6.17 Application of Nontoxic Iron Salts in Oxidative C—C Coupling Reactions

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6.17.1 Introduction

Transition metal catalysts play remarkable efficiency for the formation of carbon–carbon and carbon–heteroatom bonds over the past decades.[1–6] The current fundamental research goals for sustainable, green, clean, more efficient, and selective organic synthesis have increased the demand for such metal-based reaction promoters.

The mainstream of research in this area focuses on metals such as Pd, Ni, Pt, Rh, Ir, or Au which suffer from high costs and toxicity. Iron offers significant advantages compared with the rare and toxic metals, since it is the second most abundant metal in the earth crust (4.7 wt%). Various iron salts and iron complexes are commercially available in large scale and easy to synthesize.[7–9] Furthermore, iron is an essential metal for living organisms and biology and it plays crucial roles in the life reactivity as well as in the human body.[7,10–12]

Coupling reactions have evolved into a critical support for building molecules in modern synthetic chemistry.[4,6] Since they form chemical bonds directly, it is one of the most powerful tools in organic synthesis. A large variety of nucleophiles and electrophiles can be applied in coupling processes by using palladium or nickel complexes as catalysts. The involvement of iron in coupling reactions has recently caught much attention and significant progresses have been achieved in this emerging field.[7–9,13–21]

Compared with the traditional coupling reactions (coupling between nucleophiles and electrophiles), oxidative coupling reactions (couplings between two nucleophiles in the presence of proper oxidants) provide an alternative path for the construction of carbon–carbon and carbon–heteroatom bonds. Recently, several reviews have covered this field from different aspects.[22–24] In this chapter, the applications of nontoxic iron salts in oxidative C—C bond formations are summarized. According to the hybridization status of the carbon atom (sp, sp^2, and sp^3 hybridized), this chapter covers recent advances in the area of iron-catalyzed oxidative C—C coupling reactions respectively.

6.17.2 C_{sp}—C_{sp} Oxidative Coupling Reactions

The C_{sp}—C_{sp} oxidative coupling usually refers to the reaction between two terminal alkynes which afford the conjugated 1,3-diynes products. This reaction was also called acetylenic coupling.[25] Due to the rigid and sterically triple bond structure, interesting electronic and optical properties, di- and oligo-acetylene moieties are quite valuable as spatially and directionally well-defined structural units in diverse areas of organic chemistry including the synthesis of natural products, pharmaceuticals, materials and supramolecular construction.[26–28] Traditionally, the main methods toward the C_{sp}—C_{sp} structures synthesis cover the Glaser couplings and Cadiot–Chodkiewicz reactions, in which copper salts are usually employed as the catalysts.[25,29] Few examples of the reaction between two terminal alkynes involving iron salts have been reported yet.

One example was from Chen et al. who have reported an efficient method for constructing the symmetric and unsymmetric diynes in moderated to good yields using iron/copper (trace amount) co-catalyst.[30] Using $Fe(acac)_3$ and $Cu(acac)_2$ as co-catalyst, K_2CO_3 as base and air as oxidant in *N*,*N*-dimethylformamide (DMF), a wide variety of terminal alkynes successfully afforded the homo-coupled diynes at 50 °C (**Scheme 1**). Unsymmetric diynes were also obtained selectively using a fivefold excess of one of the alkynes. However, this is not a totally iron-catalyzed process in the strict sense, as the trace amount of copper salt in the system influenced the reactions obviously. Iron salt here might only play a role of oxidant.

6.17.3 C_{sp}—C_{sp^2} Oxidative Coupling Reactions

The most widely used methods for achieving C_{sp}—C_{sp^2} bonds are the Sonogashira reactions and Negishi reactions.[31–33] The oxidative coupling reaction between C_{sp} and C_{sp^2} nucleophiles

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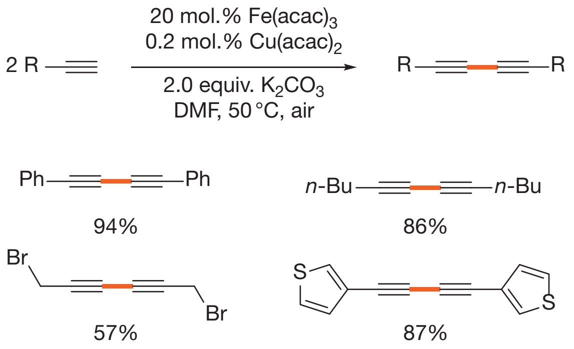


Scheme 1 Iron and copper co-catalyzed oxidative coupling between two terminal alkynes.

has also been developed in recent years.[34,35] However, this type of oxidative coupling is relatively rare due to the lack of efficient catalytic systems. A rare example has been reported which was mediated by iron catalyst.

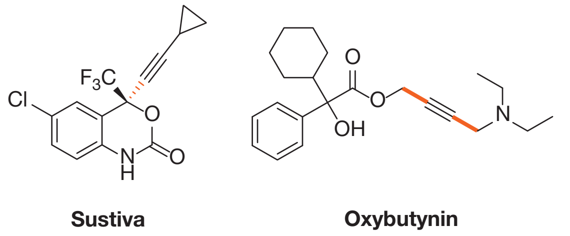
6.17.4 C_{sp}—C_{sp^3} Oxidative Coupling Reactions

The C_{sp}—C_{sp^3} structures are significant building blocks for pharmaceutical sciences which are widely used as for a synthetic intermediate compounds in organic synthesis. As the two molecules shown in Scheme 2, Sustiva, a prescription medicine used to treat people who are infected with the human immunodeficiency virus type 1 with a total sale of 0.17 billion dollars in 2008; Oxybutynin, used to control urgent, frequent, or uncontrolled urination with a total sale of 160.0 million dollars in 2007, both contain the C_{sp}—C_{sp^3} bonds and are quite similar to the target structures mentioned below.

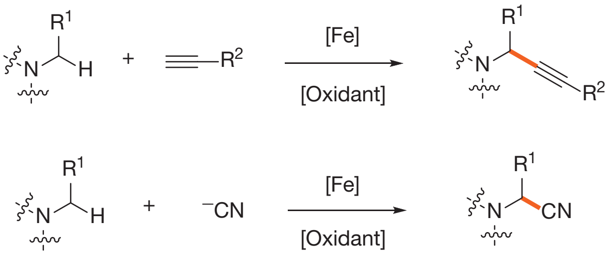
Fe-catalyzed oxidative coupling reactions in constructing C_{sp}—C_{sp^3} structures are generally the coupling between terminal alkynes or cyanides with sp^3 carbon adjacent to nitrogen atom (Scheme 3). The product propargylic amines are also key synthetic intermediates in the preparation of a large variety of biologically active compounds.[36]

In 2009, Vogel et al. reported the first iron-catalyzed chemoselective oxidative coupling between tertiary amines with terminal alkynes to achieve propargylic amines. They found that $FeCl_2$ (10 mol.%) gave the best yield by using $(t\text{-BuO})_2$ (2 equiv.) as the oxidant in a solvent-free condition.[37] Under the optimized condition, various aryl substituted *N*,*N*-dimethylanilines or even tertiary amines could be coupled with arylacetylenes, heteroarylacetylenes and nonaromatic terminal alkynes to afford the corresponding products (Scheme 4).

By employing SBA-15 (a class of mesoporous molecular sieves with large surface area, big pore size, and high porosity) supported iron terpyridine complex (3 mol.%) as catalyst, Che et al. have developed a highly efficient oxidative C—C cross-coupling of tertiary amines with carbon nucleophiles including terminal alkynes, indoles and pyrroles.[38] In the presence of iron terpyridine complex and *tert*-butyl hydroperoxide (TBHP) under reflux for 12 h, both 1,2,3,4-tetrahydroisoquinolines and *N*,*N*-dimethylanilines could react with phenylacetylenes to give the coupling products in 56–72% yields (Scheme 5). In addition, the ligand could be recycled by filtration and reused for five times without apparent loss of catalytic activity.



Scheme 2 Examples of significant pharmaceuticals containing C_{sp}—C_{sp^3} structure.

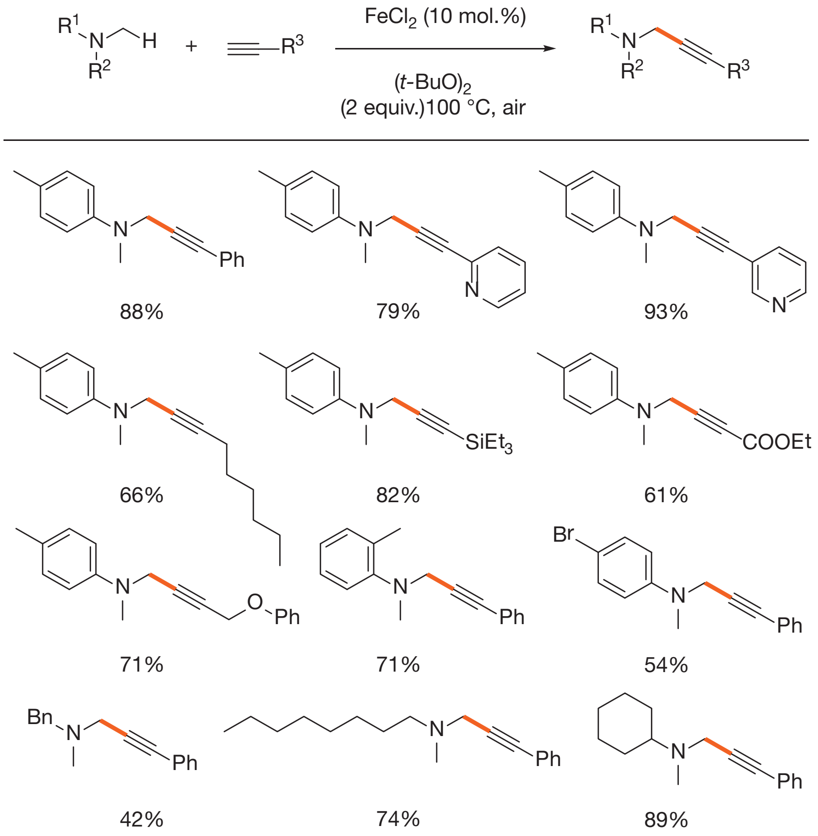


Scheme 3 Iron-catalyzed C_{sp}—C_{sp^3} oxidative coupling reactions.

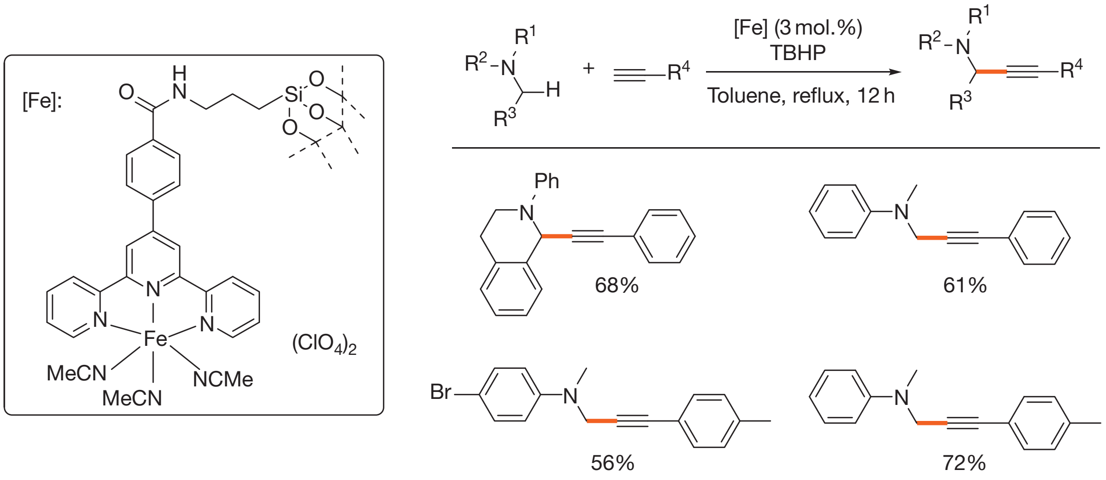
Metal-catalyzed oxidative α-cyanation of tertiary amines is another type of reaction for constructing C_{sp}—C_{sp^3} bond, which provides an access to the formation of α-aminonitriles. Miura et al. first described the iron(III) chloride-catalyzed oxidative coupling reaction between *N*,*N*-dimethylanilines and benzoyl cyanide in the presence of O_2 as oxidant to furnish α-cyanation compounds (Scheme 6).[39]

In 2009, Ofial et al. reported the selective $FeCl_2$-catalyzed oxidative reaction of tertiary amines and trimethylsilyl cyanide (TMSCN) in the presence of TBHP as the oxidant under room temperature and acid-free conditions.[40] Compared with the previous Ru and V catalyst and the highly toxic hydrocyanic acid or cyanide ion source, this system is much less toxic and is inexpensive. By using this protocol, various ring-substituted *N*,*N*-dimethylanilines reacted smoothly with TMSCN and afforded the corresponding products in good yields. 2-Aryl-1,2,3,4-tetrahydro-isoquinolines and *N*-phenyl-substituted cyclic amines could also undergo oxidative α-cyanation in good yield under the reaction conditions. With a higher excess of TMSCN, double α-cyanation of *N*-phenyl-pyrrolidine was obtained. The substrate scope is listed in Scheme 7.

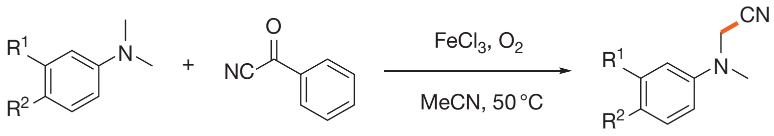
In 2010, Jain et al. developed the first heterogeneously Fe-catalyzed oxidative cyanation of various tertiary amines in good yields and selectivities by using hydrogen peroxide as the oxidant in the presence of sodium cyanide in MeOH at room temperature.[41] They employed a polymer-supported Fe(II) phthalocyanine (2 mol.%) as the catalyst which could be facilely recovered from the reaction mixture without significant loss in catalytic activity and/or leaching. *N*,*N*-dimethylanilines bearing both electron-donating and electron-withdrawing groups could react smoothly and afford the corresponding products. Similarly, cyclic amines such as piperidine, pyrrolidine and tetrahydroisoquinoline derivatives also proceeded well and gave the desired products in good yields (Scheme 8).



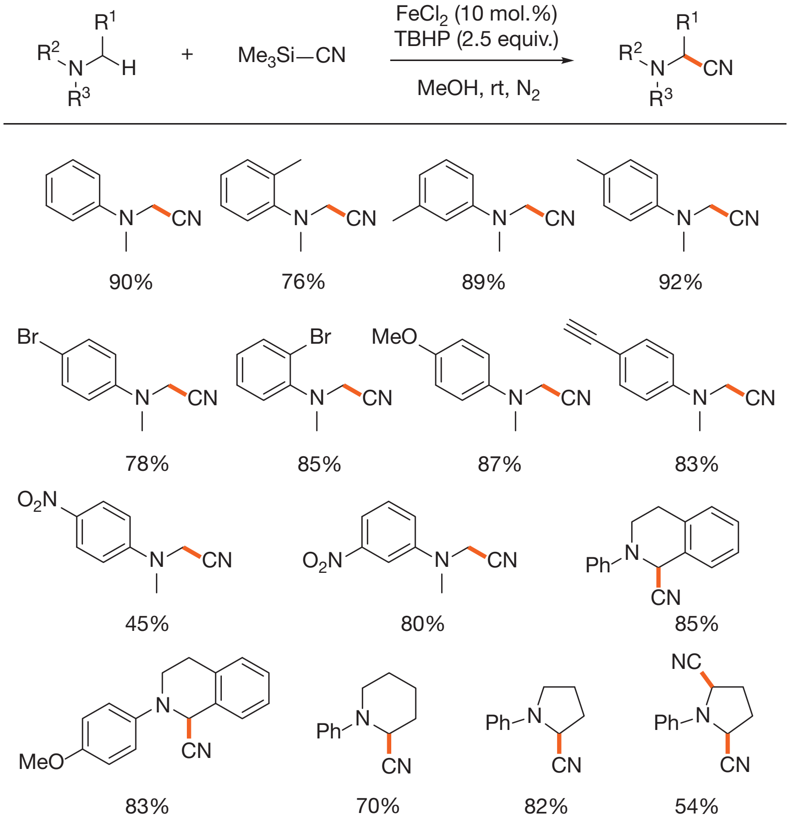
Scheme 4 Ligand and solvent-free iron-catalyzed oxidative coupling of tertiary amines with terminal alkynes.



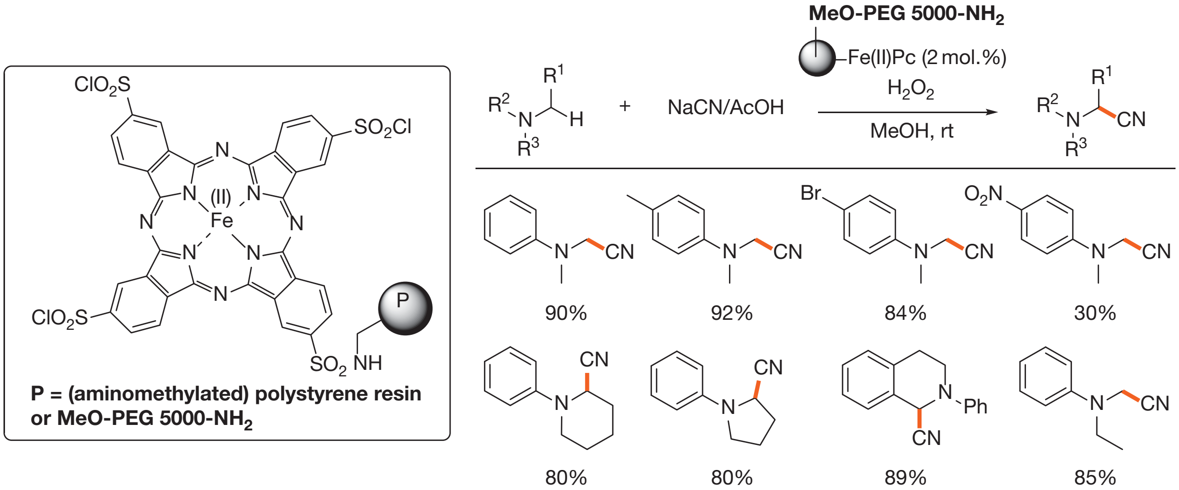
Scheme 5 SBA-15-support iron terpyridine complex catalyzed oxidative coupling of tertiary amines with terminal alkynes.



Scheme 6 $FeCl_3$-catalyzed oxidative coupling between *N*,*N*-dimethylanilines and benzoyl cyanide.



Scheme 7 FeCl$_2$-catalyzed oxidative cyanation of tertiary amines by using TMSCN.



Scheme 8 Polymer-supported iron(II) phthalocyanines catalyzed oxidative cyanation of tertiary amines with sodium cyanide.

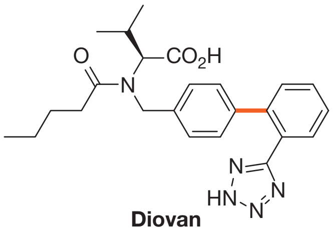
6.17.5 C_{sp^2}—C_{sp^2} Oxidative Coupling Reactions

6.17.5.1 Oxidative Couplings between Arenes

The biaryl structural motif is significant building block in many pharmaceutically relevant and biologically active compounds.[42] Diovan, for example, which is an angiotensin II receptor blocker used to treat hypertension and heart failure, has a total sale of 1.28 billion dollars in 2008 (Scheme 9). As a result, in the past several decades, organic chemists have sought to develop new efficient C_{sp^2}—C_{sp^2} bond formation methods. Till now, transition-metal-catalyzed reactions for the construction of aryl–aryl bonds are still the most widely applied methods.[42,43]

6.17.5.1.1 Oxidative couplings of phenol and naphthol derivatives

The oxidative dimerization of phenol and naphthol derivatives is a well-established method, which can be promoted stoichiometrically by iron salts. Generally, this type of oxidative

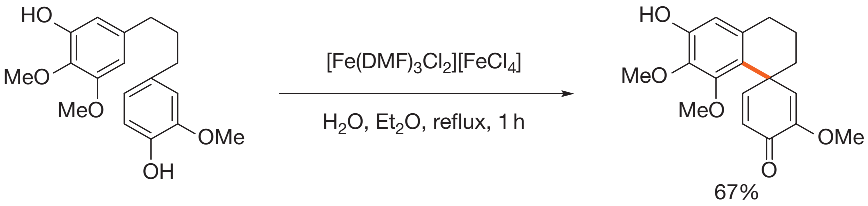


Scheme 9 Example of significant pharmaceutical containing biaryl structure.

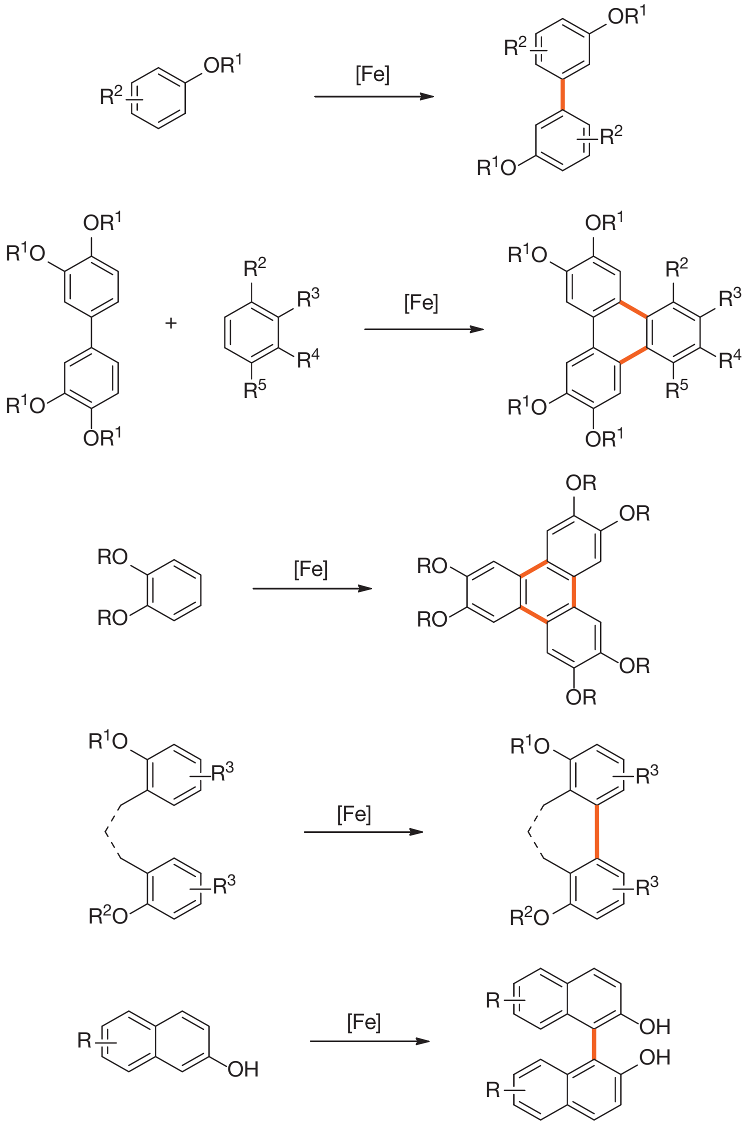
couplings belong to the large class of 'Scholl reactions,' which were discovered in 1910s.[44]

In 1972, Tobinaga et al. described the oxidative phenol coupling by using an iron complex $[Fe(DMF)_3C1_2][FeC1_4]$ (**Scheme 10**).[45] In this system, iron salts played a role more like the oxidizing agents for the oxidation of phenol compounds.

After that, many studies for the iron-promoted direct oxidative coupling of phenol and naphthol derivatives have been reported and summarized in **Scheme 11**.[46–67] In



Scheme 10 Iron-mediated oxidative phenol coupling.



Scheme 11 Summary of the iron-promoted direct oxidative coupling between phenol and naphthol derivatives.

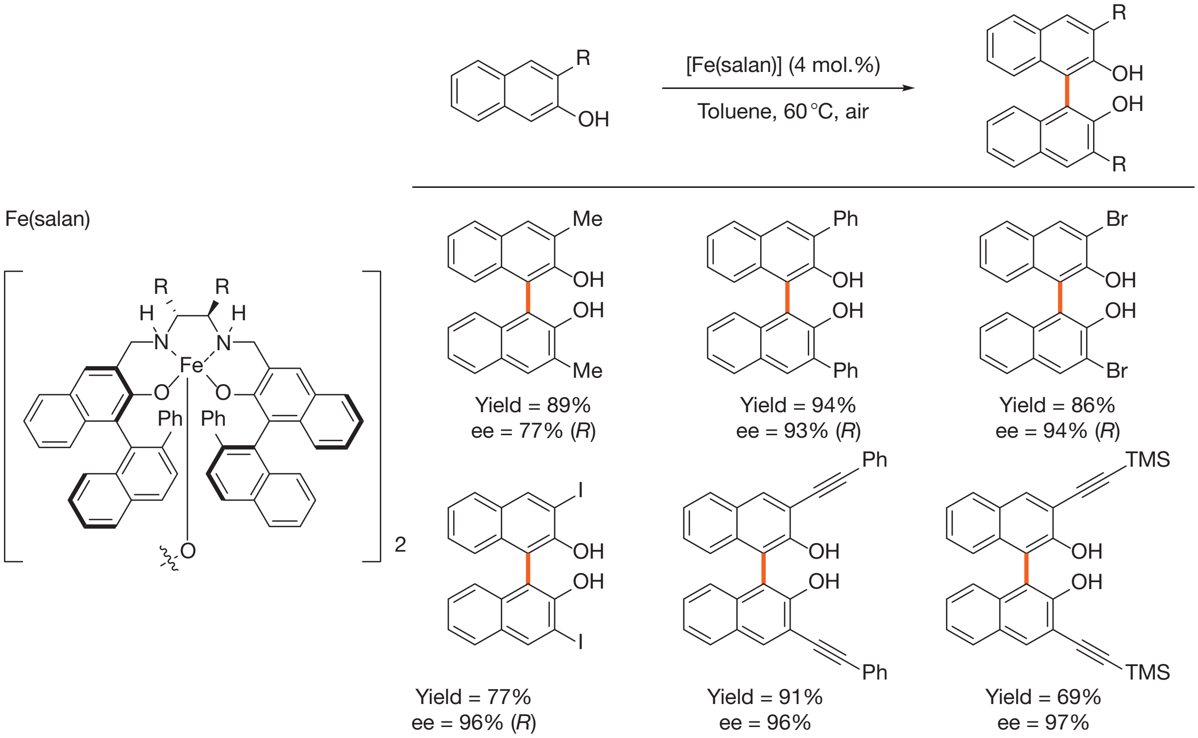
addition, this part has been reviewed by Bolm and co-authors in details.[19]

Iron-mediated oxidative coupling of naphthols is a significant tool for the synthesis of 1,1′-bi-2,2′-naphthol (BINOL), which is one of the best known representatives of axially chiral molecules and has been used as chiral ligands in a variety of transition metal-catalyzed reactions.[68–70] Very recently, Katsuki et al. developed the first asymmetric aerobic oxidative coupling of 2-naphthol derivatives by using Fe(salan) complexes (4 mol.%).[71] Corresponding chiral 3,3′-disubstituted binaphthols could be provided via this efficient and eco-friendly method. Moreover, the bulkier substituent at the C3 of naphthols, the higher enantioselectivities the reactions furnished (**Scheme 12**).

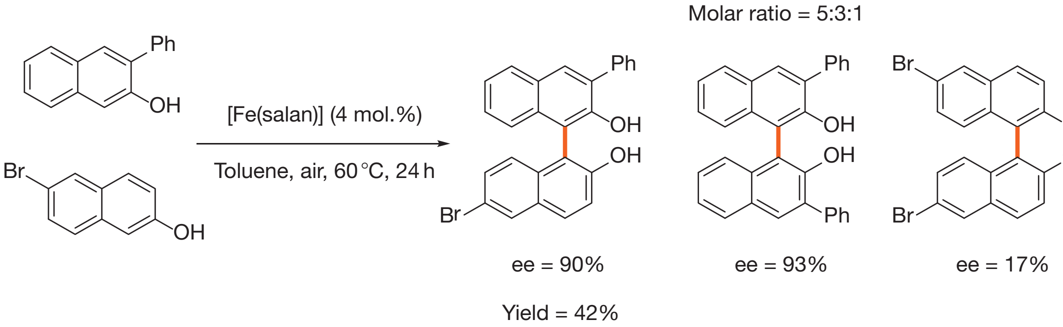
On the basis of the iron(salan) complex-catalyzed asymmetric oxidative homo-coupling, Katsuki et al. further investigated the asymmetric oxidative cross-coupling reaction between two different 2-naphthols, which could afford C1-symmetric BINOLs.[72] Based on the mechanism studies, they finally found that a combination of a 2-naphthol bearing a substituent at C3 and a less electron-rich 2-naphthol either with or without a substituent at C3 would undergo highly enantioselective cross-coupling in the presence of the iron(salan) complex (**Scheme 13**). This novel iron-catalyzed asymmetric oxidative coupling procedure not only has great potential in organic synthesis, but also gives an important clue for asymmetric oxidative coupling reactions.

6.17.5.1.2 Direct oxidative couplings with aryl metal nucleophiles

During the investigations of iron-catalyzed cross-coupling reaction between aryl Grignard reagents and alkyl halides, Hayashi et al. found the homo-coupling byproducts from arylmagnesium reagents, where iron served as the catalyst and alkyl halides acted as the oxidants. Inspired by this result, they developed the first iron-catalyzed (5 mol.% $FeCl_3$) oxidative homo-coupling of



Scheme 12 Fe(salan) complex catalyzed asymmetric aerobic oxidative coupling of 2-naphthol derivatives.



Scheme 13 Fe(salan) complex catalyzed asymmetric oxidative cross-coupling between two different 2-naphthols.

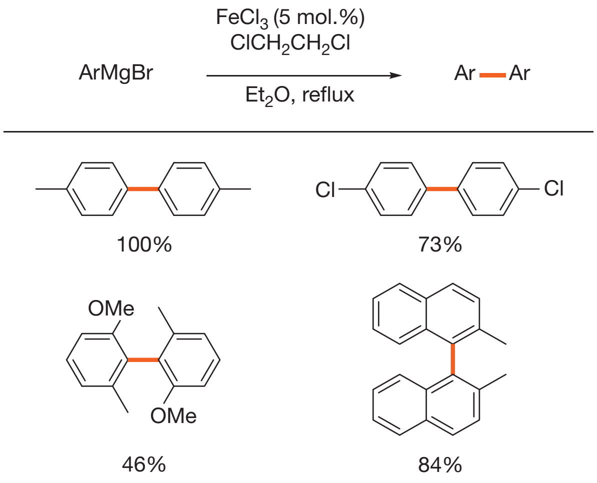
Grignard reagents by using 1,2-dichloroethane as the oxidant.[73] Notably, this system was tolerant of aryl chloride functionality (Scheme 14).

A putative reaction pathway for the iron-catalyzed homo-coupling is listed in Scheme 15. A low-valent active iron species **I** was generated by the reaction of $FeCl_3$ with Grignard reagent, the following oxidative addition of 1,2-dichloroethane to complex **I** forms an alkyl iron intermediate **II**. β-Halogen elimination gave ethylene and dihaloiron species **III**. Transmetalation of the aryl group to iron afforded a diaryliron intermediate **IV**. Then reductive elimination afforded the biaryl product and regenerates catalytically active species **I**.

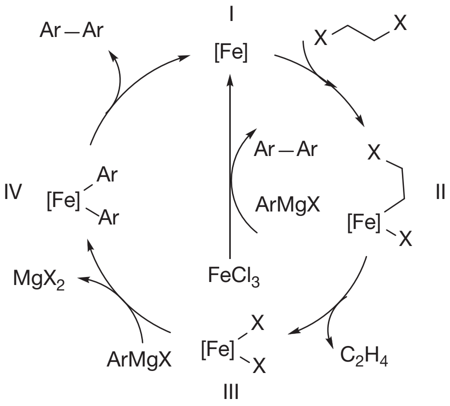
Almost at the same time, Cahiez et al. also reported $FeCl_3$-catalyzed oxidative homo-coupling of simple and functionalized arylmagnesium reagents by using 1,2-dihalogenoethane as the oxidant.[74] Different from Hayashi's work, they employed tetrahydrofuran (THF) as the solvent that the reaction underwent smoothly at room temperature or even at −40 °C. Thus, a variety of functionalized aryl and heteroarylmagnesium reagents could be successfully coupled under the conditions. Intramolecular oxidative coupling reactions could also be achieved via this protocol. For the more hindered substrates, 1,2-dibromoethane or 1,2-diiodoethane were more effective than 1,2-dichloroethane (Scheme 16).

As a natural consequence of the study, Cahiez et al. achieved the same oxidative homo-coupling of Grignard reagents by using atmospheric oxygen as the oxidant.[75] The experiments were carried out by bubbling dry air into a solution of Grignard reagents in the presence of $FeCl_3$ (5 mol.%), and then the corresponding biaryl products were provided in good yields (Scheme 17).

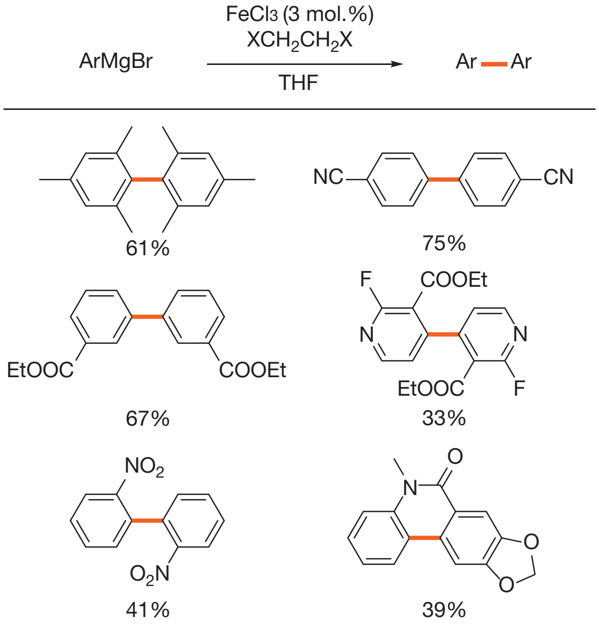
Obviously, molecular oxygen should be the best choice of green and environment-friendly oxidant for the oxidative homo-coupling reactions and other oxidation processes. Lei et al. have also developed an efficient and practical iron-catalyzed oxidative homo-coupling of aryl Grignard reagents directly by using molecular oxygen as the oxidant.[76] Moderate to good yields of the corresponding biaryl compounds were afforded at room temperature in 10 min by using $FeCl_3$/Bipy



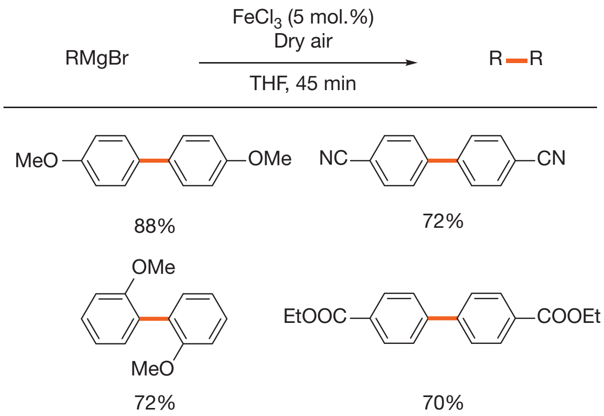
Scheme 14 $FeCl_3$-catalyzed oxidative homo-coupling of Grignard reagents.



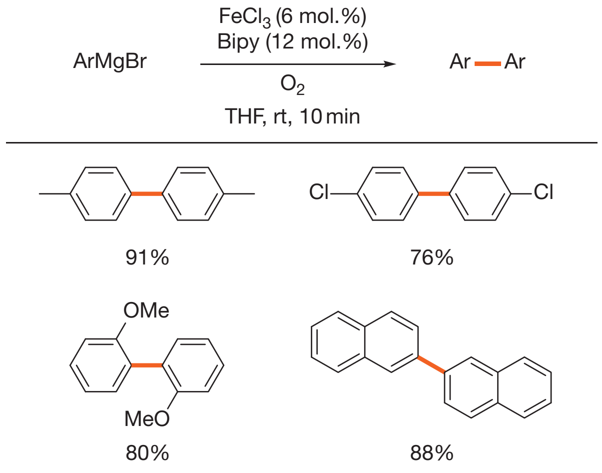
Scheme 15 Proposed mechanism for the iron-catalyzed homo-coupling of Grignard reagents.



Scheme 16 Iron-catalyzed homo-coupling of simple and functionalized arylmagnesium reagents.



Scheme 17 Iron-catalyzed homo-coupling of Grignard reagents using oxygen as the oxidant.



Scheme 18 Efficient iron-catalyzed homo-coupling of aryl Grignard reagents using O_2 as the oxidant.

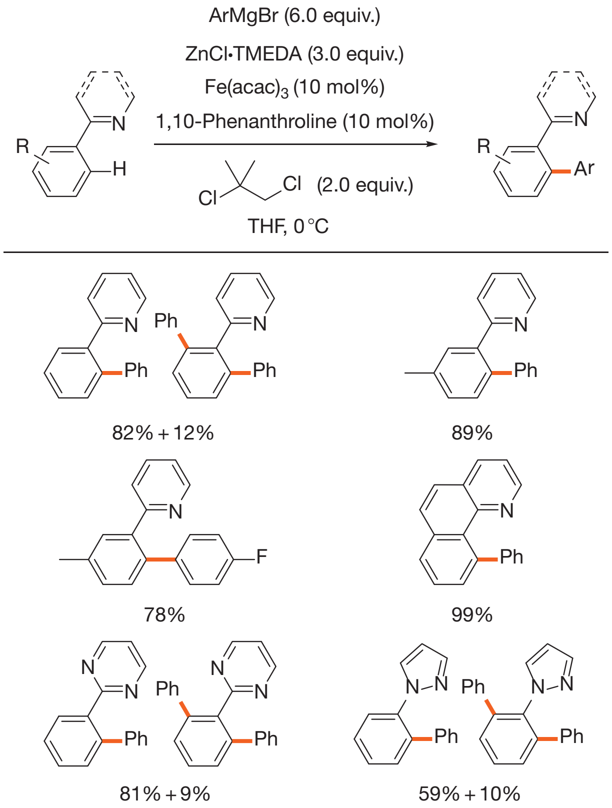
catalytic system (Scheme 18). Moreover, the reaction proceeded smoothly by using dry air as the oxidant directly at room temperature in 2 h, which provided an efficient approach for the synthesis of symmetrical biaryls.

Recently, Nakamura et al. developed a series of iron-catalyzed oxidative coupling between 2-arylpyridine derivatives or aryl imines with arylzinc reagent via C—H bond activation.[18,77–79] The nitrogen heterocycles and imino groups served as the directing groups for the iron-catalyzed C—H activation. In the presence of $Fe(acac)_3$ (10 mol.%), 1,10-phenanthroline (10 mol.%) and 1,2-dichloro-2-methylpropane (2.0 equiv.), 2-arylpyridine derivatives reacted smoothly with diarylzinc reagents (prepared from 1 equiv. of $ZnCl_2$·TMEDA and 2 equiv. of ArMgBr) via C—H activation at 0 °C.[77] Meanwhile, this protocol required a large excess of the arylzinc reagents due to their homo-coupling and oxidation. The intricate reaction conditions were quite critical for the successful arylation. The substrate scope is listed in Scheme 19.

As a similar design, ketimines were also used as directing groups for the direct displacement of the *ortho*-C—H bond of imine by the aryl group of the arylzinc nucleophiles.[78] $Fe(acac)_3$ (10 mol.%) and dtbpy (10 mol.%) catalytic system was found to be a good combination in the oxidative coupling of diarylzinc reagents and acetophenone-derived imines via C—H activation using 1,2-dichloro-2-methylpropane as the oxidant. It is noteworthy that C—Br, C—Cl, C—OTf, and C—OTs were well tolerated as functional groups which would not undergo the traditional cross-coupling reactions (Scheme 20).[78]

Later, these reactions were achieved under oxygen atmosphere.[79] By slowly employing oxygen into the system, oxidative cross-coupling of the two reactants took place smoothly to give the corresponding products in moderate to good yields.

Besides aryl Grignard reagents and arylzinc reagents, arylboron reagents can be also used as the nucleophiles in oxidative coupling reaction. Yu et al. have reported a novel stoichimetric iron-promoted direct oxidative arylation of unactivated arenes with arylboronic acids.[80] Mediated by $Fe_2(SO_4)_3·7H_2O$/cyclen/K_3PO_4/pyrazole system under air, the reactions of several simple unactivated arenes with substituted arylboronic acids afforded the desired products in good yields. Compared with



Scheme 19 Iron-catalyzed oxidative coupling between 2-arylpyridine derivatives with diarylzinc reagents.

the previous work, the reagents used here were easy to handle and of low toxicity (Scheme 21).

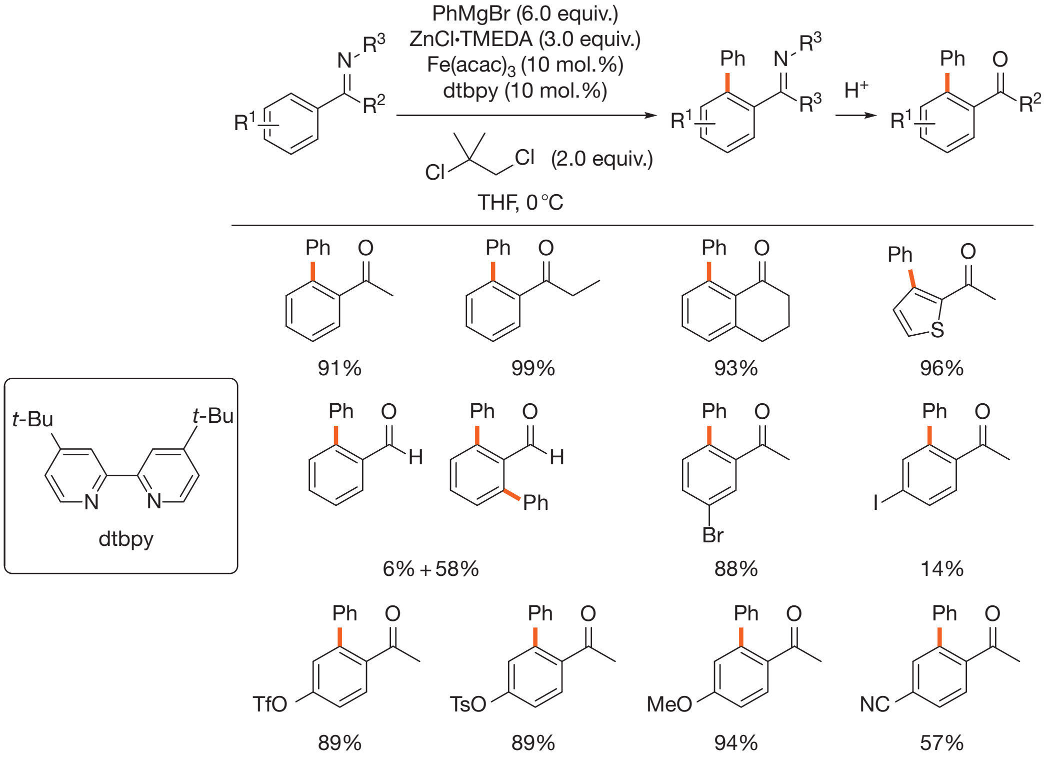
6.17.5.1.3 Oxidative couplings of heteroarenes

Due to the interesting electronic and optical properties of the heteroarenes motifs, many studies have focused on the direct oxidative couplings between heteroarenes especially thiophenes, or hetero-substituted arenes to construct polymers with defined structures and functions (Scheme 22).[81–88] These polyheteroarenes are an important class of conjugated polymers and oligomers that have been widely used as electronic and optical devices.[89] In these oxidative coupling reactions, iron played a key role as a very efficient and practical catalyst or oxidant.

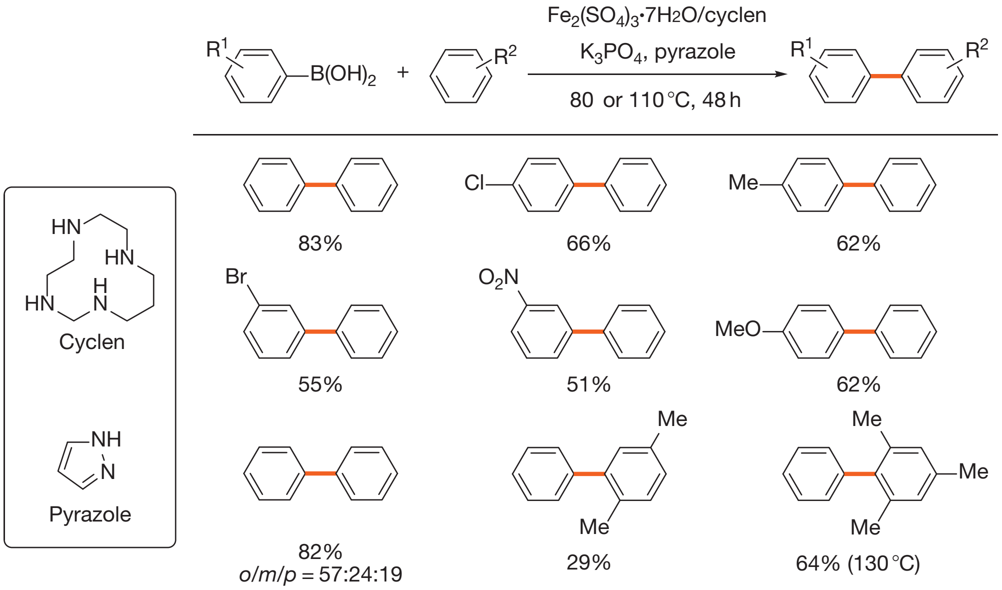
As early as 1984, Sugimoto et al. have described the synthesis of polythiophenes by treating thiophenes with $FeCl_3$.[90] After that, $FeCl_3$-mediated oxidative coupling reactions were widely used in the synthesis of various polythiophenes although excess $FeCl_3$ has to be employed to drive the reactions.[91–94] Some examples are listed in Scheme 23.

Recently, Daugulis et al. reported a series of first-row transition-metal salts-catalyzed oxidative homo-coupling of acidic arenes under the atmosphere of oxygen.[95] $FeCl_3$ (10 mol.%) was also effective for the dimerization of five- and six-membered ring heterocycles as well as electron-poor arenes in the presence of tetramethylpiperidide bases (Scheme 24).

As a consequent study of iron-catalyzed oxidative coupling reactions by using arylboronic acids as nucleophiles, Yu et al. have described the first iron-mediated direct oxidative reaction



Scheme 20 Iron-catalyzed oxidative coupling between aryl imines with diarylzinc reagents.



Scheme 21 Iron-mediated direct oxidative arylation of unactivated arenes with arylboronic acids.

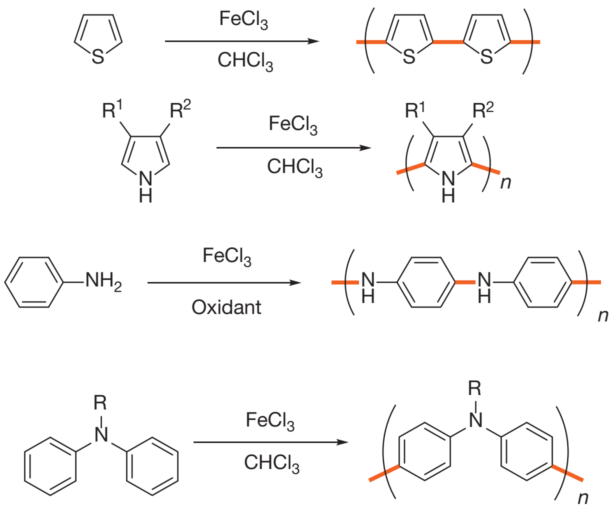
between N-heterocyclic compounds and arylboronic acids.[96] Iron-MCPA (macrocyclic polyamine ligands) complex catalytic system was found to be a good combination in this oxidative coupling for both pyrroles and pyridines. Under the optimized conditions, both electron-rich and electron-deficient heteroarenes could successfully react and give the coupling products (Scheme 25).

Based on the preliminary mechanistic studies and density functional theory (DFT) calculations, a full catalytic cycle of the iron-catalyzed direct oxidative coupling has been proposed. The active oxoiron species **B** formed first via oxidation of iron complex **A**, followed by an electrophilic attack on C-2 position of heteroarenes with the assistance of a heteroatom. After subsequent deprotonation, intermediate **C** turned into **D**.

In the presence of arylboronic acid, transmetalation and elimination would afford the desired product (Scheme 26).

6.17.5.1.4 Synthesis of polycyclic aromatic hydrocarbons

The iron-promoted oxidative coupling protocol could also be used in the synthesis of polycyclic aromatic hydrocarbons which has more and more attracted considerable attention due to their particular electronic and self-assembling properties.[97–99] Typical example of these materials was hexa-peri-hexabenzocoronene derivatives (Scheme 27). Recently, this section has been reviewed in details.[19,97–99] Thus, it will not be discussed in this chapter.



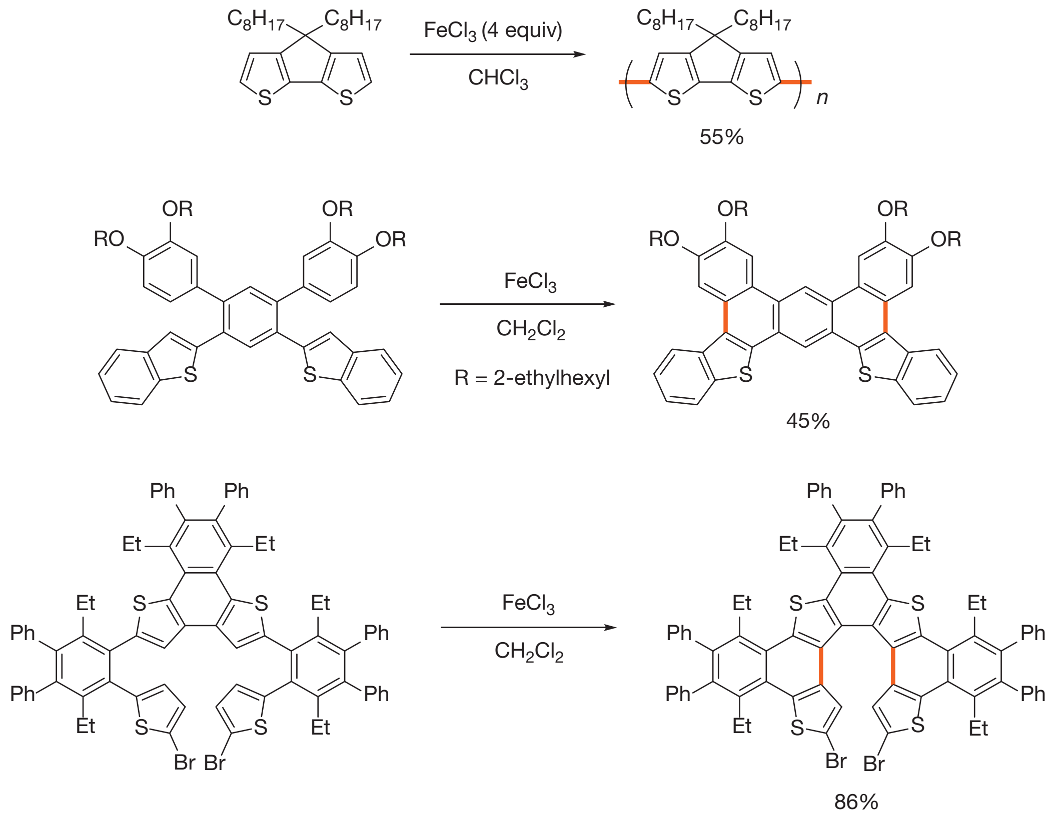
Scheme 22 Direct oxidative couplings between heteroarenes to construct polymers.

6.17.5.2 Couplings between Arenes/Alkenes and Alkenes

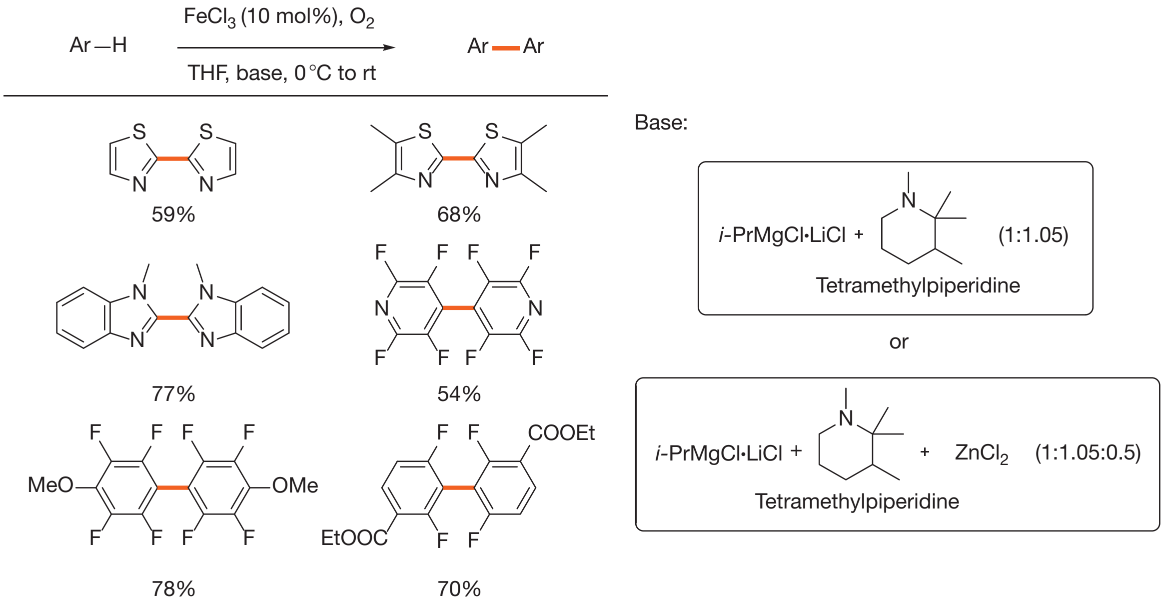
Iron-catalyzed C_{sp^2}—C_{sp^2} oxidative coupling reactions between arenes are widely developed. However, few studies on the oxidative coupling between arenes/alkenes and alkenes by iron catalyst have been reported. As mentioned in the $FeCl_3$-catalyzed homo-coupling of Grignard reagents, Cahiez et al. also employed alkenyl Grignard reagents to construct the alkene–alkene bonds.[75] The corresponding conjugated dienes were obtained in moderate yields (Scheme 28).

In order to explore some cheap and environmentally friendly catalysts for preparation indole and its derivatives, Liang et al. have described an efficient iron-catalyzed intramolecular oxidative coupling of aryl C—H and vinyl C—H bonds.[100] $FeCl_3$ (10 mol.%)/$Cu(OAc)_2 \cdot CuCl_2/K_2CO_3$ catalytic system afforded the best results in DMF at 120 °C. Under the optimized conditions, various valuable substituted indole products could be provided. Notably, Br- and I-functional groups could also be tolerated in this iron-catalyzed oxidative cyclization (Scheme 29).

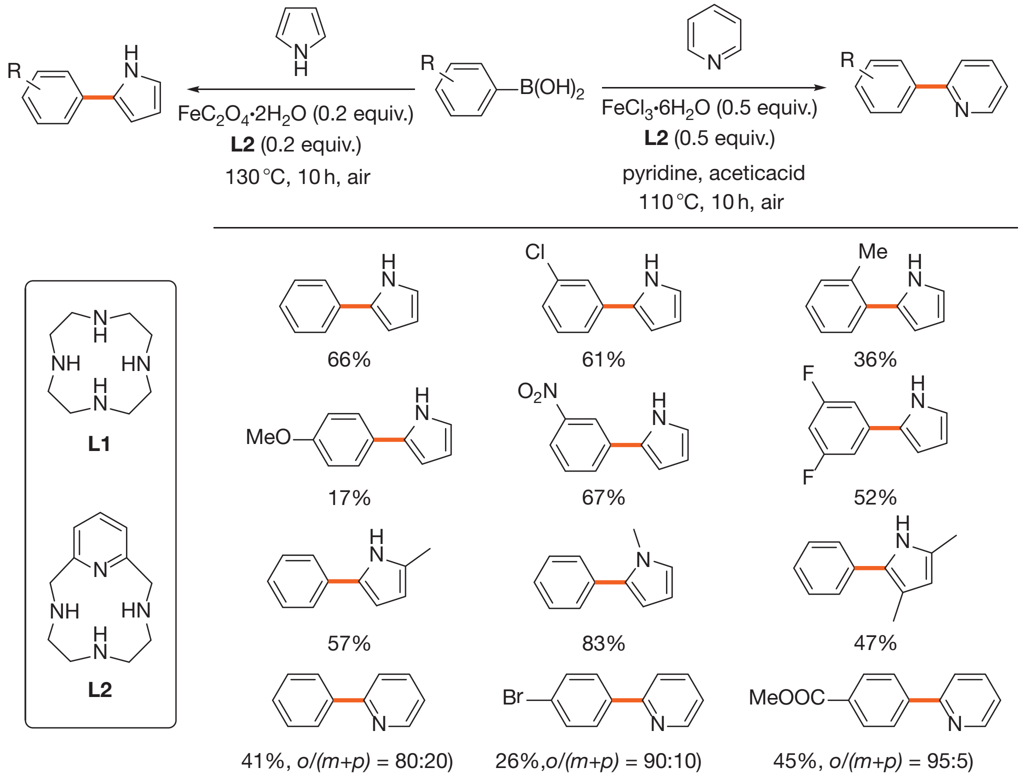
As a sequential work, Nakamura et al. reported an iron-catalyzed chelation-controlled oxidative arylation of olefins with organozinc or Grignard reagents in 2010.[101]



Scheme 23 Synthesis of polythiophenes by the $FeCl_3$-mediated oxidative coupling reactions.



Scheme 24 $FeCl_3$-catalyzed oxidative homo-coupling of acidic arenes under the atmosphere of oxygen.



Scheme 25 Iron-mediated direct oxidative coupling between *N*-heterocyclic compounds and arylboronic acids.

In the presence of $Fe(acac)_3$ and 1-bromo-2-chloroethane, 2-pyridyldimethylvinylsilane reacted with diarylzinc reagents to furnish the corresponding products in moderate yield. The pyridine directing group played a crucial role in this process. This is the first application of iron catalysis for an oxidative Heck-type reaction, which afforded a variety of olefin derivatives in good yield and with good control of regio- and stereoselectivity (Scheme 30).

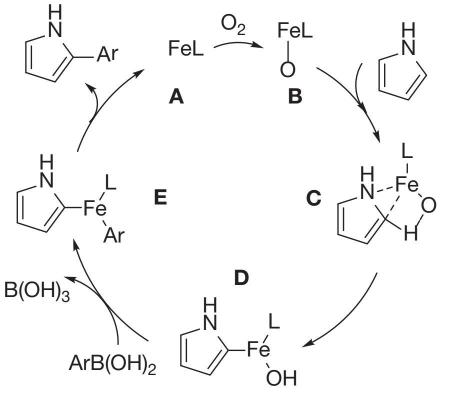
6.17.6 C_{sp^2}—C_{sp^3} Oxidative Coupling Reactions

The formations of C_{sp^2}—C_{sp^3} bonds are the basis and key steps for constructing advanced organic compounds because the aryl (or alkenyl, heteroaryl)-alkyl structures widely exist in organic compounds including medicine molecules, agrochemicals, and organic functional materials. Here are three medicine molecules with quite similar structures as we mentioned in this section. Plavix, a platelet aggregation inhibitor used to reduce stroke and heart attack risk with a total sale of 3.80 billion dollars in 2008; Lexapro, a selective serotonin reuptake inhibitor used to treat depression and anxiety with a total sale of 2.41 billion dollars in 2008; and Femara, an aromatase inhibitor used to treat breast cancer with a total sale of 0.36 billion dollars in 2008, all contain the C_{sp^2}—C_{sp^3} bond moiety (**Scheme 31**). It is noteworthy that arylation of C_{sp^3} adjacent to nitrogen usually achieved via transition-metal-catalyzed oxidative coupling reaction.

The iron-catalyzed oxidative coupling reaction between C_{sp^2}—C_{sp^3} has been reported by Baran et al. in the synthesis process of hapalindole and fischerindole.[102] However, this iron salts-mediated oxidative coupling of indoles and carvones was realized in a low yield (**Scheme 32**).

Guided by an unexpected byproduct which formed from the elimination of unsymmetrical alkyl–aryl zinc reagents in the presence of $Fe(acac)_3$ and 1,2-dibromoethane, Cahiez et al. realized an iron-catalyzed oxidative cross-coupling reaction between aryl- and alkylzinc reagents.[103] Primary or secondary aliphatic diorganozinc reagents were both applicable to this reaction under mild conditions. Ester and amide functional groups could also be tolerated in this reaction (**Scheme 33**).

Compared to the above reaction using two metal reagents as nucleophiles, several more atom-economic examples employed only one metal reagent and another hydrocarbon nucleophile were explored later.



Scheme 26 Proposed mechanism of the iron-mediated oxidative coupling between *N*-heterocyclic compounds and arylboronic acids.

Kumaraswamy et al. disclosed the first iron-catalyzed oxidative allylation to sp^2 carbon and sp^3 carbon attached to the nitrogen atom by using allyltributylstannanes.[104] When the three substrates were subjected to the reaction, allylation occurred at the *ortho*-position to amine of the aromatic ring in the presence of $FeCl_3 \cdot 6H_2O$ (10 mol.%) and T-HYDRO (70% *t*-BuOOH in H_2O) at room temperature (**Scheme 34**).

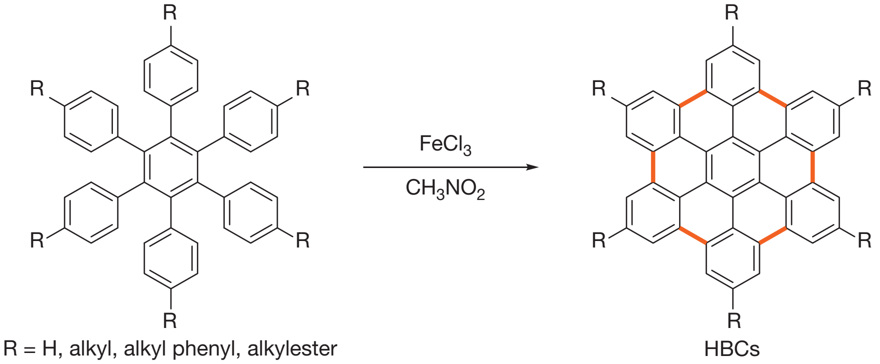
Inspired by an unexpected result, the reaction between Ph_2Zn and 4-iodotoluene producing 2-phenyltetrahydrofuran rather than biaryl products in THF in the presence of an iron catalyst, Nakamura et al. successfully developed an iron-catalyzed oxidative coupling of sp^3 C—H adjacent to the N atom bearing an *N*-(2-iodophenyl)methyl group with Grignard reagents.[105] Generally, the *N*-IBn (*N*-(2-iodobenzyl)) group in the molecule serves as an internal oxidant. Catalyzed by $Fe(acac)_3$, various aliphatic amines underwent this transformation smoothly (**Scheme 35**).

Transition-metal-catalyzed decarboxylative coupling reaction is another strategy for achieving carbon–carbon bond formation. Li et al. have reported an efficient and practical reaction system for the iron-catalyzed C_{sp^3}—C_{sp^2} decarboxylative coupling between prolines and naphthols.[106] Both α-naphthol and β-naphthol proceeded smoothly under the same conditions to afford the coupling products. The corresponding tertiary aminonaphthol products were an important class of ligands. Thus, this novel procedure would have great potential in synthesis of these ligands (**Scheme 36**).

The current requirements for clean, atom-economic, environmental protection and potential low-costing processes have increased the demand for constructing structures by only breaking C—H bonds to form new bonds under oxidative conditions. Such an oxidative coupling would eliminate the preparation of functional groups and thus make synthetic schemes shorter and more efficient, highly desirable features for the next generation of C—C bond formations.

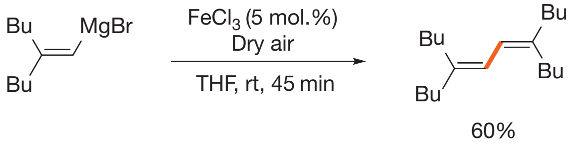
As mentioned in **Section 6.17.4**, Che et al. have reported a SBA-15-supported iron complex-catalyzed oxidative coupling between tertiary amines with carbon nucleophiles including indoles and pyrroles.[38] Under similar conditions, various indoles and pyrroles reacted smoothly with tertiary amines to give the corresponding products in good yields (**Scheme 37**).

Very recently, Hayashi and Shirakawa et al. have described iron-catalyzed oxidative coupling of alkylamides with arenes through tandem oxidation of alkylamides and Friedel–Crafts



Scheme 27 Iron-promoted oxidative coupling for the synthesis of polycyclic aromatic hydrocarbons.

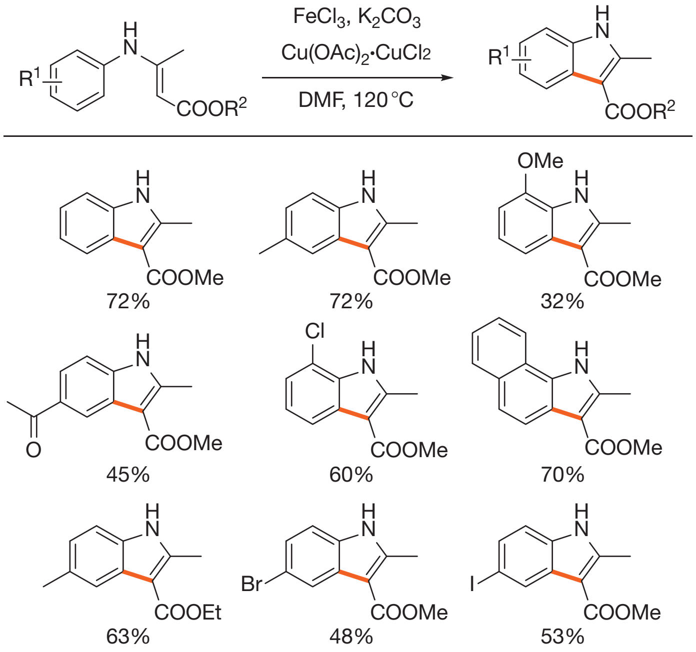
alkylation.[107] In this system, $FeCl_3$ exhibited a high catalytic activity for both oxidation and Friedel–Crafts alkylation. By using this dichotomous catalytic behavior of iron, a wide variety of alkylamides and arenes reacted smoothly to provide the desired products in good yields (**Scheme 38**).



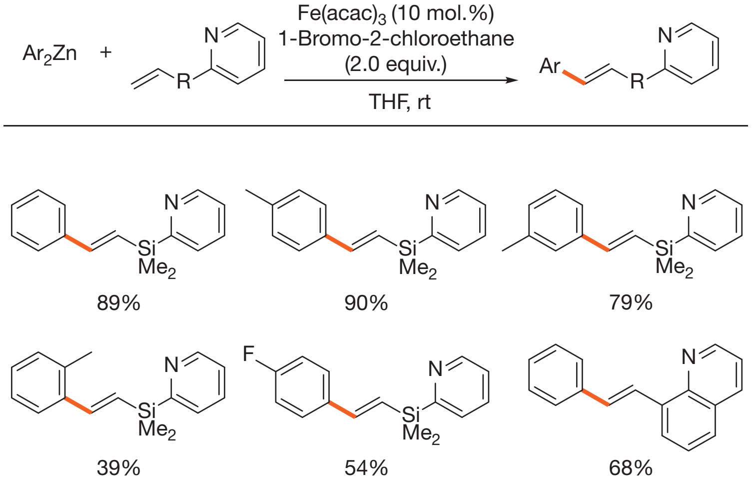
Scheme 28 $FeCl_3$-catalyzed homo-coupling of alkenyl Grignard reagents.

Shi et al. also demonstrated an efficient iron-catalyzed oxidative coupling reaction between a benzylic $C(sp^3)$—H bond and the $C(sp^2)$—H bond of an electron-rich arene.[108] In the presence of $FeCl_2$ as the catalyst and DDQ as the oxidant, two different types of C—H bonds were activated simultaneously. Under the optimized conditions, a variety of electron-rich aromatic substrates coupled with diarylmethanes in a high level of region-selectivity and gave good yields. The substrate scope is listed in **Scheme 39**.

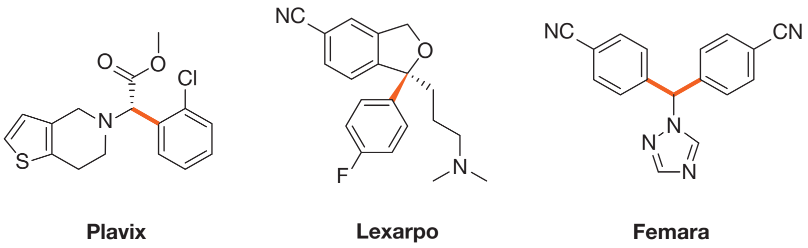
Li et al. developed a one-pot synthesis of various symmetric and unsymmetric 1,1-bis-indolylmethanes from indoles and ethers via tandem iron-catalyzed C—H bond oxidative coupling and C—O bond cleavage.[109] By using $FeCl_2$ (10 mol.%) and $(t\text{-BuO})_2$ catalytic system, a wide variety of



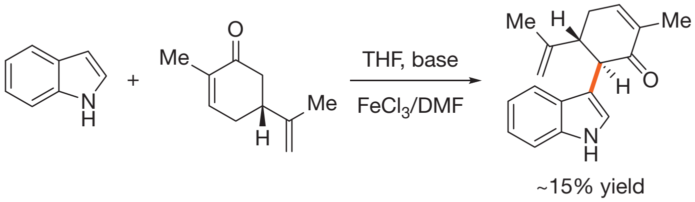
Scheme 29 Iron-catalyzed intramolecular oxidative coupling of aryl C—H and vinyl C—H bonds.



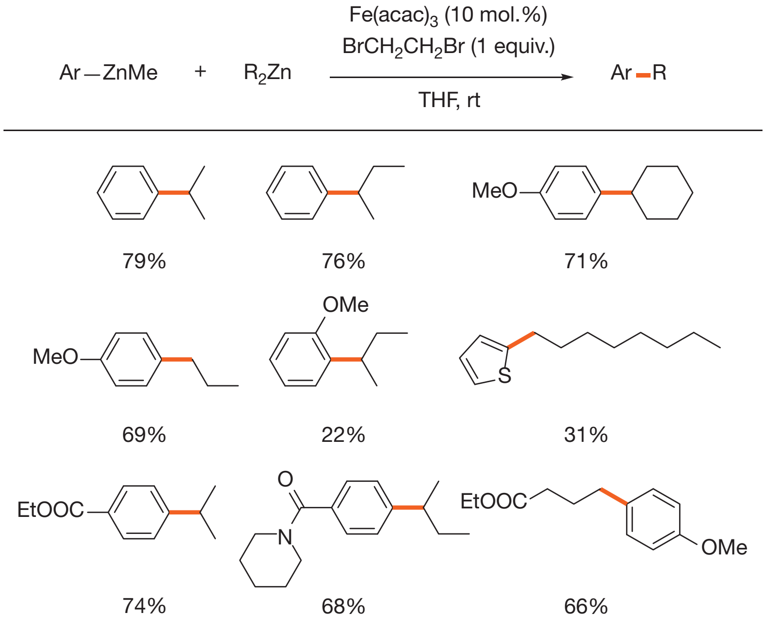
Scheme 30 Iron-catalyzed chelation-controlled oxidative arylation of olefins with organozinc or Grignard reagents.



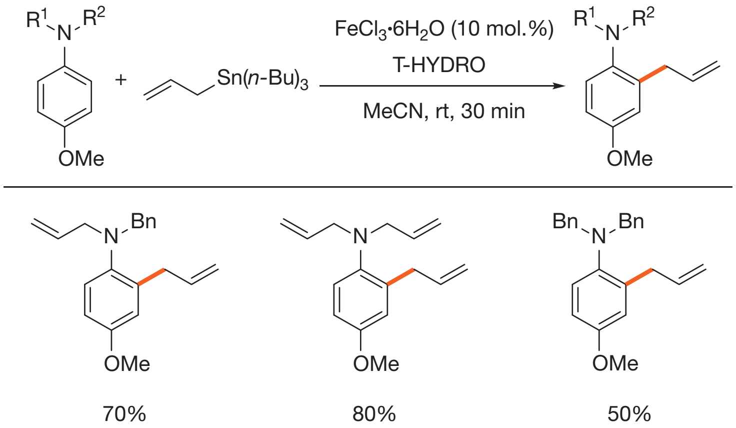
Scheme 31 Examples of significant pharmaceuticals containing aryl–alkyl structure.



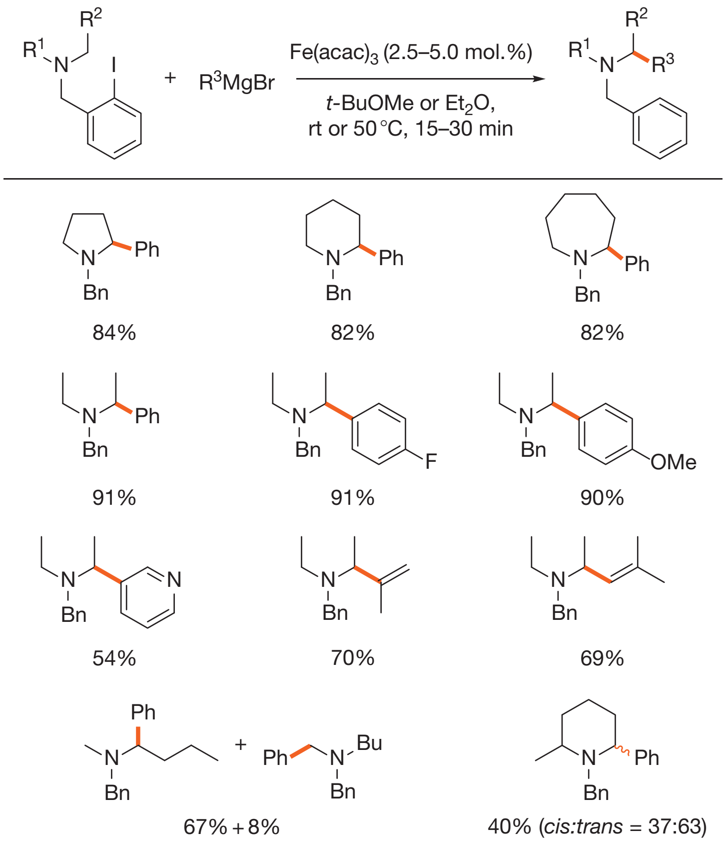
Scheme 32 Iron-mediated oxidative coupling of indoles and carvones.



Scheme 33 Iron-catalyzed oxidative cross-coupling between aryl- and alkylzinc reagents.



Scheme 34 Iron-catalyzed oxidative allylation to sp^2 C—H bond adjacent to a nitrogen atom.



Scheme 35 Iron-catalyzed oxidative coupling of sp^3 C—H adjacent to the N atom with Grignard reagents.

symmetric and unsymmetric 1,1-bis-indolylmethanes were provided in good yields (Scheme 40). This tandem process demonstrates the dichotomous catalytic behavior of the iron catalysts, which were transition metal catalyst in C—C bond oxidative coupling and Lewis acid in C—O bond cleavage.

By using the dichotomous catalytic behavior of iron (transition metal catalyst in the oxidative coupling step and Lewis acid in the condensation step), later Li et al. developed a novel and efficient method for the synthesis of multi-substituted benzofurans from simple phenols and β-keto esters by $FeCl_3 \cdot 6H_2O$ and di-*tert*-butyl peroxide catalytic system in 2009 (Scheme 41).[110] In this tandem oxidative coupling and annulation, water or various alcohols and protic acids played a crucial role to accelerate this process.

Two proposed pathways are listed in Scheme 42. In Path A, the iron-catalyzed oxidative coupling proceeds before the condensation step. In Path B, the oxidative coupling proceeds followed by the condensation step. The direct intermediate experiment might support Path A, for that the coupling intermediate could condensate into the desired benzofuran smoothly in the presence of iron catalyst.

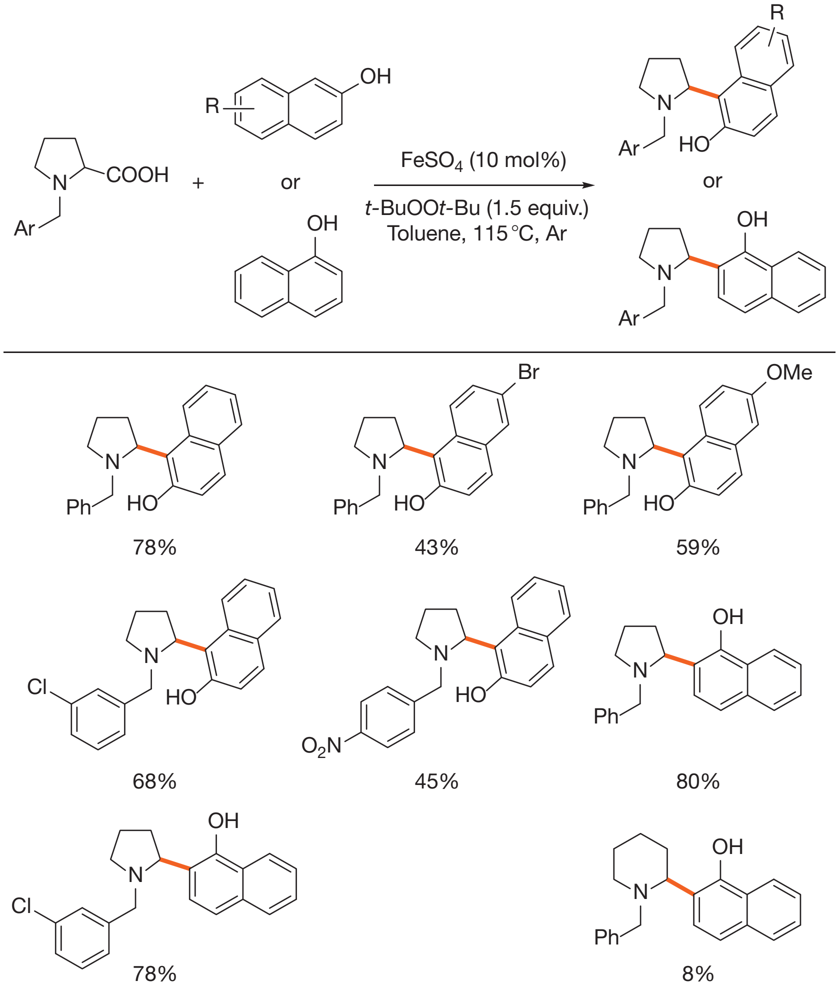
Heteroarenes and methylamines could also be cross-coupled via iron-catalyzed oxidative C—H/C—H coupling reaction. Itami et al. developed the $FeCl_2 \cdot 4H_2O$/KI/bipy/C_5H_5N–O catalytic system for the reaction between electron-rich heteroarenes and methylamines.[111] The sp^3 carbon adjacent to nitrogen atom was still important for this process. Under the optimized conditions, the coupling took place selectively at the α-position of the thiophene or furan rings. By using aqueous H_2O_2 solution (30%) instead of pyridine N-oxide at 80 °C, the reaction of indoles and methylamines afforded the corresponding products in moderate yields (Scheme 43).

6.17.7 C_{sp^3}—C_{sp^3} Oxidative Coupling Reactions

The C_{sp^3}—C_{sp^3} coupling reactions, either the traditional cross-coupling reactions or the oxidative coupling reactions, are always the most challenging work in constructing carbon–carbon bonds. In the recent years, many efforts have been put into this field for the transition-metal-catalyzed C_{sp^3}—C_{sp^3} oxidative coupling reactions. The CDC reactions named as cross-dehydrogenative couplings are typical examples of the oxidative coupling reactions.[112–114]

The oxidative coupling of the enolate anion has been examined with iron catalysts for several decades which served as an important synthetic tool in the C—C bond formation to construct 1,4-dicarbonyl compounds, although in most cases stoichiometric iron must be employed (Scheme 44).[115–118]

In 1980, Frazier et al. reported an efficient $FeCl_3$-mediated oxidative homo-coupling reaction of ketone enolates for the preparation of symmetric 1,4-diketones.[116] Stoichiometric $FeCl_3$ was used to promote the reaction of ketone enolates which were prepared with lithium diisopropylamide (LDA). $FeCl_3$ here might play roles of both a catalyst and an oxidant (Scheme 45).



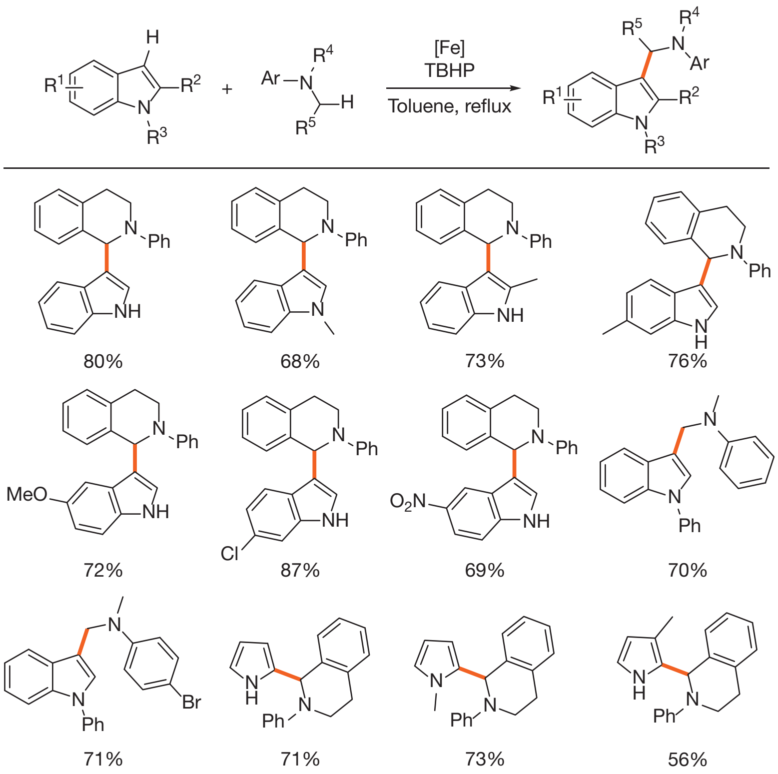
Scheme 36 Iron-catalyzed C_{sp^3}—C_{sp^2} decarboxylative oxidative coupling between prolines and naphthols.

Although the efficiency of this type iron-mediated C_{sp^3}—C_{sp^3} oxidative coupling reactions were relatively low, some good results involving this process to construct C—C bond as a key step in a total synthesis have been reported in recent years. Baran et al. demonstrated a stoichiometric iron salts mediated intramolecular oxidative coupling of carbonyl compounds, as well as the intermolecular heterocoupling of enolates which were successfully introduced into the total synthesis.[119–121] By using 2.2 equiv. $Fe(acac)_3$, the intramolecular oxidative cyclization product was obtained in 65% and 61% isolated yield as a single diastereomer.[119] This method was successfully used in the total synthesis of entstephacidin A (**Scheme 46**).

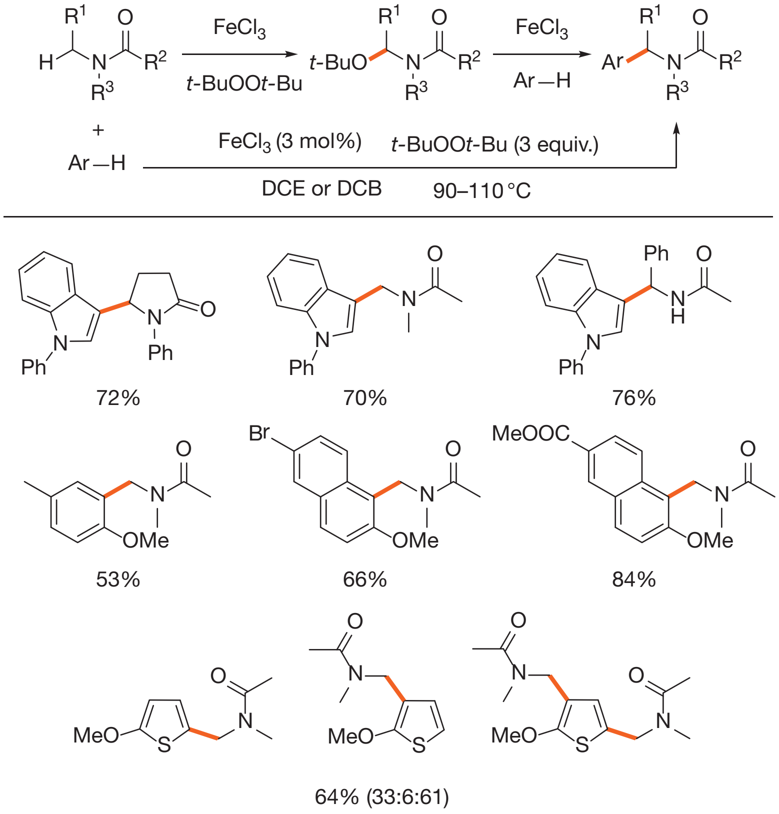
As mentioned in **Section 6.17.6**, Baran et al. have synthesized hapalindole-type products via direct oxidative coupling reactions. These natural hapalindole-type products have been isolated from soil samples in a myriad of habitats around the globe, and a broad range of biological activities arises from the different structural classes. Here is another example, by using acetylacetonate–iron complex, the C_{sp^3}—C_{sp^3} oxidative coupling between carvone and methoxymethyl (MOM)-protected oxindole could proceed efficiently, providing the desired product in good yield (**Scheme 47**).[121]

Guided by the intramolecular oxidative coupling reactions in the total synthesis, Baran et al. have developed the extensive oxidative intermolecular coupling of two different carbonyl species, which was also called intermolecular enolate heterocoupling.[120] The corresponding 2,3-disubstituted-1,4-dicarbonyl moiety is ubiquitous which is the common substructure of many natural products and medicinal compounds. It is extremely difficult to synthesize the unsymmetrical 2,3-disubstituted-1,4-dicarbonyl compounds from two carbonyl subunits because many possible side reactions, such as homo-dimerization, homo-Claisen condensation, cross-/homo-aldol condensation, overoxidation, dehydrogenation, and α-oxidation, would compete with the desired enolate heterocoupling. Based on the condition optimization, iron or copper salts could mediate this desired heterocoupling in good yield. The scope of the oxidative enolate heterocoupling is extensive and has been shown to be efficient even on a large scale (gram-scale or greater) (**Scheme 48**).

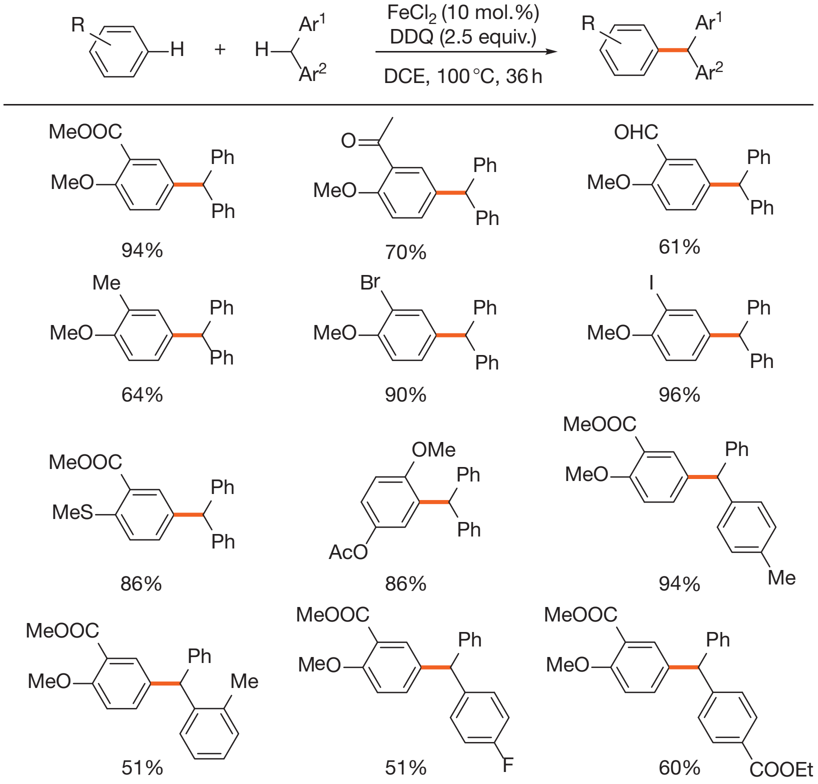
As mentioned in **Section 6.17.6**, Kumaraswamy et al. have disclosed the first iron-catalyzed oxidative allylation to sp^2 carbon and sp^3 carbon attached to the nitrogen atom by using allyltributylstannanes.[104] In the presence of $FeCl_3 \cdot 6H_2O$ (10 mol.%) and T-HYDRO (70% t-BuOOH in H_2O) in MeCN



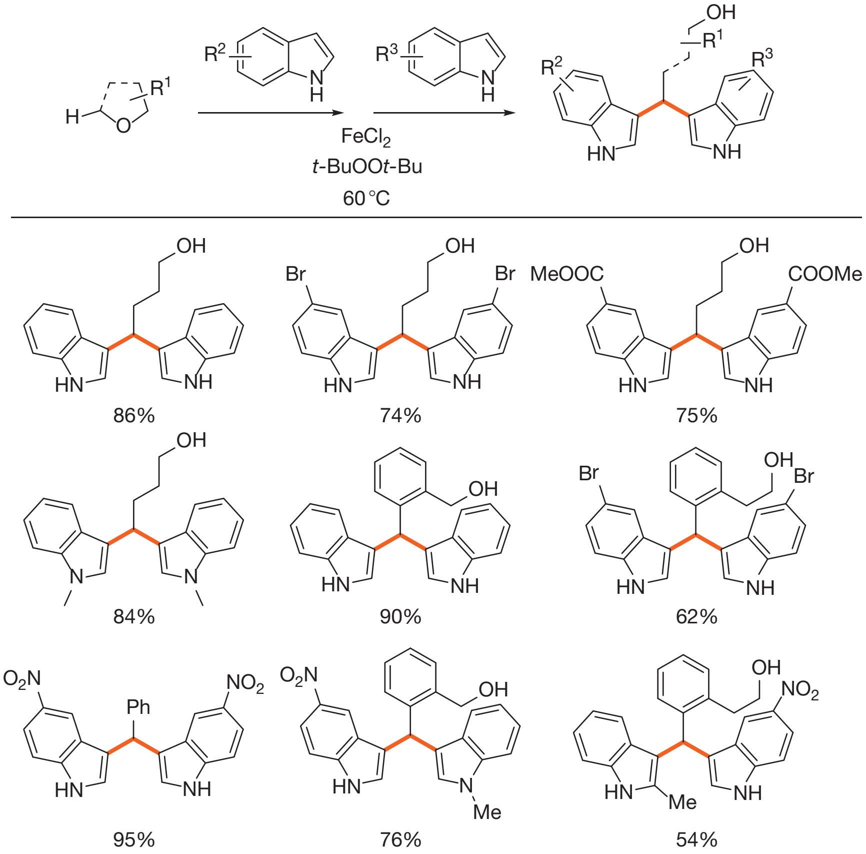
Scheme 37 SBA-15-support iron terpyridine complex catalyzed oxidative coupling of tertiary amines with indoles and pyrroles.



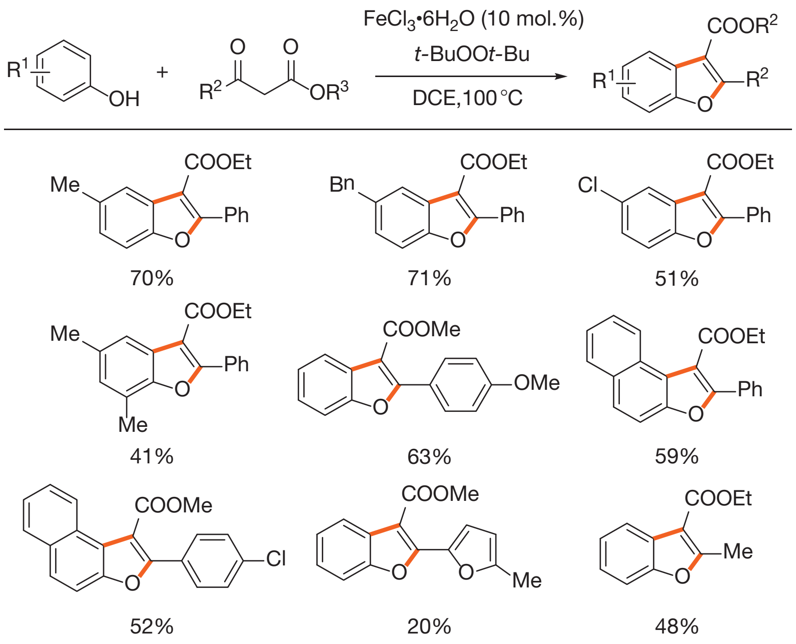
Scheme 38 Iron-catalyzed oxidative coupling of alkylamides with arenes through tandem oxidation of alkylamides and Friedel–Crafts alkylation.



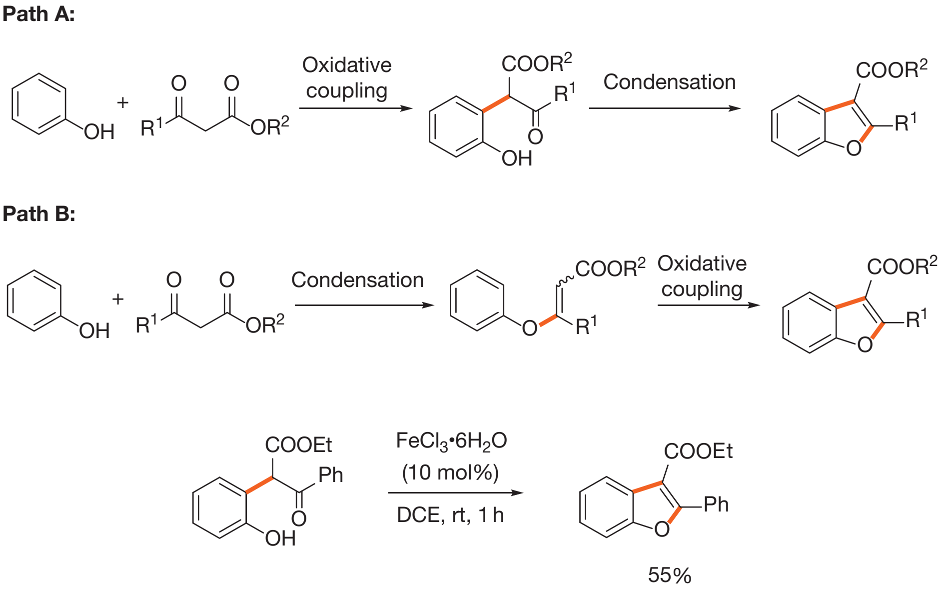
Scheme 39 Iron-catalyzed oxidative coupling between benzylic C—H bond and electron-rich arene C—H bond.



Scheme 40 Iron-catalyzed tandem C—H bond oxidative coupling between indoles with ethers and C—O bond cleavage.



Scheme 41 Iron-catalyzed tandem oxidative coupling and annulation between simple phenols and beta-keto esters.

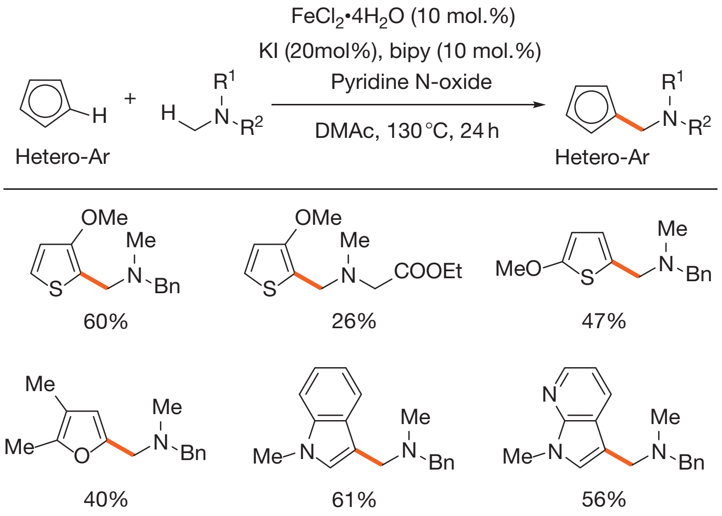


Scheme 42 Proposed pathways for the iron-catalyzed synthesis of benzofurans.

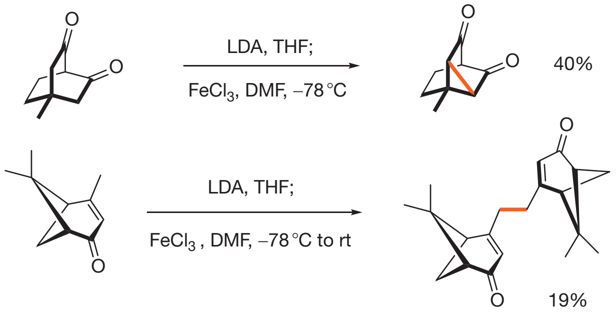
at room temperature, a wide range of tertiary amine substrates coupled with allyltributylstannanes provided the corresponding allylated products. The results are listed in Scheme 49.

Due to the interests in direct olefination through a Heck-type process via sp^3 C—H activation, Shi et al. have reported a novel method to construct C_{sp^3}—C_{sp^3} bonds via Fe-catalyzed oxidative coupling reaction between benzylic C—H and 1-aryl vinyl acetate under mild conditions.[122] By using $FeCl_2$ (10 mol.%) as the catalyst and *t*-BuOO*t*-Bu (1.2 equiv.) as the oxidant at 100 °C, various diarylmethanes reacted with different vinyl esters to give the desired products in moderate yields (Scheme 50).

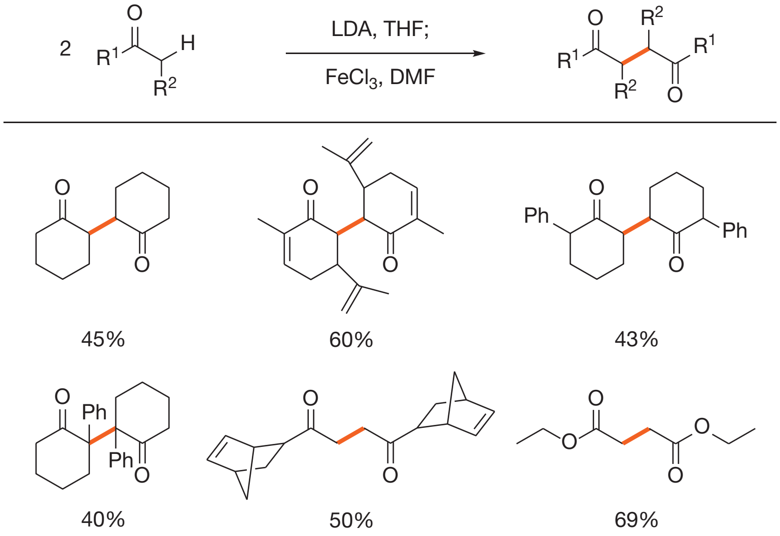
The development of sustainable, more efficient and atom-economic organic synthesis is one of the fundamental research goals in chemistry. In efforts to develop new chemical approaches that do not need extra steps for generating functional groups, Li et al. have recently developed a general oxidative CDC reaction between two C—H bonds.[112,113] By using simple, cheap copper and iron catalysts in the presence of oxidants, various sp^3 C—H bonds could be coupled with



Scheme 43 Iron-catalyzed oxidative C—H/C—H coupling between heteroarenes and methylamines.



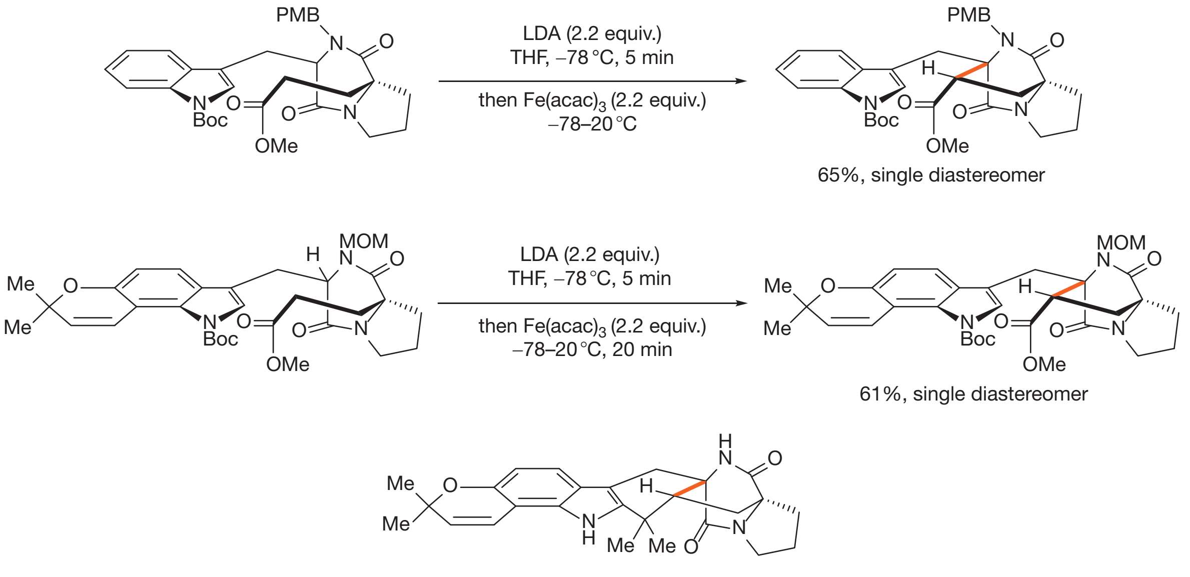
Scheme 44 Iron-mediated oxidative coupling of the enolate anions.



Scheme 45 $FeCl_3$-mediated oxidative homo-coupling of ketone enolates for the preparation of symmetric 1,4-diketones.

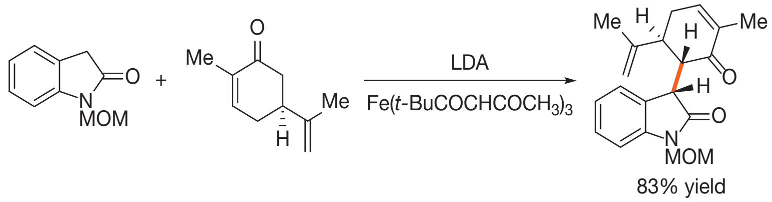
other C—H bonds without requiring pre-activation. Here we focus on the iron-catalyzed oxidative CDC reactions.

In 2007, Li et al. have developed two efficient methods to achieve C_{sp^3}—C_{sp^3} bond formation by using $FeCl_2$ as the catalyst and *t*-BuOO*t*-Bu as the oxidant.[123,124] Under the similar conditions, ether benzylic C—H bonds or cycloalkane C—H bonds could be activated and reacted with various 1,3-dicarbonyl compounds (**Schemes 51** and **52**). Notably, the



ent-1: (-)-stephacidin A

Scheme 46 Applications of iron-mediated intramolecular oxidative coupling of carbonyl compounds in total synthesis.



Scheme 47 Iron-mediated C_{sp^3}—C_{sp^3} oxidative coupling between carvone and MOM-protected oxindole.

two C_{sp^3}—C_{sp^3} bonds could be coupled directly from C—H bonds under mild conditions in the presence of catalytic simple iron salts with no ligands. Due to these advantages, this CDC protocol would have great potential in synthetic applications.

In 2008, Li et al. reported a similar iron-catalyzed direct functionalization of C—H bonds adjacent to heteroatoms.[125] In the presence of $Fe_2(CO)_9$ (10 mol.%) and *t*-BuOO*t*-Bu (3 equiv.) catalytic system, both cyclic and linear ether derivatives could react smoothly with various 1,3-dicarbonyl compounds to give the corresponding products in good yields (Scheme 53).

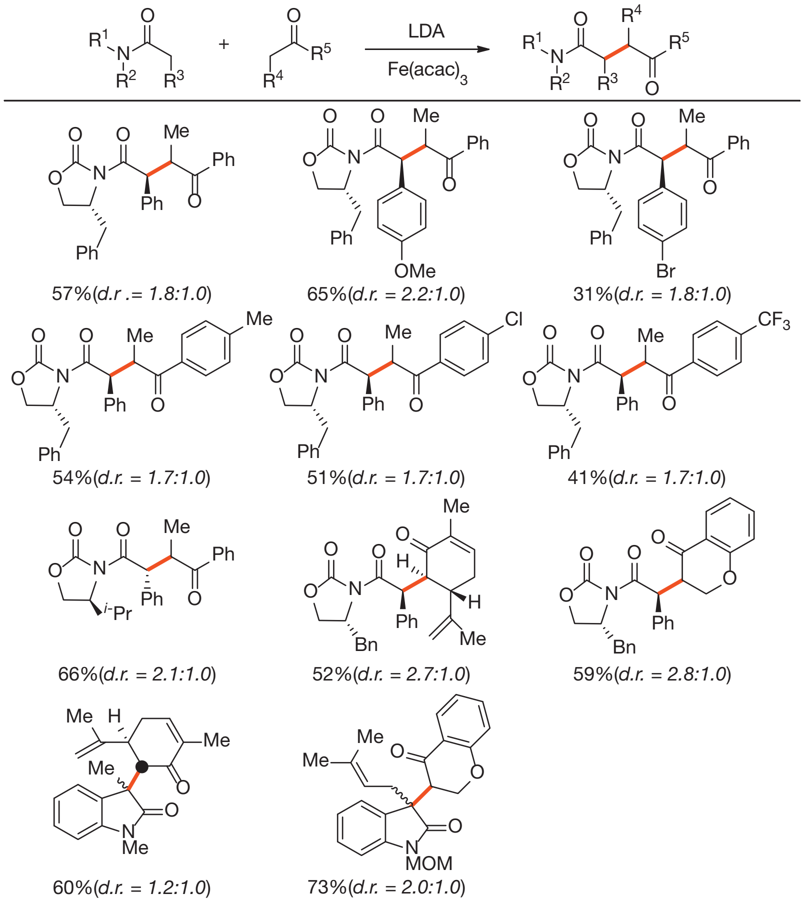
Later, in 2010, by using 2,2,6,6-tetramethylpiperidine-1-oxoammonium salts (TEMPO salts (T^+Y^-)) as alternative, mild, safe, and easy-handling oxidizing agents, Mancheño et al. also disclosed a $Fe(OTf)_2$-catalyzed oxidative CDC couplings of benzylic C_{sp^3}—H bonds adjacent to a heteroatom with enolizable carbonyls.[126] Under the optimized conditions, various corresponding α-functionalized ethers and amines could be furnished in moderate to good yields (Scheme 54).

As a sequential work of the above selective activation of C—H bonds adjacent to heteroatoms, Li et al. have demonstrated the synthesis of methylene-bridged bis-1,3-dicarbonyl derivatives by the iron-catalyzed oxidative reactions under mild reaction conditions.[127] Catalyzed by $Fe_2(CO)_9$ (2.5 mol.%) and *t*-BuOOH (2 equiv.), a wide variety of 1,3-dicarbonyl compounds reacted with *N*-methyl amines to afford the corresponding products at room temperature in 1 h (Scheme 55). This novel method provided a new efficient approach for the synthesis of such methylene-bridged compounds.

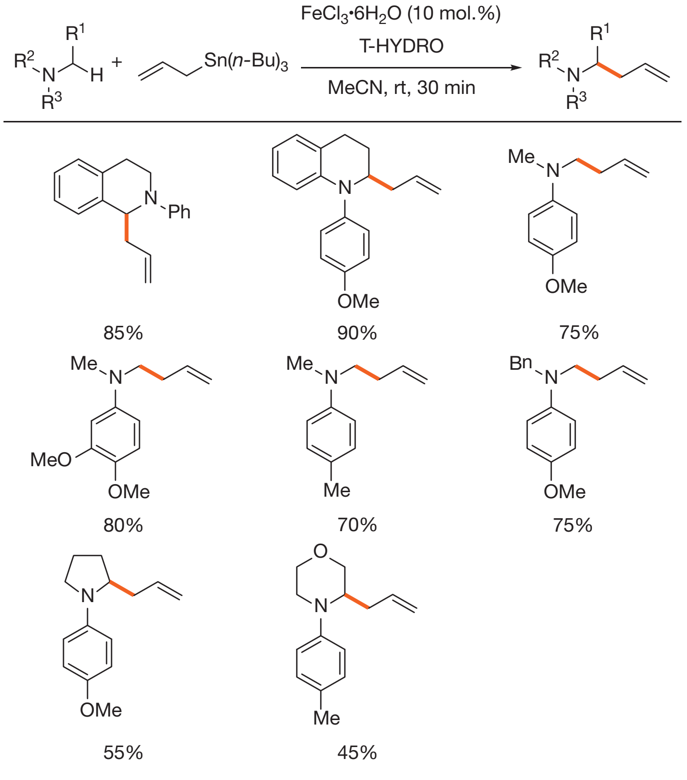
Based on the mechanism studies, a proposed pathway is listed in Scheme 56. The reaction of 1,3-dicarbonyl compounds **A** and *N*,*N*-dimethylaniline **B** firstly gave the oxidative coupling product **C**, followed by either nucleophilic substitution or the tandem reaction of Cope elimination and Michael addition via an intermediate **D**, the corresponding methylene-bridged bis-1,3-dicarbonyl product **E** was produced in the presence of iron catalyst and oxidant.

6.17.8 Conclusion

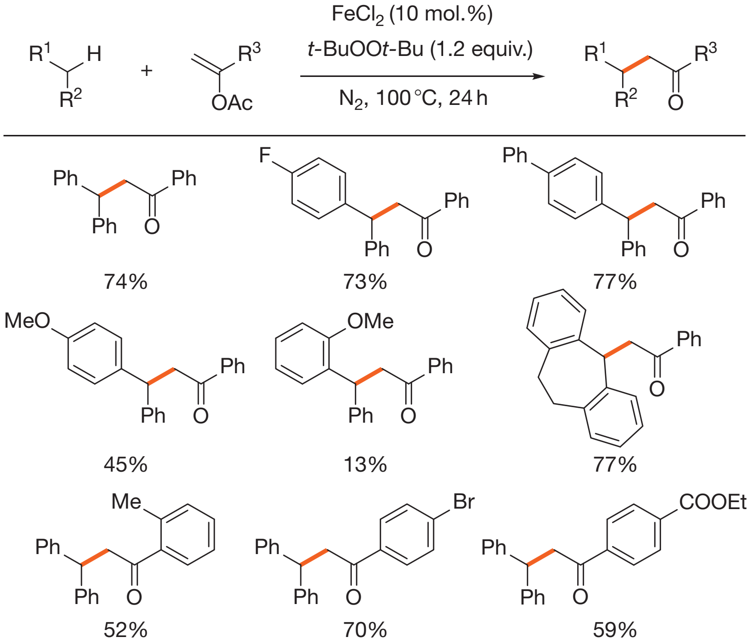
The renaissance of iron catalysis in organic synthesis blossoms out nowadays due to its sustainable, green, clean, and efficient advantages. The iron-catalyzed oxidative coupling reactions have achieved great progress in recent years, such as CDC reactions. Promoted by iron and oxidant catalytic system, various bond formations were constructed which allow for a large range of applications in organic synthesis. The research goals for more green and atom-economic organic synthesis have put chemists focusing on the bond formations directly from two hydrocarbons in the presence of the greenest oxidant, molecular oxygen.



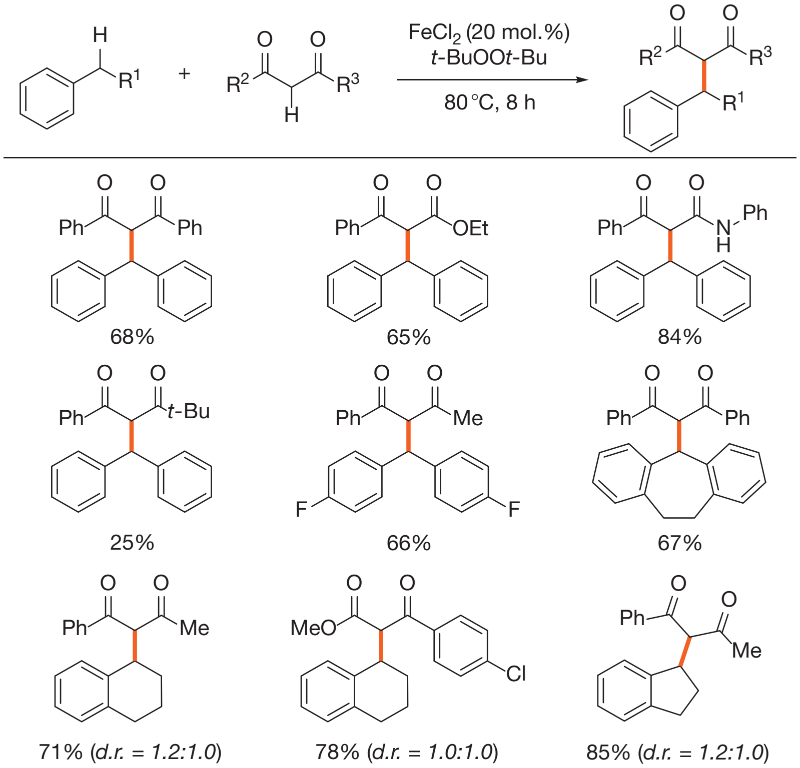
Scheme 48 Iron-mediated intermolecular oxidative enolate heterocoupling of two different carbonyl compounds.



Scheme 49 Iron-catalyzed oxidative allylation to sp^3 C—H bond adjacent to a nitrogen atom.

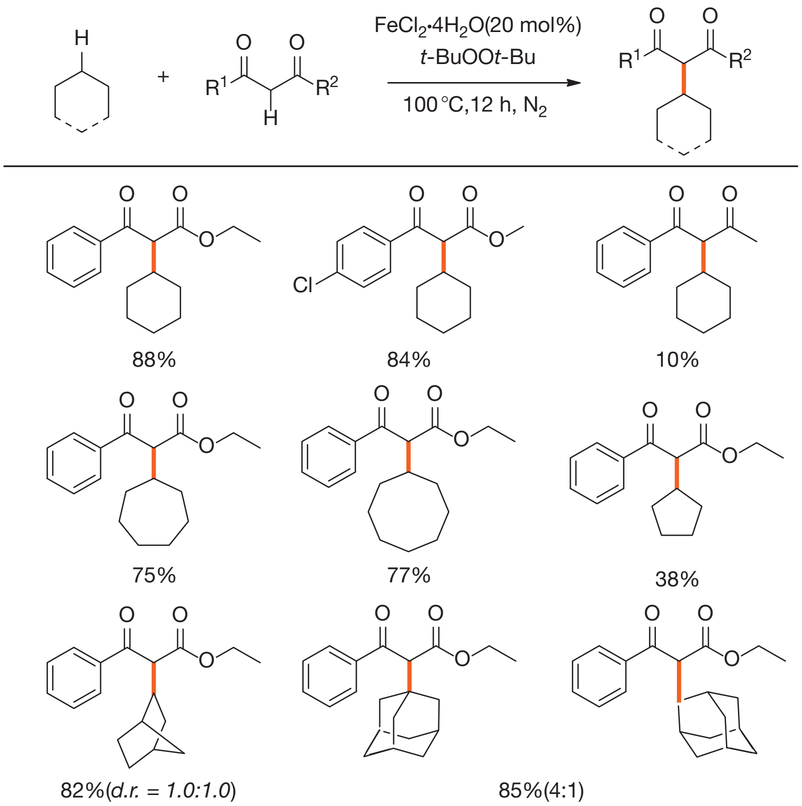


Scheme 50 Iron-catalyzed oxidative coupling between benzylic C—H bonds and 1-aryl vinyl acetates.

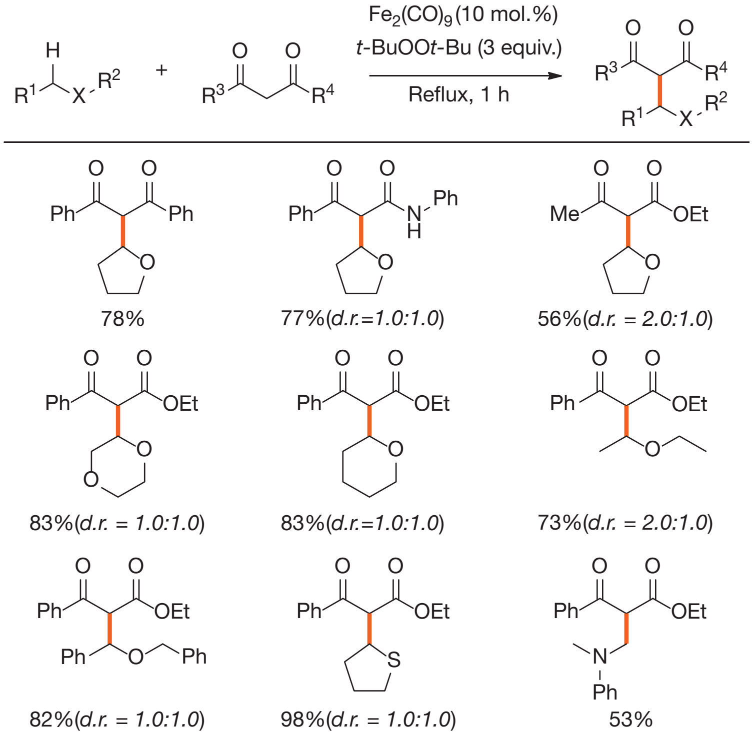


Scheme 51 Iron-catalyzed oxidative coupling between benzylic C—H bonds and 1,3-dicarbonyl compounds.

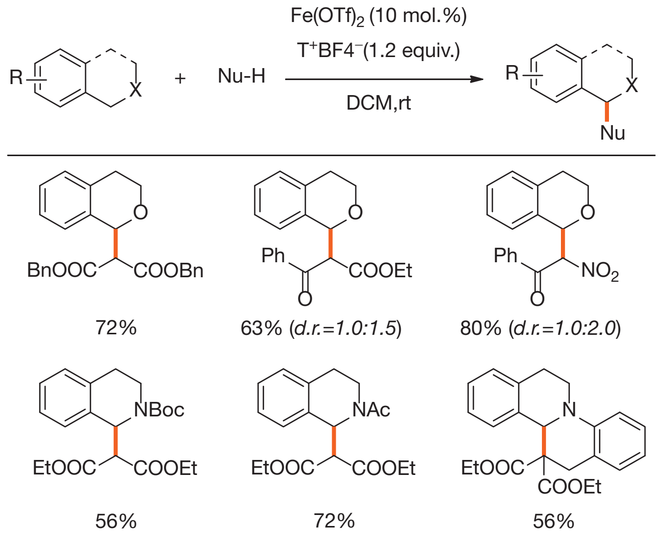
Although much significance and progress have been made, the challenge still remains. In some cases, stoichiometric or even excess amount of iron salts have to involve promoting the process. The improvement of catalyst activity and productivity is important with respect to large-scale applications. Meanwhile, the substrates scope is still narrow that only some special structures can be employed. Furthermore, there is still a strong lack of knowledge about the mechanisms in this field. More mechanistic studies are required to investigate which may guide us to know how to design, modify, control and utilize the iron-catalyzed reaction.



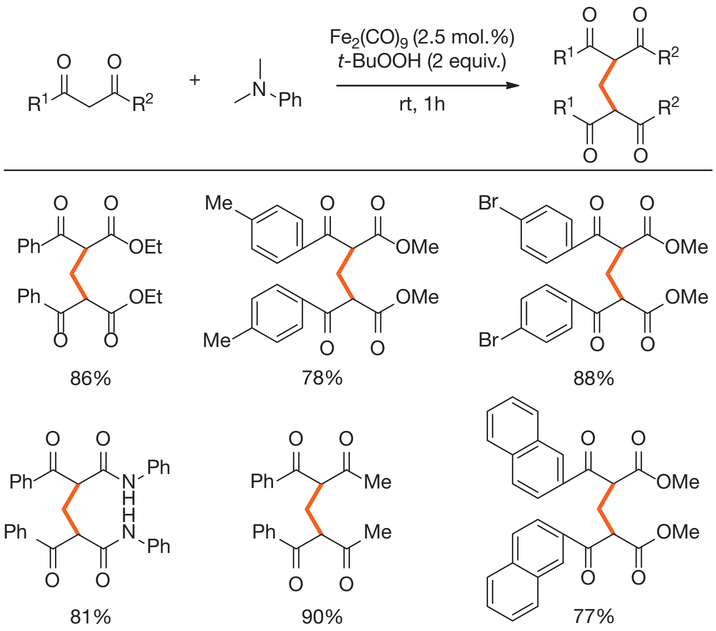
Scheme 52 Iron-catalyzed oxidative coupling between cycloalkane C—H bonds and 1,3-dicarbonyl compounds.



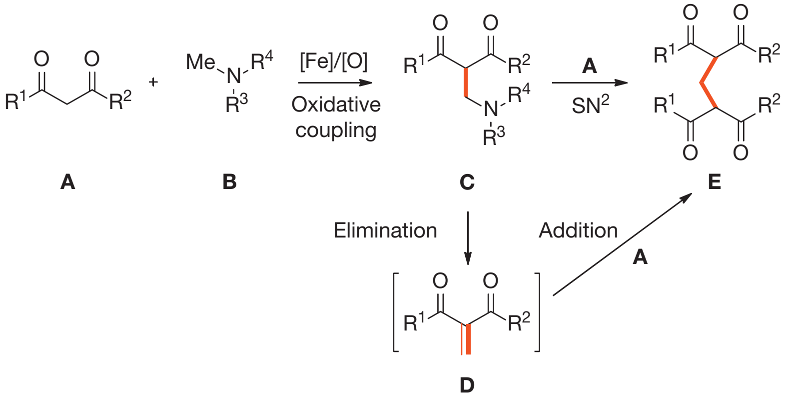
Scheme 53 Iron-catalyzed oxidative C—H/C—H coupling between ether derivatives and 1,3-dicarbonyl compounds.



Scheme 54 Iron-catalyzed oxidative coupling of benzylic C—H bonds adjacent to a heteroatom with enolizable carbonyls.



Scheme 55 Synthesis of methylene-bridged bis-1,3-dicarbonyl derivatives by the iron-catalyzed oxidative coupling reactions.



Scheme 56 Proposed mechanism of the iron-catalyzed oxidative coupling between 1,3-dicarbonyl compounds and *N*,*N*-dimethylanilines.

Undoubtedly, iron is a rising star in the organic synthesis nowadays and will indeed play an even more important role for sustainable synthesis in the future. For a related chapter in this Comprehensive, we refer to **Chapter 6.03**.

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6.18 Iron Complexes as Substitutes for Toxic Metals in Asymmetric Synthesis

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6.18.1 Introduction

The development of sustainable, efficient, and selective procedures to access organic compounds with higher values is one of the fundamental research goals in modern chemistry. Especially in the past several decades, the selective synthesis of enantiopure compounds has become one of the major issues for organic synthesis. Among all of the methodologies considered thus far, asymmetric catalysis offers an efficient and economical approach to achieve this goal.[1] In particular, transition-metal catalysts modified by chiral ligands are one of the most successful examples of practical asymmetric catalysis. Clearly, most of the applied metals (e.g., Pd, Rh, Ru, and Ir) displayed difficulties due to their high price or toxicity.[2] For instance, the current prices are as follows: palladium 1703 € per mol, iridium 5280 € per mol, rhodium 3602 € per mol, and ruthenium 281 € per mol. By contrast, the current price for 1 mol of iron is 0.01 €.[3] Hence, today's research is focused on their replacement by cheaper and less toxic metals. Here, the use of iron is of great interest because of its abundance, biological relevance (essential trace element; daily dose for humans 5–28 mg), and distinct abilities. It is surprising that, in comparison to other transition metals, the interest in iron as a catalyst core is underdeveloped. More recently, the situation has changed and the potential of iron has been demonstrated in numerous applications.[4] This chapter focuses on the recent advancements in enantioselective organic transformations applying catalytic amounts of iron as a substitute for toxic metal catalysts.[5]

6.18.2 Enantioselective Oxidation

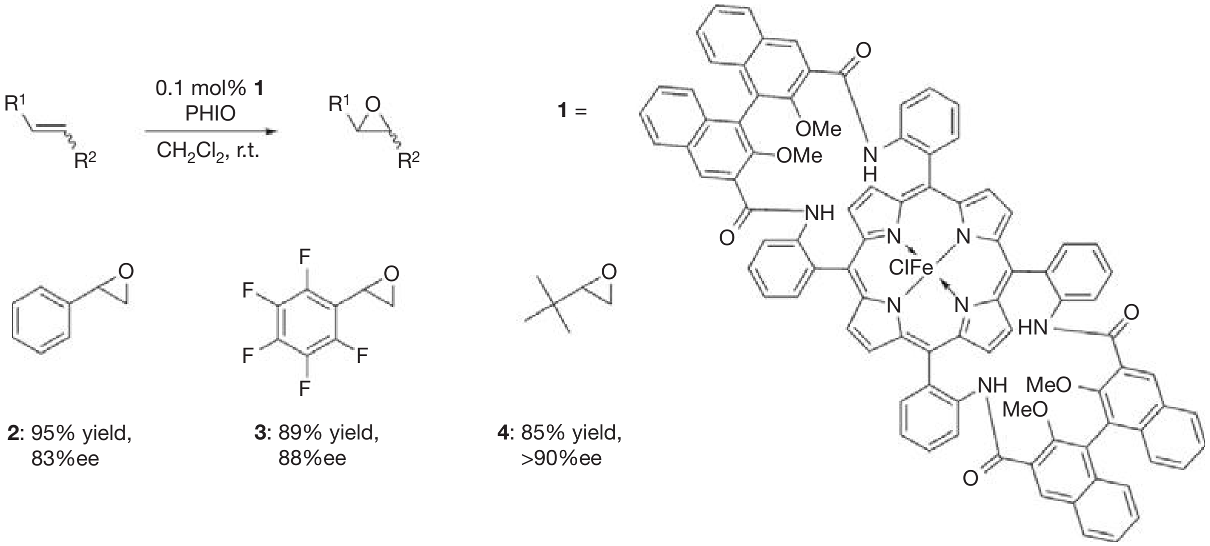
6.18.2.1 Enantioselective Oxidation of Olefins

The catalytic epoxidation of carbon–carbon double bonds has received significant attention in industry and academia as a methodology to create two carbon–oxygen bonds in one synthetic step.[6] By the formation of the epoxide, which allows easy ring-opening reactions, a versatile synthon is provided for bulk chemicals, fine chemicals, agrochemicals, and pharmaceuticals.[7] In this regard, the cheap, abundant, and biological relevant iron was the recent subject of homogeneous catalyzed epoxidation reactions.[8]

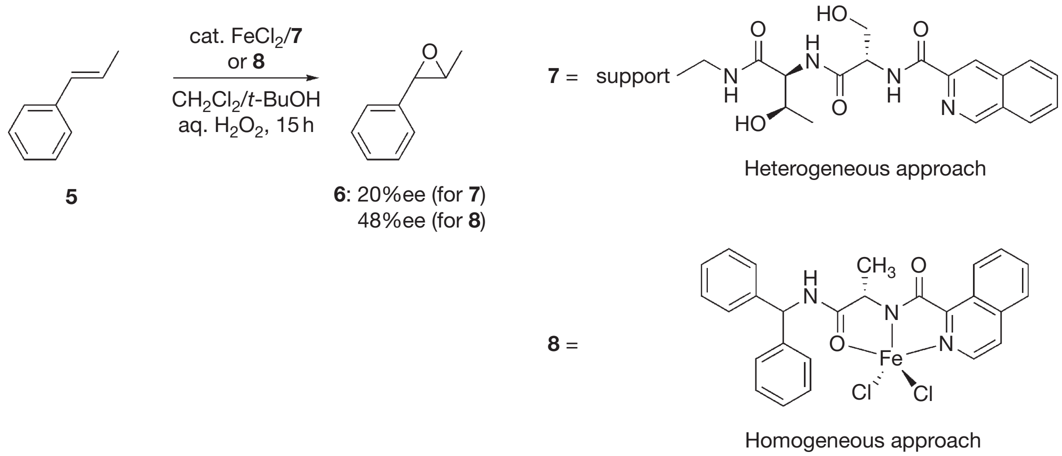
At the end of the 1990s, Collman et al.[9] presented iron porphyrin complexes for the asymmetric epoxidation of olefins (**Scheme 1**). The porphyrin scaffold is modified by chiral binaphthyl-based units. This geometry creates, on the one hand, space for substrate access and, on the other hand, substantial bulkiness to transfer the chiral information. Application of precatalyst **1** with very low catalyst loadings (0.1 mol%) in epoxidation reactions of olefin substrates with iodosylbenzene as the oxidant (**1**:PhIO:substrate 1:100:1000) resulted in good to excellent enantioselectivities for monosubstituted substrates, while for disubstituted *cis*-alkenes, lower selectivity was observed. However, an excess of substrate with respect to the oxidant was used, which lowers the overall yield of the desired products. Later, Rose et al.[10,11] improved the enantioselectivity up to 97% ee for styrene-based substrates by fine-tuning of the ligand structure.

In 1999, Francis and Jacobsen[12] reported on the setup of a huge ligand library supported on polystyrene for a combinatorial investigation (5760 combinations) with different metal precursors. After a screening of various combinations, they identified three Fe complexes with peptide-like ligands with enantioselectivities of 20% ee in the epoxidation of *trans*-β-methylstyrene (**5**) applying aqueous hydrogen peroxide as the oxidant in CH_2Cl_2/*t*-butanol (**Scheme 2**). Later, the key features of the successful ligands were transferred to a homogeneous catalysis approach, resulting in an improved enantioselectivity of 45% ee and 100% conversion of *trans*-β-methylstyrene.[13]

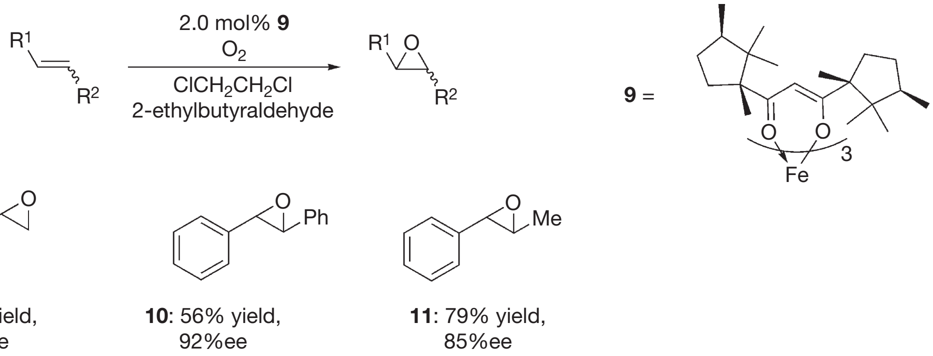
Cheng et al.[14] reported on the application of an iron complex modified by a chiral β-diketone ligand (**Scheme 3**). In contrast to earlier reports, the group applied molecular oxygen as an environmentally friendly oxidant, but a sacrificial aldehyde has to be added. The *tris*(δ,δ-dicampholylmethanato)



Scheme 1 Iron-based oxidation catalyst modified by a chiral porphyrin ligand.



Scheme 2 Epoxidation of *trans*-β-methylstyrene by a catalyst detected by a library screening.



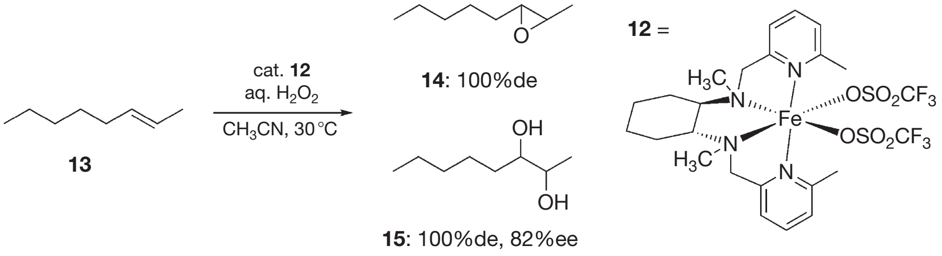
Scheme 3 Iron-catalyzed epoxidation presented by Xu et al.

iron(III) complex **9** demonstrated good performance with good enantioselectivities for styrene, accompanied by moderate yields to the desired product, while, as a significant side reaction (overoxidation), the corresponding benzaldehyde is formed (selectivity: up to 90%). The enantioselectivity was improved to 92% ee for disubstituted alkenes.

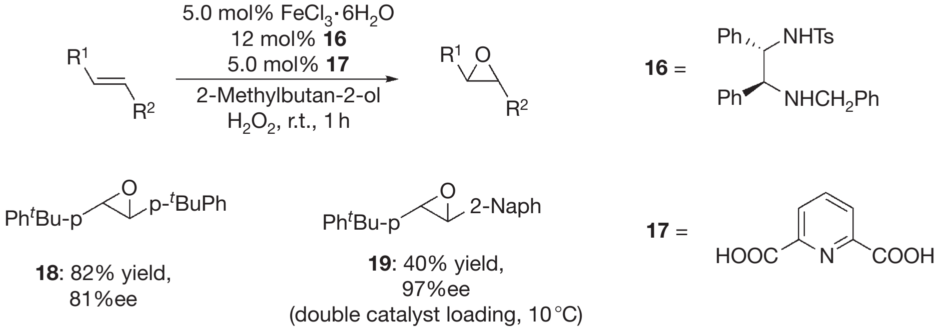
The group of Que Jr. reported on the application of the well-defined complex [Fe(bpmcn)(CF_3SO_3)$_2$] **12** in the asymmetric epoxidation of aliphatic olefins (Scheme 4). In the case of the oxidation of *trans*-2-heptene, 58% of the epoxide with 12%ee was achieved.[15] Noteworthy, as a significant side reaction or major reaction, the dihydroxylation of the carbon–carbon double bond was observed with excellent diastereoselectivities and enantioselectivities.

Recently, the group of Beller reported on a significant advancement in the iron-catalyzed asymmetric epoxidation of aromatic alkenes using hydrogen peroxide as the oxidant (Scheme 5).[16] Various chiral ligands were investigated in combination with $FeCl_3$ $6H_2O$ as the iron source in the oxidation of *trans*-stilbene as the model substrate applying environmentally friendly hydrogen peroxide as the oxidant, since only water is formed as a side product. To obtain reasonable yields and selectivity, the addition of catalytic amounts of pyridine-2, 6-dicarboxylic acid (H_2pydic) **17** was necessary. Excellent performance for an *in situ* catalyst composed of a mixture of $FeCl_3 \cdot 6H_2O$/chiral monotosylated diamine **16** and H_2pydic **17** has been found. Good to excellent isolated yields of aromatic epoxides were obtained with enantioselectivities of up to 97% ee for different substituted stilbenes, while for substituted styrenes, only low enantioselectivities were obtained. Several attempts were carried out to shed light on the underlying reaction mechanism. Spin-trapping experiments revealed the existence of radical intermediates and labeling studies to be an unsymmetrical transition state. However, various chiral iron species were detected by ESI-MS studies.

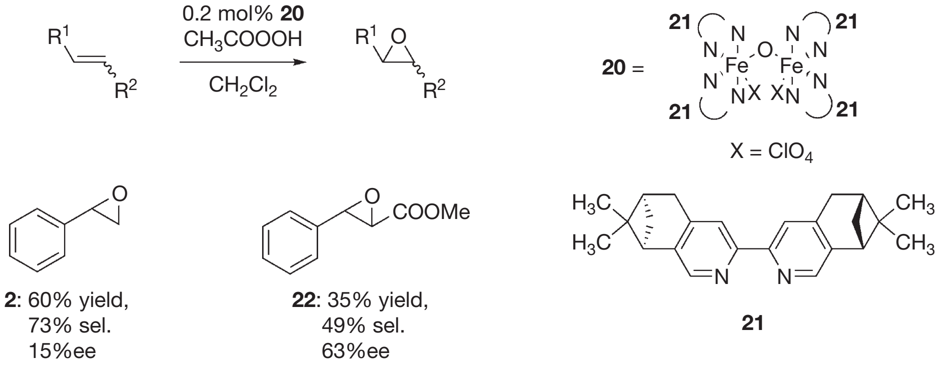
In 2007, the group of Ménage presented the application of chiral bipyridine ligands in the iron-catalyzed asymmetric epoxidation of alkenes (Scheme 6).[17] The reaction of bipyridine ligands with $Fe(ClO_4)_3 \cdot 6H_2O$ revealed the formation of a dinuclear μ-oxido iron complex containing four bipyridine units, which was proven by ESI-MS. The complex **20** performed enantioselective epoxidation with peracetic acid as the oxidant in good yields at low catalyst loadings (0.2 mol%). Various alkenes were oxidized with enantiomeric excess up to 63% ee within 2 min at 0 °C. The activity of the system was outlined in the epoxidation of *trans*-β-methylstyrene; here, with 0.1 mol% catalyst loading, Ménage and coworkers were able to perform 850 catalytic cycles, which corresponds to a turnover frequency



Scheme 4 Enantioselective epoxidation versus dihydroxylation.



Scheme 5 Epoxidation with an *in situ* catalyst by Beller et al.



Scheme 6 Epoxidation reaction with a chiral dinuclear iron complex.

(TOF) of 425 min^{-1}. Furthermore, the great importance of the dinuclearity fashion was proven by the application of a similar mononuclear species, which showed lower activity, yields, and enantiomeric excess.

A similar approach based on diiron complexes was accounted by Kwong and coworkers, but fixing all nitrogen donors in one ligand (Scheme 7).[18] The novel chiral sexipyridine was reacted with an iron precursor and resulted in the formation of the dinuclear μ-oxido iron complex **23**, which was characterized by ESI-MS measurements. The dinuclear μ-oxido iron complex **23** exhibited excellent reactivity and selectivity toward terminal and 1,2-substituted aromatic and aliphatic alkenes in the asymmetric epoxidation with H_2O_2 as the oxidant in acetonitrile/acetic acid. Enantiomeric excess up to 43% ee was achieved in short reaction times (3 min) at low temperature (0 °C). Notably, the ligand was recovered after catalysis and was recharged with iron and, subsequently, applied in epoxidation reactions to obtain the epoxides in high selectivity but lower yields.

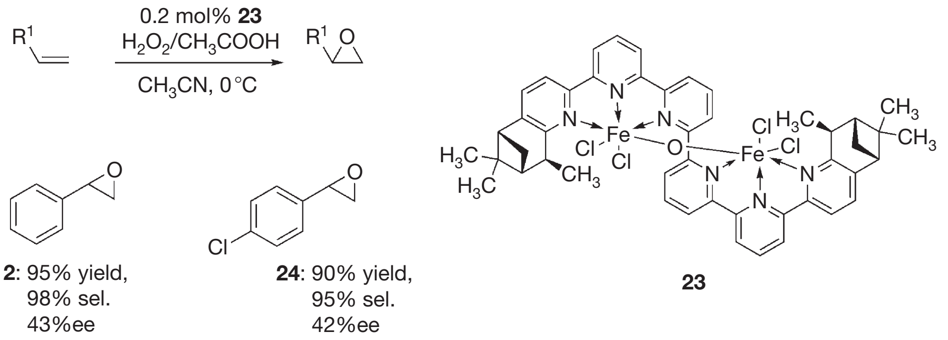
More recently, Yamamoto and coworker demonstrated the application of chiral iron catalysts in the asymmetric epoxidation of β,β-disubstituted enones with peracids as the oxidant (Scheme 8).[19] As the ligand motif, phenanthroline substituted in the 2-position with binaphthyl as the chiral function was applied. After studying various substitution patterns in the ligand backbone, with ligand **25**, the best enantioselectivities of up to 91% ee were obtained for the iron-catalyzed epoxidation of the model substrate **26** in short reaction times. After having set up suitable conditions, various substrates were transformed with excellent enantioselectivities (up to 92% ee) in the presence of an *in situ* formed catalyst composed of $Fe(OTf)_2$ and ligand **25**. Furthermore, the group was able to obtain insight into the structure of the precatalyst, in which two ligands are coordinated to the iron center. Noteworthy, the iron system was also capable of converting nonactivated alkenes, for example, *trans*-α-methylstilbene, in good enantioselectivities (87% ee).

In 2001, Que and coworkers studied the epoxidation/dihydroxylation of *trans*-2-heptene (Scheme 4). In 2008, the group reported on an improvement toward the formation of the diol with well-defined catalyst **29** containing bipyrrolidine as the chiral backbone (Scheme 9).[20] The complex **29** demonstrated general reactivity toward the dihydroxylation of several olefins using H_2O_2 as the terminal oxidant. Good results were achieved with aliphatic and aromatic olefins, for example, the oxidation of styrene resulted in the formation of styrene oxide and 1-phenylethane-1,2-diol in <1% and 65% yields, respectively. However, excellent enantioselectivity with 97% ee accompanied by 55% yield was realized for the oxidation of *trans*-2-heptene.

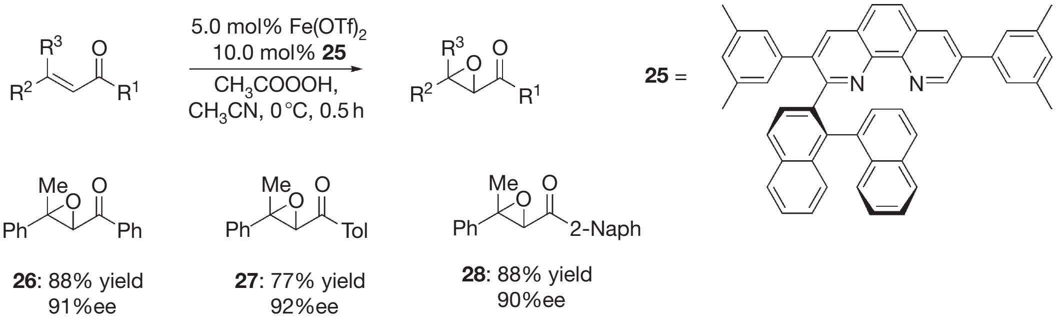
6.18.2.2 Enantioselective Oxidation of Sulfides to Sulfoxides

Chiral sulfoxide groups are abundant functionalities in organic chemistry and, in consequence, relevant for the production of numerous products in chemical industries.[21] Up to now, manifold syntheses based on chiral metal catalysts have been established to access chiral sulfoxides. However, an extensive study on chiral iron complexes was started in the year 2002.

Fontecave and Ménage and coworkers presented their investigations on the synthesis and application of dinuclear



Scheme 7 Chiral dinuclear μ-oxido iron complex as the catalyst for the epoxidation of alkenes.



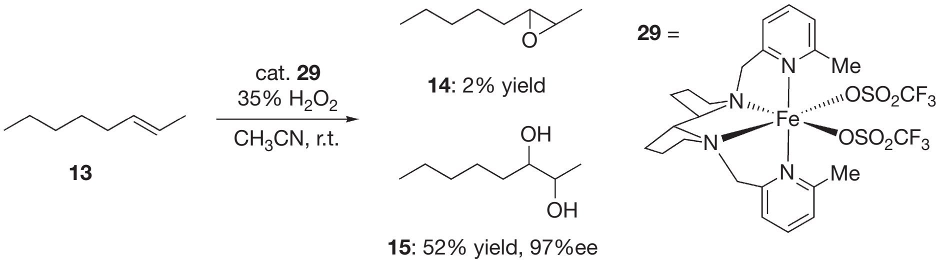
Scheme 8 Asymmetric epoxidation of β,β-disubstituted enones with an iron catalyst.

iron complex (Scheme 10).[22] The abilities of complex **30** containing chiral bipyridine ligands, which has a similar structural motif as the complex **20** active in asymmetric oxidations of alkenes, were studied in the asymmetric oxidation of sulfides to sulfoxides. Enantioselectivities of up to 40% ee were obtained under mild reaction conditions after 15 min applying hydrogen peroxide as the terminal oxidant. Specific advantages arise by the incorporation of the second metal site, while a similar mononuclear complex resulted in very low enantioselectivities. Noteworthy, a ratio of complex:sulfide:oxidant of 1:600:10 was used, which disfavors the protocol for synthetic applications. Furthermore, mechanistic investigation revealed the formation of a peroxide iron species as the catalytic active intermediate.

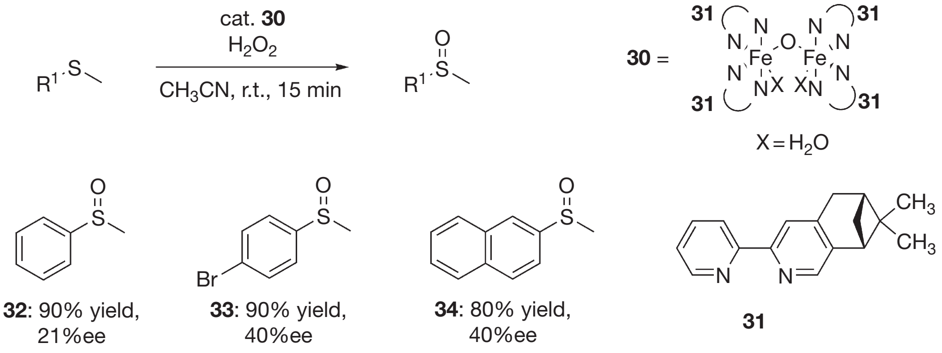
An improvement with respect to enantioselectivity was reported later on by the group of Bolm. Applying a straightforward *in situ* system composed of $Fe(acac)_3$ and a Schiff base of type **35** as the ligand, enantioselectivities of up to 90% ee were feasible (Scheme 11).[23] The system has several advantages, for example, the catalyst is highly active in the presence of water and air, hydrogen peroxide as an environmentally friendly oxidant can be applied, no overoxidation to the corresponding sulfone was detected, and the easy synthesis of the ligands. Based on that, a small ligand library was synthesized and applied in the asymmetric oxidation of sulfides to sulfoxides. Excellent performance was observed for ligand **35**. However, one limitation of the protocol was the low yield of up to 44%. Several attempts to increase the yield failed at that time. Later, the same group found that the addition of catalytic amounts of carboxylic acids or carboxylates has a positive effect on the yield as well as on the enantioselectivity.[24] After the set up of a suitable system for the asymmetric oxidation, Bolm and coworkers applied the protocol in the asymmetric synthesis of Sulindac, an anti-inflammatory drug. A key step in the synthesis to Sulindac is the formation of a chiral sulfoxide, which was achieved by the Bolm procedure in 92% ee and 69% yield.[25]

A similar approach was reported by Bryliakov and coworker dealing with tetradentate salen-type ligands (Scheme 12).[26] After synthesizing chiral iron complex **38**, the catalytic abilities were tested in the oxidation of sulfides. The best terminal oxidant with respect to enantioselectivity PhIO was noticed, while all other oxidants resulted in racemic mixtures. After the evaluation of different reaction parameters, the highest ee values were obtained for substrate **39**, with 62% ee after 2 h at 0 °C. Furthermore, as an active species, an iodosylbenzene (salen)–iron(III) complex was detected. Noteworthy, to some extent, overoxidation to the sulfone was observed. The activity of complex **38** was improved later on to 84% ee for PhS^iPr by the application of MesIO instead of PhIO at low temperature (−21 °C).[27]

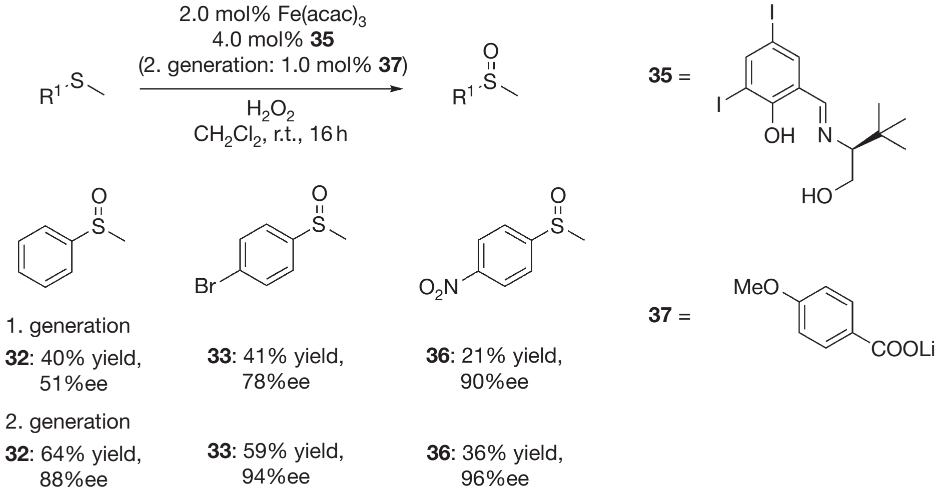
Recently, Katsuki and coworker applied a chiral salan–iron complex in the asymmetric oxidation of sulfides to sulfoxides.[28] Crucial for obtaining excellent performance was the fine-tuning of the ligand structure. In addition to the chiral cyclohexyl diamine backbone, two binaphthyl systems were introduced. Furthermore, alkylation of the nitrogen donors improved the reaction outcome. In more detail, applying complex **40** (1.0–2.0 mol%) with hydrogen peroxides as the oxidant, excellent enantioselectivities of up to 96% ee and yields of up to 99% at 20 °C after 3 h were feasible (Scheme 13). However, in some cases, significant amounts of the corresponding sulfones were detected. More recently, the group of Li encapsulated a similar chiral iron(salan) complex in nanocages and applied those materials in the oxidation of sulfides.[29] However, to some extent, lower enantioselectivities were observed compared to the homogeneous approach.



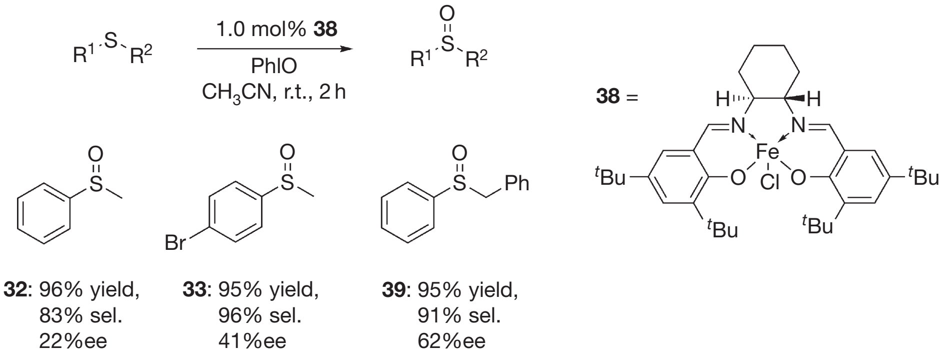
Scheme 9 Asymmetric dihydroxylation of olefins.



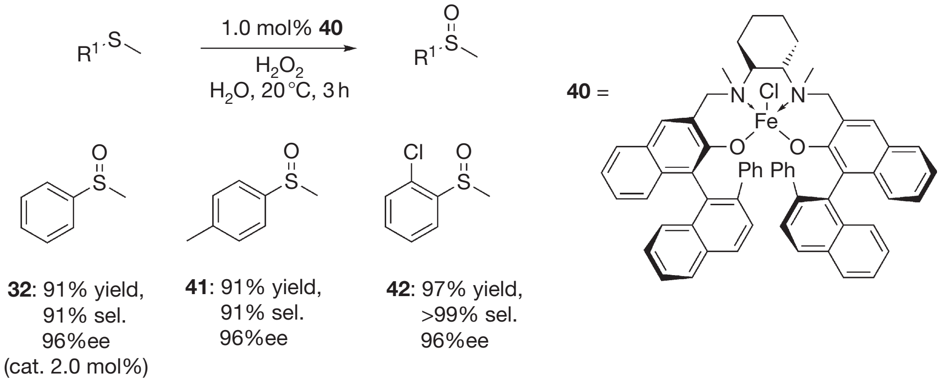
Scheme 10 Asymmetric oxidation of sulfides to sulfoxides.



Scheme 11 Asymmetric synthesis of sulfoxides by Bolm et al.



Scheme 12 Chiral salen–iron complex for the oxidation of sulfides.

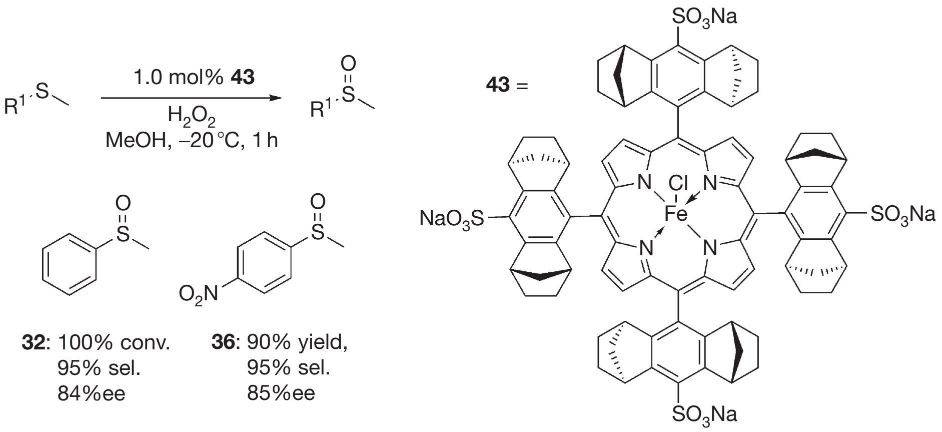


Scheme 13 Chiral salan–iron complex for the oxidation of sulfides to sulfoxides.

In 2011, the group of Simonneaux presented a chiral iron porphyrin complex for the oxidation of sulfides to sulfoxides (Scheme 14).[30] With 1.0 mol% of complex **43**, the best enantioselectivities with up to 90% ee were obtained at low temperature (−20 °C) using hydrogen peroxide as the oxidant in alcoholic solvents.

6.18.2.3 Miscellaneous Enantioselective Oxidation Reactions

Recently, the group of Katsuki investigated iron-catalyzed oxidative couplings of 2-naphthols to yield chiral binaphthols, which are useful precursors in organic synthesis and catalysis.[31]



Scheme 14 Chiral porphyrin complex in asymmetric oxidation reactions.

As chiral catalysts, complexes based on the structural motif of complex **40**, which was an excellent catalyst for sulfoxide formation, were applied. In their earlier work, the oxidative homocoupling was investigated. With 4.0 mol% **44**, excellent enantioselectivities of up to 97% ee were achieved for different substituted 2-naphthols at 60 °C with air as the oxidant, while at lower temperatures, lower yields were detected. Noteworthy, the increase of the temperature to 60 °C has no negative effect on the ee value. However, long reaction times (up to 96 h) are required in order to obtain reasonable amounts of product. Mechanistic studies revealed the formation of an iron(salan)(2-naphthoxo) complex as the intermediate in the catalytic cycle. Based on the mechanistic investigations, an oxidative heterocoupling of an electron-rich and electron-poor substituted 2-naphthol was envisaged. Indeed, the heterocoupling was feasible, but a mixture of all possible coupling products was observed.

The excellent catalytic abilities of the complex **44** were shown later on in the oxidative kinetic resolution of racemic secondary alcohols with air as the oxidant (Scheme 15).[32a] Extraordinary ee values of up to 99% ee were realized after optimization of the reaction conditions. Crucial for the reaction outcome was the addition of catalytic amounts of naphthol derivatives.

Furthermore, chiral iron complexes were applied in the enantioselective oxidation of racemic benzoins, which have some significance in the pharmaceutical industry. The group of Sekar found that iron salts modified by binaphthyl-based Schiff bases are useful catalysts for the oxidative kinetic resolution of benzoins (Scheme 16).[32b] For instance, the mixture of 5 mol% $Fe(OAc)_2$, 5 mol% ligand **50**, and 5 mol% 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) was able to realize benzoins in enantioselectivities of up to 98% ee and yields of up to 42% when utilizing molecular oxygen as the oxidant at 60 °C in hexane as the solvent.

6.18.3 Iron-Catalyzed Asymmetric Reduction Reaction

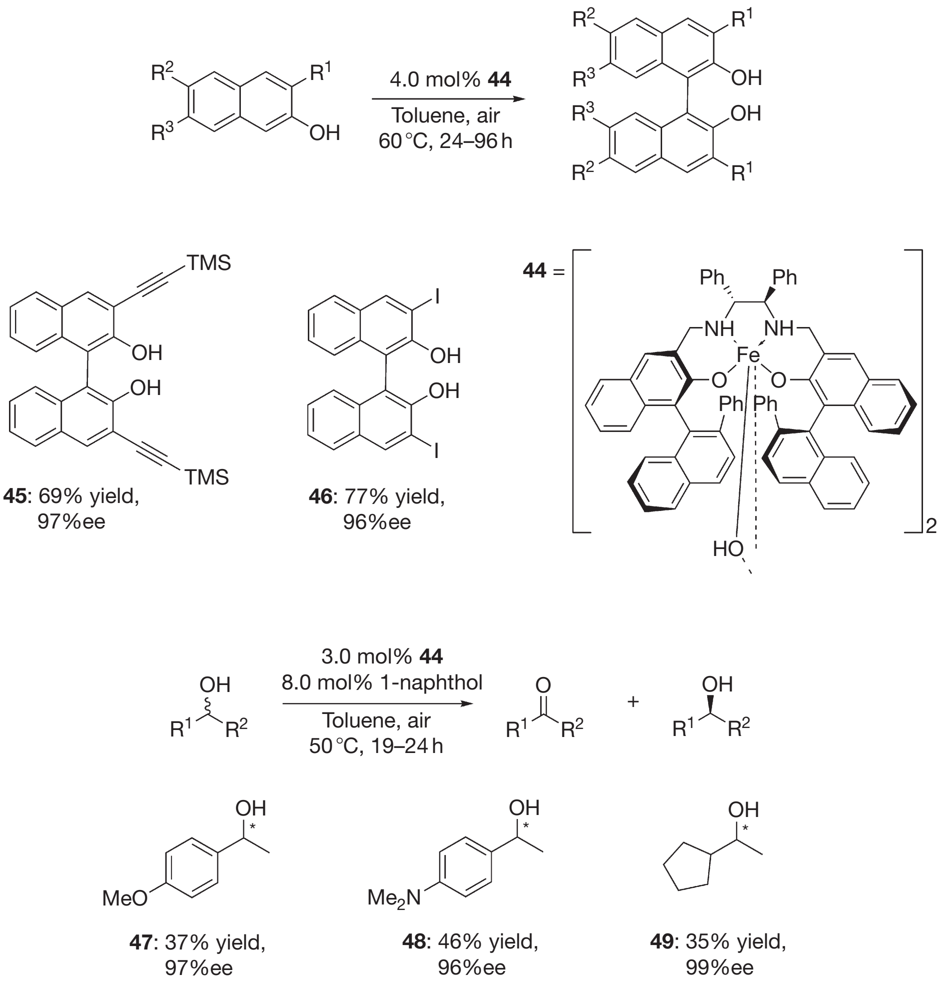
Reduction processes are one of the major transformations in organic chemistry and have some relevance in industrial applications. The addition of molecular hydrogen to unsaturated compounds, for example, C=C, C=O, C=N bonds, provides high atom efficiency and creates advantages with respect to 'green chemistry.'[33] However, for the activation of molecular hydrogen, hydrogen donors, or hydrogen equivalents, catalytic amounts of transition metals such as Rh, Ru, and Ir are required. In this regard, the cheap, abundant, and biologically relevant iron was the recent subject as the catalyst in asymmetric reduction reactions to substitute the expensive and toxic metals.[4]

6.18.3.1 Iron-Catalyzed Asymmetric Hydrogenations

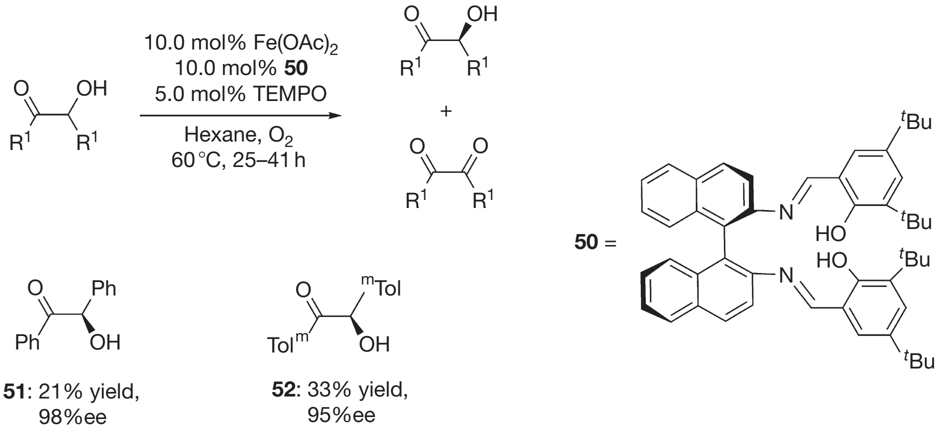
The first enantioselective hydrogenation of prochiral ketones in the presence of well-defined chiral iron complexes was presented in 2008 by Morris et al. (Scheme 17).[34] The precatalyst is easily accessible by the reaction of the PNNP-type ligand (the ligand in complex 53) with simple iron sources and was applied in the reduction of acetophenone **54** at relatively low catalyst loadings with 0.44 mol%. Noteworthy, as seen in ruthenium-based reduction systems, catalytic amounts of base were necessary. However, both the conversion and the enantioselectivity were modest (40% conversion, 27% ee) at 50 °C after 18 h. Even if the achieved enantiomeric excess was low, the group demonstrated the possibility to apply chiral iron complexes in hydrogenation reactions. Later on, Morris et al. modified the ligand backbone, but none of the derivatives was as active as **53**.[35] A DFT study revealed that the iron-based reduction catalysts work via a similar mechanism as reported for ruthenium.[36]

In 2011, Berkessel slightly improved the enantioselectivity toward 31% ee by using a modified Casey catalyst (Scheme 18).[37] By the substitution of one carbonyl ligand by a chiral phosphoramidate ligand, a chiral catalyst is generated. The complexes (10.0 mol%) were applied in the reduction of acetophenone using a hydrogen pressure of 14 bar in toluene. Furthermore, in order to succeed, light irradiation was necessary. A careful study of the complex composition revealed the formation of diastereomers after the reaction of complex **56** with hydrogen.

The group of Beller reported on the enantioselective hydrogenation of prochiral imines applying iron-based catalysts (Scheme 19).[38] A novel concept based on the cooperativity of an achiral transition-metal complex with a chiral Brønsted acid was invented. After a survey of different metal precursors, iron, especially the Knölker complex **57** in combination with chiral

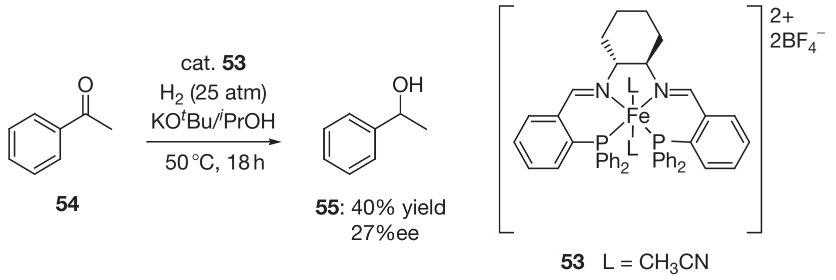


Scheme 15 Iron-catalyzed asymmetric aerobic oxidation.

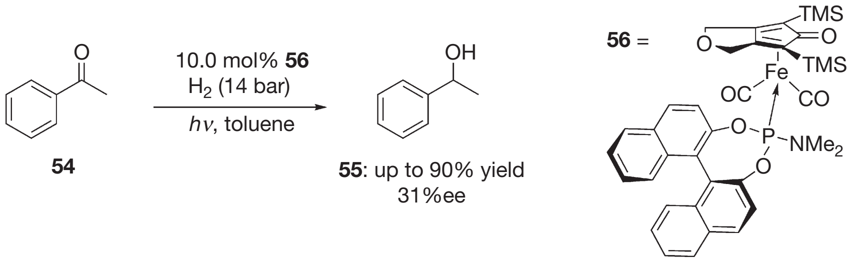


Scheme 16 Oxidative kinetic resolution of racemic benzoins.

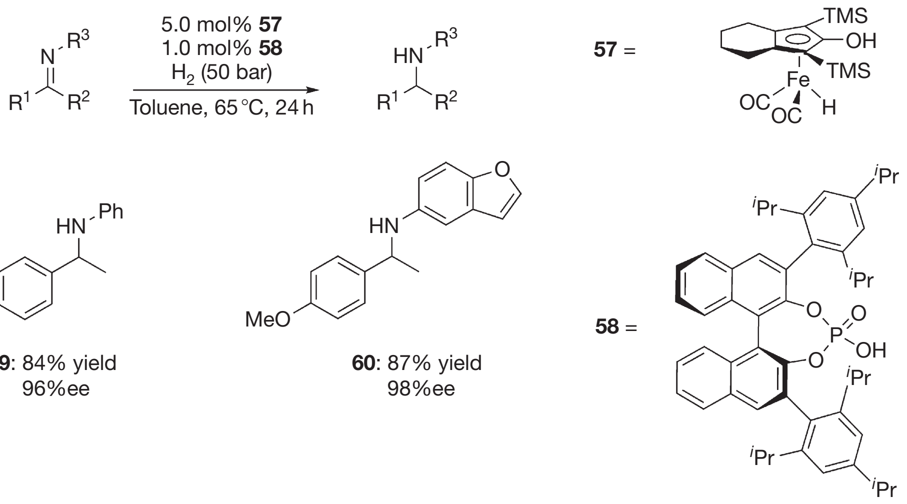
binaphthyl-based phosphates **58**, turned out to be the system of choice for realizing excellent yields and enantioselectivities. Noteworthy, for high enantioselectivities, bulky substituents in the 3,3′-position of the phosphates are required. Applying 5.0 mol% of complex **57** and 1.0 mol% of **58** under a hydrogen atmosphere (50 bar), a number of imines were reduced in excellent yields and enantioselectivities to the corresponding amines in toluene at 65 °C after 24 h. Furthermore, NMR studies showed an interaction between **57** and **58** and the formation of new species, along with the generation of hydrogen.



Scheme 17 Asymmetric hydrogenation of prochiral ketones in the presence of iron complex **53**.



Scheme 18 Iron complexes modified by chiral phosphoramidate ligands.



Scheme 19 Cooperativity of an achiral transition metal complex with a chiral Brønsted acid.

6.18.3.2 Iron-Catalyzed Asymmetric Transfer Hydrogenations

Along with hydrogen, the application of hydrogen donor molecules have been widely utilized in reduction chemistry and present a powerful strategy, because of the ease of performance and general applicability. In particular, a broad scope of products is available by transfer hydrogenation applying nontoxic hydrogen donors, for example, 2-propanol or $HCOOH/NEt_3$, under mild reaction conditions in the presence of precious metal catalysts.[39]

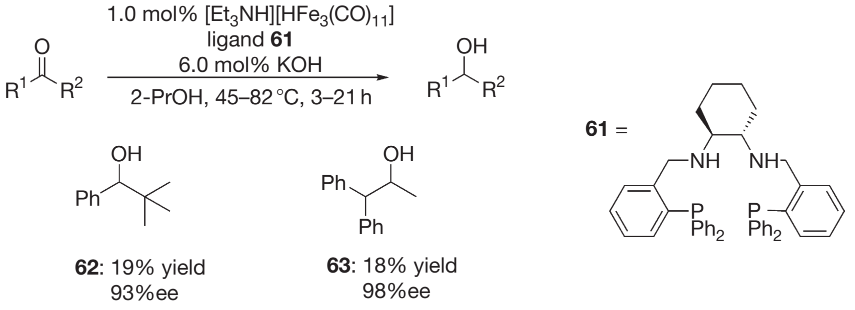
In 2004, the Gao group reported the application of an *in situ* catalyst based on the combination $[Et_3NH][HFe_3(CO)_{11}]$ and enantiopure diaminodiphosphane ligands **61** (Scheme 20).[40] The system was used in the transfer hydrogenation of prochiral ketones to obtain ee values of up to 98% ee, with moderate yields, using 2-propanol as the hydrogen donor. The highest enantioselectivities of up to 98% ee were observed for aryl/alkyl ketones with bulky groups.

Later on, Morris and coworkers investigated this reaction in more detail, demonstrating the asymmetric transfer hydrogenation at 22 °C catalyzed by well-defined iron complexes (Scheme 21). In contrast to Gao et al., enantiopure diaminodiphosphane ligands were applied. The activity of the catalyst was excellent, with TOFs of up to 1000 h^{-1}.

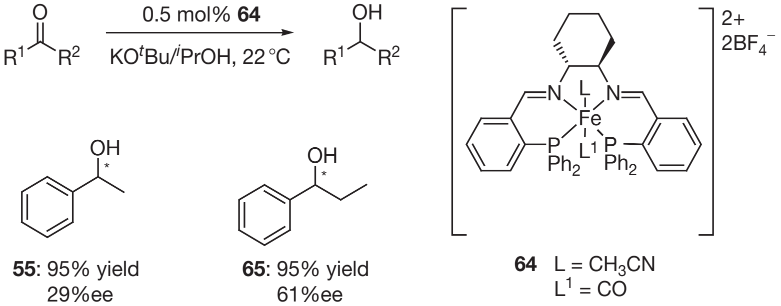
However, the realized enantioselectivities (up to 76% ee) are, to some extent, lower compared to the protocol reported by Gao et al. Interestingly, complex **64** was found to be inactive for hydrogenation applying molecular hydrogen. Based on these initial results, the group of Morris was able to improve the enantioselectivity by fine-tuning of the ligand structure (Scheme 22).[41] Replacement of the 1,2-diamino cyclohexane motif by the 1,2-diphenyl 1,2-diaminoethane showed the reduction of bulky aromatic ketones with excellent enantioselectivities of up to 99% ee, although a decrease in conversion was observed. On the other hand, with challenging substrates such as nonaromatic ketones or imines, only moderate enantioselectivities and lower activities were monitored. Furthermore, the type of counteranion was of great importance, since the replacement of BPh_4^- by BF_4^- resulted in an improvement of the catalytic activity. With a catalyst/base/substrate ratio of 1:8:600, enantioselectivities of up to 96% ee have been obtained. Various substrates were transformed with almost complete conversion after 1 h, which corresponds to TOFs of up to 2600 h^{-1}.

A further advancement was achieved after substitution of the aryl bridge by an alkyl one (Scheme 22).[42] With this precatalyst, extraordinary enantioselectivities of up to 99% ee and excellent conversions were obtained. Furthermore, TOFs of up to 4900 h^{-1} were realized. Noteworthy, the addition of base was crucial in order to obtain suitable results. A further optimization of the reaction conditions resulted in TOFs of up to 21 000 h^{-1}.[43] On the other hand, the substituents at the phosphorous were studied, but resulted in no improvement of the enantioselectivity or catalyst activity for alkyl substituents, while with tolyl substituents, activities of up to 30 000 h^{-1} were monitored.[44,45]

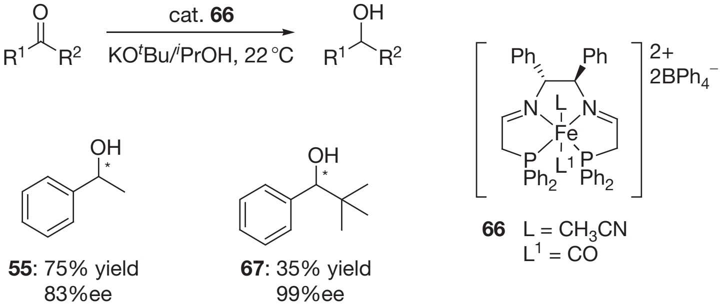
More recently, the group of Wills developed a protocol for the synthesis of chiral iron complexes (Scheme 23).[46] With a



Scheme 20 Enantioselective transfer hydrogenation.



Scheme 21 Asymmetric transfer hydrogenation according to Morris and coworkers.



Scheme 22 Transfer hydrogenation performed by iron complexes containing chiral tetradentate ligands.

straightforward route, a number of precatalysts were accessible based on the parent structure introduced by Casey. Later on, the potential of the complexes was investigated in the transfer hydrogenation of the prochiral ketone acetophenone **54**.[47] The two systems 2-propanol and $HCOOH/NEt_3$ were applied in combination with the precatalysts. The best performance with respect to enantioselectivity was observed for complex **68** and $HCOOH/NEt_3$ with 25% ee. Noteworthy, for the activation of the precatalyst, catalytic amounts of Me_3NO were added.

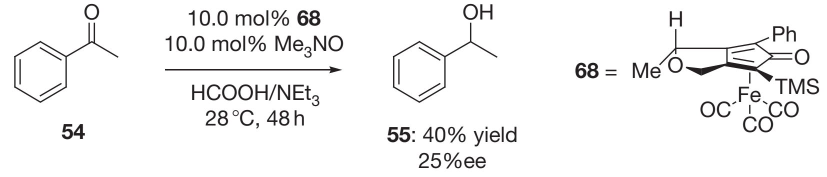
A different chiral ligand concept was presented by the group of Reiser (Scheme 24).[48] Chiral bidentate bis(isonitrile) ligands based on amino acids were coordinated to iron(II) chloride and applied as precatalysts in the transfer hydrogenation of prochiral ketones with 2-propanol as the hydrogen donor and potassium butoxide as the base. After studying the influence of the ligand structure on the reaction outcome, with complex **69**, the best performance was realized with 90% yield and 64% ee for the formation of 1-phenylethanol **55**. The complex **69** was, furthermore, active in the enantioselective reduction of various ketones, including heteroaromatic ketones, with enantioselectivities of up to 91% ee under mild reaction conditions.

In 2010, the group of Beller applied $[Et_3NH][HFe_3(CO)_{11}]$ and enantiopure diaminodiphosphane ligands **61** as precatalysts for the first iron-catalyzed enantioselective reduction of imines to produce chiral amines (Scheme 25).[49] Noteworthy, the catalytic system was introduced by the Gao group for the enantioselective reduction of ketones with excellent performance (Scheme 20).[37] After investigation of the reaction conditions, excellent enantioselectivities of up to 98% ee and yields of up to 98% were feasible within 30 min under mild reaction conditions and low catalyst loadings for a number of substrates.

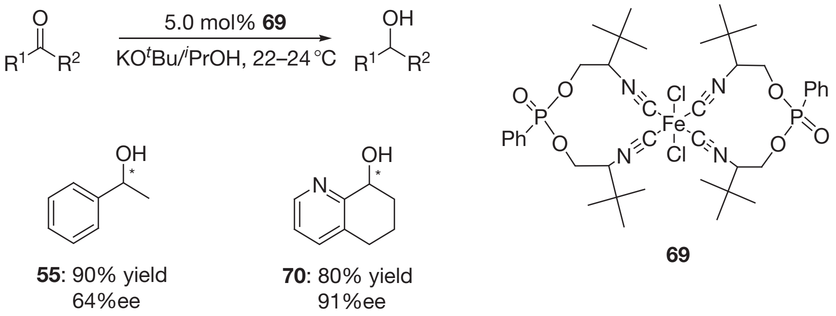
6.18.3.3 Iron-Catalyzed Asymmetric Hydrosilylations

Although enantioselective hydrogenation and enantioselective transfer hydrogenation in the presence of catalytic amounts of metal precursors are the most developed and efficient routes to chiral compounds, catalytic hydrosilylation is a desirable choice because of the mild reaction conditions and straightforwardness.[50]

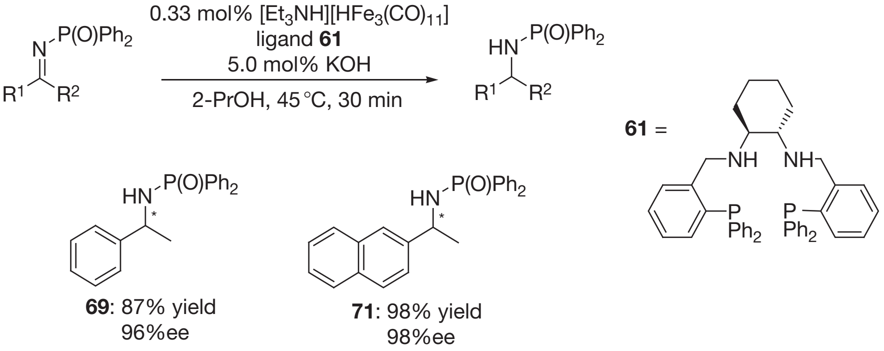
In 2007, Nishiyama and Furuta presented an efficient catalytic system based on iron for the enantioselective hydrosilylation of ketones to obtain the corresponding silyl ethers and, after acidic work-up, the chiral alcohol (Scheme 26).[51] A combination of Fe $(OAc)_2$ and a chiral nitrogen ligand, for example, pybox **72** or



Scheme 23 Application of a chiral Casey catalyst developed by Wills and coworkers.



Scheme 24 Iron(II)–bis(isonitrile) complexes as precatalysts for enantioselective ketone reductions.



Scheme 25 Enantioselective reduction of imines to the corresponding amines in accordance with Beller et al.

bopa **73**, successfully reduced methyl(4-phenylphenyl)ketone **74**. For instance, **72** gives 37% ee and **73a** increased the enantioselectivity to 79% ee. Later on, the group of Nishiyama improved the enantioselectivity to up to 95% ee by fine-tuning of the ligand structure and optimization of the reaction conditions.[52]

While Nishiyama describes an *in situ* system composed of $Fe(OAc)_2$ and pybox ligands, Chirik and coworkers investigated well-defined iron dialkyl complexes containing the pybox ligand motif **76** or bisoxazoline **77** in the hydrosilylation of ketones (Scheme 27).[53] Compared to the *in situ* system, an improvement was monitored with enantioselectivities of up to 49% ee. A further advancement was found by addition of the borane $B(C_6F_5)_3$, realizing enantioselectivities of up to 93% ee.

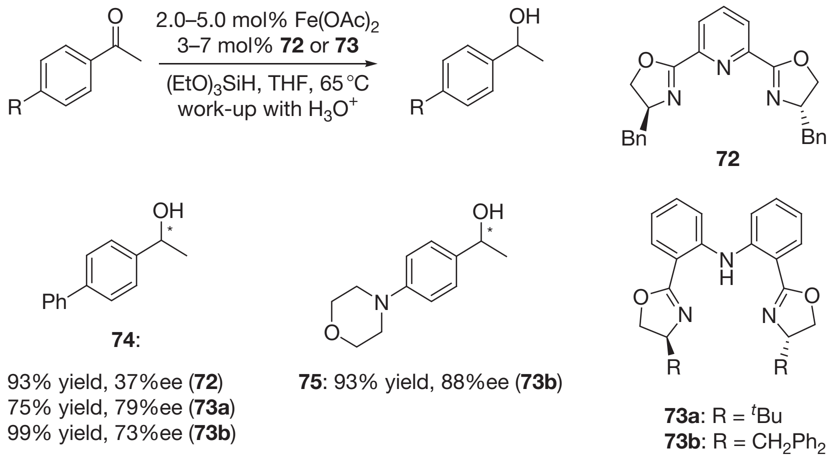
A further improvement of the enantioselectivity in the hydrosilylation of ketones was reported by the group of Beller by applying iron complexes modified by chiral phosphane ligands (Scheme 28).[54] After a survey of various chiral phosphane ligands with the *in situ* system composed of $Fe(OAc)_2$ and the bidentate ligand Me-Duphos **78**, enantioselectivities of up to 99% ee were attained for several substrates. Noteworthy, as the hydride source, also, the cheap, abundant, and safe polymethylhydrosiloxane (PMHS) was used. In addition, the non linear effect was studied, resulting in a linear behavior. The authors concluded the presence of a monomeric species as the active species.[55]

The concept of tridentate *N*,*N*,*N*-ligands was further improved by Gade and coworkers (Scheme 29).[56] They could demonstrate that catalytic amounts of iron complexes modified by chiral ligands performed the asymmetric hydrosilylation of ketones under mild conditions. After optimization of the ligand structure and the reaction conditions, a range of prochiral ketones were efficiently reduced to the corresponding alcohol with enantioselectivities of up to 93% ee. By contrast, dialkyl-based substrates gave somewhat lower enantioselectivities.

In their ongoing research, the group of Nishiyama modified the structure of the pybox ligands by replacing the pyridine nitrogen by a carbon to obtain complexes of type **82** (Scheme 30).[57] Initial tests showed an improvement of the enantioselectivity to 66% ee compared to pybox ligands.

6.18.4 Conclusion

The application of transition-metal catalysis for the creation of stereogenic centers in organic molecules is, nowadays, an established toolbox in organic chemistry. In the past, for example,



72

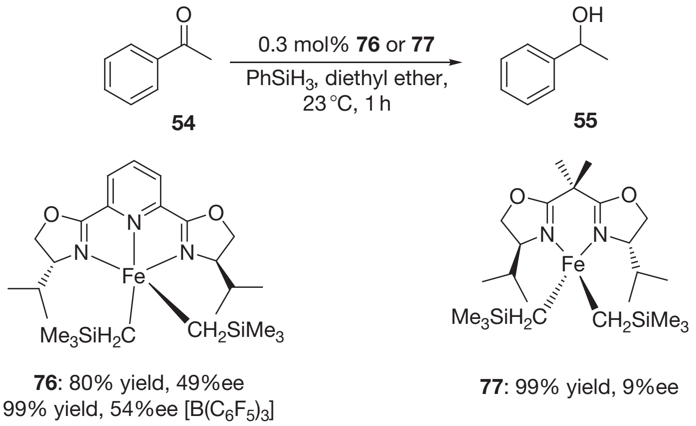
74:

93% yield, 37%ee (**72**)
75% yield, 79%ee (**73a**)
99% yield, 73%ee (**73b**)

75: 93% yield, 88%ee (**73b**)

73a: R = ^{t}Bu
73b: R = CH_2Ph_2

Scheme 26 Asymmetric hydrosilylation of ketones with iron catalysts according to the group of Nishiyama.



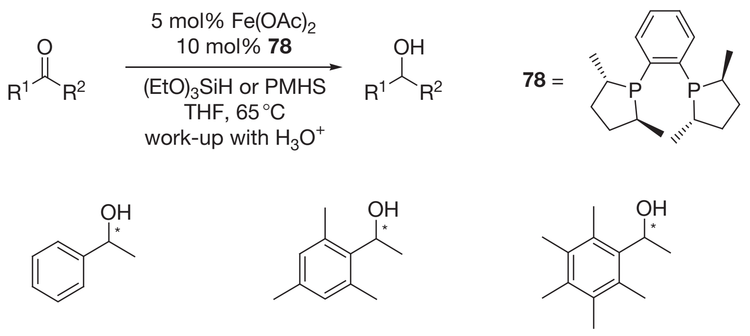
54

55

76: 80% yield, 49%ee
99% yield, 54%ee [$B(C_6F_5)_3$]

77: 99% yield, 9%ee

Scheme 27 Well-defined pybox iron complexes as precatalysts in the asymmetric catalytic hydrosilylation.

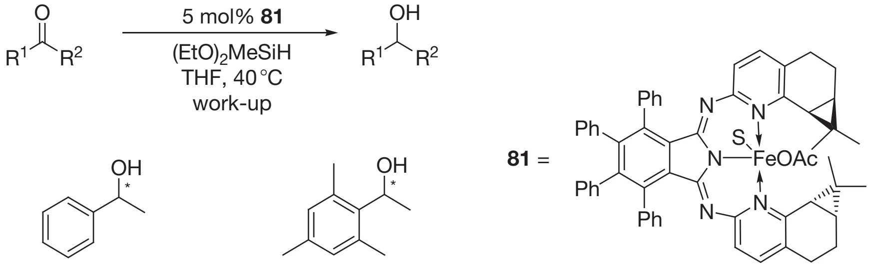


55: 85% yield
75%ee

79: >99% yield
99%ee

80: 45% yield
99%ee

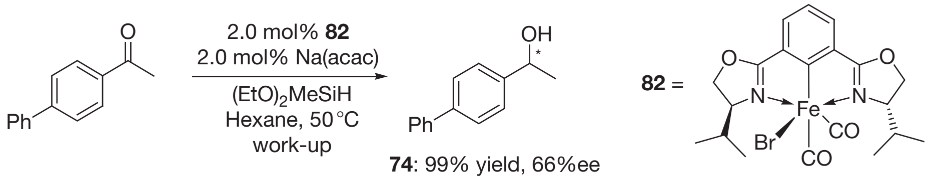
Scheme 28 Asymmetric hydrosilylation of ketones with iron catalysts modified by chiral phosphane ligands.



55: 85% yield
86%ee

79: 83% yield
93%ee

Scheme 29 Asymmetric hydrosilylation developed by Gade et al.



74: 99% yield, 66%ee

Scheme 30 Chiral iron complexes for hydrosilylation reactions.

rhodium, iridium, ruthenium, and palladium were the metals of choice. Currently, research focuses on the replacement of these metals with cheaper and low-toxic metals, such as iron. Unfortunately, a simple method transfer, in other words, the application of the same chiral ligands or the same reaction conditions, from well-established catalysts based on, for example, Rh, Ir, Ru, Pd to iron is not possible or showed difficulties. Hence, novel catalysts are highly desired. Indeed, initial studies have shown the potential of iron in asymmetric synthesis and interesting results have been observed. For the future, new catalysts, especially new chiral ligands, are desired for improved enantioselectivities and generality of the methods. Furthermore, for a deeper understanding of the reactions, the investigation of the reaction mechanism is crucial. For a related chapter in this Comprehensive, we refer to Chapter 6.12.

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6.19 From Carbon Dioxide to Valuable Products under Homogeneous Catalysis

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6.19.1 Introduction

Satisfying the energy demand of our society is mainly based on the use of fossil carbon, in its various forms: as solid coal, liquid hydrocarbons, or methane. More than 85% of the used energy comes from the conversion of chemical energy of fossil-carbon (fossil-C) into heat, electricity, mechanical energy, and other forms.[1] The combustion of wood contributes ~1–1.8% of the energy used worldwide. Such practice produces an ever-increasing amount of CO_2 that is emitted into the atmosphere and is continuously accumulated. Although there is no clear evidence but an alarming parallel among the growth of population/increase of energy consumption and the atmospheric concentration of CO_2,[2] being a greenhouse gas, the latter is considered to be the major contributor to climate change that may cause extreme events (high or low temperature, heavy rain, and dryness) that are out of human control. The average effect experienced by our planet is an increase of the average temperature, with worrisome consequences: increase of the level of the oceans, submersion of coastal areas, extreme dryness, and new illnesses and revamping of old illnesses, among others. This is pushing science and technology to find remedies that may stabilize the CO_2 concentration in the atmosphere or reduce it to lower values. The target is to keep the increase of the average temperature under control, which should not be higher than 2 °C until 2050.[3]

6.19.1.1 CO_2 Control Technologies: Efficiency Technologies Versus Capture of CO_2 from Flue Gases and Industrial Processes

The most efficient way to reduce the emission of CO_2 would be to introduce severe efficiency technologies both in the conversion of fossil fuels into other energies and in the use of such energy forms. Such an approach is winning under all aspects because it entails a correct use of energy and saves natural resources by reducing their consumption. The implementation of such technologies may be costly in some cases, for example, the transformation of power or other industrial plants with implementation of more sophisticated energy-saving technologies. Such costs should be equally shared among companies and our society, which has to pay an economic contribution for security, safety, and long-term availability of resources. Efficient technologies alone may not be able to solve the problem, but their contribution is of fundamental importance, especially for the correct use of energy that is the most immediate and economic route to cutting CO_2 emissions and implies a personal and collective responsibility.

In conjunction with efficient technologies, much attention is focused on the capture of CO_2 from flue gases generated in power plants or industrial processes,[4] For years, such technology has been considered the "solution" to the problem because, in principle, the disposal capacity of our planet is larger than the total production of CO_2,[5] and large volumes of CO_2 (60% of the total emitted CO_2) can be efficiently captured from point-continuous sources (such as power and industrial plants) before its emission into the atmosphere. The hidden trap is that such a technology has a high cost, not only economic but also energetic, and requires that more fossil carbon is extracted and more CO_2 is emitted to avoid CO_2 emission into the atmosphere: an endless spiral! The current technologies for CO_2 capture are based on the use of solids (basic[6] oxides or zeolites[7] or polymeric amines[8] or new materials[9]) or liquids (usually monoethanolamine[10] or water) that can reversibly take up CO_2 or on the use of physical methods such as membranes (which may have a selective permeability toward one or more components of a mixture of gases[11]) and cryogenic[12] techniques (which use the different liquefaction temperature of the components of a mixture of gases for their separation).

6.19.1.2 Disposal or Use of Captured CO_2?

Once CO_2 is separated from flue gases, two scenarios are possible: (i) disposal or (ii) utilization. For disposal, geological cavities,[13] aquifers,[14] or deep oceans[15] have been considered besides some curiosities, such as making an enormous solid sphere and storing it deep in the ground!

Although oceans would be able to store all CO_2 generated in the burning of all biomass and fossil-C on our planet,[15] they are not a practicable option. The effect of large volumes or masses of CO_2 (either as a labile hydrated-solid of formula $CO_2(5H_2O)$ or in a dissolved form that originates from a complex equilibrium of CO_2–H_2CO_3–HCO_3^-–CO_3^{2-} under pH control) on the marine environment is not well understood and raises concerns. In fact, preliminary studies have shown that large concentrations of CO_2 and the change in pH caused by CO_2 negatively affect the brains of fish.[16] Disposal in aquifers and depleted gas wells is already practiced by LNG extraction companies that store the CO_2 separated from methane to avoid payment of the carbon tax on carbon emitted into the atmosphere.[17] In addition, such a technology is not appropriate for general application because of the scarcity of sites and the energetic cost. A Department of Energy (DoE) study has shown that the separation and a 50-mile transport of separated CO_2 and housing cause the loss of ~20% of the energy produced by a power plant.[18] This is already a high energetic cost, and it increases with the distance of transportation, possibly reaching 40–50% for very long distances! Such a high energetic cost cannot be accepted because it would considerably shorten the availability of resources for next generations considered that, for the coming 30 years, fossil carbon will provide >80% of the necessary energy. Therefore, such technology can be practiced only under circumstances that guarantee a limited cost in terms of additional fossil carbon extraction; also, even if economically acceptable, such a solution may result not be viable because of its energetic demand.

6.19.1.3 The Utilization Option: Technological, Chemical, and Enhanced Biological Utilization

Separated CO_2 can also be used: three different approaches can be considered, namely a technological approach, chemical conversion, and enhanced biological fixation. In this volume, chemical conversion will be considered for the aspects inherent in this series. Technological utilization is discussed in Aresta[19] and enhanced biological conversion has recently been reviewed.[20]

The chemical utilization of CO_2 has been practiced for more than 150 years. The Solvay process (1861) for the synthesis of $NaHCO_3$ and Na_2CO_3, urea synthesis (1869), and the synthesis of salicylic acid (leading to aspirin, 1870) are examples of chemical utilization of CO_2. All such processes are pure thermal processes. Catalytic processes were introduced in the 1970s (conversion into methanol by addition to Syngas[21] and carboxylation of ethene epoxide).[22] In 1975, the first transition metal complex of CO_2 was reported.[23] Since then, the interest in the chemical conversion has experienced uphill and downhill trends, typically with an increase after the occasion of any oil crisis!

Today, the lack of oil or fossil carbon is not the driving force toward CO_2 utilization. Urgent environmental issues are calling for any useful action for limiting the CO_2 emission into the atmosphere.

It is interesting that the chemical utilization of CO_2, different from its disposal, is economically convenient because any use adds value to CO_2 that is considered a waste. However, the economic advantage is not enough to make chemical utilization a viable technology. In fact, any use must be environmentally beneficial and energetically viable. The chemical utilization of CO_2 is not, per se, a guarantee that CO_2 production is avoided, and avoiding CO_2 production is not synonymous with a more environmentally friendly process. The environmental impact of a product or process follows a complex pattern. **Table 1** gives the impact categories of a product emitted in soil, water, or the atmosphere; if, while reducing CO_2 emissions (that affects the impact on climate change), a process or product based on the conversion of CO_2 increases the impact on other categories, the final effect may not be beneficial. Therefore, the innovative technology used or the new synthetic pathway based on CO_2 must reduce the total environmental impact for being "environmentally more friendly" than technologies on stream; the "carbon footprint" does not tell the entire story of a process or product.

6.19.1.4 Catalysis at Work in CO_2 Conversion

This chapter considers the catalytic paths for CO_2 conversion into useful chemicals. Such conversion can be driven by homogeneous, heterogenized, heterogeneous, and enzymatic systems. For the purposes of this volume, the analysis will be

Table 1 Impact categories for emissions in soil, water, and atmosphere

Carcinogens (noncarcinogens)
Respiratory inorganics
Ionizing radiations
Ozone layer depletion
Respiratory organics
Aquatic ecotoxicity
Terrestrial acidification
Terrestrial nutrification
Land occupation
Aquatic acidification
Aquatic eutrophication
Climate change
Nonrenewable energy
Mineral extraction

limited to the conversion under homogeneous conditions, with some reference to enzymatic and heterogeneous catalyses that are not the key objectives of this chapter.

CO_2 is a molecule that lays in a potential energy well (with water, it is the end product of any combustion process, biotic or abiotic); it is a common belief that any chemical conversion of such a molecule requires energy. This is not completely true, as there are processes that are exoergonic. In fact, two categories of processes can be clearly distinguished for the use of CO_2:

(i) *Low-energy processes*: anytime CO_2 is incorporated, such as in an organic or inorganic substrate.
(ii) *High-energy processes*: anytime the oxidation state of the carbon atom is reduced from 4 down to 3, 2, 1, 0, and lower.

Table 2 shows the free energy of formation of a number of species, including C1 species, and inorganic and organic carbonates. It is quite evident that the synthesis of molecules in which the entire CO_2 moiety is used does not require a significant energy input.

Conversely, the production of C1 molecules with a reduced O content or increased H content requires energy. This brings to mind an immediate and easy-to-use tool for the rough evaluation of the energy content of a product with respect to CO_2: *given a substrate S and CO_2 that react to produce a product P, if, in the final product P, the H/C ratio is increased with respect to that of S, and the O/C ratio is decreased with respect to CO_2, the process will be endoergonic; conversely, if the H/C ratio is decreased with respect to S and the O/C ratio is increased (or remains unchanged) with respect to CO_2, the process will be exoergonic or neutral.*

A point of interest is that, although hydrogenation reactions (such as $CO_2 + 4H_2 \rightarrow CH_4 + 2H_2O$) show a decrease of the H/C ratio (that is infinite in H_2 due to the absence of C) and a decrease of the O/C ratio, they are characterized by a negative enthalpy. This result is due to the use of dihydrogen and to the formation of water. It must be taken into consideration that dihydrogen is not obtained for free and its formation requires energy.

Figure 1 shows the processes on stream, those under evaluation for potential industrial application and new processes of industrial interest. Here, attention is limited to molecules that may have a market >1 Mt per year; chemicals with a lower market may also be of scientific interest, but they will not significantly contribute to the carbon balance unless a specific case of consistent reduction of emission is encountered.

Table 2 Gibbs free energy of formation (ΔG_f°) for some C_1 and C_n compounds

Compound formula	*ΔG_f° (kJ mol^{-1})*
$CaCO_{3(s)}$	−1130
$C_2O_4{}^{2-}{}_{(aq)}$	−671
$HCO_3{}^{-}{}_{(aq)}$	−586
$CO_3{}^{2-}{}_{(aq)}$	−528
$CO_{2(g)}$	−394
$CO_{2(g)}$	−386
$HCOOH_{(l)}$	−361
$CH3OH_{(l)}$	−166
$CO_{(g)}$	−137
$CH_3C(O)CH_{3(g)}$	−113
$HC(O)H_{(l)}$	−102
$CH_{4(g)}$	−51
$C_6H_{14(l)}$	−4
$C_2H_{4(g)}$	+68
$C_6H_{6(l)}$	+124
$C_6H_{6(g)}$	+130

6.19.2 Fixation of the Entire CO_2 Molecule

In this section, the reaction of CO_2 to afford compounds in which the entire molecule is incorporated is discussed. In general, such processes occur under acceptable reaction coconditions from the energetic point of view and can be carried out also using a BAU approach.

The mild reaction conditions required can be explained by taking into account that the co-reagent is rich in energy. In fact, the species that react with CO_2 are either electron rich (e.g., all unsaturated hydrocarbons, amines, or alcohols) or are an energy vector, such as H_2. With the exclusion of dihydrogen, the coreagents considered in this section are easily available and often obtained via the petrochemical route: thus, they are interesting substrates for the fixation of CO_2 to produce species that today are prepared through tortuous, energy-intensive synthetic paths, with the production very often of large volumes of waste. At this point, it is worth recalling the concepts of 'E-factor' for a process and 'carbon utilization fraction (CUF).'

The 'E-factor'[24] expresses the ton of waste produced per ton of product. **Table 3** shows the E-factor for several processes and classes of products.

The CUF is a parameter of general application that tells how much of the starting carbon reaches the end use. One can calculate the CUF for the LNG extraction–distribution-use (how much of the extracted carbon really reaches the end user) or for a reaction (how much of the carbon content of the reagents remains in the final target product). A good process would have a CUF equal to 1, which means that no carbon is wasted. The CUF is linked to the 'carbon footprint' of a process.

6.19.2.1 Reaction with Olefins

The direct reaction of CO_2 with olefins has been attempted since 1980s because this represents an attractive route to the synthesis of a number of useful products. As an example, eqn [1] shows the synthesis of acrylic acid from ethene and CO_2.

$$CH_2 = CH_2 + CO_2 \rightarrow CH_2 = CH - COOH \qquad [1]$$

The enthalpy change of the reaction is slightly negative and, most interestingly, the CUF is equal to 1, that is, all carbon atoms of the reagents are found in the products. Such a reaction has been attempted using several transition metal systems as promoters. **Scheme 1** gives a view of the products formed: either a hydrido acrylate **(A)** is formed or a metallacyclecarboxylate **(B)**. Both **A** and **B** are stable compounds and do not release acrylic acid spontaneously. This is due to kinetic factors and to the barrier relevant to the cleavage of the M–H and M–O bonds. **Figure 2** shows the energy profile of the above reactions[25] and explains why acrylic acid is not released. Several attempts[26] have been made to push the acrylic acid out of the coordination sphere of the metal, including a recent

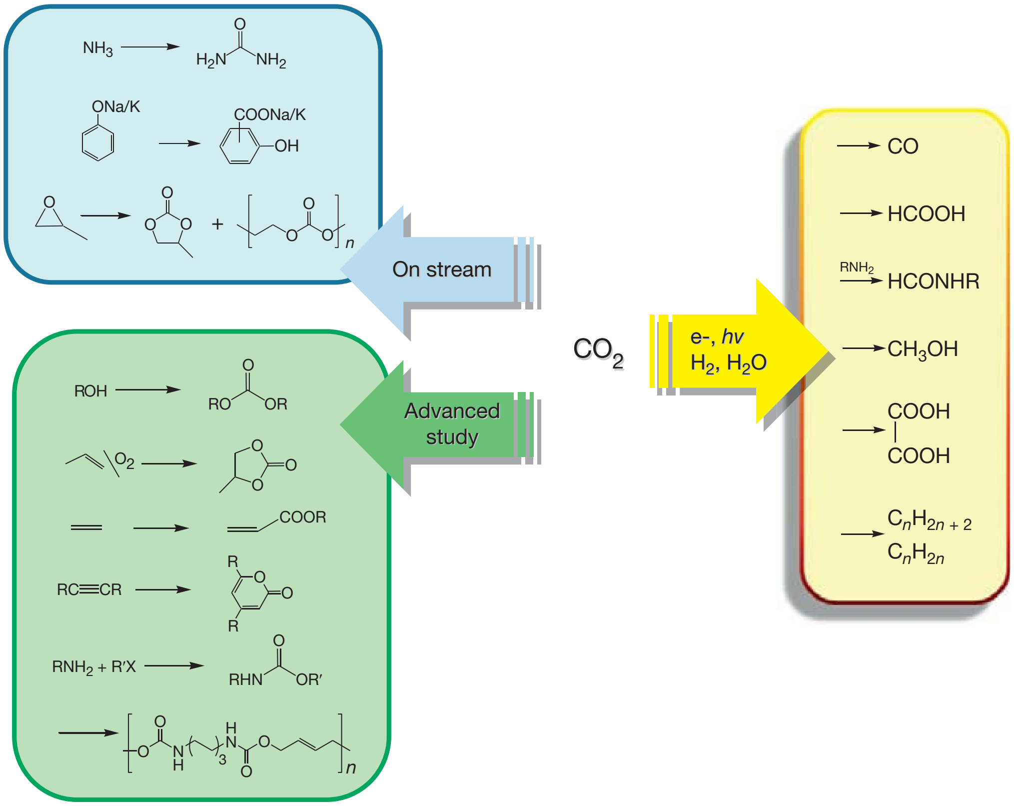
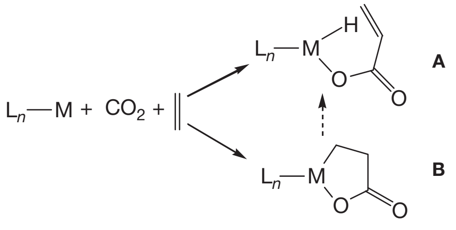


Figure 1 Synthetic processes for the production of chemicals from CO_2.

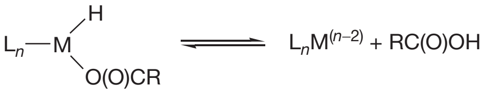
Table 3 E-factors of different classes of chemicals

Industrial application	*Market (tons year^{-1})*	*E-factor ($t_{waste}/t_{product}$)*
Petrochemicals	10^9	0.1
Intermediates	$>10^6$	0.5–1
Fine chemicals	10^5	5–100
Pharmaceuticals	10^4	100–250



Scheme 1 Reaction of CO_2 and ethylene at metal centers affording hydrido-metal-acrylate (**A**) or metalla-cycle carboxylate (**B**).

attempt based on the use of a basic phosphane.[26b] Also, in this case, as shown in Figure 3, acrylic acid was not released and a molecular rearrangement took place leading to the cleavage of P–C bonds and to the formation of stable acrylato-complexes. It is evident that the reaction depicted in eqn [2] is displaced to the left for kinetic and thermodynamic factors.



$$L_nM(H)(O(O)CR) \rightleftharpoons L_nM^{(n-2)} + RC(O)OH \qquad [2]$$

The theme of coupling ethene and CO_2 has recently been refaced. A new strategy has been investigated, namely, avoiding the formation of M–H and M–O bonds, by pushing the system toward the formation of M–C bonds of the type M–CH_2–CH_2–COOR.[26c] Such metallorganic species easily eliminate the acrylato ester CH_2=CH–COOR via a β-H shift with generation of a M–H species. Using a Pd-catalyst, it has been shown that the elimination of the acrylato ester is an easy reaction and the catalytic formation of such an ester was described, also, if limited to a few cycles. These results represent an indirect demonstration of the role of the M–H and M–O bond cleavage in preventing the elimination of acrylic acid from the hydrido acrylate complexes.

Other olefins have also been used. So, for example, norbornene and allylbromide have been coupled in the presence of CO_2 to afford double functionalized norbornane or functionalized condensed cycles.[27]

6.19.2.2 Reaction with Dienes

The chemistry of conjugated dienes (butadiene[28]) and cumulated dienes (allene[29]) has been investigated since the 1970–80s. The telomerization of 1,3-butadiene with CO_2 yields a variety of carboxylated products, such as δ- and γ-lactones, and carboxylic acids together with smaller amounts of linear

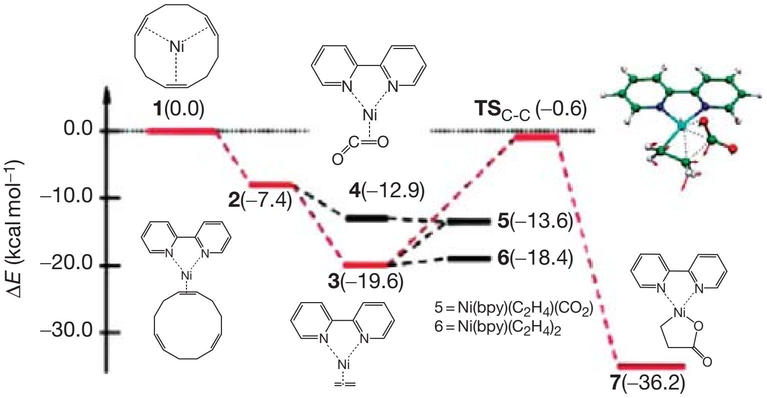


Figure 2 Energy profile for reaction of nickel complex with CO_2 and ethylene.[25]

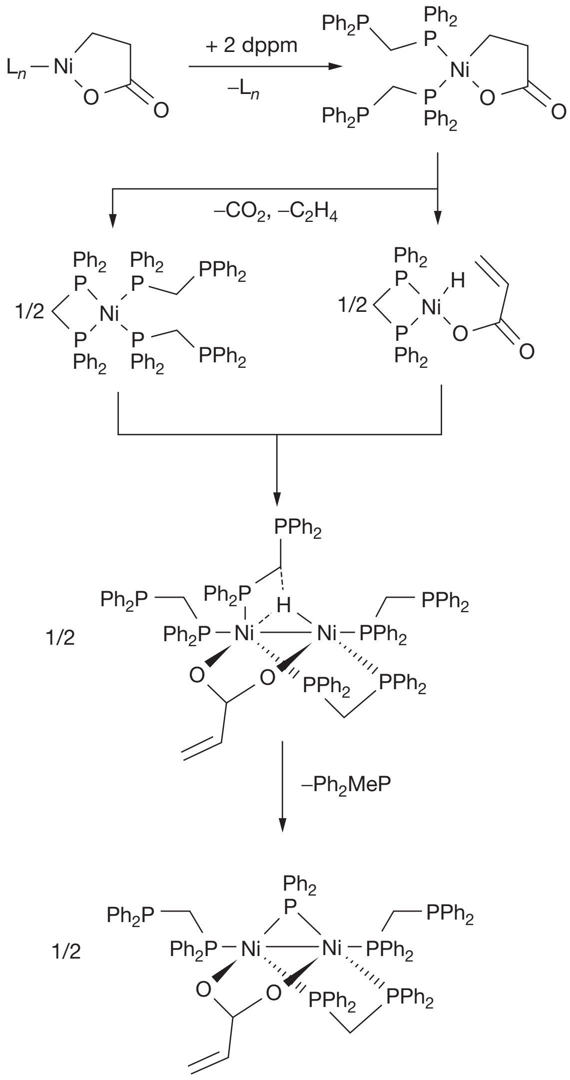
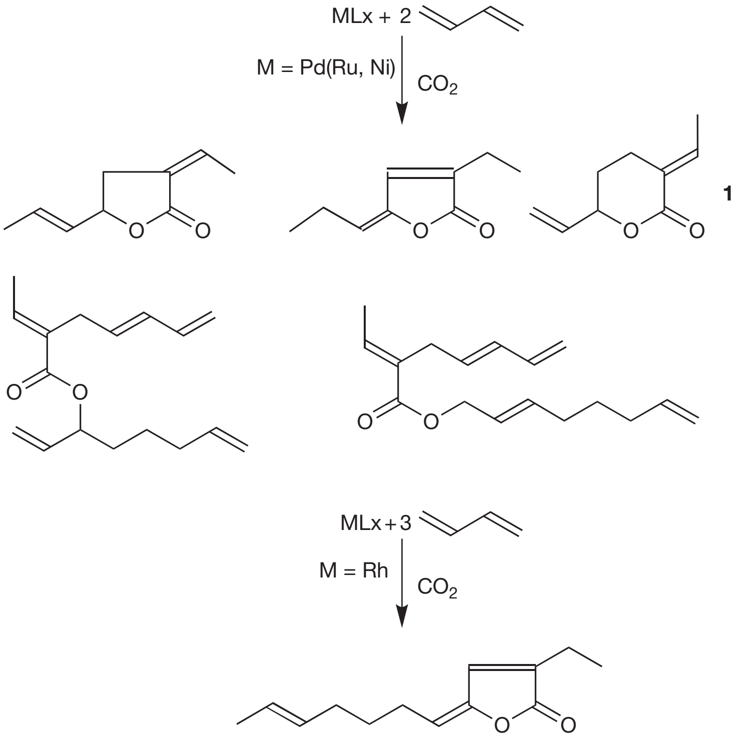


Figure 3 Formation of dinuclear Ni–Ni complex with three different bridging ligands (dppm, the carboxylato group of acrylate and a diphenylphosphido bridge).[26]

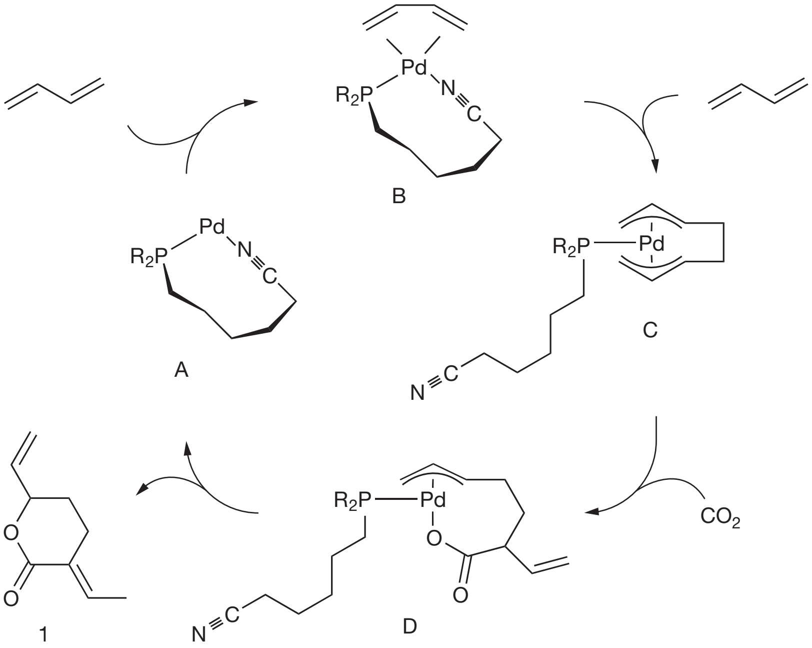
esters (Scheme 2). Further attempts[30] have been made to maximize the yield of the most interesting compound, namely, δ-lactone 2-ethylidene-6-hepten-5-olide (**1**).

Although several metal systems have been used, the most efficient catalysts were revealed to be Pd(0)-complexes of different natures.[31] The elective precursor is $Pd(acac)_2$, which is added with phosphanes having various structural characteristics, and the dependence of the activity of the Pd(0) formed in the reaction medium on the nature of the ancillary ligand has been demonstrated.[32] Both the basicity (σ-donating property) and the steric hindrance of the phosphane play key roles, and ligands with *i*-propyl and cyclohexyl groups facilitate the catalysis. Behr and coworkers have made a key contribution to improving the selectivity toward the six-membered lactone[32] by using either nitrile solvents or nitrile moieties as independent ancillary ligands in combination with phosphanes. Species such as $Pd(NCR)_x(PR_3)_4$ were proposed as the active and selective catalysts. The role of nitriles can be interpreted as that of a labile ligand able to protect–deprotect coordination sites on the metal. Such a 'nitrile effect' has been later used by incorporating the –CN moiety into a phosphane ligand to afford $R_2P–(CH_2)_n–CN$ bidentate ligands, in which one of the donating groups makes a strong bond (P) to Pd, while the –CN group may be loosely bound and can easily enter and leave the coordination sphere of the metal.[34] This tool makes it possible to carry out the reaction in any reaction medium (not necessarily nitriles), including 'CO_2-expanded' butadiene (solvent less reactions that ensure an easy recoverability of the products), affording excellent butadiene conversion (95%) with a good selectivity toward the lactone.[35]

For such systems, the reaction path can be summarized as in Scheme 3. The first step is the dimerization of butadiene (C) on Pd(0), followed by the CO_2 insertion (D) into the σ-Pd-allyl intermediate that yields a cyclic metalla-carboxylato species. The latter can undergo a reductive elimination of the lactone, thus, regenerating the active Pd(0) complex. Despite many efforts, the synthesis of optically pure isomers of the lactone has not been achieved.[36] Attempts have been made to find a large industrial use of the lactone as a co-monomer[37] or by converting it into an acyclic monomer with specific properties as a plasticizer (2-ethylheptanoic acid has been prepared in high yield by hydrogenation and ring opening[38]), or by hydroformylation and amination.[39]



Scheme 2 Conversion of butadiene into lactones and linear esters using various metal catalysts.



Scheme 3 Proposed mechanism for the Pd(0)-catalyzed telomerization of 1,3-butadiene with CO_2.

The latter approach has yielded amino acids that may have an application.[40] Such molecules have been obtained by selective 1,4-addition of morpholine to the double bond of the δ-lactone in the presence of Pt-complexes.

Behr and coworkers have also made an effort to develop strategies for catalyst recovery, and 1,2,4-butanetriol has been shown to be effective.[40,42] Immobilized catalysts were also used to simplify their recovery,[41] which has shown conversions and selectivities quite close to the soluble systems. Cyclic and linear carbonates have also been used as solvents, with the former showing a better conversion, while the selectivity remains dependent on the molecular structure of the carbonate.[43]

With Rh catalysts, butadiene is trimerized prior to CO_2 insertion.[28b] This is an interesting aspect because linear, more than cyclic compounds, can be formed that can be used in the synthesis of long-chain carboxylic acids that may find application in the sector of detergents and tensioactives.

Allene has been used in the coupling with CO_2. In general, the reaction is not selective and yields a mixture of linear esters.[29] A unique '2+2' coupling has been reported[44] that yields a tetra-atomic substituted lactone (**Scheme 4**).

In conclusion, the coupling of CO_2 with dienes is a very rich chemistry, documented by several alternative routes, depending on the catalyst used, that may afford products of industrial interest, but it still requires many fundamental studies before it can be applied.

6.19.2.3 Reaction with Alkynes

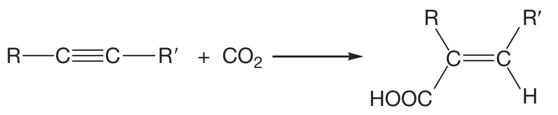
The reaction of alkynes with CO_2 is a topic investigated for a long time. After the pioneering work of Inohue et al.[45] on Ni systems for the carboxylation of alkynes, Hoberg and coworkers have greatly contributed to this chemistry in the 1980s, and discovered a number of interesting and potentially useful reactions.[46] This topic has recently been rediscovered, and efforts are currently underway to develop catalytic reactions for the carboxylation of alkynes to afford either terminal carboxylic acids or esters. Alkynes are also co-reacted with other substrates (i.e., olefins or amines) to afford organic products that are more complex. The role of catalysts in such reactions is of paramount importance.

Terminal alkynes bearing several substituents on the β-carbon (phenyl, substituted phenyl, diphenyl, thiophenyl, naphthyl, *n*-alkyl, *i*-alkyl, etc.) have been reacted in presence of Group 1 metal carbonates to produce the relevant terminal propiolyc acid with good yield (83–96%)[47] (eqn [3]).

$$R-C\equiv C-H+CO_2\xrightarrow{M_2CO_3}R-C\equiv C-COOH \qquad [3]$$

Similar results have been obtained by using a Cu(I) system with phenanthroline–phosphane ligands.[48]

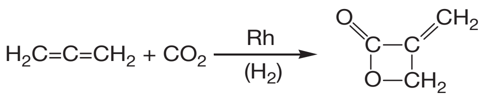
Internal alkynes and CO_2 in the presence of $Ni(COD)_2$ and diethylzinc have been shown to produce carboxylated alkenes (eqn [4]).



[4]

In ionic liquids, alkynes and γ-substituted allyl chloride in the presence of CO_2 undergo a coupling promoted by Cu(I) to produce propiolyl-acid esters with good conversion yields.[48]

The easy reactivity of alkynes is, thus, advantageously used in synthetic chemistry in conjunction with CO_2 fixation into organic molecules. Such chemistry is still worthy of investigation as it can be used for the synthesis of complex organic molecules bearing a carboxylic functionality.



Scheme 4 '2+2' coupling between CO_2 and allene affording tetra-atomic substituted lactone.[29]

6.19.2.4 Reaction with Active C–H Bonds

Transition metal-mediated carboxylation of organic substrates with CO_2 is of interest for the development of sustainable chemical processes based on the utilization of CO_2 in organic synthesis. The direct C–H carboxylation with CO_2 (eqn [5]) has been achieved only in a few cases and requires a stepwise approach based on the combination of C–H activation and CO_2 fixation. Despite efforts thus far, application of such a process, which has a tremendous potential in organic synthesis, has not yet been mastered. Only a limited number of substrates have been revealed as suitable for such direct carboxylation and the conditions are not so easy.

$$R-H+CO_2\rightarrow R-COOH \qquad [5]$$

Grignard reagents, organolithium compounds, and other metallorganic reagents, including organoboron, organozinc, and organotin reagents, usually obtained through reacting an organic halide with a metal compound or by the direct metallation of a C–H bond, have been used for stoichiometric carboxylation of organic substrates.[49]

Pioneering works have shown that Rh-phenyl complexes are easily converted into the corresponding Rh-benzoate.[50] Also, the phenate anion ($C_6H_5O^-$) coordinated in a η^6-mode to Mn(II) has been shown to be able to selectively activate the *para*-C–H bond of the benzene ring and convert the phenate into 4-OH-benzoic acid.[51] All such early examples of C–H carboxylation are more a 'metal-assisted' carboxylation in which one mol of metal is used per mol of organic product. The application is quite limited to specialty products, such as natural products and biologically active molecules, but is not usable for the synthesis of bulk chemicals, which require catalytic processes with high turnover frequency (TOF) and turnover number (TON).

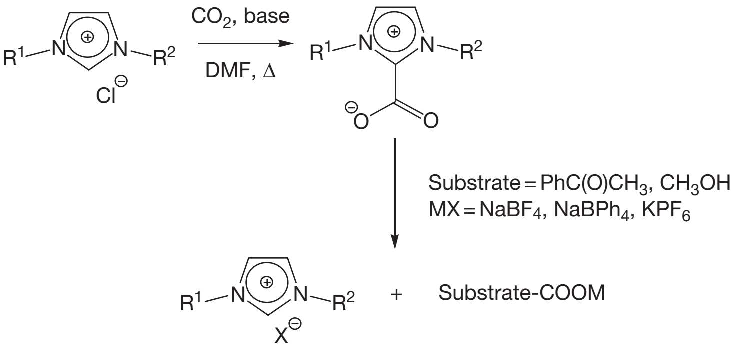
Direct catalytic C–H carboxylation has long attracted much interest.[52–56] Recently, transition metal systems, such as Pd,[57] Ir,[58,59] Rh,[60,61] Pt,[62–64] and Au,[65,67] have been used to activate the C–H bonds.

More recently, ionic liquids, such as imidazole derivatives bearing CO_2 bonded as a carbene moiety, have been shown to be able to transfer CO_2 to activated C–H bonds.[68] (**Scheme 5**).

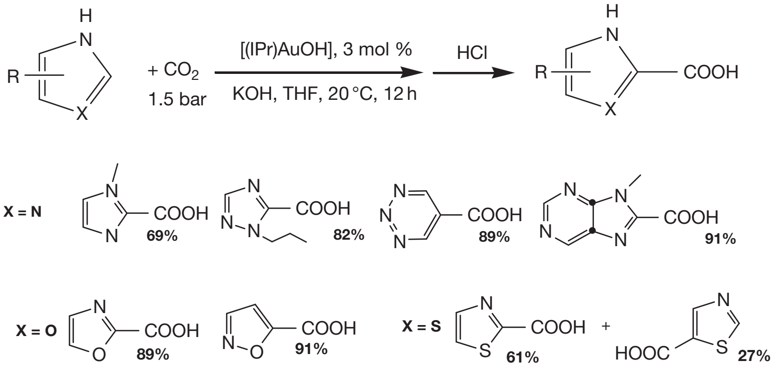
The potential of such carbene systems has been further investigated and, more recently, the catalytic carboxylation of C–H bonds promoted by gold(I) complexes has been described.[69] The N-heterocycles are activated by the Au(I) complex [(1,3-bis(diisopropyl)-phenylimidazol-2-ylidene) AuOH] and react with CO_2 in the conditions specified in **Scheme 6** to afford, after work-up, the carboxylic acid.

The overall yield is good and the regioselectivity results range from moderate to high. Interestingly, the carboxylation occurs also when two or more heteroatoms are present in the organic substrate. An interesting aspect is that the gold catalysts can be recovered and recycled and maintain their activity for up to six cycles. The N-heterocycles used in this work have very activated C–H bonds and represent unique cases.

The mechanism of such carboxylation has been explored using stoichiometric reactions and is proposed to step through the formation of a (heterocycle)C–Au bond via water elimination, implying that the –OH group is on Au and the active C–H of the heterocycle. This is followed by a CO_2 insertion and elimination



Scheme 5 Carboxylation of activated H-bonds using N-heterocyclic-CO_2 carbene moieties.



Scheme 6 Carboxylation of N-heterocycles mediated by Au(I).

of the potassium salt of the carboxylate with regeneration of the Au–OH bond. The isolated metalla-heterocycle complex and the relevant carboxylate are active in catalysis, which suggests that they are the intermediates in the catalytic cycle. Most recently, NHC–Cu complexes have been used by several groups.[70,71]

When common aromatic compounds (benzene derivatives) are used, carboxylation occurs quite efficiently only if electron-deficient groups are present in the ring, indicating that the C–H bond must be strongly activated (acidic C–H bonds) so that carboxylation may occur.[72]

With an excess of base, a double carboxylation of the aromatic substrate has also been observed.

Such direct carboxylation reactions are of great importance because, if they are developed to an application level, they may represent a revolution in the synthesis of several large market products such as carboxylic acids and similar. Such chemicals have a large market and are produced via complex or nonselective routes, often implying a low CUF due to oxidation of part of the skeleton.

The activity of the C–H bond is, thus, a crucial requisite for the carboxylation to occur. As it has been shown above, the activity is linked to the '*acidity*' of the C–H moiety that can be enhanced either (i) by controlling the *substituents* in the organic substrate or (ii) through the interaction of the substrate with an *ad hoc* designed '*intramolecular activating system*,' in general, a *metal system*. The former approach is possible with a limited number of substrates and yields products that are not of general use; the second approach is much more interesting and can bring to a variety of products of industrial use. Therefore, C–H activation plays a key role in the direct carboxylation of organic substrates, a reaction that formally can be represented as a CO_2 insertion into a C–H bond (eqn [5]).

6.19.2.5 Synthesis and Decomposition of Formic Acid

Among the processes that convert CO_2, its hydrogenation to afford formic acid and its derivatives is an extremely fashionable area of research. It must be pointed out that such process has been known for a long time, as the first report was by Farlow and Adkins in 1935 using Ni-Raney as catalyst.[73] The renewed interest toward such a process is mainly due to two important applications: (i) the easy reaction conditions for a chemical, such as formic acid, that is today produced through tortuous pathways that are energetically intensive and produce large amounts of waste[74]; (ii) the interesting prospect of using formic acid for energy-related technologies. In fact, formic acid has been identified as a potential liquid 'hydrogen carrier,' representing a very interesting alternative to solid materials for hydrogen storage and transport, issues that represent a considerable limit to the large-scale implementation of the hydrogen utilization as energy vector. The concept of using formic acid as a liquid hydrogen carrier is based on the combination of: (i) carbon dioxide hydrogenation using molecular dihydrogen; and (ii) the decomposition of formic acid into the starting carbon dioxide and hydrogen, so that a CO_2-neutral cycle can be performed. The attractive prospect of using CO_2

for hydrogen storage by converting it into a liquid carrier is subordinated to the development of process conditions, in terms of heat and pressure, that are as mild as possible in order to minimize the energy input. Homogeneous catalysis seems to be the most reliable route. Very brilliant results have been achieved in the field of homogeneously catalyzed hydrogenation of CO_2 and formic acid decomposition, as reported below in the two relevant sections. The development of a sustainable process of renewable hydrogen storage into formic acid and the decomposition of the latter to afford CO-free H_2 suitable for fuel cells represent big challenges.

The state of the art for the processes of homogeneous CO_2 hydrogenation and formic acid decomposition is summarized below, focusing mainly on the most recent achievements. These topics have recently been reviewed by several authors,[75–78] and a detailed discussion of the catalysts used can be found in these reviews.

6.19.2.5.1 Carbon dioxide homogeneous hydrogenation to afford formate salts

After Inoue reported the first example of a homogeneous catalyst for carbon dioxide hydrogenation in 1976,[79] several papers have been published and they have been reviewed by Jessop et al.[75] and Leitner,[76] in 1995, and again by Jessop et al. in 2004.[77] More recently, Beller and coworkers[78] highlighted the progress until 2010. The net reaction (eqn [6]) between

$$H_2(g) + CO_2(g) \rightarrow HCOOH\,(liq) \qquad [6]$$

gaseous H_2 and CO_2 to afford liquid formic acid is endoergonic ($\Delta G^\circ = +33$ kJ mol^{-1}) because of the strong entropic contribution. Conversely, carrying out the reaction in a condensed medium, such as dissolving the gaseous reagents in water (which results in multiple equilibria; eqn [7a]) or using a base (eqn [7b]) to afford formate salts instead of free formic acid, favors the thermodynamics of the process ($\Delta G^\circ = -4$ kJ mol^{-1} and $\Delta G^\circ = -35$ kJ mol^{-1}[75–78,80,81] for reactions [7a] and [7b], respectively). Interestingly, the hydrogenation of $HCO_3^-(aq)$ into aqueous formate, $HCO_2^-(aq)$, is also exoergonic.[81]

$$CO_2(aq) + H_2(aq) \rightarrow HCO_2^-(aq)H_3O^+(aq) \qquad [7a]$$

$$CO_2(g) + H_2(g) + NH_3(aq) \rightarrow HCO_2^-(aq)NH_4^+(aq) \qquad [7b]$$

It appears quite clear from the literature that the spontaneous release of formic acid from the catalyst, which exists in the form of a hydrido-formate complex, does not take place for kinetic and thermodynamic reasons. As a matter of fact, the elimination reaction of the acid [$\Delta H = \Delta H_{O\text{–}H} - (\Delta H_{M\text{–}H} + \Delta H_{M\text{–}O}) = 20\text{–}80$ kJ mol^{-1}] is thermodynamically not much favored if it is not an impossible process. It must be considered that the breaking of the M–O and M–H bonds can be the real barrier to smooth progression of the entire process (Scheme 7).

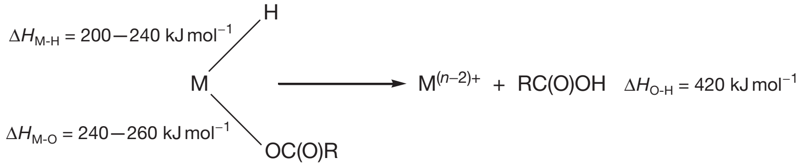
Therefore, either a cation is necessary that shuttles the formate moiety from the catalyst to the solution and keeps the anion blocked or a base is necessary that picks up the proton and again stabilizes the formate anion in solution. Free acid may easily add to the metal center in a low oxidation state in a back-reaction to afford the hydrido-formate complex thus, reverting the reaction.

As anticipated, the synthesis of formic acid has also been extensively reviewed very recently,[75–84] so this chapter is limited to presenting those systems that appear to be the most interesting from the point of view of TON and TOF (Table 4) and to showing the structural variability of ancillary ligands used by the various authors (Table 5).

As discussed above, the use of a base to afford formate is necessary for thermodynamic reasons, and, in addition, the production of formate salts should be of key importance for preventing the back dissociation of formic acid (eqn [8]). When conducting the reaction in water with strong bases, such as alkaline metal hydroxides, CO_2 is present in the form of hydrogen carbonate ions, so the hydrogenation of HCO_3^- may occur.

$$H_2 + CO_2 + B \rightarrow HCOO^-\ BH^+ \qquad [8]$$

The common active catalysts or precursors of homogeneous catalysts for CO_2 hydrogenation are transition metal-hydride complexes of group from 8 to 10. In particular, Ru(II) and Ir(III) complexes have shown very high activity, as reported below. Phosphorous ligands are often used to stabilize metal-hydride active species. Water-soluble catalysts are employed for hydrogenation in water, by using modified ligands such as

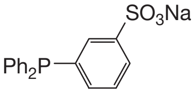
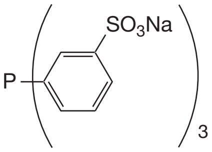
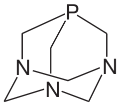
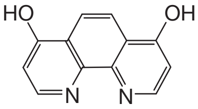
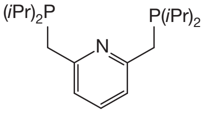


Scheme 7 ΔH for the elimination of free acid from a hydrido-metal formate.

Table 4 Recent improvement of homogeneous catalysts for CO_2 hydrogenation

Catalyst precursor	*Solvent*	*Additives*	*P(H_2,CO_2) atm*	T *(°C)*	t *(h)*	*TON*	*TOF (h^{-1})*	*Reference*
$RuH_2(PPh_3)_4$	Benzene	NEt_3, H_2O	25, 25	RT	20	87	4	79
$RhCl(tppts)_3$	H_2O	$NHMe_2$	20, 20	RT	12	3,439	287	85
$RuCl(OAc)(PMe_3)_4$	$scCO_2$	NEt_3/C_6F_5OH	70, 120	50	0.3	28,500	95,000	87
[Cp*Ir(phen)Cl]Cl	H_2O	KOH	30, 30	120	48	222,000	33,000	89
$IrH_3(PNP)$	H_2O	KOH	30, 30	120	48	3,500,000	73,000	90

Table 5 Structural features of ancillary ligands in homogeneous metal complexes active in the hydrogenation of CO_2

Ligand	*Acronym*	*Structure*	*Metal used*	*Solvent*	*$P(H_2,CO_2)$ (MPa)*	*T (K)*	*TOF (h^{-1})*	*TON*	*Reference*
Triphenyl phosphane	TPP	$P(C_6H_5)_3$	Ru	Benzene	2.5, 2.5	RT	4	87	79
Trimethyl phosphane		$P(CH_3)_3$	Ru	sc-CO_2	8, 14	323	1400	1400	88
1,1-Bis(diphenyl phosphino)methane	dppm	$(C_6H_5)_2P\text{-}CH_2\text{-}P(C_6H_5)_2$	Ru	Acetone	3.8, 3.8	RT	103	2160	94a
Tris[2-(diphenylphosphino) ethyl] phosphane	PP_3 (tetraphos)	$P(CH_2CH_2PPh_2)_3$	Fe	MeOH	6, HCO_3^-	353	31	610	91
Sodium triphenylphosphane *meta*-monosulfonate	*m*-TPPMS		Ru	Water	6, 3.5	353	9600	320	94b
Sodium triphenylphosphane trisulfonate	TPPTS		Rh	Water	2, 2	RT	287	3439	85
1,3,5-Triaza-7-phosphaadamantane	TPA		Ru	Water	10, HCO_3^-	353	409		94c
4,7-Dihydroxy-1,10-phenanthroline	DHPT		Ir	Water	3, 3	393	33 000	222 000	89
2,6-Bis-[(diisopropylphosphanyl)-methyl]-pyridine	^{i}Pr-PNP		Ir	Water	3, 3	393	73 000	3 500 000	90

sulfonated phosphanes. This is the case of the Wilkinson catalyst water-soluble analog $RhCl(tppts)_3$ (tppts = sodium triphenylphosphane trisulfonate) reported by Gassner and Leitner in 1993, who have reached a TON > 3400.[85]

Other different rhodium-based catalysts have been used and are reported in the review cited above by Jessop and Beller, who also cover ruthenium(II) water-soluble phosphane complexes employed as catalysts for CO_2 hydrogenation by Lawrenczy and coworkers (for a recent work see Jessop[86] and references therein). Here, the best performance catalyst is underlined (**Table 4**), $RuCl(OAc)(PMe_3)_4$, by Jessop and coworkers,[87] with an impressive TOF of 95 000 h^{-1}, improving the discovery of the high activity of $RuH_2(PMe_3)_4$ in supercritical carbon dioxide by Noyori in 1994.[88] Iridium(III) complexes have been found to be very active in water, as demonstrated by Himeda in 2007 (who also reviewed the water-soluble catalysts)[89] with phenanthroline–cyclopentadienyl complexes, and later by Nozaki and coworkers, who, in 2009, discovered the most active catalyst for CO_2 hydrogenation, at the state of the art, an Ir(III) hydride with PNP-pincer ligand, which has an extraordinary TON, up to 3 500 000.[90]

The latest advances in the field of homogeneous catalysis for CO_2 hydrogenation are represented by the works by the Beller group on nonprecious metal complexes such as iron complexes, and Azua et al., who very recently used *i*PrOH/base systems in place of molecular hydrogen as the hydrogen donor. Beller and coworkers reported the use of tetraphosphane ligands for in situ generation of Fe(II) catalysts active at 80°C and 6.0 MPa of H_2 for hydrogen carbonate hydrogenation in methanol with a TON of 610, comparable with the activity of $\{RuCl_2(benzene)\}_2$/tetraphos precursor.[91] $\{RuCl_2(benzene)\}_2$ has also been used in a recent publication by Federsel et al. coupled with dppm ligand for hydrogencarbonate hydrogenation in water reaching a TON of 2518 and a TOF of 1259 at 70°C and $P(H_2/CO_2) = 50/35$ bar.[92] Instead, in 2011, Azua et al. reported iridium and ruthenium carbene catalysts with TON of 151 300 for hydrogenation of CO_2 with molecular hydrogen and a TON of 2700 for hydrogenation using *i*PrOH/base as the hydrogen donor at 200°C.[93]

Such reactions are usually carried out in an organic medium, in sc-CO_2, or in water. For the reasons given above, water seems to be an excellent solvent. Unfortunately, water is not a very good solvent for CO_2 itself if the pH of the solution is not basic. The use of water requires the development of ancillary ligands that may make the catalyst water soluble. The tuning of the properties of the ligand seems to be essential for improving the activity of the catalyst. Also, the pH of the solution may affect the solubility of the catalyst, depending on the ancillary ligands. This is a crucial issue because the concentration of the metal in solution strongly affects the conversion rate and efficiency of the process. Another key issue is the stability of the starting complexes in water because they can easily de-coordinate the ancillary ligands and be converted into aqua-complexes, which may have an activity much different from that of the original catalysts.

The ancillary ligands, besides driving the solubility in water solutions, also control the catalytic activity through governing the charge density at the metal center. Theoretical calculations[95] coupled with experimental results[96] suggest that electron-donating ligands would enhance the catalytic activity of metal centers; these early findings have been confirmed by more recent, sophisticated studies based on the Hammett equation.[97]

The ancillary ligands also drive the recovery of the catalyst and products from the final reaction mixture. In fact, in some cases, ligands have been shown to undergo protonation, which reduces their solubility in the reaction medium and converts the soluble complexes into insoluble species. This latter aspect is of interest because the separation of the catalyst during the depressurization phase may prevent the reverse reaction of formate dehydrogenation. Half-sandwich catalysts with ligands dhbp and dhpt (dhbp = 4,4′-dihydroxy-2,2′-bipyridine; dhpt = 4,7-dihydroxy-1,10-phenanthroline) have intensively been investigated for their capacity of converting into insoluble species at the end of the reaction, affording an easy separation and facile work-up of the reaction medium.[98]

Very recently, the use of glycerol as H-donor for CO_2 reduction has been documented,[99] a reaction of great interest, which converts waste into useful products. In this case, the ancillary ligands play a key role in determining the species formed upon oxidation of glycerol.

6.19.2.5.2 Decomposition of formic acid to afford dihydrogen and CO_2

Even though examples of homogeneously catalyzed formic acid decomposition are as old as 1967,[100] the development of efficient catalytic system for HCOOH decomposition into H_2 and CO_2 has only recently been investigated in detail.[101] The generation of hydrogen from alcohols (such as methanol, which could be a competitor for using CO_2 for 'hydrogen storage') requires high temperatures; formic acid decomposition occurs in milder conditions, even at room temperature. Looking at reaction [6], it is obvious that the decomposition of liquid formic acid into gaseous CO_2 and H_2 (eqn [9]) is fairly thermodynamically advantageous ($\Delta G^\circ = -33$ kJ mol^{-1}), as it is the inverse reaction with respect to eqn [6]. Nevertheless, the decomposition of formic acid can follow an alternative pathway, that is, the dehydration/decarbonylation reaction [10], which is also moderately exoergonic ($\Delta G^\circ = -12$ kJ mol^{-1}).[101b]

$$HCO_2H(l) \rightarrow CO_2(g) + H_2(g) \tag{9}$$

$$HCO_2H(l) \rightarrow CO(g) + H_2O(l) \tag{10}$$

Clearly, eqn [10] is an undesired reaction in terms of producing CO-free H_2 to be used for fuel cells, so that the homogeneous catalysts under development are aimed at selectively promoting the decarboxylation/dehydrogenation pathway. **Table 6** presents some of the most active catalysts for HCOOH-selective decomposition into CO_2 and H_2.

In the last 2 years, different groups have published new catalytic systems for homogeneous formic acid decomposition. Very recently, ionic liquids have been employed to dissolve ruthenium catalyst precursors with interesting results, as in the case of $RuCl_3$ dissolved in 1-ethyl-2,3-dimethyl-imidazolium acetate, which shows a TOF of 850 h^{-1} at 120°C and a 100% H_2 yield[108] or $\{RuCl_2(p\text{-cymene})\}_2$ with a TOF of 600 h^{-1} at 60°C[109] or 1,540 h^{-1} at 80°C with 91% conversion[110] in various ionic liquids. In another very recent work,[111] $[Ru_4(CO)_{12}H_4]$ is reported to be the active homogeneous catalyst in dimethylformamides (DMF) for homogeneous formic acid decomposition. $RuCl_2(DMSO)_4$ has also been employed with a base for formic acid decomposition in a continuous-flow reactor.[112] Water-soluble catalysts have also been used for hydrogen generation from formic acid. Half-sandwich rhodium and ruthenium bearing 4,4′-dihydroxy-2,2′-bipyridine or sulfonated phosphane ruthenium complexes have been shown to be active catalysts.[113,114] A mechanistic study of $PtH(PP_3)$ [with PP_3 = tris[2-(diphenylphosphanyl)ethyl]phosphane] has also been reported at 35°C in CD_2Cl_2.[115] Finally, with a similar approach used for CO_2 hydrogenation, iron-based catalytic systems such as $[Fe(CO)_3(PBn_3)_2]$ (Bn = benzyl) + 1 equiv. of 2,2′:6′2″-terpyridine (tpy) (TON 247)[116] and inexpensive $Fe_3(CO)_{12}/PPh_3$/1,10-phenanthroline (TON 126)[117] have been used at 60°C under Xe-light irradiation assistance for degradation of triethylamine/formic acid (2:5) mixtures.

6.19.2.6 Synthesis of Carbamates and Polyurethans via Reaction with Amines

The reaction of amines with CO_2 has great importance not only for synthetic purposes[118] but also for technological applications. In fact, amines, mostly monoethanolamine (MEA), but also diamines and polyamines, are used as 'CO_2 scrubbers' for CO_2 capture from flue gases.[119,120] Carbamic moieties play a key role in biological systems, both in the photosynthetic

Table 6 Homogeneous catalysts for formic acid decomposition

Catalyst	*Substrate*	T (*°C*)	*TON*	*TOF (h^{-1})*	*Selectivity*	*Reference*
$IrH_3(PPh_3)_3$	HCO_2H in acetic acid	118	>11 000	8890	No free CO	100
$Pt(P^iPr_3)_3$	HCO_2H in acetone/water	20	25	100		102
$Ru_2(\mu\text{-}CO)(CO)_4(\mu\text{-}dppm)_2$	HCO_2H in acetone	RT	2000	~500	No free CO	103
$[Rh(Cp^*)(bpy)(H_2O)](SO_4)$	HCO_2H/HCO_2Na in water	25	80	30	No free CO	104
$[Ir\ (Cp^*)(DHbpy)(H_2O)](SO_4)$	HCO_2H in water	90	<10 000	14 000	No free CO	105
$[Ru(H_2O)_6](tos)_2$/TPPTS	HCO_2H/HCO_2Na in water	120	>40 000	460	No free CO	106
$[RuCl_2(benzene)]_2$/dppe	$5HCO_2H/4HexNMe_2$	40	5716	1905	No free CO	107

Adapted from Johnson, T.C.; Morris, D.J.; Wills, M. *Chem. Soc. Rev.* **2010**, *39*, 81; Loges, B.; Boddien, A.; Gartner, F.; Junge, H. M. *Beller Top. Catal.* **2010**, *53*, 902.

reduction of CO_2 promoted by RuBisCO (ribulose 1,5-bisphosphate carboxylase oxidase) and in the physiological elimination of N-compounds. The interaction of CO_2 with amines, mediated or not by metal or nonmetal species, yields the carbamate moiety, 'RR′NCO_2,' either ionic or covalently bound to an electrophilic center.[118,121] The direct interaction of CO_2 with some secondary amines has been shown to afford the relevant carbamic acid (eqn [11]).[125]

$$RR'NH + CO_2 \rightarrow RR'NCO_2H \qquad [11]$$

In general, primary or secondary amines alone (eqn [12a]) or in the presence of metals, metal salts, or metal complexes (eqn [12b]) react with CO_2 to afford ammonium carbamates or metal carbamates, respectively.[121]

$$2RR'NH + CO_2 \rightarrow \left(RR'NH_2\right)O_2CNRR' \qquad [12a]$$

$$RR'NH + L + MBPh_4 + CO_2 \rightarrow M\left(O_2CNRR'\right) + [HL]BPh_4 \qquad [12b]$$

$$R' = H,\ \text{alkyl},\ L = RR'NH;\ R = \text{aryl},\ R' = H,\ L = NR''3\left(R'' = \text{alkyl}\right);\ M = Li,\ Na,\ K$$

CO_2 can formally insert into the M–N bond of amides to afford metal carbamates. The carbamate moiety 'RR′NCO_2^-' thus generated can be transferred to a suitable organic substrate, or used as precursor of ureas and/or isocyanates. This innovative chemistry aims to supplant old technologies based on phosgene that have been used thus far for producing carbamic acid esters, isocyanates, and ureas. Carbamic acid, H_2NCO_2H, has been detected by neutralization–reionization mass spectrometry or by IR spectroscopy as a solid at low temperature.[122] The stability of the solid is due to intermolecular hydrogen bonding of the zwitterions form $^+H_3NCOO^-$. Carbamic acid N-coordinated to Pd(II) has been identified by ^{13}C-NMR spectroscopy (signal at 174.3 ppm) in the Pd-catalyzed hydrolysis of urea.[123] Theoretical studies have shown that the *syn* conformer is more stable than the *anti* one, and that gaseous carbamic acid exothermically yields ammonia and carbon dioxide ($\Delta H° = -26\ \text{kJ mol}^{-1}$), most probably through the zwitterion $^+H_3NCOO^{-124}$. Carbamic acids, derived from primary or secondary amines, RR′NCO_2H, are elusive species that easily give back CO_2 and the amine. Their isolation has only recently been accomplished using either dibenzylamine (Bz_2NH) or the Co-aminophosphane complex $CoCl(NO)_2[PhP(OCH_2CH_2)_2NH]$. In both cases, XRD results have shown that the acids are H-bonded dimers characterized by a O–H...O distance of 122 pm, the same as in dimeric carboxylic acids.[125,126] Such species have also been identified in solution.

A few industrially relevant amino-silanes ($H_2N(CH_2)_3Si(OMe)_3$, $H_2N(CH_2)_3Si(OEt)_3$, $H_2N(CH_2)_2NH(CH_2)_3Si(OMe)_3$, and $H_2NC(O)NH(CH_2)_2NH(CH_2)_3Si(OMe)_3$) have been shown to react with CO_2 at 300 K affording classic ammonium carbamates $(RNH_3)O_2CNHR$, while at 273 K, dimeric carbamic acids, $[RNHC(O)OH]_2$, are formed.[127]

The mechanism of reaction of amines with CO_2 to afford the acid and the ammonium salts has also been investigated with a theoretical approach[128]: an activation enthalpy of 40 kJ mol^{-1} has been calculated, in good agreement with experimental data.

Besides the Solvay process, synthesis of urea from NH_3 and CO_2,[129] new applications have recently been emerging.

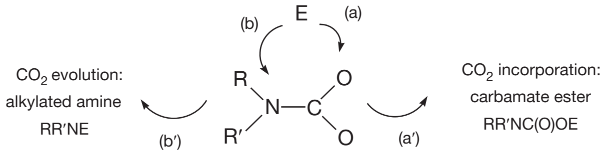
As anticipated above, amines and polymer-bound amines are used for removing CO_2 from flue gases. Several systems, including ionic liquids (eventually[130] incorporating $-NH_2$ groups in their structure and amine-containing dendrimers),[131] hydrogels,[132] and diamines[133,134] have been proposed for such uses.[135] Organogels[136] and supramolecular polymers have also been prepared.[137] Computational studies have been carried out to evaluate the parameters of the reaction.[138] Recently, the chemistry described above has been employed for preparing switching-polarity solvents.[139]

Carbamate esters are used in pharmacology (drugs, prodrugs)[140] and in agrochemicals, in synthetic chemistry as suitable intermediates for protecting amino groups,[141,142] as linkers in combinatorial chemistry,[143b] or as precursors of ureas,[143] isocyanates, and polymers.[143c] They are usually prepared from $COCl_2$.[144] The development of phosgene-free routes to carbamates is a synthetic challenge because the carbamate anion, $^+RR'NCO_2^-$, is an 'ambident nucleophile' at the oxygen ends and the carbamic nitrogen atom. The formation of a carbamate ester based on the use of the spontaneously generated carbamate anion from the amine and CO_2 implies that the attack by an electrophile (R^+) is selectively directed to one of the O-atoms, a non-trivial step. In fact, an electrophilic attack on the N-atom is possible and implies the elimination of CO_2 from the carbamic moiety, with formation of undesired side-products (**Scheme 8**, left-hand side).

Elective agents for the alkylation of the carbamate moiety are alkyl halides or dialkyl sulfates or dialkylcarbonates: the transfer of the carbamic group from a metal center or the ammonium ion to such alkylating agents has been documented in only a few cases.[121a,b,145,146] The reactivity of metal or ammonium carbamates (obtained in many different ways[147]) toward alkyl halides can be modulated by suitably changing the electrophilicity of the cation[147]: if a suitable complexing agent (crown-ether, criptand) is used,[148] the electrophilic attack occurs very selectively at the O-atom of metal carbamates or ammonium carbamates.

Carbamate esters have been prepared, under mild conditions, using suitable sterically hindered and strong organic bases B, such as amidines,[149] pentaalkylguanidines,[149] and phosphazenes.[149–151] DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) is largely used,[149,150] as well as pentaalkylguanidine superbases, such as CyTMG.[149] Tetraethylammonium superoxide,[152] basic resins,[153] triton-B (benzyltrimethylammonium hydroxide),[154] and K_2CO_3 in the presence of catalytic amounts of $(Bu_4N)I$[155] have been used, as well as alkyltosylates.[153–155]

The base has also been generated electrochemically by cathodic reduction of O_2 to superoxide.[156] The electrochemical



Scheme 8 Interaction of a carbamate group with an electrophile E.

activation of CO_2 to radical anion CO_2^{-}, in conventional solvents[157] or in ionic liquids, also promotes the formation of carbamate esters from aromatic or aliphatic amines and alkyl halides under mild conditions.[156–158]

The use of heterogeneous catalysts in the synthesis of urethanes from aliphatic and aromatic amines, CO_2, and alkyl halides has been explored only recently. Titanosilicate molecular sieves, metal phthalocyanine complexes encapsulated in zeolite-Y,[159] beta-zeolites and mesoporous silica (MCM-41) containing ammonium cations as the templates, and adenine-modified Ti-SBA-15[160] work as effective catalysts even without any additional base. Aziridines and azetidines have been co-polymerized with CO_2 to afford polymeric materials (polyurethans).

6.19.2.7 Synthesis of Acyclic Carbonates via Carboxylation of Alcohols

The substitution of phosgene ($COCl_2$) in the synthesis of organic carbonates is not an easy task because $COCl_2$ promptly reacts with alcohols (eqn [13]) already at room temperature and does not require any catalyst. Substitutes of phosgene are CO_2 (eqn [14]), urea (eqn [15]), or CO/O_2 (eqn [16]). In this chapter, only the first two reagents will be considered because they are relevant to the topic discussed here.

$$2ROH + COCl_2 + 2Base \rightarrow (RO)_2CO + 2Base \cdot HCl \quad [13]$$

$$2ROH + CO_2 \rightarrow (RO)_2CO + H_2O \quad [14]$$

$$2ROH + (H_2N)_2CO \rightarrow (RO)_2CO + 2NH_3 \quad [15]$$

$$2ROH + CO + 1/2O_2 \rightarrow (RO)_2CO + H_2O \quad [16]$$

Routes [14] and [15] can be considered (i) a direct use and (ii) an indirect use of CO_2, respectively. Ammonia formed in eqn [15] can, in principle, be recovered and reacted again with CO_2 to afford urea. Alternatively, the so-called transesterification reaction could be used, which converts a carbonate into another (eqn [22a]).

Routes [13]–[16] are characterized by a different environmental impact, and direct synthesis [14] is by far the most environmentally friendly reaction, as demonstrated by an LCA study.[161] The patent literature and the scientific literature show the industrial interest in such processes and the research efforts for identifying the most promising catalysts. A recent review on the synthesis of acyclic carbonates is available in Ballivet-Tkatchenko and Dibenedetto.[162] Several heterogeneous catalysts that are out of the scope of this chapter have been used[163]: only homogeneous catalysts are considered here.

Group 1 and 2 carbonates can be reacted with alkyl halides RX (X=Cl, Br, I) under phase-transfer conditions to afford symmetrical and unsymmetrical dialkyl carbonates below 400 K.[164] Satisfactory yields are also obtained by reacting alcohols and halides with pressurized CO_2 in the presence of strong bases[164] in ionic liquids.[165] The existing trend to reduce or exclude the use of halogenated organics limits such routes as effective alternatives to phosgene. The catalytic conversion of alcohols and CO_2 is by far the most attractive route to organic acyclic carbonates.

In principle, the reaction path for reaction [14] can be depicted as in eqns [17]–[20], where A is an acid and B is a base.

$$ROH + B \rightarrow RO^{-}\ BH^{+} \quad [17]$$

$$RO^{-} + CO_2 \rightarrow ROC(O)O^{-} \quad [18]$$

$$ROH + A \rightarrow R^{+} + AOH \quad [19]$$

$$RC(O)O^{-} + R^{+} \rightarrow ROC(O)OR \quad [20]$$

Increasing the CO_2 pressure may help to shift eqn [18] to the right, increasing the concentration of the hemicarbonate species, a key reagent for the synthesis of the organic carbonate. Reaction [14] suffers thermodynamic limitation because the ΔG° is in the range 0–4.6 kcal mol^{-1}, depending on the aliphatic group R. For aromatic phenols, the reaction is endoergonic. This means that, at the reaction temperature (above 400 K), the equilibrium position is shifted to the left and the equilibrium concentration of the carbonate may be as low as 1–2% or lower. Moreover, the use of gaseous CO_2 does not help to improve the thermodynamics because the entropic factor is also not in favor of displacing the equilibrium to the right. Only under very severe pressure (>300 MPa) is the reaction shifted to the right. These thermodynamic considerations distinguish the two possible techniques for running the catalytic process: (i) liquid alcohol pressurized with CO_2 or (ii) supercritical CO_2 plus the alcohol. Case (i) is governed by the solubility of CO_2 in the co-reagent alcohol; case (ii) improves the thermodynamics from the point of view of the availability of CO_2 but requires that alcohol and CO_2 be in a single phase in order to better react. As a matter of fact, the use of sc-CO_2 produces a better conversion of alcohols. So far, great attention has been paid to the synthesis of dimethylcarbonate (DMC) from methanol and CO_2,[162] but, recently, the synthesis of diethylcarbonate (DEC) is a target because DMC and DEC have quite similar properties and DEC can be prepared from bioethanol, giving a 'bio-derived' label to DEC and processes in which it is used.

DEC[166] has been obtained from ethanol under 1 MPa of CO_2 in a batch reactor at 443 K using $(nBu)_2Sn(OEt)_2$ as the catalyst: a ratio DEC:Sn equal to −6 has been reported. The dimethoxo stannane has been used in the synthesis of DMC in methanol at 423 K under 2.8 MPa of CO_2,[167] affording a DMC: Sn molar ratio just a bit higher than 1. The addition of dicyclohexylcarbodiimide (CyN=C=NCy) (DCC) was reported to trap water and raise the DMC:Sn to 3. Interestingly, Aresta and coworkers have shown[168] that DCC is indeed an 'organic catalyst' as it is able, under very moderated reaction conditions (330 K and 0.2 MPa CO_2), to promote the formation of DMC, DEC, and diallyl carbonate (DAC) from the relevant alcohols and CO_2 in quantitative yields. DFT calculations have demonstrated that, in the presence of DCC, the formation of DMC has a much more favorable thermodynamics (**Figure 4**), as the ΔG° is equal to −35 kcal mol^{-1}. Such a dramatic change with respect to the carboxylation of methanol is due to the simultaneous formation of dicyclohexylurea (DCU), the hydrated form of DCC; noticeably, the latter is not soluble in the alcohol and can be easily separated by filtration and quantitatively recovered.

The dehydration of DCU[169] carried out with quantitative yields closes the cycle (**Scheme 9**) and makes the process based on DCC alone of potential usefulness in the synthesis of niche carbonates or if the alcohol brings moieties sensitive to temperature.

The reaction mechanism has been demonstrated and shown to be that represented in Scheme 9, with two key TS represented by those reported in Figure 4. It is clear that, in this case, the methyl transfer to the hemicarbonate occurs intramolecularly, so that a C=O is formed. Other water-traps that raise the problem of recovery and conversion of the hydrated forms have been used.

Physical water trapping, using zeolithes,[170–172] is also a possible approach, which has a limitation in the fact that the trap works well at temperatures below 250 K, while, at the reaction temperature, the hydroxo-moieties present on the material are acid enough to promote the back conversion of carbonates into alcohol and CO_2. The temperature swing from 420 K (operative conditions) to 250 K (water trapping) does not make this approach very efficient. Moreover, the energy necessary for the dehydration of the solid inorganic materials and the pulverization that may occur during the dehydration phase make the energetic balance worse. An interesting approach is to use membranes for water separation.[185] An improvement of the catalytic properties is obtained when the stannanes are either tethered to a polystyrene matrix[173] or immobilized on mesoporous SBA-15.[174] Such systems gain in terms of recyclability and activity with respect to the soluble catalysts. A point that must be taken into consideration is that the homogeneous stannanes are easily deactivated as n-mers are formed (tri- or decamers), due to the fact that the formation of dialkyl carbonates occurs via an intramolecular transfer of an alkyl moiety to the hemicarbonate, which causes the formation of a Sn=O bond (see the similar mechanism reported for DCC) (eqn [21]).

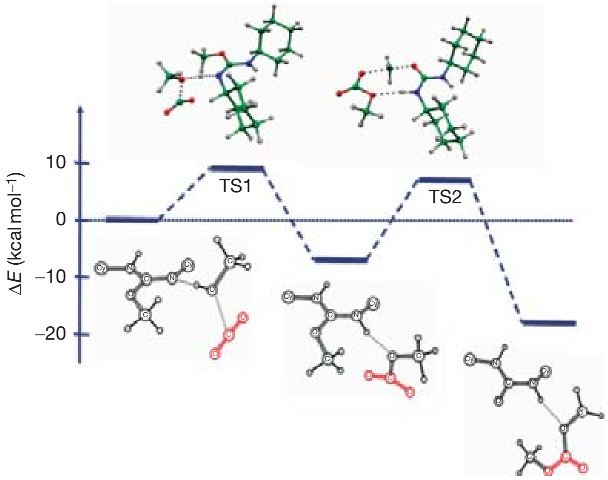


Figure 4 Energy profile and transition states calculated for DCC-promoted carboxylation of methanol.

$$n\mathrm{Bu_2Sn(OMe)} + \mathrm{CO_2} \rightarrow n\mathrm{Bu_2Sn(OCOOMe)(OMe)} \rightarrow 1/n\left[n\mathrm{Bu_2Sn} = \mathrm{O}\right]_n + \mathrm{DMC} \qquad [21]$$

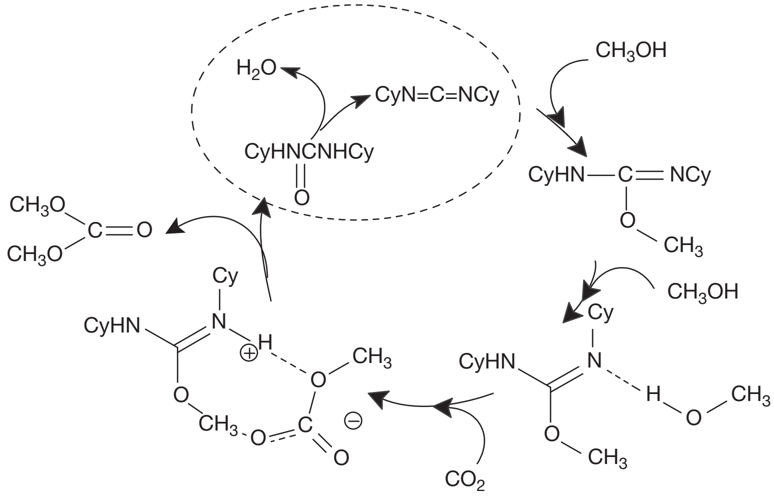
The aggregation of '$n\mathrm{Bu_2Sn{=}O}$' moieties causes loss of activity.

Other soluble alkoxides, such as those of titanium (IV)[175,176] and group 5 metals,[177,178] exhibit an interesting catalytic activity for dialkyl carbonate formation.

Coupling experiments and DFT calculations, it has been possible to suggest a reaction path with $[\mathrm{Nb(OCH_3)_5}]_2$ catalyst[178,179] based on the steps depicted in Figure 5: (i) dissociation of the dimer, (ii) insertion of CO_2 into the Nb–OCH_3 bond, and (iii) reaction with two molecules of external methanol with formation of water and DMC.

The regenerated Nb-OCH_3 restarts the catalytic cycle. The two methanol molecules are activated in different ways: one to afford the methoxo moiety (activation by a base), and the other to afford the methyl cation (activation by an acid) that, with the hemicarbonate, generates DMC. Water is formed out of the coordination sphere of the metal and is dispersed in the solution. Once the equilibrium is reached, the catalysts must be recovered for starting a new run. The Nb alkoxo can be recycled several times, maintaining its activity. It is essential that, in the new run, anhydrous methanol is used (Figure 6).

A water concentration around 20–30 ppm is admitted. For higher concentrations, the original pentamethoxo Nb-complex is converted into $\mathrm{NbO(OCH_3)_3}$ that is totally inactive. The Nb-complex, thus, presents a different mechanism than DCC



Scheme 9 Cycle of carboxylation of methanol promoted by DCC: the cycle is closed by DCU dehydration back to DCC.

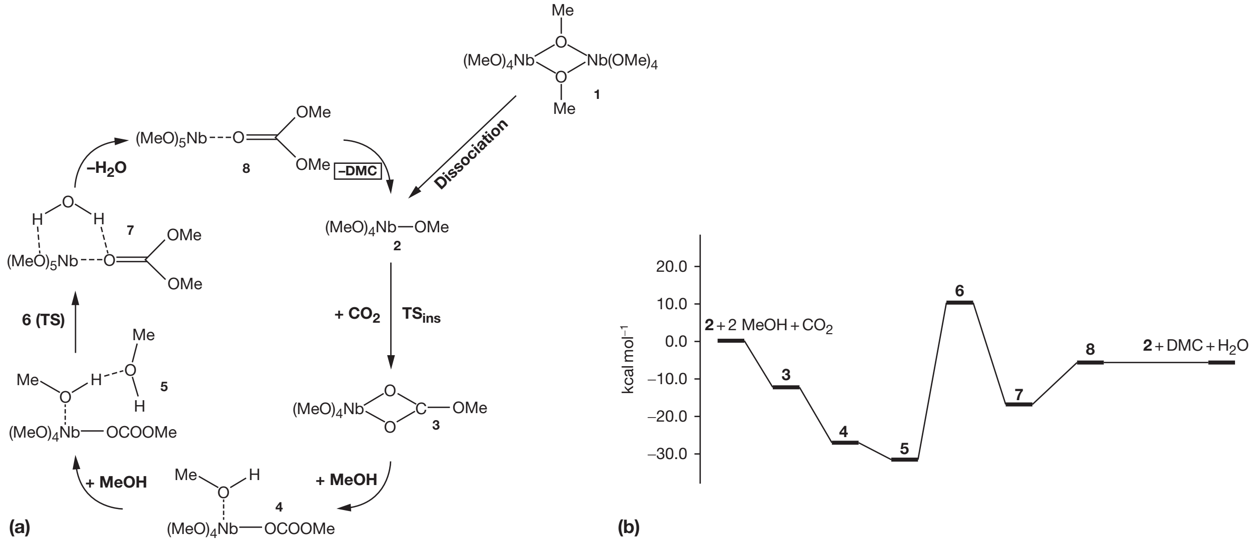


Figure 5 The reaction pathway (a) and energetic profile (b) for the $[Nb(OCH_3)_5]_2$-catalyzed conversion of methanol into DMC.

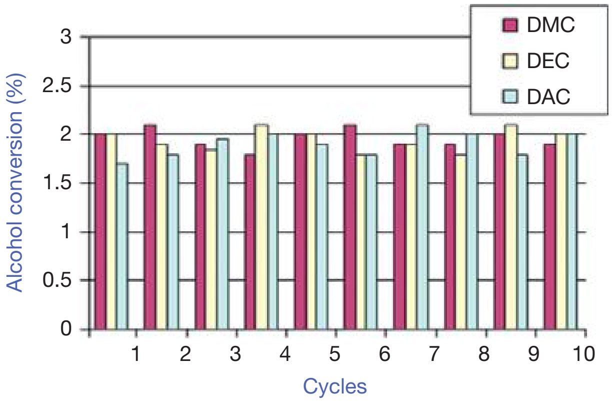


Figure 6 Activity of the recycled Nb catalysts in the carboxylation of methanol, ethanol, and allyl alcohol.

and Sn: with Nb an '*acid plus base*' activation of CH_3OH is operating, whereas, with the Sn-catalyst and DCC, two molecules of methanol are both activated by a base.

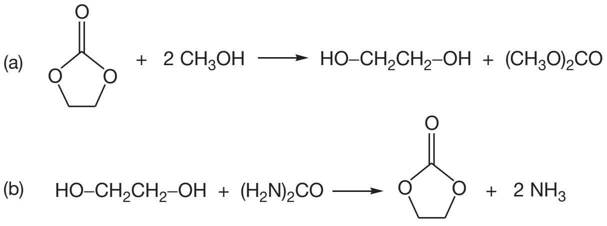
Tin systems have also been characterized at the end of the catalytic run, and 'resting species' have been identified, using $(CH_3)_2Sn(OCH_3)_2$[180] or *n*-$Bu_2Sn(OCH_3)_2$,[181–184] or else *n*-$Bu_2Sn[OCH(CH_3)_2]_2$.[184b] The species represented in Scheme 10 have been identified.

A is formed from the insertion of CO_2 into the Sn–OR bond: under the reaction conditions, **A** converts into **B** and DMC. **B** gives **C** and DMC only in the presence of methanol. With Sn-complexes, an increase of nuclearity is observed due to the formation of Sn–O–Sn linkages, in which the tin centers are pentacoordinated. The authors suggest that, most probably, monomeric species are the real catalysts.

Heterogeneous systems have been largely used, and a mechanistic study has shown that the same steps are involved as in homogeneous systems.[163]

The market of acyclic carbonates can expand much beyond the actual size if new phosgene-free processes are developed. Besides the technologies described above, the transesterification of cyclic carbonates and the reaction of alcohol with urea represent two approaches that may really contribute to implementing new sustainable synthetic routes.

The transesterification of ethene carbonate (eqn [22a]) with methanol produces ethene glycol ($HOCH_2CH_2OH$), which must be reacted with urea (eqn [22b]) to afford back the ethene carbonate.



[22]

This recycling is essential for avoiding ethene glycol becoming a waste. As mentioned above, the DMC market and that of other alkyl carbonates (DEC and DAC) may easily expand to the tens of Mt scale. DMC and DEC can be used as gasoline additives or as solvents, reagents, and monomers for polymers, and DAC is used for the synthesis of specialty polymeric materials (production of lenses).

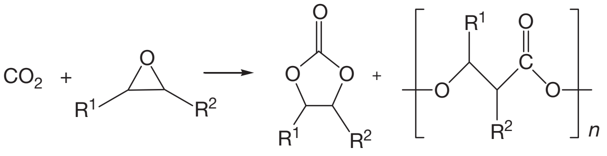
Alcoholysis of urea (eqn [23]) presents some problems of separation of products with low boiling alcohols. The reaction usually proceeds in two steps: (i) formation of an urethane $H_3CO(O)CNH_2$ and (ii) formation of DMC. Often, two catalysts are used and the two steps require different reaction conditions.

$$(H_2N)_2C=O + 2ROH \rightarrow (RO)_2C=O + 2NH_3 \qquad [23]$$

The separation is carried out using the reactive distillation technique that allows separation of DMC from methanol. The advantage of this route is the easy availability of urea, which is produced at a scale of 120 Mt per year, with a yearly foreseen increase of 7%.

6.19.2.8 Synthesis of Cyclic Carbonates

The carboxylation of epoxides (eqn [24]) has been known since 1943, and is now on stream in several plants. Such a reaction yields either cyclic carbonates[186–188] or polymers,[189] depending on the catalyst used and the reaction conditions.[190–200] Organic catalysts such as alkyl ammonium salts or phosphonium salts are active but require *quasi* equimolar amounts of the substrate, and the catalyst that results is difficult to recover and reuse. Supported on mesoporous silica,[201] 3-(triethoxysilyl)propyltriphenylphosphonium bromide has been found to have a good recyclability.



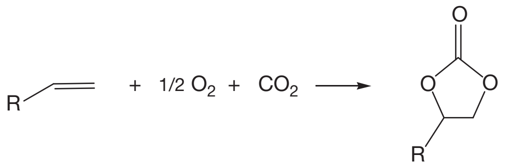
[24]

Metal halides have also been described as catalysts[202] eventually coupled to β-cyclodextrin (β-CD), which acts as a hydrogen-bonding agent and accelerates the ring opening also in the absence of organic solvents.[203] Organometallic species and metal complexes,[204] classical Lewis acids,[192] and metal phthalocyanines[205] have been used as catalysts. Heterogeneous catalysts,[206,207] including metal oxides,[208–212] have been used because they are characterized by a longer life with respect to homogeneous systems. Amides, such as DMF and dialkylacetamides, have been used as solvents and have also been demonstrated to promote the carboxylation of epoxides,[211] if to a limited extent. The synthesis of optically active carbonates has been carried out and, interestingly, metal oxides can catalyze the carboxylation of optically active epoxides with a total retention of configuration.[212]

Conversely, when a racemic mixture of the epoxides is used, an *ee* of the order of 22% is obtained using Nb(IV) complexes with optically active (N, O, and P as donor atoms) ligands: the low *ee* is due to the de-anchoring of the ligand from the metal center at the reaction temperature (415 K), as shown by an NMR study.[212] Microwaves have been shown to promote the formation of carbonate in IL.[213] Exhaustive reviews on the carboxylation of epoxides have recently been published.[162,214] Some very recent results are summarized in **Table 7**.[215]

The solvent may play a key role in the carboxylation of epoxides. As reported above, amides play a positive role due to a participation either in the ring opening of the epoxide or in a preliminary coordination of CO_2.[211,212] Sc-CO_2 is considered to be an economically viable and ecologically benign reaction medium for organic reactions; it has several advantages, such as no flammability, lack of toxicity, absence of a gas–liquid phase boundary, and possible simplifications in work-up. The advantages of using sc-CO_2 alone[216] or in combination with IL[217,218] have been described.

The oxidative carboxylation of olefins appears to be an interesting approach to the synthesis of cyclic carbonates from cheap and easily available reagents such as olefins, CO_2, and O_2 (eqn [25]).



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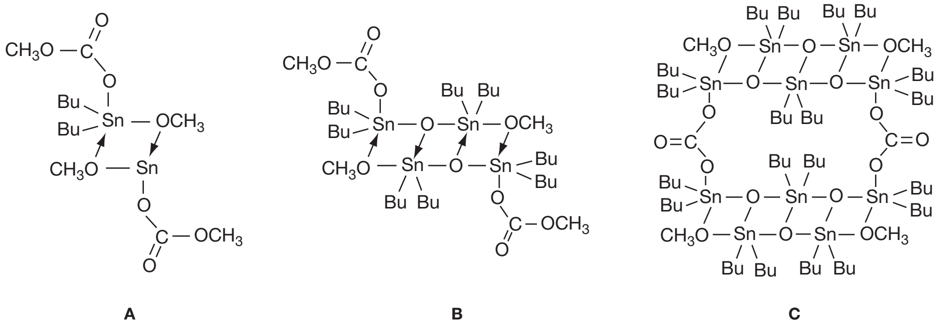


A B C

Scheme 10 Structures of isolated di-*n*-butyltin(IV) compounds.

Table 7 Features of homogeneous or heterogenized catalysts very recently employed in the carboxylation of epoxides

Catalyst	*Reaction conditions*	*Molar ratio Cat/epoxide (%)*	*Conversion yield (%)*	*TOF (h^{-1}/TON)*	*Reference*
KI on MOF-5	6 MPa, 365 K	2.5	98	NA	215a
Pd(II) and Co(II) salicylaldimine	1.8 MPa, 373 K	0.1	82	410/420	215b
KI/cellulose	2 MPa, 363 K	0.04	92–99		215c
Bimetallic Fe(II)	1 MPa, 353 K	1	70	29/700	215d
$InBr_3/PPh_3$	3.9 MPa, RT		96		215e
$FeCl_2$/bisquinoline derivative	1.5 MPa, 373 K	1	100		215f
Ru(II)	1.6 MPa, 373 K	0.2	23–62	230–627/115–314	215g
Cu(II)-Schiff bases	1.6 MPa, 373 K	0.025	95		215h

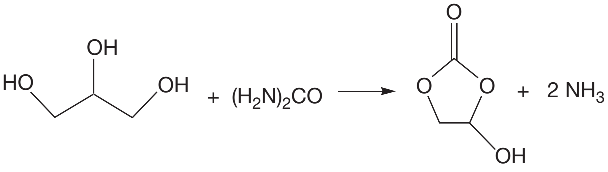
Moreover, such a reaction does not require oxygen-free carbon dioxide. The direct oxidative carboxylation of olefins couples two processes, namely, (i) the epoxidation of the olefins and (ii) the carbonation of the epoxides, an approach that avoids the separated production of the epoxide.

Only a few examples are reported in the literature of the direct carbonation of olefins, such as the direct functionalization of propene[219,220] and styrene.[221,222] So far, such an approach has shown a drawback, represented by the addition of dioxygen across the C–C double bond with formation of aldehydes or the relevant acids.[223–225] Using Rh-complexes, the active species in the epoxidation of the olefin has been shown to be the peroxocarbonate. Using $^{16(18)}$O-$^{18(16)}$O peroxo groups, it has been possible to show that the metal-bound O-atom of the peroxo group is transferred to an oxophile, like an olefin.

Several other oxidants have been used for the oxidation of olefins, like organic hydroperoxides or hydrogen peroxide,[162] but the goal must be the direct use of dioxygen under controlled conditions.

In order to reduce that cleavage of the olefin double bond, a two-step reaction has been investigated in which a metal oxide transfers one lattice oxygen to an olefin and is then reoxidized using dioxygen.[222,226]

The reaction of polyols with urea (eqn [26]) is a recent strategy to yield cyclic carbonates. Efficient catalysts have been used for the synthesis of glycerol carbonate[162,227] that has been used as a platform molecule for the synthesis of several chemicals, including epichlorohydrin.[227b]



[26]

6.19.2.9 CO_2 as Co-monomer in the Synthesis of Polycarbonates

As mentioned above, the carboxylation of epoxides may produce polycarbonates: for example, using Al–porphyrin complexes[228,229] or Zn-compounds,[230] polycarbonates are obtained. After the pioneering studies of Inoue[231] and the studies by Kuran,[232] the copolymerization of CO_2 and epoxides has been the focus of several studies in order to master the alternate insertion: copolymers that regularly incorporate CO_2 and the co-monomer have been described. A recent review in this field was published by Darensbourg[233]; that review will not be reiterated in this chapter. Here, some recent results regarding the use of discrete homogeneous metal-based catalysts for the copolymerization of epoxides and CO_2 will be discussed. Al-catalysts, among the first to be described in the literature by Inoue, are now used in a plant.

Bifunctional Co–salen complexes have been used as promoters of the alternating copolymerization of epoxides and CO_2.[234] Co(III) complexes with tetramidomacrocyclic ligands have been shown to be quite active.[235] Co(III) complexes with salen-type ligands have been demonstrated to be very efficient in the copolymerization of epoxides and CO_2, with a TOF of 15 000 h^{-1},[236] working with a quite high substrate-to-catalyst ratio (50 000). Various Co(III)–salen complexes have been used by several research groups and shown to be, in general, quite active [237, TOF = 6105 h^{-1}]. Double metal cyanide systems also show an interesting activity [238, TOF = 3856 h^{-1}].

The use of a variety of epoxides characterized by different molecular structures may be of interest because polymers with different structural properties may be obtained. In this direction, work is still necessary to discover new routes for the production of epoxides and new catalysts for the production of regular copolymers. The use of hydrogen peroxide for the synthesis of epoxides should be supplanted with that of dioxygen, which does not place any limits on use and is particularly suited for the production of epoxide at a scale of >Mt per year.

6.19.2.10 Comparison with Enzymatic Carboxylations

The approximate size of carbon fluxes and carbon deposits are represented in Figure 7. From the data reported, it is revealed that nature fixed CO_2 by autotrophic (self-nourishing) prokaryotes at a level of ~200 Gt_C per year. The anthropogenic carbon (*ca.* 7 Gt_C/y) represents, thus, only ~3.5% of the natural cycle; nevertheless, it cannot be used by the natural cycle, and thus, there is a consequent continuous accumulation in the atmosphere.

Four major pathways are used in the conversion of CO_2, namely[239a]:

(i) Calvin cycle,
(ii) Acetyl-CoA pathway,
(iii) 3-Hydroxypropionate pathway, and
(iv) Reductive tricarboxylic acid cycle.

Autotrophic organisms can be divided into two categories according to the source of energy they use. Chemoautotrophs, in the reduction of CO_2, use electrons generally derived from inorganic (mineral) sources, such as hydrogen, H_2S, elemental sulfur, metal ions (Fe^{2+}, Mn^{2+}), ammonia, and nitrite, often (but not always) involving oxidation with O_2. Most of these organisms live in dark, extreme environments. Such fixation of CO_2 is often reported as chemosynthesis.

Photoautotrophs use light from the sun as a source of energy and water as an electron donor with the formation of dioxygen. In terrestrial environments, plants and microorganisms are the predominant variety of photoautotrophs, whereas, in aquatic systems, algae and (cyano)bacteria depend on this pathway.

Biochemical and metabolic studies on carboxylation reactions have been carried out in order to verify whether a genetic manipulation of the most abundant enzyme in nature, that is, RuBisCO, may lead to an increment of carboxylase activity over oxidase activity (the two are now at 50% each). Apart from the difficulty of transferring a potential genetic manipulation to superior plants, no usable results have been obtained throughout longer than 20 years of research. The biotechnological (enzymatic) fixation of CO_2 to produce well-defined low molecular weight organic compounds or carboxylic acids, in general, could be implemented following two strategies.

(i) Genetic engineering might enable the redirecting of well-established metabolic pathways for the production of a limited number of carboxylates that are intermediates or end products in such pathways. The high substrate specificity of biosynthetic pathways makes it unlikely that the same pathways might also be exploited to convert nonnatural substrate surrogates.

(ii) Enzymes used in biodegradation pathways seem to possess a lower substrate specificity, which makes the regioselective carboxylation of various types of substrates possible. Substrates such as epoxides or electron-rich (hetero)aromatics fall into this category.

A lot of work remains necessary to expand the use of biotechnologies for CO_2 conversion. Very few attempts have been made so far to use enzymes extracted from anaerobic bacteria (**Figure 8**) for biotechnological synthesis of carboxylated products.[239b,c]

6.19.3 Reduction to CO

The 'noncatalyzed' deoxygenation of CO_2 to CO (eqn [27]) is very energy demanding (257 kJ mol^{-1}, see **Table 2**).

$$CO_2 \rightarrow CO + ½O_2 \qquad [27]$$

Conversely, such a reaction smoothly occurs at room temperature when CO_2 is coordinated to a metal system[23] or also just above 14 K in a gas matrix.[240]

The deoxygenation process is of interest because, if one O-atom of CO_2 is transferred to a suitable substrate that finds a large utilization, the process would be of interest for a cyclic *oxidation of CO to CO_2–reduction of CO_2 to CO* that would produce useful materials (during the reduction to CO) and energy (during the oxidation of CO to CO_2) (**Scheme 11**).

Unfortunately, so far, the substrates able to accept the O-atom from CO_2 have afforded products that are not usable per se nor can be used for the production of goods of large consumption. In fact, the best O-acceptor is a phosphane,[241] but the phosphane oxides do not have a large market nor do they easily transfer the O-atom to a more usable substrate; and silanes,[242] but the siloxanes do not have a very large market. Protons[243] would be possible acceptors, but such a reaction is prevented by the fact that concurrent reactions must take place to generate the protons. An interesting case is the reduction of CO_2 by PhSH in presence of Ni(0).[244] Reaction [28] shows that coordinated CO_2 is easily reduced to CO by PhSH through a one-electron transfer that generates PhS–SPh. This disulfide adds to Ni(0) to afford Ni(II), which represents the oxidated

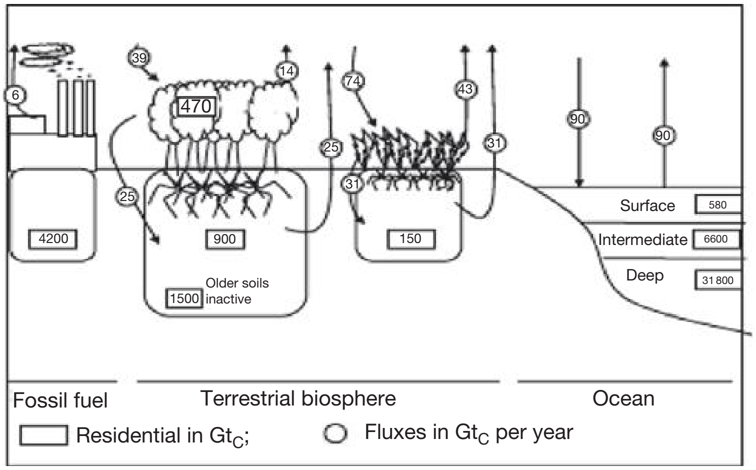


Figure 7 The natural carbon cycle. The squares represent fixed amounts of carbon in units of gigatons (Gt); the circles represent fluxes in Gt$_C$ per year. To convert to relative amounts given in CO_2 figures, all values must be multiplied by 3.67.

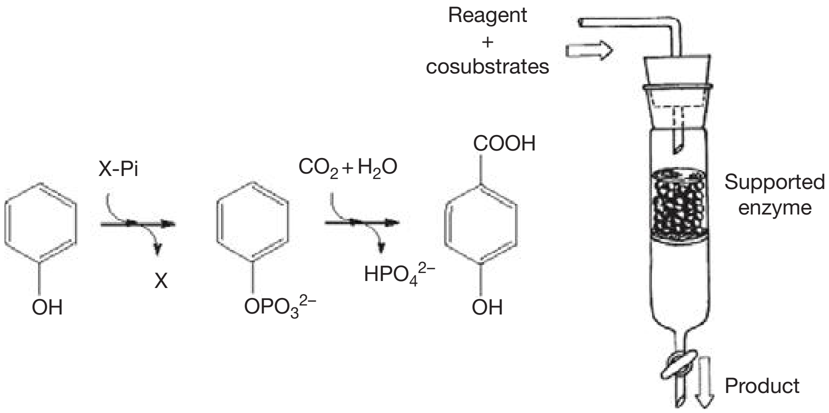


Figure 8 Biotechnological carboxylation of phenol.

product besides CO, which is the reduced product. The active metal system is, thus, converted into an inactive form (eqn [28e]).

$$PhSH \rightarrow PhSH^{\cdot+} + e^- \quad [28a]$$

$$PhSH^{\cdot+} \rightarrow PhS^{\cdot} + H^+ \quad [28b]$$

$$PhS^{\cdot} \rightarrow ½PhS-SPh \quad [28c]$$

$$Ni(CO_2)(PCy_3)_2 + 2H^+ + 2e^- \rightarrow Ni(CO)(PCy_3)_2 + H_2O \quad [28d]$$

$$Ni(CO_2)(PCy_3)_2 + PhS-SPh \rightarrow Ni(SPh)_2(PCy_3)_2 + CO_2 \quad [28e]$$

Olefins would be excellent oxophiles, if the oxygen atom could be easily transferred, which is not yet the case. The transfer of one oxygen atom from CO_2 to RNC to afford RNCO[245] would have a potential application because isocyanates are co-monomers in polymers, but, as for now, the reaction is not used because the efficiency of the O-transfer is not compatible with an industrial application.

It would also be of interest to develop cycles that would use CO_2 as an oxidant toward other chemical agents (**Scheme 12**).

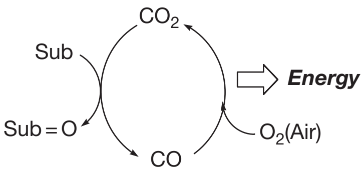
An application of this approach is the use of CO_2 as an oxidant toward alkanes derivatives[246] that can be dehydrogenated to the relevant olefin (eqn [29]). CO can be reacted with water vapor in the presence of a suitable WGS catalyst and can again produce CO_2 and dihydrogen that could be used to produce energy.

$$PhCH_2{-}CH_3 + CO_2 \xrightarrow{cat1} PhHC=CH_2 + CO + H_2O \quad [29a]$$

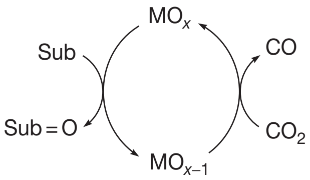
$$CO + H_2O \xrightarrow{cat2} CO_2 + H_2 \quad [29b]$$

This is a useful approach that might find a large-scale application if the use of CO_2 would result in a more selective and more controlled process than the dehydrogenation based on the use of O_2.

The electroreduction of CO_2 under homogeneous catalysis yields CO,[19] often in mixture with H_2.[19] This is not a negative case: in fact, if the two gases were produced in the correct H_2:CO = 2 molar ratio, or close to it, the mixture would be used as Syngas. Either component can be added to the gas mixture generated in such a way to reach the best ratio for the synthesis of gasoline or other compounds. High-temperature electrolysis might be convenient for the production of Syngas.



Scheme 11 Use of CO_2 as an oxidant in a cycle that produces energy.



Scheme 12 Use of CO_2 as an oxidant.

6.19.4 Reduction to Methanol, Methane, or C_n Species

The reduction of CO_2 to methanol and methane is better carried out using heterogeneous catalysis.[185,247] Nevertheless, some homogeneous systems or electrocatalyzed processes have been used for the conversion of CO_2 into methanol, methane, or C_n species. It is worth noting that while methanol is a fuel and a useful intermediate (for the synthesis of chemicals such as acetic acid and fuels) and C_n species may have industrial uses, methane is mainly used as a fuel because its chemistry, although developed for the synthesis of compounds such as HCs and syngas, is largely unexplored for application to the synthesis of specialty chemicals. Therefore, CH_3OH is a better target than CH_4.

Electrocatalysis under homogeneous conditions has good potential for CO_2 conversion, and either metal systems[248] or organic catalysts may be used.[249]

Electrocatalytic methods are currently considered with particular interest because excess electric energy (energy produced during the night or holidays, for example) could be conveniently converted into chemical energy (fuels) to be used in cars (substituting fuels produced from fossil carbon) or for generating electric energy during the peak hours.

The multielectron reduction of CO_2 is energetically more favorable than mono-electron transfer (eqn [30]).

$$CO_2 + 2H^+ + 2e^- \rightarrow CO + H_2O \quad E_0 = -0.53\,V \quad [30a]$$

$$CO_2 + 2H^+ + 2e^- \rightarrow HCO_2H \quad E_0 = -0.61\,V \quad [30b]$$

$$CO_2 + 4H^+ + 4e^- \rightarrow HCHO + H_2O \quad E_0 = -0.48\,V \quad [30c]$$

$$CO_2 + 6H^+ + 6e^- \rightarrow CH_3OH + H_2O \quad E_0 = -0.38\,V \quad [30d]$$

$$CO_2 + 8H^+ + 8e^- \rightarrow CH_4 + 2H_2O \quad E_0 = -0.24\,V \quad [30e]$$

$$CO_2 + e^- \rightarrow CO_2^{\cdot-} \quad E_0 = -1.90\,V \quad [30f]$$

Aspects of paramount importance in the electrocatalytic reductions of CO_2 to fuels are the kinetics of reaction and the electron transfer, processes in which the catalyst is implied: this requires that the catalyst must have energy levels that match the reduction potential of CO_2 to the wanted species.

Homogeneous catalysts are particularly suitable for adaptation to the different potentials required, because the properties of the metal system can be quite finely tuned through the ligands. A key point is, thus, to design metal catalysts that may work as close as possible to the thermodynamic conditions, avoiding the high over-potential that is often generated when a direct reduction of CO_2 occurs at an electrode surface. Under the latter conditions, surface deterioration and low efficiency are very often encountered, with a substantial reduction of the efficiency of the process. The ligands used to stabilize metal centers usually bear either P- or N-donors. Such anchoring sites are part of molecular structures of quite different complexity: by controlling the structural parameters of the ligands, it is possible to control the utilization of the metal complexes in the reduction of CO_2. Monodentate, didentate, and polydentate phosphanes with moieties of various basicity and acidity strongly influence the properties of the catalyst.[250] N-macrocyclic ligands have been intensively investigated,[251] as has dipyridine.[252] Cluster-soluble complexes have also efficiently been used.[253]

It is important that the metal centers may drive the reaction toward a specific product.

Table 8 gives a representation of the correlation catalyst product.

Sophisticated metal systems bearing complex ligands, such as porphyrins,[254] have been used. Porphyrin ligands have also been supported on the electrode.[255]

All of the above systems suffer an important limitation due to the possible oxidation of the ligand that may deactivate the catalyst. Recently, interesting results of catalysts that are more long living have been reported.[256]

Organic catalysts based on the use of pyridine[249] have shown, so far, a good stability, most probably due to their extreme simplicity (**Scheme 13**).

Interestingly, they can yield not only C1 reduced species (CH_2O, CO, HCOOH, CH_3OH, CH_4) but also C2 and probably C_n species. A 'radical mechanism' is most probably active in such systems that show a promising potential of application.

The reduction of CO_2 in nature occurs in several organisms, under anaerobic or aerobic conditions.

The methanation of organic substrates involves, among others, enzymes that, in a single step, are able to reduce CO_2 to CO (carbon monoxide dehydrogenases (CODH)) or to formic acid (formate dehydrogenases (F_{ate}DH)). CO_2 can be reduced to the methyl group $-CH_3$ through a tetrahydrofolate (THF)-mediated process. CO and $-CH_3$ are coupled to give the acetyl moiety using a Fe_4S_4-Ni enzyme and vitamin B12. Formate can be reduced to formaldehyde by the formaldehyde dehydrogenase (F_{al}DH) enzyme, and formaldehyde can be converted into methanol by the alcohol dehydrogenase (ADH) enzyme. Interestingly, the three enzymes that convert CO_2 into methanol (F_{ate}DH, F_{ald}DH, and ADH) are commercial. In an attempt to mimic nature, a biotechnological approach to the conversion of CO_2 into methanol has been investigated based on the use of the enzymes described above. It has been shown that the three enzymes, F_{ate}DH, F_{ald}DH, and ADH, are able to reduce CO_2 in water at ambient temperature.[257] A minimum of three molecules of NADH are consumed per molecule of CH_3OH produced (**Scheme 14**).

Table 8 Electrodes and products of reduction of CO_2 in water

Electrodes	*Products*
Cu	C_2H_4 (32–80%), C_nH_{2n+2}
Zn, Au, Ag, p-InP, p-GaAs, Pt–Pd–Rh	CO
	CO + HCOOH
RuOx on cond diamond, B-doped–Cd	MeOH, EtOH, $C_nH_{2n+1}OH$

This approach, although quite appealing, is not economically and energetically affordable, unless NAD^+ formed upon oxidation of NADH is efficiently recycled, thus, increasing the ratio CH_3OH:NADH to limits that can be acceptable for biotechnological production of methanol.

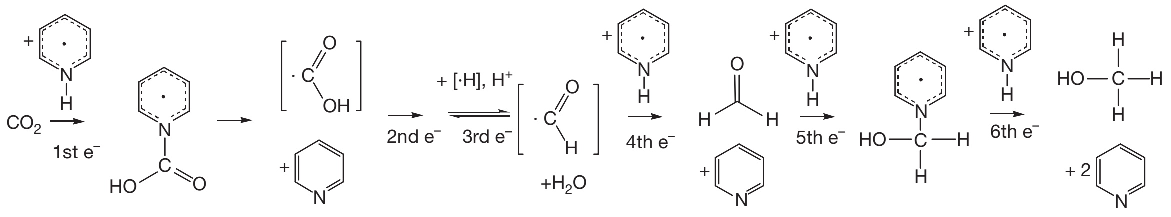
Enzymes that are more robust have been obtained[258] by encapsulation. TEOS is better used in order with Ca-alginate as an agent for producing a Ca-silicate cage, because it avoids any interference with the production of methanol in the case of noncomplete hydrolysis of TMOS.[259] Co-encapsulated enzymes (**Figure 9**) work better than singly encapsulated ones.[260]

The artificial reduction of NAD^+ to NADH can be performed in several different ways, by using (i) chemicals that act as reducing agents; (ii) metal systems that may use dihydrogen for the reduction under thermal or irradiated conditions; (iii) semiconductors, water, and light as the source of energy hydrogen for the reduction; (iv) electrocatalysts that may reduce NAD^+ under electrochemical conditions.

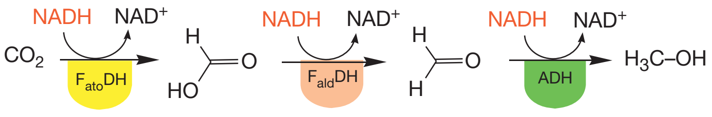
Among Class (i) reagents, cheap, easily affordable chemicals must be used. Hydrazine and sodium dithionite (SDT)[258,260] have been used, with the latter being much more efficient than the former (**Scheme 15**).

SDT must be slowly added up to a stoichiometric (eqn [31]) amount to NAD^+ after all of the NADH is oxidized to NAD^+. An addition of excess of SDT causes a rapid deactivation of the enzymes.

$$NAD^+ + S_2O_4^{2-} + 2H_2O \rightarrow NADH + 3H^+ + 2SO_3^{2-} \qquad [31]$$

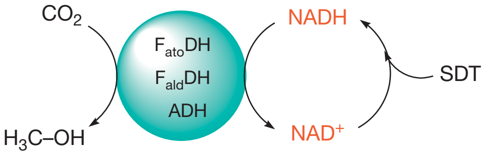


Scheme 13 Proposed mechanism for the pyridinium-catalyzed reduction of CO_2 to methanol.[248b]



Scheme 14 CO_2 reduction to methanol in water promoted by F_{ate}DH, F_{ald}DH, and ADH.

Figure 9 Beads produced from Ca-alginate and TEOS containing co-encapsulated $F_{ate}DH$, $F_{ald}DH$, and ADH.



Scheme 15 ‘One-pot’ conversion of CO_2 into CH_3OH by co-encapsulated $F_{ate}DH$, $F_{ald}DH$, and ADH enzymes, with NAD^+ reduction to NADH using SDT.

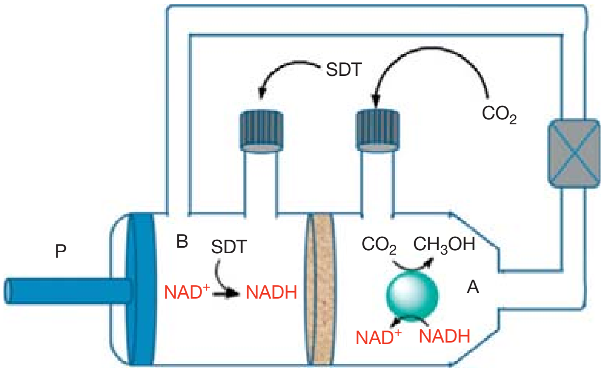


Figure 10 Two-compartment reactor for CO_2 reduction to methanol by co-encapsulated enzymes (compartment A) and NADH regeneration by SDT (compartment B). P is a plug for the transfer of the solution from B to A.

In this way, up to 5 molecules of methanol per molecule of NADH were produced.

In order to avoid such detrimental contact, the oxidation of NADH and the reduction of NAD^+ have been separated, as shown in Figure 10. With such a device, the ratio CH_3OH: NADH was further increased up to >35. This is a proof of concept that the recycling of NAD^+ is possible, and systems that are more sophisticated need to be developed for an efficient and economically viable biotechnological synthesis of CH_3OH from CO.

6.19.5 Conclusion

The utilization of CO_2 under homogeneous conditions for the production of chemicals and fuels is a well-documented process. Several products, such as fine chemicals, pharmaceutical products, bulk chemicals and intermediates, and fuels, can be obtained. Low-energy routes are available for such conversion that may make the use of CO_2 possible, effectively reducing the extraction of fossil carbon. With respect to the disposal of CO_2 in natural fields, the utilization has two key advantages: any use will generate a profit (and not costs as in the case of the disposal) and any use will save resources, because the recycling of carbon will reduce the extracted carbon (whereas disposal expands the extraction of fossil carbon). At present, it appears that the two technologies (disposal and utilization) may manage quite different volumes of CO_2, with disposal able to eliminate much larger volumes than utilization. On the other hand, utilization is a reality, as over 200 Mt/y of CO_2 are converted or used. Additionally, it must be said that disposal is not a ubiquitous technology, and site availability is an issue, whereas utilization is possible everywhere. As a matter of fact, the two technologies should not be seen as antithetical, but should be applied in parallel, each in the most correct conditions, to generate the maximum benefit. If combined in the correct way, utilization might pay the costs of disposal. For a related chapter in this Comprehensive, we refer to Chapter 8.12.

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6.20 Hydrogen Generation from Formic Acid and Alcohols

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6.20.1 Introduction

In the last several decades, hydrogen has become much more in focus as an increasingly attractive energy carrier. This interest has been enhanced recently because of the progressive depletion of fossil fuel reserves, as well as the strong demand for dramatic reduction in greenhouse gases. Hydrogen possesses an outstanding energy density of 142 MJ kg^{-1} (higher heating value) or 120 MJ kg^{-1} (lower heating value), and, after combustion, the only final product is pure water.[1,2] By the early 1970s, the idea of a hydrogen economy was born.[3,4] It includes the generation, storage, distribution, and use of hydrogen, for example, the reconversion of stored chemical energy into electric energy by fuel cells or into mechanical energy by combustion engines.

It should be noted that hydrogen is a secondary energy carrier and, therefore, a primary energy source is necessary for generating molecular hydrogen, like for the production of electric energy. Besides its role as an energy carrier, hydrogen is of basic importance for a variety of industrial processes, such as ammonia and methanol synthesis, hydrotreatment in refinery and hydrogenation processes, for example, of fats. In addition, the availability of a sufficient amount of hydrogen is the prerequisite for the conversion of biomass into synthetic fuels.

Of course, it is important how the hydrogen is generated: In 2007, 96% of hydrogen production was based on fossil fuels (48% from natural gas, 30% from refinery and chemical off-gases, 18% from coal).[5] The most common processes are steam reforming, partial oxidation, and autothermal reforming.[6] With respect to reducing CO_2 emissions and installing more environmentally friendly processes, a switch to increasing use of renewable energies as sources of hydrogen generation is pending. Obvious alternatives are the application of the energy of wind or sunlight in combination with water electrolyses or using sunlight for direct water splitting, which has a huge potential. In addition, biomass or its fermentation products, for example, alcohols, are promising feedstocks for the generation of hydrogen.

(Bio)ethanol is undoubtedly the most typical example for a biorelated alcohol. However, other alcohols such as methanol, 1-butanol, 2-propanol, glycol, or glycerol are of interest for CO_2-free hydrogen generation because they can be generated by fermentation processes with the help of different microorganisms from glucose or by the transesterification of fats.[7,8] In general, the lower homologs of the group of linear, branched, and cyclic mono-, di-, and tri-alcohols (e.g., methanol, ethanol, 1-propanol, 2-propanol, glycol, glycerol, 1-butanol, 2-butanol, butan-2,3-diol, 2-pentanol, cyclopentanol, 1-hexanol, cyclohexanol, 1-octanol, and 2-octanol) have been investigated as suitable hydrogen sources since the early 1960s. All these compounds are liquids at room temperature (RT) and contain between 8 and 14 wt.% hydrogen. However, only one molecule of hydrogen is generated per OH group of the alcohol when applying homogeneous catalysts under ambient conditions. This reduces the obtainable amount of hydrogen, especially for the longer-chain mono alcohols; therefore, C1–C3 derivatives are those that are mainly under investigation.

In contrast, alcohols can be dehydrogenated by reforming processes similar to hydrocarbons at high temperatures (above 200 °C) and resulting in higher hydrogen yields, but only in mixtures with high contents of CO and CO_2.[9] Thus, further high-temperature cleaning steps are required before their use in polymer electrolyte membrane (PEM) fuel cells becomes possible.

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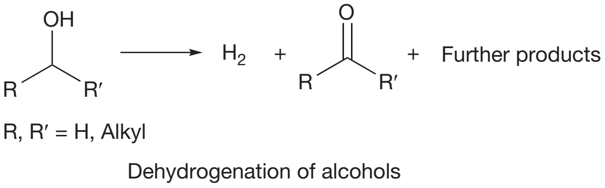
As an additional advantage in the homogeneous reaction, the organic molecules are not oxidized to CO and CO_2 but, instead, to useful products: aldehydes and ketones. These are very important compounds used directly as, for example, solvents, ingredients for perfumes, cosmetics, disinfectants, and for the further synthesis of plastics, solvents, dyes, pharmaceuticals (eqn [1]).



[1]

Widespread application of the homogeneous dehydrogenation of alcohols is the catalytic transfer hydrogenation (CTH) reaction. Here, the hydrogen is transferred directly to an acceptor, like an organic compound that contains C=C or C=O, which is reduced itself. Thus, the alcohol is used as the hydrogen source instead of gaseous molecular hydrogen. This subject has been summarized in several excellent reports.[10] In the absence of a hydrogen acceptor, the evolved hydrogen can be collected and stored for further use. Seminal work concerning acceptorless dehydrogenation of alcohols has been performed, starting in 1967 by Charman[11] as well as Dobson and Robinson[12] with rhodium- and ruthenium-containing catalysts. Approximately 20 years later, the investigations of Morton et al.[13] with catalysts of the type $[Ru(H_2)(X_2)(PPh_3)_3]$ ($X_2=N_2$, H_2) were much more successful. These results marked the state-of-the-art concerning the dehydrogenation of methanol, ethanol, 1- and 2-propanol, glycol, glycerol, and 2,3-butanediol for a long time. Turnover frequencies (TOFs; mole hydrogen per mole catalyst per hour) of 150 h^{-1} for ethanol, 330 h^{-1} for 2-propanol, and approximately 500 h^{-1} for butanol and glycol have been obtained in the presence of base (NaOH) at 150 °C. The results of this period are summarized in more detail elsewhere.[14] It is interesting that the first boom of research in this area was reached a few years after the birth of the idea of hydrogen economy and the two oil crises in 1973 and 1979. After these promising results, the interest in this field decreased again until the new millennium, which is the focus of this review.

Besides hydrogen generation, hydrogen storage is another key problem of the hydrogen economy, which is yet unsolved. This challenge is based on the very low hydrogen density, even in the condensed phase (0.0899 kg m^{-3} gas at 0 °C and ~1 bar). Thus, hydrogen has to be stored in a more compact manner for an effective distribution and usage. So far, only a few conventional techniques have been applied successfully for temporary or on-board hydrogen storage: compressed hydrogen at pressures of up to 700 bar, liquefied hydrogen at temperatures of −253 °C (70.78 kg m^{-3} liquid at −251.95 °C), or hydrogen stored in solid metal hydrides.[15] However, all these methods lack low gravimetric energy densities, cause the loss of hydrogen, or require energy-demanding storage processing.

In addition, new techniques are under development, such as cryo-physisorption in zeolites, metal organic frameworks, microporous organic polymers (e.g., polymer of intrinsic micro-porosity), or carbon-based structures (e.g., single-walled carbon nanotubes). Besides these new physical hydrogen storage technologies, also, hydrogen-rich chemical compounds, for example, methanol, ethanol, hydrazine, aminoborane, ammonia borane, or so-called 'organic hydrides' like decalin and methylcyclohexane are considered as potential materials for chemical hydrogen storage. As a prerequisite, these materials should allow for the reversible hydrogen uptake and release. Regarding the volumetric and gravimetric energy densities, especially, methanol and ethanol would be appropriate materials for hydrogen storage. However, the complete release of hydrogen requires high temperatures (see previous remarks on alcohol reformation).

Recently, the use of carbon dioxide (CO_2) or hydrogencarbonate (HCO_3^-) for the storage of hydrogen and the controlled decomposition of formic acid (HCO_2H) or formate salts (HCO_2^-) to hydrogen have received considerable attention.[14a,16]

HCO_2H is a liquid (from 8 to 100 °C), nontoxic,[17] but corrosive compound containing 4.38 wt.% hydrogen. Although the energy content (5.22 MJ kg^{-1}) is, therefore, much lower than for, for example, methanol, it is at least five times higher compared to commercially available lithium ion batteries. Besides the synthesis from carbon monoxide and methanol, which is performed, for example, at BASF in the >230 000 t scale per year, HCO_2H is also a major product of biomass processing, such as fermentation, pyrolysis, and supercritical reactions.[18] Hence, it is suitable for a CO_2-free hydrogen supply.

Basically, the cleavage of HCO_2H can proceed via two pathways: either yielding CO and water or H_2 and CO_2. Although these two reaction paths are both exergonic, the formic acid is kinetically stable at RT (Scheme 1). The spontaneous decomposition in the absence of a catalyst has been observed to be relevant at temperatures ≥78 °C, resulting mainly in CO and

			$\Delta G°$ [kJ mol^{-1}]	$\Delta H°$ [kJ mol^{-1}]	$\Delta S°$ [J mol^{-1} K^{-1}]
HCO_2H	$\longrightarrow$	$CO + H_2O$	−12.4	+28.7	+138
HCO_2H (l)	$\longrightarrow$	CO_2 (g) + H_2 (g)	−32.8	+31.5	+216
HCO_2H (l)	$\longrightarrow$	CO_2 (aq) + H_2 (aq)	+4	n.a	n.a
NH_4^+ (aq) + HCO_2^- (aq)	$\longrightarrow$	CO_2 (g) + H_2 (g) + NH_3 (aq)	+9.5	+84.3	+250
$HC(O)NMe_2$ (l) + H_2O (l)	$\longrightarrow$	CO_2 (g) + H_2 (g) + $HNMe_2$ (l)	n.a.	+239	n.a.

Scheme 1 Overview of the thermodynamic data for the decomposition and production of formic acid and its derivatives (n.a.: not available).[20]

water.[19] Applying catalysts, the selectivity with respect to the formation of hydrogen and carbon dioxide can be influenced.

Although the decomposition of HCO_2H was investigated almost 100 years ago for the first time,[21] it has been mostly neglected. However, it is the prerequisite for CTH reactions with formic acid as the hydrogen donor. Only a few examples have been published between 1967 and 1982 describing the application of platinum, ruthenium, iridium, or rhodium complexes for this reaction. More recently, especially from the middle of the 1990s, the decomposition of formates or formic acid base adducts has been studied as the unwanted backreaction of the CO_2 hydrogenation to formic acid and derivatives. In contrast, this reaction has been studied much more intensively and successfully in that period.[22] Some of the applied catalysts originally designed for the hydrogenation of CO_2 showed at least also little activity for the decomposition of HCO_2H or formates. This pivotal observation enabled the possibility of hydrogen storage based on the catalytic processes of the formation and decomposition of formic acid or formates, as depicted in Figure 1.

It is noteworthy to mention that this principle allows for CO_2-neutral hydrogen storage. Although CO_2 is available in huge amounts on the earth, to date, the use of carbon dioxide for hydrogen storage has been largely neglected and should be paid more attention in future. As a prerequisite, the development of catalysts which allow for the generation of hydrogen at higher reaction rates and under milder conditions is crucial. The best results for the homogeneously catalyzed formic acid decomposition before 2000 exhibited a TOF of 100 h^{-1} after 15 min at RT when applying a platinum phosphane catalyst[23] and a TOF of 1187 h^{-1} at 100–117 °C with an iridium phosphane complex.[24] At RT, a TOF of 30 h^{-1} has been reported.[25] A more detailed summary of this period is given elsewhere.[26]

Starting from 2008, a renaissance with a remarkable increase of research activities in this field has occurred. Since that time, very active catalyst systems for hydrogen generation from formic acid amine mixtures as well as formates have been developed. The results from 2000 until 2011 is the focus of the present chapter.

6.20.2 Hydrogen Generation from Formic Acid

6.20.2.1 Hydrogen Generation from Formic Acid Amine Adducts

In the past, the dehydrogenation of formic acid and formic acid amine adducts (FAAs) has been used mainly for the characterization of heterogeneous catalysts[21] or for transfer hydrogenation reactions,[10] respectively. In some cases, gas evolution from these reactions was observed; however, the potential of FAAs as a general hydrogen source has been largely neglected. Due to new investigations of possible candidates for potential hydrogen storage materials, the FAAs have been drawn into focus lately.[26] In order to allow for a selective dehydrogenation of formic acid from FAAs, several homogeneous precious and nonprecious metal catalysts, preferably Ru and Fe catalysts, have been applied.

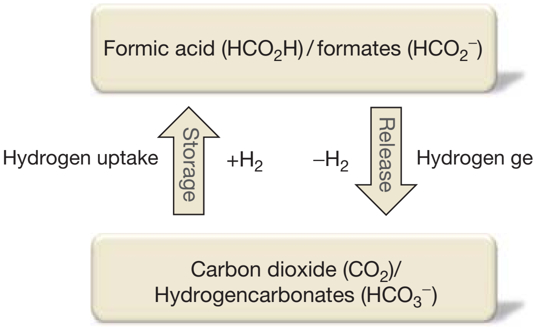


Figure 1 A CO_2-neutral cycle for the storage of hydrogen in formic acid or formates.

Between 1998 and 2000, Puddephatt et al. investigated Ru-dimers. The complex $[Ru_2(\mu\text{-}CO)(CO)_4(\mu\text{-}dppm)_2]$ (**1**; see Figure 2; dppm = 1,2-bis(diphenylphosphino)methane) was reported to be an efficient catalyst which exhibited, at RT, a TOF of 500 h^{-1} in acetone and pure formic acid. By applying *in situ* NMR spectroscopy in solution and X-ray analysis for the obtained species, they identified the Ru-hydride $[Ru_2(\mu\text{-}H)_2(CO)_4(\mu\text{-}dppm)_2]$ and the Ru-formate complex $[Ru_2H(HCO_2)(CO)_4(\mu\text{-}dppm)_2]$ as key intermediates. Since a certain amount of formate was needed, they added triethylamine and observed a significant increase in activity. In the presence of amine, the dehydrogenation of formic acid (FA) was possible, even at temperatures of −10 to −30 °C. In contrast, the reaction was fully suppressed in the presence of acids, for example, triflic acid.[27]

While investigating various Rh-complexes as potential transfer hydrogenation catalysts, Wills and coworkers observed significant gas evolution. Applying a formic acid triethylamine mixture (FA/TEA) and an Rh-complex (see Figure 3), a TOF of 490 h^{-1} at 120 °C for the dehydrogenation of FA and hydrogen liberation was obtained.[28]

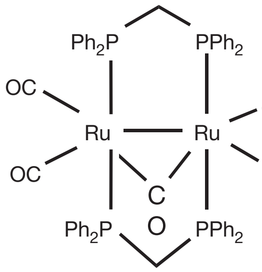


Figure 2 $[Ru_2(\mu\text{-}CO)(CO)_4(\mu\text{-}dppm)_2]$ (**1**) applied by Puddephatt and coworkers.

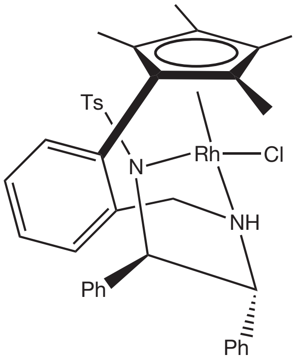


Figure 3 Rhodium-based catalyst (**2**) for FA dehydrogenation applied by Wills et al.

In addition, Wills and coworkers identified several appropriate Ru-catalysts for the hydrogen liberation from FA which are active especially at elevated temperatures (above 120 °C). They used the commercially available 5:2 FA/TEA adduct and screened various precursors, for example, $[RuCl_2(DMSO)_4]$, $RuCl_3$, or $[RuCl_2(NH_3)_6]$, in combination with triphenylphosphane (PPh_3) as the ligand. Interestingly, $[RuCl_2(DMSO)_4]$ exhibited a TOF of 18 000 h^{-1} at 120 °C, without any additional ligand. In fact, ligands like PPh_3 inhibited the reaction. Hence, during their spectroscopic investigations, they observed several Ru-carbonyl species.[28] The obtained gas mixture contained a high concentration of CO and is, therefore, not useful for a direct application in PEM fuel cells.

Furthermore, they described a method for the continuous-flow generation of hydrogen. The hydrogen generation is controlled by either an impedance-based or temperature-based feedback system to adjust the rate of FA replenishment.[29] In the continuously operated systems with $[RuCl_2(DMSO)_4]$ as the catalyst and depending on the applied amine, up to 1.5 l gas per minute over a period of 3 days were obtained with TEA. A maximum hydrogen evolution rate of 2.5 l gas per minute over a period of 6 days was witnessed with *N*,*N*-dimethyloctylamine ($OctNMe_2$) as the amine. These experiments were carried out by using the temperature drop feedback system. However, the required rate of FA replenishment was difficult to control because of the delay in temperature response. By using impedance measurements, Wills et al. were able to control the reaction much more carefully, since formates are strong electrolytes and amines are dielectric and the feedback of the changes, which occur during the reaction, was very fast. In general, this could be a suitable technique for controlling the gas evolution from FAAs and a potential technique on the path to a practical application.

In 2008, Beller and coworkers revisited FAAs as suitable hydrogen storage materials.[30] First, various metal precursors were tested and two Ru-dimer complexes were identified to be active for more than 2 h. Among them $[RuCl_2(p\text{-cymene})]_2$, which had a TOF of 7 h^{-1}, the most active complex at comparable low temperatures, for example, 40 °C. Interestingly, the addition of potassium bromide (TOF of 17 h^{-1}) or potassium iodide (TOF of 48 h^{-1}) increased the catalytic activity significantly.[31] Second, mononuclear ruthenium phosphane complexes for the hydrogen generation from FAAs at these low temperatures were investigated. Very high activity was obtained by using $[RuCl_2(PPh_3)_3]$ in an FA/TEA (5:2 molar ratio) solution and DMF as the solvent.[32] At 40 °C, this catalyst exhibited TOFs of 2288 h^{-1}. Even higher activity, with a TOF of 3630 h^{-1}, was observed applying an $RuBr_3/PPh_3$ *in situ* catalyst, which is, until today, the catalyst with the highest activity ever observed at these low temperatures. However, this system could only provide activity for a rather short time. Varying the ruthenium to phosphane ratio, it was revealed that at least 3 equiv. PPh_3 per Ru are needed. Adding 6 or more equiv. PPh_3 increased both the stability and activity of all catalytic systems. Hence, different phosphane ligands were studied by using $[RuCl_2(benzene)]_2$ and 6 equiv. of ligand. Among monodentate ligands, PPh_3 was found to provide the highest activity (TOF of 200 h^{-1}) at 40 °C, while the best bidentate phosphanes were 1,3-bis(diphenylphosphino)propane (dppp, TOF of 370 h^{-1}) and 1,2-bis(diphenylphosphino)ethane (dppe, TOF of 127 h^{-1}). In contrast to these results, only small hydrogen generation was found in the presence of alkyl phosphanes. By testing the best catalyst systems for more than 3 h, a highly stable *in situ* catalyst system was found comprising $[RuCl_2(benzene)]_2$ combined with dppe.[33] Although these catalyst systems showed a long induction period at these low temperatures, they provided a high activity combined with long-term stability. Notably, in all cases, only traces of CO (<10 ppm) were detected by GC measurements. Besides various amines, amides and heterocyclic bases have been explored and insights into the dependence of the catalyst activity on the pKa of the corresponding acids were found. In general, increases of basicity lead to enhanced activity. Furthermore, the ratio of formic acid and amine in FAAs has a tremendous impact on the catalytic activity too. Especially, by applying *N*,*N*-dimethylhexylamine ($HexNMe_2$) and $OctNMe_2$, increased activity was obtained with Ru-phosphane complexes.[32] An *in situ* catalyst system comprising $[RuCl_2(benzene)]_2$ and 6 equiv. dppe in combination with $HexNMe_2$ was further optimized towards practical application. By applying 20 ml of $5HCO_2H/4HexNMe_2$ as the substrate, a stable TOF of 1905 h^{-1} at 40 °C was reached. Notably, this catalyst system can be reactivated via the replenishment of fresh formic acid, which was shown for at least 10 times over a period of several months. The activity did not decrease significantly and an overall turnover number (TON) of more than 60 000 was achieved. Based on these results, a continuous apparatus was designed and constructed (see **Figure 4**). Notably, only a short column filled with activated charcoal was necessary for direct usage of the obtained gas mixture.

Remarkably, in a continuously driven reaction, no decrease of activity was observed over a period of 264 h and a TON of 260 000 at a constant TOF of 900 h^{-1} at a reaction temperature of 25 °C was obtained. At an FA replenishment rate of 0.74 ml h^{-1}, an average gas flow (H_2+CO_2) of 15 ml min^{-1} was found over this period.[34] This system was successfully implemented in a model car, driven with on-board hydrogen generation and combustion of the evolved hydrogen in a PEM fuel cell. Another interesting aspect of this Ru-based *in situ* catalyst is its potential photochemical acceleration. The *in situ* catalyst derived from $[RuCl_2(benzene)]_2$ and dppe exhibited an up to seven times higher activity upon visible-light irradiation. In detail, a TON of 2804 was obtained after 3 h under visible light at 40 °C, whereas, without irradiation, a TON of 407 was witnessed. Analyzing the reaction rate, it was revealed that visible-light irradiation supports the formation of the active species and accelerates the reactions in the catalytic cycle, too.[35]

In summary, highly active homogeneous catalysts for the selective dehydrogenation of formic acid from FAAs have been developed. The most active systems are described in **Table 1**.

6.20.2.2 Hydrogen Generation from Formic Acid in Ionic Liquids

Recently, ionic liquids (ILs) have gained increased attention as potential solvents and alternatives for bases. Several groups tried to implement amine functionalities to benefit from the unique attributes of ILs, such as negligible vapor pressures,

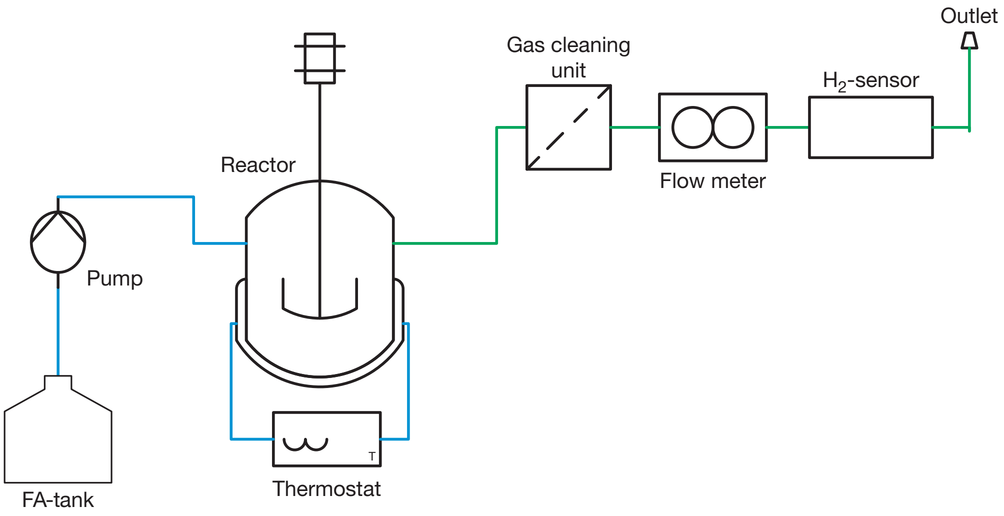


Figure 4 Apparatus for continuous hydrogen generation from FAAs.

Table 1 Homogeneous catalysts for the selective dehydrogenation of FAAs

No.	*Catalyst*	*Substrate*	*T (°C)*	*TON*	*TOF (h^{-1})*	*Reference*
I	**1**	$5HCO_2H/2NEt_3$	20	ca. 350	490	27
II	**2**	HCO_2H	RT	ca. 2000	ca. 500	28
III	$[RuCl_2(DMSO)_4]$	$5HCO_2H/2NEt_3$	120	25 000	18 000	28
IV	$[RuCl_2(p\text{-cymene})]_2$	$5HCO_2H/2NEt_3$	40	14	7	31
V	$[RuCl_2(p\text{-cymene})]_2$	$5HCO_2H/2HexNMe_2$	40	20	10	31
VI	$[RuCl_2(p\text{-cymene})]_2$	$5HCO_2H/2DBN$[a]	40	40	20	31
VII	$[RuCl_2(PPh_3)_3]$	$5HCO_2H/2NEt_3$	40	691	2288	32
VIII	$RuBr_3/PPh_3$	$5HCO_2H/2NEt_3$	40	1375	3630	33
IX	$[RuCl_2(benzene)]_2/dppe$	$5HCO_2H/2NEt_3$	40	407	136	35
X	$[RuCl_2(benzene)]_2/dppe$[b]	$5HCO_2H/2NEt_3$	40	2804	936	35
XI	$[RuCl_2(benzene)]_2/dppe$	$5HCO_2H/4HexNMe_2$	40	60 000	1905	34
XII	$[RuCl_2(benzene)]_2/dppe$	$5HCO_2H/4HexNMe_2$	25	260 000	900	34

[a] DBN = 1,5-diazabicyclo-[4.3.0]non-5-ene.

[b] 300-W xenon light with HOT mirror applied (exclusion of UV light).

tunable polarity, solubility, and miscibility properties. Especially, for practical reasons, the replacement of both solvents and amines is highly desirable, since traces of amines or solvents in the applied gas mixture can lessen the efficiency or even destroy the membranes of PEM fuel cells. For example, Beller et al. applied ILs successfully as a potential solvent.[30] Unfortunately, amines were still necessary to observe good activities. Deng, Shi, and coworkers further developed this idea and attached amine groups on imidazole units of ILs. By using $[RuCl_2(p\text{-cymene})]_2$ as the catalyst precursor in combination with the amine-functionalized IL $[Et_2NEMim]Cl$ (**3**), they could observe TOFs of 14 h^{-1} at 60 °C. By applying $[iPr_2NEMim]Cl$ (**4**), a TOF of 36 h^{-1} was achieved (Figure 5). However, only if additional $NaHCO_3$ was used, they obtained comparable activities to reactions with the present solvents and amine (TOFs of 627 h^{-1} with **4**).[36]

Unfortunately, these systems proved to be unstable and neither recycling nor long-term tests were successful.[37] A similar approach was used by Dupont and coworkers. They investigated the same system comprising $[RuCl_2(p\text{-cymene})]_2$ in combination with **3** at elevated temperatures, for example, 80 °C. At this temperature, they were able to obtain a TOF of 1540 h^{-1} (based on the Ru-dimer). Moreover, Ru-hydride ionic species were found in the reaction mixture, like $[Ru_2(p\text{-cymene})_2(H)(\mu\text{-H})(\mu\text{-HCO}_2)]^+$ and $[Ru_2(p\text{-cymene})_2(H)(\mu\text{-Cl})(\mu\text{-HCO}_2)]^+$, which were observed via ESI-MS techniques.[38]

In addition, Wasserscheid et al. designed a catalyst system which could be recycled several times. By applying [EMMIM] OAc (**5**) in combination with $RuCl_3$ as the catalyst, they observed TOFs of 150 and 850 h^{-1} at 80 and 120 °C, respectively. Moreover, this catalyst system could be reactivated by adding fresh formic acid up to 10 times (Figure 5).[39]

6.20.2.3 Hydrogen Generation from Formates or Formic Acid Base Mixtures

The generation of hydrogen from formates or formic acid base mixtures was mainly studied in the presence of catalysts based on rhodium, iridium, and ruthenium.[26] Fukuzumi, Ogo, and coworkers investigated the stoichiometric reaction of a rhodium diformate complex containing a tacn ligand ($[Rh^{III}(tacn)(HCO_2)_2]OTf$ (tacn = 1,4,7-triazacyclononane, Figure 6).

Mechanistic studies via NMR and X-ray analysis revealed that CO_2 is released via β-hydride elimination and hydrogen is formed upon protonation of the hydrido–formiato intermediate.[40] Later, in 2008, the same group came up with a catalytic version of formic acid decomposition.[41] They presented a water-soluble Rh-complex bearing a bipyridine and a substituted cyclopentadienyl ligand regime ($[Rh^{III}(Cp^*)(bpy)(H_2O)]^{2+}$, Cp* = pentamethylcyclopentadienyl, bpy = 2,2′-bipyridine, **Figure 6**). In the presence of HCO_2Na/HCO_2H, a TON of >80 and a TOF of 30 h^{-1} was determined at ambient temperature and a pH of 3.8. Notably, although no details were given on their GC setup, the investigators could not detect any CO in the gas mixture, a prerequisite for direct use of the evolved hydrogen in PEM fuel cells.

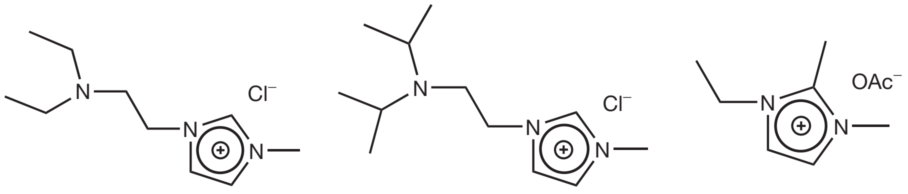
A sole example of a hetero bimetallic complex for formic acid dehydrogenation was reported in 2010.[42] The Ru–Ir complex showed a relatively high TOF of 426 h^{-1} (**Figure 6**).

Himeda and coworkers studied mainly half-sandwich complexes of iridium and ruthenium, as well as rhodium, and used an elegant way to control hydrogen release from formic acid/formate solutions.[43,44] Crucial for their success is the use of 4,4´-dihydroxy-2,2´-bipyridine (DHBP) ligands. The DHBP ligand represents a pH-tunable ligand, which can undergo deprotonation. Thus, the donor capability is dramatically influenced by the proton concentration in the reaction medium. The different electronic and polar properties of the respective hydroxyl group (acidic medium) or oxyanion (basic medium) leads to different reactivities. Applying a half-sandwich complex of iridium containing the DHBP ligand, high activities of up to TOF = 14 000 h^{-1} were obtained at 90 °C in formic acid, whereas the activity decreases dramatically when the pH is increased.

Furthermore, the pH-dependence on the reactivity enables the theoretical opportunity to build up a reversible hydrogen storage system based on formic/acid and hydrogencarbonate (**Figure 7**). Although a fully reversible system has not been demonstrated with these catalysts so far, it was shown that, on the one hand, hydrogen release can be achieved using acidic conditions, and, on the other hand, hydrogencarbonates were hydrogenated successfully to formate in basic media.[45,46] Further application of this interesting class of catalysts was demonstrated in the field of transfer hydrogenations using FA as the transfer hydrogenation reagent.[47,48]

Recently, Olah and coworkers reviewed the field of hydrogen generation from formic acid[26e] and, additionally, reported on ruthenium carbonyl hydride clusters as active catalysts. The tetramer $[Ru_4(CO)_{12}H_4]$ was obtained *in situ* from FA/TEA mixtures and was also synthesized independently. The complex proved to be an active catalyst for the dehydrogenation of formic acid/sodium formate mixtures, although the selectivity of this catalyst with respect to CO formation was not sufficient (beside CO_2 and H_2, up to 0.21 vol% CO).

A challenging but very attractive reaction is the dehydrogenation of formic acid in basic media (formates). The proton concentration in basic media is low, thus, hydrogen release from formed hydride intermediates during formic acid decomposition is slow. However, especially, aqueous basic media enables *in situ* CO_2 capture, which is transformed to solid carbonate and/or hydrogencarbonate. The consequence is the formation of pure hydrogen for fuel cell applications and an aqueous hydrogencarbonate solution, which can be hydrogenated back to formate by the use of hydrogen. The described approach leads to a fully reversible hydrogen storage system. Very recently, Beller et al. succeeded in the development of such a catalyst, formed *in situ* from $[RuCl_2(benzene)]_2$ and bis(diphenylphosphino)methane (dppm, **Figure 8**).[49,50] The catalyst is active for both transformations, the hydrogenation



[Et$_2$NEMim]Cl **3** Deng and Dupont

[*i*Pr$_2$NEMim]Cl **4** Deng and Dupont

[EMMIM]OAc **5** Wasserscheid

Figure 5 Applied ILs for the selective dehydrogenation of formic acid in the presence of a catalyst.[36,38,39]

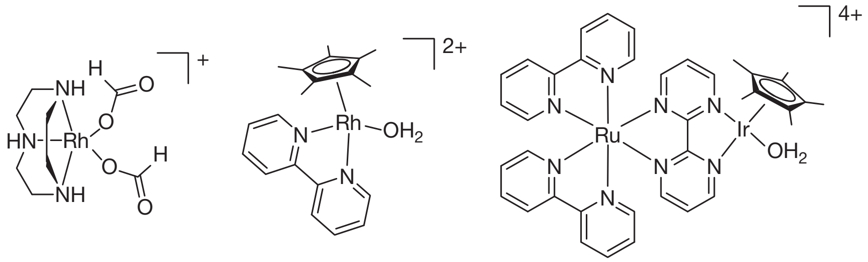


Figure 6 Hydrogen generation from formic acid/formate mixtures studied by Fukuzumi et al.[41] Rhodium complexes for stoichiometric (left), catalytic (middle), and Ru–Ir–bimetallic complex (right). Fukuzumi, S.; Kobayashi, T.; Suenobu, T. *ChemSusChem* **2008**, *1*, 827–834.

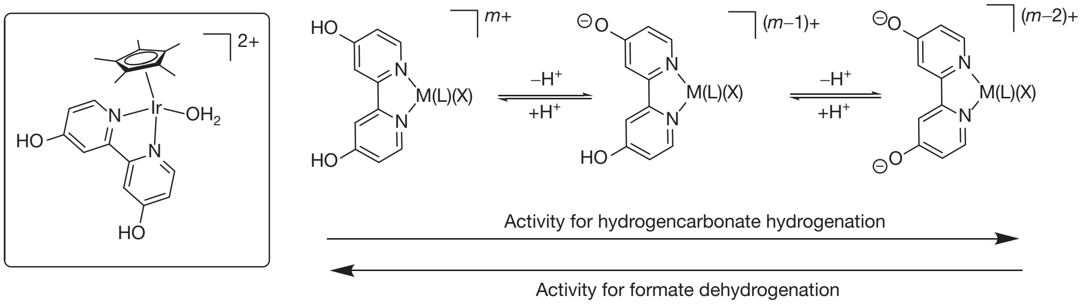


Figure 7 pH-tunable half-sandwich complexes for the catalytic dehydrogenation of formic acid and hydrogenation of hydrogencarbonates by Himeda et al.; X: Cp*, L: H_2O.

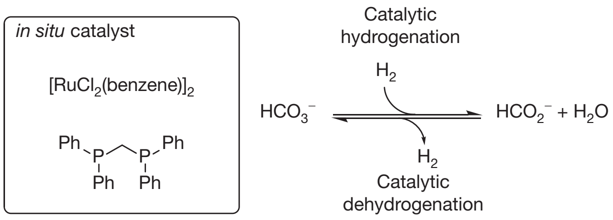


Figure 8 Concept for fully reversible hydrogen storage in a hydrogencarbonate/formate system applying an *in situ* catalyst derived from $[RuCl_2(benzene)]_2$ and dppm.[50] Boddien, A.; Gärtner, F.; Federsel, C.; Sponholz, P.; Mellmann, D.; Jackstell, R.; Junge, H.; Beller, M. *Angew. Chem. Int. Ed.* **2011**, 50*(28)*, 6411–6414. http://dx.doi.org/10.1002/anie.201101995

of hydrogencarbonate as well as the dehydrogenation of different metal formates. It was demonstrated for the first time that, by a simple switch of reaction conditions (pressure and temperature), the mode of the reaction (hydrogen uptake or hydrogen release) can be fully controlled. Sodium formate proved to be most suitable, since almost no CO_2 was detected in the gas mixture after dehydrogenation (yield >90%). Hence, the obtained hydrogencarbonate was back-transformed in high yield (80%) to sodium formate using no additional catalyst besides the one contained. Also, by the use of commercially available sodium hydrogencarbonate, it was shown that, after the hydrogenation of hydrogencarbonate (yield 95%), the obtained formate could be dehydrogenated under mild conditions (30 °C, 80% yield), without the use of additional catalyst.[50]

Hydrogencarbonate hydrogenation as well as hydrogen release from formic acid in aqueous media was also investigated intensively by the group of Laurenczy.[51–53] In 2008, this group, together with the Beller group, discussed formic acid as a potential hydrogen storage material and stimulated various groups to discover new catalysts for both hydrogen generation from formic acid as well as carbon dioxide or hydrogencarbonate hydrogenation. In their initial report, Laurenczy et al. reported an *in situ* system comprising a ruthenium precursor (e.g., commercially available $RuCl_3$ x H_2O or $[Ru(H_2O)_6](tos)_2$; tos = toluene-4-sulfonate) and the highly water-soluble phosphane ligand meta-trisulfonated triphenylphosphane (TPPTS). In an aqueous system, they decomposed an FA/formate (9:1 molar ratio) mixture with 90% yield and a TOF of 460 h^{-1} at 120 °C.[51] Notably, the system showed no decrease in activity up to a pressure of 750 bar and no CO was detected via FTIR spectroscopy (detection limit 3 ppm). Later, they described a setup for continuous hydrogen generation using $[Ru(H_2O)_6]^{2+}$ (1.5 mmol) as the catalyst precursor. An impressive gas flow of 600 ml min^{-1} was achieved at a temperature of 120 °C. Additionally, the catalyst proved to be stable over a period of 1 month, during which it was restarted and stopped several times, giving a total TON of >40 000. Detailed mechanistic studies were carried out using high-pressure NMR techniques, which led to a mechanistic proposal for the reaction.[52] Two catalytic cycles were proposed, including a monohydride and a dihydride cycle, and the authors proposed that the dihydride mechanism is predominant (Figure 9).

Moreover, a study of different water-soluble phosphanes was carried out. Besides TPPTS, the meta-disulfonated triphenylphosphane ligand (TPPDS) showed comparable activity.[53]

For large-scale and mobile applications, the recovery of the catalyst, especially if noble-metal catalysts are applied, is of central interest. In this respect, the immobilization of homogeneous catalysts is an important topic. First attempts for the immobilization of the Ru-TPPTS system of Laurenczy et al. were carried out using different techniques, such as ion exchange, coordination, and physical absorption.[54]

6.20.2.4 Application of Nonprecious Metals in the Hydrogen Generation from Formic Acid

Promising results have been reported in the field of formic acid dehydrogenation using noble-metal catalysts.[30] However, a substitution with non-noble-metal catalysts based on, for example, cobalt or iron is highly desirable to meet the needs of industry, such as low costs.[55]

In recent studies of Beller et al. aiming for new nonprecious-metal catalysts for hydrogen generation from formic acid, a range of iron phosphane complexes have been discovered, capable of generating hydrogen and carbon dioxide from formic acid (Figure 10).[56–58]

The first generation of catalysts includes *in situ*-generated iron carbonyl phosphane complexes in combination with terpyridine. In the presence of light, these catalyst systems are active for the production of hydrogen from formic acid amine mixtures. In a broad investigation of different P- and N-ligands, it was shown that, depending on the kind of ligands, TOFs of up to 200 h^{-1} at 60 °C (6,6″-(phenyl)-2,2′:6,2″-terpyridine and PPh_3 as ligands) and TONs of >100 (1,10-phenanthroline and PPh_3 as ligands) can be achieved. Mechanistic investigations via NMR and IR studies as well as DFT calculations show that iron-hydride complexes are formed exclusively in the presence of visible light and terpyridine is needed for stabilizing purposes.[56]

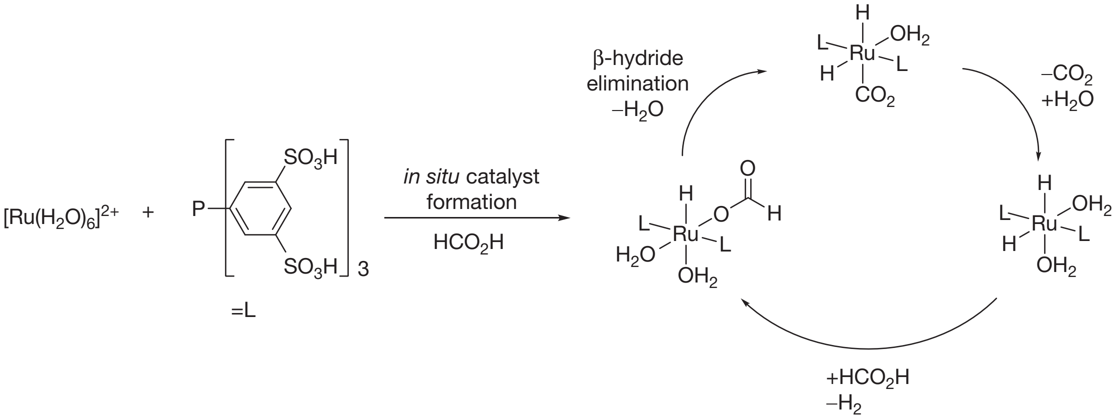


Figure 9 *In situ* catalyst formation of the Laurenczy catalyst and proposed catalytic cycle via dihydride intermediate.[52] Fellay, C.; Yan, N.; Dyson, P. J.; Laurenczy, G. *Chem. Eur. J.* **2009**, *15*, 3752–3760.

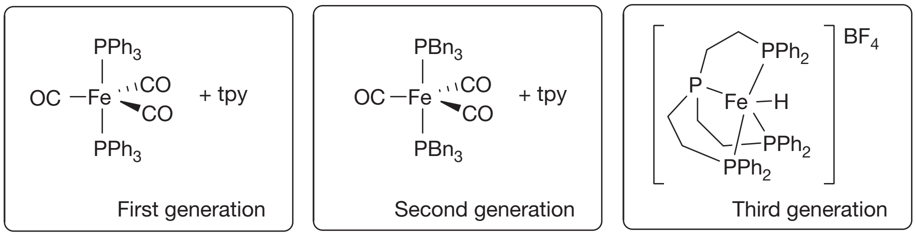


Figure 10 Nonprecious-metal catalysts capable of dehydrogenating formic acid; Bn: benzyl, tpy: terpyridine.

A second generation of iron catalysts was developed with the help of benzyl phosphanes as P-ligands.[57] Again, in the presence of terpyridine and light, hydrogen can be produced from formic acid amine mixtures with TONs as high as 1266. As the activity was found to be independent of the electronic and steric properties of the phosphane, a metallation of the benzyl phosphane was revealed as the reason for increased activity and stability. Via NMR studies and DFT calculations, it was shown that metallation of the benzyl moiety in the ligand is favored during light irradiation and is energetically downhill. This metallation might account for the observed higher activity compared to the triphenyl phosphane system.[57]

For both systems of first- and second-generation, sophisticated reaction setups, such as light source, additional base (e.g., triethylamine), and solvent (DMF), are needed to drive hydrogen generation. A much simpler system that needs no additional base, no light, and only formic acid and the fully biodegradable solvent propylene carbonate was developed on the basis of $Fe(BF_4)_2 \bullet 6\ H_2O$ and tris[2-(diphenylphosphino)ethyl]phosphane (tetraphos, PP_3).[58] A remarkably high TON of more than 92 000 was obtained in a long-term experiment at a constant TOF of 5390 h^{-1}. The highest TOF of 9425 h^{-1} was obtained at 80 °C. These numbers are the highest values ever reported for any nonprecious-metal catalyst for hydrogen generation from formic acid and are comparable to the best noble-metal catalyst systems. *In situ* NMR and kinetic studies as well as DFT calculations revealed possible reaction intermediates. Central in the mechanistic scheme is the iron hydride complex $[FeH(PP_3)]^+$, which, upon the addition of formic acid, can eliminate CO_2 as well as hydrogen via two proposed catalytic cycles.[58]

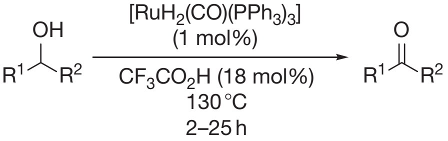
6.20.3 Hydrogen Generation from Alcohols

6.20.3.1 Synthetic Aspects of the Acceptorless Alcohol Dehydrogenation

The alcohol moiety can be regarded as the reduced congener of the carbonyl unit, the most versatile functionality found in chemistry. Comparing the two components from a reactivity point of view, the more oxidized carbonyl is much more prone towards degradation than the practically inert alcohol. It is, therefore, of great synthetic interest to keep C—O bonds in a complex molecule at the lowest possible oxidation level when either storing the compound or while performing modifications on other functionalities in the molecule. When necessary, the oxidation to the desired carbonyl functionality should then be best carried out in a single step with the least possible amount of additive and waste material. To meet these conditions, selective catalytic acceptorless dehydrogenation of an alcohol unit to a desired carbonyl counterpart would constitute the most effective approach.

Scrutinizing the literature for this type of reactions, it quickly becomes clear that this is a field that has gained ground, especially during the last decade. As such, aldehydes, ketones, esters, acetals, imines, amides, imides, and quinolines are all functionalities that have been successfully prepared using catalytic acceptorless alcohol dehydrogenation. However, what also needs to be emphasized is the fact that the majority of the publications are proof-of-concept reports, and, as such, utilization in true organic synthesis is still a future task.

In the following sections, a survey of the various developments within the distinct transformations, for example, primary



	Yield (%)
2-Octanol	81
2-Decanol	82
1-Phenylethanol	59
4-*tert*-Butylcyclohexanol	34
Menthol	51
Cyclohexanol	80

Scheme 2 $[RuH_2(CO)(PPh_3)_3]$ catalyzed acceptorless dehydrogenation of a range of secondary alcohols to their corresponding ketones.

alcohol to ester, is presented. Emphasis is placed on the reaction procedure and scope of reactions, where, in addition, hydrogen is released but not used for further reactions.

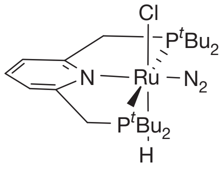
6.20.3.1.1 Alcohols to aldehydes and ketones

Since the explorative work by, for example, Cole-Hamilton,[13] Robinson,[12] and Saito[59] through the 1970s to the late 1980s, the field was very quiet for nearly a decade. The revival in catalytic acceptorless alcohol dehydrogenation could be credited to Hulshof,[60,61] Milstein,[62,63] and Williams[64] for their work on ruthenium-catalyzed dehydrogenations of secondary alcohols to ketones in the early years after the millennium. Since then, this simple transformation has been extended to include also aldehydes. Today, it constitutes the most explored reaction within this field.

The first report on acceptorless alcohol dehydrogenation to carbonyl compounds after the year 2000 was published by Hulshof in 2003, where 1 mol% of $[RuH_2(CO)(PPh_3)_3]$, together with 18 equiv. of CF_3CO_2H, were shown to catalyze the transformation of a range of secondary alcohols to ketones (**Scheme 2**).[60] For sterically nondemanding aliphatic alcohols, yields of >80% were observed. Employing benzyl-substituted alcohols led to a slightly inferior result, with a 59% yield for 1-phenylethanol. The sterically more demanding alcohols resulted in yields as low as 34% in the case of 4-*tert*-butylcyclohexanol, limiting the scope of the system. Furthermore, it was shown that a TON exceeding 200 was achieved in the case of 2-octanol as the substrate. Finally, the catalytic system could be recycled three times without noteworthy loss in catalytic activity, greatly enhancing the synthetic applicability.

Since then, several reports on catalyst complex modifications have been published.[61–65] As such, Hulshof disclosed an improved catalytic system in which $[RuH_2(CO)(PPh_3)_3]$ was treated with tetrafluorosuccinic acid followed by partial exchange of the PPh_3 ligands with bis(diphenylphosphino)-ferrocene (dppf), leading to $[Ru(\mu\text{-}OCO\text{-}C_2F_4\text{-}OCO(CO)(H_2O)(PPh_3)]_2$.[61] This led to a catalytic system capable of dehydrogenating 1-phenylethanol without adding any associated additives (TON up to 651). An attempt to employ the chiral ligand (*S*)-BINAP instead of dppf in order to obtain enantioselection, effectively a resolution, failed.

Milstein showed that the complex $[RuH(PNP)Cl(N_2)]$ (**Figure 11**) catalyzes the dehydrogenation of 2-propanol in the presence of 2 equiv. NaO^iPr with a TON of 924 after 70 h.[62] It was also shown that, under the given reaction conditions, 1-phenylethanol and cyclohexanol would also be dehydrogenated in 64.4% and 45.2% conversion, respectively. Contrary, primary alcohols were inactive towards dehydrogenation. Substrates containing both a secondary and a primary alcohol, which might be selectively oxidized only at the secondary position, were not tested.



$[RuH(PNP)Cl(N_2)]$

Figure 11 Milstein ruthenium complex for acceptorless alcohol dehydrogenation.

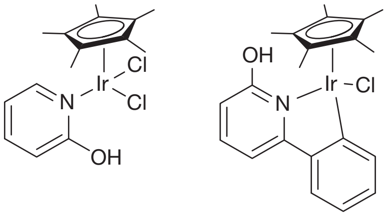


Figure 12 Fujita and Yamaguchi Cp*Ir complexes.

Williams employed an *in situ* system of 2.5 mol% $[RuCl_2(p\text{-}cymene)]_2$ with 4 equiv. of PPh_3, together with 15 mol% of LiOH in refluxing toluene under a flow of argon to achieve full conversion of 1-phenylethanol.[64] Furthermore, it was demonstrated that the reaction was independent of the electronic character of the aryl component, with both *p*-F and *p*-MeO reaching full conversion. The scope was further expanded to, for example, the bisaryl substrate benzhydrol. In addition, Grubbs' catalyst was shown to be equally active as the *in situ* system for these reactions. A single entry illustrated that primary alcohols failed to be dehydrogenated, limiting the substrate scope.

The potential of iridium as a complex metal for the acceptorless dehydrogenation of alcohols was first shown by Fujita and Yamaguchi[66,67] and Wang[68] and very recently substantiated by Gelman.[69] In 2007, Fujita and Yamaguchi reported that the Cp*Ir catalyst shown in **Figure 12** (left complex) effectively dehydrogenates a range of 1-aryl- and alkyl-substituted ethanols.[66] Performing the reactions in refluxing toluene with 0.1–1.0 mol% catalyst led to yields in the range of 75–97%. A high substrate tolerance was observed with the toleration of electron-deficient and electron-rich aryl, 2-substituted phenyl, as well as heteroaryl substituents. In addition, substrates containing cycloalkyl and *sec*-alkyl substituents were also smoothly dehydrogenated. Impressively, when using 0.025 mol% of the catalyst, a TON of up to 2120 after 100 h in boiling xylene could be achieved. The work of Gelman is discussed in **Section 6.20.3.1.2**.

Fujita and Yamaguchi then showed that a modified Cp*Ir complex (**Figure 12**, right complex) allowed for the dehydrogenation of primary alcohols to aldehydes.[67] This was the first effective aldehyde production via catalytic acceptorless dehydrogenation of primary alcohols. Thus, a wide range of 2-, 3-, and 4-aryl-substituted benzyl alcohols, both electron-deficient and electron-rich versions, were dehydrogenated to their corresponding aldehydes, with yields ranging from 51% to 95%. This was accomplished by using 2 mol% of this improved Cp*Ir complex in the presence of 5 mol% of either NaOMe or $NaHCO_3$. Aliphatic alcohols were also oxidized. However, 5 mol% of catalyst was needed in order to obtain yields in the region of 46–62%.

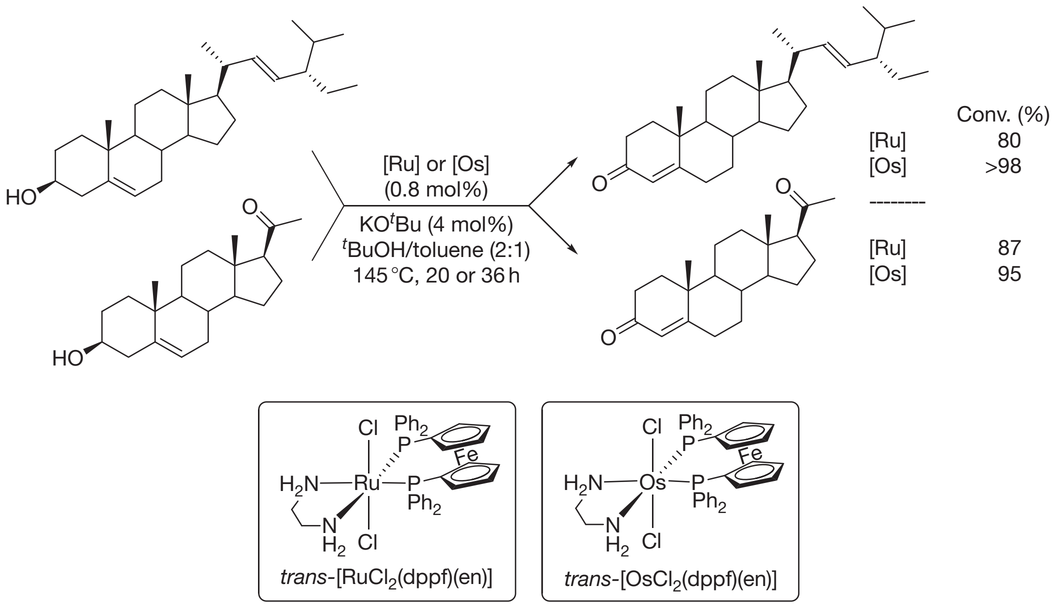
Similar results were obtained by Albrecht[65] using an Ru(II)(η^6-arene)-triazole complex. A comparable scope was shown; however, no base additive was necessary, but 5 mol% of the catalyst was used.

In 2011, Baratta reported, for the first time since 2000, the usage of catalytic acceptorless alcohol dehydrogenation for synthetic purposes in complex molecules, albeit with substrates relatively scarce in other functionalities.[70] Thus, 1.25 mmol of several sterols were shown to be effectively dehydrogenated to their corresponding steroids, of which two examples are shown in **Scheme 3**. Both ruthenium and osmium versions of *trans*-[MCl_2(dppf)(en)] (en = ethylenediamine) were shown to successfully convert the sterols with high yields, with osmium being the superior metal with nearly full conversions. Alpha-stereogenic centers to ketones already present in the sterol were shown not being epimerized (lower reaction); likewise, the presence of the ketone did not influence the conversion rate. In addition, alkene units far away from the alcohol unit were not hydrogenated, a problem observed with other catalytic systems in the field of alcohol dehydrogenation. However, the homoallylic alcohol did isomerize during the oxidation to the corresponding enone, which most likely happens after the oxidation itself.

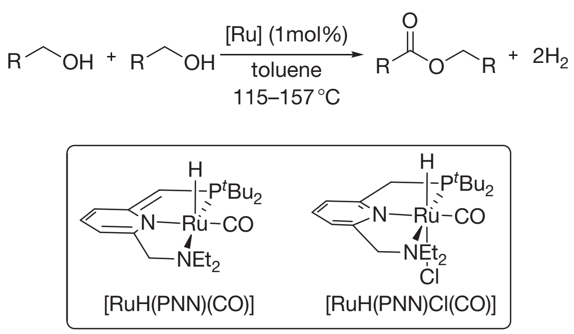
6.20.3.1.2 Alcohols to esters

In 2005, Hartwig reported the cyclization of 1,4-butanediol to γ-butyrolactone by acceptorless dehydrogenation.[71] Eighteen different iridium and ruthenium complexes were tested, of which *cis*-[$(PMe_3)_2RuCl_2$(en)] was the most active. Thus, at refluxing conditions (205 °C), 0.0058 mol% of the catalyst was able to transform the 1,4-butanediol to γ-butyrolactone in full conversion within 48 h, corresponding to an impressive TON of 17 000.

The same year, Milstein showed the intermolecular dimerization of two alcohol molecules into one ester product (**Scheme 4**).[72] 1-Butanol, 1-hexanol, and benzyl alcohol were



Scheme 3 [Ru] and [Os] catalyzed dehydrogenation reactions of sterols to steroids.



	Yield (%)
	[RuH(PNN)Cl(CO)]/[RuH(PNN)(CO)]
1-Butanol	91.5/90
1-Hexanol	94.5/99
Benzyl alcohol	99.5/92.1

Scheme 4 Ester formation from two alcohol molecules. The Milstein catalyst ([RuH(PNN)(CO)]) and the precursor ([RuH(PNN)Cl(CO)]) are also shown.

all candidates that underwent smooth conversion into their corresponding esters by reacting the given alcohol in refluxing toluene (115–157 °C) in the presence of either 1 mol% [RuH(PNN)Cl(CO)] with 1 equiv. of KOH or simply 1 mol% of the activated complex [RuH(PNN)(CO)]. With this method, the selectivity towards the ester was very high with ≤1% of the aldehydes observed, and the yield ranged from 90% to 99.5%.

In 2011, Gusev reported that the osmium complex *trans*-[OsH_2(PNP)(CO)] (**Figure 13**) is also able to form esters, albeit only from high-boiling alcohols such as isoamyl, hexanol, and benzyl alcohol.[73] Using 0.1 mol% of the catalyst in refluxing alcohol at 130–205 °C for 2–8 h led to 88–93% conversions. However, already with 1-butanol, the refluxing temperature (118 °C) proved to be too low to achieve reasonable catalytic activity, and, as a result, only 17% conversion was observed after 7 h, limiting the scope of this system.

Also in 2011, Gelman published some results from the acceptorless dehydrogenation of alcohol to esters using the PCP pincer Ir complex, as shown in **Figure 13**.[69] Both the conversion of diols to lactones and intermolecular dimerization to linear esters were shown to be catalyzed by this new complex. Thus, employing 0.1 mol% of the catalyst and 5 mol% of Cs_2CO_3 in refluxing *p*-xylene led to yields in the range of 88–98% for 1,4-butanediol and a range of electron-deficient and electron-rich benzyl alcohols. In addition, ethylene glycol was shown to form the dimerized product 1,4-dioxan-2-one in 96% yield.

6.20.3.1.3 Alcohols to amides

A major breakthrough in atom-efficient amide synthesis was made by Milstein with a publication in 2007, in which it was shown that equivalent amounts of alcohol and amine would couple to the amide product by the Milstein catalyst [RuH(PNN)(CO)], as already shown in **Scheme 4**.[74] High-boiling, mostly unbranched, alcohols were successfully employed with primary aliphatic amines in refluxing toluene with 0.1 mol% catalyst to give amides in 70–99% yields within 7–12 h. The fact that high-boiling alcohols are employed does not compromise the synthetic applicability of the system, since most alcohols to be converted into an amide in a synthetic endeavor are probably of high molecular weights. Aryl amines, represented by aniline, showed a more sluggish reactivity with a 58% yield. Secondary aliphatic amines proved to be completely unreactive, which was exploited to selectively acylate only the primary amines of diethylenetriamine in 88% yield.

The year after, Madsen showed that an *in situ* system of 5 mol% of [$RuCl_2$(COD)], the carbene precursor 1,3-diisopropylimidazolium chloride, and $PCyp_3HBF_4$ (Cyp = cyclopentyl) catalyzes the amide synthesis from alcohols and amides in toluene at 110 °C.[75] Again, high-boiling alcohols were employed, and primary aliphatic amines were showed to perform the best, with yields ranging from 60% to 100%. Both optically pure amines and alcohols, with the stereogenic center in the alpha position in the amine and beta position in the alcohol, were employed with no sign of epimerization, improving the synthetic aspects. As for the Milstein system, aryl amines and secondary aliphatic amines did not show good reactivity, although the secondary amine gave 40% yield compared to no reaction in the case of Milstein.

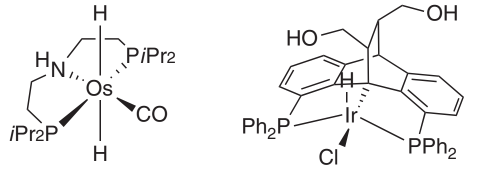


Figure 13 Gusev PNP Os pincer complex and Gelman PCP Ir pincer complex.

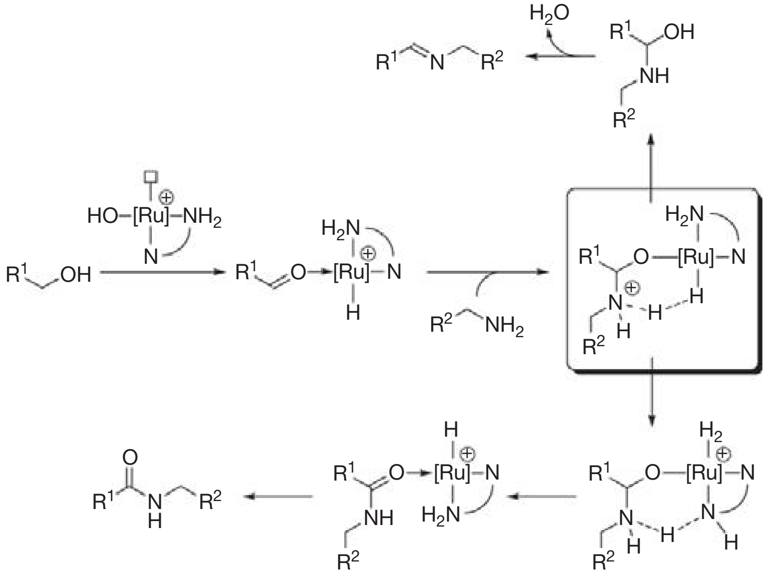
Since the Madsen publication, there have been several reports on amide synthesis from alcohols and amines using *in situ*-formed Ru—carbene complexes.[65,76–80] This has led to a single report that expands the scope to also include secondary amines as well to yield tertiary amides in good yields (76–80%).[80] In addition, for this system, no phosphane ligand is necessary, and the *in situ* catalytic system consists of 5 mol% $RuCl_3$, 1,3-diisopropylimidazolium bromide, and pyridine and 40 mol% NaH, which is refluxed in toluene for 24 h. Aryl amines still pose problems, though, with <20% yields obtained.

From a mechanistic point of view, the catalytic cycle is believed to commence with oxidation of the alcohol to the aldehyde, which is then attacked by the amine, leading to a hemiaminal. This unstable intermediate is then prone to either further oxidation to the amide or dehydration to the imine, which can be re-reduced to the alkylated amine product. The aspects of what factors that affect the switch between these distinct products are discussed in the experimental–theoretical study carried out by Crabtree and Eisenstein, in which they use *cis*-[$RuCl_2$(dppb)(2-aminomethylpyridine)] as the catalyst.[81] Mechanistic studies are beyond the scope of this chapter; however, the crude conclusion from this thorough paper is that whether the hemiaminal is coordinated to the metal or liberated is crucial. The former leads to further oxidation to the amide, whereas the latter leads to either imine or amine (**Scheme 5**).

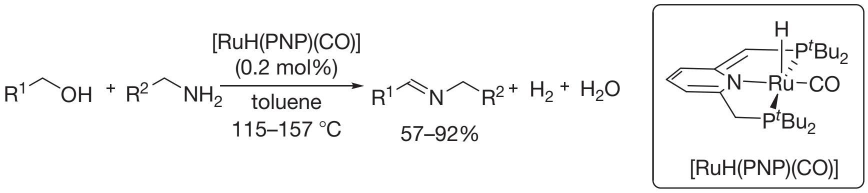
6.20.3.1.4 Miscellaneous

Very recently, the synthesis of imines from alcohols and amines has successfully been accomplished by Milstein,[82] Esteruelas,[83] and Albrecht.[65] In 2010, Milstein employed 0.2 mol% of the [RuH(PNP)(CO)] complex to convert alcohol combined with 1.01 equiv. amine to the imine product in refluxing toluene (**Scheme 6**).[82] Both benzylic and normal aliphatic versions of both alcohols as well as amines were smoothly converted to the corresponding imines in 57–92% yields. In general, the normal aliphatic alcohols showed inferior selectivity compared to the benzylic substrates, leading to yields in the lower end. Only primary alcohols underwent reasonable conversion, with cyclohexanol forming the imine of benzyl amine with merely 20% conversion after 22 h.

Already in 2002, Fujita and Yamaguchi showed that the dehydrogenation of 2-aminophenethyl alcohols led to the formation of indoles (**Scheme 7(a)**).[84] As such, this is a very early example of acceptorless alcohol dehydrogenation. However, as it utilizes the thermodynamic pull by condensating the formed carbonyl with the amine to yield indoles, it is not considered a seminal work in line with what Hulshof, Milstein, and Williams showed (*vide supra*). Nevertheless, employing 5 mol% of [Cp^*IrCl_2]$_2$ led to indole products in the range of 68–99%. Both electron-donating and electron-withdrawing substituents on the aryl were shown to be tolerated. In addition, methyl



Scheme 5 Imine or amide synthesis from a schematic mechanistic point of view.



Scheme 6 Imine formation from alcohol and amine catalyzed by the [RuH(PNP)(CO)] complex.

groups as R^2 or R^3 were applicable, demonstrating an easy synthetic approach towards substituted indoles.

In 2011, Madsen used acceptorless alcohol dehydrogenation to synthesize 2- and 3-substituted quinolines from anilines and 1,3-diols (**Scheme 7(b)**).[85] A wide range of anilines as well as both alkyl and phenyl R^2- and R^3-substituted 1,3-diols were proved to undergo conversion, albeit only in poor to moderate yields (20–61%).

Hong established a catalytic system capable of cyclic imide formation from diols and primary amines by employing an *in situ* system of 5 mol% of $[RuH_2(PPh_3)_4]$ and 1,3-diisopropylimidazolium bromide with 20 mol% of NaH in refluxing toluene (**Scheme 7(c)**).[86] Stirring for 24 h led to 23 products, with yields spanning from poor to very good (36–88%). Mostly, 5-membered cyclic imides were shown, but, also, 6-membered proved accessible. In addition, a single example of imide formation from an intramolecular cyclization of an internal amide and a primary alcohol proceeded smoothly with 70% yield. However, an attempt to form linear imides from an amine and two alcohols resulted in the amide product via a single coupling of the amine with 1 equiv. of alcohol.

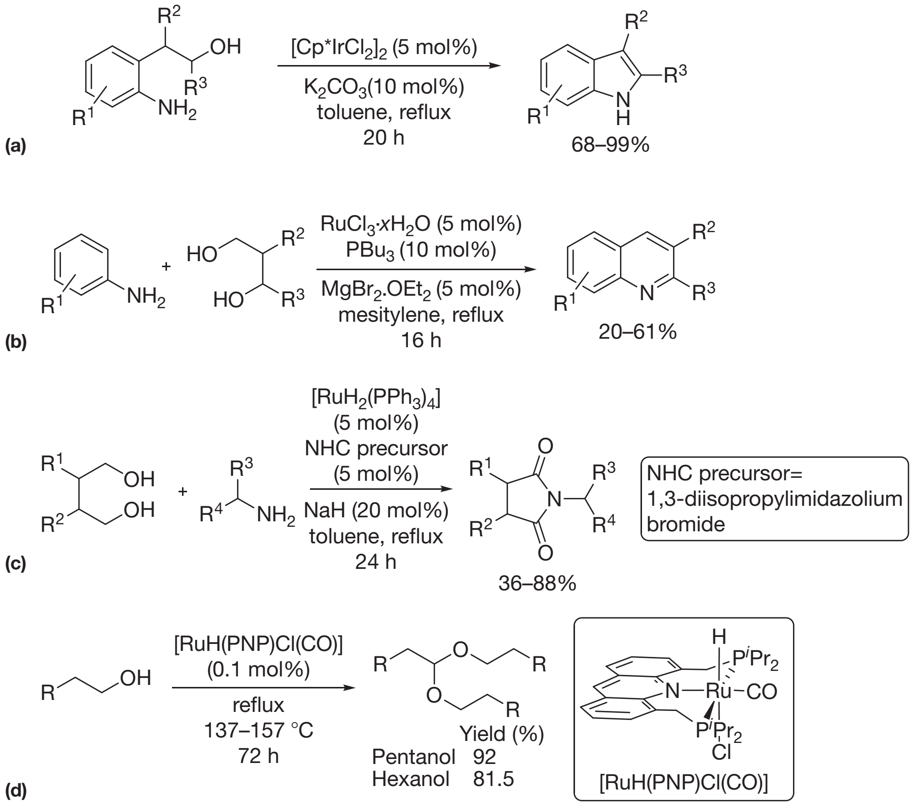
Milstein showed that, by employing the newly developed acridine-based PNP complex [RuH(A-PNP)Cl(CO)], primary alcohols could be coupled to form an acetal (**Scheme 7(d)**).[87] Only two examples, 1-pentanol and 1-hexanol, were shown to give good yields though (92% and 81.5%, respectively). Furthermore, long reaction times were necessary, considering the catalytic loading and temperature employed. Ethanol and 1-butanol were also tested but failed to give any conversion, limiting the procedure. The authors speculate that the boiling points of these two substrates (78 and 118 °C, respectively) are too low to allow for sufficient catalytic activity.

6.20.3.2 Hydrogen Generation from Alcohols with Respect to Energetic Application

Many systems are described in the literature able to dehydrogenate alcohols, giving synthetically valuable products like aldehydes, ketones, amides, or esters (see **Section 6.20.3.1**). Hydrogen is produced in these reactions as a byproduct. The amount of H_2 and the analytics of the purity of the formed gas have not been in the focus of the presented examples. However, there are some cases which go into more detail concerning the increased hydrogen generation.

In this respect, the Cole-Hamilton catalysts have to be noted as prominent candidates. Investigations in the late 1980s have shown that hydrogen can be an interesting product, although it was, in part, contaminated with methane, CO, and CO_2.[13a,13b,88] Very recently, some mechanistic investigations have been performed concerning the hydrogen generation from alcohols applying Cole-Hamilton catalysts, proving the unbroken interest.[89]

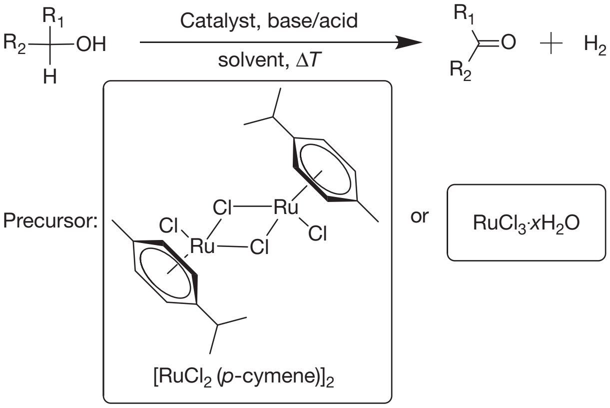
The development of new catalysts for hydrogen production was strongly related to catalysts for synthetic approaches. For both fields, a gap without significant advancement of nearly one decade can be recognized in between the mid 1990s and



Scheme 7 (a) Synthesis of indoles. (b) Synthesis of quinolines. (c) Synthesis of cyclic imides. (d) Synthesis of acetals.

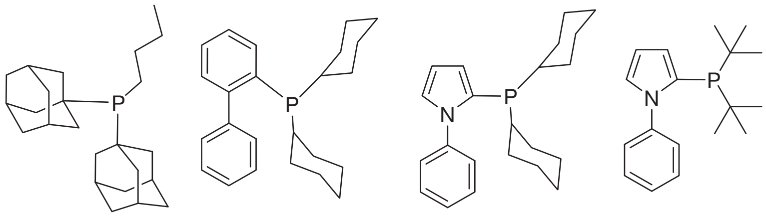
the beginning of the twenty-first century. Then, as mentioned in Section 6.20.3.1, it has been Hulshof continuing work with the Robinson catalyst in 2003 but not focusing exclusively on hydrogen. Further investigations by Milstein or Madsen mentioned hydrogen production but paid more attention to the expected more distinguished organic products.[72,74,75,87] The following examples will present primarily the production of hydrogen from alcohols (Scheme 8). This approach can easily be understood by discussing hydrogen production from biomass, for example, green plants or parts of it, like cellulose, hemicellulose, lignin, or its fermentation products, like alcohols.

At the beginning of the twenty-first century, hydrogen became more and more important. Climate change is an omnipresent topic. The old energy system starts to change to a more sustainable one. In this context, researchers are looking for reactions producing energy carriers like hydrogen in a sustainable manner. In 2005, Beller published the ruthenium-based hydrogen generation from 2-propanol with a simple *in situ* system at moderate temperature (90 °C).[14b] A broad screening of phosphane ligands in combination with a relatively cheap catalyst precursor $RuCl_3 \cdot xH_2O$ led to a very active system containing 2-di-*tert*-butyl-phosphinyl-1-phenyl-1H-pyrrole[9] (Figure 14). A TOF of 155 h^{-1} has been achieved in a 2-h experiment with a P:Ru ratio of 2:1. The NaO^{i}Pr, acting as a promoter, was freshly prepared for every experiment by the addition of sodium to 2-PrOH. Also, sodium hydroxide instead of NaO^{i}Pr was tested as the base but resulting in lower activity (Table 2, entries 8 and 9). Selected results are summarized in Table 2, and the ligands are given in Figure 14.



Scheme 8 Reaction scheme for hydrogen generation from alcohols.

In addition, another series of catalysts was presented by Beller and coworkers, focusing on nitrogen-containing ligands.[14c] Although $[RuCl_2(p\text{-cymene})]_2$ without further ligands showed a certain activity (TOF 192 h^{-1}), this could be significantly improved by applying nitrogen-containing ligands. Thus, a series of *in situ*-formed catalysts was tested. A typical experiment contained 16 ppm $[RuCl_2(p\text{-cymene})]_2$, 0.8 M NaO^{i}Pr, and an Ru:N ratio of 1:3 (tridentate ligand) or 1:2 (mono or bidentate ligands). The reaction was performed at 90 °C. The different ligands and the obtained activities (TOF (h^{-1})) after 2 h) are depicted in Figure 15. The resulting catalysts are all active in the dehydrogenation reaction of 2-propanol. A general trend



6 **7** **8** **9**

Figure 14 Phosphane ligands used in the experiments by Beller.[14b] Junge, H.; Beller, M. *Tetrahedron Lett.* **2005**, *46*, 1031–1034.

Table 2 Ligand screening for hydrogen production from 2-propanol, precursor $RuCl_3 \cdot xH_2O$

Entry	*Ligand*	*Base*	*Hydrogen volume*[a] *(ml)*	*TOF (h^{-1})*
1	PPh_3	NaOH	56	61
2	PPh_3	Na	61	66
3	PCy_3	Na	93	101
4	PCy_2Ph	NaOH	69	75
5	P^tBu_3	NaOH	49	53
6	dppf	NaOH	51	55
7	**6**	NaOH	96	104
8	**7**	NaOH	6	7
9	**7**	Na	105	114
10	**8**	NaOH	28	30
11	**8**	Na	110	120
12	**9**	Na	143	155

Reaction conditions: 315 ppm catalyst precursor $RuCl_3 \cdot xH_2O$, ratio P:Ru = 2:1 (entry 6; P:Ru = 1:1), 5.0 ml 2-PrOH, 0.8 M base, 90 °C, 2 h.

[a] Measured by gas burette.

was found: tertiary amines are better than secondary and primary amines. Favored are TMEDA (**13**) and its derivatives **14** and **18**, as well as 2-dimethylaminoethanol (**26**), *N*,*N*-dimethylaniline (**12**) and *N*,*N*,*N*′,*N*′-tetramethyl-o-phenylenediamine (N^1,N^1,N^2,N^2-tetramethylbenzene-1,2-diamine) (**21**). In contrast, for example, the tpy ligand (**24**) showed an inhibiting effect.

Interestingly, strong coordinating ligands like tpy inhibited the reaction, whereas alkylated amines showed a significantly increased reaction rate compared with the pure ruthenium precursor molecule.

By applying TMEDA (**13**) at an Ru:N ratio of 1:20, a TOF of 519 h^{-1} was obtained, which is the highest activity observed below 100 °C. This system was still active after 11 days and produced 71 mmol hydrogen, corresponding to a TON of 17 215 and a potential electric energy of 4.8 Wh. When ethanol was used instead of 2-propanol, traces of methane as a second gaseous product were found.

Another approach to produce hydrogen from renewable feedstocks has been published by Wasserscheid et al. using glucose and other carbohydrates as substrates.[90] Here, ILs were utilized to dissolve, for example, glucose and cellulose. The nature of the anion of the IL is essential for the catalytic activity. The IL $[Bu_4P][Me\text{-}P(OH)O_2]$ forms the most stable system for dehydrogenation within the investigated ILs. The catalytically active system is composed of 40 mg $[RuCl_2(p\text{-cymene})_2]_2$ and 300 mg **13** at 180 °C in 50 g IL and 3 g of glucose, resulting in a TON of 72 after 1 h. Dehydrogenation and hydrogen evolution also took place when cellulose was used. Interestingly, it was found that glucose decomposes by thermal treatment in the IL by a dehydration/rehydration process. One mole of formic acid per mole of glucose is formed in this reaction. The acid is quickly transformed to hydrogen and CO_2 in a ruthenium-catalyzed reaction, which is in agreement to the described reactions in Section 6.20.2.

6.20.4 Conclusion

Hydrogen is foreseen to play a key role as a future energy carrier, precisely because it can be efficiently used in fuel cells generating electricity and water as the only waste product.

The major issues confronted are an efficient hydrogen generation from renewables as well as a safe and reversible hydrogen storage. In this respect, the summarized results constitute a major step towards convenient hydrogen generation and storage options, and a long-striven objective, on-demand hydrogen production from a liquid source, could become reality.

Recent investigations of homogeneously catalyzed hydrogen generation from alcohols focused on temperatures below 100 °C and low-molecular-weight alcohols as biomass-related hydrogen sources.

New *in situ* ruthenium–amine and ruthenium–phosphane complexes were developed which were able to generate significant amounts of hydrogen from 2-propanol at 90 °C. Although selected catalysts were active for more than 11 days, the energy content of the produced hydrogen was only 4.8 Wh (lower heating value of H_2: 33.33 kWh kg^{-1}; 2.4 Wh taking the efficiency of a fuel cell into consideration). In addition, the progress of the reaction depends strongly on the presence of base.

These facts clearly indicate that, with respect to the purposes of energy supply, further investigations should focus on improving the catalyst activities and stabilities, upscaling experiments, and reduction of the amount of base. After these problems have been solved, the application of this technology for hydrogen generation in an industrial process seems possible in a longer-term range. Additionally, other biomass-related substrates like glucose or glycerol may play an important role. This has been already shown, for example, for the aqueous phase reforming, a heterogeneous process driven at temperatures >200 °C.[91]

The synthetic aspect of the acceptorless dehydrogenation of alcohols has recently gained much more interest, since it is a powerful method to synthesize the oxidation products of alcohols with high atom efficiency; only two hydrogen atoms are lost. A broad variety of new catalysts has been developed. Among them, especially, pincer-type Ru, Os, and Ir complexes, carbene Ru complexes, and 2-hydroxypyridine Ir complexes

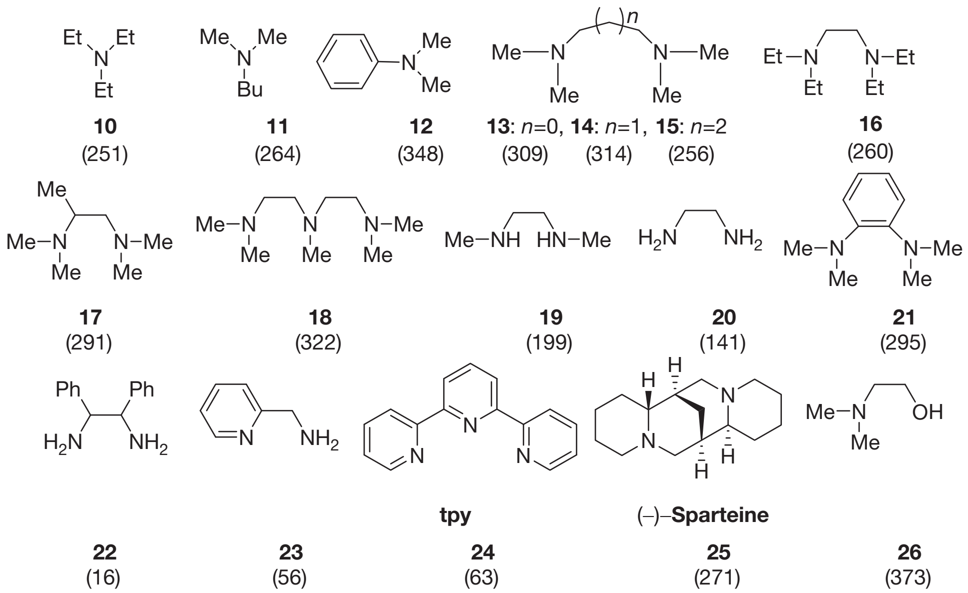


Figure 15 Nitrogen-containing ligands for the *in situ* formation of ruthenium catalysts and the activity of the catalytic system for hydrogen evolution (TOF, h^{-1}).

show very promising results for future developments. Although in these reactions the focus lays on the synthesis of oxidation products, hydrogen is generated too. This is most likely to be a great advantage considering future industrial incorporation of such processes. However, an actual application of this type of reaction and the use of acceptorless alcohol dehydrogenation on substrates other than model substrates, leading to useful products, are still future tasks.

In comparison with this, the progress in the field of hydrogen generation from formic acid is much more significant. Stable and active catalysts have been developed which are able to generate CO-free hydrogen, even at RT. The amounts of hydrogen already meet the requirements for the hydrogen supply for small mobile applications and the catalyst costs are becoming more and more neglectable due to the observed high TONs of up to 260 000 with ruthenium–phosphane-based catalyst systems. However, there has been, so far, one major disadvantage of these catalytic systems: the presence of further additives (e.g., amine or base) or a certain pH is essential.

Very recently also for a non-noble-metal-based catalyst system, an iron complex, a very high productivity (TON ca. 92 000) has been achieved. It is noteworthy to mention that this reaction works without any additive: neither base nor amine is needed. Thus, it combines the advantage of applying a much cheaper and more abundant metal precursor and the absence of additives.

In addition, progress has been achieved also with heterogeneous core-shell catalysts, which allow the hydrogen generation from formic acid at RT and without any additives.[92] However, the activities are far lower than the best homogeneous catalysts.

A very important point constitutes the potential CO_2-neutrality of the overall process of loading and releasing hydrogen. A fully reversible storage cycle based on carbon dioxide and formic acid can be envisioned, if the byproduct CO_2 is severed. At present, tremendous efforts concerning the hydrogenation of carbon dioxide are underway to complete the cycle.[93] Although having been discussed on several occasions previously, the combination of both processes using the same catalyst has been realized recently for the first time applying hydrogencarbonate and formate.[50]

In conclusion, both methods, hydrogen generation from alcohols and formic acid, constitute powerful tools for the generation of molecular hydrogen as a sustainable fuel source from a liquid organic compound. Although no application so far has been realized, achievements made in the last several years, especially for the HCO_2H decomposition, give rise to increased optimism that the hydrogen generation from liquid organic molecules may be realized in the mid-term range. This could become feasible especially for niche energy applications like small portable devices.

Among all other candidates, so far, only formic acid has the advantage to release hydrogen in ambient conditions. The combination of hydrogen generation from formic acid and a PEM fuel cell could be a suitable alternative for direct methanol fuel cells. So far, the only example is a small fuel-cell toy car that demonstrates the general feasibility of the principle of a formic-acid-based power supply system.

An upscale up to the 100-W scale seems to be already possible with the present catalysts. This would allow for the construction of power supply systems also for bigger portable electric devices (camcorders, notebooks, etc.). For related chapters in this Comprehensive, we refer to **Chapters 1.35**, **6.09**, and **7.16**.

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6.21 Catalytic Asymmetric C–C Bond Formation in Aqueous Medium

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6.21.1 Introduction

In recent years, metal-catalyzed asymmetric C–C bond formation in aqueous medium has attracted much attention, not only because any dry solvents are required for these reactions but also because water often allows unique reactivity and selectivity. Indeed, water is a safe, inexpensive, and an environmentally benign solvent. However, catalytic asymmetric reaction in aqueous medium is still immature in organic synthesis because of three main reasons (1) many chiral catalysts as well as reactive substrates are decomposed in the presence of water; (2) water generally creates heterogeneous reaction media, which often have negative effects on reaction rates; and (3) chiral ligands compete with water in coordination with metals.

To address these issues, water-compatible catalysts have been developed by utilizing original element characters. The catalysts sometimes combine with hydrophobic materials such as surfactants, polymers, and ionic liquids.

In this chapter, the progress of metal-catalyzed asymmetric C–C bond formation in aqueous medium is summarized. Examples in which even small amounts of water are essential for reactivity and selectivity are also described.

6.21.2 Allylic Substitution Reaction

Uozumi and coworkers reported amphiphilic polystyrene–poly(ether glycol) copolymer (PS–PEG) resin-supported catalysts.[1,2] A palladium complex anchored to the PS–PEG resin via coordination to the phosphane ligand catalyzed various organic reactions in water.[3–5] With a combinational strategy, it was found that **1-Pd** catalyzed the reaction of diphenylpropenyl acetate with 3-methyl-2,4-pentanedione in water to afford the corresponding product in high yield with high enantiomeric excess (Scheme 1).[6]

Uozumi et al. also designed highly functionalized, supported P,N-chelating palladium complex **2-Pd** prepared from PS–PEG–NH_2 resin, chiral P,N-ligand, and $[PdCl(\eta^3\text{-}C_3H_5)_2]_2$. For the reactions of both cyclic and acyclic substrates with dialkylmalonate, **2-Pd** worked effectively to afford the products in good yields with high to excellent enantioselectivities in water (Scheme 2).[7,8]

Cyclic isomerization of 1,6-enynes proceeded smoothly in water under heterogeneous conditions in the presence of **2-Pd** to give the corresponding cyclopentanes (Scheme 3). Multistep asymmetric synthesis of a hydrindane framework was achieved via palladium-catalyzed asymmetric π-allylic alkylation, propargylation, and cycloisomerization of 1,6-enynes, where all three steps were performed in water with recyclable polymeric catalysts.[9]

Chiral complex **3** prepared from D-glucosamine can also promote the allylic alkylation in aqueous media, and can be recycled by pH-controlled extraction (Scheme 4).[10]

Sinou and coworkers reported the palladium-catalyzed alkylation of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate in water in the presence of surfactants, using K_2CO_3 as base and chiral non-water-soluble ligands. Surfactants, especially cetyltrimethylammonium hydrogen sulfate, were beneficial additives for the allylic substitution in water catalyzed by palladium complex prepared *in situ* from $[Pd(C_3H_5)Cl]_2$ and BINAP (Scheme 5).[11]

6.21.3 Diels–Alder Reaction

Lewis acids have been used as catalysts in Diels–Alder reactions. Mikami and his coworkers reported the beneficial use of water as an additive in the hetero Diels–Alder reaction of Danishefsky's diene with butyl glyoxylate catalyzed by chiral lanthanide bis(trifluoromethanesulfonyl)amides (Scheme 6).[12]

Desimoni et al. reported that, with the same chirality of the ligand and the cationic core of the catalyst, the presence or the absence of water in the reaction of cyclopentadiene with 3-acryloyl-1,3-oxazolidin-2-one led to opposite

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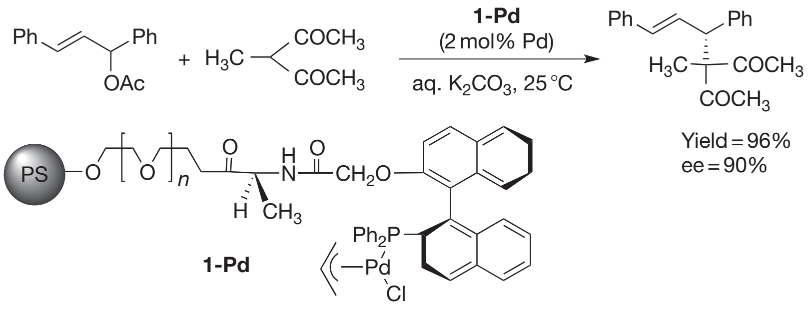
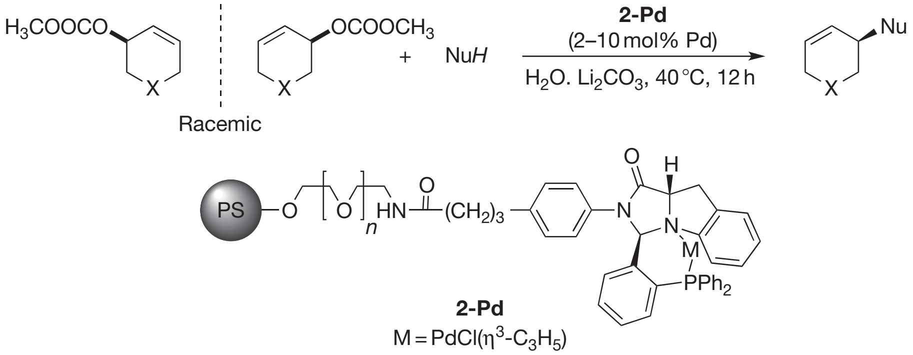
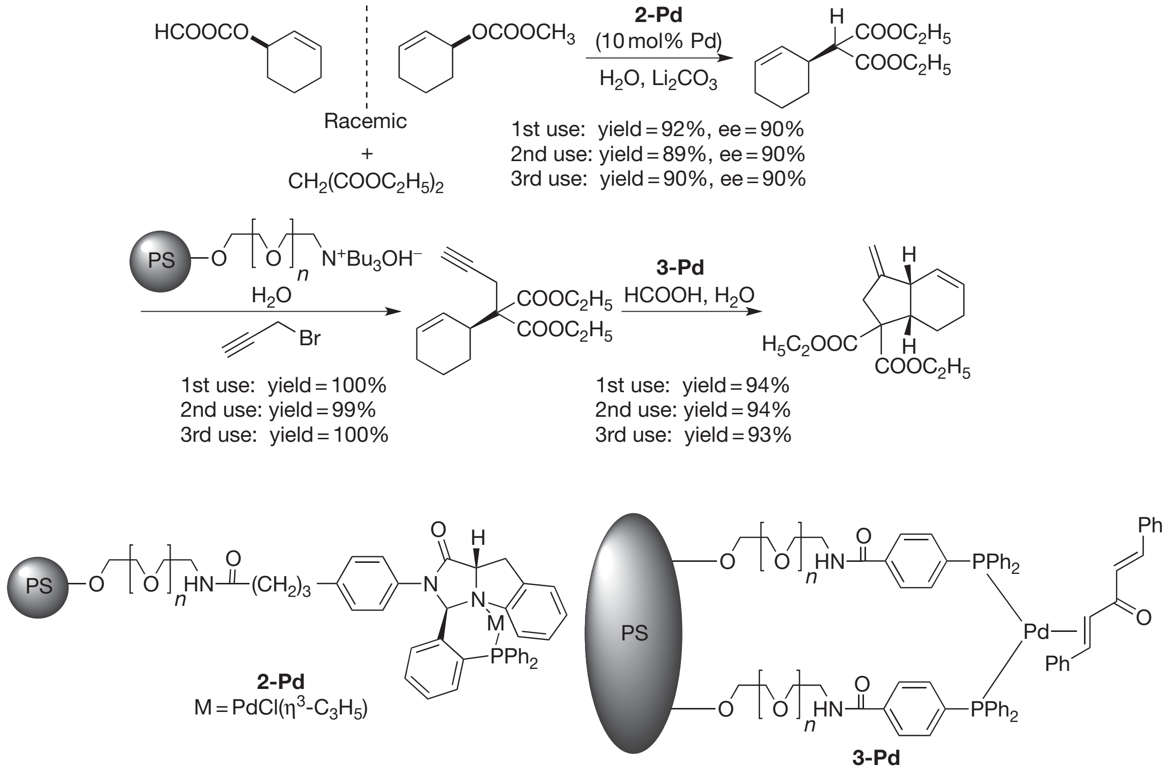


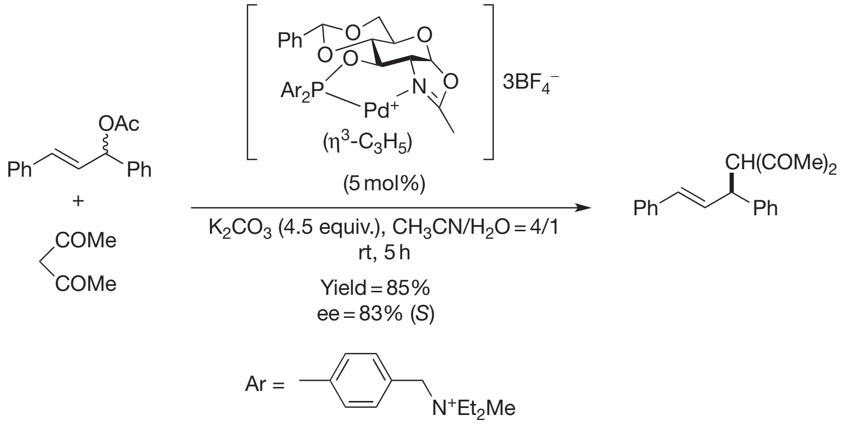
Scheme 1



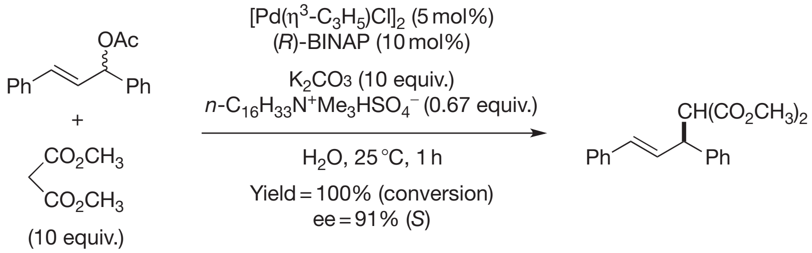
Scheme 2



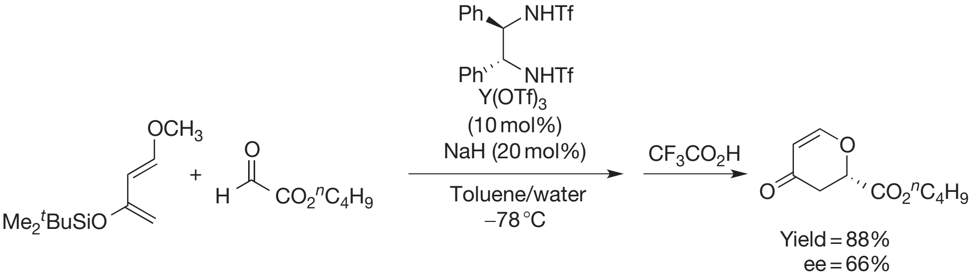
Scheme 3



Scheme 4



Scheme 5



Scheme 6

enantioselectivity. Water changed the coordination around Mg (II) from tetrahedral to octahedral, and altered the sense of the enantioselectivity (Scheme 7).[13–15]

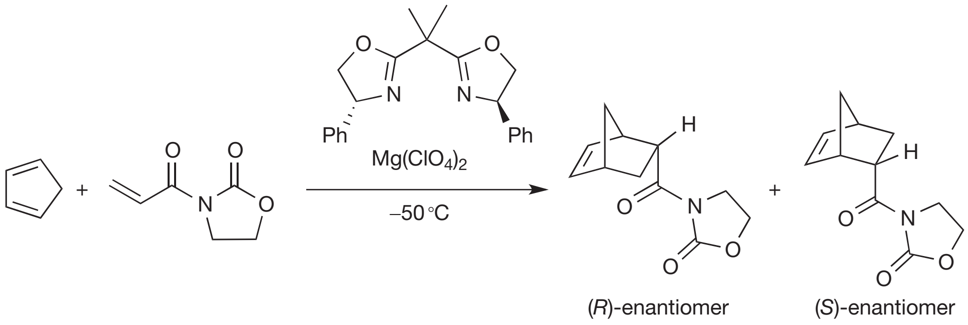
Engberts and coworkers reported asymmetric Diels–Alder reaction of 3-phenyl-1-(2-pyridyl)-2-propen-1-one with cyclopentadiene in water using a copper salt with an amino acid, especially *N*-α-methyl-L-tryptophan (L-abrine) (Scheme 8).[16,17] This was the first example of catalytic asymmetric carbon–carbon bond-forming reaction by using a chiral Lewis acid in water. The pyridine part of the substrate was crucial for its strong binding to the copper cation in a bidentate fashion. Arene–arene interactions between the substrate and the ligand, which are enhanced by water compared with organic solvents, also have beneficial effects on the high yield and the good enantioselectivity.

The DNA-based asymmetric Diels–Alder reaction in water was reported by Roelfes and Feringa (Scheme 9).[18,19] Integrating the metal-binding site and DNA anchor into one moiety resulted in a dramatic increase in the enantioselectivity.[20,21] Combination of amphiphilic phthalocyanine–copper complex with various serum albumins was also successfully applied to asymmetric Diels–Alder reaction in water.[22,23]

6.21.4 Aldol Reaction and Hydroxymethylation

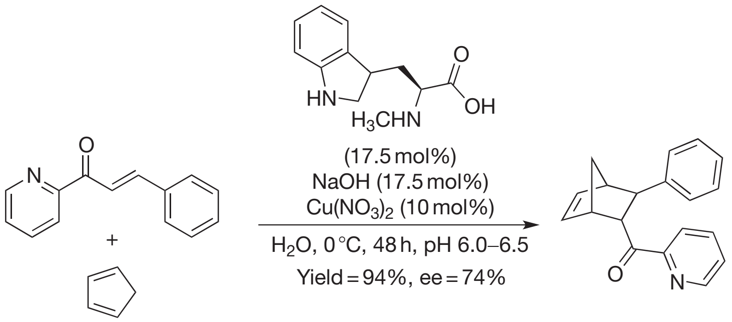
Aldol reaction is one of the most powerful carbon–carbon bond-forming processes to afford synthetically useful, optically active β-hydroxy ketones and esters.[24–26] In 1995, Shibasaki and his coworkers reported the first synthetically useful example of a catalytic asymmetric aldol reaction that proceeds via a Pd(II) enolate. Using a Pd(II)–(*R*)-BINAP-derived complex as catalyst, good chemical and optical yields were attained in the addition of silyl enol ethers to aldehydes in 'wet' dimethylformamide (DMF).[27]

Lewis acid-catalyzed, asymmetric aldol reaction in organic solvents has been intensively investigated in the past decades.

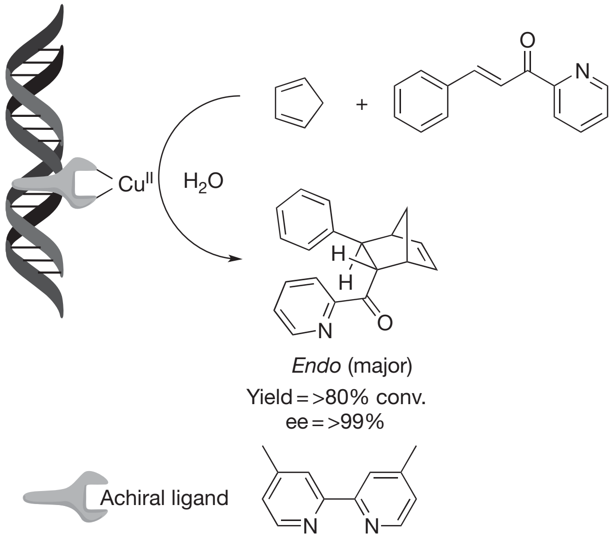


Without H_2O, *S* major ee = 68–70%
With 2 equiv. of H_2O, *R* major ee = 59–65%

Scheme 7



Scheme 8



Scheme 9

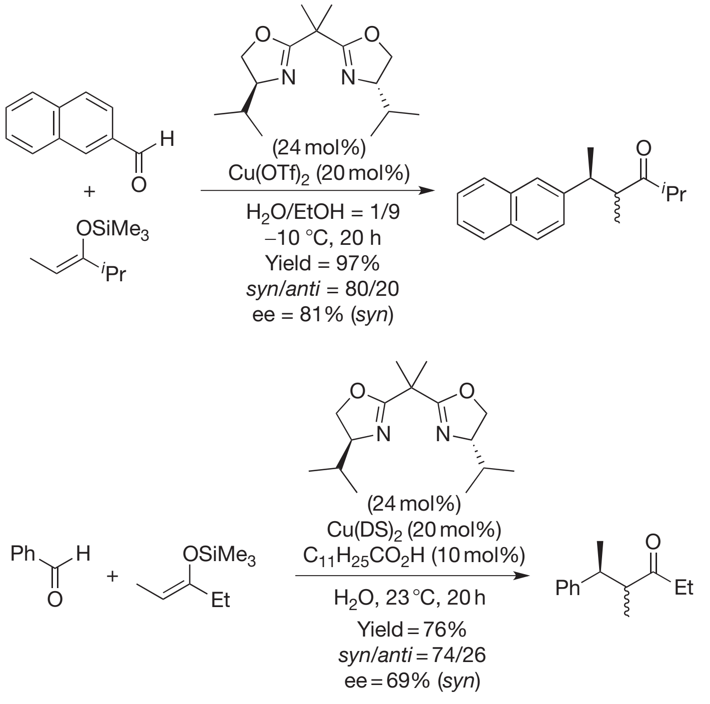
There were several successful examples of chiral Lewis acid-catalyzed reactions of silyl enol ethers with aldehydes; however, most of them required aprotic, strict anhydrous solvents such as dichloromethane (DCM), toluene, and propionitrile at low temperature.[28–30] In 1992, Kobayashi and coworkers developed water-compatible Lewis acids for aldol reactions.[31–34] The use of a catalytic amount of lanthanide triflate greatly improved the rate and the yield in the reaction of benzaldehyde with (1-trimethylsiloxy)cyclohexanone. Among the lanthanide triflates, $Yb(OTf)_3$, $Gd(OTf)_3$, and Lu$(OTf)_3$ generally gave better yields of the corresponding aldol condensation products, and the diastereoselectivities of these reactions were moderate. One of the benefits of using lanthanide triflate as a catalyst was that water-soluble aldehydes such as acetaldehyde, acrolein, and chloroacetoaldehyde were applicable, and furthermore, the catalyst could be recovered and reused in this system. Since then, various Lewis acids have been used for such reactions.[35] The catalytic activities of Lewis acids in water were related to hydrolysis constants and exchange rate constants for substitution of inner-sphere water ligands.[36] Other metals used with some success as catalysts in aqueous aldol reactions are $Bi(OTf)_3$,[37] $Cu(OTf)_2$,[38] $FeCl_3$,[39] and $InCl_3$.[40–42] In 1999, Kobayashi et al. reported asymmetric aldol reactions in aqueous media using copper triflate–bis(oxazoline) complex.[43,44] Although this complex was already used in aldol reactions of (benzoloxy)acetaldehyde with a variety of silicon enolates in dry organic solvents,[45] it should be noted that, the reaction of simple aldehydes such as benzaldehyde with silicon enolates proceeded under mild conditions in aqueous system. It was also demonstrated that water accelerated the desired chiral reaction and suppressed the undesired achiral side reaction to afford the adduct in high yield with good selectivity, while the pure ethanol or DCM favored the achiral side reaction to give rise to the corresponding product in lower yield with lower diastereo- and enantioselectivities. In a similar system, chiral bis(oxazoline) ligands, disubstituted at the carbon atom linking the two oxazolines by Frechet-type polyether dendrimers coordinated with copper(II) triflate, provided moderate yields and enantioselectivities for Mukaiyama aldol reactions in water (up to 61% ee), although diastereoselectivities of the product could be improved (up to *syn*/*anti* = 2.6/1).[46] Asymmetric aldol reaction in water without using organic cosolvents was conducted with the aid of a Lewis acid–surfactant-combined catalyst (**Scheme 10**).

The most important feature in designing a chiral ligand for the Lewis acidic metals for reactions in aqueous media is its binding property to the metal cations. A ligand with strong coordinating ability often leads to reduction of the Lewis acidity of the metal cations and, as a result, to low yields of the desired products. On the other hand, weaker binding ability of the ligand results in generating free metal cations coordinated by solvent molecules instead of the ligand. This leads to decrease in enantioselectivity of the products by competition between the chiral Lewis acid- and achiral, free Lewis acid-catalyzed pathways. This problem has to be solved by finding a chiral ligand that has strong binding ability and does not significantly reduce the Lewis acidity of the metals. $Pb(OTf)_2$[47] and $Ln(OTf)_3$–crown ether complexes (**4** and **5**)[48,49] were shown to be very efficient chiral catalysts for asymmetric aldol reaction in aqueous media. In the reactions with (*Z*)-1-phenyl-1-trimethylsiloxypropene, the desired aldol adducts were obtained in good yields with good diastereo- (*syn*/*anti* = 9/1) and enantioselectivities (in the range of 47–87% ee), depending on the structure of the aldehyde (**Scheme 11**).[50] Li and his coworkers reported that the catalyst prepared from $Ga(OTf)_3$ and chiral semi-crown **6** was effective for asymmetric aldol reactions in aqueous media. In the presence of the chiral ligand, hydrolysis of a silyl enol ether was suppressed, while rapid hydrolysis occurred in the absence of the ligand.[51,52] In addition, water was necessary to satisfy the yield and enantioselectivity of the aldol adduct. Mlynarski et al. reported a similar system using pybox-type ligand **7a**, **7b**, and $Zn(OTf)_2$ or $FeCl_2$ in asymmetric aldol reactions in aqueous media.[53–55]

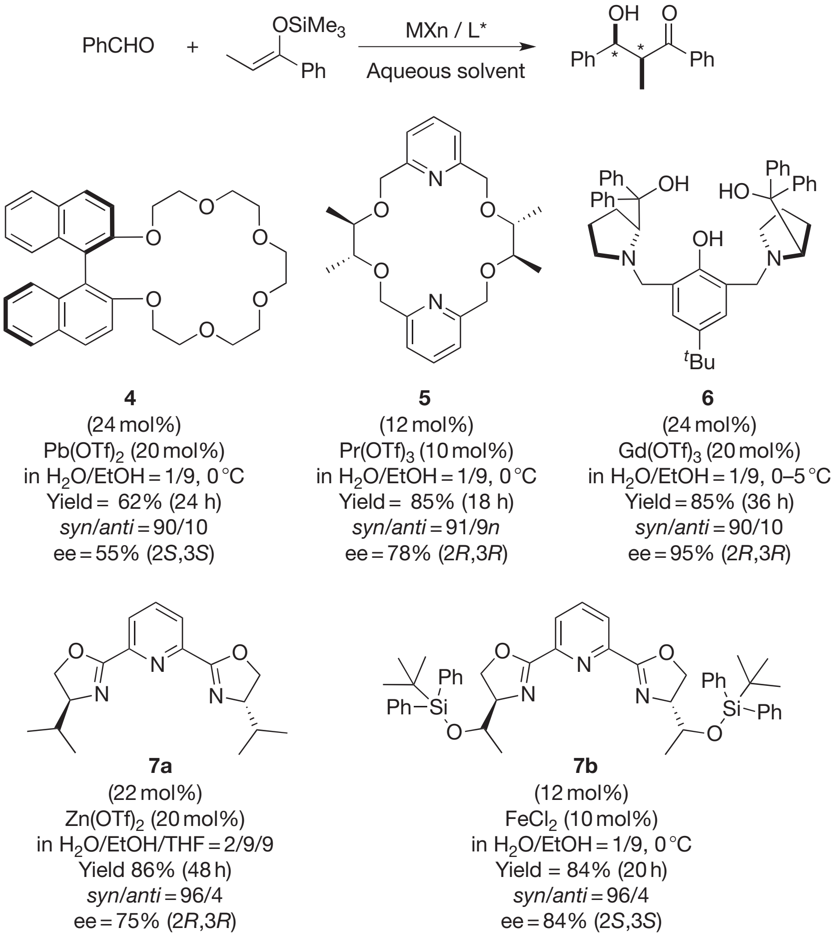
In 2002, Kobayashi et al. also developed *anti*-selective asymmetric aldol reactions using a novel chiral zirconium catalyst prepared from $Zr(OCMe_3)_4$, (*R*)-3,3′-diiodo-1,1′-binaphthalene-2,2′-diol[(*R*)-3,3′-I_2BINOL], an alcohol, and water (**Scheme 12**). Under the mild reaction conditions, the aldol reaction proceeded smoothly to afford the corresponding aldol adducts in high yields with high diastereo- and enantioselectivities.[56] The alcohol played an important role in the catalyst turnover, and water affected the formation of the catalyst. *Anti*-adducts were obtained from both *E*- and *Z*-enolates, which indicated the involvement of acyclic transition states. Coupled with *in situ* cyclization reaction (hetero-Diels–Alder reaction), this system can also be applied to the asymmetric synthesis of chiral pyran derivatives, such as (+)-prelactone.[57]

In 2003, Katsuki and coworkers reported the asymmetric Mukaiyama aldol reaction between 2-trimethylsilyloxyfuran and aldehydes catalyzed by Cr(salen) (**Scheme 13**).[58] The Mukaiyama-type aldol reaction is reversible in non protonic solvent. Water can irreversibly hydrolyze the intermediate to the product. The subsequent addition of water into the system steadily enhanced ee values of both *syn* and *anti* products, and the maxima were observed when water amounted to 10 equiv. of the catalyst. Water exerted little influence on yield. Further study showed that alcohol was a much more efficient additive than water due to its easy interdiffusion with the solvent CH_2Cl_2.[59]

$Ga(OTf)_3$ and $Cu(OTf)_2$ provided better results than Sc$(OTf)_3$ as a Lewis acid catalyst in this system.[60] $AgPF_6$–BINAP



Scheme 10



4
(24 mol%)
$Pb(OTf)_2$ (20 mol%)
in H_2O/EtOH = 1/9, 0 °C
Yield = 62% (24 h)
syn/*anti* = 90/10
ee = 55% (2*S*,3*S*)

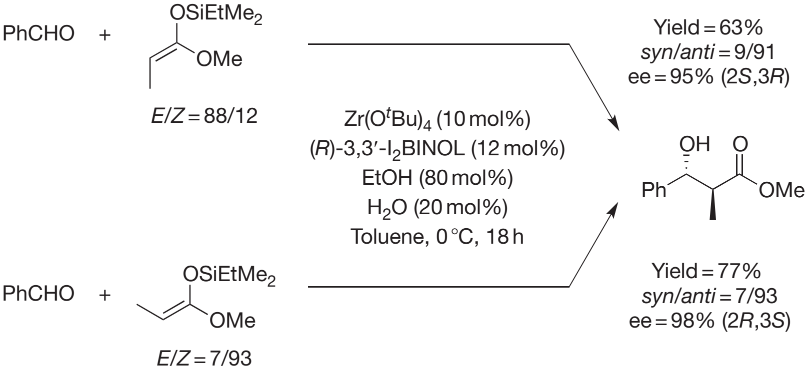
5
(12 mol%)
$Pr(OTf)_3$ (10 mol%)
in H_2O/EtOH = 1/9, 0 °C
Yield = 85% (18 h)
syn/*anti* = 91/9*n*
ee = 78% (2*R*,3*R*)

6
(24 mol%)
$Gd(OTf)_3$ (20 mol%)
in H_2O/EtOH = 1/9, 0–5 °C
Yield = 85% (36 h)
syn/*anti* = 90/10
ee = 95% (2*R*,3*R*)

7a
(22 mol%)
$Zn(OTf)_2$ (20 mol%)
in H_2O/EtOH/THF = 2/9/9
Yield 86% (48 h)
syn/*anti* = 96/4
ee = 75% (2*R*,3*R*)

7b
(12 mol%)
$FeCl_2$ (10 mol%)
in H_2O/EtOH = 1/9, 0 °C
Yield = 84% (20 h)
syn/*anti* = 96/4
ee = 84% (2*S*,3*S*)

Scheme 11



E/*Z* = 88/12

E/*Z* = 7/93

$Zr(O^tBu)_4$ (10 mol%)
(*R*)-3,3′-I_2BINOL (12 mol%)
EtOH (80 mol%)
H_2O (20 mol%)
Toluene, 0 °C, 18 h

Yield = 63%
syn/*anti* = 9/91
ee = 95% (2*S*,3*R*)

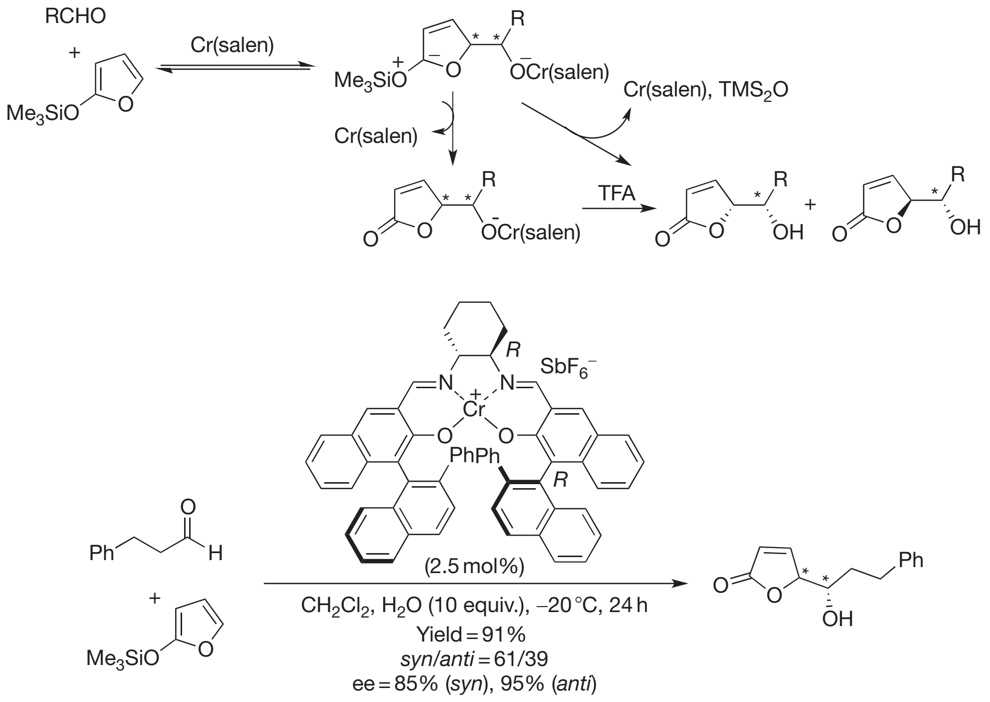
Yield = 77%
syn/*anti* = 7/93
ee = 98% (2*R*,3*S*)

Scheme 12

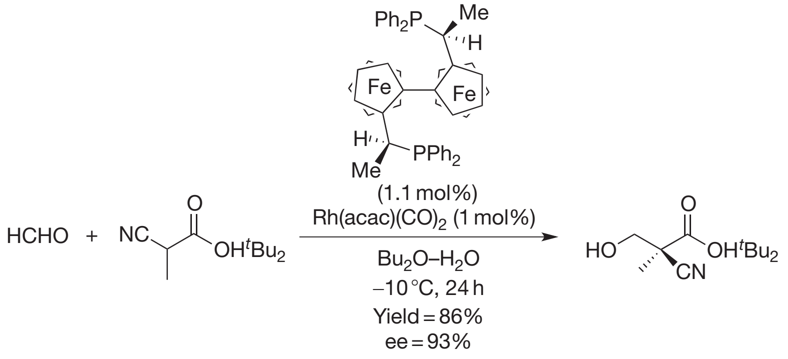
is very active in this reaction and addition of a small amount of water enhanced the reactivity.[61,62] The direct aldol reaction of acetone with some aromatic aldehydes was catalyzed by Zn–(L)-amino acid complexes in water, giving the corresponding products in high yields with moderate ees.[63,64] Similarly, it was reported that $Zn(OTf)_2$-assisted asymmetric direct-type aldol reactions of aromatic aldehydes with acyclic ketones as well as cyclic ketones proceeded smoothly in aqueous media, using a chiral C_2-symmetrical prolinamide ligand, to give the corresponding aldol adducts in moderate to good yields and selectivities.[65]

Formaldehyde is one of the most important C1 electrophiles in organic synthesis. In 1998, Ito and coworkers reported that the reaction of paraformaldehyde (10% w/w in water) with 2-cyanopropionates was catalyzed by rhodium(I)–TRAP complex (**Scheme 14**).[66]

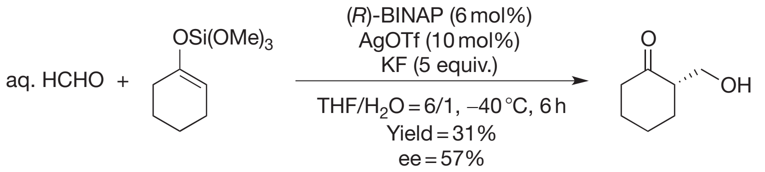
In conventional methods for hydroxymethylation in organic solvents, gaseous formaldehyde is often generated before use from paraformaldehyde with tedious procedures.[67] Formaldehyde gas is known as a causative material of the 'sick house syndrome' and, needless to say, is harmful to health. On



Scheme 13



Scheme 14



Scheme 15

the other hand, commercial formaldehyde as an aqueous solution is cheap, easy to handle, and stable. Yamamoto et al. found that fluoride ion activated silicon enolates effectively even in protic solvent,[68,69] and attempted to apply this methodology to the aldol synthesis using aqueous formaldehyde solution (aq. HCHO). In 2003, asymmetric hydroxymethylation of trimethoxysilyl enol ethers catalyzed by (*R*)-BINAP–AgOTf as Lewis acid and KF as Lewis base in aqueous media was reported (up to 57% ee) (Scheme 15).[70] On the other hand, Kobayashi et al. reported that the catalyst prepared from Pr(OTf)$_3$ and ligand **5** in H$_2$O/THF promoted the reactions of aq. HCHO with several silyl enol ethers derived from *S*-*tert*-butyl propanethioate as well as acyclic silyl enol ethers derived from aromatic ketones, although ee's of the corresponding products were moderate (up to 55% ee) (Scheme 16).[71,72]

In 2004, Kobayashi et al. reported that chiral scandium–**8** complex catalyzed highly enantioselective hydroxymethylation of silicon enolates with aq. HCHO (**Scheme 17**).

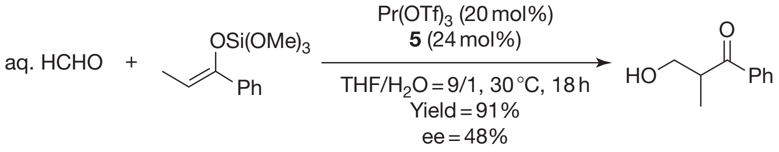
As an extension of this work, other metal salts (10 mol%) and chiral bipyridine **8** (12 mol%) were screened, and it was found that $Bi(OTf)_3$[73–76] gave promising results. This result was unexpected because (1) the ionic diameter of bismuth (2.34 Å for 8-coordination) is much bigger than that of scandium (1.74 Å for 8-coordination) and (2) $Bi(OTf)_3$ is known to be hydrolyzed.[77] Indeed, only a trace amount of the hydroxymethylated adduct was obtained using $Bi(OTf)_3$ without the chiral bipyridine. Several substrates were subjected to this catalyst system, and the hydroxymethylation proceeded smoothly using an aq. HCHO to afford the desired adducts in high yields with high enantioselectivities (**Scheme 18**).[78] It is noted that asymmetric quaternary carbons were also constructed with high selectivities by using this reaction.

$Bi(OTf)_3$ and $Ga(OTf)_3$ are unstable in the presence of water but are stabilized by the basic ligand. There are many strong Lewis acids unstable in water; however, these Lewis acids may be available in water when combined with basic ligands. In particular, the use of chiral basic ligands leading to new types of water-compatible chiral Lewis acids may enable a wide range of asymmetric catalyses in aqueous media, as $Bi(OTf)_3$–**8** and $Ga(OTf)_3$–**6** complexes have been added as water-compatible Lewis acids.

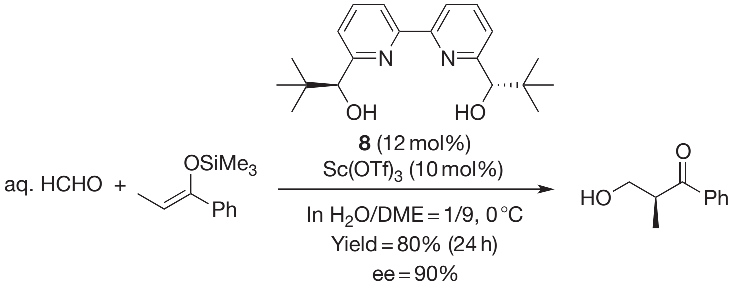
In 2010, Mlynarski et al. reported the direct-type catalytic asymmetric α-hydroxymethylation of unmodified ketones in wet solvents using $Zn(OTf)_2$ and chiral C_2-symmetrical prolinamide (**Scheme 19**).[79]

There are several chiral, Lewis acid-catalyzed organic reactions in water without any organic cosolvents.[80,81] Such reactions mostly proceeded smoothly by creating hydrophobic areas in water to stabilize and concentrate organic substrates or by suppressing undesired pathways in the reaction mechanism by water. One of the key factors for such successes is hydrophobicity of substrates; therefore, asymmetric reactions in water with hydrophilic substrates such as aq. HCHO are extremely difficult. Kobayashi and his coworkers faced such challenge and developed asymmetric hydroxymethylation in water using aq. HCHO. It was disclosed that catalytic asymmetric hydroxymethylation reactions were successfully carried out in the presence of catalytic amounts of $Sc(OSO_3C_{12}H_{25})_3$ ($Sc(DS)_3$), chiral ligand **8**[82–84] or **9**[85–87] combined with additives to afford the desired products in good to high yields with high selectivities. It is noteworthy that thioketene silyl acetals, which are known to be much less stable than silyl enol ethers (ketone-derived silicon enolates) in water, reacted smoothly under the conditions to afford the corresponding adducts in good yields with high enantioselectivities (**Scheme 20**).[88] Moreover, silica gel-supported Sc catalyst with ionic liquids was found to create efficient hydrophobic environments for several organic reactions in water. This system combined with **L-2** was applied for asymmetric hydroxymethylation using aq. HCHO in water.[89]

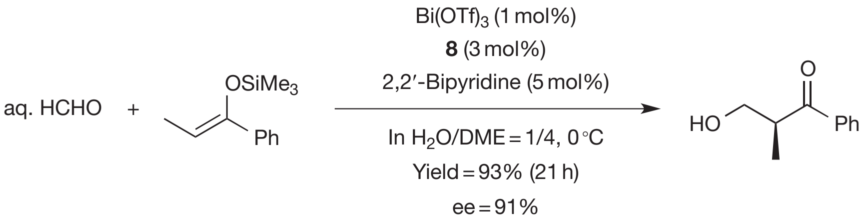
This method could be applied to the synthesis of an artificial odorant (*S*)-(+)-**10** (**Scheme 21**).[90,91] Hydroxymethylation of



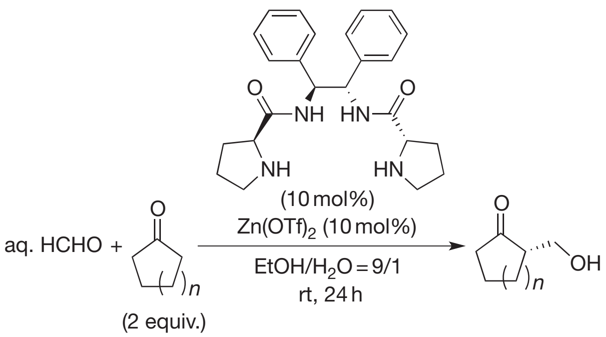
Scheme 16



Scheme 17



Scheme 18



n	Yield (%)	ee (%)[a]
1	58	98
2	60	94
3	59	93

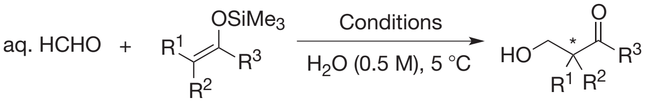
[a] Isolated yield. ee determined by HPLC analysis of the benzoate ester on a chiral phase.

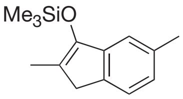
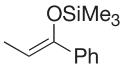
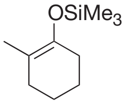
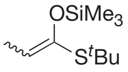
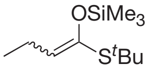
Scheme 19

2 was performed using Sc(DS)$_3$•**8** as a catalyst. After the reaction, the reaction mixture was centrifuged (3000 rpm, 20 min) to separate the colloidal white dispersion into three phases. The upper, middle, and bottom phases are water, surfactant, and organic layers respectively. After separation of the organic phase, followed by hydrogenation with polymer-incarcerated palladium (PI-Pd)[92,93] in benzotrifluoride, the compound (*S*)-(+)-**3** was obtained in 56% yield with 91% ee over two steps. It should be noted that the synthesis has been accomplished using a catalytic asymmetric reaction in water and a hydrogenation using an immobilized catalyst, which are suitable for green sustainable chemistry. Furthermore, Sc(OTf)$_3$•**8** or **9** system was applied for direct-type aldol reactions of aq. HCHO with ketones (Scheme 22).[94]

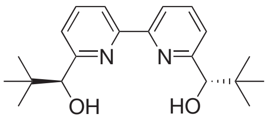
6.21.5 1,4-Conjugate Additions

In 1997, Miyaura and coworkers developed a Rh(I)-catalyzed conjugate addition of aryl- or 1-alkenylboronic acid to enones in aqueous solvent.[95] Water was found to be beneficial to the

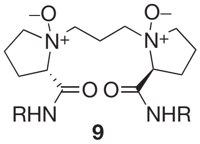


Enolate	Conditions[a]	Yield (%)[b]	ee (%)[c]
	A	81	91 (*R*)
	B	85	90 (*S*)
	B	85	91 (*R*)
	B	86	85
 *E*/*Z* = 97/3	A	73	91 (*S*)
 *E*/*Z* = 91/9	A	65	90

[a] Conditions A: Sc(DS)$_3$ (10 mol%), **L-2** (12 mol%), Triton X-705, rt, 20 h. Conditions B: Sc[O$_3$S(CH$_2$)$_{10}$CH$_3$]$_3$(10 mol%), **L-3a** (12 mol%), CH$_3$(CH$_2$)$_{10}$SO$_3$Na, 5 °C, 48 h.
[b] Yield of isolated product.
[c] Determined by chiral HPLC analysis.



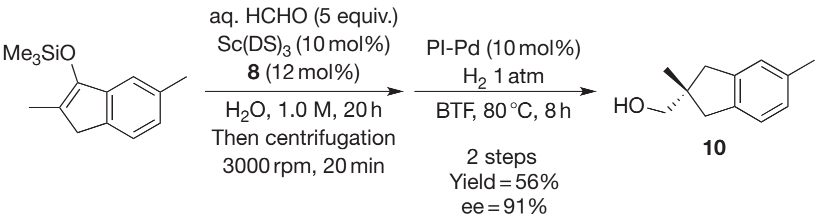
8



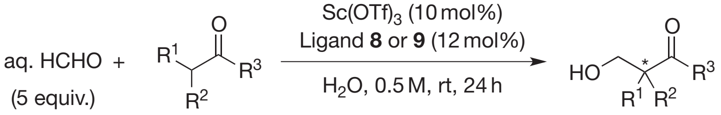
9

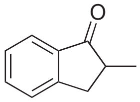
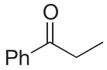
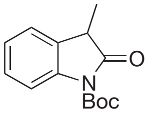
a: R = 2,5-Me$_2$-C$_6$H$_3$
b: R = cyclopentyl

Scheme 20



Scheme 21



Ketone	Conditions[a]	Yield (%)[b]	ee (%)[c]
	A	81	72
	A	29	81
	B	59	81

[a] Conditions A: **9** (12 mol%), $C_{11}H_{23}SO_3Na$ (150 mol%), pyridine (20 mol%)
Conditions B: **8** (12 mol%), SDS (150 mol%)

[b] Yield of isolated product after chromatography.

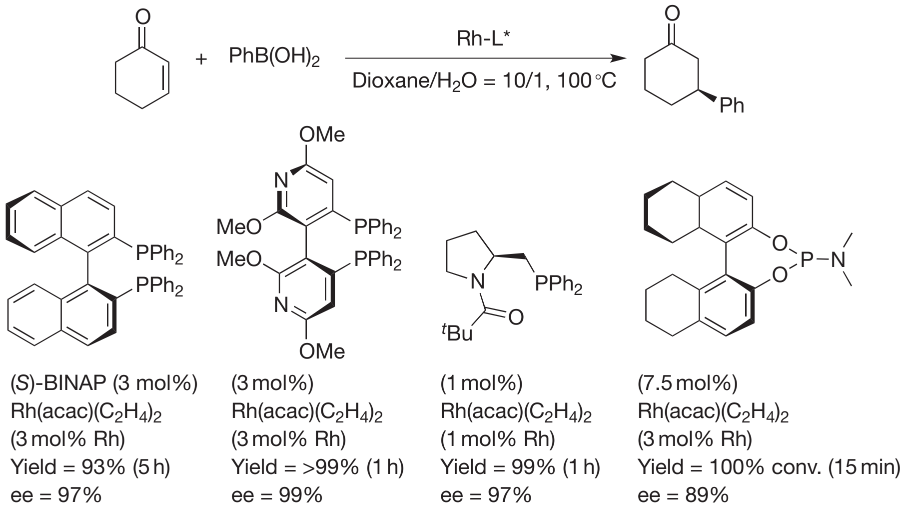
[c] Enantiomeric excess was determined by chiral HPLC analysis.

Scheme 22

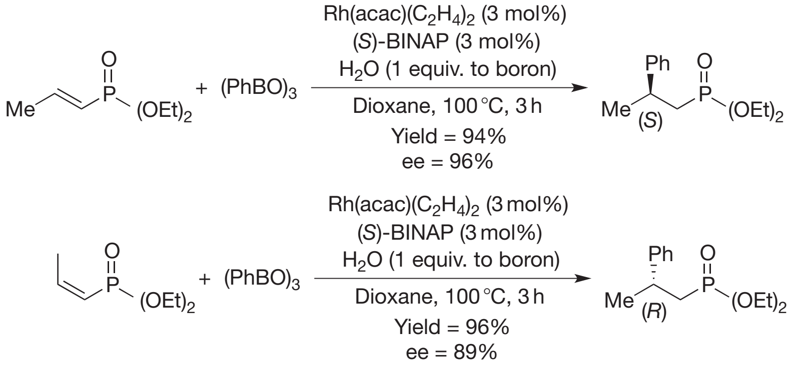
reaction. Since then, extensive studies have been carried out on the boronic acid chemistry largely related to conjugate additions, including asymmetric conjugate additions. In 1998, Hayashi and coworkers reported that asymmetric reactions of α,β-unsaturated ketones with excess arylboronic acids in the presence of a rhodium catalyst generated *in situ* from Rh(acac)(C_2H_4) and (*S*)-BINAP. This system was highly suitable for a wide range of substrates, cyclic and acyclic enones, and aryl- and alkenyl boronic acids. Interestingly, raising the reaction temperature from 40 to 120 °C greatly increased the yield, but showed no influence on the enantioselectivity.[96] After that, various chiral phosphane ligands were reported (Scheme 23).[97–103] Furthermore, supported 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) ligand permitted to carry out the reaction in water without any organic cosolvents.[104] Similar reaction conditions were applied to the reaction of nitroalkenes with organoboronic acids.[105] It was also reported that (*S*)-BINAP–rhodium(I) complex catalyzed asymmetric 1,4-addition of triarylcyclotriboroxanes to 1-alkenylphosphonates, forming 2-arylalkylphosphonates in high yields with high enantioselectivity. The *E*- and *Z*-isomers gave opposite enantiomers under the same conditions (Scheme 24).[106]

1,4-Conjugate additions of enolates to activated olefines can provide synthetically useful 1,5-carbonyl and related compounds. While several excellent chiral catalysts for the reactions have been developed in organic solvents, examples in water are still limited. In 1999, Barnes et al. recorded that water played a dual role on the Michael reaction (Scheme 25).[107,108] Addition of molecular sieves raised reaction rate and selectivity, and these sieves served only to remove the water taken into the system by $Mg(OTf)_2{\bullet}4H_2O$. However, employing dry $Mg(OTf)_2$ (containing 20 mol% water) caused a dramatic drop in the reaction rate, but the selectivity remained invariant. The reactivity of the catalyst could be restored by addition of water. Thus, while water is an inhibitor of the catalyst, it is nonetheless necessary to generate the fully active catalyst. In 2001, Kobayashi et al. reported that the complexes prepared from silver salts and BINAP derivatives could catalyze 1,4-conjugate additions effectively in water without any organic cosolvents (Scheme 26).[109] Similarly, AgOTf–PPh_3 complex-catalyzed 1,4-conjugate addition of β-ketoesters to nitroalkenes proceeded efficiently only in water but not in organic solvents. An asymmetric version of this reaction was performed using (*R*)-[2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl] ((*R*)-tol-BINAP) as a chiral ligand (Scheme 27).[110]

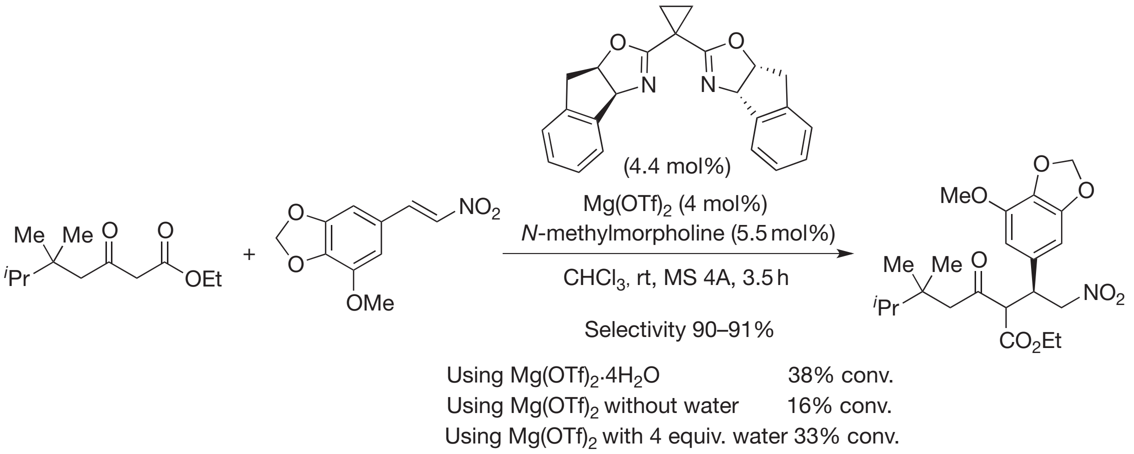
A DNA-based hybrid catalyst was used to promote a highly enantioselective Michael reaction in water (Scheme 28).[111] The Michael adducts were obtained with up to 99% ee when



Scheme 23



Scheme 24

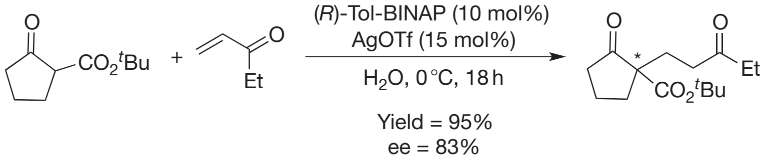


Scheme 25

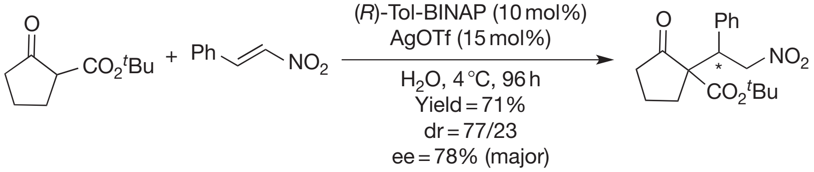
dimethyl malonate was used as the nucleophile, and an α,β-unsaturated 2-acyl imidazole was used as the Michael acceptor. The DNA hybrid catalyst was self-assembled from Salmon testes DNA and a copper complex with achiral ligand, which also promoted Diels–Alder reactions with high enantioselectivity.

6.21.6 Allylation

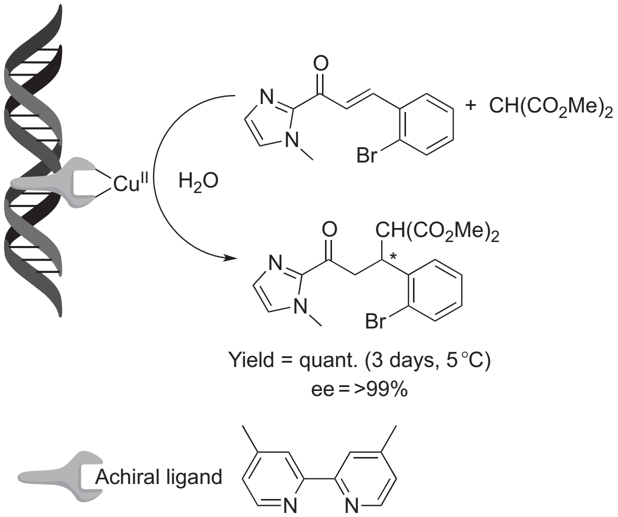
Asymmetric allylation reactions of carbonyl compounds or imine equivalents with allylmetals have been a subject of an extensive investigation. The first catalytic asymmetric allylation



Scheme 26



Scheme 27



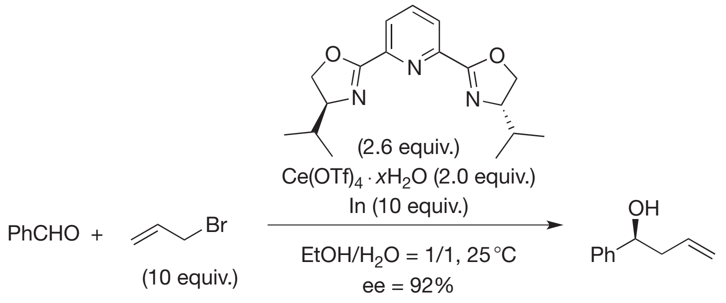
Scheme 28

reaction in aqueous media was reported by Loh and Zhou in 1999.[112] In the reaction of allyl bromide with benzaldehyde, the corresponding product was obtained with 92% ee under optimized conditions, which required the use of excess ^{i}PrPY-BOX ligand and $Ce(OTf)_4$ in $EtOH/H_2O$ (Scheme 29).

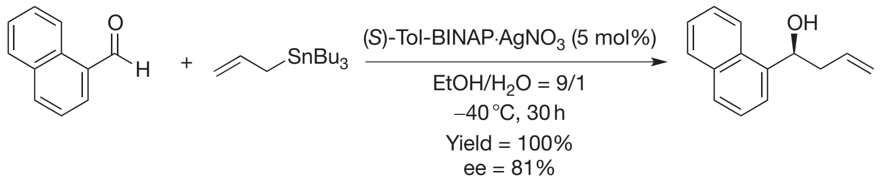
Asymmetric allylation in aqueous media using combinations of BINAP derivatives and silver salts, which were originally developed in catalytic symmetric allylation in organic solvents, was attained.[113] The complex prepared from $AgNO_3$ and (*S*)-BINAP catalyzed the reaction of aldehydes with allyltributyltin in ethanol/water (9/1) at −40 °C (Scheme 30).[114] The counterions of the silver salts exhibited no influence. The employment of $AgClO_4$, $AgNO_3$, and AgOTf led to similar results, which was probably due to complete ionic dissociation in aqueous media.

In Lewis acid-catalyzed reactions, it is often observed that Lewis acids are deactivated by coordination of ligands. Thus, ligand acceleration is a key factor to realize efficient asymmetric catalysis. In 2002, Kobayashi et al. reported that cadmium-catalyzed allylation of carbonyl compounds with allyltributyltin was dramatically accelerated by several achiral ligands in aqueous media.[115] As an extension of this work, cadmium-catalyzed asymmetric allylation was reported (Scheme 31).[116,117] Although the system has not been optimized enough, this ligand-accelerated reaction may provide a new insight into designing efficient catalytic systems that work in aqueous media.

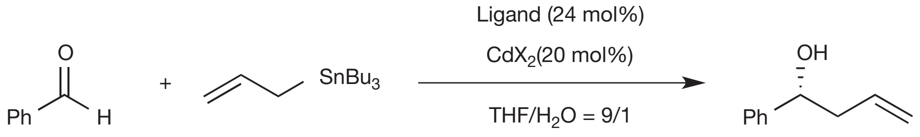
The allylation of imines is one of the most important C–C bond-forming reactions because of the versatility of homoallylic amines as useful synthetic intermediates. However, most imines are not stable in the presence of water. On the other hand, acylhydrazones are stable and isolable imine equivalents. Asymmetric allylation of acylhydrazono esters in aqueous media has been achieved with a catalytic amount of ZnF_2 and a chiral diamine ligand. While catalytic asymmetric allylation of imine derivatives is one of the most difficult reactions, the present reaction has elegantly achieved high efficiency in aqueous media (Scheme 32).[118] While the asymmetric reactions were well controlled in aqueous media, 3 equiv. of allyltrimethoxysilane are needed because of low reactivity. To address this issue, allylboronates were used as allylating reagents instead of allyltrimethoxysilanes. In the reaction of the hydrazono ester prepared from methyl glyoxylate and 4-(dimethylamino)benzohydrazide with allylboronic acid pinacol ester (1.2 equiv.), the allylation proceeded smoothly at 0 °C in the presence of 5 mol% of ZnF_2 and 12 mol% of chiral diamine **12** in water/acetone = 3/5, affording the corresponding product in high yield with good enantioselectivity (Scheme 33). Interestingly, the reaction did not proceed at all in the absence of water. (*E*)- or (*Z*)-Crotylboronate reacted with the hydrazono ester very sluggishly and ees of the crotylated products were very low. On the other hand, the reaction of α-substituted allylboronates with a hydrazono ester proceeded smoothly to afford unexpected *anti*-crotylated products in high yields with high diastereo- and enantioselectivities (Scheme 34). The crotylated products were α-addition adducts, and remarkably, no γ-addition adduct was obtained. This was the first report of catalytic regio- and stereoselective α-addition reactions. It was assumed that α-substituted allylboronates react with ZnF_2 via a six-membered chair-like transition state (γ-addition of α-substituted allylboronates toward ZnF_2) to afford *Z*-crotylzinc species, which could react with hydrazono ester stereoselectively via γ-addition, giving the crotylated product with *anti*-selectivity (Scheme 35). Further study revealed the role of water. It was hypothesized that hydrolysis of intermediate **13** might proceed



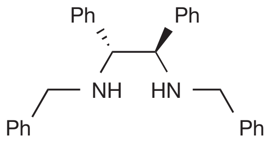
Scheme 29



Scheme 30



CdX_2	Ligand	Temp (°C)	Time (h)	Yield (%)	ee (%)
$Cd(ClO_4)_2$	None	30	4	20	–
$Cd(ClO_4)_2$	**10**	30	4	97	23 (*S*)
$CdBr_2$	**11**	0	24	88	77 (*R*)



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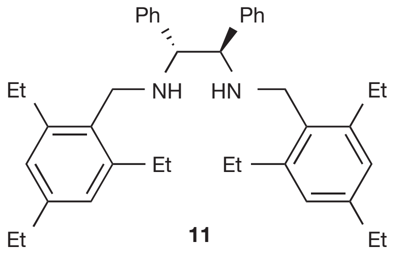

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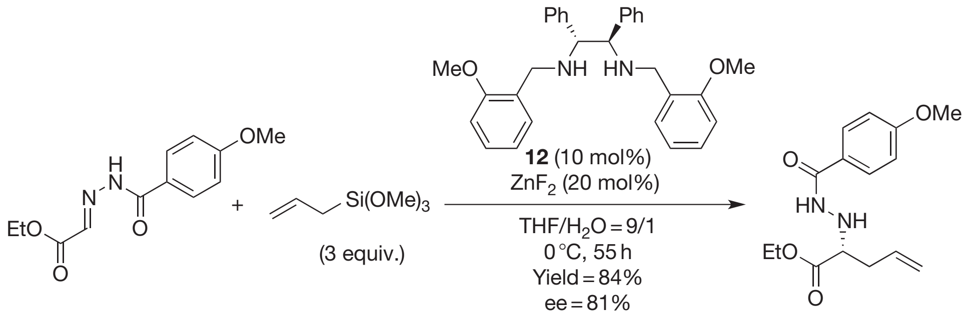
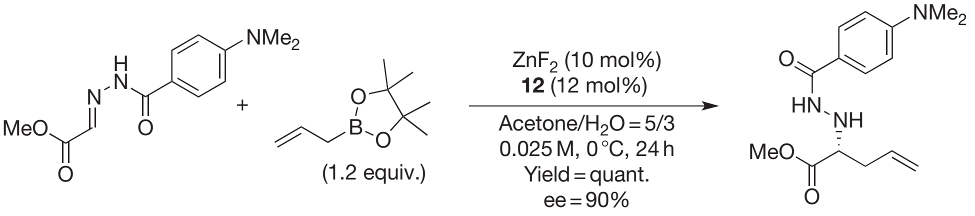
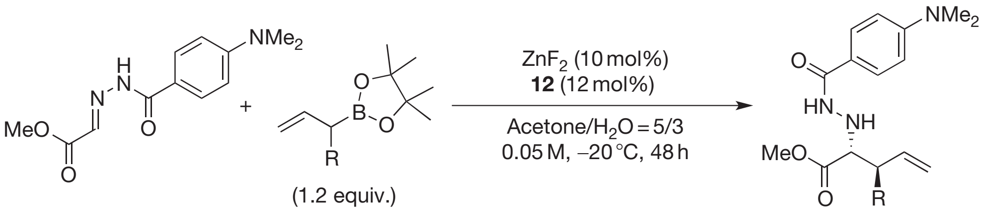
Scheme 31



Scheme 32

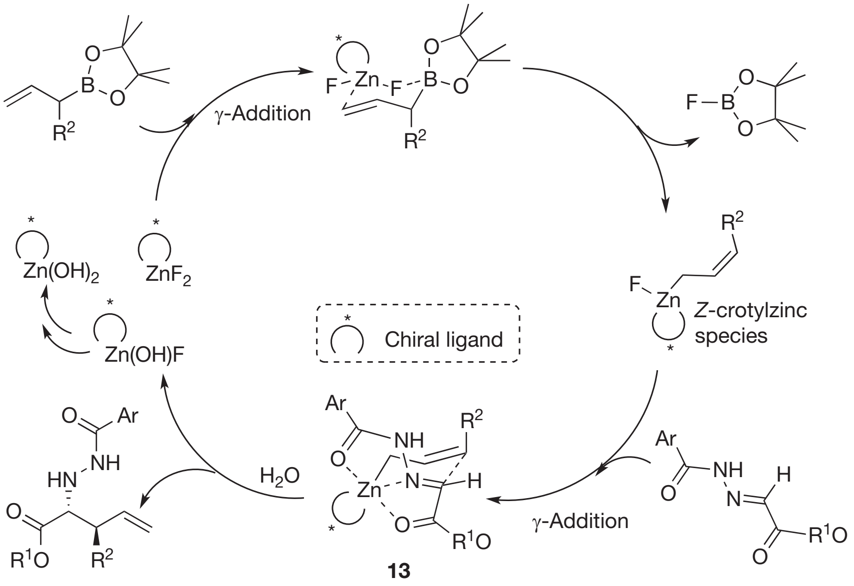


Scheme 33



R	Yield (%)	α/γ	*syn/anti*	ee (%)
Me	quant.	>99/<1	<1/>99	88
Et	98	>99/<1	<1/>99	87
Bu	88	>99/<1	<1/>99	87
^{i}Amyl	76	>99/<1	<1/>99	87
OCH_2Ph	65	>99/<1	<1/>99	82

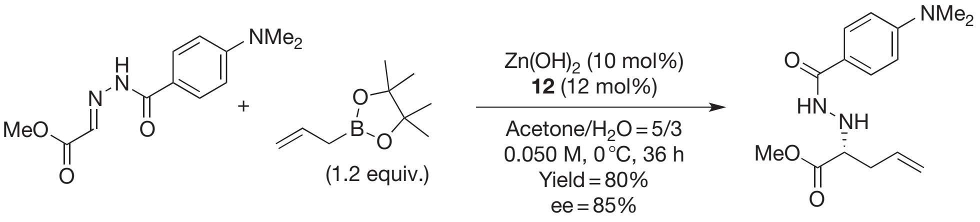
Scheme 34



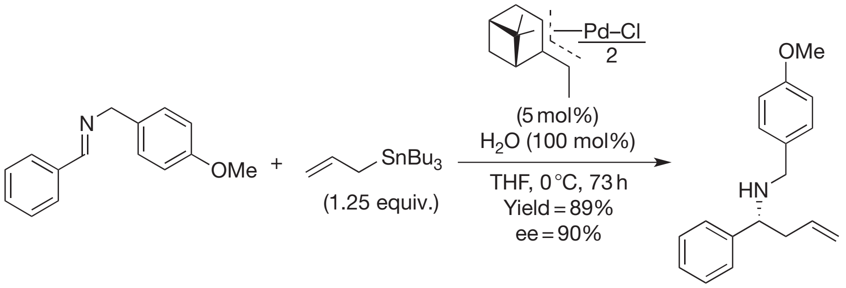
Scheme 35

smoothly to afford the product along with generation of Zn(OH)F, then $Zn(OH)_2$ after the second turnover. It was revealed that $Zn(OH)_2$ catalyzed the allylation reaction of acylhydrazone with allylboronate to afford the desired allylated product in 80% yield with 85% ee (Scheme 36). It should be noted that this was the first example of a chiral metal hydroxide-catalyzed asymmetric reaction and that metal hydroxides are ideal catalysts for organic reactions in aqueous media.[119]

Yamamoto and coworkers found that in the asymmetric allylation of imines with Pd, the addition of 1 equiv. of water increased the yield and enantioselectivity (Scheme 37).[120] Water might coordinate to the tetravalent stannane to facilitate



Scheme 36



Scheme 37

the C–Sn bond cleavage, and thereby accelerate the reaction. The Pd-catalyzed asymmetric allylation proceeds under essentially neutral conditions in contrast to Lewis acid-catalyzed reactions, making it feasible to use substrates with labile functional groups (even the halogens) and as well to apply the allylation to heterocyclic substrates which otherwise are prone to polymerization in some cases.

6.21.7 Mannich-Type Reaction

Asymmetric Mannich reactions provide useful routes for the synthesis of optically active β-amino ketones and esters, which are versatile chiral building blocks for the preparation of many nitrogen-containing biologically important compounds. Kobayashi et al. reported that Mannich-type reaction of a hydrazono ester with silyl enol ethers in aqueous media (H_2O/THF = 1/9) could be successfully achieved with ZnF_2 (100 mol%), a chiral diamine ligand **10** (10 mol%), and trifluoromethanesulfonic acid (1 mol%).[121] Further study revealed that this complex enabled reactions in water without any organic cosolvents or additives to proceed smoothly, affording the corresponding products in high yields and high stereoselectivities (Scheme 38, Entry 1). In the reaction of α-monosubstituted ketone-derived silyl enol ether with cetyltrimethyl ammonium bromide it turned out to be necessary to accelerate the reaction (Entry 2). Furthermore, in contrast to most asymmetric Mannich-type reactions, either *syn*- or *anti*-adducts were stereospecifically obtained from (*E*)- or (*Z*)-silicon enolates in the present reaction (Entries 3 and 4). Under optimized conditions, the amount of ZnF_2 and ligand **10** could be successfully reduced to 10 and 5 mol% respectively, maintaining the same level of results (Entries 2 and 5).[122,123]

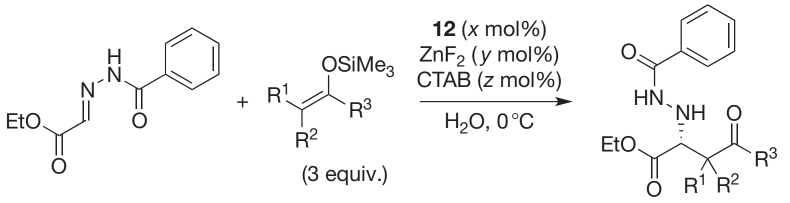
6.21.8 Propargylation

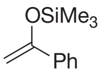
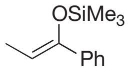
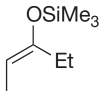
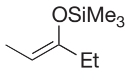
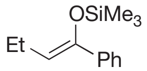
Optically active propargylamines are important synthetic intermediates for various nitrogen-containing compounds, a structural feature of many biologically active compounds and natural products.[124,125] The most reliable and efficient methods for the preparation of optically active propargylic amines are still dependent on the addition of appropriate organometallic reagents to chiral imine derivatives. Li and coworkers reported a highly efficient AA3-asymmetric aldehyde-alkyneamine (AA3) coupling in water. The one-pot process could provide a diverse range of propargylic amines in high enantioselectivity. The use of the tridentate bis(oxazolinyl)pyridines (pybox) with Cu(OTf) afforded the product with both high yield and enantioselectivity in water, although better results were obtained in some organic solvents (Scheme 39).[126,127]

Copper(I)-catalyzed conjugate addition of alkynes to a Meldrum's acid-derived acceptor was developed. The reactive copper species was formed in water by reduction of $Cu(OAc)_2•H_2O$ with sodium (+)-ascorbate. Combined with a chiral P,N-ligand, enantioselective version of this reaction could be achieved to 82–97% ee of the products with useful yields (Scheme 40).[128,129]

6.21.9 Ring-Opening Reactions of *meso*-Epoxides

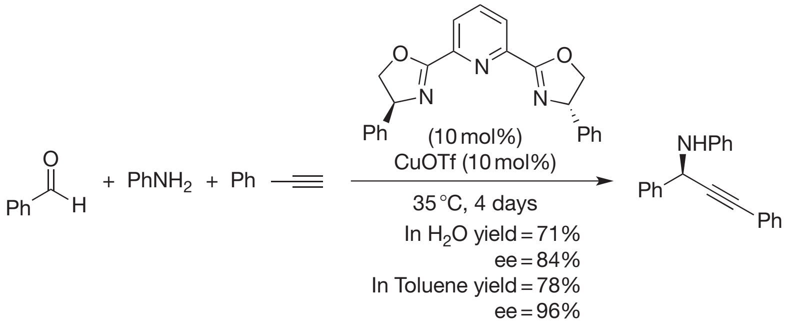
Nitrogen-containing heterocycles and their derivatives have found broad applications in synthetic and biological chemistry.[130] Moreover, the indole framework is widely represented in natural substances and medicinal compounds.[131] Therefore, generation of chiral N-heteroaromatic derivatives in optically active form, in particular those incorporating indolic architectures, is a challenging and important facet of this research area.



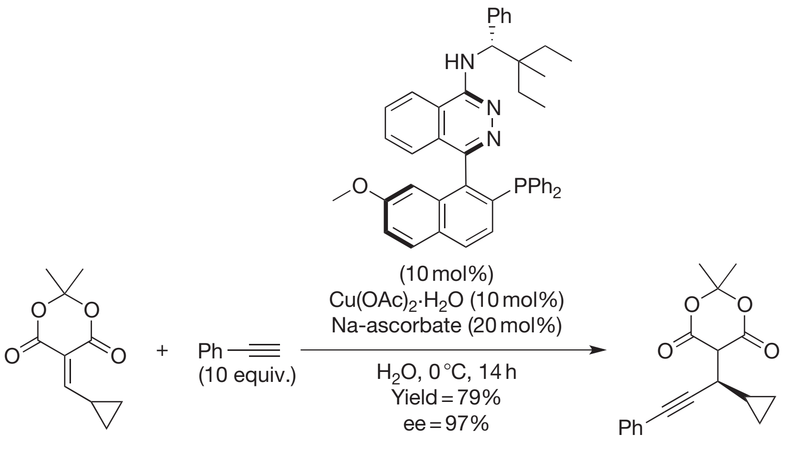
Entry	Enolate	*x*	*y*	*z*	Time (h)	Yield (%)	*syn*/*anti*	ee (%)[a]
1		10	100	–	20	91	–	95
2		5	10	2	40	87	93/7	96
3		10	10	2	155	75	13/87	92
4		10	10	2	144	63	90/10	98
5		10	5	2	40	74	96/4	96

[a] *ee* of major diastereomer

Scheme 38



Scheme 39



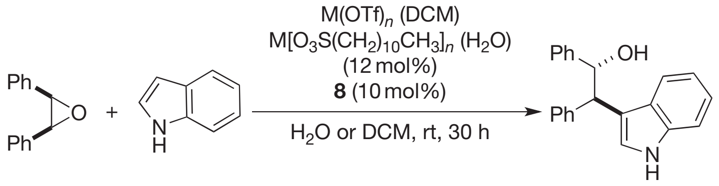
Scheme 40

Asymmetric ring-opening reactions of *meso*-epoxides with indoles can provide chiral β-indolyl alcohol. The ring-opening reactions of *cis*-stilbene oxide with indole using Sc(III) and Cu(II) catalysts were demonstrated in water and DCM (**Scheme 41**). Both catalysts gave the product in good yields with excellent enantioselectivities in water. Interestingly, enantiofacial selectivities between Sc (III) and Cu(II) were reversed. When the reaction was carried out in DCM, $Cu(OTf)_2$ gave the desired product in moderate yield with high enantioselectivity, while $Sc(OTf)_3$ gave a trace amount of the desired product along with by-product.[132–134] Furthermore, in the case of $Cu(OTf)_2$, it was revealed that the reactions proceeded faster in water than in DCM.

6.21.10 Nazarov-Type Reaction

Nazarov reaction is one of the most versatile methods for the synthesis of cyclopentenones from vinyl ketones. The reaction is believed to proceed via a conrotatory 4 π-electron cyclization of 3-oxopentadienyl cation (**14**) to oxallyl cation (**15**) in the presence of an acid (**Scheme 42**). In the conventional Nazarov reaction, proton elimination of **15** leads to cyclopentenone derivative **16**. On the other hand, when suitable cation-trapping agents are present, the intermediate **15** can be converted to various compounds. In this reaction, water can be used as a cation-trapping reagent as well as a solvent.[135]

As expected, the treatment of **17** with $Sc(DS)_3$ in water yielded water-trapping adduct **18** predominantly (**Scheme 43**).



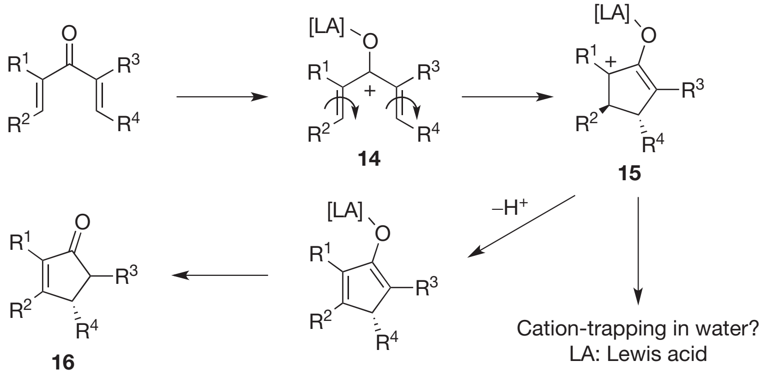
Metal	*n*	In H_2O		In DCM	
		Yield[a] (%)	ee[b] (%)	Yield[a] (%)	ee[b] (%)
Sc	3	58	92 (1*R*, 2*R*)	Trace[c]	–
Cu	2	80	96 (1*S*, 2*S*)	60	86 (1*S*, 2*S*)

[a] Isolated yield.

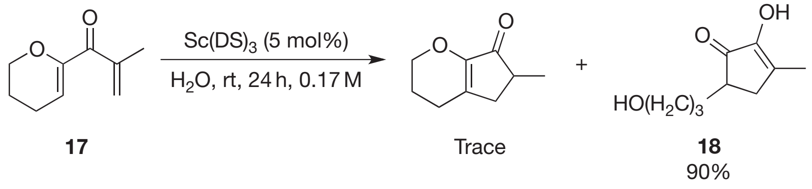
[b] ee was determined by chiral HPLC analysis.

[c] By-product was generated.

Scheme 41



Scheme 42



Scheme 43

Furthermore, chiral ligand **19** was employed in combination with Sc(DS)$_3$, although the enantioselectivity of the corresponding product needed to be improved (Scheme 44).

6.21.11 Ene Reaction

The carbonyl-ene reaction is a useful method to prepare allylic alcohols. Luo et al. have developed water-tolerant BINAP–Pd (II)- and BINAP–Pt(II)-catalyzed asymmetric carbonyl-ene reactions (Scheme 45).[136] In these catalytic systems, phenylglyoxal monohydrate worked as equally well as its anhydrous form or even better in some cases, which greatly simplified the experimental operation.

6.21.12 Pauson–Khand-Type Reaction in Water

Transition metal-catalyzed carbonylation such as Pauson–Khand-type reaction has been successful in the area of organic synthesis, and is still recognized as a powerful protocol for the direct synthesis of a wide variety of carbonyl-containing compounds.[137] The first use of a rhodium catalyst in an asymmetric Pauson–Khand reaction in aqueous media was reported in 2003 by Chung et al. (Scheme 46).[138] A combination of [Rh(cod)Cl]$_2$ and BINAP was chosen as an extension of the best catalytic systems for an asymmetric intramolecular Pauson–Khand reaction in THF.[139] When water was used as a solvent, reaction did not proceed presumably due to the insolubility of the substrate and the catalyst. Various enzymes were subject to the optimized reaction conditions, and in general, the corresponding products were obtained in moderate to high ees; however, the yields were highly dependent on the substrate itself.

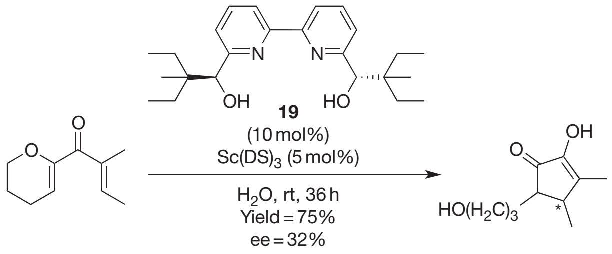
The catalyst prepared from chiral ligand (*S*)-tol-BINAP combined with [RhCl(cod)]$_2$ (cyclooctadiene rhodium chloride dimer)/TPPTS was reported to be effective for the asymmetric Pauson–Khand-type reaction in water. Formaldehyde can be used as a source of carbon monoxide directly in water (Scheme 47).[140]

In 2005, Kwong et al. reported that rhodium-catalyzed asymmetric Pauson–Khand-type reaction in water worked well in the presence of a chiral atropisomeric dipyridyldiphosphane ligand (*S*-P-Phos), transforming various enynes into the corresponding bicyclic cyclopentenones in high yields with high ees (Scheme 48).[141]

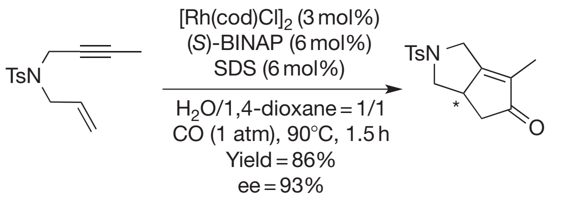
6.21.13 Conclusion

Asymmetric catalysis is now recognized as one of the most efficient methods for the preparation of optically active compounds. Although many catalytic asymmetric reactions have been developed, most reactions are carried out under strictly anhydrous conditions, because most chiral catalysts and/or reagents decompose in the presence of even small amounts of water. Catalytic asymmetric C–C bond-forming reactions in aqueous medium shown in this chapter may address the issue. The benefits to use aqueous media in catalytic asymmetric reactions are (1) water is the best solvent for environmentally benign synthesis and (2) water might have impacts on reaction rates and selectivities, which could not be obtained in organic solvents.

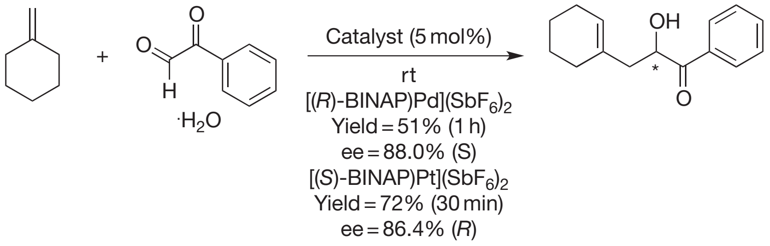
In the history of catalytic asymmetric synthesis, water has been rather recognized as a contamination, and chemists have made efforts to eliminate water for the better chance of success. On the other hand, many elegant *in vivo* reactions, mainly catalyzed by enzymes, are carried out in an aqueous environment in our bodies. Nature educates us that the fundamental organic reactions such as C–C bond formation could be performed in aqueous media. Although there are still many difficulties to achieve truly successful catalytic asymmetric reactions in aqueous media, given that nature so gracefully exploits water, it is time to unleash the potential use of water. For a related chapter in this Comprehensive, we refer to Chapter 6.17.



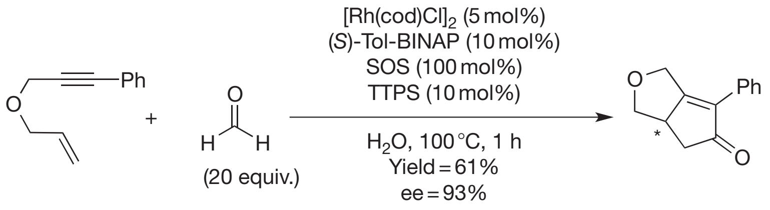
Scheme 44



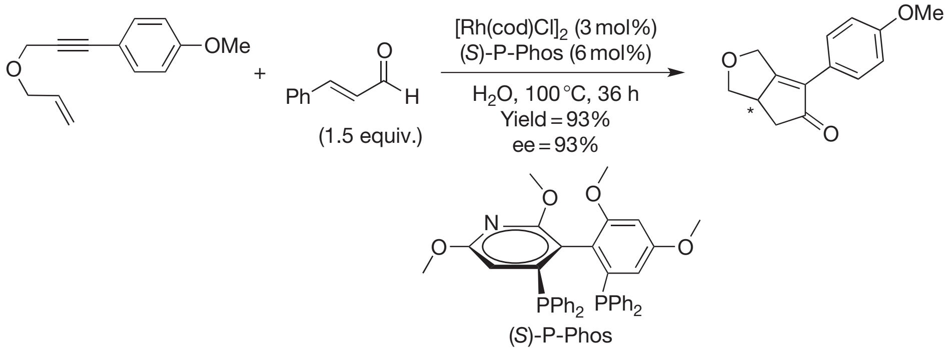
Scheme 46



Scheme 45



Scheme 47



Scheme 48

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6.22 Sustainable Asymmetric Oxidations

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Abbreviations

6-Me$_3$-tpa	tris(6-methyl-2-pyridylmethyl)amine
Ac	acetyl
AE	asymmetric epoxidation
Bn	benzyl
Boc	*t*-butoxycarbonyl
cAE	catalytic asymmetric epoxidation
CLAMPS	cross-linked aminomethylpolystyrene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
ee	enantiomeric excess
H$_2$dipic	2,6-pyridinedicarboxylic acid
IBA	isobutyraldehyde
IBA	isobutyric aldehyde
IBAc	isobutyric acid
MS	molecular sieves
MTO	methyltrioxorhenium
***N*-Me-Imd**	*N*-methylimidazole
NMO	*N*-methylmorpholine-*N*-oxide
***N*-Oct-Imd**	*N*-octylimidazole
OTf^-	trifluoromethanesulfonate (triflate) anion
Salan	*N*,*N*′-*o*-(hydroxybenzyl)-1,2-diaminoethane
Salen	*N*,*N*′-(salicylidene)-1,2-ethylenediamine
S-TBNBr	SBA-16/*N*-propyl-*N*,*N*,*N*-tri-*n*-butylammonium bromide
TEMPO	(2,2,6,6-tetramethyl-piperidin-1-yl)oxyl
TFA	trifluoroacetic acid
UHP	urea hydroperoxide

6.22.1 Introduction

Chirality is one of the major phenomena in nature, as most biological processes involve chiral reactants and catalysts; biological evolution has been entirely dependent on the occurrence of chiral recognition and asymmetric catalysis. In the last several decades, the chemistry of chiral compounds has expanded greatly, following the growing demand for optically pure compounds. In particular, chiral building blocks are indispensable for the synthesis of biologically active compounds, such as pharmaceuticals, agrochemicals, flavors, and fragrances, as well as in the creation of advanced materials.[1] Integrally, enantioselective syntheses comprise two major approaches: resolution and asymmetric synthesis. As part of the latter, catalytic asymmetric synthesis appears to be the most advantageous strategy, since one chiral catalyst molecule can serve to create millions of chiral product molecules of an optically pure compound, just as enzymes do in biological systems.[1] Additionally, this approach allows the wastes associated with the racemate resolution to be minimized.[2] Since the seminal works dating from the 1960s, catalytic asymmetric synthesis has developed into a key branch of modern chemistry, and has been crowned by the Nobel Prize in chemistry awarded to W. S. Knowles, R. Noyori, and K. B. Sharpless in 2001.[3]

In spite of the obvious success of asymmetric catalysis, there is much room for further developments. An ideal catalytic asymmetric transformation would proceed with 100%

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conversion, and would provide complete chemo-, regio-, and stereocontrol. For practical (industrial) applications, it should also withhold high turnover numbers and display high turnover frequencies, require a minimal amount of solvent and additives, and produce minimum waste. The catalyst should be inexpensive, recoverable, and nontoxic.[4] To date, few catalytic systems approach these rigorous standards, resulting in few catalytic asymmetric processes expanded to the industrial scale so far.

At the same time, it is clear, today, that the challenge of creating a sustainable future requires addressing the chemicals industry directly.[5] In particular, it is expected that the design of environmentally benign products and processes should be guided by the 12 Principles of Green Chemistry, aiming mainly at reducing (or eliminating) the use of hazardous substances, energy, and wastes.[6] Apparently, the area of catalysis is of particular importance for green chemistry, as catalytic processes may serve to minimize the quantities of reagents, reduce energy requirements, and promote the use of less toxic reagents. With respect to the asymmetric oxidation area, this implicates, at least, the use of highly active, regio- and stereoselective, and robust catalysts (desirably recyclable, metal-free, or nontoxic metals based), as well as minimum amounts of (nonpolluting) solvents, and nonhazardous oxidants.

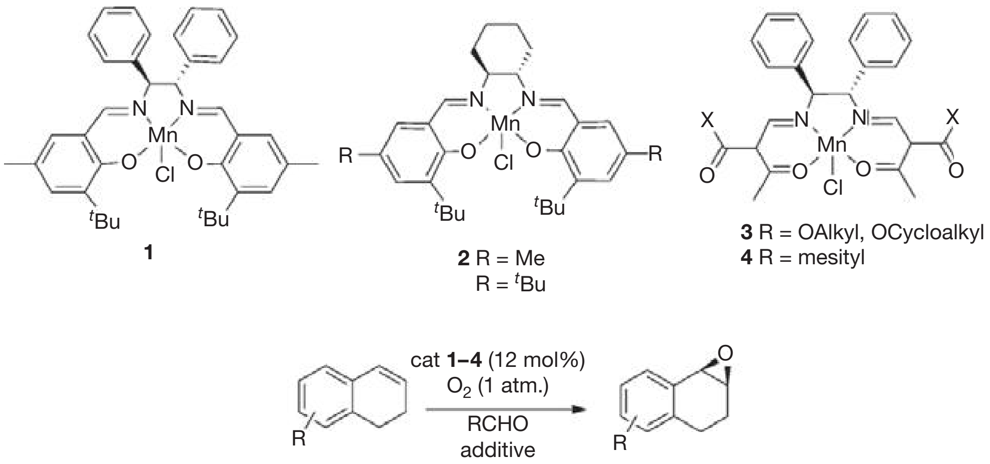
This chapter will particularly address the latter point, since, while the solvent could be distilled and recycled, the choice of an appropriate stoichiometric oxidant is often critical for achieving the overall process sustainability. Specifically, harmful oxidants (such as sodium hypochlorite, bleach) will be excluded for evident reasons, and high-molecular-weight oxidants (such as iodosylarenes, alkyl hydroperoxides, most peroxycarboxylic acids, and oxone) should be ruled out as highly waste-producing,[7] thus, leaving the cheap and nonpolluting hydrogen peroxide and dioxygen as the most viable protagonists of sustainable catalyst systems discussed hereinafter. Basically, this chapter will consider the transition-metal-catalyzed asymmetric epoxidations, sulfoxidations, Baeyer–Villiger oxidations, non-osmium-catalyzed *cis*-dihydroxylations, kinetic resolution of alcohols, and desymmetrization of *meso*-diols. Additionally, the rapidly emerging area of organocatalytic asymmetric oxidations will be discussed more concisely. Some practical applications of sustainable catalytic asymmetric oxidations will be mentioned here and elsewhere within the text.

6.22.2 Catalytic Asymmetric Epoxidations with H_2O_2 and O_2

Catalytic asymmetric epoxidations (cAEs) constitute an important class of transformations in synthetic chemistry. Olefins are rather inert compounds themselves and require functionalization (mainly oxygenation) prior to use as chemical materials, whereas enantiopure epoxides are valued as versatile and reactive, yet stable, intermediates for various small- and large-scale synthetic applications.[8] Since the mainframe work of Katsuki and Sharpless,[9] who first reported on a successful (in >95% ee) catalytic enantioselective epoxidation of allylic alcohols with *t*-butylhydroperoxide, various transition-metal-based as well as organocatalytic systems appeared. Apparently, the most reputed ones are the Katsuki[10–13] and Jacobsen[14–17] manganese–salen-based systems for the epoxidation of unfunctionalized olefins with iodosylarenes, *meta*-chloroperbenzoic acid, and hypochlorite,[18] which inspired the search for new catalyst systems worldwide. In the last 10 years, a number of critical review papers on the cAE area appeared.[19–28] Herewith, an overview of transition-metal-based catalyst systems for sustainable asymmetric epoxidation reactions will be given.

6.22.2.1 Manganese Systems

Manganese is currently among the most widely used metals for the design of oxidation catalyst systems. Apparently, one of the first successful attempts to use molecular oxygen as a readily available and safe oxidant for cAE was reported in 1992 by Mukaiyama and coworkers, who achieved the enantioselective epoxidation of dihydronaphthalene derivatives into the corresponding epoxides with 43–77% ee in the presence of catalytic amounts of chiral manganese–salen complexes **1** and **2** (R = Me).[29] For the reaction to occur, a coreductant, pivalaldehyde (3 equiv.), was essential (**Scheme 1**). In a subsequent



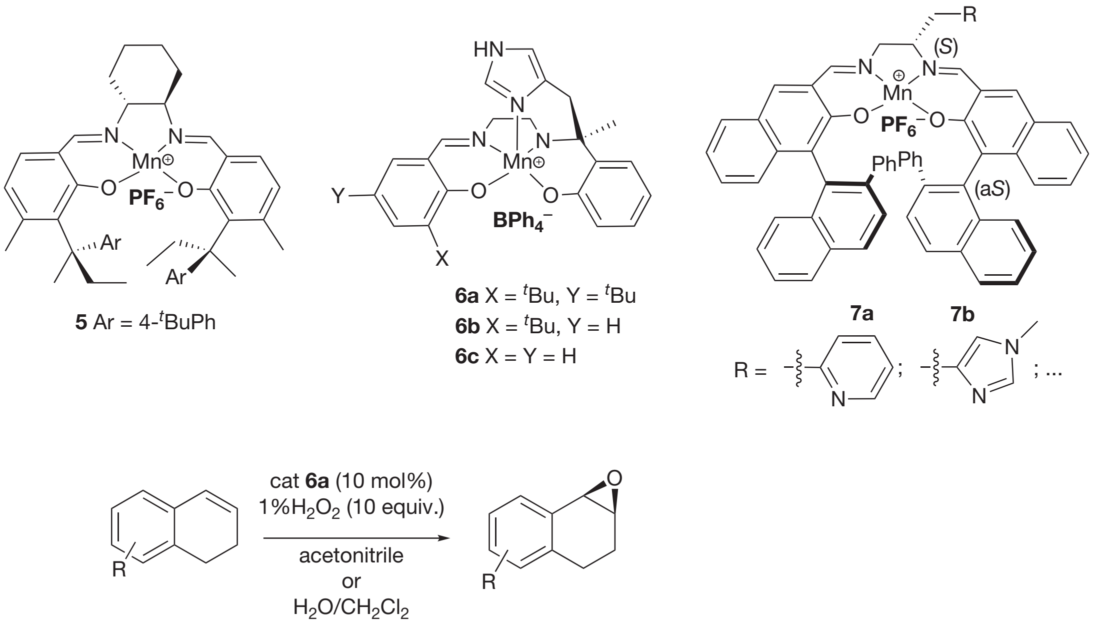
Scheme 1

fuller account, the classical Jacobsen's catalyst **2** (where R = ^{t}Bu) was reported to demonstrate even higher stereoselectivities (up to 92% ee) in the epoxidation of 2,2-dialkylchromenes, albeit with low chemical yields (24–37%).[30] The same authors also presented chiral β-ketoiminato manganese complexes **3** and **4**, which catalyzed the enantioselective epoxidations of conjugated olefins in 33–84% ee and 22–70% yield under conditions similar to those used with manganese–salen complexes.[31–33] Remarkably, in the above systems, an additive of *N*-donor ligand (0.5 equiv. of *N*-alkylimidazole) reversed the sense of asymmetric induction and enhanced the enantiomeric ratio,[30,33–35] thus, suggesting different intermediates, likely manganese(III) acylperoxo complex and manganese(v) oxido complex, to operate without and with donor additives, respectively.[36] The disadvantages of Mukaiyama-type systems are high catalyst loadings (12 mol%) and an excess of aldehyde coreductants, which eventually contaminate the reaction mixture with the corresponding carboxylic acids. On the other hand, the versatility of these systems is remarkable: besides olefins, they were successfully applied to the oxidation of substituted methyl phenyl sulfides to sulfoxides in 24–94% ee and, generally, moderate to good yields.[37,38] Despite aliphatic aldehydes, the use of 2-alkyl-2-oxocyclopentanecarboxylates as sacrificial reductants in aerobic epoxidation on Jacobsen's catalyst was reported.[39]

First attempts to use hydrogen peroxide in manganese–salen-catalyzed epoxidations are dated 1993, when Meunier and coworkers achieved a 39% ee in the epoxidation of 4-chlorostyrene with H_2O_2 catalyzed by Jacobsen's complex **2** (where R = ^{t}Bu)[40] (an earlier communication by Jacobsen and coworkers reported on the enantioselective oxidation of several alkyl aryl sulfides to sulfoxides in 84–95% yield and 34–68% ee with H_2O_2, catalyzed by manganese(ii)–salen complexes in acetonitrile[41]). We note that a donor additive (4-^{t}Bu-pyridine) was used for the epoxidation.[40] In 1994, Pietikäinen reported the epoxidation of conjugated olefins 1,2-dihydronaphthalene and *E*-β-methylstyrene in moderate yields (34–63%) and in 48–60% ee and 42–47% ee, respectively, using 5 mol% of catalysts **1** and **2** (where R = ^{t}Bu), with 2.3–3.5-fold excess of H_2O_2 and imidazole or *N*-methylimidazole as the additive.[42] Katsuki and coworkers epoxidized substituted 2,2-dimethylchromenes over catalyst **5** with 10 equiv. of 30% H_2O_2 in up to 95% ee, using *N*-methylimidazole as an auxiliary axial ligand.[43] Apparently, the role of the axial donor atom is to favor the heterolytic O—O bond cleavage and convert the initially formed manganese hydroperoxo species into the reactive oxomanganese intermediate.[44] Other examples of the use of heterocyclic nitrogen bases as external donors have been reported; see Sun et al.[45–47] and the text later.

To avoid the use of an external donor additive, Berkessel and Schwenkreis designed a pentacoordinate salalen (dihydrosalen) complex **6a** with an imidazole group.[48] Using 10 mol% of the catalyst **6a**, 1,2-dihydronaphthalene was epoxidized with dilute (1%) hydrogen peroxide in up to 64% ee and in 72% yield (Scheme 2). Later, complexes **6b** and **6c** were studied as catalysts in the epoxidation of styrene and 1,2-dihydronaphthalene derivatives.[49] A similar approach was exploited by Shitama and Katsuki, who introduced various internal *N*-donor arms into the structure of their 'second-generation' salen ligands (possessing additional elements of chirality in the aldehyde moieties).[50,51] The resulting complexes of the type **7**, used in 5 mol%, efficiently catalyzed the epoxidation of chromene derivatives with H_2O_2 in high yields and ee's up to 97–99%. The complex featuring the *N*-methylimidazole arm emerged as the best catalyst of the series.[50,51]

Different approaches to suppress the formation of hydroxo radicals or catalase activity were also exploited. In particular, Pietikäinen combined the use of catalysts of the types **1** and **2** and either aqueous H_2O_2 or urea H_2O_2 adduct as oxidants, using soluble salts (acetates, hydrocarbonates, formates, and benzoates) or nitrogen bases as additives, and reported the



5 Ar = 4-^{t}BuPh

6a X = ^{t}Bu, Y = ^{t}Bu
6b X = ^{t}Bu, Y = H
6c X = Y = H

7a **7b**

Scheme 2

epoxidation of various alkenes in 64–96% ee.[52] A similar approach was exploited by Kureshy and coworkers, who successfully used 2.5 mol% of a methylene-bridged dimeric homochiral manganese–salen complex as the catalyst in the epoxidation of several alkenes (100% conversion and ee were reported for substituted 2,2-dimethylchromene derivatives).[53,54] The role of carboxylate salts as cocatalysts is not entirely clear. Different possibilities like the formation of peroxycarboxylic species[52,55] and promotion of the formation of manganese hydroperoxo complexes due to the basicity of the salts[52] have been suggested. Alternatively, peroxymaleic acid (*in situ* preformed from urea H_2O_2 adduct and maleic anhydride) was used in manganese–salen-catalyzed epoxidations.[56]

It should be noted that only a very scanty number of substrates was reported to display ee's over 90%, mainly substituted 2,2-dimethylchromenes. Some representative epoxidation results are listed in **Table 1**.

The use of molecular oxygen for the enantioselective oxidation of alkenes (in up to 81% ee) over Jacobsen's catalyst **2** (where $R={}^t$Bu) was reported by Lee and coworkers, with the actual oxidant being dichlorocarbonyl oxide (formed *in situ* from added chloroform and hydrogen peroxide).[57] However, the conversions observed were rather low (14–38% in most cases), and the major reaction products were hem-dichlorocyclopropanes. A series of manganese–salen complexes were tested in electrocatalytic epoxidations with molecular oxygen; moderate ee's (up to 67%) and low yields (17–19%) were reported for the epoxidation of styrene.[58] In contrast, using 5 mol% of Jacobsen's catalyst **2** (where $R={}^t$Bu), Tanaka and coworkers reported moderately to highly enantioselective (30–86% ee) epoxidation of various alkenes in much higher yields (up to 93%) by using a CH_2Cl_2/aqueous NaCl two-phase solution.[59]

Despite unfunctionalized olefins, enantioselective oxidations of other substrates with hydrogen peroxide over manganese–salen-type complexes have also been reported. Brun and coworkers reported moderate ee's (50–55%) for the epoxidation of geraniol and nerol derivatives over catalyst **2**, without added external bases,[60,61] and Silva and coworkers examined the epoxidation of (*E*,*E*)-cinnamylideneacetophenones containing two C═C double bonds.[62]

Unlike the Mn(salen)/iodosylbenzene and Mn(salen)/peroxycarboxylic acids, where the nature of the reactive oxygen-transferring species has been probed by physical methods and extensively discussed (for a comprehensive account on this, see McGarrigle and Gilheany[22] and references therein), the nature of active species in the Mn(salen)/H_2O_2/additives catalyst systems remains mainly hypothetical.

Other types of manganese-based systems capable of utilizing hydrogen peroxide as the terminal oxidant in AEs appeared in the late 1990s. Namely, Bolm and coworkers employed C_3-symmetric chiral 1,4,7-triazacyclononane derivatives of the type **8** for the *in situ* generation of the catalyst from $Mn(OAc)_2$ (**Scheme 3**).[63] Using 2–3 equiv. of H_2O_2 in methanol, styrene was epoxidized in up to 43% ee, while *Z*-β-methylstyrene epoxidation yielded *trans*-epoxide with 55% ee as the major reaction product. Low ee's (15–26%) were observed for the epoxidation of substituted styrenes with H_2O_2, catalyzed by dinuclear manganese(III) complex bearing L-proline derived triazacyclononane ligand **9**.[64] Catalysts prepared *in situ* from macrocyclic ligands **10** with $Mn(OAc)_2$ or $MnSO_4$ also showed low yields and ee's.[65,66]

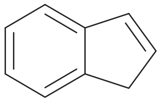
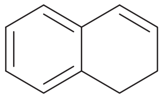
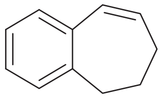
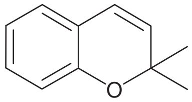
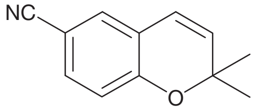
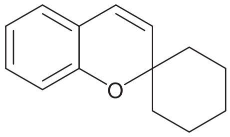
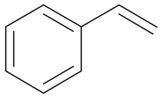
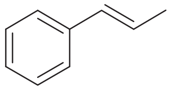
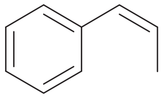
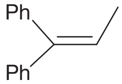
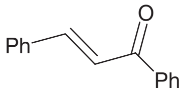
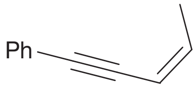
Another promising class of manganese-based catalysts employing multidentate *N*-donor ligands appeared in 2003, when Stack and coworkers reported that manganese(II) complexes with ligands **11** and **12** (similar to those previously found to be efficient for iron-catalyzed *cis*-dihydroxylation[67] and epoxidations[68] of alkenes with H_2O_2) and others could catalyze the epoxidation of various alkenes with commercial peracetic acid in nearly quantitative yield; although some of the complexes were chiral, the epoxidation enantioselectivity was not examined (**Scheme 4**).[69–71] Costas and coworkers synthesized manganese(II) complexes with more sophisticated pinene-derived ligands of the type **13** and reported ee's up to 46% for the epoxidation of various alkenes; acetonitrile emerged as the best solvent for this reaction.[72] Later, Bryliakov and coworkers examined several complexes with pyridine-derived ligands (complexes of the type **14** demonstrated the highest enantioselectivity up to 79% ee) in the enantioselective epoxidations of several alkenes with AcOOH, AlkOOH, and iodosylarenes.[73] On the basis of EPR and enantioselectivity studies, the reactions were concluded to proceed via the $[LMn^{IV}=O(OX)]^{n+}$ intermediates (OX stands for the terminal oxidant).

In 2009, the group of Costas reported that aminopyridine manganese(II) complexes (including **14**) could catalyze olefin epoxidation with hydrogen peroxide in the presence of 14 equiv. of acetic acid.[74] Although the enantioselectivities were not measured, impressive efficiency (1000 turnovers, so that 0.1 mol% of Mn catalyst was loaded) was reported. Sun and coworkers studied the enantioselective oxidation of various alkenes over catalysts prepared *in situ* from aminopyridine ligands of the type **15** and $Mn(OTf)_2$, and reported ee's in the range of 18–89% (**Scheme 5**).[75] α,β-Enones (substituted chalcones) were found to be epoxidized with the highest level of enantioselectivity (70–89% ee). The synthetic protocol of Sun required 5 equiv. of acetic acid as the additive and as much as 6 equiv. of H_2O_2; apparently, the oxidant overconsumption was caused by its decomposition in the presence of relatively high catalyst loading (1 mol%). Recently, Bryliakov and coworkers reported the epoxidation of various alkenes with 1.1–1.3 equiv. of hydrogen peroxide, catalyzed by 0.1 mol% of complexes **14** and **16**.[76] Like in the work of Costas,[74] an additive of AcOH (14 equiv.) was used. Complex **16** demonstrated better efficiencies and enantioselectivities: several electron-deficient alkenes were epoxidized in up to 100% yield and in 68–84% ee.

6.22.2.2 Iron and Ruthenium Systems

Iron is one of the most abundant metals and, as well as manganese, plays a role in the composition of many heme and nonheme enzymes, catalyzing various oxidative transformations.[77,78] Moreover, many artificial iron-based catalyst systems have also been successfully applied for alkene oxidation with H_2O_2. The first reported attempt to model the natural oxidizing systems, such as cytochrome P-450, dates 1979, when Groves and coworkers found that the treatment of iron(III)-porphyrin complex with iodosylbenzene yields an active oxoiron(IV) complex capable of epoxidizing alkenes and oxidizing adamantane to adamantanol.[79] Some years later, the first chiral iron porphyrin was prepared and reported to catalyze the epoxidation of *p*-chlorostyrene (in 51% ee) with iodosylbenzene.[80] Since that

Table 1 Asymmetric epoxidations with O_2, H_2O_2, and related oxidants catalyzed by manganese complexes

N	*Substrate*	*Catalyst*	*Oxidant*	*Additive*	*Epoxide (%)*	*ee (%)*	*References*
1		**1** **Dimeric**	H_2O_2 UHP[a]	NH_4OAc NH_4OAc	63 >99	75 76	52 54
2		**6a** **2** (R = Me)	H_2O_2 H_2O_2	– NMO[b]	72 74	64 69	48 52
3		**2** (R = Me) **1** **7b**	O_2/IBA[c] H_2O_2 H_2O_2	*N*-Me-Imd[d] NH_4OAc –	52 70 95	77 85 88	29 52 52
4		**2** (R = Me) **5** **7b**	O_2/IBA[c] H_2O_2 H_2O_2	*N*-Me-Imd[d] *N*-Me-Imd[d] –	12 55 80	91 88 98	30 43 50
5		**7b** **Dimeric** **16**	H_2O_2 UHP[a] H_2O_2	– NH_4OAc AcOH	95 >99 51	99 >99 84	51 54 76
6		**2** (R = H) **2** (R = ^{t}Bu) **7b**	H_2O_2 O_2/IBA[c] H_2O_2	NH_4OAc N-Oct-Imd[d] –	90 34 84	91 91 98	52 30 50
7		**6b** **2** (R = ^{t}Bu) **8**\Mn(OAc)$_2$ **15** (Ar = Ph)[f]	H_2O_2 O_2[e] H_2O_2 H_2O_2	– Imidazole – AcOH	67 19 15 89	52 23 43 46	49 57 63 72
8		**7b** **2** (R = ^{t}Bu)	H_2O_2 O_2[e]	– Imidazole	58 10	31 43	51 57
9		**8**/Mn(OAc)$_2$	H_2O_2	–	87[g]	55[g]	63
10		**2** (R = H)	H_2O_2	NH_4OAc	84	96	52
11		**15** (Ar = 4-^{t}BuPh)[f] **16**	H_2O_2 H_2O_2	AcOH IBAc[h]	91 100	78 82	72 76
12		**7b**	H_2O_2	–	94 (4:1 *cis*:*trans*)	83 (*cis*) 96 (*trans*)	50

[a] UHP = urea hydroperoxide.

[b] NMO = *N*-methylmorpholine-*N*-oxide.

[c] IBA = isobutyraldehyde.

[d] *N*-Me-Imd = *N*-methylimidazole, *N*-Oct-Imd = *N*-octylimidazole.

[e] In the presence of $CHCl_3$, NaOH, and Bu_4NBr.

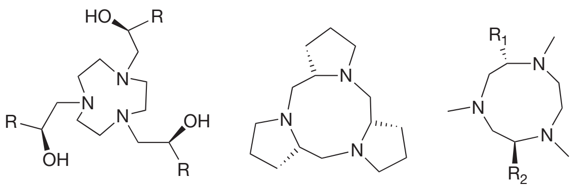
[f] Catalyst was generated *in situ* from ligand **15** and Mn(OTf)$_2$.

[g] Complete conversion observed; a 7:1 *trans*-epoxide/*cis*-epoxide mixture was formed: ee given for the *trans*-isomer.

[h] IBAc = isobutyric acid.

time, the area of iron–porphyrin-catalyzed oxidations progressed greatly, and examples of oxidations with H_2O_2 and O_2 have been reported.[81,82] Some examples of iron–porphyrin-catalyzed enantioselective epoxidations were discussed in the early reviews by Jacobsen[83] and Katsuki[84]; for none of them, however, had the use of environmentally benign hydrogen peroxide or dioxygen been achieved.

Until the 2000s, iron had remained underrepresented in stereoselective oxidation reactions with hydrogen peroxide. For a few rare exceptions, cf. a heterogeneous Fe^{II}/peptide system capable of catalyzing the epoxidation of *E*-β-methylstyrene with H_2O_2 in 20% ee,[85] an Fe–TPA catalyst system yielding capable *cis*-dihydroxylation of several alkenes (although enantiomeric excess was not measured),[86] and discussion of the works of Fontecave and coworkers in **Section 6.22.3.3** of the present chapter. In 2001, Que and coworkers[67] and Jacobsen and coworkers[68] reported structurally similar iron(II) aminopyridine complexes that catalyzed *cis*-dihydroxylation of alkenes with H_2O_2 and epoxidation of alkenes with H_2O_2 (in the presence of substoichiometric amounts of acetic acid), respectively. For the latter system, high isolated yields of the epoxide were achieved by using only 1.5 equiv. of H_2O_2 and 3 mol% of the catalyst prepared from $Fe(ClO_4)_2$ and ligand **11.**[68] On the other hand, Que and coworkers reported ee's of 3–82% for the *cis*-diols formed in the course of oxidation over the catalyst [{(*R*,*R*)-**17**}Fe(OTf)$_2$] (although the yields did not exceed 11.2%, and 10–20 equiv. of H_2O_2 had to be used), while chiral epoxide formed only as a byproduct with 12% ee.[67] More recently, Kwong and coworkers reported chiral polypyridine ligand **18**, which, upon complexation, gave an active epoxidation catalyst (presumably, [Fe_2O{**18**}Cl_4] complex); in the

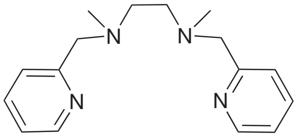


8 R = Me, ^{i}Pr

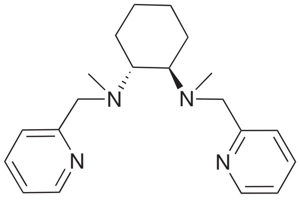
9

10 R_1, R_2 = Me, ^{i}Pr

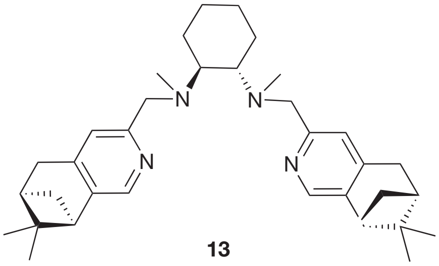
Scheme 3



11



12



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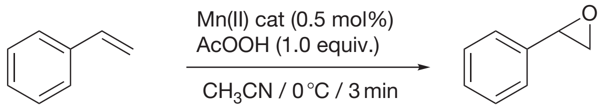
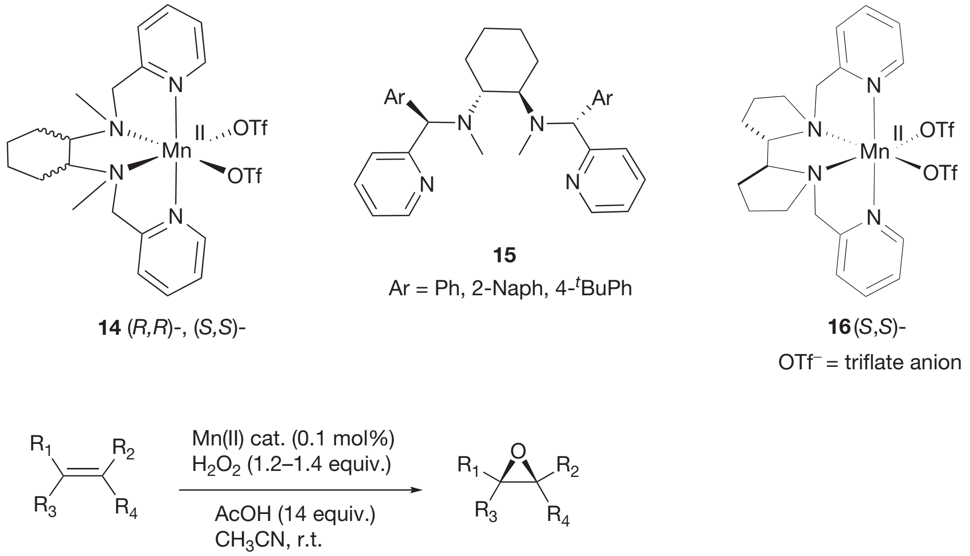


Scheme 4

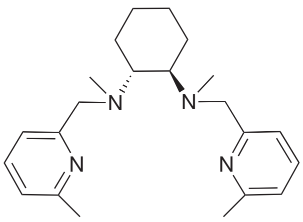


14 (*R*,*R*)-, (*S*,*S*)-

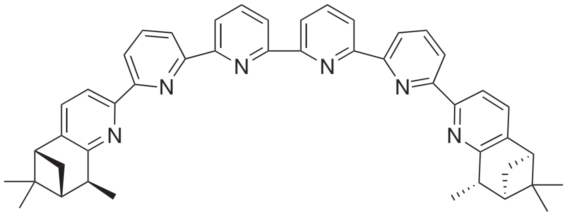
15
Ar = Ph, 2-Naph, 4-^{t}BuPh

16 (*S*,*S*)-
OTf$^-$ = triflate anion

Scheme 5



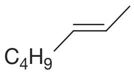
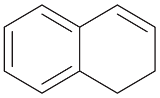
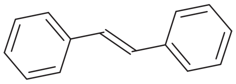
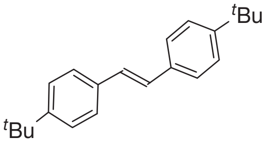
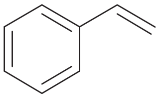
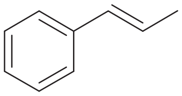
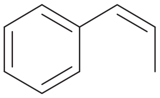
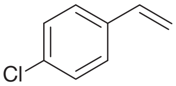
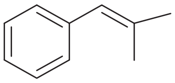
17



18

Scheme 6

Table 2 Asymmetric epoxidations with O_2 and H_2O_2 catalyzed by iron and ruthenium complexes

N	*Substrate*	*Catalyst*	*Oxidant*	*Additive*	*Epoxide (%)*	*ee (%)*	*References*
1		[{(*R*,*R*)-**11**}Fe(OTf)$_2$]	H_2O_2	–	–[a]	12	87
2		[Fe_2O\{**18**\}Cl_4] **21** [Ru(**22**)Cl]PF_6	H_2O_2 O_2 H_2O_2	AcOH – –	50 14[b] 55	31 56 41	88 94 95
3		$FeCl_3 \cdot 6H_2O$/**19** **24** (R = 2-naphthyl) **24** (R = 2-naphthyl)	H_2O_2 H_2O_2 H_2O_2	H_2dipic[c] – –	97 100 99	47 54 54	90 98 100
4		$FeCl_3 \cdot 6H_2O$/**19**	H_2O_2	H_2dipic[c]	82	81	90
5		[Fe_2O\{**18**\}Cl_4] **20** **21** [Ru(**22**)Cl]PF_6 **24** (R = 2-naphthyl)	H_2O_2 O_2/IBA[d] O_2 H_2O_2 H_2O_2	AcOH PyNO[e] – – AcOH	95 85 10[b] 28 85	43 24 70 37 59	88 93 94 95 98
6		[Fe_2O\{**18**\}Cl_4] $FeCl_3 \cdot 6H_2O$/**19** **24** (R = 2-naphthyl)	H_2O_2 H_2O_2 H_2O_2	AcOH H_2dipic[c] –	96 94 67	37 28 74	88 90 98
7		[Fe_2O\{**18**\}Cl_4] **21** **24** (R = 2-naphthyl)	H_2O_2 O_2 H_2O_2	AcOH – –	100 21[b] 96	40 73 60	88 94 100
8		**20** **21**	O_2/IBA[d] O_2	– –	78 11[b]	30 52	93 94
9		**24** (R = 2-naphthyl)	H_2O_2	AcOH	91	84	98

[a] 5.8 mmol of epoxide per mmol of the catalyst.

[b] Turnover number.

[c] Dipicolinic acid.

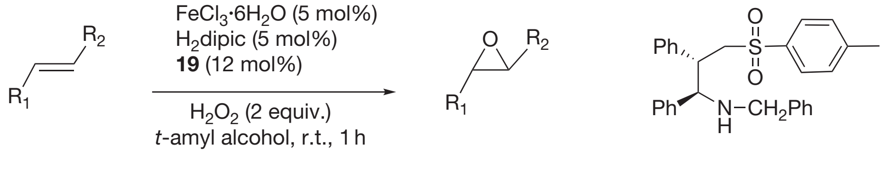
[d] IBA = isobutyraldehyde.

[e] Pyridine-*N*-oxide.

presence of acetic acid, various alkenes were epoxidized with H_2O_2 in 50–100% yield and in 15–43% ee (Scheme 6).[87] Some representative epoxidation results can be found in Table 2.

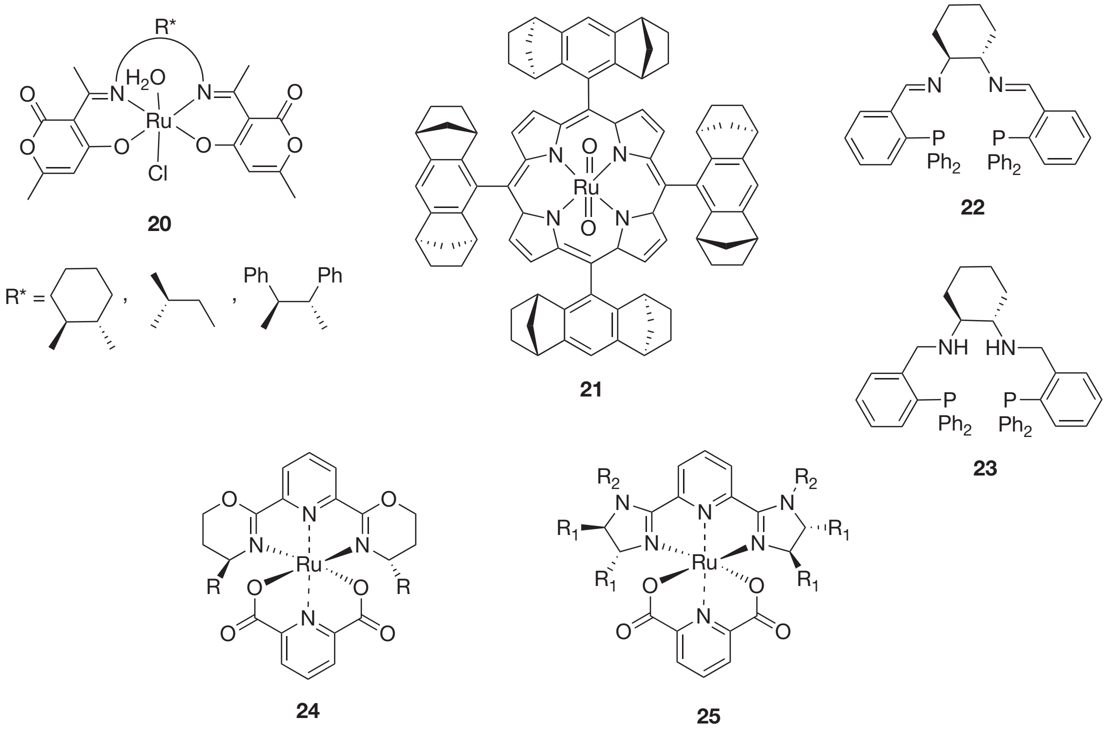
A major breakthrough was made by Beller and coworkers, who found that combinations of $FeCl_3 \cdot 6H_2O$, dipicolinic acid (H_2dipic), and an organic base (such as benzylamine, 4-methylimidazole, and pyrrolidine) led to active and highly selective epoxidation catalyst with H_2O_2.[88] The authors have extended their approach to asymmetric epoxidations: several (including commercially available) chiral ligands combining chiral 1,2-diamine and sulfonyl moieties were screened, and one of them emerged as an efficient chiral auxiliary for iron-catalyzed enantioselective epoxidations (Scheme 7).[89] The catalyst was formed *in situ* from ferric chloride, H_2dipic, and the chiral auxiliary **19**; the epoxidations of several *trans*-alkenes (with 2 equiv. of H_2O_2) proceeded in 40–94% isolated yield and 10–97% ee.[89] Formation of a high-valent active oxoiron intermediate was suspected; the authors noted, however, that no ^{18}O label incorporation into the epoxide was observed in the course of epoxidation in the presence of an excess of $H_2^{18}O$ that could argue against the oxoferryl active species.[90]

Ruthenium, as an analog to iron, has also found many applications in asymmetric catalytic oxidations: chiral ruthenium-porphyrin, Schiff base, oxazoline, and polypyridine-based catalysts, to mention just a few.[91] However, the systems employing hydrogen peroxide or dioxygen as terminal oxidants have remained rather scarce. In 1997, Kureshy and coworkers reported three chiral ruthenium(III)-Schiff base complexes of the type **20** (Scheme 8) that were found to catalyze the enantioselective epoxidation of *p*-substituted styrenes by molecular oxygen, in the presence of 1 equiv. of sacrificial reductant (isobutyraldehyde).[92] The addition of pyridine-*N*-oxide resulted in some improvement of the conversion and enantioselectivity. Remarkably, 0.3 mol% of the catalyst was enough to attain high conversions (in most cases, 70–92%), but the enantioselectivities were low (16–30%). One year later, Che and coworkers synthesized chiral ruthenium(VI) porphyrin complex **21**, which was shown to catalyze the epoxidation of several alkenes with molecular oxygen (at 8 atm pressure) without any coreductant.[93] Moderate ee's (52–73% ee) have been reported, and the catalyst efficiency was rather low (generally, 1–14 turnovers, and up to 21 in one case).



19

Scheme 7



20 **21** **22** **23** **24** **25**

R = Ph, 2-naphthyl

Scheme 8

The use of hydrogen peroxide in ruthenium-catalyzed asymmetric epoxidations was first achieved in 1999, when Mezzetti and coworkers reported ruthenium(II) complexes with *P*,*N*,*N*,*P*-donor chiral ligands **22** and **23**.[94–96] The synthetic protocol they used required 1 mol% of the Ru catalyst and 7 equiv. of H_2O_2, and the observed conversions were in the range 6–100%. Along with the epoxide, significant amounts of aldehydes were detected in most experiments, and the enantioselectivity was generally low (10–42% ee). Systems of this type could also use O_2/heptaldehyde as the terminal oxidant, albeit with lower conversion and ee.[94]

Some years later, Beller and coworkers reported the ruthenium(II) complexes **24** that, when added in 5 mol%, were capable of catalyzing enantioselective epoxidations of alkenes with 2 equiv. of 30% hydrogen peroxide.[97] Increased steric bulk of the R substituent (2-naphthyl instead of Ph) in most cases increased the enantioselectivity, and additives of acetic acid (20 mol%) improved the epoxide yields (up to 99% in some cases) and ee's (typically, 50–80%, and up to 84% ee in one case).[98,99] We note that ruthenium catalysts showed significantly lower reactivities compared to the iron ones (**Table 2**). Indeed, at identical catalyst loadings and concentrations, Ru-catalyzed reactions required 12–20 h versus 1 h for Fe-catalyzed reactions (cf. Gelalcha[90] and Tse[97]). A series of structurally related pyridinebis(imidazoline) complexes of ruthenium(II) **25** were prepared and screened as catalysts in asymmetric epoxidations with H_2O_2 by the same group.[100–102] Using 3 equiv. of the oxidant, good yields (63% to >99%) and low to moderate enantioselectivities (1–84%) were achieved. Some mechanistic considerations have been made.[99,102]

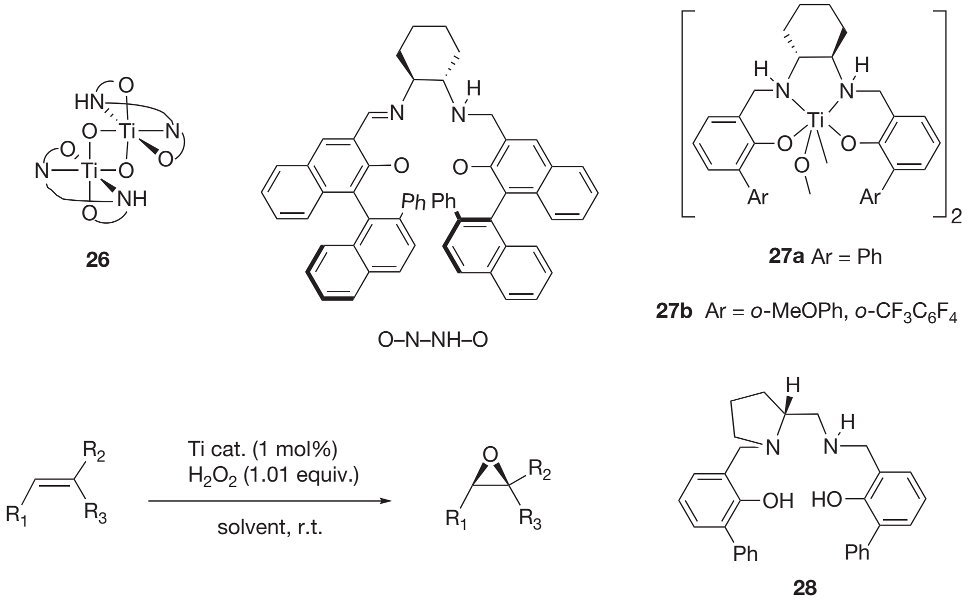
To date, aerobic asymmetric oxidations catalyzed by iron and ruthenium complexes are rather scarce. Apart from the ruthenium–porphyrin asymmetric epoxidation catalyst system by Che,[93] there have been some reports on iron–salen and ruthenium–salen-catalyzed aerobic (without sacrificial reductants) oxidative kinetic resolution of α-hydroxy ketones, allylic alcohols, and *meso*-diols,[103–108] while asymmetric epoxidations under similar conditions remain a challenge.

6.22.2.3 Titanium Systems

Titanium is one of the most challenging metals for asymmetric catalytic synthesis. It is one of the cheapest transition metals (and the seventh most abundant metal on Earth), and products of its hydrolysis are nontoxic, which is in distinct contrast to those of other widespread transition metals, such as Mn, Cr, Ni, V, etc.[109] One of the first asymmetric catalyst systems, the Sharpless system for the enantioselective epoxidation of allylic alcohols, exploited a catalyst formed from titanium alkoxide and chiral tartrate.[9]

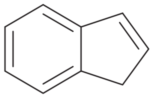
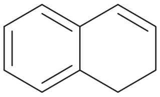
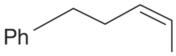
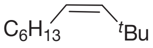
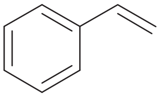
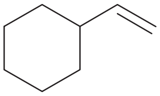
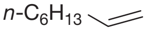
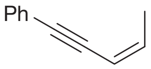
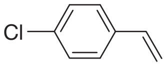
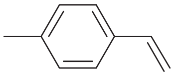
It is quite surprising, therefore, that no enantioselective epoxidation with hydrogen peroxide in the presence of titanium catalysts was reported until 2005, when Katsuki and coworkers reported that bis(μ-oxido) titanium(IV) salalen complex **26** is capable of efficiently promoting the epoxidation of unfunctionalized olefins with 30% hydrogen peroxide (**Scheme 9**).[110] Good yields (generally, 70% to >99%) and excellent enantioselectivities (82% to >99% ee) were achieved for several alkenes using only 1 mol% of the catalyst (**Table 3**); moreover, in one case, the catalyst performed 4600 turnovers with no loss of enantioselectivity. Remarkably, aliphatic alkenes, which are known to be poorly reactive toward electrophilic oxidants, could also be epoxidized in moderate to high yields and ee's.[111]

The same authors discovered that synthetically more easily available dinuclear titanium(IV) salan complexes could also catalyze the enantioselective epoxidations. The authors screened several complexes and identified the best catalyst, **27a**. Compared to the titanium–salalen catalysts, **27a** required higher catalyst loadings (5 mol%), while the yields and enantioselectivities were somewhat lower.[112] The introduction of *ortho*-substituents in the aryl rings at the C3 and C3′ positions



Scheme 9

Table 3 Asymmetric epoxidations with O_2 and H_2O_2 catalyzed by titanium complexes

N	*Substrate*	*Catalyst*	*Oxidant*	*Epoxide (%)*	*ee (%)*	*References*
1		**26** **27a** **27b** (Ar = *o*-MeOPh) **31** $(R_1,R_3=Ph)/Ti(O^iPr)_4$	H_2O_2 H_2O_2 H_2O_2 H_2O_2	87 72 98 88	99 95 97 97	111 113 114 119
2		**26** **27a** **27b** (Ar = *o*-MeOPh)	H_2O_2 H_2O_2 H_2O_2	>99 79 99	>99 98 98	111 113 114
3		**26**	H_2O_2	51[a]	82	112
4		**26**	H_2O_2	90	77	112
5		**26**	H_2O_2	19	97	112
6		**26** **27b** $(Ar=o\text{-}MeOC_6H_4)$ **28**$/Ti(O^iPr)_4$ **29**$/Ti(O^iPr)_4$	H_2O_2 H_2O_2 H_2O_2 H_2O_2	90 86 71 78	93 88 98 80	111 114 116 118
7		**26** **29**$/Ti(O^iPr)_4$ **31** $(R_1,R_3=Ph)/Ti(O^iPr)_4$	H_2O_2 H_2O_2 H_2O_2	72 75 14	95 67 84	112 118 119
8		**26** **27a** **31** $(R_1,R_3=Ph)/Ti(O^iPr)_4$	H_2O_2 H_2O_2 H_2O_2	70 25 6	82 55 60	111 113 119
9		**26** **29**$/Ti(O^iPr)_4$	H_2O_2 H_2O_2	64 97	88 82	111 118
10		**28**$/Ti(O^iPr)_4$ **30**$/Ti(O^iPr)_4$	H_2O_2 H_2O_2	66 73	98 76	116 118
11		**28**$/Ti(O^iPr)_4$	H_2O_2	80	98	116

[a] 1,2-Epoxide:6,7-epoxide ratio of 20:1; ee for the major product given.

(complexes **27**), however, was found to improve both the yield and enantioselectivity.[113,114] Complex **27b** with *o*-methoxy substituents gave the highest enantioselectivity, and the use of a phosphate buffer improved the efficiency (so that only 1 mol% of the catalyst could be used).

Despite the high efficiency and enantioselectivity of the Katsuki's titanium–salalen and titanium–salan systems, the enantioselectivities that they demonstrated in the epoxidation of styrenes remained insufficient. The same group synthesized the C_1-symmetric salan ligands of the type **28**, with chiral proline moiety as the chirality source. The catalyst, generated *in situ* from $Ti(O^iPr)_4$ (10 mol%) and **28** (10 mol%), afforded epoxides of substituted styrenes with 96–98% ee, in 16–84% yields.[115] The applications of titanium–salalen and *in-situ*-prepared titanium–salan catalysts were successfully extended to the epoxidation of *cis*-alkenylsilanes.[116]

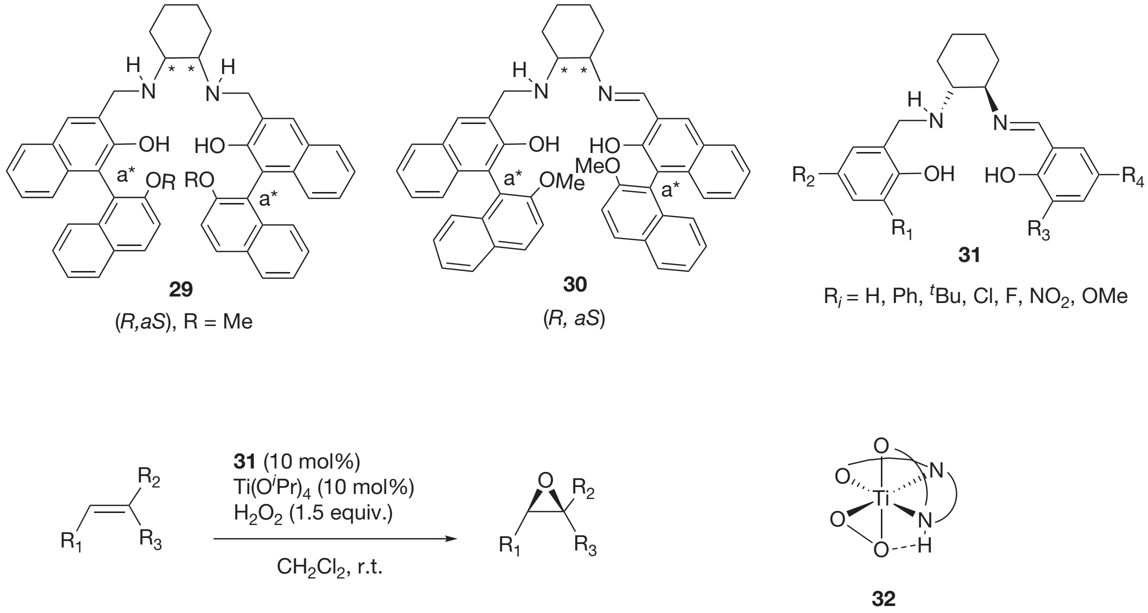
More recently, Sun and coworkers synthesized a series of binaphthol-derived salalen and salan ligands of the types **29** and **30** (Scheme 10).[117] The synthetic protocol they exploited for the enantioselective epoxidations required 10 mol% of the active catalysts (formed *in situ* from $Ti(O^iPr)_4$ and ligand **29** or **30**), and 3 equiv. of 50% H_2O_2 as the oxidant. However, the enantioselectivities achieved were inferior to those demonstrated by the Katsuki's systems (generally, 44–82% ee, and 99% ee in one case). Berkessel and coworkers reported another route for the synthesis of salalen ligands of the type **31**; the ligand with $R_1=R_3=Ph$ yielded the most stereoselective catalyst when combined *in situ* with $Ti(O^iPr)_4$.[118] The system gave acceptable yields with electron-rich olefins; for nonconjugated alkenes, the yields did not exceed 20%, even with 4.5 equiv. of H_2O_2.

Of major importance is the nature of the real catalysts and the active oxidizing species operating in the titanium–salan- and titanium–salalen-based catalyst systems. Katsuki and coworkers isolated and x-ray-characterized a μ-oxido–μ-peroxido titanium–salan complex (formed after the interaction of the dinuclear catalyst with H_2O_2), which they believed to be the precursor of the real active epoxidizing species.[119] Berkessel and coworkers identified the titanium–salalen complexes formed *in situ* from the salalen ligand and $Ti(O^iPr)_4$ as mononuclear species.[118] They also supposed that mononuclear peroxotitanium(IV) species could be the active oxidizing species.[120] Significantly, the presence of at least one N–H moiety seems to be essential for efficient catalysis: neither Ti (salen)[120] nor the *N*,*N*′-dimethylated derivative of **27**[112] displayed catalytic activity in the epoxidation of olefins. The structure of the plausible reactive species **32**[112,115,118–120] is presented in Scheme 10.

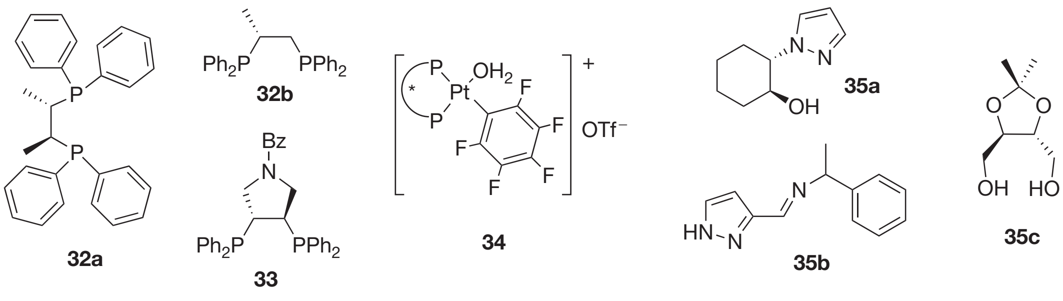
6.22.2.4 Systems Based on Other Metals

Metals other than Mn, Fe, Ru, and Ti have been rather moderately represented in asymmetric epoxidation catalysts systems with hydrogen peroxide. The first published platinum-based system appeared in 1987, when Strukul and coworkers reported the asymmetric version of their diphosphane-modified Pt(II)- based catalyst system.[121] Some of the ligands **32** they considered are presented in Scheme 11. The catalysts with general formula $[(\mathbf{32})Pt(CF_3)(CH_2Cl_2)][BF_4]$, used in <1 mol%, afforded epoxides of 1-propene and 1-octene with low to good yields and 31–41% ee (Table 4). Some years later, the same group developed a series of new chiral diphosphanes; complex $[(\mathbf{33})Pt(CF_3)(CH_2Cl_2)][BF_4]$ was found to catalyze the epoxidation of α,β-unsaturated ketones with low yields and ee's.[122] The 'second-generation' catalyst systems were reported in 2006, when the authors presented the platinum (II) catalysts **34** capable of catalyzing the epoxidation of terminal alkenes in moderate to good yields and in 58–87% ee.[123] After screening several chiral ligands, the optimal ligand **32a** was found. The system required 2 mol% catalyst (of the type **34**) load and 1.0 equiv. of H_2O_2. The enantioselectivities were improved by reducing the temperature to −10 °C. The reactions proceeded rather slowly and required 20–48 h to complete. While styrene was not oxidized, the epoxidation of dienes containing both a terminal and an internal double bond led to selective epoxidation of the terminal double bond, indicating nucleophilic oxidant, which is rather uncommon for transition-metal-catalyzed epoxidations.[23,123,124] Shortly after, this reaction was realized in a water–surfactant media instead of chlorinated organic solvents, albeit with lower enantioselectivities.[125]

The first enantioselective epoxidation of alkenes with H_2O_2 over rhenium complexes was reported in 2002 by Corma and

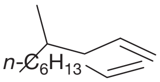
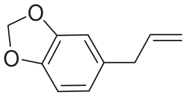
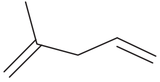
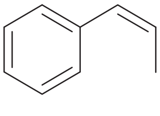
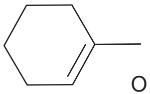
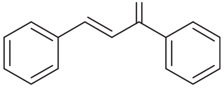
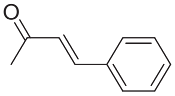
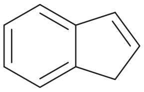


Scheme 10



Scheme 11

Table 4 Asymmetric epoxidations with O_2 and H_2O_2 catalyzed by other complexes

N	*Substrate*	*Catalyst*	*Oxidant*	*Additive*	*Epoxide (%)*	*ee (%)*	*References*
1		**34**	H_2O_2	–	63	78	124
2		[(**32a**)Pt(CF_3)(CH_2Cl_2)][BF_4]	H_2O_2	–	81	36	122
		34	H_2O_2	–	88	79	124
		37	O_2/IBA[a]	–	80	30	131
3		**34**	H_2O_2	–	64	87	124
4		**34**	H_2O_2	–	66[b]	98	124
5		MTO/amine	H_2O_2	–	8	35	127
		MTO/**35a**	H_2O_2	–	6[c]	27	128
		MTO/**35a**	H_2O_2	–	5	41	128
6		MTO/amine	H_2O_2	–	37	20	127
7		**36**/$CuCl_2$, INC-2[e]	UHP[d]	Et_3N	72	84	130
8		**36**/$CuCl_2$, INC-2[e]	H_2O_2	Et_3N	89	82	130
9		**37**	O_2/IBA[e]	–	66	41	131

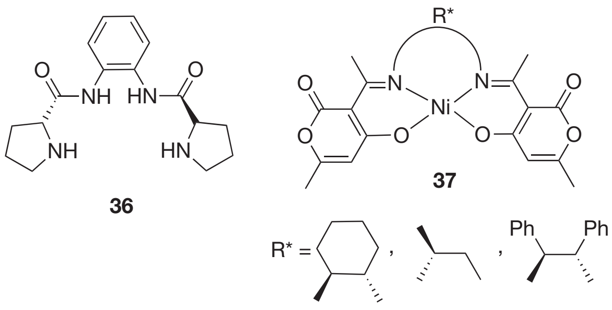
[a] Isobutyraldehyde.

[b] 2-(2-Methyl-allyl)-oxirane/2-allyl-2-methyl-oxirane = 100/0.

[c] Alkene conversion.

[d] Urea hydroperoxide.

[e] INC-2 – mesoporous silica.[129]



Scheme 12

coworkers.[126] Particularly, the catalysts generated *in situ* from methyltrioxidorhenium (methyltrioxorhenium, MTO) and a series of chiral amines promoted the epoxidation of 1-methylcyclohexene, substituted styrenes, and α-pinene at low temperatures, with 4–41% ee. However, the conversions were low (from 9% up to 59%), and significant amounts of diol formed. Herrmann and coworkers tested a number of chiral pyrazoles and diols of the type **35** in the MTO-catalyzed epoxidations of *Z*-β-methylstyrene with H_2O_2, but the conversions and ee's were generally low, despite the high (12 mol%) catalyst load.[127] A series of chiral pyridine-ester and pyridine-amide ligands were tested by Burke and coworkers for the MTO-catalyzed epoxidations with urea hydroperoxide (UHP); however, the conversions were low and the enantioselectivities were very poor (below 12%).[128]

Catalyst systems based on other metals have also been reported. Park and coworkers prepared copper(II) complex with ligand **36**, immobilized on mesoporous silica, which catalyzed the epoxidation of several α,β-unsaturated ketones with 2 equiv. of H_2O_2 or UHP under solvent-free conditions (Scheme 12).[129] The reported conversions varied from 54% to 92%, and the enantioselectivities were up to 84% ee. The solid catalyst was recycled and reused five times without any loss of enantioselectivity. Kureshy and coworkers synthesized several nickel(II) chiral Schiff base complexes **37**, which were tested as catalysts in the epoxidation of several olefins with O_2 in the presence of isobutyraldehyde.[130] The catalysts demonstrated remarkable efficiency (over 300 turnovers), but the enantioselectivities reported were rather moderate (14–41% ee). Very small (2–4% ee) enantioselectivities were observed in Co(salen)-catalyzed aerobic oxidation of styrene in the presence of isobutyraldehyde.[131]

Very recently, Katsuki and coworkers reported the first asymmetric epoxidation of allylic alcohols with H_2O_2 and UHP.[132] The process was catalyzed by niobium–salan complexes with chiral ligands similar to those of titanium–salan complexes **26**. Moderate to good yields (40–82%) and ee's (74–95%) were achieved through the use of 4 mol% of the catalyst.[132]

6.22.3 Catalytic Enantioselective Sulfoxidations with H_2O_2 and O_2

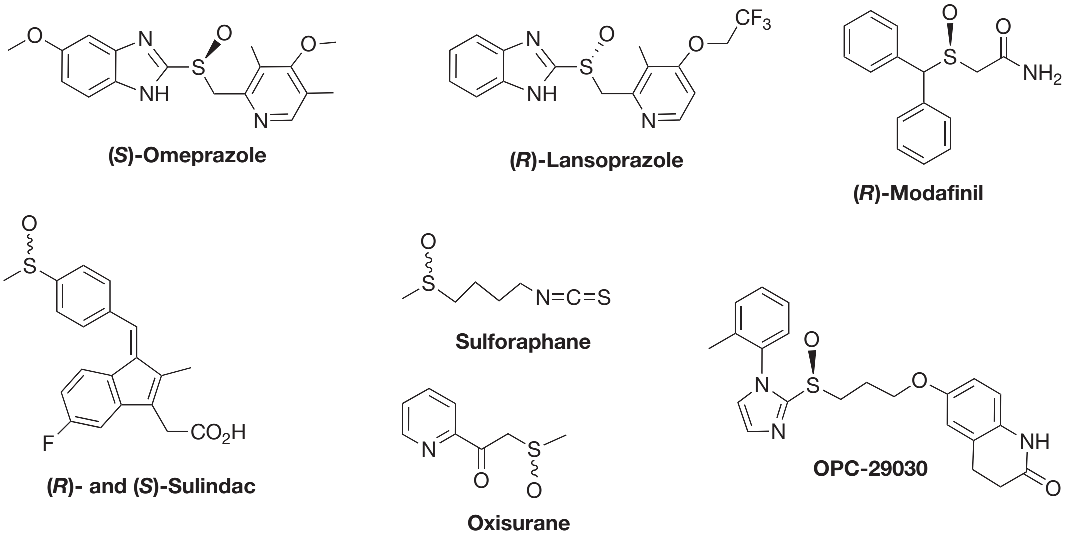
Chiral sulfoxides are finding increasing use as auxiliaries in asymmetric synthesis, the chiral sulfinyl group being one of the most efficient and versatile chiral controllers in C—C and C—X bond formations.[133–141] Moreover, enantiopure sulfoxides have established biological activity and are used in pharmaceutical industry: some representative examples are (Scheme 13) the antiulcer agents (*S*)-omeprazole (inhibitor of gastric acid secretion, commercialized as Nexium™ by AstraZeneca, with $7.9 bn. worldwide sales in 2011[142–144]) and (*R*)-lansoprazole (Kapidex™ or Dexilant by Takeda Pharmaceuticals[144]), stimulant-like drug (*R*)-modafinil,[144] nonsteroidal anti-inflammatory drug sulindac, anticancer-active sulforaphane, immunosuppressor oxisurane, the platelet adhesion inhibitor OPC-29030, and others.[141–151] In 1984, the groups of Kagan[152,153] and Modena[154] adapted the Sharpless titanium-tartrate asymmetric olefin epoxidation system[9] for the enantioselective oxidation of sulfides. Since then, a good deal of catalyst systems for asymmetric sulfoxidations have appeared.[146–150]

To date, quite a number of metal-based catalyst systems are known. Only very recently, has the first use of molecular oxygen for asymmetric sulfoxidations (over ruthenium–salen catalyst) been reported.[155] In contrast, various catalyst systems are known that successfully use hydrogen peroxide, another cheap and environmentally benign terminal oxidant. An overview of the asymmetric sulfoxidations with H_2O_2 over chiral metal complexes will be given below.

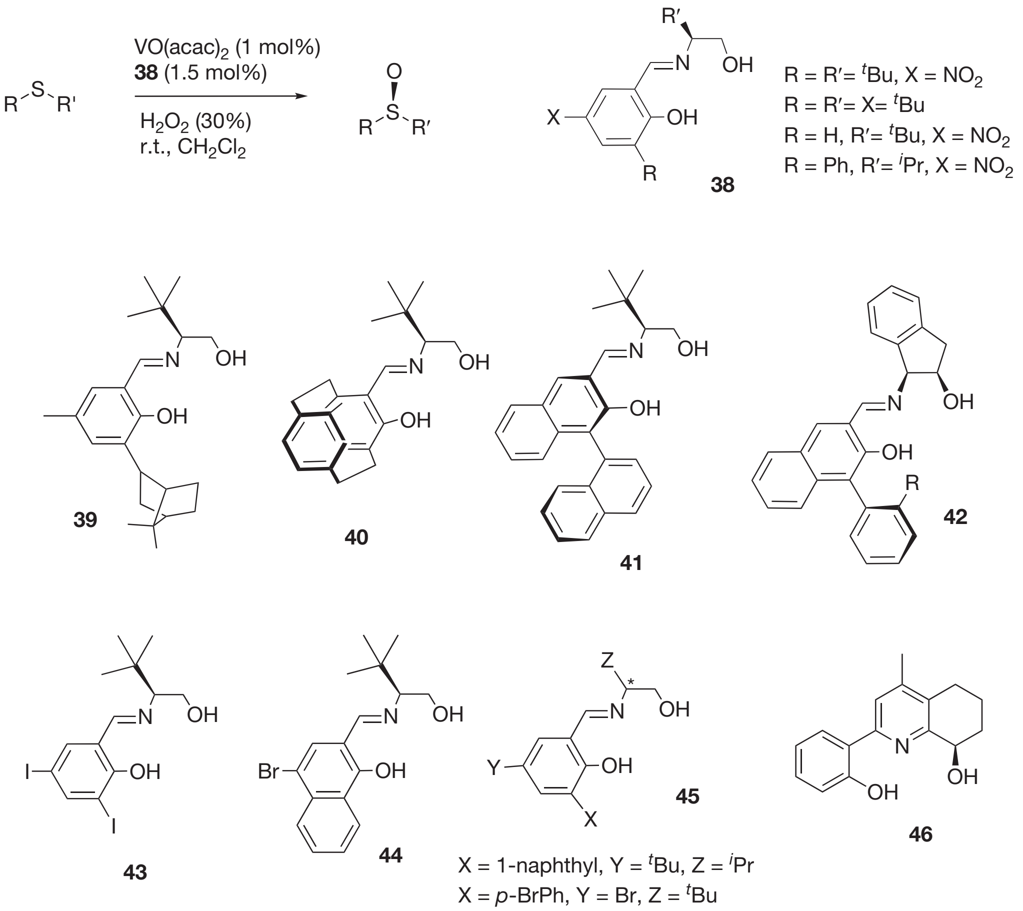
6.22.3.1 Vanadium Systems

So far, vanadium has been one of most popular metals in enantioselective sulfoxidations. This is particularly the case for the oxidations with H_2O_2. In 1995, Bolm and Bienewald discovered the vanadium catalysts formed *in situ* from vanadyl (IV) acetylacetonate and 1.5 equiv. of the Schiff bases of the type **38** (Scheme 14).[156] Remarkably, the system could use 1.1 equiv. of 30% H_2O_2 as the oxidant, and high efficiency (so that the catalyst load could be reduced to 0.01 mol% vanadium) was demonstrated. The enantioselectivities (Table 5) were in the range of 53–76% ee and reached 85% ee in the monooxidation of 2-phenyl-1,3-dithiolane to the sulfoxide (Entry 3).[156,157] Later, the authors examined the oxidation of a variety of dithioacetals and dithioketals.[158] On the basis of experimental findings (the reaction was ligand-accelerated, and the enantioselectivity was proportional to the ligand optical purity), the authors concluded that the active sites contained one chiral ligand per vanadium.[156,157] Based on ^{51}V NMR data, they reported the formation of several vanadium(V) species upon the addition of H_2O_2.[158] Later, Karpyshev and coworkers detected two major peroxovanadium(V) complexes by ^{51}V NMR,[159] and Bryliakov and coworkers found an equilibrium between peroxovanadium(V) species with bis- and tris-coordinated chiral ligand.[160] A discussion on the structure of the catalyst was continued by Ellman[161] and Maeda.[162]

The seminal works of Bolm and Bienewald were followed by those of others. Skarzewski and coworkers discovered ligand **38** (R = Ph, R′ = ^{i}Pr, X = NO_2) to be the most effective for the asymmetric oxidation of various bis(arylthio)alkanes into the corresponding mono- and bis-sulfoxides.[163,164] Vetter and Berkessel synthesized more sophisticated ligands bearing additional elements of chirality (central, planar, and axial) in the aldehyde moiety (**39–41**, Scheme 14),[165] and the ligand **39** that showed the best enantioselectivity in the oxidation of thioanisole: 78% ee at 0 °C. Katsuki and coworkers focused on the asymmetric oxidation of aryl methyl sulfides using a variety of similar axially chiral ligands. The highest ee they reported was achieved with methyl 2-naphthyl sulfide (93%



Scheme 13



Scheme 14

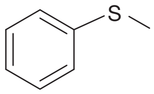
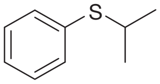
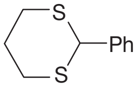
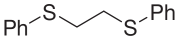
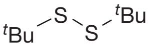
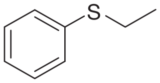
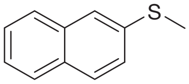
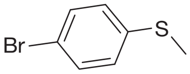
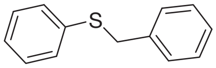
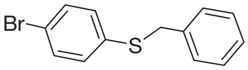
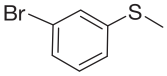
at 0 °C), using the ligand **42**.[166] Ellman and coworkers chose the ligand **38** (R = R′ = X = ^{t}Bu) as the most suitable for the asymmetric mono-oxygenation of *t*-butyl disulfide (91% ee) – the key step of the synthesis of chiral *t*-butanesulfinamide.[167] Somanathan and coworkers synthesized a library of Schiff base ligands starting from various salicylaldehydes and chiral β-amino alcohols. The ligands were tested in vanadium-catalyzed oxidation of sulfides to sulfoxides and demonstrated moderate enantioselectivities (up to 59% ee).[168,169]

Anson and Jackson with coworkers tested a library of Schiff base ligands derived from natural and synthetic β-amino alcohols, and aromatic *o*-hydroxy aldehydes.[170] The ligands **43** and **44** containing electron-withdrawing substituents in the aromatic ring demonstrated the highest enantioselectivities in the vanadium-catalyzed enantioselective oxidation of sulfides with H_2O_2 in dichloromethane, giving oxides of alkyl aryl sulfides in 74–86% yield and 89–97% ee. Later, it was found that vanadium–Schiff base systems could catalyze the oxidative kinetic resolution of racemic sulfoxides: ligand **43** and its (*R*)-enantiomer showed higher stereoselectivity factor *S* (which is equal to the ratio of the rate constant of fast-reacting and slow-reacting enantiomers) in $CHCl_3$ (10.5 to >30 at 0 °C) and lower in toluene.[171] A combined asymmetric oxidation/kinetic resolution procedure was exploited to obtain a set of alkyl aryl sulfoxides in over 70% yield and up to 99.5% ee using the ligand **43** (or its (*R*)-enantiomer)/$VO(acac)_2/H_2O$ system in $CHCl_3$.[172]

Maguire and coworkers also exploited the vanadium-based catalyst systems (ligand **43** and its enantiomer exhibited the best results) for the enantioselective oxidation of sulfides to sulfoxides. Due to the combined asymmetric oxidation/kinetic resolution procedure, a series of bulky sulfoxides were synthesized in 56–99% ee, albeit with low yield (generally, below 50%).[173,174] The authors noted that the efficiency of the kinetic resolution is substrate- and solvent-dependent; the highest ee's were achieved for substituted benzyl aryl sulfoxides in CH_2Cl_2,[174] while the effect of kinetic resolution was negligible in the oxidations of aryl methyl sulfides.[157]

Recently, Sun and coworkers have tested a series of 3-arylsubstituted Schiff bases of the type **45**; some of them appeared to be rather effective chiral ligands in vanadium-catalyzed oxidations of aryl methyl sulfides (53–90% ee).[175] They also reported another tridentate ligand **46**, which showed enantioselectivities ranging from 8% to 77% ee in asymmetric oxidations of several aryl methyl sulfides in acetone, the yields of sulfoxides being good to high (80–95%).[176] Gau and coworkers prepared and x-ray-characterized a series of vanadium(V) complexes of the type **47** (Scheme 15) and used them as precatalysts for the asymmetric oxidation of methyl phenyl sulfide with H_2O_2.[177] Moderate to high yields (61–80%) and ee's (26–98%) were reported; the enantioselectivity increased at low temperatures, and the use of CH_2Cl_2/toluene solvent instead of CH_2Cl_2 afforded methyl phenyl sulfoxide in 98% ee

Table 5 Asymmetric sulfoxidations with H_2O_2 catalyzed by vanadium complexes

N	*Substrate*	*Catalyst*	*Oxidant*	*Sulfoxide (%)*	*ee (%)*	*References*
1		VO(acac)$_2$/**38** (R,R′=^{t}Bu, X=NO_2)	H_2O_2	94	70	158
		VO(acac)$_2$/**39**	H_2O_2	97	78	166
		VO(acac)$_2$/**43**	H_2O_2	81	90	171
		VO(acac)$_2$/**43**	H_2O_2	70	96.7	173
		47 (R_1,R_2=H, R_3=^{t}Bu, R_4=I)	H_2O_2	61	98	178
		VO(acac)$_2$/**50**	H_2O_2	81	99	181
		VO(acac)$_2$/**59** (X=H, Y,Y=–C_2H_4–)	H_2O_2	81	95	194
2		VO(acac)$_2$/**38** (R,R′=^{t}Bu, X=NO_2)	H_2O_2	64	62	158
3		VO(acac)$_2$/**38** (R,R′,X=^{t}Bu)	H_2O_2	84[a]	85[b]	158
		VO(acac)$_2$/**38** (R=Ph, R′=^{i}Pr, X=NO_2)	H_2O_2	80[a]	88[b]	164
4		VO(acac)$_2$/**38** (R=Ph, R′=^{i}Pr, X=NO_2)	H_2O_2	60[c]	95	164
5		VO(acac)$_2$/**38** (R,R′, X=^{t}Bu)	H_2O_2	98[d]	91	168
		VO(acac)$_2$/**54**	H_2O_2	90	85	185
6		VO(acac)$_2$/**44**	H_2O_2	74	90	171
		VO(acac)$_2$/**43**	H_2O_2	76	97.4	173
		VO(acac)$_2$/**50**	H_2O_2	84	99	181
7		VO(acac)$_2$/**43**	H_2O_2	78	97	171
		VO(acac)$_2$/**46**	H_2O_2	73	>99.5	173
		VO(acac)$_2$/**45** (X=4–BrC_6H_4,Y=Br,Z=^{t}Bu)	H_2O_2	85	90	176
		VO(acac)$_2$/**49** (X_1=I, X_2, X_3=H, R=^{t}Bu)	H_2O_2	61	99	180
8		VO(acac)$_2$/**43**	H_2O_2	79	95.5	173
		VO(acac)$_2$/**46**	H_2O_2	95	76	177
		VO(acac)$_2$/**49** (X_1,X_2=Br, X_3=H, R=^{t}Bu)	H_2O_2	65	97	180
		VO(acac)$_2$/**50**	H_2O_2	81	>99	181
		VO(acac)$_2$/**53** (X=I, R=^{i}Pr)	H_2O_2	82	92	184
9		VO(acac)$_2$/**43**	H_2O_2	51	91	175
		VO(acac)$_2$/**51** (R_1=C(Et_2)OMe, R_2=O_2C^tBu)	H_2O_2	80	96	183
		VO(acac)$_2$/**59** (X=H, Y,Y=–C_2H_4–)	H_2O_2	78	72	194
10		VO(acac)$_2$/**43**	H_2O_2	41	>99	175
11		VO(acac)$_2$/**59** (X=H, Y,Y=–C_2H_4–)	H_2O_2	83	92	194

[a] Monoxide yield.

[b] ee of monosulfoxide reported.

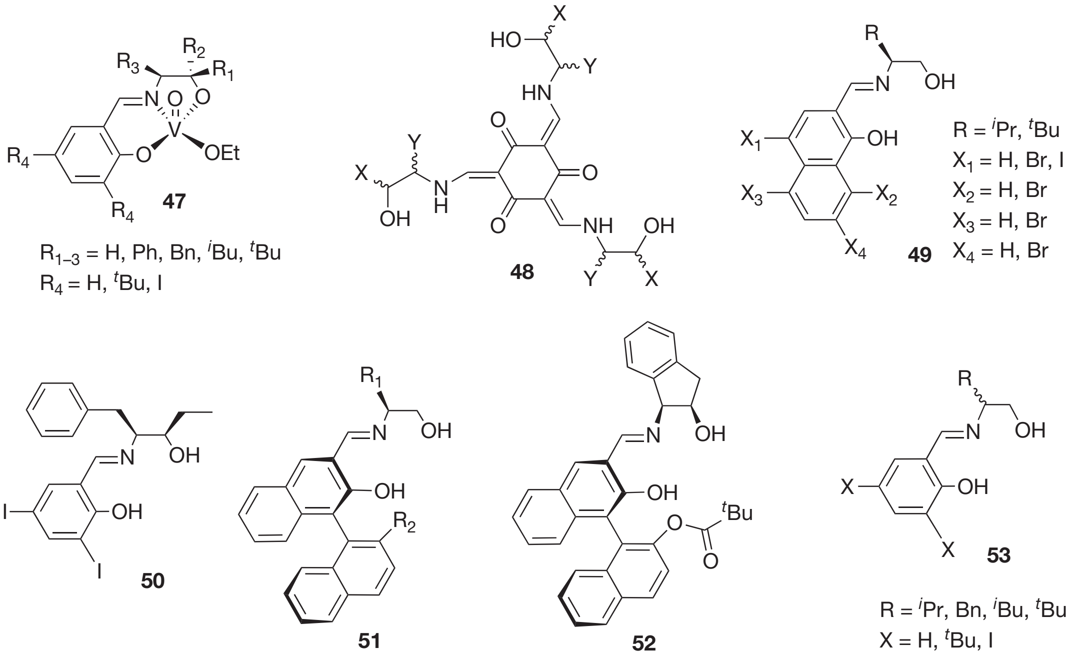
[c] Yield of (*R*,*R*)-bis-sulfoxide.

[d] Sulfide conversion reported.

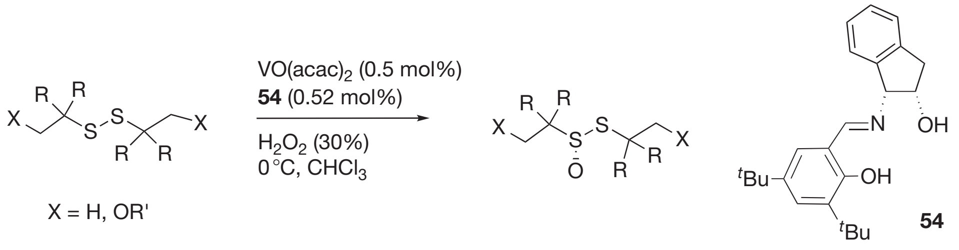
(at the expense of lowered yield: 61%). Apparently, the effect of kinetic resolution of sulfoxides is more pronounced upon the addition of toluene. Pati and coworkers developed a trimeric version of Bolm's system, using 0.6 mol% of ligands of the type **48** and 1.0 mol% of VO(acac)$_2$ as the catalyst, to yield sulfoxides in up to 89% ee.[178]

Very recently, Wang and coworkers presented a new library of tridentate ligands derived from β-amino alcohols and bromo- and iodo-functionalized hydroxynaphthaldehydes **49** that were reported to be efficient chirality carriers for the vanadium-catalyzed oxidation of methyl phenyl sulfide (67–82% ee in CH_2Cl_2 and up to 94% ee in toluene) and its *p*-substituted derivatives (95–97% ee), as well as methyl-2-naphthyl sulfide (98–99% ee).[179] The reactions required 1 mol% of vanadium and could be successfully carried out in toluene rather than methylene chloride. The authors claimed the results to have industrial potential; however, the observed yields were rather low (51–67%), apparently due to a pronounced kinetic resolution of sulfoxides, which was facilitated in toluene.[179]

Li and coworkers introduced the second stereogenic center into the aminoalcohol moiety of the tridentate Schiff bases.[180] One of the resulting ligands **50** (Scheme 15) appeared to be a



Scheme 15



Scheme 16

very efficient chiral inducer for the vanadium-catalyzed sulfoxidations with H_2O_2. Particularly, aryl methyl sulfides were oxidized in 80–85% yield and in 99% ee, and, also, bulkier substrates (ethyl 2-naphthyl sulfide, 2-naphthyl propyl sulfide, butyl 2-naphthyl sulfide) were oxidized in 80–81% yield and 98–99% ee.[180] The reactions were performed in $CHCl_3$ at 0 °C, and took 48 h to complete. The high ee's were achieved in a tandem enantioselective oxidation/kinetic resolution process (which required the use of 1.35 equiv. of H_2O_2). The ligand–solvent–temperature combination found by the authors is one of the best ever reported for the asymmetric oxidation of alkyl aryl sulfides with H_2O_2; it is challenging as to whether these conditions could be applied for the practical syntheses of biologically active chiral sulfoxides or their precursors.

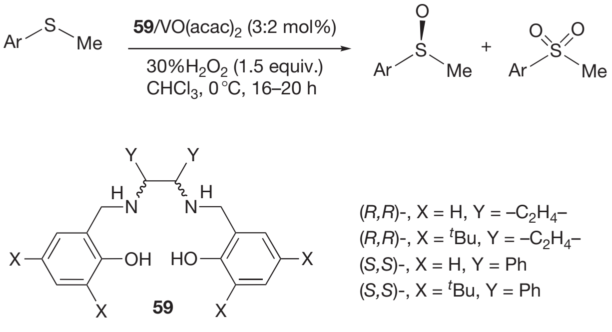
Ahn and coworkers focused on the synthesis of sterically hindered Schiff base ligands of the type **51** possessing additional elements of chirality.[181,182] They found that it is the chirality of the imine moiety that determines the absolute configuration of the sulfoxide. The ligand **51** (where $R_1={}^t\mathrm{Bu}$, $R_2=O_2C{}^t\mathrm{Bu}$) showed high enantioselectivities in the oxidation of thioanisole (86% ee at 90% yield) and up to 98–99% ee in the oxidation of benzyl phenyl sulfide and benzyl *p*-bromophenyl sulfide.[181] High yield and ee (80% and 96%, respectively) were achieved in the oxidation of bulky benzyl phenyl sulfide in CH_2Cl_2 at 0 °C using ligand **51** ($R_1=C(Et_2)OMe$, $R_2=O_2C{}^t\mathrm{Bu}$).[182] Ligand **52** exhibited a similar catalytic performance.[182] Gao and coworkers prepared a series of ligands **53** featuring different alkyl substituents at the asymmetric carbon.[183] The authors found that valinol-derived ligands ($R={}^i\mathrm{Pr}$) demonstrated a better performance (*p*-bromophenyl methyl sulfoxide was obtained in 82% yield with 92% ee).

Khiar and coworkers aimed at the monooxidation of disulfides to enantiomerically pure thiosulfinates (Scheme 16).[184] The best vanadium catalyst ($VO(acac)_2$/**54**) catalyzed the oxidation of *t*-butyl disulfide in up to 85% ee, which was, yet, inferior to the original Ellman method[167] and to the results obtained with organocatalysts and oxone.[184] A number of Schiff base ligands featuring carbohydrate-derived chiral diamine moieties were tested in asymmetric sulfoxidations and exhibited generally low ee's (0–45% ee, and 60% ee in one case).[185,186] Volcho and coworkers synthesized several tridentate Schiff base ligands by the condensation of various salicylaldehydes with chiral aminoalcohols derived from α-pinenes and 3-carene; however, the enantioselectivities reported for the oxidation of methyl phenyl sulfide were rather low (1–32% ee).[187,188]

Several groups reported attempts to immobilize vanadium–Schiff base catalysts. Jackson and coworkers screened 72 chiral ligands fixed on Wang resin, but, even with the best ligand **55** (Scheme 17), they could oxidize methyl phenyl sulfide with only 23% ee.[189] Anson and Jackson screened a library of 29 Schiff bases of the type **56** supported on Merrifield resin; however, the enantioselectivity in the oxidation of methyl phenyl sulfide with H_2O_2 was low (4–21% ee, with the best chiral ligand featuring *tert*-leucinol moiety R*).[170] Maeda and coworkers immobilized several oxovanadium(IV) Schiff base complexes of the type **57** on Merrifield resin that catalyzed the oxidation of thioanisole with *tert*-butylhydroperoxide in high yield (90%) and moderate ee (up to 40%).[190] Barbarini and coworkers attached a series of Schiff base ligands of the type **58** to polystyrene or polyacrylate support; however, the oxidation of alkyl aryl sulfides showed poorer results compared to their homogeneous counterparts (61% ee for methyl phenyl sulfide).[191]

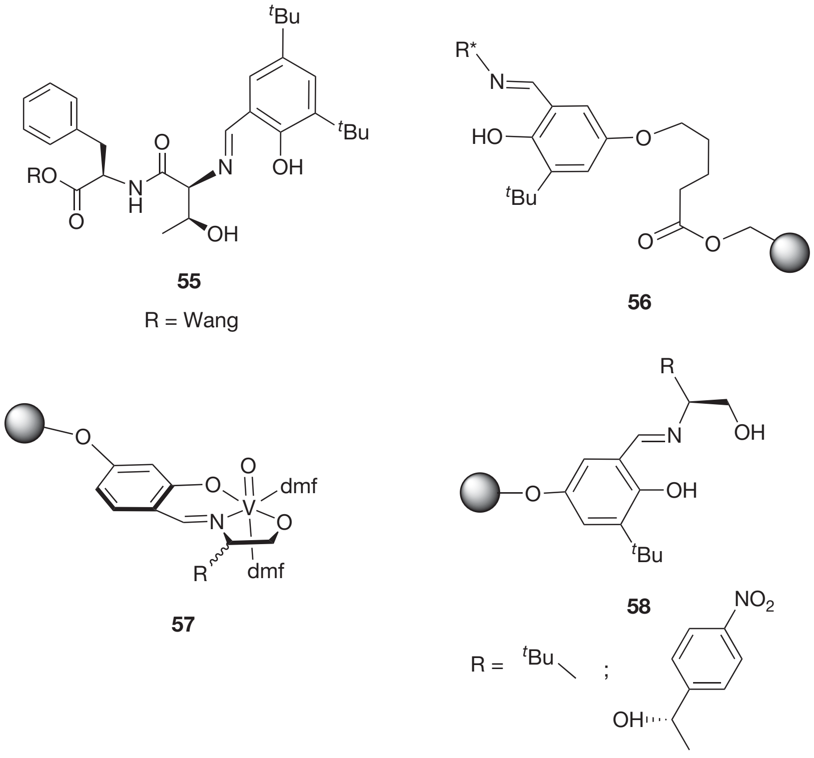
There have been some attempts to apply vanadium–tridentate Schiff base catalyst systems for the enantioselective syntheses of biologically active sulfoxides.[145,192] Overall, vanadium–tridentate Schiff base catalyst systems have high potential. In some cases, they demonstrate even better results than the Kagan–Modena systems (e.g., for 2-aryl-1,3-dithianes oxidation, disulfides oxidation). Other advantages of such systems are high efficiency and activity, ease of handling (open vessels, usually room temperature, no moisture control required), and the use of cheap and safe oxidant. Practical applications of such types of systems are foreseen.

Other vanadium-based systems are rather scanty. In 2004, Zhu and coworkers examined chiral salan (tetrahydrosalen)-type ligands as chirality sources in vanadium-catalyzed asymmetric sulfoxidations with H_2O_2, reporting ee's from 5% to 95% for the oxidation of aryl methyl sulfides.[193] The best results were achieved with ligand **59** (X=H, Y,Y=–C_2H_4–) (Scheme 18), which was particularly suitable for the oxidation of aryl methyl sulfides (Table 5). The authors did not observe a significant effect of kinetic resolution on the sulfoxide ee under the experimental conditions applied. We should note, however, that the encouraging results of Zhu and coworkers were not reproduced by others.[194] Correia and Pessoa with coworkers isolated and characterized several $V^{IV}O$(salan) and $V^{IV}O$(salen) complexes, which were further examined as precatalysts for the enantioselective oxidation of methyl phenyl sulfide with H_2O_2.[195] The enantioselectivities reported by the authors varied from 3% to 47% ee (higher for vanadium–salan and lower for vanadium–salen complexes). Further studies are needed in order to analyze the scope of vanadium–salan-catalyzed sulfoxidations with H_2O_2.



(*R*,*R*)-, X = H, Y = –C_2H_4–
(*R*,*R*)-, X = ^{t}Bu, Y = –C_2H_4–
(*S*,*S*)-, X = H, Y = Ph
(*S*,*S*)-, X = ^{t}Bu, Y = Ph

Scheme 18



Scheme 17

6.22.3.2 Titanium Systems

Titanium is probably the most important metal in asymmetric sulfoxidations. The majority of practical applications are based on Kagan–Modena-type systems that use alkyl hydroperoxides as oxidants.[153–155] In contrast, successful titanium-mediated oxidations with H_2O_2 had been relatively rare until the 2000s. So far, all titanium/H_2O_2 catalyst systems reported are based on titanium complexes with chiral Schiff bases and related ligands.

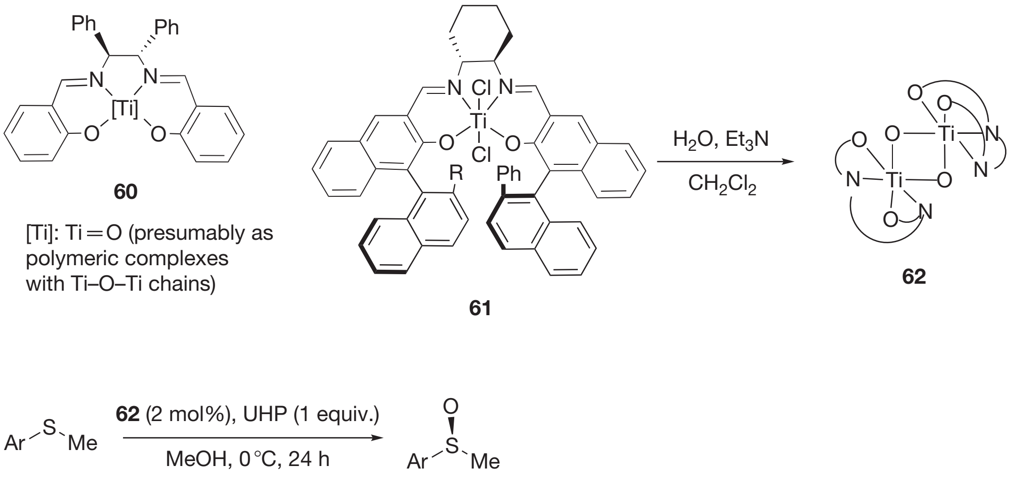
Apparently, the earliest example was the titanium(IV)-Schiff base catalyst **60** reported by Pasini and coworkers in 1986 (Scheme 19).[196] Catalyst **60** demonstrated excellent turnover numbers (1000–1500) in the oxidation of methyl phenyl sulfide by H_2O_2 in aqueous methanol or dichloromethane, but the enantioselectivities were rather low (<20% ee). The authors' suggestion was that, instead of the formation of active peroxotitanium species, sulfide coordination precedes the attack of hydrogen peroxide.

Much later, Katsuki tested the mononuclear 'second-generation' titanium–salen complex **61** containing additional elements of (axial) chirality (Scheme 19) as a catalyst for the oxidation of methyl phenyl sulfide with aqueous hydrogen peroxide, and found only poor enantioselectivity.[197] Surprisingly, when **61** was converted to the corresponding di-μ-oxido dinuclear titanium complex **62**, the latter (used in 2 mol%) appeared to be a very active and enantioselective catalyst of alkyl aryl sulfides oxidation with H_2O_2 or UHP (which gave even better results) in methanolic solution (Table 6). In a subsequent paper, the authors discussed the possible reaction mechanism and proposed the mononuclear titanium peroxo complex to be the likely oxidizing species.[198] Later, the system **62**/UHP was applied to the asymmetric oxidation of cyclic dithioacetals (with ee's of the resulting mono-sulfoxides ranging from 39% to 99%).[199]

In 2001, Jackson and coworkers explored the oxidation of several alkyl aryl sulfides with H_2O_2 over solid catalysts formed upon the treatment of Wang-supported Schiff base ligand **55**.[189] Moderate enantioselectivities (45–72% ee) have been reported for the reaction in CH_2Cl_2 upon the use of 1.5 mol% of the solid catalyst and 1.1 equiv. of H_2O_2. In 2007, Bryliakov and Talsi published a new family of titanium(IV) complexes with *N*-salicylidene-L-amino alcohols **63** and **64** capable of asymmetric oxidation of prochiral sulfides with H_2O_2 (Scheme 20).[200,201] The sulfoxidation reactions proceeded with high selectivity and conversion levels, but with moderate enantioselectivity (Table 6; the maximum ee of 65% was achieved for the oxidation of benzyl phenyl sulfide over a ligand with R=^{i}Pr, X, Y=cumyl, see Table 6, Bryliakov[201]). Based on NMR measurements, the active-site precursors were concluded to be mononuclear titanium species containing one chiral ligand per titanium center. The effect of kinetic resolution was found to be negligible.[200] Titanium–tridentate Schiff base systems appeared to be more active than analogous vanadium and iron-based systems: oxidations were successfully performed within hours at catalyst and substrate concentrations one order of magnitude lower than in Fe and V systems. As distinct from vanadium(V) systems, the replacement of the ^{t}Bu substituent in the amine moiety with ^{i}Pr led to higher ee's.

Somanathan and coworkers also examined a series of chiral β-aminoalcohol-derived Schiff bases of the type **65** in vanadium- and titanium-catalyzed asymmetric oxidation of methyl phenyl sulfide with H_2O_2.[168] Despite the existence of two asymmetric centers in the aminoalcohol moiety, the ee's were moderate (35–64%), with titanium catalysts demonstrating enantioselectivities higher than their vanadium counterparts. Very recently, Wang and Sun with coworkers prepared a series of dicumenyl-substituted aminoalcohol-derived Schiff bases **66** and tested them in titanium-catalyzed oxidations of aryl methyl sulfides.[202] From a series of catalytic experiments, ligand **66** with R=^{t}Bu emerged as the most efficient chiral inducer, yielding methyl phenyl sulfoxide in 89% yield and 73% ee. Also, the effect of solvents was extensively studied, revealing CH_2Cl_2 as the most suitable in terms of enantioselectivity.

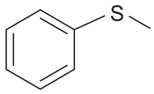
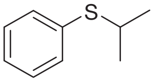
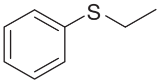
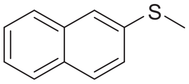
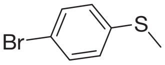
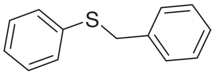
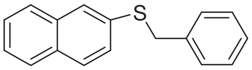
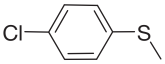
Titanium–salan complexes constitute another new but very challenging class of sulfoxidation catalysts with H_2O_2. Inspired by the titanium–salan-catalyzed epoxidations proposed by Katsuki and coworkers,[112–114] Bryliakov and Talsi examined a



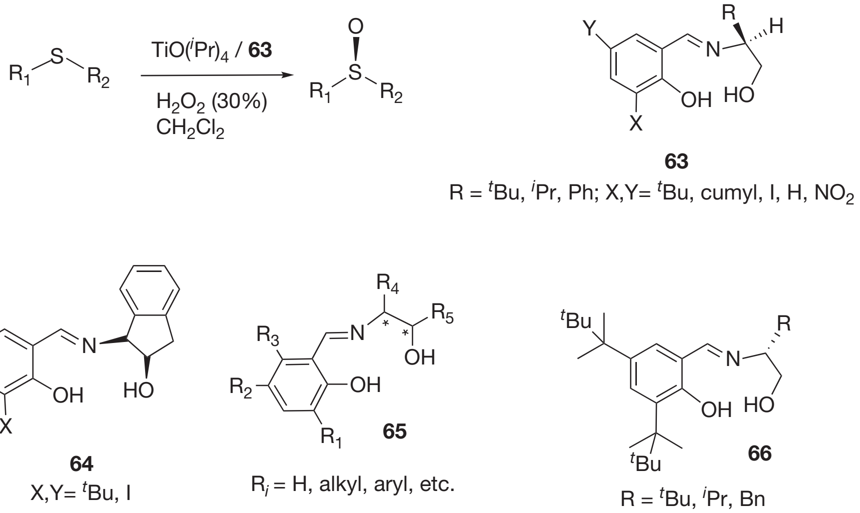
[Ti]: Ti=O (presumably as polymeric complexes with Ti–O–Ti chains)

Scheme 19

Table 6 Asymmetric sulfoxidations with H_2O_2 catalyzed by titanium complexes

N	*Substrate*	*Catalyst*	*Oxidant*	*Sulfoxide (%)*	*ee (%)*	*References*
1		Ti(O^{i}Pr)$_4$/**55** Ti(O^{i}Pr)$_4$/**66** (R=^{t}Bu) **68** (R_1=C_2H_4, R_2,R_3,R_4=H, Y=CH)	H_2O_2 H_2O_2 H_2O_2	100[a] 89 97	64 73 51	190 203 206
2		**67** (*Z*,*Z*=C_2H_4, X=Ph, Y=H)	H_2O_2	53	73	205
3		**62** **55**/Ti(O^{i}Pr)$_4$	UHP[b] H_2O_2	91 96	93 64	198 190
4		**55**/Ti(O^{i}Pr)$_4$	H_2O_2	87	72	190
5		**62** Ti(O^{i}Pr)$_4$/**63** (R=^{i}Pr, X,Y=^{t}Bu) Ti(O^{i}Pr)$_4$/**66** (R=^{t}Bu)	UHP H_2O_2 H_2O_2	93 82 84	96 42 54	198 201 203
6		**63**/Ti(O^{i}Pr)$_4$ (R=^{i}Pr, X,Y=cumyl) **67** (Z,Z=C_2H_4, X=Ph, Y=H)	H_2O_2 H_2O_2	85 73	65 98.5	202 205
7		**67** (Z,Z=C_2H_4, X=Ph, Y=H)	H_2O_2	78.5	96.5	205
8		**62** **55**/Ti(O^{i}Pr)$_4$	UHP H_2O_2	88 90[c]	99 58	198 190

[a] Conversion reported.
[b] Urea hydroperoxide.
[c] Sulfide conversion reported.



63
R = ^{t}Bu, ^{i}Pr, Ph; X,Y= ^{t}Bu, cumyl, I, H, NO_2

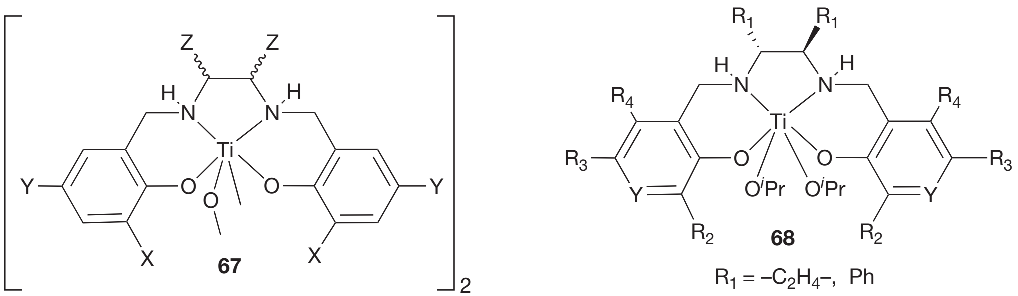
64
X,Y= ^{t}Bu, I

65
R_i = H, alkyl, aryl, etc.

66
R = ^{t}Bu, ^{i}Pr, Bn

Scheme 20

series of titanium–salan complexes of the type **67** as catalysts for the enantioselective oxidation of prochiral sulfides with H_2O_2 (Scheme 21).[203] Moderate to good enantiomeric excess values (up to >98.5% ee) were achieved in a tandem stereoconvergent asymmetric oxidation/kinetic resolution process, with the catalyst performing over 500 turnovers with no loss of stereoselectivity. Later, the oxidation of bulky (mainly substituted aryl benzyl) sulfides was studied in more detail.[204] The role of kinetic resolution was found to be crucial for the high optical purity of sulfoxide, so that the ee was in the range of 85–90% at oxidant/substrate ratios of <1.0 and increased to 95–98.5% at ratios of 1.2–1.6. A proper adjustment of experimental conditions allowed reasonably high yield of sulfoxides (75–87%) and good ee's at the same time.[204]



Z,Z = $-C_2H_4-$, Ph
X = H, Ph, ^{t}Bu, Me
Y = H, Me, ^{t}Bu, Br, NO_2

$R_1 = -C_2H_4-$, Ph
R_2 = H, Me, OMe
R_3 = H, OMe
R_4 = H, CH_2OH
Y = CH,N

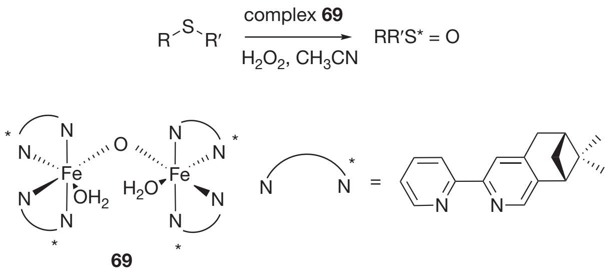
Scheme 21

In 2010, Pessoa and Correia with coworkers presented several titanium–salan complexes **68** featuring chiral (*R*,*R*)-1,2-cyclohexanediamine or 1,2-diphenylethylenediamine moieties; one of them crystallized in a tetranuclear μ-oxido-bridged structure.[205] Low to moderate enantioselectivities (up to 51% ee) have been reported for the oxidation of methyl phenyl sulfide with hydrogen peroxide, the sulfoxide yields ranging from 16% to 71%. Nevertheless, due to the encouragingly high enantioselectivities achieved for the oxidation of bulky thioethers, titanium–salan catalyst systems may find use in the practical oxidation of bulky sulfide precursors of biologically active chiral sulfoxides.

6.22.3.3 Iron Systems

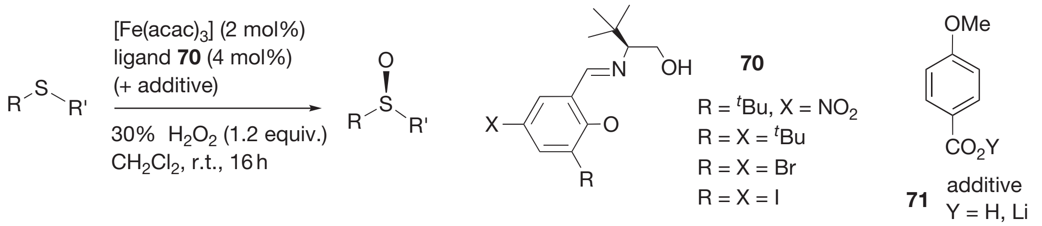
In 1997, Fontecave and coworkers published a model dinuclear iron-based catalyst system for the enantioselective oxidation of sulfides with H_2O_2. In particular, nonheme dinuclear iron(III) complex **69** (Scheme 22) afforded *p*-bromophenyl methyl sulfoxide in 40% ee (and 90% yield) in the oxidation of *p*-bromophenyl methyl sulfide (we note that the system was tested at the iron:substrate:oxidant ratio of 1:600:10).[206] The active species was concluded to be the peroxo adduct of **69**, and the reaction proceeded through the nucleophilic attack of the sulfide to the peroxoiron intermediate.[207] A possible explanation for the synergistic effect of two iron sites was given in a subsequent mechanistic study in terms of peroxide coordination to one iron site, and the sulfide coordinated to the second.[208]

In 2003, Bolm and Legros proposed a new iron-based catalyst system which used β-aminoalcohol-derived tridentate Schiff base ligands **70** similar to those previously used for vanadium-catalyzed sulfoxidations,[157–159] and iron(III) acetylacetonate as the metal source (Scheme 23).[209] Despite the generally low yields of alkyl aryl sulfoxides (15–44%), the system showed moderate to good enantioselectivities (13–90% ee) (Table 7).[209] Later, the catalyst was improved significantly by the introduction of special additives (substituted benzoic acids or their lithium salts: compound **71** was the additive of choice). The addition of 0.5 equiv. (with respect to iron) of the additive improved both the chemical yields and ee's (up to 95–96%) (Table 7).[210] The mechanistic rationale for the use of 0.5 equiv. of the additive is not entirely clear; the authors supposed that monocarboxylate-bridged diiron(III) complexes could be involved.[210] A broader range of additives was considered in a conclusive work.[211] No effect of kinetic resolution on the sulfoxidation enantioselectivity was observed, and the possible participation of more than one chiral ligand in the stereochemistry-determining step was supposed based on the nonlinear dependence of the sulfoxide ee on the ligand ee.[211] It is worth noting that the iron system described by Bolm and Legros had been used for the synthesis of sulindac **57** (sulfoxidation was performed in up to 92% ee and 71% yield).[212]



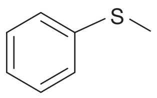
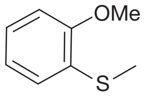
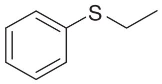
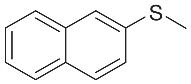
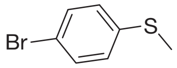
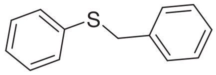
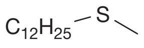
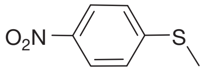
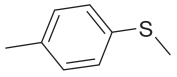
Scheme 22

Katsuki and Egami reported a series of iron(III)–salan complexes **72** (Scheme 24) that efficiently catalyzed the oxidation of several thioethers to sulfoxides with H_2O_2, in generally high yields (76–99%) and ee's (81–96%).[213] Remarkably, the oxidations were successfully performed in water as a solvent. One of the catalysts **72** ((a*R*,*S*), R=Me) showed the best results (Table 7). In most cases, significant amounts of sulfone (7–24%) formed; the presence of *o*-substituent in the sulfide aryl ring effectively suppressed overoxidation. In a subsequent publication, the authors broadened the scope of the oxidation and optimized the reaction conditions (by lowering the temperature and reducing the catalyst loading to 0.2 mol%).[214] More recently, Yang and coworkers encapsulated a chiral Fe(salan) complex **72** in the nanocages of modified mesoporous silicas[215]; the authors reported that the heterogeneous catalyst demonstrated higher turnover numbers than that of the homogeneous catalyst. A series of aryl methyl sulfides were oxidized to sulfoxides with high yields and good selectivities, but the ee's were significantly lower than those of the homogeneous system (Table 7).



Scheme 23

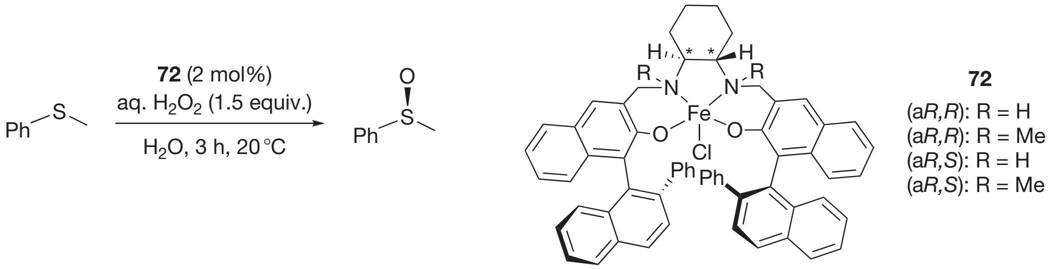
Table 7 Asymmetric sulfoxidations with H_2O_2 catalyzed by iron complexes

N	*Substrate*	*Catalyst*	*Oxidant*	*Additive*	*Sulfoxide (%)*	*ee (%)*	*References*
1		Fe(acac)$_3$/**70** (R,X=I) Fe(acac)$_3$/**70** (R,X=I) **72** ((a*R*,*S*), R=Me) **72** ((a*R*,*S*), R=Me)/S-TBNBr	H_2O_2 H_2O_2 H_2O_2 H_2O_2	– **71** (Y=Li) – –	36 63 92 81	59 90 96 73	210 211 214 216
2		**72** ((a*R*,*S*), R=Me)	H_2O_2	–	99	95	214
3		**72** ((a*R*,*S*), R=Me)	H_2O_2	–	78	81	214
4		Fe(acac)$_3$/**70** (R,X=I) Fe(acac)$_3$/**70** (R,X=I)	H_2O_2 H_2O_2	– **71** (Y=H)	44 67	70 95	210 211
5		Fe(acac)$_3$/**70** (R,X=I) Fe(acac)$_3$/**70** (R,X=I)	H_2O_2 H_2O_2	– **71** (Y=Li)	41 59	78 94	210 211
6		Fe(acac)$_3$/**70** (R,X=I) Fe(acac)$_3$/**70** (R,X=I)	H_2O_2 H_2O_2	– **71** (Y=H)	40 73	27 79	210 211
7		**72** ((a*R*,*S*), R=Me)	H_2O_2	–	82	94	214
8		Fe(acac)$_3$/**70** (R,X=I) Fe(acac)$_3$/**70** (R,X=I)	H_2O_2 H_2O_2	– **71** (Y=Li)	21 36	90 96	210 211
9		**72** ((a*R*,*S*), R=Me) **72** ((a*R*,*S*), R=Me)/S-TBNBr	H_2O_2 H_2O_2	– –	91 87	96 85	214 216

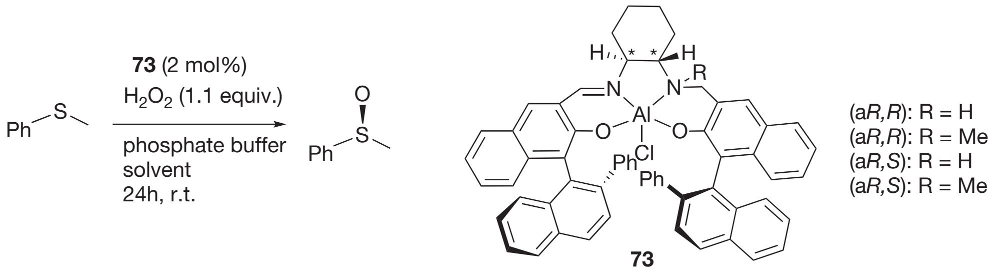
6.22.3.4 Systems Based on Other Metals

To date, other metals have been rather poorly represented in asymmetric sulfoxidations with hydrogen peroxide. Apparently, one of the most challenging catalyst systems is based on the aluminum–salalen complexes **73** proposed by Katsuki and coworkers (Scheme 25).[216] A set of aryl methyl sulfides were oxidized to sulfoxides using 2 mol% of the Al catalysts in 97–99% ee and 81–91% yield, with the yield of sulfones being rather low (1–10%); the high enantioselectivities resulted in a stereoconvergent asymmetric oxidation/kinetic resolution process. Complex **73** ((a*R*,*S*), R=Me) demonstrated the highest enantioselectivity; methanol was the best solvent in terms of both high enantioselectivity and low overoxidation to sulfone. Later, the authors found that the same system could effectively operate under solvent-free conditions and at lowered catalyst load (0.01–0.002 mol%), yielding sulfoxides in similarly high ee's (whereas the yields were lower in some cases).[217] The system also proved to be capable of efficient highly enantio- and diastereoselective asymmetric monooxidation of cyclic dithioacetals.[218,219]

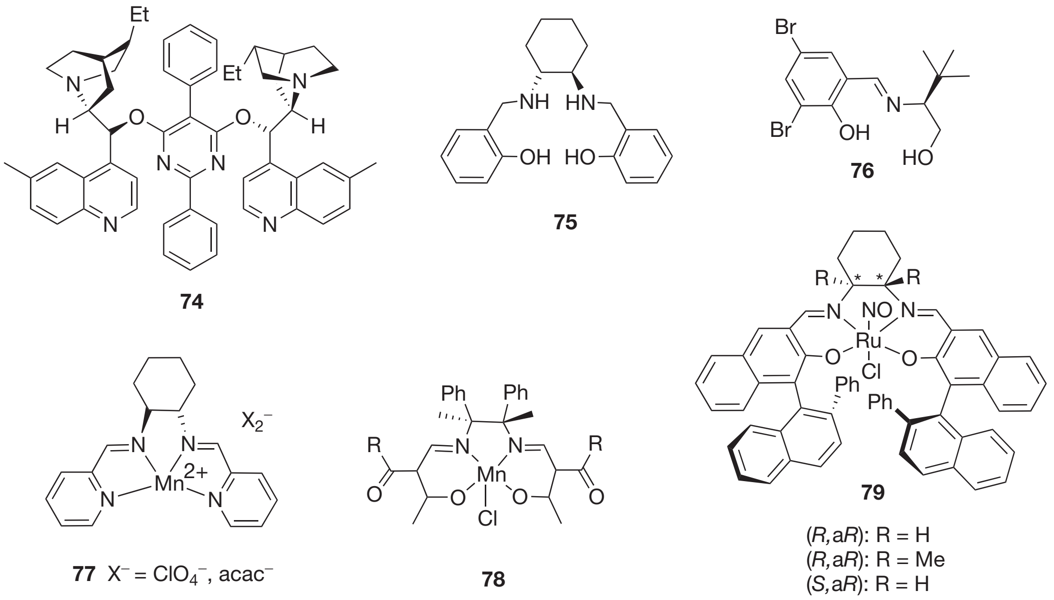
Several tungsten-based catalyst systems have been published. In 2003, Sudalai and Thakur reported a heterogeneous solid catalyst based on WO_3 and cinchona alkaloids; the system catalyzed the oxidation of several alkyl aryl sulfides with H_2O_2 in up to 90% ee.[220] The best results were obtained by using WO_3 (5 mol%) and $(DHQD)_2$-PYR **74** (10 mol%, Scheme 26). The existence of kinetic resolution of sulfoxides (resulting in higher ee's and lower yields) was observed in most cases. However, the antiulcer sulfoxide drug (*R*)-lansoprazole was prepared in good yield (84%) and ee (88%).[220] Zhang and Zhu with coworkers



Scheme 24



Scheme 25



Scheme 26

published a heterogeneous catalyst system based on WO_3/salan ligands, which, in combination with the best salan ligand **75** (5 mol% of W and 5 mol% of ligand **75**), catalyzed the oxidation of aryl methyl sulfides with H_2O_2 in 27–67% ee.[221]

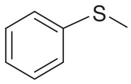
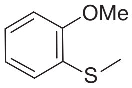
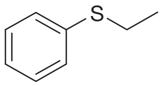
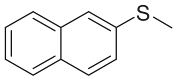
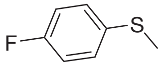
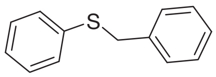
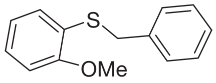
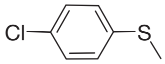
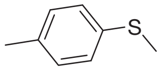
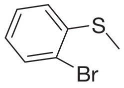
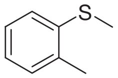
Maguire and coworkers reported on the copper–tridentate Schiff base catalyzed sulfoxidations with H_2O_2. Namely, when $Cu(acac)_2$ (2 mol%) was combined with *t*-leucinol-derived Schiff bases (4 mol%), chiral aryl benzyl sulfoxides formed in CCl_4 in 14–49% isolated yield and 13–81% ee, with the ligand **76** (Scheme 26) being the best one.[222] No formation of sulfone was detected during the oxidation. Two modified β-cyclodextrin derivatives with catechol-type ligands were prepared and tested as ligands in the Mo- and Cu-catalyzed oxidation of aromatic sulfides with H_2O_2 in water,[223] and molybdenum-based catalysts showed better results (yields 28–99%, ee's 35–65%). Some other attempts to use copper complexes as sulfoxidation catalysts led to only poor ee's.[224–226]

Fontecave and coworkers reported manganese(II)–Schiff base complexes **77** that could catalyze the oxidation of aryl methyl sulfides.[227] Enantiomeric excesses ranged from 20% to 62% ee, with the yields being rather low (8% up to 70%). However, the authors tested their system at the manganese:substrate:oxidant ratio of 1:600:10, and, thus, it remained unclear as to whether it could be used for preparative syntheses.

Transition-metal-catalyzed asymmetric sulfoxidations with dioxygen have been very rare so far. In 1995, Mukaiyama and coworkers reported a family of β-oxo aldiminatomanganese(III) complexes of the type **78**. These complexes were found to be capable of asymmetric oxidation of sulfides with molecular oxygen in the presence of coreductant pivalaldehyde.[37,38] Using 5.5 mol% of the catalyst, aryl methyl sulfoxides were formed in up to 70% ee with moderate to good yields (**Table 8**). In 2010, Katsuki and coworkers reported ruthenium–salen complexes of the type **79** capable of aerobic photopromoted enantioselective oxidation of sulfides to sulfoxides without any sacrificial reductant.[155] Using 5 mol% of complex **79** ((*R*,a*R*), R = Me), the system oxidized aryl methyl sulfides and 1,3-dithianes by air oxygen to give sulfoxides in 18–98% yield and 84–98% ee. These results can lay the foundation for future sustainable aerobic stereoselective catalyst systems.

Overall, transition-metal-catalyzed asymmetric epoxidations and, particularly, sulfoxidations with hydrogen peroxide have established their prospects and significance in the research laboratory. The progress in the catalyst systems

Table 8 Asymmetric sulfoxidations with H_2O_2 catalyzed by other complexes

N	*Substrate*	*Catalyst*	*Oxidant*	*Additive*	*Sulfoxide (%)*	*ee (%)*	*References*
1		**73** ((a*R*,*S*), R = Me)	H_2O_2	–	86	98	217
		73 ((a*R*,*S*), R = Me)[a]	H_2O_2	–	92	96	218
		WO_3/**74**	H_2O_2	–	88	59	221
		WO_3/**75**	H_2O_2	–	83	47	222
		79/((*R*,a*R*), R = Me)	O_2	H_2O	74	94	156
2		**73** ((a*R*,*S*), R = Me)	H_2O_2	–	91	99	217
		73 ((a*R*,*S*), R = Me)[b]	H_2O_2	–	88	96	218
3		**73** ((a*R*,*S*), R = Me)	H_2O_2	–	80	91	217
		73 ((a*R*,*S*), R = Me)[c]	H_2O_2	–	48	97	218
		WO_3/**74**	H_2O_2	–	82	51	221
4		**78** (R = O-cyclo-C_5H_9)	O_2/IBA[d]	–	57	51	38
5		WO_3/**75**	H_2O_2	–	65	67	222
6		WO_3/**74**	H_2O_2	–	88	61	221
		Cu(acac)$_2$/**76**	H_2O_2	[e]	57	71	223
7		Cu(acac)$_2$/**76**	H_2O_2	NMO[f]	57	81	223
8		**73** ((a*R*,*S*), R = Me)	H_2O_2	–	83	97	217
		73 ((a*R*,*S*), R = Me)[c]	H_2O_2	–	73	99	218
		WO_3/**75**	H_2O_2	–	70	61	222
9		**73** ((a*R*,*S*), R = Me)	H_2O_2	–	82	98	217
		73 ((a*R*,*S*), R = Me)[c]	H_2O_2	–	86	98	218
		78 (R = OEt)	O_2/IBA[d]	–	58	44	38
		79/((*R*,a*R*), R = Me)	O_2	H_2O	61	91	156
10		**78** (R = Me)	O_2/IBA[d]	–	93	70	38
11		**79**/((*R*,a*R*), R = Me)	O_2	H_2O	86	96	156

[a] Under solvent-free conditions, 0.002 mol% of the catalyst.

[b] Substrate concentration 5 M, 0.004 mol% of the catalyst.

[c] Substrate concentration 5 M, 0.01 mol% of the catalyst.

[d] Isobutyraldehyde.

[e] Ionic liquid.

[f] *N*-Methylmorpholine-*N*-oxide.

development is closely related to the understanding of the detailed reaction mechanisms, which, in turn, facilitates the prediction of catalytic activity and stimulates the rational design of new systems, and suggests new approaches to the synthesis of valued chiral organic molecules. Practical applications of sustainable asymmetric catalyst systems are foreseen.

6.22.4 Miscellaneous Catalytic Asymmetric Oxidations with H_2O_2 and O_2

In this section, some examples of asymmetric *cis*-dihydroxylations, Baeyer–Villiger oxidations, and kinetic resolution of secondary alcohols will be given.

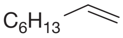
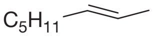
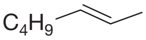
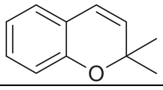
6.22.4.1 *cis*-Dihydroxylations

1,2-*cis*-Diols are common motifs in many natural products and intermediates.[228] So far, most synthetic approaches have been based on the direct osmium-catalyzed *cis*-dihydroxylation (either stoichiometric or catalytic) proposed initially by Sharpless and coworkers.[229–231] The major drawbacks of the osmium-based systems are their high toxicity and volatility (one of the possible ways to obviate that is the heterogenization of the osmium catalyst[232]), which inspired the search for catalyst systems based on other metals.

Among non-osmium-mediated *cis*-dihydroxylations with H_2O_2, iron occupies the central place, since significant efforts have been directed on modeling the reactivity of nonheme iron enzymes (and Rieske dioxygenases affording *cis*-diols in particular). However, most of the catalyst systems reported afforded racemic diols (for a recent review on iron-mediated *cis*-dihydroxylations, see Bataille and Donohoe[228]). In 2001, Que and coworkers reported that iron(II)–triflate complexes with tetradentate aminopyridine ligands **12** and **17** catalyzed the *cis*-dihydroxylation of various alkenes with 10–20 equiv. of H_2O_2 (Table 9); the ee's reported by the authors ranged from 3% to 82%.[67] We note that the diol yields were rather low: the authors reported 0.9–11.2 mmol of diol per mmol of the catalyst when loading 0.7 mmol of Fe, 700 mmol of olefin, and 10–20 (relative to Fe) equiv. of H_2O_2. Later, the authors identified another complex **80** (Scheme 27), which yielded *cis*-diols in higher ee's (up to 97%), with the yields remaining similarly low.[233] The authors ascribed the improved stereoselection of **80** to the more rigid bipyrrolidine backbone (relative to that of 1,2-diaminocyclohexane) and the *cis*-α-topology of **80** versus the *cis*-β topology of [Fe(**17**)(CF_3SO_3)$_2$].[233]

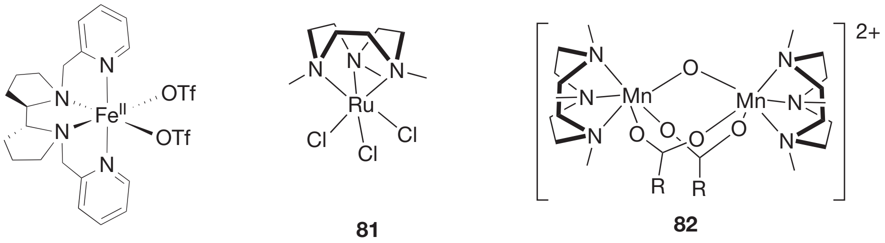
To date, no ruthenium-based catalyst systems for asymmetric *cis*-dihydroxylations with H_2O_2 have been reported. Noteworthy, in 2008, Che and coworkers reported on an environmentally friendly catalyst system based on [Ru(Me_3tacn)Cl_3] (Me_3tacn = *N*,*N*′,*N*″-trimethyl-1,4,7-triazacyclononane) complex **81** (Scheme 27); using 10 mol% of the catalyst, aqueous H_2O_2 as the oxidant, and Al_2O_3 and NaCl as the additives, the system yielded racemic *cis*-diols in good to high (59–96%) yields, starting from cyclic, aliphatic, and conjugated alkenes.[234] It is possible that a proper choice of a chiral auxiliary ligand could lead to an asymmetric version of this system. The first asymmetric manganese-based system was reported by Feringa and coworkers in 2008; they demonstrated that dinuclear manganese complexes **82** (0.4 mol%) with *N*-Boc or *N*-Ac protected chiral α-amino acids (4.0 mol%) catalyzed the asymmetric

Table 9 Asymmetric *cis*-dihydroxylations with H_2O_2 catalyzed by metal complexes

N	*Substrate*	*Catalyst*	*Oxidant*	cis-*Diol*[a]	*ee (%)*	*References*
1	 C_6H_{13}	[Fe(**17**)(CF_3SO_3)$_2$] **80**	H_2O_2 H_2O_2	8.1 6.4	60 76	67 234
2	 C_5H_{11}	[Fe(**17**)(CF_3SO_3)$_2$]	H_2O_2	7.5	82	67
3	 C_4H_9	[Fe(**17**)(CF_3SO_3)$_2$]	H_2O_2	3.8	79	234
4		**80** **82** (RCO_2OH = Ac-D-PhgOH)	H_2O_2 H_2O_2	5.2 [b]	97 54	234 236

[a] mmol of diol per mmol of catalyst.

[b] 55% conversion reported.



80
$OTf^- = CF_3SO_3^-$

81

82
RCO_2H = Boc-aminoacids

Scheme 27

cis-dihydroxylation of 2,2-dimethylchromene with 50% H_2O_2 in low to moderate optical yields (28–54% ee).[235]

6.22.4.2 Baeyer–Villiger Oxidations

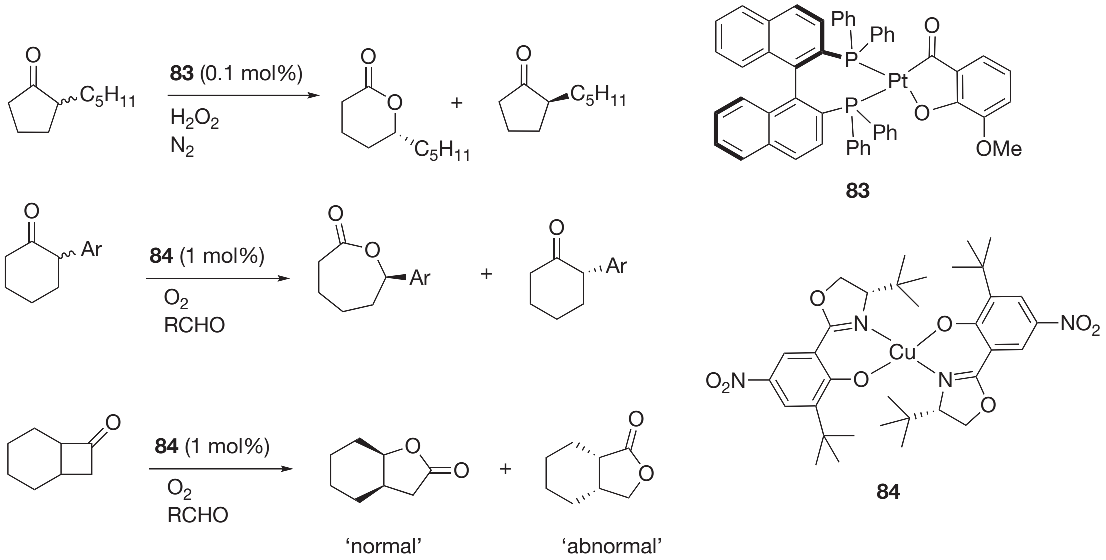
The Baeyer–Villiger oxidation converts ketones to the corresponding esters or lactones. Since its discovery in 1899,[236] the reaction has been upgraded several times, from the original use of persulfuric acid as the oxidant, toward more sustainable oxidants, such as hydrogen peroxide.[237,238] Also, catalytic (including asymmetric) versions of the Baeyer–Villiger oxidations appeared. In 1994, Strukul and coworkers found a chiral platinum catalyst **83** which was active in the oxidative kinetic resolution of the racemic mixture of cyclic ketones with aqueous hydrogen peroxide as the oxidant, yielding chiral lactones with up to 58% ee (Scheme 28), the reaction being performed in neat ketone (Scheme 28).[239,240] Platinum complex **83** and those with other chiral diphosphanes were later shown to catalyze the desymmetrization of *meso*-cyclohexanones (Table 10).

Bolm and coworkers discovered copper-catalyzed asymmetric Baeyer–Villiger oxidation of cyclic ketones with molecular oxygen in the presence of sacrificial reductant – pivalaldehyde.[241] Complex **84** afforded chiral lactones in up to 47% yield and 69% ee. The latter complex **84** catalyzed the oxidation of saturated cyclobutanones to form 'normal' and 'abnormal' lactones (Scheme 28 and Table 10), with high yield and good to high ee's,[242] while the oxidation of 3-substituted cyclobutanones proceeded with moderate enantioselectivities (up to 47% ee).[243] Later, Feng and Jiang with coworkers reported on structurally similar copper oxazoline complexes that showed rather low conversions and enantioselectivities (below 25% ee) in the oxidation of 2-phenylcyclohexanone.[244]

Katsuki and Uchida reported a series of chiral cobalt(III)–salen complexes that were found to catalyze the enantioselective Baeyer–Villiger oxidation of 3-phenylcyclobutanone with UHP (Scheme 29), yielding the corresponding lactone in moderate to good yields and moderate ee's (50–77%).[245] The authors used 5 mol% of catalyst (with **85** being the best one) and ethanol appeared to be the best solvent. Aqueous hydrogen peroxide could also be successfully used as the oxidant. The same group reported zirconium(IV)–salen catalyzed Baeyer–Villiger oxidations with UHP.[246] The results achieved with zirconium catalysts were better than with Co catalysts: zirconium complex **86**, used in 5 mol%, catalyzed the oxidation of 3-phenylcyclobutanone with up to 87% ee. Zr–salen complexes also promoted parallel kinetic resolution of racemic bicyclo [4.2.0]octan-7-one, affording 'normal' and 'abnormal' lactones in up to 85% ee and >99% ee, respectively.[246] Structurally related hafnium(IV) complexes demonstrated rather similar reactivity toward 3-phenylcyclobutanone.[247]

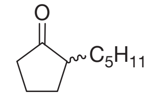
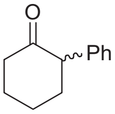
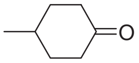
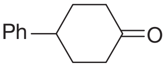
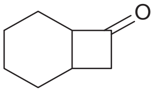
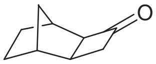
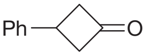
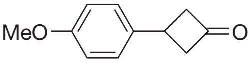
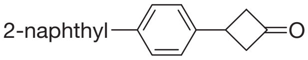
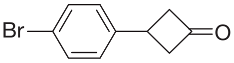
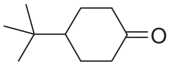
In 2003, Katsuki and coworkers reported that cationic palladium(II) complex formed *in situ* upon the interaction of $PdCl_2(PhCN)$ (5 mol%) and chiral ligand **87** (5.5 mol%), and $AgSbF_6$ (10 mol%) catalyzed the Baeyer–Villiger oxidation of 3-aryl substituted cyclobutanones with UHP, to yield the corresponding lactones in 76–94% yield and 73–83% ee (Table 10).[248] Tricyclic ketone was oxidized in >99% ee.[248] Later, Malkov and coworkers reported that terpene-derived ligands of the type **88** also served as an effective chiral inducer in Pd-catalyzed oxidation of 3-cyclobutanones, to yield lactones in good to excellent yields and moderate to good ee's (Table 10).[249]

Worth mentioning are the catalyst systems capable of operating in aqueous media. In particular, Strukul and coworkers found that chiral platinum diphosphane complexes of the type **89** catalyzed the enantioselective Baeyer–Villiger oxidation of substituted cyclobutanones and cyclohexanones in aqueous solution with H_2O_2 (high yields were only achieved with cyclobutanones, whereas the less reactive cyclohexanones demonstrated yields below 25%, generally 3–9%) (Scheme 30).[250] For the solubilization of the hydrophobic catalyst and substrate, micelles were used as surfactants and nanoscopic reactors.



Scheme 28

Table 10 Asymmetric Baeyer–Villiger oxidations with H_2O_2 and O_2

N	*Substrate*	*Catalyst*	*Oxidant*	*Additive*	*Lactone (%)*	*ee (%)*	*References*
1		**83**	H_2O_2	$HClO_4$	4	58	240
2		**84** ((a*R*,*S*), R = Me)	O_2/PIA[a]	–	47	69	242
3		**83** **89**	H_2O_2 H_2O_2	– –	10 5	53 66	241 251
4		**83** **89**	H_2O_2 H_2O_2	– –	9 7	68 79	241 251
5		**84**	O_2/PIA[a]	–	61[b]	67/92[c]	243
6		**84**	O_2/PIA[a]	–	32[b]	76/95[c]	243
7		**85** **Zr-86** **Hf-86** $PdCl_2(PhCN)$/**87** $PdCl_2(PhCN)$/**88** **89**	UHP[d] UHP[d] UHP[d] UHP[d] UHP[d] H_2O_2	– – – $AgSbF_6$ $AgSbF_6$ –	72 68 62 76 97 99	77 87 82 73 81 56	246 247 248 249 250 251
8		**85**	H_2O_2	–	75	78	246
9		$PdCl_2(PhCN)$/**87** $PdCl_2(PhCN)$/**88**	UHP[d] UHP[d]	$AgSbF_6$ $AgSbF_6$	94 83	83 71	249 250
10		$PdCl_2(PhCN)$/**88**	UHP[d]	$AgSbF_6$	95	76	250
11		**89**	H_2O_2	–	8	92	251

[a] Pivalaldehyde.
[b] Isolated yield.
[c] ee normal/ee abnormal.
[d] Urea hydroperoxide.

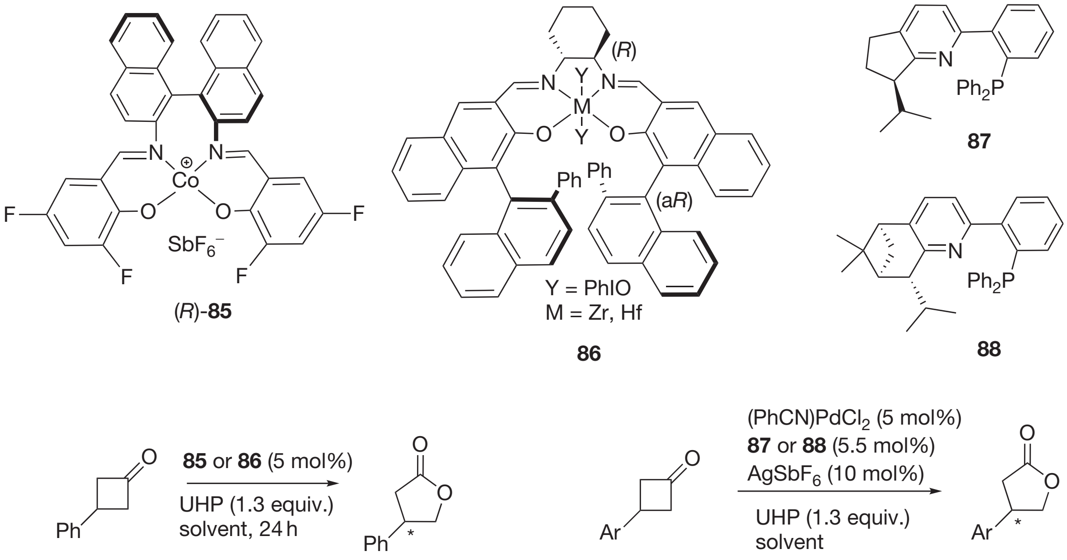
A similar approach was applied when using the cobalt–salen catalyst **90** as the catalyst in aqueous media.[251] Note that the latter catalyst was inefficient in common organic solvents. Although the yields and enantioselectivities in the oxidation of 3-substituted cyclobutanones were poor, catalyst **90**, used in 1 mol%, demonstrated moderate yields and ee's up to 90% for the oxidation of bicyclic cyclobutanones, such as *cis*-bicyclo (3.2.0)hept-2-en-6-one.[251]

Despite the substantial progress achieved in the last 15 years, examples of metal complexes catalyzed asymmetric Baeyer–Villiger oxidations remain rather scarce. In contrast, biocatalytic and organocatalytic[238,252–254] oxidations with hydrogen peroxide have made significant progress in recent years. Furthermore, most of the known organometallic catalyst systems have rather narrow scope (mainly limited to most reaction-prone substituted cyclobutanones) and cannot be applied to cycloalkanones with larger rings. Other approaches that are to be developed for the metal-catalyzed asymmetric Baeyer–Villiger oxidations could find practical applications.

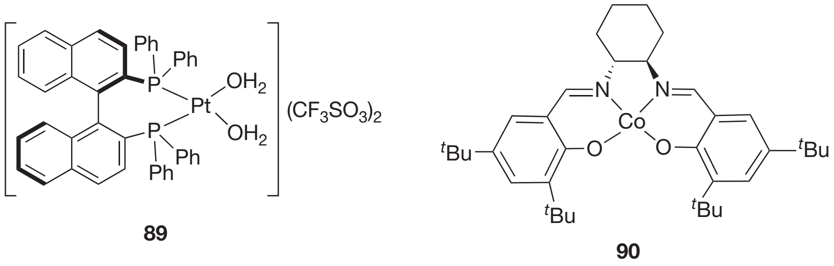
6.22.4.3 Oxidative Kinetic Resolution of Secondary Alcohols

Among other types of asymmetric oxidations, the oxidation of alcohols to the corresponding carbonyl compounds is worth mentioning. These processes are mainly divided into two classes: kinetic resolution of racemic secondary alcohols and desymmetrization of *meso*- or prochiral diols.[255] Remarkably, various catalyst systems employing molecular oxygen have appeared over the recent years.

In 2001, Sigman found that palladium complexes combined with naturally occurring amine, (−)-sparteine, catalyzed the oxidative kinetic resolution of secondary alcohols with molecular oxygen in dichloroethane.[256] A series of substituted benzyl alcohols demonstrated moderate to good k_{rel}, to recover



Scheme 29



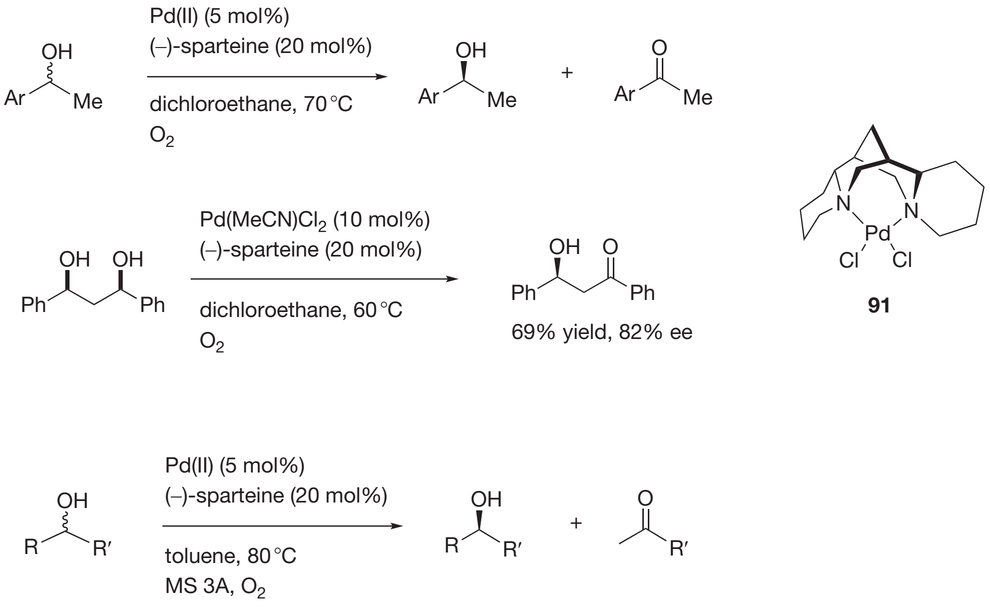
Scheme 30

enantiomerically enriched alcohols with 66–99% ee (Scheme 31). This catalyst system was also used for the oxidative desymmetrization of *meso*-1,3-diphenylpropane-1,3-diol (Scheme 31). Later, the authors discovered that the palladium(II)-(−)-sparteine complex **91** could only promote the asymmetric kinetic resolution in the presence of exogenous (−)-sparteine, thus, revealing the dual role of the latter: as a chiral ligand and as a base serving for the β-hydrogen elimination from the palladium-alkoxide intermediate.[257] Complex **91**, in the presence of (−)-sparteine, was further used in an extensive study on a broad range of alcohol substrates in the media of *t*-butanol.[258]

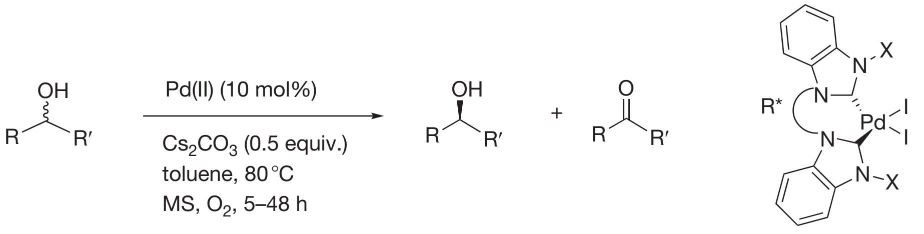
Simultaneously to Sigman, Stolz and Ferreira reported a very similar catalyst system (using toluene as a solvent and molecular sieves; see Scheme 31). They screened several racemic alcohol mixtures and reported isolated yields of enantioenriched alcohols of 29–49% (i.e., close to the theoretical yield) and ee's of 68–99%.[259] The same group reported that the addition of Cs_2CO_3/*t*-butanol accelerated the reaction,[260] so that the latter could be conducted at 60 °C (instead of 80 °C), typically with comparable selectivity. Further improvements were achieved by using 1 atm ambient air as the oxidant and chloroform as the solvent (in that case, the addition of *t*-butanol was no longer required); the process could be performed at 23 °C.[261] Note that the palladium(II)-catalyzed asymmetric oxidative kinetic resolution was utilized for the syntheses of a series of some key pharmaceuticals.[262,263]

Other chiral ligands have been tested in the palladium-catalyzed oxidative kinetic resolutions of secondary alcohols. Stolz and Trend synthesized and tested C_2-symmetric (−)-α-isosparteine and (+)-β-isosparteine that showed reactivity and enantioselection inferior to (−)-sparteine.[264] A series of sparteine-like diamines were prepared by O'Brien and coworkers, and tested as chiral auxiliaries in the palladium-catalyzed resolution of 1-indanol; the ee's were also found to be inferior to those demonstrated by (−)-sparteine.[265] Sacchetti and coworkers synthesized a set of novel chiral keto-dispidines that were tested in Pd-catalyzed oxidative kinetic resolution of 1-phenyl ethanol in toluene; the ee's were in the range of 4–42% (vs. 96% for (−)-sparteine under these conditions).[266] Shi and coworkers reported two axially chiral palladium complexes **92** as efficient catalysts (when used in 10 mol%) for the oxidation of a series of alcohols (Scheme 32). Enantiomeric excesses of 61–99% were reported at 61–75% conversions.[267,268]

In 2000, Katsuki and coworkers reported chiral ruthenium–salen complexes **79** (R=H) capable of oxidative kinetic resolution of secondary alcohols with air oxygen.[104] The reaction



Scheme 31



X = Me, Et, Bn

92a: R* = (*R*)-1,1′-binaphthalenyl

92b: R* = (*R*)-1,1′-octahydrobinaphthalenyl

Scheme 32

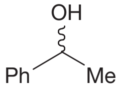
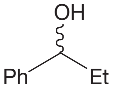
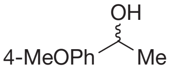
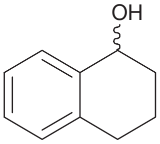
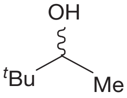
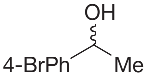
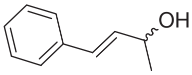
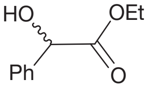
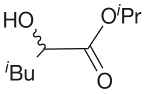
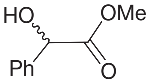
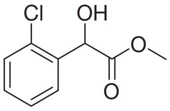
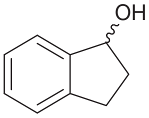
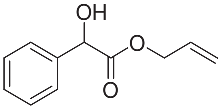
proceeded upon irradiation with visible light; 2 mol% of the ruthenium catalyst was loaded. Three different alcohols were oxidized, and enantiomeric excesses of 11% to >99.5% were reported (Table 11). Later, the performance of this catalyst system was improved by the addition of 1,3-diketones,[105] whereas catalyst **79** (R = Me) was found to catalyze the oxidative desymmetrization of 1,4-*meso*-diols.[106,107]

Toste and coworkers reported moderate to high ee's (50–99%) achieved in the vanadium-catalyzed oxidative kinetic resolution of α-hydroxy esters with molecular oxygen (Scheme 33).[269] The authors used VO(O^{i}Pr)$_3$ (5 mol%) as the metal source and L-*t*-leucinol-derived Schiff base **38** ($R_1 = R_2 = R_3 = {}^t$Bu) as the chirality source. In one case (Table 11, entry 8), a very high k_{rel} of >50 was observed.[269] One year later, Chen and coworkers reported a successful use of vanadium complexes **93** with chiral *N*-salicylidene carboxylates for the enantioselective oxidation of α-hydroxy esters (Scheme 33).[270] In 2010, Li and coworkers tested a series of vanadium(V) complexes, generated *in situ* from VO(O^{i}Pr)$_3$ and aminoalcohol-derived tridentate Schiff base ligands of the type **38** (with R_1, $R_2 = {}^t$Bu, H, I, and various R_3) in the aerobic oxidation of methyl *o*-chloromandelate.[271] Moderate to high ee's for the recovered ester were reported (17–99.7%, Table 11). Starting from tridentate Schiff base chiral ligands of the type **38**, Jones and coworkers developed polymer-supported vanadium catalysts that exhibited good to high ee's (up to 98%) for the oxidative kinetic resolution of ethyl mandelate.[272]

High ee's were reported by Ikariya and coworkers, who tested a series of chiral half-sandwich iridium, rhodium, and ruthenium complexes of the type **94–96** (10 mol%) for the kinetic resolution of secondary alcohols with air oxygen (Scheme 34).[273,274] Iridium catalysts demonstrated higher k_{rel} values compared to Rh and Ru catalysts. Sekar and Alamsetti reported the cobalt-catalyzed kinetic resolution of a series of α-hydroxy esters (Scheme 35), using molecular oxygen as the oxidant.[275] Chiral ligand **97** was identified as the most efficient of the series. Good to high ee's (78–99.9%) were achieved for a series of mandelates.

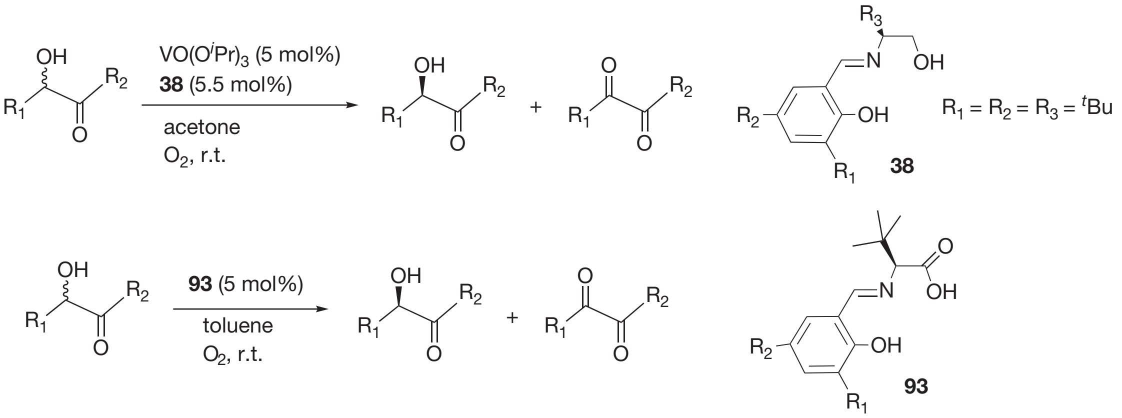
Generally, transition-metal-catalyzed asymmetric oxidations other than epoxidations and sulfoxidations are less developed and, correspondingly, less often employed.

Table 11 Oxidative kinetic resolution of racemic secondary alcohols

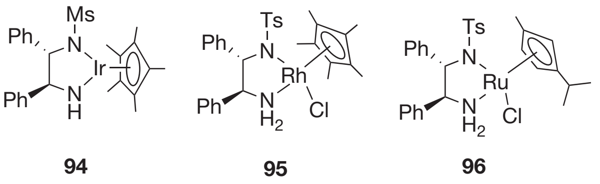
N	*Substrate*	*Catalyst*	*Oxidant*	*Additive*	*Conversion (%)*	*ee (%)*	*References*
1		Pd(II)/(−)-sparteine	O_2	–	54	87	257
		Pd(II)/(−)-sparteine	O_2	–	60	99	260
		92ª (X=Me)	O_2	Cs_2CO_3	62	87	268
		79 ((*R*,a*R*), R=H)	O_2	–	41	50	106
		79 ((*R*,a*R*), R=H)	O_2	[b]	62	97	106
		94	O_2	–	48[a]	98	274
		95	O_2	–	46[a]	93	274
		96	O_2	–	78[a]	23	274
2		Pd(II)/(−)-sparteine	O_2	–	58	89	257
		Pd(II)/(−)-sparteine	O_2	–	59	93	260
		Pd(II)/(−)-sparteine	O_2	$Cs_2CO_3/^tBuOH$	63	98	261
3		Pd(II)/(−)-sparteine	O_2	–	67	99	257
		Pd(II)/(−)-sparteine	O_2	–	67	98	260
		Pd(II)/(−)-sparteine	O_2	$Cs_2CO_3/^tBuOH$	67	99.5	261
4		Pd(II)/(−)-sparteine	O_2	–	69	99.8	260
		91/(−)-sparteine	O_2	–	62	99	259
		92b (X=Me)	O_2	Cs_2CO_3	64	>99	268
		94	O_2	–	46[a]	>99	274
5		**91**/(−)-sparteine	O_2	–	61	97	259
6		**92b** (X=Me)	O_2	Cs_2CO_3	68	93	268
7		**79** ((*R*,a*R*), R=H)	O_2	–	65	>99.5	105
8		$VO(O^iPr)_3$/**38** ($R_i=^tBu$)	O_2	–	51	99	270
9		$VO(O^iPr)_3$/**38** ($R_i=^tBu$)	O_2	–	55	98	270
10		**93** ($R_1=R_2=^tBu$)	O_2	–	54	93	271
		93 ($R_1=R_2=Ph$)	O_2	–	55	97	271
		93 ($R_1=^tBu$, $R_2=OMe$)	O_2	–	54	98	271
11		$VO(O^iPr)_3$/**38** ($R_1=R_2=^tBu$, $R_3=^iPr$)	O_2	–	62	99.7	272
12		**94**	O_2	–	50[a]	>99	274
13		$Co(OAc)_2$/**97**	O_2	TEMPO	61	99.9	276

[a] Yield of recovered alcohol.

[b] 2,2,6,6-Tetramethyl-heptane-3,5-dione.



Scheme 33



Ms = methanesulfonyl
Ts = *p*-toluenesulfonyl

Scheme 34

6.22.5 Sustainable Organocatalytic Oxidations: An Alternative?

In recent years, asymmetric organocatalysis has emerged as a new challenging branch of modern catalytic chemistry, providing a number of powerful tools for metal-free catalytic procedures.[24,277–280] The advantages of organocatalysis over the conventional metallocomplex catalysis are their easy availability from relatively cheap raw materials (from the 'chiral pool' or simple derivatives thereof), stability and nontoxicity of organocatalysts, and, in most cases, moisture and air insensitivity.[276–278] Since transition metals are not involved, organocatalytic methods seem to be especially attractive for the preparation of compounds that do not tolerate metal contamination, for example, some pharmaceuticals.[276]

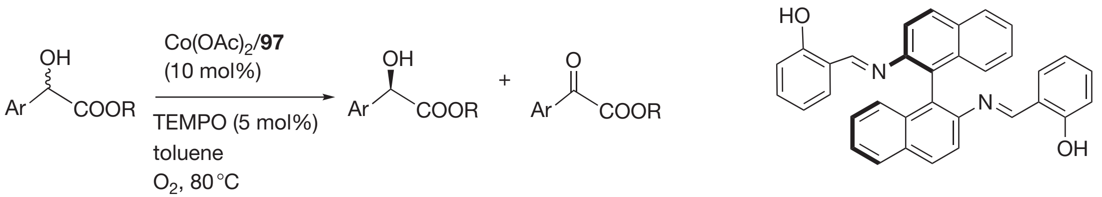
Regarding the asymmetric oxidations, various organocatalytic techniques for the epoxidation of unfunctionalized olefins as well as α,β-unsaturated ketones, oxidation of sulfides, kinetic resolution of secondary alcohols, and desymmetrization of *meso*-diols have been reported. As organocatalysts are purely organic substances, composed of carbon, hydrogen, nitrogen, sulfur, and phosphorus, a detailed review of existing organocatalytic processes is beyond the scope of this chapter. However, a brief survey of asymmetric oxidations with H_2O_2 will be given for comparison with the transition-metal-catalyzed processes discussed above.

6.22.5.1 Organocatalytic Epoxidation with H_2O_2

The majority of existing nonmetal-catalyzed olefin epoxidations exploits either chiral ketones or iminium salts as catalysts.[24] Those rely on the catalytic generation of chiral dioxiranes or oxaziridinium cations (Scheme 36), acting as the chiral oxidizing agents.[277] Until 1999, active oxidants were generated exclusively from the ketone (or iminium salt) and oxone (potassium persulfate $KHSO_5$), in the form of its triple salt with K_2SO_4 and $KHSO_4$. However, in 1999, Shi and Shu demonstrated that the use of oxone could be avoided by using the reaction of hydrogen peroxide with acetonitrile in the presence of an appropriate concentration of K_2CO_3 (to yield peroxyimidic acid) which effected the formation of the desired dioxirane, thus, opening the path for using H_2O_2 as the green terminal oxidant.[280,281] H_2O_2 provided enantioselectivities similar to those by oxone (Scheme 36). Using fructose-derived ketone **100** as the catalyst, enantioselectivities of 89–99% ee have been achieved for a wide range of *trans*- and trisubstituted alkenes (Table 12); one disadvantage is the use of 15–30 mol% of the ketone.[280,281] Later, Shi and coworkers found that oxazolidinone-containing ketones of the type **101** could also catalyze the epoxidation of *cis*- and terminal olefins by H_2O_2 in the presence of CH_3CN.[282] Crucially, *n*-butanol was identified as the optimal solvent for this reaction; H_2O_2/CH_3CN (3.0/3.8 equiv.) was employed as the terminal oxidant. Chiral catalyst **100** was also used for the enantioselective epoxidation of *cis*-1-propenylphosphonic acid, the key intermediate in the synthesis of fosfomycin (with up to 68% ee); however, a chiral amine-based catalyst demonstrated higher enantioselectivity (74% ee).[283]

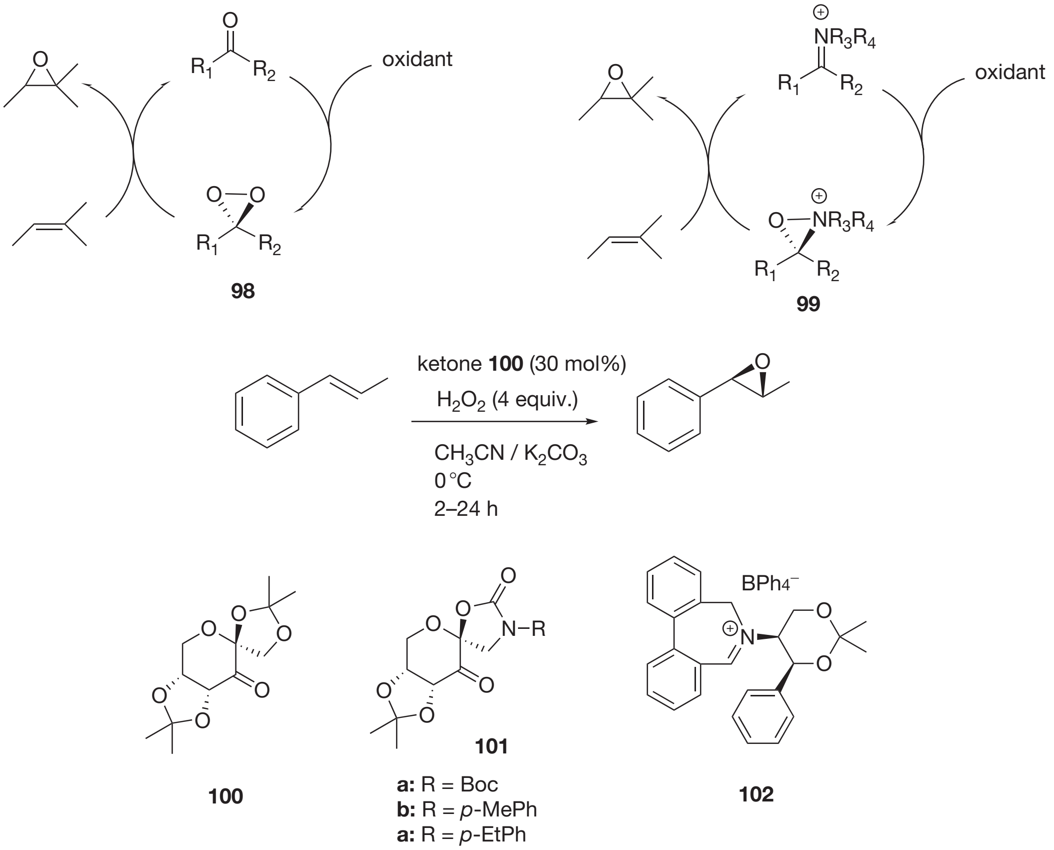
So far, there have been no examples of the iminium-catalyzed alkene epoxidations by hydrogen peroxide; apparently, the latter could not directly serve to convert the iminium cation into the corresponding oxaziridinium cation. This limitation, however, could be avoided by the use of a cocatalyst (carbonates and hydrocarbonates) which was able to transfer oxygen to the iminium salt **102** (Scheme 36).[284] Using this approach, moderate ee's were obtained in the epoxidation of 1-phenylcyclohexene (15–46% ee).

While very few examples of asymmetric organocatalytic unfunctionalized olefin epoxidations with H_2O_2 have been reported so far, synthetic methods for the epoxidation of electron-poor olefins (such as α,β-unsaturated ketones) are more elaborate and mainly based on peptide catalysts. In particular, it was in the early 1980s that Juliá and Colonna reported the epoxidation of chalcone with basic hydrogen



97

Scheme 35



98

99

100

101

a: R = Boc
b: R = *p*-MePh
a: R = *p*-EtPh

102

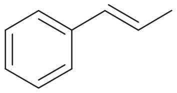
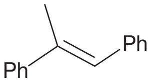
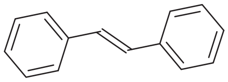
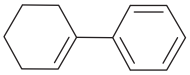
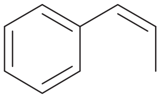
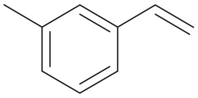
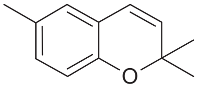
Scheme 36

peroxide in the presence of poly-L-alanine **103a** with 85% yield and 93% ee (Scheme 37).[285–288] Despite the simplicity (room temperature and ambient atmosphere) and high enantioselectivity (which, after optimization, was improved to 96% with poly-L-alanine and to 97% with poly-L-leucine **103b**[288]), high excess of the oxidant (generally more than 10 equiv.) and poor catalyst recyclability remained serious disadvantages of the reported 'synthetic enzyme' system.

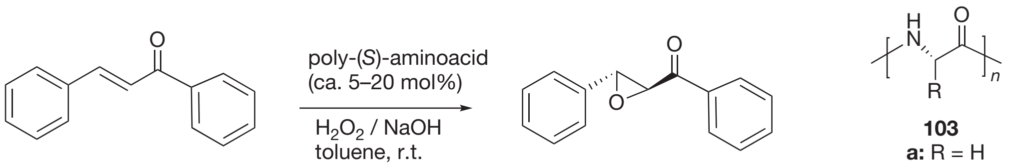
Nevertheless, the Juliá–Colonna method for the epoxidation of enones was regarded as one with high practical potential and inspired a number of works by other research groups relying on polypeptide-based epoxidation catalysts. The method was found to be applicable to the epoxidation of enynones, enediones, and unsaturated ketoesters.[289] The original three-phase (toluene–aqueous H_2O_2–solid catalyst) reaction system was replaced by a two-phase nonaqueous one (such as THF or DME), employing UHP (1.2 equiv.) as the oxygen source and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as the non-nucleophilic base.[290–295] The two-phase system demonstrated a higher reactivity, allowing dramatically shorter reaction times. The poor catalyst recyclability was overcome by the use of supported polyaminoacids.[291–293,295–298] Interestingly, the use of sodium percarbonate as the oxygen source did not require the addition of rather expensive DBU as an external base.[293,297,298]

A couple of significant improvements were introduced by Geller and coworkers, who developed a novel high-temperature polypeptide preparation procedure; thus-prepared catalysts required no preactivation and demonstrated very high activity (in the presence of tetrabutylammonium bromide as a phase-transfer agent), so that the reaction required only 7 min under the triphasic conditions, with retention of high

Table 12 Organocatalytic asymmetric epoxidations with H_2O_2

N	*Substrate*	*Catalyst*	*Oxidant*	*Additive*	*Epoxide (%)*	*ee (%)*	*References*
1		**100**	H_2O_2	K_2CO_3	93	92	282
2		**100** **101c**	H_2O_2 H_2O_2	K_2CO_3 K_2CO_3	94 78	95 88	282 283
3		**100**	H_2O_2	K_2CO_3	78	99	282
4		**100** **102**	H_2O_2 H_2O_2	K_2CO_3 $NaHCO_3$	94 100[a]	98 46	282 285
5		**101c**	H_2O_2	K_2CO_3	83	82	283
6		**101c**	H_2O_2	K_2CO_3	93	83	283
7		**101c**	H_2O_2	K_2CO_3	89	91	283

[a] Conversion reported.



103
a: R = H
b: R = ^{i}Pr

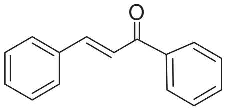
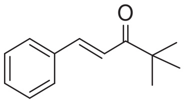
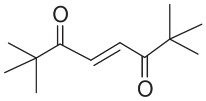
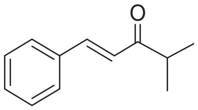
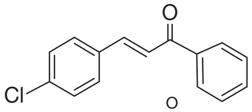
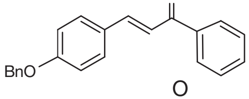
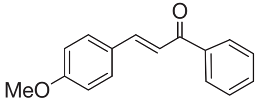
Scheme 37

enantioselectivities.[299,300] Furthermore, the authors found that the amount of oxidant (H_2O_2) could be reduced from 30 equiv. to only 1.3 equiv.,[301] and developed a scaled up procedure applicable to 100-g substrate loading.[302] More recently, Tang and coworkers reported the preparation of imidazolium-modified poly-L-leucine catalyst, which catalyzed the epoxidation with sodium percarbonate without preactivation, and could be easily recovered by simple filtration and reused seven times without loss of enantioselectivity (Table 13).[303]

Apart from the 'classical' systems based on insoluble polypeptide catalysts, 'homogeneous' versions of the Juliá–Colonna epoxidations have been reported. In particular, polyethyleneglycol- and polystyrene-bound oligo-L-leucines were prepared and showed high activities and enantioselectivities in chalcone epoxidations in the UHP/DBU processes.[304,305]

Another attractive approach to the enantioselective epoxidation of α,β-unsaturated ketones is based on phase-transfer catalysis. In 1976, Wynberg and coworkers reported the first asymmetric epoxidation of several enones in up to 25% ee using cinchona alkaloid-derived quaternary ammonium salt **104** (Scheme 38).[306] In subsequent communications, the authors reported improved enantioselectivities up to 54% ee.[307–310] Much later, Arai and coworkers screened a number of cinchona catalysts of the type **105** bearing electron-withdrawing substituents in the *p*-position of R and suggested to add inorganic base (LiOH) to the reaction mixture.[311] Substituted chalcones were reported to be epoxidized in up to 92% ee (Table 14).[311,312] Concurrently, Corey and Zhang synthesized a quaternary salt **106** that demonstrated even higher enantioselectivities, albeit at very low temperatures (−40 °C).[313] Dehmlow and coworkers demonstrated that quaternary salts of structural analogs of cinchona alkaloids of the type **107** could also efficiently catalyze the enantioselective epoxidation of 2-isopropyl-1,4-naphthoquinone, with moderate to good enantioselectivities.[314] Moderate enantioselectivities (up to 61% ee) were also reported by Gao and coworkers for the epoxidation of enones over phase-transfer catalysts prepared from cinchona alkaloids and Fréchet dendritic wedges.[315]

Table 13 Polypeptide-catalyzed asymmetric epoxidations with H_2O_2

N	*Substrate*	*Catalyst*	*Oxidant*	*Additive*	*Epoxide (%)*	*ee (%)*	*References*
1		Poly-L-alanine	H_2O_2	NaOH	85	93	286
		Poly-L-leucine	H_2O_2	NaOH	80	97	289
		Poly-L-leucine	UHP	DBU	85	>95	291
		Poly-L-leucine/CLAMPS	UHP	DBU	93	96	293
		Poly-L-leucine/CLAMPS	$Na_2CO_3 \cdot 1.5H_2O_2$	–	>99	96	294
		Poly-L-leucine	$Na_2CO_3 \cdot 1.5H_2O_2$	–	95[a]	95	298
		Poly-L-leucine/silica	$Na_2CO_3 \cdot 1.5H_2O_2$	–	94	93	299
2		Poly-L-leucine	H_2O_2	NaOH	92	>98	290
		Poly-L-leucine[b]	UHP	DBU	99[a]	97	295
3		Poly-L-leucine	H_2O_2	NaOH	>95	>95	290
4		Poly-L-leucine	H_2O_2	NaOH	60	62	291
		Poly-L-leucine/silica	UHP	DBU	78	93	292
		PLN[c]/silica	UHP	DBU	88	92	298
5		Poly-L-leucine/PSDVB[d]	H_2O_2	NaOH	98	99	297
6		Poly-L-leucine	H_2O_2	NaOH[e]	78[f]	97.3	303
7		Poly-L-leucine[g]	$Na_2CO_3 \cdot 1.5H_2O_2$	–	98	99	304

[a] Conversion reported.

[b] Diaminopropane-bound poly-L-leucine.

[c] Poly-L-*neo*-pentylglycine.

[d] Poly(styrene-*co*-divinylbenzene)-supported poly-L-leucine.

[e] With phase-transfer catalysis tetrabutylammonium bromide.

[f] Reaction performed at 100-g substrate loading.

[g] Imidazolium-modified.

An important improvement introduced by Jew and Park and coworkers consisted of the addition of a commercially available surfactant, such as Span 20 (sorbitan monolaurate), into the reaction mixture; in effect, the dimeric cinchona phase-transfer catalyst **108**, used in only 1 mol%, afforded epoxides of chalcone derivatives in very high yields and ee's (**Table 14**).[316]

Besides the cinchona alkaloid-derived phase-transfer catalysts, binol-derived quaternary ammonium salts **109** were reported to catalyze the epoxidation of chalcones with basic hydrogen peroxide, showing moderate ee's; the enantioselectivity level could be controlled by the length of the alkyl chains at the quaternary nitrogen atom.[317]

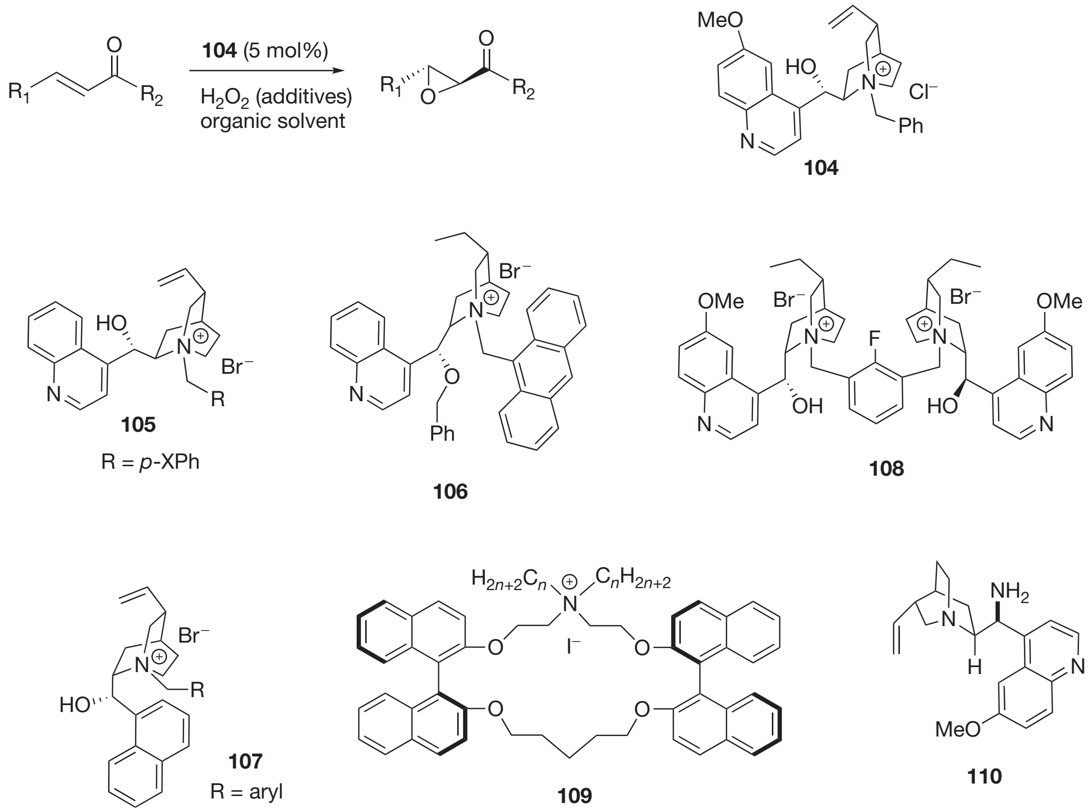
Overall, to date, the epoxidation of chalcones under phase-transfer catalytic conditions has, in most cases, been reported to be more stereoselective with sodium hypochlorite as the oxidant, with hydrogen peroxide demonstrating inferior results.[279]

In 2008, List and coworkers reported the use of cinchona alkaloid-derived amine catalysts of the type **110**, which (in the form of trichloro- or trifluoroacetic acid salt) showed high enantioselectivities (over 90% ee in two cases) in the epoxidation of simple acyclic aliphatic α,β-unsaturated ketones (**Table 14**).[318] The authors suggested a plausible catalytic cycle, including the basic hydrolysis of an intermediate peroxyhemiketal. The same group extended their studies on a series of salts of chiral amines and diamines with chiral acids, and reported the highly enantioselective epoxidation of several cyclic enones (mainly substituted cyclohexenones) with H_2O_2.[319]

A very interesting system was presented by Tanaka and Nagasawa, who prepared a guanidine–urea bifunctional organocatalyst of the type **111** (**Scheme 39**), which promoted the successful epoxidation of chalcone derivatives with basic H_2O_2 with high enantioselectivities.[320]

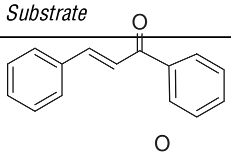
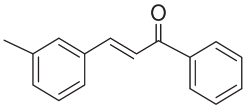
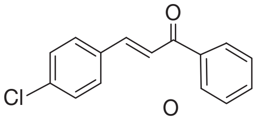
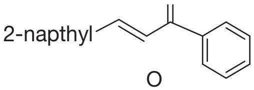
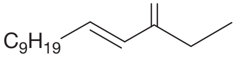
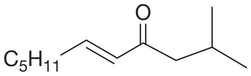
6.22.5.2 Miscellaneous Organocatalytic Oxidations with H_2O_2

To date, only two organocatalytic techniques for the enantioselective oxidation of sulfides to sulfoxides with H_2O_2 have been documented. In particular, Page and coworkers reported that



Scheme 38

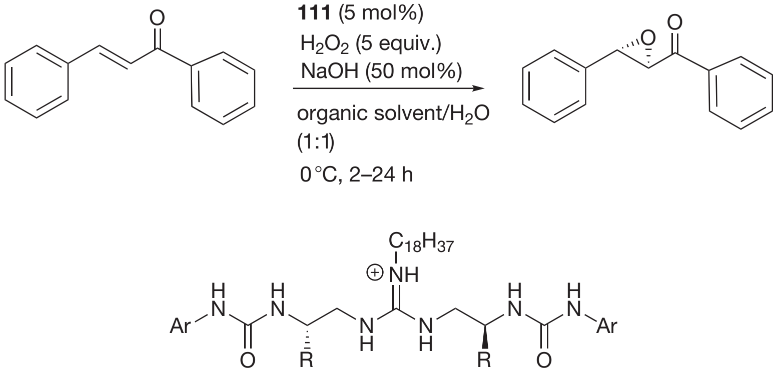
Table 14 Asymmetric epoxidations with H_2O_2 using cinchona alkaloid-derived and related catalysts

N	*Substrate*	*Catalyst*	*Oxidant*	*Additive*	*Epoxide (%)*	*ee (%)*	*References*
1		**104** **106** **108** **111** (R = Bn, Ar = 3,5-$(CF_3)_2$Ph)	H_2O_2 H_2O_2 H_2O_2 H_2O_2	LiOH KOH KOH, Span 20 NaOH	97 96 95 99	84 93 >99 94	313 314 317 321
2		**105** (R = *p*-IPh) **108**	H_2O_2 H_2O_2	LiOH KOH, Span 20	100 95	92 97	313 317
3		**106**	H_2O_2	KOH	94	92	314
4		**109** (*n* = 9) **111** (R = Bn, Ar = 3,5-$(CF_3)_2$Ph)	H_2O_2 H_2O_2	KOH NaOH	90 98	83 96	318 321
5		**110**	H_2O_2	TFA[a]	82	98	319
6		**110**	H_2O_2	TFA[a]	81	97	319

[a] Trifluoroacetic acid.

camphor-derived *N*-sulfonyl imines of the type **112** (Scheme 40) could mediate sulfoxidations with H_2O_2, but satisfactory enantioselectivities (up to 98% ee) were only achieved when they were employed in stoichiometric amounts.[326,327] Apparently, the only truly catalytic oxidation was reported by Shinkai and coworkers, who used chiral flavinium cation **113**: moderate ee's of up to 65.4% were reported, with the organocatalyst performing up to eight turnovers.[328]

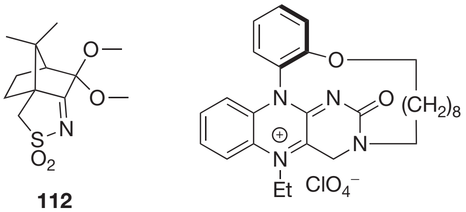
There have been several examples of asymmetric organocatalytic Baeyer–Villiger oxidations. Apparently, the first example of such a process was reported by Murahashi, who demonstrated that a planar–chiral bisflavinium perchlorate



111

R = Bn, ^{i}Pr, Me; Ar = Ph, 3,5-$(CF_3)_2$Ph, 3,5-$(F)_2$Ph

Scheme 39



112 **113**

Scheme 40

114 (**Scheme 41**, 10 mol%) catalyzed the asymmetric Baeyer–Villiger reaction of cyclobutanones with hydrogen peroxide (1.5 equiv.) to give the corresponding optically active lactones with up to 74% ee, the yields ranging from 17% to 81%.[329] Later, Ding and coworkers discovered that chiral phosphoric acids of the type **115** could catalyze the Baeyer–Villiger oxidation of 3-substituted cyclobutanones with hydrogen peroxide.[330,331] With the catalyst of choice, **115** (Ar = pyren-1-yl), the process featured high yields (65–99%) and moderate to high ee's (55–93%). Very recently, chiral phosphoric acid catalysts of the type **115** have been successfully applied to the enantioselective oxidation of several bicyclic and tricyclic cyclobutanones, to achieve excellent yields and moderate to good ee's (up to 99% in a few cases).[332] Peris and Miller used an aspartate-derived oligopeptide as the chiral acid catalyst (25 mol%) for the Baeyer–Villiger oxidation of two cyclic ketones; with 12.5 equiv. of H_2O_2, yields of 74% and 29% and enantiomeric excesses of 33% and 42% ee, respectively, were reported.[333]

Overall, the design of organocatalytic epoxidation processes with H_2O_2 remains a challenging task, as long as existing techniques could only be applied to certain classes of electron-deficient substrates (mostly *E*-enones). The search and rational design of sustainable asymmetric organocatalytic oxidations other than epoxidations is, so far, in its initial stage. There are rare and specific examples of organocatalyzed oxidations that could hardly be performed over conventional metal-based catalysts; for example, the epoxidation of α,β-unsaturated aldehydes[321–324] or trisubstituted olefins bearing carbamate functionality[325] with H_2O_2.

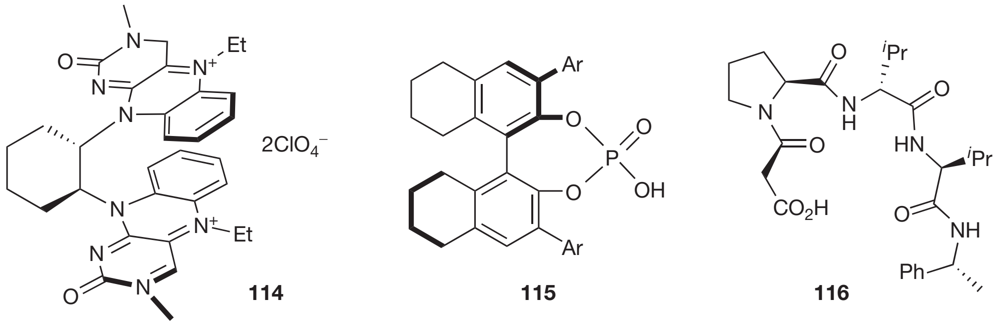
The only spectacular success of organocatalytic oxidations with H_2O_2 is the polyamino acids catalyzed Juliá–Colonna-type epoxidation of chalcones that developed greatly from the discovery of Juliá[285] to industrial applications and attracted a significant interest of key chemical producers such as Bayer AG and Degussa AG.[276,278,279]

Nevertheless, the majority of organocatalyzed asymmetric oxidation processes are just making the first step on the long path from the laboratory to practice. Further improvements are expected, mainly aimed at broadening the substrate scope, reduction in the oxidant consumption to stoichiometry or slightly higher, and increasing the catalysts' efficiencies and scalabilities.

6.22.6 Conclusion

The area of catalytic asymmetric oxidations with H_2O_2 and O_2 has expanded greatly, mainly since 1990 (see also Part 2 of the present Volume). The developments related to metal–Schiff base catalyzed oxidations are probably the most impressive to date.[26] In the last few years, other perspective asymmetric catalyst systems have been reported. Particularly, the metal–salan catalysts have demonstrated remarkable stereoselectivities and versatilities; some new metal-free organocatalytic catalysts have emerged. It is apparent, however, that existing organocatalytic systems could not yet compete with the much better developed metal-based catalysts in the arena of sustainable asymmetric oxidations: the latter demonstrate broader substrate scope, efficiencies, and (in many cases) enantioselectivities.

Chemical synthesis is currently undergoing a shift toward new products and processes, based on sustainable catalysis (refer also to Part 3 of the present Volume). It is gratifying to see that researchers are becoming keener on sustainable catalyst systems, and the number of those employing environmentally benign dioxygen and hydrogen peroxide as oxidants is steadily expanding. The present chapter was written aiming to address mainly the issue of green oxidants. Basically, asymmetric epoxidations, sulfoxidations, non-osmium-mediated



114 **115** **116**

Scheme 41

cis-dihydroxylations, Baeyer–Villiger oxidations, and kinetic resolution of secondary alcohols have been overviewed.

The chapter discussed mostly artificial catalyst systems, with regard to existing synthetic applications, while the structure of catalytically active sites and the mode of oxidant activation were, because of limited space, left beyond the consideration. On the other hand, these issues are, in many cases, still insufficiently studied or controversial. Interested readers should better address original accounts and thematic reviews. The author also avoided mentioning and discussing the so-called *biomimetic approach* (i.e., focusing on mimicking the structure and reactivity of natural enzymes' active sites by low-molecular-weight models). The latter, however, has often been exploited by the researchers working in the area of asymmetric oxidations (see van Eldik and Reedij[28] and Part 4 of the present Volume). Enzymatic oxidations are also believed to have a significant potential and bright future.

From a practical point of view, however, only a few of the catalyst systems considered demonstrate truly satisfactory results. In most cases, improvement of chemo- and enantioselectivity, as well as catalyst efficiency and recyclability, is needed before they could be put into practice. The author looks forward to witnessing future studies that will provide novel opportunities and the basis for innovative applications. For related chapters in this Comprehensive, we refer to Chapters 6.08 and 6.26.

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6.23 Cobalt(II) Carboxylate Chemistry and Catalytic Applications

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Abbreviations

2-MeIm	2-Methylimidazole
acac	2,4-Pentanedionate; acetylacetonate
ATRP	Atom transfer radical polymerization
bipy	Bipyridine
Bu	Butyl
DME	Dimethoxyethane
DMF	*N*,*N*-dimethylformamide
Et	Ethyl
H_3tmp	1,1,1-Tris(hydroxymethyl)propane, EtC$(CH_2OH)_3$
HB	3,5-Bis(6-methyl-2-pyridyl)pyrazole
Hdbm	Dibenzoylmethane
Im	Imidazole
Me	Methyl
NHPI	*N*-Hydroxyphthalimide
Ph	Phenyl
py	Pyridine
quin	Quinolone
RAFT	Reversible addition–fragmentation chain transfer
tBHP	*tert*-Butyl hydroperoxide
THF	Tetrahydrofuran
TOF	Turnover frequency
trien	Triethylenetetramine

6.23.1 Introduction

The interest in cobalt carboxylate chemistry predominantly stems from the large-scale industrial use of these complexes as oxidation catalysts. Cobalt carboxylates find widespread industrial application in the homogeneously catalyzed oxidations of hydrocarbons[1,2] and carboxylic acids[3,4] and in polymerizations.[5] The industrial use of the salts became widespread in the years immediately following World War II with the commercialization of polyester fibers (in particular, polyethylene terephthalate[6]). Increased demand for polyethylene terephthalate resulted in a concomitant increase in demand for the precursor terephthalic acid, which at that point was not a large-volume industrial chemical and an efficient large-scale synthesis was not available. A few years earlier, Du Pont had patented the cobalt-catalyzed oxidation of toluene to benzoic acid[7] and by the 1950s ICI and Du Pont had developed processes for the large-scale production of terephthalic acid via the cobalt-catalyzed oxidation of *p*-xylene. Cobalt carboxylate-catalyzed oxidations are now so widespread that cobalt carboxylates are today the most widely used homogeneous metal catalysts in industry.[8] Although the chemistries of other metal carboxylates have received considerable attention, that of the cobalt carboxylates has been infrequently reviewed.[9–12]

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In terms of citations to the beginning of 2012, the most significant complexes are those of the following ligands: acetate (6127) > stearate (1061) > 2-ethylhexanoate (1026) > octanoate (846) ≫ neodecanoate (183) > oxalate (161) ~ oleate (156) > benzoate (116) ~ decanoate (111) > laurate (86) ~ palmitate (80) ~ propionate (74) > pivalate (39) ~ abietate (37) > myristate (32) ~ hexanoate (30) > butanoate (24) ~ heptanoate (21) > *p*-toluate (16) ~ valerate (15). In terms of citations, the field is clearly dominated by complexes of four ligands: acetate, stearate, 2-ethylhexanoate, and octanoate; of which the acetate ligand is clearly preeminent. By late 2011, there had been approximately 6100 reports on cobalt acetate (43% patents and 57% journals) alone while patents account for the bulk of the citations of the other three of these ligands. Paradoxically, the reaction and structural chemistries of complexes of these ligands are among the least well understood. With regard to the other ligands (with the exception of pivalate, hexanoate, dodecanoate, tetradecanoate, and stearate), the number of patents is ≥50% of the citations. In some cases (2-ethylhexanoate, octanoate, and neodecanoate), the patent citations dramatically dominate the literature. Some materials (e.g., cobalt neodecanoate) are classified as an 'incompletely defined substance' and, in some cases, particularly the heavily patented compounds, the journal citations describe applications almost exclusively, with few or no characterization studies reported.

The patent applications can be quite varied. As a very broad generalization, acetate complexes are important as oxidation catalysts in acetic acid, the mid-carbon number complexes are employed as polymerization catalysts in hydrocarbon solvents, and while the long-chain fatty acid complexes also find application as catalysts and polymer stabilizers, they are also used as lubricants, corrosion inhibitors, and germicides, and in the paint, varnish, and color printing industry.

In this chapter, we focus on the more common structural motifs of given nuclearity for molecular homometallic near-homoleptic complexes of cobalt(II) and mixed-valence cobalt (II/III) complexes. For a more detailed treatment of the structures of cobalt(II) carboxylates, including discussions of their physical and chemical properties and the relationship of these properties to structure, refer to Volume 8 of this series. We have provided a uniform presentation of structures reproduced herein. Generally, ligand hydrogen atoms (and frequently all but the O_2C–C carbon atoms) have been omitted for clarity. The diagrams are color coded as follows: cobalt, orange; chlorine, green; fluorine, dark green; oxygen, red; nitrogen, cyan; carbon, dark blue; and hydrogen, yellow. Hydrogen bonds, where shown, are illustrated as dashed red lines. A search of the Cambridge Structural Database with an O_2C–C framework, a cobalt atom, and 'cobalt(II)' as keyword nets 6257 structures, with Co–O(carboxylate) bond lengths between 1.795 and 2.622 Å (mean 2.073 Å).

6.23.2 Structures of Cobalt(II) Carboxylate Complexes

Given the diverse range of binding modes exhibited (12 are possible[9,13–18]) by the carboxylate ligand at a metal center, it is not surprising that a correspondingly large number of structural motifs exist in the chemistry of cobalt(II) with these ligands. Within these structures there are a number of carboxylate-binding modes that predominate over the rest: unidentate coordination, *syn–syn* bidentate bridging, and monodentate bridging. Of the possible binding modes, all but two (*syn–anti* bridging and multiple bridging) have been observed structurally in cobalt carboxylate chemistry (see **Chapters 2.11**, **2.12**, and **8.05**). The geometries of cobalt(II) carboxylate complexes range from tetrahedral or octahedral mononuclear complexes to bridged dinuclear and trinuclear complexes, to distorted heterocubane structures, to linear polymeric materials, and finally to large clusters consisting of up to 32 cobalt atoms.

Herein we focus our attention on the predominant structural characteristics of single-molecule homoleptic cobalt(II) carboxylates (and in a few cases, mixed cobalt(II)/cobalt(III) species) of the various nuclearities in order to give a general overview of this extremely rich area and as a structural background for a discussion of the catalytic chemistry. Where possible, multiple examples have been given; however, an exhaustive treatment of all possible species is beyond the scope of this chapter and an extensive treatment is given in **Chapter 8.05**. We also limit the coverage to structurally characterized examples and do not cover metal–organic framework compounds.

6.23.2.1 Mononuclear Complexes

One of the earliest isolated cobalt(II) carboxylate complexes was that of the mononuclear octahedral complex $[Co(\eta^1\text{-}O_2CCH_3)_2(H_2O)_4]$, which possesses two *trans* unidentate carboxylate ligands (**Figure 1**).[19,20] A crystal of this material was reported in 1853;[21] however, its structure was only definitively solved a century later.[20] A variety of mononuclear distorted octahedral complexes can also be isolated when complexes $[Co(O_2CR)_2]$ (R = CF_3, CCl_3, CCl_2H) are reacted with monodentate (e.g., pyridine,[22] 2-methylpyridine,[22] 4-methylpyridine,[22] quinoline,[23] isoquinoline,[23] and 8-hydroxyquinoline[24]) or bidentate (e.g., *N*,*N*-dimethylethylenediamine[25] and 2,2′-bipyridine[26]) Lewis basic ligands.

The nature of the coordination mode and the coordination number can be readily manipulated in some cases. An example is provided by the imidazolium complexes $[Co(O_2CCH_3)_2(2\text{-RIm})_2]$ (R = H, Me, Et). When R = H, the resulting complex has a distorted tetrahedral geometry with the carboxylate ligands coordinated in a unidentate fashion (**Figure 2(a)**) while a distorted octahedral complex in which the carboxylate ligands are coordinated in a bidentate fashion is isolated when R = Me (**Figure 2(b)**).[27,28] A similarly distorted tetrahedral geometry was also observed in the structure of the homoleptic complex $[Ph_4As]_2[Co(O_2CCF_3)_4]$. In this complex, the cobalt atom is coordinated to four unidentate carboxylates in which the four noncoordinated oxygen atoms of the carboxylate ligand are in close proximity to the metal center.[29]

6.23.2.2 Dinuclear Complexes

Perhaps the most recognizable of the cobalt carboxylate structures is the dinuclear 'Chinese lantern' structure that was first described for cobalt pivalate complexes with quinoline (quin) and 2-methylpyridine (2-Mepy).[30] Such complexes are characterized by two five-coordinate cobalt atoms bridged by four *syn–syn* bidentate carboxylate ligands and the coordination

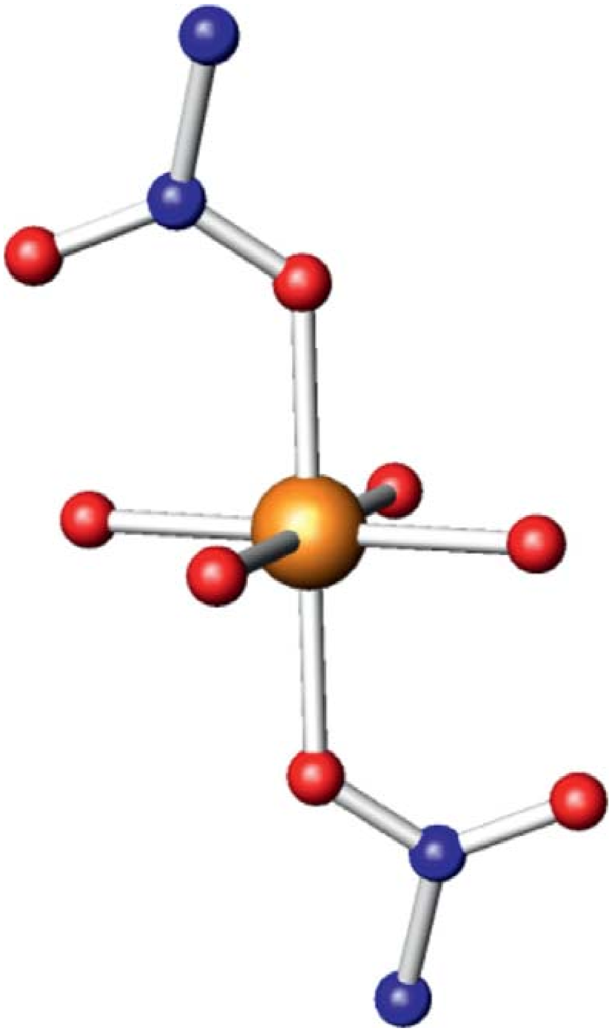

Figure 1 Structure of the nonhydrogen atoms of a molecule of $[Co(\eta^1\text{-}O_2CCH_3)_2(H_2O)_4]$.[19,20]

sphere being usually completed by a monodentate Lewis base (such as pyridine or quinoline). The most common examples of such complexes usually possess pivalate[31] or benzoate[32–35] ligands; however, examples exist for acetate[36] and crotonic acid.[37] An example of such a 'Chinese lantern' structure, the complex $[Co_2(O_2CPh)_4(quin)_2]$, is shown in **Figure 3(a)**.[32]

A structure closely related to the 'Chinese lantern' arises when a bridging water molecule displaces two of the bridging *syn–syn* carboxylate ligands. The result is a dinuclear complex in which the two cobalt atoms are bridged by two *syn–syn* bidentate carboxylate ligands and one μ-OH_2 ligand with the coordination sphere of each cobalt atom completed by two unidentate carboxylate ligands and two monodentate (or one bidentate) Lewis base ligands. The free oxygen atoms of the unidentate carboxylate ligands are hydrogen bonded to the hydrogen atoms of the bridging water molecule. Such complexes are observed for a variety of different carboxylate ligands, such as acetate,[38,39] trifluoroacetate,[40] trichloroacetate,[39] and pivalate.[31] The crystal structure of $[Co_2(\mu\text{-}OH_2)(\mu\text{-}O_2CCF_3)_2(O_2CCF_3)_2(py)_4]$ is shown in **Figure 3(b)**.

This motif can be further altered to create new structures. For example, when the sterically hindered acid 2,6-di(*p*-tolyl) benzoic acid (O_2CAr^{Tol}) was used, the resulting complex $[Co_2(\mu\text{-}OH_2)_2(\mu\text{-}O_2CAr^{Tol})_2(O_2CAr^{Tol})(C_5H_2N)]$ was found to be bridged by two *syn–syn* bidentate carboxylate ligands and two μ-OH_2 ligands.[41] A crystal structure of the complex $Et_4N[Co_2(O_2CCH_3)_5(H_2O)(py)_2]$ (**Figure 4(a)**) revealed an asymmetric dimeric core in which the two cobalt atoms were bridged by the two *syn–syn* bidentate carboxylate ligands and the μ-OH_2 ligand; however, one of the cobalt atoms was coordinated to two unidentate acetate ligands while the other was coordinated to a bidentate acetate ligand (in both cases, the coordination sphere was completed by pyridine ligands).[42] A further modification of this structure can arise as a result of a change to the binding mode of one of the carboxylate ligands as seen in the structure of the $[Co_2(O_2CCMe_3)_5]^-$ anion;[43] in this structure, the two cobalt atoms are bridged by two *syn–syn* bidentate carboxylate ligands and one chelating and bridging carboxylate ligand (**Figure 4(b)**).

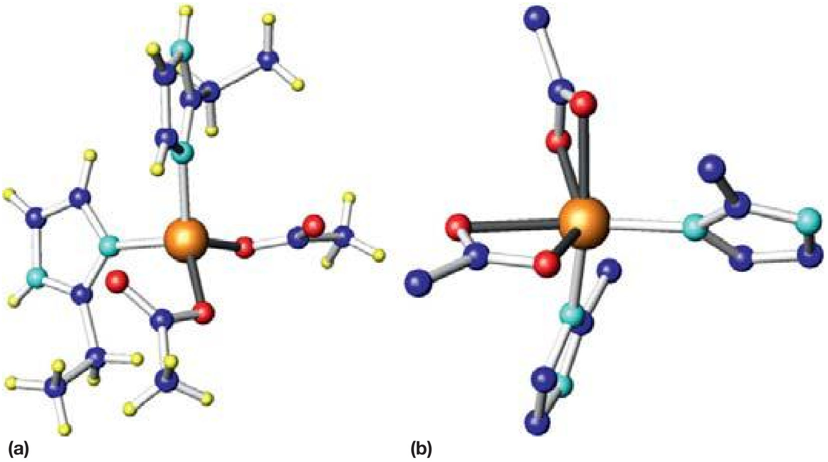

Figure 2 Structure of (a) $[Co(O_2CCH_3)_2(2\text{-EtIm})_2]$ and (b) $[Co(O_2CCH_3)_2(2\text{-MeIm})_2]$ showing the variation in coordination geometry of these closely related complexes.[27]

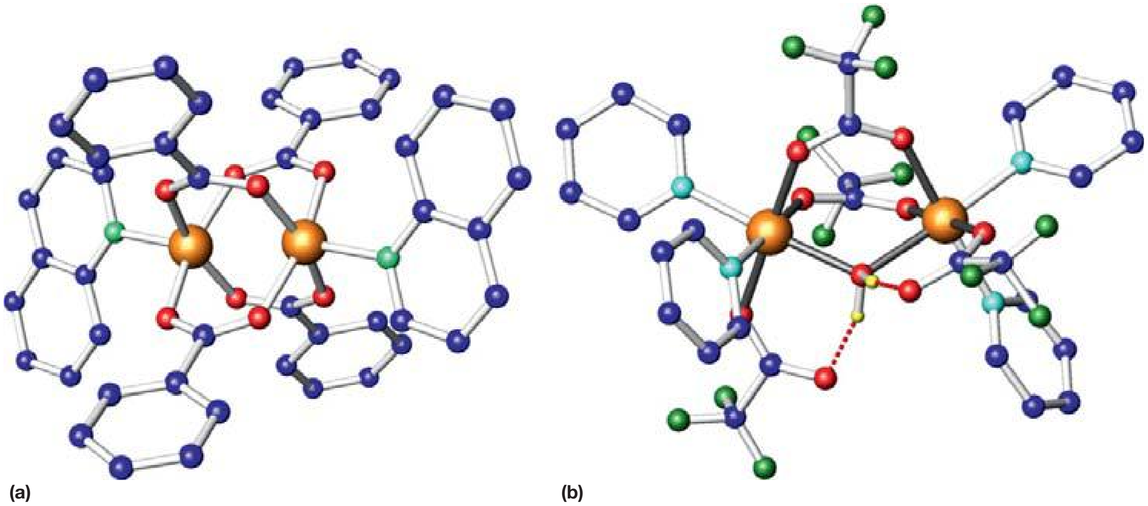

Figure 3 Structure of (a) $[Co_2(O_2CPh)_4(quin)_2]$[32] and (b) $[Co_2(\mu\text{-}OH_2)(O_2CCF_3)_4(py)_4]$.[40] Intramolecular H-bonds drawn as dashed lines.

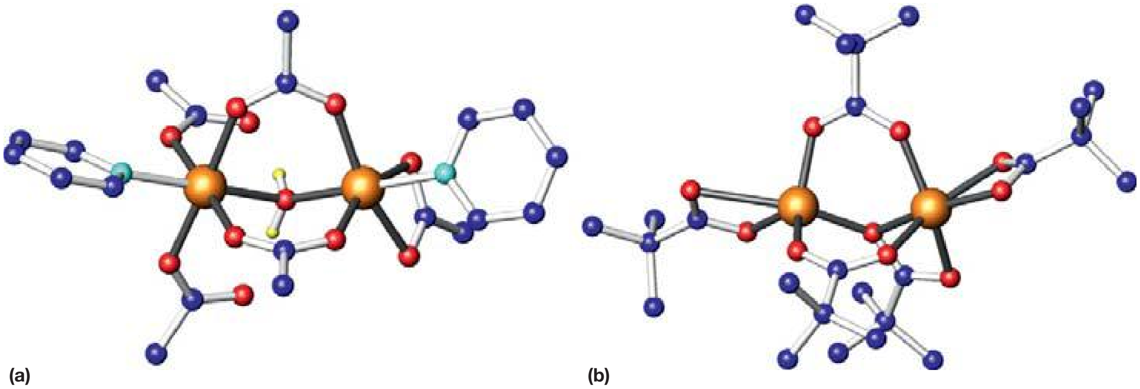

Figure 4 Crystal structures of (a) the $[Co_2(O_2CCH_3)_5(H_2O)(py)_2]^-$ anion,[42] and (b) the $[Co_2(O_2CCMe_3)_5]^-$ anion.[43]

6.23.2.3 Trinuclear Complexes

The trinuclear cobalt(II) carboxylate complexes fall into two distinct structural types: linear and triangular.

The linear complexes are seen for a variety of carboxylate ligands (acetate,[44,45] trifluoroacetate,[46,47] and benzoate[48]), and, as the name suggests, their structures are characterized by a linear arrangement of the pseudo-octahedral cobalt atoms. The archetypal structure involves neighboring cobalt atoms being bridged by two *syn–syn* bidentate carboxylate ligands and one monodentate bridging carboxylate ligand. The coordination spheres of the terminal cobalt atoms are completed by either bidentate carboxylate ligands (as seen for the complex $[Co_3(O_2CCH_3)_2(O_2CCH_3)_2(O_2CCH_3)_4]^{2-}$ (**Figure 5**))[44] or Lewis base ligands (as seen for the complexes $[Co(O_2CCH_3)(2,2'\text{-bipy})_2](ClO_4)$[45] and $[Co_3(O_2CPh)_6(quin)_2]$ (2,2′-bipy= 2,2′-bipyridine)).[48]

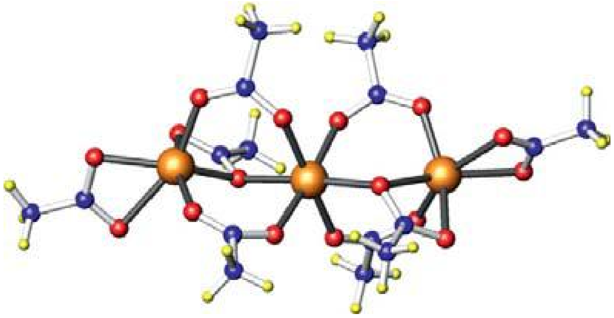

Figure 5 Structure of the $[Co_3(O_2CCH_3)_2(O_2CCH_3)_2(O_2CCH_3)_4]^{2-}$ dianion.[44]

Variations of this structure also exist. Thus, the neighboring cobalt atoms of the complex $[Co_3(O_2CCF_3)_6(HO_2CCF_3)_6]$[47] are bridged by three *syn–syn* bidentate trifluoroacetate ligands and the coordination spheres of the terminal cobalt atoms are completed by two unidentate trifluoroacetic acid molecules, the hydrogen atoms of which hydrogen bond to the oxygen atoms of the bridging carboxylate ligands. Similarly to the dinuclear complexes, the replacement of bridging carboxylate ligands with bridging water molecules is also possible in the case of linear trinuclear complexes. For example, the complex $[Co_3(O_2CCF_3)_4(O_2CCF_3)_2(HO_2CCF_3)_2(OH_2)_4]$ possesses neighboring cobalt atoms bridged by two *syn–syn* carboxylate ligands and one bridging water molecule (**Figure 6**). In this example, one unidentate carboxylate ligand, one unidentate trifluoroacetic acid ligand, and a water molecule complete the coordination sphere of the terminal cobalt atoms.