydrogen elimination is still geometrically difficult, reductive elimination to the most unusual cyclobutene **54** occurs (Equation 1.61, path a). On the other hand, the Pd-based method leads to the usual *cis*-type product **55** (Equation 1.61, path b).



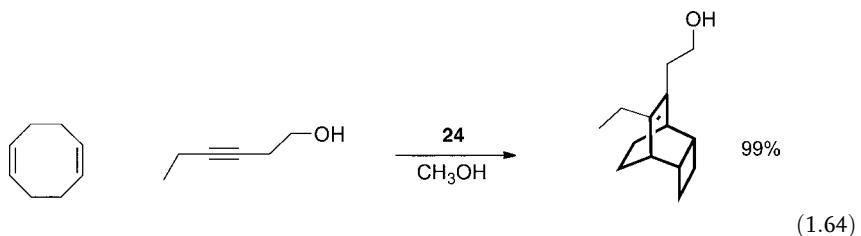
1.6 Reactions of Alkenes

1.6.1 Allene–Alkene Coupling

Can an allene serve as a surrogate for an alkene in these reactions? Initial results of alkene–allene coupling proved problematic. On the other hand, use of vinyl ketones with appropriate allenes led to well-defined pathways. Whereas the alkene partner cannot serve as the source for β -hydrogen elimination in the ruthenacycle **56**, the allene can (Equation 1.62, path a). The net result is the useful formation of a 1,3-diene (Equation 1.63) [56]. Most interestingly, using $\text{CpRu}(\text{cod})\text{Cl}$ as the precatalyst in DMF in the presence of a Lewis acid to generate a cationic Ru complex led to modest reactivity. The 1,3-diene produced serves as an excellent partner for the Diels–Alder reaction, the cycloadduct of which then nicely reacts in methanol to form the bicyclic lactone in a highly atom economic sequence with the only by-product being methyl acetate.

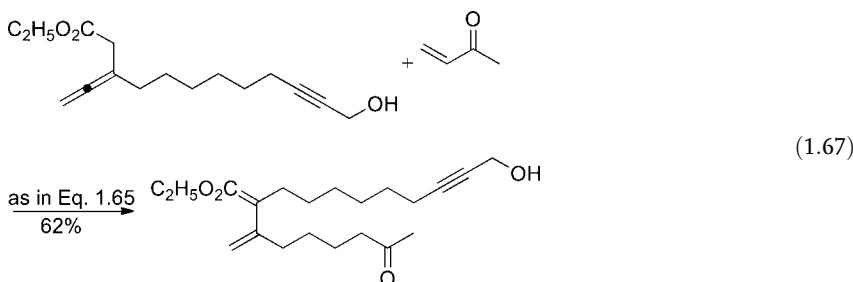
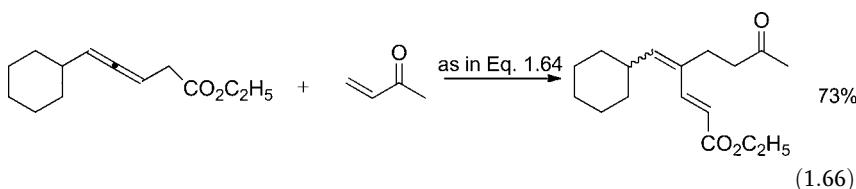
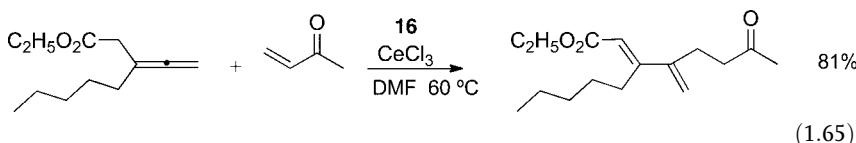


We had established in previous catalytic reactions involving complex **24** that this precatalyst was activated by the removal of the cod (1,5-cyclooctadiene) from the ruthenium by its reaction with the alkyne substrate via a [2 + 2 + 2] cyclization as illustrated in Equation 1.64 [57]. Thus, not only does this reaction constitute an activation of the Ru complex **24** by reacting off the cod, it also serves as a novel atom economic reaction in its own right. Both internal and terminal alkynes participate. The overall atom economy of this process is outstanding since cod itself is simply available by the nickel-catalyzed dimerization of butadiene. Thus, the tricyclic product is available by the simple addition to two molecules of butadiene and an alkyne with anything else only needed catalytically.

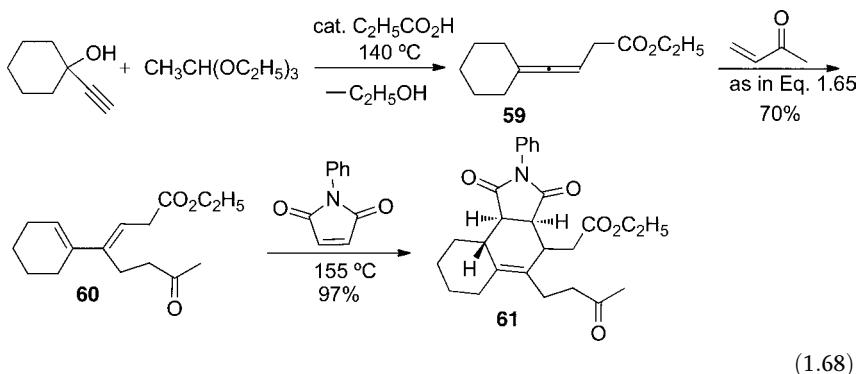


Adding a catalytic amount of an alkyne to the reaction in Equation 1.63 indeed enhanced the yield dramatically. The quantitative yield for the activation step obtained using 3-hexyn-1-ol made this alkyne the one of choice as the activator for the allene addition. Taking advantage of this atom economic synthesis of 1,3-dienes by employing the [4 + 2] cycloaddition then allows complex cyclic entities to be available with high atom economy.

Both 1,1- and 1,2-disubstituted allenes participate well. If both substituents bear allylic hydrogen, the issue becomes regioselectivity of β -hydrogen elimination. An obvious solution is to activate one of the possible β -Hs by proper choice of the substituent. A carbonyl group serves that role, as illustrated in Equations 1.65 and 1.66 [58]. In these cases, the tris-acetonitrile precatalyst was employed, which does not require the addition of an alkyne as a cocatalyst. Interestingly, competing the reaction of a propargyl alcohol with that of an allene as in the case of allenyne **58** (Equation 1.67) showed complete chemoselectivity for reaction of the allene.



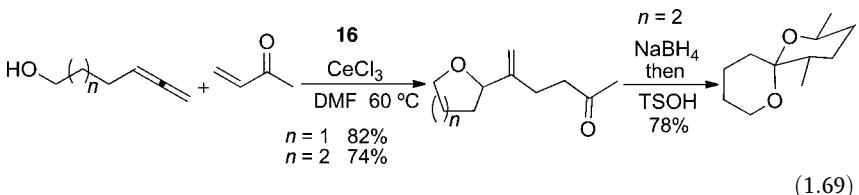
The activation of an ester for β -hydrogen elimination can be overridden by release of strain. For example, trisubstituted allene **59** adds methyl vinyl ketone to migrate a double bond that is exocyclic to a six-membered ring endocyclic to relieve the steric stress of such a double bond. Thus, the ester activation of the β -hydrogen elimination is insufficient to overcome this strain component. The atom economy of this process is highlighted in Equation 1.68. Thus, the allene precursor evolves from an acid-catalyzed addition of ethyl orthoacetate to a propargyl alcohol wherein the only stoichiometric by-product is ethanol. Further, the propargyl alcohol derives from the addition of an acetylene to cyclohexanone. Thus, the 1,3-diene **60** derives from the addition of three building blocks with ethanol as the sole by-product. Further, the resultant 1,3-diene allows further ring construction by simple additions with typical dienophiles. We are now able to construct such complex molecular arrays as tricycle **61** with nearly perfect atom economy.



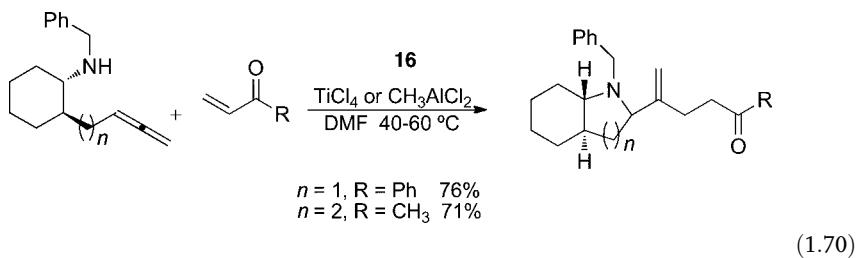
1.6.2

Heterocycles via Allene–Alkene Coupling

The metallacycle **56** (Equation 1.62) is also a σ -bonded tautomer of a π -allylruthenium complex. As such, it can be envisioned that it might be possible to capture this species with a nucleophile as illustrated in Equation 1.62, path b [58, 59]. Tethering a judiciously placed alcohol to the allene partner does indeed lead to such a product with excellent regioselectivity (Equation 1.69) [60]. Both tetrahydrofurans and -pyrans form with equal efficiency. Interestingly, reduction followed by acid treatment forms the spiroketal efficiently and reasonably atom economically (Equation 1.69).



An even better nucleophile is nitrogen. The incompatibility of basic amines for almost every one of these reactions catalyzed by these coordinatively unsaturated Ru complexes led us to examine sulfonamides and carboxamides. However, no productive results ensued. A basic amino group was also examined to verify its incompatibility. In contrast to that expectation, cyclization proceeded without problems as summarized in Equation 1.70 [61]. A Lewis acid was required as a cocatalyst. For formation of pyrrolidines, titanium tetrachloride proved most efficacious; whereas for formation of piperidines, methylaluminum dichloride proved best. In principle, any nucleophile, such as carbon, that satisfactorily reacts in ruthenium-catalyzed allylic alkylations should function here also.



1.7 Conclusion

Efficiency in synthesis must include the efficiency with which the raw materials are utilized. In a resource-limited world, maximal use of starting materials and minimal

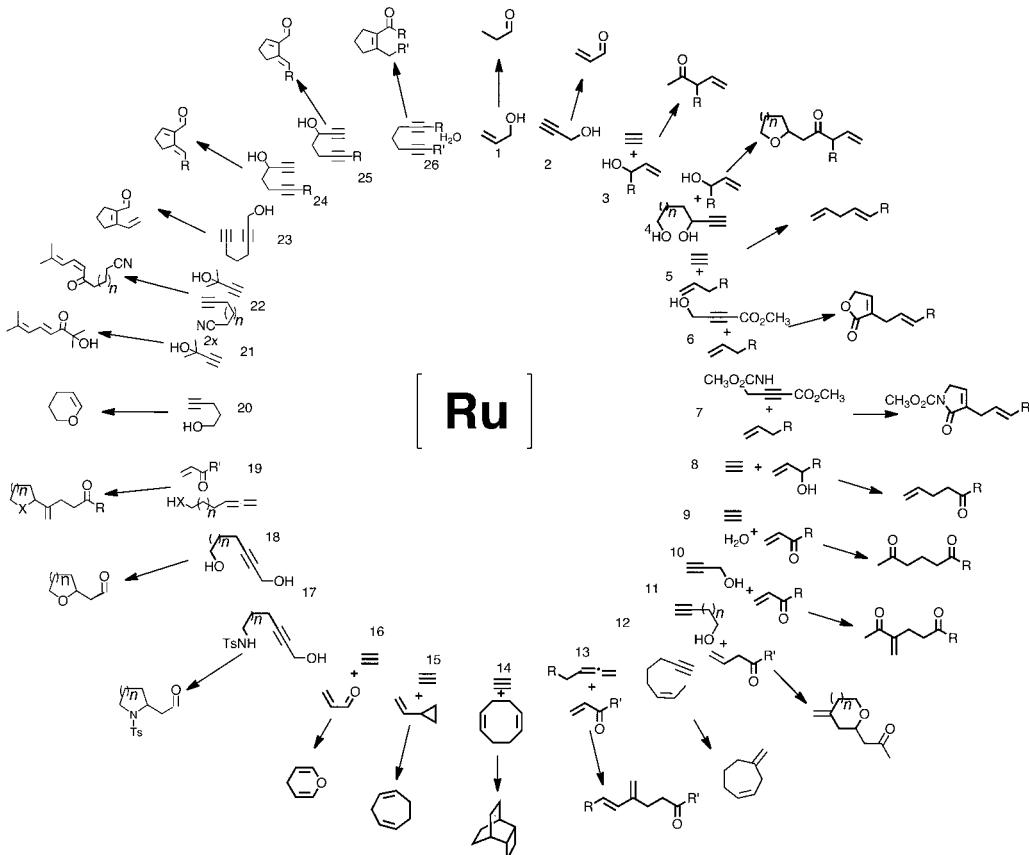


Figure 1.1 New atom economic Ru-catalyzed reactions.

generation of waste must be attempted. To meet this challenge, we must expand our toolbox of synthetic reactions which have high atom economy. The results reported in this chapter are very promising. Using one metal and, further, with one type of complex structure, a plethora of processes, all of which are simple additions, have emerged. Figure 1.1 summarizes the new reactions reported herein. Furthermore, this list is not comprehensive. Opening up so many new concepts to construct complex structures and in addition doing so by maximizing atom economy can significantly advance making organic synthesis more “environmentally benign by design.” More importantly, it is absolutely clear that we have only begun to open up the potential for new reaction invention.

Acknowledgments

I thank a great group of co-workers, all of whom are identified in the references, for making this chemistry possible. Financial support for the work in my laboratories from the National Science Foundation and, to a lesser extent, the National Institutes of Health is gratefully acknowledged.

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2

Evaluating the Greenness of Synthesis

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2.1

General Considerations About Green Chemistry and Green Engineering Metrics

Over the past several decades, a considerable amount has been written about the characteristics of metrics, or what constitutes a good metric [1–4]. Condensing all the relevant material written on the subject would be a formidable task, but most would agree that metrics must be clearly defined, simple, measurable, objective rather than subjective, and must ultimately drive the desired behavior [5].

There has also been a vast amount written about how to assess the economic or commercial viability of chemical processes [6, 7], some things written about how to assess comparatively chemistries, processes, or products from a green chemistry or engineering perspective [6–17], and there have been several reviews of various metrics systems [17–20]. Given this backdrop of writing on metrics and comparisons, one might find it confusing in a particular situation or context to decide which few key metrics should be used to allow us objectively to discover those things that have the greatest impact or potential to make our processes more sustainable.

Now, if you asked most any person who practices synthetic organic chemistry, you are likely to find agreement that the art and science of synthetic chemistry requires an encyclopedic knowledge of many different types of chemistries, named reactions, and approaches to making molecules. While this is a skill that can be learned, it does demand a considerable amount of practice and practical experience before chemical synthesis becomes intuitive and a person has a “feel” for what needs to be done.

You may also find that once a synthetic organic chemist hears about green chemistry, they will tell you that they think they already practice green chemistry because green chemistry is just “good” synthetic chemistry. After all, would you knowingly design a process that is inefficient or that produces toxic waste? Although such a position is understandable, it should be seen for what it is: a fallacious argument. There should be no doubt in anyone’s mind that green chemistry adds an additional level or two of complexity to a synthetic organic chemist’s jobs. Now they

must not only design a molecule, they must design it in such a way that it has as few adverse impacts as possible and do this using materials that are derived from sustainable sources. This is no small feat!

In general, discussions around green chemistry metrics are plagued by what is best described as a boundary problem, that is, where should the boundaries be drawn during a consideration of the “greenness” of a synthetic route and the process associated with that route? In the case where we may be evaluating one step of a synthesis, is the boundary only drawn to include reactants? Or do we include everything in the flask? How about all the materials that were required to make the reagents, reactants, and solvents that are in our round-bottomed flask? How about other impacts that would only be apparent as the chemistry is scaled up (e.g., production of utilities)? It is our considered opinion that a life cycle approach must be comprehensively applied to green chemistry metrics to evaluate appropriately the “greenness” of a new chemistry, a synthetic route, the associated processes, and the final products. Although we briefly cover in this chapter a general description of life cycle inventory and assessment (LCI/A) metrics used, you would be well advised to develop a greater understanding of LCI/A methodologies and apply what you learn to greening your syntheses [21–24].

In addition to the boundary problem, green chemistry metrics are also frequently plagued by a tendency for people to ignore a systems, systems-wide, or holistic view of a chemical synthesis and the processes that are associated with them. In undergraduate- and graduate-level chemistry curricula, there is almost no practical training about industrial processes and scale-up issues, even those that use the chemistries studied in the laboratory. In the case of engineering students and/or an engineer early in their career, it is probably the case that they do not have a good feel or first-hand experience for what a “typical” chemical or petrochemical plant might look like. Changes to a reaction sequence or in the choice of reagents may affect the type of reactor, for example, and that would most likely bring a cascade of effects to other unit operations such as the separation train. It is imperative that the metrics that are used take into consideration the cause-and-effect relationships that comprise “typical” chemical synthetic processes.

A systems-wide view will also tend to force you into collecting more than one or one kind of metric. Univariate metrics approaches are popular because they are simple, and a simplistic approach often leads to simplistic error-prone conclusions. The world of green chemistry and engineering is complex and a multivariate view is really the only way to understand greenness properly. The underlying complexity in most chemical operations inevitably leads to trade-offs amongst different metrics, which makes it very hard work indeed to find the few key metrics that best delineate the greenness of a given system or operation. For example, a change in a critical reagent, reactant, or solvent that leads to an improved yield may have an adverse impact on the overall environmental and safety profile of the process. A systems approach that is based on a carefully chosen set of metrics should allow an objective evaluation of all the trade-offs and show the “greenness” of your chemistry, process, or product for data-based decision making.

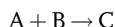
Another general principle about metrics that should be understood is that one size does not fit all; the context is important, so metrics must be continuously adapted, evaluated, and validated to ensure that they drive the desired behaviors and objectives. Metrics must also be easily understood by those that have an interest in what is being evaluated. A good approach is that they be simple, but that does not mean that they are simplistic or inelegant.

Metrics for green chemistry and engineering should also promote strategic analysis and continuous improvement. Collecting but not evaluating metrics and trends and comparing these with desired outcomes needs to be done on a regular basis; otherwise, why collect the metrics? This may seem like a very obvious point, but metrics are sometimes collected and not always routinely questioned, assessed, evaluated, and evolved. Reviewing metrics should be used to help make strategic decisions, find the areas of more promise for improvement, or to make them more useful to key stakeholders, or to guide future research.

2.2

Selected Metrics Used in the Past

As chemists have become more aware of green chemistry and the impact of chemical syntheses on the environment and society over the past dozen or so years, a number of metrics have been proposed. Before considering some of these metrics, however, it would be helpful to consider how chemists have historically evaluated the success of their reactions. The most obvious and prevalent measure of chemical efficiency for a synthetic chemist would be, of course, yield. For any given reaction:



the yield can be considered as follows.

2.2.1

Yield

Theoretical yield = ([A] moles of limiting reagent) \times (stoichiometric ratio: [C/A] desired product/limiting reagent) \times (MW of desired product [C])

$$\text{Percentage yield} = (\text{actual yield}/\text{theoretical yield}) \times 100$$

where MW is molecular (formula) weight. As is readily apparent, yield does not take into account other materials that participate in a reaction or end up in the final molecule, so several chemists have attempted to find other metrics to account for these materials, such as the effective mass yield.

2.2.1.1 Effective Mass Yield

Hudlicky *et al.* [25] were among the first to propose a non-traditional metric in a 1999 paper describing effective mass yield. Effective mass yield was defined as

“the percentage of the mass of desired product relative to the mass of all non-benign materials used in its synthesis.” Stated mathematically:

$$\text{effective mass yield} = \frac{\text{mass of products}}{\text{mass of non-benign reagents}} \times 100$$

This metric is an attempt to define yield in terms of the mass of the product that is made from non-toxic materials. This was one of the first times that reagent and reactant toxicity were included as an important part of determining what is considered to be “green,” and it is something that was absent from traditional yield measures. Hudlicky *et al.* did make an attempt to define benign (i.e. “those by-products, reagents, or solvents that have no known environmental risk associated with them, for example, water, low-concentration saline, dilute ethanol, autoclaved cell mass, etc.”), but the explanation suffers from a lack of definitional clarity.

In practice, defining “non-benign” is difficult, especially when you are working with complex reagents and reactants that have limited environmental or occupational toxicity information. Because ecotoxicity and human toxicity information is currently frequently not available, and believable quantitative structure–activity relationship (QSAR) estimations are not available for the wide diversity of chemicals used in chemical synthesis, it is difficult to apply this metric to most synthetic chemical route evaluations. Moreover, while Hudlicky *et al.* suggested that “benign” includes such things as saline and dilute ethanol, depending on the situation all have environmental impacts of one kind or another that would have to be evaluated and addressed.

2.2.2

E-Factor

The *E*-factor, a metric proposed by Sheldon [26], has become one of the most cited and commonly used metrics in the batch chemical processing industry. It is defined as follows:

$$E\text{-factor} = \frac{\text{total waste (kg)}}{\text{kg product}}$$

The original publication was ambiguous about whether the *E*-factor included or excluded water, but it could be used to describe either case. This metric meets our requirement for simplicity, is relatively easy to calculate from a mass balance, and has done a good job in drawing attention to the quantity of waste that is produced for a given quantity of product. Because of Sheldon’s time working in industry, in addition to consulting with a variety of industrial sectors after joining academia, he was able to calculate comparatively the relative wastefulness of different parts of the chemical processing industries. His well-known comparison includes industries as diverse as petrochemicals, specialties, and pharmaceuticals.

Despite the simplicity of the metric, it may be subject to ambiguity depending on how waste is defined and where one draws system boundaries for any given

comparison. The following examples illustrate the complexity of the boundary problem. Do we include waste:

- Only if it passes over the fence line? (e.g., what if we buy increasingly more complex chemicals to make the same product?).
- Produced as a consequence of emissions treatment (e.g., acid gas scrubbing, pH adjustment in wastewater treatment plants)?
- That results from our production of energy to heat or cool reactions, or operate abatement technology, etc.?
- Solvent that is passed on to a waste handler to be burned in a cement kiln?

These types of questions will undoubtedly complicate our use of the metric and the interpretation of the results as we attempt to put it into routine use. In addition, this metric does not consider the degree of hazard of the waste that is being created; for instance, is it better to generate 100 kg of non-hazardous waste that is difficult to treat, or 50 kg of highly hazardous waste?

An additional point to note is that this metric is focused on the waste part of the equation, and not on the efficiency or productivity side of the equation. This is linked to our final general experience that drawing a chemist's attention to waste does not always lead them to think about what steps they might take to avoid creating the waste in the first place. Instead, experience suggests that chemists focus on what they think is "good science," novelty (for patent protection), and precedent (using what they know works) to the exclusion of most other things. However, because they tend to focus solely on these areas, they ignore the impacts and implications of the materials they use and the wastes that are generated by the chemical reactions they are developing. It is certainly easier to leave it to others to focus on waste treatment at a later date, as has been done traditionally.

2.2.3

Atom Economy

Maximizing chemical selectivity and yield is probably the premier objective of most synthetic organic chemists. Since we have reviewed chemical yields above, let us briefly review chemical selectivity. This is an important digression, despite the fact that it may be obvious to many that the more chemoselective a reaction is, the more inherently green the reaction should be. Or, stated slightly differently, much of what is not "green" in chemistry is not green by virtue of a lack of chemical selectivity when chemists are busy assembling molecules. The definitions of chemical selectivity are given here by way of reminder:

- **Chemoselectivity** – A chemoselective reagent is one that reacts with one functional group (e.g., a halide, R–X), but not another (e.g., a carbonyl group, R–C=O)
- **Enantioselectivity** – This refers to a chemical reaction in which an inactive substrate (a molecule of interest) is converted selectively to one of two enantiomers. Enantiomers are isomers (compounds with the same numbers and types of

atoms but possessing different structures, properties, etc.) that differ only in the left- and right-handedness of their orientations. Enantiomers rotate polarized light in equal but opposite directions and react at different rates with other chiral compounds.

- **Stereoselectivity** – Any reaction in which only one of a set of stereoisomers (isomers whose relative spatial positions of atoms or functional groups differ) is formed exclusively or predominantly.
- **Regioselectivity** – When a reaction can potentially give rise to two or more structural isomers (e.g., R–O–C=N or R–N=C=O) but actually produces only one.

As you have been reminded of these definitions, you have also seen several important concepts related to chemical selectivity that will inform any discussion and debate around what is green. We can readily see, for example, that when working with chiral molecules we not only have to worry about reacting with a particular type of bond or functional group, but we also have to do it in such a way that only the bond of interest forms that preserves or creates the desired isomer. As any synthetic organic chemist knows, there remains a considerable amount of chiral chemistry that suffers from a lack of selectivity (stereo-, regio-, and enantioselectivity) and in many cases more than 50% of the starting material ends up as waste.

In recent years, another metric, introduced by Trost and known as atom economy [27], is an attempt to prompt synthetic organic chemists to pursue “greener chemistry.” Atom economy is a good organizing concept for synthetic chemists as it focuses attention on including all of the reactants in the final product. Ideally, atom economy is applied equally to any reaction or series of reactions, whether it is a single chemical transformation, a series of chemical transformations in a single stage of a multistage synthetic route, or the entire route to a final product.

Atom economy is deliberately kept simple by making certain key assumptions; it ignores the reaction yield, molar excesses of reactants, solvents, and reagents. Before discussing the pros and cons of atom economy, it is worth clarifying what atom economy means.

2.2.3.1 Key Assumptions About Atom Economy

Reactants

A reactant is a chemical compound that in most cases is incorporated in whole or part into an intermediate but not necessarily into the final product. When calculating atom economy, consideration of only key reactants helps to simplify things. For example, stoichiometric “catalysts,” or acids and bases used for hydrolysis, should be considered as reactants. Including these materials stands in contrast to common inorganic reagents that are not included, as in the case of potassium carbonate used for a Williamson ether formation, even though it may be used in stoichiometric quantities. Other materials, including organic reagents and/or solvents, are not included in atom economy calculations as the focus is on the two or three reacting substances in the flask; however, solvents and other organic reactants can contribute significantly to the environmental impacts of a synthesis.

Reactants also include those materials that may be temporarily incorporated into a reaction intermediate, as in the case of the addition and removal of a protecting group. Even though it is not included in the final product, it was a part of the intermediate and is therefore included in the overall atom economy for the synthesis. Examples include the common protection strategies for primary amines where *tert*-butoxycarbonyl chloride (Boc) is used, or for carboxyl groups where *tert*-butyl or benzyl esters are used. In each case, the protecting agent would be included in the atom economy calculation, despite the fact that no part of the protecting group, or the reagents involved in deprotection, are included in the atom economy calculation.

Stoichiometry

The use of excesses of reagents and reactants to maximize reaction yield/selectivity, although a very common practice, is not part of the atom economy calculation. Reaction stoichiometry is, however, part of the calculations. This means that when 2 mol of one reactant combine with a single mole of a second reactant to form a new molecule that is either a reaction or process intermediate, the relevant stoichiometric ratio would be used to calculate the overall atom economy of the reaction.

Working with Chiral Selectivity: Regio-, Stereo-, or Enantioselectivity

When calculating atom economy for a chiral resolution step, the reaction stoichiometry must be adjusted to account for that portion of the mass to be discarded as the unwanted enantiomer. This includes those cases where the resolving agent is in a 1:1 or 2:1 ratio with respect to the desired enantiomer, or 1:2 as in the case where the desired enantiomer is difunctional.

2.2.3.2 How Atom Economy Is calculated

For a generic reaction:

we have



$$\text{Atom economy} = \left(\frac{\text{m.w. of product } C}{\text{m.w. of } A + \text{m.w. of } B} \right) \times 100$$

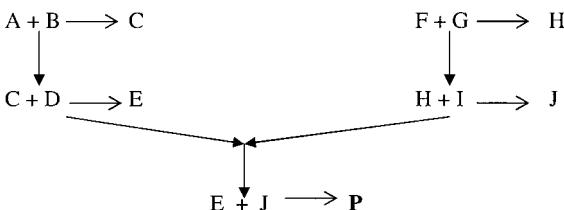
It should be noted that the calculation considers only the reactants and ignores intermediates made in one step or stage and consumed in the next. *Because of this, one must not multiply the atom economy of each stage to produce an overall atom economy for a synthetic scheme.* Overall atom economy must be calculated as follows:

For a generic linear synthetic process:

- 1) $A + B \longrightarrow C$
- 2) $C + D \longrightarrow E$
- 3) $E + F \longrightarrow G$

$$\text{Atom economy} = \left(\frac{\text{m.w. of product } G}{\text{m.w. of } A + \text{m.w. of } B + \text{m.w. of } D + \text{m.w. of } F} \right) \times 100$$

Synthetic schemes with two or more separate branches are treated analogously by taking into account all of the reactants but none of the intermediates in the calculation. Thus, for the following branched synthetic process:



where C, E, H, and J are intermediates and E and J are coupled in the final step, atom economy is calculated as follows:

$$\text{atom economy} = \frac{\text{FW P}}{\sum(\text{MW A, B, D, F, G, I})} \times 100$$

2.3

Reaction Mass Efficiency

Reaction mass efficiency (RME) is a metric that was first introduced by Curzons *et al.* [4] as a means of including the concept of atom economy (AE), while adding yield and the reactant stoichiometry. RME is defined as the percentage of the mass of the reactants that remain in the product. There are two ways to calculate RME.

For a generic reaction $A + B \rightarrow C$:

$$\text{reaction mass efficiency} = \frac{\text{MW of product C}}{\text{MW of A} + (\text{MW of B} \times \text{molar ratio B/A})} \times \text{yield}$$

or more simply:

$$\text{reaction mass efficiency} = \frac{\text{mass of product C}}{\text{mass of A} + \text{mass of B}} \times 100$$

Because reaction mass efficiency includes the stoichiometry of a reaction and the yield, it is thought to be a more accurate reflection of the true efficiency of a given chemical reaction. But why would this be the case? Experienced chemists know that many reactions require significant molar excesses to drive the reaction to completion. They also are well aware of the fact that poor chemical selectivity in all its forms leads to yields that are considerably less than 100%, especially as molecules become more complex (greater functionality), as is the case when making chiral molecules.

This means that if we would like to account more accurately for the impacts of a chemical synthesis, we need to be more careful about what we include in our metrics. As is readily apparent to any synthetic organic chemist, reagents and solvents promote reactivity and/or at the very least provide a means for heat and mass transfer that ensures good kinetics and chemical selectivity. Although the *E*-factor may be a good measure for focusing attention on waste, it ignores the product and what we buy in to make our product, that is, the raw materials. Because it looks at the

end of the process and not at the beginning, the tendency on the part of many is to be concerned only about waste treatment and end-of-pipe solutions that inherently require more mass and energy to resolve. Consequently, a different metric that is related to the *E*-factor was proposed and is known as mass intensity.

2.4

Mass Intensity and Mass Productivity (Mass Efficiency)

This metric has been discussed elsewhere [4] and is defined as follows:

$$\text{mass intensity (MI)} = \frac{\text{total mass used in the synthesis (kg)}}{\text{mass of product (kg)}}$$

It may also be useful to compare MI with the *E*-factor, where

$$E\text{-factor} = \text{MI} - 1$$

By simply adding up the masses of all substances placed in a reaction flask and the materials used for extractions and other separations, MI accounts for the yield, reaction and reagent stoichiometry, catalysts, and the solvent. MI is expressed on a mass basis rather than as a percentage and, in the ideal situation, MI would approach 1. Total mass usually includes everything that is put into a reaction vessel but often excludes water, as water can sometimes be the major mass contribution to the reaction and tends to skew the data. However, it is not too much of a stretch to calculate MI with or without water, and there are advantages in looking at both metrics. Total mass also includes all mass used in acid, base, salt, and organic solvent washes, and organic solvents used for extractions, crystallizations, or for solvent switching.

Let us briefly revisit water in mass metrics as its inclusion may be a somewhat contentious issue for some. Most would agree that water as plain or potable water generally does not constitute a significant environmental impact. However, much of the water used in the chemical processing industries is water that has been highly purified; this is especially the case in the pharmaceutical, semiconductor, and related industries such as some parts of the fine chemicals industry. There may also be some significant life cycle impacts related to the chemicals and equipment used to purify the water, depending on where and how the water is obtained. In addition to the front-end impacts, there are also problems at the back end of the process. It is at that point that we encounter mixed aqueous–organic reaction mixtures that lead to the need for separation, treatment, and subsequent disposal of wastes. These operations often lead to increased solvent use, additional unit operations, waste treatment operations, and most certainly increased energy use. Finally, but by no means of lesser importance, water and the competition for potable (drinking) water are becoming more of an issue in many parts of the world. Water will continue to be an issue of public concern in the future and, consequently, metrics that include water use are being collected on a more frequent basis.

If we express mass intensity as its reciprocal and convert it to a percentage, its form is similar to effective mass yield and atom economy. This metric is generally known as mass productivity or mass efficiency, which is the percentage of the materials that we use in a chemical synthesis that is actually incorporated into a saleable product:

$$\text{mass productivity} = \frac{1}{\text{MI}} \times 100 = \frac{\text{mass of product}}{\text{total mass used in the synthesis}} \times 100$$

Table 2.1 contains averaged data for 28 different chemistries commonly used in industry. The stoichiometry, yield, atom economy, reaction mass efficiency, mass intensity, and mass productivity are shown for each type of chemistry.

Analysis of the chemical reactions and these data has yielded the following conclusions:

- 1) Most of the reactions studied were run with significant stoichiometric excesses. This added mass would be lost if a metric such as atom economy was the only metric used.
- 2) Reaction yield, a metric universally used by synthetic chemists to evaluate their success, does not include poor reaction mass efficiencies. The correspondingly significant waste of resource (mass or energy) may be an obvious consequence to some, but many do not think about the wasted resource and the expense that this represents from both a direct materials cost and a more comprehensive life cycle costing perspective.
- 3) Extensive statistical analysis of the mass intensity, yield, atom economy, and stoichiometry show that these data do not correlate with each other in any meaningful way. Because these metrics appear to be of discretely different types, following one metric in isolation from others may not drive the best behavior for “greening” reactions. This is illustrated in Table 2.2, which contains an example of three different chemistries of similar mass intensity that have generally different and conflicting data trends for the other metrics.
- 4) Because reaction mass efficiency includes all the mass used for a given reaction (whether or not it includes or excludes water), and includes yield, stoichiometry, and atom economy, we believe that this metric is the most helpful metric for chemists to focus their attention on how far from “green” a given reaction or reaction scheme may be.
- 5) Mass productivity has been found to be a useful metric for business leaders since it highlights resource utilization, and it is more focused on efficiency rather than waste. This is illustrated in Table 2.3, where the average atom economy is compared with the average mass productivity for 38 drug manufacturing processes.

If synthetic organic chemists looked at the data in Table 2.3, most of them would probably agree that an average atom economy of 43% for a seven-stage synthesis of a complex molecule is pretty good. Remember that to achieve this average atom economy of 43% for the entire synthesis, the atom economy for each individual step or stage would have to be somewhere in the mid-80% range. For complex chemical syntheses characteristic of the pharmaceutical industry, this degree of synthetic efficiency represents the state-of-the art.

Table 2.1 Comparison of metrics for different chemistries.

Chemistry	Stoichiometry of B (mol%)	Yield (%)	Atom economy (%)	Reaction mass efficiency (%)	Mass intensity excluding water (kg kg^{-1})	Mass productivity excluding water (%)
Acid salt	135	83	100	83	16.0	6.3
Base salt	273	90	100	80	20.4	4.9
Hydrogenation	192	89	84	74	18.6	5.4
Sulfonation	142	89	89	69	16.3	6.1
Decarboxylation	131	85	77	68	19.9	5.0
Esterification	247	90	91	67	11.4	8.8
Knoevenagel condensation	179	91	89	66	6.1	16.4
Cyration	122	88	77	65	13.1	7.6
Bromination	214	90	84	63	13.9	7.2
N-Acylation	257	86	86	62	18.8	5.3
S-Alkylation	231	85	84	61	10.0	10.0
C-Alkylation	151	79	88	61	14.0	7.1
N-Alkylation	120	87	73	60	19.5	5.1
O-Arylation	223	84	85	58	11.5	8.7
Epoxidation	142	78	83	58	17.0	5.9
Borohydride	211	88	75	58	17.8	5.6
Iodination	223	96	89	56	6.5	15.4
Cyclization	157	79	77	56	21.0	4.8
Amination	430	82	87	54	11.2	8.9
Lithal	231	79	76	52	21.5	4.7
Base hydrolysis	878 ^a	88	81	52	26.3	3.8
C-Acylation	375	86	81	51	15.1	6.6
Acid hydrolysis	478	92	76	50	10.7	9.3
Chlorination	314	86	74	46	10.5	9.5

(Continued)

Table 2.1 (Continued)

Chemistry	Stoichiometry of B (mol%)	Yield (%)	Atom economy (%)	Reaction mass efficiency (%)	Mass intensity excluding water (kg kg^{-1})	Mass productivity excluding water (%)
Elimination	279	81	72	45	33.8	3.0
Grignard	180	71	76	42	30.0	3.3
Resolution	139	36	99	31	40.1	2.5
N-Dealkylation	2650 ^a	92	64	27	10.1	9.9

a) Inflated by use of solvent as reactant.

Table 2.2 Comparison of three different chemistries with similar mass intensities.

Chemistry	Stoichiometry of B (mole%)	Yield (%)	Atom economy (%)	Reaction mass efficiency (%)	Mass intensity excluding water (kg kg^{-1})
S-Alkylation	230.9	85.3	83.8	61.3	10.0
Chlorination	313.6	86.0	73.6	45.8	10.5
Acid hydrolysis	478.4	92.4	75.6	50.0	10.7

Table 2.3 Comparing atom economy and mass productivity for 38 late-phase and/or pharmaceutical manufacturing processes. Average number of stages: 7.

Parameter	Overall process average (%)	Range (%)
Atom economy	43	21–86
Mass productivity	1.5	0.1–7.7

However, before we pat ourselves on the back, we should have a look at the average mass productivity for these 38 late-phase or manufacturing processes. As can be seen from Table 2.3, a mass productivity of 1.5% means that 98.5% of the total mass used to make our average active pharmaceutical ingredient is not ending up as the desired substance. Even if the atom economy for individual steps of the process were to be raised above 95%, this may not necessarily increase the overall average mass intensity of the process to a significant extent. Since a majority of the mass in a given process is not accounted for by atom economy, it may be argued that atom economy may not be the most robust measure or the best measure of sustainability for synthetic chemistry.

2.5

Cost Implications and Green Chemistry Metrics

Although we could end our discussion here at the point of only focusing on metrics that apply to chemistry and mass, to do so would be a mistake without due consideration of cost. The life cycle implications of material production, and energy requirements and waste treatment/disposal, undoubtedly have a cost component that frequently remains hidden.

Before we begin to discuss this, however, we need to think about a few important points as we attempt to apply a green perspective to metrics and cost. First, most people do not really consider what lies behind the goods and services that we extract from the environment for “free.” For example, we do not pay significantly for the air

that we use for its oxygen content, or for the water we extract from an aquifer. This means that in many areas of everyday commerce, what we pay for materials is not a true reflection of the overall cost required to make the material. Clearly, there is a purchase cost that must be paid to a supplier for a chemical, but the maker of that chemical is not paying for everything they use, and these costs are currently not accounted for in the price we pay. Happily, over the past several decades there have been a number of people developing approaches to total cost assessment [28] or environmental accounting [29] that help to throw light on the more non-traditional costs. The reader is strongly encouraged to seek elsewhere for more information about how this is done.

A second important point that many in the chemistry community seem to ignore is that for many chemically useful materials that we use in our laboratories every day, there are limited supplies, and dwindling supplies of key materials. Moreover, the supply of these materials comes with a significant and growing cost to the environment. An example of the types of materials in mind would be some transition metals and platinum group metals that are key components of catalytic systems and novel synthetic pathways. Think about this for a moment. Not only do we have impacts related to the extraction, refinement, and use of these materials in catalyst systems, but these materials, or a portion of these materials, are being widely dispersed into the environment, again in a form that makes them inaccessible. Even synthetic organic chemists are subject to the second law of thermodynamics: entropy happens. Although some materials or a large proportion may be recovered, complete recovery from process streams is not always possible. This is because some of the catalysts that we use are homogeneous and they are difficult to extract and recover from reaction mixtures. Even in those cases where we use heterogeneous catalysts, a loss of 5–10% of the catalyst with the filter or filter aid is not unusual. Although we make great efforts to collect these materials, it is undoubtedly very difficult and costly to collect it all. It is also difficult and costly to find alternatives that perform the same function, but that is what green chemists need to be doing!

It is now readily seen from the example of atom economy that reactions having poor atom economy will be more costly, because:

- 1) Those portions of each reactant molecule that are not incorporated into the final molecule are lost, that is; materials (and energy) are not used efficiently and therefore more materials and energy need to be acquired.
- 2) Different synthetic strategies affect the length and complexity of the route:
 - (a) Portions of the molecule may be in the wrong oxidation state.
 - (b) Protection/deprotection may be required.
 - (c) Chiral resolutions may be required.
- 3) By-products, reactants, reagents, solvents, and so on may lead to additional purifications and separations to remove them, which will require additional materials and energy.
- 4) Environmental, safety, and health costs will attend the management of materials and treatment of waste products.

2.6

Life Cycle Assessment Metrics

We have stated that to evaluate greenness, a life cycle approach must be applied to green chemistry metrics to evaluate a new chemistry appropriately. A true green chemist can no longer look at the reaction of A, B, and D in isolation, but has to consider the wider impacts of producing reactants, purifying products, and disposing of waste. In other words, it is necessary to expand the boundaries to evaluate greenness. It is therefore worth spending some time looking at the typical metrics used in evaluating processes within a life cycle assessment (LCA) framework. The scope of this chapter does not allow a detailed review of LCA methodologies, and these are reviewed in detail elsewhere [30–36]. Our focus in this chapter is to provide a brief overview of the type of LCA metrics that can be used to evaluate our progress towards greening our synthetic routes.

LCA is a methodology used to evaluate the environmental impacts of processes and activities throughout their entire life cycle. This is typically known as a “cradle-to-grave” assessment, in which the resource consumption, pollutants emitted, and their environmental impacts are measured and assessed at each step, from the extraction of raw materials, production, transportation, sales, distribution, use, through their final fate. Depending on the goal and scope of the assessment, the boundaries can be set differently; for instance, a “cradle-to-gate” assessment might be adequate when comparing two chemical routes to the same API, or a “gate-to-grave” boundary may suffice when comparing two different solvent treatment processes.

LCA methodology provides a framework of directly applicable green metrics at wider boundaries. These metrics can be reported as direct inventory data, for example, life cycle energy, life cycle mass, life cycle emissions; measures of individual potential impacts (such as global warming, acidification, etc.); or as an aggregate score or index for high-level comparison (e.g., EcoIndicator 99). Examples of some metrics for life cycle inventory (LCI) or impact assessment (LCIA) are shown in Table 2.4 [37–39].

It is worth noting that the type of LCA metrics shown above will include total waste, the hazards, and the potential impacts from the use of particular chemistries. As we discussed earlier, the LCIA framework is arguably the best way to date to provide the multivariate set of metrics to evaluate the greenness of chemical synthesis. Having said that, estimating the life cycle environmental impacts of synthetic chemistry routes and their associated processes is not a straightforward endeavor under the best of circumstances. Perhaps the main challenge that one faces when attempting to evaluate a new chemistry is the large amount of information required from a variety of sources. The synthesis of a typical fine chemical may involve 20 or so chemicals and life cycle inventory data are needed for each of these chemicals. The problem that we face is that life cycle information for complex chemicals is normally not readily available at this time. This challenge has driven the use of streamlined life cycle analysis techniques in order to estimate the greenness of synthetic chemistries within reasonable timelines.

Table 2.4 Examples of life cycle inventory (LCI) and life cycle assessment (LCA) metrics.

LCI metrics	LCA metrics
Cumulative energy demand	<i>Impact metrics</i>
Exergy	Resource consumption
Total mass	• Biotic
Land use	• Abiotic
Emissions (total and itemized)	• Renewable
• Air	• Non-renewable
• Water	Global warming potential
• Land	Acidification potential
	Photochemical ozone creation potential
	Human toxicity
	Eco-toxicity
	Workplace hazards
	etc.
	<i>Index metrics</i>
	Eco-indicator 99 [37]
	GSK's FLASC™ score [38]
	BASF's eco-efficiency fingerprint [39]

2.7

Process Metrics

Now that we have covered some metrics that have been used by chemists in the past and given a very brief overview of life cycle metrics, it is important to keep in mind that industrial-scale chemistry is not the same as what chemists carry out in the round-bottom flasks of the laboratory. With the scale-up of an exploratory synthetic route comes the inevitable drive for increased efficiency as the cost of buying and disposing of large quantities of materials is fairly high and continues to grow. Some might argue that as synthetic routes become processes, and these processes are scaled up to industrial sizes, process considerations become most important. This assertion should be seen for what it is, as something of a false dichotomy, as the chemistry is the backbone of the process. However, it is useful to take a moment and consider them separately so we might draw a few distinctions between them.

Table 2.5 contains a small collection of process-related areas of interest that make good targets for establishing metrics related to route and process development. The areas encompassed by this list are not new and would generally be found in many texts on process-related metrics. It is also generally true that each area in Table 2.5 could be further dissected for additional attributes or areas of interest in ever-increasing levels of detail, but this table was not intended to be comprehensive; merely illustrative. In addition to the potential for greater scrutiny and detail, one should also remember that life cycle considerations impact on each category and aspect contained in the table, as we discussed above.

It should be understood from consideration of the items in Table 2.5 that choices of materials (chemicals, solvents, reagents, etc.) will directly affect choices about which

Table 2.5 General areas of interest for process metrics.

Materials	Equipment	Operability	EHS risk	Quality
Physical form and properties (i.e., gas, liquid, solid)	Unit operation type	Throughput/cycle time	Occupational exposure	Purity/impurity profile
Mass (i.e., total, solvent, reactant, process, etc.)	No. of unit operations	Robustness	Environmental – air, water, land	
Inherent hazard (e.g., toxicity, stability, reactivity)	Size (volume)	Energy (i.e., total, heating, cooling, recovery, treatment, etc.)	Safety/process safety	
Cost	Scalability			
Renewability	Controllability			
Recyclability		Ease of cleaning and maintenance		

unit operations are used. Also, the combination of materials choices and equipment choices will directly impact the operability of a given process. Choices about materials, equipment, and operability all have environmental, health, and safety (EHS) implications and opportunities and ultimately impact the product and product quality. The remainder of this chapter discusses the categories shown in Table 2.5 and suggested approaches to “green” metrics development.

2.7.1

Materials

2.7.1.1 Physical Form and Properties

The physical form and properties of intermediates and final molecules are directly linked to and impact other parts of a process such as the reactor type, the type of mixing (static or continuous), the overall process throughput, the rate at which a chemical will dissolve in a solvent or precipitate out, the ease of which liquids are separated, and so on. There will also be knock-on impacts related to energy used for heating, cooling, recovery if applicable, cleaning, and wastes.

An approach to metrics for this area could be profitably divided into three different aspects, depending on the questions that we are trying to answer with the metrics:

- summing the number of materials that possess a particular attribute as in the case of the number of materials that have different phases, the number of different solvents containing azeotropes or close boiling points, and so on
- summing the masses of all materials that possess a particular attribute, as in the case of the mass of all solvents, or the mass of all gases
- or a combination of number and mass to arrive at a score that could be a proxy for material complexity.

We might want to follow things such as large numbers and masses of different materials because increases in these are likely to lead to increased use or quantities of equipment or energy, slow throughput, and an increase in general materials management. By combining several metrics of this type, we may be able to develop a metric that can be used as an index of process complexity. Increased process complexity tends to drive costs higher and can lead to increases in waste in one part of the life cycle or another.

2.7.1.2 Mass

Mass has been discussed previously, but there are a few additional metrics to consider. These are clearly just variations on a theme, but they may be important metrics depending on the type of process that is being developed or run. These additional mass metrics could allow for additional scrutiny on the areas that might require additional investment of time to improve:

$$\text{solvent intensity} = \frac{\text{total solvent input excluding water}}{\text{total mass input}}$$

$$\text{specific compound } (i) \text{ released} = \frac{\text{amount of compound } (i) \text{ released as an emission}}{\text{total mass input}}$$

2.7.1.3 Inherent Hazard

The inherent hazard a particular material or group of materials in a process possess represents a major component of the overall environmental, safety, and health risk profile of a process. It is also a key driver for such process-related activities as equipment design and material of construction selection, storage and handling of chemicals, throughput, and process robustness. If one thinks about highly reactive materials such as vinyl chloride monomer, aziridines, acetylenes, and hydrogen fluoride, one knows that they require considerable care during their manufacture, storage, transport, and use. While these materials are routinely and safely used, there is a need to maintain careful thermodynamic and kinetic control so adverse events may be avoided.

As was the case in our discussion of mass metrics, we can use different metrics approaches to highlight the inherent hazards of the materials used in our processes. One can sum numbers and/or masses of chemicals possessing hazards in different areas, as in the case of all materials possessing a particular process safety hazard, or those that possess an occupational exposure hazard, or those that possess one or more environmental hazards. Many companies in recent years have adopted a banding approach to materials hazard assessment that puts compounds into different hazard categories. This allows one to group quickly materials of similar hazard and it is common practice for a hazard category to be associated with a suggested control approach such as adding different layers of protection, pressure relief valves, and so on, as the hazard increases. Banding helps people to identify potential issues rapidly and provides standard options for elimination, substitution, or control.

As an example of how this might look, materials may be first grouped according to their type, that is, as a solvent, as an inorganic, as a reagent, and so on. A hazard ranking is then applied that is typically based on all the different potential hazards that a given material or group of materials possess. We can also construct a composite ranking based on the different types of hazards, or the ranking may be computed for each individual hazard category. There are different means of scoring, such as a simple weighted average (hazard ranking times the mass of material used), or a score based on weighted averages for each category of materials [hazard ranking times mass of (solvent, reagent or process chemical) used]. By calculating a geometric mean of the scores for each category, we will highlight those materials possessing the greatest hazard. In this way, a category score may be used to focus efforts on those areas of a process that are in most need of change. The score may also be used as a means of prioritizing which processes or parts of processes are addressed first.

It is appropriate at this point, and perhaps critically important, to ensure there is no confusion about what constitutes the inherent hazard of materials and what constitutes a risk. Risk is usually defined as a function of a material's inherent hazard and the potential for, or likelihood of, exposure:

risk = $f(\text{the inherent hazard of a material, the potential for or likelihood of exposure})$

The risk equation is often expanded to include a severity rating for discrete probabilities. From a green perspective, this is useful to bear in mind. One may attempt to use highly hazardous materials for a particular reaction or part of a process while designing the overall process to have less impact and a lower risk. A good example of this might be the *in situ* generation of highly hazardous materials in small volumes that are immediately consumed, as has been done in the case of phosgene production for isocyanate production [40].

2.7.1.4 Cost

Refer to the discussion above and to reference [11] for an example of cost implications.

2.7.1.5 Renewability

The ability to obtain the materials of interest for the maintenance and extension of human society is perhaps one of the most important unsolved problems of the twenty-first century. As one looks around, it is obvious that very few chemicals used routinely in commercial operations are currently available from renewable sources. Occasionally we may find an example of a material that is from renewable sources, but these are usually accompanied by considerable life cycle environmental impacts. Or, we find that there are undesirable trade-offs between environmental impacts, such as a reduction in global warming potential, which at the same time significantly increases the eutrophication potentials associated with the material. A very relevant example of this sort of trade-off is seen in the production of bioethanol or biodiesel, where considerable controversy surrounds the sustainability of both of these fuels.

So, what is the relevance of such debates to metrics for assessing the greenness of syntheses? First, assessments about what constitutes a renewable material have to be made from a life cycle perspective. Second, new technologies are generally at a disadvantage to existing technologies. This is seen when one compares, for example, a highly developed chemical processing route based on non-renewable resources with processes that use potentially renewable materials and processing approaches that have not been optimized over the course of many years as the chemical routes. This is a very real dilemma that currently inhibits the adoption of many biologically based fermentation or biotransformation processes. When compared with chemical synthetic processes, biological processes typically cannot immediately compete on favorable terms.

Because the state-of-the-art of new technologies continuously evolves over time, comparisons one might wish to make are not always possible on an “apples-to-apples” basis. It is also true that materials and energy use in a biological or potentially renewable process can be several times larger than a chemical synthetic process, given the differences in process and volume intensity, the ease of separating the product from the biomass, and the efficiency of the organisms in converting substrate into the desired product.

2.7.1.6 Recyclability

Both in-process and post-processing recycling is desirable, depending on the context. Although in-process recycling is the preferred approach whenever possible, it is largely restricted to the petrochemical and commodity chemicals industries. In-process recycling is generally very difficult to execute in the kinds of batch chemical operations that are common to the fine chemical, pharmaceutical, and agrochemicals businesses. If, however, these batch operations are converted to continuous processes, they are more likely to incorporate in-process recycling.

Out-of-process or post-process recycling has been taking place more routinely in recent years and is performed on- and/or off-site, depending on the solvent and the local recycling infrastructure. Although each option has a common set of issues and impacts, transport and storage of bulk solvent on- and off-site generally leads to greater numbers of potential impacts to manage. Depending on the type of reaction mixture, the scale of the process, and the throughput, recycling can create some problems, as in the case of aqueous–organic reaction mixtures containing solvents with similar boiling points or those that form azeotropic mixtures. These situations may, on balance, result in less than desirable solutions or solutions that are technically or economically close to impossible with existing technology for recycling, and it would be better simply to obtain virgin solvent. One clearly needs to balance costs and impacts across the entire life cycle to evaluate recycling opportunities appropriately.

Recyclability metrics approaches are generally similar to those for other aspects. It is possible to sum the masses or numbers of potentially recyclable chemicals, solvents, water, and so on. However, no matter which recyclability metrics are developed and ultimately chosen, they should drive chemists and engineers to explore different solvent systems that facilitate the desired chemistry while ensuring facile recovery and reuse.

No matter where recycling occurs, either in-process or out-of-process, the total mass metric will necessarily be reduced by the amount of recycled materials in the process. It is therefore important not only to account for the reduced impacts from a life cycle viewpoint, but also to account for the environmental and resource usage impacts that result from recycling materials (e.g., distillation energy for solvent recovery). It should be noted that in most cases the benefits associated with the avoidance of manufacturing impacts tend to dwarf the energy and resources requirements for recycling the materials.

2.7.2

Equipment and Operability Intertwined

Earlier in this chapter, we made several general points about metrics principles that are especially relevant to equipment selection and operability. It is worth revisiting these principles to note that good process metrics for these categories require a very good understanding of the overall chemical synthetic process and that optimization of a process should be done from a multivariate perspective. Metrics in these categories should be seen as having considerable dependencies on each other and on the materials and chemicals used in the process.

Given the current economic climate and the shift in chemical manufacturing to other regions, established industries are generally not building new plants to accommodate new processes or products. The consequence of this is that the type of unit operations in common use is generally fairly small and fixed over time, and for a multi-purpose batch chemical synthetic operation process designers typically tend to “make do” with what is available to avoid capital expenditure, plant shutdown for modifications, and so on. It is also true that where new synthetic chemical plants are being built, they are merely copies of existing technology, so the state-of-the-art is not moving significantly forward. In terms of metrics for this area, then, it is important to understand the resulting complexity of a given process that is being fitted into an established processing train. The plus side of this is that there is a great opportunity to take relatively simple, modular, standardized approaches to process assessment.

2.7.2.1 Type and Number of Unit Operations

For any process associated with a chemical synthesis, there will be a number of different unit operations and there will be a variety of options that one can choose to carry out the desired operation (e.g., reactions, distillations, extraction). Metrics in this category therefore provide an indication of the overall process complexity. As a way of illustrating this, one can think about how one might go about isolating a solid from a liquid reaction mixture. Such approaches as gravity settling and decanting, solvent switching, filtration, centrifugation, and/or variations on, or combinations of all of the above, may be used to carry out the isolation. Each isolation strategy will have its own particular challenges and different impacts that will need to be assessed and evaluated. The chosen strategy will impact the overall mass and energy efficiency of the final process and, as a result, there will be the potential for various and different EHS impacts such as occupational exposure risks, process safety risks, and/or environmental risks.

2.7.2.2 Size of Unit Operations

The size of a unit operation is likely to affect energy and mass transfer and therefore the efficiency of mixing, the reaction rate, by-product formation, and control of exo- or endotherms, and separations in general become more challenging. As processes are scaled up, one needs to pay closer attention to determining and maintaining optimal control over mass and energy transfer in any unit operation, as with larger size it will be more difficult to achieve efficient mass and energy transfer to allow the reactions and separations. Optimal control may sometimes be challenging to achieve if a chemical plant is not specifically designed with the process involved. As was mentioned previously, in the batch chemical business this is often not the case, so inefficiency is inherently a part of most processes.

2.7.2.3 Scalability

Scalability is a term that is used to describe the ease and capacity for changing a process to accommodate different production volumes. To scale chemical processes

safely and successfully, one must develop sufficient process understanding and control to ensure that when changes to larger or smaller equipment sizes occur, product quality and yield will not be adversely affected. Although scalability in large petrochemical or bulk chemical manufacturing plants is generally a given, scaling up a new technology is by no means a trivial endeavor. Scalability is also required if a product becomes commercially successful.

In contrast to the petrochemical context, in the batch chemical multi-purpose chemical plant context there are frequent struggles to achieve facile transitions from the R&D laboratory to bench scale to pilot scale to commercial scale. Although there are many reasons for this, the issues and challenges during scale-up can result in reduced product quality and yield, increased by-product formation, and longer cycle times. In some cases, scalability issues will lead to failures in key product properties such as color, size, or crystal structure. The green downside to scalability caused by longer cycle times, decreased yields, by-product formation, or an inability to reproduce key product properties is that waste increases and more materials and energy will be used to rectify the problems.

Metrics for scalability require a specification of the critical quality attributes and a good understanding of the chemistry and the associated processes. One can then probe the limits of acceptability of these critical attributes, and by so doing will discover the scalability limits of the process. As a process is scaled up, one needs to ensure that it is operationally simple and that there are no unacceptable environmental, safety, and health risks.

2.7.2.4 Controllability

In the petrochemical and bulk commodity chemical manufacturing industries, automated, real-time process control has been an essential element of their success. Considerable process understanding and control of critical process parameters are tightly maintained to achieve statistical process control or six sigma performance, that is, the occurrence of one defect in a million. This performance has only been possible through the use of real-time process analysis that is linked to programmable logic circuits that make continual changes to various process inputs, both material and energy, as required.

For batch chemical operations, real-time process control and understanding are rarely achieved despite recent attempts to achieve greater statistical process control. The batch chemical industry is typically able to operate at no more than about three or occasionally four sigma, or one defect in 1000–10,000.

The green downside to three or four sigma processes is that they will produce more waste, and in the process consume more materials and energy per unit of finished product while reducing throughput and cycle time. When processes are out of control, product specifications will not be met and there is likely to be a need to reprocess the off-specification product or, in the worse-case scenario, to discard it. In either case, an out-of-control process is a problem.

Controllability metrics might be something as simple as recording the number of excursions from statistical process control, but process capability indices are probably

the most useful metrics for assessing controllability. Simply stated, a process capability index is a comparison of the output from an in-control process with its specification limits, with an in-control process being one where most of the measurements fall inside the specification limits. The comparison is made by taking the ratio of the spread between the process specifications (the specification “width”) to the spread of the process values (the process “width”). In a six-sigma environment the process “width” is six standard deviation units for the process. The general equation for a six-sigma process capability index is

$$\text{process capability} = C_p = \frac{USL - LSL}{6\sigma}$$

where USL is the upper specification limit, LSL is the lower specification limit, and σ is the standard deviation of the process. As can be seen from this equation, if $C_p > 1.0$, then the process specifications cover almost all of the process measurements.

Additional indirect proxies for assessing controllability might include such things as the mass or volume of waste produced for each kilogram of final product, or the amount of materials and/or energy consumed for each kilogram of out-of-control product caused by excursions outside the control zone. An example of how this might work would be the case where a rejected batch becomes waste that requires additional mass and energy to replace, treat and dispose of, or to rework the rejected batch.

2.7.2.5 Robustness

A process that is not greatly affected by variations in process temperature, mixing, minor variations in rates of addition, and so on would be considered robust if these excursions did not adversely affect product quality. The main difference between robustness and controllability is that a capable or controlled process will stay within the desired parameters whereas a robust process may experience excursions outside the control parameters, but these excursions will not affect the critical quality attributes.

A good understanding of key process inputs and parameters may be obtained through careful statistical design of experiment and will lead to a good understanding of how robust a process is. Factors that can adversely affect process robustness include non-selective chemistry or unwanted side reactions, physical and chemical stability of the reactants or reagents, and the complexity of the process separation train.

2.7.2.6 Throughput/Cycle Time

Throughput is best understood as the time required to produce a quantity of average saleable product and cycle time is best understood as the average rate at which products are manufactured. Throughput will be affected by such things as the efficiency and rate of chemical conversion, the isolated process yield, plant capacity, the availability of equipment, process time, cycle time, the number of chemical steps, the number of unit operations, plant layout, warehouse processes, raw material availability, process bottlenecks, labor availability, and others.

As a synthetic chemist, there are several important objectives to ensure good cycle times and throughput which are likely to seem obvious upon a moment's reflection. The first is to find reactions that proceed to completion as rapidly as possible under statistical control. Second, high isolated yields as close to theoretical as possible are desirable. Third, the fewer number of steps required, the better. Although these may seem obvious, it is common for reactions and processes to be transferred into manufacturing that do not meet these criteria. It is worth noting that a recent survey of processes within AstraZeneca established a clear relationship between the number of synthetic steps and the throughput; when the number of steps decreased linearly, the throughput increased exponentially.

For continuous processing operations, maintaining high throughputs is essential for economic viability and profitability. For a typical multi-purpose batch chemical plant, continuous utilization of multiple processing trains is extremely difficult and rarely achieved. It is not uncommon to find significant processing barriers related to extended reaction, reflux, filtration and/or drying times, and so on. Each unit operation, series of processing steps, or multiple stages lengthens the cycle time and throughput, which will in turn lead to increased consumption of materials, energy, and labor.

Several different approaches may be investigated to track throughput in a plant. These include such things as tracking the volume or mass of the product or intermediate manufactured over a given period of time, the number of products produced over a given period of time, and others.

For a standard batch chemical operation, a process that can be run repeatedly over long periods of time without cleaning or maintenance of the processing train will significantly improve throughput and cycle time. Any metrics for throughput and cycle time should therefore include the time required for cleaning, but also for transportation, and maintenance, as these can dramatically affect the overall cycle times and utilization rates of a plant. A simple model developed from the AstraZeneca survey calculated the time for a manufacturing campaign as

$$\text{time for manufacturing} = T_m = \frac{N_B}{P} + \text{misc}$$

where N_B is the number of batches, P is the productivity and "misc" accounts for any time needed for additional activity, such as plant cleaning and maintenance.

2.7.2.7 Energy

For the large integrated petrochemical and chemical manufacturing enterprise, process integration and modifications are continually pursued as a means of reducing the enormous amounts of energy consumed. However, the attention to energy efficiency is comparatively much less in the batch chemical environment.

This lack of attention starts with route development because, as a synthetic organic chemist, it is common when executing many different kinds of chemistries for there to be a need to heat and/or cool reaction liquors in any given step or stage of a synthesis. Although it may be possible to avoid such temperature changes through

closer attention to route strategies and how chemistries might be combined with different reactor types and configurations, this is generally not what chemists do. It is also generally true that because there is a large installed base of reactors with their supporting unit operations, the implementation of newer technologies is very difficult. For either the batch environment or the continuous environment, existing processing trains that have been paid for many times over will continue to be used unless the gains in efficiency or the reduction in processing costs are overwhelming.

The metrics that we might use for energy are, not surprisingly, very similar to the mass metrics. It is clearly possible to compute the total energy used per kilogram of product to highlight key materials use, or to track the different energy uses in the form of heating or cooling. In addition to our processing energy, we should also remember to account for the life cycle energy requirements, such as the energy required to produce raw materials, to recycle materials, and to carry out waste treatment. Some potential metrics might include the following:

$$\text{Energy Intensity} = \frac{\text{Total process energy [MJ]}}{\text{kg of final product}}$$

$$\begin{aligned}\text{Life Cycle Energy} &= \frac{\text{Life Cycle energy requirements [MJ]}}{\text{kg of final product}} \\ &= \frac{\sum(\text{process, material manufacturing, recovering, treatment})}{\text{kg of final product}}\end{aligned}$$

$$\text{Waste Treatment Energy} = \frac{\text{Waste treatment energy requirements [MJ]}}{\text{kg of final product}}$$

$$\text{Solvent Recovery Energy} = \frac{\text{Solvent Recovery energy requirements [MJ]}}{\text{kg of final product}}$$

Or we can express metrics as a fraction of the total energy input, such as:

$$\text{Solvent Energy Ratio} = \frac{\text{Total energy for solvent use and recovery}}{\text{total energy input}}$$

$$\text{Waste Energy Ratio} = \frac{\text{Total waste produced}}{\text{total energy input}}$$

2.7.2.8 Cleaning and Maintenance

Cleaning equipment is something that a synthetic organic chemist is unlikely to think about or spend a great amount of time being concerned about. After all, it has nothing to do with chemistry, right? However, it should be something that is thought about because of the impacts that cleaning has on throughput, cycle time, labor costs, and the environment. Each individual unit operation in a batch chemical operation is utilized for multiple products so the processing train is usually subjected to long

clean-out periods where large solvent volumes and/or aqueous detergents, or both, are used. Because cleaning solvents and detergents are not generally considered to be part of the process, their use is not optimized in the same manner as are other process-related materials and solvents. This means that where it is possible to use them, clean-in-place protocols as opposed to those that specify equipment dismantling and reassembly are preferred. Frequency of cleaning, length of cleaning, volumes of solvent, water, and detergent, energy use, and so on will all affect the overall mass and energy intensity of a process, in addition to cycle time and throughput, amongst others.

A combination of volume or mass per unit of time and/or energy would be potentially useful metrics for cleaning. However, the intrinsic hazards of these materials should also be evaluated, just as for any process reagent, solvent, or reactant.

2.7.3

EHS Hazards and Risk

It is not uncommon practice for many to focus on one region of the EHS risk universe and ignore other parts that are of equal or greater significance. For example, a person with a process safety background may be more concerned with dust explosibility and not pay sufficient attention to the fact that extremely potent or toxic compounds are being handled. In another situation, a person may focus on the environmental risks of wastes and not consider storage risks associated with the reagents or solvents used in the process. It is therefore extremely important to address EHS risks as an integrated problem and not as isolated concerns.

A second common undertaking is for people to make lists of regulations that do or do not apply to a particular chemical. This can be problematic on two accounts. First, most regulatory lists are based on hazard and not risk, which means that many chemicals will appear unacceptable that in reality can be used without too much concern. There is a clear debate within the green chemistry community over the fact that very hazardous materials continue to be used but that they should not be used under any circumstances. Although application of the precautionary approach is understandable, there are those situations where highly hazardous materials may be used with less associated risk than the use of a larger quantity of less hazardous material. As is the case elsewhere, it is important to take a holistic view and weigh the alternatives carefully and objectively. The classic example of this was the Boots ibuprofen process, where the use of hydrogen fluoride and carbon monoxide reduced the number of synthetic steps, increased the mass efficiency, and dramatically decreased the quantity of waste [41].

Second, some compounds are not on lists because they do not meet certain volume requirements, or there has been little EHS hazard testing carried out on the materials. In this case, one might be lulled into believing that a compound is fine to use when in reality it is not, or not enough data are available to know whether it is fine or not. In recent years, there has been a movement towards chemicals legislation, for example, the European REACH legislation, that should overcome the problem of a lack of EHS information. However, the implementation of the legislation and the

required testing will take some time, and for low-volume chemicals credible EHS hazard information is likely to be hard to obtain.

Another important area for metrics to evaluate the greenness of syntheses is toxicology, the study of the effects that chemicals have on living systems. Within toxicology, it is important to understand that effects can be acute (effects that are immediate and/or of short duration) or chronic (effects that occur following long-term exposure to the chemical). In general, most attention in the past has been and continues to be directed towards acute hazards. This is largely because the links between long-term chemical exposure and ill health in humans or other species are often difficult to determine conclusively, much less predict.

Apart from avoiding chemicals of known chronic effect, there are several strategies that one may employ to avoid potential problems. One thing that is often proposed is to apply the precautionary principle uniformly. This means that until the hazard potential of a chemical is known, use of that chemical should be avoided if at all possible. Frequently, for practical reasons, the precautionary principle is not something that can be rigorously followed. A good strategy in that instance is to assess chemicals by analogy, that is, if the chemical is structurally similar to another chemical with known chronic hazards, then it may be prudent to avoid it. In some instances, it may be possible to take a more sophisticated approach [42–44] through the use of quantitative structure–activity relationships (QSARs). QSARs require a good database of relevant chemicals with known cause and effects for ill health or other toxic effects to be successful. QSARs may allow one to screen out chemicals of concern, but this requires an understanding of the compound of interest and a reasonably high degree of understanding of human or ecotoxicity to make good use of the predictive capability of any type of modeling.

2.7.3.1 Occupational Exposure Hazards and Risk

Occupational exposure hazards associated with process materials may be assessed through the use of permissible or occupational exposure limits (OELs or PELs). OELs are generally available for many high-volume chemicals but not for a large number of compounds used by synthetic organic chemists, especially for developmental or route exploration work. If the OEL or the occupational hazard category is available, one may assess occupational exposure risk by careful evaluation of all the materials and the unit operations employed in a process or by developing an exposure assessment that is based on a given type or class of hazard to estimate the occupational exposure risk, as in the case of Dow's exposure index [44].

A variety of metrics approaches to assess occupational exposure risk are possible and include simply summing the number of materials in a given hazard band to slightly more sophisticated approaches that apply different weightings to toxicological concerns such as the potential for carcinogenicity, mutagenicity, reproductive effects, and so on. Simply summing the masses of materials in a given band or performing a high-level assessment of potential risk based on the mass may also be used, as discussed above. Assessments may also be based on a chemical's physical form, the type of unit operations employed in a process train, or the potential for accidental release into the workspace.

2.7.3.2 Process Safety Hazards Risk

In the laboratory, precipitous changes in temperature and or pressure that lead to secondary events such as detonations, explosions, over-pressurizations, fires, and so on are generally not considered to be major issues. A sudden rise in temperature or popping a stopper off a reaction flask can be managed without a great deal of effort. However, when these things occur on a larger scale, as in a batch chemical operation, they can cause major problems. As with most things related to greening syntheses, the best way, indeed the most cost-effective way, of avoiding these sorts of risks is through appropriate synthetic design. The synthetic chemist is fortunately not without assistance about what to do as a number of practices and principles have been developed over many years, and these are known as inherent safety principles [45]. Inherent safety principles are very similar and complementary to pollution prevention principles, and each area has benefited from knowledge of the other. In pollution prevention and inherent safety, one attempts to use a hierarchy of approaches to avoid and/or reduce the risk of an adverse event.

For the synthetic chemist scouting out routes, or for the process chemist developing the final process, the most cost-effective means of avoiding potential risk is to eliminate inherently unsafe materials. The problem from a synthetic chemistry standpoint is that this generally includes materials whose physical or physico-chemical properties lead to them being highly reactive or unstable. As is well known, chemists exploit chemical instability because the inherent reactivity of a material ensures that a reaction will proceed to completion at a rapid enough rate to be useful, that is, the reaction is kinetically and thermodynamically favored. Another problem is that without a full battery of tests to determine, for example, flammability, upper/lower explosivity limits and their variation with scale, minimum ignition temperatures, and so on, it is almost impossible to tell how a particular chemical will behave under a given set of reaction conditions.

Our approaches to process safety metrics will be analogous to those that might be used to assess occupational exposure risk. One can also use different indices that have been developed as metrics for estimating and ranking the safety of a given process or chemical reaction. These include indices such as the Dow fire and explosion index [44], the Stoessel index [46] for hazard assessment and classification of chemical reactions, the Inherent safety index, the prototype index for inherent safety, and others [47, 48].

2.7.3.3 Environmental Hazards and Risk

There are a number of ways to approach the assessment of the environmental risk that may be associated with a process. Whatever strategy might be chosen, however, some general risk areas should be part of the overall assessment. First, the inherent hazard, fate, and effects of the materials in the process need to be determined and assessed from an environmental perspective. Second, the potential for any process or unit operations releases need to be identified and evaluated. Third, environmental impacts from transportation, storage, and disposal options associated with the materials used in the process need to be identified and evaluated. Finally, the environmental life cycle impacts of producing those materials need to be collected and assessed.

It should be understood that to develop process metrics based on a credible risk assessment will require a considerable number of tests to assess appropriately the potential environmental hazards associated with the process and the materials used in the process. One typically needs to screen compounds to assess their environmental hazard and their tendency for persistence, bioaccumulation, and toxicity. Depending on how a compound is ultimately used, environmental testing might lead you to the conclusion that it is best to avoid the commercial production of a particular compound. Alternatively, you might devise a process that uses the compound but controls the environmental risk to acceptable levels. For the latter case, performing a process-specific risk assessment would be imperative to assess the impact of the inherent hazard and environmental fate and effects of a given chemical or set of chemicals. In addition, the unique characteristics of the process, available treatment, and volumes will need to be taken into consideration.

2.7.4

Quality

2.7.4.1 Purity

It is probably universally true that synthetic chemists seek reactions with very high yields and as few impurities as possible in the isolated intermediates and the final product. Although a purity of as close to 100% is sought in every case, this is often very difficult to achieve in practice, especially for complex molecules and the processes used to make them. In general, as a chemical synthesis becomes more complex, it becomes more difficult to separate and isolate the desired target compound easily. It is therefore not uncommon to require one or more recrystallizations of the final product and/or intermediates to achieve the desired purity, crystal structure (including polymorphs), or particle size characteristics, but each of these lead to an increase in solvent use. Although it is true that solvents may be recycled, this is not always the case and recycling comes with a cost (economic and environmental) in energy and the additional capital invested in storage and distillation and other types of recovery infrastructure.

Metrics for purity may simply be a statement of the purity or the impurity profile of the final product for any given process. However, if one is interested in purity from a perspective of greening syntheses, we might be more interested in how many times we isolate intermediates and or how many times we recrystallize the final substance to achieve the desired purity. Another point worthy of consideration is the idea that “quality” is defined as delivering the exact requirements needed in the eyes of the customer, and it is therefore possible for higher purity to go beyond the customer’s needs. Additional purification steps will, in almost every case, add to the mass and energy intensity of a product without necessarily adding value to the customer.

Other metrics to be considered may be combinations of such things as net waste per isolation or the quantity of energy per isolation. Although these may be more insightful metrics to derive and use, it should be understood that they are more difficult and time-consuming metrics to develop.

2.8

Conclusions

The preceding discussion has hopefully illustrated the need to develop green metrics for chemical processes in a holistic fashion and from a systems point of view across a range of disciplines, where trade-offs are often encountered amongst the metrics. It is also hoped that a case has been made for metrics being context dependent, with one kind or one set of metrics not fitting all situations. The discussion above will also help to make it clear that different organizations or companies will have to undertake some very hard work to identify, assess, and implement metrics that meet their needs, and then analyze the information given by those metrics to design strategies for the development of greener, more sustainable, chemistries.

The good news is that there are a large number of metrics from other companies and many of these metrics, or variations of these metrics, are likely to meet the needs of most organizations or companies. It is imperative, however, that in developing metrics, organizations bring together a diversity of disciplines to identify the few key metrics that will achieve the best results, that is, the metrics that drive synthetic chemists towards designing greener chemistries. Metrics that are developed in a compartmentalized fashion are destined to be less useful in the quest for greener synthetic pathways.

Ideally, metrics should not be collected for the sake of being seen to do something, but they should drive meaningful behavior around greening syntheses and their associated processes. Finally, it is important to follow liberally the 80:20 rule, that is, do not strive for the perfect or most comprehensive set of metrics; rather, find the few key metrics that will result in the greatest benefit. Above all, begin to apply metrics and use them to improve the synthetic routes!

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3

Alternative Feedstocks for Synthesis

Arno Behr and Leif Johnen

3.1

Introduction

3.1.1

Renewable Resources as Natural Feedstock

For more than 50 years, industrial chemistry has been based on coal, oil, and gas. Hence renewable resources have become less important, but shortage of resources, the greenhouse effect, growth of the world population, and the pursuit of sustainable development have awoken great interest in the energetic and substantial use of renewable resources in industry and research. A lower dependence on crude oil imports and raw material costs is currently accelerating the shift towards chemical products derived from renewable biological feedstocks.

About 170–200 billion tonnes of biomass are provided yearly by photosynthesis with the aid of sunlight. Only 4% of this enormous amount is currently used as food, fuel, or basic material. The worldwide consumption of raw materials totals about 245 million tonnes, of which only 20 million tonnes are renewable resources (8%). The aim of the United States and the European Union is to increase this proportion to 20–25% by 2020.

Which renewable resources can be used industrially? From forestry, wood and resins are available; from agriculture, oleiferous fruits, sugar beets, sugar cane, corn, and potatoes; and from the meat and fish industries, animal waste such as bones. From these primary products the following ingredients – the actual renewable resources – are obtained:

- *Carbohydrates*, which have the general formula $C_nH_{2n}O_n$ and are classified as mono-, di-, oligo-, or polysaccharides depending on their carbon chain length.
- *Lignin*, which is a macromolecule occurring in wood that is predominantly composed of coumaryl, coniferyl, and sinapyl alcohols and therefore has a high aromatic percentage.
- *Fats and oils*, which are mainly triesters of glycerol with long-chain carbon acids (C_8 – C_{22}), the so-called fatty acids.

- *Proteins*, which are obtained from animal waste (whey and bones) or vegetable raw materials (soya, rapeseed, and wheat) and which are poly(amino acids).
- Further renewable resources that occur only in smaller amounts are often summarized as “*vegetable secretions and extracts*.” Waxes, natural rubber, colophony, turpentine oils, herbal dyes, and essential oils are important examples.

3.1.2

Challenges of Using Renewable Resources

In industrial chemistry, the current processes are mainly based on the bulk chemicals carbon monoxide, hydrogen, ethylene, propylene, and benzene, all obtained from oil and gas. By means of classical chemical processes, chemical intermediates are produced, which – due to versatile combinations – can be converted into a multitude of higher value molecules. This synthetic approach yields a broad range of applications from low-cost plastics up to expensive highly designed drugs. The utilization of oil and gas as starting materials, which contain almost exclusively hydrocarbons, requires the insertion of functional groups to generate the desired intermediates. Hence the big challenge of using oil and gas is selective functionalization. By contrast, most renewable resources contain too many functional groups. This “hyper-functionality” synthesized by Nature is a common problem in the direct conversion of renewable resources to hydrocarbon fuels. The difference between fossil and renewable feedstocks becomes apparent on comparison of their elemental composition: Crude oil consists of about 85–89% carbon, 10–14% hydrogen, and less than 1% oxygen. Renewable resources, however, contain only 50–75% carbon and 6–13% hydrogen, but 11–45% oxygen [1].

In addition to these substantial differences, several barriers currently impede the market entry of renewable resources: Predominantly today’s chemical industry is orientated towards fossil raw materials and thus the existing processes are incompatible with the new resources. Currently, the use of renewable resources leads to disadvantages in price compared with crude oil. Further, the qualitative and quantitative availability of the natural products hampers a major breakthrough. The supply and the composition of the renewables often change with year and location. Additionally, some renewable resources with special properties, such as palm oil, cannot be cultivated everywhere because of unfavorable climatic conditions and must therefore be imported via long routes. Furthermore, the increasing competition between using crops for food and feed on the one hand and for biofuels on the other hand causes ethical problems.

Nevertheless, renewable resources may provide promising chances in the future. Taking the whole process chain into consideration, renewables can make substantial contributions to climate protection. The products can be made and used locally. A wide product platform can be offered and the natural product origin leads to a positive image. Particularly bio-based products usually show high biodegradability and biocompatibility. For selected resources, the synthetic pathway in plants is superior to chemical synthesis.

However, extensive efforts in biotechnology, chemistry, and chemical engineering will be essential to meet the challenges of renewable resources. An outstanding tool for the selective conversion and improvement of renewables will be the high potential of catalysis. For the utilization of renewable resources, three approaches can be distinguished:

- The biomass is thermally gasified to C₁ building blocks (e.g., to carbon monoxide,) which are converted catalytically to bulk chemicals.
- By catalysis, the natural materials are decomposed into smaller building blocks (C₂–C₆) that provide a basis for larger molecules.
- The natural materials are directly converted into useful products. In this way, the chemical structure of the renewables is optimally used. This is the smartest and most energy-saving option.

In the following sections, the renewable resources are presented as alternative feedstocks for chemical syntheses, giving a short overview of newer and already established routes. It is not intended to give an extensive review, but rather to exemplify that catalysis is a versatile tool to convert alternative feedstocks directly into valuable products. References to detailed review articles are given as appropriate. Lately, some surveys focusing on catalysis and renewable resources were published by Gallezot [2, 3] and van Bekkum [4].

3.2 Carbohydrates

As a product of photosynthesis, carbohydrates are the major part (75%) of annually generated biomass. Only 4% of these are used by humans and the rest decays and recycles along natural pathways. Obviously, carbohydrates represent a nearly inexhaustible raw material. Industrially, carbohydrates are traditionally used for food, lumber, paper, and heat production. Carbohydrates are defined as the “hydrates of carbon” and contain mainly carbon, hydrogen, and oxygen. According to the carbon chain length of their constituent repeating units, they are divided into mono-, oligo-, and polysaccharides. Monosaccharides contain a single hydroxylated hydrocarbon backbone, whereas oligosaccharides contain a few monosaccharides connected via glycosidic linkages [5]. Carbohydrates as renewable raw materials have been reviewed in detail by Lichtenthaler [6–8] and van Bekkum, Röper, and Voragen [9].

3.2.1 Polysaccharides

3.2.1.1 Cellulose

Cellulose is an unbranched polysaccharide that consists of several hundred up to 10 000 1,4-linked β -D-glucose molecules (Figure 3.1). The key resource of cellulose is wood, which is lumbered worldwide in an amount of 2 billion tonnes per year.

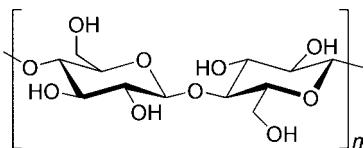


Figure 3.1 Cellulose.

The major part is used as firewood or timber; only 13% is further processed by mechanical and chemical treatment. The common process to convert wood into wood pulp is the Kraft process, which uses a mixture of sodium hydroxide and sodium sulfide to separate lignin and cellulose. The resulting cellulose is predominantly used for the production of paper and board. Only a small percentage (4%, 4–5 million tonnes) is further processed chemically.

An important process is the manufacture of regenerated cellulose applied to make fibers (e.g., rayon) and films (e.g., Cellophane). Solvents used classically in cellulose regeneration are a mixture of carbon disulfide and sodium hydroxide or ammoniacal copper solutions. More recent solvents include *N*-methylmorpholine-*N*-oxide and phosphoric acid [4]. The cellulose solution is extruded through nozzles into an acidic precipitation bath and is spun into fibers. Recently, the partly toxic and strong-smelling solvents have been replaced by ionic liquids which are even able to improve the solubility of the slightly soluble cellulose [10]. For example, 1 l of 1-butyl-3-methylimidazolium chloride dissolves 100 g of cellulose at 100 °C [11].

Other important secondary products of cellulose are esters and ethers. Esters can be used for fibers and films, but also for varnishes and molding materials. The most important representative of ether derivatives is carboxymethylcellulose, which has widespread applications as a thickener, binder, and graying inhibitor in detergents. Despite the versatile possibilities to derivatize cellulose, only 0.5% of worldwide felling is used for chemical refining. Detailed information about the fundamentals and functionalization of cellulose can be found in [12, 13].

3.2.1.2 Starch

Starch consists of polysaccharides, in fact of the branched amylopectin and the linear amylose (Figure 3.2). Starch can be obtained from very different plants, such as corn, wheat, rice, and potatoes. Most of the starch raw material is used directly for food (“native starch”); only a small percentage is modified either by partial hydrolysis or by total saccharification, for example to glucose or fructose. The enzymatic hydrolysis of starch to high-fructose corn syrup (HFCS) is described in Section 3.2.3.2.

By means of partial hydrolysis, the chain length of the polysaccharide can be shortened, but the polymer structure is maintained. The resulting maltodextrins and dextrans are useful compounds for dietary foods and thickeners. The utilization of starch in industry was reviewed thoroughly by Röper [14].

Several investigations have been carried out to modify starch catalytically with the aim of obtaining specific hydrophilic properties. For example, selective oxidation of the hydroxymethyl groups of starch molecules leads to polycarboxylic acids, which can be used as adsorbers in diapers (nappies). A suitable catalyst for the synthesis of

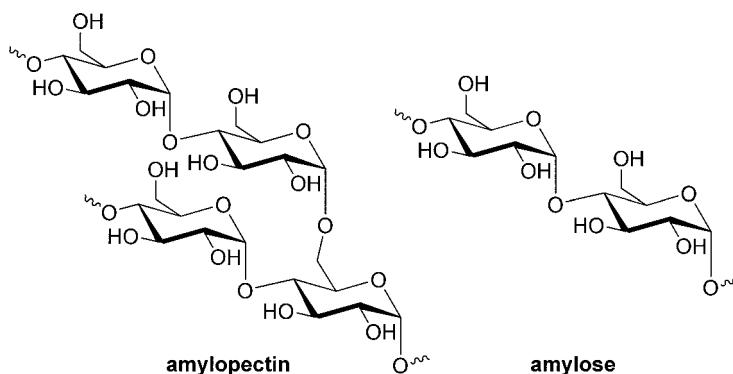


Figure 3.2 Starch.

this “carboxyl starch” is a three-compound system consisting of hydrogen peroxide, methyltrioxorhenium, and sodium bromide [15].

With iron phthalocyanine as catalyst, the glucose units of starch can be selectively cleaved between the C-2 and C-3 atoms along with the formation of aldehyde groups. Another possibility for modifying the hydrophilic properties of starch is grafting with hydrocarbon chains. Due to their numerous hydroxy groups, maltodextrins and glucose are convenient building blocks for the combination of hydrophilic sugar molecules with hydrophobic fat molecules, yielding a surfactant which is built up only by natural compounds. These alkylpolyglucosides (APGs) represent an important class of nonionic surfactants with bright prospects. They can be synthesized selectively, are completely biodegradable, and their properties can be specifically adjusted by the ratio of the two starting compounds. Analogous to cellulose, starch can also be converted into ethers and esters.

3.2.2

Disaccharides

Sucrose (“sugar”) and lactose (“milk sugar”) are the most important disaccharides (Figure 3.3). Sucrose as the “royal carbohydrate” [16] is produced on a scale of 160 million tonnes annually, whereas 300 000 t of lactose are produced each year. In the period 2005–2006, the bulk-quantity price of sucrose was about €0.25 kg⁻¹ and that of lactose about €0.60 kg⁻¹ [6]. Due to these prices, which are comparable to those of basic organic chemicals, and their large-scale accessibility, intense efforts to boost

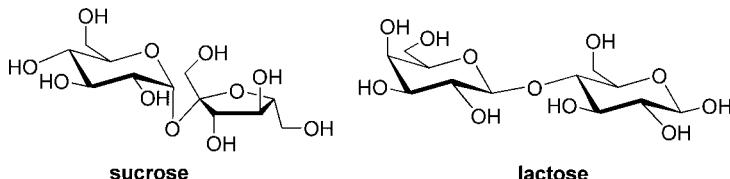


Figure 3.3 Sucrose and lactose.

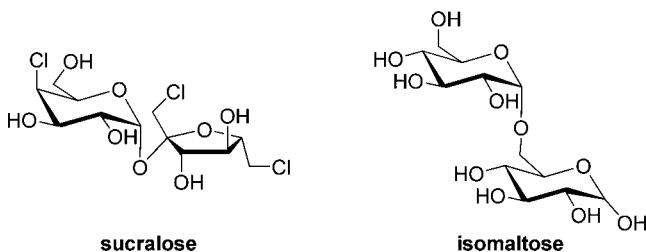


Figure 3.4 Sucralose and isomaltose.

carbohydrates as renewable key compounds in the chemical industry have been undertaken.

3.2.2.1 Sucrose

Sucrose is a disaccharide of α -1,2-linked α -glucose and β -fructose and the most important sugar in plants. Due to its sweetness and its structure-forming properties, sucrose is ubiquitous in food preparations as the most common sweetener. Many industrial applications are based on further processing by fermentation [8]. Thereby sucrose can be directly used or the synthesis starts with the monomer constituent glucose (cf. Section 3.2.3.1). Splitting of sucrose into its components glucose and fructose by a glycoside hydrolase enzyme (invertase) yields the so-called “invert sugar syrup,” which is sweeter than the original sucrose solution. Typical applications with a preserved disaccharide structure are the manufacture of sucralose, a zero-calorie sugar substitute artificial sweetener with chlorine substituents, and isomaltose, a tooth-friendly sucrose replacement favored in products for diabetics (Figure 3.4).

3.2.2.2 Lactose

Lactose contained in milk and dairy products consists of β -galactose and β -glucose units bonded through a β -1,4 glycosidic linkage. Lactose has its most applications in the food industry, particularly in infant nutrition, and in the pharmaceutical industry as a matrix material [17]. Recently, lactose has been developing into a key molecule because of its secondary products. For example, hydrogenation affords lacitol, appreciated as a low-caloric sweetener, oxidation leads to the metal-complexing lactobionic acid, and the laxative lactulose is obtained by isomerization (Figure 3.5). A simple hydrolysis gives a glucose–galactose syrup.

3.2.3

Monosaccharides

The monosaccharides are the monomeric units of the high molecular weight carbohydrates. They are the actual carbohydrate raw material for the synthesis of organic chemicals with tailor-made industrial applications. In particular, D-glucose and D-fructose are still by far the key compounds.

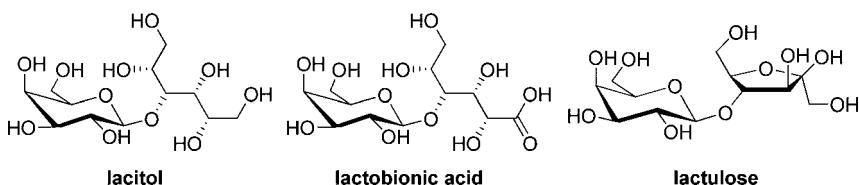


Figure 3.5 Lactose derivatives.

3.2.3.1 D-Glucose

D-Glucose is not only a very important energy source and metabolic intermediate in Nature, but also one of the main products of photosynthesis. Glucose is the starting material for several very valuable industrial applications – often by selective fermentation. Generally, the fermentation process is carried out in such a way that several naturally occurring complex compounds can be produced in large volumes based on glucose, much more effective than with petrochemical routes. The largest fermentation process is the production of ethanol (“bioethanol”) by the ascomycetous yeast *Saccharomyces cerevisiae*. About 300 million hectoliters are produced annually, not to replace the ethylene-based processing lines but to use bioethanol as a direct or indirect fuel additive, for example as ethyl *tert*-butyl ether. Starting from glucose, various amino acids, such as L-lysine and L-glutamic acid, citric acid, and most notably lactic acid, are accessible by fermentation with fungi or bacteria. The major amount of the lactic acid is polymerized to poly(lactic acid) (PLA) via polycondensation because of its very suitable properties for the fabrication of fibers and films. Additionally, PLA is biodegradable and compostable.

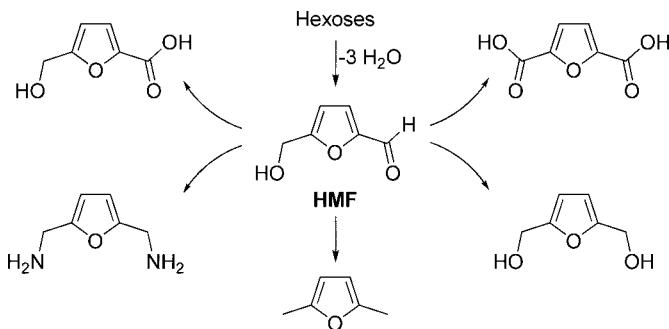
Current investigations are focused on microbial glucose conversions towards 1,4-acids (malic, fumaric, and succinic acid) and itaconic acid. Also, 1,3-propanediol is formed, which is an important component for poly(trimethylene terephthalate), a high-performance polyester [6]. Apart from these biotechnological processes, metal-catalyzed functionalizations are in use. For instance, the hydrogenation of glucose yields D-sorbitol which is used not only as a non-caloric sweetening agent but also as an interesting key intermediate in the synthesis of vitamin C.

3.2.3.2 D-Fructose

In Nature, fructose occurs primarily in fruits, such as berries, melons, and beets, and in honey. Fructose is the sweetest of all naturally occurring carbohydrates (1.73 times sweeter than sucrose). As a result of economic and logistic advantages, the synthetically manufactured “high-fructose corn syrup” (HFCS) increasingly superseded the use of sucrose. This sugar concentrate is produced by treating hydrolyzed corn starch with enzymes to convert it partially into fructose. There are different types on the market with varying proportions of fructose. Especially in the United States, HFCS is used in the overwhelming majority of all soft drinks as an inexpensive caloric sweetener as a consequence of subsidized corn production. It can be found ubiquitously in a multitude of processed foods and beverages.

In contrast to these food applications, the highest industrial non-food application for a fructose compound is attributed to the key compound

5-(hydroxymethyl)furfural (HMF). This is directly accessible from fructose by an acid-induced elimination of water. However, acid catalysts cause various side reactions, leading to high purification costs in an industrial process for this desired key compound. Zhang and co-workers reported on ionic liquids (ILs) and various metal halides as catalysts in the conversion of fructose to HMF [18]. In the presence of 6 mol% CrCl_2 and 1-ethyl-3-methylimidazolium chloride, even glucose can be converted to HMF. Later work showed that the reaction based on fructose could also be carried out in an IL biphasic system [19]. Although the estimated market price of HMF of $\text{€}2500 \text{ t}^{-1}$ is currently too high for a bulky starting material, plenty of versatile applications have already been well investigated. For example, the resulting 5-hydroxymethylfuroic acid, the 2,5-furandicarboxylic acid, and the 1,6-diamine are promising alternatives to replace adipic acid, alkanediols, and hexamethylenediamine in polyamides and polyesters (Scheme 3.1).



Scheme 3.1 Versatile applications of HMF.

Hydrogenation of HMF leads to 2,5-dimethylfuran, an interesting compound for use as a booster due to its high research octane number. Kuster [20] has reviewed intensively the manufacture of HMF and a detailed review of the synthesis, chemistry, and applications of HMF has been published by Lewkowski [21].

3.3 Lignin

Along with cellulose and hemicellulose, lignin also is found in wood as a major constituent. Lignin is a macromolecule that is predominantly composed of coumaryl, coniferyl, and sinapyl alcohols and therefore is a very important source of aromatics (Figure 3.6). Naturally most lignin is located in the secondary wall of the wood cells and decreases the permeation of water across the cell walls due to its lipophilic character. In addition, lignin works as a binder between the cells, generating a composite structure with outstanding strength and elasticity. Lignified material also resists effectively attacks by microorganisms by impeding penetration of destructive enzymes into the cell walls. These protective properties of lignin make it the greatest

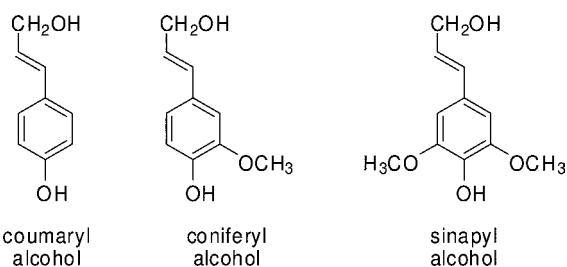


Figure 3.6 Monomeric lignin constituents.

challenge to chemists and biologists to find efficient and low environmental impact ways of unlocking Nature's greatest store of aromatic molecules.

The complex chemical structure of lignin leads to expensive degradation processes and ultimately high levels of impurities, for example, solubilized carbohydrates and considerable amounts of inorganic amounts such as sulfur, which necessitate costly purification processes. Up to now commercial lignins have been obtained exclusively as by-products from the chemical pulping industry [22] – mostly as lignosulfates. The main applications of lignins and lignosulfates are based on their dispersing, binding, complexing, and emulsion-stabilizing properties: dispersants in cement applications, water treatment formulations, and textile dyes, additives in specialty oil field applications and agricultural chemicals; and even as environmentally sustainable dust suppression agent for roads. However, only catalytic vanillin synthesis is known as a sustainable source of aromatic compounds using lignin as starting material [23]. Very recently, Partenheimer of DuPont oxidatively cleaved different lignin samples using metal bromide catalysts in acetic acid–water mixtures, yielding hydroxyaromatic benzaldehydes and carboxylic acids; 11 wt.% of the lignin was converted to these aromatic products [24]. Further investigations should be aimed at improving catalysts and biotechnology to make Nature's store available.

3.4 Fats and Oils

Fats and oils of vegetable and animal origin belong to the most important renewable raw materials used in the chemical industry. The fats and oils are mainly applied in human alimentation; only 10% of the oils are converted into technical products. The total global market for fats and oils amounts to about 130 million tonnes. Soybean oil (31 million tonnes per year), a by-product of soybean flour production, and palm oil (31 million tonnes per year) are the most important fatty raw materials worldwide. Animal fats (22 million tonnes per year) arise as by-products of meat fabrication and processing and are used for nutrition and technical purposes.

From the chemical point of view, fats and oils offer fairly consistent structures. Nearly the total amount of the worldwide commercial material consists of triglycerides (Figure 3.7).

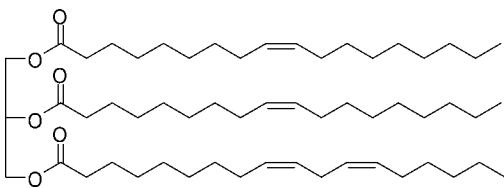


Figure 3.7 Chemical structure of fats and oils (example).

In plants they are composed of CO₂ and water due to solar energy and mostly stored in seeds. As in organisms the nonpolar carbon chain is generated from C₂ units, nearly exclusively even-numbered carbon chains exist. The constitution of the triglycerides is very specific according to the plant species. Coconut and palm kernel oil possess high levels of lauric acid (C₁₂), which leads to the general term lauric oils or “laurics” for these oils. Lauric acid is an important raw material for the production of detergents. The preponderant number of technically available triglycerides particularly consist of C₁₆ and C₁₈ fatty acids. Numerous C₁₈ fatty acid chains include one, two, or three *cis*-C=C double bonds; oleic acid (C_{18:1}) is the most commonly occurring unsaturated fatty acid. The fatty acid spectrum can be changed by plant breeding and gene modification.

The technical conversion of fats and oils starts with a triglycerides cleavage leading to glycerol and fatty acids. This can be done by cleavage with water to give fatty acids or by transesterification mostly with methanol to yield methyl esters. The by-product glycerol is used in a variety of technical applications, but also as an additive for nutrition and as a pharmaceutical excipient (cf. Section 3.4.2). Due to the considerable subsidized production of biodiesel, a methyl ester based on rapeseed oil, substantial amounts of glycerol are pushed into the European market.

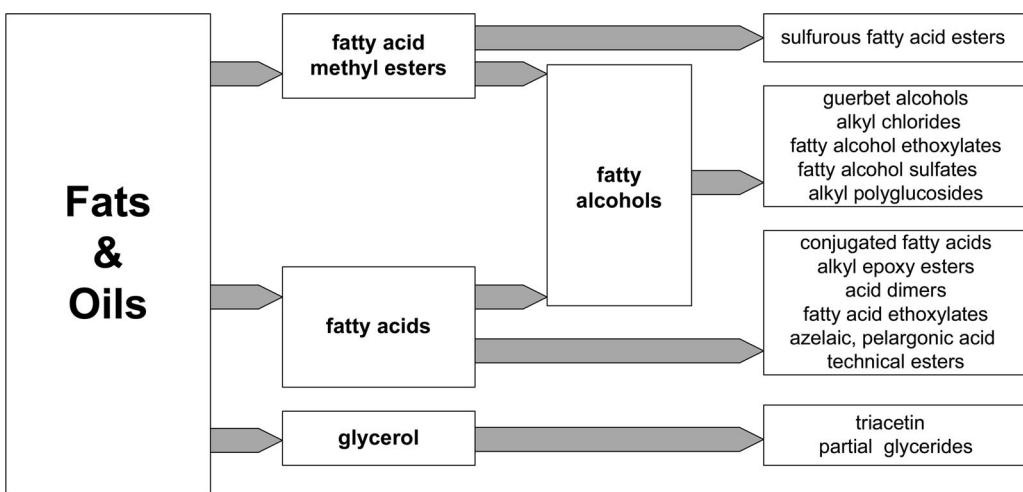
The fatty acids or esters can be further converted into fatty alcohols by high-pressure hydrogenation in continuously working reactors. Approximately 1 million tonnes of alcohols are produced in this way, mainly on the basis of coconut and palm kernel oil. The alcohols are used as raw materials for a range of different detergents. Fatty alcohol ethoxylates (nonionic detergents), fatty alcohol sulfates, and ether sulfates (anionic detergents) make up the highest production volume and are often applied in of washing and cleaning agent formulas.

The chemical products stemming from native fats and oils can be classified in different classes of oleo-base chemicals: fatty acids, alcohols, esters, and specialties, which are expanded in a range of products (Scheme 3.2). The basic chemicals are either used directly as raw materials or they form the basis for the production of specialties.

3.4.1

Catalytic Derivatization of Unsaturated Fatty Compounds

The basic oleochemical chemicals, fatty acids, esters, and alcohols, are so far almost exclusively derived via classical organic reactions at the carboxylate or alcohol



Scheme 3.2 Overview of oleochemistry.

function yielding fatty acid chlorides or amides, fatty amines, or fatty acid salts, the so-called soaps. However, many fats have further reactive centers in addition to their carboxyl function: they contain between one and three C=C double bonds. In oleochemistry, numerous existing homogeneous catalyzed reactions lead to the conclusion that selective functionalizations at these double bonds are possible. These functionalizations provide very interesting follow-up products. Some important applications of oleochemicals are presented briefly in the following. Readers who are interested in more detailed knowledge of fat chemistry are referred to reviews by Behr and co-workers [25–27].

3.4.1.1 Selective Catalytic Hydrogenation

An example of functionalization is hydrogenation, in which hydrogen is added to the C–C double bond with the view to obtaining saturated fatty compounds. This process, which is called “hardening” in oleochemistry, is very well known, for example, in the production of margarine: liquid unsaturated oils are mainly converted into solid saturated fats using heterogeneous Raney nickel catalysts.

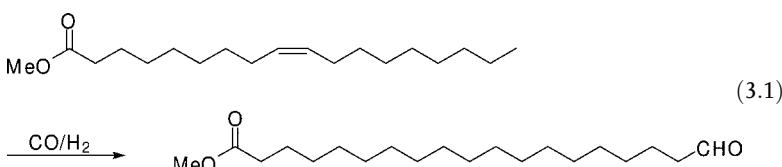
However, a selective hydrogenation, for instance, the hydrogenation of only one of the two double bonds of linoleic acid ($C_{18:2}$) to yield the *cis*- and *trans*- $C_{18:1}$ fatty acids, is much more difficult. In this case, the formation of the completely saturated stearic acid $C_{18:0}$ is to be avoided. This selective hydrogenation was investigated in detail by using homogeneous transition metal catalysts: Examples are metal carbonyls, platinum–tin systems, and catalysts of the Ziegler type (iron, cobalt, and nickel salts activated by triethylaluminum). Neutral precious metal phosphine complexes such as Wilkinson’s catalyst $[RhCl(PPh_3)_3]$ and cationic complexes, e.g. $[Rh(cod)(PPh_3)_2]BPh_4$, were tested, but with only moderate success. The best results were achieved with a palladium nanocatalyst stabilized with propylene carbonate [28].

3.4.1.2 Selective CC Linkage Reactions

Hydroformylation

The first investigations concerning the hydroformylation of fatty compounds were accomplished by Ucciani and co-workers with cobalt catalysts such as cobalt bislaurate and dicobalt octacarbonyl [29]. Later, Frankel and co-workers found that the cobalt-catalyzed hydroformylation of methyl oleate also leads to the corresponding fatty alcohols [30]. In recent investigations on the hydroformylation of fatty compounds, the preferred catalyst is based on rhodium. For instance, the hydroformylation of methyl oleate catalyzed by $[\text{Rh}(\text{acac})(\text{CO})_2]/\text{biphephos}$ yields an isomeric mixture of formylstearic acid methyl esters [31].

A particularly ambitious synthesis is isomerizing hydroformylation (Equation 3.1). In this reaction, first the internal double bond of the methyl oleate isomerizes to the terminal position, which is then hydroformylated to the ω -aldehyde [32].



Metathesis

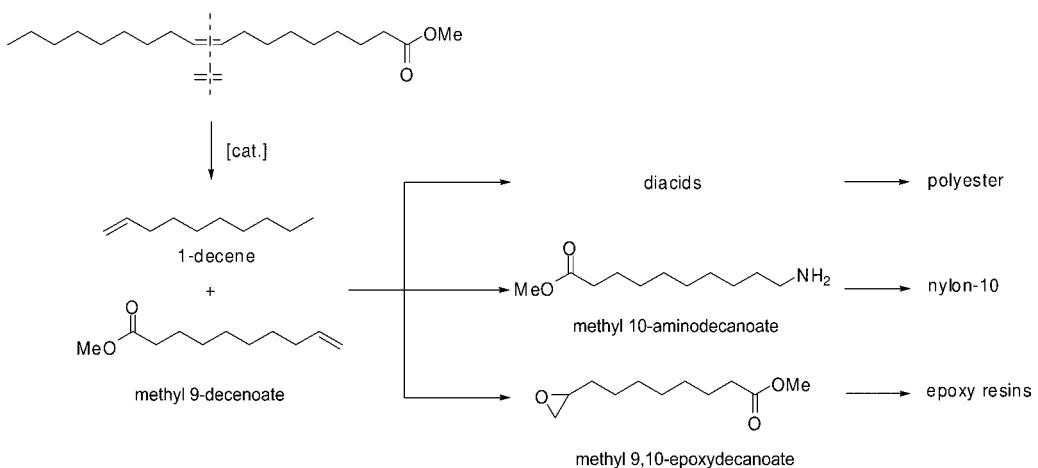
Metathesis has been applied in oleochemistry for many years, but only fairly recently technical realization comes within reach [33, 34]. As typical catalysts, ruthenium carbene complexes of the Grubbs type are applied because of their very high activity (turnover numbers up to 200 000). In principle, oleochemical metathesis can be divided into two different types: in self-metathesis the same fatty substrate reacts with itself and in cross-metathesis a fatty substrate reacts with, for example, a petrochemical alkene. The simplest case, the self-metathesis of methyl oleate forms 9-octadecene and dimethyl 9-octadecenedioate. The resulting diester can be used along with diols for the production of special, comparatively hydrophobic, polyesters. An interesting example of cross-metathesis is the reaction of methyl oleate with an excess of ethene, so-called ethenolysis. This provides two products, each with a terminal double bond, 1-decene and methyl 9-deenoate (Scheme 3.3).

This ω -unsaturated ester is an excellent substrate for a number of important polymers: It can be converted into a C_{11} -dicarboxylic acid, which can be utilized for the manufacture of polyesters, or into 10-aminodecanoic acid, which leads to nylon 10. The epoxidation of the terminal double bond provides 9,10-epoxydecanoic acid, which can be used for the production of epoxy resins.

Other exemplary reactions are the cross-metathesis of methyl oleate with allylamine, methyl acrylate and dimethyl maleate. In just a single reaction step, very different multifunctional products can be produced in this way.

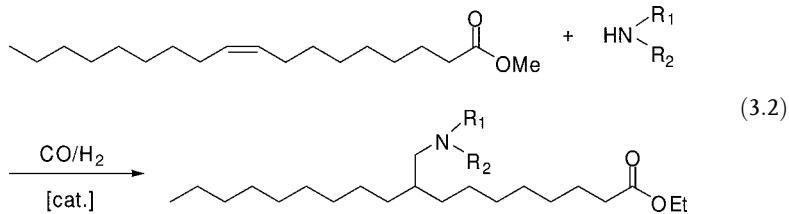
3.4.1.3 CN Linkage Reactions

Hydroaminomethylation is an excellent method to connect an amino function to a fatty acid chain [35, 36]. Mechanistically it is a tandem or domino reaction,



Scheme 3.3 Cross-metathesis of methyl oleate with ethene and the follow-up chemistry.

which consists of several interlocked steps (Equation 3.2): first the unsaturated oleo substrate reacts with the synthesis gas to give an aldehyde. After the reaction of this aldehyde with an amine, the resulting enamine is finally hydrogenated to the desired fatty amine.



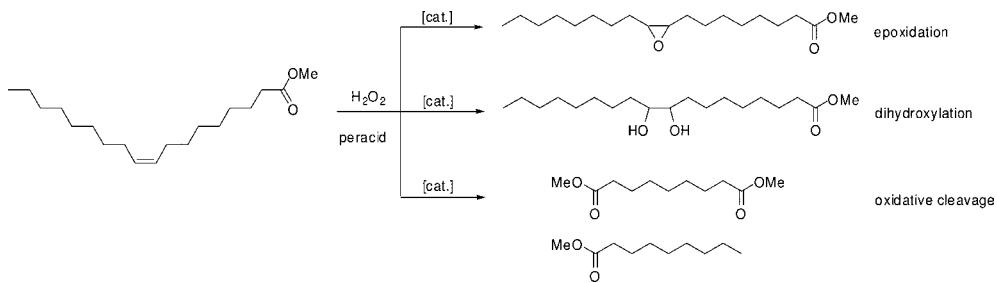
For hydroaminomethylation, homogeneous rhodium complexes are preferentially used as catalysts, for example, $[\text{Rh}(\text{cod})\text{Cl}]_2$.

3.4.1.4 CO Linkage Reactions

Unsaturated fats can react in various ways with oxidants such as hydrogen peroxide, hydroperoxides and peracids (Scheme 3.4):

- The double bond is oxidized to an epoxide.
- Hydrogen peroxide is added and a vicinal diol is formed.
- The double bond is cleaved and a mono- and a dicarboxylic acid are formed.

The *epoxidation* of petrochemical alkenes is an intensely investigated oxidation reaction and in recent years numerous homogeneous catalysts have been developed for this reaction. However, so far the catalytic epoxidation of fatty compounds has been investigated only marginally. Sobczak and Ziolkowski reported on the epoxidation of oleic acid with organic hydroperoxides catalyzed by molybdenum complexes [37]. Typical homogeneous catalysts include $\text{Mo}(\text{CO})_6$ and $\text{MoO}_2(\text{acac})_2$.

**Scheme 3.4** Possible oxidations of unsaturated fatty acids.

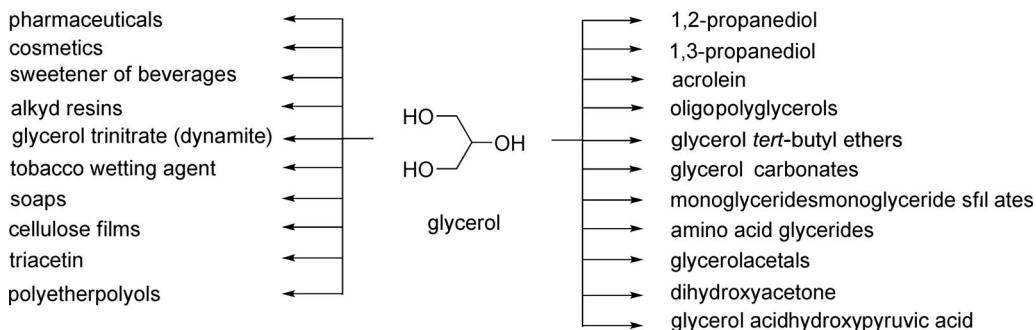
Vicinal diols can be generated from alkenes by *dihydroxylation*. There are various techniques, among others using potassium permanganate or the very toxic osmium tetroxide as oxidizing agents. Formerly, these versions required stoichiometric amounts of oxidants; more recently, catalytic versions have also been developed. Excellent hydroxylation catalysts are rhenium catalysts, such as methyl trioxorhenium CH_3ReO_3 , used by Herrmann [38].

The *oxidative cleavage* of unsaturated fats is an interesting possibility for generating selectively short-chain mono- or dicarboxylic acids (C_9) from longer chain carboxylic acids (C_{18}). This process is performed industrially using ozonolysis. Suitable catalysts for this reaction with other oxidants are compounds of tungsten, ruthenium, and palladium. Oleic acid, for instance, can be cleaved with peracetic acid into azelaic acid and pelargonic acid in the presence of RuCl_3 as catalyst.

3.4.2

Glycerol

As glycerol is formed automatically in the hydrolysis, saponification, or transesterification of natural fats and oils as by-product (cf., Section 3.4.1), the catalytic derivatization of glycerol will also be considered. As it is produced on a large scale in the manufacture of biodiesel, the classical markets for glycerol (Scheme 3.5, left

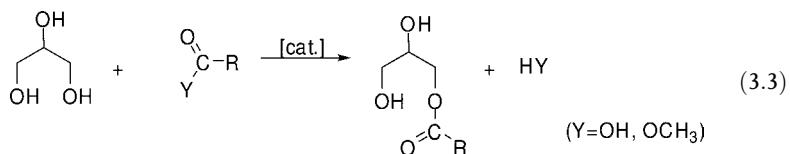
**Scheme 3.5** Applications and derivatives of glycerol.

column) are more or less saturated and cannot accommodate substantially greater sales of glycerol. Therefore, the synthesis of a number of new glycerol derivatives has been developed in recent years (Scheme 3.5, right column), in particular esters, ethers, and acetals of glycerol, but also products of reduction and oxidation.

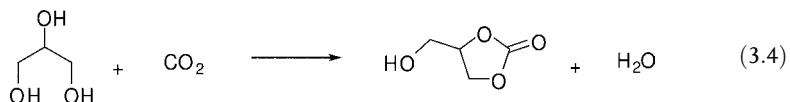
A complete overview of these products is given in review articles by Behr and co-workers [39, 40] and Pagliaro *et al.* [41].

3.4.2.1 Glycerol Esters

Partial glycerol esters are mainly applied as emulsifiers, which can be produced by two different ways. The first route is the conversion of glycerol with fatty acids or fatty acid methyl esters using appropriate catalysts (Equation 3.3). The second is known as transesterification, involving the conversion of fats with glycerol. Glycerol can be replaced by glycerol oligomers, which lead to polyglycerol esters. Metal oxides [42] and mesoporous catalysts [43] have been investigated as potential catalysts for the synthesis of glycerol esters.



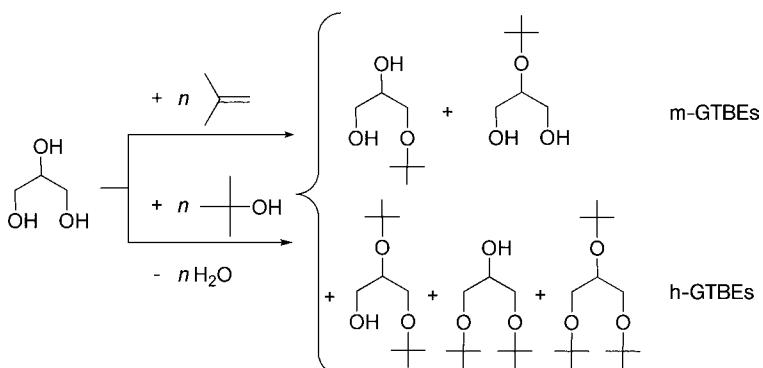
Glycerol carbonate, a cyclic glycerol ester, is also a very interesting derivative of glycerol. It can be used as a solvent in many applications (colors, varnishes, glues, cosmetics, and pharmaceuticals) and for the synthesis of glycitol by cleaving off carbon dioxide. The classical synthesis of glycerol carbonate is a multi-step reaction starting from ethylene oxide. Apparently, it would be more economic to convert glycerol directly into the carbonate (Equation 3.4). Therefore, two different approaches exist, one using a tin catalyst to convert carbon dioxide and glycerol [44], and the other using a heterogeneous zinc catalyst in the reaction of glycerol with urea leading to glycerol carbonate and ammonia [45].



3.4.2.2 Etherification

Among the manifold possibilities of utilizing glycerol, the ethers of glycerol play a predominant role, particularly glycerol oligomers and glycerol *tert*-butyl ethers (GTBEs). Glycerol oligomers can be used, for example, as ingredients of body care products, as lubricants, and as food additives. The conventional catalysts for glycerol oligomerizations are sodium or potassium hydroxide, resulting, however, in a broad product spectrum which cannot be utilized completely. A more selective formation of the lower oligomers can be achieved by the use of heterogeneous catalysts such as metal ion-modified mesoporous materials [46].

At present, glycerol alkyl ethers, especially GTBEs, are of particular interest, because the higher ethers (h-GTBEs) can be used as octane boosters in automotive fuels analogously to methyl *tert*-butyl ether (MTBE), but they do not exhibit the same environmental problems. Glycerol can be converted with isobutene [47–49] or with *tert*-butanol [50] to the desired fuel additives (Scheme 3.6). When using on *tert*-butanol, water is a by-product and must be removed.

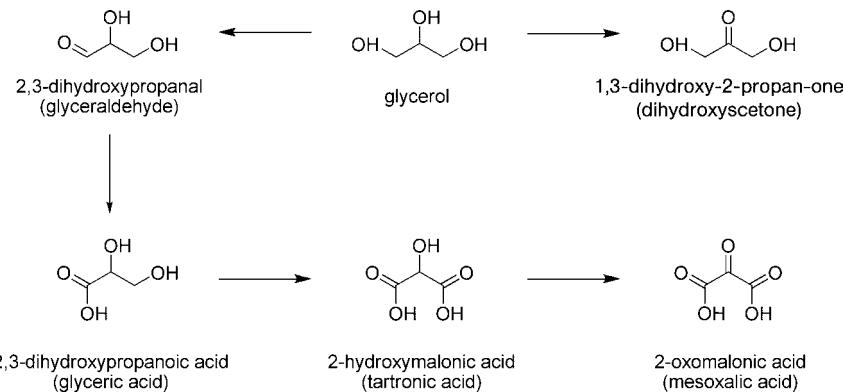


Scheme 3.6 Synthesis of GTBEs via reaction of glycerol with isobutene or *tert*-butanol.

Another important etherification is the palladium-catalyzed telomerization of glycerol with butadiene yielding octadienyl ethers of glycerol, which can be used as starting materials for detergents [51, 52].

3.4.2.3 Glycerol Oxidation and Dehydration

A large number of products can be obtained from glycerol oxidation processes (Scheme 3.7). If the secondary hydroxy group of glycerol is oxidized selectively, dihydroxyacetone (DHA) is formed. DHA has been used for years as an active



Scheme 3.7 Oxidation products of glycerol.

substance in sunless tanning lotions. The oxidation of the primary hydroxy groups of glycerol leads to glyceraldehyde, an intermediate in carbohydrate metabolism.

Further oxidation of glyceraldehyde produces carboxylic acids, such as glyceric acid, tartronic acid, and mesoxalic acid. These acids are mainly converted into various market products such as polymers and biodegradable emulsifiers.

Platinum and palladium are well-known metal catalysts for the glycerol oxidation process. Gold, as a relatively new metal catalyst for catalytic glycerol oxidation, has a better resistance to oxygen poisoning and gives higher yields of glyceric acid compared with platinum [53].

3.5

Terpenes

Terpenes belong to the most widespread and chemically interesting groups of natural products [54, 55]. For hundreds of years terpenes have been known as flavors and fragrances extracted from essential oils. According to Wallach's rule, terpenes are composed of isoprene units (C_5) and therefore are classified in monoterpenes (C_{10}), sesquiterpenes (C_{15}), diterpenes (C_{20}), sesterterpenes (C_{25}), and triterpenes (C_{30}). As acyclic or mono- to pentacyclic derivatives, they can be found almost everywhere in organisms, particular in higher plants, and each plant has its own characteristic composition of terpenes. Perfumes and fragrances are the most important applications of pure or crude terpenes. They serve as excellent solvents and diluting agents for dyes and varnishes. Natural and synthetic resins of terpenes are produced, and also many pharmaceutical syntheses, for example, for vitamins and insecticides, start from terpenes.

The most important natural source of terpenes is turpentine [56] – a collective name for the volatile compounds of the crude tree resin from conifers. In the ecosystem of trees, turpentine plays an important role in metabolism and in the protection system. Up to 1 l of monoterpenes can be produced starting from the amount of needles spread on an area of 1 m^2 under a conifer. Depending on the starting material and the production method, gum, sulfate, and wood turpentine are produced. Gum turpentine is obtained from the balsam of living trees by vacuum distillation. Wood turpentine derives from steam distillation of chopped stumps, whereas sulfate turpentine is a by-product in pulp production (cf., Section 3.2.1.1). The main components of turpentine are α -pinene, β -pinene, limonene, and 3-carene, serving as important key molecules for a multitude of flavors, fragrances, and pharmaceuticals (Figure 3.8).

In the following, it will be shown on selected examples that with the help of catalysis these key molecules can be converted into valuable fine chemicals. Catalytic transformations of terpenes into fine chemicals were reviewed in detail by Swift [57] and Monteiro and Veloso [58].

α -Pinene is of considerable industrial importance in the synthesis of a wide variety of flavors and fragrances (Scheme 3.8). The major part serves for the technical manufacture of camphor, which is used as a plasticizer in celluloid production and

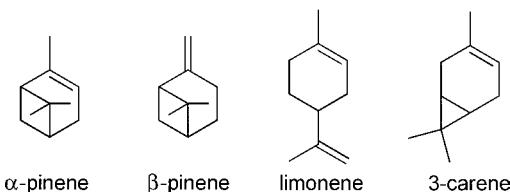
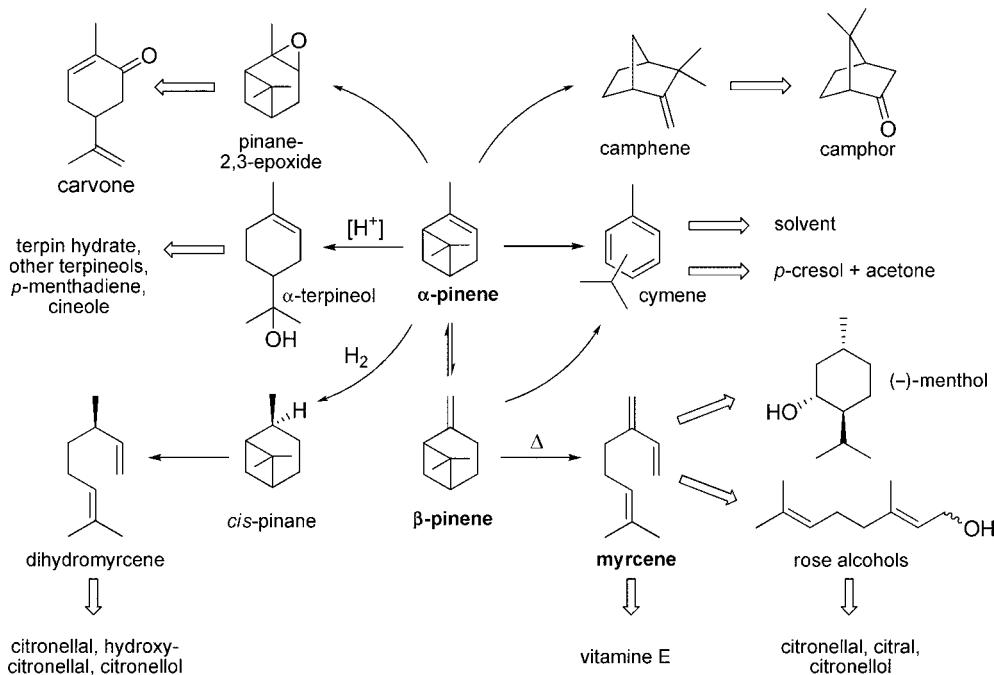


Figure 3.8 Major components of turpentine.

for medical formulations. With weakly acidic TiO_2 catalysts or activated clays, α -pinene isomerizes to camphene, which is treated with aqueous acids to give isoborneol. Isoborneol is finally dehydrogenated over a copper catalyst, yielding camphor. Direct isomerization of α -pinene with mineral acids, for example phosphoric acid, leads to the odoriferous classes of terpineols, *p*-menthadienes, and cineoles. Hydrogenation of α -pinene leads to *cis*-pinane – an important precursor for the synthesis of enantiomerically pure dihydromyrcene and citronellol. Suitable catalysts are based on nickel, palladium, or ruthenium.

In hydrogen peroxide solution, α -pinene can be epoxidized with methyltrioxorhenium/pyridine as catalyst, giving a precursor for the synthesis of carvone, known as an odor component from caraway [59]. Aromatization to cymene can be accomplished by catalysts which have a dual functionality for isomerization and hydro-



Scheme 3.8 Overview of important routes starting from α - and β -pinene.

genation/dehydrogenation, for example, palladium-impregnated catalysts [60]. Cymene serves as a flavor compound and as a starting material for cresols and acetone.

As in the 1960s the demand for β -pinene far exceeded its availability owing to its versatile applications, a large part of the more commonly occurring α -pinene was isomerized to β -pinene using, for example, basic catalysts such as calcium amide and alkaline earth metal oxides. A major amount of β -pinene is converted to resins with adhesive properties and by pyrolysis to the acyclic monoterpene myrcene.

Myrcene is one of the most important starting materials for the manufacture of olefinic scents. A considerable advantage of this natural hydrocarbon compound is the application of the classic “built-up” chemistry known from olefin chemistry, whereas the most renewable resources, especially carbohydrates, are “hyper-functionalized.” Copper catalyzed halogenation of myrcene, saponification, and final hydrolysis yield the top-selling scents nerol, geraniol (the so-called “rose alcohols”), and linalool. In the Takasago process, myrcene serves also as the starting material for the manufacture of enantiomerically pure menthol. In this process, two remarkable catalytic reactions are used: the synthesis starts with a lithium-catalyzed hydroamination and is continued with an enantioselective isomerization to an enamine catalyzed by rhodium/BINAP. Rhône-Poulenc applies myrcene as the starting material for the synthesis of vitamin E.

After α -pinene, the monocyclic monoterpene *limonene* (cf., Scheme 3.8) is the most widely distributed terpene in Nature and occurs as two enantiomers with a *p*-menthane structure. The racemic mixture of these two enantiomers is also called “dipentene.” *D*-Limonene is obtained industrially from orange skins with high purity and, owing to its fruity flavor, it is often used as an odorant in industrial and household specialty products. In addition, it is preferentially used in aqueous cleaning compositions due to its good properties as a solvent, its orange oil fragrance, and its biodegradability. Most of the *D*-limonene is used in the commercial manufacture of (*–*)-carvone as the main component of spearmint oil via a non-catalytic process. The racemic mixture dipentene is a good solvent for paints, varnishes, and synthetic resins. By passing over γ -alumina and activated clays, terpinene and terpinolene as important intermediates and additives of perfumes are accessible via isomerization of the terminal double bond. Conversion to the valuable *p*-cymene (cf., α -pinene) has also been achieved using several catalysts [57]. Additionally, *p*-cymene can be obtained by pyrolysis in the presence of platinum on carbon from *3-carene* (cf., Scheme 3.8) [61]. *3-Carene* also serves as an intermediate in perfume synthesis and as a precursor for insecticides of the pyrethroid type.

3.6 Carbon Dioxide

Due to the enormous supplies of carbon dioxide in the atmosphere (10^9 t), in the hydrosphere (10^{14} t), and in the lithosphere (10^{16} t), the question arises of whether they could be used economically in chemistry. Several industrial reactions have already been realized: the synthesis of urea from CO₂ and ammonia, the addition of

CO_2 in methanol synthesis, the synthesis of cyclic carbonates from CO_2 and epoxides, and the production of salicylic acid according to the Kolbe–Schmitt process.

The greatest barrier to the economic usage of CO_2 is the high stability of the molecule. The carbon atom in CO_2 is in its highest oxidation state (+4). Many reactions of CO_2 , however, are fortunately exothermic, such as its reaction with hydrogen to give methanol ($\Delta H_R = -131.0 \text{ kJ mol}^{-1}$) or with hydrogen and methanol to give acetic acid ($\Delta H_R = -138.1 \text{ kJ mol}^{-1}$). By taking the entropy effect and additionally the kinetics into account, the use of CO_2 as a C₁ building block is in principle possible. For activation, catalysts are essential with respect to thermal or electric energy. In particular, homogeneous catalysis can make an important contribution to activate the CO_2 and to convert it into valuable base chemicals. Detailed information about carbon dioxide recovery and utilization can be found in various publications [62–71].

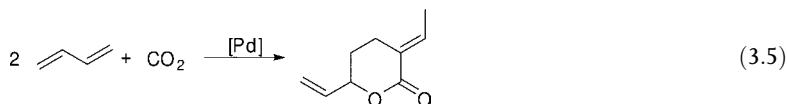
3.6.1

Reactions with Alkanes, Alkenes, and Dienes

Activated alkanes, such as cyclohexanone, acetone, and aliphatic nitro compounds, can react with carbon dioxide even without metal catalysis. A typical example is the phenolate-catalyzed reaction of acetophenone with CO_2 to the corresponding carbon acid. A catalytic conversion of the non-activated methane with CO_2 to give acetic acid was reported by Fujiwara and co-workers [72]. The reaction was carried out in the presence of palladium and copper acetate and also stoichiometric amounts of the oxidant $\text{K}_2\text{S}_2\text{O}_8$.

Homs and co-workers described the linkage of ethene and CO_2 on a supported platinum/tin complex yielding 3-hydroxypropionic acid [73]. Another approach to utilizing CO_2 was pursued by Tominaga and Sasaki, namely hydroformylation with CO_2 [74]. 1-Hexene, for instance, reacts with a mixture of CO_2 and H_2 in the presence of ruthenium clusters giving heptanals, heptanols, and, in small amounts, the undesired hexane as a result of simple hydrogenation. Mechanistically it is assumed that a retro water gas shift reaction occurs, in which CO and H_2O are formed from CO_2 and H_2 . This carbon monoxide undergoes ordinary hydroformylation with the alkene and H_2 .

1,3-Dienes can also react with the C₁ building block CO_2 . In the 1970s, the catalyzed telomerization of CO_2 with 1,3-butadiene was reported by Inoue and co-workers, which yields, in the presence of catalytic amounts of palladium and phosphine ligands, a δ -lactone with up to 90% selectivity (Equation 3.5) [75]. Behr's group scaled up this reaction from the laboratory to the miniplant scale and it could be carried out in a full-scale plant in the near future [76–80].



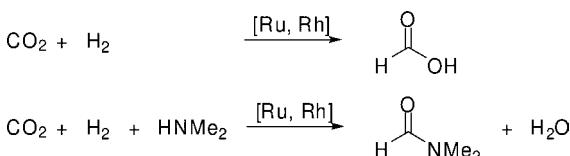
Among the hydrogenation, hydroamination, hydroformylation, and oxidation of δ -lactones, hydrogenation is of particular interest owing to its facile approach to a

suitable precursor for the synthesis of the plasticizer di(2-ethylheptyl) phthalate. Also, the resulting diols are potential starting compounds for new polyesters and polyurethanes. Homogeneous, bimetallic complexes based on molybdenum and rhodium are the best catalysts for the hydrogenation of δ -lactones to diols [81–83].

3.6.2

Conversion to Formic Acid and Dimethylformamide

CO_2 can also be used in the synthesis of formic acid and *N,N*-dimethylformamide (DMF). From the transition metal-catalyzed reaction of CO_2 with H_2 , formic acid is obtained, and addition of diethylamine leads to DMF in a consecutive reaction (Scheme 3.9).



Scheme 3.9 Syntheses of formic acid and *N,N*-dimethylformamide (DMF).

These reactions have been investigated since the 1970s. Palladium, rhodium, nickel, ruthenium, and iridium complexes proved to be active catalysts, but at first with only low conversions. In the 1990s, these reactions were picked up again, first by Graf and Leitner [84] with Rh catalysts, then by Jessop and co-workers [85] and Baiker and co-workers [86] with Ru complexes. An enormous increase in activity was achieved: in the synthesis of formic acid a turnover frequency (TOF) of $95\,000\,\text{h}^{-1}$ was obtained and for DMF a TOF of $370\,000\,\text{h}^{-1}$.

Both reactions could be carried out in a liquid–liquid two-phase system with the advantages of easy product separation and efficient catalyst recycling. In the presence of a water-soluble ruthenium catalyst with the ligand triphenylphosphine trisulfonate, simultaneous extraction of the organic product phase by *N,N*-dibutylformamide can be achieved [87, 88].

3.6.3

Plasma Activation of Carbon Dioxide

A non-catalyzed method to activate carbon dioxide is conversion with methane to synthesis gas using an argon plasma (Equation 3.6) [89–91].



This process is an interesting alternative to the conventional steam reforming of methane and water to synthesis gas, because an expensive purification of the natural gas can be avoided. From natural gas with a high CO_2 concentration, synthesis gas is

generated by plasma activation which is suitable for hydroformylation reactions due to its high CO concentration. Accordingly, the advantages of this process are the high reaction rate and the lack of expensive catalysts. However, high investment costs, intensive maintenance, and high energy costs are disadvantages.

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4

Synthesis in Green Solvents

László Orha, Geoffrey R. Akien, and István T. Horváth

4.1

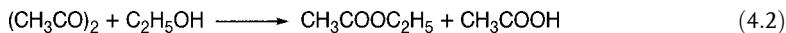
The Role of Solvents in Synthesis

Chemical reactions can proceed in gaseous, liquid, supercritical, or solid phases. Most chemical transformations are performed in the liquid phase by providing an additional component, which is a liquid used in excess and called the solvent [1], to dissolve the reactants, products, reagents, and/or catalysts. The use of one or more of the reactants, products, or reagents as solvent can be considered a greener or *no (external) solvent* approach. There are various reasons why solvents have been used frequently in chemical processes, on both small and large scales. Most importantly, solvents can provide a common place for reactants, which can include and involve dissolved atoms, molecules, and neutral and ionic materials, and also the surfaces of solids, to collide efficiently and so leading to chemical reactions. Since solids themselves have limited surface areas to interact with each other, dissolution of their constituents in a common medium can facilitate chemical reactions. Reaction rates can be increased to economically favorable values by assisting reactants in moving faster; dissolving the reaction mixture in a solvent can lower the viscosity. This can allow stirring rates to be increased, which can have significant impacts on reactions, especially when mass transfer (for example, from gaseous to liquid phases) is a limiting factor. Solvents have been used to control the temperature of solutions by the boiling point (reflux) probably since as long as humans have cooked using hot water. Solvents can remove or deliver heat for exo- and endothermic reactions, respectively. Solvents have been used to purify reaction mixtures by filtration, centrifugation, extraction, recrystallization, azeotropic distillation, chromatography, and so on. In addition to the simple physical role of solvents, they can alter reaction rates by virtue of their polarity, solvation, and dielectric constants, all based on molecular level interactions [2]. For example, a polar solvent can accelerate a reaction if the products are more polar than the reactants. Since tetraethylammonium iodide is ionic and much more polar than triethylamine and ethyl iodide, the rates of

reaction (4.1) can be increased 700-fold by replacing hexane with the more polar acetophenone [3].



On the other hand, a polar solvent can decrease the reaction rate if the reactants are more polar than the products, as in reaction (4.2).



A polar solvent will have very little or no effect if the reactants and products are non polar, such as in reaction (4.3).



Solvation of, or the interaction of the solvents with, one of the reactants or reaction intermediates can have a significant influence on the rate or the selectivity of a reaction. When the solvation results in a lower potential energy, the activation energy increases, depressing the reaction rate. On the other hand, if the activated complex has a stabilizing interaction with the solvent, the activation energy decreases, which accelerates the reaction. If both the activated complex and the reactants are solvated, the effect of solvent on the rate may be negligible. The influence of the solvation of products does not have any effect on the rate except in the case of reversible reactions. Finally, in the case of ionic reactions, the dielectric constant of the solvents can have an important role.

4.2

Types of Solvent

Solvents can be atomic liquids (low-melting metals such as mercury, having metallic bonding), molecular liquids (possessing mainly covalent bonding), and ionic liquids (molten salts, a combination of covalent and ionic bonding) [4].

4.2.1

Atomic Liquids

Liquid metals, such as mercury and liquid sodium, have been rarely used as reaction media. Chemical reactions in liquid alkali metals were reviewed some time ago [5].

4.2.2

Molecular Liquids

Nonaqueous organic solvents consist of the following classes of compounds: aliphatic and aromatic hydrocarbons and their halogenated and nitro derivatives, alcohols, carboxylic acids, esters, ethers, ketones, aldehydes, amines, nitriles, unsubstituted and substituted amides, sulfoxides, and sulfones. In general, a compound

dissolves more easily in a solvent that has similar functional groups than in one of a completely different nature, since it has been well known for centuries that “like dissolves like” or “*similia similibus solvuntur*.” The preferred solvent should also avoid undesired reactions between the solutes and the solvent. For example, condensation reactions should not be carried out in solvents having carbonyl groups, or hydrolyses in esters, amides, or nitriles.

Liquid crystals or mesomorphic compounds are formed by long, flat, and fairly rigid molecules, and have a special position among solvents [6]. Unlike normal isotropic liquids, which have a completely random arrangement of molecules, liquid crystals are substantially ordered. Liquid crystals are usually good solvents for other organic compounds. The anisotropic solute–solvent interaction leads to a significant orientation of the guest molecules dictated by the axis preferred by the solvent. Ordered solvent phases have been used as reaction media, particularly for photochemical reactions [7].

4.2.3

Ionic Liquids

Ionic liquids are molten salts which are also liquids at, or close to, room temperature (usually below 100 °C) [8]. Although these solvents have been known since 1914 ($[\text{CH}_3\text{CH}_2\text{NH}_3^+][\text{NO}_3^-]$) [9], their popularity increased significantly after the recognition of the importance of their extremely low vapor pressure. Ionic liquids are electrically conductive and many have low combustibility, in addition to excellent thermal stability and favorable solvating properties for a range of different types of compounds. The miscibility of ionic liquids with water or organic solvents depends on the structure of the cation and anion. Typical cations are ammonium, phosphonium, imidazolium, pyridinium, and pyrrolidinium ions, and typical anions are formate, acetate, benzoate, halides, phosphate, hexafluorophosphate, hydrogensulfate, methanesulfonate, trifluoromethanesulfonate, nitrate, tetrafluoroborate, thiocyanate, and tosylate ions.

4.2.4

Solvent Polarity

The polarity of the solvent can be defined as the solvent’s “overall solvating power,” which can affect both chemical equilibria and reaction rates. The overall solvating power depends on all interactions, nonspecific and specific, intermolecular solute–solvent interactions, excluding such interactions leading to any eventual chemical changes of the ions or molecules of the solute [10]. Typical polar solvents include water, short-chain alcohols, carboxylic acids, and ketones, and apolar solvents include long-chain esters (such as triglycerides), hydrocarbons (aliphatic and aromatic), and halogenated hydrocarbons. Polarity has an important role in the liquid–liquid biphasic separations of products, since the solvent for the reactants, reagents, or catalysts should not dissolve the products.

4.2.5

Protic Solvents

Solvents can be differentiated according to the availability of dissociable hydrogen atoms attached to a more electronegative atom. Protic solvents readily form hydrogen bonds and can stabilize cations by electron pair donation and anions via hydrogen bonding. Examples include water, alcohols, carboxylic acids, ammonia, and amines.

4.3

Problems with Solvents

The most commonly used solvents usually have properties which make them dangerous, causing serious environmental and health problems. For example, the destruction of ozone by chlorofluorocarbons (CFCs) in the upper atmosphere is well established and led to the replacement of CFC refrigerants. Many of the chlorinated solvents are dangerous to workers who handle them and, if they enter the environment, to all of us (laboratory use: carbon tetrachloride, chloroform, trichloroethylene; all are carcinogenic). Solvents frequently cause fires and/or explosions [11]. One of the causes of these problems can be the solvent's high vapor pressure at ambient temperature, so that the solvent can easily enter the environment. For example, volatile organic compounds (VOCs) have high vapor pressures, such as diethyl ether 400 mmHg at 18 °C and 1,2-dichloroethane 387 mmHg at 20 °C. Another problem can be the formation of peroxides on standing in air [12]. Peroxides in solvents may cause explosions and fires, so before using such solvents one has to either remove the peroxides or, preferably, use solvents which do not form peroxides.

4.4

Application of Green Solvents

The elimination of solvents in chemical processes, or the replacement of hazardous solvents with environmentally benign ones, is one of the Twelve Principles of Green Chemistry [13]. The main advantage of solventless chemistry is that it is conceptually the simplest solution for the problems with solvents. However, not many reactions can be carried out under such conditions, as exothermic reactions can be dangerous, heating and stirring can be inefficient, especially if solid reactants or products are present, and usually solvents are needed for working up the product from solventless reaction media.

4.4.1

Water

The most abundant and perhaps the most obvious solvent is water. It is cheap, readily available, nonflammable, nontoxic, and useful for certain types of reaction

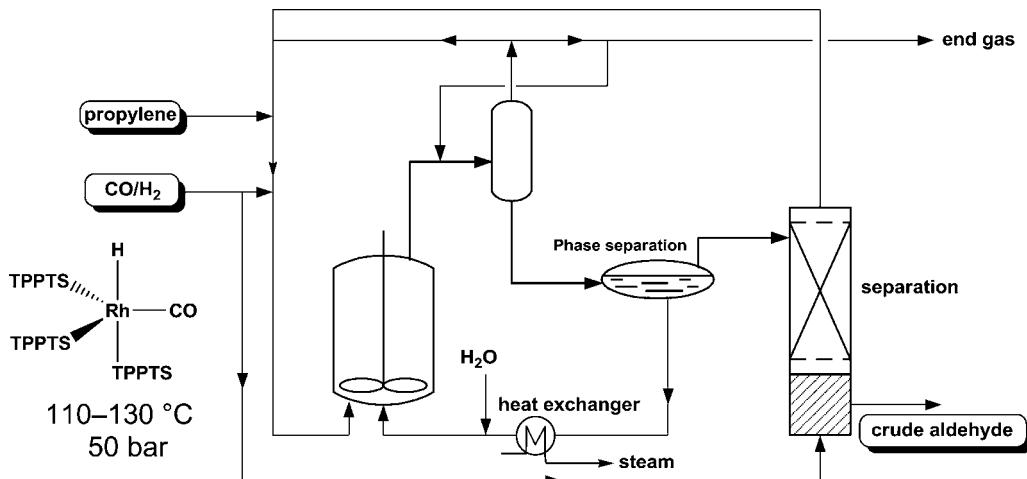


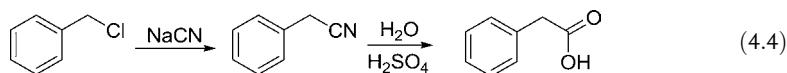
Figure 4.1 Flow diagram of the Ruhrchemie/Rhône-Poulenc Oxo process.

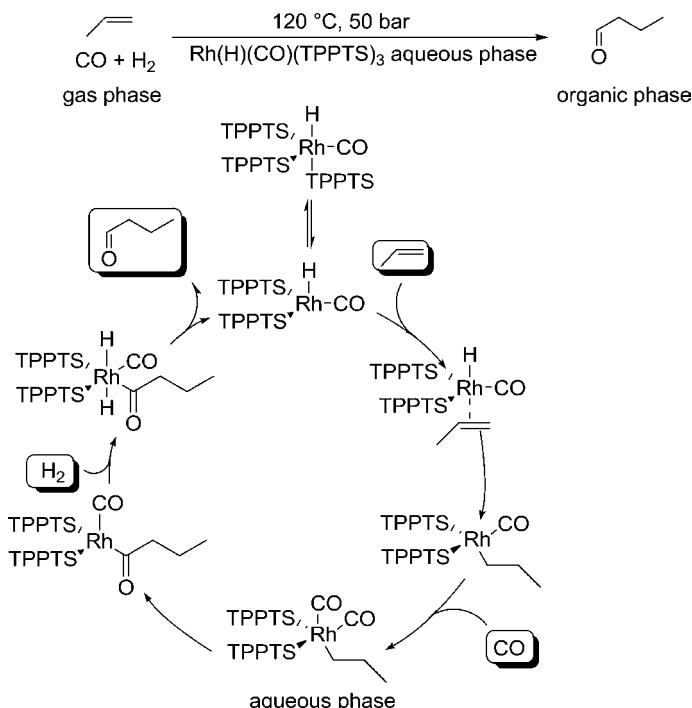
such as ionic reactions, because it can readily solvate both anions and cations. It can serve as both a solvent and a ligand, also stabilizing coordinatively unsaturated species, which is a key issue for long-term catalyst stability. Water is a strong σ-donor with only a weak back-donating capability. Since water has strong O–H bonds which do not permit easy reactions with radicals in solution, it is an attractive medium for radical reactions. The key properties of water as a solvent are in stabilizing structures and effecting reactions by hydrogen bonding. Water has a limited role in some reactions, because it is a poor solvent for many organic substrates, and is incompatible with some reagents. It can be the major component in one of the phases in biphasic processes, but often the clean-up of the aqueous phase is difficult.

The Ruhrchemie/Rhône-Poulenc Oxo process (Figure 4.1, Scheme 4.1) was developed for the synthesis of butyraldehyde from propylene and synthesis gas, where the water-soluble tris(*m*-sulfonated-phenyl)phosphine (TPPTS)-modified rhodium catalyst operates in the aqueous phase [14].

In the synthesis of phenylacetic acid, the Pd-TPPTS system was used as a catalyst by Kohlpaintner and Beller (Hoechst) [15] in a biphasic carbonylation of benzyl chloride as a greener alternative to the classical process: the reaction of benzyl chloride with sodium cyanide (Equations 4.4 and 4.5). Although in the new process 1 equiv. of sodium chloride is formed, this is far less salt waste than in the original process. Moreover, sodium cyanide is about seven times more expensive per kilogram than carbon monoxide.

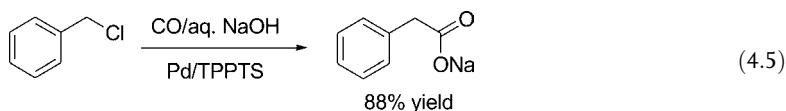
Classical process:



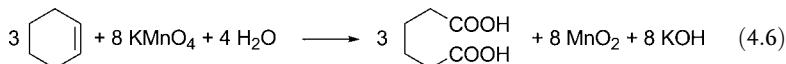


Scheme 4.1 The Ruhrchemie/Rhône-Poulenc Oxo process.

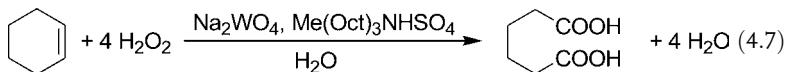
New process:



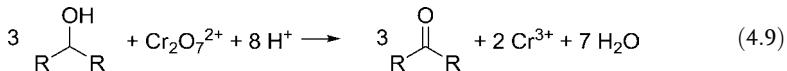
The synthesis of adipic acid in the laboratory can be carried out by the oxidation of cyclohexene with potassium permanganate (Equation 4.6). The *E*-factor of this reaction is 2.61, which means that for 1 kg of adipic acid 2.61 kg waste (mainly MnO₂ and KOH) is produced. The atom economy is 27.8%, indicating that only 27.8% of the atoms in the reactants will be incorporated into the product.



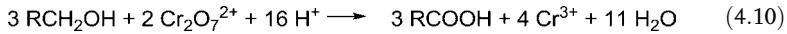
A greener method has been developed using hydrogen peroxide as the oxidant, with catalytic amounts of sodium tungstate and a quaternary ammonium phase-transfer catalyst (Equation 4.7) [16]. Since the solvent and the by-product are water, the reaction is indeed much greener (*E*-factor = 0.49, atom economy 67%).



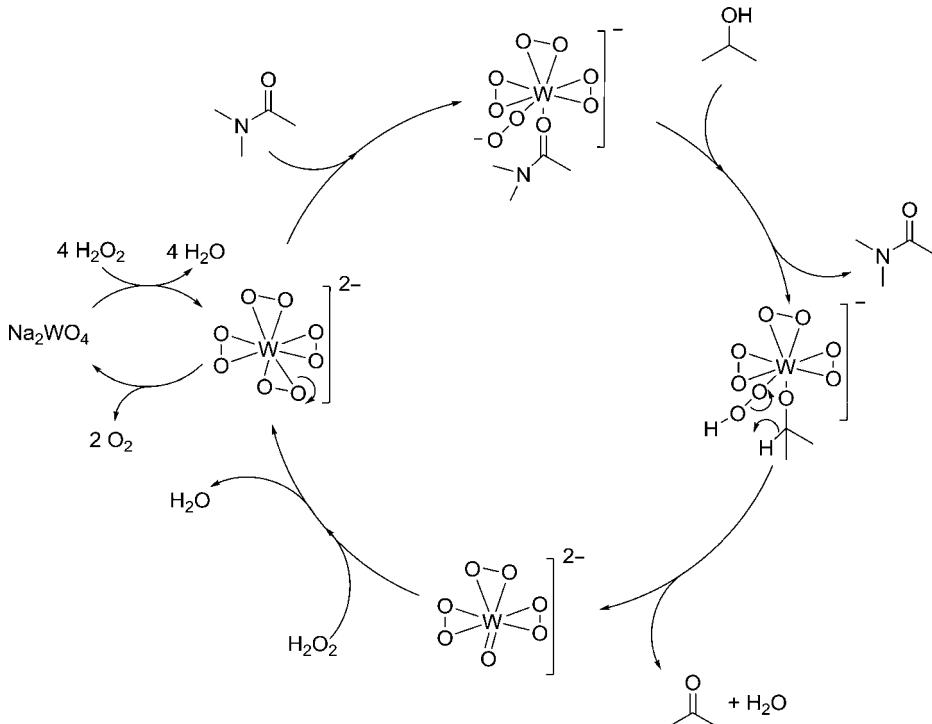
The oxidation of alcohols to aldehydes or ketones can be performed using the very toxic potassium dichromate. The oxidizing agent in these reactions is a solution of $\text{Na}_2\text{Cr}_2\text{O}_7$ or $\text{K}_2\text{Cr}_2\text{O}_7$, acidified with sulfuric acid (Equation 4.8). If the oxidation takes place, the orange dichromate(VI) ions in the solution are reduced to green Cr(III) ions (Equation 4.9).



The oxidation of primary alcohols with an excess of an oxidizing agent produces carboxylic acids (Equation 4.10). The *E*-factor for the oxidation of ethanol to acetaldehyde is 1.74 and the atom economy is only 36.5%.



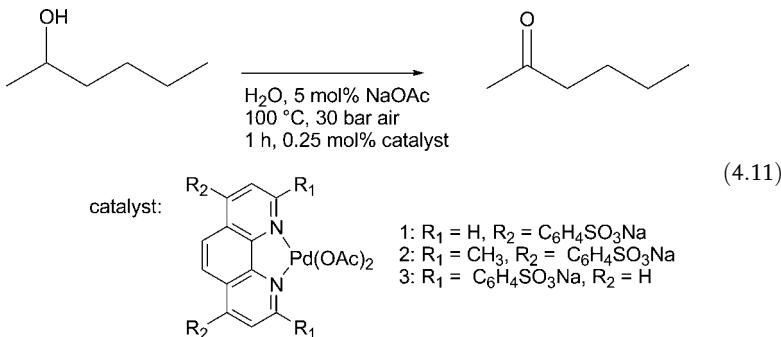
A practical and efficient oxidation of an alcohol to a ketone or aldehyde under neutral conditions using H_2O_2 as the oxidizing agent and Na_2WO_4 as the catalyst was developed in water-*N,N*-dimethylacetamide media (Scheme 4.2) [17]. This method is



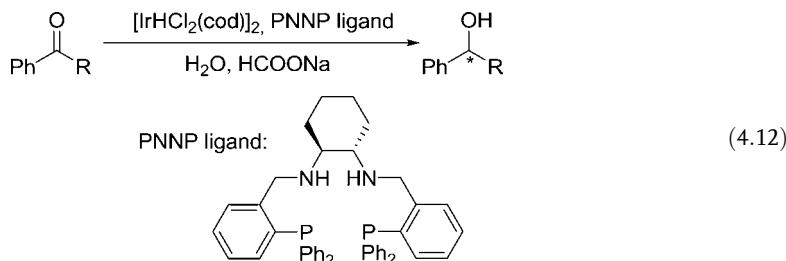
Scheme 4.2

very simple, practical for large-scale manufacturing, and has wide applicability to a variety of substrates including acid-sensitive compounds.

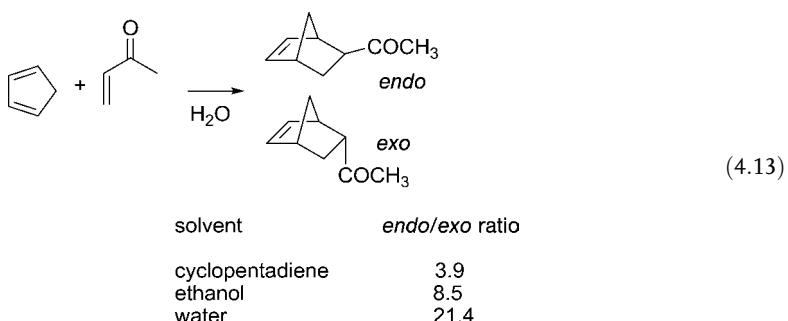
Oxidation with oxygen gas can be carried out in aqueous biphasic systems. Primary and secondary alcohols have been oxidized to the corresponding aldehydes or ketones, respectively, using a palladium(II) complex (Equation 4.11) [18]. No organic solvents were used, except the substrate is a solid, and the catalyst could be easily recycled and reused by simple phase separation, because the aqueous phase is the lower layer and so can be recycled. The only disadvantage of water as a solvent for oxidations with oxygen/air is the low solubility of oxygens in water.



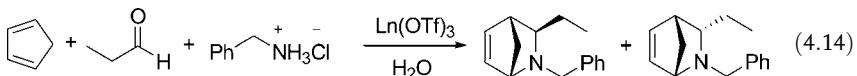
Reductions can also be performed in water. Systems for reduction of ketones in water can be water-compatible sodium and lithium borohydrides, amino acid-based cationic surfactants to reduce aryl ketones [19], iridium hydrides used in transfer hydrogenations, such as $[Cp^*\text{Ir}^{III}(\text{bpy})\text{H}]^+$ ($Cp^* = \eta^5\text{-C}_5\text{Me}_5$, bpy = 2,2'-bipyridine) [20], and $[\text{IrHCl}_2(\text{cod})]_2$ with a chiral diaminodiphosphine ligand to form secondary alcohols in high enantioselectivity and almost quantitative yield (Equation 4.12) [21].



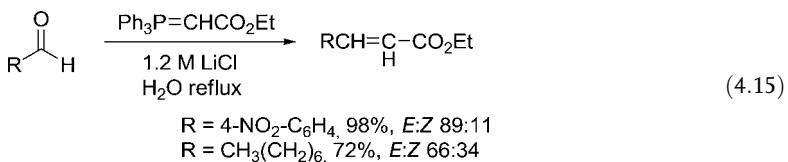
In the 1980s, Breslow's group found that an increased reaction rate occurred in water in the reaction between cyclopentadiene and butanone (Equation 4.13) [22]. Curiously, the reaction rate in methanol was similar to that in other organic solvents, and the strange acceleration in water was assigned to hydrophobic and hydrogen bonding interactions [23].



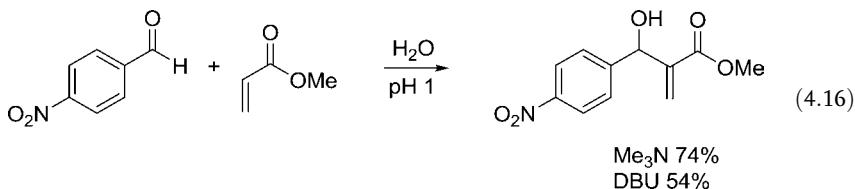
Additives that can be added to aqueous reactions include Lewis acids, which have roles as catalysts in organic transformations, mainly in Diels–Alder reactions [24]. A number of Lewis acids which can be used in water have been described, such as nitrates, for example, $\text{Cu}(\text{NO}_3)_2$ and Zn^{2+} , Ni^{2+} , Co^{2+} analogs [25], lanthanide triflates, $\text{Ln}(\text{OTf})_3$ [26], and others, including indium trichloride [27]. Increased yields and product selectivities have been observed in several systems. A typical example is the three-component hetero-Diels–Alder reaction catalyzed by lanthanide triflate (Equation 4.14). Lanthanide triflates were used in the pH range 5–7, and when no $\text{Ln}(\text{OTf})_3$ was added, the product was isolated in only 4% yield; however, with added lanthanide catalyst the yield was increased to 64% [28].



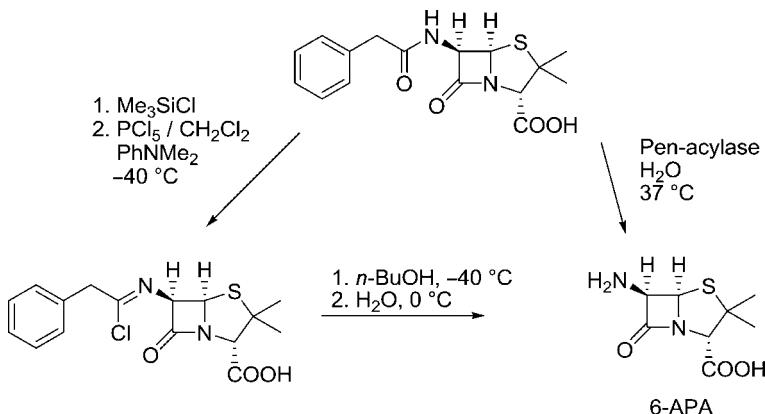
The Wittig reaction is widely used in synthetic chemistry and is conventionally carried out in dry organic solvents in the presence of a base. However, it has been found that when using stabilized phosphorus ylids the reaction can easily be carried out in water; and in fact the reactions were faster than when performed in organic solvents [29]. Most reactions were complete in 5–60 min in water at boiling point, and the presence of LiCl (1.2 M) as a salting-out agent was advantageous (Equation 4.15). When aromatic aldehydes were used, the *E/Z* selectivities were similar to those observed in toluene, but lower selectivities and yields were achieved with aliphatic aldehydes.



The Baylis–Hillman reaction takes place in several polar aprotic organic solvents with different kinetic data [30]. In acidic aqueous media, the reaction yield can be up to 74%, depending on the substrate and tertiary amine used (Equation 4.16) [31].



Water is an excellent medium for biocatalytic transformations. 6-Aminopenicilanic acid (6-APA), a key raw compound for semi-synthetic penicillin and cephalosporin antibiotics, was produced by using 0.6 kg of Me₃SiCl, 1.2 kg of PCl₅, 1.6 kg of PhNMe₂, 0.2 kg of NH₃, 8.4 l of *n*-BuOH and 8.4 l of CH₂Cl₂ to obtain 1 kg of the product (Scheme 4.3). In contrast, the enzymatic cleavage of penicillin G is performed in water at 37 °C and the only reagent used is NH₃ (0.09 kg per kg of 6-APA), to adjust the pH [32].



Scheme 4.3

Solid-phase peptide synthesis is an easy synthetic method in which synthetic reactions are performed on a solid support. Since all synthetic steps are carried out in a biphasic (solid and liquid phase) system, the building blocks and reagents are generally well soluble in organic solvents, such as *N,N*-dimethylformamide (DMF) or CH₂Cl₂. It is environmentally friendly to use water for this process, by using water-soluble protecting and coupling reagents (Figure 4.2). Hojo and co-workers developed a fluorenylmethyloxycarbonyl (Fmoc) amino acid nanoparticle system, which was used efficiently in water to produce peptides [33].

4.4.2

Fluorous Solvents

As an analog to the term aqueous, the term fluorous was introduced to highlight the fact that one of the phases of a biphasic system is richer in fluorocarbons than the other [34]. Perfluorinated alkanes, dialkyl ethers, and trialkylamines have unusual

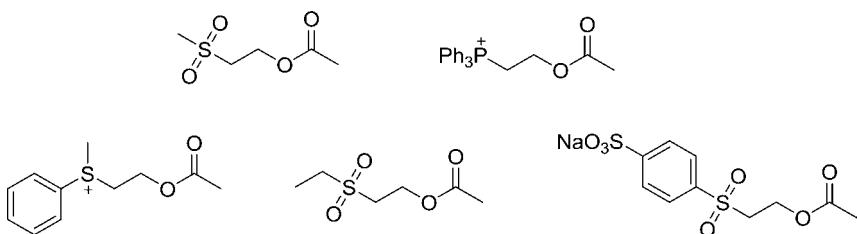
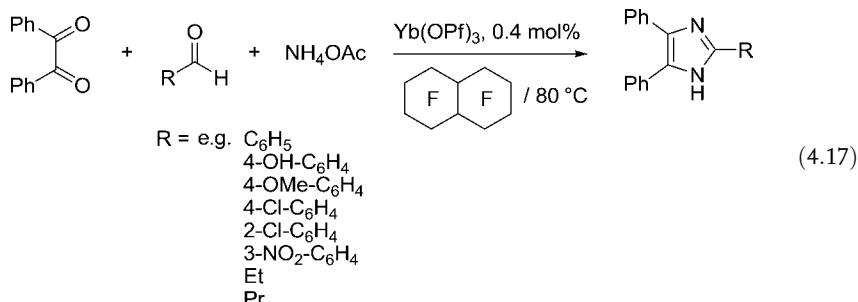


Figure 4.2 Reagents for solid-phase peptide synthesis.

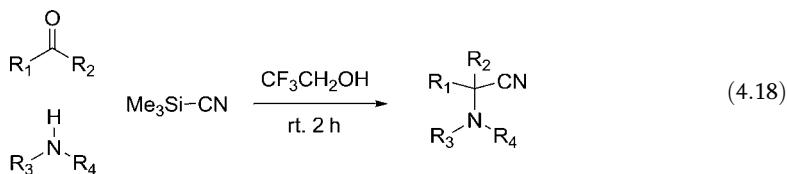
properties, such as having an extremely nonpolar character and also showing small intermolecular attractions. Their miscibility with common organic solvents is low at room temperature, hence these materials can form fluorous biphasic systems. By immobilizing reagents and catalysts in the fluorous phase, fluorous biphasic systems have been widely studied in stoichiometric and catalytic chemical transformations [35]. A fluorous biphasic system is made up of a fluorous phase containing a fluorous-soluble reagent or catalyst, and a second product phase, which may be any organic or nonorganic solvent with a limited solubility in the fluorous phase. Reagents and catalysts can be made more fluorous soluble by attaching fluorocarbon groups to ligands of adequate size and number. The most effective fluorocarbon moieties are linear or branched perfluoroalkyl chains with high carbon number that may contain other heteroatoms ("fluorous ponytails"). Depending on the solubilities of the substrates in the fluorous phase, a fluorous biphasic reaction can proceed either in the fluorous phase or at the interface between the two phases. When the solubilities of the substrates are very low in the fluorous phase, the chemical reaction may still occur at the interface; phase-transfer agents can also be added to promote the reaction. It should be noted that a fluorous biphasic system might become a single phase on increasing the temperature. Therefore, by running the reaction at higher temperatures and separating the products at lower temperatures, using a fluorous catalyst combines the advantages of single-phase catalysis with biphasic product separation. Fluorous solvents are inert under common reaction conditions and dissolve gases very well (for example, the solubility of oxygen in perfluorotributylamine is 38.9 ml per 100 ml) [36]. This latter property, along with their low toxicity, allows them to be used in medicine, in addition to using them in chemical reactions involving gases. The application of fluorous solvents has been severely limited by the persistence, toxicity, and long half-lives in humans of compounds containing C₇- and C₈-perfluoroalkyl groups [37]. Although limiting the exposure to these compounds could lower the risks, their replacement with shorter perfluoroalkyl groups has been demonstrated, some of which are now considered safe.

The synthesis, reactions, and biological properties of substituted imidazoles have a significant role in modern heterocyclic chemistry. Multi-substituted imidazoles, an important group of pharmaceutical compounds, show a wide spectrum of biological activity [38]. Synthesis of trisubstituted imidazoles was successfully carried out using rare earth(III) perfluorooctanesulfonates [RE(OPf)₃, RE = Sc, Y, La–Lu] as catalysts in fluorous solvents. Ytterbium perfluorooctanesulfonate [Yb(OPf)₃] catalyzes the

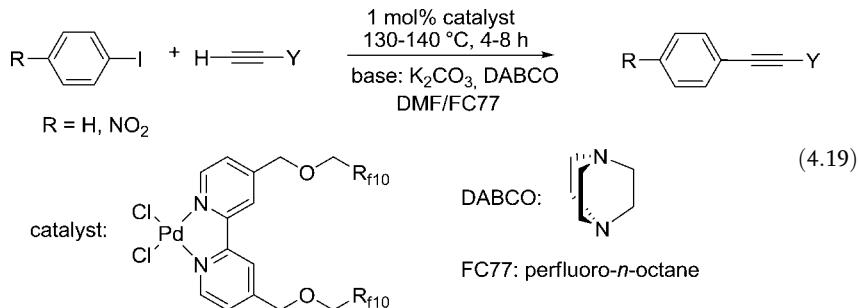
efficient synthesis of trisubstituted imidazoles in fluorous solvents (Equation 4.17). After separation, the fluorous phase only contains the catalyst and can be reused several times [39].



1,1,1-Trifluoroethanol is an efficient and recyclable solvent in helping one-pot, three-component coupling reactions of aldehydes or ketones, amines, and trimethylsilyl cyanide or trimethyl phosphate to yield the corresponding α -amino nitriles or α -amino phosphonates in high yields (Equation 4.18). This method does not require the use of either an acid or base catalyst [40].

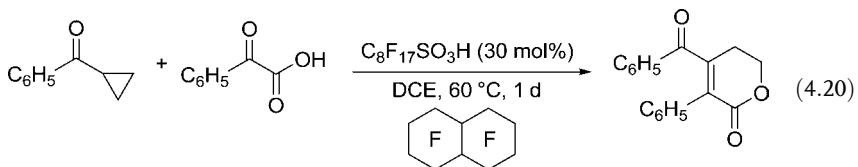


The Sonogashira coupling reaction of terminal alkynes with aryl or vinyl halides is a useful tool for carbon–carbon bond formation, and has found wide employment in areas such as natural product synthesis, the pharmaceutical industry, and material sciences. Novel recyclable Pd catalysts with fluorous ponytails in the ligand 2,2'-bipyridine were reported in a copper-free Pd-catalyzed Sonogashira reaction in a fluorous biphasic system (FBS) (Equation 4.19). The catalysts are only soluble in perfluorinated solvents at room temperature [41].

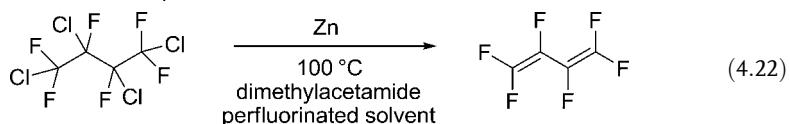
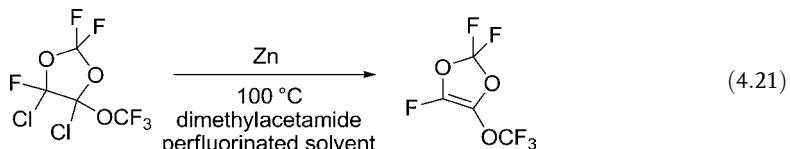


The FBS technique was employed in the reactions of cyclopropyl aryl ketones with α -ketoacetic acids catalyzed by C₈F₁₇SO₃H (30 mol%) using perfluorodecalin

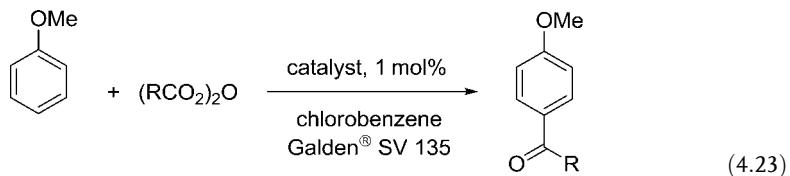
(C₁₀F₁₈, *cis*- and *trans*-mixture) and DCE as a co-solvent to give 5,6-dihydropyran-2-ones in good yields (Equation 4.20). Moreover, the reaction could be repeated several times without replacing the catalyst or fluorous solvent [42].



The dehalogenation of halofluorinated alkanes and fluorinated ethers (linear and cyclic), and also halofluorinated alkanes containing an aromatic group, to their unsaturated species in a biphasic fluorinated/organic solvent system was studied (Equations 4.21 and 4.22). The reactions in the biphasic system give higher selectivities and better yields than those obtained by driving the reaction in the traditional organic monophasic system. With this method, the concentrations of hydrogenated by-products of general formula RCF₂H or RCFHR' were below 100 ppm. Hence this novel biphasic system provides a useful synthetic route to materials and chemicals for electronics, optical polymers, plasma etching, and so on, which require high purity of all compounds used [43].



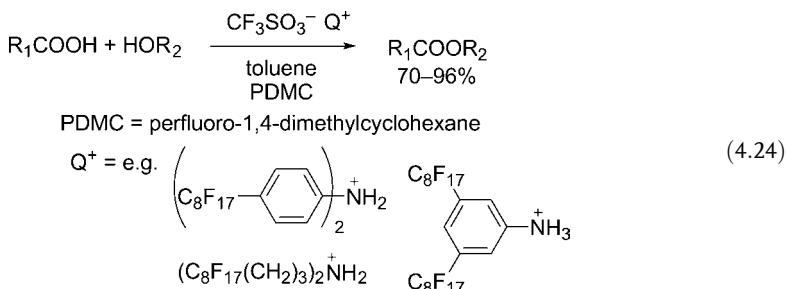
Hafnium(IV) bis(perfluoroctanesulfonyl)amide complex {Hf[N(SO₂C₈F₁₇)₂]₄} is a highly reactive and recyclable Lewis acid catalyst in Friedel–Crafts acylation and Prins reactions in fluorous biphasic systems at low catalyst loadings (≤ 1 mol%) (Equation 4.23). In these reactions, Hf[N(SO₂C₈F₁₇)₂]₄ is selectively soluble in the fluorous phase and can be recovered after reaction by simple phase separation. In addition, the catalyst can be reused without any loss of activity [44].



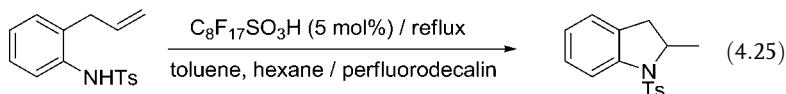
$$\text{Galde}^{\circledR} \text{ SV 135} = \text{CF}_3\text{-(O-CF(CF}_3\text{-CF}_2)_n\text{-}(O\text{-CF}_2)_m\text{-O-CF}_3$$

$$\begin{aligned} \text{R} &= \text{Me} \\ &= n\text{-Pr} \\ &= \text{Ph} \end{aligned}$$

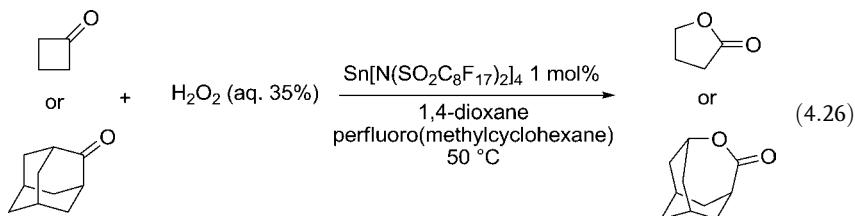
The direct condensation of carboxylic acids with aliphatic alcohols has been investigated by the use of fluorous ammonium salts as metal-free catalysts (Equation 4.24). Esterification reactions were carried out under mild fluorous biphasic conditions, in the presence of 1 mol% of fluorous ammonium triflate and without any water removal techniques. In the case of primary and secondary aliphatic alcohols, good to excellent ester yields were obtained. The fluorous ammonium triflate salt was easily recovered by simple phase separation and reused at least three times without any significant loss of activity [45].



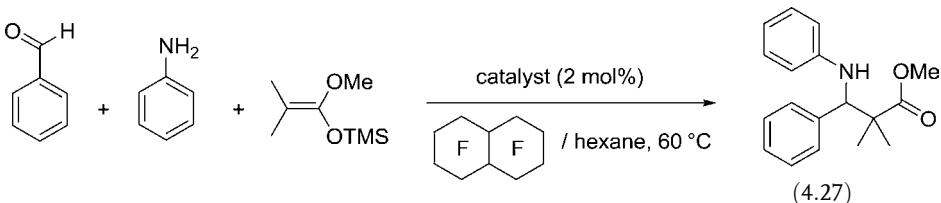
Nitrogen-containing heterocycles (e.g., pyrrolidines, piperidines, indolines, and quinolines) are found in many natural products and have various biological activities. In FBS, a practical, efficient, and environmentally benign intramolecular hydroamination of olefinic sulfonamides was carried out using commercially available heptadecafluorooctanesulfonic acid ($C_8F_{17}SO_3H$) as a catalyst and perfluorodecalin ($C_{10}F_{18}$, *cis*- and *trans*-mixture) as a fluorous solvent to synthesize the corresponding cyclic products in good yields (Equation 4.25). The Brønsted acid $C_8F_{17}SO_3H$ is easily recovered and recycled at least five times [46].



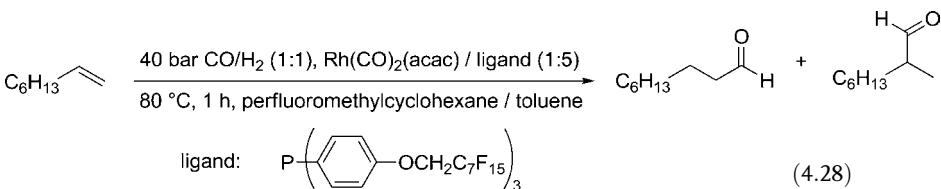
An important application of metal bis(perfluorooctanesulfonyl)amides in fluorous biphasic systems is the Baeyer–Villiger oxidation. Especially $\text{Sn}[\text{N}(\text{SO}_2\text{C}_8\text{F}_{17})_2]_4$ could be reused more than four times in the Baeyer–Villiger oxidation of adamantone and cyclobutanone without significant decomposition of the catalyst (Equation 4.26). It was found that there was almost no difference for the formation rate of γ -butyrolactone between the first and fourth cycles within a 1 h reaction time, which showed that there was not only no loss of the catalyst, but also no decrease in catalytic activity during the repetition [47].



A useful Mannich-type reaction can be carried out in an fluorous biphasic system, by use of perfluorodecalin ($C_{10}F_{18}$, *cis*- and *trans* mixture) as the fluorous solvent and hexane as the organic solvent and perfluorinated rare earth metal salts such as $Sc(OSO_2C_8F_{17})_3$ or $Yb(OSO_2C_8F_{17})_3$ (2.0 mol%) as the catalyst. The Mannich-type reaction of arylaldehydes with aromatic amines and (1-methoxy-2-methylpropenyl)trimethylsilane can be carried out many times without reloading the catalyst and the fluorous solvent (Equation 4.27) [48].



Rhodium complexes with the fluororous phosphine $P(C_6H_4\cdot 4\text{-OCH}_2C_7F_{15})_3$ are active catalysts in the hydroformylation of 1-octene in fluororous biphasic systems [the turnover frequency (TOF) was 380 h^{-1}] (Equation 4.28). Selectivity in aldehydes was as high as 99% and regioselectivity for the linear aldehyde up to an *n/iso* ratio of 2.8 [49].



4.4.3

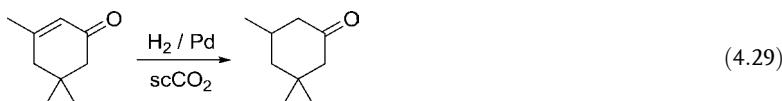
Supercritical Carbon Dioxide

Non-classical reaction media have, in the last few years, come to the forefront of attempts to eliminate environmentally unattractive solvents and improve catalyst recovery and recycling. For example, attention has increasingly focused on supercritical carbon dioxide ($scCO_2$) as an alternative reaction medium [50]. Carbon dioxide shares some of the advantages of water: it is cheap, plentiful, it is a by-product of some industrial processes (e.g., ammonia synthesis, combustion, fermentation), and is nontoxic to the environment and to humans (although is an asphyxiant in high concentrations), but it is a greenhouse gas. The critical temperature and pressure are $31.1\text{ }^\circ\text{C}$, and 73.8 bar , respectively. It can be easily removed and recycled from the reaction mixture by simple depressurization. CO_2 is an aprotic solvent, a weak Lewis acid or base, and does not react with radicals and oxidizing agents, but reacts with moderately strong nucleophiles [51]. Gases (H_2 , O_2 , CO) are

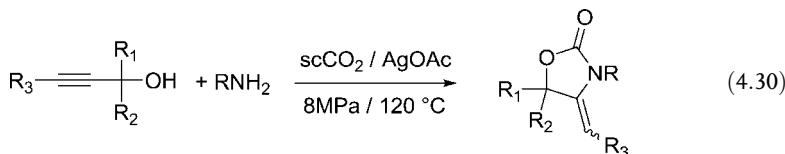
completely miscible with scCO₂, so it is a good medium for reactions involving gases. However, to use scCO₂ special equipment is required, energy is needed to compress the CO₂ (this can be minimized by partial decompression and recycling), and poorly dissolves polar substrates.

The most common use of scCO₂ is in the extraction of caffeine from coffee or tea, nicotine from tobacco, and essential oils from plants. The isolation of products is simple, with the evaporation of the solvent with no residue. Another important application is in supercritical fluid chromatography (SFC).

Poliakoff and co-workers developed a catalytic hydrogenation process which has been commercialized by Thomas Swan and Co. for the manufacture of trimethylcyclohexanone by Pd-catalyzed hydrogenation of isophorone (Equation 4.29) [52].

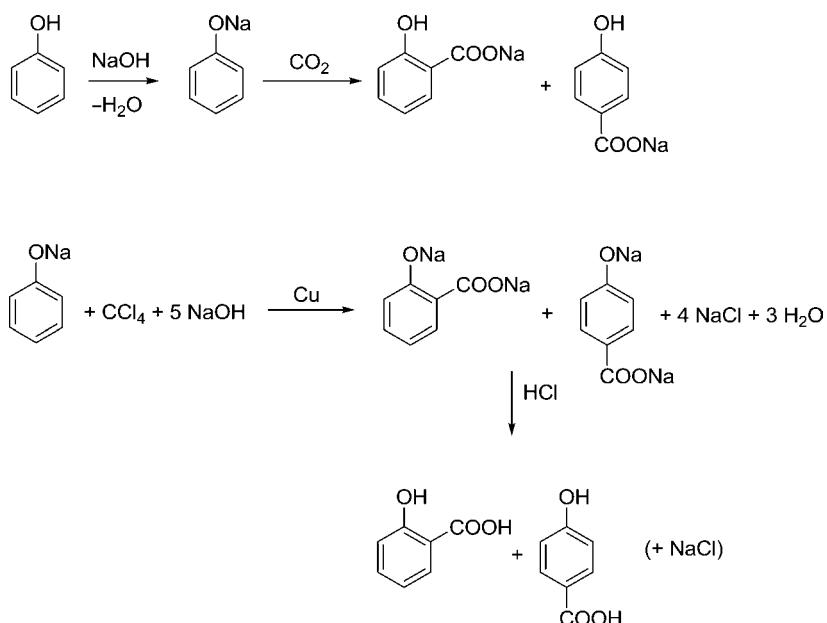


Oxazolidinones are useful heterocyclic compounds in organic synthesis. They have a wide range of applications in asymmetric syntheses as chiral reagents and, since they have good antibacterial properties, in medicinal chemistry [53]. Oxazolidinones can be synthesized in traditional solvents such as acetonitrile [54] or DMF [55], but it is more environmentally friendly to use scCO₂ [56]. In the reaction an internal propargyl alcohol, carbon dioxide, and a primary amine participate in a cycloaddition reaction under supercritical conditions to give 4-alkylene-1,3-oxazolidin-2-ones (Equation 4.30).

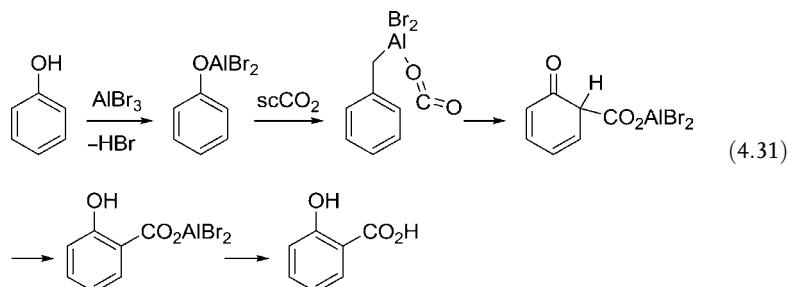


Aromatic hydroxycarboxylic acids, especially salicylic acid, have a wide range of applications, for example, as valuable raw materials and intermediates in the production of pharmaceutical chemicals. Originally, salicylic acid was synthesized by the Kolbe–Schmitt reaction [57], which consists of two steps: (1) the synthesis and purification of alkali metal phenoxides and (2) carboxylation (Scheme 4.4). Another possible synthetic method is via the attack of a trichloromethyl cation (generated by a copper catalyst from carbon tetrachloride) on the phenoxide anion, followed by hydrolysis of the C–Cl bonds with concentrated sodium hydroxide, because it is fairly difficult to replace an aromatic hydrogen with carboxyl functionality [58].

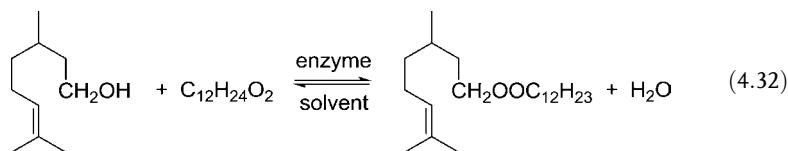
Iijima and Yamaguchi published an efficient and regioselective carboxylation of phenol in supercritical carbon dioxide in the presence of aluminum bromide to form salicylic acid (Equation 4.31) [59]. They also reported the K₂CO₃-catalyzed direct synthesis of salicylic acid from phenol and scCO₂ [60].



Scheme 4.4



Enzymatic esterification of β-citronellol with lauric acid to obtain citronellol laurate was studied in traditional organic solvents (*n*-heptane, 2-methyl-2-butanol, ethyl methyl ketone, acetone) and compared with scCO₂ (Equation 4.32) [61].



Poly(heptadecafluorodecyl acrylate) and poly(heptadecafluorodecyl methacrylate) (Figure 4.3) were synthesized in a high-pressure reactor using solution polymerization methods in scCO₂ at 70 °C and 300–310 bar for 24 h with azobisisobutyronitrile (AIBN) as the initiator (1.0 wt% of monomer) [62].

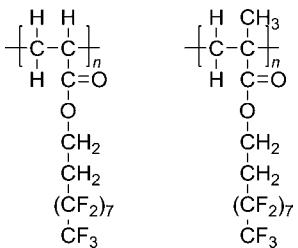
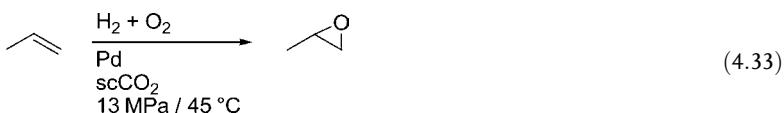


Figure 4.3 Poly(heptadecafluorodecyl acrylate) and poly(heptadecafluorodecyl methacrylate).

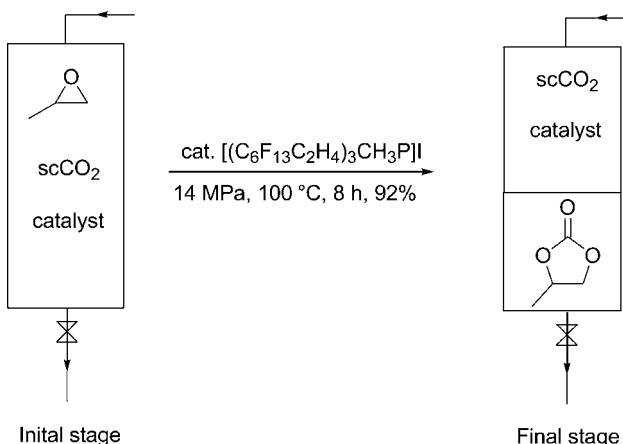
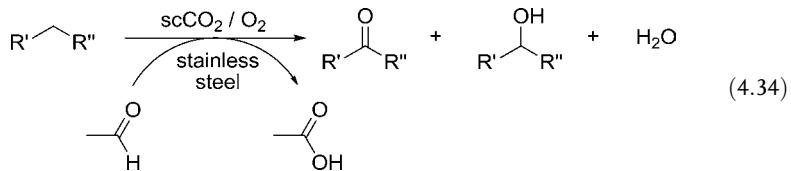
Hydroformylation is one of the mildest and most efficient methods of producing aldehydes and hence it has a wide range of applications in the petrochemical industry. The cleanest, industrially important hydroformylation process is the aqueous biphasic system developed by Ruhrchemie/Rhône-Poulenc [63]. However, the applicability of this system is limited to substrates which have a low solubility in water, such as propene and 1-butene. It is advantageous to use scCO₂ because there is no gas–liquid phase boundary and because of the ability of scCO₂ to dissolve gases in high concentrations, combined with effective product and catalyst separation [64].

scCO₂ is an ideal inert solvent for performing catalytic aerobic oxidations, because it is nonflammable and completely miscible with oxygen. Recently, attention has focused on catalytic oxidations with hydrogen peroxide, generated *in situ* by the Pd-catalyzed reaction of hydrogen with oxygen, in scCO₂–water mixtures (Equation 4.33). These reactions probably involve the intermediate formation of peroxy-carbonic acid by reaction of H₂O₂ with CO₂ [65].

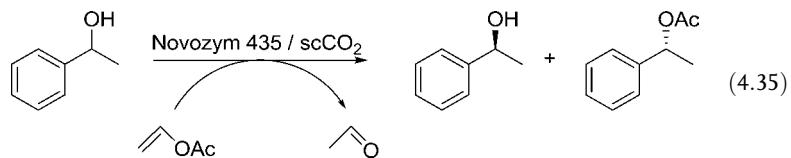


Alkylene carbonate synthesis in scCO₂ is an ideal system for solvent–product and product–catalyst separation. Initially, starting epoxides such as propylene oxide form a single homogeneous phase with scCO₂. As the reaction takes place, the resulting alkylene carbonate (propylene carbonate) spontaneously separates from the supercritical CO₂ phase as a lower liquid phase. The product is removed from the bottom of the reactor, while maintaining the CO₂ pressure and temperature inside the reactor. In addition, CO₂-philic polyfluoroalkylphosphonium iodides {e.g., [(C₆F₁₃C₂H₄)₃CH₃P]I} can be applied as catalysts that can be used repeatedly, since they have high solubility in scCO₂ (Scheme 4.5) [66].

The oxidation of cycloalkanes or alkylarenes with molecular oxygen and acetaldehyde as a co-reductant takes place efficiently in scCO₂ under mild conditions. No catalyst is required and high-pressure ATR-FTIR online measurements showed that a radical reaction pathway was heterogeneously initiated by the stainless steel of the reactor walls (Equation 4.34) [67].

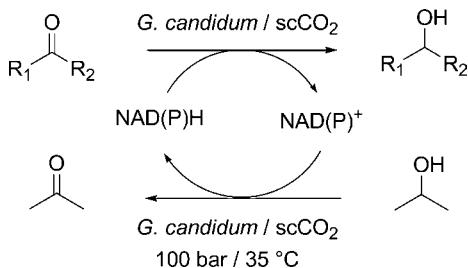
**Scheme 4.5**

scCO_2 is also an interesting solvent for performing bioconversions. Enzymes can be more stable in scCO_2 than in water and the *Candida antarctica* lipase (Novozym 435)-catalyzed resolution of 1-phenylethanol was successfully performed at temperatures under 100 °C in this solvent. A kinetic resolution of 1-phenylethanol at 9 MPa CO_2 and 40 °C gave the (*R*)-acetate in 99.8% *ee* and the (*S*)-alcohol in 90.6% *ee* at 48% conversion (Equation 4.35) [68].

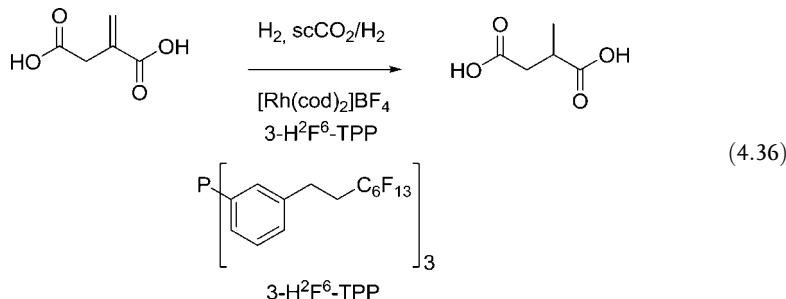


The enantioselective reduction of prochiral ketones catalyzed by whole cells of *Geotrichum candidum* proceeded smoothly in scCO_2 in a semi-continuous flow system (Scheme 4.6) [69].

An inverted scCO_2 -aqueous biphasic system has been used as reaction medium for Rh-catalyzed hydrogenation of polar substrates (Equation 4.36). Chiral and achiral CO_2 -philic catalysts were efficiently dissolved and immobilized in scCO_2 as the (upper) stationary phase, while water, as the mobile phase, contained the polar substrates and products. Notably, product separation and catalyst recycling were conducted by maintaining the pressure in the reaction vessel. The catalyst phase was reused several times with high conversion and product yields of more than 85% [70].



Scheme 4.6



4.4.4

Ionic Liquids

Ionic liquids (ILs) are molten salts which are liquid at, or close to, room temperature and generally consist of larger organic cations and smaller anions (Figure 4.4) [71].

One of the most advantageous properties of ILs is their very low vapor pressure. This is why they cannot contaminate the atmosphere and are a potential candidate for green chemistry. Reaction products can be separated from ILs by distillation. ILs can dissolve many organic, inorganic, and organometallic compounds. Compared with

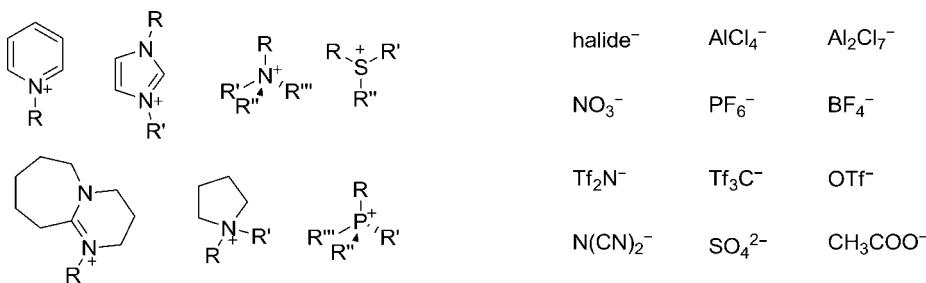
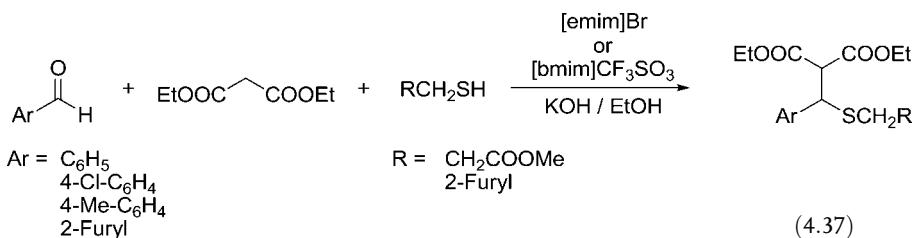


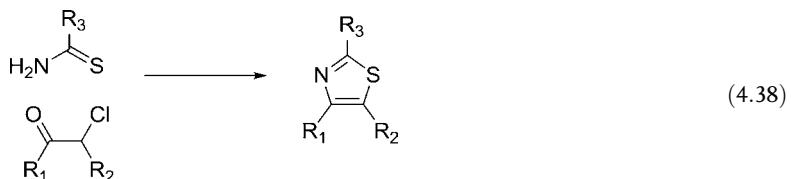
Figure 4.4 Components of ionic liquids.

traditional organic solvents, much higher kinetic control can be attained because they are stable over a wider range of temperature. As they are immiscible with several organic solvents, they can be used in biphasic systems. The products can be extracted with an organic solvent, while the catalyst remains in the IL and can be reused. Furthermore, they have reasonable thermal stability and are liquid over a wide range of temperature. They can behave as Lewis acids and serve as a solvent at the same time or they can be a ligand, catalyst, and solvent simultaneously. According to their chemical structure, they are easily tunable. However, the effects of ILs on aquatic organisms and ecosystems are not well known. The toxicity of imidazolium-based ILs is close to that of many chemicals used currently in manufacturing and disinfection processes (e.g., ammonia and phenol), showing that these “green” chemicals may be more malign to aquatic organisms than current volatile organic solvents [72].

1-Ethyl-3-methylimidazolium bromide and 1-butyl-3-methylimidazolium trifluoromethanesulfonate were used as a green recyclable alternative to volatile organic solvents for KOH-catalyzed three-component syntheses of diethyl alkylsulfanyl methylmalonates from aldehydes, diethyl malonate, and alkanethiols (Equation 4.37) [73].

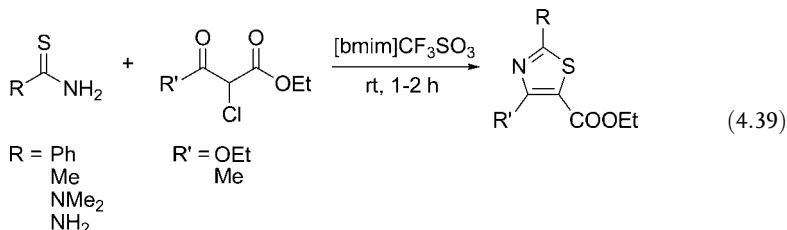


Thiazole and its derivatives are useful compounds in medicinal and agricultural chemistry. The thiazolium ring is present in vitamin B₁, and its coenzyme form is important for the decarboxylation of α -keto acids [74]. This heterocyclic system has broad application in drug development for the treatment of inflammation [75] and bacterial [76] and HIV infections [77]. Hence the thiazole nucleus has been much studied in organic and medicinal chemistry. Originally it was synthesized by the Hantzsch reaction (α -halo ketones with thioamides or thioureas) (Equation 4.38) [78].

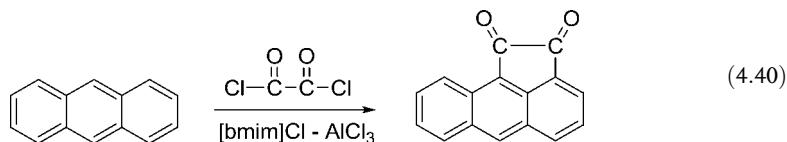


With a simple one-pot reaction of 2-chloro-1,3-dicarbonyl compounds with thiourreas or thioamides in the presence of 1-butyl-3-methylimidazolium trifluorometha-

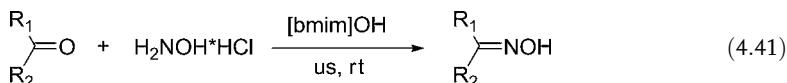
nesulfonate, functionalized ethyl 1,3-thiazole-5-carboxylates were synthesized (Equation 4.39)[79].



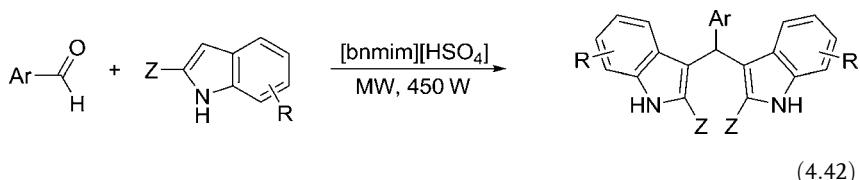
Friedel–Crafts acylations can be catalyzed by some inorganic Lewis acidic catalysts, of which AlCl_3 has the highest catalytic activity. In order to compare these, the acylation of anthracene with oxalyl chloride was carried out with 1 equiv. of AlCl_3 as catalyst where CS_2 was used as solvent, and also in the system $[\text{bmim}] \text{Cl}-\text{AlCl}_3$ (Equation 4.39). The results showed that $[\text{bmim}] \text{Cl}-\text{AlCl}_3$ is an environmentally friendly catalyst, and its catalytic efficiency is higher than that of AlCl_3 . The yields of 1,2-acanthrylenedione when using $[\text{bmim}] \text{Cl}-\text{AlCl}_3$ and AlCl_3 were 88.2 and 83.8%, respectively, and the selectivities of 1,2-acanthrylenedione were 98.2 and 92.3%, respectively. Furthermore, in the presence of $[\text{bmim}] \text{Cl}-\text{AlCl}_3$ IL, the separation and isolation of the products were easier and the acylation synthetic step is free of any volatile organic solvent since the IL plays two roles: Lewis acid catalyst and solvent. However, for AlCl_3 as catalyst, some problems arose, such as heavy environmental pollution, problematic recovery and purification of the product, and difficulty in recovering the catalyst [80].



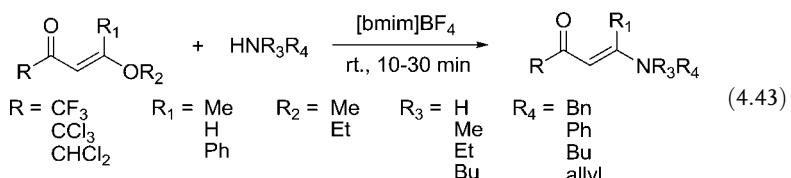
The basic IL 1-butyl-3-methylimidazolium hydroxide ($[\text{bmim}] \text{OH}$) efficiently catalyzes the condensation reaction of aldehydes and ketones with hydroxylamine hydrochloride with ultrasound irradiation (Equation 4.41). Compared with conventional methods, the main advantages of this procedure are milder conditions, shorter reaction times, and higher yields [81].



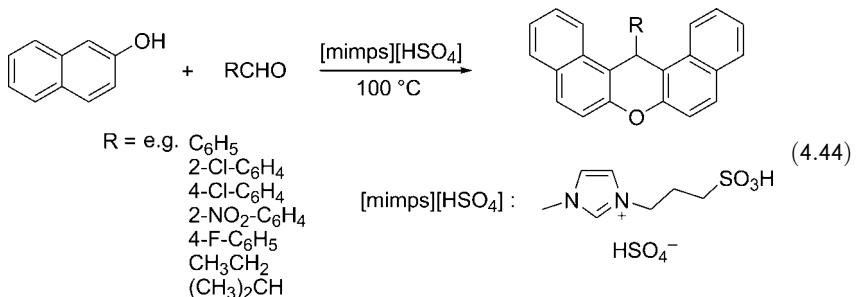
1-Benzyl-3-methylimidazolium hydrogensulfate ($[\text{bnmim}] [\text{HSO}_4]$) was found to be an effective catalyst for the condensation reaction of indoles and derivatives with benzaldehydes under microwave irradiation with shorter reaction times and higher yields to give bis(indolyl)methanes (Equation 4.42). Bis(indolyl)methanes are very active substances for promoting beneficial estrogen metabolism and are used in tumor chemotherapy by inducing apoptosis in human cancer cells [82]. A mixture of indole and aldehyde in an IL was irradiated at 450 W in a microwave oven [83].



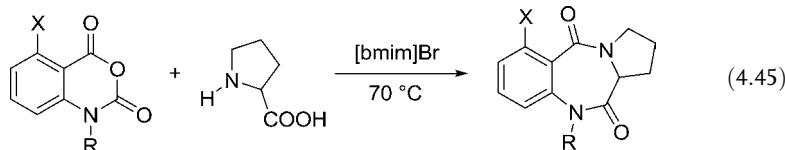
A series of halomethylated β -enaminones were synthesized using the IL [bmim] BF_4 at room temperature (Equation 4.43). It was demonstrated that this IL is suitable as a reaction medium for the amination of β -alkoxyvinyl halomethyl ketones. This method is advantageous because of the absence of solvents, short reaction times, and good yields [84]. These compounds are now widely used as important materials in research, having interesting functionalities for use in medicinal and agricultural sciences [85].



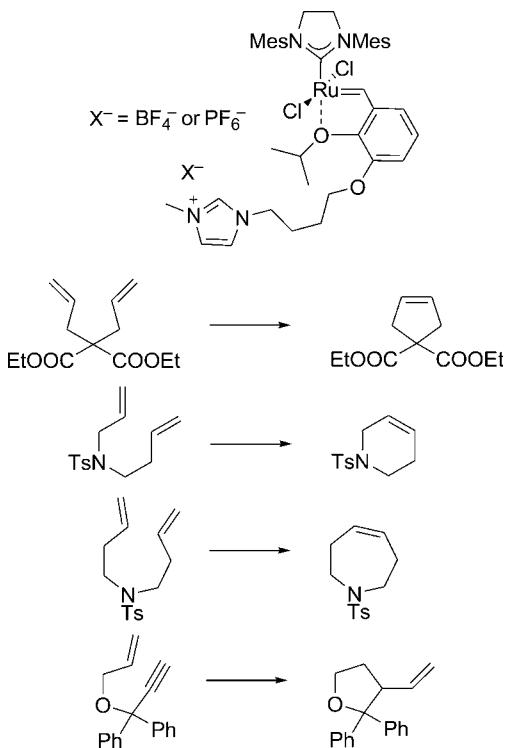
A Brønsted-acidic IL, 1-methyl-3-propanesulfonic imidazolium hydrogensulfate ($[\text{mimps}][\text{HSO}_4]$), was applied as a catalyst for the synthesis of 14-alkyl- or -aryl-14*H*-dibenzo[*a,j*]xanthenes by the one-pot condensation of β -naphthol with aliphatic or aromatic aldehydes (Equation 4.44). Numerous aliphatic and aromatic aldehydes have been used in the reaction and, in all cases, the desired products were synthesized successfully. The novel synthesis method has the advantages of high yields, short reaction times, and a simpler and easier work-up compared with the conventional method. The catalyst could be recycled and reused five times without a decrease in its activity. The synthesis of xanthenes, especially benzoxanthenes, has come to the forefront in recent years because of their wide applicability in biological and pharmaceutical sciences due to their antiviral, antibacterial, and anti-inflammatory properties and also an efficacy in photodynamic therapy and an antagonism for the paralyzing action of zoxazolamine. These compounds also can be used as dyes, as pH-sensitive fluorescent materials for visualization of biomolecules, and in laser technology [86].



The importance of 1,4-benzodiazepine-2,5-diones (BZDs) has increased due to their valuable pharmacological properties in the treatment of cancer, AIDS, hypertension, inflammation, pain, muscle tension, and depression. The green reaction of isatoic anhydrides with α -amino acids in the presence of the IL 1-butyl-3-methylimidazolium bromide gave 1,4-benzodiazepine-2,5-diones in excellent yields with no catalyst (Equation 4.45). The reaction work-up is simple and the IL was easily separated from the reaction and reused. The methodology was fairly general and numerous cyclic and acyclic α -amino acids were used to produce 1,4-benzodiazepine-2,5-diones [87].

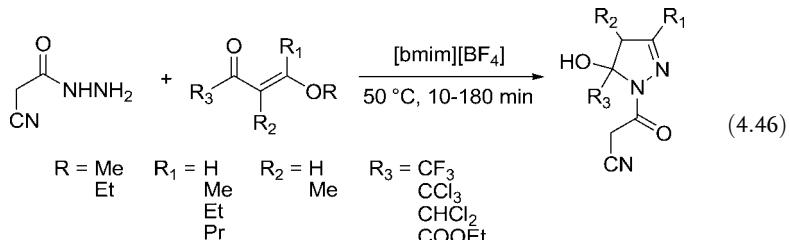


Pyrazolines are important nitrogen-containing five-membered heterocyclic compounds, and are employed as dyestuffs, analytical reagents, and agrochemicals. In addition, pyrazolines have important pharmacological activities and hence they are useful materials in drug research. Several pyrazolines have played an important role



Scheme 4.7

in the development of theoretical studies in heterocyclic chemistry and are also very useful building blocks in organic chemistry [88]. 1-Cyanoacetyl-5-hydroxy-5-halo-methyl-4,5-dihydro-1*H*-pyrazoles were synthesized in [bmim][BF₄] from 4-alkoxy-3-alken-2-ones and cyanoacetohydrazide (Equation 4.46) [89].



Olefin metathesis is a powerful tool for the synthesis of carbon–carbon double bonds, and many applications in natural product synthesis have already been reported using ruthenium- or molybdenum-catalyzed ring-closing metathesis. On the other hand, attention has increased on ILs as reaction media in organic chemistry, due to their interesting properties that provide wide applicability to organic and inorganic compounds. New IL-supported ruthenium–carbene complexes and their application have been reported in ring-closing metathesis for the construction of 5–8-membered rings with high activity and good recyclability (Scheme 4.7) [90].

4.5

Conclusion

One of the key principles of green chemistry is the elimination of solvents in chemical synthesis or the replacement of hazardous solvents with environmentally benign solvents. The development of solvent-free alternative syntheses is, of course, the best solution, especially when either one of the substrates or the product is a liquid and can be used as the natural solvent of the reaction. However, if solvents are crucial to a process, we can select from solvents that will have no or limited impact on health and the environment and the selection should be an intrinsic part of green innovation. The most important rule is that we should match the solvent properties with the synthesis objectives and then identify the best available solvent or design a new solvent.

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5

Development and Application of Isocyanide-based Multicomponent Reactions

Jieping Zhu, Qian Wang, and Mei-Xiang Wang

5.1

Introduction

The waste production in a chemical process parallels to the number of synthetic steps that are involved. For a given target, the length of a synthesis depends upon the average molecular complexity produced per operation, which depends in turn on the number of chemical bonds being created [1, 2]. Therefore, devising reactions that achieve multiple-bond formation in one operation can save synthetic operations and is becoming one of the major challenges in searching for eco-compatible syntheses. By nowadays' standards, in addition to being regio-, chemo-, and stereoselective, an ideal multiple-bond-forming process should satisfy the following additional criteria: (a) use readily available starting materials; (b) be operationally simple; (c) be easily automatable; (d) be resource effective (personnel, time, cost etc); (e) be atom economic; and (f) be ecologically benign. A multicomponent reaction (MCR) is a process in which three or more reactants are combined in a single chemical operation to produce a compound that incorporates substantial portions of all starting materials (Figure 5.1). They are by definition sustainable chemistry and are inherently (a) chemo- and regioselective, a prerequisite for a successful MCR since at least three reactive functional groups are involved and they react in an ordered and selective fashion; (b) atom-economic [3], since most of them involve addition rather than substitution reactions, and indeed, addition reactions are susceptible to generate new reactive functionalities essential for the multicomponent domino process, whereas substitution reactions consume the functional groups; (c) step-efficient since they create at least two chemical bonds in one operation; (d) convergent and efficient in generating molecular complexity and diversity [4]; (e) cost-effective, since they reduce significantly waste production by minimizing the number of costly end-of-pipe treatments by decreasing the number of synthetic steps; and (f) operationally simple, since most of the MCRs are performed under mild reaction conditions and in some cases even proceed spontaneously in the absence of external reagent. In short, MCRs constitute a gateway to the ideal organic syntheses in which the target molecule is made from readily available starting materials in one

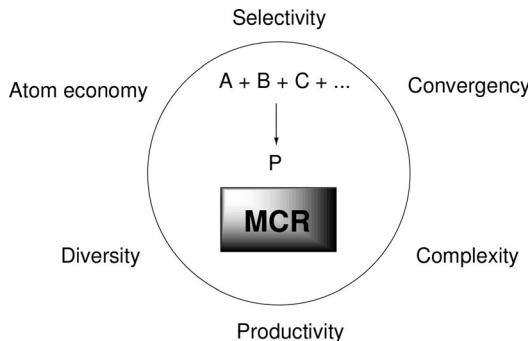
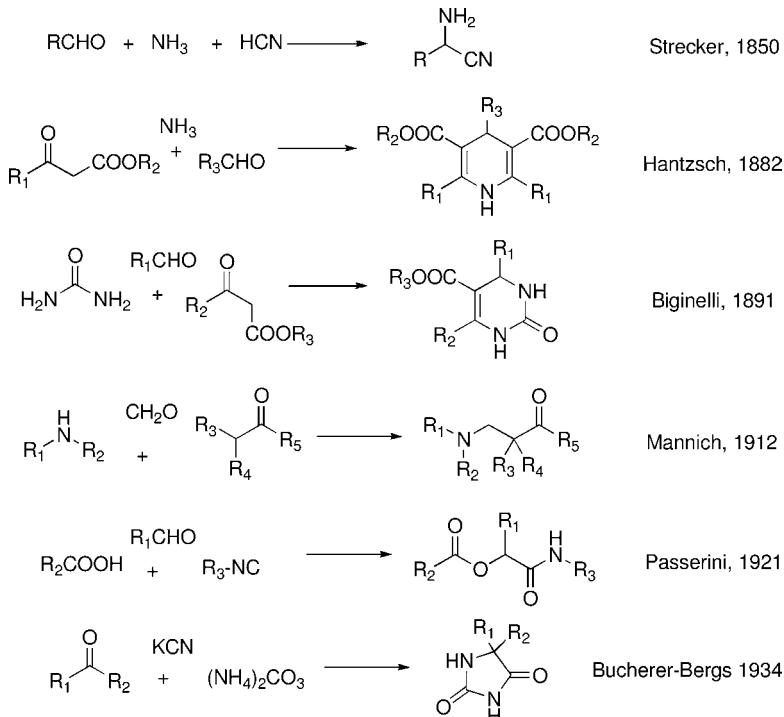


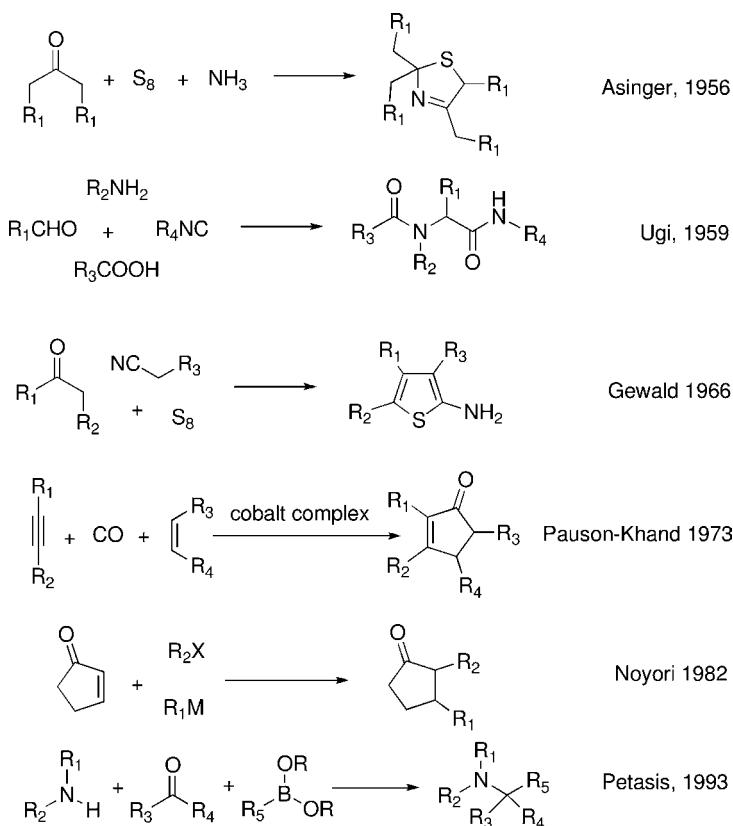
Figure 5.1 Multicomponent reactions: tools for developing eco-compatible chemistry.

simple, safe, environmentally acceptable, and resource-effective operation that proceeds quickly and in high yield[5].

Multicomponent reactions, although fashionable these days, have in fact a long history. Indeed, many important reactions such as the Strecker amino acid synthesis (1850)[6], the Hantzsch dihydropyridine synthesis (1882) [7], the Biginelli dihydropyrimidine synthesis (1891)[8], the Mannich reaction (1912) [9], and the isocyanide-based Passerini reactions (1921) (Scheme 5.1) [10], among others, are all



Scheme 5.1 Text-book MCRs developed before the 1950s.



Scheme 5.2 Text-book MCRs developed after the 1950s.

multicomponent in nature. In spite of the significant contribution of MCRs to the state-of-art of modern organic chemistry and its potential use in complex organic synthesis¹⁾ [11], little attention was paid to the development of novel MCRs for the past half a century, with some important examples being listed in Scheme 5.2. However from the mid-1990s, research dedicated to the development and application of MCRs increased steadily, parallel to the introduction of molecular biology and high-throughput biological screening. By virtue of its inherent convergence, high productivity, and its exploratory and complexity-generating power, research on MCRs has become a rapidly evolving field and has attracted attention from both academic and industrial scientists. Indeed, many reviews dealing with the discovery and application of MCRs in drug development and in syntheses of heterocycles and bioactive natural products have appeared in recent years [12]. Therefore, it is not our intention to make this chapter comprehensive (impossible anyway); rather, we try to use isocyanide-based MCRs as examples to illustrate the recent development and

1) Robinson's three-component synthesis of tropinone remained illustrative.

applications of this family of MCRs in the context of green chemistry. For this reason, most of the MCRs discussed in this chapter satisfied the following criteria: (a) need no external reagent, or if required only in a catalytic amount; (b) produce minimum amounts of side products, in most cases water and low molecular weight alcohols; (c) require no protective groups; and (d) create more than two chemical bonds.

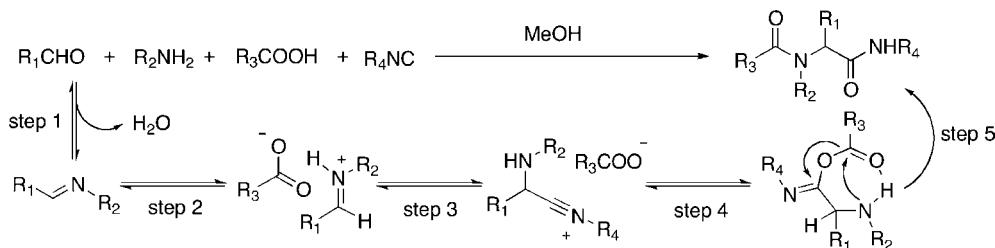
5.2

Basic Principle of MCRs

MCRs could be roughly divided into three categories: [13]

Each elementary step is reversible. At first glance, this type of reaction should afford a complex reaction mixture of product, all possible intermediates, and starting materials. However, if the desired adduct is thermodynamically more stable than any other intermediates, the reaction can still be high yielding and become synthetically useful. The Strecker reaction is a typical example. Although the condensation of an aldehyde, an amine leading to iminium intermediate and subsequent nucleophilic addition of cyanide are in principle reversible under aqueous acidic conditions. The α -aminonitrile can be obtained in high yield under appropriate conditions.

Last irreversible step in combination with other equilibrium steps. Notable examples are the Passerini and the Ugi reactions. As detailed in Scheme 5.3, the Ugi four-component reaction (U-4CR) produced α -acetamidoamide by simply stirring a methanolic solution of an aldehyde, an amine, a carboxylic acid, and an isocyanide. The Mumm rearrangement (step 4), being irreversible, drove the reaction towards the formation of the Ugi adduct in good to excellent yield under extremely mild conditions. Evidently, having an irreversible step, especially if it occurred at the end of the reaction sequence, is advantageous, as the equilibrium steps will consequently be shifted to the final product.



Scheme 5.3 Ugi four-component reaction: proposed mechanism.

Each elementary step is irreversible. This type of reaction implies that each reaction step must be highly chemoselective in order to avoid the formation of side products, and examples belong to this class are relative rare. Nevertheless, the Noyori

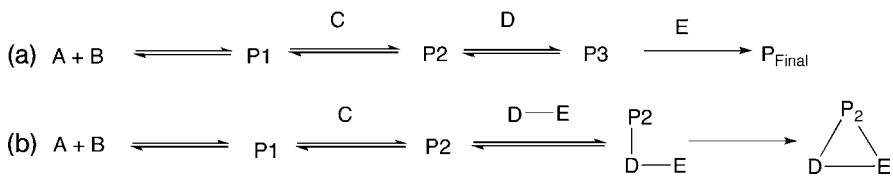


Figure 5.2 Linear versus cyclic adducts.

three-component reaction involving the Michael addition of an organometallic species followed by trapping of the resulting enolate by an alkyl halide could be categorized in this family²⁾. In addition, with the recent advent of transition metal-catalyzed multicomponent reactions, more and more MCRs of this type will be discovered.

Of course, the above classification is just a guideline and not a strict definition. A key point that one can draw and that should be kept in mind from this analysis is that the presence of equilibrium steps is generally beneficial to MCR sequences.

5.3

Discovering Novel MCRs

It is fair to say that a multicomponent reaction was rarely devised aiming at exploring new chemical reactivity of individual functional groups. Rather, the process is designed on the basis of well-known bimolecular reactions. The novelty of an MCR resides in how these individual reactions were combined and the outcome of the overall reaction sequence. A proper combination of a sequence of already existing reactions is essential for the development of novel MCRs: (a) two components (A and B) must combine to generate a substructure (P1) that reacts with another component (C); (b) component C must not react irreversibly with either A or with B and so on; and (c) in an ideal case, an irreversible step is incorporated to drive the reaction along the desired pathway. This last requirement, however, is not an obligation, as discussed in Section 5.2.

Linear adducts would be produced from monofunctional inputs whatever the number of components employed [Figure 5.2, reaction (a)]. If one aimed at developing multicomponent syntheses of heterocycles, one simple solution would then be the use of polyfunctional substrates since these imply an intramolecular reaction at a certain stage of the sequence, leading eventually to heterocycles [Figure 5.2, reaction (b)]. Some very simple functional groups such as cyanide and carbonic acid are bifunctional in nature, as in the Bucherer–Bergs reaction.

As shown in Scheme 5.3, the Ugi 4CR provides a linear peptide-like adduct. However, it provided an ideal starting point to reach heterocycles. A conceptually simple approach consisted of tethering two out of four inputs and performing a

2) Michael addition could be reversible depending on the nature of the nucleophiles. However, when RM ($R = \text{alkyl, alkene, M} = \text{metal}$) were used as nucleophiles, the 1,4-addition became essentially irreversible.

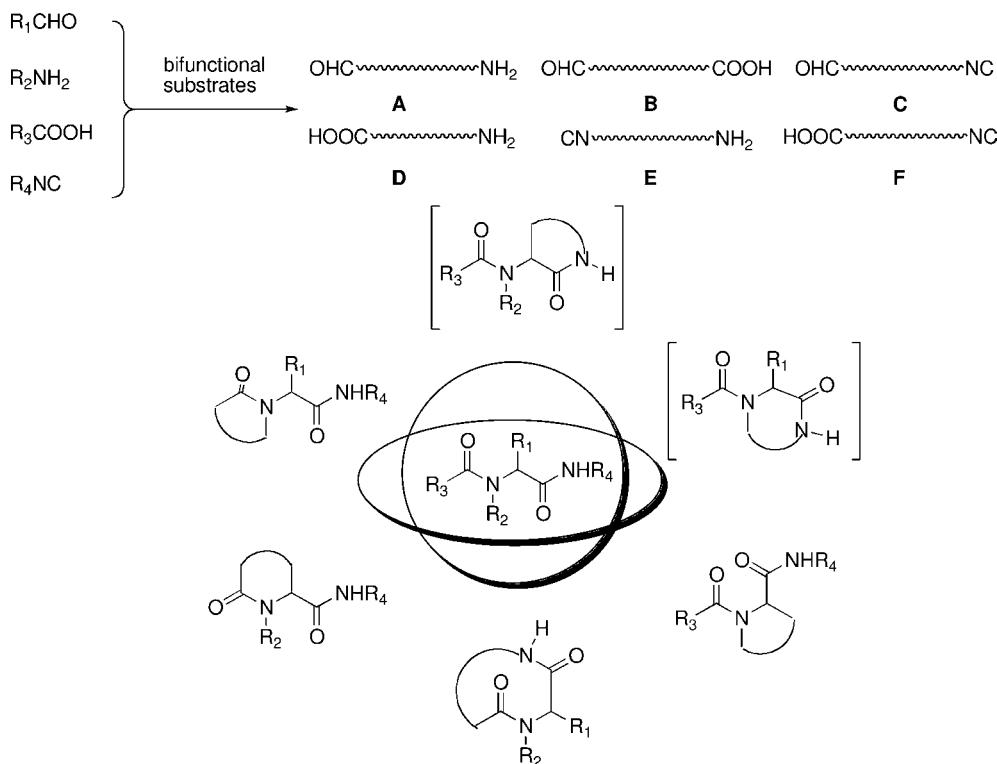
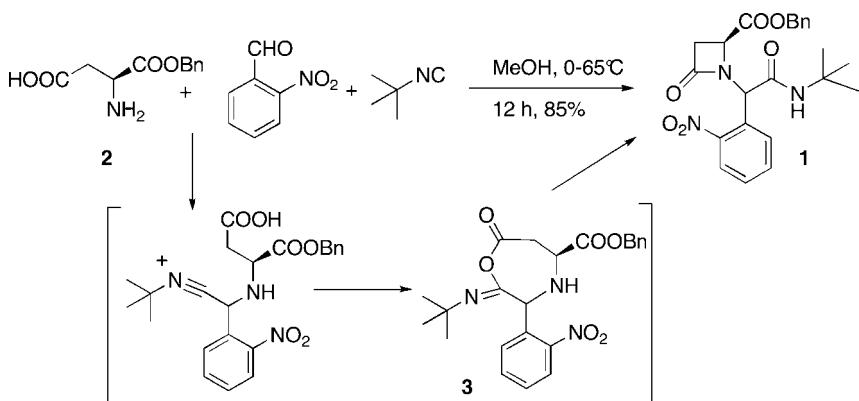


Figure 5.3 From linear peptide-like adducts to heterocycles.

Ugi three-component/four-center condensation. Theoretically, random combination of four functional groups would lead to six different bifunctional substrates, which, once engaged in a Ugi reaction, would produce six topologically different cyclic scaffolds (Figure 5.3). In practice, four types of cyclic structures have been synthesized employing an aminoaldehyde (or cyclic Schiff base) (A), keto acid (B), amino acid (or peptide) (D), and isocyanocarboxylic acid (F) as bifunctional starting materials. Using ketoisocyanide (C) and aminoisocyanide (E) in Ugi-three-component/four-centers remained to be exploited.

Scheme 5.4 shows a one-step three-component synthesis of the medicinally important β -lactam **1** by simply mixing a β -amino acid, an aldehyde, and an isonitrile. In this example, the amine and carboxylic acid were tethered together in the form of a β -amino acid. The reaction proceeded according to the Ugi mechanism leading to a cyclic imidate intermediate, which upon intramolecular transacylation afforded the observed cyclic product [14].

Both computational methods and diversity-oriented reaction searches have been successfully applied to the discovery of novel MCRs [15]. However, MCRs can also be devised on rational grounds, and we give a few examples in the following sections to illustrate the basic principles that were used for the development of novel isocyanide-based MCRs (IMCRs) [16].

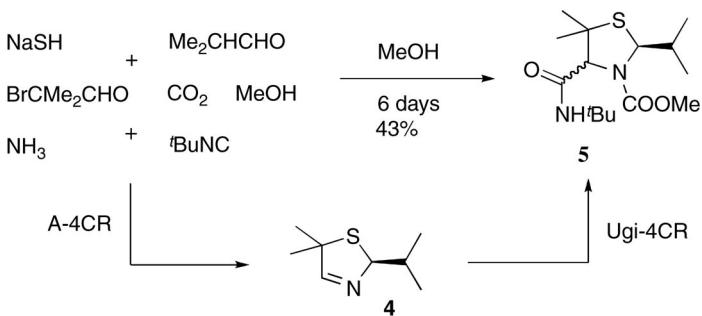


Scheme 5.4 Ugi-three-component/four-centers for the synthesis of a functionalized β -lactam.

5.3.1

Union Concept

Ugi and colleagues developed the concept of unifying MCRs in order to obtain new MCRs [17]. Indeed, the Ugi-4CR could be considered as a combination of Schiff base formation and Passerini-3CR. By combining the Asinger and Ugi MCRs, Dömling and Ugi found a novel seven-component reaction as shown in Scheme 5.5 [18]. In this reaction, the Asinger adduct, the thiaoxazoline 4, a cyclic imine, serves as the starting material for the subsequent Ugi condensation leading to the formation of thiazolidine 5. In fact, the Ugi reaction is known to proceed especially well when a preformed imine is used.



Scheme 5.5 Union of Asinger and Ugi MCRs leading to a seven-component reaction.

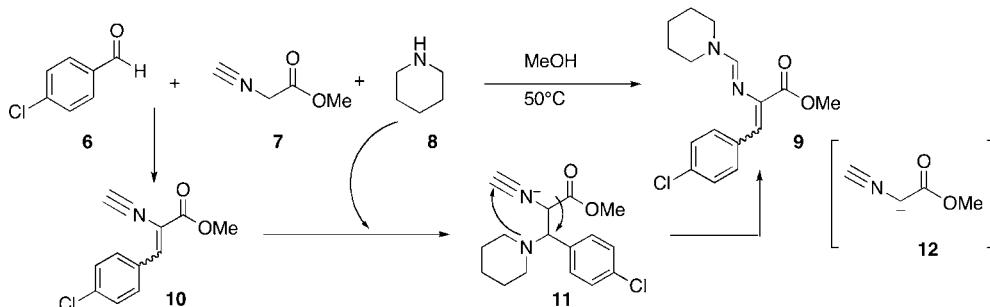
5.3.2

Rational Substrate Design

The MCR is a combination of a series of two-component reactions where the product of the first reaction reacts with the third input to give a second product, which in turn

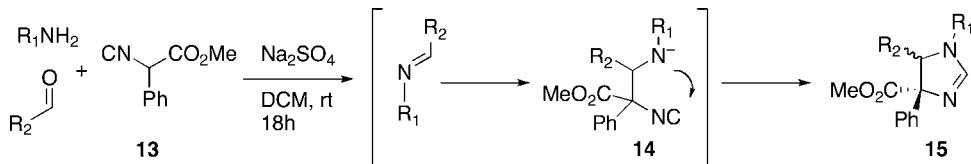
may react with a fourth starting material, and so on. Thus, by carefully considering the chemical reactivities of individual starting materials and relevant intermediates, it is possible to design novel MCRs. If polyfunctionalized substrates were designed and programmed in such a way that they will react in a highly ordered and productive fashion to produce in high yield an interesting scaffold, then a novel MCR would be uncovered.

Matsumoto and co-workers reported in 1978 that simply heating a solution of 4-chlorobenzaldehyde (**6**), methyl α -isocyanoacetate (**7**), and piperidine (**8**) in MeOH led to the formation of an amidine (**9**) in about 50% yield (Scheme 5.6) [19]. The reaction is suggested to be initiated by the Knoevenagel condensation followed by a formal α -addition of the secondary amine to the isocyano group. It is evident from this work that the α -proton of α -isocyanoacetate **7** is relatively acidic and is readily deprotonated under even weakly basic conditions [20]. The nucleophilicity of the α -carbanion of the enolate **12** produced is apparently higher than that of the terminal divalent carbon of the isonitrile, thus initiating the overall reaction sequence by the Knoevenagel condensation.



Scheme 5.6 Three-component synthesis of amidine from α -isocyanoacetate.

By introducing a substituent, especially an aryl group, into the α -position of an α -isocyanoacetate (e.g., **13**) and using a primary amine as reaction partner of an aldehyde, a completely different product was obtained by Orru's group (Scheme 5.7) [21]. The reaction was also initiated by nucleophilic addition of the enolate anion of **13** to the imine (iminium); however, the lack of an additional acidic proton α to the ester group in the intermediate **14** (Mannich adduct) made β -elimination impossible. Therefore, the secondary amine would attack intramolecularly the divalent isocyano carbon leading,

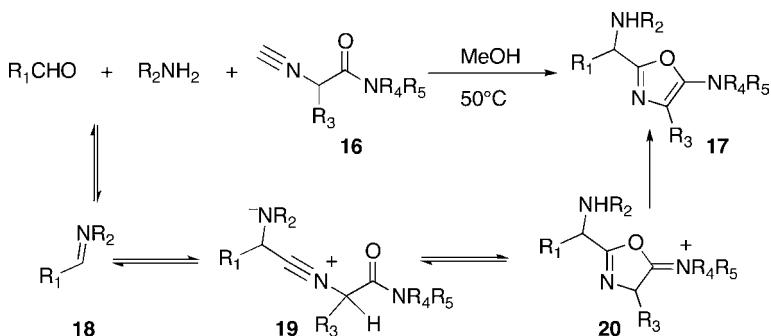


Scheme 5.7 Three-component synthesis of imidazoline.

after protonation, to the imidazoline in excellent yield and diastereoselectivity. The presence of an α -phenyl group was considered to contribute further to the acidity of the α -proton in **13**, thus allowing the deprotonation to occur even under mild conditions (CH_2Cl_2 , room temperature).

It is conceivable that if one used α -isocyanoacetic acid derivatives having a less α -acidic proton and if the reaction conditions were sufficiently mild to prevent the α -deprotonation, then one could expect to have a reaction sequence initiated by the nucleophilicity of the isocyanide, consequently leading to a completely different product.

The $pK_{\alpha(\alpha\text{CH})}$ of amide is 3–5 units higher than that of ester. Consequently, the α -methylene proton of the α -isocyanoamide **16** should be less prone to deprotonation than that of α -isocyanoacetate. The fact that the amide function is less electron withdrawing than the ester function should also render the isonitrile carbon slightly more nucleophilic. This consideration led us to perform the same reaction as described by Matsumoto and co-workers but using α -isocyanoacetamide **16** [22] instead of the α -isocyanoacetate as a reaction partner. As shown in Scheme 5.8, the reaction indeed proceeded in a completely different way to afford a 5-aminooxazole (**17**) in excellent yield [23]. We hypothesized that under these mild conditions, the deprotonation of the α -proton of amide **16** did not occur. Consequently, the sequence is initiated by a nucleophilic addition of the isonitrile carbon to the *in situ*-generated imine **18** led to the nitrilium intermediate **19**, which was in turn trapped by the amide oxygen to afford the oxazole **17**. This example demonstrated how subtle structural modification of one input in a given MCR could modify the reaction sequence and diversify the structure of the resulting adducts³⁾.

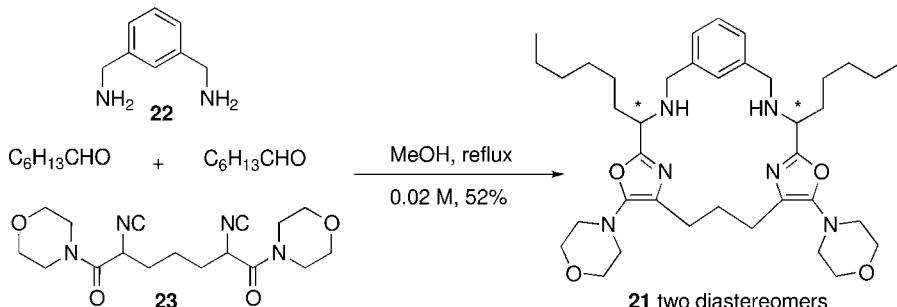


Scheme 5.8 Three-component synthesis of 5-aminooxazoles.

Based on this novel three-component synthesis of 5-aminooxazoles and by designing reaction partners, a two-fold four-component (ABC₂) synthesis of *m*-cyclophane **21** was devised by reacting a diamine (**22**), a bis- α -isocyanoacetamide

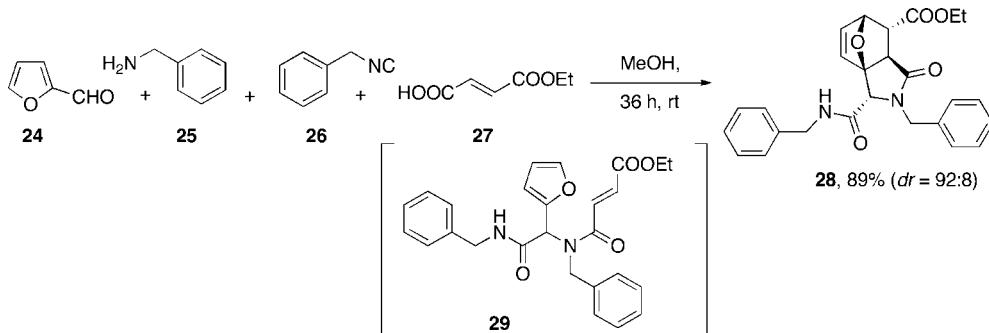
3) Reaction of methyl α -(4-nitrophenyl) α -isocyanoacetate with an amine and an aldehyde afforded the 5-methoxyoxazole instead of imidazoline. In this case, the high acidity of the α -proton of substituted α -isocyanoacetate made the resulting enolate very stable, and hence inactive [24].

(23) and 2 equiv. of heptaldehyde (Scheme 5.9) [25]. In this MCR, one macrocycle embedded with two heterocycles was produced via the creation of six chemical bonds, and water was the only by-product generated.



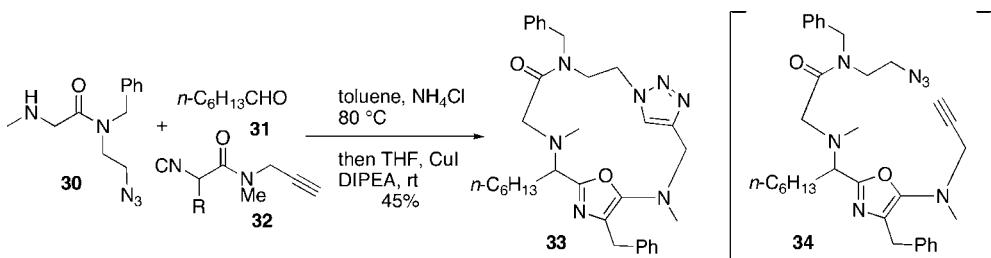
Scheme 5.9 Four-component (ABC₂) synthesis of *m*-cyclophane.

An MCR allows the build-up of a scaffold with a multitude of substituents. One highly rewarding approach in devising novel MCRs involved the incorporation of paired functional groups into the starting materials that can subsequently react intramolecularly after all components have been assembled. In this context, Paulvannan reported an elegant synthesis of bridged tricyclic compounds by combination of a Ugi-4CR and an intramolecular Diels–Alder reaction (IMDA) [26]. Key to this process is the incorporation of a diene and a dienophile in two of the four components of the Ugi reaction. As shown in Scheme 5.10, stirring a methanolic solution of furaldehyde (24), benzylamine (25), benzyl isonitrile (26), and ethyl fumarate (27) at room temperature for 36 h provided the cycloadduct (28) in 89% yield (*dr* = 92:8). The initially formed Ugi adduct 29, isolable, underwent intramolecular [4 + 2] cycloaddition to afford the observed heterocycle. The relative stereochemistry of the major isomer, undetermined at that time, was drawn in the light of the X-ray structure of a similar compound obtained by Schreiber and co-workers [27].



Scheme 5.10 Four-component Ugi-4CR followed by intramolecular Diels–Alder reaction to give an oxa-bridged heterocycle.

Based on the same principle, we developed a three-component synthesis of macrocycles starting from an azidoamide (**30**), an aldehyde (**31**), and an α -isocyanoacetamide (**32**) bearing a terminal triple bond (Scheme 5.11) [28]. The reaction involved a sequence of three-component synthesis of an oxazole followed by an intramolecular [3 + 2] cycloaddition. The azido and alkyne functions were not directly involved in the three-component construction of the oxazole, but reacted intramolecularly once the oxazole (**34**) had been assembled. The reaction created five chemical bonds with concurrent formation of one macrocycle, one oxazole, and one triazole.



Scheme 5.11 Three-component synthesis of macrocycles by a sequence of 3CR-[3 + 2] cycloaddition.

The above examples illustrate an approach wherein two paired functional groups were appended into the starting materials that reacted intramolecularly after the multicomponent process was terminated [Figure 5.4, reaction (a)]. Another approach consisted in introducing a functionality that was in principle inert to all functionalities incorporated in starting materials in addition to all possible transient intermediates, but could react with the seemingly stable functionality found in the final adduct [Figure 5.4, reaction (b)]. In these two approaches, both multicomponent adducts **A** and **B** could be stable and isolable, but transformable under appropriate conditions, consequently increasing the molecular diversity and complexity.

Oxazoles are reactive dienophiles that readily undergo Diels–Alder cycloaddition [29]. Thus the three-component synthesis of oxazoles detailed in Scheme 5.8 could in principle be further elaborated to more complex heterocycles by using the

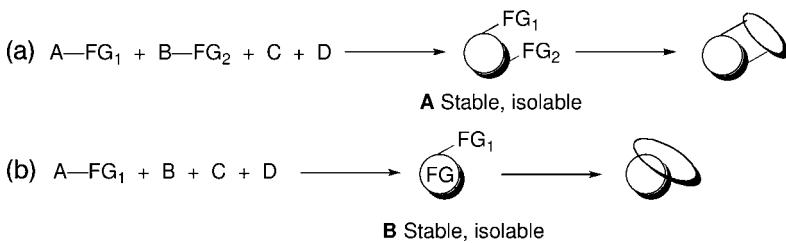
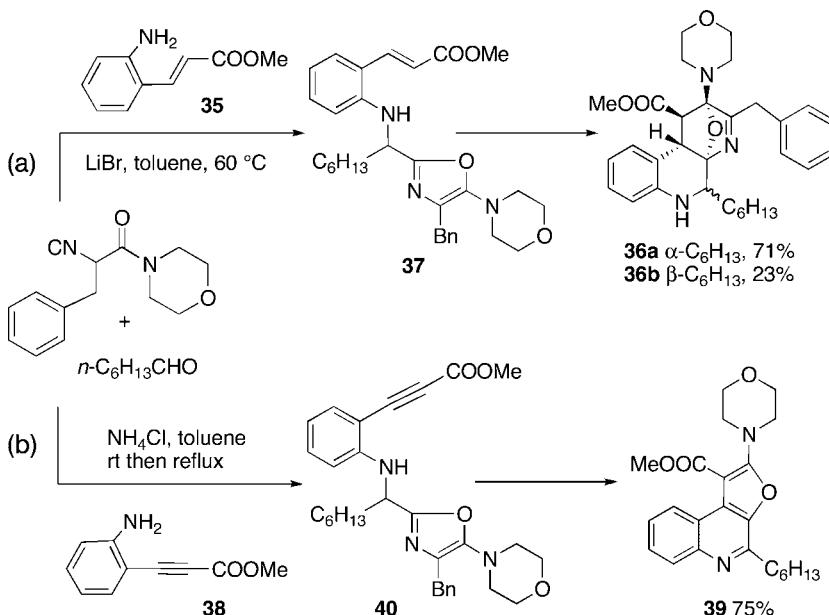


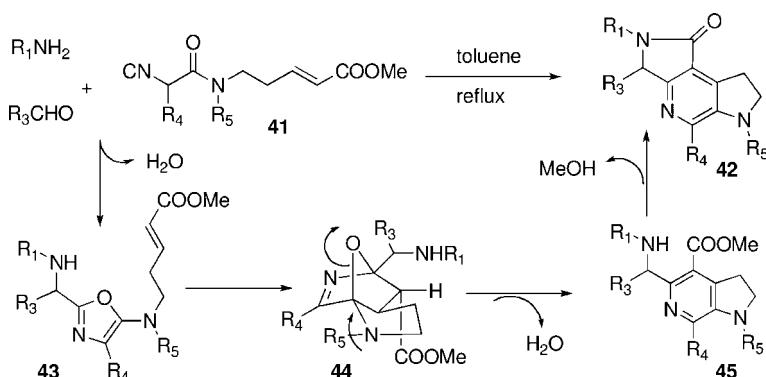
Figure 5.4 *In-situ* post-transformation of multicomponent adduct.

resulting 5-aminooxazole as a springboard. Scheme 5.12 illustrates an LiBr-catalyzed three-component synthesis of oxa-bridged polyheterocycles **36** by using methyl 2-aminocinnamate (**35**) as an input [route (a)] [30]. The initial three-component adduct **37** underwent *in situ* Diels–Alder (D–A) reaction with the tethered double bond to afford **36** as a mixture of two separable diastereomers in 94% yield. It is worth noting that one C–N, one C–O, and three C–C bonds were formed with the concomitant creation of five asymmetric centers in this one-pot process. The efficiency of this reaction was thus truly remarkable if one looks at the yield per bond formed. The oxazole **37** could be isolated if the reaction was performed at room temperature. Significantly, the same reaction using the *o*-aminophenylpropiolate **38** instead of **35** in the presence of ammonium chloride furnished the furoquinoline **39** in 75% yield [route (b)] [31]. The intramolecular D–A cycloaddition of **40** followed by retro-D–A reaction and dehydrogenation accounted for the formation of **39**. These two examples demonstrate how subtle structural modification of one input (**35** versus **38**) in a given MCR can diversify the structure of the reaction product. Compound **36** is a product with up to five stereocenters, whereas **39** is a flat aromatic heterocycle.



Scheme 5.12 Three-component synthesis of polyheterocycles using an oxazole as template.

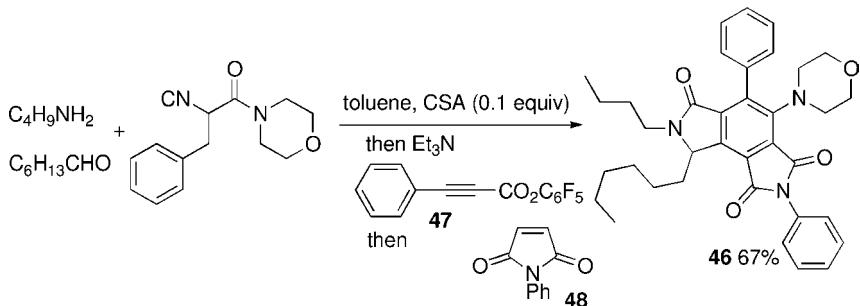
Using the *N*-(*ω*-alkynyl)-*N*-alkyl-*α*-isocyanoacetamide **41** as a polyfunctional substrate, three-component synthesis of the azaindoline **42** was developed. By simply heating a toluene solution of **41**, a primary amine and an aldehyde afforded tricyclic compound **42** in good to excellent yield [32]. A possible reaction sequence that accounted for the formation of **42** is depicted in Scheme 5.13. The sequence involved (a) a three-component synthesis of oxazole **43**, (b) intramolecular D–A cycloaddition



Scheme 5.13 Three-component synthesis of a pyrrolidinone-fused 6-azaindoline.

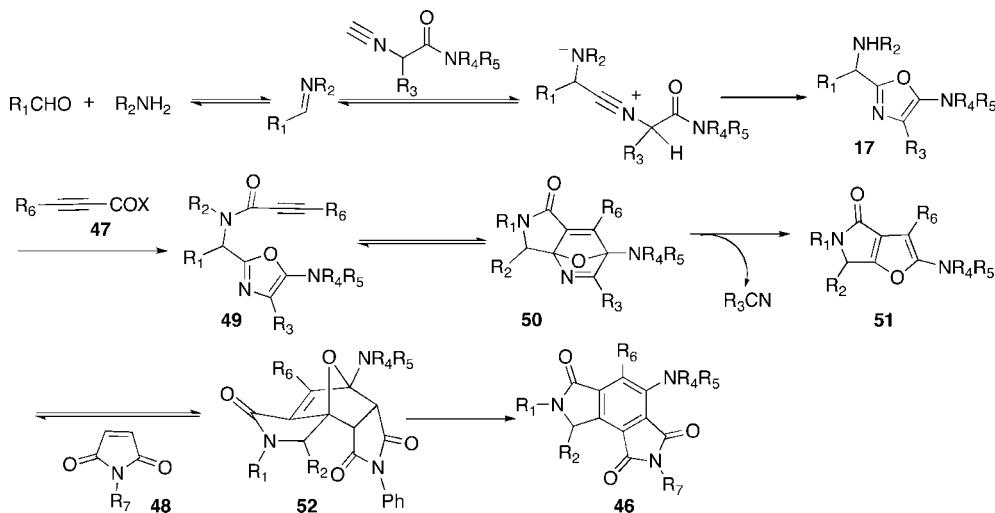
of **43** leading to **44**, (c) fragmentation of the bridged amino ether function assisted by the lone pair of nitrogen to give the 6-azaindoline **45**, and (d) intramolecular transamidation to **42**. In this 3CR, the designed substrate **41** contains four functionalities: an isocyano group, an amide, a double bond, and an ester. Initiated by nucleophilic addition of the isocyano carbon to an iminium generated *in situ*, all these reactive functionalities participated in the reaction sequence in a highly ordered manner to afford the observed product. No external reagent was required and heating was the only external energy needed to promote this MCR, leading to the creation of five chemical bonds with the concurrent formation of a tricyclic ring system. Water and methanol were the only by-products produced in this MCR. We stress that under these conditions, Michael addition between the amine and the enoate moiety of isocyanoacetamide **41** did not occur, which could otherwise interrupt the entire reaction sequence. The condensation between amine and aldehyde is apparently a much faster process or thermodynamically more favorable than the undesired Michael addition in this circumstance.

Based on the same design principle and by careful pairing of the reactivity of each component and also intermediates generated in the course of the reaction, we have developed a five-component synthesis of polyheterocycles with a hexasubstituted benzene core (**46**, Scheme 5.14) [33].



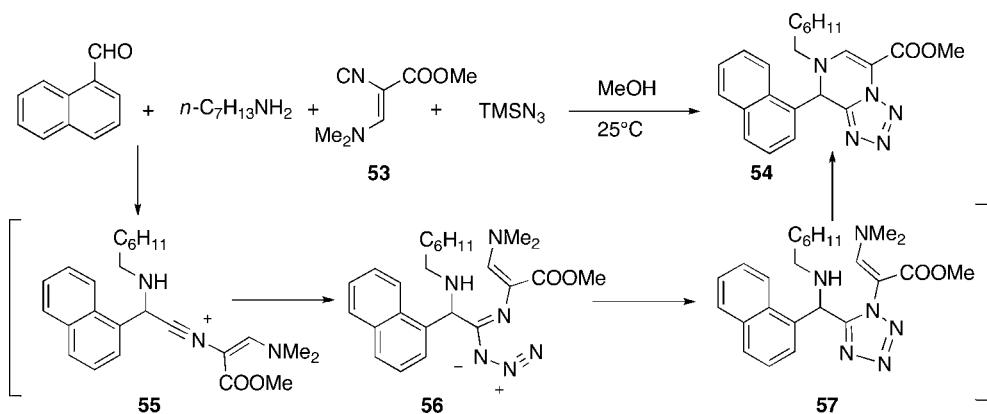
Scheme 5.14 Five-component synthesis of heterocycles with a hexasubstituted benzene core.

A possible reaction scenario explaining the formation of **46** is shown in Scheme 5.15. Thus, three-component condensation of an amine, an aldehyde, and an isocyanoacetamide provided the 5-aminooxazole **17**. Reaction of **17** with pentafluorophenyl 3-arylprop-2-ynoates **47** delivered the pyrrolofuran **51** via a sequence of acylation, intramolecular D–A cycloaddition and retro-D–A cycloreversion. The subsequent cycloaddition between the furan unit of **51** and the dienophile **48** (*N*-phenylmaleimide, quinone, etc.) followed by fragmentation of the oxa-bridged amino ether would then provide the observed product **46**. In this one-pot transformation, seven functional groups reacted with each other in a highly ordered fashion leading to the creation of seven chemical bonds and a polyheterocyclic scaffold with a hexasubstituted benzene core. Not less than nine elementary reactions were involved in this experimentally simple MCR. Two dienes (an oxazole and a furan; both are isolable) were generated in the course of the reaction and subsequently reacted with two different dienophiles. A catalytic amount of camphorsulfonic acid (CSA, 0.1 equiv.) is the only reagent required to catalyze the entire reaction sequence.



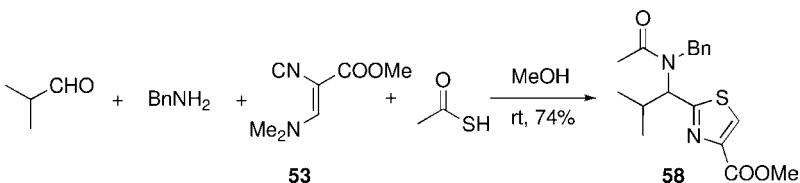
Scheme 5.15 Possible reaction sequence of the five-component reaction.

Taking advantage of the multifunctionalities and ready accessibility of methyl (*Z*)-3-(dimethylamino)-2-isocyanoacrylate (Schollkopf's isocyanide) (**53**), Bienaymé and Bouzid developed a four-component synthesis of bicyclic tetrazole **54** (Scheme 5.16) [34]. Simply stirring a methanolic solution of an aldehyde, an amine, **53**, and TMSN₃ afforded **54** in good to excellent yield. Trapping the nitrilium **55** by azide afforded the intermediate **56**, which was subsequently cyclized to furnish the tetrazole **57**. A sequence of intramolecular Michael addition followed by β -elimination of dimethylamine then provided the final product **54**. The intermediate tetrazole **57** could be isolated and was found to cyclize to the bicyclic tetrazole **11** in essentially quantitative yield under the reaction conditions.



Scheme 5.16 Four-component synthesis of bicyclic tetrazoles.

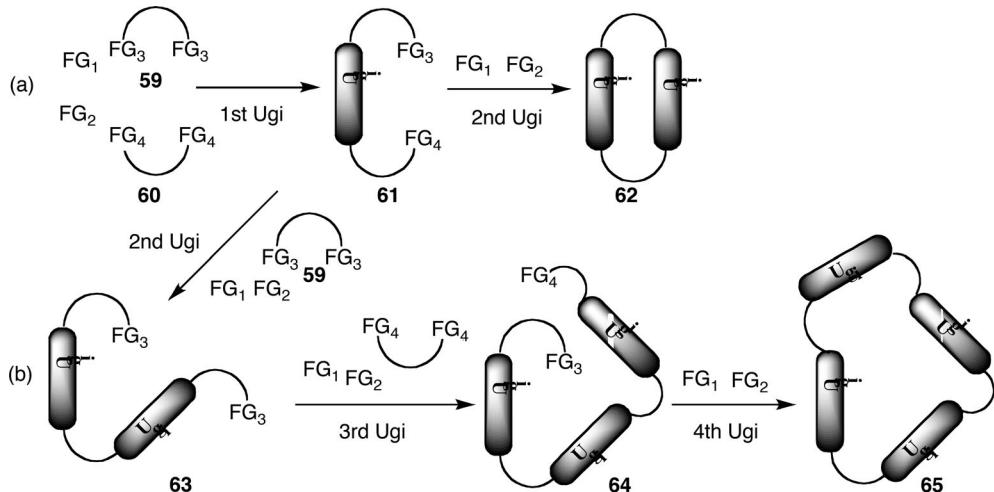
Using thiocarboxylic acid and **53** as a key component, Heck and Dömling devised an efficient synthesis of the highly functionalized thiazole **58** by a similar reaction sequence (Scheme 5.17) [35].



Scheme 5.17 Four-component synthesis of thioazole.

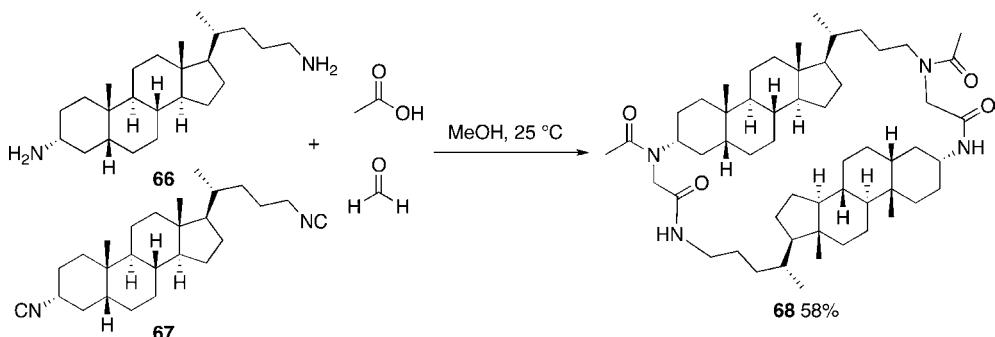
Wessjohann *et al.* developed an elegant approach termed “multiple multicomponent reactions including bifunctional building blocks (MiBs)” [36]. The basic principle is that the use of bifunctional building blocks with the same functionality on either side leads to bidirectional macrocycles. These “symmetric” bifunctional building blocks can be synthesized in a more straightforward manner than the unsymmetrical ones and problems of functional group incompatibility are avoided. In this approach, two different symmetric bifunctional building blocks are required and the minimum number of MCRs forming the macrocycle is two. Using the Ugi-4CR as a prototypical reaction, a possible reaction leading to two- and four-fold cyclic adducts is shown in Scheme 5.18. The first Ugi adduct **61** could react further with FG₁ and FG₂ to afford the cyclic product **62** [Scheme 5.18, route (a)]. Alternatively, the adduct **61** can react with **59**, FG₁, and FG₂ to provide the two-fold Ugi adduct **63**, which could be further transformed to the four-fold Ugi cyclic adduct **65** via intermediate **64** [Scheme 5.18, route (b)]. The higher order oligomer/cyclic oligomer could in principle be produced, making this reaction difficult to control.

Using relatively rigid, umbrella-shaped or kinked bifunctional building blocks can often result in the conformational preorganization of cyclization precursors, which can in turn favor the formation of one particular macrocycle [37]. In practice, high



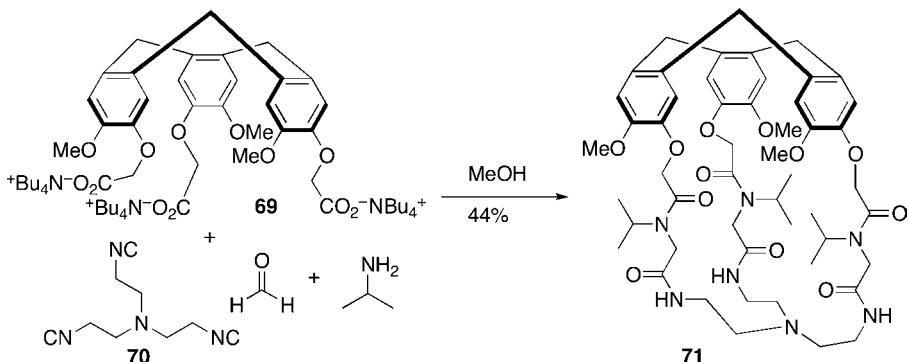
Scheme 5.18 Synthesis of macrocycles by multiple multicomponent reactions including bifunctional building blocks (MiBs).

dilution or pseudo-dilution conditions achieved by slow addition of at least one input are generally used to disfavor the non-productive oligomerization process. Using a steroid as supporting scaffold, the reaction of diamine **66**, diisocyanide **67** (both derived from lithocholic acid), acetic acid, and formaldehyde afforded the macrocycle **68** in 58% yield as a mixture of head-to-tail and head-to-head cyclic dimers [38]. For the sake of clarity, only the head-to-tail regioisomer is shown in Scheme 5.19.



Scheme 5.19 Double Ugi-4CR to give a cyclic dimer.

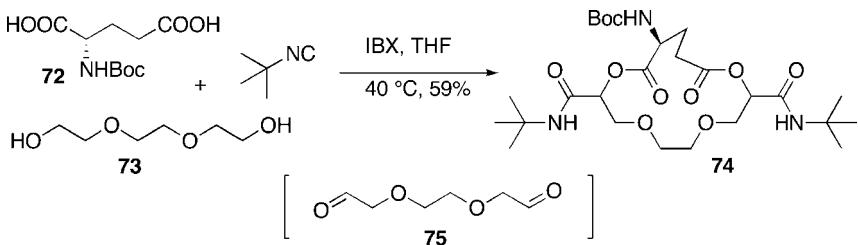
An impressive threefold Ugi reaction using carefully designed trifunctional building blocks was subsequently developed by Rivera and Wessjohann [39] (Scheme 5.20). This reaction unified eight components (**69**, **70**, 3 equiv. each of formaldehyde and isopropylamine) via 12 reaction steps in a one-pot fashion to produce hemicryptophane **71** in 44% yield. This approach should be very useful in



Scheme 5.20 Synthesis of hemicryptophane by a threefold Ugi reaction.

the rapid synthesis of supramolecular receptors due to its efficient and diversity-oriented nature [40].

A Passerini-3CR approach has also been used for the synthesis of macrocycles using the same MiBs concept. Scheme 5.21 shows an example of oxidative double P-3CR using a diacid and a diol as bifunctional substrates. Simply heating a THF solution of *N*-Boc-glutamic acid (72), triethylene glycol (73) and *tert*-butyl isocyanide in the presence of IBX afforded the macrolide 74 in 44% yield [41]. In this reaction, triethylene glycol (73) was oxidized *in situ* to the unstable dialdehyde, which then participated in the double P-3CR [42].



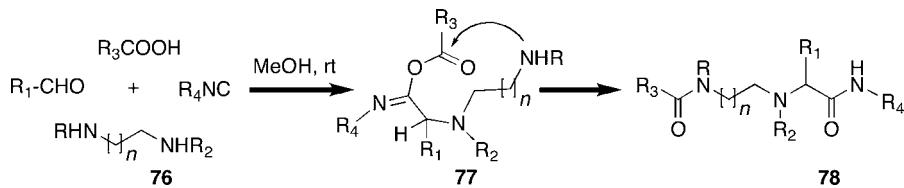
Scheme 5.21 Oxidative double P-3CR to give macrolides.

5.3.3

Mechanism-Based Design

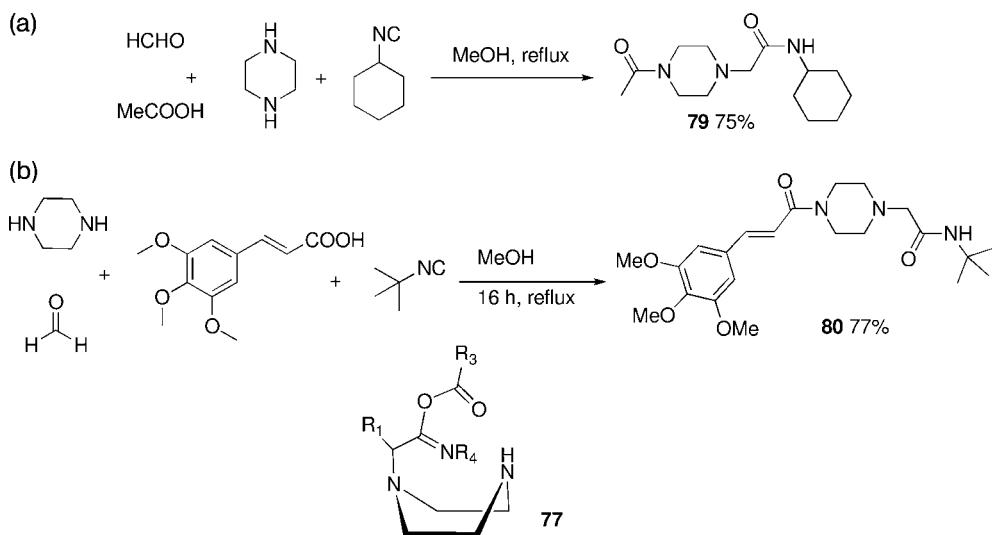
5.3.3.1 “Split-Ugi” Reaction

In a classic Ugi reaction, a primary amine is used, which is converted to a tertiary amide at the end of the reaction [43]. Giovenzana and Tron *et al.* developed a so-called “split-Ugi” reaction [44]. The basic idea (Scheme 5.22) is to “split” the primary amine into a two-tethered secondary amine (76). One reacts with the carbonyl group to afford an iminium ion, which then interacts with the isocyanide and the carboxylate

**Scheme 5.22** Working hypothesis of the “split Ugi” reaction of bis-secondary amines.

moiety to form the imidate 77. Subsequently, the resulting intermediate undergoes transacylation in which the remaining secondary amine would act as a nucleophile to afford 78 [45].

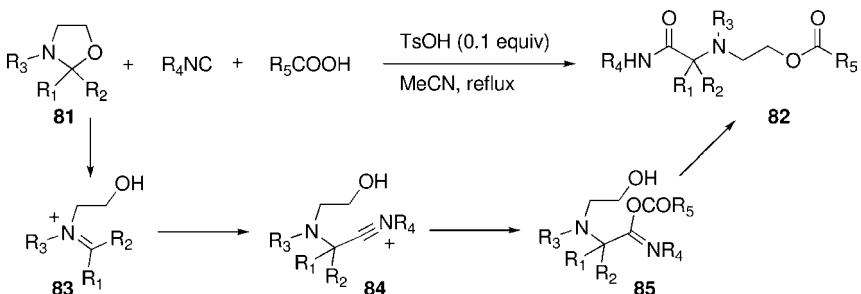
The reaction indeed worked well. Thus, heating to reflux a methanolic solution of piperazine, formaldehyde, acetic acid, and cyclohexyl isocyanide afforded the “split-Ugi adduct” 79 in 75% yield. Note that in this reaction, the symmetric diamine has been effectively desymmetrized since one nitrogen atom was alkylated while the other was acylated. The piperidine ring in intermediate 77 has to adopt a boat conformation in order for the transacylation to take place smoothly [Scheme 5.23, reaction (a)].

**Scheme 5.23** Examples of “split-Ugi” reaction.

Compound 80, a known vasodilator, has been synthesized in four steps following the standard transformation [46]. By applying the split-Ugi reaction, Tron *et al.* were able to prepare it in one step in 77% yield from simple and commercially available starting materials [Scheme 5.23, reaction (b)] [44].

Motherwell and co-workers independently developed a similar approach using N-alkyloxazolidines as imine precursors having a hidden β-amino alcohol unit [47].

Thus a TsOH-catalyzed three-component reaction of **81**, an isocyanide, and a carboxylic acid afforded the *N*-the acyloxyethylaminoacetamide **82** in good yield. The reaction was proposed to go through the iminium intermediate **83**, which was in turn converted to imidate **85** via α -addition to an isocyanide. Subsequent *O*-transacylation then gave the observed product **82** (Scheme 5.24).



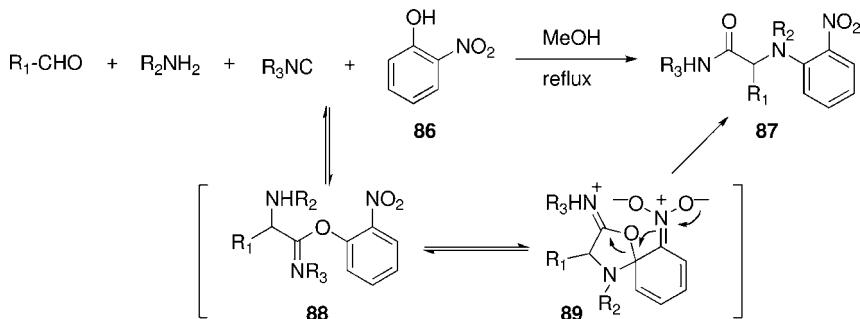
Scheme 5.24 Three-component synthesis of an *N*-acyloxyethylaminoacetamide.

An attempt to combine the oxazolidine synthesis (from *N*-methylethanamine and heptanal) with the above 3CR also gave the desired product, albeit with reduced yield (13%).

5.3.3.2 Ugi–Smiles 4CR

Isocyanides have a high tendency to react with an electrophilic sp^2 carbon, but they are nevertheless moderately reactive and fairly stable towards aldehydes and imines in the absence of an acidic component. This observation is key to the development of the Passerini reaction and the Ugi reaction. In addition to carboxylic acids, thiocarboxylic acids, carbonic acid, isocyanic acids, isothiocyanic acid, hydrazoic acid, hydrogen selenide, thiosulfate, and so on have been successfully employed in Ugi reactions leading to interesting adducts. Alcohols and phenols are known to be unable to promote the coupling of aldehydes/amines with isocyanides due to their low acidities [48]. Recently, El Kaim *et al.* discovered that *o*-nitrophenol (**86**) is sufficiently acidic to activate the imine and therefore to promote the Ugi-type reaction. Thus a four-component reaction of an aldehyde, an amine, an isocyanide, and *o*-nitrophenol afforded an *N*-arylacetamide in good to excellent yields (Scheme 5.25) [49]. The reaction is believed to proceed via the α -adduct **88**, which then undergoes an intramolecular S_NAr reaction (Smiles rearrangement) to afford the observed product **87**. This elegant MCR was denoted “Ugi–Smiles coupling” by the authors.

Subsequent to this disclosure, the same group found that other aromatic and heteroaromatic derivatives having a strong electron-withdrawing group are able to trigger this reaction sequence [50]. Some representative examples are given in Figure 5.5. In heteroaromatic series such as pyridine, pyrimidine, triazine, and so on, the presence of an additional electron-withdrawing group is not required since the Smiles rearrangement takes place readily with these electron-deficient aromatics.



Scheme 5.25 Ugi–Smiles four-component reaction developed by El Kaim *et al.*

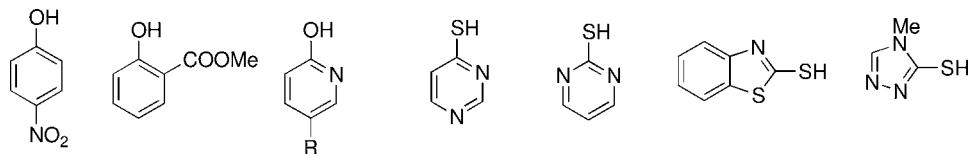
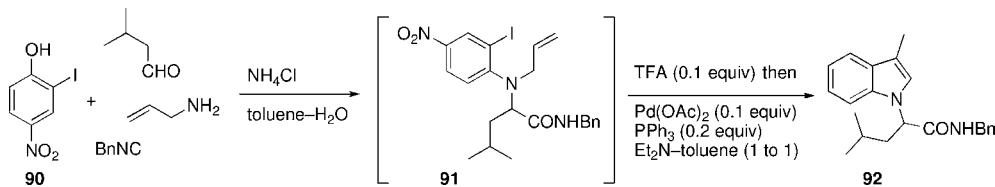


Figure 5.5 Phenols and thiophenols used in Ugi–Smiles coupling.

The adduct resulting from this Ugi–Smiles coupling contains an *N*-aryl unit that offers great synthetic potential for further functionalization. Scheme 5.26 shows just one such an example. The reaction of 2-iodo-4-nitrophenol (**90**) with allylamine, 3-methylbutanal, and benzyl isocyanide in the presence of ammonium chloride afford the Ugi–Smiles adduct **91**, which, without purification, underwent palladium-catalyzed Heck cyclization to afford indole **92** in 72% yield. Trifluoroacetic acid (0.1 equiv.) was introduced before addition of the palladium catalyst in order to destroy any remaining isocyanide, which was harmful to the subsequent cyclization due to catalyst poisoning [51].

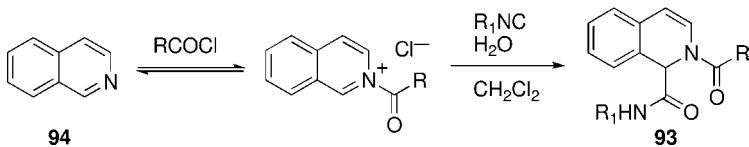


Scheme 5.26 *In situ* conversion of Ugi–Smiles adduct to give an indole.

5.3.3.3 Activation of Imines by Other Electrophiles

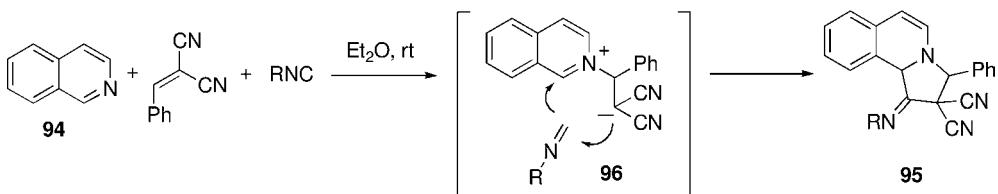
The formation of a salt between an imine and a carboxylic acid leading to a more reactive electrophile was proposed as an essential step in the Ugi reaction. In parallel to the Reissert reaction, wherein the azine nitrogen was activated as

an *N*-acyliminium salt, Lavilla and co-workers developed an elegant multicomponent synthesis of α -carbamoylated 1,2-dihydroazines (**93**) by reaction of an azine (**94**), an acyl chloride, an isocyanide, and water (Scheme 5.27) [52]. This reaction turned out to be fairly general and a wide range of azines and acylating agents, including acyl halides, chloroformates, and sulfonyl chloride, have been used with success.



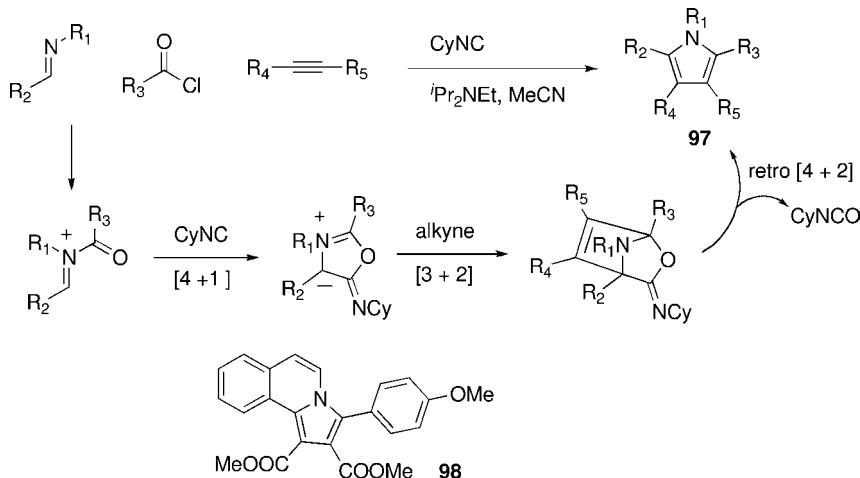
Scheme 5.27 Three-component synthesis of 1,2-diacylated-1,2-dihydroazines.

The formation of an iminium salt via Michael addition between an azine and an electron-poor olefin was nicely exploited by Mironov *et al.* for the development of a three-component synthesis of benzo-fused heterocycles (**95**) (Scheme 5.28) [53]. In this case, the intermediate **96** underwent a formal [4 + 1] cycloaddition with isocyanide that led to the observed heterocycle **95**.



Scheme 5.28 Three-component synthesis of benzo-fused heterocycles.

Arndtsen and co-workers developed an isocyanide-mediated three-component synthesis of the polysubstituted pyrroles **97**, wherein an acyclic imine was activated *in situ* by acylation [54]. Thus, reaction of an imine, an acyl chloride, an alkyne, and an isocyanide in the presence of $^{\text{i}}\text{PrNET}_2$ afforded **97** in good to excellent yields (Scheme 5.29). A complex reaction sequence involving formation of the *N*-acyliminium by [4 + 1] followed by [3 + 2] cycloadditions and a retro-cycloaddition was proposed to account the formation of **97**. The isocyanide participated actively in this reaction sequence; however, it was not incorporated in the final adduct since it was lost as isocyanate by a retro-D–A reaction. The aliphatic imine was shown to be an appropriate substrate, at least in one case, leading to the corresponding pyrrole ($\text{R}_2 = \text{isopropyl}$) in 72% yield. Azenes participated in this reaction in a similar manner. Thus, the isoquinoline **94** was converted to the benzo-fused pyrrole **98** in 50% yield.



Scheme 5.29 Isocyanide-mediated three-component synthesis of pyrroles.

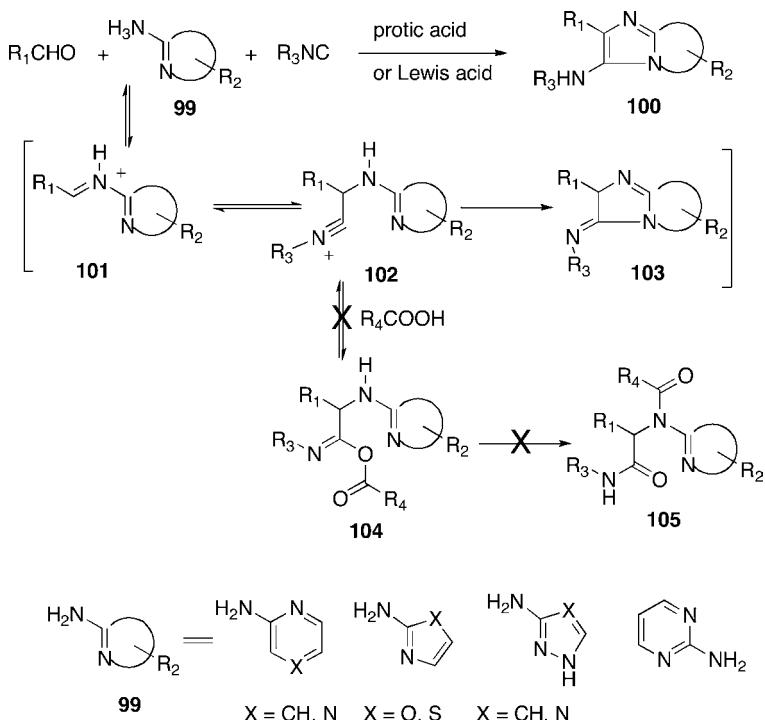
5.3.4

Serendipity

In chemistry, many important chemical transformations have been discovered accidentally. Indeed, serendipity, which emanates from researchers with keen observation, open-mindedness, good instincts, and scientific intuition, has played a key role in science in general.

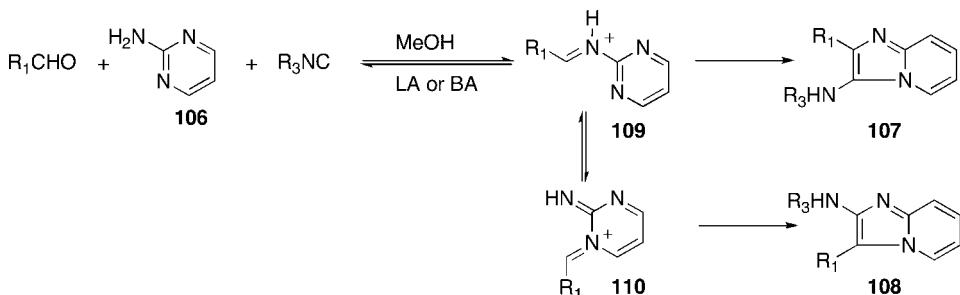
While investigating the Ugi four-component reaction using 2-aminopyridine as amine input, three industrial research groups, led by Bienaymé at Rhône-Poulenc [55], Groebke at Hoffmann-La Roche [56], and Blackburn at Millennium Pharmaceuticals [57], discovered that the normal Ugi adduct was not produced. Instead, a medicinally relevant imidazo[1,2-*a*]pyridine was formed in excellent yield. The acetic acid used in these reactions did not participate in the Ugi reaction as it is not incorporated in the final product; instead, it promoted the formation of the imidazo[1,2-*x*]heterocycles. The proposed mechanism accounting for the formation of **100** (Scheme 5.30) involved the nucleophilic addition of isocyanide to iminium **101** leading to nitrilium **102**, which was then trapped intramolecularly by the neighboring nitrogen atom to afford a formal [4 + 1] cycloadduct (**103**). A subsequent [1,3-*H*] prototropic shift gave then the final product **100**. The conversion of intermediate **102** to **103** is apparently kinetically faster (a 5-*exo*-dig cyclization) than the classic Ugi pathway involving the addition of carboxylic acid to the nitrilium that would furnish the normal Ugi adduct **105** via imidate **104**. Other acids such as HClO₄ and Sc(OTf)₃ catalyzed the above three-component reactions efficiently.

Performing the reaction in methanol using 2-aminopyrimidine as input, two regioisomers (**107** and **108**) were produced, probably via the two possible iminium intermediates (Scheme 5.31) [58]. A simple solution was proposed that involved performing the reaction in toluene in the presence of ammonium chloride [59].



Scheme 5.30 Three-component synthesis of an azine-fused imidazole.

Under these conditions, **107** was produced exclusively at the expense of **108**. It was proposed that nonpolar solvent (toluene) would disfavor the charged intermediate **110**, thus favoring the production of **107**. For the very electron-deficient 4-amino-pyrimidine, heating a toluene solution to 100 °C in the presence of TsOH or InCl₃ was necessary to ensure the formation of imidazol[1,2-*a*]heterocycles [60]. Using TMSCN as a source of both cyanide and isocyanide equivalent, Hulme and co-workers combined the above reaction with the Strecker reaction under microwave irradiation conditions to provide highly functionalized heterocycles [61]. Other



Scheme 5.31 Reaction divergence with 2-aminopyrimidine.

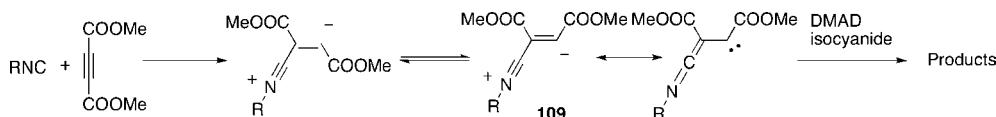
solvents, including water [62] and ionic liquids [63], or even under neat conditions [64], have been proposed for this three-component reaction. The methodology has been adapted to solid-phase synthesis using either a supported aldehyde [65] or universal Rink-isonitrile resin [66]. Fluorous-tagged aldehydes have also been employed in this reaction to facilitate purification [67].

There seems to be no major limitation regarding the selection of aldehydes and isonitriles. For 2-aminoazenes, both heteroaromatic amidines and heteroaromatic guanidines participated in this novel 3CR. However, aliphatic amidines were found to be inactive. Many variants have since been reported by different research groups, both academic and industrial, due to the medicinal importance of this family of heterocycles [68].

5.4

MCRs Imitated by Addition of Isocyanides to Alkynes

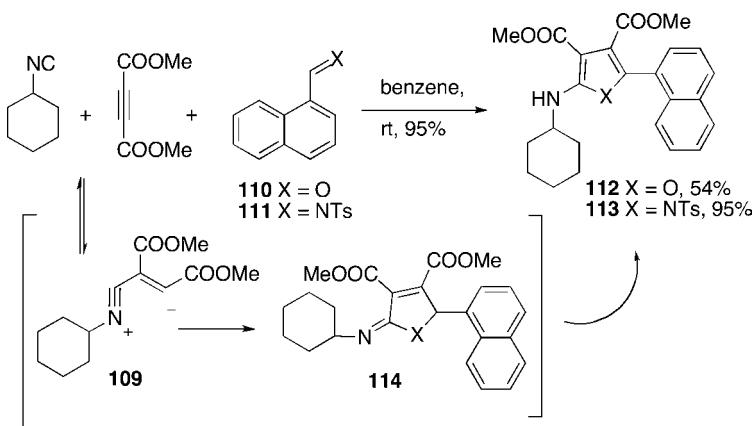
Carbonyl compounds and imines are the electrophilic partner of isocyanides in the Passerini-3CR and the Ugi-4CR, respectively. Other highly electrophilic multiple bonds, such as in dimethyl acetylenedicarboxylate (DMAD), are also known to react with isocyanides. The initially formed 1:1 zwitterionic species having carbanion, carbene character can undergo further reaction with DMAD and isocyanides in different molar ratios, leading to a variety of heterocyclic systems (Scheme 5.32) [69].



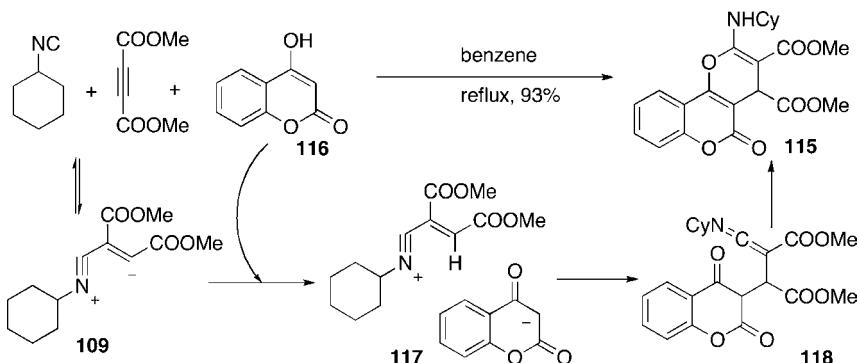
Scheme 5.32 Zwitterionic adduct from an isocyanide and DMAD.

The 1:1 zwitterionic adduct **109** has been trapped by alcohols, but earlier attempts to trap it by other electron-deficient olefins failed. More recently, Nair and co-workers demonstrated that aldehydes and tosylimines did not interrupt the formation of **109** and were capable of intercepting **109** to afford, after cyclization, 2-aminofurans and 2-aminopyrroles, respectively, in good to excellent yields (Scheme 5.33) [70]. The results led the authors to develop original three-component syntheses of these two important families of heterocycles.

Nair *et al.* subsequently developed a three-component synthesis of the pyran-annulated heterocycle **115** (Scheme 5.34) [71]. Thus, heating to reflux a benzene solution of 4-hydroxycoumarin (**116**), DMAD, and cyclohexyl isocyanide gave the pyranocoumarin **115** in 93% yield. It was hypothesized that protonation of the zwitterionic intermediate **109** by the hydroxycoumarin **116** occurred to afford ion pair **117**. Subsequent 1,4-addition of enolate to nitrilium would furnish the ketamine **118**, which would then cyclize to provide the heterocycle **115**.



Scheme 5.33 Three-component synthesis of 2-aminofurans and 2-aminopyrroles.

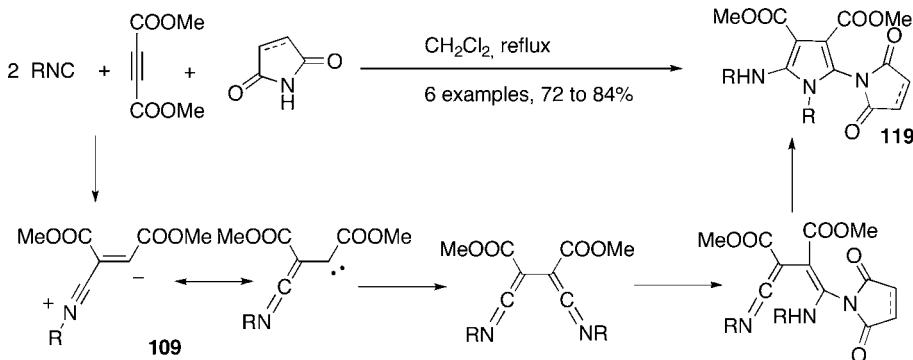


Scheme 5.34 Three-component synthesis of pyranocoumarins.

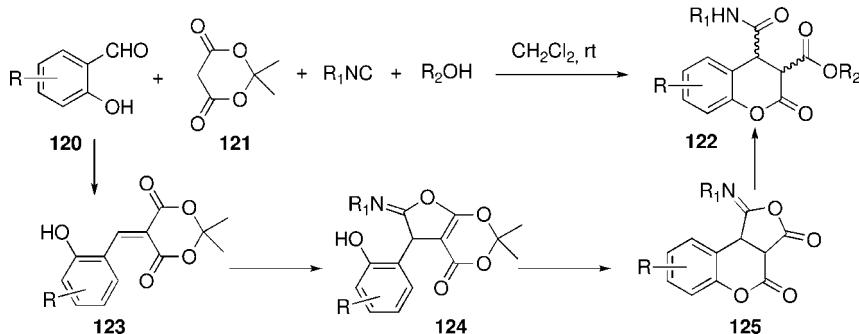
2-Hydroxy-1,4-naphthoquinone, 4-hydroxy-6-methylpyrone, and α -naphthol can be used instead of 116 to afford the corresponding condensation products in good to excellent yields.

Shabbani *et al.* found that a similar reaction sequence occurred using tetroneic acid, leading to 4*H*-furo[3,4-*b*]pyrans [72]. The same group also developed an alternative synthesis of the pyrrole 119 using succinimide or maleimide having an acidic NH group as reaction partner [73]. The reaction is a pseudo-four-component process since 2 equiv. of isocyanides are consumed and incorporated into the final adduct (Scheme 5.35).

More recently, the same group reported that acetic anhydride can also act as an electrophile to trap the zwitterionic intermediate 109 and developed a three-component synthesis of 2,5-dihydro-5-imino-2-methylfuran-3,4-dicarboxylates [74]. More significantly, they developed an elegant four-component synthesis of 3,4-dihydrocoumarin derivatives by reaction of salicylaldehyde, Meldrum's acid, isocyanide, and

**Scheme 5.35** Pseudo-four-component synthesis of pyrroles.

alcohol (Scheme 5.36) [75]. Mechanistically, the reaction may be rationalized by initial Knoevenagel condensation of the 2-hydroxybenzaldehyde **120** and Meldrum's acid **121** to afford the conjugated ester **123** followed by its [4 + 1] cycloaddition reaction with isocyanide to provide an iminolactone intermediate **124**. Ring opening of the iminolactone by an internal hydroxy group and subsequent loss of acetone would lead to **125**. Finally, nucleophilic attack of alcohol on the activated carbonyl moiety of **125** would afford the product **122**. Two diastereomers were generally produced; however, with bulky isocyanides and alcohols, excellent diastereoselectivity was observed, favoring the *cis*-diastereomer.

**Scheme 5.36** Four-component synthesis of 3,4-dihydrocoumarins.

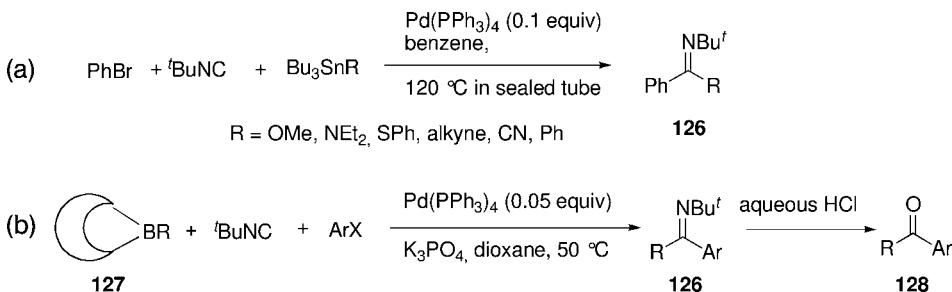
5.5

Metal-Catalyzed IMCRs

Addition of isocyanides to polarized multiple bonds generally occurs under catalyst-free conditions and indeed most of the isocyanide-based MCRs (IMCRs) described above took place readily in the absence of an external reagent, which

undoubtedly fits into the concept of green chemistry. However, using appropriate catalysts, especially transition-metals, some interesting IMCRs have been developed allowing access to otherwise inaccessible chemical entities by classical isocyanide chemistry.

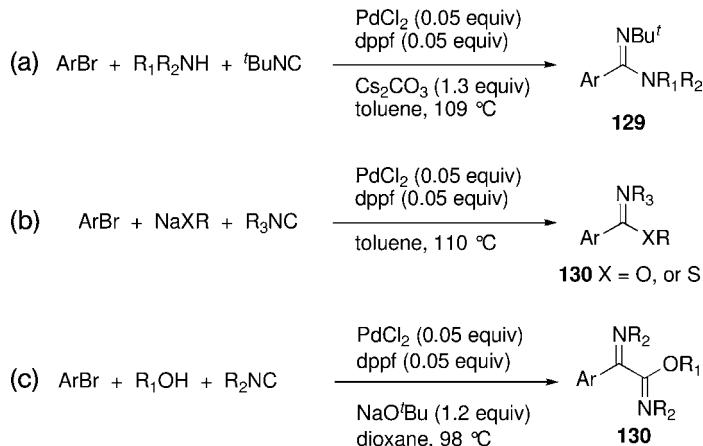
Kosugi *et al.* in 1986 reported a palladium-catalyzed three-component coupling of bromobenzene, isocyanide, and organotin compound [Scheme 5.37, reaction (a)] [76]. The reaction was nevertheless limited in scope and yields were typically low to moderate. Miyaura and co-workers subsequently reported a three-component coupling of alkylborane, isocyanide, and aryl halide for the synthesis of imines, which were readily hydrolyzed to aryl ketones [Scheme 5.37, reaction (b)] [77]. The use of 9-alkyl-9-BBN derivatives (**127**) was mandatory, since the same coupling reaction using trioctylborane under otherwise identical conditions did not provide the coupling products. The stoichiometry between isocyanide and **127** is also very important and the use of an excess of isocyanide relative to **127** decreased significantly the yield of ketone **128**. The 9-alkyl-9-BBN derivatives were prepared *in situ* by hydroboration of an alkene with 9-BBN.



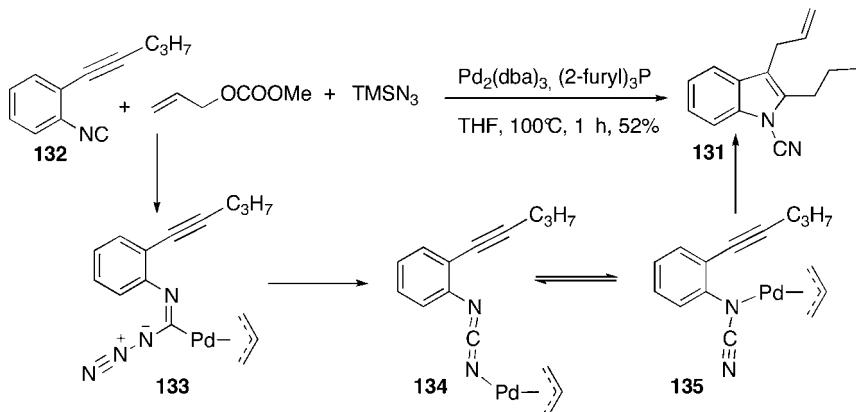
Scheme 5.37 Palladium-catalyzed three-component coupling involving isocyanides.

Whitby and co-workers developed general methods for the synthesis of amidines (**129**) [78] and imidates (**130**) [79] by palladium-catalyzed three-component reactions without using an organometallic reagent as coupling partner [Scheme 5.38, reactions (a) and (b)]. Using an excess of isocyanide, conditions were established for the synthesis of α -iminoimidates [Scheme 5.38, reaction (c)] [80]. The use of a bidentate ligand was found to be important for the success of these reactions.

Kamijo and Yamamoto developed a palladium-catalyzed three-component synthesis of *N*-cyanoindoles (**131**) (Scheme 5.39) [81]. The reaction of a 2-alkynylisocyanobenzene (**132**), allyl methyl carbonate, and trimethylsilylazide in the presence of $\text{Pd}_2(\text{dba})_3$ (2.5 mol%) and tri(2-furyl)phosphine (10 mol%) at 100 $^\circ\text{C}$ afforded the *N*-cyanoindoles **131** in good yield. Key steps of this reaction involved the formation of π -allylpalladium complex **133**, its Curtius-like rearrangement to intermediate **134**, and subsequent isomerization to the π -allylpalladium cyanamide complex **135**. A wide range of functional groups is tolerated at the *para*, *meta*, and even *ortho* positions of the aromatic ring.

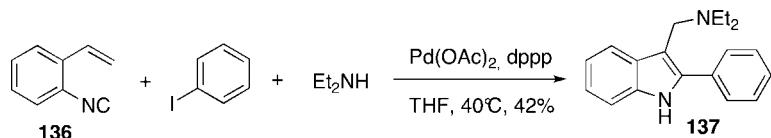


Scheme 5.38 Palladium-catalyzed three-component synthesis of amidines, imidates, and α -iminoimidates.



Scheme 5.39 Palladium-catalyzed three-component synthesis of α -cyanoindoless.

Takahashi and co-workers reported an alternative three-component synthesis of indoles (137) (Scheme 5.40) [82]. Thus, reaction of an aryl iodide, an *o*-alkenylphenyl isocyanide (136), and a secondary amine in the presence of a palladium catalyst produced 2,3-disubstituted indoles in moderate yields. A chelating ligand such as dppp was found to be superior to a monodentate ligand such as PPh₃.



Scheme 5.40 Palladium-catalyzed three-component synthesis of indoles.

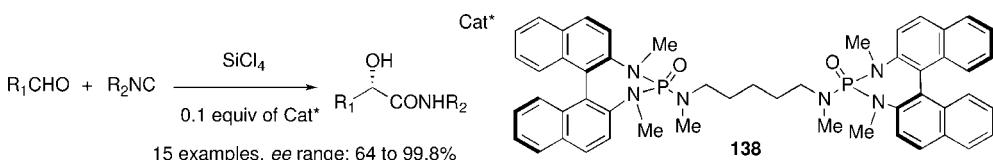
5.6

Enantioselective P-3CR

The field of catalytic enantioselective transformation has blossomed into a mainstay of chemistry. Although many reactions can currently be run with high yields and high enantiomeric excesses (*ees*), progress still remains to be made in terms of reaction efficiency, atom economy, and environmental safety. While marrying all of these concepts will take time, the development of enantioselective domino and multicomponent reactions certainly represents an important step in this direction [83].

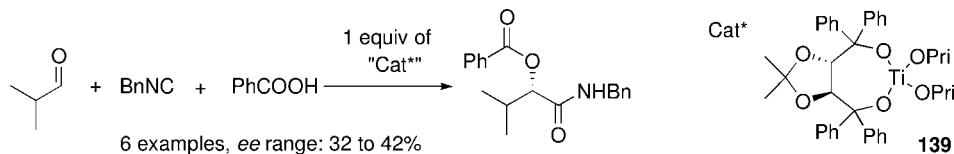
In P-3CR and U-4CR, one chiral center is created resulting from the α -addition of divalent isonitrile carbon to polarized double bonds (e.g., carbonyl group, imine), hence the ability to control the stereochemical outcome would further extend their synthetic utility. However, the development of a truly catalytic enantioselective three-component P-3CR and U-4CR of wide application scope remains a significant challenge, in sharp contrast to the formidable progress recorded in the field of asymmetric synthesis in general. Several obstacles exist that make this task particularly challenging: (a) the complexity of the reaction mechanism; (b) the competitiveness of the uncatalyzed background reaction; (c) all components are Lewis bases and can potentially coordinate to or deactivate the catalyst; and (d) the problem of catalyst turnover due to product inhibition. Indeed, starting from a non-chelating aldehyde, the reaction produces an imide intermediate that is bidentate in nature. Furthermore, the P-3CR adduct itself is also a bidentate ligand and consequently can compete with the substrate to coordinate to the catalyst. No enantioselective U-4CR have been developed to date. However, several groups have succeeded in developing catalytic enantioselective P-3CR.

Denmark and Fan developed a chiral Lewis base (138)-catalyzed asymmetric α -addition of isocyanides to aldehydes with good to excellent enantioselectivity (Scheme 5.41) [84]. The protocol is applicable to non-chelating aldehydes, but it is a bimolecular transformation since the carboxylic acid is excluded from the reaction.

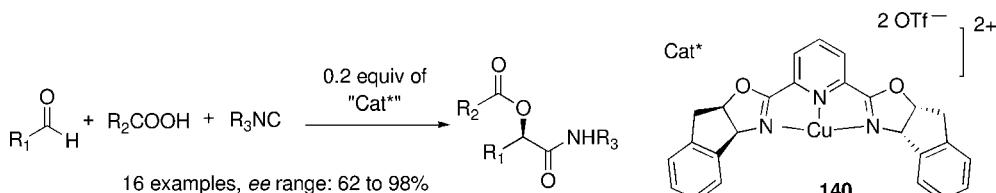


Scheme 5.41 Lewis base-catalyzed enantioselective truncated Passerini reaction.

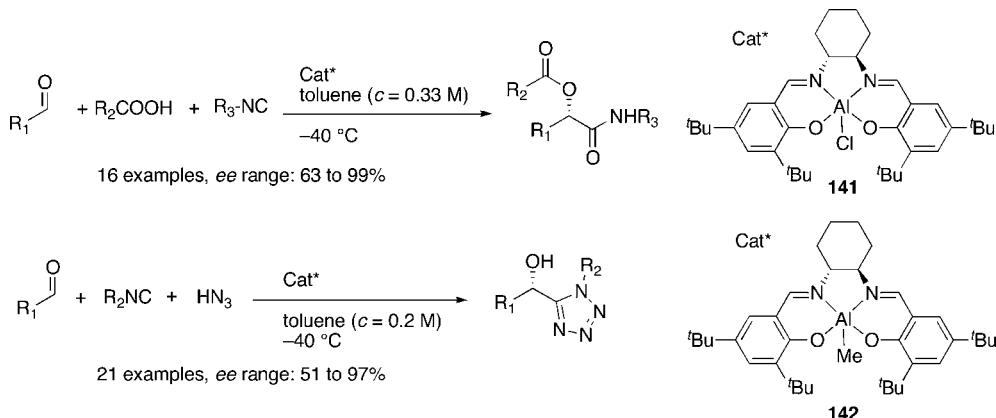
Dömling and co-workers performed a massive parallel screening of a large number of metal–ligand combinations and found that a stoichiometric amount of the Ti-Taddol complex 139 was capable of promoting the P-3CR to afford α -acyloxymides in low to moderate *ee* (Scheme 5.42) [85].

**Scheme 5.42** Ti-Taddol complex-promoted P-3CR.

Schreiber and co-workers demonstrated that an indan (PyBox)–Cu(II) complex (**140**) was able to catalyze the P-3CR (Scheme 5.43) [86]. Nevertheless, the enantio-enriched Passerini adduct was obtained only when the chelating aldehyde was used as a reaction partner.

**Scheme 5.43** PyBox–Cu complex-catalyzed enantioselective P-3CR.

We have developed a (salen)AlCl (**141**)-catalyzed enantioselective three-component Passerini reaction (Scheme 5.44) [87]. In order to overcome the catalyst turnover dilemma, using a chiral catalyst with only one coordination site available was the working hypothesis of our research, and this turned out to be rewarding. A variety of non-chelating aldehydes, including α -branched compounds, carboxylic acids, and isocyanides participated in this catalytic enantioselective process to afford Passerini adducts in good to excellent *ee*. Unfortunately, aromatic aldehydes were not acceptable as substrates under these catalytic conditions. The similar catalyst (salen)AlMe (**142**)

**Scheme 5.44** (Salen)–Al complex-catalyzed P-3CR.

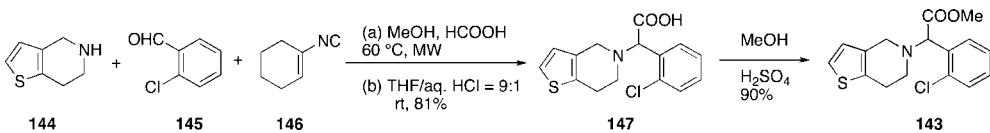
(142) has been developed to catalyze the three-component reaction of aldehydes, isocyanides, and hydrazoic acid to furnish the 5-(1-hydroxylalkyl)tetrazole in good to excellent enantioselectivity [88].

5.7

Application in Medicinal Chemistry and in Natural Product Synthesis

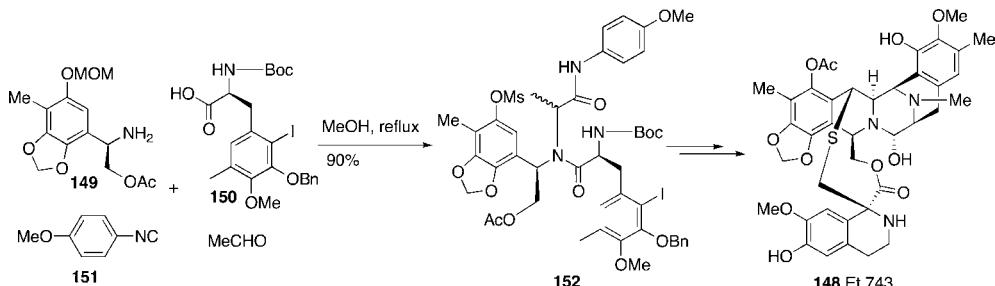
As an enabling technology, the development and application of multicomponent reactions are now an integral part of medicinal chemistry. It is nevertheless important to point out that MCR has contributed to drug development, from lead discovery and lead optimization to production, long before the advent of combinatorial technologies. The one-step synthesis of nifedipine (Adalat®), a highly active calcium antagonist, by a Hantsch reaction is a classic demonstration.

There are many reviews dealing with this important aspect [89]. We give here just one recent example to show how one of the world's highest selling products, clopidogrel (Plavix®) (143) can be synthesized by applying the Ugi reaction (Scheme 5.45) [90]. Thus, three-component Ugi reaction of the secondary amine 144, 2-chlorobenzaldehyde (145), and 1-isocyanocyclohexene (146) in the presence of formic acid under microwave irradiation conditions afforded, after hydrolysis of the initial amide adduct, the acid 147. Esterification of 147 under acidic conditions provided (\pm)-clopidogrel in 72% overall yield. This synthesis appeared to be competitive with the original synthesis patented by Sanofi (overall yield: 31%).



Scheme 5.45 Synthesis of (\pm)-clopidogrel featuring a key Ugi reaction.

The Passerini reaction and the Ugi reaction provide α -acyloxyamides and α -acetamidoamides, respectively. Naturally, these reactions have been applied in the synthesis of peptides and cyclopeptides/cyclodepsipeptides [91]. Recently, the application of these reactions in the synthesis of heterocycles was reported. One of the most notable examples is Fukuyama and co-workers' total synthesis of ecteinascidin 743 (Et 743) (148), a complex natural product recently commercialized as an anticancer drug (Scheme 5.46) [92]. Thus, reaction of the amine 149, the amino acid 150, 4-methoxyphenyl isocyanide (151) and acetaldehyde afforded the corresponding Ugi adduct 152 in 90% yield. After a series chemical transformations, 152 was ultimately converted to Et 743. The connection between the structure of Et 743 and the peptidic nature of Ugi adduct is not obvious, but with the deep insight of an experienced synthetic chemist, the non-trivial link can be drawn and be put into practice [93, 94].

**Scheme 5.46** From Ugi-4C adduct to Et 743.

5.8

Conclusion

The ultimate goal in organic synthesis will be “mix and adding up of reaction components” with anything else needed only catalytically and with minimal loss of atoms [95]. “It is better to prevent waste than to treat or clean up waste after it has been created” [96]. From the examples that we described in this chapter, we can indeed conclude that MCRs satisfy intrinsically the criteria of green chemistry and should therefore find application in many areas where chemistry plays the key role.

The development of novel MCRs is an intellectually challenging task, since one has to consider not only the reactivity match of the starting materials, but also the reactivity of the intermediate functions generated *in situ*, their compatibility, and their compartmentalization. In return, they are powerful tools for developing ideal syntheses and may also provide chemists with interesting problems that are worthy of being solved. As with any discovery process, there are many possibilities, such as combinatorial methods, for discovering novel MCRs. We think that the rational “substrate design approach” could be a highly rewarding approach. Indeed, with the critical mechanistic insight of various classical bimolecular reactions, the development of new reactive chemical entities, new methods for activation of otherwise “inactive” functional groups, and the enthusiasm of chemists towards the subject, we can be optimistic that many new and synthetically useful MCRs will be developed on a rational basis in the coming years. Nature did this in a wonderful way, as Echenmoser stated in analyzing the biosynthesis of vitamin B₁₂: “These outwardly complex structural elements are found to ‘self assemble’ with surprising ease under structurally appropriate preconditions; the amount of ‘external instruction’ required for their formation turns out to be surprisingly small in view of the complexity and specificity of these structural elements”[97].

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6

Flow Syntheses

Charlotte Wiles and Paul Watts

6.1

Introduction

With the chemical industry acknowledging its pivotal role in the development and application of sustainable processes [1], the emergence of micro reaction technology, and more broadly flow chemistry [2, 3], has captured the attention of chemists in all disciplines, ranging from those involved in research and development to large-scale production [4]. From a financial perspective, there are several drivers for the chemical industry to adopt greener/sustainable practices; these include increasing costs associated with petrochemicals and hazardous waste disposal, along with problems associated with the supply of chemicals; recently highlighted by the worldwide shortage of acetonitrile. Such improvements might include increasing atom efficiency, achieved through the use of catalysts, reducing the number of reaction steps or through moving towards multicomponent reactions, all of which reduce the volume of waste generated and raw materials consumed. Although steps such as these are routinely investigated when processes are evaluated for scale-up [5], at the present time these approaches are not widely considered at a research level. Consequently, providing researchers with the tools required to evaluate more sustainable synthetic practices will permit the development of lower impact processes from an early stage rather than redeveloping processes for production once a synthetic route has been identified. This strategy will therefore reduce the time, cost, and impact associated with taking a chemical through the many stages of development leading to production.

6.1.1

Continuous Flow Reactors: What Are They and How are They Used?

Over the past decade, continuous flow reactors have been fabricated from a wide range of substrates, including glass [6, 7], metals [8], silicon [9], ceramics [10], and polymers [11], with the material selection being based on chemical compatibility, reactor temperature and pressure, along with the fabrication technique [12] employed and the complexity of any micro structures required.

Flow reactions are conducted by bringing together solutions of substrates within a reaction channel (10 µm–10 mm), where they mix rapidly by diffusion and subsequently undergo reaction for the duration that they are within the channel; to increase the rate of reaction and reduce the processing time, the reactors can be heated and pressurized [13]. Fluids are manipulated within the reactors using a pumping mechanism determined by the reactor material, the chemicals under investigation, the flow rate required, and the system pressure. Of the numerous techniques available, pressure-driven flow (using HPLC or syringe pumps), negative pressure (peristaltic pumps), or electroosmotic flow (EOF) [14] have featured most widely in the development of the field.

It is the rapid mixing and precise control over reaction conditions that afford operational advantages over conventional batch reactors [15]. Once the optimal reaction conditions have been identified within a laboratory-scale reactor, unlike conventional up-scaling, which involves increasing the reactor volume to attain the required production volume, flow reactors use an approach called scale-out. This principle is based on numbering-up or parallelization, whereby the number of reactors employed is simply increased (internally or externally) to afford the required process throughput. Consequently, the reaction characteristics used within the production module are the same as those identified by the R&D chemist, leading to considerable reductions in development time and cost, while removing the risks associated with failing to scale a process [16]. With this in mind, production quantities of synthetically challenging compounds have been realized within flow reactors and examples are provided in Section 6.3. Micro reactors therefore have a valuable role to play in all stages of chemical development, ranging from reaction optimization and catalyst evaluation to product purification and production. With these factors in mind, this chapter serves to illustrate the potential that flow reaction methodology has to contribute towards the development of sustainable chemical processes, through the use of examples found within the scientific literature.

6.2

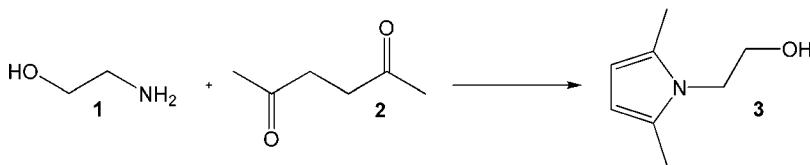
Examples of Their Use as Tools for the Research Chemist

6.2.1

Liquid Phase

6.2.1.1 Solvent Free

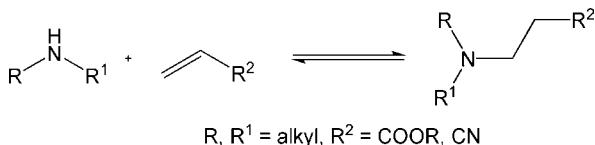
A facile approach to increasing the sustainability of a chemical process is to perform reactions in the absence of a solvent, thus reducing the volume of waste generated. Unfortunately, when reactions are conducted in this way, problems are often encountered with the efficient removal of heat generated, leading to the need for lengthy dosing times. The ability of micro reactors to readily dissipate heat makes them particularly useful for highly exothermic reactions; this is illustrated for the solvent-free Paal–Knorr reaction reported by Schwalbe *et al.* (Scheme 6.1) [17].



Scheme 6.1 Paal–Knorr synthesis of pyrrole **3** conducted under continuous flow in the absence of a solvent.

When performing the reaction of ethanolamine (**1**) and acetonylacetone (**2**) in batch, owing to the evolution of heat it was found necessary to add the amine **1** to the ketone **2** slowly over an extended period. Consequently although the reaction itself was rapid, the rate of dosing required to maintain control over the reaction temperature led to a significant increase in the processing time. Conversely, conducting the reaction in a CYTOS flow reactor, consisting of a stainless-steel micro mixer and a tubular residence time unit, the authors were able to add **1** to **2**, in the absence of a solvent, at a total flow rate of 6.1 ml min^{-1} . Employing a reactor temperature of $65\text{ }^\circ\text{C}$ and a residence time of only 5.2 min, the authors were able to synthesize the target 2-(2,5-dimethylpyrrol-1-yl)ethanol (**3**) in 91% yield, which corresponds to a throughput of 260 g h^{-1} , affording significant time savings and increased process safety compared with batch protocols.

In a second solvent-free example, Löwe *et al.* [18] demonstrated the addition of secondary amines to α,β -unsaturated carbonyl compounds (Scheme 6.2) in a micro structured reactor. Conventionally, the exothermic nature of such reactions requires them to be conducted in dilute solutions, in conjunction with long dosing times (85% yield, 17–25 h), where poor thermal control results in the reverse reaction dominating at temperatures in excess of $200\text{ }^\circ\text{C}$. Using flow methodology [mixer dimensions = $40\text{ }\mu\text{m}$ (width) \times $200\text{ }\mu\text{m}$ (depth), tube reactor = $1/4$ in o.d. (74.5 ml) and $1/8$ in o.d. (9.8 ml)], the authors were able to add the secondary amine continuously to an unsaturated ketone, with the heat of reaction being readily dissipated (heat exchange surface = $12\,800\text{ m}^2\text{ m}^{-3}$, heat transfer coefficient = $4000\text{ W m}^{-2}\text{ K}^{-1}$), without the need for external cooling. Employing mixing times in the range 0.8–5.0 ms, the authors were able to conduct the reaction of acrylonitrile **4** with dimethylamine (40 wt% in H_2O) in 1.6 min and the less reactive diethylamine in 7.2 min, affording the respective acrylic acid ethyl esters in 96.4 and 61.1% conversion.



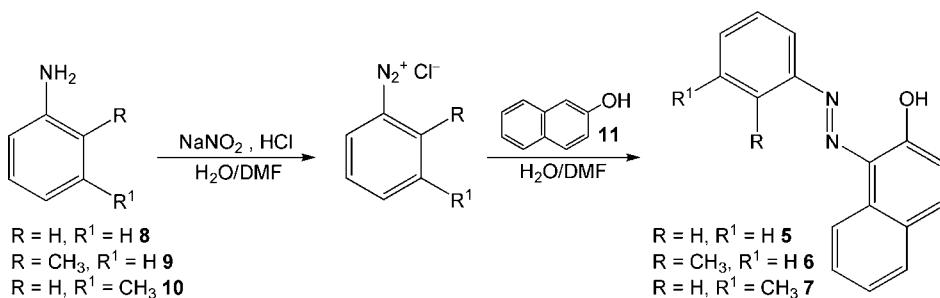
$\text{R}, \text{R}^1 = \text{alkyl}, \text{R}^2 = \text{COOR, CN}$

Scheme 6.2 General reaction scheme illustrating the addition of secondary amines to α,β -unsaturated compounds.

In addition to demonstrating the excellent reaction control obtained through the use of continuous flow reactors, these examples also illustrate the ability to reduce reaction

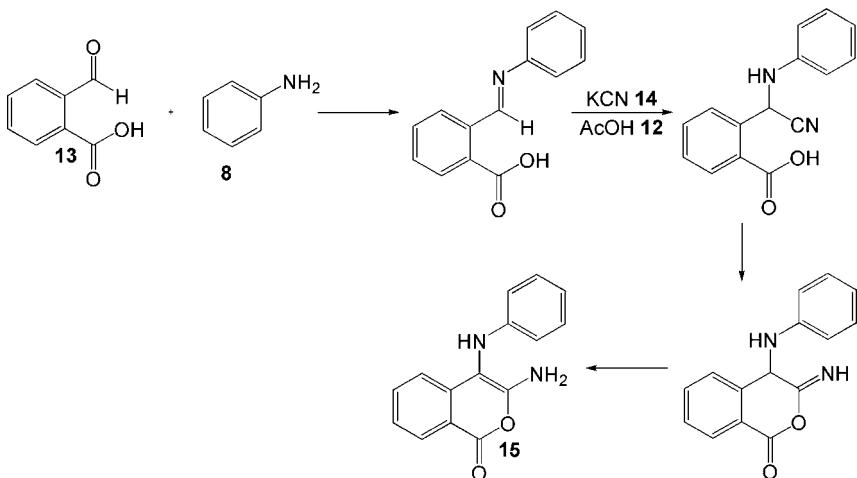
times dramatically, a feature that is attributed to the efficient mixing and dissipation of heat, preventing the need for lengthy addition times or dilute reactants as observed in conventional batch reactors. Mostly, however, reaction solvents are required in order to maintain dissolution of solid substrates, reaction products, and by-products, thus preventing blockage formation within the micro structures of the flow reactors.

One of the earliest examples of a liquid-phase reaction conducted within a micro reactor [channel dimensions = 190 µm (width) × 90 µm (depth)] was reported by Harrison and co-workers [19], who demonstrated the synthesis of an azo dye under EOF conditions. This was an important example as it served to illustrate the potential associated with performing hazardous reactions under continuous flow and, based on these preliminary findings, many research groups have subsequently investigated the continuous flow synthesis of azo dyes; one example, reported by de Mello and co-workers [20], is illustrated in Scheme 6.3. Within a glass reactor [channel dimensions = 150 µm (width) × 50 µm (depth) × 8.0 cm (length)], the authors evaluated the synthesis of three azo dyes (**5**, **6** and **7**), using pressure-driven flow to manipulate reactant streams. Using a stepwise approach, the formation of a series of highly unstable diazonium salts, via the diazotization of aniline (**8**), 2-toluidine (**9**), and 3-toluidine (**10**), followed by their *in situ* reaction with β-naphthol (**11**) to afford the various azo dyes, Sudan 1 (**5**) (52%), 1-(2-methylphenylazo)-2-naphthol (**6**) (23%) and 1-(3-methylphenyl)-2-naphthol (**7**) (9%). Section 6.3.1 gives an industrial example of azo dye synthesis utilizing continuous flow methodology.



Scheme 6.3 Reaction scheme illustrating the protocol used for the continuous flow synthesis of azo dyes.

Employing a stacked-plate micro reactor (channel dimensions = 100 µm, volume = 2 ml), Acke and Stevens [21] investigated the continuous flow synthesis of a series of pharmaceutically relevant chromen-1-ones via the multicomponent route illustrated in Scheme 6.4. To ensure that HCN was formed within the confines of the micro reaction channel, solutions of acetic acid (**12**) (2 equiv.)–2-formylbenzoic acid (**13**) (1 equiv.) and aniline (**8**) (2 equiv.)–potassium cyanide (**14**) (1.2 equiv.) were introduced into the reactor from separate inlets. A maximum concentration of 0.15 M was selected for **13** as this prevented precipitation of the reaction products and intermediates within the micro reactor. Employing a reactant residence time of 40 min, the authors obtained 3-diamino-1*H*-isochromen-1-one (**15**) in 66% yield;



Scheme 6.4 Summary of the reaction pathway used to synthesize 3-diamino-1*H*-isochromen-1-one (**15**) in a stacked-plate micro reactor.

equating to a throughput of 1.80 g h^{-1} . To demonstrate the flexibility of the methodology, the authors evaluated a series of amines, isolating the isocoumarins in 6–75% yield.

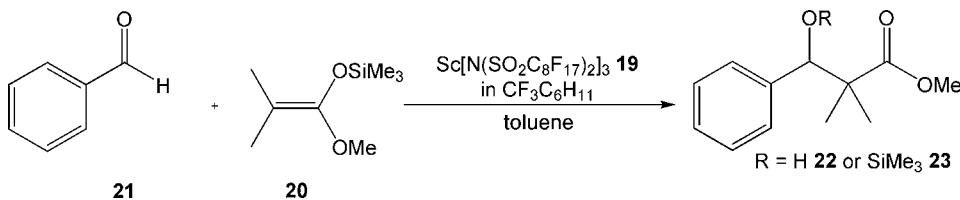
Building on these initial findings, the same group [22] subsequently investigated the ring closing of vicinal amino groups in order to introduce an imidazole core into the compound's skeleton and investigated the effect of solvent, temperature, concentration, and stoichiometry on the synthesis of 1*H*-isochromen[3,4-*d*]imidazol-5-ones. Using this screening approach, the authors identified the optimal conditions to be a reactant concentration of 0.2 M, dimethylformamide (DMF) as the reaction solvent, 22 °C as the reaction temperature, 10 mol% *p*-TsOH (17) and 5 equiv. of the orthoester 18. Under the aforementioned conditions, the target compound 16 was obtained in 88% yield with a residence time of 118 min. The generality of the reaction was subsequently demonstrated for an array of substituted isochromen-1-ones, with outputs in the range 0.18–2.21 g h⁻¹, a selection of which are illustrated in Table 6.1.

6.2.1.2 Liquid–Liquid Phase

In addition to the use of conventional organic solvents as diluents, researchers have investigated the use of fluorous solvents, exploiting the laminar flow conditions within micro reaction channels [dimensions = 30 μm (width) × 30 μm (depth) × 1, 2 or 3 cm (length)] to conduct fluorous biphasic catalysis (FBC), demonstrating facile recycling of the solvent/catalyst. Using the Mukaiyama aldol reaction (Scheme 6.5), Mikami *et al.* [23] employed scandium bis(perfluoroctanesulfonyl)amide (19) as the catalyst (6.3×10^{-5} M) and perfluoromethylcyclohexane–toluene as the biphasic solvent system. Using a 2:1 ratio of the silyl enol ether 20 to benzaldehyde (21) (0.1 M), the effect of residence time on the yield and ratio of the silylated (22) and desilylated (23) aldol products was evaluated. Initial reactions employing a residence

Table 6.1 Summary of the throughputs obtained for the synthesis of 1*H*-isochromen[3,4-*d*]imidazole-5-ones.

Product (R)	Yield (%)	Throughput (g h^{-1})
Phenyl 16	80	2.21
3-Methoxyphenyl	55	0.39
3-Tolyl	27	0.18
4-Tolyl	78	0.52
4-Methoxyphenyl	75	0.53
4-Fluorophenyl	92	0.62

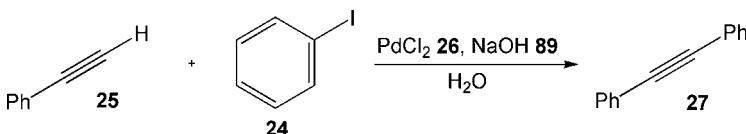
**Scheme 6.5** Illustration of the use of fluoruous materials as recyclable solvents in continuous flow systems.

time of 5.4 s afforded 50% conversion (**23:22** 1.5:1); this was readily increased, however, to 92% (**23:22** 2.2:1) by doubling the residence time to 10.8 s. For comparative purposes, the reaction was also conducted in a stirred batch reactor, whereby only 11% yield was obtained after 2 h. The dramatic increase in yield within the flow reactor is attributed to the large interfacial area obtained between the phases, compared with the relatively small surface area within a stirred batch reactor.

6.2.1.3 Elevated Reaction Temperatures

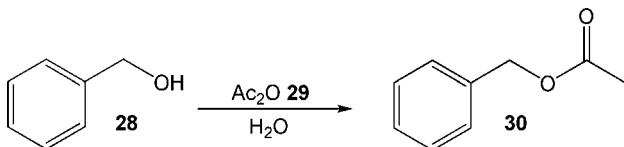
In addition to performing reactions at room temperature, the excellent thermal control obtained within flow reactors enables conditions that would conventionally be termed “extreme” to be used with ease. An excellent example of this was demonstrated by Kawanami *et al.* [24], whereby a superheated Hastelloy micro mixer (0.5 mm i.d.) and tubular flow reactor [1.7 mm i.d. \times 10 m (length)] was used to create rapid collision mixing between a substrate and water, the resulting particle dispersion was then rapidly heated, to induce a reaction, and cooled to afford a binary

phase containing the reaction products and water. To illustrate the potential of the technique, the authors employed copper-free Sonogashira C–C coupling as a model reaction (Scheme 6.6), demonstrating the benefits associated with this approach compared with the use of more conventional organic solvents. Employing a reaction temperature of 250 °C at 16 MPa, nearly quantitative coupling of 4-iodobenzene (24) to phenylacetylene (25) was obtained, employing 2 mol% of catalyst 26 and reaction times ranging from 0.1 to 4.0 s. In addition to the rate acceleration observed, the technique of rapid mixing and heating afforded an unprecedented catalytic turnover frequency of $4.3 \times 10^6 \text{ h}^{-1}$. As the reaction product 27 floated on the surface of the water and the catalyst precipitated as Pd⁰, diphenylacetylene (27) was isolated by a facile process of filtration and phase separation. Using this approach, the authors subsequently investigated the C–C coupling reactions of 25 and a further nine aryl halides to afford yields ranging from 62 to 100%.



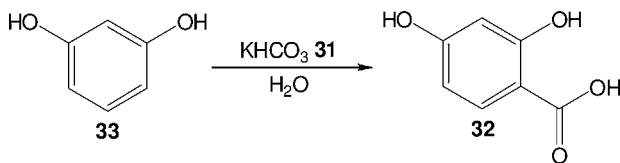
Scheme 6.6 Reaction used to demonstrate the rate acceleration attained using superheated water under flow.

In a second example, the authors demonstrated the use of subcritical water as a solvent in the selective hydrolysis-free *O*-acylation of alcohols. Using a reaction temperature of 200 °C and a pressure of 5 MPa, the acylation of benzyl alcohol (28) using acetic anhydride (29) was achieved in <10 s (Scheme 6.7). Under the aforementioned conditions, the target compound benzyl acetate (30) was obtained in 99% yield, representing a dramatic increase of 82% compared with analogous batch processes.



Scheme 6.7 Hydrolysis-free *O*-acylation of benzyl alcohol (28) conducted in subcritical water.

Another example illustrating the safe operation of micro reactors at elevated temperatures and pressures was reported by Hessel *et al.* [25], for the industrially relevant Kolbe–Schmidt reaction (Scheme 6.8). Potassium hydrogencarbonate (31) was selected as a raw material as it is cheap and readily available, making it suitable for the industrial-scale preparation of 2,4-dihydroxybenzoic acid (32); water was selected as the reaction solvent as it is inexpensive ($100\text{--}1000 \text{ l h}^{-1}$). To optimize the continuous flow conditions, the authors employed a stainless-steel capillary reactor and evaluated the effect of pressure for a fixed reaction time of 6.5 min at 120 °C.

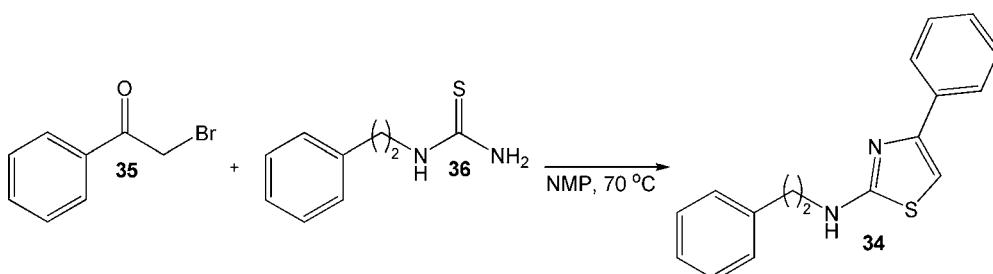


Scheme 6.8 The flow synthesis of 2,4-dihydroxybenzoic acid (**32**) via the Kolbe–Schmidt reaction of resorcinol (**33**).

Using this approach, the authors observed an increase in the yield of product **32** formed, from 23 to 47% between 1 and 32 bar, respectively. This represented an increase in reaction efficiency compared with batch reactions (2 h), conducted at reflux, whereby **32** was obtained in 40% yield, and only 90% selectivity. By overpressurizing the flow reactor to 40 bar, the authors were able to superheat the reaction mixture, allowing the formation of a single liquid phase compared with the biphasic system observed at lower pressures. Compared with a 1 l flask, this approach afforded a 440-fold increase in the space–time yield, providing a throughput of 110 g h⁻¹ of **32**.

The use of subcritical water as a solvent, coupled with the advantages of micro reaction technology, has the potential to remove the need for organic solvents, enabling reactions to be performed in a cheap, readily available, and environmentally benign solvent, while providing a facile means of isolating the reaction products and permitting re-use of the reaction solvent.

In addition to those examples reporting the use of elevated temperatures and pressures in conjunction with aqueous solvent systems, many authors have investigated the use of elevated reaction temperatures as a means of increasing the efficiency of reactions conducted using more conventional reaction solvents. An early such example was reported by Garcia-Egido *et al.* [26], and involved placing a glass micro reactor [channel dimensions = 300 µm (width) × 115 µm (depth) × 3.0 cm (length)] on a Peltier heater. Using this approach, the authors reported the synthesis of 2-aminothiazoles such as fanetizole (**34**) (Scheme 6.9). Employing EOF as the pumping mechanism, 2-bromoacetophenone (**35**) (1.4×10^{-2} M) and 3-phenethylthiourea (**36**) (2.2×10^{-2} M, 1.6 equiv.) were reacted in *N*-methylpyrrolidone (NMP) at 70 °C to afford **34** in 99% conversion; as determined by LC–MS.



Scheme 6.9 Synthesis of a 2-aminothiazole (**34**) in a heated micro reactor.

Seeberger and co-workers [27] demonstrated a facile approach for the fluorination of alcohols, carboxylic acids, aldehydes, and ketones by harnessing the synthetic utility of diethylaminosulfur trifluoride (DAST) (37) in a PTFE flow reactor (reactor volume = 16.0 ml) maintained at 5 bar and 70 °C.

To conduct a reaction, the substrate and DAST were introduced into the reactor from separate inlets and mixed within a T-mixer, reacted, and quenched with a solution of saturated aqueous NaHCO₃. Using this approach, the authors identified dichloromethane (DCM) as the best solvent, employing a reactor temperature of 70 °C, coupled with 1.0 equiv. of DAST for the deoxyfluorination of alcohols and 2.0 equiv. when using substrates containing a carbonyl moiety. Under the aforementioned conditions, the effect of reactant residence time (8–32 min) was evaluated and the authors quickly identified 16 min as being the optimum residence time. As Table 6.2 illustrates, using this approach an array of fluorinated materials were synthesized in moderate to excellent yield.

Employing a stainless-steel continuous flow reactor (reactor volume = 4, 8, and 16 ml) with an in-line scavenger cartridge, containing tosylhydrazine resin, Ley and co-workers [28] investigated the metal-free reduction of ketones. Using substrate concentrations of 0.3–0.4 M, ⁱPrOH as the reaction solvent and a residence time of 30 min, LiO^tBu (38) (10 mol%) was identified as a superior catalyst to the analogous Na or K salts, affording the respective secondary alcohol in high yield when a reaction temperature of 180 °C (160 bar) was employed. After passing the reaction mixture through the scavenger cartridge and evaporation of the reaction solvent, the corresponding secondary alcohols were obtained in excellent yield and purity (Table 6.3), with the ⁱPrOH sufficiently pure to be re-used in subsequent reactions. The reaction was found to be versatile, permitting the efficient reduction of ketones in the presence of nitriles; however, halogenated ketones experienced dehalogenation.

Kappe and co-workers [29] recently demonstrated the advantages associated with performing homogeneous organic reactions at elevated temperatures and pressures, typically between 50 and 200 bar and 350 °C. Utilizing a stainless-steel micro reactor (channel dimensions = 1 mm i.d., reactor volumes = 4, 8 and 16 ml) and a series of HPLC pumps, the authors demonstrated the advantages of this mode of operation compared with that of microwave-promoted chemistry. Using the Diels–Alder reaction of dimethylbutadiene (39) and acrylonitrile (4) as a model, the authors evaluated the formation of 3,4-dimethylcyclohex-3-enecarbonitrile (40) (Scheme 6.10a). Employing toluene as the reaction solvent, the reaction mixture (2.0 M) was pumped through the micro reactor at a flow rate of 800 µl min⁻¹, where it was heated to 250 °C and maintained at 68 bar. Using the aforementioned reaction conditions, the authors obtained the target compound 40 in excellent yield (>99%) with a residence time of 5 min; representing a time saving compared with conventional batch methodology under microwave heating. In a second example, the authors evaluated the Claisen rearrangement of allyl phenyl ether (41), as depicted in Scheme 6.10b, whereby heating the reactor to 240 °C (100 bar) afforded 2-allylphenol (42), in 95% yield, with a reaction time of 4 min.

The authors also evaluated the use of supercritical solvents as it enabled reactions to be conducted in low-boiling solvents that could easily be removed from the reaction

Table 6.2 A selection of the substrates fluorinated using DAST (37) within a PTFE reactor.

Substrate	Product	Yield (%) ^{a)}
		70 ^{b)}
		61 ^{c)}
		89
		81
		89

a) Isolated yield, determined after purification by column chromatography.

b) 5:1 mixture of diastereomers.

c) 6:1 mixture of diastereomers.

products. Due to the high ionic product of supercritical alcohols, the solvents were also found to act as an acid catalyst, thus promoting reactions such as transesterifications (85% yield) (Scheme 6.10c) and esterifications (87% yield) (Scheme 6.10d).

Along with increasing the throughput of synthetic reactions, the ability to perform reactions at elevated temperatures under continuous flow has the advantage of unprecedented levels of reaction control. This is elegantly demonstrated using the synthesis of a key intermediate of Sildenafil® (43) (Figure 6.1), 2-methyl-4-nitropropyl-2*H*-pyrazole-3-carboxylic acid (44); Scheme 6.11 illustrates that when the nitration of 1-methyl-3-propyl-1*H*-pyrazole-5-carboxylic acid (45) is performed under poor

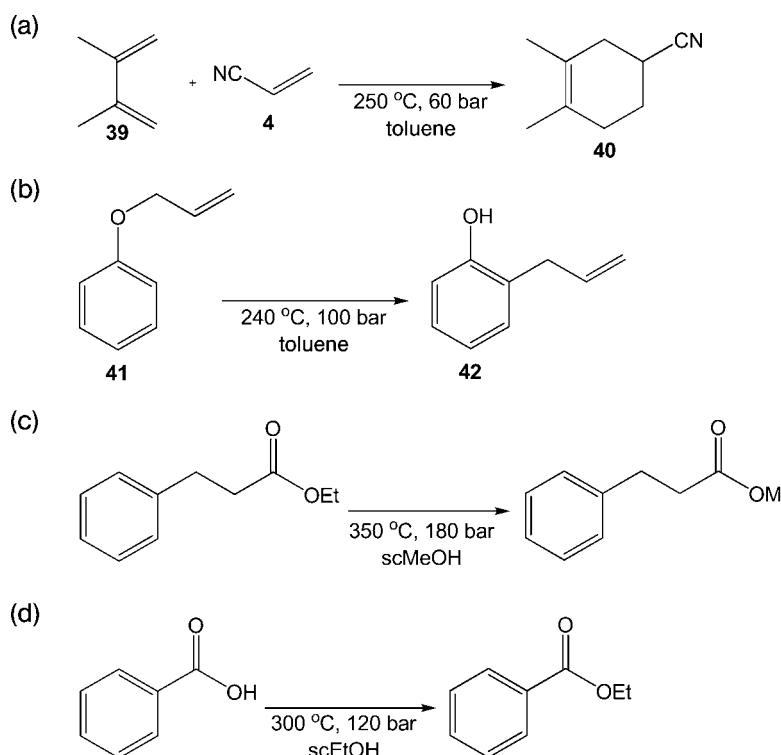
Table 6.3 A selection of the metal-free transfer hydrogenations performed under high temperature and pressure.

Ketone	Alcohol	Yield (%)
		94
		92
		92 ^{a)}
		88
		90

a) In addition, 5% dehalogenated alcohol was detected.

thermal control, decarboxylation of the target compound **44** occurs to afford the unwanted by-product 1-methyl-4-nitro-3-propyl-1*H*-pyrazole (**46**).

Due to the exothermic nature of the nitration reaction, which results in a rise in temperature from 50 to 92 °C upon addition of the nitrating solution, researchers identified the need to add the reactant solution in aliquots in order to reduce the temperature to 70 °C. Although this approach afforded increased reaction control, it also increased the processing time from 8 to 10 h. Conducting the reaction in a continuous flow reactor, where the heat of reaction was readily dissipated, Taghavi-Moghadam and co-workers [30] were able to maintain a reaction temperature of 90 °C, while adding the nitrating solution continuously, thus preventing the undesirable decarboxylation of the target compound **44** to 1-methyl-4-nitro-3-propyl-1*H*-pyrazole (**46**). Using a reaction time of 35 min, the authors were able to synthesize the target compound **44** in an overall yield of 73% (5.5 g h⁻¹), dramatically reducing processing time and increasing process safety compared with the conventional process.



Scheme 6.10 A selection of the flow reactions performed at elevated temperatures by Kappe and co-workers.

Microwave Heating

Along with the introduction of thermal energy into continuous flow reactors via thermal jackets, oil/water baths and convective heating, the use of microwaves as a heating mechanism for continuous flow reactors [31] has been demonstrated on both micro- and meso-scales; coupling these emerging technologies has afforded

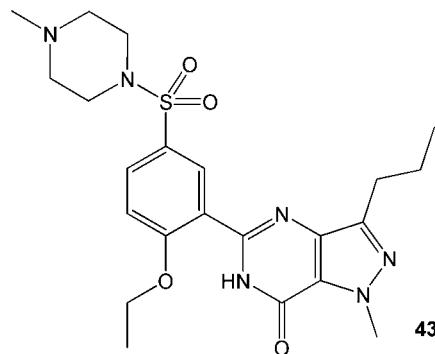
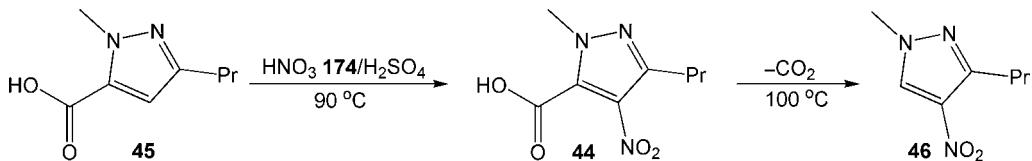
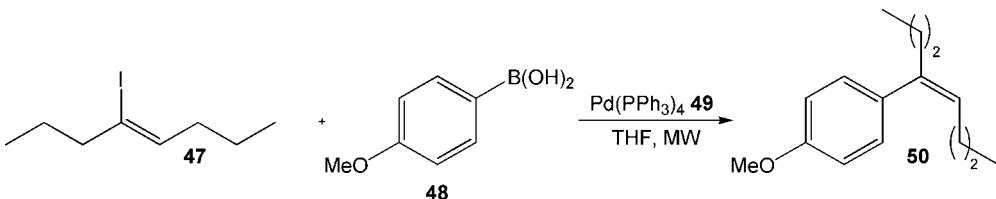


Figure 6.1 Sildenafil[®] (43), a pulmonary hypertensive agent and lifestyle drug, marketed as Viagra[®].



Scheme 6.11 Schematic illustrating the by-product **46** formed as a result of poor thermal control.

advantages such as enhanced reaction rates, reduced reaction times, higher yields, and increased product selectivity. An early example demonstrating the use of microwave irradiation as a heat source for continuous flow reactors was reported by Comer and Organ [32] and used Suzuki–Miyaura cross-coupling as a model reaction (Scheme 6.12). Introducing reactants into glass capillary reactors (200 µm i.d.) via a stainless-steel mixing chamber, the coupling of 4-iodooct-4-ene (**47**) (0.20 M) and 4-methoxyboronic acid (**48**) (0.24 M) was initially investigated using THF as the reaction solvent and palladium tetrakis(triphenylphosphine) (**49**) as the catalyst.



Scheme 6.12 Schematic illustrating the Suzuki–Miyaura reaction conducted using microwave heating.

Using pressure-driven flow and 100 W, the authors obtained 100% conversion to 1-methoxy-4-(1-propylpent-1-enyl)benzene (**50**) with a residence time of 28 min. Compared with conventional batch reactions, this result represented a dramatic improvement in yield, which was attributed to the suppression of competing side reactions. Consequently, the reaction was repeated for a series of aryl halides and boronic acids, affording the target compounds in yields ranging from 37 to 100%.

Other reactions evaluated by the authors included Wittig–Horner olefination and a series of ring-closing metathesis (RCM) reactions, employing Grubbs's II catalyst. In all cases, a reduction in power consumption, increase in yield, and reduction in reaction time were obtained as a result of employing microwave-assisted continuous flow reactions [33].

More recently, Shore and Organ [34] reported a series of Diels–Alder reactions conducted in Pd-coated capillaries, identifying the Pd film as having a dual role: that of a heat source and a catalyst. As Table 6.4 illustrates, on conducting the reaction in the absence of the Pd coating, in an oil bath at 205 °C, 54% conversion to (1*R*,4*S*)-dimethyl 7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-carboxylate (**51**) was obtained; this was subsequently increased to 72% upon employing a Pd-coated capillary. Utilizing microwave irradiation as a means of heating the flow reactor, the authors obtained 10% conversion to **51** in the absence of Pd; 47% conversion was detected when the

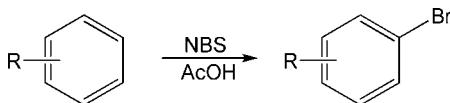
Table 6.4 An illustration of the microwave effect on Diels–Alder reactions conducted in Pd-coated capillaries.

Capillary treatment	Temperature (°C)	Heat source	Conversion (%) ^{a)}
None	205	Oil bath	54
Pd-coated, inside	205	Oil bath	72
None	115	MW	10
Pd-coated, outside	205	MW	47
Pd-coated, inside	205	MW	90

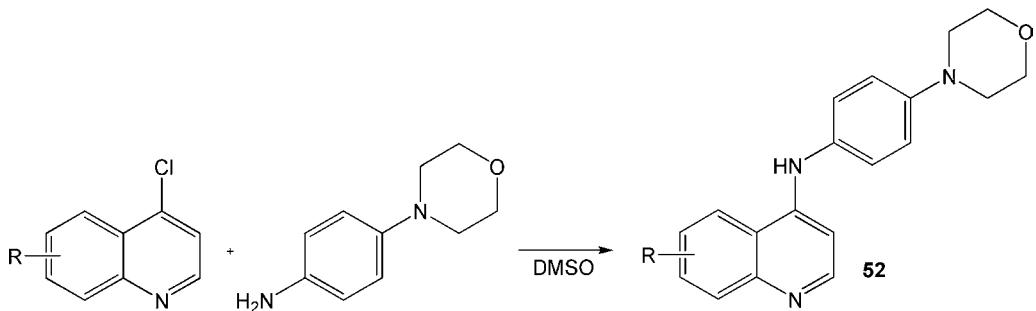
a) Conversion determined by ^1H NMR spectroscopy.

reactor was coated on the outside, with the increase being attributed to a thermal effect, and 90% **51** when the Pd coating was in contact with the reactant solution; confirming the presence of a catalytic effect. Based on these findings, the authors performed a series of Diels–Alder cycloadditions, within the coated capillary reactor, affording conversions consistently higher than in analogous reactions performed in an oil bath, typically $>90\%$ conversion.

Using a coiled perfluoroalkoxyalkane (HP-PFA) tube, of $750\text{ }\mu\text{m i.d.}$ (total volume = 3 ml), Benali *et al.* [35] investigated the effect of microwaves on a bromination reaction (Scheme 6.13), the product of which was required in a large amount for a drug discovery program. Employing microwave power of 300 W, affording a reaction temperature of $120\text{ }^\circ\text{C}$, coupled with a flow rate of $650\text{ }\mu\text{l min}^{-1}$, the authors were able to obtain the target compound in 89% yield and 91% purity. Unfortunately, the time taken for the system to reach a steady state resulted in a large amount of waste generation and the authors sought an alternative method for microwave reaction optimization.

**Scheme 6.13** Bromination reactions used to evaluate continuous flow microwave-assisted reaction optimization.

To increase the rate of optimization and reduce the volume of material used, the authors subsequently investigated the formation of discrete sample plugs separated by a fluorous solvent, perfluoromethyldecalin (PFMD), enabling a large number of reactions to be performed in series, each with a relatively small reactant volume. Focusing on the halide displacement reaction illustrated in Scheme 6.14, the authors identified that analogous conversions were obtained across plug volumes ranging



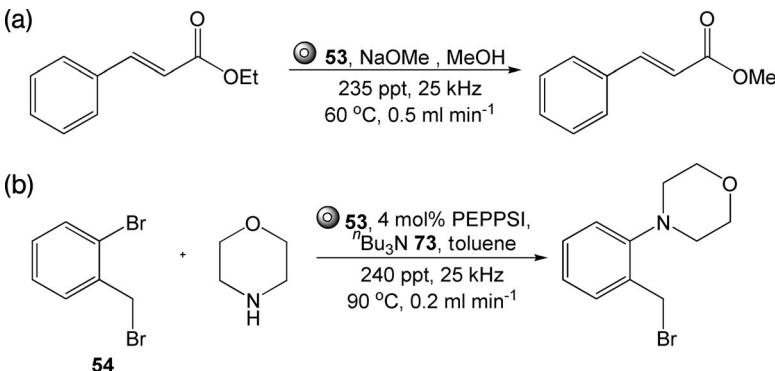
Scheme 6.14 Microwave-assisted displacement of an aromatic chloride by a secondary amine.

from 200 to 4000 μl (\sim 85% conversion to **52**), meaning that reactions could readily be scaled once optimization had been performed using 200 μl aliquots of the reactant mixture.

Electromagnetic Heating

More recently, Kirschning and co-workers [36] demonstrated the indirect heating of a series of solution-phase micro reactions via the application of an electromagnetic field on silica-coated magnetic nanoparticles (**53**). Housed within an inductor, the reactor consisted of a glass fixed bed [9 mm i.d. \times 14 cm (length)] which contained the nanoparticles **53**, application of an electromagnetic field (200–400 ppt, 25 kHz) allowed inductive heating of the reactants flowing through the fixed bed (40–220 °C).

Using this approach, the authors demonstrated a series of reactions including transesterifications (88% yield) (Scheme 6.15a) and the Buchwald–Hartwig amination of an aryl bromide (**54**) (75% yield) (Scheme 6.15b). Employing flow rates in the range 200–500 $\mu\text{l min}^{-1}$ and temperatures of 60–90 °C, the authors obtained excellent yields in a single pass through the reactor, demonstrating significant

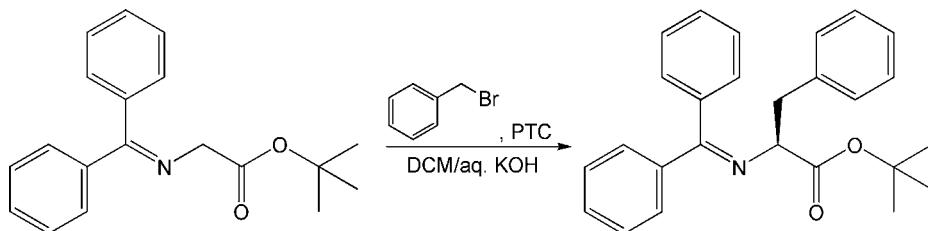


Scheme 6.15 A selection of the reactions demonstrated under continuous flow utilizing the inductive heating effect from magnetic nanoparticles (**53**): (a) transesterification and (b) Buchwald–Hartwig amination.

improvements in yield compared with analogous flow reactions using conventional heating. See Metal-Catalyzed Flow Reactions in Section 6.2.2.1 for an example utilizing functionalized magnetic nanoparticles (**53**), in a magnetic field, as a heat source within micro reactors, demonstrated using the Suzuki–Miyaura and Heck couplings as model reactions.

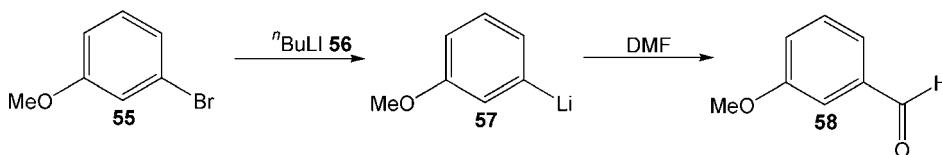
6.2.1.4 Reduced Reaction Temperatures

During their investigations into synthetic transformations within micro reactors, Kitamori and co-workers [37] identified an interesting phenomenon that allowed the supercooling of fluids. Employing octadecylsilane-treated Pyrex micro channels, the authors were able to tune the freezing point of water to between -20 and $-28\text{ }^{\circ}\text{C}$, as a result of changing the channel width (300 – $100\text{ }\mu\text{m}$), independent of the fluid flow rate. Using the model reaction illustrated in Scheme 6.16, the authors investigated the performance of an asymmetric reaction within their supercooled micro reactor, identifying an increase in *ee* from 43 to $>50\%$ as a result of decreasing the reaction temperature from 20 to $-20\text{ }^{\circ}\text{C}$.



Scheme 6.16 The model reaction used to illustrate the thermal control obtained in supercooled micro channels.

Schwalbe *et al.* [38] anticipated that performing lithiation reactions under continuous flow would not only be safer and higher yielding than in conventional stirred tank reactors, but also be more energy efficient and environmentally friendly. To assess this hypothesis, they conducted the bromolithium exchange between 3-bromoanisole (**55**) and *n*-butyllithium (**56**) to afford intermediate **57**; this was followed by the addition of DMF and hydrolysis to afford 3-methoxybenzaldehyde (**58**) (Scheme 6.17).



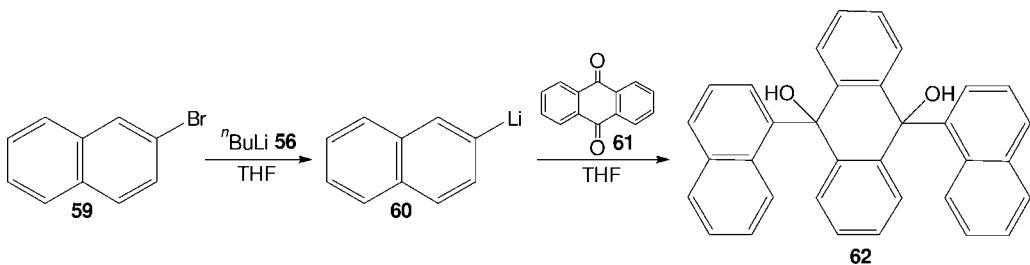
Scheme 6.17 Halogen–lithium exchange reaction conducted in a CPC micro reactor.

Due to the exothermic formation of intermediate **57**, and its well-known thermal instability, prolonged dosing times are conventionally required in order to obtain high yields and selectivities; furthermore, reductions in yield and purity are

frequently observed upon increasing the scale of the reaction ($0.04\text{ mol} = 100\%$ yield, $0.80\text{ mol} = 76\%$ yield) and mean that reactions employing lithiated intermediates are not exploited in production chemistry. With these problems in mind, the authors believed that by conducting the reaction under continuous flow, increased thermal control would permit access to the target product in high yield and purity due to the reduced processing time required.

Employing a two-stage reactor (reactor 1 = 2 ml and reactor 2 = 2 ml), maintained at 0°C in a cooling bath, the authors first conducted the lithiation step by mixing **56** (1.6 M in hexane, 6.0 ml min^{-1}) and 3-bromoanisole (**55**) (1.9 M in THF, 4.7 ml min^{-1}) to afford intermediate **57** with a residence time of 11.4 s. In the second reactor, intermediate **57** was mixed with DMF (5.0 M) in THF, where it underwent electrophilic addition to afford 3-methoxybenzaldehyde (**58**) with a residence time of 9.0 s. Using this approach, the target product **58** was obtained in 88% yield, affording a throughput of 0.4 mol h^{-1} with an overall reaction time of 20.4 s compared with $>7\text{ h}$ in batch.

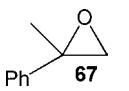
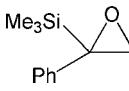
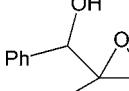
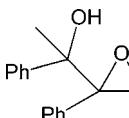
Song and co-workers [39] also reported a continuous flow lithium–halide exchange reaction, using the synthesis of two light-emitting diode materials, one of which is illustrated in Scheme 6.18. To perform the reaction, the authors employed two caterpillar split–recombine micro mixers, connected in series, maintained at -20°C in an external bath, with a solution of bromonaphthalene (**59**) (0.2 M) in THF pumped into one inlet of the micro mixer and a solution of **56** (2.5 M) in hexane into the second inlet. The lithiated intermediate **60** was subsequently fed into the second micro mixer, where a solution of 9,10-anthraquinone (**61**) was introduced; the reactions were quenched by the addition of saturated ammonium chloride (at 1°C), affording 85% conversion of **61** and the target compound **62** in 97% purity.



Scheme 6.18 Illustration of a light-emitting diode material synthesized in a two-stage continuous flow reactor.

Yoshida and co-workers [40] subsequently demonstrated the use of *sec*-butyl-lithium (**63**) in a continuous flow reactor, for the *in situ* preparation of an oxiranyl anion, derived from styrene oxide (**64**) and **63**. As Table 6.5 illustrates, the authors constructed a library of substituted epoxides derived from the reaction of 1,2-epoxyethylphenyllithium (**65**) with a series of electrophiles. The generation of **65**, from styrene oxide (**64**) (0.10 M) and **63** (0.75 M), was conducted in the first micro mixer and was followed by trapping, with MeI (**66**) (0.45 M), in the second micro

Table 6.5 Summary of the results obtained for the reaction of 1,2-epoxyethylphenyllithium (**65**) under flow.

Electrophile	Product	Yield (%) ^{a)}	Throughput (g h ⁻¹)
MeI 66		88	4.2
Me ₃ SiCl		72	5.0
Benzaldehyde 21		84 ^{a)}	6.8
Acetophenone		70 ^{b)}	6.1

a) Diastereomer ratio 82:18, as determined by ¹H NMR spectroscopy.

b) Diastereomer ratio 67:33, as determined by ¹H NMR spectroscopy.

mixer. Using this approach, the authors investigated the effect of reaction temperature, from -78 to -48 °C, and residence time, from 1 to 25 s, on the formation of 2-methyl-2-phenyloxirane (**67**), identifying that a reaction temperature of -78 °C permitted stabilization of the oxiranyl anion for up to 25 s.

Using a similar approach, the authors also demonstrated the use of **63** in the anionic polymerization of styrene (**68**), demonstrating the ability to obtain a high degree of control over the molecular weight distribution of the resulting polymers [41]. From the examples provided, it can be seen that this two-step reaction approach represents a facile route for the preparation and reaction of highly reactive intermediates, without the need for the intense cooling and lengthy reaction/dosing times currently required in batch, making the processes faster and more energy efficient.

6.2.2

Solid–Liquid Phase

Over the past two decades, the use of solid-supported reagents, catalysts, and scavengers has revolutionized the way in which the modern synthetic chemist performs transformations such as oxidations, reductions, and coupling reactions [42–44]. Their growing application can be attributed to the ease of product

isolation compared with homogeneous reagents and catalysts along with allowing the rapid generation of compound libraries. However, the use of such materials in stirred or shaken reactors is not without its drawbacks, with the most problematic being the mechanical degradation of the solid support, which makes recovery of the reagent/catalyst from the reaction products difficult. In the case of solid-supported metal catalysts, this can lead to the leaching of undesirable quantities of trace metals into the final product at levels unacceptable to the pharmaceutical industry.

To address these shortcomings, numerous researchers have investigated the incorporation of solid-supported reagents, catalysts, and scavengers into continuous flow reactors as a means of facilitating product isolation, in addition to reducing the time taken to obtain the target compounds in high yield and purity. With this in mind, the following section provides examples of the different methods employed for the use of solid-supported reagents, catalysts, biocatalysts, and scavengers under continuous flow including packed beds, monoliths, and wall coating [45, 46].

6.2.2.1 Solid-Supported Catalysts

Metal-Catalyzed Flow Reactions

The replacement of stoichiometric reagents with a catalyst is an efficient method of increasing the atom economy of synthetic transformations and is an area that has benefited greatly from the coupling of solid-supported catalysts with flow reactor methodology, not only from a product purity perspective but also as a means of increasing catalyst lifetimes.

Employing a flow reactor comprising polyvinylpyridine-coated Raschig rings, functionalized with a palladacycle (**69**) (10 mmol Pd per ring), Kirschning and co-workers [47] evaluated the activity of an immobilized oxime–palladacycle, under continuous flow, towards a series of cross-coupling reactions. The authors initially evaluated the Suzuki–Miyaura reaction by circulating a solution of aryl bromide (1.00 mmol), boronic acid (**70**) (1.50 mmol), and cesium fluoride (**71**) (2.4 mmol) in DMF–H₂O (10:1, 5 ml), through the heated reactor (100 °C) at a flow rate of

Table 6.6 Results obtained for the continuous flow Suzuki–Miyaura reaction with Pd(II) catalyst **69**.

R ¹	Residence time (h)				Yield (%)
H	24				89
CH ₃	24				56
COCH ₃	9				91
OCH ₃	24				50

Table 6.7 A selection of the results obtained for the Heck reaction performed under continuous flow.

R¹	Residence time (h)	Yield (%)
CO ₂ Cy	2	99
CO ₂ ^t Bu	4	99
CN 4	4	97 (5:1) ^{a)}

a) The number in parentheses represents the *E*:*Z* ratio.

2.5 ml min⁻¹ (Table 6.6). After 24 h, the reactor was washed with DMF–H₂O and the reaction products were purified by flash chromatography, to afford the target products in moderate to excellent yield.

In addition to the Suzuki–Miyaura reaction, the authors also found the catalyst **69** to be active in the arylation of olefins with aryl halides (Table 6.7). Again, to conduct a reaction the authors circulated a solution containing 4-iodoacetophenone (**72**) (1.0 mmol), the alkene (3.0 mmol) under investigation, and tributylamine (**73**) (3.0 mmol) in anhydrous DMF (3 ml), through the heated reactor (120 °C) at a flow rate of 2 ml min⁻¹. After 24 h, the flow reactor was rinsed with DMF and the reaction products were diluted with water prior to extraction into ethyl acetate, to afford the target product in excellent purity.

In a more recent example, Kirschning and co-workers [48] reported the use of silica-coated magnetic nanoparticles (**53**) as a means of introducing heat into micro reaction channels and, in an extension to this, surface functionalization afforded a Pd⁰ solid-supported catalyst (**74**) (Scheme 6.19). Incorporation of the material **74** into a fixed bed enabled the solution-phase reactants to be heated, upon application of an electromagnetic field, and Pd-catalyzed reactions to be performed. As illustrated in Table 6.8, the authors demonstrated their synthetic strategy using the Suzuki–Miyaura and Heck coupling reactions. Conducting the reactions on a 1.0 mmol scale, at a flow rate of 2 ml min⁻¹ and a reaction temperature of 100 and 120 °C,

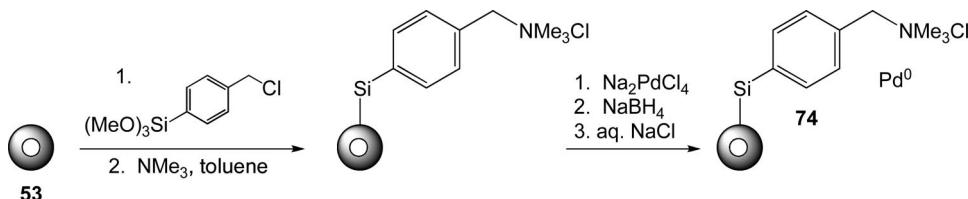
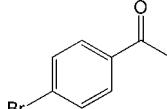
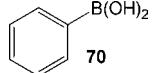
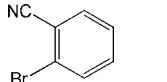
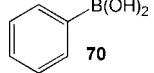
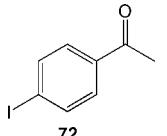
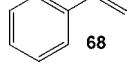
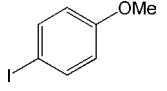
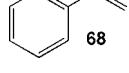
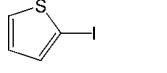
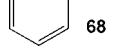
**Scheme 6.19** Protocol used to functionalize silica-coated Fe₃O₄/Fe₂O₃ nanoparticles (**53**).

Table 6.8 Summary of the results obtained for C–C cross-coupling reactions conducted in the presence of functionalized magnetic nanoparticles (**74**).

Halide	Boronic acid/alkene	Conditions ^{a)}	Yield (%)
	 70	A	77
	 70	A	83
 72	 68	B	76
	 68	B	84
	 68	B	63

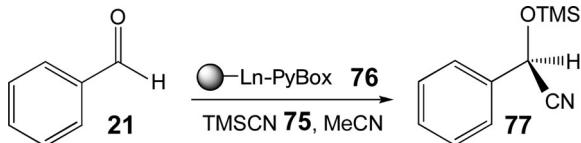
a) A, 1.5 equiv. phenylboronic acid (**70**), 1.0 equiv. aryl halide, 2.4 equiv. CsF (**71**), 2.8 mol% **74** in DMF–H₂O at 100 °C; B, 1.0 equiv. aryl halide, 3.0 equiv. styrene (**68**), 3 equiv. ⁷Bu₃N (**73**), 2.8 mol% **74** in DMF at 120 °C.

respectively, the authors obtained moderate to excellent yields in all cases, as a result of cycling the reaction mixture through the system for 1 h.

Along with the inclusion of heterogeneous metal catalysts in continuous flow reactors, numerous authors have evaluated the advantages associated with the incorporation of acid and base catalysts in these reaction systems, using a range of packed beds, monoliths, and wall-coated reactors.

Acid-Catalyzed Flow Reactions

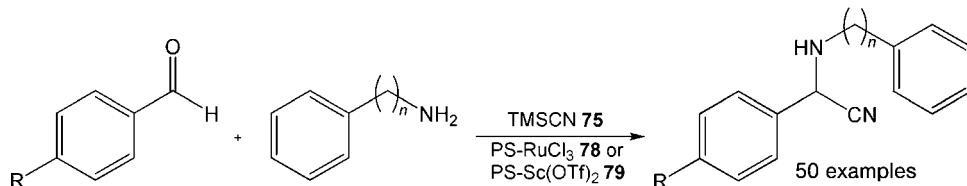
An early example of Lewis acid-catalyzed reactions conducted under continuous flow was demonstrated by Möberg and co-workers [49] and employed the enantioselective addition of trimethylsilyl cyanide (TMSCN) (**75**) to benzaldehyde (**21**) (Scheme 6.20).



Scheme 6.20 The use of polymer-supported Lewis acid catalyst **76** for the enantioselective synthesis of the cyanohydrin **77**, using EOF as the pumping mechanism.

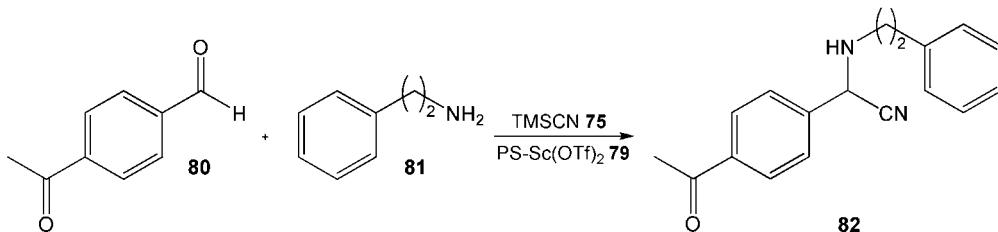
Under EOF, solutions of **21** and **75** were pumped through a packed bed containing the polymer-supported lanthanide–PyBox catalyst **76**, and the reaction products were analyzed off-line by GC, allowing both the conversion and enantioselectivity of the cyanohydrin to be determined. Compared with standard batch protocols, the use of an EOF-based flow reactor enabled the authors to screen rapidly a series of reaction conditions and additives, while demonstrating excellent recyclability of the catalyst.

Wiles and Watts [50, 51] subsequently reported the fabrication of an integrated borosilicate glass reactor in which they performed a solution-phase and a heterogeneously catalyzed reaction in series (Scheme 6.21). Initial investigations were conducted using polymer-supported ruthenium(III) chloride (PS-RuCl₃) (**78**) as the catalyst (0.01 g, 0.26 mmol g⁻¹). Reactions were conducted by pumping a solution of aldehyde and amine (each 0.4 M in MeCN) into a central micro reaction channel [150 µm (width) × 50 µm (depth) × 5.6 cm (length)] to afford the intermediate aldimine, followed by a solution of TMSCN (**75**) (0.2 M, 1 equiv.) from a third inlet. The reaction mixture then entered the packed bed, where the nucleophilic addition of cyanide afforded the target α-aminonitrile (17.2–25.4 mg h⁻¹).



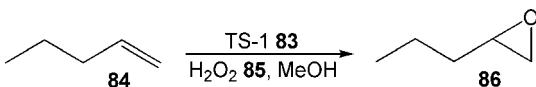
Scheme 6.21 Schematic illustrating the Lewis acid-catalyzed aldehydic Strecker reaction.

The throughput of the system was subsequently doubled as a result of employing polymer-supported scandium triflate [PS-Sc(OTf)₂] (**79**) as the Lewis acid catalyst, under the aforementioned reaction conditions. Using this approach, the authors demonstrated the generality of the technique, synthesizing a 10 × 5 array of α-aminonitriles, derived from 10 aliphatic and aromatic aldehydes and five amines. The chemoselectivity of the technique was also demonstrated using the reaction of 4-acetylbenzaldehyde (**80**) and 2-phenylethylamine (**81**) (Scheme 6.22); whereby 2-(4-acetylphenyl)-2-(phenethylamino)acetonitrile (**82**) was obtained, in 99.8% yield, as the sole reaction product.



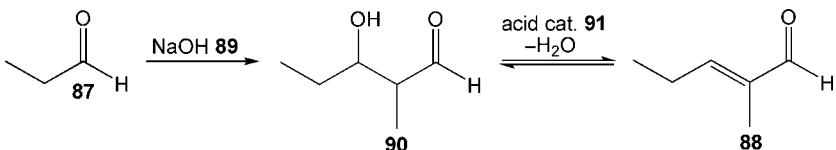
Scheme 6.22 Illustration of the chemoselective nature of the Strecker reaction conducted under continuous flow.

Employing a silicon micro reactor [channel dimensions = 500 or 1000 µm (width) × 250 µm (depth)], wall-coated with the acidic zeolite titanium silicate-1 (TS-1, Si:Ti ratio = 17) (83) (3 µm), Gavrilidis and co-workers [52] demonstrated a facile method for the epoxidation of 1-pentene (84) (Scheme 6.23). Using H₂O₂ (85) (0.18 M, 30 wt%) as the oxidant and 84 (0.90 M) in MeOH, the effect of reactant residence time on the formation of epoxypentane (86) was evaluated at room temperature. The authors observed increased productivity within the 500 µm reaction channel compared with the 1000 µm channel, a feature that is attributed to an increase in the surface-to-volume ratio and thus a higher effective catalyst loading.



Scheme 6.23 Schematic illustrating the epoxidation of 1-pentene (84) to afford epoxypentane (86).

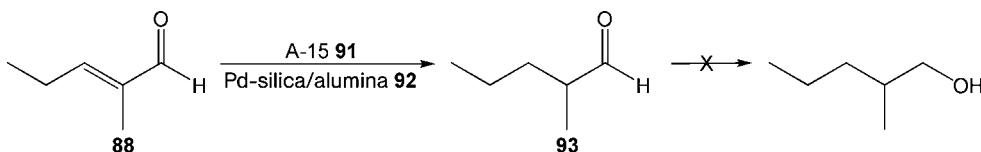
More recently, Poliakoff and co-workers [53] reported the continuous self-aldo condensation of propionaldehyde (87) in supercritical carbon dioxide (scCO₂) as a selective route to 2-methylpentenal (88), a component used within the fragrance, flavor, and cosmetics industries. Conventionally the compound is prepared via the base-catalyzed self-condensation using stoichiometric quantities of aqueous NaOH (89) or KOH, affording 99% conversion of aldehyde 87, with 86% enal 88 selectivity. Using a 316 stainless-steel tube [12 mm o.d. × 10 cm (length)] packed with catalyst, the authors evaluated the activity of a series of solid-supported materials, including acidic and basic materials, for activity towards the condensation reaction depicted in Scheme 6.24. Employing propionaldehyde (87) at a flow rate of 100 µl min⁻¹ and a CO₂ flow rate of 1.0 ml min⁻¹ (at 10 MPa), the effect of temperature and catalysts on the reaction selectivity was investigated, with the reaction products being analyzed by GC. Using this approach, the authors identified Amberlyst-15 (91) as a viable catalyst for the selective synthesis of 2-methylpentenal (88) and undertook further optimization of the reaction conditions.



Scheme 6.24 Schematic illustrating the self-condensation of propionaldehyde (87) to afford 3-hydroxy-2-methylpentenal (90) and the dehydration product 2-methylpentanal (88).

Conducting reactions in the absence of CO₂, the authors detected insignificant quantities of the enal 88 at temperatures <130 °C, compared with reactions conducted in the presence of CO₂ where 48% conversion to 88 was obtained with 92% selectivity (90 °C). This increase in product formation is attributed to the relative insolubility of the aldol intermediate in the polar scCO₂, affording a higher affinity for the catalyst surface and hence greater reactivity. Reducing the flow rates

to $75 \mu\text{l min}^{-1}$ and 0.75 ml min^{-1} respectively, the authors obtained 51% conversion and 95% selectivity towards **88**. Increasing the reaction temperature resulted in a decrease in selectivity, as did reducing the proportion of CO_2 within the system. Doubling the reactor bed volume, by adding a second packed-bed reactor, did, however, afford an increase in conversion to 65% (90°C), which rose to 80% at 105°C ; this was also accompanied by an increase in selectivity to $>99\%$. By employing a mixed catalyst bed containing Amberlyst-15 (**91**) and Pd on silica/alumina (**92**), the authors subsequently demonstrated the ability to perform an *in situ* hydrogenation to afford 2-methylvaleraldehyde (**93**), as illustrated in Scheme 6.25; significantly, no further reduction was observed.



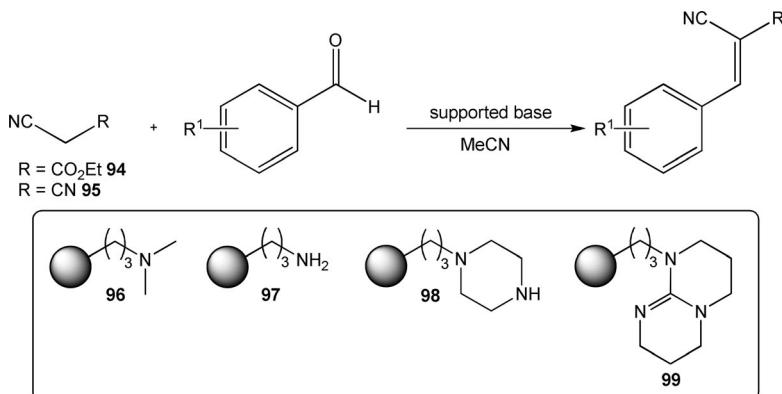
Scheme 6.25 The *in situ* hydrogenation of 2-methylpentenal (**88**) to 2-methylvaleraldehyde (**93**).

Base-Catalyzed Flow Reactions

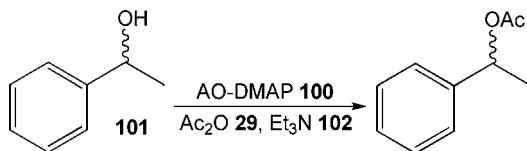
Haswell and co-workers [54, 55] demonstrated the incorporation of a series of silica-supported bases into a capillary reactor, operated under EOF, as a means of increasing the efficiency of the Knoevenagel condensation compared with conventional stirred reactors. The reactors were constructed from borosilicate glass capillaries [$500 \mu\text{m}$ i.d. $\times 3.0 \text{ cm}$ (length)] and the solid-supported base held in place by two microporous silica frits. To conduct flow reactions, a premixed solution of the aldehyde and ethyl cyanoacetate (**94**) or malononitrile (**95**) (1.00 M in MeCN) was placed in a reservoir and mobilized through the packed bed via the use of an applied field (V cm^{-1}). As the reactant solution passed through the solid-support, the base-catalyzed condensation reaction occurred, and the reaction products were collected at the reactor outlet in MeCN. Analysis of the reaction products off-line by GC-MS enabled the conversion of aldehyde to product to be determined. Using this approach, the authors investigated the reactivity of a range of substituted aromatic aldehydes, obtaining conversions in the range 99–100%, and evaluated solid-supported catalysts **96**–**99** (Scheme 6.26). Reduced degradation of the solid-supported catalyst was observed, leading to enhanced reagent lifetimes and reaction reproducibility.

McQuade and co-workers [56] subsequently evaluated the acylation of secondary alcohols using the supported base AO-DMAP (**100**), employing a pre-mixed solution of *rac*-phenyl-1-ethanol (**101**), Et₃N (**102**), and acetic anhydride (**29**) (0.33, 0.50, and 0.50 M, respectively) in hexane (Scheme 6.27). Reactions were conducted at room temperature and the effect of residence time was evaluated (10–50 s) using a 60 cm packed bed (1.6 mm i.d.). Employing residence times of <20 s, the authors obtained nearly quantitative conversions, affording superior results to those obtained in analogous batch reactions.

Baxendale *et al.* [57] reported a bifurcated approach to the synthesis of thiazoles and imidazoles by coupling a glass micro reactor and a packed-bed reactor to achieve a



Scheme 6.26 Illustration of the solid-supported bases evaluated for the Knoevenagel condensation under flow.



Scheme 6.27 Evaluation of AO-DMAP (100) as a catalyst for the acylation of secondary alcohols.

base-mediated condensation. Initial investigations employed a reaction temperature of 55 °C and a flow rate of 100 $\mu\text{l min}^{-1}$, with ethyl isocyanoacetate (**103**) (0.75 M) and 4-bromophenyl isothiocyanate (0.75 M) reacted in the presence of PS-BEMP (**104**). Although the target thiazole was obtained in excellent purity (95%), the authors were surprised by the low yield of 58%. Assuming that the remainder of the thiazole was trapped on the polymer-supported base **104**, the authors passed a solution of electrophile (0.75 M) through the packed bed to afford a new product, the corresponding imidazole (38%), with optimal conditions found to be a 1:1 ratio of coupling reagents (0.75 M in MeCN), 1.6 equiv. of PS-BEMP (**104**) and a flow rate of 50 $\mu\text{l min}^{-1}$ (for each reactant solution employed); as summarized in Table 6.9, an electronic effect was observed, with methoxy substituents favoring the selective thiazole formation.

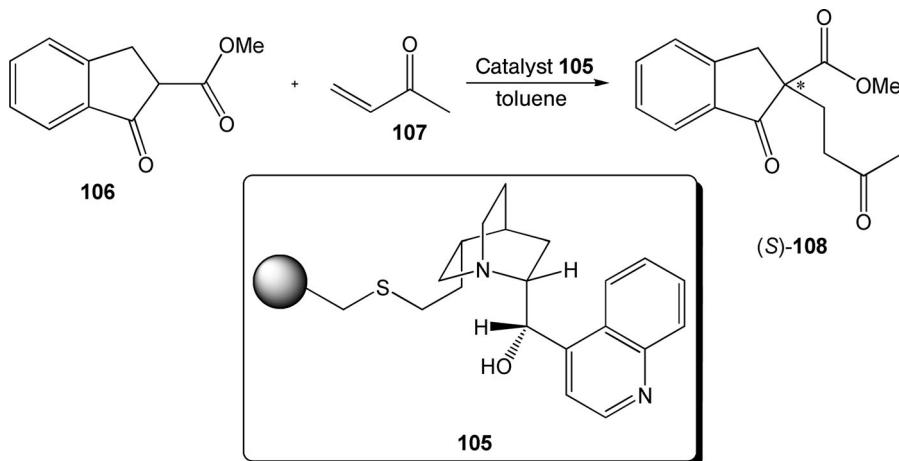
Using a polymer-supported cinchonidine derivative (**105**), Hodge and co-workers [58] evaluated the enantioselective Michael addition between methyl 1-oxoindan-2-carboxylate (**106**) and methyl vinyl ketone (**107**) to afford the *S*-enantiomer of the Michael adduct **108** (Scheme 6.28). Employing a glass tube reactor [1.4 cm i.d. \times 36 cm (length)], sealed at one end, containing 15 g of PS-cinchonidine **105** (reactor volume = 28.9 ml), the authors introduced solutions of **106** (0.50 M) and **107** (0.53 M) in toluene from separate inlets at a total flow rate of 0.83 $\mu\text{l min}^{-1}$.

Maintaining the reaction temperature at 50 °C, in a water bath, the target compound was obtained in 97% yield and 52% *ee*. Compared with batch, the flow reactor afforded similar yields and higher *eess*, providing a facile route to the synthesis of Michael adduct **108** with a throughput of \sim 10 g day⁻¹.

Table 6.9 Summary of the results obtained for the continuous flow synthesis of thiazoles and imidazoles.

R ¹	R ²	Thiazole yield (%)	Imidazole yield (%)	Combined yield ^{a)} (%)
4-OMe	H 35	96.0	4.0	100.0
3-F	Br	68.0	28.0	96.0
3-OMe	Br	84.0	5.0	89.0
2-OMe	H 35	90.0	7.0	97.0
3,4-Cl	CN	53.0	26.0	79.0

a) Reactions conducted in MeCN at 55 °C and a flow rate of 50 µl min⁻¹ for each reactant solution.

**Scheme 6.28** Illustration of enantioselective Michael addition performed using the PS-cinchonidine 105.

In addition to the preparation of packed beds and monoliths, wall coating is an alternative method for the introduction of catalysts into continuous flow systems, due to the short diffusion distances obtained within micro reaction channels. An early example of this was demonstrated by Yeung and co-workers [59], who employed a stainless-steel micro reactor [channel dimensions = 300 µm (width) × 600 µm (depth) × 2.5 cm (length)] coated with an NaA zeolite membrane, followed by a layer of

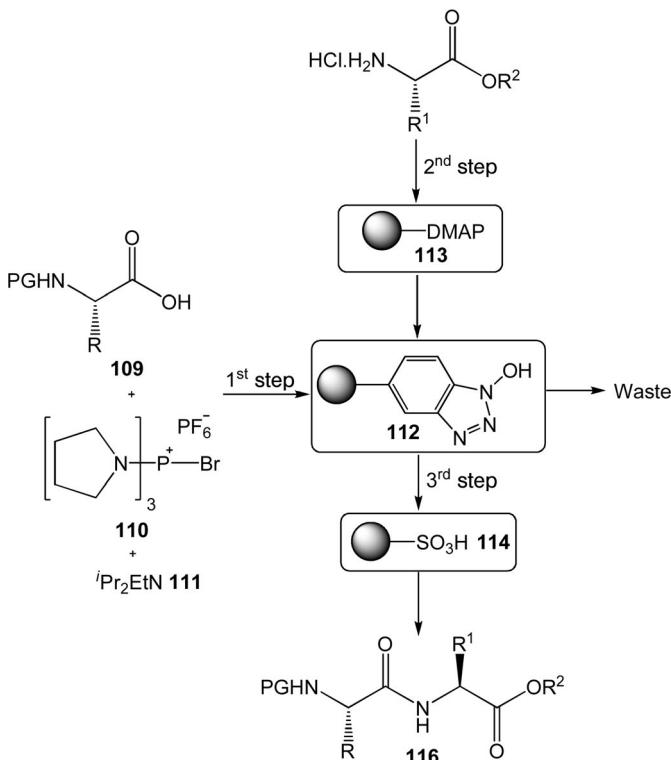
poly(diallyldimethylammonium chloride), which enabled the catalyst CsNaX-NH_2 to be immobilized via an ion-exchange process.; heating of the micro reactor at 523 K for 12 h, afforded catalyst adhesion to the micro channels. To evaluate the catalytic micro reactor, the authors employed the Knoevenagel condensation (Scheme 6.26, R = CO₂Et) of benzaldehyde (21) and ethyl cyanoacetate (94) as a model reaction and evaluated the effect of reactant flow rate on the conversion to ethyl 2-cyano-3-phenylacrylate. Employing a residence time of 48 min, the authors obtained 80% conversion of 21, demonstrating an increase of 25% compared with a packed-bed reactor.

More recently, Verboom and co-workers [60] developed a nanostructure, based on poly(glycidyl methacrylate) (PGMA) polymer brushes (50, 150 and 400 nm), as a means of introducing catalytic material on to the surface of glass micro channels [dimensions 100 μm (width) × 100 μm (depth) × 10.3 cm (length)]. Functionalization of the PGMA brushes with 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) afforded an organic base-coated micro channel that was subsequently evaluated for catalytic activity in the Knoevenagel condensation. Employing benzaldehyde (21) and malononitrile (95) as the reactants, in MeCN at 65 °C, the authors investigated the effect of flow rate (0.2–20 μl min⁻¹) on the formation of 2-benzylidenemalononitrile, detected by in-line UV-Vis spectrophotometry (Scheme 6.26, R = CN). Using this approach enabled the authors to determine the rate constant of the reaction as $1.3 \times 10^{-2} \text{ s}^{-1}$ (± 0.1) and an hourly output of $7.5 \times 10^{-5} \text{ M}$ nitrile. Importantly, no sign of catalyst leaching was observed over the course of 25 reactions and identical results were obtained when the system was re-evaluated 30 days later. The catalyst nanostructure did, however, require regeneration after each reaction, which was achieved by pumping a solution of Et₃N (102) (0.1 M) through the micro reactor.

6.2.2.2 Solid-Supported Reagents

Peptide Couplings

Utilizing the principle of “catch and release,” Ley and co-workers [61] reported the synthesis of a series of Boc and Cbz *N*-protected peptides under continuous flow. Employing a commercially available meso-fluidic pumping system, the authors developed a serial process that permitted the coupling of carboxylic acids and amines to develop a small molecule library. To perform a reaction, the authors placed the reactant solutions in sample loops that were connected to a flow stream which passed through a series of columns containing polymer-supported reagents, affording the target peptide at the reactor outlet. As Scheme 6.29 illustrates, the catch and release principle employed involved passing a solution of an *N*-protected carboxylic acid (109), a phosphonium coupling reagent (110), and diisopropylethylamine (111) through a packed bed containing polymer-supported 1-hydroxybenzotriazole (112), sequestering the carboxylic acid 109 on the solid support as the activated ester. The column was then washed with DMF in order to remove any free 109 and contaminants. The column was subsequently placed in-line with a polymer-supported DMAP (PS-DMAP) (113) column and a solid-supported sulfonic acid (PS-SO₃H) (114) column, forming the series illustrated in Scheme 6.31. At this stage, a second amino acid, a protected HCl salt (115), was passed through the 113 column,



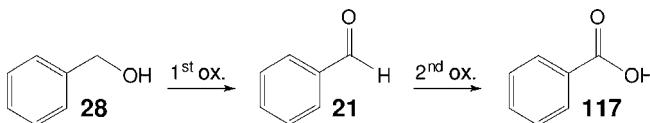
Scheme 6.29 Schematic illustrating Ley's principle of catch and release employed for the coupling of peptides.

liberating the amine, which was subsequently coupled with the active ester affording the target dipeptide **116**. Upon passing through the third and final **114** column, any unreacted amine **115** was removed from the reaction mixture and the dipeptide **116** was isolated from the reaction stream via evaporation of the solvent (DMF). The resulting reaction products were subsequently analyzed by ¹H NMR spectroscopy and LC-MS in order to evaluate the product purity, which was >95%.

In addition to demonstrating the synthesis of dipeptides, the authors also reported the preparation of a tripeptide (59% yield, 95% purity), with an overall processing time of 6–7 h compared with batch protocols which take ~24 h to complete. The authors noted that an additional advantage associated with the use of a continuous flow process is that the reagents spend very little time in contact with the supported reagents, hence racemization is negligible.

Oxidations

By exploiting the high surface-to-volume ratio obtained within a packed-bed continuous flow reactor, Watts and co-workers [62] were able to oxidize selectively an array of primary alcohols to either the aldehyde or carboxylic acid, depending on the residence time employed, demonstrating a higher degree of reaction control unattainable in conventional stirred reactor vessels (Scheme 6.30). In addition to investigating a



Scheme 6.30 Illustration of the potential reaction products obtained upon oxidation of primary alcohols.

method for the selective oxidation of aldehydes, the authors evaluated the use of a solid-supported oxidizing agent as it represented a facile means of reducing the toxic residues associated with conventional oxidants; enabling any chromium residues formed to remain supported, facilitating containment and disposal.

To perform such reactions, the authors fabricated a borosilicate glass reactor [3 mm i.d. \times 5.0 cm (length)] containing silica-supported Jones reagent (0.15 g, 0.15 mmol), a solution of benzyl alcohol (**28**) (1.0×10^{-2} M) in DCM was pumped through the packed bed and the reaction products were collected at the reactor outlet and analyzed by GC–MS. Using this approach, the authors investigated the effect of flow rate ($50\text{--}650 \mu\text{l min}^{-1}$) on the reaction products obtained and sought to identify a link between reactant residence time and product selectivity. Conducting initial investigations at $300 \mu\text{l min}^{-1}$ (equating to a reaction time of 21 s), the authors observed complete reaction of the benzyl alcohol **28**; however, the resulting reaction products contained a mixture of benzaldehyde (**21**) and benzoic acid (**117**). Increasing the reaction time to 126 s, achieved by reducing the flow rate to $50 \mu\text{l min}^{-1}$, afforded complete oxidation of the alcohol **28** to the respective carboxylic acid **117**. In order to prevent over-oxidation, the flow rate was increased to $650 \mu\text{l min}^{-1}$, with a residence time of 9.7 s, affording quantitative conversion of the alcohol **28** to aldehyde **21**. Having identified a means of selectively oxidizing **28** to **21**, an additional 14 primary alcohols were investigated in order to identify any substituent effects. As Table 6.10

Table 6.10 A selection of the oxidations performed using silica-supported Jones reagent in a flow reactor.

Alcohol	Flow rate ($\mu\text{l min}^{-1}$)	Product distribution (%)	
		Aldehyde	Carboxylic acid
Benzyl alcohol 28	650	100 (99.1) ^{a)}	0
	50	0	100 (99.6)
4-Cyanobenzyl alcohol	650	100 (98.5)	0
	50	0	100 (99.0)
Methyl-4-formylbenzyl alcohol	650	100 (99.2)	0
	50	0	100 (99.6)
4-Benzoyloxybenzyl alcohol	650	100 (99.5)	0
	50	0	100 (99.8)
4-Aminobenzyl alcohol	650	100 (100)	0
	50	0	100 (99.8)
4-Acetylbenzyl alcohol	650	100 (99.8)	0
	50	0	100 (99.8)

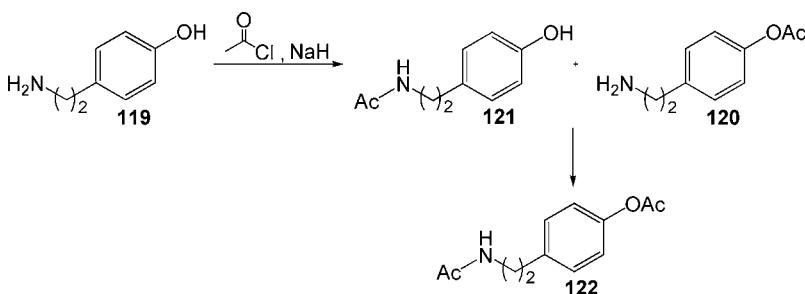
a) The number in parentheses represents the isolated yield (%).

illustrates, no substrate dependence was observed, with all alcohols readily oxidized to the respective aldehyde when employing a residence time of 9.7 s and the carboxylic acid when a reaction time of 126 s was employed. In addition to the unprecedented chemoselectivity attained using this strategy, the authors also found that the reaction products generated contained negligible quantities of Cr ($<6.9 \times 10^{-7}$ % w/w).

O-Acylations/Alkyations

With careful synthetic design, reaction pathways can be devised to waste as few atoms as possible, through, for example, the utilization of catalysts. One area of synthetic chemistry that is atom inefficient is that of protecting group chemistry, and although the use of protecting groups can increase the selectivity of a synthetic pathway, their incorporation can generate a large amount of waste upon deprotection.

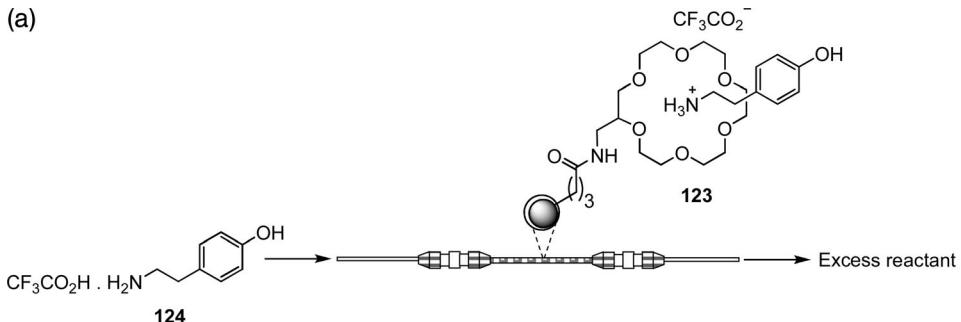
With the increasingly popular view that conventional protecting group strategies are atom inefficient, it was the aim of a recent study conducted by Wild *et al.* [63] to develop a non-covalent protecting group strategy that would allow the facile *N*-protection of bifunctional compounds, while enabling the protecting group to be recycled with ease. With this aim in mind, the authors investigated the use of crown ethers as non-covalent protecting groups, as they have been shown to sequester ammonium ions efficiently, forming a stable adduct via hydrogen bonding. To permit re-use of the crown ether, Wild *et al.* embarked upon the preparation of a solid-supported 18-crown-6 ether derivative (**118**) and subsequently demonstrated its use as a novel *N*-protecting group in a borosilicate glass continuous flow reactor. To illustrate the synthetic utility of this chemoselective technique, the *O*-acetylation of tyramine (**119**) was first conducted in the absence of a protecting group, whereby a complex reaction mixture consisting of the desired tyramine acetate (**120**) (23%), tyramine *N*-acetate (**121**) (12%), tyramine diacetate (**122**) (20%), and residual starting material **119** (45%) resulted (Scheme 6.31).



Scheme 6.31 Schematic illustrating the reaction products obtained when conducting the acetylation of tyramine (**119**) in the absence of a protecting group.

In comparison, employing the reaction strategy depicted in Scheme 6.32, whereby tyramine (**119**) was effectively *N*-protected as **123** by passing a solution of the tyramine TFA salt **124** in THF through a packed bed containing the crown ether

(a)

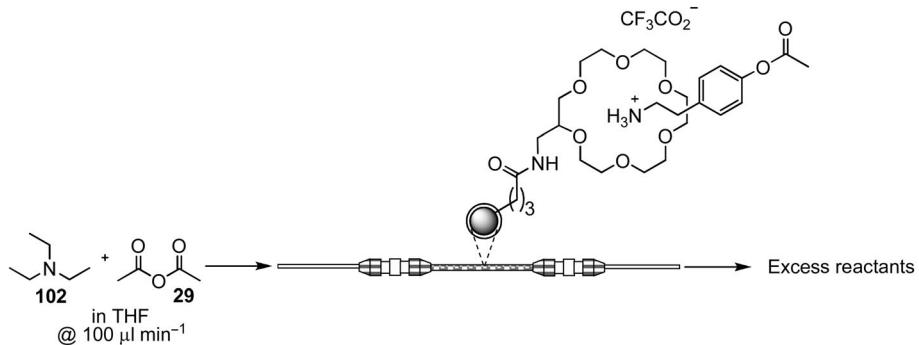


(b)

^{in THF}
@ 100 µl min⁻¹

Solvent wash (THF @ 100 µl min⁻¹)

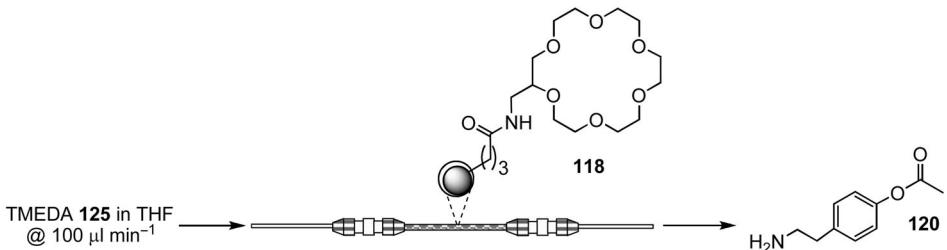
(c)



(d)

Solvent wash (THF @ 100 µl min⁻¹)

(e)



Scheme 6.32 Reaction protocol employed for the continuous flow acetylation of tyramine (**119**), using the immobilized 18-crown-6 ether derivative **118** (0.15 g, 0.16 mmol g⁻¹).

(0.15 g, 0.16 mmol g⁻¹) [step (a)], then O-acetylated by reacting the protected tyramine **123** with acetic anhydride (**29**) in the presence of an organic base (**103**) [step (c)], and subsequently simultaneously deprotected and the crown ether regenerated using a solution of *N,N,N',N'*-tetramethylethylenediamine (**125**) [step (e)], the target compound tyramine acetate (**120**) was obtained in quantitative yield (2.4×10^{-2} mmol per reaction) and selectivity.

Furthermore, the authors demonstrated the ability to protect, and react, several bifunctional compounds, obtaining esters and ethers in quantitative yield and

regioselectivity without the need for chemical derivatization; providing an atom-efficient alternative to covalent protecting group chemistry.

6.2.2.3 Solid-Supported Scavengers

A wide range of chemistries employed within the pharmaceutical industry use metal-based catalysts; however, with regulations becoming increasingly stringent with respect to the quantities of trace metals tolerated within final products, novel techniques are finding application in such reactions.

Although the field of micro reaction technology has provided overwhelming evidence to show that reactions are more efficient and products can be synthesized in higher purity compared with conventional batch procedures, trace metal contamination of the resulting compounds can still present a problem.

With this in mind, Pitts and co-workers [64] recently developed a reactor capable of removing trace metal contaminants, such as Pd, Co, Cu, and Hg, from reaction mixtures generated under continuous flow. Using the Pd-catalyzed Suzuki reaction as a model reaction, the authors screened a series of commercially available solid-supported scavengers, including silica gel, carbon, and various QuadraPure™ resins (thiourea, iminodiacetate, and aminomethylphosphonic acid), for the removal of Pd at a concentration of 60 ppm. Of the materials evaluated, thiourea-derived QuadraPure was found to be the best scavenger, removing >99% of Pd from the reaction mixture in a single pass.

Coupled with the fact that the proportion of trace metal contaminants detected within continuous flow reaction products is inherently low, due to reduced catalyst degradation, the use of a scavenger cartridge at the end of a reaction sequence represents a relatively long-term solution to this problem. Other examples of the use of solid-supported scavengers have been reported by Ley and co-workers [65], where in one example, two scavenger modules, comprising QuadraPure TU (126) and phosphane resin, were used in the synthesis of 1,4-disubstituted-1,2,3-triazoles [66], and by Watts and co-workers [67], where silica-supported copper sulfate was used for the removal of residual dithiol (ppb) in the synthesis of 1,3-dithiolanes and 1,3-dithianes.

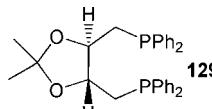
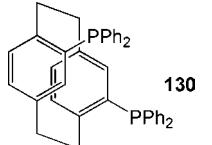
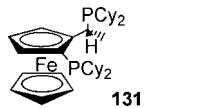
6.2.3

Gas–Liquid Phase

Owing to the complex and often dedicated equipment required to perform gas–liquid phase reactions within research laboratories, this area of synthetic chemistry is somewhat underutilized. Over the past decade, however, numerous research groups have developed an array of continuous flow reactors capable of conducting such reactions in a safe and efficient manner, including microchannel contactors, falling film micro reactors, and packed-bed reactors [68, 69].

With thin-film nickel reactors, Chambers and co-workers demonstrated the biphasic fluorination of numerous organic substrates including diketones [70], substituted toluenes [71], and more recently benzaldehyde derivatives [72], using

Table 6.11 Catalyst screening for the asymmetric hydrogenation of methyl-2-acetamidoacrylate (**127**).

Ligand	Yield (%)	<i>ee</i> (%)	<i>ee</i> (%) (lit.)
 129	38	57 (<i>R</i>)	67
 130	95	98.5 (<i>R</i>)	80
 131	0.7	70 (<i>R</i>)	86

10% elemental fluorine in a carrier stream of nitrogen and an aprotic or acidic media. Using this approach, the authors observed increases in reaction selectivity, conversion, and product purity, along with noting the ability to scale reactions with ease [73]. This use of elemental fluorine is also advantageous as it is readily available, cost-effective, and, when handled correctly, provides a viable alternative to hazardous reagents such as HF.

More recently, de Bellefon and co-workers [74] demonstrated the asymmetric hydrogenation of methyl-2-acetamidoacrylate (**127**) to **128**, within a glass capillary reactor (530 µm i.d.). Employing MeOH as the reaction solvent, H₂ (1–5 bar), and a residence time of 1 min, the chiral phosphines (*R,R*)-DIOP (**129**), (*R*)-PHANPHOS (**130**), and (*R,S*)-Cy,Cy-JOSIPHOS (**131**) were evaluated as chiral promoters in the model reaction (Table 6.11). Using this approach, the authors were able to screen the catalysts using only 100 µl of reaction mixture, readily identifying **130** as the most suitable catalyst for the transformation.

6.2.4

Gas–Liquid–Solid Phase

One of the most interesting and green continuous flow techniques to be developed emerged from the ability to perform triphasic reactions, whereby a gas–liquid phase is pumped through a packed bed containing a heterogeneous catalyst. Using this

approach, Darvas and co-workers [75] developed an automated system capable of conducting continuous flow hydrogenations (H-cube®). In addition to dramatically reducing the time taken to perform common hydrogenations, typically from hours to minutes, the authors were also able to reduce the hazards associated with hydrogenations by generating the H₂ *in situ* via the electrolysis of distilled water, removing the need for H₂ cylinders within the research laboratory. To perform such reactions, a continuous liquid stream is introduced into the reactor, where it is mixed with H₂, prior to passing through the catalyst cartridge or packed-bed reactor. The reaction product is then collected at the outlet and the solvent removed to afford the hydrogenated product. Under the aforementioned conditions, a series of hydrogenations have been performed, as illustrated in Table 6.12, including nitro groups, alkenes, oximes, and nitriles, along with debenzylations and deuteration.

Table 6.12 A selection of the model reactions performed in the continuous flow hydrogenator^{a)}.

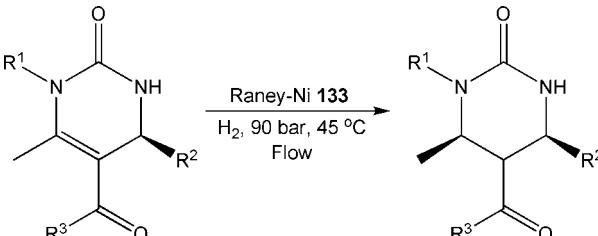
Substrate	Product	Catalyst	Temperature (°C)	Yield (%) ^{b)}
		10% Pd/C 132 25		95
		10% Pd/C 132 80		89
		10% Pd/C 132 25		94
		10% Pd/C 132 25		85
		Raney-Ni 133 70 ^{c)}		88
		Raney-Ni 133 70 ^{c)}		99

a) Unless otherwise stated, reactions were conducted at 1 bar.

b) -Isolated yields.

c) 70 bar.

Table 6.13 A selection of the diastereoselective hydrogenations performed under flow conditions.

	R¹	R²	R³	Yield (%)^{a)}	dr^{b)}	Purity (%)^{c)}
PhCH ₂	Ph	OCH ₃	85	>20:1	>98	
EtOCOCH ₂	Ph	CH ₃	83	19:1	95	
Et	(CH ₂) ₂ Ph	CH ₃	82	17:1	>98	
EtOCOCH ₂	Ph	OCH ₃	86	19:1	95	
MeO(CH ₂) ₂	(CH ₂) ₂ Ph	OCH ₃	87	16:1	>98	

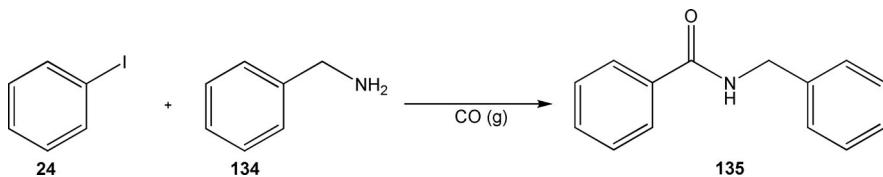
a) Isolated yield.

b) *dr* determined by LC–MS–ELSD.

c) Purity after preparative RP-HPLC (LC–MS–UV–ELSD).

Employing the H-cube, Schaus and co-workers [76] subsequently demonstrated the ability to perform a series of diastereoselective hydrogenations, under continuous flow, as a key step in a predominantly batch-led investigation. Initial investigations focused on the identification of a suitable catalyst [Pd/C (132), Pt/C, Pt/Al₂O₃, and Raney-Ni (133)], solvent system, and reaction temperature for the hydrogenation and, after extensive studies, the authors identified 133, MeOH, and 45 °C as the optimal reaction conditions. Employing a packed-bed reactor [3.3 cm (length)], the authors pumped a solution of dihydropyrimidone, in MeOH, through the reactor at a flow rate of 500 µl min⁻¹ to afford the respective *cis,cis*-tetrahydropyrimidone. The resulting reaction mixture was then analyzed by LC–MS–UV–ELSD, which confirmed complete conversion of the starting material to product. Evaporation of the reaction solvent afforded the target *cis,cis*-tetrahydropyrimidone in excellent yield and purity without the need for additional purification (Table 6.13). To afford the respective *trans,trans*-tetrahydropyrimidones, the *cis,cis*-derivatives were stirred in a methanolic solution of K₂CO₃ (1 mol%) for up to 3 days and the product was isolated by elution with EtOAc through a silica plug.

As an extension to a biphasic system reported previously, de Mello and co-workers [77] described the incorporation of a silica-supported Pd catalyst into a fluidic system and investigated the gas–solid–liquid carbonylation reaction of an aryl halide (24), an amine (134) and carbon monoxide (Scheme 6.33), to afford the respective *N*-benzylbenzamide (135). To conduct the reaction, a solution of aryl halide and amine, in THF, was pumped through the reactor at a flow rate of 10 µl min⁻¹, where it was mixed with CO (2 sccm) in a T-mixer, prior to passing through the packed-bed reactor [1 mm i.d. × 45 cm (length)]. Maintaining the system at 75 °C,



Scheme 6.33 An example of multi-phase carbonylation reactions performed under continuous flow.

coupled with a residence time of 12 min, the authors isolated **135** in 63% yield. The reactions of several aryl halides were subsequently investigated, affording five benzamide derivatives with yields ranging from 23 to 99%.

6.2.5

Biocatalysis

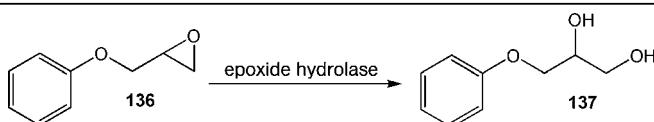
6.2.5.1 Liquid Phase

One of the areas to benefit from the speed and efficiency of reaction optimization afforded by continuous flow processes is that of biochemical transformations involving enzymes, whole cells, or lysates [78]. Biocatalysis is an important area of synthetic chemistry that has been extensively studied for application within industry for the synthesis of amino acids, lipids, sugars, pharmaceuticals, and fine chemicals; however, the long-term instability of biocatalysts precludes application within industry.

An early example by Reetz and co-workers [79] demonstrated the evaluation of a series of biocatalysts for the hydrolytic kinetic resolution of chiral glycidyl phenyl ethers. Employing a fused-silica reactor, the authors developed an integrated reaction system capable of performing biocatalytic hydrolysis, along with separation and detection of the reaction products. Using the enantioselective hydrolysis of 2-phenoxymethyloxirane (**136**) to 3-phenoxypropane-1,2-diol (**137**) as a model reaction (Table 6.14), the authors evaluated the biocatalytic activity of a series of epoxide

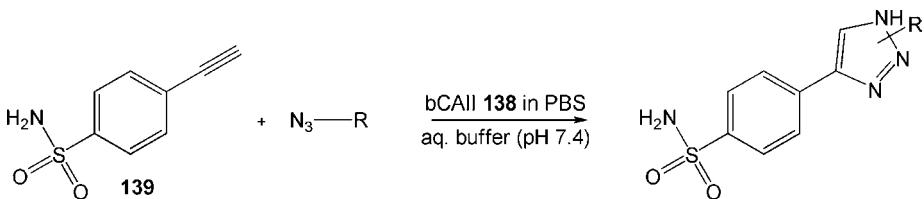
Table 6.14 Results obtained for the evaluation of epoxide hydrolases in a microfluidic reactor ($n = 3$).

Enzyme	Conversion (%)	<i>ee</i> diol (%)	<i>E</i>	
			1	2
Wild type	38	49		4
LW080	22	90		23
LW086	43	84		21
LW144	28	93		37
LW202	41	95		101



hydrolase mutants, with reactants manipulated by application of a vacuum. They investigated a series of epoxide hydrolase mutants from *Aspergillus niger* (whole cell), and also the wild type (cell lysates). As Table 6.14 illustrates, a selectivity factor of $E = 4$ was obtained for the wild type versus $E = 101$ for mutant LW202. Using this approach, the authors were able to screen the enzymes rapidly using only 10 μl of a 0.02 mg ml⁻¹ solution of enzyme and 10 μl of 0.75 mM epoxide 136 solution with the potential to follow the kinetics of a reaction, enabling a wealth of information to be collected from minute quantities of substrate and enzymes. In addition, the use of online reaction monitoring leads to a reduction in the quantity of waste generated compared with conventional analytical methodology.

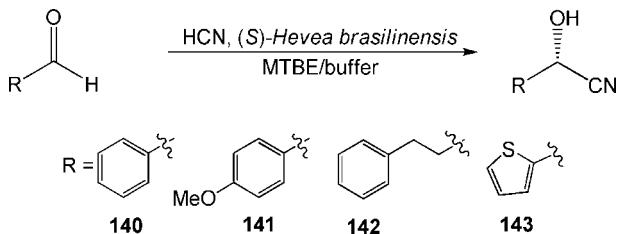
In a second screening example, Tseng and co-workers [80] demonstrated the use of a PDMS microfluidic reactor to screen bovine carbonic anhydrase II (bCAII) (138) for activity towards the click reaction of the acetylene 139 and 10 azides (Scheme 6.34). The micro reactor consisted of several components, including a nanoliter rotary mixer, a chaotic mixer, and a microfluidic multiplexer, which enabled discrete aliquots of reactants to be introduced into the micro reaction channel, allowing multiple reactions to be performed in parallel.



Scheme 6.34 General reaction scheme illustrating biocatalyzed click reactions evaluated under flow.

Using this approach, 32 *in situ* click reactions were performed between the acetylene 139 and 10 azides (a) in the presence of bCAII (138), (b) in the presence of 138 and an inhibitor, and (c) in the absence of 138. Two blank solutions were also employed containing only 138 and a PBS solution. Once the reaction mixtures had been mixed and deposited into the respective micro well, they were heated at 37 °C for 40 h prior to analysis by LC–MS. In addition to the speed of processing, the use of a micro reactor is advantageous for screening applications, such as this, as the technique affords a dramatic reduction in the quantities of reactants and enzymes required. For example, a typical micro reaction employs 4 μl of reaction mixture (19 μg of 138, 2.4 nmol of 139, 3.6 nmol of azide) compared with 100 μl (94 μg of 138, 6.0 nmol of 139, 40.0 nmol of azide) in a batch protocol; affording a 2–12-fold reduction depending on the reactant.

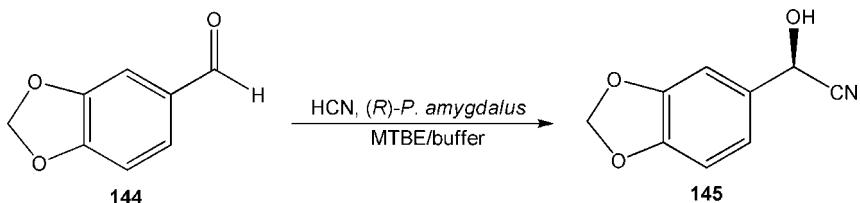
A more recent example of enzyme-catalyzed synthesis performed in micro reactors was reported by Rutjes and co-workers [81], who demonstrated the use of crude enzyme lysates, containing hydroxynitrile lyase, for the enantioselective synthesis of cyanohydrins. Employing a wet-etched borosilicate glass micro reaction channel, containing pillars to promote biphasic laminar flow, the authors evaluated the



Scheme 6.35 Biphasic enzyme-catalyzed (*S*)-cyanohydrin formation.

synthesis (*S*)-cyanohydrins under continuous flow (Scheme 6.35). To perform the reaction, an organic phase containing an aldehyde (0.23 M) and anisole (0.18 M) was introduced into the reactor from one inlet and an aqueous solution of KCN (14) (0.23 M) and crude lysates [(*S*)-HbHNL] (10% v/v) were introduced from a second inlet. The reaction products were collected in dilute HCl (1.0 M)–MTBE, which acted as a quench solution, and the MTBE layer was diluted with IPA and hexane prior to analysis by chiral HPLC. Under stoichiometric conditions, the authors found that the optimal conversions for all aldehydes were obtained with a residence time of 12.5 min (equivalent to a flow rate of $0.25 \mu\text{l min}^{-1}$) affording the (*S*)-cyanohydrins in yields of 65% (140), 37% (141), 90% (142), and 30% (143). In the case of aromatic substrates, the authors obtained enantioselectivities >95%; however, the aliphatic substrate 142 afforded lower enantioselectivity of ~85%.

The authors subsequently developed an automated platform capable of screening reaction conditions such as residence time and the aqueous-to-organic ratio, whereby conversion of aldehyde 144 to (*R*)-cyanohydrin (145) (Scheme 6.36), in the presence of 4% v/v *Prunus amygdalus* [(*R*)-PaHNL, EC 4.2.10] was determined off-line by GC and the enantioselectivity was quantified using chiral HPLC analysis. Employing reaction times ranging from 1 to 5 min and an aqueous-to-organic ratio from 1:1 to 5:1, the authors performed 58 reactions in only 4 h, leading to a dramatic reduction in substrate consumption compared with conventional screening protocols.



Scheme 6.36 Model reaction used in the development of an automated screening platform for the optimization of biocatalytic reactions.

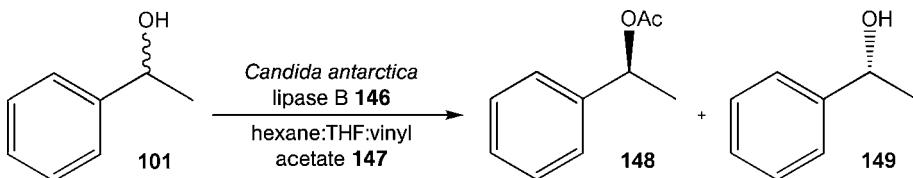
In addition to concerns associated with the cost of enzymes and their efficient re-use with respect to preparative-scale synthesis, the difficulties associated with the recovery and re-use of enzyme cofactors, which are frequently more expensive than

the enzymes themselves, has also contributed to the limited uptake of biocatalysis in industry. A potential solution to this issue was presented by Kenis and co-workers [82] and consisted of a PDMS microfluidic system in which nicotinamide cofactors were electrochemically regenerated. The authors observed that by employing co-flowing laminar streams, comprising a buffer and a reagent, regeneration of the cofactor could be achieved at the surface of a gold electrode. Employing the conversion of achiral pyruvate to L-lactate in the presence of the enzyme lactate dehydrogenase, the authors were able to demonstrate efficient enzyme/cofactor regeneration affording a turnover number of 75.6 h^{-1} .

6.2.5.2 Immobilized Biocatalytic Flow Reactors

Due to their cost, instability, and limited longevity, enzymes are not widely employed in production-scale syntheses; however, through their immobilization and incorporation into flow reactors, biocatalysts have the potential to be employed in the synthesis of high-value products. Although the use of microfabricated reactors for the screening of biocatalysts for organic synthesis is a relatively new area of research, the field has been quick to employ those techniques developed for the use of solid-supported catalysts under continuous flow, a feature that is illustrated by the diverse array of immobilization techniques reported to date.

Utilizing a similar approach to that demonstrated for solid-supported catalysts, Urge *et al.* [83] recently demonstrated the enantioselective acylation of racemic alcohols in a continuous flow packed-bed reactor (Scheme 6.37). Employing *Candida antarctica* lipase B (CaLB) (146) (0.40 g) and pumping a solution of *rac*-phenyl-1-ethanol (101) (10 mg ml⁻¹) in hexane–THF–vinyl acetate (147) (2:1:1) at a flow rate of 100 µl min⁻¹ (at 25 °C), the authors found that the reactor reached a steady state after 30 min of operation. Under the aforementioned conditions, the (*R*)-acetate 148 was obtained in 50% conversion and 99.2% ee and the residual (*S*)-alcohol 149 in 98.9% ee with a residence time of 8.2 min. Analogous results were obtained in batch, but a reaction time of 24 h was required in order to obtain 50% conversion of 101 to 148.

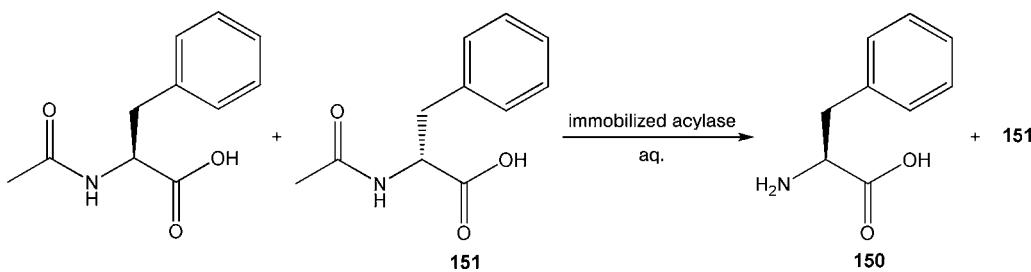


Scheme 6.37 Schematic illustrating the enantioselective acylation of *rac*-phenyl-1-ethanol (101).

Having developed a technique for the rapid evaluation of immobilized biocatalysts, the authors subsequently compared a series of lipase enzymes for the model reaction depicted in Scheme 6.39, whereby CaLB (146), lipase *Pseudomonas cepacia* IM and Amano lipase AK were found to afford the highest throughputs of 10.2, 10.2, and 10.6 µmol 148 min⁻¹ g⁻¹, respectively. The synthetic applicability of the kinetic

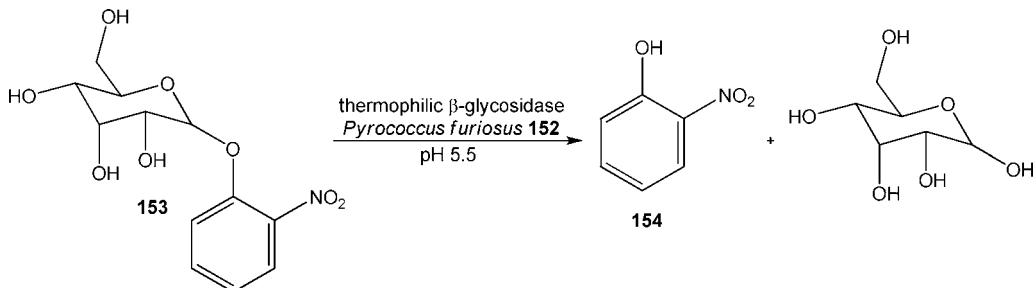
resolution was subsequently demonstrated on a preparative scale, whereby 20 ml of solutions of each racemic alcohol were passed through the bioreactor (3.3 h). It was found that analogous results were obtained during the reaction optimization and preparative stages. In addition to immobilized enzymes, the technique was also found to be useful for lyophilized enzymes and represents a synthetically viable approach to the kinetic resolution of racemic alcohols.

As a means of further increasing the efficiency of biocatalytic transformations conducted under flow, Maeda and co-workers [84] reported the use of an integrated microfluidic system which consisted of an immobilized enzyme reactor, containing L-aminoacylase, and an in-line micro extraction device. Using this approach, the authors developed a system that was capable of performing the optical resolution of racemic amino acids while being able to recycle the biocatalyst efficiently. As depicted in Scheme 6.38, the first step of the process was the enzyme-catalyzed enantioselective hydrolysis of a racemic mixture of acetyl-D,L-phenylalanine to afford L-phenylalanine (**150**) (99.2–99.9% ee) and unreacted acetyl-D-phenylalanine (**151**). Acidification of the reaction products, prior to the addition of EtOAc, permitted extraction of **150** into the aqueous stream, whereas **151** remained in the organic fraction (84–92% efficiency). Employing the optimized reaction conditions of a flow rate of $0.5 \mu\text{l min}^{-1}$ for the enzymatic reaction and $2.0 \mu\text{l min}^{-1}$ for the liquid–liquid extraction, the authors were able to resolve 240 nmol h⁻¹ of the racemate.



Scheme 6.38 Illustration of the optical resolution of *rac*-acetylphenylalanine conducted under continuous flow.

In 2007, Nidetzky and co-workers [85] demonstrated the use of wall coating as a means of immobilizing the thermophilic β -glycosidase enzyme within a PDMS micro reaction channel [350 μm (width) \times 250 μm (depth) \times 64 mm (length)] containing silicic acid as a filler. Wall coating of the reactor was achieved via silanization of the channel walls, followed by derivatization of the surface with glutaraldehyde. In a final step, the protein was immobilized by pumping a solution of thermophilic β -glycosidase (**152**) (7 ml, 95 $\mu\text{g l}^{-1}$) through the reactor for <15 h. Employing the hydrolysis of 2-nitrophenyl- β -D-galactopyranoside (**153**) (1.3×10^{-2} M, pH 5.5) as a model reaction, the authors evaluated the immobilized enzyme reactor (Scheme 6.39). Using the generation of 2-nitrophenol (**154**) (detection at 405 nm) as a reaction indicator, the authors found that heating the reactor to 80 °C allowed the



Scheme 6.39 Biocatalytic hydrolysis of 2-nitrophenyl- β -D-galactopyranoside (**153**) in a wall-coated micro reactor.

continuous hydrolysis of the substrate **153**. In addition, the authors employed the same reactor to determine the flow rate dependence on the hydrolysis of lactose.

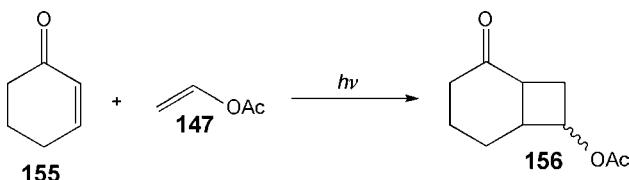
6.2.6

Photochemistry

Photochemistry affords a facile means of performing synthetically useful transformations, such as alkene isomerizations, proton abstractions, cycloadditions, and bond cleavages, and although the approach has been shown to be of use within research and development laboratories, the technique is marred with problems when attempts to scale up successful reactions are made, namely how to irradiate large reaction vessels. Through the use of continuous flow reactors, several authors have demonstrated the ability to employ commercial light sources for high-throughput syntheses, attaining excellent quantum yields compared with conventional batch reactors.

6.2.6.1 Homogeneous Photochemical Reactions

Utilizing a commercially available micro reactor, fabricated from Foturan® glass, Ryu and co-workers [86] evaluated a series of [2 + 2] cycloadditions as a means of reducing the reaction times conventionally associated with the synthetic transformation. Using a high-pressure mercury lamp (300 W), the reaction of cyclohex-2-enone (**155**) with vinyl acetate (**147**) (Scheme 6.40), to afford the cycloadduct **156**, was used to compare photochemical efficiency within the micro reactor [1000 μ m (width) \times 500 μ m (depth)] and a conventional batch reactor (10 ml).



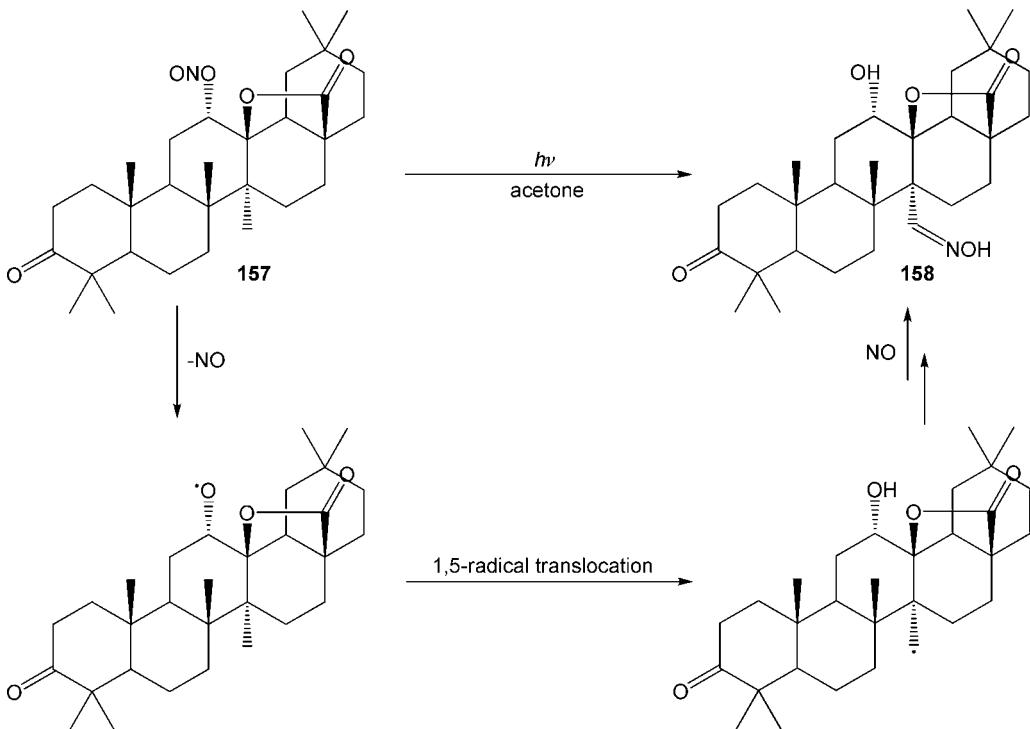
Scheme 6.40 Photochemical [2 + 2] cycloaddition of cyclohex-2-enone (**155**) with vinyl acetate (**147**).

Table 6.15 The photochemical [2 + 2] cycloadditions conducted in a Foturan® micro reactor.

Substituted cyclohex-2-enone	Vinylic substrate	Cycloadduct	Irradiation time (h)	Yield (%)
			2	70
			3.2	62
			3.2	64
			3.2	67

Based on literature precedent, the batch reactor was irradiated for 2 h, affording only 8% of **156**; however, on employing a residence time of 2 h within the micro reactor and a flow rate of $8.3 \mu\text{L min}^{-1}$, the authors obtained adduct **156** in 88% yield. The enhanced irradiation efficiency obtained within the flow reactor therefore allowed a dramatic increase in reaction yield, coupled with a reduction in the overall reaction time required. With this in mind, the authors investigated the generality of the technique and, as Table 6.15 illustrates, moderate to good yields were obtained for a range of substituted cyclohex-2-enones and vinylic compounds.

In a second example, Ryu and co-workers [87, 88] demonstrated the nitrite photolysis (Barton reaction) of the steroidal substrate **157** to afford **158** (Scheme 6.41), a key intermediate in the synthesis of an endothelin receptor antagonist, using a 300 W high-pressure mercury lamp. Maintaining a gap of 7.5 cm between the stainless-steel/glass reactor [channel dimensions = $1000 \mu\text{m}$ (width) $\times 107 \mu\text{m}$ (depth) $\times 2.2 \text{ m}$ (length)] and the light source, an acetone solution of the nitrite **157** (9 mM) and pyridine (0.2 equiv.) was pumped through the reactor at a flow rate of $33 \mu\text{L min}^{-1}$ to afford the rearranged product **158** in 59% yield (determined by HPLC). The authors suggested that undesirable heating of the reactor was preventing further increases in yield and subsequently replaced the light source with a 15 W black light, placed 3.0 cm from the reactor, affording the oxime **158** in 21% yield (6 min). By increasing the residence time to 12 min, the authors obtained the target compound **158** in 71% yield (23.7 Wh). The throughput of the reactor was subsequently



Scheme 6.41 Schematic illustrating the Barton reaction of steroid 157 to oxime 158.

increased by employing two serially connected micro reactors (16 channels each), which afforded a throughput of 0.16 g h^{-1} of 158.

With numerous researchers investigating the advantages associated with the thermal or biocatalytic control of asymmetric reactions, Ichimura and co-workers [89] considered the potential of photochemical asymmetric syntheses performed in continuous flow reactors. To investigate the hypothesis, the authors employed the asymmetric photochemical addition of MeOH to *(R)*- $(+)$ -*(Z)*-limonene (159) as a model reaction, comparing three quartz micro reactors, with a standard laboratory cell as a means of highlighting the synthetic potential of this approach.

Employing a low pressure Hg lamp (λ 254 nm), the authors evaluated the effect of channel geometry on photon efficiency and diastereomeric excess (*de*) (see Table 6.16) by pumping a methanolic solution of 159 (25 mM) and toluene (10 mM) through the various quartz reactors. Initial investigations were conducted using a micro reactor with channel dimensions of $500 \mu\text{m}$ (width) \times $300 \mu\text{m}$ (depth) and were focused on determining the effect of irradiation time on the conversion of 159. Using this approach, a linear relationship between irradiation time and conversion was observed; however, the authors observed a decrease in *de* with prolonged exposure times. Based on this observation, a series of microchannel geometries were subsequently evaluated and it was found that shallow channels, typically $<40 \mu\text{m}$, afforded

Table 6.16 Summary of the results obtained for the asymmetric addition of MeOH to (*R*)-(+)-(Z)-limonene (**159**) with an irradiation time of 36 s.

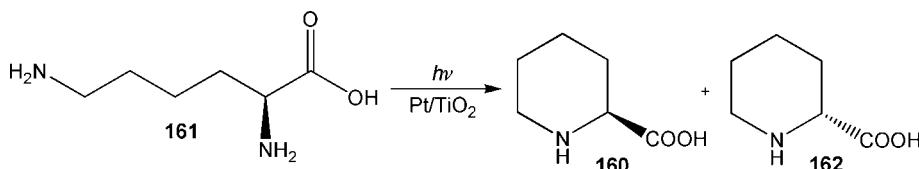
Reactor	Dimensions	Photon efficiency	de (%)
Batch	100 μm × 3 mm	0.06	28.7
Micro	500 μm × 300 μm	0.11	30.6
Micro	400 μm × 40 μm	0.27	29.4
Micro	200 μm × 20 μm	0.29	30.0

increased photon efficiency, which was attributed to illumination homogeneity. Furthermore, a slight increase in *de* was observed in all flow experiments compared with the batch cell, a feature that was explained by the suppression of side reactions within the continuous flow reactors.

6.2.6.2 Heterogeneous Photochemical Reactions

Continuous flow photochemistry is not limited to homogeneous reactions, however, with many synthetically useful transformations conducted utilizing catalytic processes. While miniaturized catalytic photochemistry initially focused on the photodegradation of substrates [90, 91], more recently researchers have reported the use of such systems for a series of common organic reactions.

An example of a photochemical cyclization was reported by Takei *et al.* [92], who demonstrated the synthesis of L-pipecolinic acid (**160**) from an aqueous solution of L-lysine (**161**), as illustrated in Scheme 6.42. To achieve this photocatalytic transformation, the authors fabricated a Pyrex micro reactor in which the channel cover plate was coated with a 300 nm layer of anatase TiO₂ (100 nm particles), to afford a titania-coated micro reactor (TCM); the titania film was subsequently loaded with platinum (0.2 wt%), by photodeposition, to enable the TCM to be used

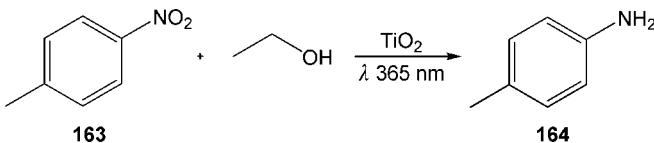


Scheme 6.42 Schematic illustrating the photocatalytic synthesis of L- and D-pipecolinic acid (**160** and **162**, respectively).

for redox-combined photosynthesis. A solution of **161** (2.0 mM) was subsequently irradiated using a high-pressure mercury lamp (110 mW cm^{-1}) and the resulting reaction mixture was analyzed by chiral HPLC in order to determine the proportion of **161** converted to L- and D-pipecolinic acid (**160** and **162**, respectively).

Employing a flow rate of $1 \mu\text{l min}^{-1}$ and a residence time of 0.86 min, the authors obtained 87% conversion of **161**, exhibiting 22% selectivity for pipecolinic acid (**160** and **162**) and 14% L-pipecolinic acid (**160**). For comparative purposes, the authors also performed the reaction in batch, employing 2 wt% Pt-loaded TiO₂ particles, which afforded the same surface-to-volume ratio of catalyst as the TCM, where a 70 times longer reaction time (60 min) was required in order to obtain analogous results to the TCM. The authors concluded that the increased reaction efficiency, within the TCM, was attributable to the efficient irradiation of the reaction mixture; however, for a true comparison they noted that measurement of the quantum yield of each system would be required.

Using a quartz micro reactor [channel dimensions = 500 μm (width) \times 100 μm (depth) \times 0.4 cm (length)] in which the bottom and sides of the micro channel were coated with TiO₂ (anatase), Matsushita *et al.* [93] investigated the photocatalytic reduction of 4-nitrotoluene (**163**) (Scheme 6.43) using a UV LED (λ 365 nm, 2.2 mW cm^{-2}). As the photoreduction requires a corresponding oxidation step to occur, a series of alcohols were evaluated to act as potential solvents/reactants.

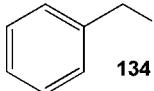
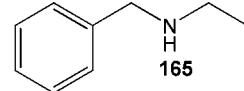


Scheme 6.43 Photocatalytic reduction conducted by Matsushita *et al.* [93] using a quartz micro reactor.

Due to the kinetic instability of the methoxy radical, the authors found the reductions to be more successful when conducted in EtOH. In addition, it was found that saturating the reactant stream with nitrogen, thus excluding dissolved oxygen, promoted the reaction as the electrons in the conduction band of the excited TiO₂ layer were not captured by oxygen. With this knowledge in hand, the authors evaluated the efficiency of the TiO₂-coated quartz reactor in the reduction of 4-nitrotoluene (**163**) to afford 4-aminotoluene (**164**), as a function of reactant residence time within the micro reactor. Employing **163** in N₂-saturated EtOH ($1.0 \times 10^{-4} \text{ M}$), in the absence of light, 0% conversion to **164** was observed; this was subsequently increased to 8.3% with an irradiation time of 10 s and finally to 45.7% when a residence time of 60 s was employed.

Matsushita *et al.* subsequently demonstrated the ability to N-alkylate amines under continuous flow within the aforementioned micro reactor. As Table 6.17 illustrates, increasing the surface-to-volume ratio by reducing the channel depth affords a more efficient reaction system and, compared with batch operation where no N-ethylbenzylamine (**165**) was obtained using TiO₂, excellent yields of **165** were obtained with

Table 6.17 Effect of illuminated specific surface area for the ethylation of benzylamine (**134**).

		
Channel depth (μm)	Illuminated surface area ($\text{m}^2 \text{ m}^{-3}$)	Yield (%)
300	7.3×10^3	98
500	6.0×10^3	94
1000	4.0×10^3	70

irradiation times as low as 1.5 min. It was also encouraging to see that the use of different solvent systems also enabled the authors to access *N*-methyl and *N*-propyl derivatives, providing a facile route to *N*-alkylamines with no competing dialkylation products detected.

Although photochemical transformations provide the synthetic chemist with an attractive, atom-efficient approach to the synthesis of complex molecules, the inability to increase the scale of reactions beyond the bench-scale has hampered the adoption of this technique. As can be seen from the examples described below, the use of continuous flow reactors affords a facile means of increasing the throughput of photochemical reactions while employing laboratory-scale light sources such as low-energy LEDs.

6.3

Process Intensification Achieved Through the Use of Flow Reactors

Conventional synthetic processes undergo several stages of up-scaling as they progress along the route from chemical development to production, and at each point problems may be encountered that prevent the compound or process from being developed further. Successful scale-up was defined by Paul [94] as “plant operation that achieved the same conversion, selectivity and product distribution as defined in the laboratory.” Difficulties are often encountered, however, when attempting to scale up a synthetic process; these include practical problems such as the need to meter reactant addition and the efficient removal of heat, along with unexpected physical changes in the process as a result of surface-to-volume effects. As such, the process of scale-up is costly from a development perspective and time consuming due to the need for continual reoptimization as a result of changes such as reactor shape and volume [95]. It is these factors that has led to the burgeoning level of research into the use of continuous flow processes, which have the ability to be employed in various numbers in order to meet the production volumes of each stage of chemical development.

Through a process known as scale-out, parallelization, or numbering-up [96], continuous flow reactors enable a chemical process to be investigated on a small scale

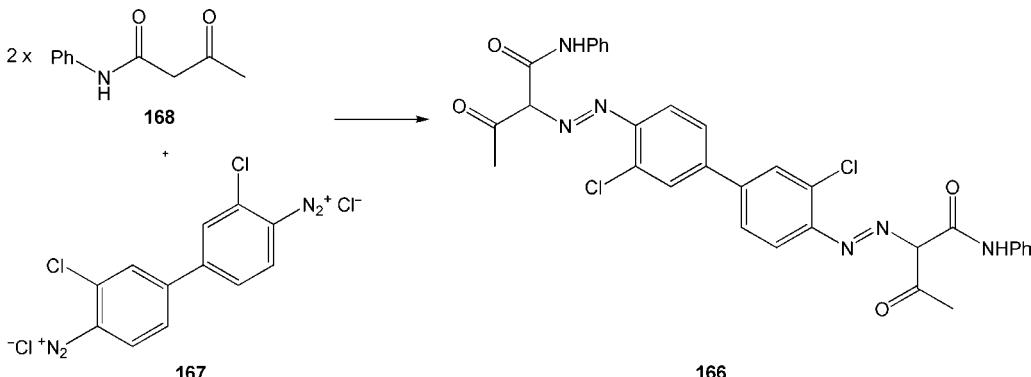
using a single reactor. The process information generated from this reaction screening can then be used on a pilot scale via the use of multiple reaction units in parallel. Further increases in scale, to attain production quantities, can then be accessed through the construction of reactor banks. Consequently, at no stage does the process require reoptimization, with production systems operated under conditions identical with those initially identified within the research and development laboratory. As a result, thorough and rapid screening of a reaction can be performed using small quantities of reactants prior to translating the reaction to production, without the risk of failure to scale, significantly reducing the volume of waste generated and energy required during a chemical campaign. With this in mind, the following section describes a series of key synthetic examples that have employed the theories associated with continuous flow reactors for the large-scale preparation of organic compounds.

6.3.1

Synthesis of Azo Dyes

One of the first examples of micro reactors used for manufacturing was reported by Cellular Process Chemistry (CPC) [97] and involved a three-step process for the synthesis of a diazo pigment: (a) diazotization, (b) coupling, and (c) pigmentation. As discontinuous batch reactions are notorious for affording a broad particle size distribution, with even agglomerated and aggregated particles resulting, the pigment industry requires a means of preparing dyes with narrow particle distributions so as to obtain the highest possible pigment quality, that is, glossiness, transparency, and tinctorial power. Up to this point it was believed that the manipulation of slurries and suspensions would be problematic within microstructured reactors and consequently this example was an important illustration of the operational capabilities of continuous flow reactor methodology. One of the most important findings of this investigation was the improved color properties obtained in the micro reactor compared with batch methodology, arising from the narrower particle size distribution of the pigment (Clariant's PV-Fast Yellow H2GR) generated under continuous flow; attributed to rapid and efficient mixing. The authors also demonstrated an improvement in pigment quality when scaling the reactions from the laboratory (60 ml h^{-1}) to a continuous flow pilot plant (301 h^{-1}) owing to a more efficient dosing mechanism.

Pennemann *et al.* [98] subsequently published data confirming this to be a general observation, reporting the semicontinuous flow synthesis of Yellow 12 (**166**), from the preformed diazonium salt **167** and nucleophile **168**, using an interdigital micro mixer (Scheme 6.44). Employing an interdigital micro mixer, diazotized 3,3'-dichlorobenzidine (**167**) in dilute HCl (0.12 M) and acetanilide (**168**) in aqueous NaOH (89) (0.24 M, 2 equiv.) were mixed using a range of flow rates (10, 30, and 50 ml min^{-1}) and the reaction products were collected in a beaker of distilled water. After 5 min, a resin solution was added to the beaker and stirring continued for an additional 16 h prior to filtration and assessment of the pigment quality, using a commercially available sample of **166** as a benchmark. Using this approach, the authors obtained a



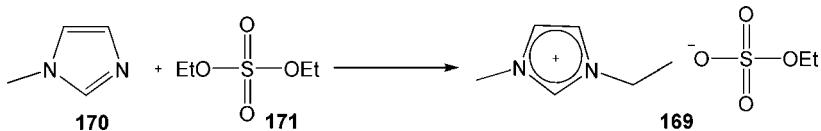
Scheme 6.44 Synthetic protocol employed for the flow synthesis of the pigment Yellow 12 (**166**).

monomodal particle size distribution compared with the bimodal distribution obtained in the commercial sample. As would be expected, no changes in hue and tinctorial power were observed as a result of employing continuous flow; however, the transparency and glossiness were improved by 66 and 73%, respectively. Consequently, with respect to the pigment industry, micro reaction technology has the potential not only increase to product quality but also to reduce operational costs and increase process safety.

6.3.2

Synthesis of Ionic Liquids Under Continuous Flow

Ionic liquids (ILs), in particular room temperature ionic liquids (RTILs), have attracted a great deal of interest from the synthetic community over the past decade, owing largely to the diverse array of physical properties accessible via tuning of the ionic components [99]. Of particular importance from a sustainability standpoint is the ability to recover the solvents, a property that results from their thermal stability and low vapor pressure. Furthermore, even the synthesis of RTILs from fructose, itself a renewable feedstock, has been demonstrated [100]; the synthesis of these materials and solvents is, however, far from simplistic. The traditional synthetic approach is based on the use of stirred-tank reactors, either batch or semi-batch; however, owing to the fast reaction kinetics and exothermic nature of the reaction, heat management limits the scale of the process and has an effect on the product purity, characterized by a yellow coloration. Therefore, as a means of reducing the risk of thermal runaway and increasing productivity, in 2007 Renken *et al.* [101] reported the use of a microstructured reactor (MSR) for the continuous flow synthesis of ethylmethylimidazole ethylsulfate [EMIM][EtSO₄] (**169**) using a solvent-free alkylation reaction ($\Delta H_r = -100 \text{ kJ mol}^{-1}$). Using this two-pronged approach, the authors were able to intensify the process and prepare the target compound **169** with a throughput of 2.0 mol h^{-1} (specific performance = $4 \text{ kg m}^{-3} \text{ s}^{-1}$), increasing the process efficiency by three orders of magnitude compared with conventional methodology.



Scheme 6.45 Synthetic protocol employed for the preparation of $[EMIM][EtSO_4]$ (169).

As Scheme 6.45 illustrates, the procedure involved the combination of methylimidazole (170) with diethyl sulfate (171) to afford the target material 169 under solvent-free conditions, within a reactor comprising a caterpillar micro mixer [channel dimensions = 600 μm (width) \times 600 μm (depth)] and a microstructured reactor containing stacked plates with parallel micro channels [channel dimensions = 1000 μm (width) \times 650 μm (depth) \times 12.5 cm (length), volume = 10.8 ml]. The MSR was then connected to two tubular reactors ($R_2 = 1750 \mu\text{m}$ i.d. (volume = 6.7 ml) and $R_3 = 4370 \mu\text{m}$ i.d. (volume = 13.8 ml)), both of which were housed within separate thermostated baths maintained at 70 and 95 $^{\circ}\text{C}$, respectively. The product was subsequently reduced to ambient temperature by passing through a heat exchanger prior to collection, then analysis by HPLC was used to quantify product purity. Using this approach, the authors were able to attain 99.8% conversion to 169 with a production capacity of 0.5 kg h^{-1} and a volumetric throughput of 0.41 h^{-1} ; consequently, the reaction set-up described is under long-term evaluation by an industrial partner.

6.3.3

DSM Nitration

Harnessing the safety and processing advantages associated with continuous flow methodology, DSM recently disclosed their investigations into the preparation of the pharmaceutical naproxinod (172) (Figure 6.2) [102], obtaining a pilot-scale process capable of delivering hundreds of kilograms of material; developed in conjunction with Corning [103].

As nitration reactions are notoriously difficult to perform on a commercial scale, the main challenge for the researchers was to develop a process that was capable of generating production volumes that were in the range of tonnes per day. The authors commented that although the reaction enthalpy is moderate, it is the potential exothermic decomposition of the product 172 that represents a safety risk. Furthermore, side reactions can also arise from the oxidation of the starting material, hence careful control of the reaction conditions is paramount on a production scale.

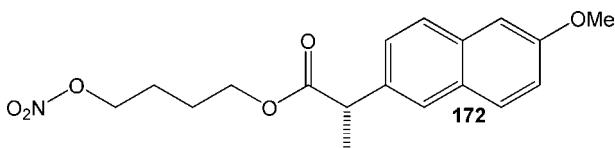
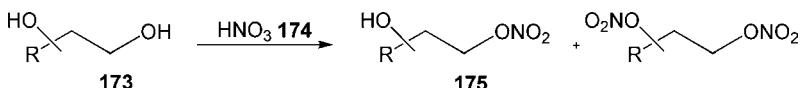


Figure 6.2 The pharmaceutical agent naproxinod (172), synthesized on a pilot scale using MRT.

To perform the organic nitration, the substrate **173** and solvent were brought together in a glass micro structure that afforded a fine emulsion [104]; this was followed by the addition of neat HNO_3 (**174**), at which point the reaction started immediately (Scheme 6.46). After the reaction had proceeded for the desired period of time, water was added to stop the reaction, prior to neutralization with NaOH ; to control the release of heat into the micro reactor, neutralization was performed in stages. Using this approach, the authors employed a reactor volume of 150 ml, through which they were able to produce 13 kg h^{-1} of the target compound **175**, attaining higher levels of reaction control and hence safety compared with the conventional batch protocol.



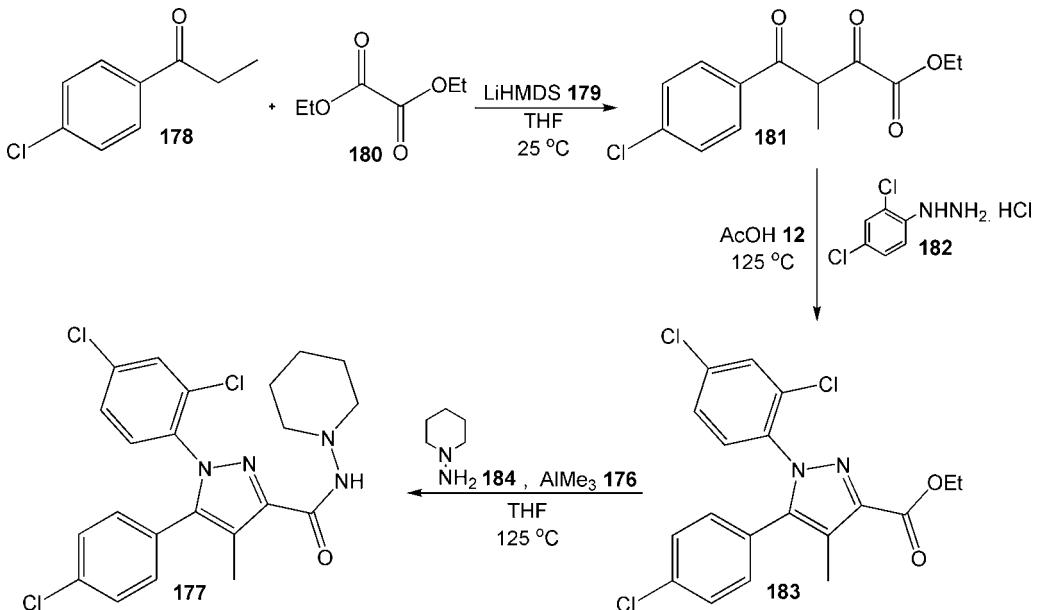
Scheme 6.46 Illustration of the selective nitration performed by DSM under continuous flow conditions.

Having demonstrated the viability of the system, no scale-up was required in order to meet the production targets; the authors simply employed a production unit comprising eight micro reactors operated under the aforementioned conditions. Using this production unit affords DSM the capacity to produce 100 kg h^{-1} of **175**, which is equivalent to an annual production volume of 800 t. This investigation therefore serves to illustrate the feasibility of performing what are considered to be hazardous reactions on a large scale through the use of continuous flow reactors.

6.3.4

Synthesis of Rimonabant

In addition to the continuous flow synthesis of fine chemicals and solvents, significant efforts have been made towards the large-scale synthesis of pharmaceutical substances using continuous flow methodology. Having previously demonstrated the use of AlMe_3 (**176**) for the efficient synthesis of amides from a series of simple methyl and ethyl esters [105], Seeberger and co-workers [106] extended their investigations to include the synthesis of the anti-obesity drug rimonabant (**177**) (SR141716) under continuous flow. As Scheme 6.47 illustrates, the first step of the flow synthesis of **177** involved the treatment of 4-chloropropiophenone (**178**) with LiHMDS (**179**) for 1 min prior to the addition of ethyl oxalate (**180**) at 50°C where it reacted for 5 min; after work-up and purification, the resulting β -keto ester **181** was isolated in 70% yield. Treatment of **181** with 4-chlorophenylhydrazine·HCl (**182**), afforded the pyrazole **183** in 80% yield with a residence time of 16 min. The final step of the synthesis involved the formation of an amide bond, which was achieved via the treatment of **183** with **176** and 1-aminopiperidine (**184**) in THF at 125°C for 2 min. Using this approach, the authors reported the isolation of **177** in an overall yield of 49%, demonstrating the continuous synthesis of drug molecules on a gram scale.

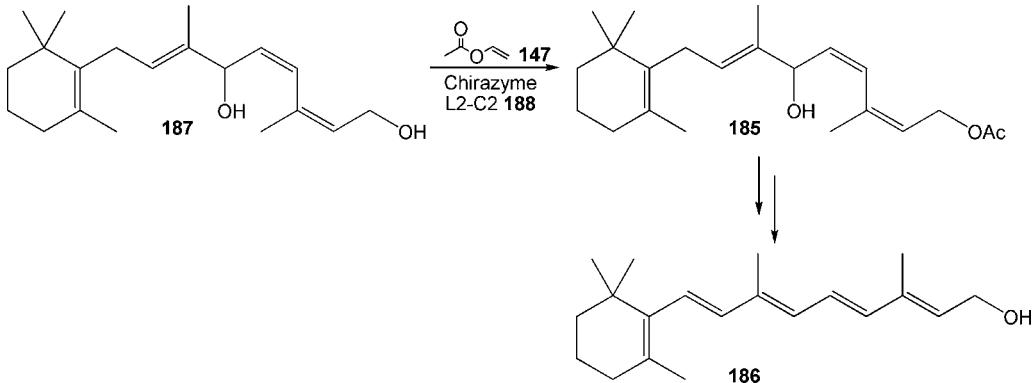


Scheme 6.47 Synthetic route employed for the continuous flow synthesis of rimonabant (177) on a gram scale.

6.3.5

Biocatalytic Synthesis of Vitamin A

In 1999, Orsat *et al.* [107, 108] discussed the lipase-catalyzed synthesis of (*E*)-retinyl acetate (185), an intermediate used in the synthesis of retinol (vitamin A) (186) (Scheme 6.48). Pumping a solution of the alcohol 187, in vinyl acetate (147) (10% w/v), through a packed bed containing 5.0 g of biocatalyst 188, the authors were



Scheme 6.48 Synthetic strategy for the synthesis of (*E*)-retinyl acetate (185), an intermediate in the synthesis of retinol (vitamin A) (186).

able to generate 49 g day⁻¹ of **185** (>97% selectivity). In order to employ the strategy in a mini-plant (120 g of biocatalyst **188**), the authors found that the long-term stability of the enzyme had to be addressed as a decrease in conversion was observed after a few days of operation. The source of inactivation was found to be the presence of impurities in the feedstock, the effect of which was reduced by the incorporation of a precolumn containing EDTA tetrasodium salt coupled with the addition of Et₃N (**102**) (100 ppm) and hydroquinone (100 ppm) to the feedstock. Using this strategy and a feedstock containing 30% w/w **186** in **147**-acetone (30:70), the system was operated at 10 g min⁻¹ of **185** for over 100 days before the precolumn required replacing. Under the conditions described, 99% conversion of **186** to **185** was observed with >97% selectivity for the primary hydroxyl group and a throughput of 1.6 kg ay⁻¹. Isolation of the target product **185** was achieved by distillation of acetaldehyde (**165**), followed by rectification of residual **147**, permitting its re-use in the process.

6.4

Conclusions and Outlook

To date, the development of sustainable synthetic processes has focused on improving the cleanliness and efficiency of chemical production; however, little has been done to address these issues from a research and development perspective. Through the employment of emerging technologies, such as micro- and meso-flow reactors, there is an opportunity to develop sustainable methods from an early stage in the chemical process, rather than the current approach of retrospectively improving processes that fail to meet the current ideals of atom economy, reduced waste generation, energy efficiency, and safety. Furthermore, the ability to employ the same flow reactor in all stages of the development process provides researchers with a tool capable of bridging the gap between the laboratory and production, removing the risks currently associated with scale-up.

From an industrial perspective, however, for companies to implement such a new technology it must first be shown to provide a fiscal advantage over continuing to use conventional techniques. The development of commercially available systems for laboratory use is therefore of paramount importance if this technology is going to progress from the research laboratory to widespread application within the chemical sector. Whether or not flow reactors will replace round-bottomed flasks and stirred-tank reactors remains to be seen; however, the current uptake of the technology within both industry and academia appears promising.

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7**Synthesis Without Protecting Groups**

Reinhard W. Hoffmann

7.1**The Present Use of Protecting Groups**

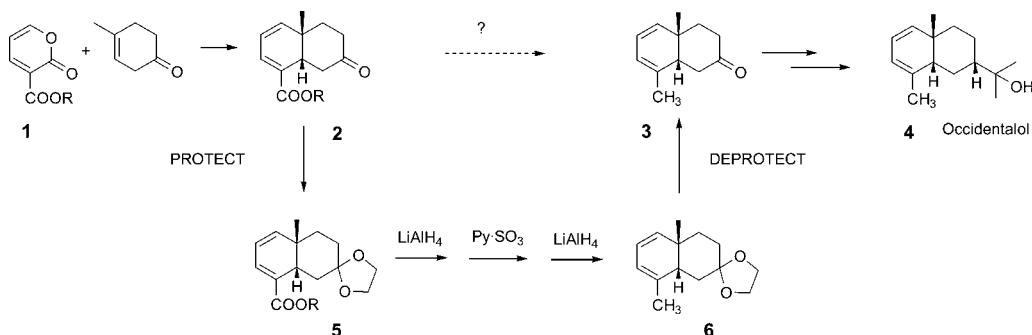
The use of protecting groups in organic synthesis has become so widespread that the necessity to do so is rarely reflected upon. Among the situations that lead chemists to use protecting groups, one is an (external) incompatibility between a reagent and a functional group present in the substrate. This may be illustrated with Watt and Corey's synthesis of occidentalol (Scheme 7.1) [1].

The *cis*-decalin core of occidentalol (**4**) was assembled by a Diels–Alder addition using methyl α -pyronecarboxylate (**1**) as diene. The ester group of **1** was destined to become the methyl group of occidentalol. In order to effect a selective reduction of **2** to **3**, the keto group of **2** had to be protected as an acetal, because a method for chemoselective reduction of an ester in the presence of a keto group was and still is not available. After effecting the reduction of **5** to **6**, the keto group was deprotected to allow the final conversion of **3** to occidentalol. The reason for introducing a protecting group was the incompatibility of the reducing conditions with the aim of maintaining a keto group in the molecule, that is, an incompatibility between a functional group and reagent(s).

In addition to an external incompatibility between a functional group and a reagent, an internal incompatibility of two functional groups in an intermediate may also be the cause of the introduction of protecting groups. A hypothetical scheme addresses the conversion of the aminoalkene **7** into the amino alcohol **9**. This suggests an ozonolysis of **7** to generate the amino ketone **8** on the way to the alcohol **9** (Scheme 7.2). However, amino ketones are amphoteric molecules [2] with a high tendency of these two functional groups to react with each other, in this case to give a tetrahydropyridine (**10**). This will be a dead end in the route to the amino-alcohol **9**.

In order to overcome this internal incompatibility, one tends to protect the amino function in **7** as an amide, whereupon the reaction sequence can be carried out requiring at the end a final deprotection of the amine to reach the target **9**.

The most common cause of the use of protecting groups is the necessity to differentiate between two (or more) similar functional groups. Let it be alcohol groups in a polyol. For instance, a differentiation between the primary and secondary

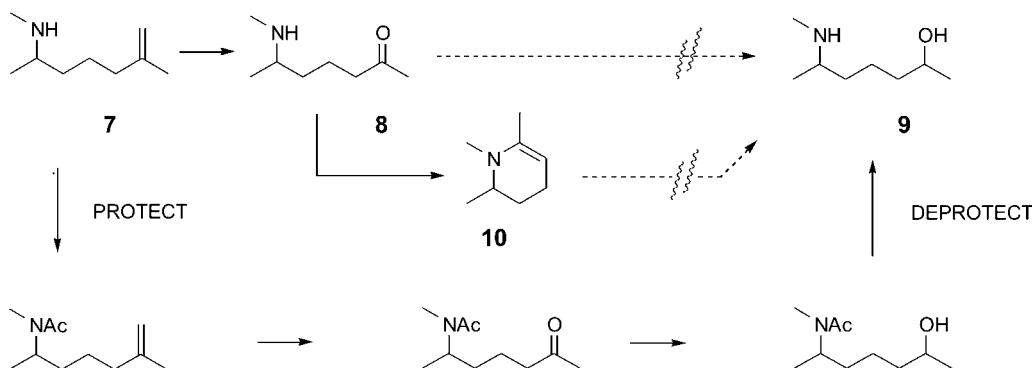
**Scheme 7.1** External incompatibility of functional group and reagent.

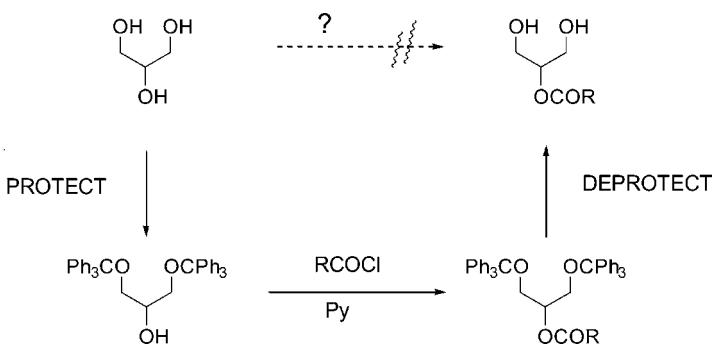
alcohol functions has been effected long ago, by selective protection of the primary alcohol functions. The reagent, triphenylmethyl chloride, exerts for steric reasons sufficient chemoselectivity to allow such a differentiation (Scheme 7.3) [3].

Thus a selective tritylation of the primary hydroxyl functions of glycerol allows for a subsequent clean acylation of the secondary alcohol group. In all the typical examples shown in Schemes 7.1–7.3, it is the introduction of a protecting group that compensates for our inability to carry out transformations with a desirable level of chemoselectivity or regioselectivity. The price to pay are the two extra steps for the attachment and later removal of the protecting group. These two extra steps lengthen a synthesis in a principally unnecessary manner [4] and, considering the input of material and the generation of side products, detract from the efficiency of the overall synthesis effort.

When hydroxyl groups of a polyol have to be differentiated, the situation in Scheme 7.3 is the favorable one, in which the more reactive primary alcohol have to be blocked. When the task calls for blocking of a less reactive secondary alcohol function, a protective group dance is staged with an even higher number of protecting group management steps. This can be seen in the example shown in Scheme 7.4 [5].

It is easy to project that differentiation of a higher number of hydroxyl groups (functional groups) in a polyol such as one faces in carbohydrate chemistry may

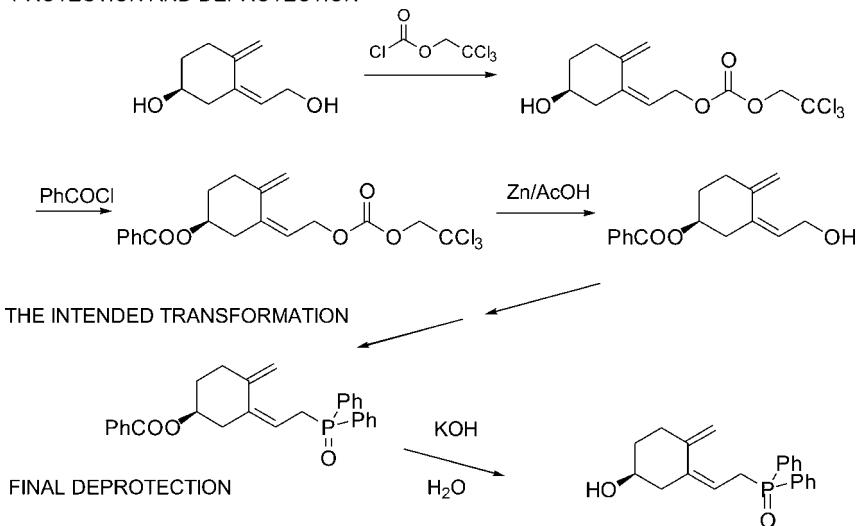
**Scheme 7.2** Internal incompatibility between two functional groups.

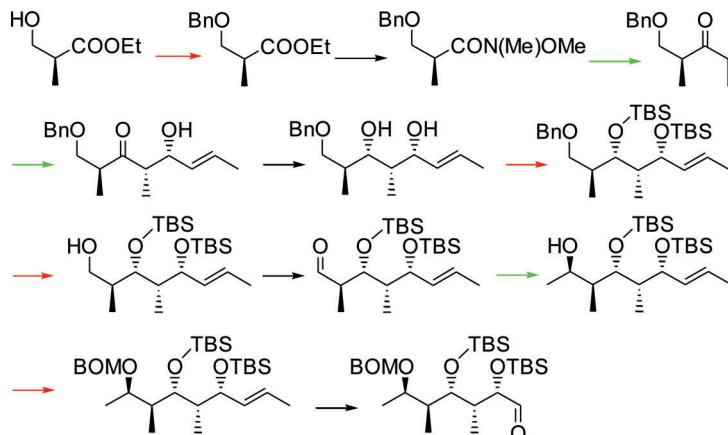
**Scheme 7.3** Differentiation of functional groups by selective protection.

evolve into an opera of protecting group steps. It has, therefore, become customary to protect hydroxyl groups (reactive functional groups) in a synthesis as soon as they have been generated; see the sequence in Scheme 7.5 [6].

This scheme encompasses four protecting group management steps (marked in red) to effect three skeleton-building operations (marked in green), which entailed four redox operations. The overall step economy [7] of this scheme is indeed rather low. On analysis of the individual protecting group steps in this scheme, one recognizes that the initially introduced benzyl group serves as a *medium-term protecting group*, as it has to come off after lasting for five steps. The *tert*-butyldimethylsilyl (TBS) groups serve as *long-term protecting groups*, which probably will stay in place until the very end of the total synthetic endeavor. They have to be orthogonal to the benzyl group, allowing its earlier removal without being affected themselves.

PROTECTION AND DEPROTECTION

**Scheme 7.4** Protecting group dance to block a less reactive hydroxyl group.

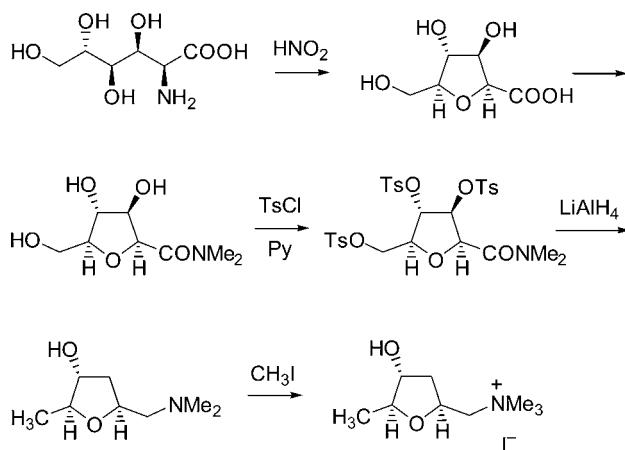
**Scheme 7.5** Immediate protection of alcohol groups for later differentiation.

The BOM group likewise is orthogonal to the TBS group and serves to differentiate that particular hydroxyl group to be unveiled at later stage of the synthesis.

7.2

Protecting Group-Free Synthesis?

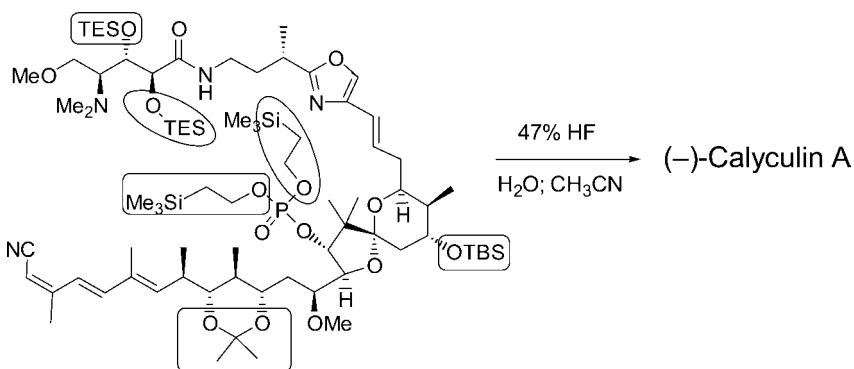
Seeing all this effort that goes into protecting group manipulations, one is led to query whether all this is really necessary. Would protecting group-free synthesis schemes [8] not be much more preferable? In fact, protecting group-free syntheses are not so rare in the synthetic endeavors published in the 1950s to 1970s [9]; see, for instance, Hardeger and Lohse's synthesis of muscarine (Scheme 7.6) [10].

**Scheme 7.6** Protecting group-free synthesis of muscarine from 1957.

Chemists in the last century were rather thrifty in using protecting groups, a situation that lasted until the introduction of the silyl [11] and *p*-methoxybenzyl [12] protecting groups. These groups were so easy and reliable to apply and to remove that even inexperienced undergraduate students could successfully handle them. From that moment on, protecting groups were applied more and more indiscriminately in organic synthesis. One is led to the conclusion that the use of protecting groups went out of control by the end of the last century. It is therefore no surprise that a backlash started, making protecting group-free synthesis [8] a programmatic goal [13].

Such a goal is not utopian, as Nature demonstrates that it can be done: the biosynthesis of even the most complex natural products occurs without recourse to protecting groups! And, in fact, in the twenty-first century there is an increasing number of total syntheses [14] that are free of protecting groups. It is now time to analyze and to discuss the strategies for achieving protecting group-free syntheses.

Such a discussion can be guided by the purpose that individual protecting groups serve in synthesis. It will be realized that *long-term protecting groups* will be the most difficult to dispense with. Long-term protecting groups guarantee that individual functional groups, the number of which increases during a total synthesis, can be differentiated. As we will see the use of long-term protecting groups for decades to come, their impact on the step count of a synthesis has to be considered. In the epochal synthesis of palytoxincarboxylic acid, 43 functional groups were present at the end of the synthesis carrying 42 protecting groups comprising eight different protecting group types such as ethers, esters, and silyl groups [15]. It took five concluding steps to deprotect the multitude of functional groups and to liberate the carefully constructed target. There is nothing wrong in using different long-term protecting groups in a particular synthesis. However, they should be chosen such that they can be removed in a single deprotection step. This is called a *convergent* protecting group scheme, as illustrated in Scheme 7.7 [16].



TES = Et₃Si; TBS = 'BuMe₂Si

Scheme 7.7 Convergent protecting group scheme.

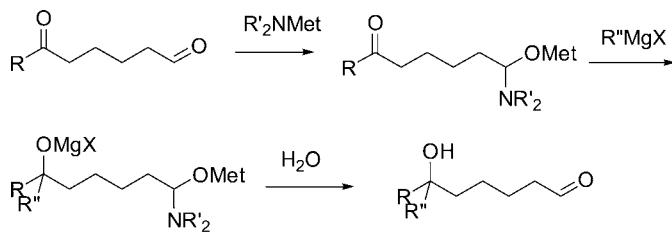
A convergent protecting group scheme does not preclude that the introduction of each protecting group causes one extra step in the synthesis, but guarantees that global deprotection can be carried out in just a single operation.

7.3

Use of *In Situ* Protections in Lieu of Short-Term Protecting Groups

In terms of protection group economy, *short-term protecting groups* are the most aggravating, since they are introduced just to allow a single synthesis step to be carried out, after the execution of which they are immediately removed. This suggests combining all these three steps into a one-pot operation, which then turns into an *in situ* protecting group scheme.

This strategy has been applied to protect an aldehyde function in an ketoaldehyde, allowing a selective transformation at the keto function (Scheme 7.8) [17].

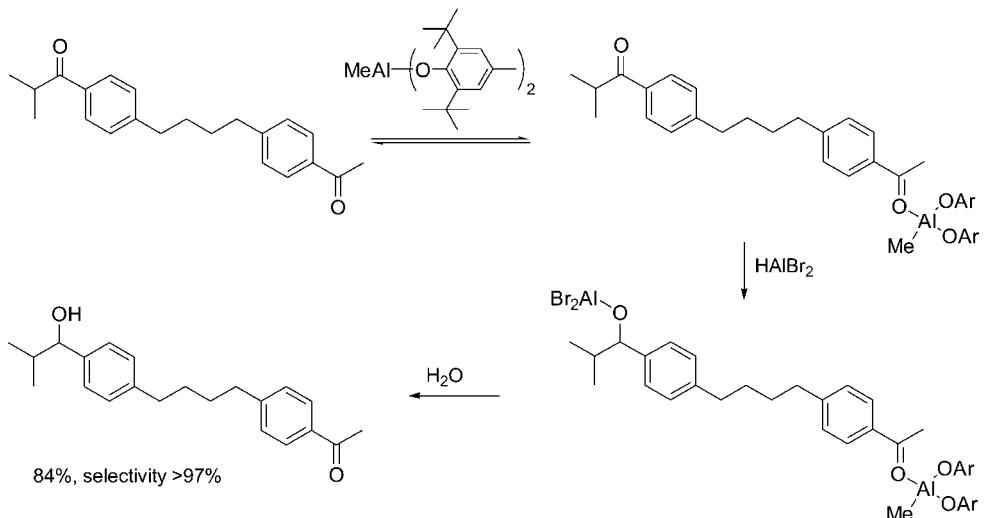


Met: $(\text{R}'_2\text{N})_3\text{Ti}$; Me_2Al ; Li

Scheme 7.8 *In situ* protection of an aldehyde in the presence of a ketone function’.

The one-pot sequence is initiated by addition of a metal amide, which adds into the aldehyde function to give a metal-chelated stable hemiaminal. At this point, the intended reaction – addition of a Grignard reagent – at the keto function can be carried out. On aqueous workup the aldehyde is liberated, thus allowing the desired transformation without requiring separate protection and deprotection steps. Another example, shown in Scheme 7.9, involves an *in situ* differentiation of two keto functions in a diketone. Here, the sterically more accessible carbonyl group is complexed selectively by a sterically demanding Lewis acid, allowing subsequent reduction of the sterically more hindered ketone with high selectivity. Aqueous workup liberates the alcohol generated and also the non-reduced ketone function. [18]

A further common situation with *in situ* protection applies when an acidic group in the substrate interferes with an intended transformation elsewhere in the molecule. In this case, it is advantageous just to deprotonate the acidic group *in situ* by addition of 1 equiv. of LiHMDS, methylolithium, or methyl-Grignard reagent. On final aqueous workup, the initial acidic group is regenerated [19], allowing an overall protecting group-free synthesis as shown in Scheme 7.10.

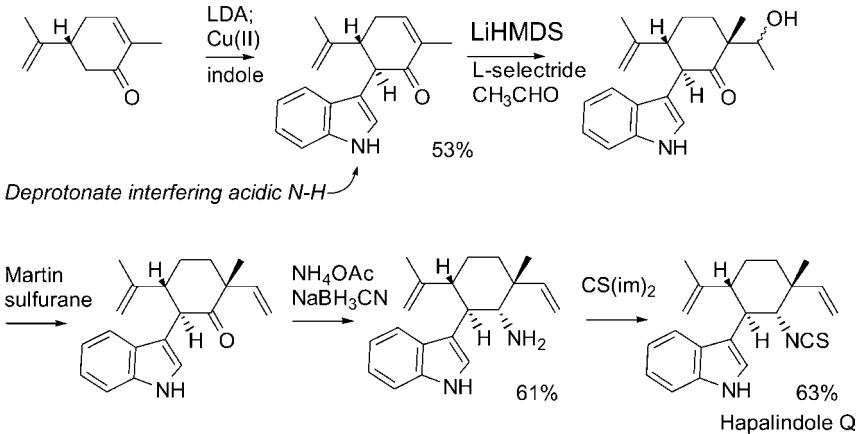


Scheme 7.9 *In situ* blocking of a less hindered carbonyl group during reduction of a more hindered ketone.

7.4

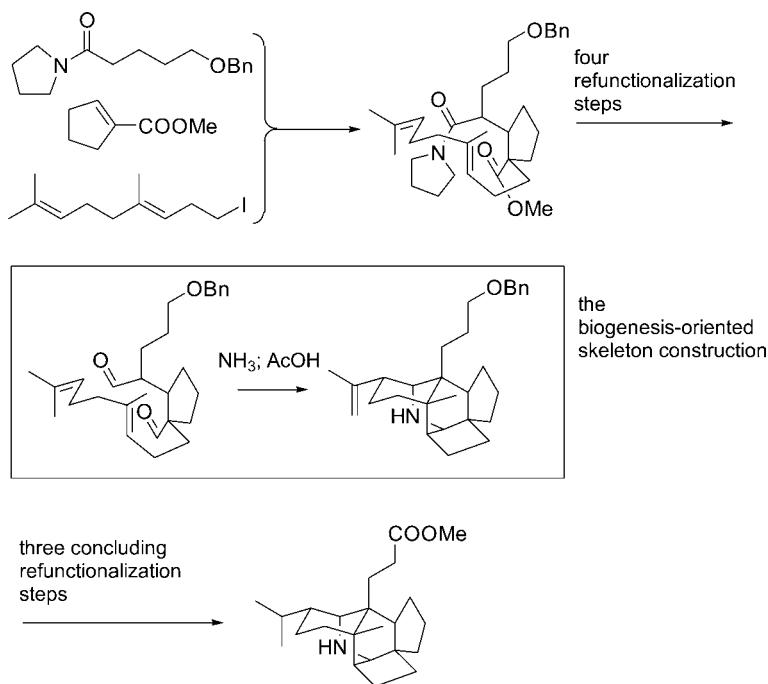
Follow Nature's Biogenetic Routes to Avoid Protecting Groups

With reference to other situations in which protecting groups are commonly used, it takes more strategic considerations to render them dispensable. To develop some guidelines, it is appropriate to look again at Nature and to point out that Nature



Scheme 7.10 *In situ* deprotonation of an interfering acidic group allowing an overall protecting group-free synthesis of hapalindole Q.

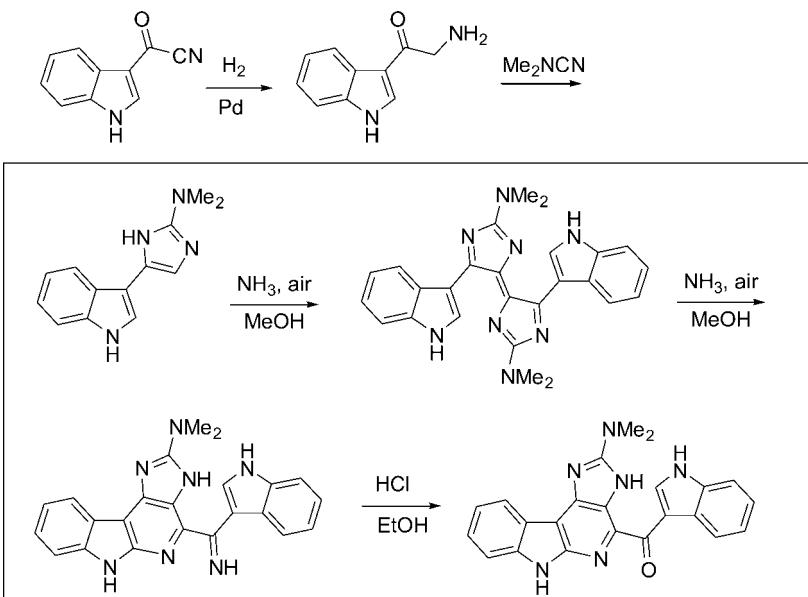
performs biosynthesis without protecting groups. It becomes clear that performing synthesis in a biomimetic manner should ultimately allow protecting group-free synthesis. The general state of biomimetic synthesis of natural products is such [20] that just the key step of biosynthesis is reproduced in an *in vitro* synthesis, whereas the steps after and the steps before this key step are carried out in the ordinary way. Hence, although the key (biomimetic) step of the synthesis does not require the presence of protecting groups, the generation of the precursor molecule and the end point of the synthesis sequence may involve protecting groups in the usual format. This can be seen in the (biomimetic) synthesis of the daphniphylline alkaloids by Heathcock (Scheme 7.11) [21].



Scheme 7.11 Biomimetic construction of the daphniphylline skeleton.

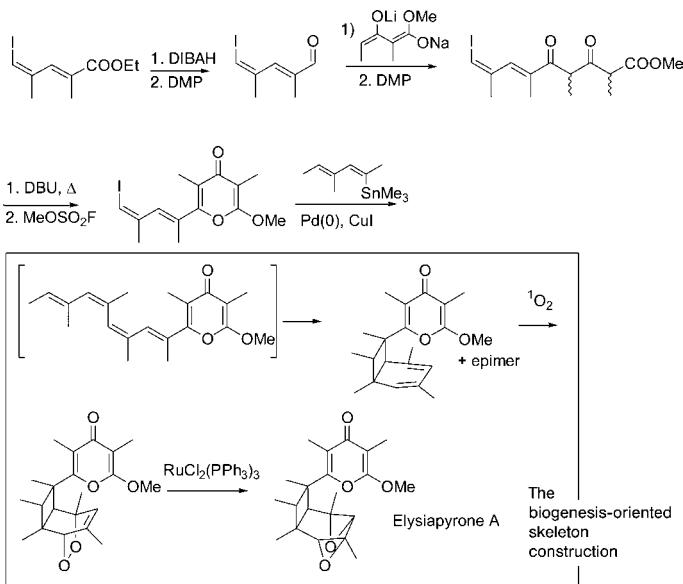
In this outstanding synthesis, a single protecting group was used. It was not required by the biomimetic tetracyclization step, but served rather to carry the ultimate ester group through the synthesis as a (benzyl-protected) alcohol, that is, to differentiate it from another ester group occurring in the precursor preparation.

Nevertheless, biomimetic syntheses have the potential to be free of protecting groups overall, as seen in the examples in Schemes 7.12 [22] and 7.13 [23]. In the syntheses of both grossularine and of elysiapyrone, the key steps of biosynthesis were electrocyclic reactions, dehydrogenations, and oxidations, reaction types that render it easy to reproduce them in biomimetic synthesis without recourse to protecting groups.



The biogenesis-oriented skeleton construction

Scheme 7.12 Biomimetic synthesis of grossularine-1.

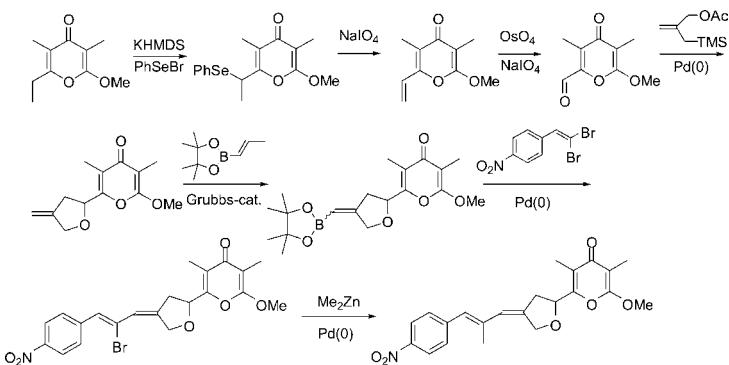


Scheme 7.13 Biomimetic synthesis of elysiapyrone A.

7.5

Apply Functional Group-Tolerant Construction Reactions to Avoid Protecting Groups

However, to achieve an overall protecting group-free synthesis, the main issue is that of chemoselectivity, the ability to use functional group-tolerant construction reactions. Looking at the early steps in Trauner and co-workers' elysiapyrone synthesis [23] (Scheme 7.13), one notes the use of the Stille coupling, a typical representative of transition metal-catalyzed reactions that have a notoriously high functional group tolerance. A particular example is given by Baldwin and co-workers' synthesis of aureothin [24] (Scheme 7.14), a synthesis in which all skeleton-forming steps are carried out by transition metal catalysis. This made it easy to achieve the goal "protecting group-free synthesis."



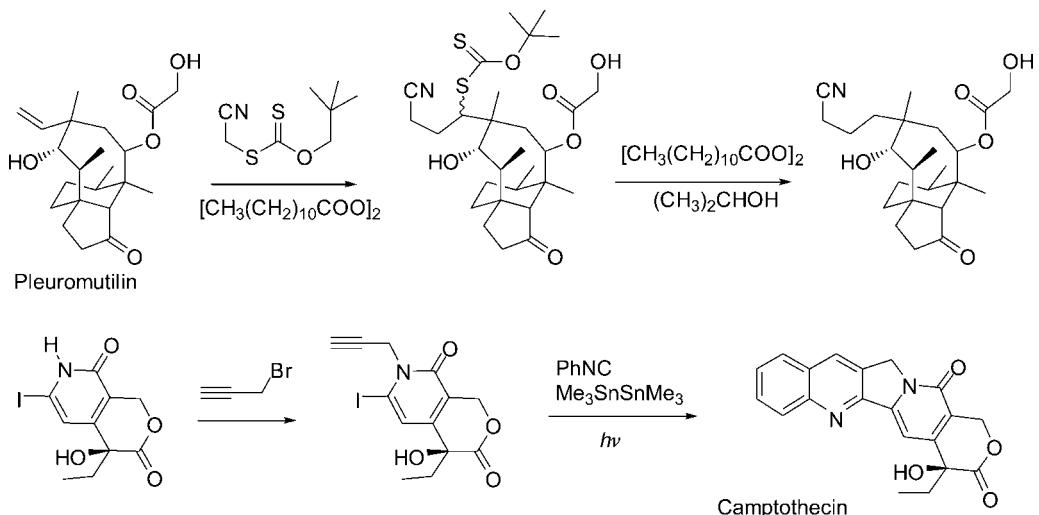
Scheme 7.14 Protecting group-free synthesis of aureothin.

There is yet another class of skeleton-forming reactions that is functional group tolerant, namely free radical chain reactions. Obviously they lend themselves to realizing protecting group-free syntheses, as has been repeatedly pointed out [25, 26]. The potential of free radical chain reactions in this regard can be illustrated with a sequence to modify the structure of pleuromutilin [26] or the final step of Curran *et al.*'s camptothecin synthesis [27], neither of which required any protecting groups (Scheme 7.15).

7.6

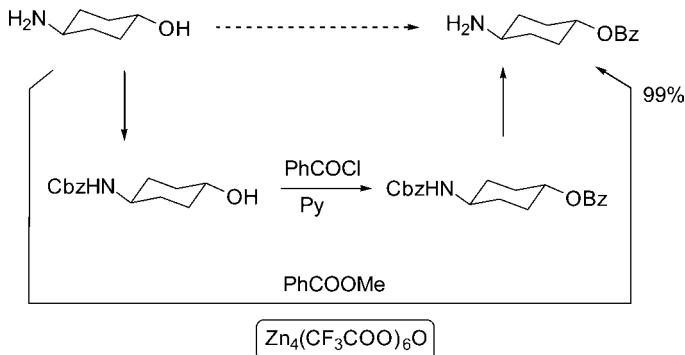
Aim for Higher Chemoselectivity to Avoid Protecting Groups

Chemoselectivity is still one of the big issues in organic chemistry. Accordingly, the development of functional group-tolerant skeleton-forming reactions will see



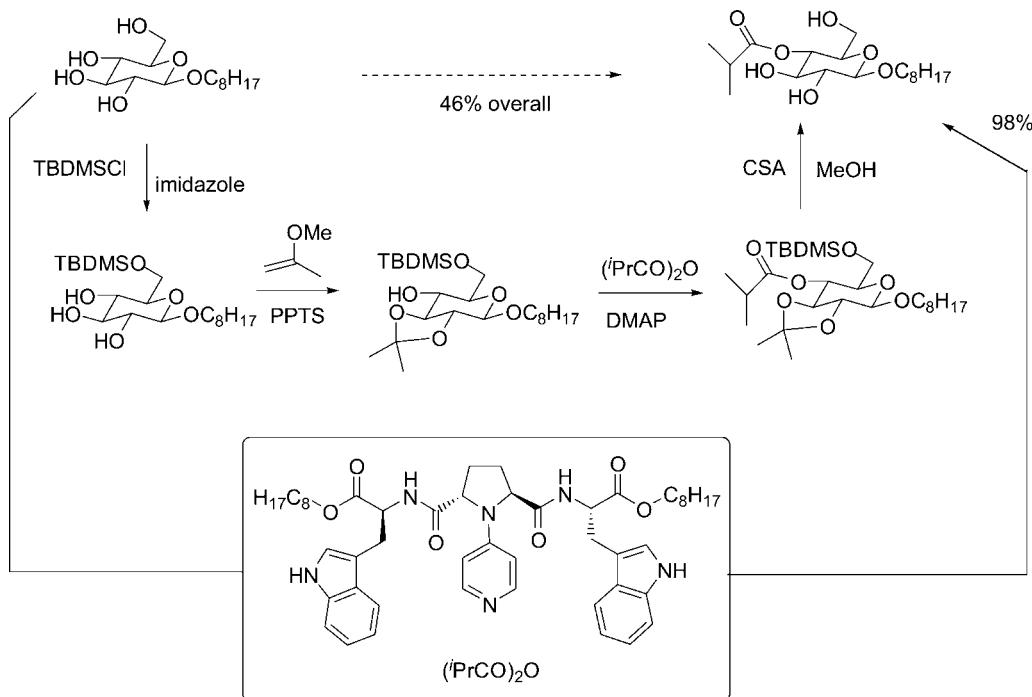
Scheme 7.15 Free radical chain modification of elaborate structures without protecting groups.

considerable progress in the years to come. Then the use of protecting groups will become more and more obsolete at a similar pace. When standard reactions show low or no chemoselectivity, the advice may be deceptively simple: just find the right catalyst! Then one can do away with protecting groups. For instance, consider the old problem of acylating a hydroxyl group in the presence of an amine: at last, the catalyst to achieve this chemoselectively has been found (Scheme 7.16)! [28].



Scheme 7.16 Chemoselective acylation of a hydroxy group in the presence of an amine.

A more spectacular case of chemoselective acylation using the right catalyst [29] is shown in Scheme 7.17. Here the catalyst addresses selectively the 4-position of a glycoside, obviating the previously used route with two protecting groups:



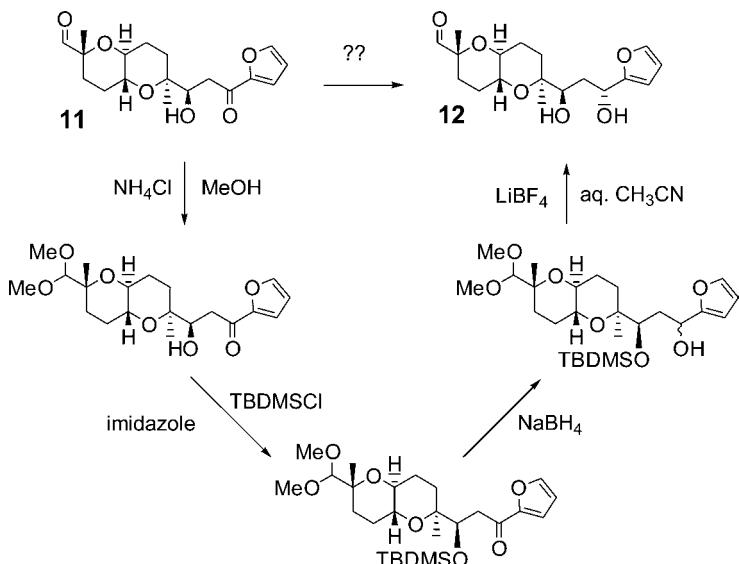
Scheme 7.17 Position-selective acylation of a glycoside using the appropriate catalyst.

Although such catalysts cannot be found overnight, one sees the direction which synthesis method research is taking these days, and with every new such catalyst developed, the need for using protecting groups will diminish.

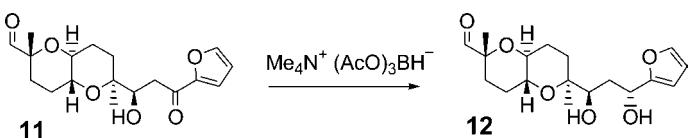
Chemoselectivity, for example, the differentiation between a ketone and an aldehyde, can in favorable cases be realized by capitalizing on the inherent reactivity of a specific functional group environment. Consider the conversion of **11** to **12** (Scheme 7.18). Traditionally, one tends to apply two short-term protecting groups to achieve the selective reduction of the keto function.

Yet the experienced chemist will recognize that the keto group in **11** is in a β -hydroxy ketone arrangement. This combined functionality offers as distinct reactivity pattern, to differentiate it from an ordinary ketone: β -hydroxy ketones may be reduced in the presence of a ketone (for example, in acetone as solvent!) with the specific reagent triacetoxyborohydride [30]. Using this reagent, the above task was mastered without recourse to any protecting groups (Scheme 7.19) [31].

This example demonstrates that exploitation of the innate reactivity [13] of a functional group (combination) may allow for chemoselective transformations and may thus render the use of protecting groups obsolete.



Scheme 7.18 Protecting group pathway for selective reduction of a ketone in the presence of an aldehyde.



Scheme 7.19 Chemoselective reduction of a β -hydroxy ketone in the presence of an aldehyde.

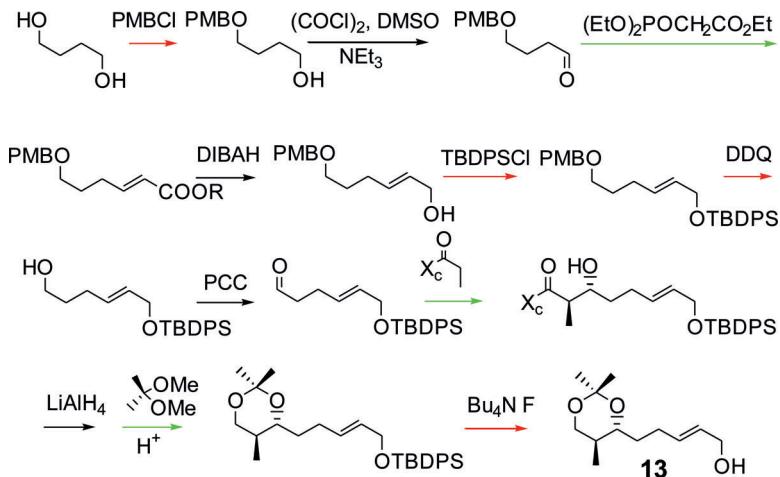
7.7

Change the Order of Synthesis Steps to Avoid Protecting Groups

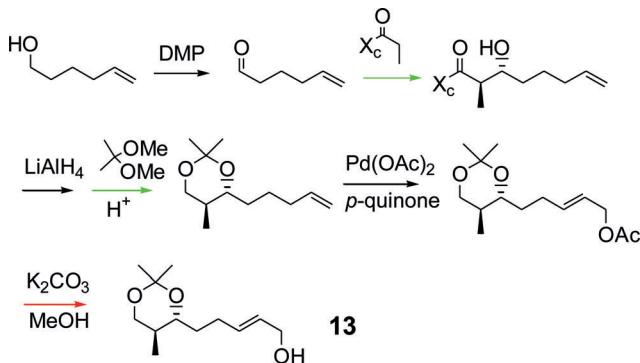
Are there other steps that can be taken today to avoid the use of protecting groups in multistep organic synthesis? Here it is the sequence of the individual steps in a synthesis that merits the closest attention. Given the bonds one wants to construct on the way from the starting materials to the target, chemists have a large degree of freedom in which order they are formed. Permutation of these steps offers the potential that a certain functional group, which interferes with a particular construction reaction, could be introduced at a later stage, thereby obviating the necessity to protect it.

This can be illustrated by comparing two syntheses of the same intermediate **13**. The one shown in Scheme 7.20 follows conventional wisdom of the last century, involving four protecting group management steps, not counting the formation of the acetonide, which was part of the target [32].

The same intermediate **13** has been also synthesized recently featuring the late introduction of the second hydroxyl group. This obviated the necessity to differentiate

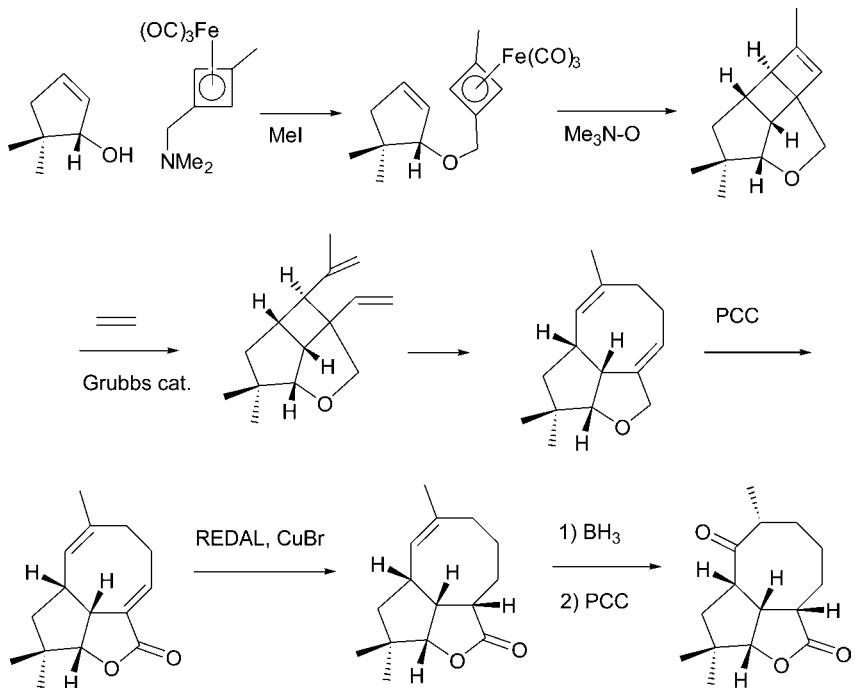
**Scheme 7.20** Conventional synthesis of the intermediate **13**.

two hydroxyl groups as in Scheme 7.20. Hence the synthesis depicted in Scheme 7.21 succeeds with at most one protecting group step, the removal of the acetyl group at the end [33].

**Scheme 7.21** Modern synthesis of the intermediate **13**.

One realizes that it may be advantageous to introduce functional groups late in a synthesis sequence, when it is no longer necessary to protect them during the skeleton-forming steps. In terms of step count, this is better than following Hendrickson's guideline [4] to generate the functional groups in the skeleton-forming steps, when these have to be protected immediately and deprotected at the end. This can be illustrated with a spectacular synthesis of asteriscanolide (Scheme 7.22) [34], in which the functionality was introduced at the end of the synthesis. It thus succeeded without the assistance of any protecting groups.

Another synthesis of asteriscanolide was completed at about the same time [35], this time introducing oxygen functionality early and during the assembly of the



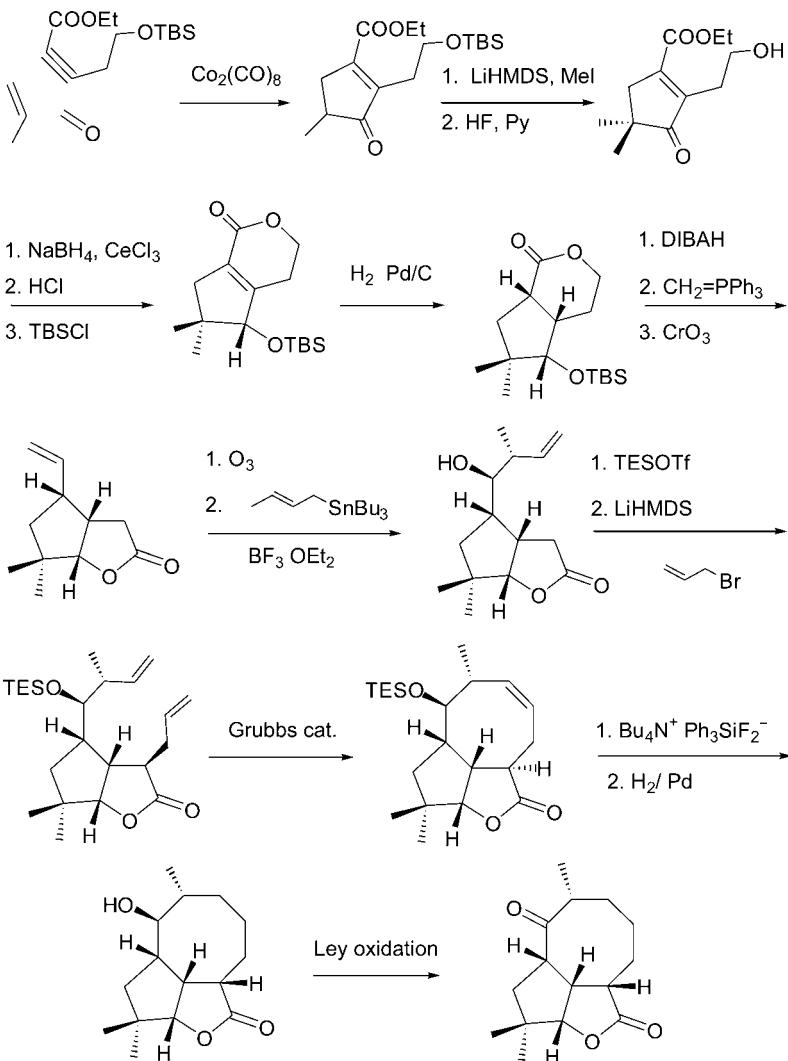
Scheme 7.22 Limanto and Snapper's synthesis of asteriscanolide.

molecular skeleton. This necessitated the enlistment of protecting groups. This synthesis (Scheme 7.23) is accordingly longer, requiring four protecting group management steps.

7.8

Enlist Latent Functionality to Avoid Explicit Protecting Group Steps

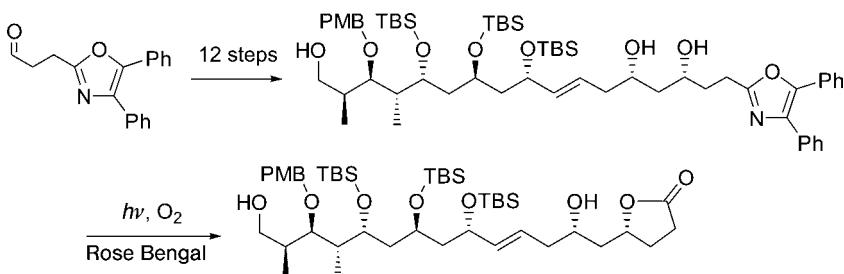
The tactic of first synthesizing the backbone of the target and decorating it later with the functional groups is worth considering, but it is not a “magic bullet.” Rather, it may be equally attractive to introduce a functional group early in the synthesis not as such, requiring subsequent protection, but rather it should be introduced as a latent functionality. Latent functionality is a long-known tactic [36] to provide functional groups in a step-economic manner. That is, the functional group is introduced in the form of a chemically inert precursor function, which can be carried through a multitude of steps. Only at the appropriate moment is the precursor function converted in a specific reaction to the desired functional group. Of course, this latter step adds to the overall step count, but it is only that single step and not the two steps of protection and deprotection. A case is given in Scheme 7.21, where the terminal alkene in the starting material serves as a latent allyl alcohol function to be revealed in



Scheme 7.23 Krafft and co-workers' synthesis of asteriscanolide.

the last step. A typical example of using latent functionality can be found in Evans and co-workers' synthesis of oasomycin A (Scheme 7.24) [37].

In this example, a diphenyloxazole unit is used right from the start. The C-29–C-46 part of oasomycin is then elaborated with a conventional long-term protecting group pattern. At the desired moment, the diphenyloxazole is selectively oxidized with singlet oxygen to a carboxyl function that immediately forms the desired γ -lactone. In a similar vein, Kishi and co-workers used a furan residue as a latent carboxyl function during their benchmark lasalocid synthesis [38]. It is the chemical inertness of the aromatic isoxazole or furan rings that renders them suitable as latent functional groups.



Scheme 7.24 Diphenyloxazole as a latent carboxyl function.

7.9

Summary

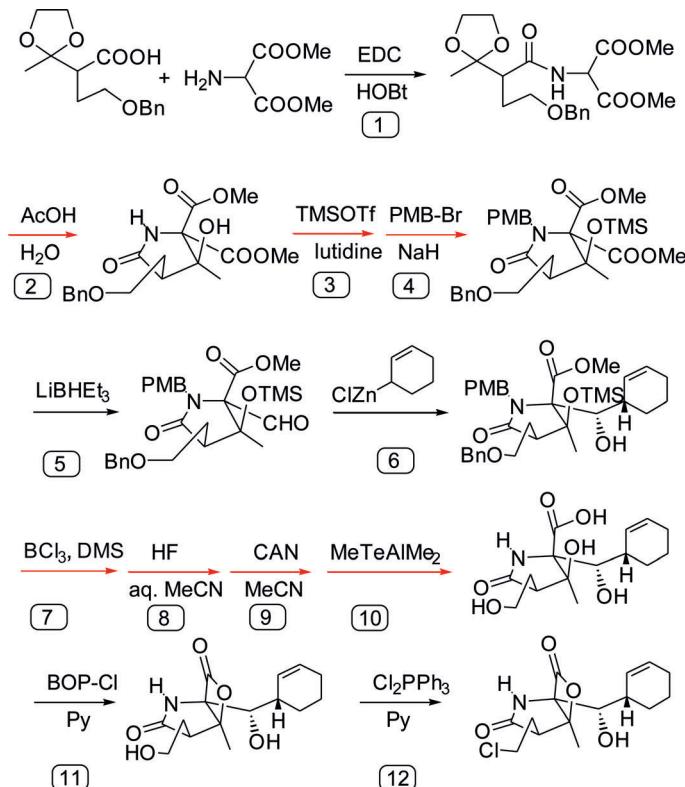
At this point, the strategies to attain synthesis without protecting groups should be summarized. The highest return may result when reconsidering the sequence of steps in a planned synthesis:

- Can the timing of the steps be changed to avoid incompatibilities between reaction conditions and functional groups present? Consider the late introduction of potentially interfering functional groups or the introduction of such functional groups as a latent equivalent.
- When synthesizing a natural product, try to follow the known or hypothetical biogenesis.
- Evaluate the extent to which it is possible to use highly chemoselective skeleton bond-forming reactions, such as transition metal-catalyzed or free radical chain reactions.

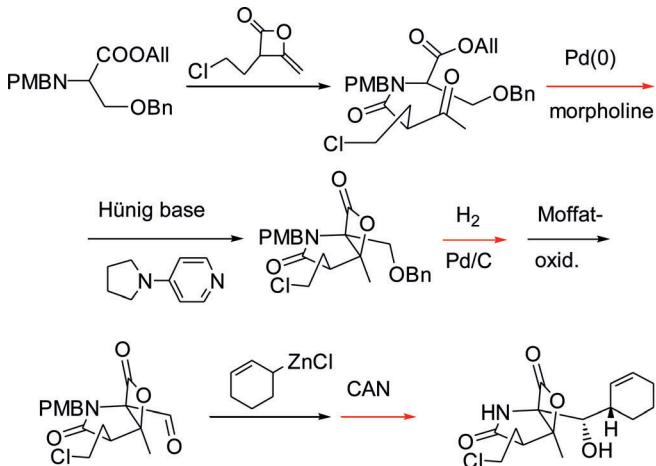
It may be instructive to see the extent to which streamlining of a synthesis becomes possible by following these rules, reducing the number of protecting group management steps. An example is a recent conventional synthesis [39] of salinosporamide A (Scheme 7.25), involving eight protecting group steps.

This synthesis can be compared with another one [40] in Scheme 7.26 which follows the same bond set [41]. This means that the same skeletal bonds are made in both syntheses. Any differences between these two syntheses therefore arise from differences in the refunctionalization and protecting group steps.

Since the bond set is the same in both syntheses, they are biomimetic to the same extent. Both syntheses use cyclohexenylzinc chloride as a chemoselective building block [42] which tolerates the presence of an ester, lactone, and amide group. It is the ordering of the steps that makes the difference. For instance, the second synthesis forms the β -lactone ring rather early, avoiding the protecting group steps (3), (8), and (10) in the former synthesis. The second synthesis introduces the chlorine substituent right at the beginning. This avoids the protecting group step (7) and the refunctionalization step (12) in the former synthesis. It is instructive to learn how much can be gained by thoughtful reordering of the sequence of the essential skeleton-building operations of a synthesis.



Scheme 7.25 Conventional synthesis of salinosporamide A.



Scheme 7.26 Biomimetic synthesis of salinosporamide A.

Such streamlining of multistep syntheses of complex targets is one of the current objectives of present-day organic chemistry. Avoiding protecting groups in syntheses is a powerful strategy in this regard. The necessary change in attitude is slowly gaining momentum. It is like the discussion of climate change: most people realize the importance of the problem, but before taking action themselves they look first at what their neighbor does or does not do.

Acknowledgments

The author thanks Georg Thieme Verlag, Stuttgart, for permission to reproduce Schemes 7.10, 7.13, 7.14, 7.20, and 7.21 from [8] and Springer-Verlag, Heidelberg, for permission to reproduce Schemes 7.4, 7.7, 7.8, 7.22, and 7.23 from R. W. Hoffmann, *Elements of Synthesis Planning*, 2008, ISBN 978-3-540-79219-2.

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8

Biological Synthesis of Pharmaceuticals

Junhua Tao and Alex Chu

8.1

Introduction

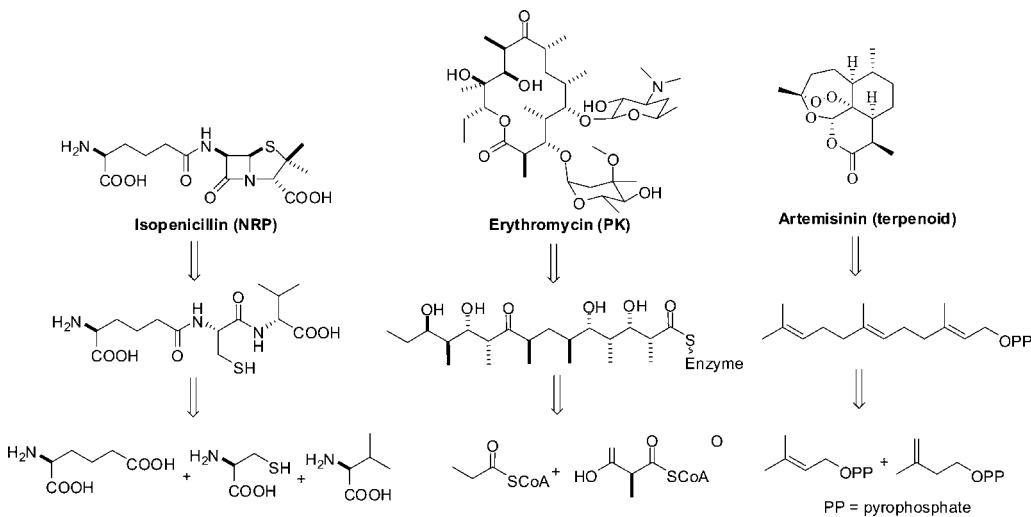
As a result of recent advances in large-scale DNA sequencing and enzyme-directed evolution technologies, biocatalysis is becoming a transformational technology uniquely suited for the development of green synthesis. For example, as a result of the availability of a wide range of expression hosts to produce biocatalysts cost efficiently, instead of designing synthetic pathways around limited toolboxes of biocatalysts, we are now able to ask what the optimal synthetic sequences are and then develop chemoenzymatic routes to meet process requirements on cost efficiency, waste reduction, energy consumption, throughput, and intellectual property [1]. Nature has evolved enzymes to create molecules that range from simple gases to complex natural products, yet many of these tools remain unutilized by synthetic chemists. In order to expand further the synthetic applications of biotransformations, it is essential that biocatalysts display attributes complementary or superior to chemical catalysis, such as high synthetic efficiency, exquisite stereocontrol, and use of economic and even renewable starting materials [2–5]. This chapter focuses on (1) some new classes of enzymatic transformations derived from natural product biosynthesis; (2) the development of pharmaceutical processes for small-molecular active pharmaceutical ingredients (APIs) using isolated enzymes; and (3) whole cell production of pharmaceuticals.

8.2

New Enzymes for Chemical Synthesis

The past decade has seen an explosion in our understanding of enzyme pathways through which natural products are produced [6, 7]. For example, linear non-ribosomal peptide (NRP), polyketide (PK), and terpenoid (terpene) scaffolds are usually assembled from amino acids (isopenicillin) [8], acyl-CoAs (erythromycin) [9], and pentenyl pyrophosphates (artemisinin), respectively [10] (Scheme 8.1). These

linear products are further modified enzymatically through cyclization, reduction, oxidation, halogenation, glycosylation, acylation, epimerization, and methylation. Despite the complexity and diversity of individual natural products, each transformation is often catalyzed by a discrete enzyme with high selectivity and turnover. This section focuses on enzymatic halogenation, macrocyclization, glycosylation, heterocyclization, methylation, and oxygenation.

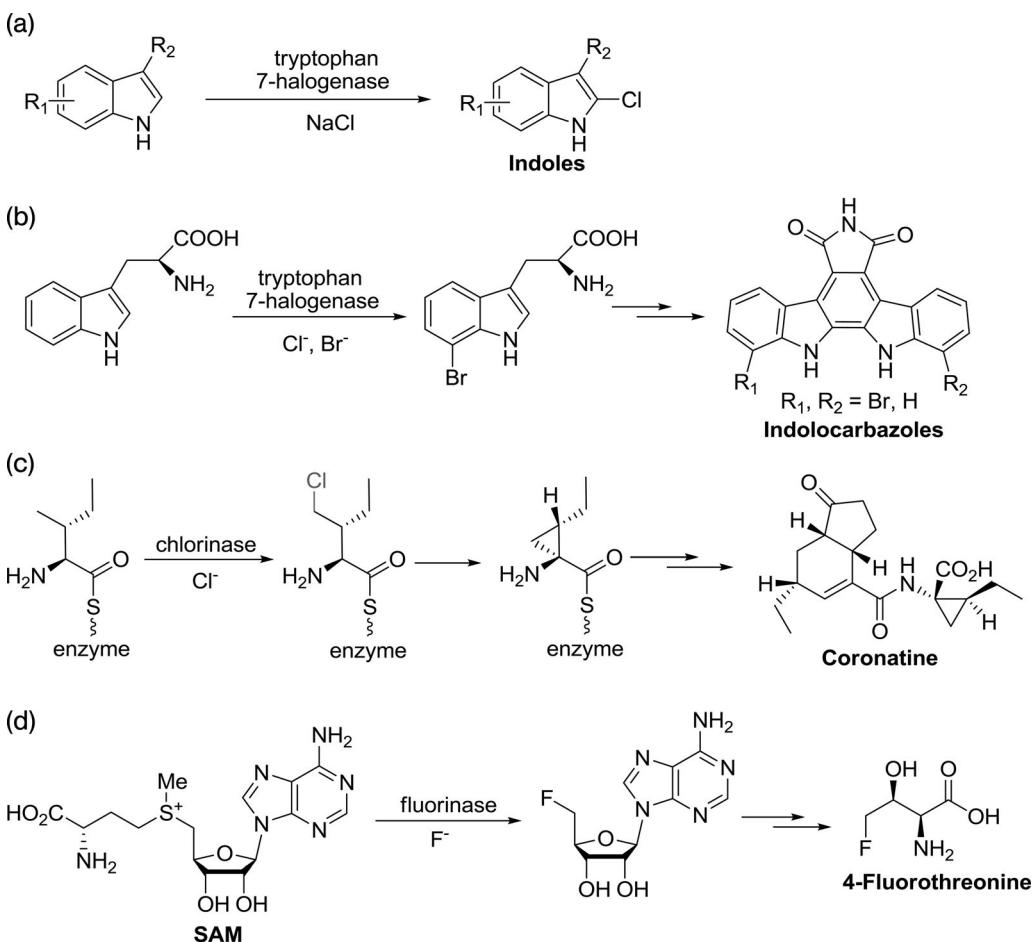


Scheme 8.1

8.2.1

Enzymatic Halogenation

Natural products require halogens to be strategically placed to achieve the desired biological activities [11], usually using flavin-dependent halogenases or haloperoxidases for enzymatic chlorination, bromination, or iodination of electron-rich substrates [reactions (a) and (b), Scheme 8.2], and mononuclear iron halogenases of electron-deficient molecules such as alkanes [reaction (c), Scheme 8.2] [12–15]. On the other hand, fluorination relies on a nucleophilic substitution mechanism [reaction (d), Scheme 8.2] [16, 17]. Halogenation by haloperoxidases often occurs with poor regio- and stereoselectivity since the activated hypohalous acids are freely diffusible from enzymes. As a result, their synthetic utility is largely limited. However, both flavin-dependent and mononuclear iron halogenases elicit high regio- and stereoselectivity [18, 19]. FADH₂ halogenases such as tryptophan 7-halogenases have been reported to catalyze the regioselective halogenation of a number of indole derivatives and aromatic heterocycles [reactions (a) and (b), Scheme 8.2] [20, 21].



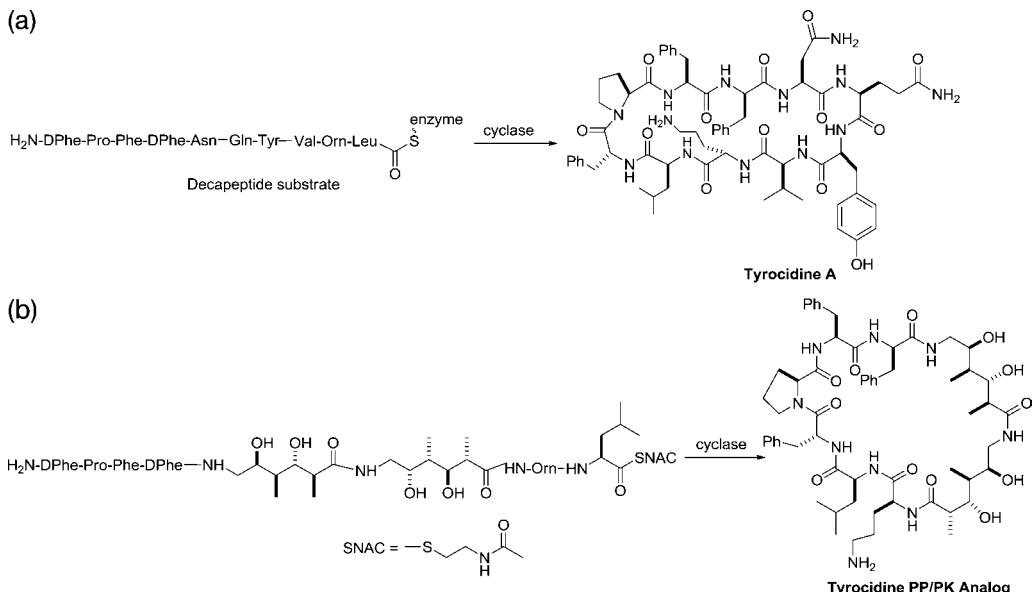
Scheme 8.2

8.2.2

Macrocyclization

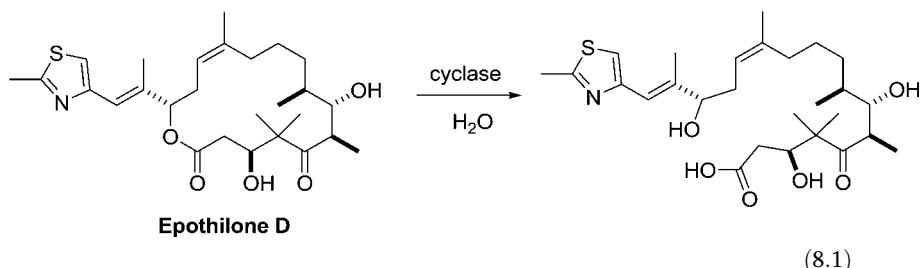
Macrocyclic motifs are usually essential for the unique biological properties of natural products. In most cases, linear NRP and PK scaffolds are cyclized to form macrolactones or macrolactams prior to further post-modification. Macrocyclization is usually carried out by cyclases towards the end of elongation. For example, in the biosynthesis of the antibiotic tyrocidine A, a linear enzyme-bound decapeptide is cyclized via an intramolecular S_N2 reaction between the N-terminal amine nucleophile and the C-terminal thioester, which is covalently linked to the synthase [reactions (a) and (b), Scheme 8.3] [22]. This cyclase shows great versatility. Not only does it catalyze the formation of macrolactams of ring sizes from 18 to 42 atoms from

linear thioester substrates with excellent catalytic efficiency, in fact all residues except two may be replaced by other functionalities. For example, in one study, four amino acids [Asn, Gln, Tyr, Val; reaction (b), Scheme 8.3] could be replaced by polyketide moieties, leading to the production of hybrid peptide/polyketide (PP/PK) cyclic molecules [23]. In contrast to chemical macrocyclization, no protection was required for the linear precursors. As the enzyme is highly flexible with respect to the template, this chemoenzymatic macrocyclization strategy has been extended to the synthesis of a library of glycosylated natural product-like molecules [24].



Scheme 8.3

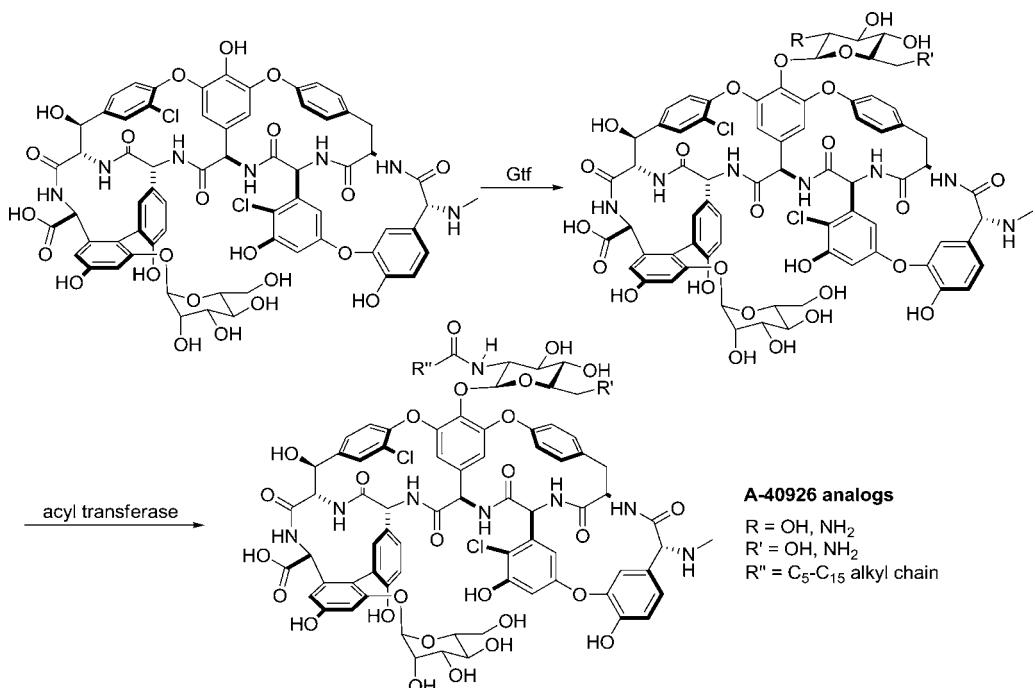
Cyclases are also responsible for NRP depsipeptide and PK lactone cyclization. For example, a di-domain excised from fengycin synthase was able to catalyze the formation of a macrolactone through the formation of a C–O bond [25]. Several cyclases from PK synthases have also been characterized to be functional, including the epothilone D cyclase [26, 27] (Equation 8.1).



8.2.3

Glycosylation

A wide range of bioactive natural products are glycosylated through O, N, or C linkages to their respective aglycones, which is often essential to confer biological activity on the parent molecules [28]. The recent discovery of a variety of glycosyltransferases (Gtfs) has greatly facilitated the synthesis of glycosylated molecules, often through processes complementary or superior to chemical approaches [29]. For example, one Gtf from a glycopeptide A-40926 synthase accepts a variety of sugar substrates allowing the creation of new glycopeptides (Scheme 8.4), which can be further modified to generate a library of novel lipoglycopeptides by acyl transferases [30, 31]. In another example, the glyco moiety was further randomized through copper-catalyzed 1,3-dipolar cycloaddition via incorporation of azido sugars [32]. The availability of a wide range of diversified Gtfs and sugar biosynthesis genes also provides a general strategy to generate glycosylated molecules *in vivo* [33]. For example, a glycosyltransferase from picromycin biosynthesis was able to take a wide range of sugars, leading to *in vivo* production of novel polyketides [34].

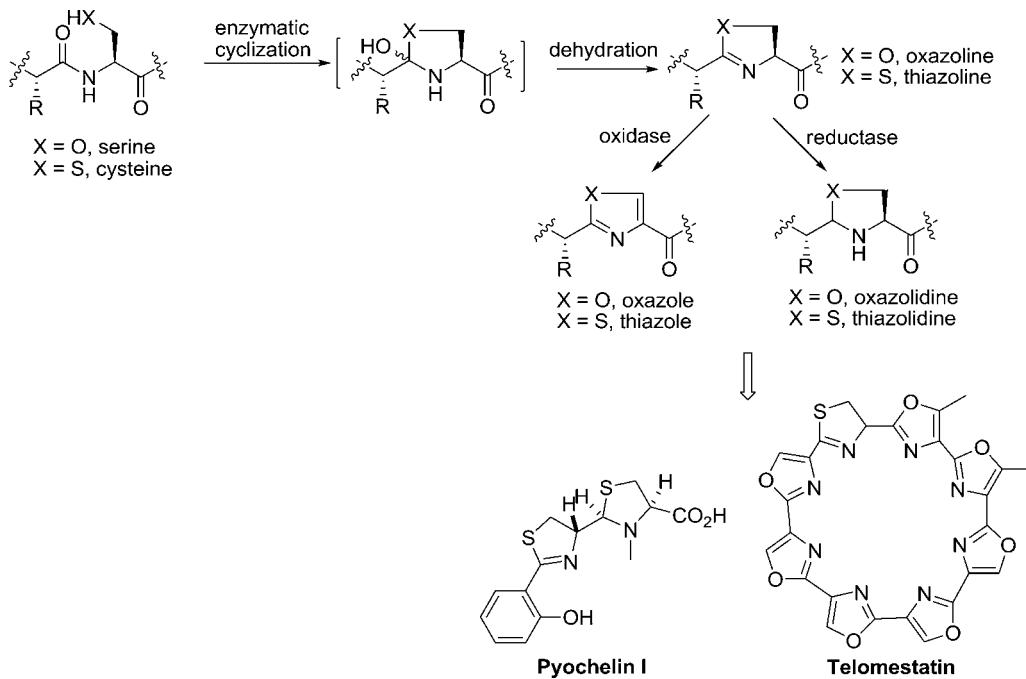


Scheme 8.4

8.2.4

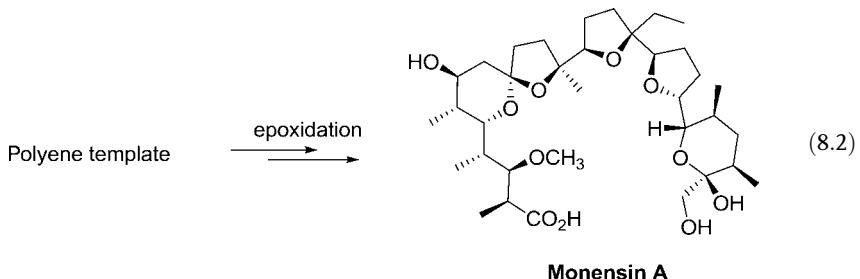
Heterocyclization

Heterocycles are common motifs in natural products, which may occur as single, tandem, and multiple moieties within a given molecule (Scheme 8.5) [35–37]. These motifs often provide molecular interaction with nucleotide and protein targets. In the biosynthesis of NRPs, an oxazoline was usually formed from a dipeptide containing serine in the second position upon dehydration (Scheme 8.5) [38]. The syntheses of a thiazoline from cysteine and a 2-methyloxazoline from threonine follow a similar mechanism. These heterocycles can be further custom-made to provide thiazolidines/oxazolidines upon reduction or thiazoles/oxazoles upon oxidation. Enzymatic heterocyclization can be portable, as demonstrated in the synthesis of novel chiral heterocyclic carboxylic acids by hybrid enzymes [39].



Scheme 8.5

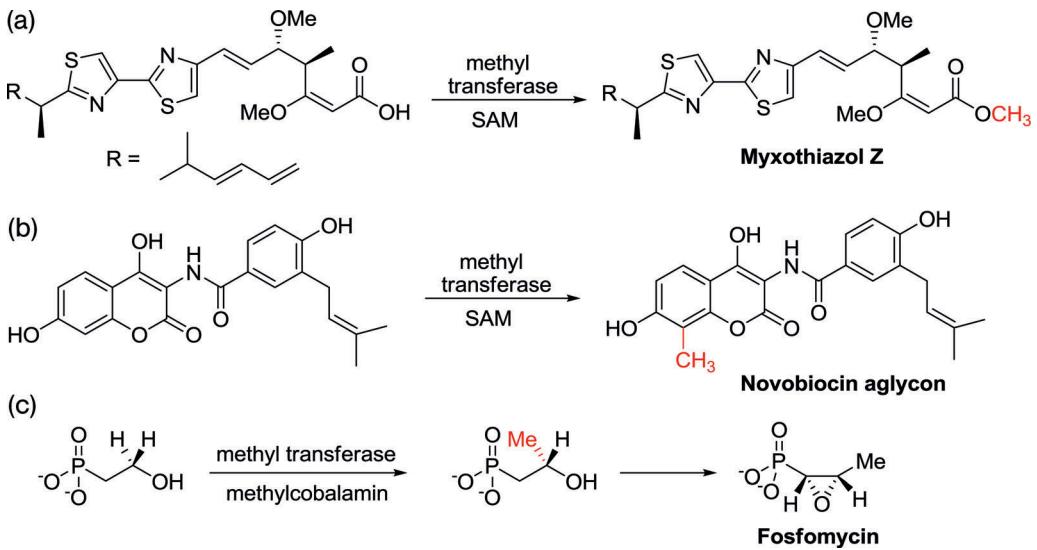
A different mechanism was adopted in the biosynthesis of cyclic polyethers such as monensin. These PK-derived polycycles are formed in a cascade fashion with other enzymatic transformations. For example, in the biosynthesis of monensin (Equation 8.2), the cascade polyether formation is triggered by epoxidation of a polyene template [40]. Similar mechanisms can probably be used to make other polyether antibiotics containing tetrahydrofurans and tetrahydropyrans [41].



8.2.5

Methylation

Methylation of amines in nucleotides and proteins plays important roles in biological function. Methyl transferases accept a wide range of nucleophiles such as halides, amines, hydroxyls, and enolates [reactions (a) and (b), Scheme 8.6] [42–44]. For example, in the biosynthesis of novobiocin, methylation takes place at only one phenolic carbon and not the remaining three hydroxyl groups [45, 46]. On the other hand, methyl transfer to electron-deficient substrates often occurs under radical mechanisms requiring methylcobalamin as the cofactor, as shown in the biosynthesis of fosfomycin, where only one of the two enantiotopic hydrogen was replaced by the methyl group [reaction (c), Scheme 8.6] [47].

**Scheme 8.6**

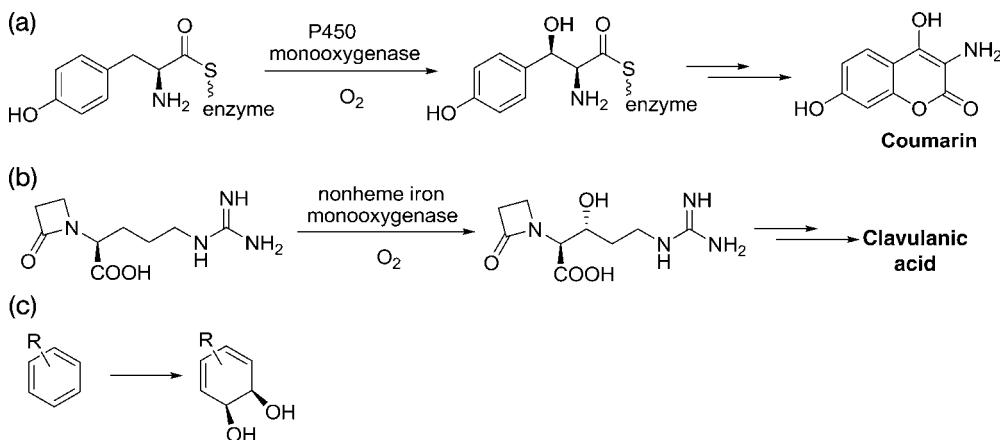
Despite higher selectivity of enzymatic methyl transfer over chemical methylation, where toxic or hazardous reagents are often utilized such as methyl sulfonate and diazomethane, the synthetic applications of these enzymes have been largely ignored.

due to the high cost of the cofactor SAM. Recent efforts have been directed at *in vivo* methylation, where SAM is regenerated inside cells. For example, methyl benzoate production was engineered in recombinant *Saccharomyces cerevisiae* and *in vivo* methylation was accomplished through heterologous expression of benzoic acid methyl transferase [48].

8.2.6

Oxygenation

Oxygenated natural products are often created by oxygenases, which are categorized as either monooxygenases or dioxygenases, depending on whether they insert one or both atoms of dioxygen into a substrate (Scheme 8.7) [49–51]. For example, aromatic dioxygenases are an important pathway in the degradation of aromatics into *cis*-dihydrodiols (Scheme 8.7) [52, 53]. It should be noted that dioxygenation may also take place in the absence of cofactors [54–56]. C–H activation has perhaps the highest potential of all enzyme-catalyzed transformations for synthetic applications. At the same time, these transformations are often difficult to carry out on a practical scale when using isolated enzymes. Currently, they require whole-cell processes and the outcome can be unpredictable. The discovery of new oxygenases and efficient expression hosts is key to expanding applications of enzymatic oxygenation.



Scheme 8.7

8.3

Synthesis of Pharmaceuticals via Isolated Enzymes

8.3.1

Penicillins and Cephalosporins

Penicillins are a group of β -lactam antibiotics sharing the same 6-aminopenicillanic acid (6-APA) nucleus (Figure 8.1). Cephalosporins, on the other hand, share a

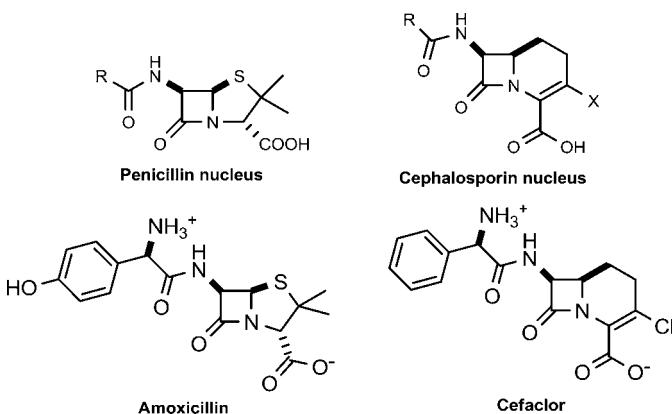
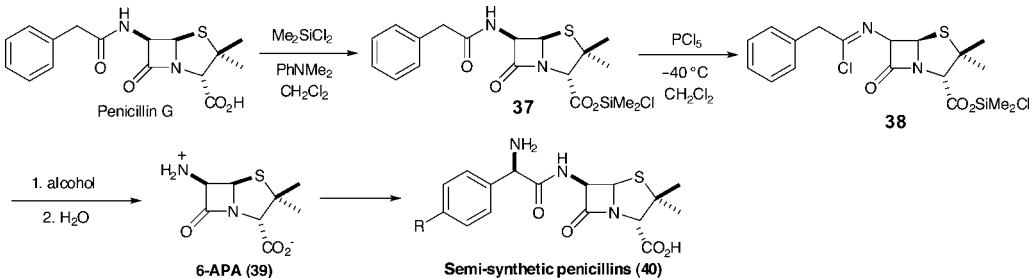


Figure 8.1

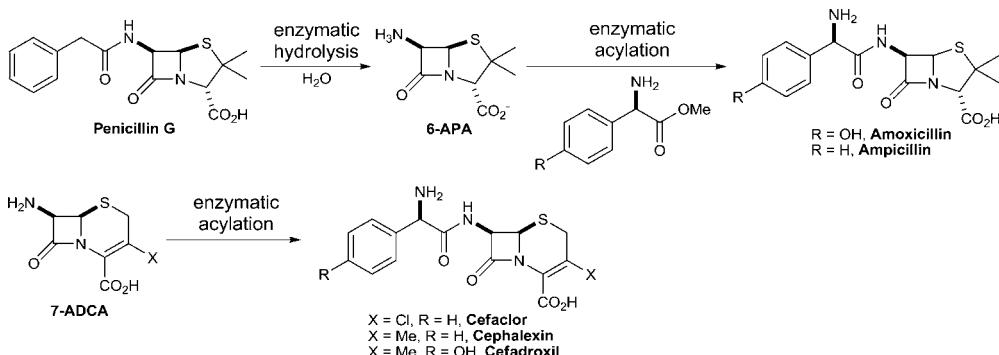
7-aminodeacetoxycephalosporanic acid core (7-ADAC) (Figure 8.1). Both have the same mode of action. To enhance the therapeutic index, a variety of semi-synthetic β -lactam antibiotics have been developed by modifying natural penicillins and cephalosporins, including amoxicillin and cefaclor (Figure 8.1).

Until recently, most of these semi-synthetic penicillin antibiotics were manufactured from penicillin G by chemical methods (Scheme 8.8) [57], which involve many green chemistry issues, including the use of stoichiometric amounts of the silylating agents, phosphorus chloride, and *N,N*-dimethylaniline, and a large volume of dichloromethane. Moreover, the chlorination has to be carried out at -40°C .



Scheme 8.8

More recently, a biocatalytic manufacturing route was developed in which deacylation was accomplished by penicillin G acylase in water at room temperature, requiring no protection and deprotection (Scheme 8.9) [58]. Moreover, through reaction engineering, penicillin G acylase also catalyzes the acylation of 6-APA with either amino esters or aminoamides to produce a wide range of semi-synthetic β -lactam antibiotics such as amoxicillin and ampicillin. A similar approach could be applied to the synthesis of the 7-ADCA derivatives cefaclor, cephalexin, and cefadroxil.

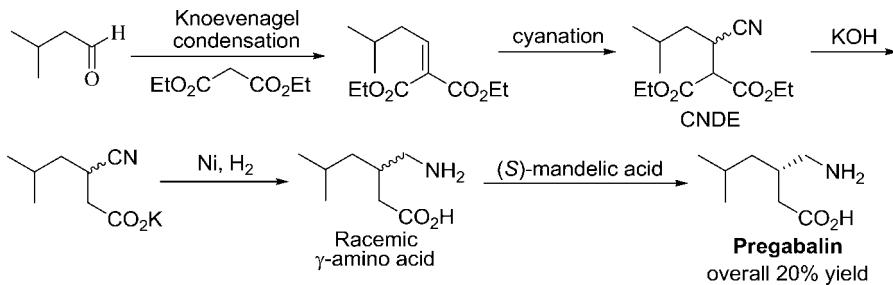


Scheme 8.9

8.3.2

Pregabalin

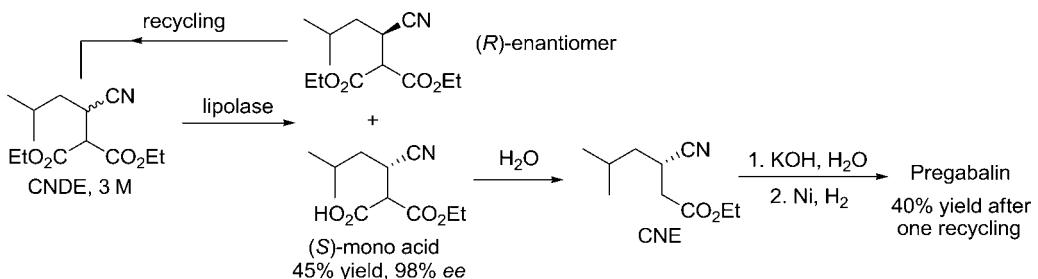
Pregabalin is the active ingredient of Lyrica® for the treatment of neuropathic pain and epilepsy. The regulatory starting material of the first-generation manufacturing process is a cyano diester (CNDE) synthesized from valeraldehyde after Knoevenagel condensation and cyanation (Scheme 8.10) [59]. Upon basic hydrolysis and Ni-catalyzed hydrogenation, CNDE was converted to a racemic γ -amino acid and then pregabalin upon resolution under a stoichiometric amount of (*S*)-mandelic acid. The overall yield of the process is only about 20%. Since the undesired γ -amino acid enantiomer could not be recycled, this chemical process suffers from high process mass intensity.



Scheme 8.10

To address both the green chemistry and cost issues, a novel biocatalytic process was recently developed involving a lipolase-catalyzed resolution of a CNDE to produce the desired (*S*)-mono acid enantiomer, which was subsequently converted to pregabalin upon decarboxylation, hydrolysis, and hydrogenation (Scheme 8.11) [60]. The enzymatic step has an excellent volumetric activity of $>500 \text{ g l}^{-1}$ per day. Since the undesired *R*-enantiomer could be readily racemized to CNDE, the yield of

the new process was more than doubled from the yield of the chemical route. Moreover, all three steps after CNDE were conducted in water. As a result, the biocatalytic process is significantly greener than the chemical route, with the *E*-factor being reduced from 86 to 17.

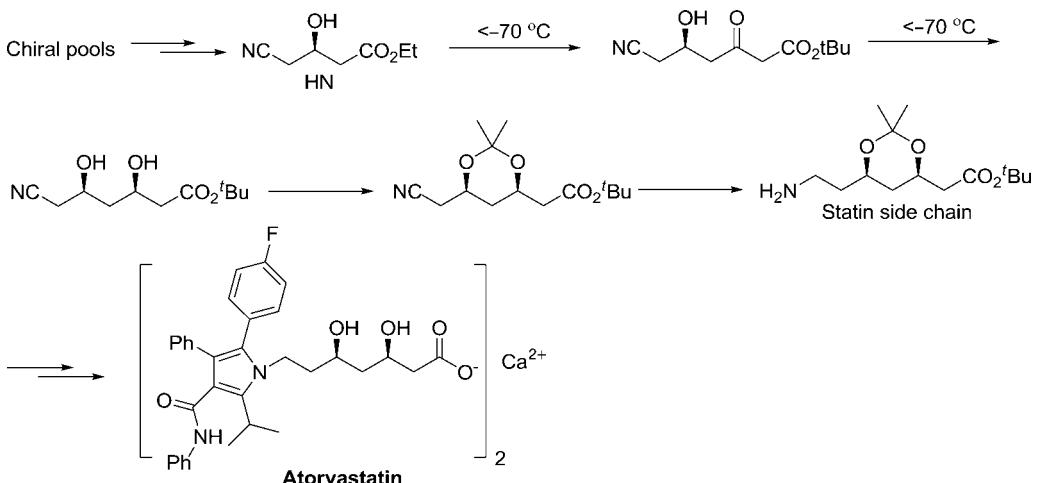


Scheme 8.11

8.3.3

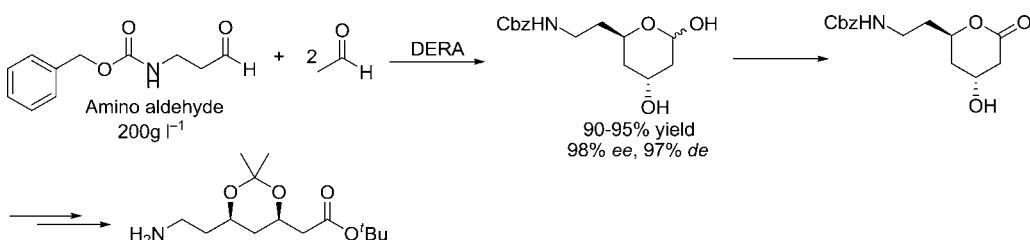
Atorvastatin

Atorvastatin is the active ingredient of Lipitor®, a cholesterol-lowering drug with sales exceeding US\$13 billion in 2008. Although the current manufacturing process is robust, it suffers from high process mass intensity due to the extreme linearity of the synthetic sequence and high energy consumption as a result of two cryogenic reactions (Scheme 8.12) [61].



Scheme 8.12

More recently, a biocatalytic process was reported to target the statin side chain directly by applying a DERA (deoxyribose-5-phosphate aldolase)-catalyzed sequential aldol condensation between 1 equiv. of an aminoaldehyde and 2 equiv. of acetaldehyde to form an aminolactol, which was then converted to the statin side chain (Scheme 8.13) [62]. The enzymatic step meets excellent process metrics: high throughput (200 g l^{-1} per day), high yields (90–95%), and excellent stereocontrol [98% enantiomeric excess (*ee*), and 97% diastereomeric excess (*de*)]. Moreover, the overall process was shortened significantly by removing the two energy-intensive chemical steps.

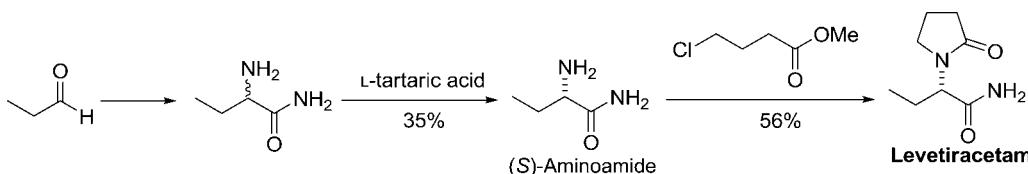


Scheme 8.13

8.3.4

Levetiracetam

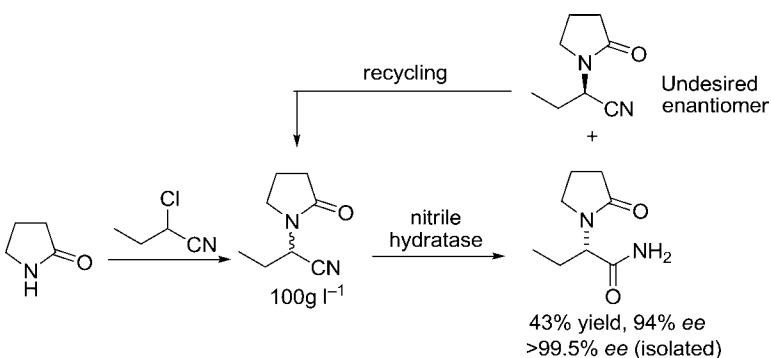
Levetiracetam is the active ingredient of Keppra® approved for the treatment of epilepsy. The key step of the current manufacturing route involves resolution of a racemic 2-aminoamide by L-tartaric acid to provide the desired (*S*)-aminoamide, the penultimate precursor to levetiracetam (Scheme 8.14) [63, 64]. This approach involves many green chemistry issues as a result of poor resolution and cyclization yields (35 and 56%, respectively).



Scheme 8.14

A biocatalytic process was recently disclosed in which the strategic step involves kinetic resolution of a racemic 2-pyrrolidinonyl nitrile by nitrile hydratases (Scheme 8.15) [65, 66]. Using an engineered nitrile hydratase mutant, the enzymatic step proceeds with high productivity (100 g l^{-1} per day), good resolution yield (43%), and high stereoselectivity (94% *ee*). The biocatalytic process can potentially be much

more atom efficient than the chemical route due to easy recycling of undesired *R*-enantiomer.



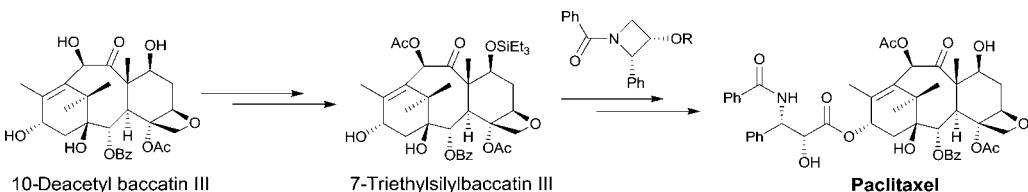
Scheme 8.15

8.4 Synthesis of Pharmaceuticals via Whole Cells

8.4.1

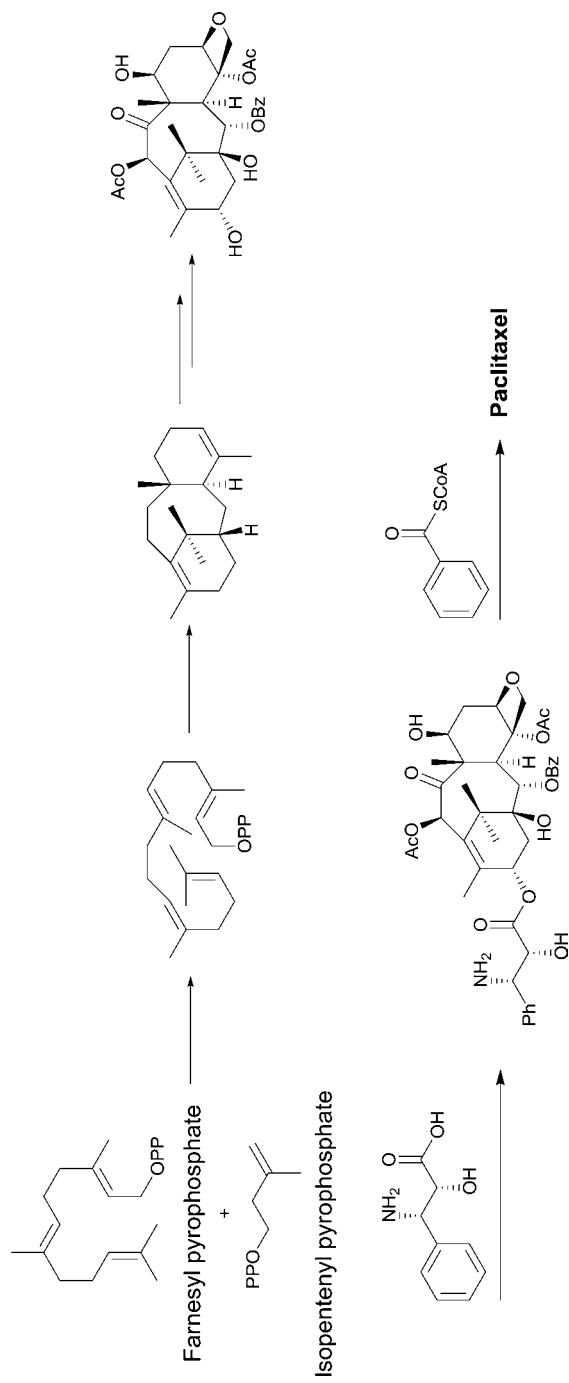
Paclitaxel

Paclitaxel (Taxol®) is an anti-cancer agent originally obtained from Pacific yew tree bark. The complexity of the molecule makes chemical synthesis from simple compounds economically unfeasible. For instance, one of the most efficient semi-syntheses starts from 10-deacetyl baccatin III, a more abundant taxoid obtained from needles of the European yew tree (Scheme 8.16) [67, 68]. However, the process is still long, requiring 11 chemical transformations.



Scheme 8.16

A more efficient process to paclitaxel involves fermentation [69–71]. The biosynthesis starts from isoprenyl diphosphate and farnesyl diphosphate (Scheme 8.17). To achieve a high titer of paclitaxel production, cell cultures from various species of *Taxus* were investigated. For example, methyl jasmonate was able to enhance paclitaxel production to 55 mg l^{-1} per week in a cell suspension culture. The plant

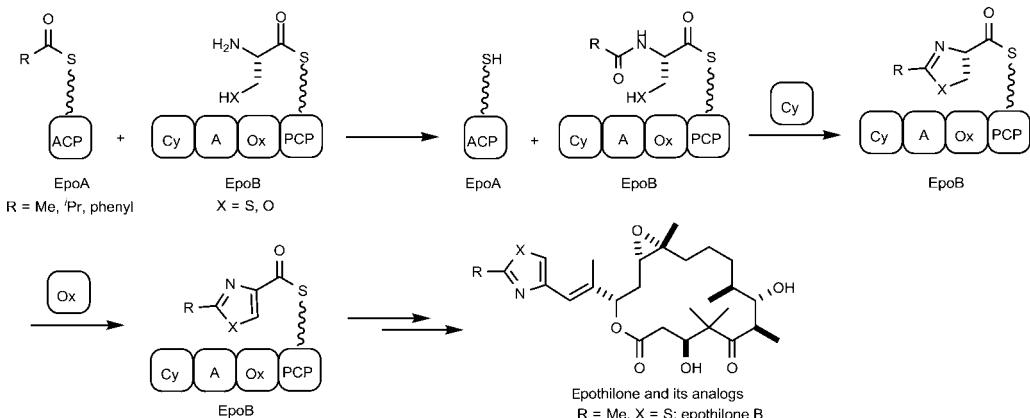


Scheme 8.17

cell fermentation process eliminates the 11 chemical transformations and the large amounts of hazardous wastes required by the semi-synthetic route.

8.4.2 Epothilones

Epothilones are a new class of anti-cancer compounds with simpler structures than paclitaxel. The complete genome of the epothilone-producing strain *Sorangium cellulosum* has recently been reported [72–74]. Heterologous expression of the whole gene cluster in the actinomycete *Streptomyces coelicolor* gave epothilone A and B (Scheme 8.18). Inactivation or deletion of the P450 epoxidase produced epothilone C and D. Heterologous expression of the epothilone synthetic gene cluster has also produced epothilone C and D in recombinant *Escherichia coli* [75]. The biosynthesis of epothilones starts with EpoA responsible for loading and decarboxylation of malonyl-CoA to generate an acetyl-(S)-EpoA (Scheme 8.18) [76, 77]. EpoB contains four domains responsible for the formation of a dipeptide, heterocyclization to form an enzyme-bound thiazoline (X=S) or oxazoline (X=O), and their oxidation to give thiazole and oxazole, respectively. Subsequent carbon chain elongation and macrocyclization release epothilones. The promiscuity of these domains provides an efficient pathway to for large-scale production of epothilones. For example, substitution of the acetyl-(S)-ACP (acyl carrier protein) of EpoA with isobutyl-(S)-ACP ($R = ^3\text{Pr}$) or benzoyl-(S)-ACP ($R = \text{phenyl}$) leads to isopropylthiazoyl-(S)-EpoB and phenylthiazoyl-(S)-EpoB ($R = ^3\text{Pr}$, phenyl), respectively (Scheme 8.18).

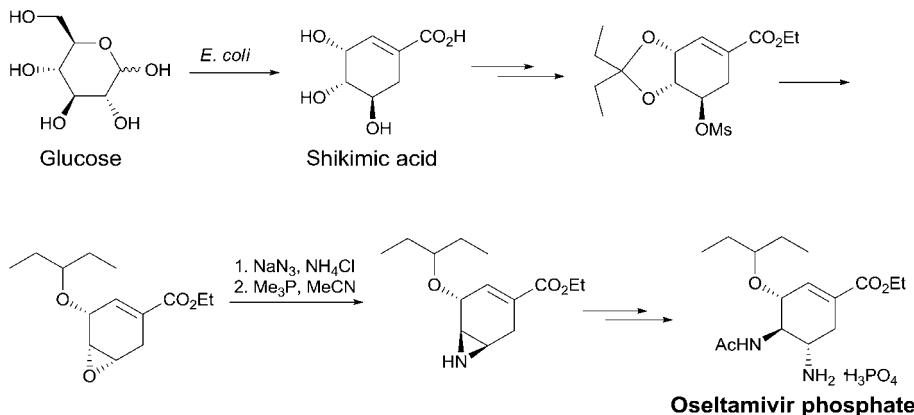


Scheme 8.18

8.4.3 Oseltamivir

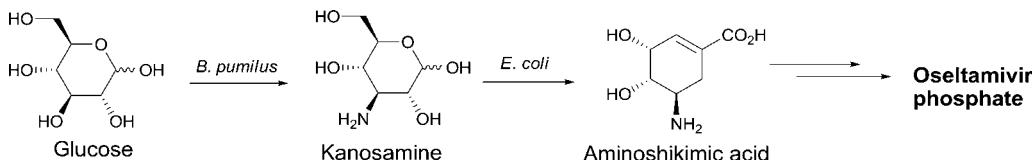
Oseltamivir phosphate (Tamiflu®) was developed for the treatment and prevention of influenza virus infections. The key starting material of one commercial route is

shikimic acid, which is produced with a titer of 84 g l^{-1} and a yield of 33% by a genetically engineered *E. coli* strain deficient in both shikimate kinase isozymes (Scheme 8.19) [78–80]. This acid was then converted to oseltamivir phosphate after side chain installation, reductive opening of the ketal, base-catalyzed epoxide ring closure, and azidination.



Scheme 8.19

Letelyan azide-free synthesis of oseltamivir phosphate was reported, where the key intermediate is aminoshikimic acid produced by a two-step microbial process: *Bacillus pumilus* to generate kanosamine followed by engineered *E. coli* to give aminoshikimic acid (Scheme 8.20) [81–83].



Scheme 8.20

8.4.4

Avermectins

Avermectins are a mixture of 16-membered macrocyclic polyketide aglycones with a dimeric *o*-methyl- α -L-oleandrose attached to C-13, and are widely used for broad spectrum parasite control (Figure 8.2). They vary in three substituents R_1 , R_2 and R_3 , where R_1 can be either a hydroxyl or hydrogen, in which case there is a double bond

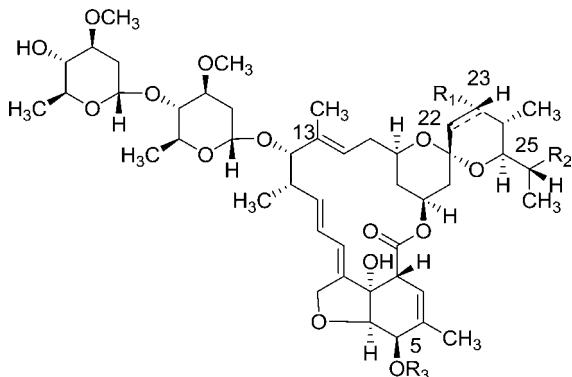


Figure 8.2

between carbons C-22 and C-23, R₂ is either methyl or ethyl and R₃ either hydrogen or methyl [84].

Based on the sequence of the gene clusters and alignment with known homologous enzymes, methylation at the C-5 hydroxyl group was found to be catalyzed by a methyl transferase. As a result, inactivation of the gene encoding the methyltransferase led to a mutant of *Streptomyces avermitilis* producing only avermectins with R₃ = H, which are biologically more active than those with R₃ = methyl. In addition, the genetic architecture shows that biosynthesis of the avermectin A1a (R₁ = H, R₂ and R₃ = methyl) probably starts with the loading of 2-methylbutanoyl-CoA to the polyketide synthase [85] (not shown). After 12 chain extensions catalyzed by the polyketide synthase in a modular fashion, the final linear polyketide is cyclized by a cyclase to form the macrocyclic aglycone. Avermectin A1a was eventually generated after ketalization, benzofuran ring formation, and disaccharide decoration (not shown). By following the same mechanism, the loading of 2-methylpropionyl-CoA to the same synthase produced avermectins (where R₂ = methyl). Since 2-methylbutanoyl-CoA and 2-methylpropionyl-CoA are synthesized from isoleucine and valine, respectively, by amino acid transaminases followed by branched-chain α -keto acid dehydrogenase complex (bkd complex) (not shown), mutants of *S. avermitilis* lacking the bkd complex should allow the preparation of novel avermectins with diverse substituents at C-25 by feeding with exogenous carboxylic acids [86, 87]. Indeed, avermectins B1 and B2 with a cyclohexyl group at C-25 showed the highest efficacy (Figure 8.3).

In avermectin B1, there is a double bond between C-22 and C-23, whereas in avermectin B2 R₁=OH. The product ratio of B2 to B1 is 1.6:1. Since the B1 analog is much more effective as an antiparasite, there is a desire to improve the B1:B2 ratio, which can be achieved by a dehydratase domain [88, 89]. Its directed evolution and mutant screening led to a mutant giving an excellent fermentation titer of B1:B2 = 1:0.07 [90, 91]. As a result of understanding the biosynthesis, pathway engineering, and directed evolution, a biologically superior new product, doramectin (Dectomax[®]), was evolved from a mixture of eight natural products.

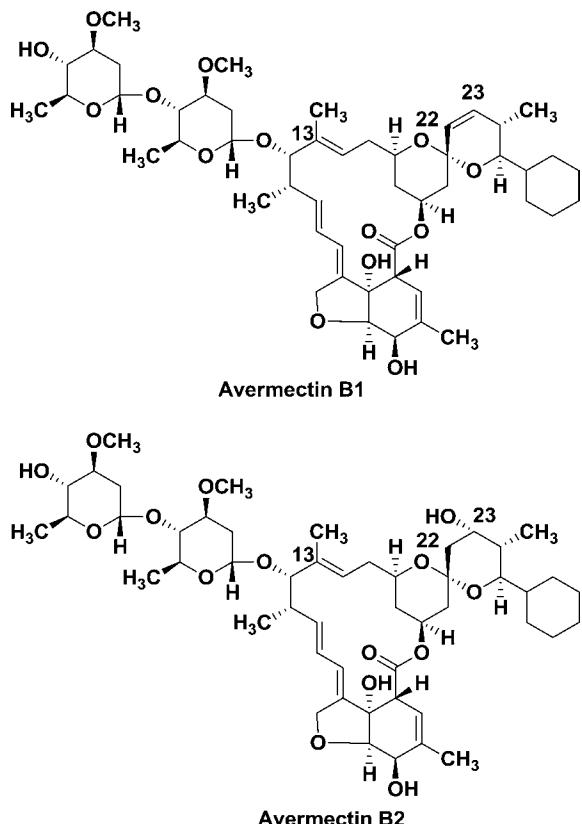


Figure 8.3

8.5 Conclusion

The green chemistry momentum opens up a new landscape of opportunities for more efficient synthetic tools. Recent advances in large-scale DNA sequencing and enzyme-directed evolution have rendered biocatalysis a much more practical technology to provide green chemistry solutions for the industrial production of chemicals. As illustrated in the power of biosynthetic enzymes in halogenation, macrocyclization, glycosylation, heterocyclization, methylation, and oxygenation, and also recent examples of developing biocatalytic pharmaceutical processes for semi-synthetic lactam antibiotics (penicillin and cephalosporin derivatives), pregabalin, atorvastatin, levetiracetam, paclitaxel, epothilones, oseltamivir, and doramectin, enzymatic catalysis provides a new dimension to meet green chemistry metrics.

Acknowledgments

The authors would like to thank Dr. Mel Luetkens of Elevance Renewable Sciences for generous support. J.T. would also like to thank Ben Borer, Stephen Bowlin, Shanghai Hu, Sean Kelly, Carlos Martinez, Ningqing Ran, Robert Scott, John Tucker, Jean Xie, Lan Xu, Weihong Yu, and Lishan Zhao, who made this chapter possible.

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9**Syntheses via C–H Bond Functionalizations**

Lutz Ackermann, Anant R. Kapdi, Harish K. Potukuchi, and Sergei I. Kozhushkov

9.1**Introduction**

Among synthetic methods in organic chemistry, those based upon direct regioselective functionalizations of a C–H bond appear to be the most promising, as they allow for the synthesis of complex molecules from easily available and less expensive precursors in fewer reaction steps. Undoubtedly, a majority of organic reactions involves homo- or heterolytic cleavages of a C–H bond. However, the efforts of a number of synthetically oriented groups around the world have focused on direct functionalizations of unactivated C–H bonds which possess high bond dissociation energies (BDEs), or in which protons cannot be abstracted by simple reactions of bases with moderate strengths. Commonly, the pK_a s of such C–H bonds are between 41 and 51, as estimated in water as solvent [1], or between 41 and 56, as measured in DMSO as solvent [2], and exceed the pK_a of the heterolytic cleavage of molecular hydrogen itself ($pK_a \approx 35$, $BDE \approx 104 \text{ kcal mol}^{-1}$) [3]. Typical examples of such compounds are benzene ($pK_a \approx 43$, $BDE \approx 113 \text{ kcal mol}^{-1}$), methane ($pK_a \approx 48$, $BDE \approx 105 \text{ kcal mol}^{-1}$), and ethane ($pK_a \approx 50$, $BDE \approx 111 \text{ kcal mol}^{-1}$). Functionalization of such inert C–H bonds became possible along the route of employing transition metal-catalyzed cross-coupling reactions [4–6]. The current scope of such functionalizations of unactivated C–H bonds is summarized in Figures 9.1 and 9.2, which demonstrate the most relevant C–H bond functionalizations in arenes [7] and in some non-aromatic compounds [8], respectively.

In an effort to develop environmentally benign syntheses, a versatile methodology to synthesize functional molecules by directly utilizing two different C–H bonds was established recently, which was termed cross-dehydrogenative coupling (CDC) (Scheme 9.1) [9–14]. Thereby, a variety of C–C bonds can be formed via oxidative functionalization of sp^3 C–H bonds in substrates, with a representative example being depicted in Scheme 9.1 [9]. Importantly, this methodology was extended to asymmetric catalytic C–C bond-forming reactions [15].

A protocol for cross-dehydrogenative oxidative coupling of the 2-arylpyridine **4** with the cycloalkane **5** under ruthenium catalysis was elegantly developed by Li and

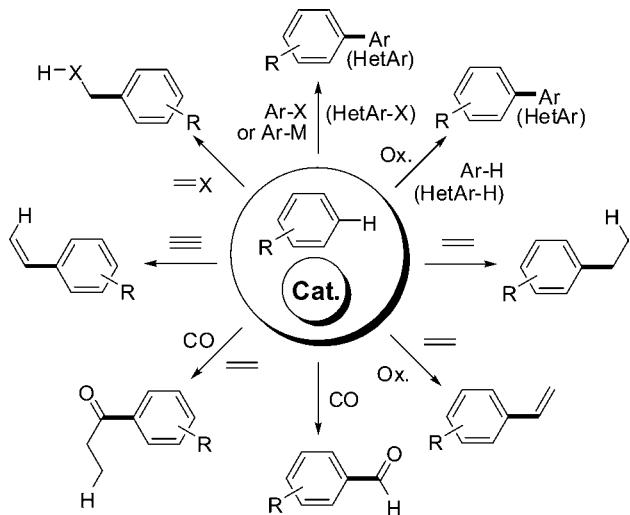


Figure 9.1 Representative C–H bond functionalizations of arenes.

co-workers [16]. Here, peroxides served as a sacrificial oxidant for achieving oxidative couplings (Scheme 9.2). Excellent regioselectivities were observed for 2-arylpyridines with either electron-withdrawing or electron-donating substituents.

Similarly, chelation-assisted palladium-catalyzed oxidative functionalizations of C–H bonds with, for example, hypervalent iodine(III) reagents turned out to be particularly valuable. These protocols allowed for, *inter alia*, regioselective acetoxylation or etherification of aromatic and aliphatic C–H bonds [17–19], and also halogenations of arenes (Scheme 9.3) [20, 21].

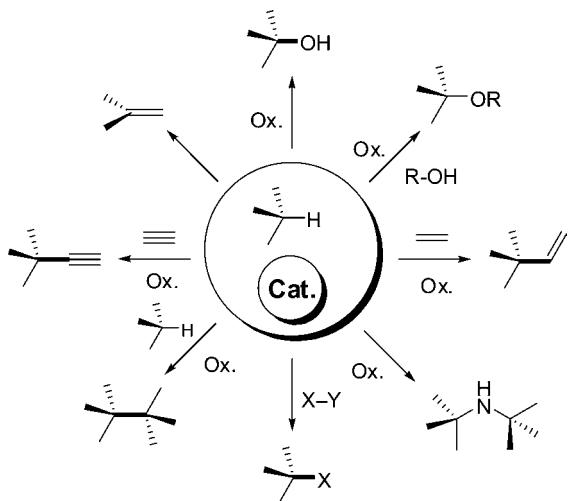
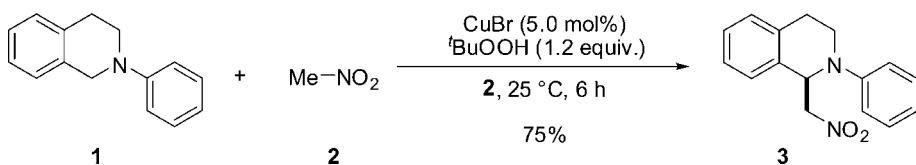
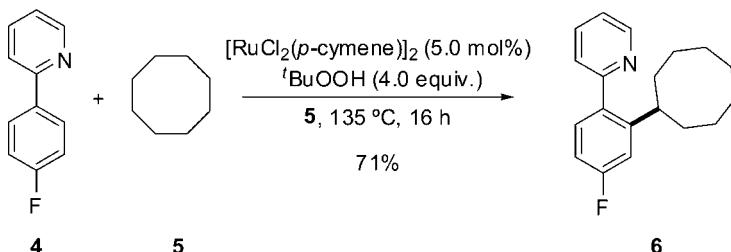


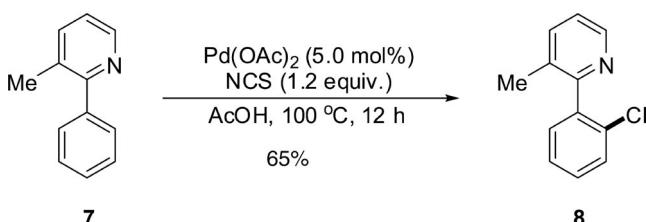
Figure 9.2 Selected C–H bond functionalizations in non-aromatic compounds.



Scheme 9.1 Copper-catalyzed cross-dehydrogenative coupling.



Scheme 9.2 Ruthenium-catalyzed cross-dehydrogenative coupling between the 2-arylpyridine **4** and the cycloalkane **5**.



Scheme 9.3 Palladium-catalyzed chelation-assisted oxidative functionalization of the arene **7**.

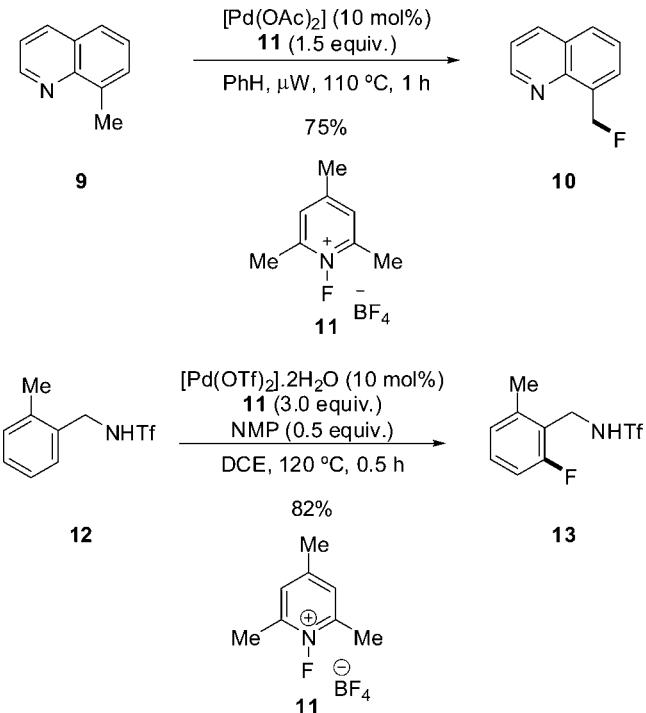
Furthermore, the use of the electrophilic fluorinating reagent **11** to effect oxidative formation of C–F bonds in 8-methylquinoline (**9**) was reported [22]. More recently, a versatile palladium-catalyzed *ortho*-fluorination of the triflamide-protected benzylamine **12** was disclosed, which also made use of electrophilic fluorinating reagents (Scheme 9.4) [23].

However, given that transition metal catalysis had arguably the strongest impact through the development of efficient methods for bi(hetero)aryl formations, we focus here largely on C–H bond functionalizations for catalytic direct arylations of (hetero)arenes [24].

9.2

Direct Arylations of Arenes

The development of methods for the synthesis of compounds with aryl–aryl or aryl–heteroaryl moieties is of the utmost importance for modern organic synthesis,

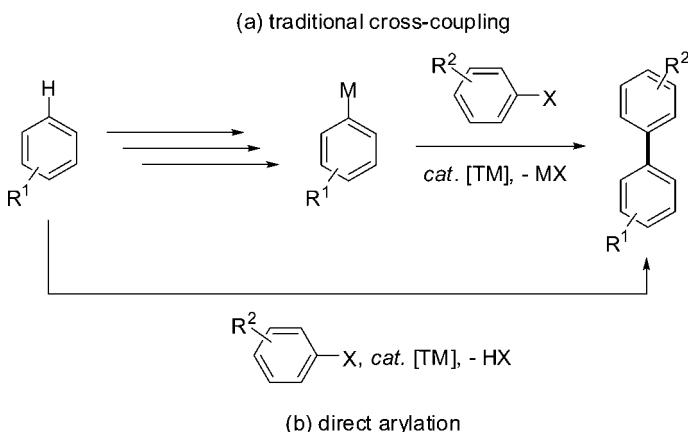


Scheme 9.4 Palladium-catalyzed regioselective fluorinations.

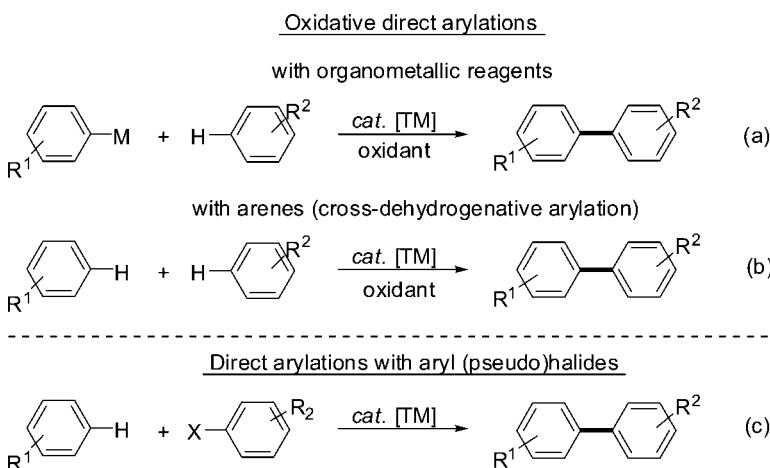
because these structural motifs are often found as indispensable substructures of naturally occurring compounds, pharmaceutical and agrochemical products, and organic (semi)conductors. Regioselective syntheses of these bi(hetero)aryls predominantly make use of transition metal-catalyzed cross-coupling reactions between organic (pseudo)halides and stoichiometric amounts of organometallic reagents (Scheme 9.5a) [25–27], which have matured to being reliable tools for the formation of C(sp²)–C(sp²) bonds.

However, the required organometallic nucleophilic reagents, particularly when being functionalized, are often not commercially available or are expensive. Their syntheses from the corresponding arenes usually involve a number of reactions, during which undesired by-products are formed, as they are during the traditional cross-coupling reactions themselves. An environmentally sound and economically more attractive strategy is represented by intermolecular direct arylation reactions through cleavages of C–H bonds (Scheme 9.5b). Importantly, this strategy is not only advantageous with respect to the minimization of overall by-product formation, but also allows for a significant reduction in the number of reaction steps [6b].

Catalytic direct arylations can be accomplished in an oxidative fashion, provided that stoichiometric oxidants are present. These transformations can be achieved either with stoichiometric amounts of organometallic reagents as arylating reagents (Scheme 9.6a) or directly with (hetero)arenes (Scheme 9.6b). Unfortunately, oxidative



Scheme 9.5 Traditional cross-coupling (a) versus direct arylation (b).



Scheme 9.6 Direct arylation-based strategies for biaryl synthesis.

direct arylations employing organometallic reagents are associated with the formation of stoichiometric amounts of undesired by-products. In contrast, cross-dehydrogenative arylations are significantly more desirable, but often proved to be inapplicable with the use of air as sacrificial oxidant [28]. Moreover, controlling regioselectivities in intermolecular cross-dehydrogenative arylation reactions continues to represent a significant challenge. Therefore, this approach was found useful for mainly or intramolecular processes, and also selected intermolecular transformations of electronically biased (hetero)arenes. Consequently, direct arylations with (pseudo)halides as arylating reagents (Scheme 9.6c) had arguably the most significant impact so far on the synthesis of biaryls.

Achieving C–H bond cleavages is generally believed to be difficult given their inherent strengths. Indeed, the bond dissociation energies for Ph–H, Ph–Cl, Ph–Br, and Ph–I are 113–110, 96, 81, and 65 kcal mol⁻¹, respectively [1–3, 29]. Despite these obstacles, the fundamental features of using C–H bonds as functional groups in organic synthesis were delineated, and a number of fascinating protocols for C–H bond cleavages involving predominantly palladium, rhodium and ruthenium catalysis were developed during the last decade. Accordingly, selected reviews were published, which partly cover the state-of-the-art of catalytic direct C–H bond arylations of (hetero)arenes [7, 8, 28, 30, 31]. Therefore, we mainly discuss here more recently reported protocols in more detail.

9.2.1

“Green” Aspects of Direct Arylation of Aryl C–H Bonds

At the outset, we wish to compare ecological aspects of direct C–H bond arylations with those of traditional coupling chemistry. Arguably, the Suzuki–Miyaura reaction is currently the most widely used method for the preparation of bi(hetero)aryls in “usable” solvents [32] with low catalyst loadings at slightly elevated reaction temperatures. The recent achievements towards performing the Suzuki–Miyaura coupling in “greener” aqueous media and employing immobilized ligand-free recyclable palladium catalysts under microwave irradiation [33] allowed this reaction to meet most of the Twelve Principles of Green Chemistry (TPGC, Figure 9.3) [34].

However, the true “greenness” of this reaction remained far from being ideal, as the necessity to prepare initially the arylboronic acids (or their derivatives) as nucleophilic starting material and to recycle (or to eliminate) the associated waste thereafter violate several of the TPGC. Hence this not only contradicts the concept of “atom economy” [35], but also increased Sheldon’s environmental impact factor *E* (*E* = kg_{waste}/kg_{product}) [36]. As a consequence, this resulted in a decrease in the value of the reaction mass efficiency (RME) for the Suzuki–Miyaura reaction. The value RME = 1 characterizes an “absolutely green” reaction, but all reactions with RME ≥ 0.618,

Twelve Principles of Green Chemistry

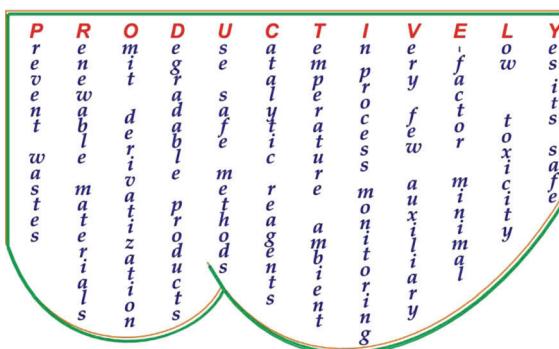


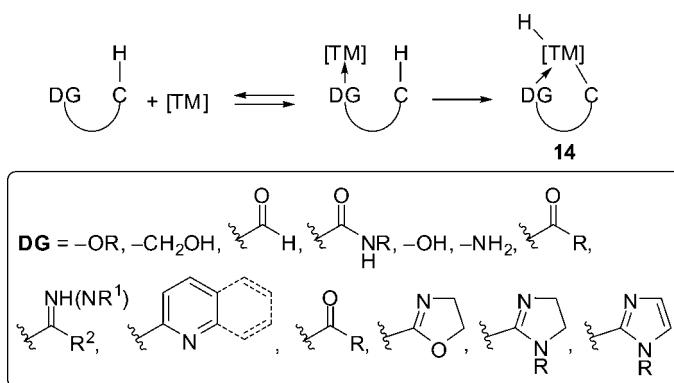
Figure 9.3 The twelve principles of green chemistry [34].

the so-called “golden ratio,” can still be considered “green” [37]. The RME values for Suzuki–Miyaura couplings, as calculated by the generalized Markush structures, are close to 0.55–0.66. However, the necessity to recycle or to eliminate the boron-based wastes decreases these values to 0.24–0.27 [37]. In contrast, when being compared with Suzuki–Miyaura reactions, direct arylations of C–H bonds of (hetero)arenes exhibit obvious advantages in at least four of the TPGC, that is, “prevent wastes,” “omit derivatization,” “*E*-factor,” and “low toxicity.”

9.2.2

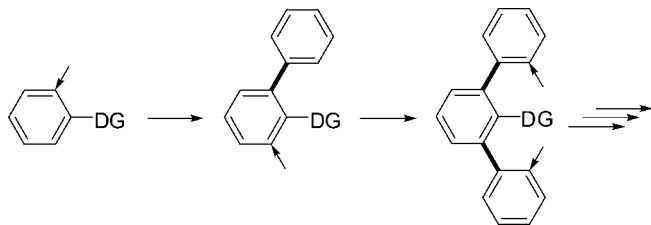
Chelation-Assisted Direct Arylations of Arenes

The above-mentioned advantages of direct arylations of arenes are less relevant when these reactions occur with only moderate regioselectivities. The most generally applicable strategy to address this problem is through the use of directing groups to control the regioselectivities of C–H bond metalation [38]. Accordingly, selectivities can be achieved with Lewis basic directing groups (DGs) (Scheme 9.7). These can precoordinate to the transition metal catalyst [TM], thereby bringing the metal in close proximity to the C–H bond to be functionalized and thus promoting the necessary substrate–catalyst interactions. This allows direct regioselective arylation, usually through the formation of five- or six-membered metallacycles (14) [31, 39].

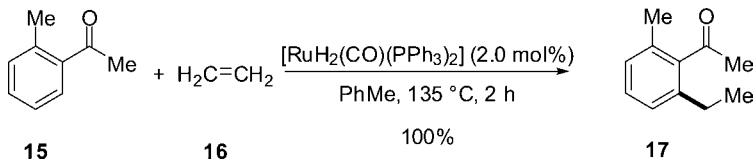


Scheme 9.7 Directing groups for regioselective C–H bond cleavages.

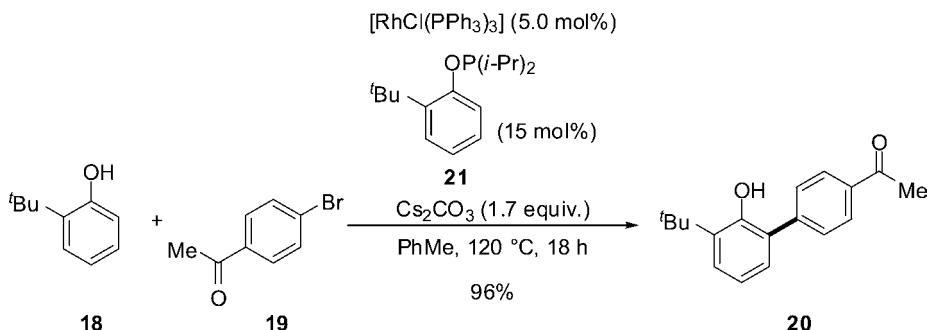
The most widely applied DGs include alkoxy, hydroxymethyl, formyl, amido, hydroxy, amino, keto, ketimino, pyridyl (quinolinyl), oxazolinyl, imidazolinyl, and pyrazolyl substituents. The first four DGs, however, have been used mainly in palladium-catalyzed arylations, whereas reactions with the last three DGs were performed almost exclusively with ruthenium catalysts [40]. A peculiar problem of selectivity complicates direct arylations of organic compounds, in that monoarylation can be accompanied by the formation of di- or oligoarylated species (Scheme 9.8).

**Scheme 9.8** Selectivities in direct arylations using directing groups.

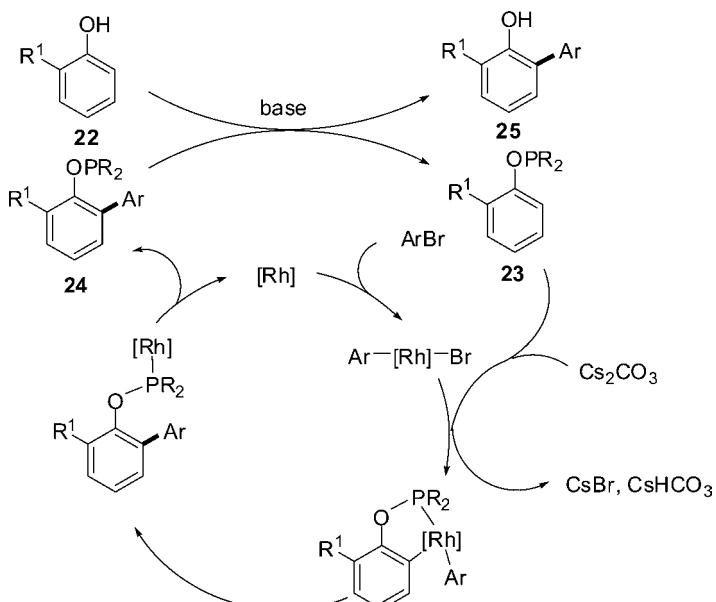
Pioneering studies on C–C-bond formations through C–H bond cleavages employed phenols [41] or aromatic ketones [42] for arylations of alkenes through chelation assistance (Scheme 9.9).

**Scheme 9.9** Ruthenium-catalyzed hydroarylation of ethene (**16**).

Arylations of phenols with palladium catalysts are preparatively valuable mainly when using substituted 2-phenylphenols, since otherwise difficult to separate mixtures of oligoarylated products were obtained [43]. The problem was addressed by the application of rhodium catalysts. Thus, the use of $\text{P}(\text{iPr})_2(\text{OAr})$ (**21**) as a co-catalyst allowed for the selective *ortho*-arylation of a variety of 2-substituted phenols such as **18** with the aryl bromide **19** in good to excellent yields (Scheme 9.10) [44].

**Scheme 9.10** Rhodium-catalyzed regioselective arylation of the phenol **18** in the presence of the phosphinite co-catalyst **21**.

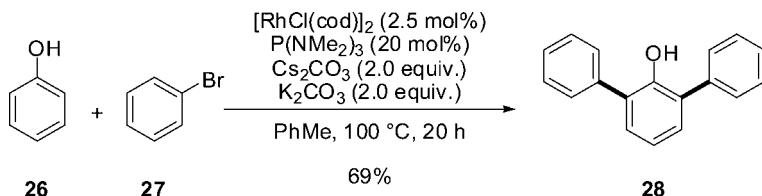
According to the proposed mechanism (Scheme 9.11), the reaction proceeds via *ortho*-metalation and arylation of a phosphinite (**23**), which is regenerated by



Scheme 9.11 Proposed mechanism for regioselective arylations of phenols.

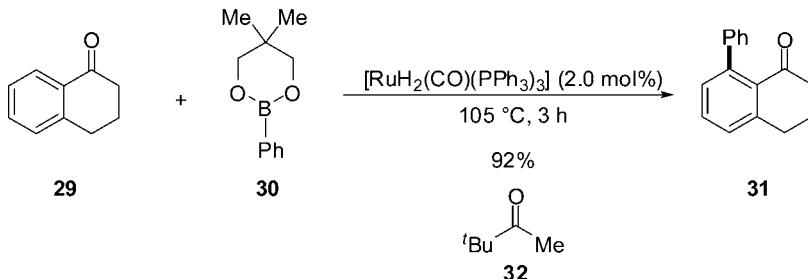
transesterification of its arylated derivative **24** with the starting phenol **22**. This furnishes the 2-arylated product **25**. Consequently, the corresponding phosphinite co-catalyst **23** had to be prepared from each starting material prior to its use, to avoid contamination with undesired and difficult to separate byproducts.

An alternative solution was developed through the use of hexamethylphosphorous triamide [HMPT; $\text{P}(\text{NMe}_2)_3$] as an additive, along with $[\text{RhCl}(\text{cod})_2]$ as precursor (Scheme 9.12) [44c,45]. In this transformation, aryl phosphites were initially generated *in situ* from the corresponding phenols and $\text{P}(\text{NMe}_2)_3$.



Scheme 9.12 Rhodium-catalyzed direct phenylation of phenol **(26)**.

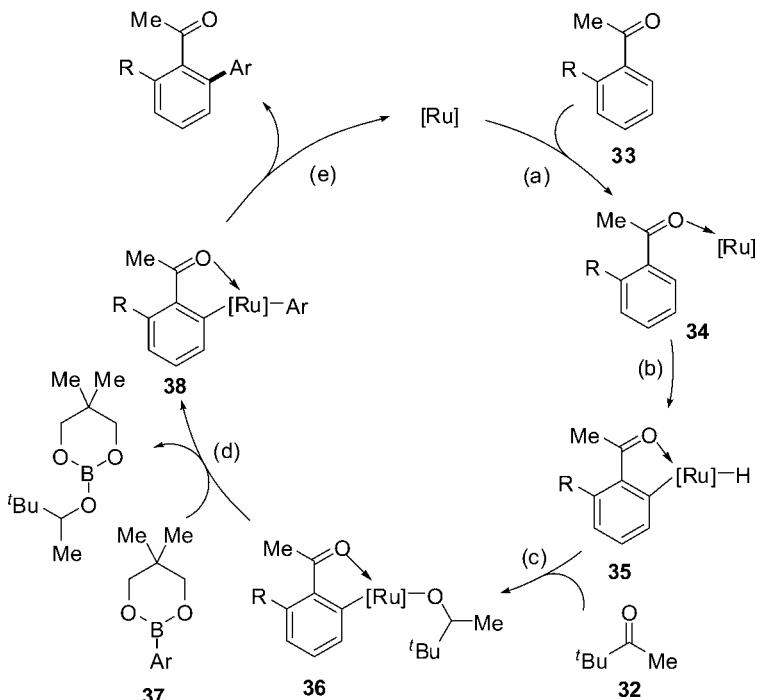
Palladium-catalyzed ketone-directed arylations with substituted aryl bromides furnished a mixture of differently arylated products in moderate yields [46]. However, direct arylations of aryl-substituted ketones can be achieved using substituted boronates with ruthenium catalysts [47]. This protocol was not only applied to the monoarylation of aryl ketone **29** (Scheme 9.13) [47], but also more recently enabled



Scheme 9.13 Ruthenium-catalyzed direct arylation of the ketone **29** with the arylboronic ester **30** in pinacolone (**32**).

oligoarylations of anthraquinones to be achieved [48]. Furthermore, regioselective α -arylations of saturated heteroarenes proved viable through chelation assistance [49].

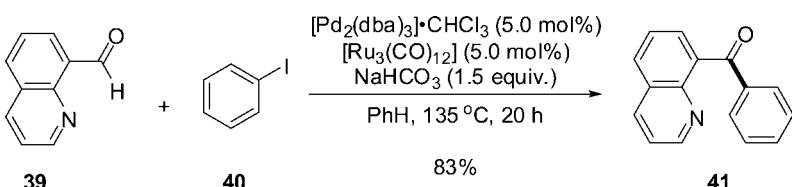
Elegant mechanistic studies revealed that pinacolone not only served as a solvent, but was also required as a sacrificial oxidizing agent (Scheme 9.14). Additionally, inter- and intramolecular competition experiments with isotopically labeled ketones provided evidence for a precoordination of the ruthenium catalyst by the oxygen of the aryl ketone. Thus, a mechanism was elaborated consisting of (a) coordination, (b)



Scheme 9.14 Mechanism of ruthenium-catalyzed direct arylation of ketones (**33**) with a substituted boronic ester (**37**).

oxidative addition to yield *ortho*-metalated ruthenacycle **35**, (c) insertion of pinacolone into the [Ru]–H bond, (d) transmetalation, and final (e) reductive elimination.

Substituted benzaldehydes, with a formyl substituent as directing group, were selectively arylated at their *ortho*-position with aryl bromides as electrophiles in the presence of palladium(0) catalysts [50]. The use of a ruthenium complexes within a cooperative multi-catalytic system [51] altered the chemoselectivity dramatically [52]. Thus, reactions of 8-formylquinoline (**39**) with iodoarenes proceeded regioselectivity at the formyl group itself to give the corresponding ketones in moderate to very good yields (Scheme 9.15) [52].

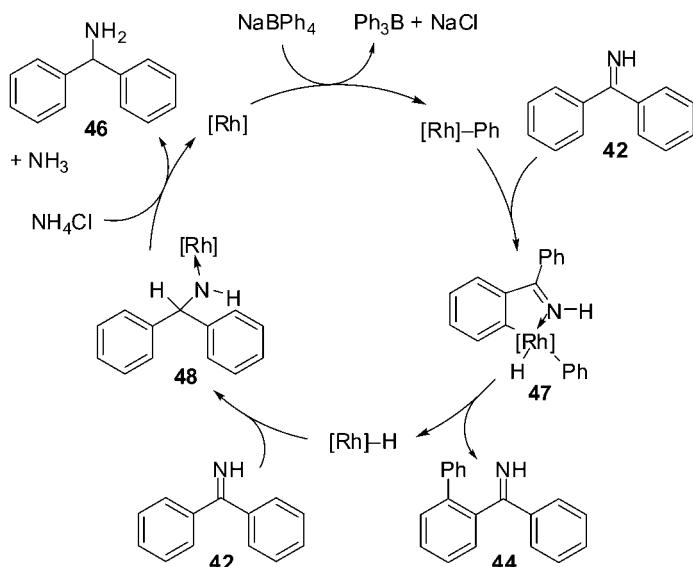
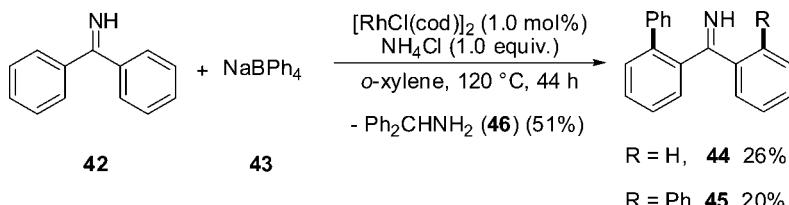


Scheme 9.15 Palladium-catalyzed arylation of 8-formylquinoline (**39**).

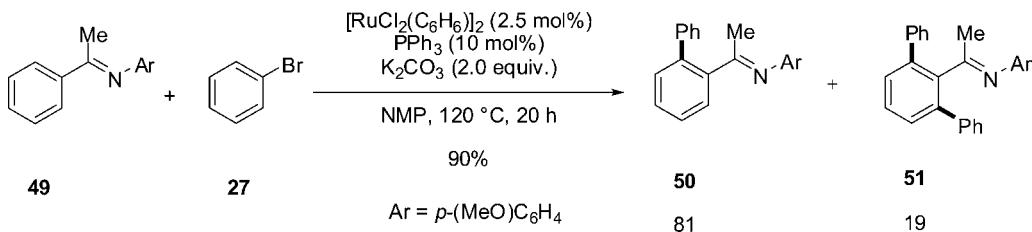
Arylation reactions of aromatic ketimines were developed, and in many cases the products of the reaction were isolated after subsequent hydrolysis. Therefore, these arylations constitute an indirect method for the preparation of arylated aromatic ketones, the direct functionalizations of which are often more difficult. Thus, direct arylation of imine **42** with sodium tetraphenylborate catalyzed by $[\text{RhCl}(\text{cod})]_2$ afforded a mixture of mono- and diarylated benzophenone imines (**44** and **45**) (Scheme 9.16) [53]. The formation of the corresponding amine **46** clearly indicated that **42** also acted as a hydride acceptor in this transformation. Most likely, the reaction occurs via initial coordination by the benzophenone imine to a phenylrhodium intermediate followed by *ortho*-rhodation to afford the five-membered rhoda-cycle intermediate **47** (Scheme 9.16). Subsequent reductive elimination generates the monophenylation product **44** and a rhodium hydride, which then reduces imine **42** in the presence of ammonium chloride as proton donor to regenerate the catalytically active species.

Synthetically useful direct arylations of a variety of substituted ketimines with aryl bromides were achieved with $[\text{RuCl}_2(\text{C}_6\text{H}_6)]_2$ as precursor, along with PPh_3 as ligand and K_2CO_3 as base, to give the corresponding arylated imines in high yields [54]. In the absence of any *meta*-substituent, as in imine **49**, mixtures of mono- and diarylated products **50** and **51**, respectively, were obtained (Scheme 9.17).

An alternative approach to ensure selective monoarylations of ketimines, including those without *meta*-substituents, was based on the development of a novel catalytic system. Significant progress was achieved with air-stable (heteroatom-substituted) secondary phosphine oxides (HA)SPOs, since these preligands gave rise to arylation reactions also with less reactive, yet inexpensive, aryl chlorides as electrophiles. Here, the sterically hindered derivative $(1\text{-Ad})_2\text{P}(\text{O})\text{H}$ (**54**) was found



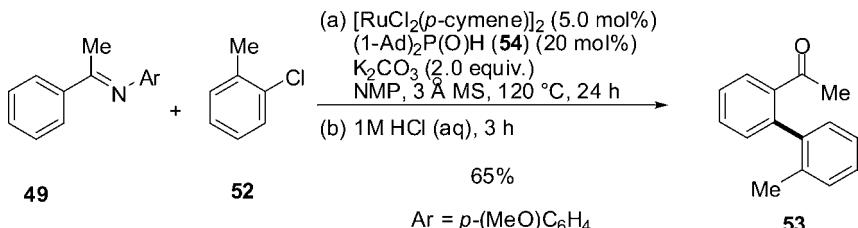
Scheme 9.16 Rhodium-catalyzed phenylation of benzophenone imine (**42**) with NaBPh₄.



Scheme 9.17 Ruthenium-catalyzed direct arylation of the ketimine **49** with the aryl bromide **27**.

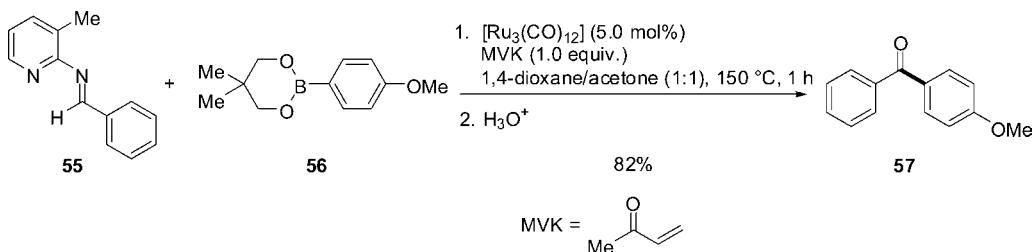
particularly useful for direct arylations of substituted imines with aryl chlorides (Scheme 9.18) [55]. These reactions yielded selectively the monoarylated products, which were isolated after hydrolysis as the corresponding arylated ketones in high yields even when *ortho*-substituted aryl chlorides were employed.

Fewer examples of direct arylations of aldimines have thus far been reported. Aldimines with *N*-(2-pyridyl) substituents displayed a unique reactivity, in that the



Scheme 9.18 Ruthenium-catalyzed monoarylation of ketimine **49** with aryl chloride **52** using $(1\text{-Ad})_2\text{P}(\text{O})\text{H}$ (**54**) as preligand.

directing effect of the 2-pyridyl moiety suppressed those exposed by the imino moiety. As a consequence, these reactions resulted in regioselective arylations of the formyl group itself. Thus, ruthenium-catalyzed arylations of the aldimine **55** with the boronic ester **56** and methyl vinyl ketone (MVK) as hydride scavenger afforded after hydrolysis the corresponding ketone **57** in good yield (Scheme 9.19) [56]. Thus, this reaction constituted a convenient method for the conversion of aromatic aldehydes into the corresponding benzophenone derivatives.

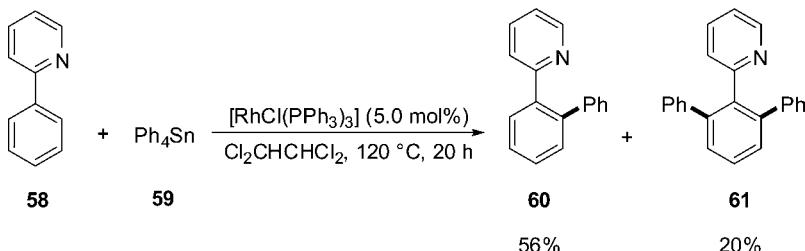


Scheme 9.19 Ruthenium-catalyzed arylation of the aldimine **55**.

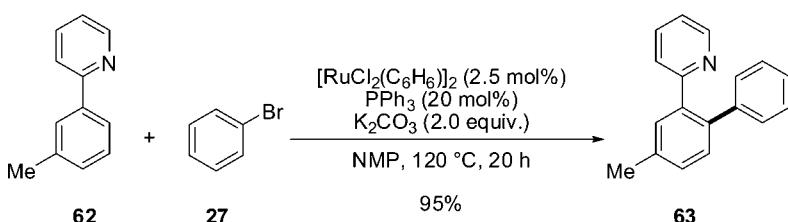
2-Pyridyl and 2-quinolinyl substituents are known to be among the most powerful directing groups for direct arylation reactions [57]. Palladium-catalyzed direct arylations of arenes displaying these directing groups with aryl iodides, bromides, or hypervalent iodonium salts as arylating agents were reported in recent years [31e]. Furthermore, direct arylation reactions of such arenes were also accomplished with tin-based arylating reagents (Scheme 9.20) [58]. Similar products were obtained through ruthenium-catalyzed direct arylations of 2-(3-methylphenyl)pyridine (**62**) (Scheme 9.21) [59].

Ruthenium-catalyzed direct arylations of the arene **58** with the secondary phosphine oxide $(1\text{-Ad})_2\text{P}(\text{O})\text{H}$ (**54**) as preligand allowed for the use of inexpensive aryl chlorides as electrophiles (Scheme 9.22) [55]. Importantly, the protocol proved applicable to both electron-deficient and electron-rich aryl chlorides.

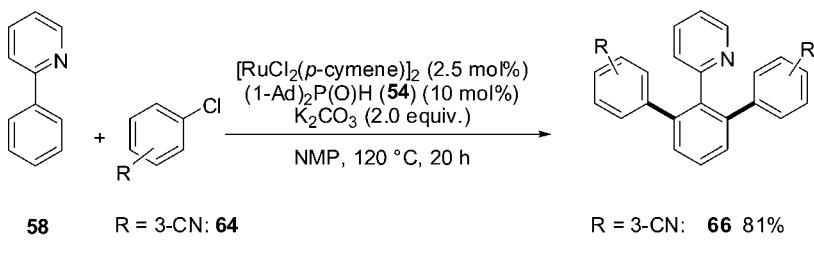
The problem of achieving selective monoarylations of 2-arylpyridines was solved by applying a sterically hindered diaminophosphine oxide (**72**) as preligand [60]. This air-stable preligand allowed the use of tosylates as electrophiles, which are easily



Scheme 9.20 Rhodium-catalyzed direct arylation of 2-phenylpyridine (**58**).



Scheme 9.21 Ruthenium-catalyzed direct arylation with bromobenzene (**27**).

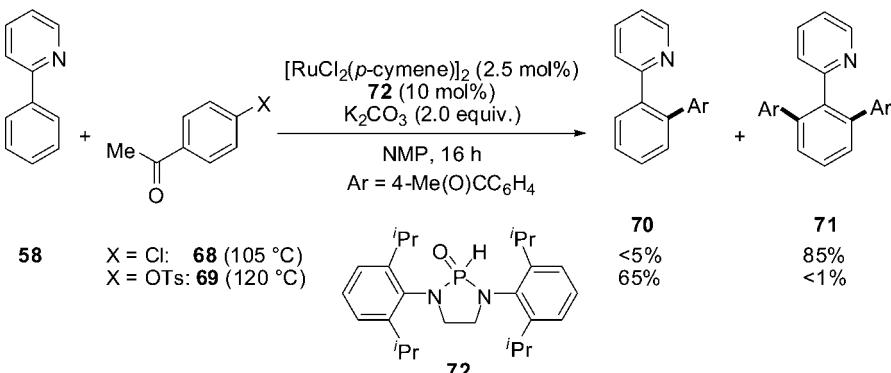


Scheme 9.22 Ruthenium-catalyzed direct arylations with the aryl chlorides **64** and **65**.

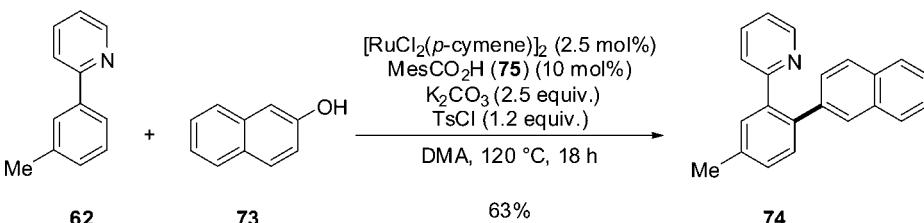
available from inexpensive phenols. Importantly, reactions with aryl tosylates as electrophiles selectively yielded the monoarylated products, whereas the corresponding aryl chlorides gave rise to diarylated arenes (Scheme 9.23) [60].

Furthermore, tosylates could be generated *in situ* by employing phenols directly as proelectrophilic reagents. Thus, monoarylations of 2-arylpyridines were accomplished through chemo- and regioselective functionalizations of C–H and C–OH bonds via a formal dehydrative cross-coupling (Scheme 9.24) [61].

In ruthenium-catalyzed direct arylations, the directing abilities of 2-oxazolinyl, 2-imidazolinyl, and 1-pyrazolyl groups turned out to be comparable to those observed for 2-pyridyl substituents [60]. As a consequence, a number of nitrogen-containing five-membered heterocycles have been employed as directing groups in intermolecular *ortho*-arylation reactions [60, 62]. As an example, the 2-aryloxazoline **76** was

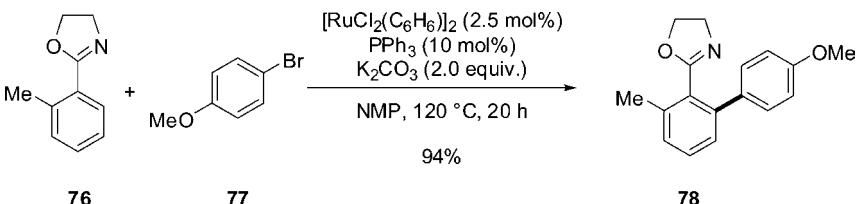


Scheme 9.23 Selective ruthenium-catalyzed mono- or diarylation of 2-phenylpyridine (**58**).



Scheme 9.24 Selective ruthenium-catalyzed monoarylation with the phenol **73**.

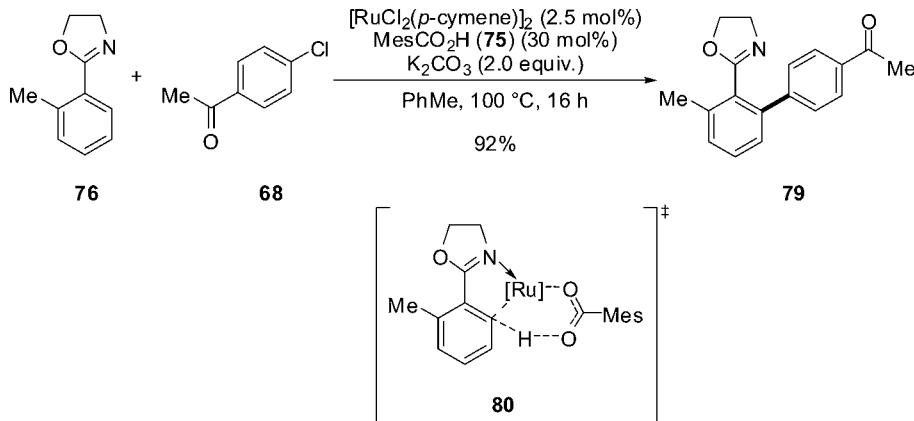
arylated with 4-bromoanisole (**77**) using a ruthenium catalyst derived from PPh_3 (Scheme 9.25) [63].



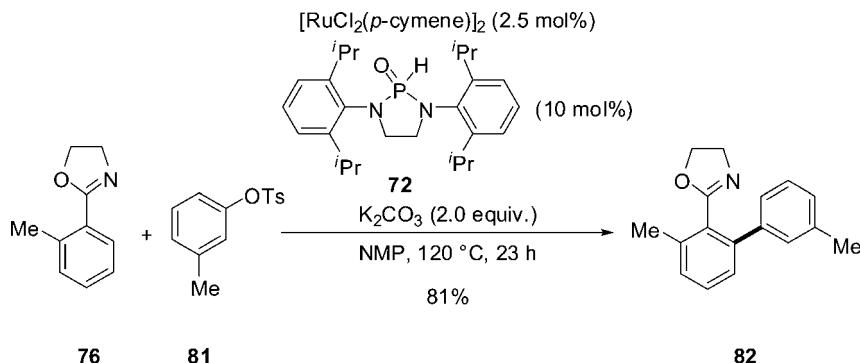
Scheme 9.25 Ruthenium-catalyzed direct arylation of the 2-aryloxazoline **76** with the aryl bromide **77**.

A significantly more active catalytic system was recently reported, with a ruthenium complex generated from carboxylic acid **75**. This allowed for direct arylations to occur also in apolar solvents likely via a concerted metalation–deprotonation mechanism (CMD) and set the stage for the use of aryl bromides, chlorides, and tosylates as electrophilic substrates (Scheme 9.26) [64].

Efficient direct arylations of 2-aryloxazolines with aryl tosylates as electrophiles were further accomplished with HASPO preligand **72** (Scheme 9.27) [60].

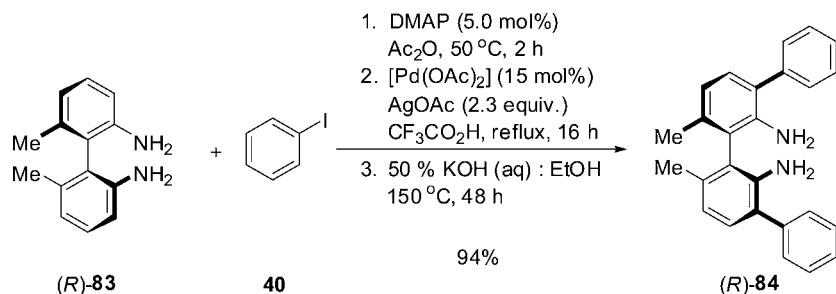


Scheme 9.26 Ruthenium-catalyzed direct arylation with MesCO_2H (**75**) as additive.



Scheme 9.27 Selective ruthenium-catalyzed *ortho*-arylation of the oxazoline **76** with the aryl tosylate **81**.

An elegant application of regioselective palladium-catalyzed direct arylations of anilides in the presence of stoichiometric amounts of AgOAc in trifluoroacetic acid [65] permitted the preparation of chiral diamines with varying steric demands (Scheme 9.28) [66].

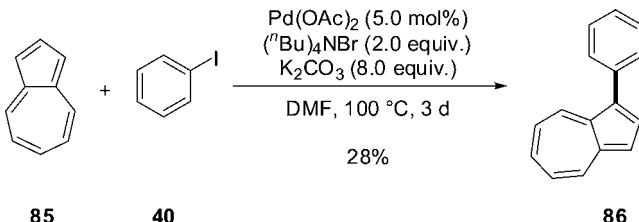


Scheme 9.28 Palladium-catalyzed synthesis of the chiral diamine **84** via direct arylation.

9.2.3

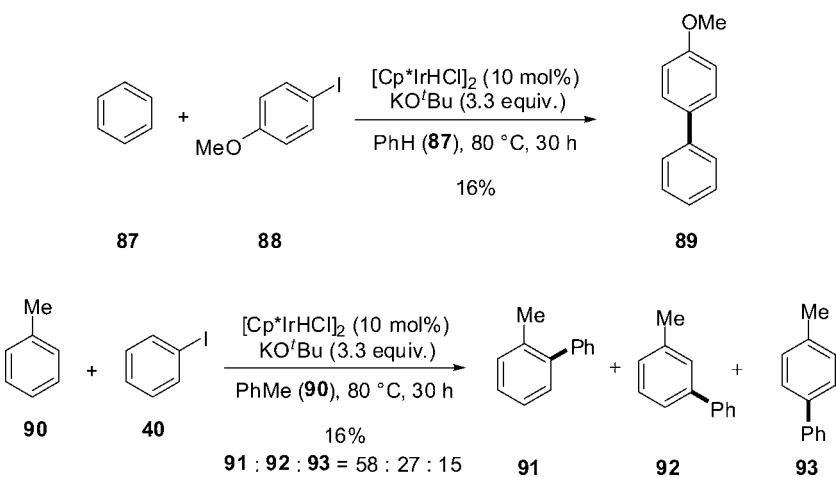
Non-Directed Direct Arylations of Arenes

Among the few known methods for catalytic direct arylations of simple arenes with aryl halides, early examples are represented by direct arylations of azulene (Scheme 9.29) [67] and of benzene [68].



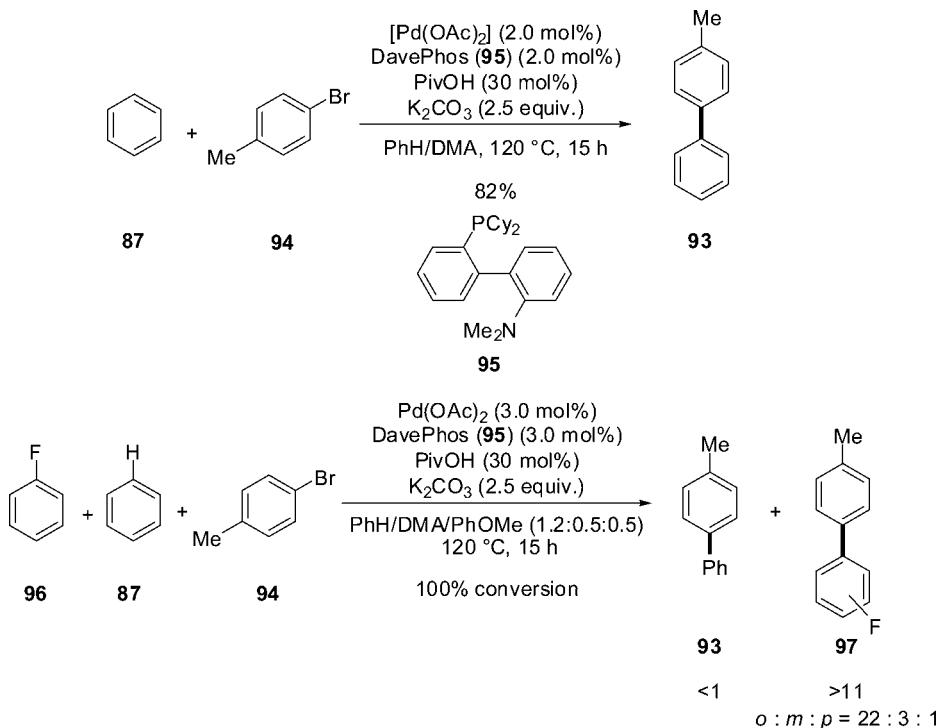
Scheme 9.29 Palladium-catalyzed direct arylation of azulene (85).

Direct arylations of arenes are, however, not restricted to palladium-catalyzed transformations, but were also accomplished with, *inter alia*, iridium complexes. Thus, the direct coupling of various aryl iodides with an excess of benzene in the presence of $[\text{Cp}^*\text{IrHCl}]_2$ afforded the corresponding biaryl products, but usually in moderate yields only (Scheme 9.30) [69]. The reaction is believed to proceed via a radical-based mechanism with initial base-mediated reduction of iridium(III) followed by electron transfer from iridium(II) to the aryl iodide. Rather high catalyst loadings were required and the phenylation of toluene (90) under these reaction conditions provided a mixture of regioisomers 91, 92, and 93 in an overall low yield (Scheme 9.30) [69].



Scheme 9.30 Iridium-catalyzed direct arylations of benzene (87) and toluene (90).

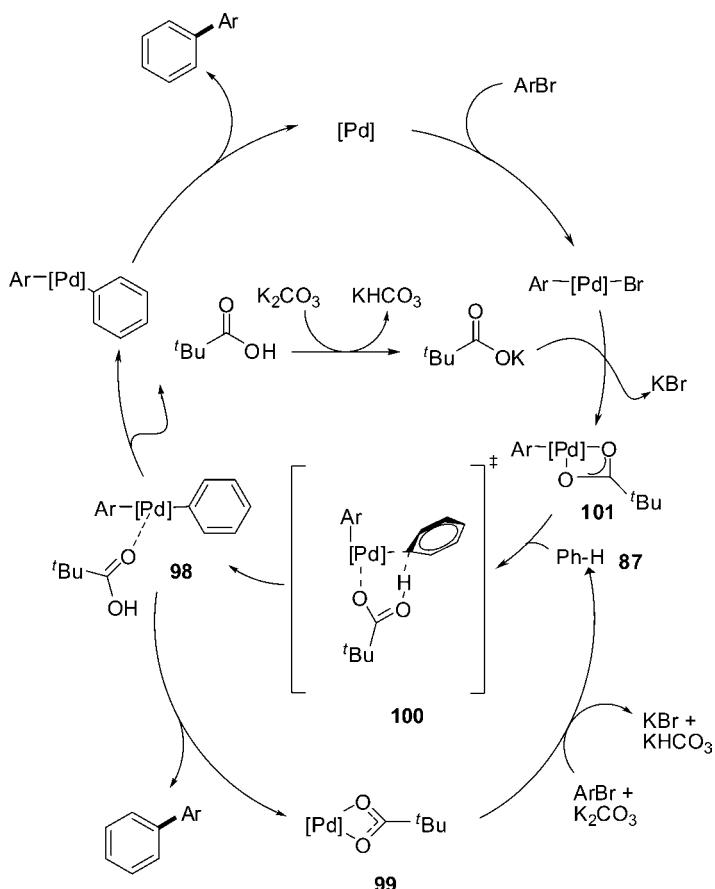
Further improvements in palladium catalysis were achieved with a larger excess of benzene as co-solvent, and also with DavePhos (**95**) as ligand and pivalic acid as additive (Scheme 9.31) [70]. This catalytic system tolerated various valuable functional groups, such as a nitro substituent. These reaction conditions allowed not only for the achievement of better yields of biaryls with aryl bromides as electrophiles, but also improved chemoselectivities of these transformations. Thus, in competition experiments between benzene (**87**) and fluorobenzene (**96**), the latter reacted preferentially in a ratio of $>11 : <1$ (Scheme 9.31) [70].



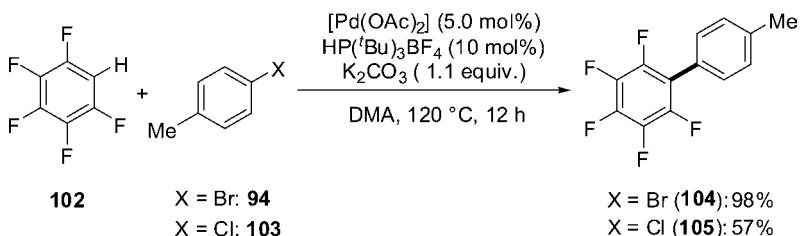
Scheme 9.31 Palladium-catalyzed direct arylation of arenes with the aryl bromide **94** and pivalic acid as additive.

These competition experiments and also a large intermolecular kinetic isotope effect of 5.5 highlighted the importance of the C–H bond acidity for such arylations. These results were not compatible with an $S_{\text{E}}\text{Ar}$ -type mechanism or radical processes, but were in agreement with a proton-transfer mechanism [70]. According to this mechanism, the pivalic acid was involved as a proton shuttle (Scheme 9.32). Experimental and computational studies further indicated that the pivalate anion is a key component in C–H bond cleavage, lowering the energy of the activation barrier for C–H bond cleavage [71].

From a mechanistic viewpoint, direct arylations of electron-deficient oligofluorobenzene with various aryl halides are somewhat related (Scheme 9.33) [72].



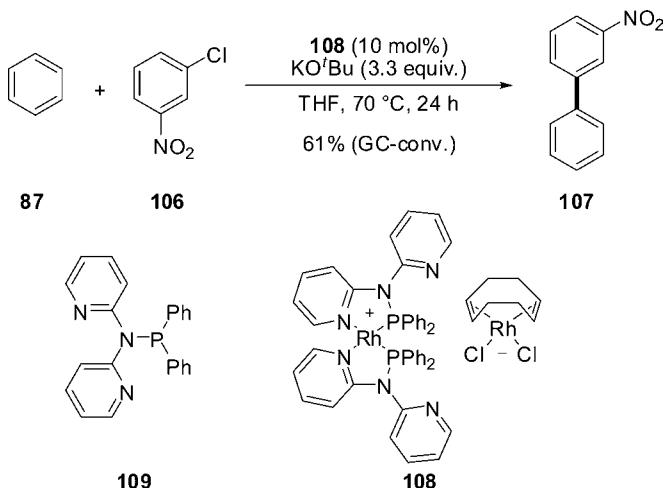
Scheme 9.32 Proposed mechanism of palladium-catalyzed direct arylation with pivalic acid as additive.



Scheme 9.33 Palladium-catalyzed direct arylation of pentafluorobenzene (**102**) with aryl halides **94** and **103**.

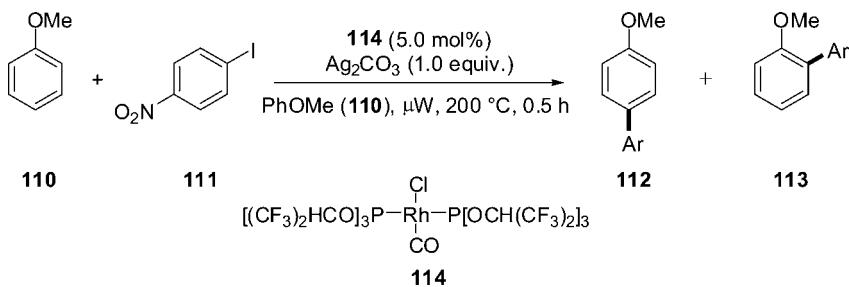
Importantly, aryl chlorides, bromides, and iodides led to the desired biaryl products. In particular, aryl bromides gave rise to the most efficient catalysis, whereas aryl iodides required AgOTf as stoichiometric additive to obtain satisfactory yields.

A highly active catalytic system for direct arylation reactions of nonactivated arenes relied on a homobimetallic rhodium complex. Thus, treatment of [bis(2-pyridyl)amino]diphenylphosphane (**109**) with $[\text{Rh}(\text{cod})\text{Cl}]_2$ led to the formation of a complex **108**, which, according to X-ray crystal structure analysis, consisted of $[\text{Rh}(\text{cod})\text{Cl}_2]^-$ anion and a rhodium cation stabilized by two P,N-ligands (Scheme 9.34) [73]. This bimetallic rhodium complex (**108**) allowed the direct arylation of benzene (**87**) with the aryl chloride **106** with a turnover number (TON) of 780 under comparably mild reaction conditions.



Scheme 9.34 Rhodium-catalyzed direct arylation reaction of benzene (**87**) with the homobimetallic rhodium catalyst **108**.

Further progress was made with the use of rhodium complexes with a strongly π -accepting phosphite ligand [74]. Here, the regioselectivities of direct arylations of anisole (**110**) and 1,3-dimethoxybenzene with rhodium complex **114** bearing strongly π -accepting phosphite ligands were consistent with an electrophilic metalation mechanism (Scheme 9.35) [74b].



Scheme 9.35 Rhodium-catalyzed direct arylation of anisole (**110**) with 4-iodonitrobenzene (**111**) catalyzed by the rhodium complex **114**.

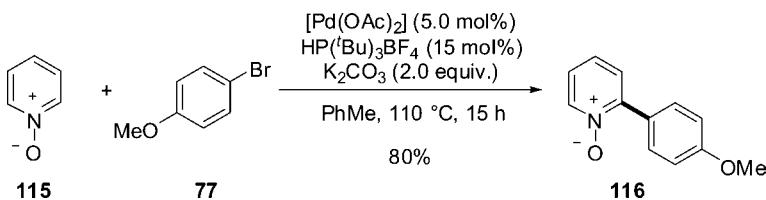
9.2.4

Direct Arylations of Heteroarenes

Intermolecular direct arylations of heteroarenes with aryl halides were thus far predominantly accomplished with palladium or rhodium complexes [31, 39, 75, 76]. Hence rhodium catalysts proved applicable to various electron-rich heteroarenes. In contrast, less expensive and more versatile palladium catalysts allowed for direct arylations of both electron-rich and electron-deficient substrates. Generally, the problem of achieving regioselectivities in direct arylation reactions of heteroarenes is less pronounced than it is for simple arenes, since in many cases the heteroatom can be considered as an “endocyclic” directing group.

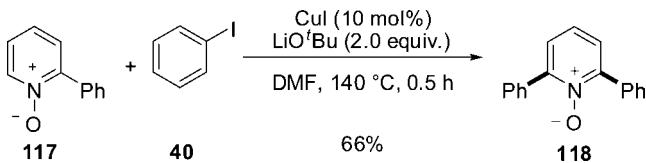
9.2.4.1 Direct Arylations of Electron-Deficient Heteroarenes

C–H bond arylations of electron-deficient heteroarenes, such as azines, remain highly challenging. An elegant and versatile solution was recently elaborated, however, through a redistribution of electron density in the starting pyridine by chemical modification [77, 78]. It was found that pyridine *N*-oxides smoothly underwent regioselectively palladium-catalyzed direct arylations with a variety of aryl bromides (Scheme 9.36) [77a].



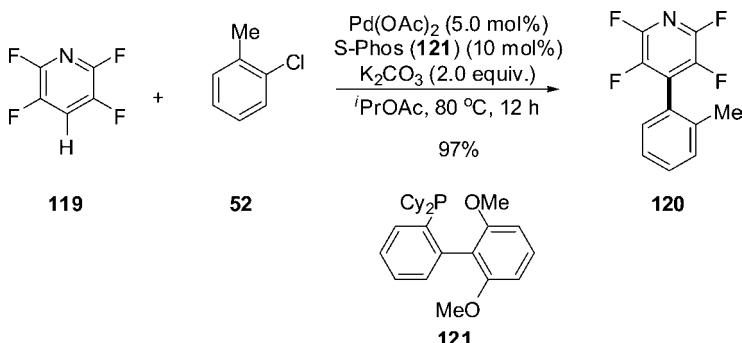
Scheme 9.36 Palladium-catalyzed direct arylation of pyridine *N*-oxide (115).

The arylated pyridine *N*-oxides could easily be reduced to give arylated pyridines. This methodology proceeded well with substituted diazine-*N*-oxides and also a wide range of electron-rich and electron-deficient aryl iodides, bromides, and chlorides [77b]. The second arylation in monoarylated pyridine *N*-oxides (117) was further achieved selectively in the 6-position when using an inexpensive copper catalyst (Scheme 9.37) [79].



Scheme 9.37 Copper-catalyzed direct arylation of the monoarylated pyridine *N*-oxide 117.

Direct phenylation of pyridine was accomplished with a heterogeneous palladium catalyst in the presence of zinc and water, albeit in only moderate yield [80]. In contrast, 2,3,5,6-tetrafluoropyridine (**119**) can easily be directly arylated with aryl bromides or chlorides such as **52** as electrophiles, furnishing substituted products in high yields (Scheme 9.38) [72].



Scheme 9.38 Palladium-catalyzed direct arylation of tetrafluoropyridine (**119**).

However, for the preparation of compounds with Ar–HetAr or HetAr–HetAr bonds bearing 3-, 4- or 5-substituted electron-deficient heterocyclic moieties, direct arylations using halogenated electron-deficient heteroarenes as electrophiles are usually superior. Selected examples of such couplings are summarized in Table 9.1.

9.2.4.2 Direct Arylations of Electron-Rich Heteroarenes

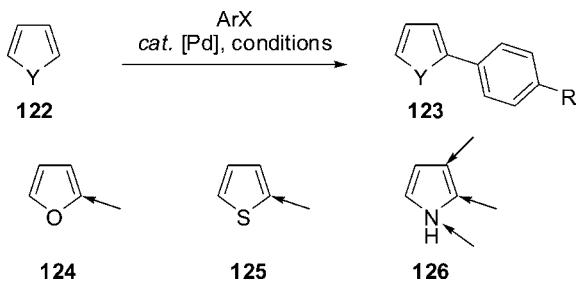
Palladium-catalyzed arylations of simple electron-rich five-membered heteroarenes with one heteroatom, such as furans, thiophenes, and pyrroles, with aryl iodides, bromides, or chlorides are among the most frequently studied direct arylation reactions [31, 39, 85]. These reactions usually afforded five-membered heterocycles, which were arylated at the position adjacent to the heteroatom in moderate to good yields. These reactions were mainly accomplished with electrophilic catalysts and proceeded more efficiently using aryl bromides with electron-withdrawing groups. This is in agreement with an electrophilic $S_{\mathrm{E}}\mathrm{Ar}$ -type mechanism relying on a palladium(0)/palladium(II) manifold [86]. Selected results of catalytic direct arylations of simple electron-rich five-membered heteroarenes (**124–126**) with aryl iodides, bromides, or chlorides are summarized in Table 9.2.

By switching the mechanism of palladium-catalyzed direct arylations from a palladium(0)/palladium(II) catalytic cycle to a palladium(II)/palladium(IV) manifold [92] effective arylations were achieved for both *N*-protected and *N*-unprotected pyrroles. However, this protocol required a 10-fold excess of the arylating reagent $[\text{Ph}_2\text{I}] \text{BF}_4^-$ [92]. Selective high-yielding 2-arylations of unprotected pyrrole (**126**) with aryl iodides were viable with a catalytic system consisting of $[\text{Rh}(\text{coe})_2\text{Cl}_2]_2$, along with the electron-deficient phosphine $[p\text{-}(\text{CF}_3)\text{C}_6\text{H}_4]_3\text{P}$ as ligand and pivalate as base (Scheme 9.39) [93].

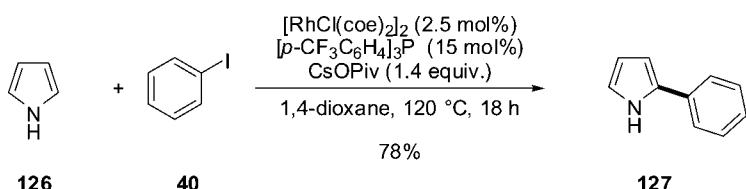
Table 9.1 Selected arylation reactions of (hetero)arenes with halogenated electron-deficient heteroarenes (where necessary arrows indicate the position of C–H bond functionalization).

(Hetero)arene	HetArX	Reaction conditions	Yield (%)	Ref.
		[Pd(OAc) ₂ (5.0 mol%), S-Phos (10 mol%), K ₂ CO ₃ (2.0 equiv.), ⁱ PrOAc, 80 °C, 12 h]	79	72
		108 (10 mol%), PhH (10 equiv.), 70 °C, 24 h	59	73
		108 (5.0 mol%), PhH (10 equiv.), 70 °C, 24 h	83	73
		[Pd(OAc) ₂ (5.0 mol%), Ad ₂ "BuP (10 mol%), K ₃ PO ₄ (2.0 equiv.), NMP, 125 °C, 24 h]	67	75m
		[Pd(OAc) ₂] (5.0 mol%), HN(ⁱ Pr) ₂ (3.0 equiv.), DMA, 125 °C, 48 h	25	75p
		CuI (10 mol%), LiO ^t Bu (2.0 equiv.), DMF, 140 °C, 10 min	89	81
		[PdCl ₂ (dppf)]·CH ₂ Cl ₂ (5.0 mol%), Ph ₃ P (10 mol%), Ag ₂ CO ₃ (2.0 equiv.), H ₂ O, 60 °C, 24 h	99	82
		[Pd(OAc) ₂] (2.0 mol%), Ph ₃ P (4.0 mol%), Cs ₂ CO ₃ (2.0 equiv.), 1,4-dioxane, 100 °C, 18 h	55	83
		[Pd(Ph ₃ P) ₄] (5.0 mol%), KOAc (2.0 equiv.), DMA, 150 °C, 6 h	25–82	84
		[Pd(OAc) ₂] (7.0 mol%), Ph ₃ P (14 mol %), K ₂ CO ₃ (2.5 equiv.), ⁱ Bu ₄ NHSO ₄ (1.0 equiv.), H ₂ O, 95 °C, 24 h	50	84

Table 9.2 Representative examples of palladium-catalyzed direct arylations of furan (124), thiophene (125) and pyrrole (126).

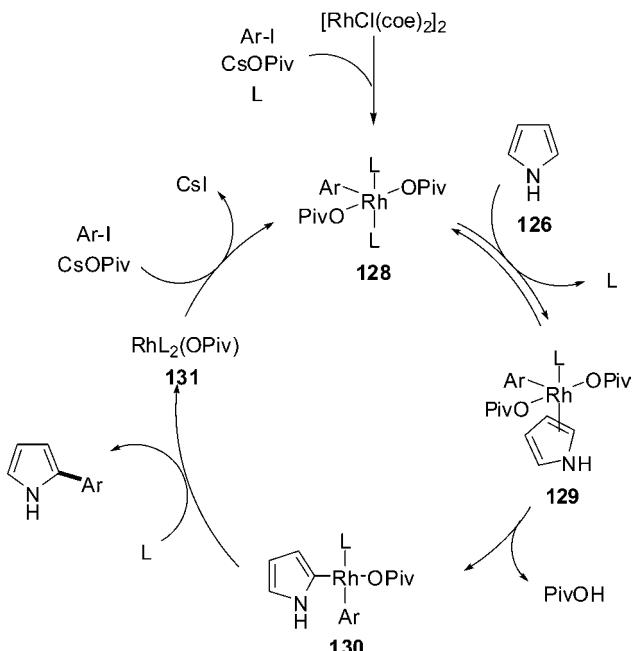


Entry	Y	X	R	Reaction conditions	Yield (%)	Ref.
1	S	Cl	3-AcN(H)	[Pd(OAc) ₂] (5.0 mol%), Ad ₂ ⁿ BuP (10 mol%), K ₃ PO ₄ (2.0 equiv.), NMP, 125 °C, 24 h	54	75m
2	O	Br	H	[Pd(PPh ₃) ₄] (5.0 mol%), KOAc (1.5 equiv.), DMA, 125 °C, 18 h	61	87
3	O	Br	NO ₂	[Pd(PPh ₃) ₄] (5.0 mol%), KOAc (1.5 equiv.), DMA, 150 °C, 12 h	59	88
			CHO		40	
			Ac		48	
			CO ₂ Me		52	
			CN		33	
4	S	I	OMe	[PdCl ₂ (dppb)] (3.0 mol%), AgF (1.0 equiv.), DMSO, 60 °C, 5 h	43	89
5	NZnCl	Br	H	[PdCl ₂ (PPh ₃) ₂] (10 mol%), Ph ₃ P (20 mol%), NMP, 140 °C, 2 h	75	90
6a	NZnCl	I	H	[Pd(OAc) ₂] (2.0 mol%), John-Phos (4.0 mol%), THF, 60–100 °C, 16–25 h	90	91
6b		Br	NMe ₂		48	
6c		Cl	“Bu		71	
7a	NH	–	H	Ph ₂ I ⁺ BF ₄ [–] (1.0 equiv.) [IMesPd(OAc) ₂] (5.0 mol%), AcOH, 25 °C, 15–24 h	69	92
7b	NMe	–	H		67	



Scheme 9.39 Rhodium-catalyzed direct arylation of pyrrole (**126**) with the aryl iodide **40**.

This *in situ*-generated rhodium complex functionalized C–H bonds selectively in the presence of more acidic N–H bonds. This chemoselectivity was explained in terms of a greater electrophilicity of the Ar–Rh(III) species compared with the corresponding Ar–Pd(II) species. The proposed mechanism was supported by a large kinetic isotope effect at the 2-position, together with an X-ray crystal structure analysis of the key intermediate **130** ($\text{Ar} = p\text{-Tol}$) (Scheme 9.40).



Scheme 9.40 Proposed mechanism of rhodium-catalyzed direct arylations of pyrroles.

In contrast, *N*-methylpyrrole underwent direct arylations at the 3-position [93], and a comparable result was obtained in direct arylations of *N*-phenylpyrrole employing the electron-deficient rhodium complex **114**, in combination with Ag_2CO_3 under microwave irradiation [74b]. Selected examples of regioselective arylations of substituted five-membered heteroarenes are summarized in Table 9.3.

Studies on the regioselectivity of catalytic direct arylation reactions of 3,4-disubstituted five-membered aromatic heterocycles are scarce. Published examples of such reactions are largely limited to palladium-catalyzed twofold arylations of 3,4-disubstituted thiophenes possessing identical substituents with aryl bromides as electrophiles [99]. Thus, diarylated derivatives **143** and **147** were obtained in moderate to good yields starting from 3,4-dicyanothiophene (**142**), arylated analogs of which are interesting because of their optical properties [102], and from 3,4-ethylenedioxythiophene (EDOT) (**145**) [99], which is used as a building block for the preparation of organic conducting materials (Scheme 9.41).

Table 9.3 Representative examples of catalytic direct arylations of substituted furans (124), thiophenes (125), and pyrroles (126).

Entry	Y	R ¹	Ar-X	Conditions	Yield (%)	Ref.
1a	S	Et	Ph-I	114 (3.0 mol%), Ag ₂ CO ₃ -DME (1.0 equiv. each), <i>m</i> -xylylene, μW, 150–200 °C, 0.5 h	76	74b
1b		Et	4-AcC ₆ H ₄ -I		79	
1c		Et	4-MeC ₆ H ₄ -I		50	
1d		2-Thienyl	4-AcC ₆ H ₄ -I		64	
2a	NH	CO ₂ Me	Ph-I	[Pd(OAc) ₂] (2–5 mol%), CsOAc (2.8 equiv.), iPr ₂ NH (1.0 equiv.), DMA, 125 °C, 48 h	30	75p
2b		Ph		4-(MeO ₂ C)C ₆ H ₄ -Br	58	

3	S	CHO	Ph-I	[Pd(OAc) ₂] (5.0 mol%), Ph ₃ P (10 mol%), CuI (10 mol%), Cs ₂ CO ₃ (2.0 equiv.), DMF, 140 °C, 21 h	82	86
4a	S	Ph	4-(MeO)C ₆ H ₄ -I	[PdCl ₂ (dpbb)] (3.0 mol%), AgF (1.0 equiv.), DMSO, 60 °C, 5 h	55	89
4b	S	Ph	4-(MeO)C ₆ H ₄ -I	[Pd(OAc) ₂] (10 mol%), Ph ₃ P (20 mol%), Cs ₂ CO ₃ (2.0 equiv.), DMSO, 60 °C, 5 h	0	
5a	NZnCl	2-(MeO)C ₆ H ₄	4-MeC ₆ H ₄ -Br	[Pd(OAc) ₂] (5.0 mol%), John-Phos (10 mol%), THF, 100 °C, 17–54 h	83	91
5b		2-(MeO)C ₆ H ₄	4-(Me ₂ N)C ₆ H ₄ -Br	[PdCl ₂] (5.0 mol%), PCy ₃ (10 mol%), ⁿ Bu ₄ NBr (1.0 equiv.), KOAc (2.0 equiv.), DMF, 110 °C, 10 h	82	
5c	O ^{a)}	2-(MeO)C ₆ H ₄	3,5-(F ₃ C) ₂ C ₆ H ₃ -Br	[PdCl ₂] (5.0 mol%), PCy ₃ (10 mol%), ⁿ Bu ₄ NBr (1.0 equiv.), KOAc (2.0 equiv.), DMF, 110 °C, 10 h	92	
6a	O ^{a)}	CHO	Ph-I	[Pd(OH) ₂]/C (10 mol%), KOAc (3.0 equiv.), ⁿ Bu ₄ NBr (2.0 equiv.), DMF, 145 °C, overnight	70	94
6b			4-NCC ₆ H ₄ -Br	[Pd(Ph ₃ P) ₄] (5 mol%), KOAc (2 equiv.), PhMe, 110 °C, 24 h	71	
6c			4-(O ₂ N)C ₆ H ₄ -I	[Pd(Ph ₃ P) ₄] (5 mol%), KOAc (2 equiv.), PhMe, 110 °C, 24 h	88	95
7	O	CHO	Ph-Br	[Pd(Ph ₃ P) ₄] (5 mol%), KOAc (2 equiv.), PhMe, 110 °C, 24 h	75	95
8a	O ^{b)}	CO ₂ Et	3-(O ₂ N)C ₆ H ₄ -Br	[Pd/C (10 mol%), KOAc (2.0 equiv.), NMP, 110 °C, 24 h	73	96
8b			3-(MeO ₂ C)C ₆ H ₄ -Br	[Pd/C (10 mol%), KOAc (2.0 equiv.), NMP, 110 °C, 24 h	69	
8c			4-(O ₂ N)C ₆ H ₄ -Br	[Pd/C (10 mol%), KOAc (2.0 equiv.), NMP, 110 °C, 24 h	59	
9	O	CO ₂ Et	3-(O ₂ N)C ₆ H ₄ -Br	[Pd/C (10 mol%), KOAc (2.0 equiv.), NMP, 110 °C, 24 h	13	96
10a	S ^{c)}	Br	4-(MeO)C ₆ H ₄ -I	[PdCl ₂ (Ph ₃ P) ₂] (5.0 mol%), AgNO ₃ (1–2 equiv.), KF (2.0 equiv.), DMSO, 60–100 °C, 5–8 h	42	97
10b		Br	4-(EtO ₂ C)C ₆ H ₄ -I	[PdCl ₂ (Ph ₃ P) ₂] (5.0 mol%), AgNO ₃ (1–2 equiv.), KF (2.0 equiv.), DMSO, 60–100 °C, 5–8 h	60	93
10c		Br	4-NC-C ₆ H ₄ -I	[PdCl ₂ (Ph ₃ P) ₂] (5.0 mol%), AgNO ₃ (1–2 equiv.), KF (2.0 equiv.), DMSO, 60–100 °C, 5–8 h	64	64
11a	S ^{d)}	R ¹ = R ² = Br	4-(EtO ₂ C)C ₆ H ₄ -I	[PdCl ₂ (Ph ₃ P) ₂] (5.0 mol%), AgNO ₃ (1–2 equiv.), KF (2.0 equiv.), DMSO, 60–100 °C, 5–8 h	72	

(Continued)

Table 9.3 (Continued)

Entry	Y	R ¹	Ar-X	Conditions	Yield (%)	Ref.
11b	S	R ¹ = Br, R ² = Me Ph	4-(MeO)C ₆ H ₄ -I Ph-Br	[Pd(OAc) ₂] (10 mol%), John-Phos (20 mol%), Cs ₂ CO ₃ (2.4–4 equiv), o-xylene, 145 °C, 24–65 h	61 90	98
12a		CO(<i>c</i> C ₅ H ₁₀ N)	Ph-Br		7	7
12b		COPh	Ph-Br		82	82
12c					12	12
13a	S ^{e)}	MeO	4-ClC ₆ H ₄ -Br	[Pd(OAc) ₂] (10 mol%), ⁿ Bu ₄ NBr (1.0 equiv.), KOAc (3.0 equiv.), DMF, 80 °C, 1 h	62	99
13b		MeO	4-(O ₂ N)C ₆ H ₄ -Br		73	
13c		MeO	4-(MeO)C ₆ H ₄ -Br		41	
14a	S	Me	4-NCC ₆ H ₄ -Br	[Pd(OAc) ₂] (0.1–0.01 mol%), KOAc (2.0 equiv.), DMA, 150 °C, 20 h	92	100
14b		ⁿ Bu	4-HC(O)C ₆ H ₄ -Br		89	
14c		CN	4-(F ₃ C)C ₆ H ₄ -Br		80	
15a	N-SEM ^{f)}	CN	Ph-I	141 (5.0 mol%), CsOAc (2.0 equiv), DMA, 125 °C, 24 h	59	101
15b		CN	3-Py-I		49	

a) Yields 60–88% (10 examples).

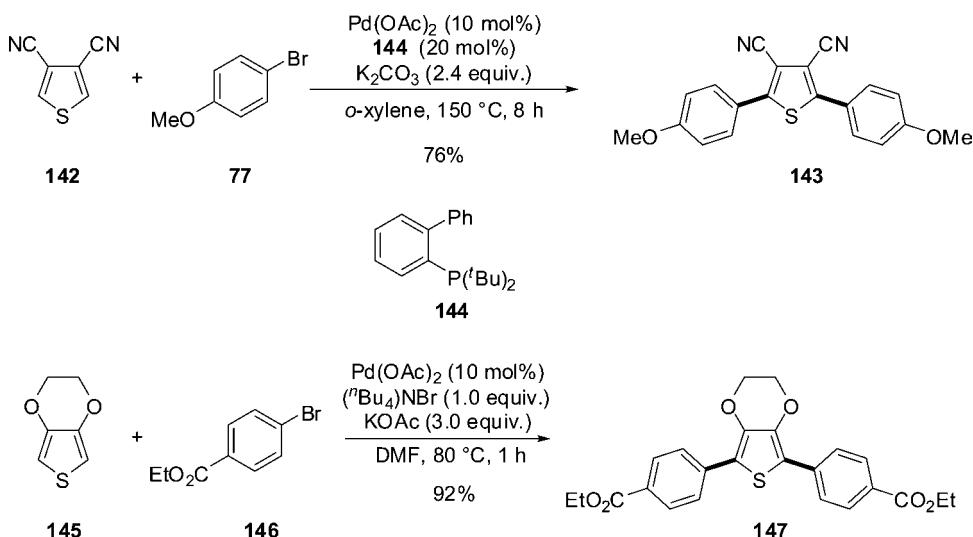
b) Yields 59–83% (7 examples).

c) Yields 60–93% (6 examples).

d) Yields 51–87% (8 examples).

e) Yields 23–73% (12 examples).

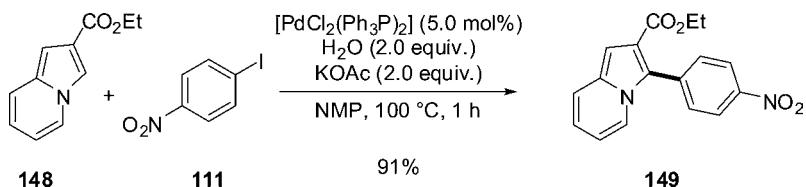
f) SEM = [2-(trimethylsilyl)ethoxymethyl]; 141 = [(NHC)PdI₂]₂.



Scheme 9.41 Palladium-catalyzed direct arylations of 3,4-disubstituted thiophenes **142** and **145**.

Palladium-catalyzed direct (hetero)arylations of indolizines proceeded in a highly efficient and regioselective manner (Scheme 9.42) [103]. Mechanistic studies strongly supported an electrophilic substitution-type mechanism for this transformation.

Direct arylations of benzo[*b*]furans, benzo[*b*]thiophenes, and indoles displayed different regioselectivity patterns. The chemical behavior of benzo[*b*]furans and benzo[*b*]thiophenes are rather similar to those of non-benzannelated furans and thiophenes, respectively (Table 9.4).

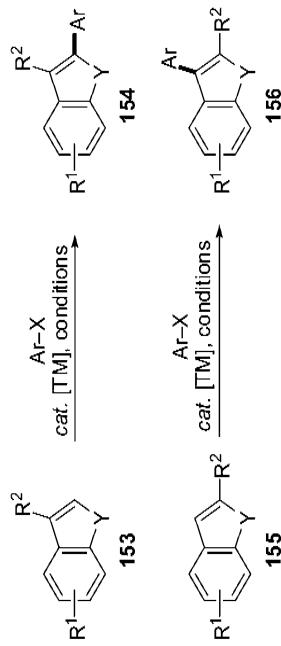
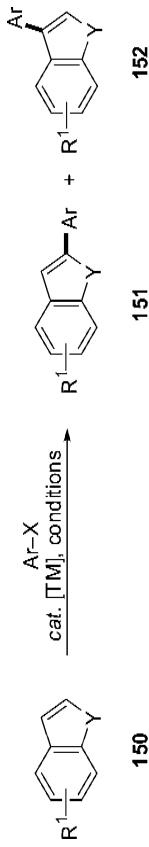


Scheme 9.42 Palladium-catalyzed regioselective direct arylation of the indolizine **148**.

1,3-Azoles are another class of heterocycles which could be directly arylated efficiently. Direct arylations of benzannelated azoles usually occurred regioselectively at position C-2, since both heteroatoms function as “endocyclic directing groups” [75g]. For example, a pivalic acid-derived palladium catalyst proved to be versatile [75a,b]. Rhodium catalysis was also exploited for direct arylations of 1,3-azoles. Thus, Bergman and co-workers reported on the use of $[\text{RhCl}(\text{coe})_2]$ in combination with PCy_3 and Et_3N for direct arylations of various benzimidazoles, benzothiazoles, quinazolines, dihydroquinazolines, and oxazolines with aryl iodides as electrophiles (Scheme 9.43) [110].

Table 9.4 Catalytic direct arylations of benzofurans, benzothiophenes, and indoles.

Entry	Y	R ¹	R ²	Ar-X	Conditions	Yield (%)	Ref.
1a	O	H	H	4-(O ₂ N)C ₆ H ₄ -Br	[Pd(PPh ₃) ₄] [5.0 mol%], KOAc (1.5 equiv.), DMA, 150 °C, 12 h	20	
1b	O	H	H	4-AcC ₆ H ₄ -Br			
1c	O	H	H	2-(O ₂ N)C ₆ H ₄ -Br			
1d	O	H	H	Ph-Br			
2a	S	H	H	4-NCC ₆ H ₄ -Br	[Pd(PPh ₃) ₄] [5.0 mol%], KOAc (1.5 equiv.), DMA, 150 °C, 12 h	36	88



2b	S	H	H	4- <i>AcC₆H₄-Br</i>	64
2c	S	H	H	2-(O ₂ N)C ₆ H ₄ -Br	65
2d	S	H	H	Ph-Br	35
3	O	H	H	Ph-Cl	75 ^a
4	S	H	H	4-MeO-2-O ₂ N-C ₆ H ₃ -Br	104
5a	S	H	H	Ph-I	86
5b	S	H	H	Ph-Br	89
6	S	H	H	Ph-Cl	75 ^m
7a	S ^b	H	CHO	4-(MeO)C ₆ H ₄ I	63
7b	S	H	CHO	4-(MeO)C ₆ H ₄ -Br	64
7c	S	H	MeO	2-NCC ₆ H ₄ -Br	69
7d	S	H	CN	4-ClC ₆ H ₄ -Br	69
7e	S	H	CN	2-NCC ₆ H ₄ -Br	63
7f	S	H	MeO	Ph-I	51
8a	N-Ph	H	H	Ph-I	80
8b	N-Me	H	H	Ph-I	91

(Continued)

Table 9.4 (*Continued*)

12a	N-H ^e	H	H	Ph-I	66
12b	N-H	5-OMe	H	Ph-I 2-Tol-I	75p
12c	N-H	5-Cl	H	4-BrC ₆ H ₄ -I	64
12d	N-H	5-Me	H	[Ph ₂ I] ⁺ BF ₄ ⁻	60
13a	N-H ^f	H	H	Ar ₂ I ⁺ BF ₄ ⁻ (1-6 equiv.) [IMesPd(OAc) ₂] (5.0 mol%), AcOH, 25-60 °C, 15-24 h	44
13b	N-H	5-OMe	H	[Ph ₂ I] ⁺ BF ₄ ⁻	81
13c	N-Me	5-NO ₂	H	[Ph ₂ I] ⁺ BF ₄ ⁻	58
13d	N-Me	H	H	(2-Tol) ₂ I ⁺ BF ₄ ⁻	70
14a	N-H ^g	H	H	Ph-Br	62
14b	N-H	H	5-OMe	[PdCl ₂ (ⁱ Pr ₂ POH) ₂] (5.0 mol%), K ₂ CO ₃ (3.0 equiv.), 1,4-dioxane, 100 °C, 24 h	72
14c	N-H	H	H	Ph-Br	80
15	NH	H	H	4-NCC ₆ H ₄ -Br	107
16a	NH	H	H	4-(MeO)C ₆ H ₄ -I	53
16b	NH	H	H	[Pd(OAc) ₂] (5.0 mol%), Cul (2.0 equiv.), DMF, 140 °C, 48 h	35
16c	NH	H	H	[Pd(OAc) ₂] (5.0 mol%), Cul (2.0 equiv.), DMA, 160 °C, 48 h	108
17a	N-H ^h	H	H	4-(F ₃ C)C ₆ H ₄ -I	53
17b	N-H	7-TsNH	H	Ph-I	29
18a	N-SEM	H	Me	Ph-I	33
				[Rh(coe) ₂ C] ₂ (2.5 mol%), (<i>p</i> -CF ₃ -C ₆ H ₄) ₃ P (15 mol%), CsOPiv (1.4 equiv.), 1,4-dioxane, 120 °C, 18-36 h	82
				141 (5.0 mol%), CsOAc (2.0 equiv.), DMA, 125 °C, 24 h	65
					67
					93
					101

(Continued)

Table 9.4 (Continued)

Entry	Y	R ¹	R ²	Ar-X	Conditions	Yield (%)	Ref.
18b	N-SEM	H	CO ₂ Me	Ph-I	Ph ₂ I ⁺ BF ₄ ⁻ (1–3 equiv), [IMesPd(OAc) ₂] (5.0 mol%), AcOH, 25 °C, 15–24 h	22	89
19	N-Me	H	Me	[Ph ₂ I] ⁺ BF ₄ ⁻	[Pd(OAc) ₂] (5.0 mol%), AcOH, 25 °C, 15–24 h	89	92
20a	N-H ⁱ⁾	H	Me	2-Tol-I	[Pd(OAc) ₂] (1–5 mol%), CsOAc (2.8 equiv), Pr ₂ NH (1.0 equiv), DMA, 125 °C, 24–48 h	28	
20b	N-H	H	Me	Ph-Br		63	
20c	N-H	H	Me	4-AcC ₆ H ₄ -Br		70	75p
20d	N-H	H	EtO ₂ C-CH ₂	Ph-Br		46	
21	N-H	H	Ph	4-(O ₂ N)C ₆ H ₄ -Br	[Pd]/SBA-15 (1.0 mol%), NaOAc (1.1 equiv), NMP, 140 °C, h	55	109
22a	N-H	H	H	PhBr	[Pd(OAc) ₂] (5.0 mol%), (HA) SPO-preligand (10 mol%), K ₂ CO ₃ (3.0 equiv), 1,4-dioxane, 95 °C, 20 h	81	
22b	N-H	H	H	4-(MeO)C ₆ H ₄ -Br		66	
22c	N-H	H	H	4-(Me ₂ N)-C ₆ H ₄ -Br		61	75d

a) 2,3-Diphenylbenzofuran was obtained.

b) Yields 21–76% (over 60 examples).

c) SEM = [2-(trimethylsilyl)ethoxymethyl].

d) Yields 0–92% (17 examples).

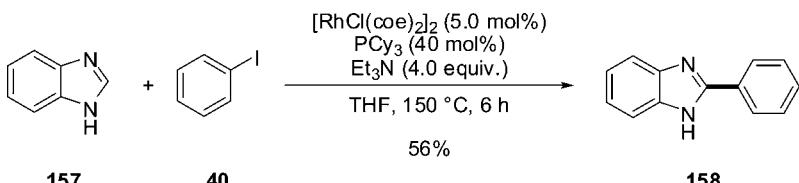
e) Yields 23–75% (8 examples).

f) Yields 58–90% (14 examples).

g) Yields 0–80% (7 examples).

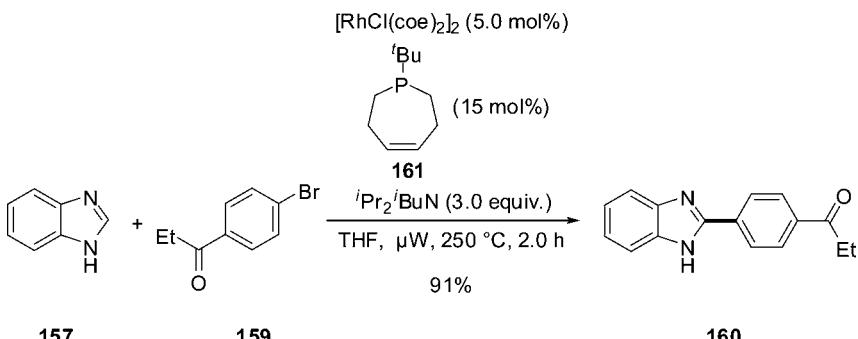
h) Yields 59–82% (5 examples).

i) Yields 28–70% (7 examples).



Scheme 9.43 Rhodium-catalyzed direct arylation of 1*H*-benzimidazole (**157**) with the iodobenzene (**40**).

Recently, a more reactive catalytic system was devised which allowed the use of less expensive aryl bromides as arylating reagents. This was accomplished with sterically hindered ligand **161** under microwave irradiation (Scheme 9.44) [111]. Note that more recently direct arylations of azoles were achieved with less expensive copper [112] or nickel complexes [113].



Scheme 9.44 Rhodium-catalyzed direct arylation of 1*H*-benzimidazole (**157**) with the aryl bromide **159**.

Mechanistic studies revealed that the dimeric complex **162** is formed (Scheme 9.45). Coordination of complex **162** by heterocycle **157** provides the heterocyclic complex **163**. This then undergoes tautomerization followed by oxidative addition with aryl bromide to generate the N-heterocyclic carbene complex **165**. Elimination of HBr from complex **165** takes place and is followed by reductive elimination to release the arylated product and regenerate the rhodium catalyst **162**.

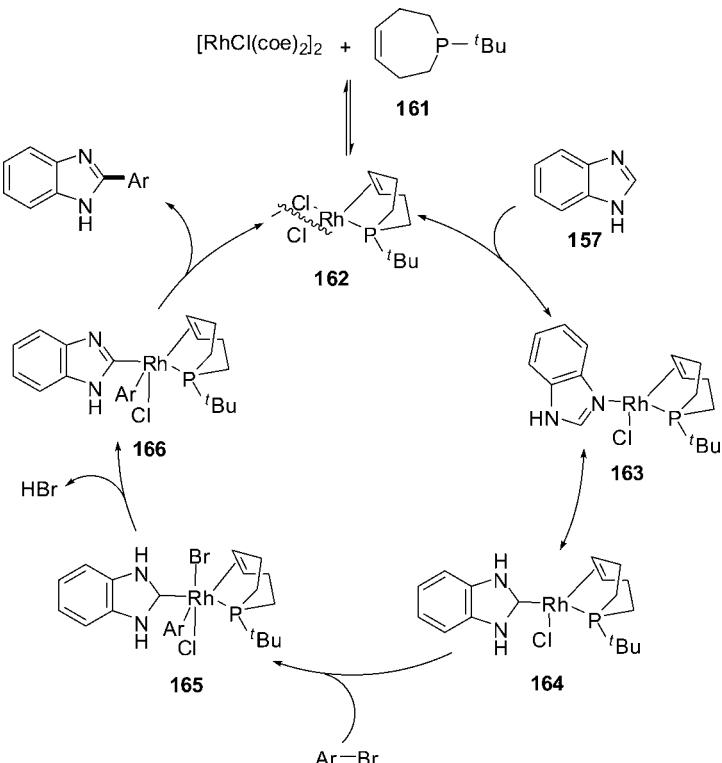
9.3

Catalytic Oxidative Arylations of (Hetero)arenes

9.3.1

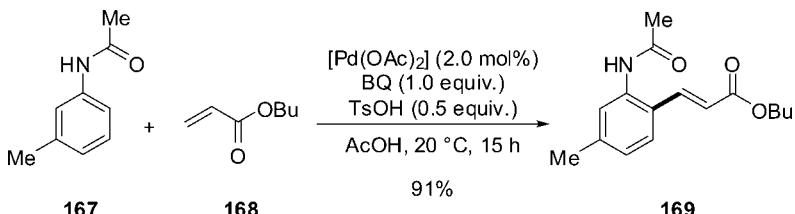
Introduction

Early examples of the formation of C(sp²)–C(sp²) bonds via oxidative direct C–H bond functionalizations were described by Moritani, Fujiwara and co-workers [114, 115].



Scheme 9.45 Proposed mechanism for rhodium-catalyzed direct arylations of benzimidazoles.

This transformation matured to being a highly efficient tool for the synthesis of substituted alkenes [116–118]. Thus, for instance, effective palladium-catalyzed regioselective oxidative arylation of alkenes [119] were developed, which enabled oxidative coupling to proceed at ambient temperature (Scheme 9.46).



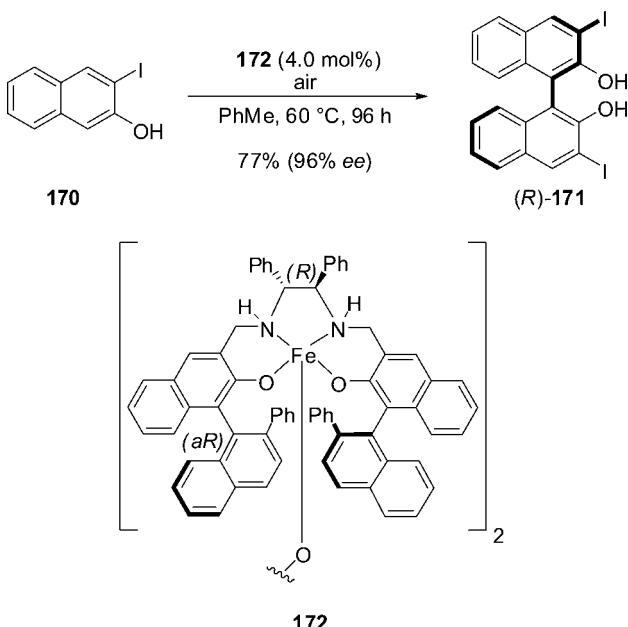
Scheme 9.46 Palladium-catalyzed direct arylation of alkene 168.

The pioneering studies by Moritani and co-workers set the stage for further applications of palladium-catalyzed C–H bond functionalizations to oxidative $\text{C}(sp^2)\text{–C}(sp^2)$ bond-forming processes. Thus, catalyzed oxidative arylations for biaryl syntheses could be accomplished with either stoichiometric [120] or catalytic [121] amounts of palladium complexes.

9.3.2

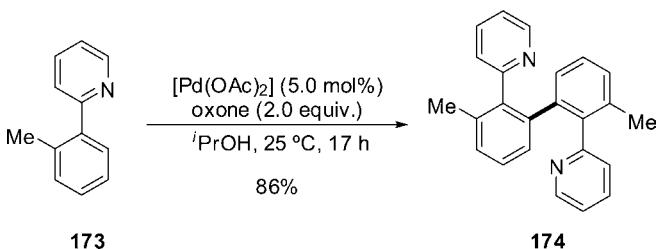
Oxidative Homocouplings

Intermolecular dehydrogenative oxidative homocouplings of (hetero)arenes turned out to be among the most important methods for the synthesis of symmetrically substituted biaryls [122]. A recent illustrative example is oxidative coupling reactions of 2-naphthols, which were accomplished in an asymmetric fashion employing an inexpensive iron catalyst (Scheme 9.47) [123].



Scheme 9.47 Iron-catalyzed enantioselective aerobic homocoupling of iodonaphthol (**170**).

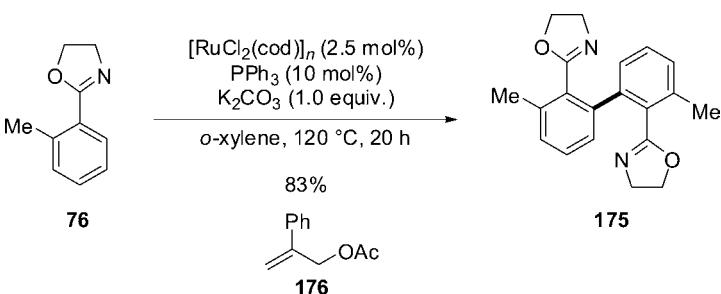
2-Arylpyridines underwent palladium-catalyzed regioselective oxidative homocoupling reactions through chelation assistance, using $[\text{Pd}(\text{OAc})_2]$ as catalyst and Oxone as stoichiometric oxidant in 2-propanol as solvent (Scheme 9.48) [124]. Interestingly,



Scheme 9.48 Palladium-catalyzed homo-dehydrogenative coupling of the 2-arylpyridine **173**.

these reactions occurred readily at ambient temperature and mechanistic studies suggested the formation of palladium(IV) species as intermediates [20, 124, 125]. Note that the same transformation was more recently accomplished with stoichiometric amounts of copper in the presence of iodine [126].

Dehydrogenative homocouplings could also be accomplished using ruthenium catalysts. Thus, a catalytic system consisting of $[\text{RuCl}_2(\text{cod})]_n$ and PPh_3 , along with the allyl acetate **176** as stoichiometric oxidant, recently allowed the dimerization of 2-aryloxazolines (Scheme 9.49) [127]. Furthermore, arenes bearing imidazole, pyrazole, or thiazole moieties could also be homocoupled in a regioselective fashion.



Scheme 9.49 Ruthenium-catalyzed oxidative homocoupling of the aryloxazoline **76**.

9.3.3

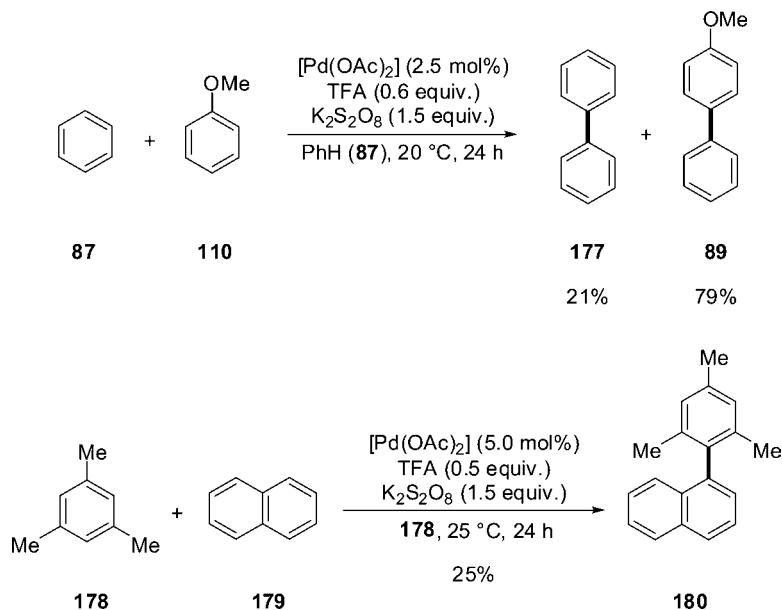
Cross-Dehydrogenative Arylations

While intramolecular oxidative arylations and also intermolecular homocouplings can be performed in a highly selective fashion, a significant challenge is to achieve chemoselectivities in intermolecular oxidative arylations between two different (hetero)arenes.

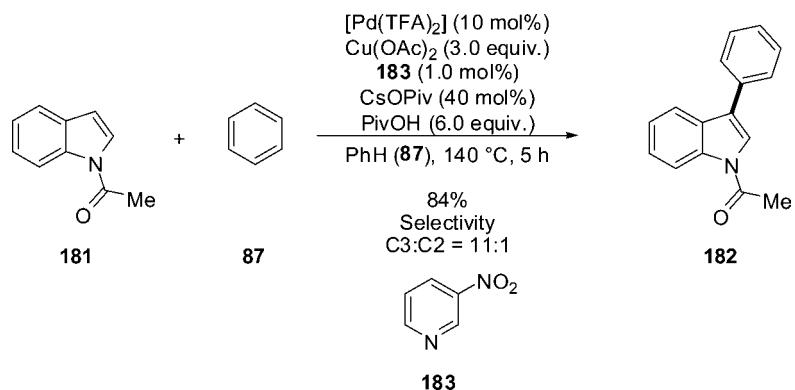
Recently, the formation of unsymmetrically substituted biaryls from simple arenes was achieved with a catalytic system consisting of $[\text{Pd}(\text{OAc})_2]-\text{CF}_3\text{CO}_2\text{H}$ and $\text{K}_2\text{S}_2\text{O}_8$ under mild reaction conditions (Scheme 9.50) [128]. The chemo- and regioselectivities of these reactions were controlled by the use of an excess of the less reactive coupling partner as solvent [129].

More promising results were obtained for cross-dehydrogenative arylations with heteroarenes, since pronounced differences in reactivities gave improved chemoselectivity. In elegant studies it was shown that palladium-catalyzed oxidative arylations of indoles could be accomplished with unactivated arenes, which were used as solvents, in the presence of $\text{Cu}(\text{OAc})_2$ as terminal oxidant [130]. Notably, these reactions proceeded with high regioselectivities, leading predominantly to arylations at position C-3 (Scheme 9.51).

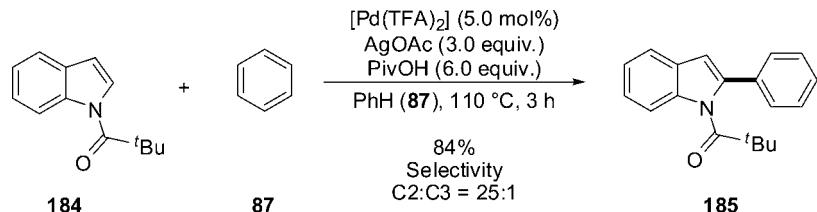
Interestingly, this selectivity could be inverted towards predominant arylations at position C-2 when using AgOAc as a sacrificial oxidant (Scheme 9.52) [131]. It is



Scheme 9.50 Palladium-catalyzed oxidative direct arylations of simple arenes.



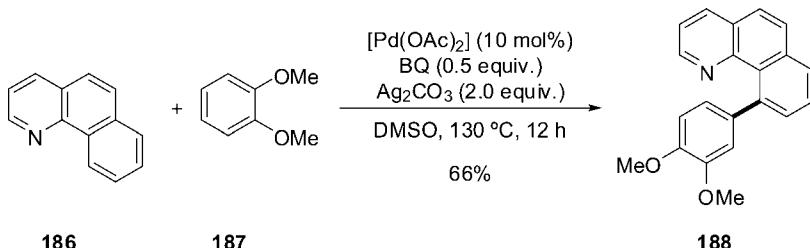
Scheme 9.51 Palladium-catalyzed cross-dehydrogenative arylation of the indole 181 at position C-3.



Scheme 9.52 Palladium-catalyzed cross-dehydrogenative arylation of the indole 184 at position C-2.

noteworthy that the presence of valuable functionalities such as chloro substituents did not affect the reaction course, and that pyrroles could be arylated regioselectively at position C-2 under otherwise identical reaction conditions.

Based on studies directed towards chelation-assisted oxidative homocouplings of 2-arylpyridines, a protocol was developed for intermolecular coupling reactions [132]. Thus, benzo[*h*]quinoline (**186**) was efficiently arylated with a variety of arenes using silver salts and benzoquinone as additives (Scheme 9.53).



Scheme 9.53 Palladium-catalyzed cross-dehydrogenative arylation.

9.4 Conclusion

Direct arylations of (hetero)arenes through C–H bond cleavages have matured to being increasingly viable alternatives to traditional cross-coupling reactions. Indeed, effective methodologies for metal-catalyzed oxidative direct arylations with either organometallic reagents or simple arenes have been developed. The use of the latter is particularly attractive. As a valuable alternative, aryl (pseudo)halides have been widely employed as electrophiles in catalytic direct arylation reactions.

Acknowledgments

The authors thank the Alexander-von-Humboldt foundation (Fellowship to A.R.K.) and the DAAD (Fellowship to H.K.P.) for financial support.

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10

Synthesis Without Metals

Takahiko Akiyama

10.1

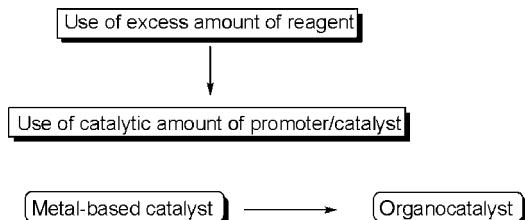
Introduction

One of the most important objectives of organic chemistry is the efficient synthesis of organic compounds, which are required to study the function of the compounds, phenomena exerted by the substances, and to supply them for pharmaceuticals, agrochemicals, and so on. Ideally, the targeting compounds should be synthesized in 100% yield and with 100% selectivity without producing wastes [1]. In order to realize this goal, the chemical processes should be economical, efficient in resources, and environmentally benign. Organic chemists should take into account the atom economy proposed by Trost [2] and the *E*-factor suggested by Sheldon [3]. Disposal of poisonous by-products and/or reagents should be avoided. Green chemistry is an indispensable discipline of chemical community in order to sustain the civilized society.

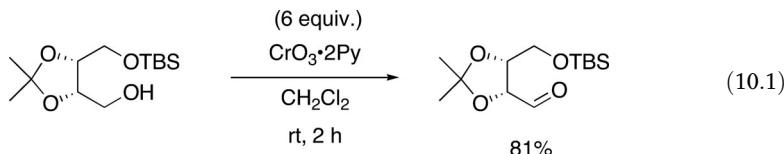
In order to achieve the goal, the use of stoichiometric amount of a promoter is avoided and the use of just a catalytic amount of promoter (catalyst) is desirable (Figure 10.1). Metal-based catalysts have played important roles in synthetic organic chemistry. Due to the potential toxicity and sensitivity towards oxygen and moisture of metal-based catalysts, the development of metal-free catalysts has attracted much attention from synthetic organic chemists and is desired from the standpoint of green chemistry.

An advantage of organocatalysts lies in their stability towards oxygen and moisture, hence they are easy to handle. Due to the stability towards water, phase-transfer catalysis in aqueous–organic two-phase solvent system is used. Another advantage is economy of the catalyst, because many organocatalysts are of economic interest, such as alkaloids, tartaric acid, (*S*)-proline, and natural amino acids. Although the use of small organic molecules for organic synthesis has been reported for more than half a century, the past decade has witnessed an explosion of growth in the organocatalysis, in particular enantioselective catalysis.

In this chapter, examples of achiral organocatalysts are briefly described and chiral organocatalysts are mainly discussed.

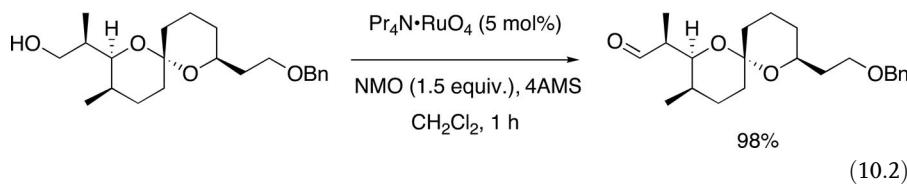
**Figure 10.1****10.2****Organic Reactions Promoted by Non-Metallic Catalysts**

Oxidation of primary alcohols to aldehydes constitutes one of the most important oxidation reaction for the preparation of biologically active compounds, and a range of oxidizing agents have been reported [4]. In the 1980s, a number of chromium-based reagents were developed. Although the Collins oxidation is a useful method for the oxidation of primary alcohols to aldehydes, a large excess of the reagent was required and isolation problems persisted (Equation 10.1) [5].

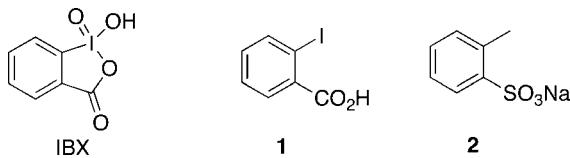


Because the use of a stoichiometric amount of chromium-based oxidant is not desirable from the standpoint of green chemistry, a number of approaches to employ catalytic amount of oxidant in combination with a stoichiometric amount of re-oxidant have been reported.

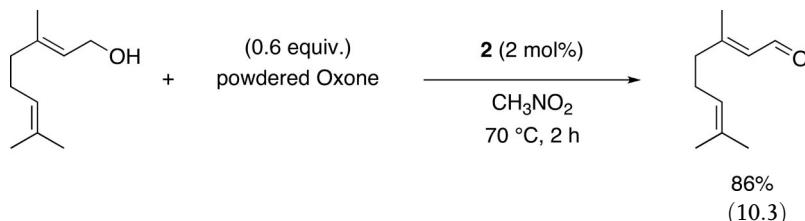
Ruthenium derivatives have been used for oxidation reactions. Ley and co-workers reported a useful method for the oxidation of primary alcohols to aldehydes by means of catalytic amount of $\text{n-Pr}_4\text{N}^+\text{RuO}_4^-$ (TPAP) in the presence of a stoichiometric amount of *N*-methylmorpholine oxide (Equation 10.2) [6].



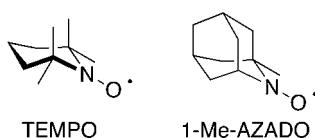
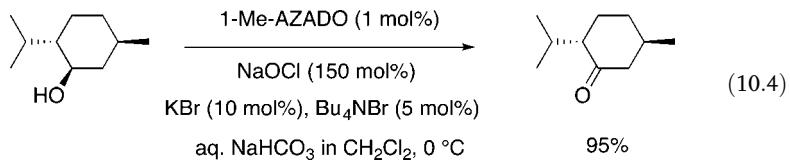
Hypervalent iodine reagents have also attracted much attention as oxidizing agents for alcohols. IBX is readily prepared starting from 2-iodobenzoic acid (**1**) (Figure 10.2) and is a useful oxidizing reagent for the oxidation of primary alcohols to aldehydes [7].

**Figure 10.2**

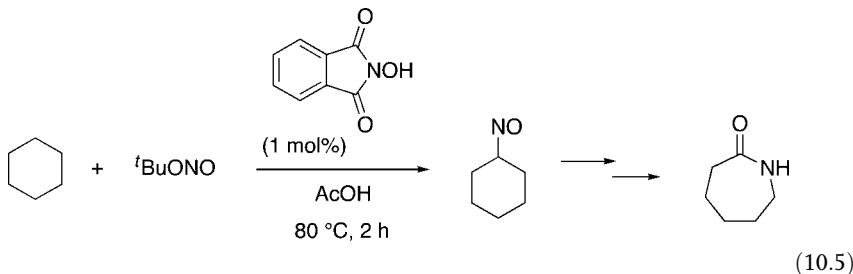
Recently, Ishihara and co-workers developed a more powerful hypervalent iodine catalyst, generated *in situ* from 2-iodobenzoic acid and furthermore demonstrated that its sulfonic acid analog **2** is more reactive as a precatalyst (Equation 10.3) [8]. They reported that it was not necessary to isolate hypervalent iodine compounds, which are potentially explosive oxidants, and furthermore that more powerful oxidants could be generated *in situ*.



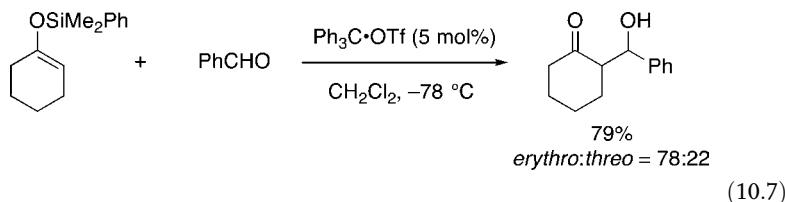
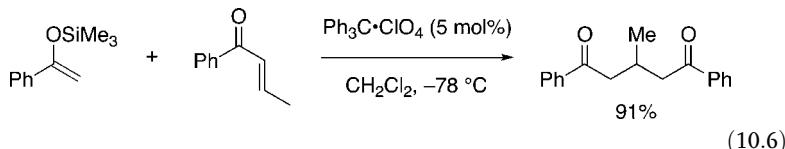
2,2,6,6-Tetramethyl-1-piperidinyloxy (TEMPO), a nitroxyl radical (Figure 10.3), is an effective catalyst for the oxidation of primary alcohols in the presence of secondary alcohols [9]. Iwabuchi and co-workers reported excellent catalytic activity of 2-azaadamantane-N-oxyl (1-Me-AZADO) towards a variety of alcohols. Oxidation of secondary alcohols was effected by means of 1 mol% of 1-Me-AZADO (Equation 10.4) [10].

**Figure 10.3**

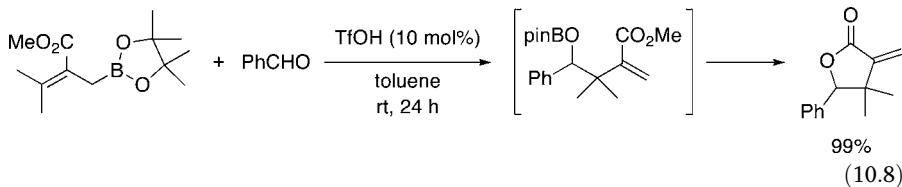
Ishii and co-workers reported the *N*-hydroxyphthalimide (NHIP)-catalyzed nitrosation of cyclohexane with *tert*-butyl nitrite (*t*BuONO) to give nitrosocyclohexane in high yield (Equation 10.5) [11]. Subsequently, they reported an efficient one-pot procedure for the preparation of ϵ -caprolactam from cyclohexane by means of cyanuric acid chloride [12]. The present route towards ϵ -caprolactam obviates the use of corrosive NOCl in the photonitrosation of cyclohexane.



The Mukaiyama aldol reaction is an important and fundamental reaction for the preparation of polyols. Mukaiyama and co-workers reported that trityl salts are effective as catalysts for Michael reactions (Equation 10.6) and Mukaiyama aldol reactions (Equation 10.7) in addition to traditional Lewis acids such as $TiCl_4$ and $SnCl_4$ [13].



Allylations of aldehydes and imines also constitute important carbon–carbon bond-forming reactions [14]. A range of metal-based Lewis acid catalysts have been reported. Hall and co-workers described the Brønsted acid-catalyzed allylation of aldehydes with allyl boronate (Equation 10.8) [15].



10.3

Asymmetric Organocatalysts

10.3.1

Introduction

The enantioselective synthesis of organic compounds is one of the key issues to be resolved in the field of synthetic organic chemistry because chiral organic compounds are important as pharmaceutical products, agrochemicals, and fine chemicals.

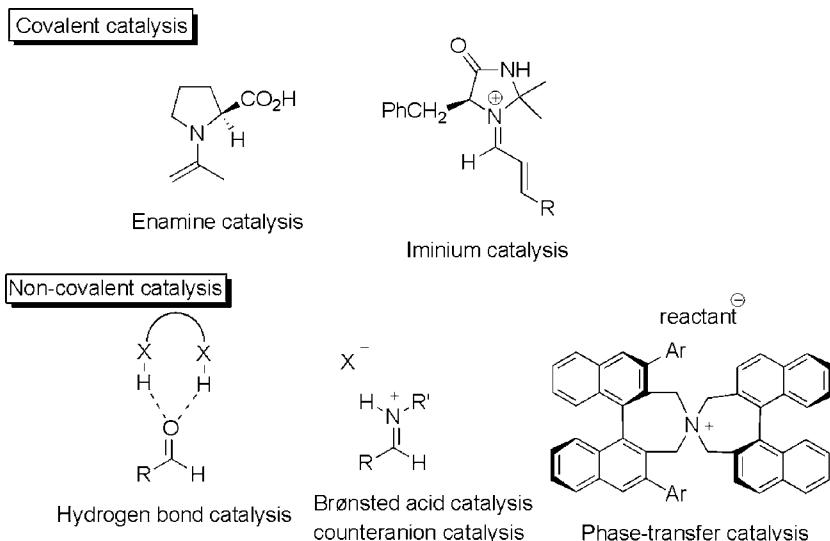
Metal-based catalysts have been extensively studied in both academia and industry. The award of the Nobel Prize in Chemistry in 2001 to William R. Knowles and Ryoji Noyori for their work on metal-catalyzed enantioselective hydrogenation reactions and to K. Barry Sharpless for his work on catalyzed enantioselective oxidation reactions was a landmark in chiral catalysis studies. Enzymes and biocatalysts have also played a pivotal role as asymmetric catalysts [16].

Until fairly recently, primarily transition metal complexes and enzymes were utilized as catalysts for enantioselective synthesis [17]. Nicolaou and Sorensen wrote the following statement in their book published in 1996 [18]: “In a catalytic asymmetric reaction, a small amount of an enantiomerically pure catalyst, either an enzyme or a synthetic, soluble transition metal complex, is used to produce large quantities of an optically active compound from a precursor that may be chiral or achiral.”

In the past, synthetic organic chemists rarely employed small organic compounds as catalysts, although some of the very first asymmetric catalysts were purely organic molecules.

Prelog reported cinchona alkaloid-catalyzed cyanohydrin formation in 1954. It was not until the 1970s that truly highly enantioselective catalysts were reported by two independent groups who discovered that a simple amino acid worked efficiently as a catalyst for enantioselective aldol reactions. Cinchona alkaloids and proline were popular organocatalysts for some time. Meanwhile, although metal catalysts played a predominant role as asymmetric catalysts at the end of the last century, the perception has changed in the last few years and several studies have indicated that small organic molecules could work efficiently as chiral catalysts. List, Lerner, and Barbas reported intramolecular aldol reactions catalyzed by (*S*)-proline in the early 2000s [19]. Subsequently, MacMillan reported iminium catalysis. Those two reports paved the way to organocatalysis [20],

Chiral metal-based catalysts are generally unstable in the presence of moisture and oxygen and are therefore prepared *in situ* from a metal salt and a chiral ligand and employed directly. In contrast, asymmetric organocatalysts are generally stable and thus easy to handle. Recently, chiral organocatalysts were found to complement metal-based catalysts. In this chapter, an overview of chiral organocatalysts, including the seminal work, is presented, focusing on the recently developed chiral Brønsted acid catalysts.

**Figure 10.4****10.3.2****Classification by Reaction Types**

Chiral organocatalysts are classified into non-covalent and covalent catalysts on the basis of their transition states (Figure 10.4).

10.3.2.1 Covalent Organocatalysis

Proline derivatives form enamine intermediates to activate the HOMO of a nucleophile. In contrast, iminium salts are generated with MacMillan's catalyst to activate the LUMO of an electrophile. The formation of the enamine intermediate from proline is reminiscent of the general catalysis of class 1 aldolase in enzymatic catalysis [21].

10.3.2.2 Non-Covalent Organocatalysis

In contrast to covalent bond catalysts that form covalent substrate–catalyst adducts, hydrogen bond catalysts activate carbonyl compounds via weak interactions such as hydrogen bonding. Brønsted acid catalysts form ion pairs by protonating imines. The concept of counteranion catalysis has also been proposed. Phase-transfer catalysts also form ion pairs.

10.3.3**Organocatalysts****10.3.3.1 Cinchona Alkaloids and Derivatives**

Cinchona alkaloids such as quinine and quinidine are readily available chiral compounds. Prelog and Wilhelm reported in 1954 cinchona alkaloid-catalyzed

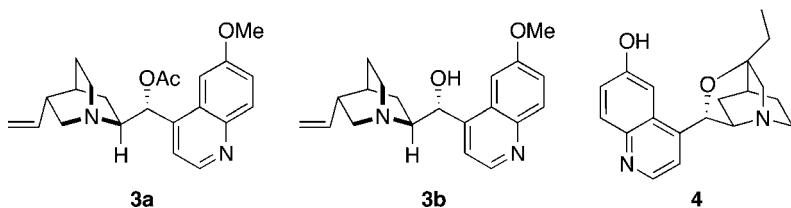
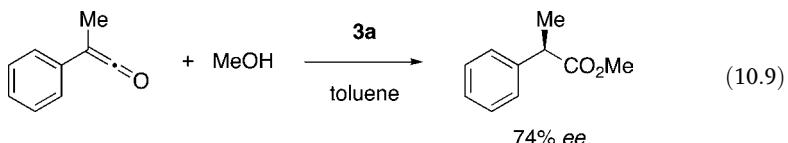
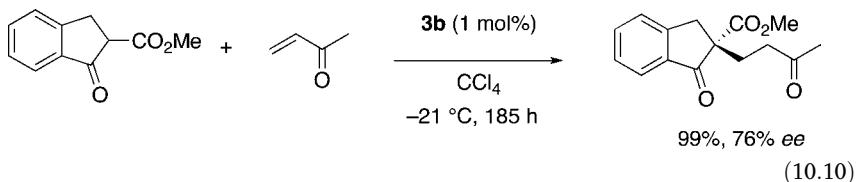


Figure 10.5

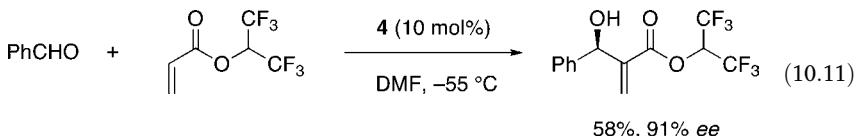
cyanohydrin formation with modest enantioselectivity [22]. In 1960, Pracejus reported that the addition reaction of methanol with methyl phenyl ketene, which is catalyzed by the *O*-acetylquinine **3a** (Figure 10.5), yielded (−)- α -phenyl methylpropionate in 74% enantiomeric excess (*ee*) (Equation 10.9) [23].



Hermann and Wynberg reported the Michael reaction of a β -keto ester with methyl vinyl ketone under the influence of the quinine **3b** to give the Michael adduct with 76% *ee* (Equation 10.10) [24].



Hatakeyama and co-workers reported the highly enantioselective Baylis–Hillman reaction of 1,1,1,3,3,3-hexafluoroisopropyl acrylate with an aldehyde, which is catalyzed by the cinchona alkaloid catalyst **4** that was readily available from (+)-quinidine (Equation 10.11) [25].

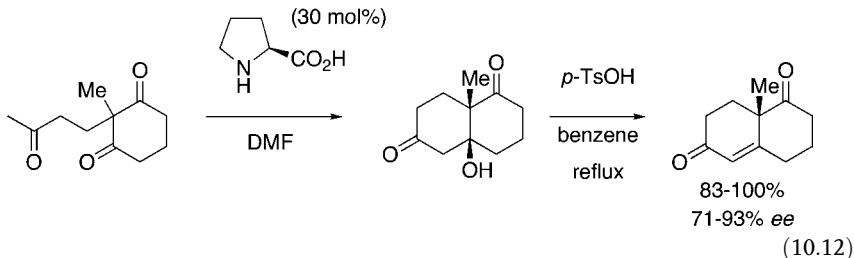


Deng reported the cinchona alkaloid-catalyzed desymmetrization of meso and achiral cyclic anhydrides by alcoholysis [26].

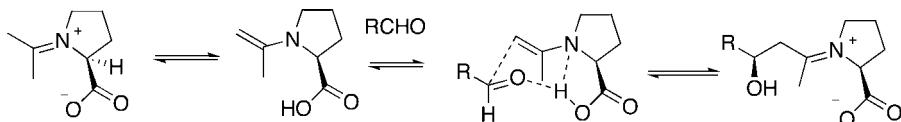
10.3.3.2 Proline Derivatives and MacMillan's Catalyst

Efficient L-proline-catalyzed Robinson annulation was reported in the early 1970s by two separate groups in industry: one at Schering in Germany [27] and the other at

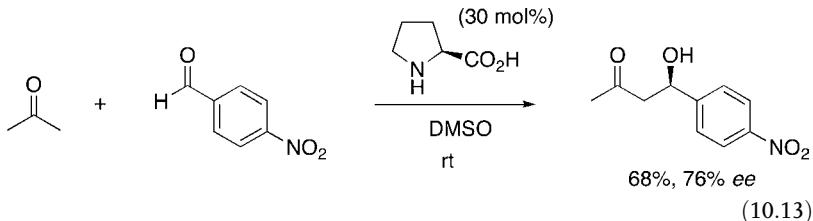
Hoffman-La Roche in the USA [28]. The so-called Hajos–Parrish–Eder–Sauer–Wiechert reaction provided access to key intermediates for the synthesis of natural products and offered a practical route to the Wieland–Miescher ketone (Equation 10.12).



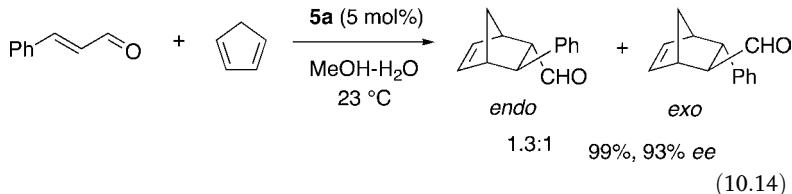
However, the proline-catalyzed intramolecular cyclization reaction was considered to be a special reaction and the application of the catalyst to other reactions was not attempted until List, Lerner, and Barbas reported the proline-catalyzed intermolecular aldol reaction in 2000 (Equation 10.13) [29]. The aldol reaction proceeds via an enamine intermediate through a six-membered transition state (Scheme 10.1) [30].

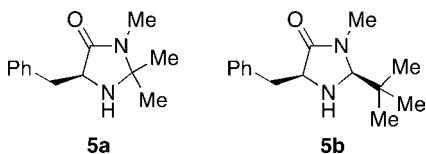
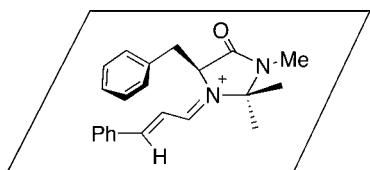


Scheme 10.1

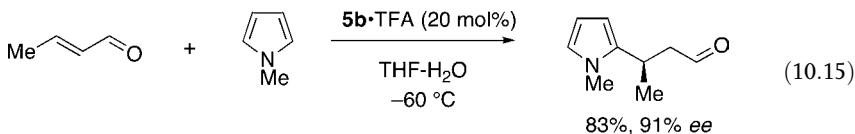


Around the same time, MacMillan and co-workers developed imidazolidinone **5a** (Figure 10.6) and demonstrated its catalytic activity in the Diels–Alder reaction (Equation 10.14) [31]. MacMillan’s catalyst works as an iminium ion catalyst, thereby lowering the LUMO level, as shown in Figure 10.7.



**Figure 10.6****Figure 10.7**

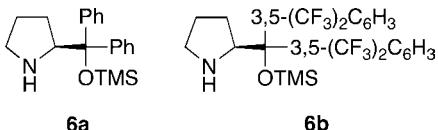
Subsequently, MacMillan reported the second-generation MacMillan's catalyst **5b** for the Friedel-Crafts alkylation reaction of pyrrole to, form α,β -unsaturated aldehydes (Equation 10.15) [32].



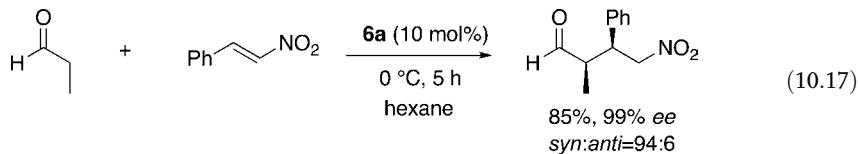
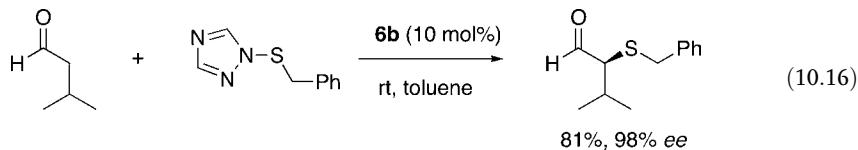
Following the seminal work on proline-catalyzed reactions, a range of proline- and proline derivative-catalyzed asymmetric reactions, including the Mannich reaction, Michael reaction, α -functionalization of carbonyl compounds, and cycloaddition reactions, have been developed [33].

One disadvantage of proline lies in its low solubility in less polar organic solvents, thereby requiring the use of polar solvents such as DMSO and DMF. Furthermore, the catalyst activity is not always high whereas the catalyst load is generally high. To circumvent the disadvantages of using proline, two groups independently developed in 2005 diarylprolinol trimethylsilyl ethers **6** as efficient organocatalysts (Figure 10.8).

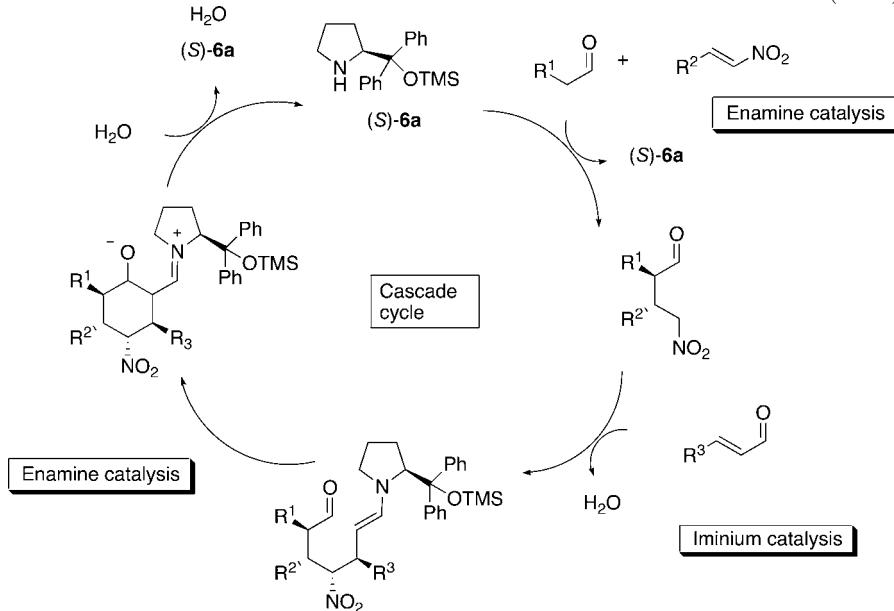
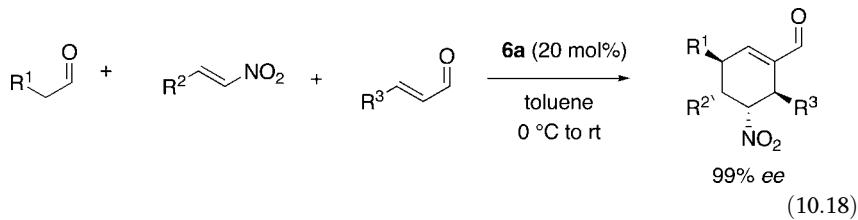
Jørgensen and co-workers reported the enantioselective α -sulfonylation of aldehydes catalyzed by **6b** (Equation 10.16) [34]. Hayashi *et al.* reported the 1,4-addition reaction of acetaldehyde with nitrostyrene in the presence of **6a** (Scheme 10.17) [35]. The introduction of a siloxy group into proline increased its catalytic activity, thus allowing for a decrease in catalyst load and reaction time without compromising the

**Figure 10.8**

enantioselectivity, in addition to broadening the substrate scope. This improved activity can be attributed to the increased solubility of **6a** in organic solvents.



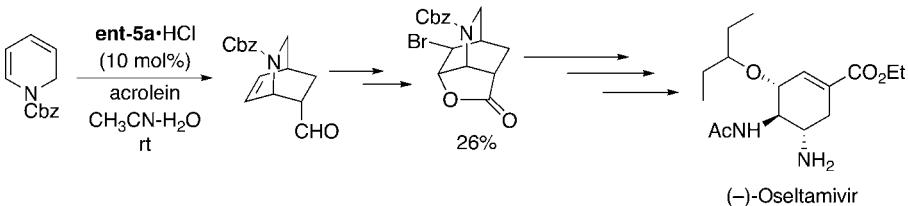
Enders *et al.* elegantly applied diphenylprolinol silyl ether **6a** as a catalyst for triple cascade reactions (Scheme 10.18), wherein **6a** played the roles of both enamine catalyst and iminium catalyst. It should be noted that the four stereocenters were completely controlled [36]. The proposed catalytic cycle of the triple cascade is shown in Scheme 10.2.



Scheme 10.2

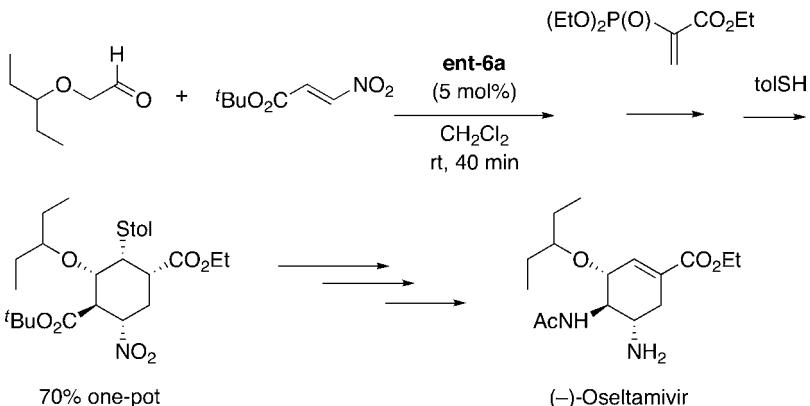
Recently, two Japanese groups independently synthesized the anti-influenza neuramidase inhibitor (*(*)-oseltamivir by using a chiral organocatalyst in the key reactions.

Fukuyama and co-workers constructed the [2.2.2]azabicyclohexane framework enantioselectively via the asymmetric Diels–Alder reaction and MacMillan’s catalyst **ent-5a** and obtained a lactone without purification. Subsequent transformation led to the preparation of (*(*)-oseltamivir in 22% yield from benzyl chloroformate (Scheme 10.3) [37].



Scheme 10.3

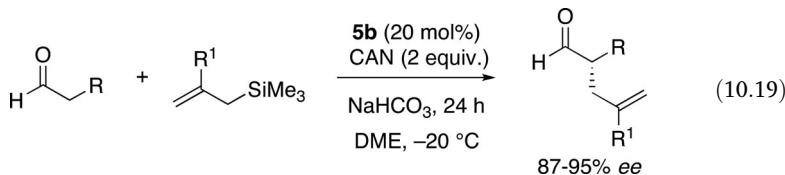
Hayashi and co-workers took advantage of the organocatalyzed reaction for the stereoselective synthesis of the cyclohexane structure. Diphenylprolinol silyl ether **ent-6a** proved to be effective for the domino Michael addition/Horne–Wardsworth–Emmons reaction. They synthesized (*(*)-oseltamivir by three one-pot operations, with a total yield of 57% (Scheme 10.4) [38].



Scheme 10.4

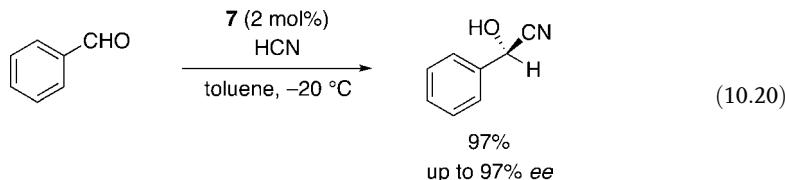
In 2007, MacMillan and co-workers reported conceptually novel reactions employing MacMillan’s catalyst **5b** [39]. This catalyst worked as a singly occupied molecular orbital (SOMO) catalyst in the presence of cerium (IV) ammonium nitrate (CAN) as a single-electron oxidant and the enantioselective α -allylation of aldehydes

was achieved (Equation 10.19). Subsequently, they reported the α -vinylation of aldehydes [40] and the carbo-oxidation of styrenes [41].

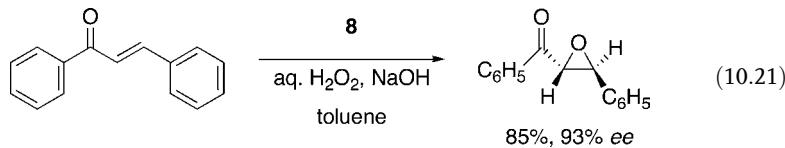


10.3.3.3 Peptide Catalysts

Inoue's group pioneered studies on the cyclic peptide (diketopiperazine) **7** (Figure 10.9), which is readily available from L-histidine and L-phenylalanine, and used it as a catalyst for the addition of hydrogen cyanide to benzaldehyde with up to 97% *ee* (Equation 10.20) [42].



Polyamino acid **8** catalyzed the epoxidation of chalcones in the presence of alkaline hydrogen peroxide. The Juliá-Colonna reaction furnished the corresponding oxiranes with excellent enantioselectivities (Equation 10.21) [43].



Recently, Miller and co-workers developed a number of peptide-based catalysts for asymmetric acyl transfer reactions [44]. For example, the catalytic asymmetric monophosphorylation of 2,4,6-tri-O-benzyl-*myo*-inositol was achieved by means of

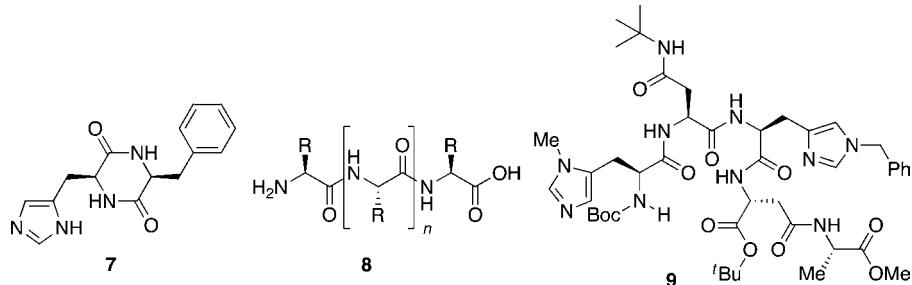
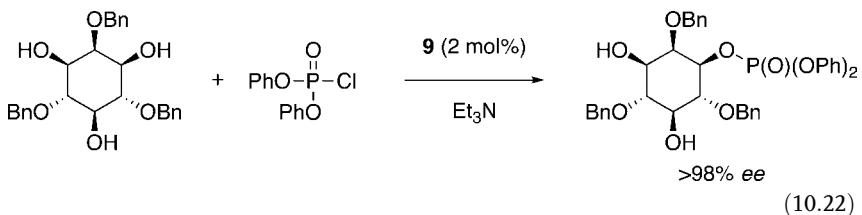


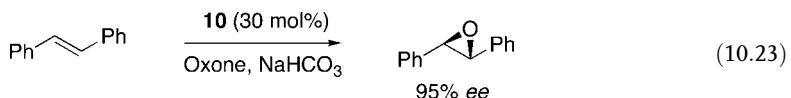
Figure 10.9

a polypeptide catalyst (**9**) to furnish the corresponding monophosphate with excellent enantioselectivity, which provided an expedient route for the asymmetric synthesis of D-*myo*-inositol-1-phosphate (Equation 10.22) [45].



10.3.3.4 Ketone Catalysts

Shi and co-workers reported in 1996 the enantioselective epoxidation of unfunctionalized alkenes mediated by the fructose-derived ketone **10** (Figure 10.10) [46]. Corresponding oxiranes were obtained with excellent enantioselectivities (Equation 10.23). Yang and co-workers also reported the enantioselective epoxidation of alkenes, employing a cyclic ketone derived from binaphthylidicarboxylic acid [47].



10.3.3.5 Phase-Transfer Catalysts

Wynberg and co-workers reported the first example of a chiral quaternary ammonium fluoride-catalyzed Michael addition of nitromethane to chalcone [48]. Although the enantioselectivity in the initial report was modest, a range of chiral phase-transfer catalysts, in particular based on cinchona alkaloids, were reported.

The asymmetric synthesis of α -alkyl- α -amino acids using a chiral catalyst is a useful method for the preparation of both natural and unnatural amino acids. O'Donnell *et al.* developed the cinchona alkaloid-catalyzed alkylation of glycine derivatives [49]. However, almost all of the chiral phase-transfer catalysts were restricted to cinchona alkaloid derivatives. In 1999, Maruoka and co-workers designed a chiral ammonium salt bearing a binaphthyl backbone as a chiral phase-transfer catalyst (**10a**) (Figure 10.11), and demonstrated its catalytic activity

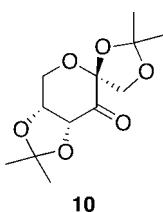
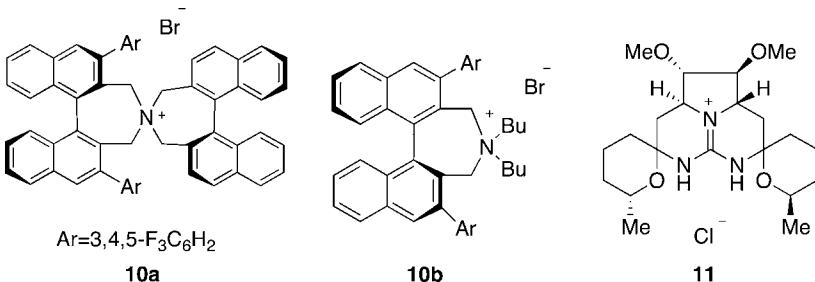
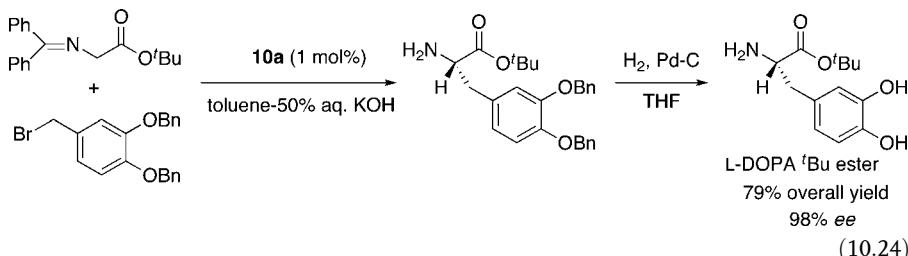


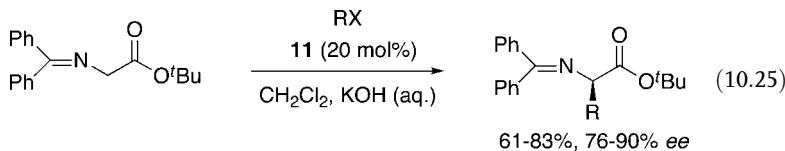
Figure 10.10

**Figure 10.11**

in the alkylation of a glycine derivative (Equation 10.24) [50, 51]. Recently, they reported a simplified version of a chiral phase-transfer catalyst bearing a monobinaphthyl backbone (**10b**) [52].

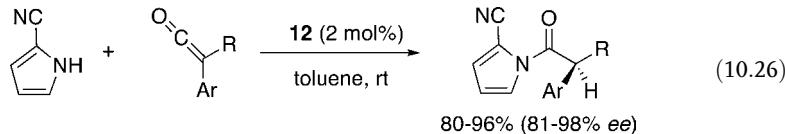


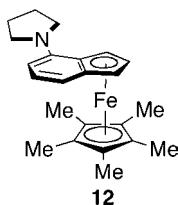
Nagasawa and co-workers developed the C_2 -symmetric chiral pentacyclic guanidine **11** as a chiral phase-transfer catalyst for the enantioselective alkylation of *tert*-butyl glycinate Schiff base (Equation 10.25) [53].



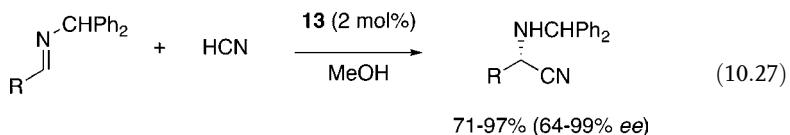
10.3.3.6 Amine Catalysts

In 2002, Hodous and Fu and co-workers reported the enantioselective addition of amines to ketenes catalyzed by the planar chiral 4-(pyrrolidino)pyridine derivative **12** (Figure 10.12) to furnish acylpyrroles with good to excellent enantioselectivities (Equation 10.26) [54].

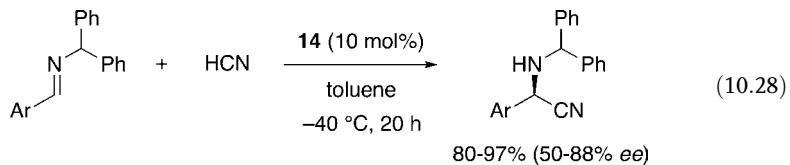


**Figure 10.12****10.3.3.7 Guanidinium Salts [55]**

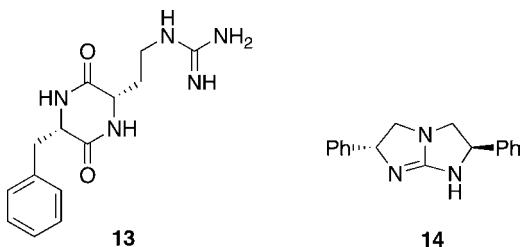
Lipton and co-workers employed the cyclic dipeptide **13** (Figure 10.13) bearing a guanidinium moiety as a catalyst in the Strecker synthesis in 1996. Corresponding α -aminonitriles were obtained with high enantioselectivities (Equation 10.27).

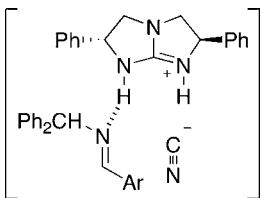
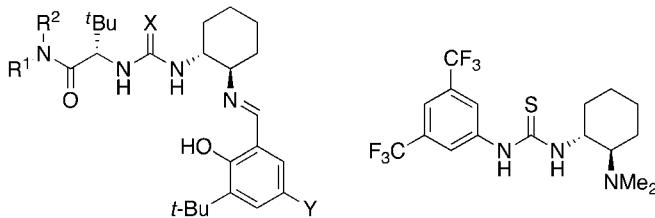
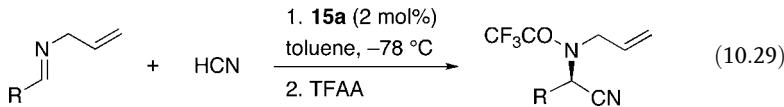


Corey and Grogan reported an enantioselective Strecker reaction via the C_2 -symmetric guanidine **14** (Equation 10.28) [56]. They proposed the transition-state structure shown in Figure 10.14, where the imine is activated by hydrogen bonding.

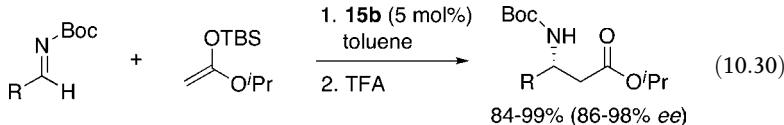
**10.3.3.8 Hydrogen Bond Catalysts [57]**

During the study of ligands for metal-catalyzed asymmetric reactions, Sigman and Jacobsen identified urea **15a** as an efficient catalyst for the Strecker reaction in 1998 (Figure 10.15, Equation 10.29) [58].

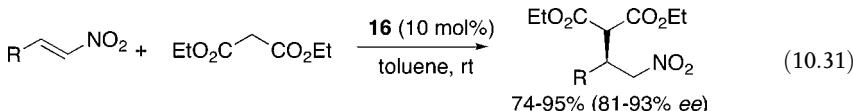
**Figure 10.13**

**Figure 10.14****15a:** $R^1 = \text{Bn}$, $R^2 = \text{H}$, $X = \text{O}$, $Y = \text{O}(\text{CO})^t\text{Bu}$ **15b:** $R^1 = \text{Bn}$, $R^2 = \text{Me}$, $X = \text{S}$, $Y = ^t\text{Bu}$ **16****Figure 10.15**

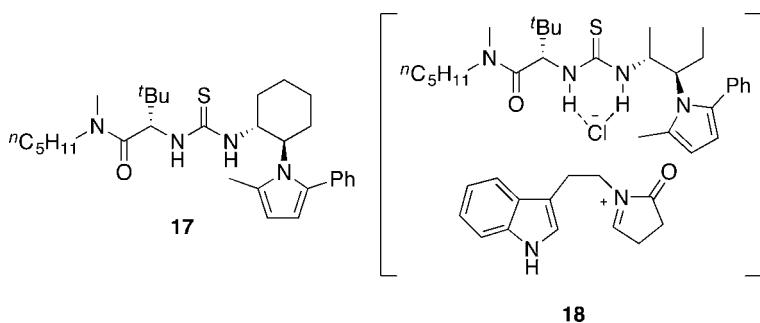
Wenzel and Jacobsen reported the thiourea **15b**-catalyzed Mannich-type reaction of a ketene silyl acetal with an *N*-Boc-aldimine, furnishing β -amino esters with excellent enantioselectivities (Equation 10.30) [59]. Subsequently, Jacobsen and co-workers reported the hydrophosphonylation of dialkyl phosphites with aldimines to yield α -amino phosphonates [60].



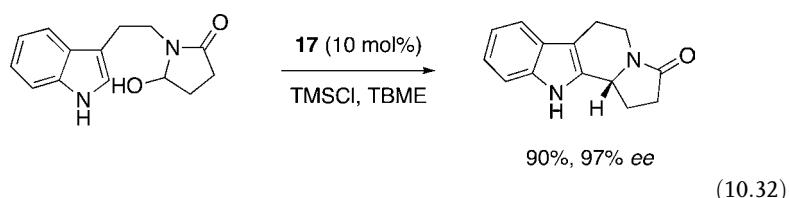
The bifunctional thiourea catalyst **16** was developed by Takemoto and co-workers in 2003 [61, 62]. The Michael reaction of diethyl malonate with nitroalkenes proceeded with excellent enantioselectivities (Equation 10.31).



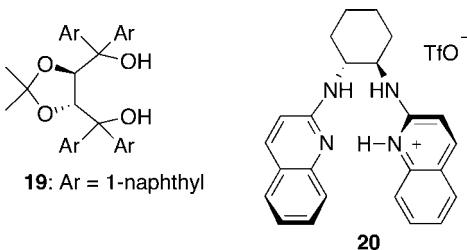
Following the pioneering work of Jacobsen's and Takemoto's groups, a range of chiral thiourea catalysts were reported [63].

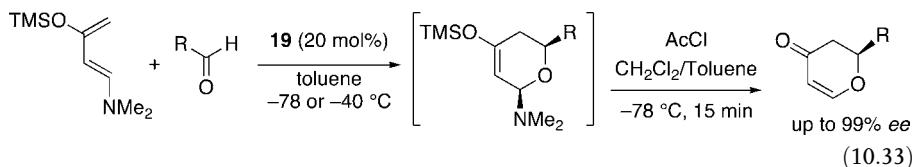
**Figure 10.16**

Recently, Jacobsen and co-workers reported conceptually novel counteranion catalysis employing the thiourea **17** (Figure 10.16) [64]. Thiourea **17** catalyzed the Pictet–Spengler-type cyclization of hydroxylactams and the corresponding cyclization products were obtained with excellent enantioselectivities (Equation 10.32). The authors proposed the cationic intermediate **18**, in which the thiourea coordinates to the chloride anion.

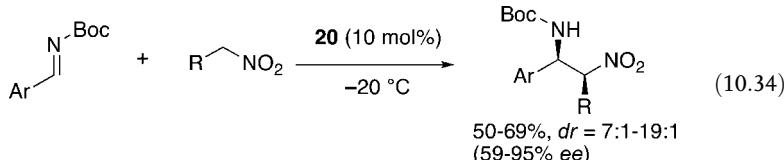


In 2002, Huang and Rawal found that the hetero Diels–Alder reaction of aminosiloxydienes with aldehydes was accelerated in alcoholic solvents [65]. They subsequently elucidated that TADDOL (**19**) is an efficient chiral catalyst for the hetero-Diels–Alder reaction (Figure 10.17, Equation 10.33) [66]. The internal hydrogen bond in TADDOL observed in its crystal structure is expected to render the hydroxy proton more acidic, hence enabling it to participate better in intermolecular hydrogen bonding with the carbonyl group of the dienophile [67]. The Mukaiyama aldol reaction was also reported [68].

**Figure 10.17**

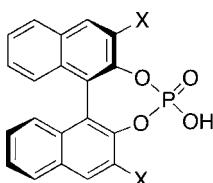
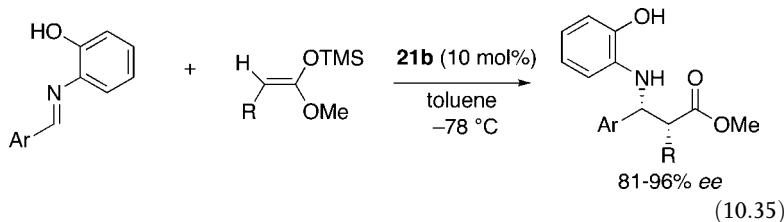


Johnston and co-workers developed amidinium salt **20** from cyclohexanediamine and employed it as a catalyst for the aza-Henry reaction (Scheme 10.34) [69].



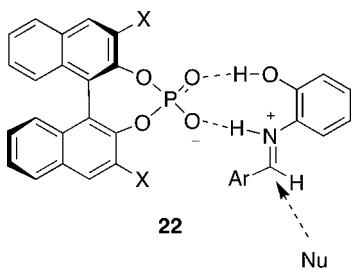
10.3.3.9 Stronger Brønsted Acid Catalysts

The chiral phosphoric acid **21a** (Figure 10.18) is derived from (*R*)-BINOL and is employed as a chiral resolving agent [70]. Alper and Hamel used **21a** as a chiral ligand for the metal-catalyzed reaction [71]. Inanaga *et al.* employed its lanthanide salt as a catalyst for the hetero-Diels–Alder reaction [72]. However, its catalytic activity has not been studied. In 2004, Akiyama’s and Terada’s groups independently reported that the chiral phosphoric acid derived from (*R*)-BINOL exhibited excellent catalytic activity as a chiral Brønsted acid for the Mannich and related reactions. Whereas weak Brønsted acids such as thiourea and TADDOL were reported, strong Brønsted acids had not been investigated as chiral catalysts. Akiyama and co-workers reported the Mannich-type reaction of ketene silyl acetals with aldimines derived from *o*-anisidine by means of chiral phosphoric acid **21b**, giving α -substituted β -amino esters with high *syn* selectivity and excellent enantioselectivities (Equation 10.35) [73].



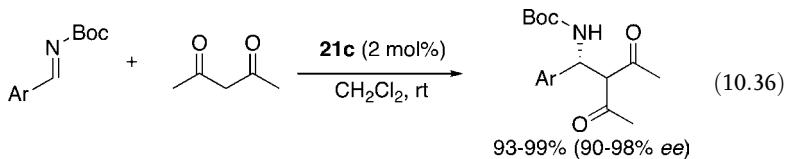
- | | |
|---|---|
| 21a: X = H | 21g: X = 9-phenanthryl |
| 21b: X = 4-NO ₂ C ₆ H ₄ | 21h: X = 3,5-dimesitylphenyl |
| 21c: X = 4- β -naph-C ₆ H ₄ | 21i: X = SiPh ₃ |
| 21d: X = 3,5-(CF ₃) ₂ C ₆ H ₃ | 21j: X = 9-anthryl |
| 21e: X = 2,4,6-(Pr) ₃ C ₆ H ₂ | 21k: X = 2,6-(Pr) ₂ -4-(9-anthryl)C ₆ H ₂ |
| 21f: X = SiPh ₃ | |

Figure 10.18

**Figure 10.19**

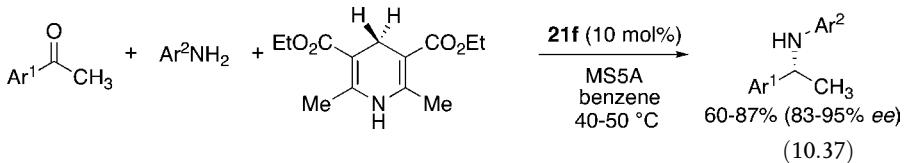
Based on experimental results showing that the use of aldimines derived from *o*-hydroxyaniline is essential to achieve excellent enantioselectivity, and also from theoretical studies [74], the present reaction proceeds via a dicoordination pathway through nine-membered zwitterionic cyclic transition state **22**, consisting of the aldimine and the phosphoric acid (Figure 10.19).

Terada and co-workers reported the direct Mannich reaction of 1,3-pentanedione with *N*-Boc-aldimines catalyzed by **21c**, leading to β -amino ketones with excellent enantioselectivities (Equation 10.36) [75].

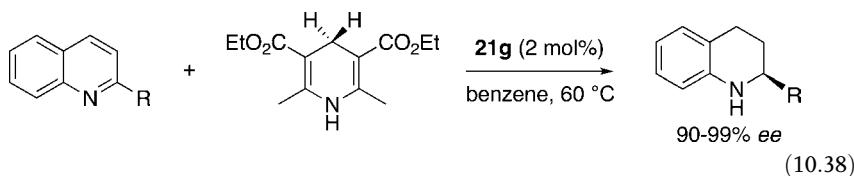


Following the pioneering reports on chiral Brønsted acid catalysis, a range of chiral phosphoric acid-catalyzed reactions have been reported [76].

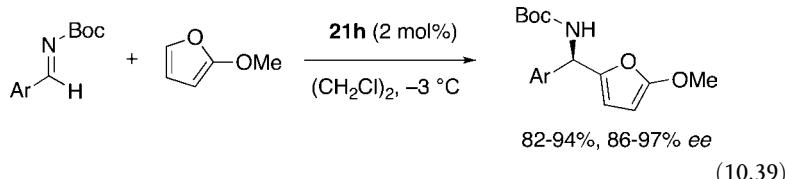
Transfer hydrogenation reactions of ketamines were successfully catalyzed by phosphoric acid with the use of a Hantzsch ester as a hydrogen source. Rueping *et al.* and List and co-workers independently reported the reaction by means of **21d** and **21e** [77]. MacMillan and co-workers reported reductive amination (Equation 10.37) [78–80].



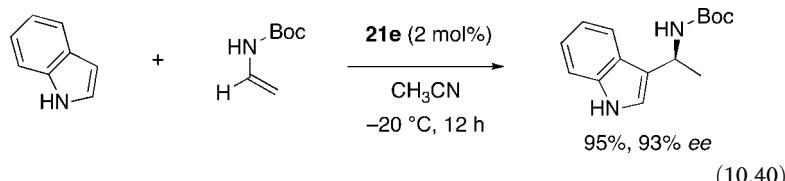
Rueping *et al.* extended the biomimetic approach to the reduction of quinolines, benzoxazines, benzothiazines, and benzoxazinones (Equation 10.38) [81]. The reduction of benzoxazines, in particular, is highly stereoselective, reducing the catalyst load of **21g** to as low as 0.01 mol% without a substantial loss of reactivity or selectivity.



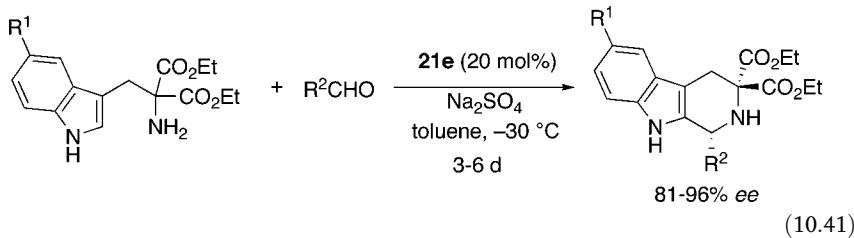
Terada and co-workers reported the aza-Friedel–Crafts alkylation of furans to aldimines by means of 2 mol% of **21h** (Scheme 10.39) [82, 83].



Enantioselective Friedel–Crafts reaction of indole with electron-rich alkenes by means of **21e** furnished 1-indolyl-1-alkylamines, which are of pharmaceutical and biological importance, with excellent enantioselectivity (Equation 10.40) [84].

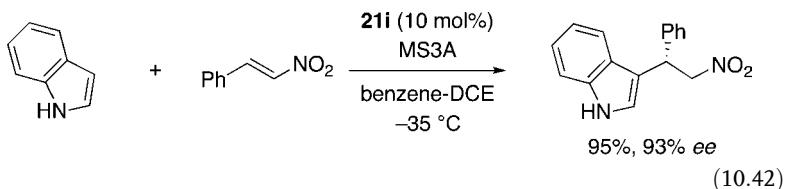


The Pictet–Spengler reaction is important for the preparation of tetrahydro- β -carbolines and tetrahydroquinolines. List and co-workers applied phosphoric acid catalysis to the Pictet–Spengler reaction starting from geminally disubstituted tryptamines (Equation 10.41) [85, 86]. The presence of the bis(ethoxycarbonyl) group facilitated the cyclization reactions by virtue of the Thorpe–Ingold effect. Both aliphatic and aromatic aldehydes turned out to be good substrates.

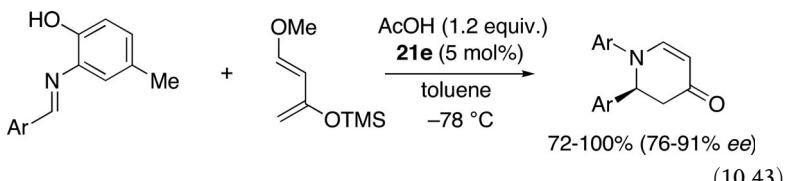


Hiemstra and co-workers also reported the Pictet–Spengler reaction of *N*-sulfenylamines by use of 5 mol% **21d**, in which geminal disubstitution is not required and the *N*-substituent is readily removed [87].

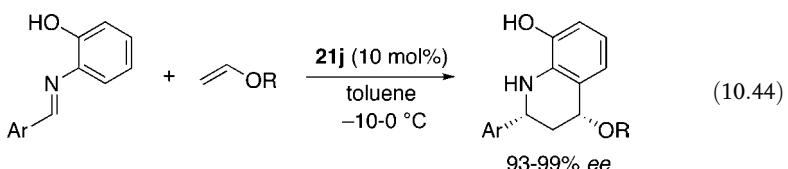
Friedel–Crafts alkylation of indole with nitroalkenes was also effected by chiral phosphoric acid **21i** (Equation 10.42) [88].



Chiral phosphoric acid is also effective for aza-Diels–Alder reactions. Danishefsky’s diene underwent aza-Diels–Alder reaction with aldimines by means of **21e** in the presence of acetic acid to give the cycloadducts with high enantioselectivities (Equation 10.43) [89]. Brassard’s diene also participated in the aza-Diels–Alder reaction under the influence of **21j** to give δ -lactams with excellent enantioselectivities [90].



The reverse electron-demand aza-Diels–Alder reaction of electron-rich alkenes with 2-azadienes was catalyzed by **21j** to give tetrahydroquinoline derivatives in favor of the *cis*-isomer with excellent enantioselectivities (Equation 10.44) [91].



Phosphoric acid catalysis is also effective for multicomponent reactions. Gong and co-workers reported a highly enantioselective Biginelli reaction catalyzed by means of **23a** (Figure 10.20) to furnish 3,4-dihydropyrimidinones with high enantioselectivities (Equation 10.45). Gong and co-workers also reported three-component 1,3-dipolar cycloadditions, furnishing pyrrolidine derivatives with excellent enantioselectivity and

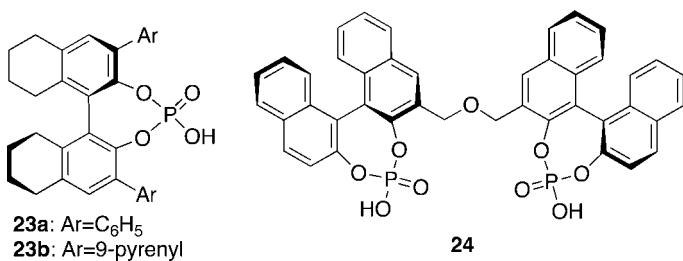
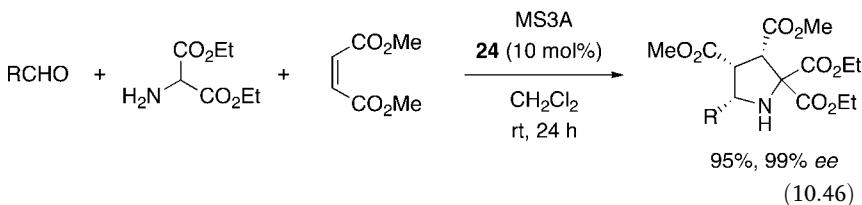
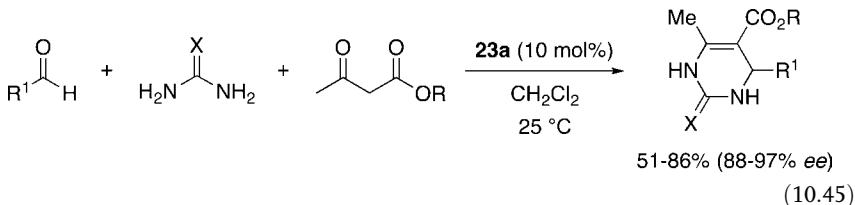
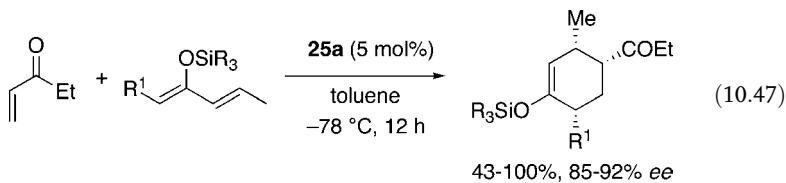


Figure 10.20

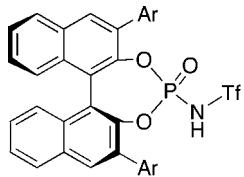
diastereoselectivity by means of a bisphosphoric acid derived from (*R,R*)-linked BINOL **24** (Equation 10.46) [92].



Most of the reactions catalyzed by phosphoric acid involved activation of imines. In order to activate carbonyl compounds, Nakashima and Yamamoto introduced an *N*-triflyl (NTf) group, thereby increasing the acidity of the phosphoric acid. Thus, Diels–Alder reaction of electron-rich dienes with α,β -unsaturated ketones proceeded highly enantioselectively by means of *N*-triflylphosphoramide **25a** (Figure 10.21) to furnish cyclohexenes with high enantioselectivities (*N*-triflyl 10.47) [93].

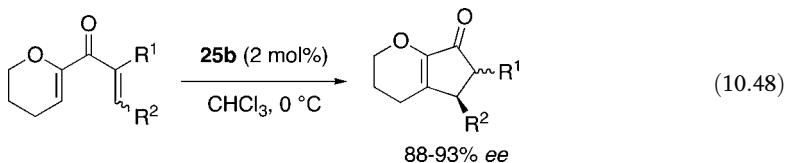


Rueping *et al.* reported the Nazarov cyclization reaction catalyzed by **25b** (Equation 10.48) [94]. This was the first example of an organocatalyzed electrocyclization reaction.

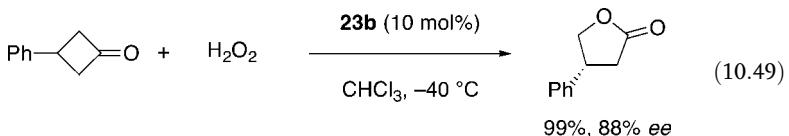


25a: Ar = 2,4,6-(*i*Pr)₃C₆H₂
25b: Ar = 9-phenanthryl

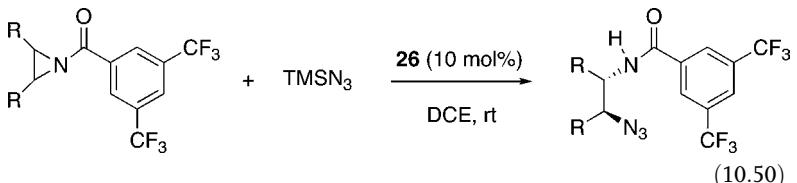
Figure 10.21



Ding and co-workers reported the Baeyer–Villiger reaction of cyclobutanones by means of **23b**, giving access to γ -lactones with high enantioselectivities (Equation 10.49) [95].

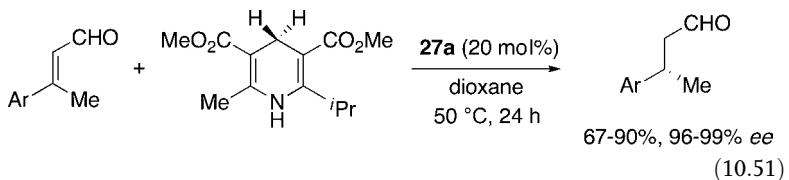


Antilla and co-workers reported desymmetrization of *meso*-aziridines catalyzed by the (*R*)-VAPOL-derived phosphoric acid **26** (Equation 10.50, Figure 10.22) [96].

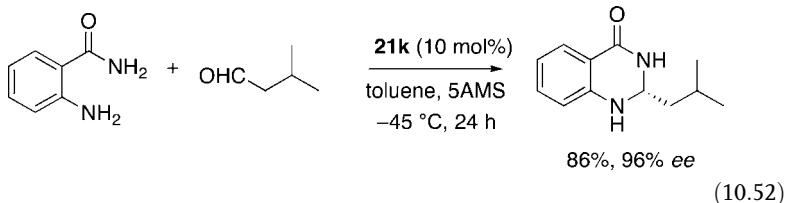


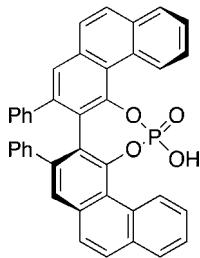
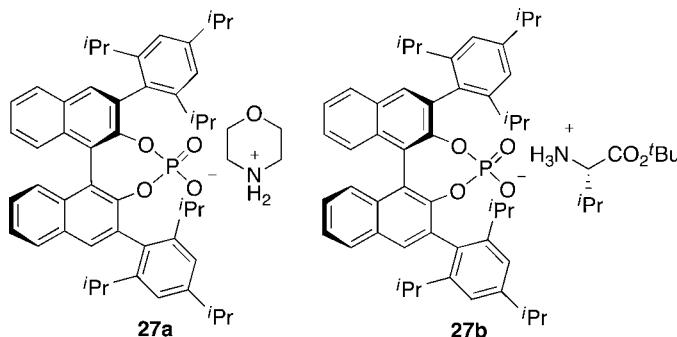
10.3.3.10 Counteranion Catalysis [97]

List and co-workers [98] reported a counteranion-directed transfer hydrogenation reaction involving the phosphoric acid ammonium salt **27a** (Figure 10.23). The reduction proceeded via an iminium salt intermediate, wherein phosphate anion effectively shielded one of the enantiofaces of the iminium salt (Equation 10.51).



Antilla and co-workers reported the enantioselective formation of *N,N*-aminals catalyzed **26** [99]. Recently, List's and Rueping's groups independently applied the methodology for the asymmetric synthesis of 2,3-dihydroquinazolinones, which exhibit potent tubulin inhibitory activities (Equation 10.52) [100].



**26****Figure 10.22****Figure 10.23**

10.4 Conclusion

Some of the seminal studies of organocatalysts have been described, focusing on chiral Brønsted acid catalysts. Because this review is not comprehensive, there are a number of topics not covered in this chapter, such as carbene catalysts, bifunctional catalysts, and so on.

Although asymmetric reactions catalyzed by small chiral organic compounds date back to the mid-twentieth century, organocatalysis was overlooked by synthetic organic chemistry until 2000, when List, Lerner, Barbas, and MacMillan reported their seminal work on iminium and enamine catalysis. The scope of the transformation has expanded significantly in the last 10 years. Viability as a catalyst for the total synthesis of natural products has been recognized. Application to large-scale syntheses in industry has also been reported lately. Although organocatalysts are not always satisfactory in terms of conversion and/or catalyst loading, more efficient catalyst systems will be developed.

It is difficult to predict the future of organocatalysis, but it will continue to attract the attention of synthetic chemists. It is important to find novel transformations and reactivities so far not realized in metal catalysis. The first century of the organocatalysis is almost over, and it is exciting to expect a further explosion of the field in the next decade.

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11

Chemistry Beyond Functional Group Transformation

Zhiping Li and Rong Yu

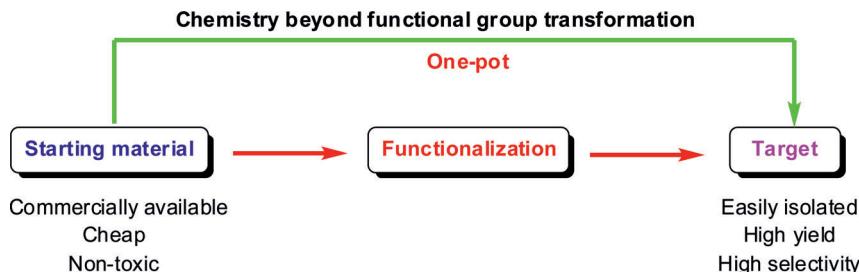
11.1

Introduction

Organic chemistry is one of the fundamental areas of chemistry, which broadly is the science of the compositions, structures, properties, and reactions of substances. The essence of organic chemistry is to construct desired highly functionalized products from simple starting materials using various synthetic methods in an efficient manner. Since urea, the first artificially synthesized organic molecule, was made in 1828, the field of organic synthesis has witnessed tremendous developments. Synthetic chemists now have an almost unimaginable variety of reagents and reactions in their synthetic toolboxes. All these achievements provide invaluable knowledge and useful tools for the development of human society.

In most organic textbooks, the context of organic chemistry was predominated by the chemical properties of organic functional groups. Students started learning organic chemistry by following the classification of these functional groups. In fact, functionalized molecules are always the ultimate products of organic synthesis and, historically, organic synthesis is the transformation of one functional group into another. These methodologies are useful in providing the desired products from starting substances, which already contain transformable functional groups. However, most precursors are not commercially available and needed to be prepared via additional synthetic steps from simpler and more easily available compounds. Consequently, a series of problems, such as pollution and process safety, became issues of serious concern to human society. As one of results, organic chemistry is often blamed as a source of pollution. Is there anything wrong with organic chemistry itself? The answer is, of course, “no.” How can we fit synthetic work into our new society? How to face these problems becomes the challenge for synthetic chemistry. Fortunately, “green chemistry” appeared at an opportune time [1]. Green chemistry, also known as sustainable chemistry, is the design of chemical processes that reduce or eliminate the use

or generation of hazardous substances. Green chemistry has attracted much attention due to its potential to revolutionize the development of chemistry. As one of the fundamental innovations in organic chemistry, “chemistry beyond functional group transformation,” which uses readily available, cheap, and nontoxic materials to construct targeted molecules in high yields under mild conditions, is highly desirable (Scheme 11.1) [2].



Scheme 11.1 Desirable synthesis versus traditional synthesis.

The concept of “chemistry beyond functional group transformation” concerns mainly reaction participants, and this chapter is aimed at providing a summary of some recent development in that respect. The contents of this chapter include (1) sp^3 C–H and sp^2 C–H bond activation, (2) C–C bond activation, (3) C–O bond activation, (4) C–F bond activation, (5) C–N bond activation, and (6) small molecule activation (H_2 , O_2 , and CH_4). More detailed information can be found in the cited references.

11.2 C–H Bond Activation

C–H bonds are ubiquitous in organic compounds. However, C–H bonds are generally inert to most reagents and are not considered as a type of functional group. Strong bases were generally used to deprotonate C–H bonds, followed by further transformation in traditional synthetic chemistry. Direct and selective functionalization of C–H bonds brings us new opportunities and fresh ideas for organic synthesis [3]. Selective and efficient functionalization of C–H bonds has attracted much attention in both academia and industry in the last few decades. A variety of strategies for C–H bond activation have been developed, including lithiation, radical, metal-catalyzed, oxidative coupling, and carbene insertion processes. A number of reviews and monographs on C–H bond activation have been published [4]. In this section, the topics are organized according to the types of C–H bonds (sp^3 and sp^2 C–H bonds). C–C, C–N, and C–O bond formation are covered in each subsection.

11.2.1

***sp*³ C–H Bond Activation**

11.2.1.1 C–C Bond Formation

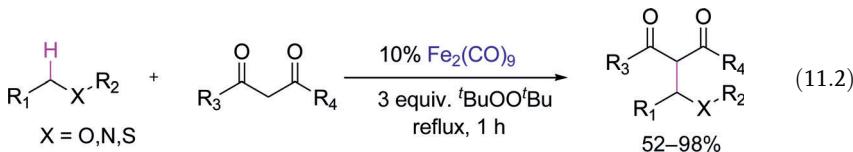
C–C bond formation reactions are among the most important processes in chemistry, because they provide key steps in building more complex molecules from simple precursors. After over a century of fundamental development, traditional synthetic methods are widely used in industrial production and also small-scale laboratory synthesis. To obtain the desired products, prefunctionalized starting materials are generally used. Therefore, for a single chemical bond formation, an extra step (or multiple steps) is needed for the preparation of these prefunctionalized starting materials. To address the challenge of making synthesis more efficient, C–H bond activation or direct utilization of activated C–H bonds followed by subsequent C–C bond formation have attracted much interest in recent years.

Iron Catalysts The applications of iron catalysts have attracted much attention in organic chemistry due to their advantages of being inexpensive, easily available, and nontoxic [5]. Recently, some pioneering work on iron-catalyzed organic reactions and selective C–H bond activation has been reported, which were previously achieved only by noble metal catalysts [6].

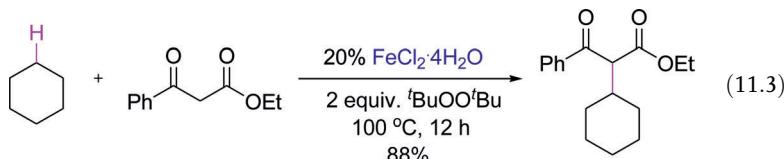
The syntheses of benzyl derivatives from benzylic C–H are well developed. Traditionally, multi-step syntheses had to be used. Furthermore, a stoichiometric amount of base was used and toxic halides were produced. To avoid such problems, various catalytic methods have been developed recently via direct functionalization of benzylic C–H bonds. More recently, our group has reported the FeCl₂-catalyzed oxidative activation of benzylic C–H bonds followed by a cross-coupling reaction to form C–C bonds (Equation 11.1) [7]. The reactions selectively cleave benzylic C–H bonds and avoid further oxidation. The present methodology opens a window for iron-catalyzed C–H bond oxidation and C–C bond formation.



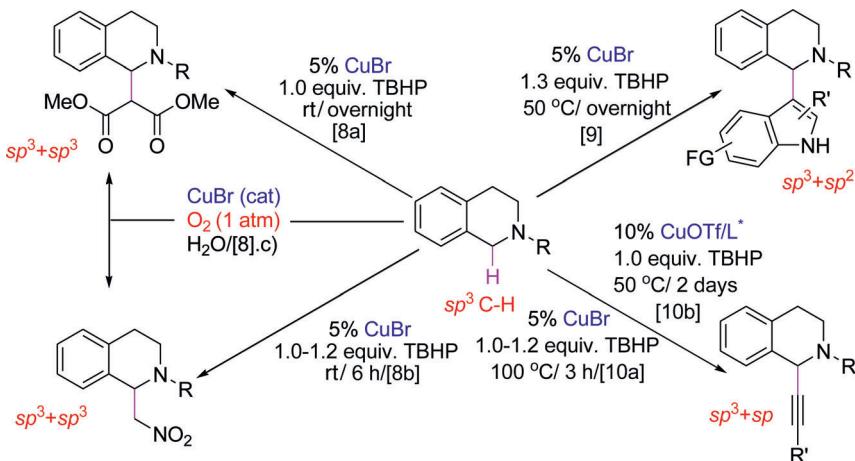
Direct oxidative activation of *sp*³ C–H bonds adjacent to a heteroatom is an ideal synthetic route to heteroatom-containing derivatives. Recently, our group has developed an efficient method for the alkylation of 1,3-dicarbonyl compounds using Fe₂(CO)₉ as a catalyst (Equation 11.2) [8]. The scope of this transformation is fairly broad and various heteroatom-containing compounds have been shown as effective alkylation reagents. Kinetic isotopic effect (KIE) experiments have shown that the reaction has a $k_{\text{H}}/k_{\text{D}}$ value of 5.4 ± 0.1 , which supports a rate-determining C–H bond cleavage step for the overall transformation.



Direct functionalization of simple alkanes is one of the great challenges in organic synthesis. A simple iron salt, $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$, has shown high efficiency in the catalytic alkylation of activated methylene groups. The reactions of cycloalkanes and various 1,3-dicarbonyl compounds have led to desired oxidative cross-coupling products with reasonable to good yields (Equation 11.3) [9]. Importantly, not only cycloalkanes but also simple alkanes can be applied in the alkylation reactions under mild conditions, although the selectivity is problematic at the present stage.



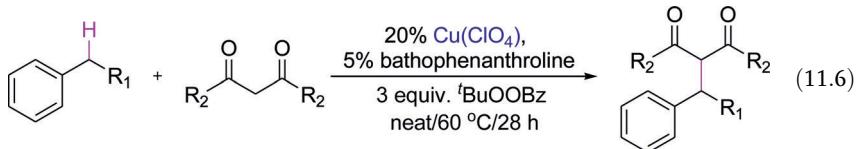
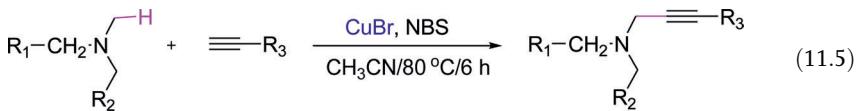
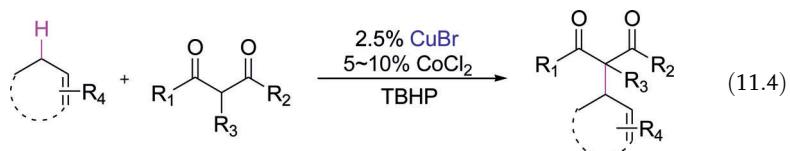
Copper Catalysts Direct oxidative functionalization of tertiary amines is of importance both enzymatically and synthetically. The combination of CuBr –TBHP has proved to be as an efficient system in the oxidative activation of sp^3 C–H bonds adjacent to a nitrogen atom [10]. Various types of cross-dehydrogenative coupling (CDC) reactions have been developed, including compounds with activated methylene groups [11], indoles [12], and terminal alkynes (Scheme 11.2) [13]. Because 1,2,3,4-tetrahydroisoquinoline derivatives are important structure motifs of natural



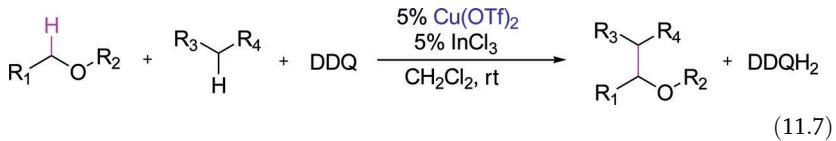
Scheme 11.2 Cu-catalyzed cross-dehydrogenative coupling (CDC) reactions.

products and pharmaceuticals, these catalytic reactions will be efficient methods for the synthesis of such compounds. These CDC reactions have provided an alternative to traditional synthetic chemistry which uses functional groups. In addition, the CDC reactions make synthetic schemes shorter and more efficient.

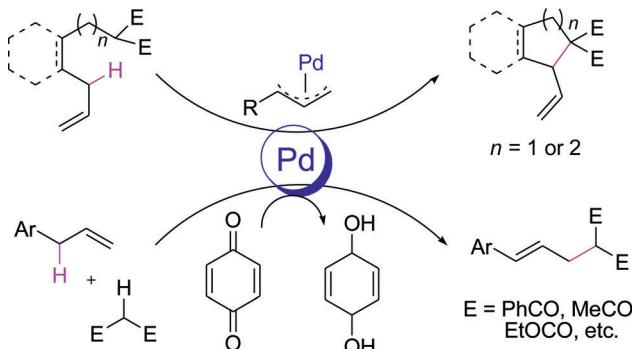
When CoCl_2 is used as a co-catalyst, the CDC reactions of allylic sp^3 C–H and 1,3-dicarbonyl compounds smoothly afford Trost–Tsuji-type products, which are traditionally prepared from allyl halides or acetates (Equation 11.4) [14]. Moreover, when NBS is used instead of TBHP, selective C–H cleavage of tertiary aliphatic amines is possible (Equation 11.5) [15]. For benzylic C–H bonds, direct C–C bond formation can be achieved using copper perchlorate (Equation 11.6) [16].



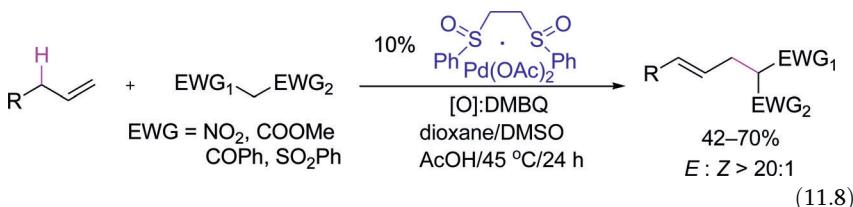
Compared with the tertiary amine system, there are few examples of oxidative activation of C–H bonds adjacent to an oxygen atom. DDQ was an effective oxidant for the oxidative activation of α -C–H bonds of ethers (Equation 11.7) [17].



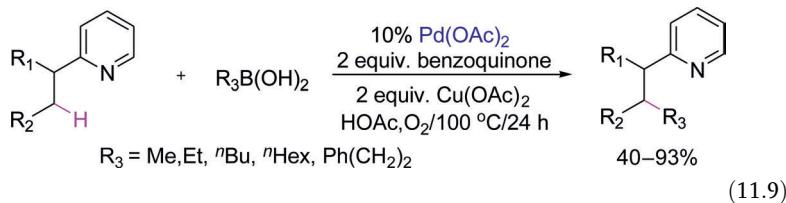
Palladium Catalysts Palladium catalysts are effective and powerful for C–H bond functionalization. Carbene precursors and directing groups are commonly used strategies. Generally, sp^3 C–H bond activation is more difficult than sp^2 C–H bond activation due to instability of potential alkylpalladium intermediates. By choosing specific substrates, such as these with allylic C–H bonds, palladium catalytic systems have been successful. Both intramolecular and intermolecular allylic alkylation have been developed (Scheme 11.3) [18]. This methodology has presented another alternative way to achieve the traditional Tsuji–Trost reactions.

**Scheme 11.3** Pd-catalyzed Tsuji–Trost reactions via C–H coupling.

Another excellent example of allylic C–H alkylation has been developed using a $\text{Pd}(\text{OAc})_2$ -bis-sulfoxide catalyst (Equation 11.8) [19]. Bis-sulfoxide is a crucial and efficient ligand for the transformation. The regioselectivity of the allylation reactions is controlled by steric effects. The synthetic utility of this method is highlighted by the subsequent transformation of its product.

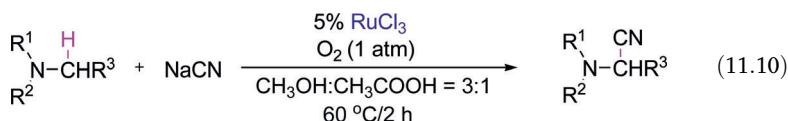


With the strategy of directing group (DG)-assisted C–H bond activation, there are many examples of Pd-catalyzed alkylation of sp^3 C–H bonds. Two representative examples are shown here. A one-pot procedure for sp^3 C–H bond activation with nontoxic and readily available methylboroxine and alkylboronic acids using pyridine (Py) as a directing group has been reported (Equation 11.9) [20]. Later, the same group reported the alkylation of sp^3 C–H bonds using COOH [21] and CONHOMe [22] as directing groups. The feasibility of using air as the final oxidant is advantageous for the potential synthetic utility of this methodology.



Other Metal Catalysts Murahashi's group has carried out systematic studies on the oxidation of C–H bonds adjacent to a nitrogen atom. An effective

ruthenium-catalyzed oxidative cyanation of tertiary amines was reported in 2003 (Equation 11.10) [23]. This approach represents not only a novel methodology for organic synthesis, but also an environmentally benign and useful process for synthesizing α -amino acids and 1,2-diamines under simple and mild conditions. Mechanistic studies have shown that Ru-based catalysts are more effective than other transition metals in aerobic oxidative cyanation [24]. The reactions are dramatically influenced by the solvents. Methanol and ethanol are excellent solvents for these transformations. It should be noted that acetic acid is essential. No cyanation takes place in the absence of acetic acid, indicating that the cyanation reagent is HCN rather than CN^- . Hydrogen peroxide is also an effective oxidant for the transformation [25].



In order to clarify the mechanism, the Hammett linear free energy relationship [26] and the intra- and intermolecular deuterium isotope effects (k_H/k_D) have been investigated (Table 11.1). The negative ρ values indicate cationic intermediacy in the rate-determining step [27]. The intramolecular and intermolecular deuterium isotope effects (k_H/k_D) for the RuCl_3 -catalyzed oxidative cyanation of *N,N*-dimethylanilines and their deuterated analogs have been determined as 2.40 and 2.62, respectively (entry 1 in Table 11.1). These observed isotope effects are larger than those observed for *N*-demethylation with cytochrome P450 (1.6–3.1 [28] and 1.0–1.1 [29]) (entry 5), suggesting that cleavage of the C–H bond proceeds via an intermediate with greater ionic character. The intramolecular deuterium isotope effect for the *p*-X-C₆H₄NMeCD₃ (X = MeO, Me, H, Br) is dependent on the substituent ρ values: the k_H/k_D values are 4.2, 3.1, 2.4, and 1.1, respectively [30]. Thus, the values decrease from electron-donating to electron-withdrawing substituents, indicating that electron transfer from the amine to the ruthenium would

Table 11.1 KIE of catalytic oxidative cyanation of XC₆H₄N(CH₃)₂ to XC₆H₄N(CH₃)CH₂Y.

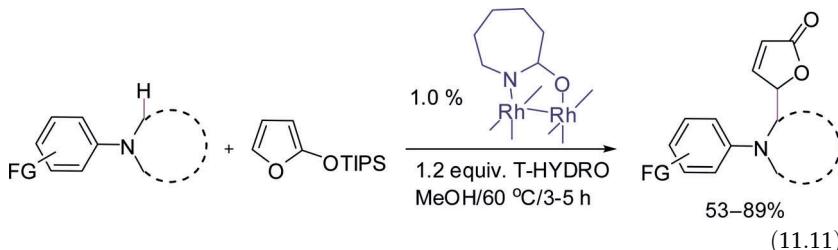
Entry	Catalyst	Oxidant	Y	ρ	k_H/k_D ^{a)}	k_H/k_D ^{b)}	Ref.
1	RuCl_3	O_2	CN	−3.35	2.40	2.62	24
2	RuCl_3	H_2O_2	CN	−3.61	4.06	3.74	24
3	$\text{RuCl}_2(\text{PPh}_3)_3$	^t BuOOH	^t BuOOCH ₃	−0.84	3.53	1.64	27
4	RuCl_3	H_2O_2	OCH ₃	−3.60	3.47	3.72	30
5	Cytochrome P450	O_2	(OH)	−0.74	1.6–3.1	1.0–1.1	[28, 29]

a) Intramolecular deuterium isotope effect.

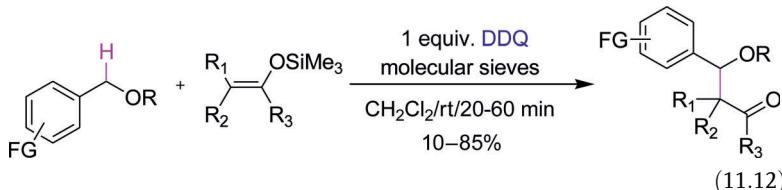
b) Intermolecular deuterium isotope effect.

take place in the initial step [31]. These studies provide an excellent understanding of amine oxidation.

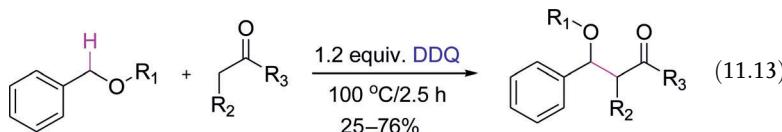
An oxidative iminium ion formation strategy allows the synthesis of valuable γ -aminoalkyl butenolides from readily available amines in the presence of a rhodium catalyst (Equation 11.11) [32]. 2-Triisopropoxysilylfuran reacted with the iminium ion formed *in situ* from catalytic C–H oxidation to afford the corresponding oxidative Mannich products.



Metal Free Transition metal catalysts are highly effective for C–H bond activation. However, transition metal complexes are not only expensive, but also difficult to remove from the reaction products, resulting in toxicity concerns. DDQ is a well-known oxidant in organic chemistry [33]. For many years, it has been used for the oxidation of alcohols to ketones and aromatization. The first intermolecular C–C bond formation was realized by DDQ-mediated Mukaiyama-type aldol reactions [34]. The reactions of electron-rich benzyl ethers and silyl enol ethers afforded 3-alkoxy-3-phenylpropionyl derivatives at ambient temperature with moderate to excellent yields (Equation 11.12).

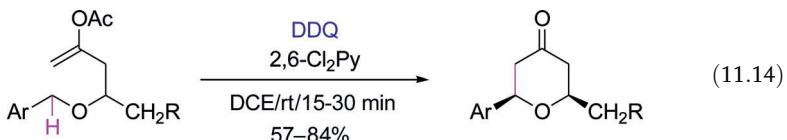


Furthermore, a convenient direct CDC between benzyl ethers and simple ketones has been reported using DDQ as a stoichiometric oxidant (Equation 11.13) [35]. In this reaction, DDQ serves dual roles: oxidizing benzylic C–H bonds and acting as a base to abstract proton from the α -position of the ketone.

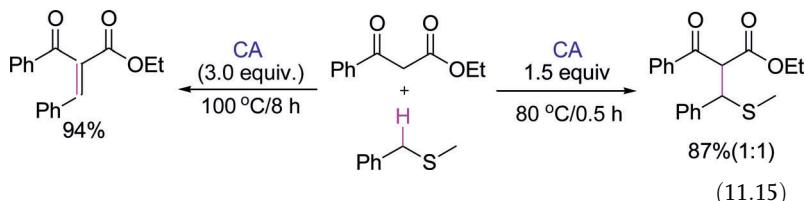


Recently, DDQ has been nicely used for oxidative activation of sp^3 C–H bonds of benzylic and allylic ethers to construct tetrahydropyrone selectively

(Equation 11.14) [36]. Intramolecular enol acetate served as the nucleophile. The reactions tolerate various functional groups. The products were obtained as single isomers. The stable chair conformation contributes to the high *trans* selectivity.

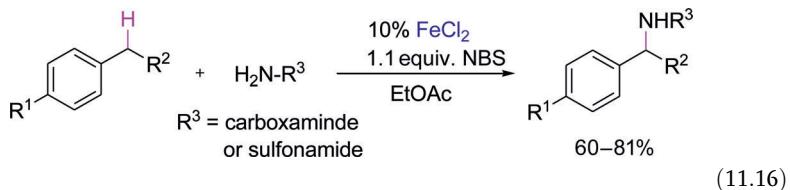


o-Quinones can also be used in C–H bond oxidation and C–C bond formation. Our group has reported tetrachloro-*o*-benzoquinone(CA)-mediated oxidative benzylic sp^3 C–H bond activation of sulfides (Equation 11.15) [37]. This method represents a novel Pummerer-type reaction that avoids preactivation steps. It is noteworthy that Knoevenagel-type products have also be obtained via multiple C–H bond activation by controlling the reaction conditions.



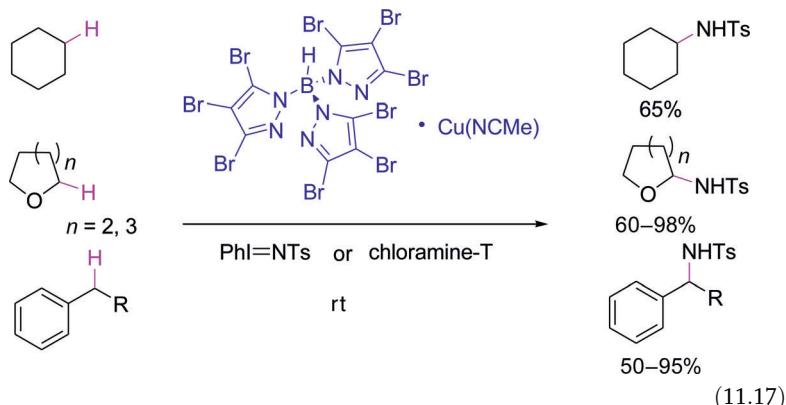
11.2.1.2 C–N Bond formation

Iron Catalysts Direct amidation of C–H bonds presents an efficient method for C–N bond formation. A combination of simple air-stable FeCl_2 and NBS has been successfully used in the amidation of benzylic sp^3 C–H bonds (Equation 11.16) [38]. The reactions are insensitive to atmospheric moisture and oxygen. Neither a dried solvent nor an inert atmosphere is required. An iron–nitrene intermediate has been proposed [39]. The carbene insertion of benzylic C–H bonds provides the final products.

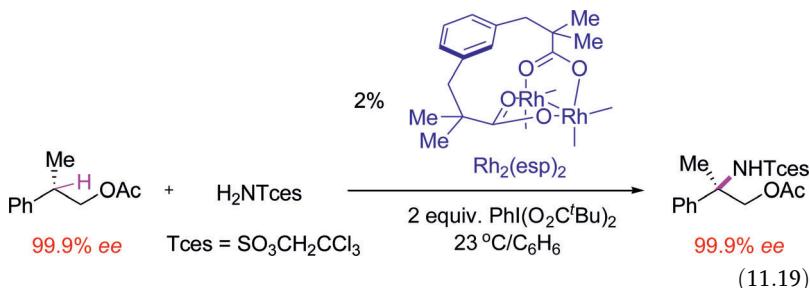
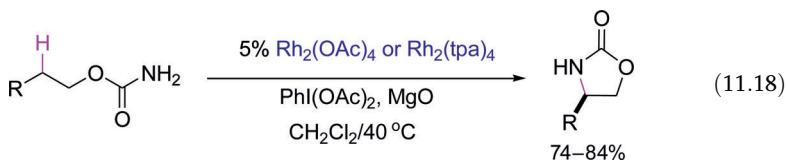


Copper Catalysts Copper is an excellent catalyst for nitrogen transfer reactions via copper–nitrene intermediates. Benzylic hydrocarbons are selectively converted to the corresponding sulfonamides [40]. The intermolecular amidation of saturated C–H bonds of cyclic ethers has been reported using $\text{TsNH}_2\text{-PhI(OAc)}_2$ or PhI=NTs as the nitrene source [41]. The copper-catalyzed amidation of unactivated sp^3 C–H bonds adjacent to a nitrogen atom has also been achieved using *tert*-butyl hydroperoxide or

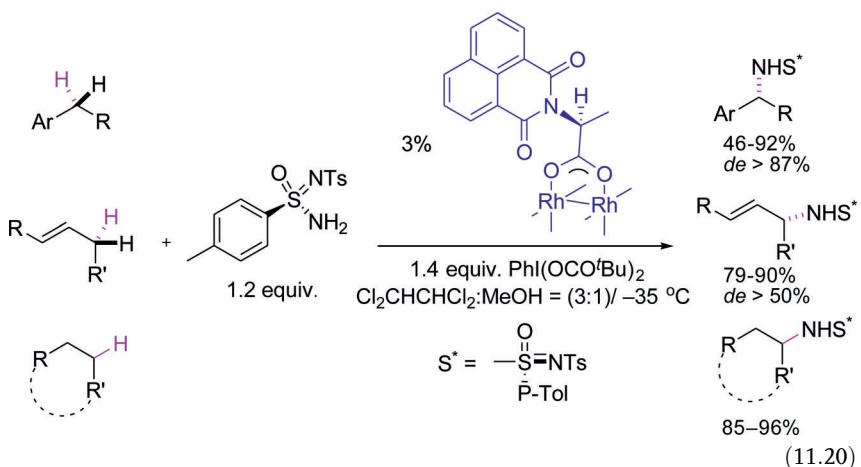
N-halosuccinimide (NBS or NCS) [42] as the oxidant. The complex $\text{Tp}^{\text{Br}3}\text{Cu}(\text{NCMe})$ displays high activity towards nitrene-transfer reactions (Equation 11.17) [43]. Various substrates can be used under the same catalytic conditions.



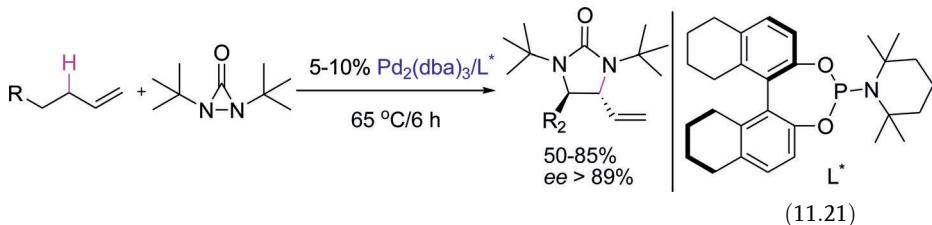
Rhodium Catalysts Rhodium catalysts have been widely used in C–N bond formation via the Rh–nitrene intermediates. Du Bois and co-workers have developed various types of Rh-catalyzed intramolecular C–N bond-forming reactions (Equation 11.18) [44] and intermolecular C–N bond-forming reactions (Equation 11.19) [45]. The mechanism of these C–H amidation reactions proceeds via a concerted asynchronous two-electron oxidation pathway.



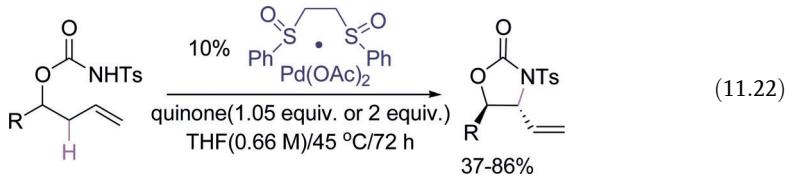
Recently, efficient rhodium-catalyzed intermolecular C–H amination reactions have been reported where a sulfonimidamide is used as the nitrene precursor [46]. The functionalizations of various C–H bonds proceed smoothly in this type of intermolecular amidation reaction (Equation 11.20) [47]. When chiral sulfonimidamides are used, moderate to excellent diastereoselectivities can be achieved.



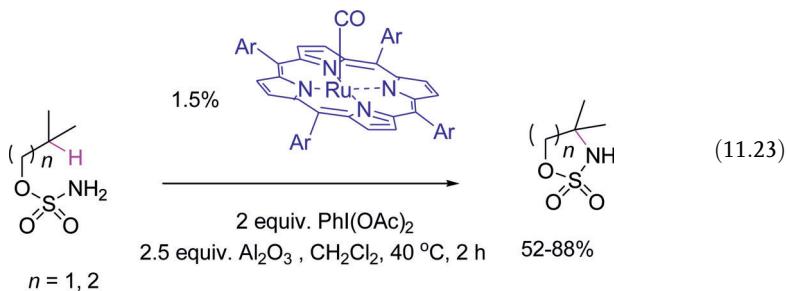
Other Metal Catalysts Palladium catalysts are most widely used for C–N bond formation, particularly in Buchwald–Hartwig coupling reactions [48]. Halides or pseudohalides are generally used. Recently, direct amination of C–H bonds has been developed with palladium catalysts. Pd(0)-catalyzed diamination of terminal olefins at allylic and homoallylic carbons takes place via formal sp^3 C–H activation under solvent-free conditions [49]. More recently, an asymmetric version of allylic and homoallylic diamination has been successfully achieved using di-*tert*-butyldiaziridine as the nitrogen source (Equation 11.21) [50].



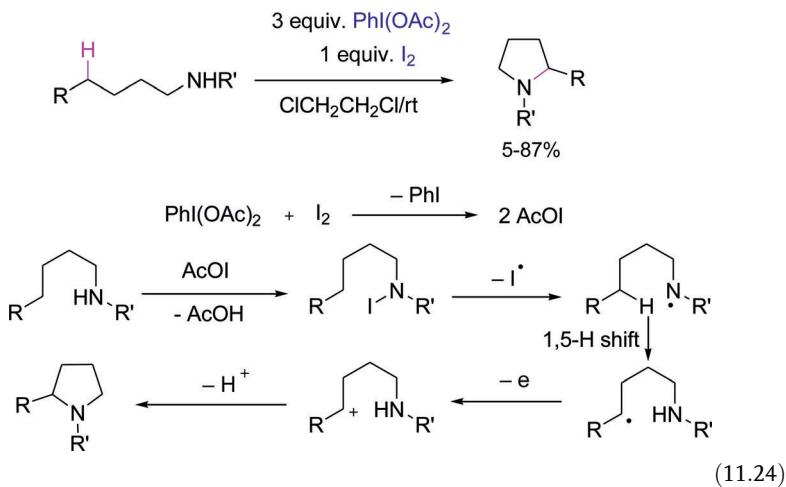
Pd(II)-catalyzed allylic C–H amination reactions have been developed using quinone as an stoichiometric oxidant (Equation 11.22) [51]. The excellent diastereoselectivity and functional group tolerance have paved the way for the broader utilization of this method. Importantly, the functionalized *anti*-oxazolidinone products can be rapidly transformed into useful *syn*-1,2-amino alcohols. Mechanistic studies support a Pd(II)/bis-sulfoxide mediated C–H cleavage to form a π -allyl Pd intermediate followed by a Pd(II) counterion-mediated deprotonation of the nitrogen nucleophile to achieve functionalization. The same group has also demonstrated selective Pd(II)/Cr co-catalytic intermolecular allylic C–H amination reactions [52]. Liu *et al.* have recently developed an even more practical method for the highly regioselective synthesis of linear (*E*)-allylimides [53]. In this case, oxygen is used as an external oxidant.

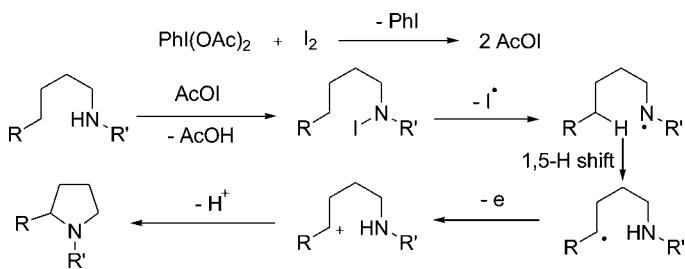


Ruthenium catalysts can also be used in nitrene transfer reactions. The intramolecular amidation reactions of saturated C–H bonds have been developed with ruthenium catalysts (Equation 11.23) [54]. In addition, the Ru-catalyzed asymmetric amination of benzylic and allylic C–H bonds has also been reported [55].



Metal Free Although transition metal catalysts are effective and selective for C–N bond formation via direct C–H bond functionalization, metal-free methodologies are more attractive. Molecular iodine acts as a radical initiator and can be used to direct γ -/ α - sp^3 C–H bond oxidation of sulfonamides in the presence of PhI(OAc)₂ (Equation 11.24) [56]. The reaction provides a practical route to pyrrolidines, N-sulfonylimines, and various sulfonamide derivatives. A tentative mechanism is



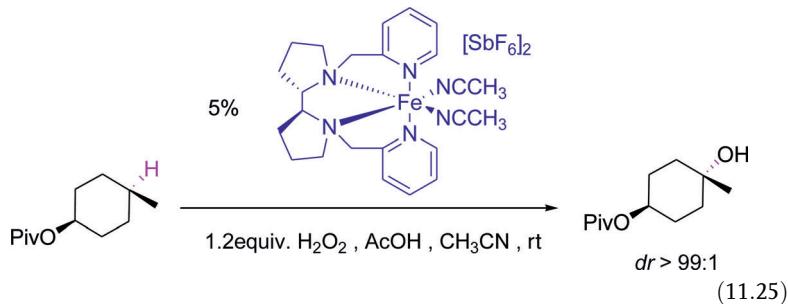


Scheme 11.4 A tentative mechanism for pyrrolidine formation.

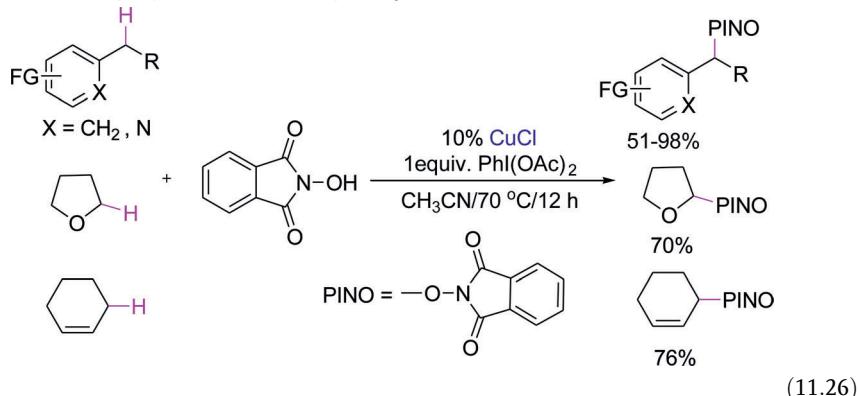
shown in Scheme 11.4. The reaction between $\text{PhI}(\text{OAc})_2$ and iodine generates iodobenzene and acetyl hypoiodite. Sulfonamides react with acetyl hypoiodite to form sulfonamidyl radicals [57]. After a 1,5-H shift and single-electron transfer, five-membered ring products are generated [58].

11.2.1.3 C–O Bond Formation

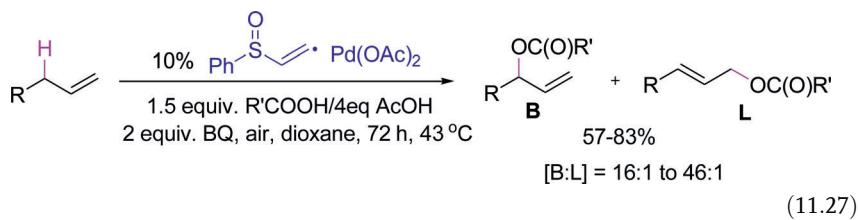
Iron Catalysts Iron-catalyzed C–H oxidation systems such as the Gif [59] and Fenton [60] reactions are well-known examples of C–H functionalization. However, stereospecific sp^3 C–H bond oxidation is still a great challenge for the application of iron-catalyzed C–H oxidations. Recently, selective oxidation of non-activated sp^3 C–H bonds has been realized (Equation 11.25) [61]. Various complex substrates are converted into the corresponding alcohols with high diastereoselectivity under mild reaction conditions.



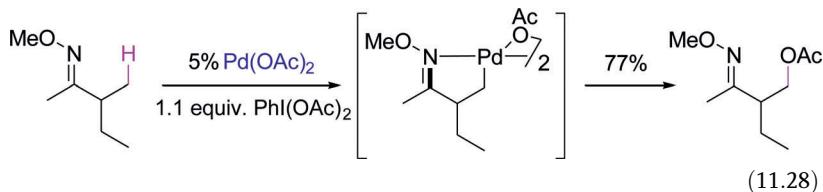
Copper Catalysts When *N*-hydroxyphthalimide is used as an oxygen source, a range of substrates can be selectively oxygenated using $\text{PhI}(\text{OAc})_2$ as an oxidant in the presence of CuCl catalyst (Equation 11.26) [62]. When a radical trap, TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy), is added to the reaction mixture, a TEMPO-trapped compound can be isolated (21%) along with 23% of the desired product. Therefore, a radical intermediate is most likely involved in this transformation [63].



Palladium Catalysts Pd-catalyzed allylic oxidation proceeds effectively using vinyl sulfoxide as a ligand for Pd and benzoquinone (BQ) as a serial ligand under acidic conditions (Equation 11.27) [64]. Mechanistic studies have established that vinyl sulfoxide promotes the step of allylic C–H bond cleavage and BQ acts as a promoter for the reductive elimination to form the final product. The reactions tolerate various functional groups and the products are generated with high chemo- and regioselectivity. The intramolecular Pd-catalyzed macrolactonization of α -alkenoic acids has also been achieved [65].



Significantly, unactivated sp^3 C–H bond oxidation has been achieved using oxime or pyridine as a directing group and Phi(OAc)_2 as a stoichiometric oxidant in the presence of a palladium catalyst (Equation 11.28) [66]. γ -C–H bonds are selectively oxygenated. The selectivity is dramatically influenced by the steric and electronic properties of the alkane substrates.

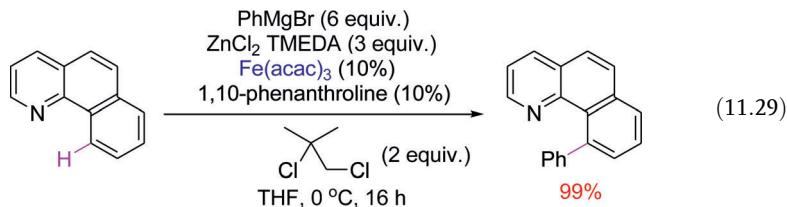


11.2.2

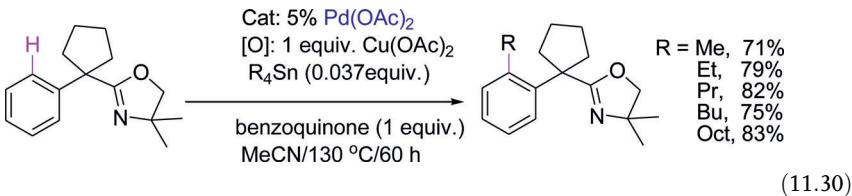
***sp*² C–H Bond Activation**

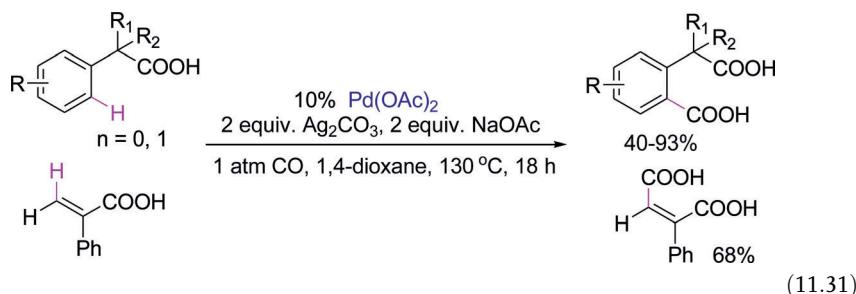
11.2.2.1 C–C Bond Formation

Iron Catalysts Iron catalysts have been used in various reactions of *sp*³ C–H bond functionalization as shown above; however, there are few examples of direct *sp*² C–H bonds functionalization. Significantly, the first cross-coupling of an arylzinc reagent and 2-arylpyridine has been reported recently (Equation 11.29) [67]. This reaction represents an excellent example of synthetically viable iron-catalyzed C–C bond formation through C–H bond activation. The combination of iron, zinc, magnesium, 1,10-phenanthroline, TMEDA, and 1,2-dichloro-2-methylpropane is important for the success of the reaction. It has been speculated that the phenanthroline coordinates to the iron and TMEDA coordinates to the zinc. The reactions proceed via a redox cycle of iron with the 1,2-dichloro-2-methylpropane acting as an electron acceptor.

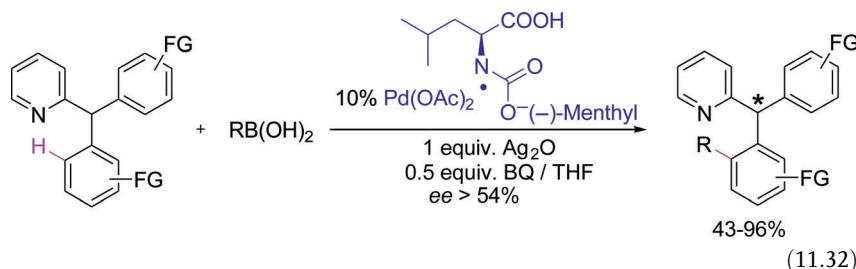


Palladium Catalysts Yu's group has carried out systematic studies on Pd-catalyzed alkylations of aryl C–H bonds. Stille-type cross-coupling reactions have been developed by directed C–H activation (Equation 11.30) [68]. The reaction rate is enhanced by benzoquinone and microwave irradiation. Significantly, carboxylic acid functionality can be used as an efficient directing group for aryl C–H bond activation (Equation 11.31) [69]. The reaction conditions can be applied to the carboxylation of vinyl C–H bonds. The possible intermediacy of a palladacycle has been confirmed by NMR spectra and X-ray crystallography.

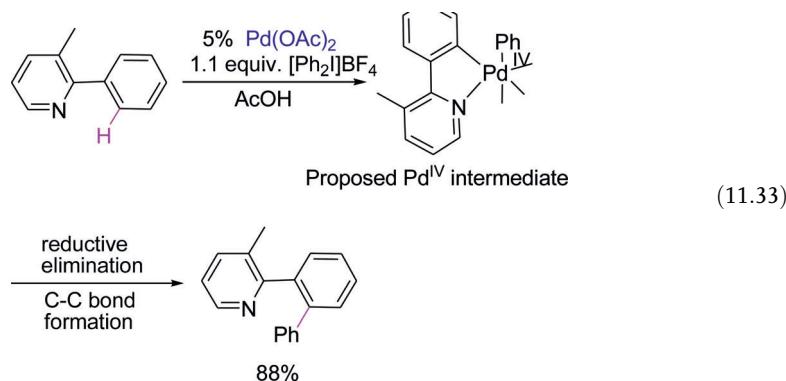




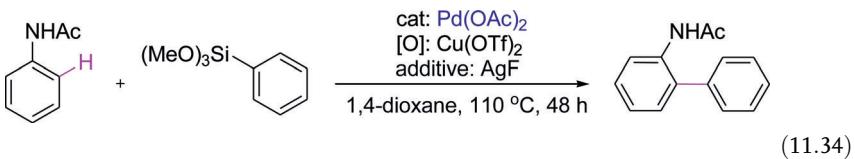
A promising Pd(II)-catalyzed enantioselective C–H activation reaction has been demonstrated using monoprotected α -amino acids as chiral ligands (Equation 11.32) [70]. The coordination of a chiral nitrogen atom at the metal center is believed to be crucial for the enantiocontrol. This approach opens the door for chiral recognition in the C–H activation step.



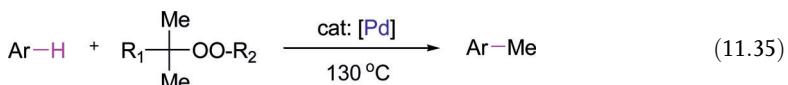
A Pd(II)/(0) catalytic cycle is common in Pd catalytic reactions. Sanford's group has demonstrated a Pd(II)/(IV) catalytic cycle for arylation of aromatic C–H bonds (Equation 11.33) [71]. The method demonstrated high functional group tolerance, high regioselectivity, and broad scope under mild conditions. Preliminary mechanistic experiments have provided evidence supporting a Pd(II)/(IV) catalytic cycle for this transformation.



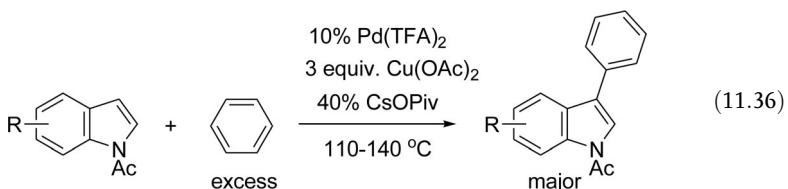
Shi and co-workers have developed various types of C–H bond functionalization and C–C bond formation. Recently, they reported a novel transformation to realize *ortho*-arylation of acetanilides with trialkoxyarylsilanes through direct C–H functionalization (Equation 11.34) [72]. Furthermore, they also demonstrated a novel method for the direct construction of biaryl C–C bonds via Pd(II)-catalyzed cross-coupling of (hetero)arenes and various arylboronic acids [73]. Various aromatic rings show good selectivity, even without directing groups, under mild conditions.



Recently, Li's group reported an unexpected efficient Pd-catalyzed methylation of aryl C–H bonds using a peroxide as a source of methyl groups (Equation 11.35) [74]. This study provided a new avenue for the direct alkylation of aryl C–H bonds using alkyl radicals rather than organometallic reagents. Moreover, this work presents an excellent example of the control of radical decomposition.

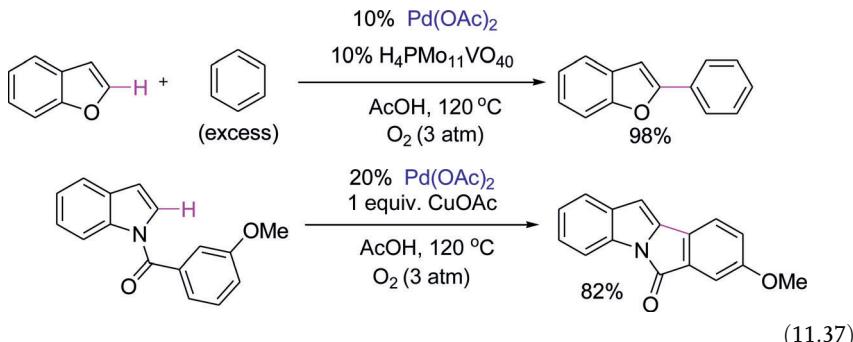


Selective cross-coupling of two different aromatic compounds is a great challenge for C–H bond activation. Recently, a breakthrough has been achieved without a directing group and/or a functional group. The Pd-catalyzed cross-coupling reactions of *N*-acetylindoles and benzenes have been developed using a copper oxidant (Equation 11.36) [75]. These reactions are highly selective for cross-coupling and no homo-coupling products of indoles or benzene have been observed by spectroscopic analysis.

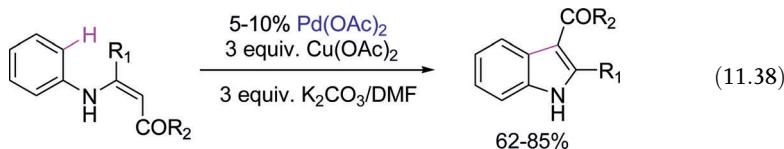


The oxidative coupling reactions of benzofuran and *N*-substituted indoles with benzene and derivatives have also been achieved using oxygen as an oxidant (Equation 11.37) [76]. This methodology for synthesizing heterocoupled biaryls

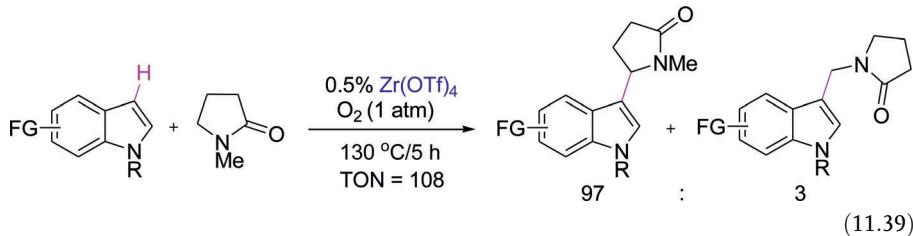
takes place in both inter- and intramolecular scenarios. This method represents a practical way to construct biaryl derivatives.



Indole derivatives are biologically important natural products. Many efforts have been made to achieve the synthesis of this motif. Various innovative and powerful methodologies for the synthesis of indole derivatives have been developed. Recently, Glorius and co-workers reported an efficient oxidative synthesis of indoles from *N*-arylenamines using $\text{Pd}(\text{OAc})_2$ as a catalyst and $\text{Cu}(\text{OAc})_2$ as a stoichiometric oxidant (Equation 11.38) [77]. This method represents an excellent example of constructing C–C bonds by direct use of two C–H bonds. This conversion of anilines into indoles can also be carried out in a one-pot sequence.

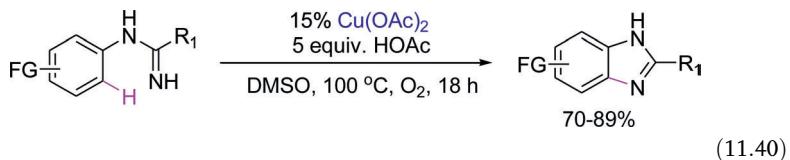


Zirconium Catalysts Early transition metal catalysts are rarely used for C–H functionalization. Tsuchimoto *et al.* reported the first example of a Zr-catalyzed oxidative coupling reaction of lactams with heterocyclic arenes (Equation 11.39) [78]. The reactions show a high turnover number (TON) and high regioselectivity. Significantly, the coupling reactions can be carried out under atmospheric oxygen. This instructive study opens the window for the application of early transition metal catalysts in C–H functionalization.

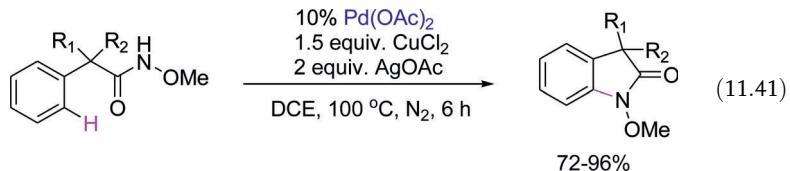


11.2.2.2 C–N Bond Formation

Copper Catalysts Brasche and Buchwald reported a direct Cu-catalyzed C–H functionalization and C–N bond-forming approach which provides benzimidazoles from readily available amidines (Equation 11.40) [79]. The new method requires only inexpensive reagents, such as copper(II) acetate, acetic acid, and oxygen, and tolerates a variety of useful functional groups.

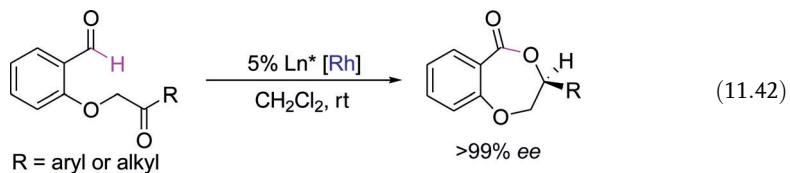


Palladium Catalysts Pd(II)-catalyzed intramolecular amination of sp^2 and sp^3 C–H bonds has been demonstrated (Equation 11.41) [80]. It was proposed that a Pd(II)/(IV) catalytic cycle is most likely for this transformation. CuCl_2 and AgOAc are used as co-oxidants. This method provides practical access to a range of β -, γ -, and δ -lactams.



11.2.2.3 C–O Bond Formation

Compared with C–C and C–N bond formation, there are fewer examples of C–O bond formation reactions via direct sp^2 C–H bond activation. Dong and co-workers reported a novel approach to form chiral lactones (Equation 11.42) [81]. This C–H bond functionalization strategy involves an unprecedented Rh-catalyzed hydroacylation of ketones. The basicity of the phosphine ligand plays a critical role in promoting hydroacylation over competitive decarbonylation.



11.3

C–C Bond Activation

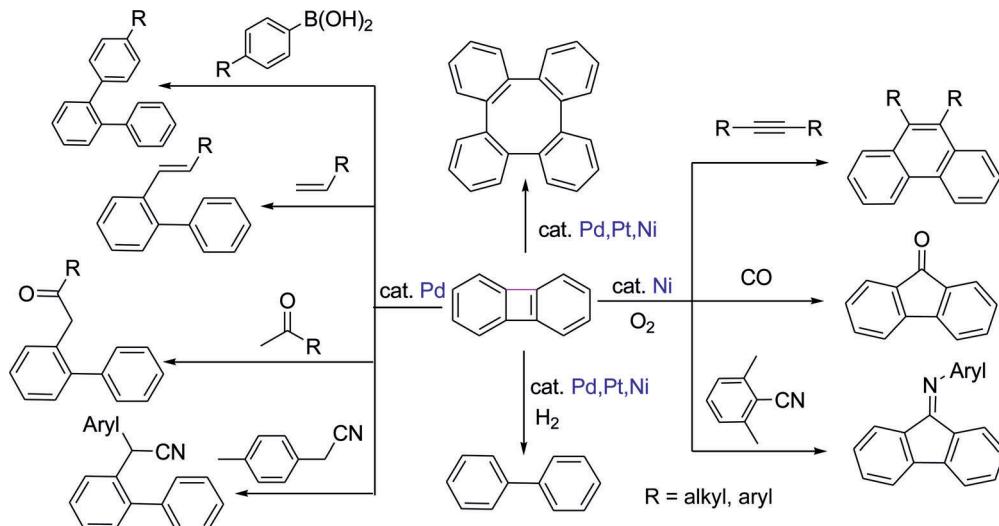
C–C bond activation is more difficult than C–H bond activation due to the inertness of C–C bonds to transition metals. In order to overcome thermodynamic

and kinetic challenges, selective C–C bond activation usually occurs to C–C bonds which are close to functional groups [82]. Various C–C bond transformations have been achieved using transition metals in the past two decades [83]. In this section, three different strategies for C–C bond cleavage are discussed.

11.3.1

Utilization of Strained Molecules

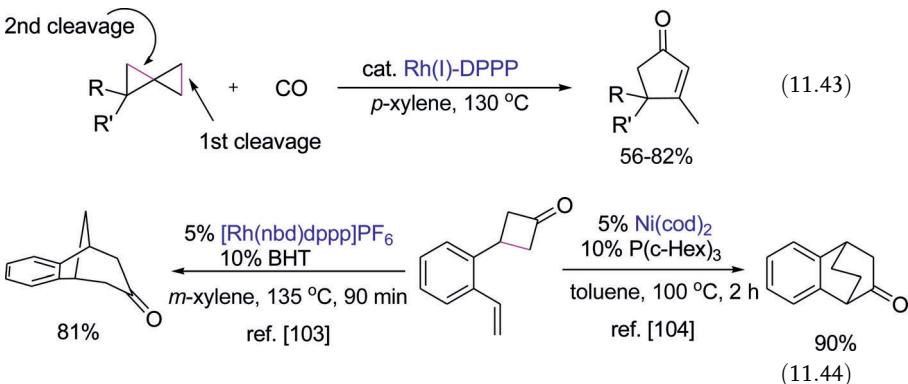
The utilization of ring strain is an effective strategy for transition metal-catalyzed C–C bond cleavage. A variety of late transition metal complexes have been found to cleave the C–C bond of biphenylene to give insertion complexes and relieve ring-strain [84]. These metal complexes participate in various insertion reactions with small unsaturated molecules, such as CO, olefins, and alkynes, to give functionalized products (Scheme 11.5) [82].



Scheme 11.5 Cleavage of C–C bonds of biphenylene.

Murakami's group has developed various rhodium-catalyzed C–C bond cleavages of small rings. Recently, they reported rhodium-catalyzed carbonylation reactions of spiropentanes involving two different types of C–C bond cleavage processes (Equation 11.43) [85]. The reaction allows for the synthesis of a series of 3-methylcyclopent-2-enones, one of which has been utilized as an intermediate in the concise synthesis of (\pm)- β -cuparenone. Another example is the rhodium-catalyzed intramolecular olefin insertion of 3-(*o*-styryl)cyclobutanone to generate

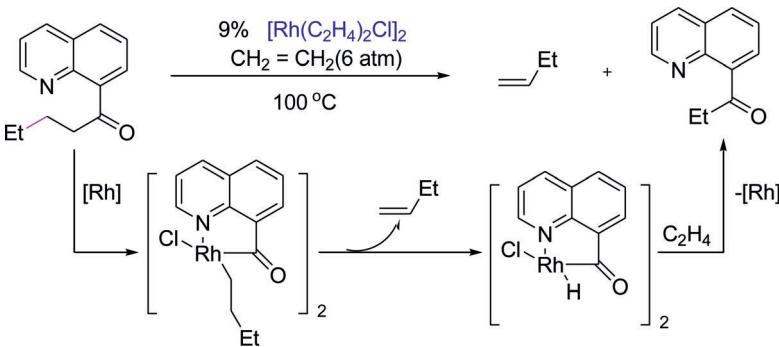
benzobicyclo[3.2.1]octenone [86]. Interestingly, the reaction with a nickel catalyst affords benzobicyclo[2.2.2]octenone (Equation 11.44) [87].



11.3.2

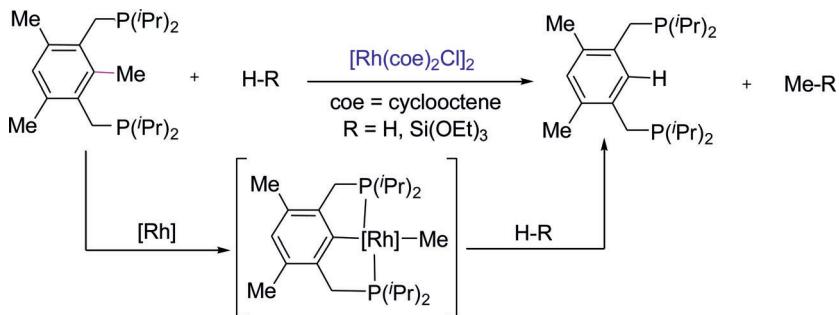
Utilization of Chelating Substrates

A chelation-assisted strategy is another useful method for C–C bond cleavage. In this method, the substrates containing a coordinating functional group will first coordinate to a metal and form a stable metallacycle. A representative example of this strategy is the activation of the α -C–C bond to the carbonyl group in 8-quinolinyl alkyl ketones (Scheme 11.6) [88].

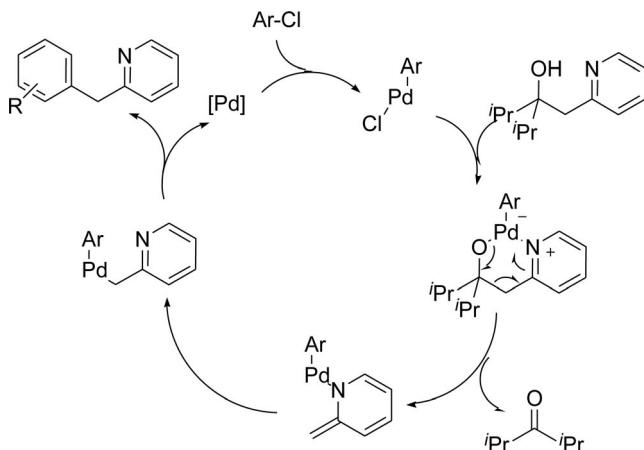
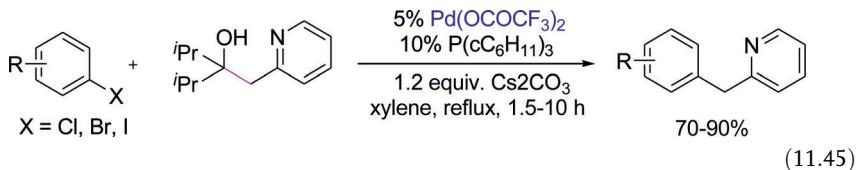


Scheme 11.6 Chelation-assisted C–C bond cleavage of an 8-quinolinyl alkyl ketone.

The pincer-type ligand has the advantage of forming two stable metallacycles and thus favors C–C bond cleavage. Despite the high enthalpy of the Ar–Me bond, the reaction between $\{[\text{Rh}(\text{coe})_2\text{Cl}]_2\}$ ($\text{coe} = \text{cyclooctene}$) and a P–C–P pincer-type ligand under H_2 pressure or silane results in catalytic cleavage of the aryl C–C bond to give the cleavage product (Scheme 11.7) [89].

**Scheme 11.7** Pincer-assisted C–C bond cleavage.

Recently, Oshima and co-workers reported Pd-catalyzed 2-pyridylmethyl transfer reactions by chelation-assisted cleavage of unstrained C–C bonds (Equation 11.45) [90]. A tentative mechanism has been proposed (Scheme 11.8). The key step is the coordination of nitrogen to the palladium center. With the aid of this coordination, the intermediate is likely to undergo cleavage of the C–C bond to yield a palladium amide [91]. This amide immediately isomerizes to aryl(2-pyridylmethyl)palladium to restore the aromaticity. Reductive elimination affords the final product.

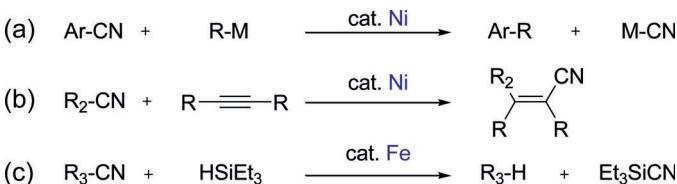
**Scheme 11.8** A tentative mechanism for 2-pyridylmethyl group transfer.

11.3.3

Utilization of Activating Functional Groups

The α -C–C bonds adjacent to carbonyls, alcohols, and nitriles are often the targets for activation [92]. This section focuses on recent developments of transition metal-catalyzed C–CN bond cleavage.

An efficient cross-coupling reaction of aryl cyanides and organometallic reagents has been achieved using a nickel catalyst [Scheme 11.9, reaction (a)] [93]. The carbocyanation of internal alkynes has also been reported using organonitriles in the presence of a nickel catalyst [Scheme 11.9, reaction (b)] [94]. In addition, the decyanation of acetonitrile and aryl cyanides was achieved using $\text{Cp}(\text{CO})_2\text{FeMe}$ as a catalyst and Et_3SiH as a reducing reagent [Scheme 11.9, reaction (c)] [95].



Scheme 11.9 Transition metal-catalyzed C–CN bond cleavage.

11.4

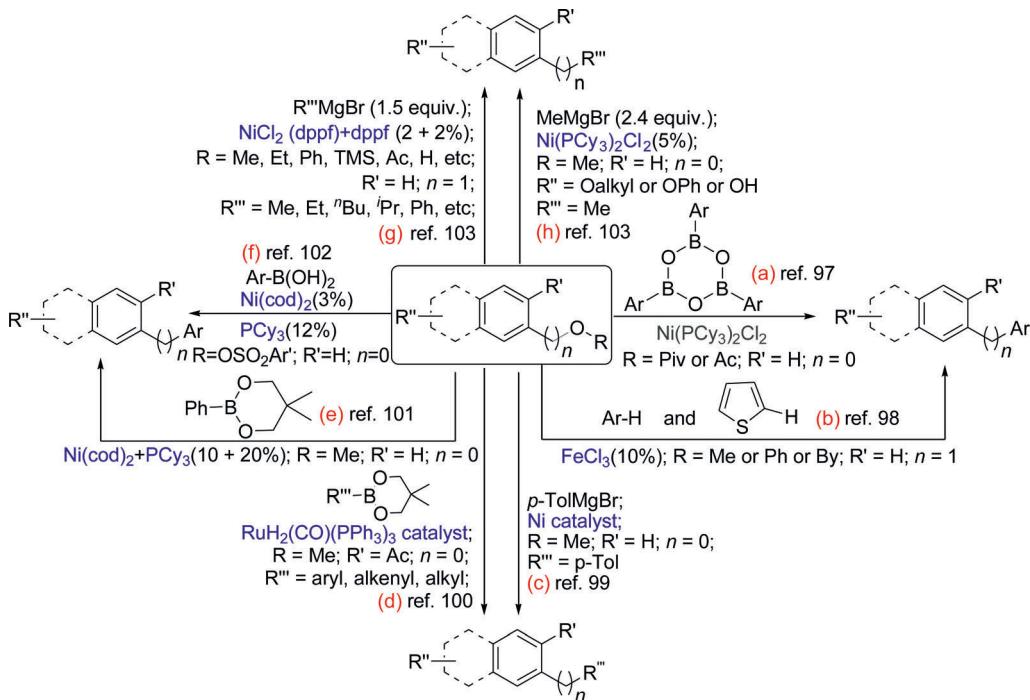
C–O Bond Activation

sp^2 C–O bonds and C–OH bonds are versatile functional groups and are widely applied in synthetic chemistry. For example, various organometallic reagents could react with sp^2 C–O bonds to afford alcohols or ketones, and Brønsted acids activate C–OH bonds to generate carbocations. However, the transformation of simple sp^3 C–O bonds has been less studied. Most studies take advantage of a good leaving group, such as OTs, and show successful activity towards C–O cleavage [96]. The challenges of sp^3 C–O bond activation are the following: (1) the sp^3 C–O bond has a relatively high bond dissociation energy (BDE); (2) the selectivity for one of the two different sp^3 C–O bonds of an ether molecule is challenging; and (3) how to use C–O bonds to construct C–C bonds. At the present stage, aryl s and benzyl C–O bonds have been efficiently applied in various C–O bond transformations. Nickel catalysts are effective for C–O bond cleavage. A summary of recent achievements by Shi, Chatani, Dankwardt, and Hu groups is shown in Scheme 11.10.

11.5

C–F Bond Activation

The C–F bond is the strongest single bond to carbon, and selective C–F transformation is still a great challenge under mild conditions [105]. Ozerov and co-workers



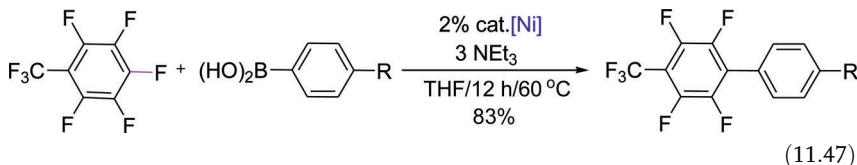
Scheme 11.10 Transition metal-catalyzed cleavage of sp^3 C–O bonds. (a) Ni-catalyzed cleavage of aryl carboxylates [97]; (b) FeCl_3 -catalyzed cleavage of benzyl ethers [98]; (c) Kumada–Corriu-type cross-coupling of aromatic ethers with an aryl Grignard reagent [99]; (d) chelation-assisted cleavage of

unreactive aryl C–O bonds [100]; (e) Ni-catalyzed cross-coupling of aryl methyl ethers with boronic esters [101]; (f) reactions of aryl arenesulfonates and boronic acids [102]; (g) cross-coupling of relatively stable benzyl ether [103]; (h) methylation of simple phenol derivatives [104].

reported a hydrodefluorination reaction with widely accessible silanes under mild conditions (Equation 11.46) [106], and indicated that the reactions are completely selective for aliphatic C–F bonds in preference to aromatic C–F bonds [107].



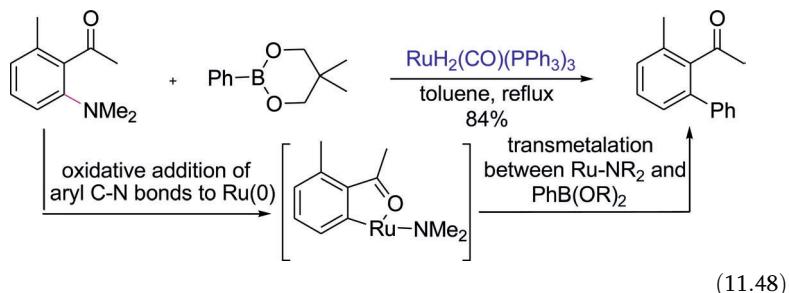
For aromatic C–F bonds, the Suzuki-type cross-coupling of perfluorinated arenes, such as octafluorotoluene and perfluorobiphenyl, in the presence of nickel catalysts has been developed (Equation 11.47) [108]. In these reactions, triethylamine is used as a base, whereas stronger inorganic bases are typically used in Suzuki coupling reactions.



11.6

C–N Bond Activation

Ru-catalyzed Suzuki-type cross-coupling reactions of aniline derivatives and organoboronates have been achieved via unreactive aryl C–N bond cleavage (Equation 11.48) [109]. The proposed reaction pathway is a sequence of oxidative addition of an unreactive aryl C–N bond to the late transition metal complex, followed by transmetalation between the Ru–NR₂ species and organoboronates, and reductive elimination.



11.7

Small Molecule Activation

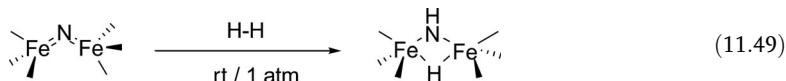
Small molecules such as H₂, O₂, and CH₄ are ubiquitous reservoirs of chemical energy. They are widely used as (1) fuels for biological systems, (2) synthons for the construction of more complex molecules, and (3) signaling agents for triggering complex protein expression and regulation processes. Therefore, activation of small molecules is still a very important challenge in both academia and industry [110]. Here, a brief summary of recent achievements is given, focusing on the activation of H₂, O₂, and CH₄.

11.7.1

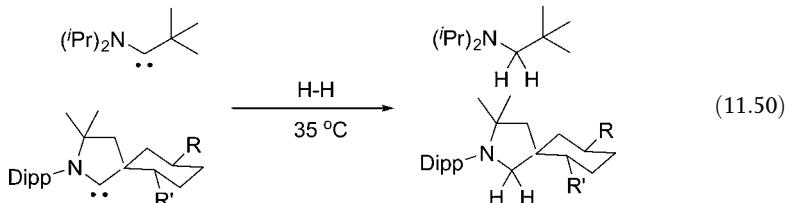
H₂

H₂ is the simplest molecule, consisting of two protons and two electrons. Because its oxidation leads to water as the sole product, it has been regarded as a “clean” proton source. In many industrially important reactions, such as hydroformylation and hydrogenation, dihydrogen gas serves as a reducing agent or H-atom source. The BDE of H₂ is +103.25(l) kcal mol⁻¹ [111]. Therefore, H₂ is an “unreactive” molecule.

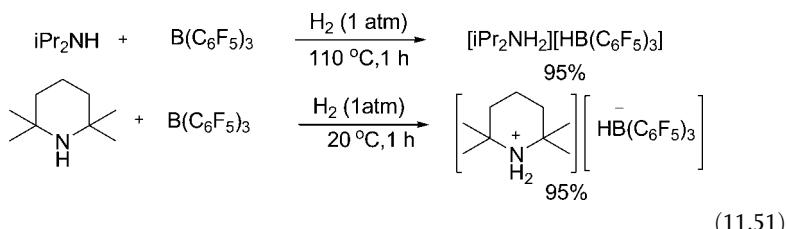
Transition metals are the main promoters for H–H bond cleavage assisted by the coordination of σ-H–H bond to metal atoms. An example is presented here. The reaction of low-coordinate L₃Fe–(μ-N)–FeL₃ complexes and H₂ generates Fe(μ-NH)(μ-H)Fe species under mild conditions (Equation 11.49) [112].



Significantly, stable singlet carbenes could mimic the transition metals for H_2 activation under mild conditions (Equation 11.50) [113]. Mechanistically, in contrast to transition metals that act as electrophiles towards H_2 , the carbenes behave as nucleophiles. As a result, this nucleophilic behavior also allows carbenes to activate NH_3 .



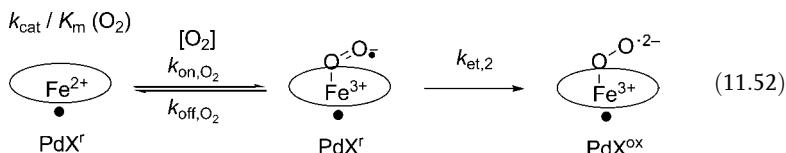
In addition, a heterolytic cleavage of H_2 was achieved via the cooperation of $\text{B}(\text{C}_6\text{F}_5)_3$ and amines (Equation 11.51) [114]. As an application, benzaldehyde is reduced by the present system.



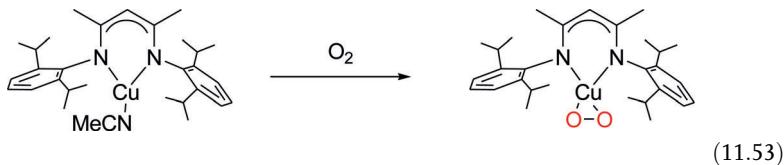
11.7.2 O_2

Oxidation is one of the basic chemical processes in Nature. Molecular oxygen (O_2) is an ideal oxidant, owing to its abundance, atom efficiency, and benign byproducts (H_2O_2 or H_2O). A transition metal ion is usually intimately related to oxidation chemistry, and understanding the relationship between metal ions and oxidants is necessary for the development of efficient and clean oxidative processes.

Klinman and co-workers investigated the mechanism of O_2 activation by cytochrome P450cam, including the study of isotope effects and transient state kinetics (Equation 11.52) [115]. The observed second-order kinetics for the interaction between cytochrome P450cam and O_2 suggested that the binding for O_2 is largely the rate-determining step.



Tolman and co-workers reported dioxygen activation at a single copper site (Equation 11.53) [116]. The existence of the copper peroxide species was supported by both experimental and computational studies.

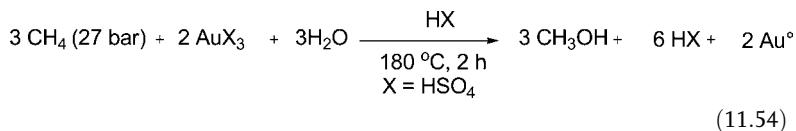


11.7.3

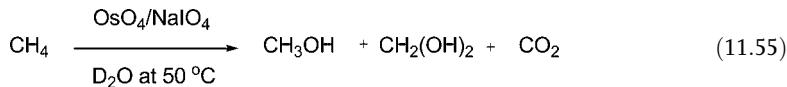
CH₄

Petroleum is our primary hydrocarbon feedstock; however, at the current rate of consumption its supply is projected to last only about 50 years. Methane (CH₄) is the major component of natural gas (75–90%), and is one of the most abundant hydrocarbons on the planet. Conversion to heat is the major use of hydrocarbon feedstock. Therefore, methane as a replacement for petroleum for the production of materials is highly desirable.

Periana *et al.* reported the Pd-catalyzed oxidative functionalization of CH₄ to CH₃COOH via C–H activation [117]. The conversion of 2 equiv. of methane into acetic acid, which is also an important petrochemical, brightens the future use of natural gas. Recently, the same group also reported that cationic gold catalyzes the selective and low-temperature oxidation of methane to methanol in a strongly acidic solvent using Se^{VI} ions as the stoichiometric oxidant (Equation 11.54) [118]. The reaction does not appear to proceed through free radicals and DFT calculations indicate that Au^I or Au^{III} species are both viable catalysts. Possibly the mechanism involves overall electrophilic C–H activation and oxidative functionalization.



Mayer and co-workers reported that aqueous solutions of OsO₄ and NaIO₄ oxidize methane to methanol under mild aqueous conditions. Mechanistic studies showed that further oxidation of methanol is competitive with methane oxidation (Equation 11.55) [119]. The presence of methane substantially inhibits the over-oxidation of methanol.



11.8

Conclusions and Outlook

The transformation of non-functional groups or small molecules has shown a promising start with many efforts in the past few decades. Such reactions represent the most direct and efficient synthetic methods for chemical bond formation and provide the pillar for the next generation of chemical syntheses with an eye on green chemistry. The essence of non-functional group chemistry is consistent with the philosophy of organic synthesis, which emphasizes efficiency, selectivity, and practicality. With “chemistry beyond functional group transformation” in mind, a synthetic process can be free of functional groups and protecting groups, while maintaining concise synthetic steps and stereocontrolled outcomes.

Some breakthroughs have been achieved and used in the total synthesis of complex molecular and natural products. Although these recent successes in this area have proved to be very valuable for organic synthesis, the generalities and scale-up are still problematic for their practical application. Novel methodologies and strategies are still waiting to be discovered. Additionally, the mechanistic details of these transformations remain to be determined. As the reaction stands, the catalysts and oxidants should be nontoxic, cheap, and easily available. These challenges are awaiting further investigation.

List of Abbreviations

acac	acetylacetone
AIBN	2,20-azobisisobutyronitrile
Ar	aryl
Bn	benzyl
BQ	benzoquinone
Bz	benzoyl
CAN	ceric ammonium nitrate
Cp	cyclopentadienyl
DBU	1,5-diazabicyclo[5.4.0]undec-5-ene
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DMAC	dimethylaluminum chloride
DMAD	dimethyl acetylenedicarboxylate
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
EDG	electron-donating group
EDTA	ethylenediaminetetraacetate

<i>ee</i>	enantiomeric excess
EWG	electron-withdrawing group
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
MVK	methyl vinyl ketone
MW	molecular weight
NBS	<i>N</i> -bromosuccinimide
NMR	nuclear magnetic resonance
Nu	nucleophile
PE	photoelectron
PPA	polyphosphoric acid
PPE	polyphosphate ester
Py	pyridine
TBHP	<i>tert</i> -butyl hydroperoxide
TCE	2,2,2-trichloroethanol
Tf	trifly (trifluoromethanesulfonyl)
TFA	trifluoroacetyl
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMEDA	tetramethylethylenediamine [1,2-bis(dimethylamino)ethane]
TMS	trimethylsilyl
TMSCl	trimethylsilyl chloride
Tol	tolyl
Tr	trityl (triphenylmethyl)
Ts	4-toluenesulfonyl (tosyl)
X	halogen or leaving group

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12

Synthesis Assisted by Electricity

Jun-ichi Yoshida and Seiji Suga

The synthesis of organic compounds using electron transfer-driven transformations assisted by electricity (electroorganic synthesis) has been widely utilized both in laboratory synthesis and in the industrial production of chemicals [1, 2]. For example, electrohydrodimerization of acrylonitrile to adiponitrile for the production of nylon 66, which was developed by Monsanto in the early 1960s, is still in operation. Because the electrodes work as an oxidizing reagent or a reducing reagent, a chemical oxidizing or reducing agent is, in principle, unnecessary in electrochemical processes. For this reason, electrochemical reactions serve as inherently environmentally friendly processes. However, electrochemical processes suffer from some disadvantages from the viewpoint of green sustainable chemistry, such as the use of hazardous organic solvents, separation of products, and disposal of supporting electrolytes as waste. In this chapter, we discuss the development of new methodologies that solve such problems and make electrochemical processes more environmentally friendly. This chapter is not intended to present an exhaustive compilation of all known reactions, but provides examples of sufficient variety to illustrate the scope of this field.

12.1

Electroorganic Synthesis in Green Reaction Media (Homogeneous System)

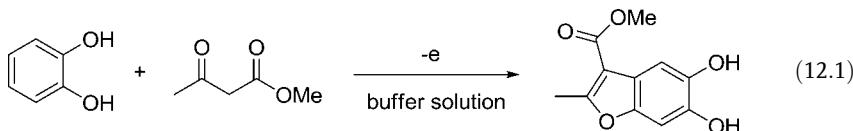
Most organic reactions are carried out in organic solvents as reaction media, because organic substrates and products are soluble in organic solvents. However, the use of organic solvents is problematic from the viewpoint of green sustainable chemistry. Therefore, many attempts have been made to replace organic solvents with greener reaction media such as water [3]. In this section, we discuss electroorganic synthesis in such green reaction media.

12.1.1

Electroorganic Synthesis in Aqueous Solutions

Water is one of the most environmentally friendly solvents, and the use of water as a solvent for electroorganic synthesis seems to be attractive, although many organic

compounds do not dissolve in water. Kolbe oxidative coupling of carboxylic acids [4], which is one of the most popular and powerful reactions in electroorganic synthesis, can be carried out, in some cases, in aqueous solution because some organic carboxylate anions dissolve in water. Some other electroorganic reactions using water-soluble organic substrates have been reported. For example, Nematollahi's group reported a method to prepare benzofuran derivatives by the electrooxidation of catechols in the presence of 1,3-dicarbonyl compounds in an aqueous solution [5]. The anodic oxidation of catechol in the presence of methyl acetoacetate involves a 1:1 addition reaction in a phosphate buffer solution at ambient temperature to give methyl 5,6-dihydroxy-2-methyl-1-benzofuran-3-carboxylate, as shown in Equation 12.1. In this reaction, the product precipitated at the end of the reaction and was easily separated by filtration.



12.1.2

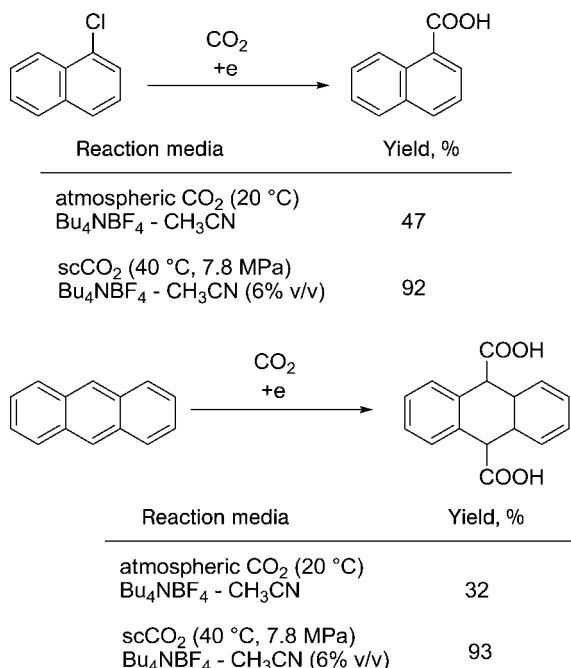
Electroorganic Synthesis in Supercritical Carbon Dioxide

Supercritical carbon dioxide (scCO_2) has attracted significant attention as an environmentally benign solvent because it is nontoxic, inexpensive, and miscible with many organic compounds. However, early attempts to perform electrolysis in scCO_2 were not successful because of the limited solubility of supporting electrolytes in scCO_2 due to its inherent non-polarity. Successful electrochemical carboxylations in scCO_2 can be achieved by adding a small amount of an organic solvent. Tokuda and co-workers reported the electrochemical carboxylation of 1-chloronaphthalene and anthracene in scCO_2 in the presence of a small amount of acetonitrile as co-solvent (Scheme 12.1) [6]. It is interesting that the yields of products were much higher than those obtained by cathodic carboxylation in acetonitrile containing CO_2 at atmospheric pressure. Faster diffusion in supercritical fluids than that in conventional reaction media and the “naked” property of carboxylate anions seem to be responsible.

12.1.3

Electroorganic Synthesis in Ionic Liquids

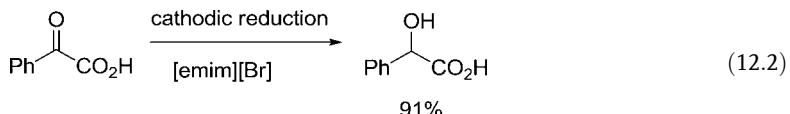
Ionic liquids have also attracted significant research interest as environmentally benign reaction media because they are expected to replace hazardous and volatile organic solvents. The advantages of ionic liquids include easy recovery and re-use, in addition to minuscule vapor pressure, nonflammability, and relative inertness. For electroorganic synthesis, ionic liquids serve as good reaction media, because they have relatively wide potential windows and high conductivity. Because ionic liquids



Scheme 12.1

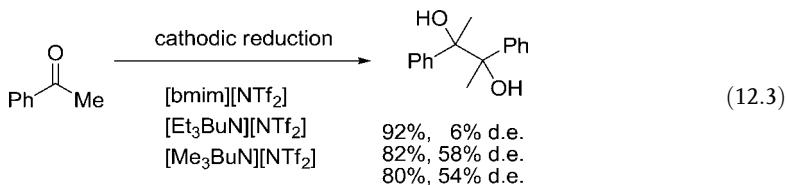
themselves play the role of supporting electrolyte, electrolyses can be conducted without any intentionally added supporting electrolyte.

Simple electrochemical reductions of carbonyl compounds and organic halides have been achieved in ionic liquids. For example, the electrochemical reduction of benzoylformic acid in [emim][Br] (emim = 1-ethyl-3-methylimidazolium) gave mandelic acid in 91% yield (Equation 12.2) [7].

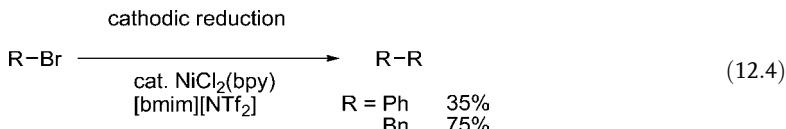


Cathodic reduction of organic dihalides using a Co(II)-salen complex in [bmim][BF₄] (bmim = 1-benzyl-3-methylimidazolium) was carried out successfully to give the corresponding dehalogenated compounds [8]. The catalyst–solvent system was readily recycled with little loss of reactivity.

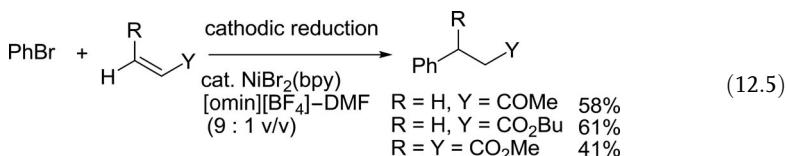
Ionic liquids are also effective for electrochemical reductive coupling reactions. For example, the cathodic reduction of benzaldehyde in [bmpyr][NTf₂] (bmpyr = 1-butyl-1-methylpyrrolidinium; NTf₂ = bis(trifluoromethylsulfonyl) imide) gave rise to dimerization [9]. Electroreductive coupling of acetophenone in ionic liquids gave the corresponding pinacol as a mixture of diastereomers (Equation 12.3) [10].



Homocoupling reactions of organic halides such as bromobenzene and benzyl bromide were successfully carried out in the presence of an Ni(II) complex catalyst in $[\text{bmim}][\text{NTf}_2]$ (Equation 12.4) [11].



In some cases, a small amount of cosolvent such as DMF was added to attain good conductivity. For example, the Ni-catalyzed electroreductive coupling of organic halides with activated olefins was carried out in $[\text{omin}][\text{BF}_4]$ (omin -1-octyl-3-methylimidazolium) using DMF as a cosolvent (Equation 12.5) [12].



12.2

Electroorganic Synthesis in Liquid–Liquid Biphasic Systems

Separation is one of the central issues of organic synthesis from the viewpoint of green sustainable chemistry, and several fundamental approaches have been studied to propose a solution to this problem [13]. Among various approaches, extensive studies have been carried out on synthesis using biphasic systems because of easy separation. Products are separated by simple phase separation. Easy separation and re-use of reagents or catalysts are also advantages of biphasic systems. In this section we discuss electroorganic synthesis using liquid–liquid biphasic systems.

Anodic oxidation of alcohols in water using water-soluble N -oxyl compounds (WS-TEMPOs, Figure 12.1) has been developed by Tanaka and co-workers [14]. An alcohol

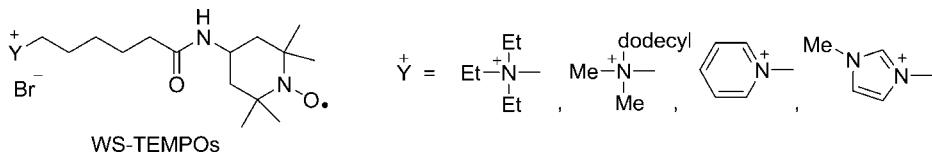


Figure 12.1 Water soluble N -oxyl compounds (WS-TEMPOs).

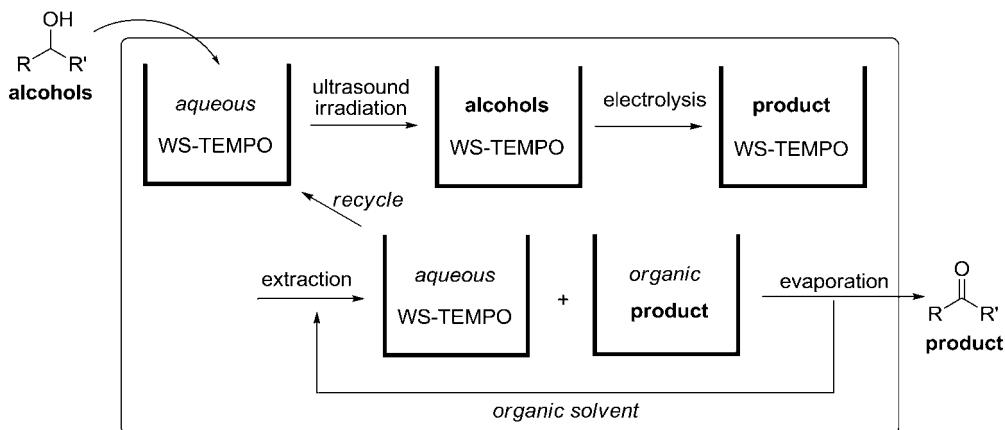


Figure 12.2 General procedure for anodic oxidation of alcohols mediated by WS-TEMPOs.

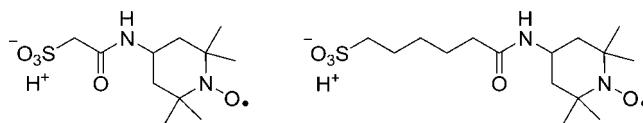


Figure 12.3 Water soluble anionic *N*-oxyl compounds.

substrate was dispersed in water by ultrasound irradiation and electrolysis with NaBr in the aqueous phase afforded the corresponding ketones in good yields. After the electrolysis, the product in the organic phase was easily separated and isolated (Figure 12.2). It is noteworthy that most of the WS-TEMPO in water remained unchanged after the electrolysis, and the aqueous solution containing WS-TEMPO was easily recovered and re-used.

Halide-free anodic oxidation of alcohols mediated by an anionic WS-TEMPO (Figure 12.3) was also accomplished. It was suggested that the anionic WS-TEMPO might form an anionic oil-in-water emulsion including alcohol, and the attractive force between the sulfonate ion and the positive charge of anode would facilitate direct electron transfer from the *N*-oxyl moiety to the anode.

12.3

Electroorganic Synthesis in Thermomorphic Liquid–Liquid Biphasic Systems

Thermomorphic liquid–liquid biphasic systems have attracted significant research interest owing to the easy separation. The system forms a monophasic solution by heating and a biphasic system by cooling, reversibly. Chiba and co-workers reported an interesting application of thermomorphic biphasic systems to electroorganic synthesis [15]. They found that the combination of cyclohexane and a polar organic solvent in the presence of electrolytes forms an effective thermomorphic biphasic system, which permitted electrolysis at relatively high current density. As

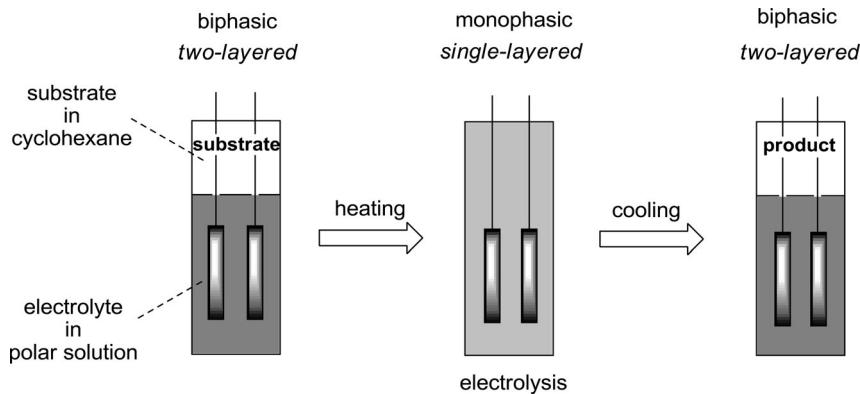
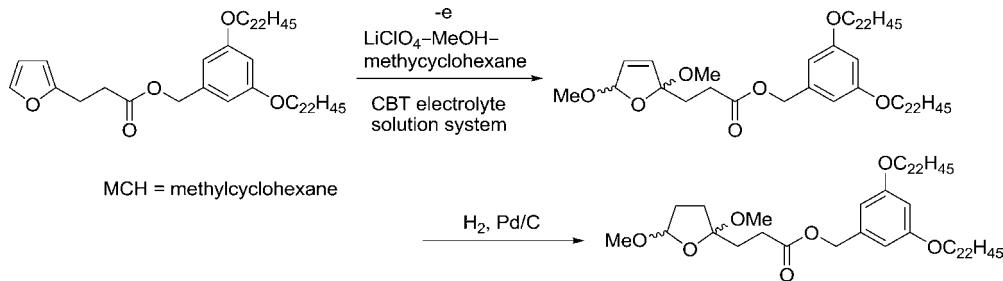


Figure 12.4 A cycloalkane-based thermomorphic (CBT) electrolyte solution system.

outlined in Figure 12.4, the electrolysis of a hydrophobic phase-tagged substrate was carried out under monophasic conditions, and after electrolysis the solution was cooled and the product was easily separated from the electrolyte by simple phase separation.

Scheme 12.2 illustrates the anodic oxidation of a substrate bearing a highly hydrophobic 3,5-didocosyloxybenzyl group as a phase tag by using a methylcyclohexane/LiClO₄-MeOH-methycyclohexane system to give the dimethoxylated product. The product, which was separated by phase separation, was subjected to catalytic hydrogenation to afford the final product.



Scheme 12.2

12.4

Electroorganic Synthesis in Solid–Liquid Biphasic Systems

Solid–liquid biphasic systems that utilizes reagents or catalysts bound to insoluble materials are also an effective approach. Various mediators and carriers of electricity bound to insoluble materials have been developed for electroorganic synthesis. We discuss such approaches in this section.

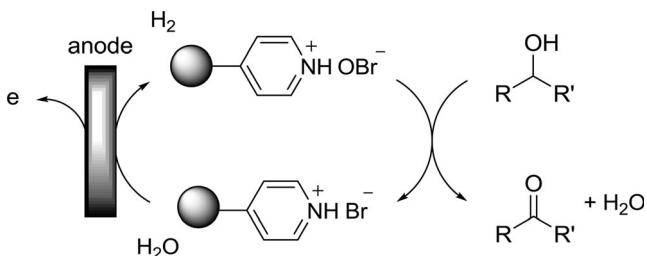


Figure 12.5 Anodic oxidation of alcohols using a polymer-supported pyridinium bromide as a mediator.

12.4.1

Solid-Supported Mediators

Yoshida and co-workers reported the oxidation of alcohols mediated by cross-linked poly(4-vinylpyridinium bromide) in the presence of a small amount of water (Figure 12.5) [16]. The electrolysis can be carried out without intentionally added electrolyte, and therefore ketone products are easily separated by simple filtration and the mediator can be recovered and re-used. This method has also been applied successfully to the oxidation of sulfides, epoxidation of olefins, and side-chain oxidation of alkylbenzenes. A similar polymeric system has also been reported by Zupan and Dolenc [17].

Unique aqueous electrolysis media have been developed and highly efficient electrochemical oxidations of alcohols were accomplished using these systems. Tanaka's group developed the anodic oxidation of alcohols mediated by *N*-oxyl in an aqueous silica gel disperse system (Figure 12.6) [18]. The system could be successfully applied to the kinetic resolution of *sec*-alcohols and the enantioselective oxidation of *meso*-1,4-diols, affording optically active γ -lactones (Scheme 12.3).

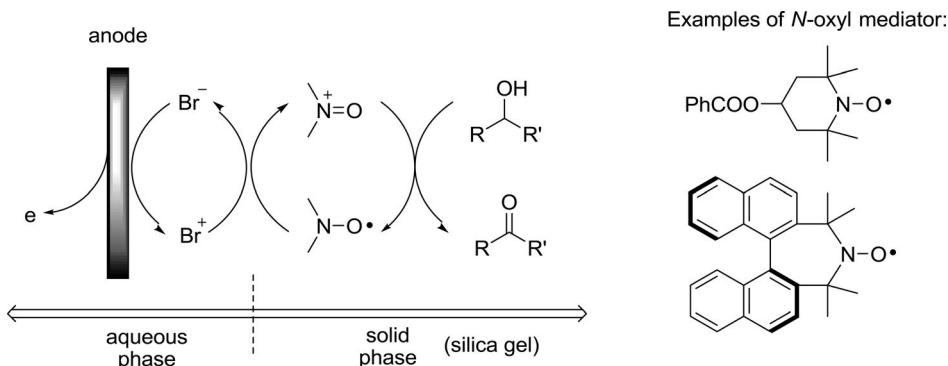
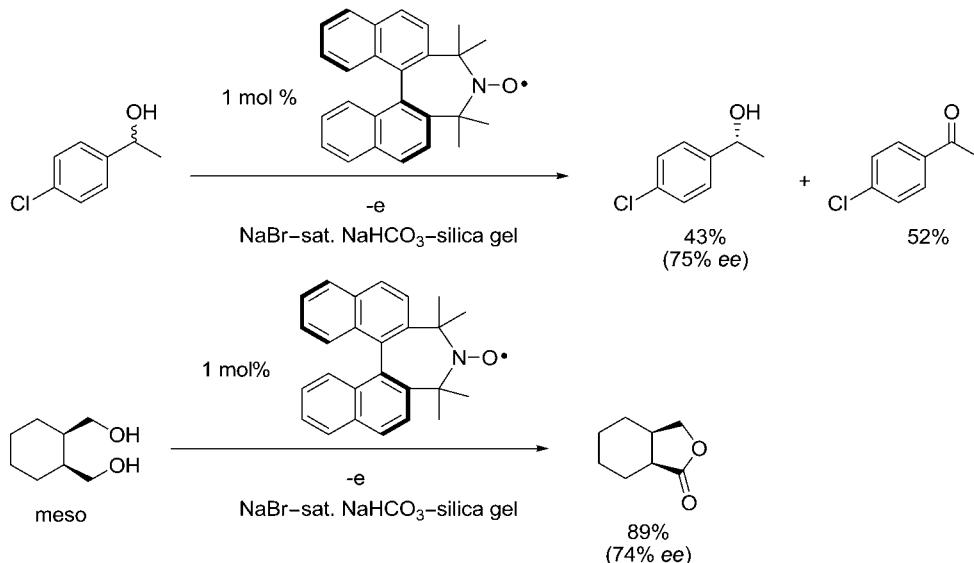


Figure 12.6 Anodic oxidation of alcohols mediated by *N*-oxyl in an aqueous silica gel disperse system.



Scheme 12.3

The same group also reported a disperse system consisting of *N*-oxyl-immobilized polyethylene particles as disperse phase and aqueous NaHCO₃-NaBr as disperse medium [19]. *N*-Oxyl-immobilized poly(*p*-phenylenebenzobisthiazole) network polymer particles (PBZTNT-*N*-oxyl) have also been developed. The polymer is effective for the anodic oxidation of alcohols to afford the corresponding ketones, aldehydes, and/or carboxylic acids [20]. These achievements nicely demonstrate the potential of liquid-solid disperse systems for electroorganic synthesis.

12.4.2

Solid-Liquid Biphasic System for Electrolysis Without Intentionally Added Supporting Electrolyte

To provide sufficient electrical conductivity to solvents for electrolysis, the use of a supporting electrolyte is essential under conventional electrolysis conditions. For organic electrolysis, tetraalkylammonium salts such as Et₄NOt and Bu₄NBF₄ are often used because of their good solubility in organic solvents. However, separation of the products from the supporting electrolyte after electrolysis, which usually needs column chromatography, is problematic from the viewpoint of green sustainable chemistry. To solve such problems, new technologies such as insoluble polymer-supported electrolytes have been developed.

12.4.2.1 SPE Technology

Supporting electrolyte-free electrolysis is an ideal way to realize perfect green synthesis assisted by electricity. Solid polymer electrolyte (SPE) technology, devel-

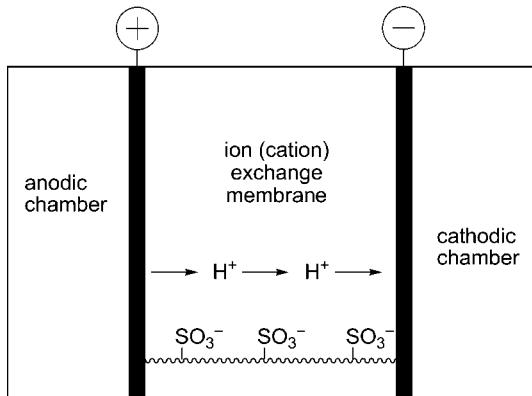


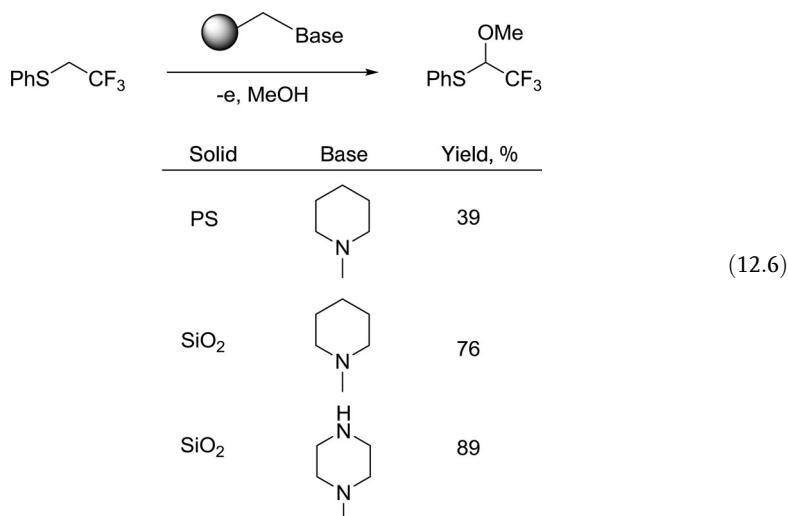
Figure 12.7 Scheme of an SPE cell with cation-exchange membranes.

oped by Ogumi and co-workers [21], permits electrochemical reactions in the absence of a conductive fluid containing supporting electrolyte (Figure 12.7). Therefore, separation and recycling of a supporting electrolyte after the electrolysis are not necessary. Jorissen and co-workers [22] and Tallec and co-workers [23] also reported independently that ion-exchange membranes could function as solid polymer electrolytes in non-conductive liquids. The electrochemical reactions take place at the interfaces between the ion-exchange membrane and electrocatalytically active layers of porous electrodes. In the case of a cation-exchange membrane, H^+ ions, which are formed by the anodic reaction, migrate with their solvation shell through the membrane, and are usually reduced to hydrogen gas at the cathode. Therefore, the cation-exchange membrane works like immobilized sulfuric acid. SPE technology has been successfully applied to the methoxylation of *p*-methoxytoluene, which is of significant interest in industry.

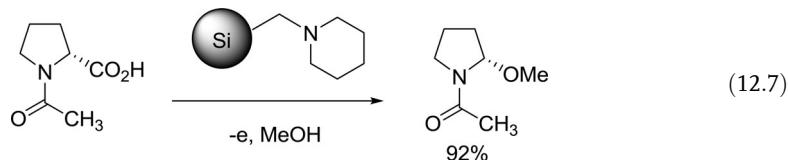
12.4.2.2 Electrolysis Using Solid-Supported Bases

Tajima and co-workers have developed a novel environmentally friendly electrolytic system using solid-supported bases and protic organic solvents such as methanol [24]. This method permits electrolysis without an intentionally added supporting electrolyte. Solid-supported bases are not oxidized at the electrode surface because electron transfer between two solids is, in principle, very difficult [25]. Therefore, protons generated by the reaction of a solid-supported base and a protic solvent may serve as carriers of electronic charge. After the electrolysis, the solid-supported base can be easily separated by filtration and can be re-used.

Anodic α -methoxylation of phenyl 2,2,2-trifluoroethyl sulfide was carried out using various solid-supported bases as shown in Equation 12.6. Polystyrene and silica-gel are suitable as the solid support for an organic base such as piperidine. It is noteworthy that anodic methoxylation was successfully carried out even after 10 recycles of the solid-supported base. The method has also been successfully applied to electrochemical acetoxylation in acetic acid/acetonitrile.



The anodic oxidation of carboxylic acids has also been carried out using a solid-supported base in methanol. Non-Kolbe-type electrolysis takes place to give the corresponding methoxylated product (Equation 12.7). The acid–base reaction between a carboxylic acid and a solid-supported base seems to reduce the cell voltage and makes the electrochemical reaction possible. Kolbe-type carbon–carbon coupling using aliphatic and benzylic carboxylic acids has also been accomplished using this method [26]. Based on a similar concept, anodic fluorination by an alkali metal fluoride using a solid-supported acid has been developed [27].



12.5

Electroorganic Synthesis in Microflow Systems

Recently, microflow systems have attracted significant research interest from both academia and industry [28, 29]. Microflow systems are expected to serve as a much better reaction environment than conventional macrobatch reactors because of the inherent advantages of microspaces, such as fast molecular diffusion by virtue of small sizes and fast heat and mass transfer by virtue of large surface-to-volume ratios. In electroorganic synthesis, the use of a microflow reactor serves as a solution to the problems with conventional macrobatch electrochemical reactors, such as difficulty in mass transfer on the surface of the electrodes and high ohmic drop between the electrodes.

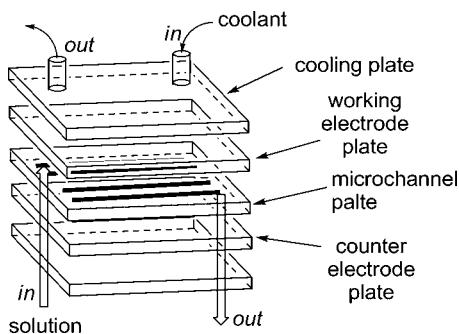


Figure 12.8 A microflow electrochemical reactor having a plate-to-plate configuration.

12.5.1

Electrochemical Microflow Cells

Löwe and co-workers developed a microflow electrochemical reactor having a plate-to-plate electrode configuration mounted in a non-conducting housing (Figure 12.8) [30, 31]. The working electrode and the counter electrode are separated using a 75 μm thick polyimide foil between them. The microflow reactor was used for the anodic oxidation of *p*-methoxytoluene to give *p*-methoxybenzaldehyde dimethyl acetal. The authors reported that the efficiency (98%) was higher than that of the conventional macrobatch industrial processes (85%).

A different type of electrochemical microflow reactor was developed for the generation of highly reactive organic cations (the “cation flow” method) (Figure 12.9 and Scheme 12.4) [32]. A solution of a cation precursor is introduced into the anodic chamber, and a solution of trifluoromethanesulfonic acid (TfOH) as a proton source is introduced into the cathodic chamber. The reaction can be monitored by inline FTIR spectroscopy (ATR method). The organic cation thus generated is immediately transferred to a vessel in which a nucleophilic reaction takes place to give the desired coupling product. A unique serial combinatorial synthesis has been achieved based on the cation flow method.

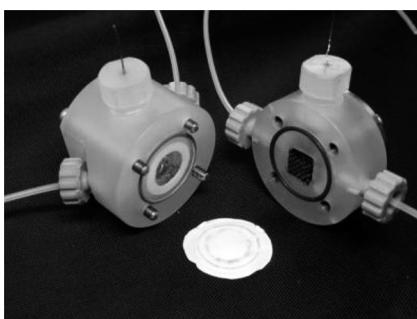
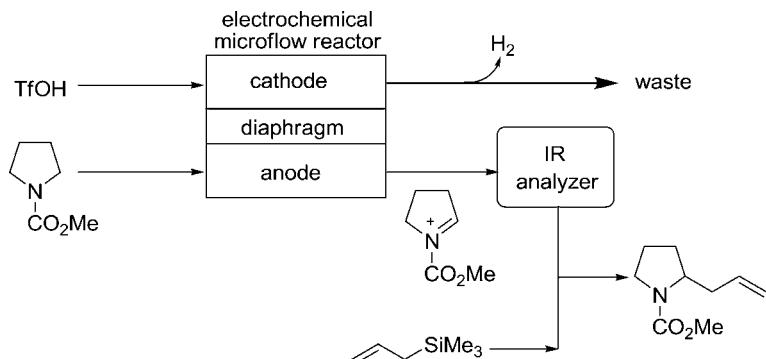


Figure 12.9 An electrochemical microflow reactor for the “cation flow” method.



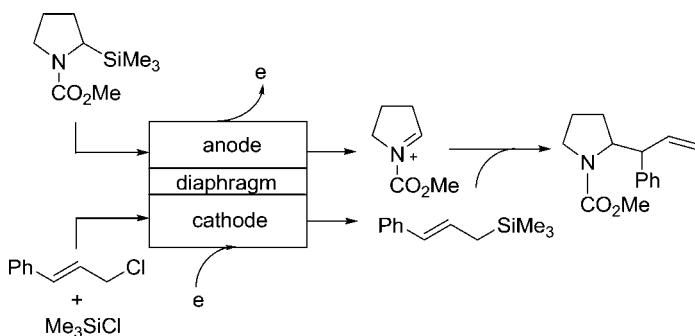
Scheme 12.4 A schematic diagram of the “cation flow” method.

12.5.2

Paired Electrolysis in Microflow Systems

Paired electrolysis [33], in which both the anodic oxidation and the cathodic reduction contribute to the formation of the final product(s), is highly advantageous from the viewpoint of green chemistry, because of the efficient use of electric energy and avoidance of disposal of by-products produced at the counter electrode.

A paired microflow electrochemical system has been developed. An organic cation is generated by anodic oxidation and a carbanion equivalent is generated by cathodic reduction; these intermediates are allowed to react to give the corresponding coupling product [34]. For example, a silyl-substituted carbamate is oxidized at the anode to generate a solution of *N*-acyliminium ion, and cinnamyl chloride is reduced at the cathode in the presence of chlorotrimethylsilane to generate the corresponding allylsilane [35] in the continuous microflow system (Scheme 12.5). In the next step, the *N*-acyliminium ion is allowed to react with the allylsilane to give the coupling product.



Scheme 12.5

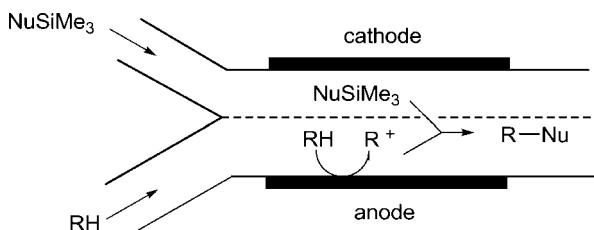


Figure 12.10 Parallel laminar microflow system for the electrochemical generation and reaction of *N*-acyliminium ion.

Atobe and co-workers reported that the use of parallel laminar flow in a microflow electrochemical reactor permits the effective generation of an *N*-acyliminium ion (R^+) from a carbamate (RH), followed by trapping with an easily oxidizable carbon nucleophile (NuSiMe₃) such as allylsilane (Figure 12.10) [36]. The oxidation potentials of carbon nucleophiles are often lower than those of organic substrates, and therefore the presence of nucleophiles would prevent the oxidation of organic substrates. In this case, however, the carbamate is oxidized dominantly to generate an *N*-acyliminium ion, while oxidation of carbon nucleophiles is avoided. The *N*-acyliminium ion thus generated at the anode diffuses rapidly to the bulk solution and reacts with the allylsilane to afford the desired products. The yield was improved when ionic liquids such as 1-ethyl-3-methylimidazolium tetrafluoroborate ([emim] [BF₄]), 1-ethyl-3-methylimidazolium bis(trifluoromethanesulfonyl)imide ([emim] [TFSI]), and *N,N*-diethyl-*N*-methyl-*N*-(2-methoxyethyl)ammonium bis(trifluoromethanesulfonyl)imide ([deme][TFSI]) were used as reaction media. The ionic liquids seem to serve as both a reaction medium and an electrolyte. These results suggest that ionic liquids might stabilize the *N*-acyliminium ion intermediate, which would otherwise decompose before the coupling reaction.

12.5.3

Electroorganic Synthesis in a Microflow System Without Using Intentionally Added Supporting Electrolyte

Electrochemical microflow systems have also attracted significant research interest from the viewpoint of electrolysis without an intentionally added supporting electrolyte, because the short distance between the electrodes and the high electrode surface to reactor volume ratio are advantageous for conductivity and reaction efficiency.

Marken and co-workers accomplished electrolysis without an intentionally added electrolyte by using a simple microflow electrochemical cell having a parallel electrode configuration [37]. Two electrodes are placed facing each other at a distance of the order of micrometers, and a substrate solution flows through the chamber. In this system, the liquid flow and the current flow are perpendicular.

The anodic oxidation of furans in methanol was also carried out without an intentionally added electrolyte (Figure 12.11) [38, 39]. 2,5-Dimethoxy-2,5-dihydrofuran was obtained in 98% yield. The anodic methoxylation and acetoxylation of various organic compounds was also achieved using this system.

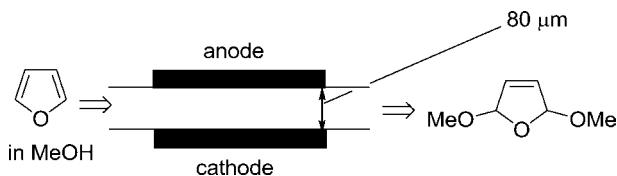
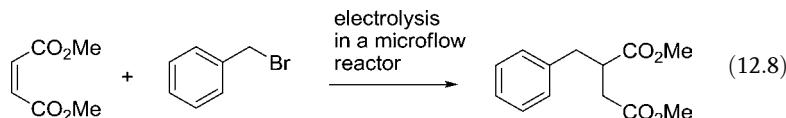


Figure 12.11 Electrochemical oxidation of furan.

Using a similar type of the microflow cell, Haswell's group reported the electroreductive coupling of activated olefins and benzyl bromide derivatives (Equation 12.8) [40]. The microflow electrochemical reactor can be easily multiplexed to generate a number of parallel flow cells, which offer the performance of a single cell while increasing the volumetric throughput of the system.



There is another type of microflow system that can be used for electrolyte-free electrolysis (Figure 12.12) [41]. In this system, two carbon fiber electrodes are separated by a spacer (porous PTFE membrane, pore size 3 μm, thickness 75 μm) at a distance of the order of micrometers. An anodic solution flows through the spacer membrane into the cathodic chamber and the product solution leaves the system from the cathodic chamber. In this system, the electric current flow and the liquid flow are parallel.

Using this electrochemical microflow system, the anodic methylation of *p*-methoxytoluene was accomplished effectively without an intentionally added electrolyte. The oxidation of *p*-methoxytoluene was carried out in methanol. The anodic reaction

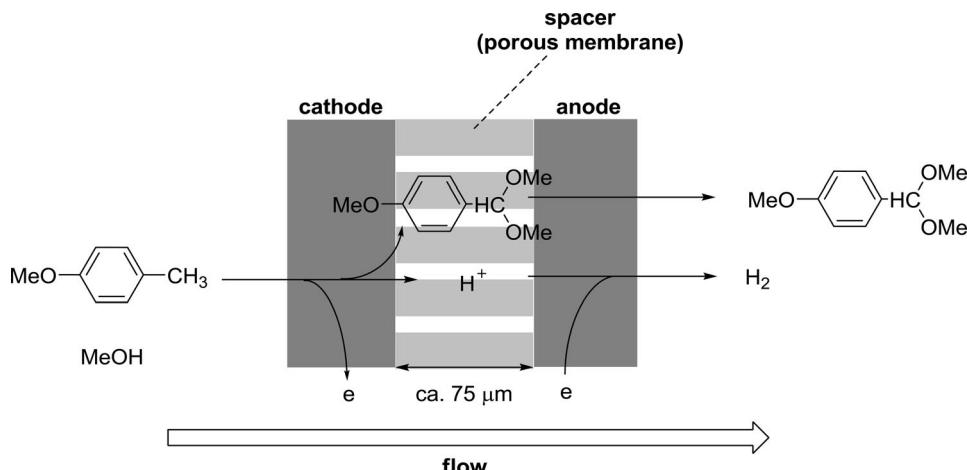


Figure 12.12 Methylation of *N*-methoxycarbonylpyrrolidine using an electrochemical microflow system without an intentionally added electrolyte.

generates protons, and it is most likely that protons are the carriers of the electricity as described in Figure 12.6. It was difficult, however, to increase the current density. The addition of a small amount of a proton source in the reactor only at the initial stage was found to be fairly effective at improving the reaction efficiency. Other types of anodic oxidation, such as the methoxylation of *N*-methoxycarbonylpyrrolidine and the methoxylation of acenaphthylene, were also successful using the microflow system.

12.6

Future Outlook

The examples presented in this chapter demonstrate that a variety of new strategies have been developed in electroorganic synthesis from the view point of green sustainable chemistry. Such strategies allow easy separation of products and supporting electrolyte. Strategies that permit electrolysis without using an intentionally added supporting electrolyte have also been developed. It is hoped that these strategies will provide solutions to the problems of conventional electrochemical processes and serve as powerful methods for environmentally benign electroorganic synthesis in laboratories and industry. It is also hoped that a wide range of new strategies based on different principles will be exploited and will work together to meet the great demands for green sustainable chemistry in the future.

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13

Parameterization and Tracking of Optimization of Synthesis Strategy Using Computer Spreadsheet Algorithms

John Andraos

13.1

Introduction

The study of green metrics [1–9] is now an established tool used to gauge and rank material and energy efficiencies of a set of synthesis plans to a given target molecule. The pillar green metrics for material efficiency are atom economy (*AE*) [10–12], *E*-factor (*E*) [13–16], and reaction mass efficiency (*RME*) [1, 2, 4]. Recently, important relationships and algorithms were determined that described the global and kernel *RME* for individual reactions and for synthesis plans for any degree of complexity [17–23]. In particular, the latest computer spreadsheet algorithm for determining global material consumption and waste production for any kind of synthesis plan was disclosed and illustrated for various synthetic routes to the anti-influenza drug oseltamivir phosphate [24]. Material consumption green metrics may be conveniently divided into two broad classes. Kernel metrics refer to intrinsic chemical performance and are based on atom economy and reaction yield only, whereas global metrics also account for excess reagent, reaction solvent, and all auxiliary material consumption in work-up and purification procedures.

For the purpose of identifying potential bottlenecks in synthesis plans, a radial pentagon analysis [22] was introduced that gave a visual representation of the four individual factors contributing to the global *RME* for a given reaction, namely reaction yield, atom economy, stoichiometric factor (excess reagent contribution), and material recovery parameter (auxiliary material contribution). Kernel metrics are useful for quickly ranking synthesis plans so as to identify both obvious inefficient plans and leading candidates based on intrinsic chemical performance. It is important to rank plans using a consistent set of assumptions and limitations for the fairest comparisons. In this chapter, we focus on synthesis strategy, that is, how the target molecules are put together by establishing which target bonds are made, and so we wish to evaluate plans under the best-case scenario conditions possible at the level of kernel metrics in order to highlight the achievements of good strategies. Auxiliary material consumption such as reaction solvents and all other materials used in work-up and purification procedures are therefore considered extraneous.

Another important practical reason for choosing to evaluate plans at the kernel metrics level when attempting to understand the essence of synthesis strategy is that not all of the material consumption information is disclosed in literature experimental procedures. This observation is the single most important reason why the progress of establishing a strong synergy between green metrics implementation and serious synthesis planning that adhere to green chemistry principles is currently slow. The synthesis tree diagram [20] was introduced as a new tool to facilitate the computation of kernel metrics for both simple and complex synthesis plans, including overall yield along the longest branch, and overall, individual, and cumulative atom economies and kernel reaction mass efficiencies. From the synthesis tree, one can easily identify the number of reaction steps, reaction stages, intermediates, input materials, branches, molecular weights of all chemical species, and reaction yields for a plan. Most important is the easy determination of the molar scale of any reagent or intermediate in the tree diagram relative to a reference molar scale of target product by a simple connect-the-dots approach. In addition to material efficiencies, synthesis tree diagrams also allow the determination of new parameters based on their shapes that can be used to describe synthetic elegance quantitatively [20]. These parameters are degree of asymmetry (β), degree of convergence (δ), and molecular weight first moment building up parameter (μ_1). It was concluded that material-efficient synthesis plans generally were those that had high values for atom economy, kernel reaction mass efficiency, and overall yield, low values for *E*-factor based on molecular weight and kernel mass of waste produced, and fewer numbers of reaction steps, reaction stages, and input materials. All of these observations are intuitively obvious.

Synthetically elegant plans were those that had strongly negative values for μ_1 , that is, they utilized low molecular weight molecules that progressively built up towards the target structure. They also had values of β close to zero (most symmetric) and values of δ close to one (highly convergent). One interesting finding from an ongoing exhaustive analysis of over 500 plans for about 100 target molecules is that the statement that convergent plans are *always* more atom economic, have higher overall yields, and are more material efficient than linear ones is not entirely true, as there is no mathematical proof that demonstrates this and, more importantly, there are several counter examples documented in the literature which refute this statement. Prior discussions [25, 26] on this point always used identical yields for all reaction steps to illustrate that convergent plans are *generally* more efficient than linear ones; however, clearly the reaction yields will never be the same for all reaction steps in a plan, which means that each plan must be evaluated separately before drawing any meaningful conclusions. Zhang [27] gave a good discussion of the pitfalls of using overall yield as a reliable metric of synthesis efficiency and performance for both linear and convergent plans. The best metric that simultaneously takes into account branching, yield performance, and atom economy for each reaction step in a plan is kernel reaction mass efficiency.

The most important overall conclusion drawn from all of these studies is that true synthesis plan optimization is achieved when all good material efficiency and synthetic elegance attributes coincide in the *same* plan. Typically, a set of reported plans for a given target have scattered attributes. For example, one plan may have the

best atom economy but an average overall yield, whereas another plan may have the reverse situation. Or, one plan may have the highest overall yield even though it has more steps than a shorter plan with poorer yield performances. Clearly, a synergy of all parameters must result to effect a true gravitation to the most optimum plan possible. Since the evaluation of greenness of a set of synthesis plans to a common target is a comparative analysis, claims of greenness are not valid in an absolute sense, that is, on the basis of the existence of a single plan for a given target molecule. The optimization of synthesis is necessarily an iterative exercise that is open-ended in that in principle an infinite number of appropriate starting materials may be used to make the final desired target product structure. Even if one believes that they have made a significant advance in improving synthesis performance to a given target, one should also keep an open mind in accepting that the possibility of coming up with an even better performing plan always exists, so the job is essentially never done.

In contrast to the rigorous analysis of material consumption and waste production summarized above, the parameterization of synthesis strategy is less well defined in quantitative terms. In practice, retrosynthetic analysis to “cheap, readily available starting materials in the fewest number of steps” is done largely by chemical intuition but is guided by a thorough knowledge of the large, ever-growing database of known reaction transformations from which to draw upon that is constantly updated. In developing strategies to a given target molecule, there are a number of paradigms that synthetic chemists follow, with the top priority being that a newly disclosed plan be distinctly different from others previously reported. Paradigms include developing a plan to prove the correctness of a postulated structure assignment, or developing a plan around a particular newly discovered reaction for the purpose of highlighting its synthetic methodology and scope of generality with the long-term goal of developing chemical libraries of potentially useful derivatives for screening against some desired property, or developing a plan that mimics how it *could* have been made biosynthetically in Nature, or simply developing a plan from an unusual starting material that bears no structural resemblance to the final target just for the purpose of demonstrating the synthetic prowess of a chemist.

The imposition of various constraints suggested by these common paradigms may or may not be consistent with the goal of designing a synthetic strategy that is also truly the most material efficient and environmentally friendly, even if that means using classical nineteenth century chemistry and “non-fancy” reagents. There is no doubt that it is a challenging task to achieve all of these aims in a single plan and even harder to envisage some kind of algorithm that could somehow code the creative aspect of efficient synthesis design, given that the problem is entirely open-ended and limitless. Essentially, the problem in chemistry of conducting a retrosynthetic analysis from a given target structure to a set of potential building block structures is completely analogous to the classical problems in number theory or algebra of factorizing natural numbers to their prime factors or complex polynomials to the multiplicative product of simple non-factorizable ones. However, despite the challenges posed by this inverse problem, the pursuit of developing useful tools for capturing the essence of what makes a given strategy good or not is worthy. With such tools available, it is possible to catalogue and study in detail what has already been

done, to frame the problem using well-defined parameters in such a way that iterative cycles of optimization will truly lead to the “best” possible method of synthesizing a given target, to learn from the successes and failures of the past, and then, armed with this knowledge, to move forward and develop future plans that are indeed well designed and can be called “green.” This argument is certainly not a negative criticism of existing synthesis plans, for it must be remembered that it is necessary first to go through a number of poorly performing plans before hitting on one that shows promise, hence all reported plans are valuable for future trials.

With the current thrust to implement green chemistry principles seriously in synthesis design, future reported plans for known targets of interest should take into consideration the value of green metrics as guiding tools in this quest. Green metrics are a great “after-the-fact” analysis of synthesis plan performance. What is advocated here is that green metrics be incorporated from the start at the design phase in conjunction with discovering new methodologies and chemistries in order to monitor plan performance and to make the necessary changes along the way to achieve the prior stated goal of synergy of optimization with respect to all available metrics.

13.2

Synthesis Strategy Parameterization

With these views in mind, this chapter introduces four new tools that describe and track synthesis strategy for a given plan: (1) target bond structure maps, (2) target bond-forming reaction profiles from which the number of target bonds per reaction step is determined, (3) molecular weight fraction of sacrificial reagents used, and (4) hypsicity (oxidation level) index. A target bond structure map is simply a drawing of the target product structure showing which target bonds are made and at what reaction step. A target bond is denoted with a heavy connecting line and its associated circled reaction step number is given alongside. From such a diagram, it is possible to trace the origin of each atom in the target structure back to the associated atoms in the reagents used. In effect, the set of reagent atoms is mapped on to the set of atoms comprising the target structure. From such a map, it is possible to determine the molecular weight fraction of sacrificial reagents whose atoms never become incorporated in the final target structure according to Equation 13.1.

$$f(\text{Sac}) = 1 - \frac{\sum \text{MW}_{\text{reagents in whole or in part ending up in target product}}}{\sum \text{MW}_{\text{all reagents}}} \\ = 1 - \frac{(AE)_{\text{overall}} \sum \text{MW}_{\text{reagents in whole or in part ending up in target product}}}{\text{MW}_{\text{target product}}} \quad (13.1)$$

Sacrificial reagents include those that serve as protecting groups, those that change the electronic states of key atoms so that skeletal building bond-forming reactions are possible, those that are used to control stereochemistry, those that are used in substitution reactions to switch poor leaving groups into better ones, and those that are reducing or oxidizing agents that are used in *subtractive* redox reactions, that is,

where oxygen atoms or hydrogen atoms are *removed* from a structure. The condition concerning redox reactions is important as it is *additive* redox reactions that are desirable to reduce $f(sac)$ since they contribute oxygen or hydrogen atoms to the target structure. It is obvious that the ultimate goal is to minimize the magnitude of $f(sac)$. One can deduce readily from Equation 13.1 that when the overall atom economy is unity, that is, when all atoms in all of the reagents used end up in the target structure, the two sums in the first part of the equation become equal to each other and, hence, $f(sac)$ is equal to zero. Also, from the target structure map it is possible to construct a bar graph of the number of target bonds made versus the reaction step count. Gaps in such bar graphs coincide with the use of sacrificial reagents in those steps and bars indicate productive steps. The number of target bonds made per step may be used as an indicator of synthetic efficiency and elegance, since good synthesis strategies are characterized by fewer steps and the accomplishment of more target bonds made per step. The above discussion is consistent with the following general guidelines with respect to synthesis strategy made by Baran *et al.* [28]:

The percentage of C–C bond-forming events within the total number of steps in a synthesis should be maximized. Where possible, cascade (tandem) [domino and multicomponent] reactions should be designed and incorporated to elicit maximum structural change per step. The innate reactivity of functional groups should be exploited so as to reduce the number of (or perhaps even eliminate) protecting groups.

The target structure map also provides the set of atoms in the target structure that are involved in bond-making and bond-breaking processes throughout the synthesis. These atoms are precisely the ones connected by the heavy lines in the target structure map. It is possible to trace the oxidation numbers of these atoms from the target structure back to the progenitor reagent used via the intervening intermediate products. In a manner similar to the determination of the molecular weight first moment building up parameter, the difference between the oxidation number of an atom in an intermediate structure and that same atom in the final target product is determined for each atom involved in this special set of atoms as a function of reaction stage. This idea of tracking the changes in oxidation state, or hypsicity (Greek: *hypnos*, meaning level or height), of key atoms involved in bond-making and bond-breaking steps was introduced by Hendrickson [29]. He proposed that good synthesis plans aim for the *isohypsic* condition, which is characterized by a zero net change in oxidation state of all atoms of starting materials and intermediates involved until the target product is reached. This can be achieved by designing synthesis plans that eliminate redox reactions entirely as it is consistent with the conclusion that such reactions are to be minimized in a plan because they are the most material inefficient class of organic reaction and therefore contribute to significant attenuations in kernel and global *RMEs*. If these cannot be avoided due to practical considerations, then the next best thing to achieve the *isohypsic* condition is to sequence redox reactions strategically in such a way that for every increase in oxidation level of an atom occurring in a step it is matched by a concomitant decrease in oxidation level of equal

magnitude in the next step, or vice versa. This cuts down on the accumulation of excess gains or losses in oxidation level of atoms, as the case may be, in starting materials and intermediates with respect to the oxidation levels of those atoms in the final target molecule over the course of the synthesis. This second option of achieving the isohypsic condition is purely due to an algebraic cancellation of all the “ups” and “downs” in oxidation state changes and hence will coincide with appreciably higher kernel *E*-factor values and lower kernel *RME* values for such plans, since generally redox reactions are the least material efficient. The first option, however, will coincide with lower kernel *E*-factor values and higher kernel *RME* values since redox reactions would be completely eliminated.

Formally, we may define an hypsicity index, *HI*, as

$$HI = \frac{\sum_{\text{stages},j} \left[\sum_{\text{atoms},i} [(Ox)_{\text{stage},j}^{\text{atom},i} - (Ox)_{\text{stage},N}^{\text{atom},i}] \right]}{N + 1} = \frac{\sum_{\text{stages},j} \Delta_j}{N + 1} \quad (13.2)$$

where (Ox) represents the relevant oxidation number of an atom. If *HI* is zero, then the synthesis is *isohypsic*. If *HI* is positive valued, then to get to the target molecule a net reduction is required over the course of the synthesis since an accumulated gain in oxidation level has resulted. Such a condition is termed *hyperhypsic*, by analogy with the term *hyperchromic*, which describes increases in intensities of absorption bands in spectroscopy. Conversely, if *HI* is negative valued, then to get to the target molecule a net oxidation is required over the course of the synthesis since an accumulated loss in oxidation level has resulted. Such a condition is termed *hypohypsic*, again by analogy with the term *hypochromic*. It is important to note that changes in oxidation number can occur for atoms in reactions that are not formally classified as reductions or oxidations with respect to the substrate of interest. A good example of this is the Grignard reaction, which is classified as a carbon–carbon bond-forming reaction and yet involves a formal oxidation with respect to magnesium in the preparation of the Grignard reagent. Another is electrophilic aromatic substitution, which begins with an oxidation state of -1 for the ArC-H carbon atom, which then increases to $+1$ when hydrogen is substituted for chlorine, for example. The hypsicity index therefore accounts for all such changes in oxidation numbers of atoms regardless of the reaction type.

The following sequence of steps may be followed to determine *HI* for a synthesis plan:

- 1) Enumerate atoms in the target structure that are only involved in the building up process from corresponding starting materials according to the structure map. This set of atoms defines those that are involved in bonding changes occurring in the relevant reaction steps.
- 2) Work backwards intermediate by intermediate to trace the oxidation numbers of the above set of atoms back to original starting materials as appropriate following the reaction stages back to the zeroth stage.
- 3) For each key atom, i , in each reaction stage, j , determine the difference in oxidation number of that atom with respect to what it is in the final target structure. Hence $(Ox)_{\text{stage},j}^{\text{atom},i} - (Ox)_{\text{stage},N}^{\text{atom},i}$.

- 4) Sum the differences determined in step 3 over all key atoms in stage j . This yields the term $\sum_{\text{atoms},i} \left[(\text{Ox})_{\text{stage},j}^{\text{atom},i} - (\text{Ox})_{\text{stage},N}^{\text{atom},i} \right] = \Delta_j$.
- 5) Finally, take the sum $\sum_{\text{stages},j} \Delta_j$ over the number of stages and divide by $N + 1$, accounting for the extra zeroth reaction stage.

From the above discussion, for a material-efficient synthesis plan it is not a sufficient condition just to aim for an HI value of zero. Statements suggesting that “the overall oxidation level of intermediates should linearly escalate during assembly of the molecular framework” [28] are also incomplete. What matters is that as many of the atoms as possible in oxidizing and reducing agents end up in the target structure. These can only arise from oxidation and reduction reactions that are of the *additive* type where oxygen and hydrogen atoms are added to a structure in a reaction and remain there until the final target structure is reached, and not of the *subtractive* types as described earlier in the discussion of sacrificial reagents. This idea is consistent with Baran *et al.*’s statement that “redox reactions that do not form C–C bonds should be minimized” [28]. Hence it is possible to have HI values that are strongly positive or negative and still be material efficient provided that those key atoms are incorporated as part of the final target structure. It is preferable to have a hypsicity profile that exhibits either a steadily increasing or a steadily decreasing oxidation level rather than an undulating one. Increases and decreases in oxidation levels parallel the types of redox reactions employed in a plan. This will depend, of course, on the oxidation levels of atoms in the selected reagents used throughout the synthesis. Hence careful correlation of HI values and overall AE , kernel RME , and $f(\text{sac})$ values need to be made to understand the synergy between material efficiency and oxidation level changes. It is impossible to make inferences solely on the basis of the magnitude of HI . One needs to examine the shape or distribution of the bar graph that tracks the changes in oxidation level as a function of reaction stage for a given synthesis plan.

13.3

Case Study: Lysergic Acid [30–40]

This section presents a detailed analysis of nine documented synthesis plans for [30–40] the alkaloid lysergic acid, the structure of which is shown in Figure 13.1.

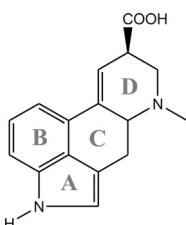


Figure 13.1 Structure of lysergic acid showing ring designations.

In the chemistry literature, lysergic acid is one of several famous targets for total synthesis since many research groups have made pioneering contributions in developing various synthesis design strategies and methodologies. Table 13.1 shows all of the relevant metrics and the plans are ranked in order from the highest kernel percent *RME* value (lowest kernel *E*-factor and lowest kernel mass of waste produced with respect to 1 mol of target product) to the lowest. The best parameters are shown as bold entries in the table. For each plan, figures are given for the molecular weight first moment building up, target bond forming reaction, hypsicity profiles, and the corresponding target structure maps. Also, included in each set of target structure maps is a structure map showing the most common bonds made in all of the plans examined according to frequency. A combinatorial pairwise comparison between various target maps for a given molecule is a useful way to pick out common and different strategy themes and patterns using the Tanimoto similarity index [41]. Coefficients having values close to unity imply that very similar strategies were used and those close to zero imply very different strategies. It should be mentioned that even if two plans have the same Tanimoto similarity index, they may still differ in the order in which those common target bonds were made during the course of each plan. Plans are compared with respect to strategy and greenness and highlights are discussed accordingly. Of particular importance is the construction of the ring system, which is the main reason why synthetic chemists were attracted to such compounds in the first place once their structures had been firmly elucidated. What is suggested by this compilation is that future attempts to make this compound, for example, should start first by careful study of these data to take stock of what has been achieved and then to devise new plans having green metrics parameters discussed here that hopefully would be better than those reported in the tables and the graphs for the documented plans. The long-term goal is to use green metrics of all types, dealing with synthesis material efficiency and synthesis strategy efficiency, as an additional tool to predict and identify new disconnections in retrosynthetic analysis, particularly in the construction of ring systems, which is a key characteristic of the example lysergic acid presented here. This philosophy can in principle be applied to any synthetic target.

Table 13.1 shows that the convergent Hendrickson plan is the most material-efficient overall with the highest overall yield (6.3%), highest kernel RME (1.1%), lowest kernel mass of waste (23.9 kg per mole lysergic acid). It also has the highest degree of building up toward the target molecular weight (-68.64 g mol^{-1} per stage), is the most symmetric ($\beta = 0.887$), and has the highest number of target bonds made per step (0.83). The linear Rebek plan has the least number of reaction steps (11) and input materials (22) required. The linear Ramage plan has the least molecular weight fraction of sacrificial reagents (0.682). The convergent Ortar plan has the fewest number of reaction stages (9) and has the highest degree of convergence ($\delta = 0.463$). The oldest Woodward plan has the highest atom economy (11.2%), slightly ahead of the overall best-performing Hendrickson plan.

These data clearly show that no plan reported to date has all the best attributes in the same plan and so the optimum synthesis has yet to be achieved for this target molecule. Hence the next effort to synthesize lysergic acid should aim to design a

Table 13.1 Summary of metrics for syntheses of lysergic acid arranged in ascending order of kernel waste production.

Plan	Year	Type	N^a	M^b	ρ^c	μ_1^d	β^e	δ^f	$f(sac)^g$	B/M^h	HI^i	Yield (%)	AE^j (%)	RME^k (%)	Kernel mass of waste (kg) ^l
Hendrickson	2004	Convergent	10	12	26	-68.64	0.887	0.439	0.763	0.83	+4.18	6.30	10.2	1.10	23.9
Rebek	1984	Linear	11	11	22	+59.82	0.896	0.395	0.755	0.64	+0.67	1.20	10.0	0.46	58.3
Ramage	1981	Linear	16	16	30	+57.97	0.911	0.375	0.682	0.63	+0.18	1.70	7.9	0.30	88.8
Kurihara	1987	Linear	13	13	35	+40.32	0.929	0.425	0.796	0.54	+0.43	1.00	7.2	0.18	148.4
Ortar	1988	Convergent	9	13	28	-15.66	0.897	0.463	0.859	0.54	-0.10	1.30	9.7	0.17	160.9
Woodward	1956	Convergent	15	17	29	-19.78	0.971	0.367	0.789	0.71	+1.19	0.69	11.2	0.16	168.6
Oppolzer	1981	Convergent	16	17	32	+18.05	0.913	0.385	0.817	0.71	+1.59	0.96	6.1	0.14	193.3
Szantay	2004	Convergent	15	17	33	-10.26	0.911	0.401	0.764	0.59	+1.31	0.53	9.1	0.12	228.0
Ninomiya	1985	Linear	19	19	36	+27.67	0.933	0.370	0.835	0.58	-0.95	0.45	7.7	0.10	261.6

a) Number of reaction stages.

b) Number of reaction steps.

c) Number of input materials.

d) Molecular weight first moment building up parameter.

e) Degree of asymmetry.

f) Degree of convergence.

g) Fraction of sacrificial reagents by molecular weight.

h) Number of target bonds made per reaction step.

i) Hypsicity index.

j) Basis is 1 mol of lysergic acid target product.

k) j)

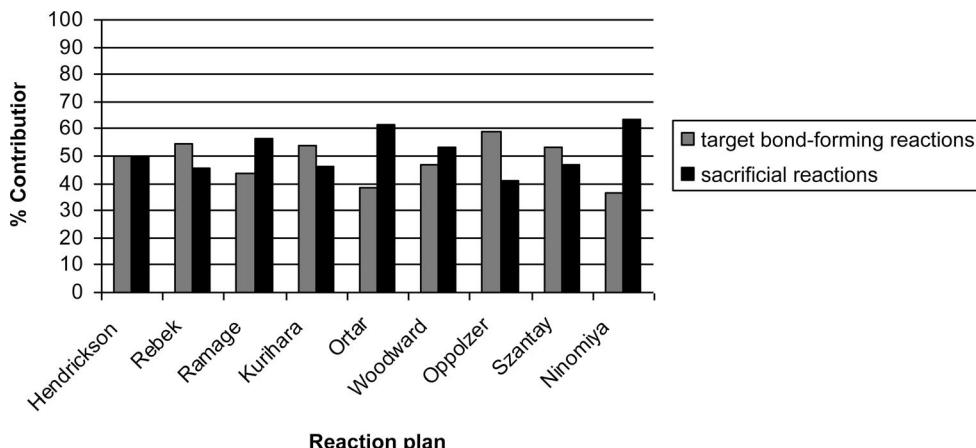


Figure 13.2 Percentage contributions to target bond-forming and sacrificial reactions for the nine synthesis plans to lysergic acid.

plan framed by the following constraints: (a) the number of reaction stages should be no more than nine, (b) the number of total reactions should be no more than 11, (c) the molecular weight building up parameter should be less than -69 g mol^{-1} per reaction stage, (d) the overall reaction yield along the longest branch should exceed 6%, (e) the overall atom economy should exceed 11%, (f) the overall kernel mass of waste should not exceed 24 kg mol^{-1} of lysergic acid (E -kernel < 90), (g) the number of target bonds made per step should exceed 0.8, (h) the degree of convergence should exceed 0.46, (i) the degree of asymmetry should be less than 0.89, and (j) the fraction of sacrificial reagents should be less than 0.68. The priority metrics to aim for are step

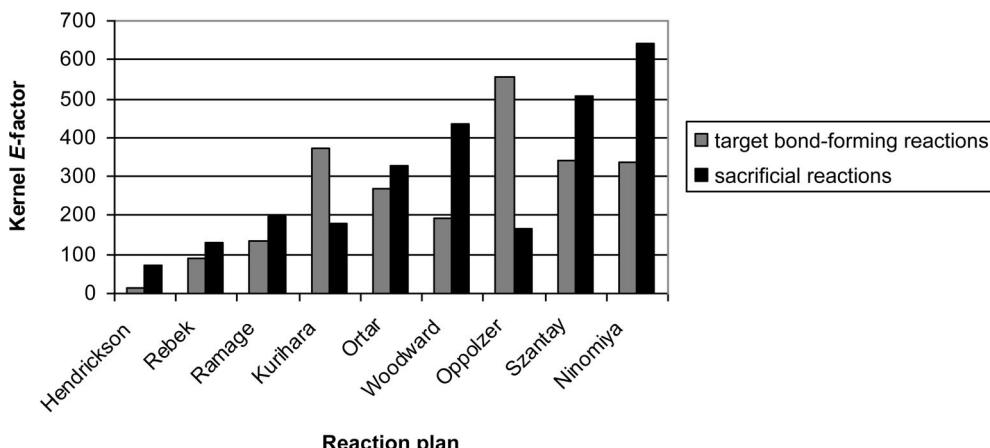
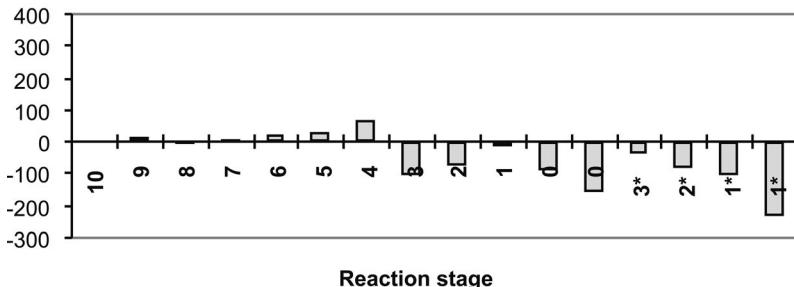


Figure 13.3 Kernel E -factor contributions from target bond-forming and sacrificial reactions for the nine synthesis plans to lysergic acid.

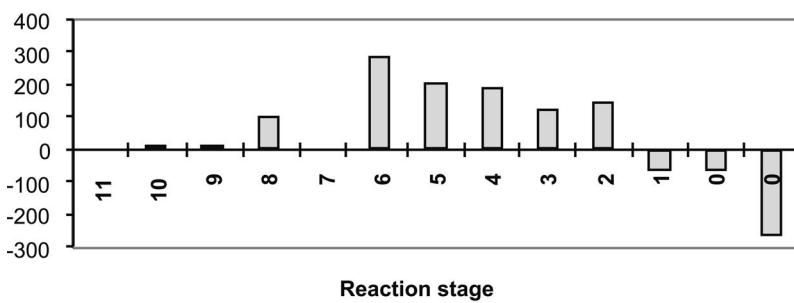
count, atom economy, overall kernel reaction mass efficiency or *E*-factor, $f(sac)$, and number of target bonds made per step.

The order of plan performance given in Table 13.1 can be readily understood by categorizing all reaction steps in each plan into either target bond-forming or or sacrificial reactions, and then determining the waste contribution of each category.

(a) Lysergic acid - Hendrickson plan



(b) Lysergic acid - Rebek plan



(c) Lysergic acid - Ramage plan

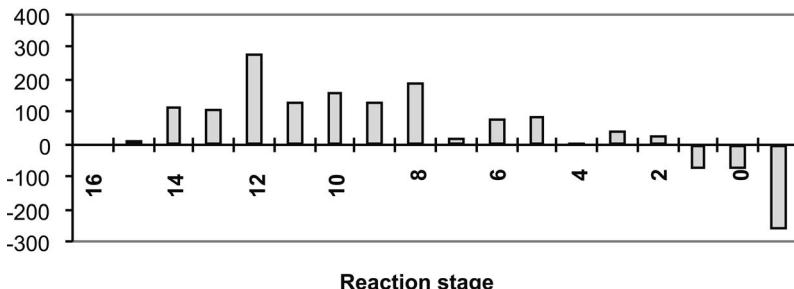
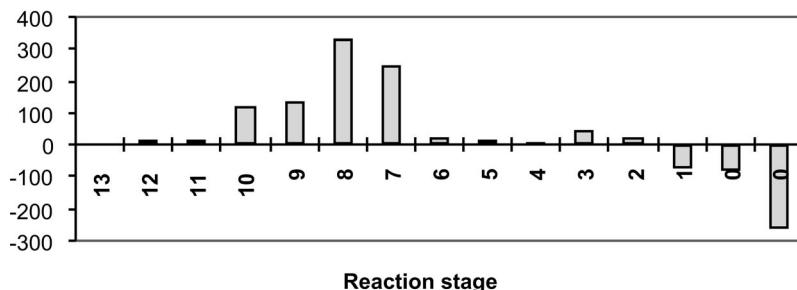


Figure 13.4 Molecular weight first moment profiles for various plans to lysergic acid:
 (a) $\mu_1 = -68.64$; (b) $\mu_1 = +59.82$;
 (c) $\mu_1 = +57.97$; (d) $\mu_1 = +40.32$;
 (e) $\mu_1 = -15.66$; (f) $\mu_1 = -19.78$;
 (g) $\mu_1 = +18.05$; (h) $\mu_1 = -10.26$;
 (i) $\mu_1 = +27.67 \text{ g mol}^{-1}$ per stage. Ordinate scale is g mol^{-1} per reaction stage.

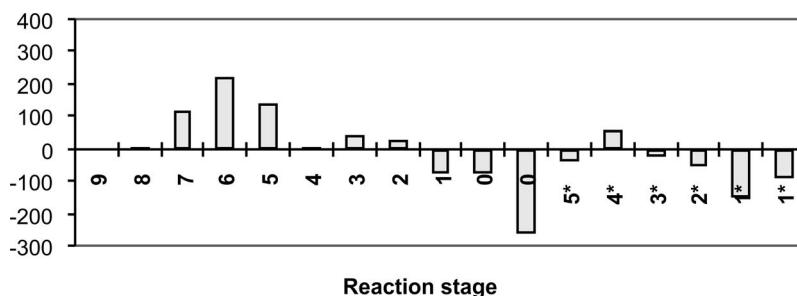
Figures 13.2 and 13.3 show the percentage contributions and kernel *E*-factors for target bond-forming and sacrificial reactions in each plan, respectively.

The best performing Hendrickson plan has an even distribution of target bond-forming reactions and sacrificial reactions and overall it has the least kernel *E*-factor. The worst performing Ninomiya plan has the highest proportion of sacrificial reactions and these contribute the bulk of the waste, giving this plan the highest overall kernel *E*-factor. The Rebek, Kurihara, Oppolzer, and Szantay plans employ more target bond-forming reactions than sacrificial reactions, with the Oppolzer plan

(d) Lysergic acid - Kurihara plan



(e) Lysergic acid - Ortar plan



(f) Lysergic acid - Woodward plan

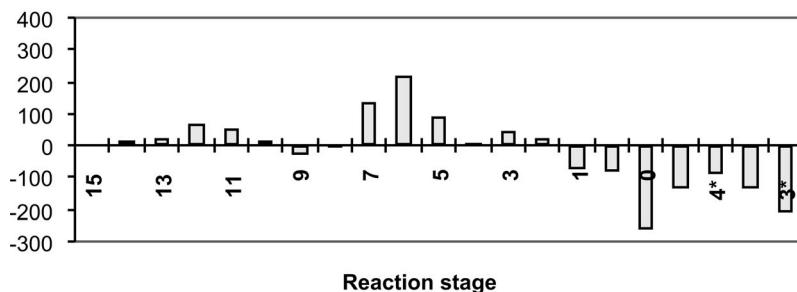
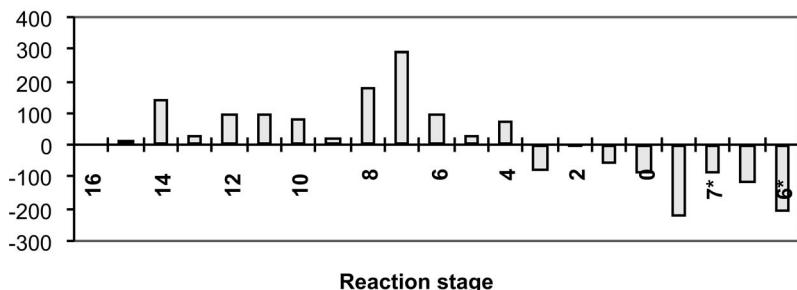


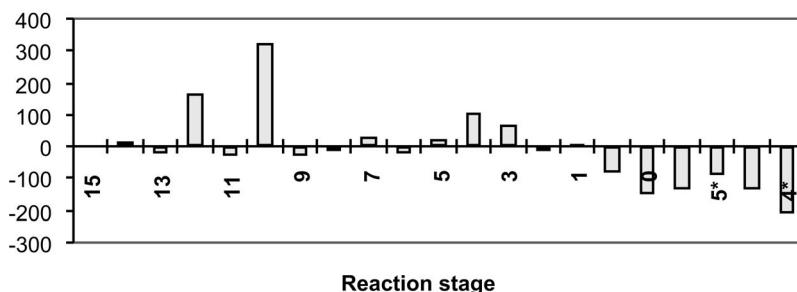
Figure 13.4 (Continued)

being the best of these. The Ninomiya, Ortar, and Ramage plans employ the highest proportion of sacrificial reactions compared with target bond-forming reactions. In terms of kernel *E*-factor contributions, the Ninomiya, Woodward, and Szantay plans have higher contributions from sacrificial reactions, whereas the Oppolzer and Kurihara plans have higher contributions from target bond-forming reactions. The last two plans have the property of having proportionally more target bond-forming reactions that in turn contribute the bulk of the waste produced. Although these plans have comparable overall atom economies to the others, it is the lower reaction yield

(g) Lysergic acid - Oppolzer plan



(h) Lysergic acid - Szantay plan



(i) Lysergic acid - Ninomiya plan

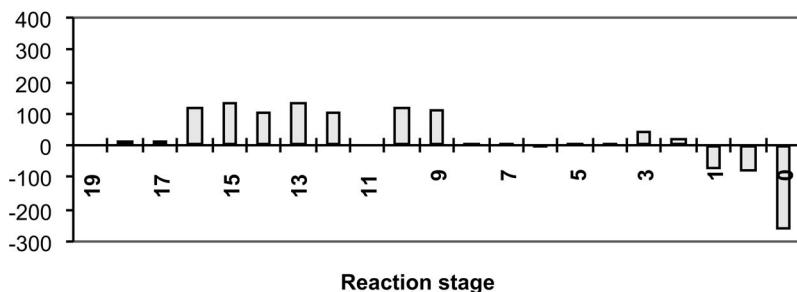
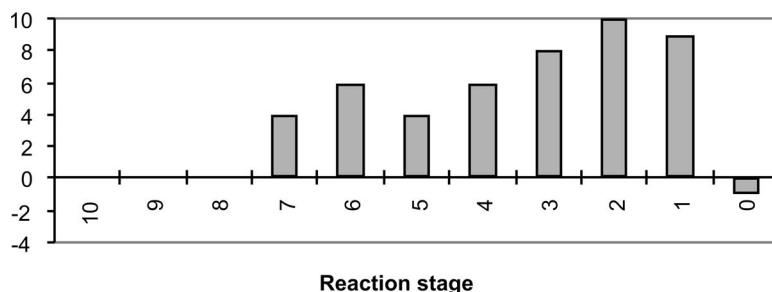
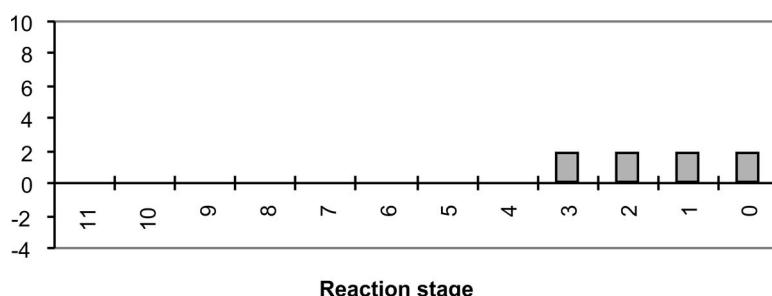


Figure 13.4 (Continued)

(a) Lysergic acid - Hendrickson plan



(b) Lysergic acid - Rebek plan



(c) Lysergic acid - Ramage plan

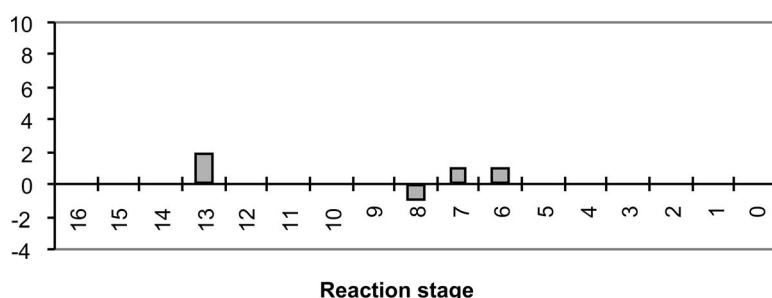
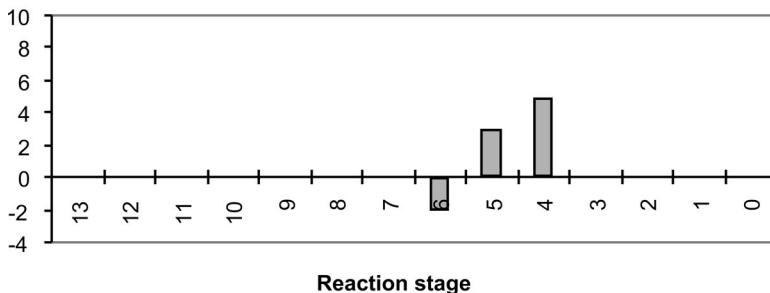


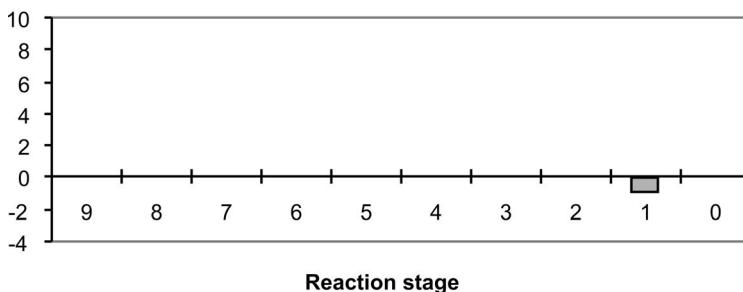
Figure 13.5 Hypsicity profiles for various plans to lysergic acid: (a) $HI = +4.18$; (b) $HI = +0.67$; (c) $HI = +0.18$; (d) $HI = +0.43$; (e) $HI = -0.10$; (f) $HI = +1.19$; (g) $HI = +1.59$; (h) $HI = +1.31$; (i) $HI = -0.95$. Ordinate is sum of oxidation number changes.

performances that weigh down these plans in terms of waste production. Such plans therefore have the potential to be optimized by increasing both reaction yield and atom economy performance with respect to the target bond-forming reactions. The Szantay plan, which has more target bond-forming reactions but a higher kernel *E*-factor contribution from sacrificial reagents, may be optimized by increasing both reaction yield and atom economy performance with respect to the sacrificial reactions

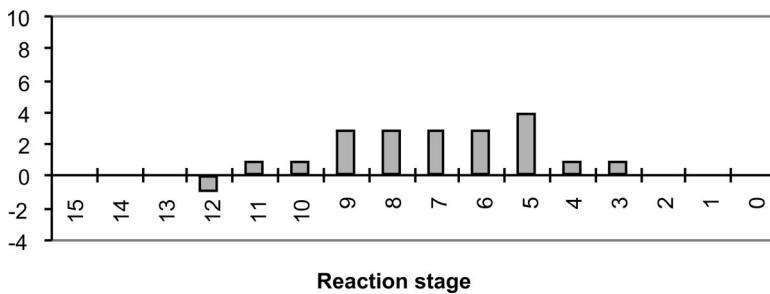
(d) Lysergic acid - Kurihara plan



(e) Lysergic acid - Ortar plan



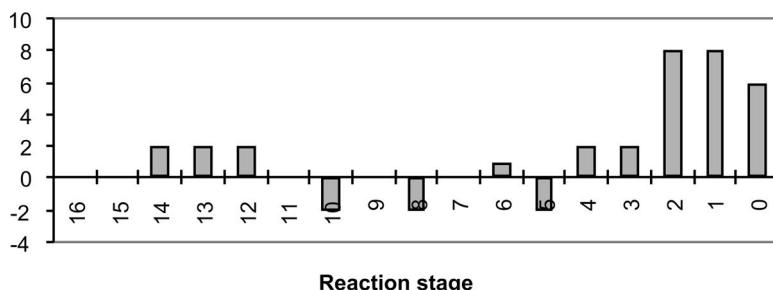
(f) Lysergic acid - Woodward plan

**Figure 13.5 (Continued)**

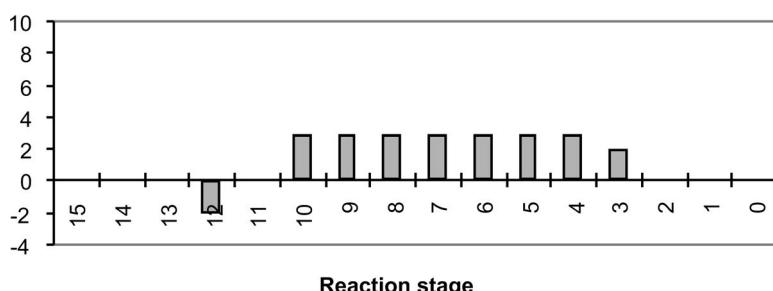
so that the overall kernel *E*-factor is brought down. Plans such as the Ninomiya plan that have a high proportion of sacrificial reactions which in turn contribute the bulk of the waste are those having the least chance of further optimization, hence their intrinsic design strategy needs a complete overhaul.

By the reasoning described, the most optimum situation is to have a plan made up of the least number of steps that are entirely target bond-forming reactions having both high atom economies and reaction yields that contribute to a low overall kernel *E*-factor. Examples of good target bond-forming reactions are skeletal building

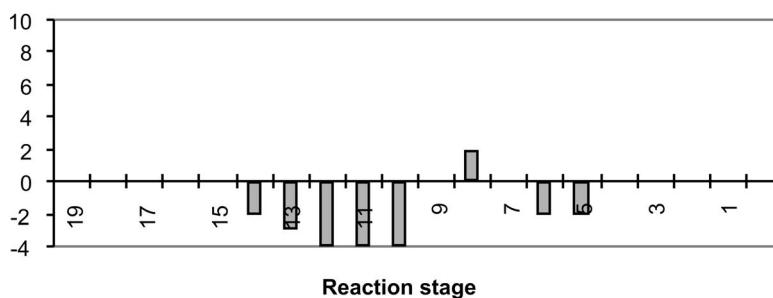
(g) Lysergic acid - Oppolzer plan



(h) Lysergic acid - Szantay plan



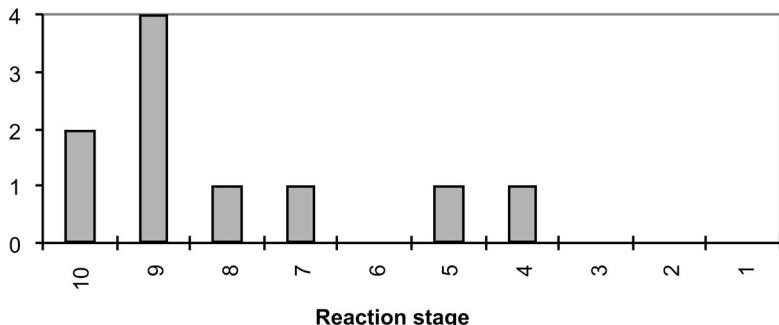
(i) Lysergic acid - Ninomiya plan

**Figure 13.5 (Continued)**

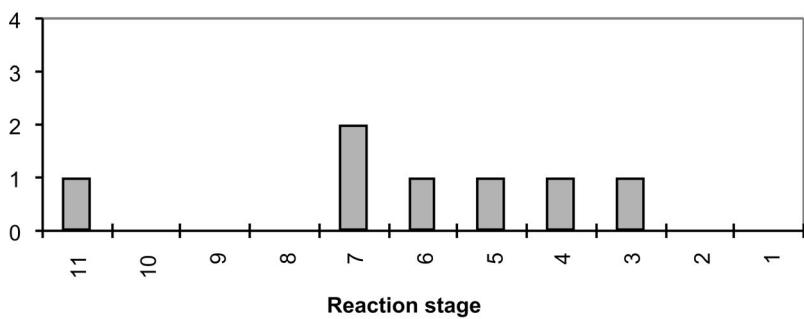
reactions that form carbon–carbon and non-carbon–carbon bonds and/or additive redox reactions that contribute oxygen or hydrogen atoms to the target structure. The more such reactions are involved in ring constructing steps, the better.

The molecular weight first moment profiles in Figure 13.4 show significant overshoots above the target molecular weight of lysergic acid for the Rebek, Ramage, Kurihara, Ortar, Woodward, Oppolzer, Szantay, and Ninomiya plans, thus driving the μ_1 values in a positive direction. The Hendrickson plan is clearly the best plan with respect to this parameter since it is the most negative. From the hypsicity profiles in

(a) Lysergic acid - Hendrickson plan



(b) Lysergic acid - Rebek plan



(c) Lysergic acid - Ramage plan

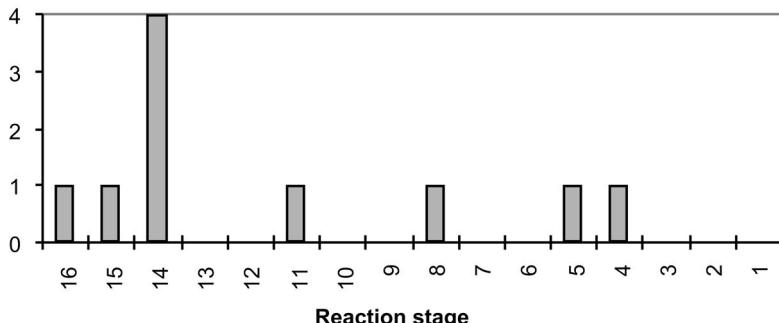
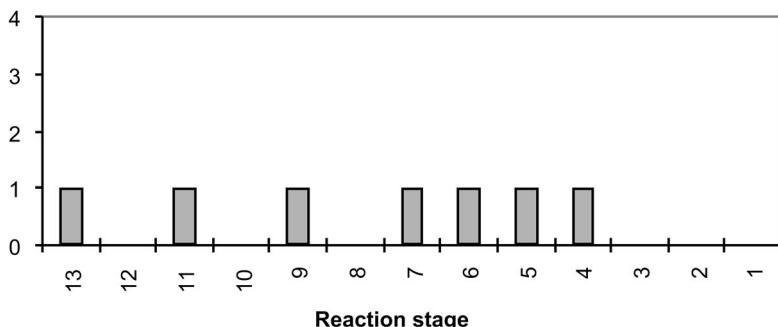
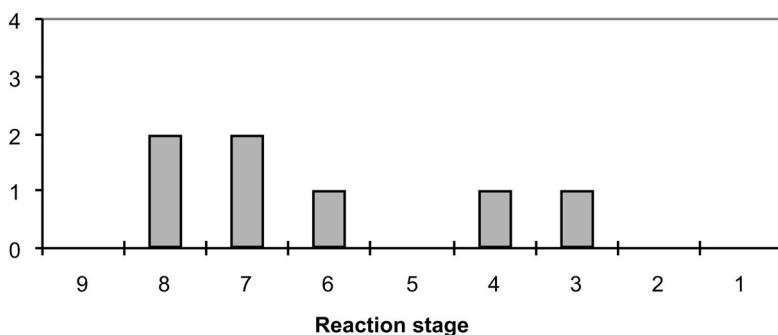
**Figure 13.6** Target bond-forming reaction profiles for various plans to lysergic acid. Ordinate is number of target bonds made per reaction stage.

Figure 13.5, the Ortar plan is very close to being isohypsic followed by the Rebek, Ramage, and Kurihara plans. The Ortar plan achieves the target oxidation level sooner than any other plan, followed closely by the Rebek plan. The Rebek plan may be considered monotonically decreasing. The Hendrickson plan has the most positive *HI* and the Ninomiya the most negative *HI*.

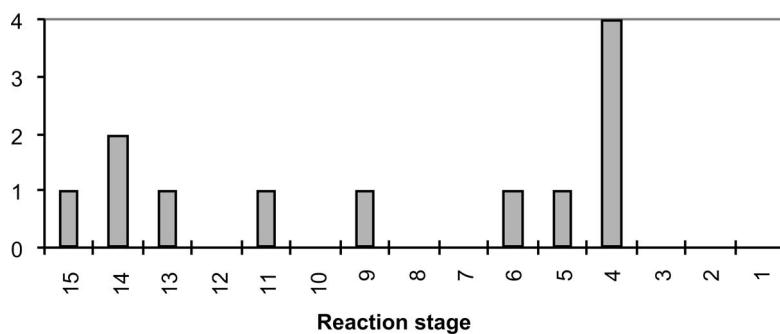
(d) Lysergic acid - Kurihara plan



(e) Lysergic acid - Ortar plan

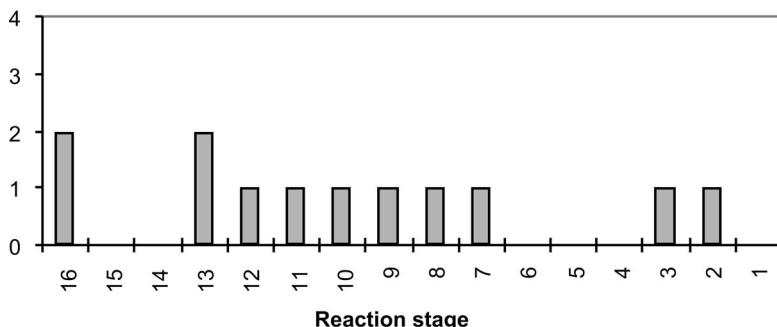


(f) Lysergic acid - Woodward plan

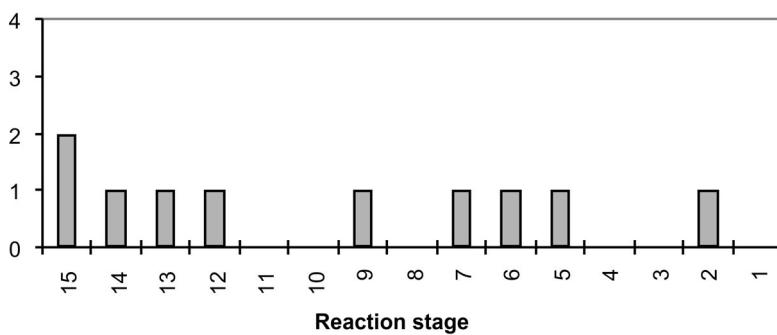
**Figure 13.6 (Continued)**

From the target bond-forming reaction profiles in Figure 13.6, one can see that the Hendrickson, Ramage, Ortar, and Szantay plans are most productive in the late stages; whereas, the Rebek, Kurihara, Woodward, Oppolzer, and Ninomiya plans are most productive in the early to middle stages. A Tanimoto pairwise structure comparison shows that the Woodward–Szantay, Ramage–Ortar–Rebek,

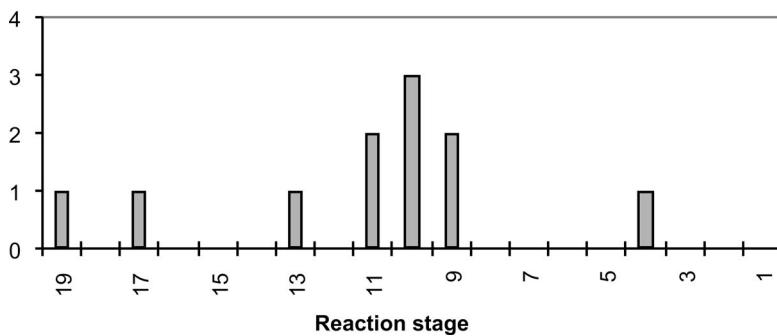
(g) Lysergic acid - Oppolzer plan



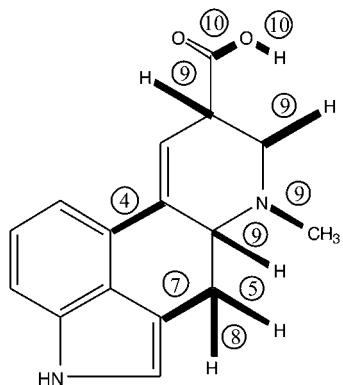
(h) Lysergic acid - Szantay plan



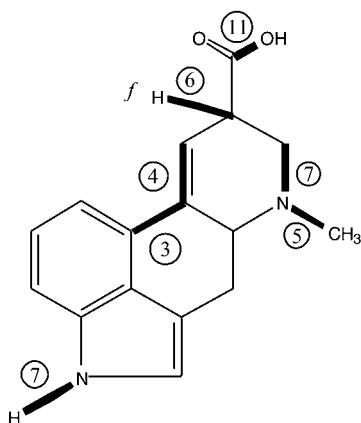
(i) Lysergic acid - Ninomiya plan

**Figure 13.6** (Continued)

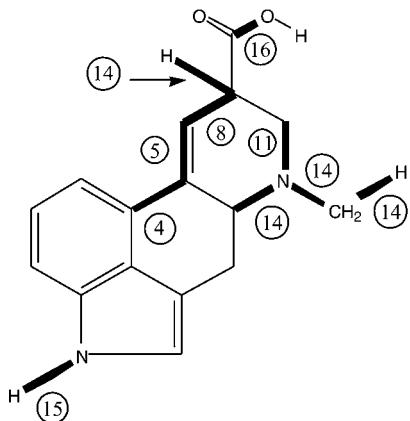
and Woodward–Ninomiya plans have the highest similarity coefficients of 0.9, 0.7, and 0.667, respectively. On the other hand, the Kurihara–Hendrickson, Oppolzer–Hendrickson, Szantay–Hendrickson, and Woodward–Hendrickson pairs have the lowest Tanimoto indices of 0.067, 0.158, 0.176, and 0.188, respectively, indicating that the synthetic strategy of the Hendrickson plan is distinctly different from the others.

Hendrickson

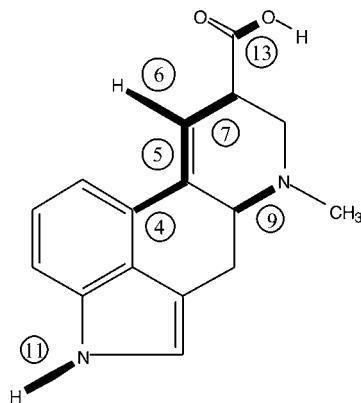
3-carboxymethylindole (1),
pyridine-2,5-dicarboxylic acid (2*),
 $\frac{1}{4}$ Ca(BH₄)₂ (5), $\frac{1}{3}$ BH₃ (8), CH₃-I (9),
 $\frac{1}{2}$ NaBH₄ (9), water (9), NaOH (10), HCl (10).

Rebek

(S)-tryptophan (1), BrCH₂C(COOEt)=CH₂ (4),
CH₃-I (5), HBr (6), water (7), water (11).

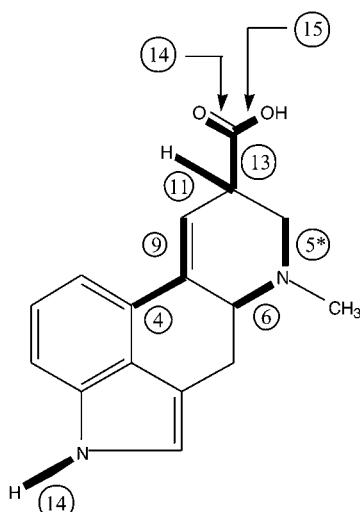
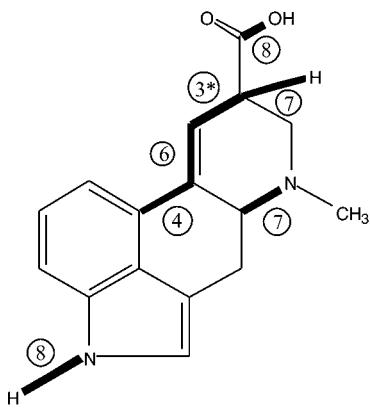
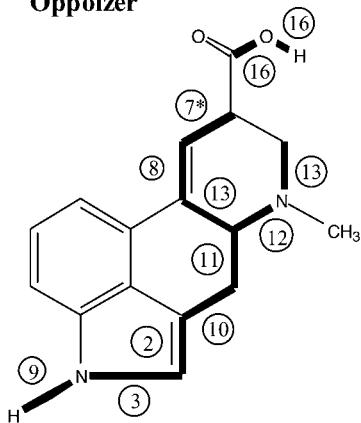
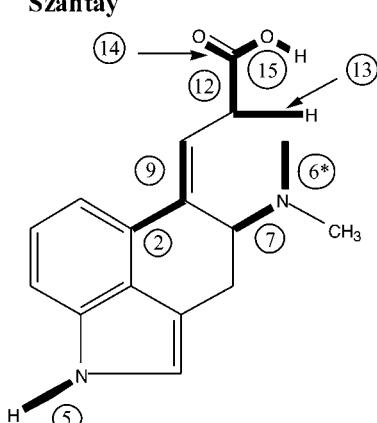
Ramage

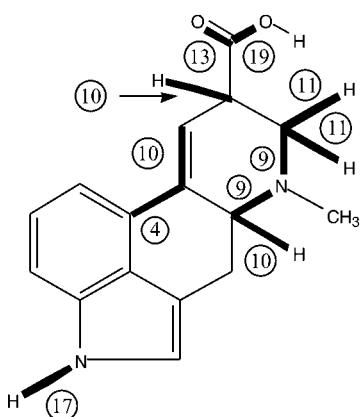
3-(3'-indolyl)propanoic acid (1), ClCH₂COOEt (5),
MeOOC=(PPh₃)CH₂COO'Bu (8),
tetramethylguanidinium azide (10), CH₂=O (14),
HCOOH (14), MeOH (15), KOH (16).

Kurihara

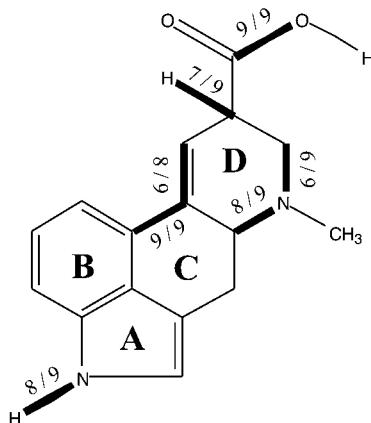
3-(3'-indolyl)propanoic acid (1),
(EtO)₂(PO)CN (5), ⁱBu₂AlH (6),
EtOOCCH₂CH₂N(Me)COO'Bu (7),
water (11), water (13).

Figure 13.7 Target bond reaction maps of lysergic acid by plan showing which bonds were made and at what reaction step. Lists of reagents used that in whole or in part end up in the target structure are shown below each structure map.

Woodward**Ortar****Oppolzer****Szantay****Figure 13.7** (Continued)

Ninomiya

3-(3'-indolyl)propanoic acid (1),
3-carboxychloridefuran (9), CH_3NH_2 (9),
 MeOH (10), $\frac{1}{4} \text{NaBH}_4$ (10), LiAlH_4 (11),
 $\text{Me}_3\text{NO}\cdot 2\text{H}_2\text{O}$ (13), water (17), water (19).

**Target bond frequencies
for most common bonds****Figure 13.7 (Continued)**

Consider the target structure maps in Figure 13.7 and the ring sequence strategies given in Table 13.2.

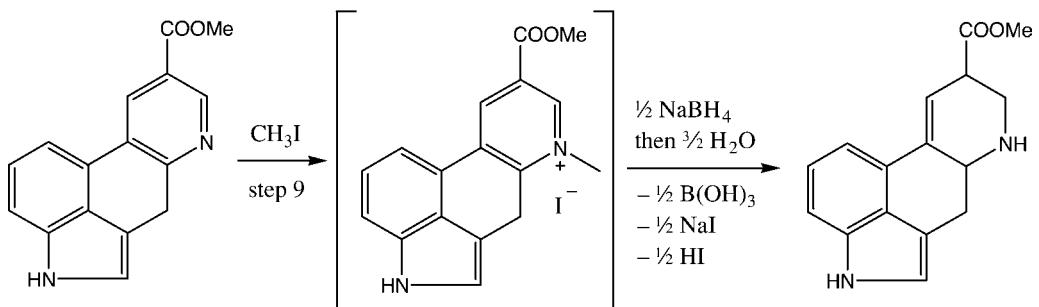
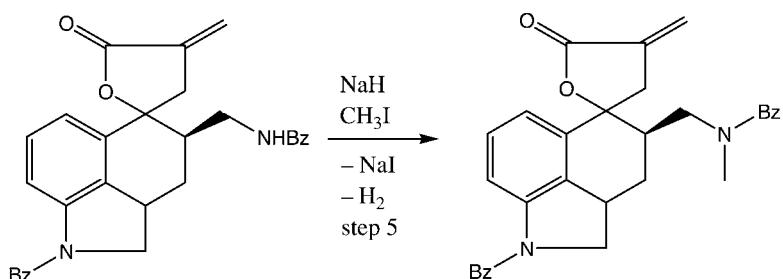
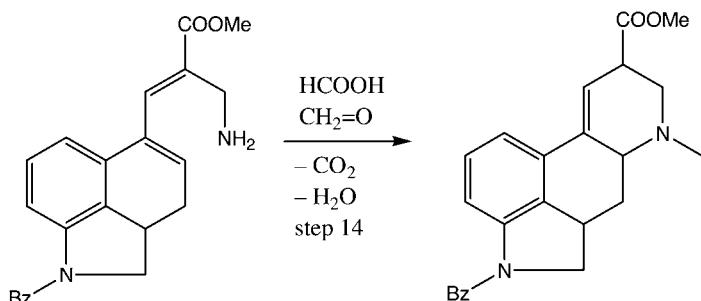
From these, we may deduce the following similarities among the lysergic acid plans:

Table 13.2 Ring sequence strategies for synthesis plans of lysergic acid^{a)}.

Plan	Ring sequence	Comments
Hendrickson	$(\text{A} + \text{B})_0 \rightarrow \text{D}_{2*} \rightarrow \text{C}_7$	No sacrificial rings cleaved
Rebek	$(\text{A} + \text{B})_0 \rightarrow \text{C}_2 \rightarrow \text{D}_7$	Sacrificial ring cleaved in step 8 (lactone methanolysis)
Ramage	$(\text{A} + \text{B})_0 \rightarrow \text{C}_4 \rightarrow \text{D}_{14}$	Sacrificial ring cleaved in step 6 (epoxide opening and decarboxylation to an aldehyde which is captured by semicarbazide)
Kurihara	$(\text{A} + \text{B})_0 \rightarrow \text{C}_4 \rightarrow \text{D}_9$	No sacrificial rings cleaved
Ortar	$(\text{A} + \text{B})_0 \rightarrow \text{C}_4 \rightarrow \text{D}_6$	No sacrificial rings cleaved
Woodward	$(\text{A} + \text{B})_0 \rightarrow \text{C}_4 \rightarrow \text{D}_9$	No sacrificial rings cleaved
Oppolzer	$\text{B}_0 \rightarrow \text{A}_3 \rightarrow (\text{C} + \text{D})_{13}$	Sacrificial ring cleaved in step 13 (thermolysis of norbornene ring liberates cyclopentadiene)
Szantay	$(\text{A} + \text{B})_0 \rightarrow \text{C}_2 \rightarrow \text{D}_9$	No sacrificial rings cleaved
Ninomiya	$(\text{A} + \text{B})_0 \rightarrow \text{C}_4 \rightarrow \text{D}_{10}$	Sacrificial rings cleaved in step 8 (epoxide to ketone transformation catalyzed by BF_3 etherate), step 14 (oxidative cleavage of cyclic diol with NaIO_4)

a) Numerical subscripts denote step numbers where rings are formed. Asterisk designates second branch in synthesis plan.

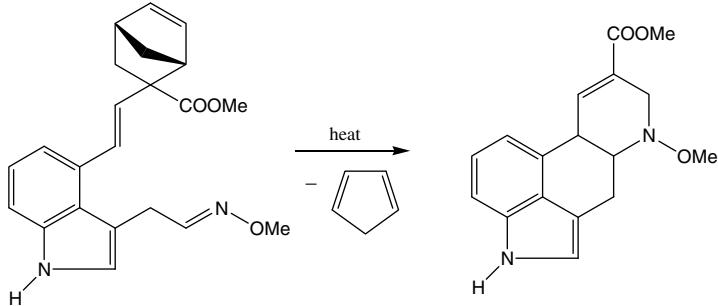
- 1) The Szantay and Woodward plans have identical bonding patterns.
- 2) The Ninomiya plan is the next similar one to the Szantay and Woodward plans.
- 3) The Oppolzer plan has the longest continuous bonding pattern connecting all the rings.
- 4) The Ortar and Rebek plans have the fewest number of target bonds made (seven).
- 5) The Ninomiya, Rebek, Ortar, Ramage, and Kurihara plans involve hydrolysis of a benzoyl protecting group on the indole nitrogen atom; the Oppolzer plan

Hendrickson**Rebek****Ramage****Scheme 13.1** Key *N*-methylation steps in lysergic acid plans.

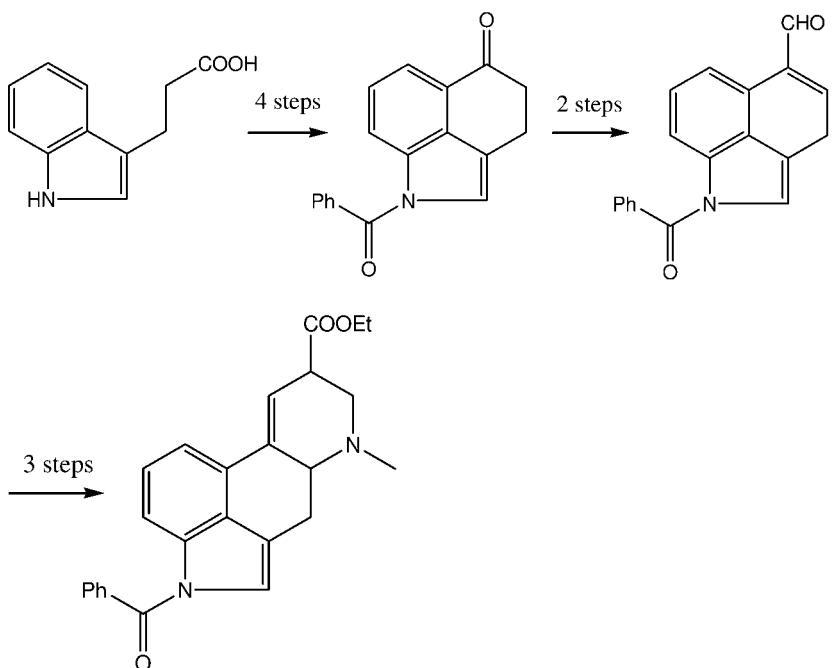
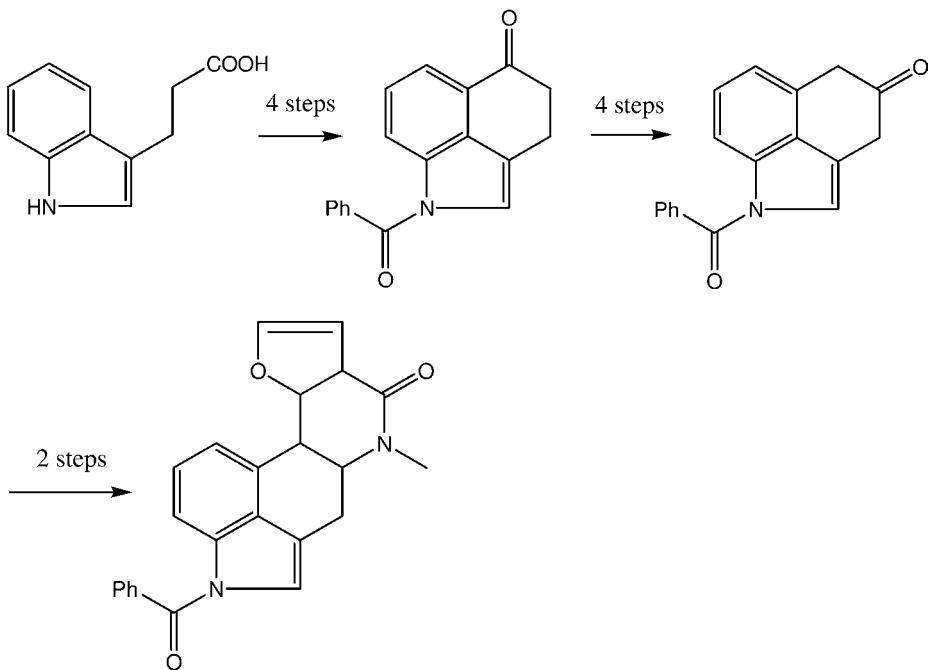
involves hydrolysis of a tosyl protecting group; the Szantay plan involves hydrolysis of a pivaloyl protecting group; and the Woodward plan involves hydrolysis of an acetyl protecting group.

- 6) All plans except the Oppolzer plan involve making a bond connecting the indole benzenoid ring B and ring D.
- 7) The Hendrickson, Rebek, and Ramage plans (Scheme 13.1) involve N-methylation of ring D according to the following strategies: methylation of a pyridine ring with methyl iodide, methylation of an *N*-benzoyl-protected amino group with methyl iodide, and methylation of an amino group using formic acid and formaldehyde, which also effects cyclization to form ring D.
- 8) The hydrogen atom alpha to the carboxylic acid group is introduced by a reduction reaction in the Woodward plan with sodium borohydride, or by protonation reactions in the Ramage (formic acid), Rebek (hydrobromic acid), Hendrickson and Szantay (water), and Ninomiya (methanol) plans.
- 9) The Oppolzer plan makes rings C and D simultaneously in step 13 according to Scheme 13.2.
- 10) The Kurihara, Ninomiya, Woodward, Ortar, Szantay, Ramage, and Rebek plans (Scheme 13.3) follow the same ring sequence strategy beginning with an indole starting material: (A + B) → C → D.

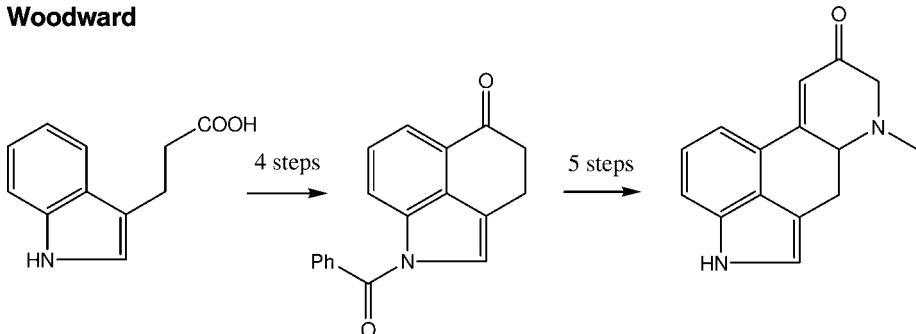
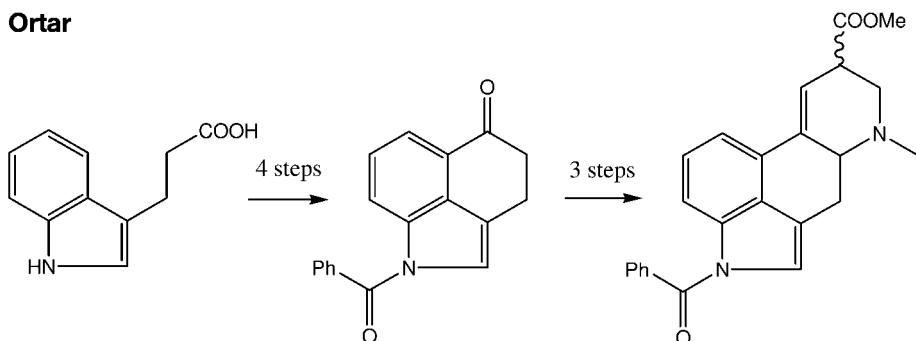
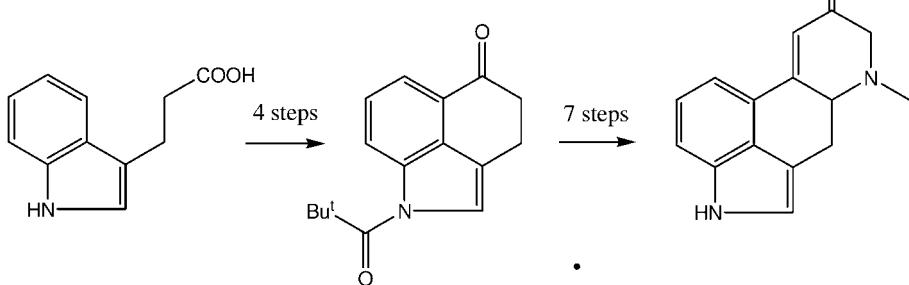
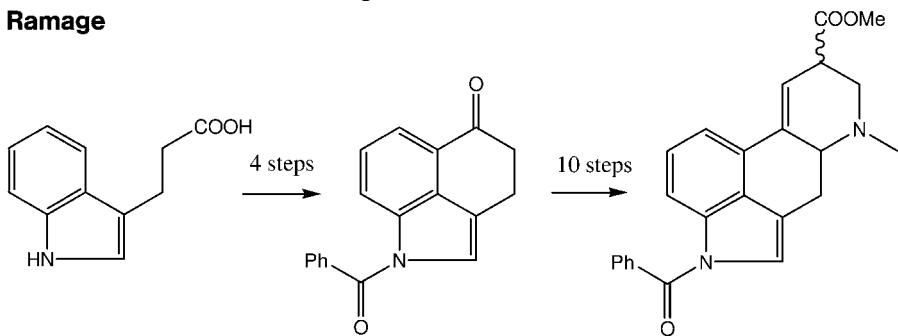
Oppolzer

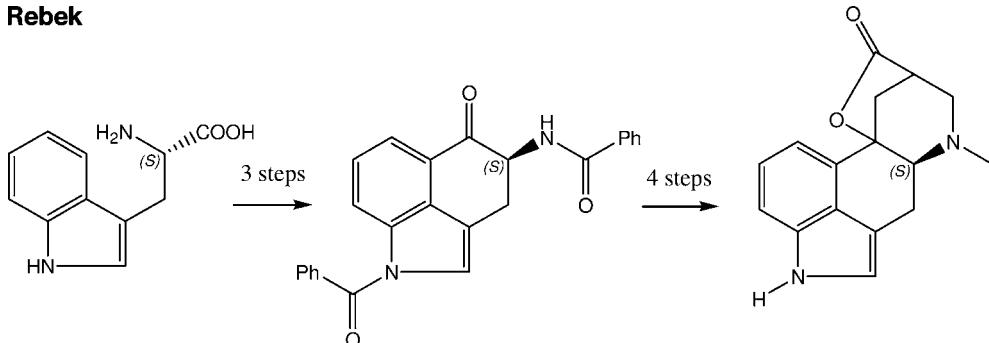


Scheme 13.2 Key ring forming step in Oppolzer plan.

Kurihara**Ninomiya**

Scheme 13.3 Key (A + B) → C → D ring-forming steps in lysergic acid plans.

Woodward**Ortar****Szantay****Ramage****Scheme 13.3 (Continued)**

Rebek**Scheme 13.3 (Continued)****References**

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Since the writing of this chapter six new plans [1–6] have been published for lysergic acid that will result in a reshuffling of the hierachal ranking of plan efficiencies. The pharmaceutical industry has adopted the process mass intensity (PMI) as the best metric to gauge material efficiency for chemical processes [7, 8]. This metric is just the reciprocal of the global RME (including reaction solvent and all other auxiliary materials used) described in this work. The reader is directed to a recent book which compiles similar analyses for other synthesis plans of important target molecules [9].

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