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## CATALYTIC ASYMMETRIC SYNTHESIS IN NONCONVENTIONAL MEDIA/ CONDITIONS

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### 1.1. INTRODUCTION

Conventionally, catalytic asymmetric synthesis has been carried out in organic solvents, because most organic materials are not soluble in other solvents. However, asymmetric catalysis in other solvents (nonconventional solvents) is now of interest for many reasons. First and most significantly, the negative characteristics of organic solvents have come to the fore recently; many organic solvents are volatile, flammable, sometimes explosive, and have a damaging effect on human health (e.g., mutagenic or carcinogenic) or on the environment. On the other hand, recovery and reuse of catalysts is crucial in organic synthesis not only from an economical aspect but also from an environmental point of view. Use of nonconventional solvents often enables the recovery and reuse of catalysts.

In this chapter, water, fluorosolvents, supercritical fluids (SCFs), and ionic liquids (ILs) are discussed as nonconventional solvents, and characteristic features of asymmetric catalysis are surveyed. Microwave-assisted catalytic asymmetric synthesis is also described.

### 1.2. CATALYTIC ASYMMETRIC SYNTHESIS IN WATER

Water is remarkable in nature; indeed, nature chooses water as a “solvent.” Many elegant *in vitro* reactions, mainly catalyzed by enzymes, are carried out in an aqueous

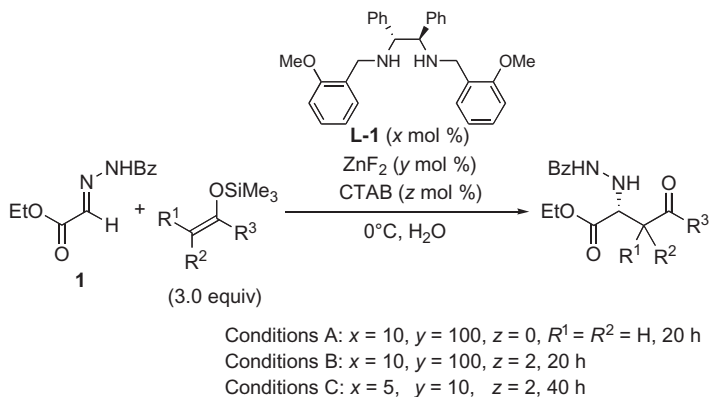
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environment in our bodies. Given that nature so gracefully exploits water, why should mankind not perform synthesis in water too?

### 1.2.1. Chiral Lewis Acid Catalysis in Water

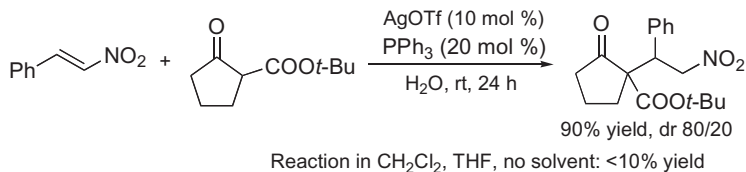
In general, the formation of chiral Lewis acid complex is much more difficult in water than in organic media, since a chiral ligand competes with water in coordination with Lewis acid. Although there are successful reports to realize chiral Lewis acid catalyzed asymmetric reactions in *aqueous media*, it is still very challenging to use *water as sole solvent* [1,2].

**1.2.1.1. Mannich-Type Reaction in Water** Asymmetric Mannich reactions provide useful routes for the synthesis of optically active  $\beta$ -amino ketones and esters, which are versatile chiral building blocks for the preparation of many nitrogen-containing biologically important compounds [3]. Diastereo- and enantioselective Mannich-type reactions of  $\alpha$ -hydrazono ester **1** with silicon enolates in aqueous media can be successfully achieved with a  $\text{ZnF}_2$ -chiral diamine **L-1** complex (Scheme 1.1) [4]. This complex enables reactions in water without any organic cosolvents or additives to proceed smoothly, affording the corresponding products in high yields and high stereoselectivities (Conditions A) [5]. In the reaction of  $\alpha$ -monosubstituted ketone-derived silyl enol ether with **1**, cetyltrimethyl ammonium bromide (CTAB) is necessary to accelerate the reaction. It is also noted that, in contrast to most asymmetric Mannich-type reactions, either syn- or anti-adducts are stereospecifically obtained from (E)- or (Z)-silicon enolates in the present reaction (Conditions B). Moreover, the amount of  $\text{ZnF}_2$  and **L-1** can be successfully reduced to 10 and 5 mol %, respectively, maintaining the same level of result (Conditions C).



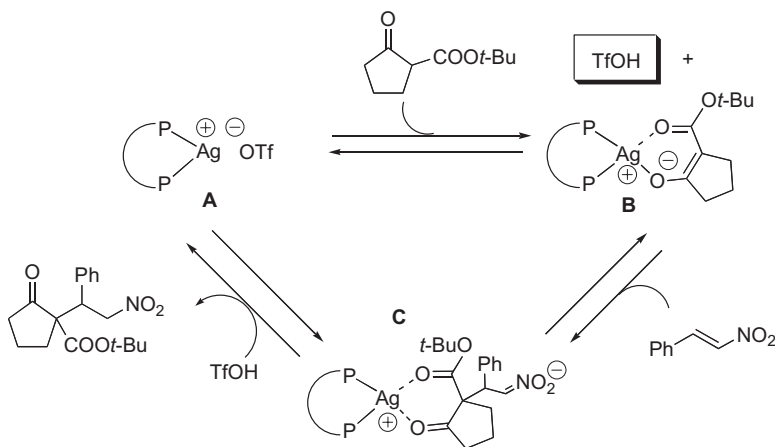
**Scheme 1.1.**

**1.2.1.2. Michael Reaction in Water**  $\text{AgOTf-PPh}_3$  complex-catalyzed Michael additions of  $\beta$ -ketoesters to nitroalkenes proceed efficiently only in water but not in organic solvents (Scheme 1.2).



Scheme 1.2.

Based on these results, a plausible mechanism is shown in Scheme 1.3. In the formation of metal enolate B, TfOH is generated and the reaction mixture becomes heterogeneous, where metal enolate B stays in organic phase, while TfOH is excluded to water phase because of the difference of hydrophobicity between them. On the other hand, in the case of a normal organic solvent system, the reaction mixture becomes homogeneous, leading the reverse reaction from B to A fast. As a result, metal enolate B does not make contact with TfOH, and the reverse reaction from B to A is suppressed. Metal enolate B and nitrostyrene would thus combine in high concentration, and the Michael addition step (B to C in Scheme 1.3) may proceed smoothly. Moreover, this reaction system can be applied to catalytic asymmetric synthesis in water (Scheme 1.4) [6,7].

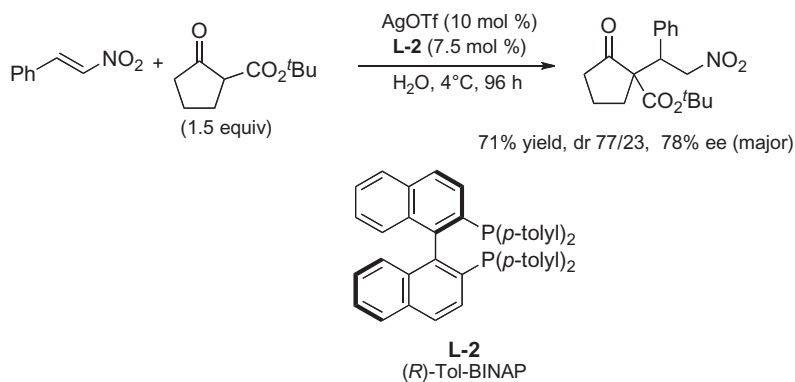


Scheme 1.3.

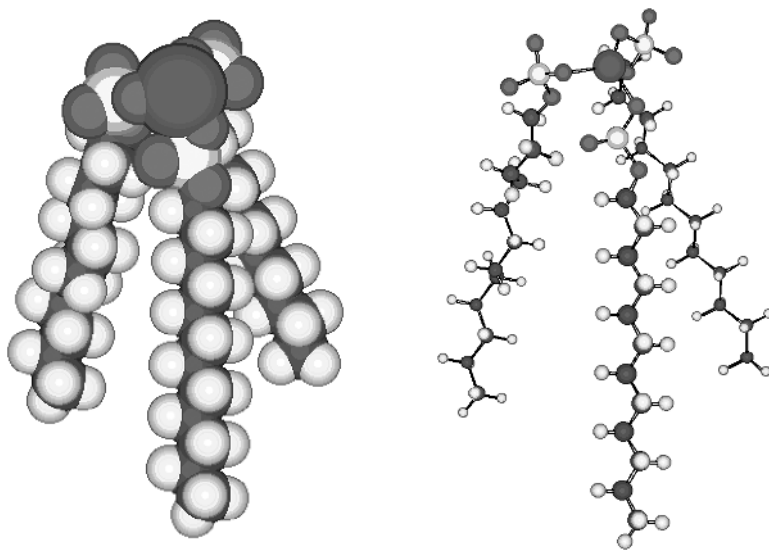
**1.2.1.3. Epoxide Ring-Opening Reaction in Water** Scandium trisdodecylsulfate (Sc(DS)<sub>3</sub>) was designed as a Lewis acid as well as a surfactant as illustrated in Scheme 1.5. In the model reaction of benzaldehyde with the silyl enol ether derived from propiophenone in water, Sc(DS)<sub>3</sub> catalyzes the reaction smoothly, while the reaction proceeds sluggishly when Sc(OTf)<sub>3</sub> is used as a catalyst (Scheme 1.6).

A key to the success in this system is assumed to be the formation of stable emulsions. Physical property of the droplets was investigated, and transmission electron microscopy (TEM) analysis revealed that only about 0.08 mol % of Sc(DS)<sub>3</sub> is sufficient to form

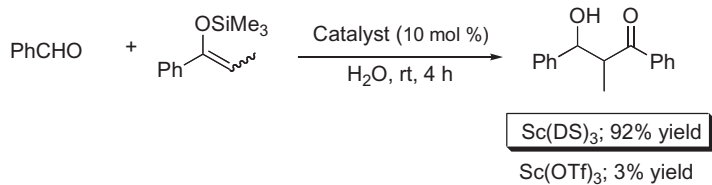
4 CATALYTIC ASYMMETRIC SYNTHESIS IN NONCONVENTIONAL MEDIA/CONDITIONS



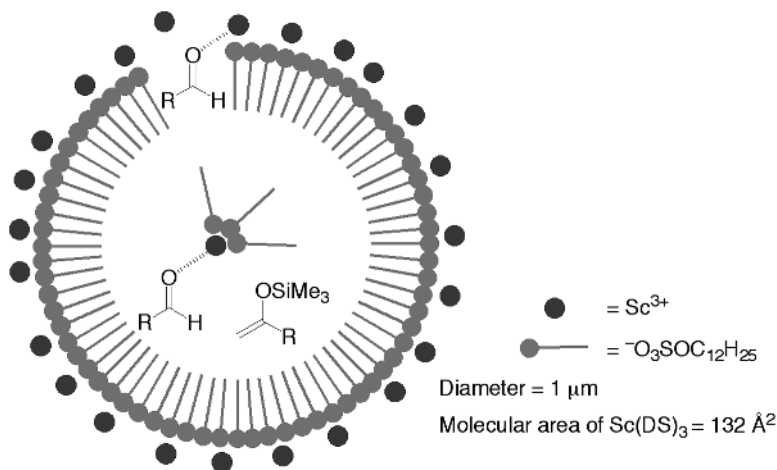
Scheme 1.4.



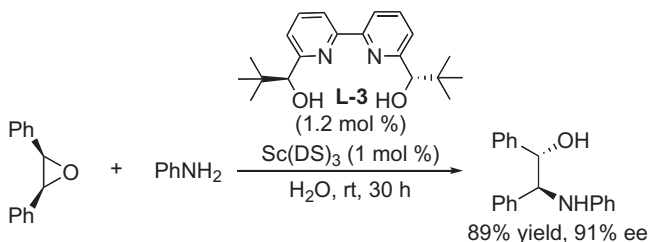
Scheme 1.5.



Scheme 1.6.



Scheme 1.7.



Scheme 1.8.

monolayers (Scheme 1.7). Based on these results, it is expected that highly hydrophobic environment is formed inside of the emulsion.

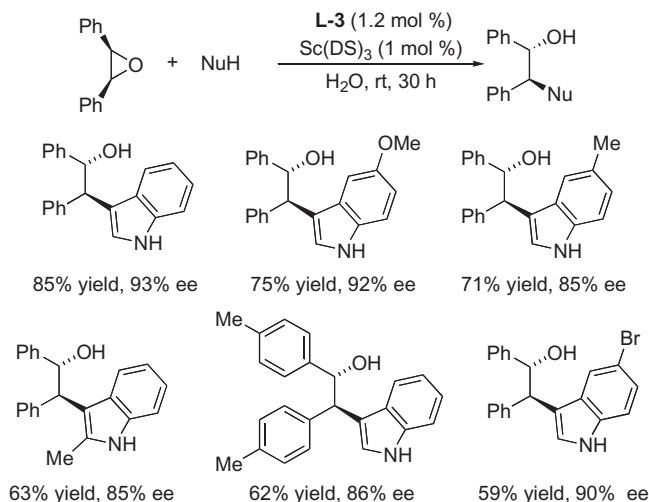
To explore this catalyst further, chiral  $\text{Sc}(\text{DS})_3$  catalyst has been investigated. The complex  $\text{Sc}(\text{OTf})_3 \cdot \mathbf{L-3}$  was found to be effective in asymmetric hydroxymethylation using aqueous formaldehyde solution in DME (1,2-dimethoxyethane)/ $\text{H}_2\text{O}$  cosolvent condition [8,9]. Therefore, there was a possibility that  $\text{Sc}(\text{DS})_3$  could form chiral complex with  $\mathbf{L-3}$  in water. First, the asymmetric ring opening of *cis*-stilbene oxide with aniline in water was investigated.

Chiral  $\beta$ -amino alcohol units can be found in many biologically active compounds and chiral auxiliaries/ligands used in asymmetric reactions [10]. Catalytic enantioselective synthesis of these chiral building blocks mainly relies on the asymmetric ring opening of *meso*-epoxides. Indeed, several examples using a chiral catalyst (typically a chiral Lewis acid) are reported in literature [11]; however, all these reactions proceeded in organic solvents. It is probable that epoxides are readily decomposed under acidic conditions in water.

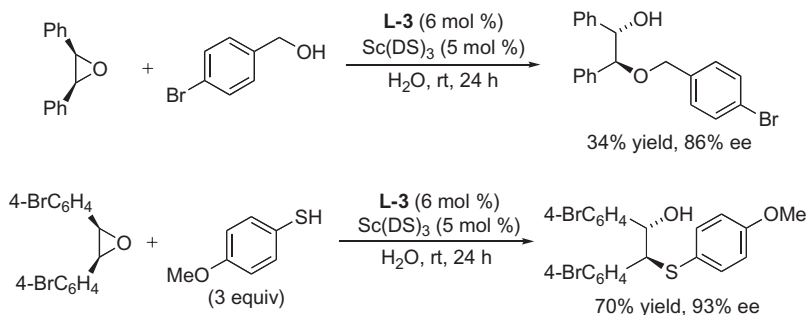
Using 1 mol% of  $\text{Sc}(\text{DS})_3$  and 1.2 mol% of  $\mathbf{L-3}$  in water, the reaction proceeded smoothly in high yield with high enantioselectivity (Scheme 1.8). It is noted that the

ring-opening reaction proceeded smoothly in water, and that no diol formation was observed. This is to date the first example of an asymmetric epoxide ring opening in water as a sole solvent [12,13].

Moreover, catalytic asymmetric ring-opening reactions of *meso*-epoxides with indoles, alcohols, and thiols proceed smoothly in the presence of catalytic amounts of  $\text{Sc}(\text{DS})_3$  and chiral bipyridine ligand **L-3** in water to afford  $\beta$ -amino alcohols in high yields with high enantioselectivities (Schemes 1.9 and 1.10) [14,15]. These results suggest that an excellent asymmetric environment is created in water.



Scheme 1.9.



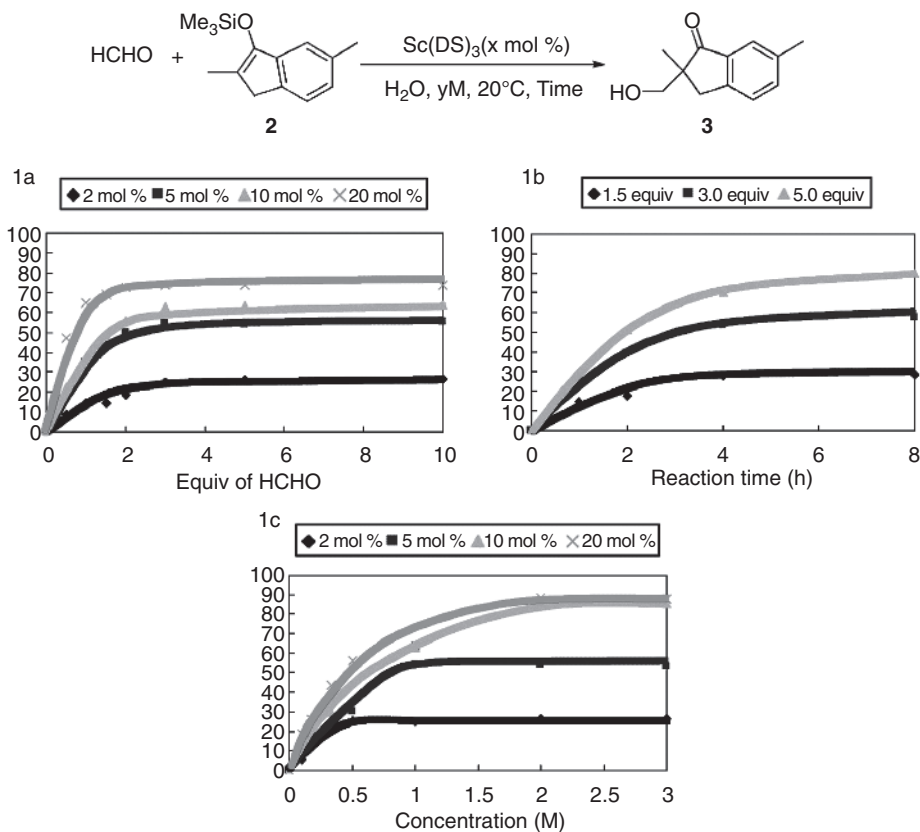
Scheme 1.10.

**1.2.1.4. Hydroxymethylation in Water** Several asymmetric organic reactions have been achieved in water without any organic cosolvents. These reactions proceeded smoothly by creating hydrophobic areas in water to stabilize and concentrate organic substrates or by suppressing the undesired pathway in the reaction mechanism by water.

One of the key factors for these successes is hydrophobicity of substrates. Therefore, asymmetric reactions in water with hydrophilic substrates are far more challenging.

An aqueous formaldehyde solution, or formalin, is one of the most important C1 electrophiles as well as a representative of hydrophilic substrates. Asymmetric hydroxymethylation using an aqueous formaldehyde solution has been investigated in water-organic cosolvent systems [16,17]. Since the hydrophobicity of a substrate is an important factor, it is assumed that hydrophilic substrates are very difficult to handle in water.

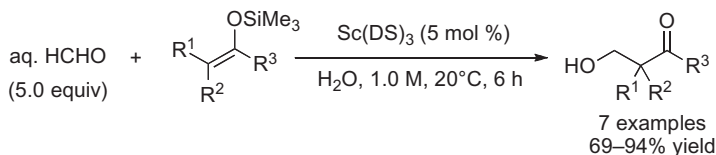
Hydroxymethylation of silicon enolate **2** with 36% aqueous formaldehyde solution (aq. HCHO) was studied in detail. The yield of **3** was improved when the amount of formaldehyde was increased from 1 to 5 equiv with a catalyst loading dependency (Scheme 1.11, **Part 1a**) and for an 8-h reaction (**Part 1b**). The concentration of aq. HCHO also affected the yield of **3** (**Part 1c**). With an Sc loading level (10 and 20 mol %) in the presence of 5 equiv of aq. HCHO, the yields were improved to >80% as the concentrations increased up to 2.0M; however, no improvement was observed by further



**Scheme 1.11. Part 1a.** Hydroxymethylation of **2** (catalyst loading and HCHO equiv, reaction concentration was 1.0M, reaction time was 1 h). **Part 1b.** Hydroxymethylation of **2** (reaction time and HCHO equiv, reaction concentration was 1.0M). **Part 1c.** Hydroxymethylation of **2** (catalyst loading and concentration, reaction time was 8 h).

increasing the concentration. In the cases of the lower Sc loading level (2 and 5 mol %), the yields leveled off at much lower concentrations, 0.5 and 1.0M, respectively. These results indicated that Sc(DS)<sub>3</sub> might be saturated by aq. HCHO. Based on the experiments, it can be said that, in spite of the extreme solubility of HCHO in water, *the population of HCHO in the hydrophobic environment increases in the presence of Sc(DS)<sub>3</sub> due to Lewis acid–Lewis base interaction between Sc(DS)<sub>3</sub> and HCHO*, and therefore, the reaction of HCHO with silicon enolate **2** can proceed smoothly even in water.

Furthermore, the hydroxymethylation of various silyl enol ethers proceeded smoothly (Scheme 1.12). Consequently, these experiments suggest that Lewis acid-surfactant combined catalyst (LASC) reaction system can be applied to hydrophilic substrates as well as hydrophobic substrates.



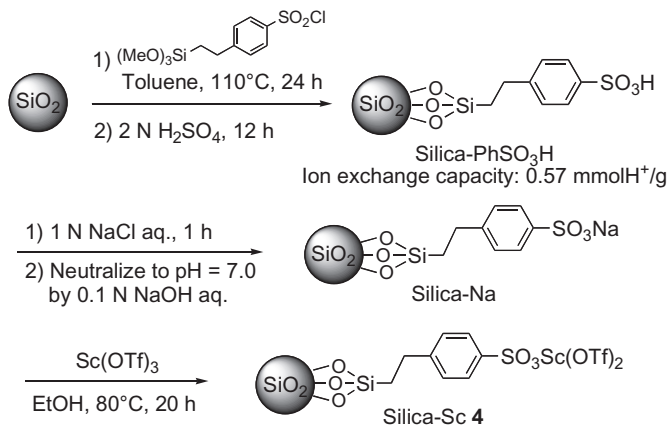
**Scheme 1.12.**

Lewis acid-catalyzed asymmetric reactions in water using hydrophilic substrates are recognized as highly challenging [18], considering the importance of *Lewis acid–Lewis base interactions*, since Lewis acids lose their acidity upon coordination from chiral ligands. Additionally, chiral ligands compete with substrates and water molecules for coordination with Lewis acids. Therefore, the development of chiral Lewis acid-catalyzed hydroxymethylation using aq. HCHO with water as the sole solvent would make a great impact in the field.

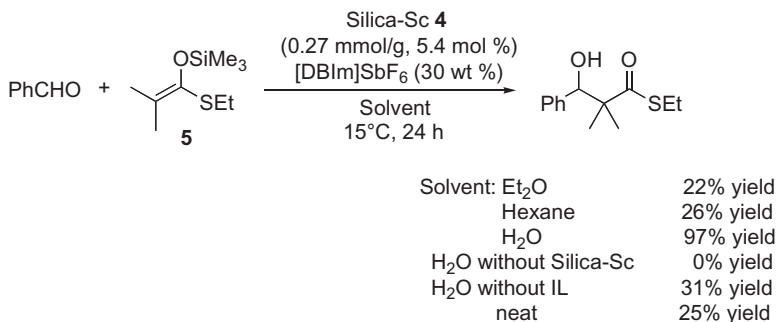
The investigation of asymmetric variants of hydroxymethylations using aq. HCHO revealed that the addition of a chiral ligand and a small amount of a surfactant suppressed the competitive hydrolysis of silicon enolates. Eventually, catalytic asymmetric hydroxymethylation reactions are successfully carried out in the presence of a catalytic amount of Sc(DS)<sub>3</sub>, chiral ligand **L-3** [19], or **L-4** [20] in the presence of additives to afford the desired products in 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 desired hydroxymethylated adducts in good yields with high enantioselectivities (Scheme 1.13).

This method could be applied to the synthesis of an artificial odorant (S)-(+)-**3** (Scheme 1.14) [12]. Hydroxymethylation of **1** was performed using Sc(DS)<sub>3</sub>•**L-3** 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 the separation of organic phase, followed by hydrogenation with polymer incarcerated palladium (PI-Pd) [13] in benzotrifluoride (BTF), 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 with an immobilized catalyst, which are suitable for green sustainable chemistry [3,14].

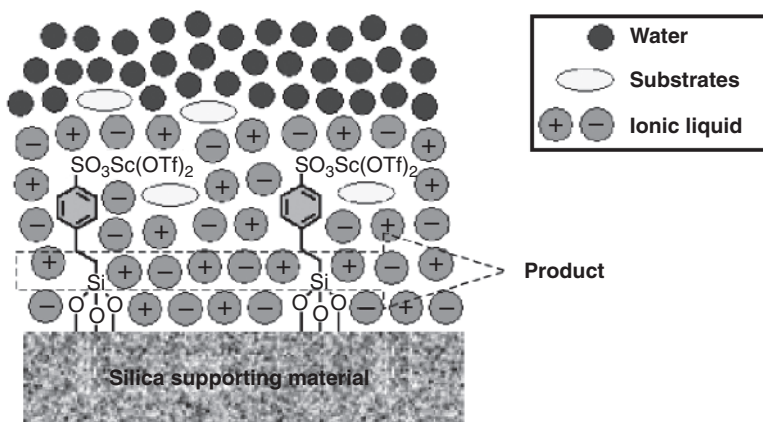




Scheme 1.15.



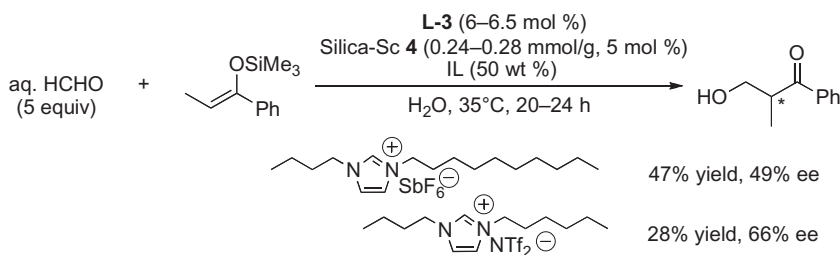
Scheme 1.16.



Scheme 1.17.

such as **5** can work well in water under the conditions, and that this is the first demonstration of a combination of silica gel-supported metal catalysts and ILs to create efficient hydrophobic environments for organic reactions in water.

Although there is room to improve the results, an asymmetric catalysis can be realized using Silica-Sc-IL combined with a ligand **L-3** (Scheme 1.18).



**Scheme 1.18.**

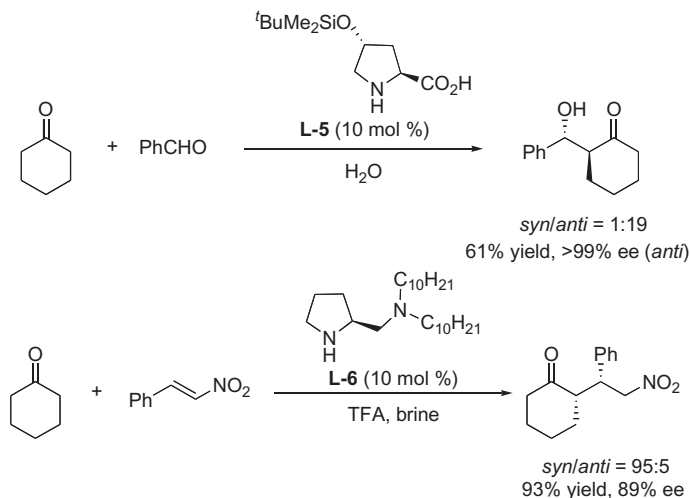
### 1.2.2. Chiral Organocatalysis in Water

In contrast to metal-based catalysts, organocatalyses are easy to handle, since they are, in general, stable in water. Amino acids are representative of organocatalysts and their derivatives have been widely investigated. Tert-butyldimethylsilyl (TBS)-protected hydroxyproline **L-5** catalyzes a direct-type aldol reaction, leading to the aldol adduct in good yield with high diastereo- and enantioselectivities. And a Michael reaction of a ketone or an aldehyde with  $\beta$ -nitrostyrene in brine can be catalyzed by a proline derivative **L-6** to afford the corresponding product in good yield with good diastereo- and enantioselectivities (Scheme 1.19). Moreover, a threonine derivative **L-7** catalyzes Mannich reaction to produce the product in good yield with high diastereo- and enantioselectivities (Scheme 1.20) [22].

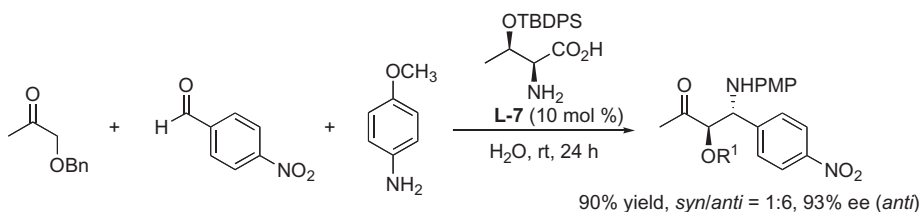
The Diels–Alder reaction is a powerful transformation method in organic chemistry. Chiral imidazolidinone can successfully catalyze the reaction of  $\alpha,\beta$ -unsaturated ketones with dienes, where chiral Lewis acid catalysts showed lower enantioselectivities (Scheme 1.21) [23,24].

### 1.2.3. Others

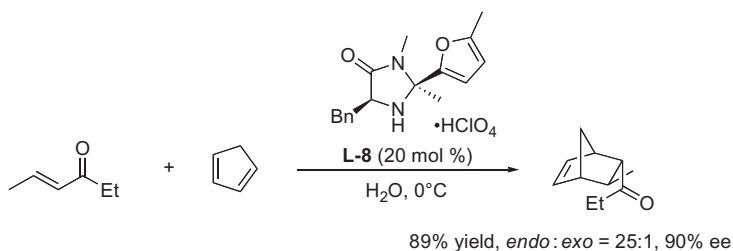
**1.2.3.1. Asymmetric Reactions Using Alkynes** [25] Optically active propargylamines are important synthetic intermediates for various nitrogen-containing compounds, a structural feature of many biologically active compounds and natural products. The most reliable and efficient methods for the preparation of optically active propargylic amines are still dependent on the addition of appropriate organometallic reagents to chiral imine derivatives. While methods for catalyzed preparation of optically active propargylic amines are still limited, highly enantioselective direct-type alkyne-imine addition was recently reported using a chiral Cu(I)•**L-9** complex. The process is simple and provides a diverse range of propargylic amines in high enantioselectivity (Scheme 1.22) [26].



Scheme 1.19.

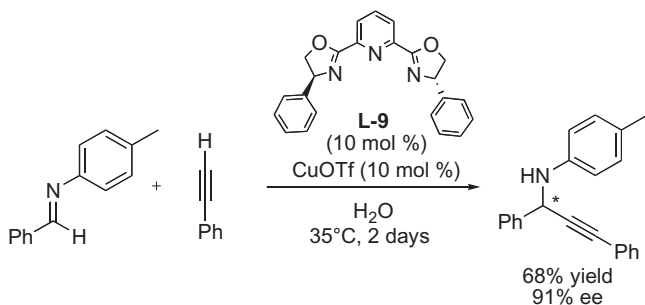


Scheme 1.20.

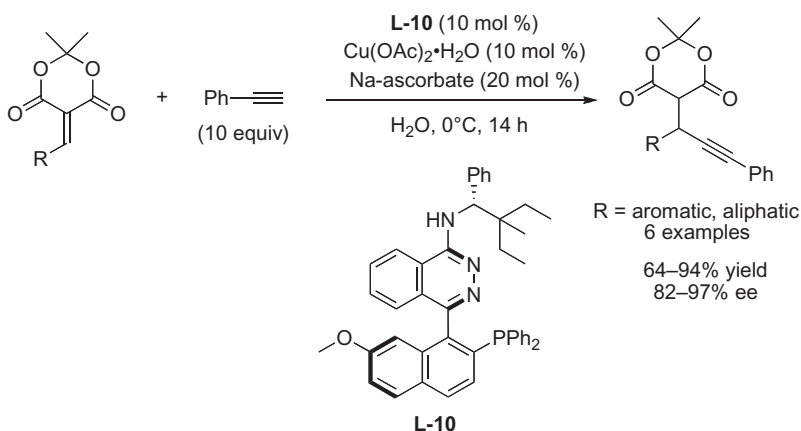


Scheme 1.21.

The conjugate addition reaction of terminal alkynes to C=C bond can be catalyzed by copper in water. The reaction only proceeds with derivatives of Meldrum's acids in the presence of Cu(I) produced by Cu(OAc)<sub>2</sub> and sodium ascorbate in water, and a large excess amount of phenylacetylene. Combined with chiral ligand **L-10**, enantioselective versions of this addition reaction can be achieved to 82–97% ee of products with useful yields [27] (Scheme 1.23).



Scheme 1.22.

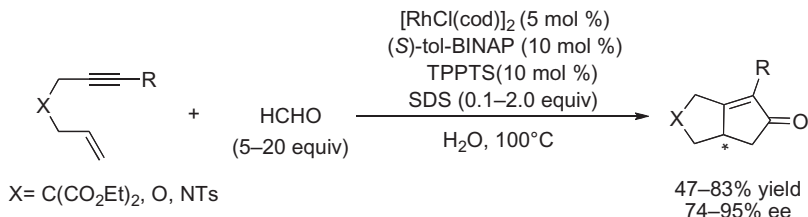


Scheme 1.23.

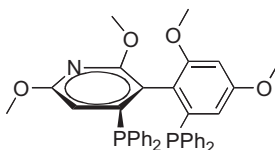
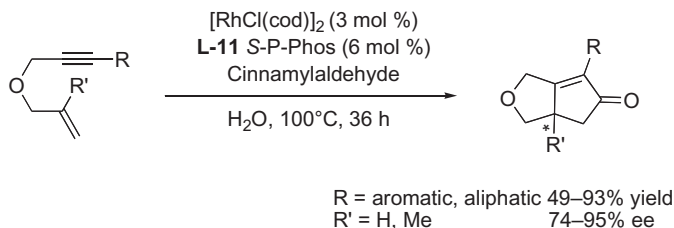
**1.2.3.2. DNA-Based Asymmetric Catalysis in Water** The DNA-based asymmetric Diels–Alder reaction proceeds in water. There are three key structural features: a DNA-intercalating moiety, a spacer component, and a metal-binding group, which intimately anchored the metal complexes to DNA to use its chiral information. The substituent and the spacer length of the ligand are crucial for both of enantioselectivity and the enantiopreference [28].

**1.2.3.3. Pauson–Khand-Type Reaction in Water** The chiral ligand BINAP [2,2'-bis(dip-tolylphosphino)-1,1'-binaphthyl] together with  $[\text{RhCl}(\text{COD})]_2/\text{TPPTS}$  (trisodium salt of 3,3',3''-phosphanetriyl benzene sulfonic acid) is effective for the asymmetric Pauson–Khand-type reaction in water. Formaldehyde can be used as a source of carbon monoxide directly in water (Scheme 1.24) [29].

Rhodium-catalyzed asymmetric Pauson–Khand-type reactions in water work well in the presence of a chiral atropisomeric dipyridyldiphosphane ligand (*S*-P-Phos), transforming various enynes into the corresponding bicyclic cyclopentenones in good yields and ees (up to 95% ee) (Scheme 1.25) [30].



Scheme 1.24.



L-11 S-P-Phos

Scheme 1.25.

### 1.2.4. Conclusion and Perspective

Organic reactions in other, nonconventional solvents instead of organic solvents are now of interest in many aspects related to green sustainable chemistry. The first choice of a nonconventional solvent is water. Water is a clean, nontoxic, inexpensive, and the most environmentally friendly solvent. In addition, acid catalysis has occupied major parts of organic transformations. Therefore, the chiral acid catalysis in water we have discussed here will play a key role in this field.

As we described, organic reactions in water are difficult because most organic materials are not soluble and many reactive intermediates and catalysts are not stable in water. In addressing these issues, many focused research efforts have led to rapid progress, exemplified by elegant asymmetric catalysis in water, which was believed to be impossible 10 years ago. Moreover, systems have been developed for the recovery and reuse of catalysts utilizing biphasic reaction conditions that incorporate water.

As for the future of asymmetric catalysis in water, several important developments are predicted. Stereoselective carbon–carbon bond-forming reactions are still an important challenge in organic synthesis, and in particular, control of the stereogenic centers of products is crucial. From this aspect, the development of catalytic asymmetric reactions in water is still a major task, which represents significant challenges since most asymmetric catalysts, except for some late transition metal-based systems, are not stable in water.

As such the design of water-compatible catalysts will be the key to the future of this work. Asymmetric aerobic oxidation in water is an important research target for the future. It will not be necessary to mention the importance of environmentally benign oxidation processes to this readership, but due to the high heat capacity and stability of water, the process is promising. The use of water-soluble small molecules such as formaldehyde and ammonia will be another critical area. These molecules are inexpensive and potentially useful carbon and nitrogen building blocks; however, they are not well utilized in conventional organic synthesis in organic solvents. Asymmetric catalysis using formaldehyde and ammonia will be a key project not only in academia but also in industry.

### 1.3. CATALYTIC ASYMMETRIC SYNTHESIS IN ALTERNATIVE REACTION MEDIA

Since many chiral catalysts are valuable and indeed expensive, recovery and reuse of the catalysts is especially important in industry. For this purpose, nonconventional solvents have been investigated. In this section, fluorosolvents, SCFs, and ILs are described.

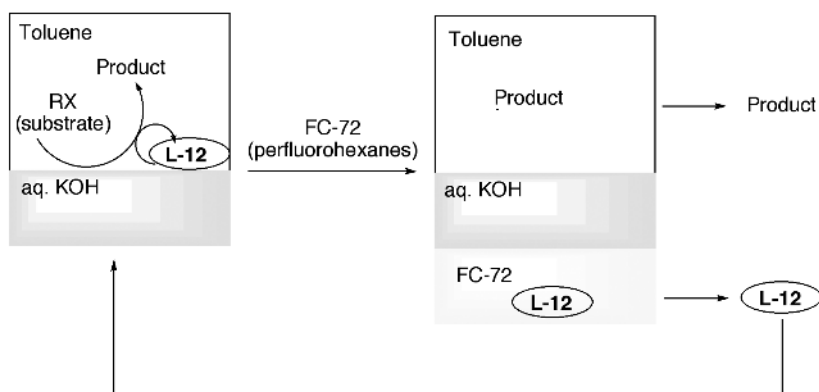
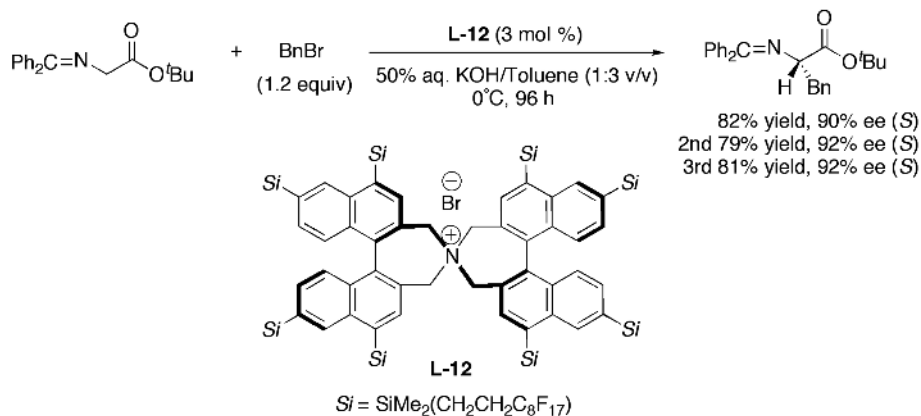
#### 1.3.1. Fluorous Solvents

Fluorous compounds with appropriate melting and boiling points can be used as solvents. Interestingly, these fluorosolvents are remarkably different from the corresponding hydrocarbons and form bilayers with conventional organic solvents. In terms of recovery and reuse of catalysts, fluorosolvents are of great interest. Since fluorosolvents tend to mix poorly with common organic solvents, some catalysts can be immobilized in fluorosolvents in biphasic systems. In addition, one of the characteristic points in fluorosolvent-organic biphasic systems is that some combination of fluorosolvent and organic solvents demonstrates increased miscibility at elevated temperature, and that heating can result in a completely homogeneous mixture in such cases. This is remarkably different from water-organic biphasic systems. Accordingly, in fluorosolvent-organic biphasic systems, it is possible to carry out reactions under homogeneous conditions at elevated temperature, and after the reactions occur, the mixture is cooled to become two phases. While products are separated from organic solvent phases, catalysts can be recovered from fluorosolvent phases.

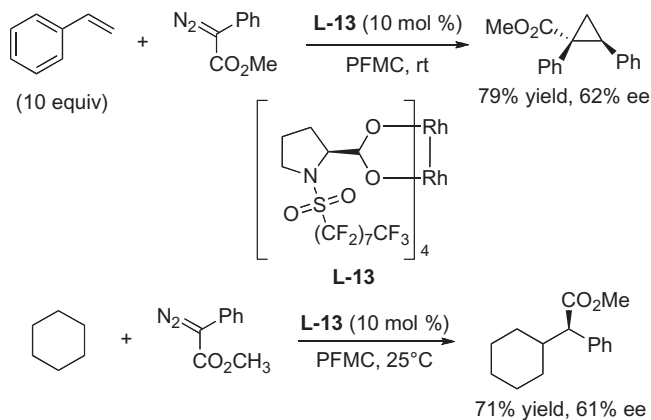
Since the first report of fluorosolvent biphasic systems (FBSs) [31], reactions using fluorosolvents have been recognized as green reactions due to simple procedures and use of chemically inert and low toxicity fluorosolvents. In the past decade, FBSs have been widely applied to asymmetric reactions.

A typical and very successful application of FBS is chiral phase transfer catalyst for  $\alpha$ -amino acid synthesis. Synthetically convenient 4,4',6,6'-tetrasubstituted symmetrical chiral phase-transfer catalysts promote asymmetric alkylation of *t*-butylglycinate-benzophenone schiff base [32]. The substituent of the 4,4',6,6'-positions of binaphthyl effects on chiral efficiency and the SiMe<sub>2</sub>(CH<sub>2</sub>CH<sub>2</sub>C<sub>8</sub>F<sub>17</sub>)-substituted catalyst designed as a recyclable fluorosolvent chiral phase-transfer catalyst can promote the reaction's good chiral efficiency and reusability (Scheme 1.26).

The chiral fluorosolvent complex tetrakis-dirhodium(II)-(*S*)-*N*-(*n*-perfluorooctylsulfonyl)prolinate (**L-13**) displays good chemo- and enantioselectivity in intermolecular cyclopropanation and C–H bond activation reactions (Scheme 1.27). The catalyst can be simply and thoroughly separated from the reaction mixture and is recyclable [33].

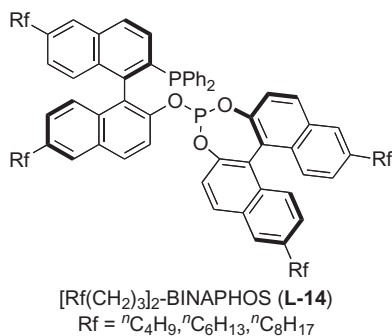


Scheme 1.26.



Scheme 1.27.

Rh-[Rf(CH<sub>2</sub>)<sub>3</sub>]<sub>2</sub>-BINAPHOS complex catalyzes hydroformylation of alkynes in fluorous solvents. The desired branch product from styrene is obtained in comparable or even higher regio- and enantioselectivities than those of the conventional Rh-BINAPHOS (**L-14**) system [34].

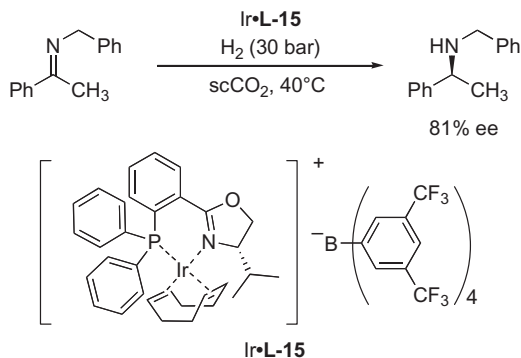


More applications of FBSs to asymmetric reactions such as the hydrogenation of ketones [35], epoxidations [36], and C–C bond formations [37–41] have been reported.

### 1.3.2. Catalytic Asymmetric Synthesis in SCFs

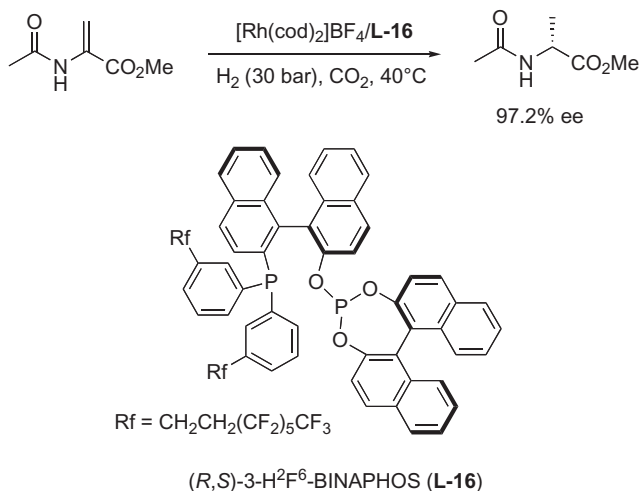
SCFs are also focused as nonconventional solvents. SCFs are probably best known through their use for the decaffeination of coffee, which employs supercritical carbon dioxide (scCO<sub>2</sub>). SCFs represent a different type of nonconventional solvent from water, fluorous solvents, ILs, and even organic solvents, because they are not in the liquid state. An SCF is defined as a substance above its critical temperature (*T<sub>c</sub>*) and pressure (*P<sub>c</sub>*), but below the pressure required for condensation to a solid. The critical point represents the highest temperature and pressure at which the substance can exist as a vapor and liquid under equilibrium. Hence, in a closed system, as both temperature and pressure are increasing, the liquid becomes less dense due to thermal expansion, and the gas becomes dense as the pressure rises. The densities of both phases thus converge until they become identical at the critical point. At this point, the two phases become indistinguishable and an SCF is obtained. In such SCFs, remarkable reactivities and selectivities are sometimes observed. From a process perspective, scCO<sub>2</sub> offers the advantage that simple depressurization removes residual scCO<sub>2</sub>, and, therefore, no hazardous solvent effluent is produced. This leads to a facile separation of products. This organic solvent-free process is of great interest in the pharmaceutical, cosmetic, food, and electronic industries where highly pure materials are very important.

Catalytic asymmetric synthesis in SCFs has been investigated. Iridium-catalyzed asymmetric hydrogenation of imines is successfully carried out in scCO<sub>2</sub> [42]. Cationic Ir(I)•**L-15** complex with a perfluoroalkyl group in the counter anion is very effective for efficient asymmetric catalysis. In the presence of 0.078 mol % of the catalyst, an imine derived from acetophenone is reduced within 1 h in scCO<sub>2</sub> at 40°C under H<sub>2</sub> (30 bar) to afford the corresponding amine in high yield with high enantioselectivity (Scheme 1.28). It is noted that the catalyst loading is decreased dramatically by using scCO<sub>2</sub> instead of conventional solvents such as dichloromethane (DCM). The product is readily separated from the catalyst, which can be reused several times without significant loss of activity.



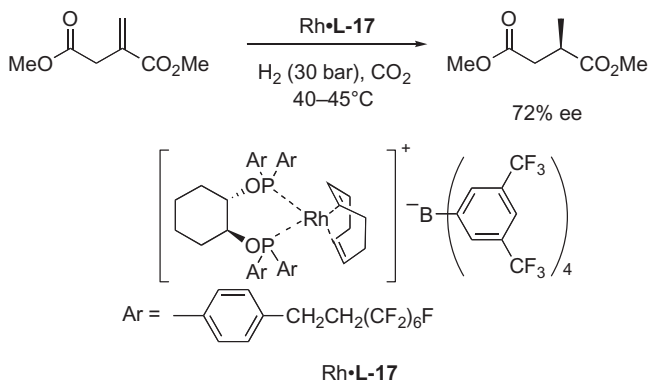
Scheme 1.28.

Asymmetric hydrogenation also proceeds smoothly in  $\text{scCO}_2$  by using the perfluoroalkyl-substituted ligand (*R,S*)-3- $\text{H}^2\text{F}^6$ -BINAPHOS (**L-16**) and Rh complex (Scheme 1.29) [43]. Another  $\text{Rh}\cdot\text{L-17}$  complex for asymmetric hydrogenation in  $\text{scCO}_2$  has also been reported (Scheme 1.30) [44]. In these cases, the catalysts are soluble in  $\text{scCO}_2$  to form homogeneous systems during the reactions.

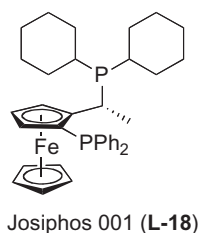


Scheme 1.29.

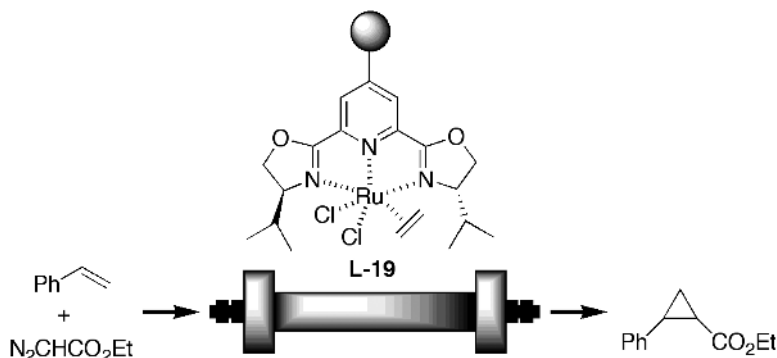
On the other hand, the continuous flow  $\text{scCO}_2$  system [45] has been applied to asymmetric hydrogenation using  $[\text{Rh}(\text{COD})_2]^+[\text{BF}_4]^-/\text{H}_3\text{O}_{40}\text{PW}_{12}/\text{alumina}$  (CATAXA®) and Josiphos 001 ligand (**L-18**) as an immobilized chiral catalyst [46]. A mixture of  $\text{H}_2$ ,  $\text{CO}_2$ , and a substrate (dimethyl itaconate) in 2-propanol is poured into a hydrogenation reactor with the chiral Rh catalyst, and the product is obtained with 83% ee (Scheme 1.31). In this system, neither perfluoroalkyl-substituted ligands nor counter anions with



Scheme 1.30.



Scheme 1.31.



Scheme 1.32.

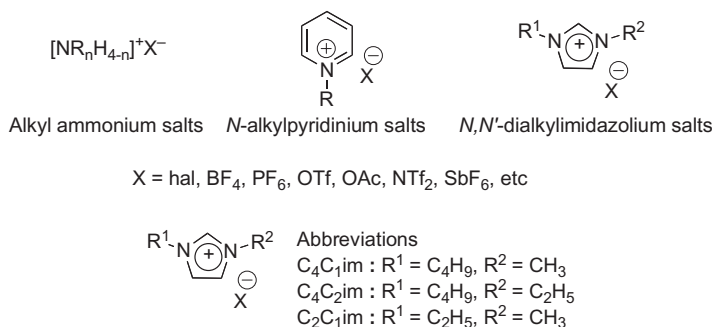
perfluoroalkyl groups are used.  $\text{scCO}_2$  is utilized to dissolve  $\text{H}_2$  and for ease of product separation.

A similar flow system with an immobilized chiral  $\text{Ru}\cdot\text{L-19}$  complex for asymmetric cyclopropanation reaction in  $\text{scCO}_2$  has been reported. It is demonstrated that productivity in  $\text{scCO}_2$  has been increased 7.7-fold compared with that in DCM. Environmental friendliness and ease of product separation are further merits (Scheme 1.32) [47].

An inverted  $\text{scCO}_2$ /aqueous biphasic system has been used as reaction media for Rh-catalyzed asymmetric hydrogenation. Chiral  $\text{CO}_2$ -philic catalysts are efficiently immobilized in  $\text{scCO}_2$  as the stationary phase, while polar substrates and products are contained in water as a mobile phase. The catalyst phase is reused several times with high conversion and product recovery of more than 85%. The chiral ligand (*R,S*)-3- $\text{H}^2\text{F}^6$ -BINAPHOS (**L-16**) allows highly enantioselective hydrogenation of itaconic acid and methyl-2-acetamidoacrylate under these conditions [48].

### 1.3.3. IL

ILs are defined as materials that are composed of ions and have melting points below  $100^\circ\text{C}$  (the temperature may be flexible). ILs have many properties that lend themselves to clean chemical synthesis, perhaps most notably that they are nonvolatile and are therefore not lost to the atmosphere. The main advantages are that catalyst lifetimes can be extended, often considerably, and rates of reactions are accelerated in many cases. In addition, recovery and reuse of catalysts is possible using biphasic or multiphase catalyst systems. Efficient reactions with organic compounds under homogeneous conditions in an IL, followed by extraction of the products with  $\text{scCO}_2$ , provide an ideal process without any volatile organic solvents. Typical ILs are shown in Scheme 1.33.

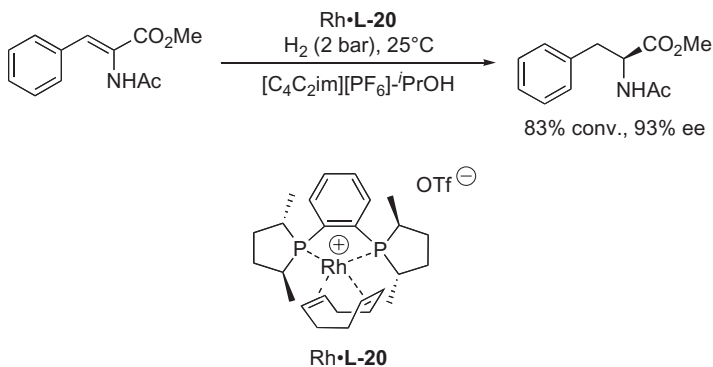


**Scheme 1.33.** Major classes of ionic liquids.

**1.3.3.1. Asymmetric Hydrogenation in ILs** The catalytic enantioselective hydrogenation of unsaturated bonds such as  $\text{C}=\text{C}$ ,  $\text{C}=\text{O}$ , and  $\text{C}=\text{N}$  in the presence of molecular hydrogen or hydrogen donor is one of the most useful chemical transformations. Since molecular hydrogen is used as the reactant in many cases, it is clear that the solubility of hydrogen gas in ILs is an important factor in catalyzed reactions. It has been suggested that increased reaction rates in biphasic hydrogenation reactions in ILs could be due to high solubility of hydrogen in the IL, and the correlation of ILs and the solubility of molecular hydrogen has been studied [49].

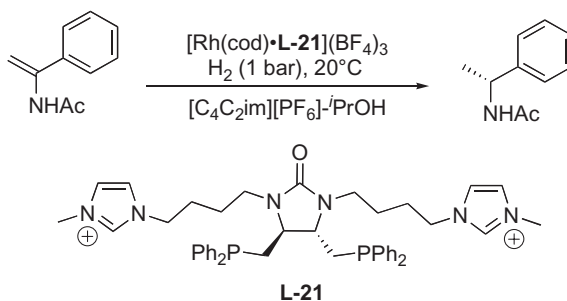
Since the first report of enantioselective metal-catalyzed reaction in ILs [50], asymmetric hydrogenation of carbon-carbon double bonds and carbon-heteroatom double bonds has been the most investigated transformation. Several combinations of transition metals, chiral ligands, and ILs have been studied for these reactions [51].

Rh and Ru-chiral phosphine or Ru-chiral diamine complexes are often combined with *N,N'*-dialkylimidazolium salts [52,53]. The Rh-catalyzed hydrogenation of C=C bond such as  $\alpha$ -acetoamide cinnamic acid and related enamides works well to give the corresponding products with high enantioselectivities (Scheme 1.34). The catalyst can be reused, and IL can suppress the catalyst aging in some cases; however, in other cases, the catalyst loses its activity in the process of recycling, probably because of leaching or deactivation [54].



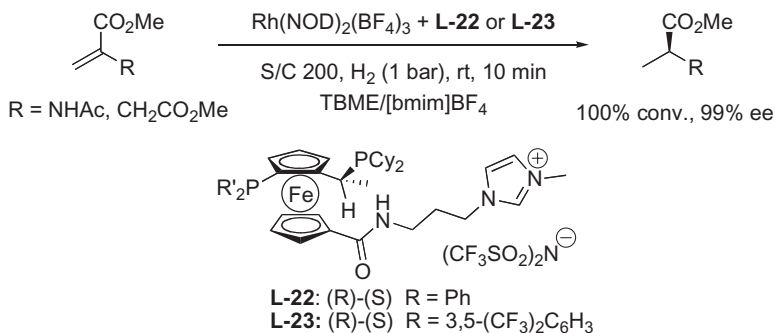
Scheme 1.34.

Imidazolium moieties were introduced to chiral diphosphine ligand (**L-21**) in order to attach the catalyst to the IL phase. The modified catalyst can work efficiently in the hydrogenation and can be recovered and reused without significant loss of activity (Scheme 1.35) [55].



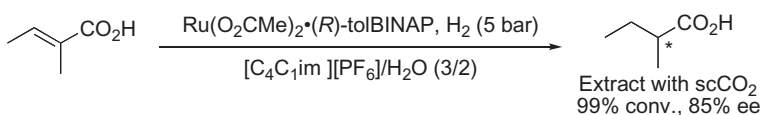
Scheme 1.35.

With a similar concept, Josephos ligands with an imidazolium tag can be applied to the asymmetric hydrogenation of methyl acetamidiacrylate and dimethyl itaconate in biphasic cosolvent/IL combinations (Scheme 1.36) [56,57]. The introduction of an imidazolium group in the Josephos ligand improves the affinity of the Rh complex for the IL to lead the suppression of catalyst leaching in the combination of *t*-butyl methyl ether (TBME)/[bmim]BF<sub>4</sub>. The catalyst can be recycled and reused with efficient product isolation.



Scheme 1.36.

Ru-BINAP and its derivative complexes are very common reagents for asymmetric hydrogenation [58].  $[\text{Ru}(\text{O}_2\text{CMe})_2 \cdot ((R)\text{-tolBINAP})]$  in  $[\text{bmim}][\text{PF}_6]/\text{H}_2\text{O}$  system promotes the hydrogenation of tiglic acid to give the corresponding product in excellent conversion with good ee (Scheme 1.37). The enantioselectivity depends on hydrogen pressure, and water enhances enantioselectivity at high pressure, while there is no effect of adding water at low pressure. To avoid the use of organic solvents, supercritical carbon dioxide ( $\text{scCO}_2$ ) can be applied to this reaction to recover the organic product from the reaction mixture. Since Ru catalyst is not soluble in  $\text{scCO}_2$ , the product can be extracted from IL by  $\text{scCO}_2$  and is contaminated only by water. The catalyst can be immobilized to the IL layer, therefore efficiently reused multiple times without loss of activity and even with enhanced enantioselectivity [59].

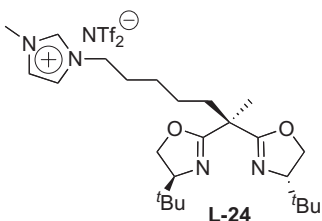
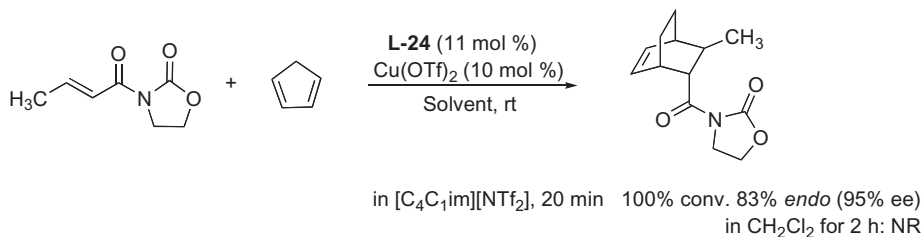


Scheme 1.37.

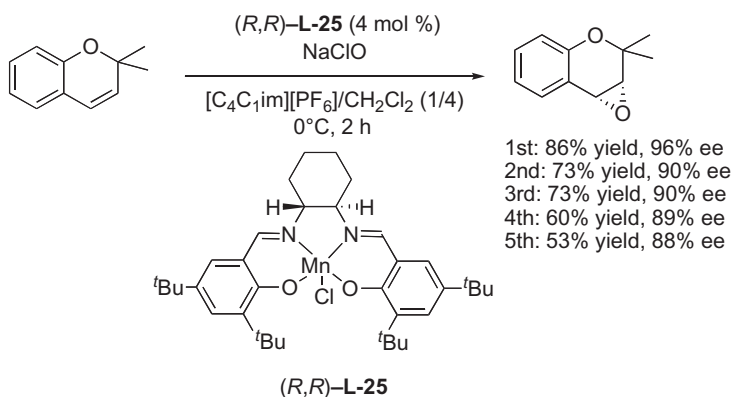
**1.3.3.2. Asymmetric Diels–Alder Reaction in ILs** Copper catalysts based on imidazolium-tagged bis(oxazolines) enhance the reaction rate and enantioselectivity of the corresponding product in the reaction of *N*-acyloyl and *N*-crotonyloxazolidinones with cyclopentadiene and 1,3-cyclohexadiene (Scheme 1.38) [60].

The introduction of an imidazolium tag into bis(oxazolines) significantly improves the recovery and reuse of the catalyst for reactions performed in IL. The catalyst can be recycled at least 10 times without loss of activity and enantioselectivity. Furthermore, the imidazolium-functioned ligand does not leach into the organic phase [61,62].

**1.3.3.3. Asymmetric Epoxidation in ILs** Mn-salen complex **11** catalyzes asymmetric epoxidation of alkenes efficiently in IL [63,64]. Since IL is solidified at the reaction temperature, the reaction requires the use of DCM to form homogenous solution. IL



Scheme 1.38.

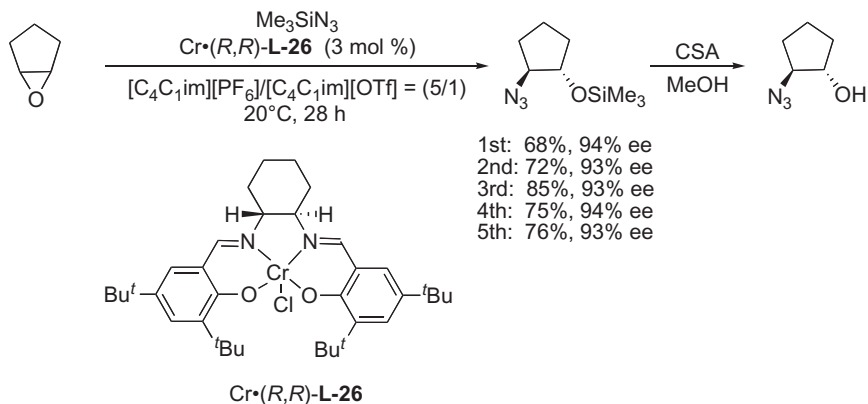


Scheme 1.39.

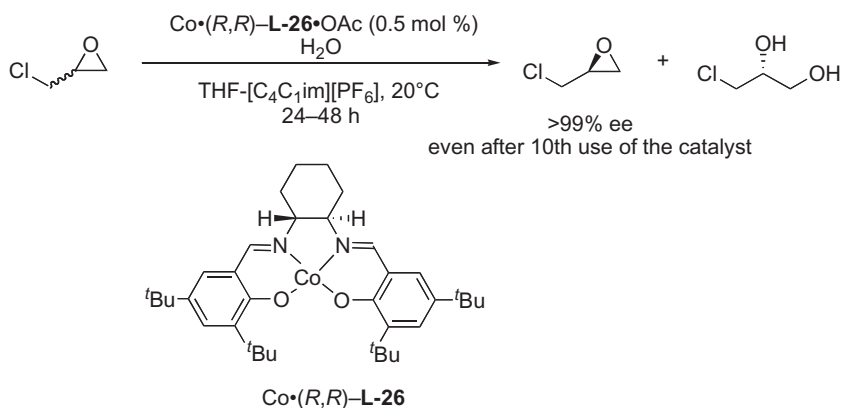
enhances the catalyst's reactivity, and, moreover, IL and chiral complex can be recycled up to five times with only slight loss of ee and catalyst activity (Scheme 1.39).

**1.3.3.4. Asymmetric Ring Opening of Epoxides in ILs** Cr(salen) complex ( $\text{Cr}\cdot\text{L-26}$ ) catalyzes ring opening of epoxides with  $\text{TMSN}_3$  in  $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$  and  $[\text{C}_4\text{C}_1\text{im}][\text{OTf}]$  at room temperature. The catalyst can be recycled up to five times without loss of ee and can even enhance its activity [65] (Scheme 1.40).

Chiral Co(III)(salen) complex catalyzes hydrolytic kinetic resolution of racemic epoxides in ILs. Co(II)(salen) complex is oxidized without acetic acid to catalytically active Co(III)(salen) complex during the reaction, and this oxidation state is stabilized



Scheme 1.40.

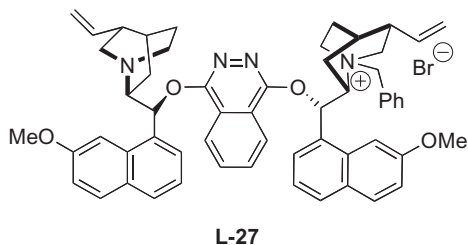


Scheme 1.41.

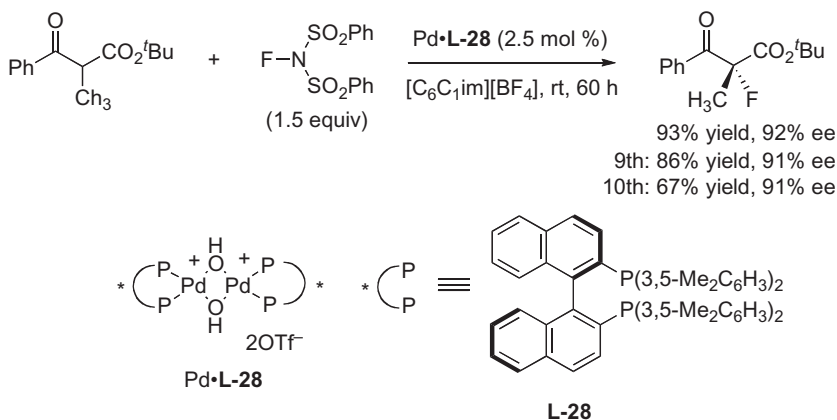
against reduction to Co(II) complex. The catalyst can be reused 10 times without loss of ee and reactivity [66] (Scheme 1.41).

**1.3.3.5. Asymmetric Dihydroxylation in ILs** Osmium-catalyzed asymmetric dihydroxylation constitutes a versatile method for the synthesis of chiral vicinal diols from alkenes. Its industrial utility suffers from several disadvantages, mainly the high cost of osmium and chiral ligands and the toxicity of the metal, which may contaminate the optically active product. To address these issues, many efforts to modify these catalysts have been made. The main way to utilize chiral  $\text{OsO}_4$  catalysts efficiently is to immobilize the catalyst to polymers [67], porous resins [68], and the other various solid supports [69]. IL can also provide functions to support the catalysts [70]. In the asymmetric dihydroxylation of *trans*-stilbene catalyzed by  $\text{OsO}_4$  (1.5 mol %) and ligand **L-27** (2.0 mol %) in the presence of *N*-methylmorpholine *N*-oxide (NMO) (2.6 mol %) and  $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$  (2 mL for 2-mmol scale) in acetone–water (v/v, 10/1) at 0°C, the catalyst can be recovered in IL phase and reused up to three times without significant loss of activity and ee with

only a small amount of  $\text{OsO}_4$  (<2% of the total amount) leaching from IL phase to organic phase [71].



**1.3.3.6. Asymmetric Fluorination in ILs** Chiral Pd-BINAP complex-catalyzed enantioselective fluorination of  $\beta$ -ketoesters and  $\beta$ -ketophosphonates can be achieved in ILs (Scheme 1.42). The reactions proceed smoothly to afford the corresponding products in good yields with ees in most cases [72]. The catalyst can be reused up to 10 times with slight loss of activity.



**Scheme 1.42.**

**1.3.3.7. Others** There are some more reactions such as asymmetric allylic substitution [73], asymmetric cyclopropanation [74], asymmetric synthesis of cyanhydrines [75], asymmetric allylation [76], asymmetric addition of alkynes to imines [77], and asymmetric hydroamination [78]. These reactions have been investigated in ILs; however, considering the property, character, and aim of using ILs, reuse of the catalysts should be further investigated.

## 1.4. MICROWAVE-ASSISTED CATALYTIC ASYMMETRIC SYNTHESIS

Microwave irradiation has been widely accepted in academic chemical laboratories as well as pharmaceutical companies. The use of this nonconventional method in chemical

transformations can be traced back several decades, and since the first reports were published [79], the number of publications regarding microwave-assisted organic synthesis has been increasing. Chemists generally use a microwave to heat chemical reactions on a laboratory scale [80]. Direct microwave heating can reduce chemical reaction times from days or hours to minutes or even seconds, and therefore suppress undesired side reactions, increase chemical yields, and improve reproducibility. Thus, microwave-assisted organic chemistry is an aspect of green chemistry. Two microwave effects are known.

#### (1) Microwave-enhanced thermal effects

Each material such as a solvent, a reagent, a reaction intermediate, and a catalyst has its own ability to absorb microwave energy and convert it into heat. Microwave-enhanced chemistry is based on this ability, induced by the electric dipole of the material. Compared with conventional heating, some specific features of microwave heating include (i) selective heating of specific reaction components, (ii) rapid heating rates and temperature gradients, (iii) elimination of reaction vessel wall effects, and (iv) superheating of solvents.

#### (2) Nonthermal microwave effects

These effects have been proposed in order to explain unusual observations in microwave chemistry, and do not involve the transfer of microwave energy into thermal energy, as the name suggests. The details are still under discussion.

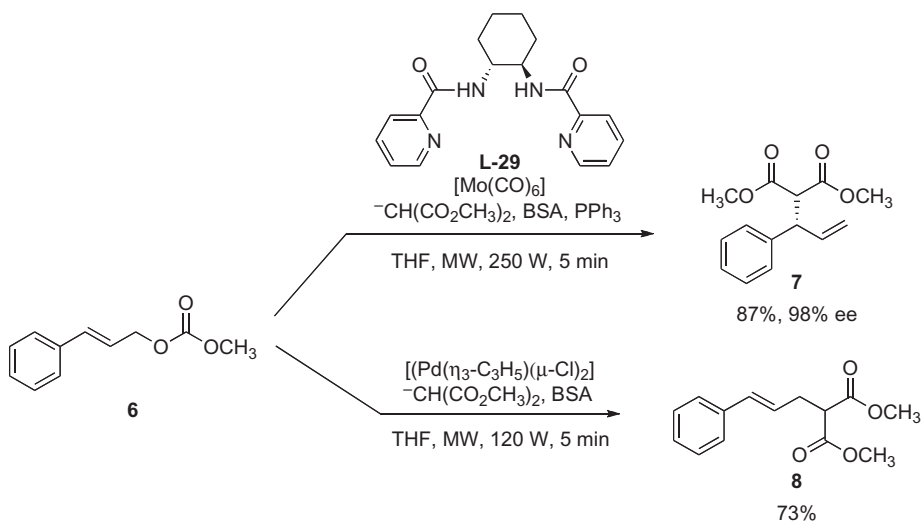
In general, high reaction temperatures will invariably lead to the loss of selectivities. This phenomenon may be one of the reasons why comparatively few enantioselective processes under microwave heating have been reported, in contrast to non-enantioselective procedures. In this chapter, several representative examples of enantioselective reactions are described.

### 1.4.1. Asymmetric Allylic Alkylations

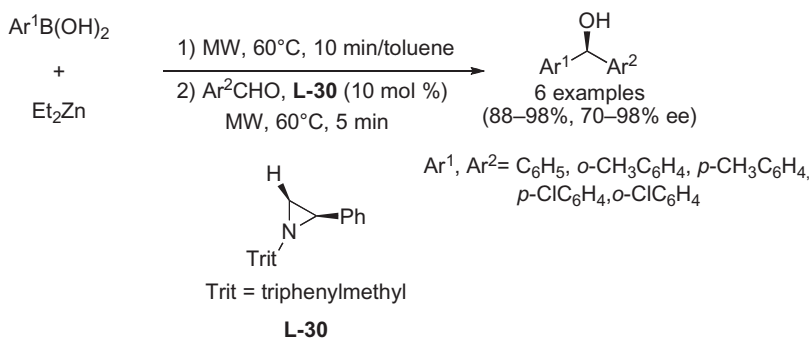
Molybdenum • ligand **L-29** complex catalyzes asymmetric allylic alkylation of the carbonate **6** with dimethyl malonate under microwave heating with a shortened reaction time, affording the product **7** with excellent regio- and enantioselectivities, whereas **8** is obtained predominantly in the presence of a palladium catalyst (Scheme 1.43) [81,82]. The reaction proceeds at 220°C by *flush heating* in tetrahydrofuran (THF), far above its boiling point under normal pressure. Under microwave conditions, the reaction systems are exposed to considerable pressure in closed vessels. Any rate acceleration in such cases might be caused by high temperature and the change of the physical properties of the solvents. Therefore, it is difficult to compare microwave conditions and conventional heating conditions directly.

### 1.4.2. Enantioselective Arylation and Alkylation of Aromatic Aldehydes

Microwave irradiation also has an impact on arylation of aromatic aldehydes via arylzinc addition using aziridine-based ligand [83,84]. A reactive arylzinc is generated from an aryl boronic acid and Et<sub>2</sub>Zn by microwave irradiation for 10 min. Followed by the addition of an aldehyde and a ligand, further microwave heating for 5 min accelerates the reaction. The reaction time can be reduced from 1 h to 15 min by changing conventional heating to microwave radiation (Scheme 1.44).



Scheme 1.43.

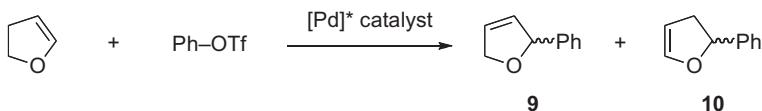


Scheme 1.44.

### 1.4.3. Asymmetric Heck Reactions (1)

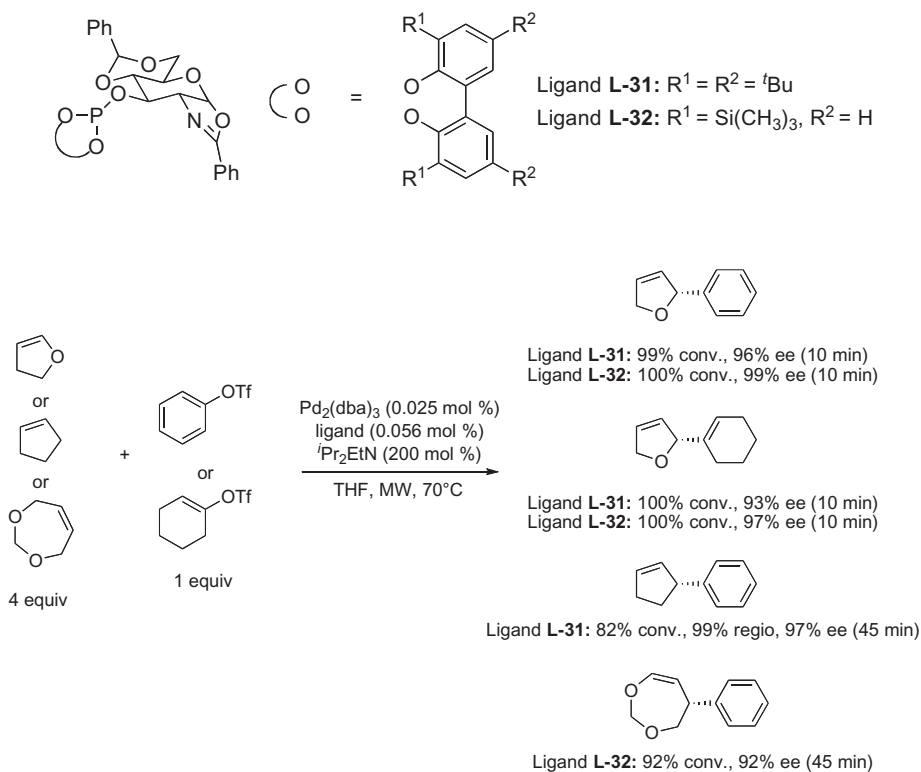
Asymmetric Pd-catalyzed Heck reaction, that is, coupling of an aryl or alkyl halide or triflate and an alkene, is one of the most powerful and versatile procedures in carbon-carbon bond-forming reactions, since it tolerates several functional groups. In an intermolecular Heck reaction such as 2,3-dihydrofuran with phenyl triflate, regioselectivity is problematic because the undesired product **10** is obtained in addition to **9** due to an isomerization in the reaction process (Scheme 1.45).

Several ligands such as phosphanyloxazoline (PHOX) ligands have been successfully discovered for intermolecular Heck reactions [85,86]. In spite of their accomplishments, one of the drawbacks with N, P ligands is long reaction times for full conversion. To address this issue, microwave irradiation has been applied to asymmetric Heck reactions



Scheme 1.45.

[87–89]. The reaction of 2,3-dihydrofuran, cyclopentene, and 4,7-dihydro-1,3-dioxepin with phenyl- or cyclohexenyl triflate employing either ligand **L-31** or **L-32** combined with Pd catalyst produces the corresponding products in excellent conversion yields with high regio- and enantioselectivities (Scheme 1.46). Compared with the optimized conditions that require conventional heating at 50°C, microwave heating at 70°C dramatically shortens the reaction time from up to 2.5 days to 10–45 min.

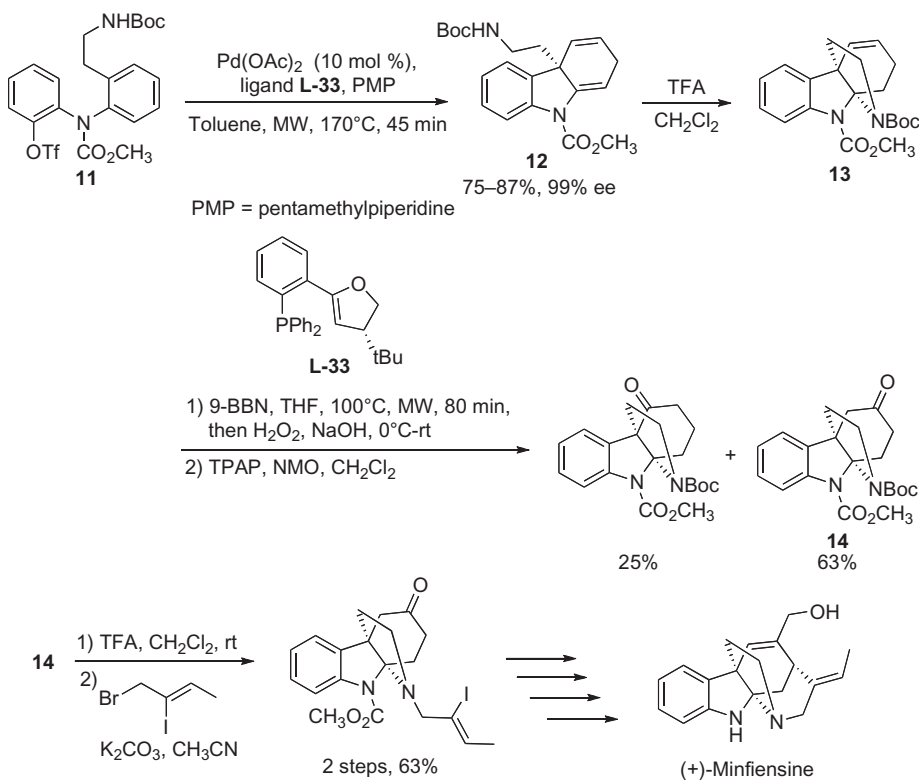


Scheme 1.46.

#### 1.4.4. Asymmetric Heck Reactions (2); Total Synthesis of (+)-Minfiensine [90]

Microwave irradiation has been applied to a key step, intramolecular asymmetric Heck reaction of substrate **11**, in the total synthesis of (+)-minfiensine. The reaction is conducted at 170°C for 45 min to afford **12** in high yield with excellent ee. Furthermore, the

shorter reaction time allowed the catalyst loading to be reduced to 10 mol % of Pd. In the second generation of the total synthesis of (+)-minfiensine, hydroboration of **13** proceeds under microwave heating with 9-BBN at 100°C in THF, whereas no reaction takes place under reflux conditions. Followed by the oxidation with trans-chelating chiral bisphosphine ligands (TPAP)/NMO, the desired ketone **14** is obtained as a major product in 63% yield. Consequently, (+)-minfiensine is successfully synthesized in 6.5% overall yield (15 steps) (Scheme 1.47).

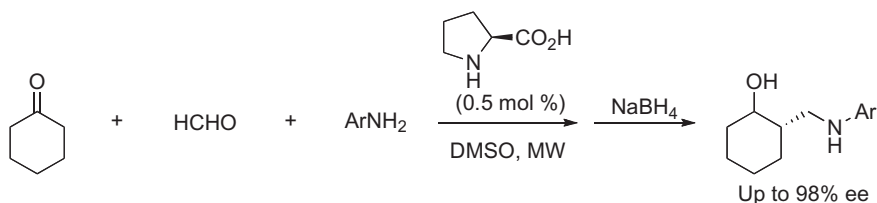


Scheme 1.47.

### 1.4.5. Organocatalyzed Asymmetric Reactions

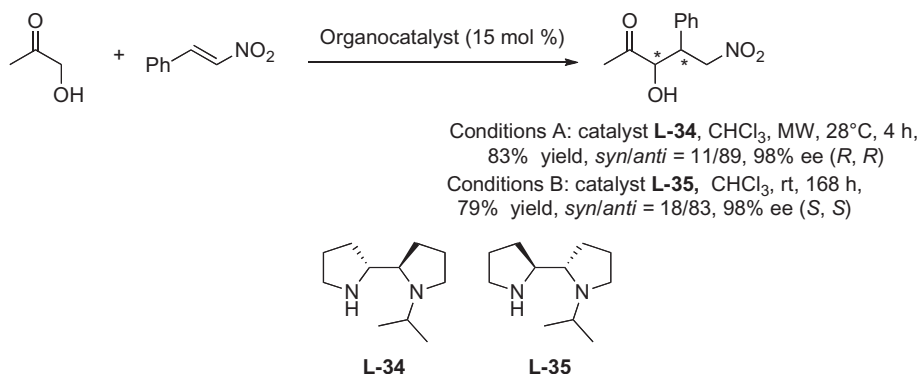
Proline-catalyzed Mannich reactions have been intensively investigated [91,92]. Although high enantioselectivities and high yields have been achieved for several substrates, two drawbacks have been pointed out: relatively high catalyst loading and relatively longer reaction times.

Direct asymmetric Mannich reactions among cyclohexanone, formaldehyde, and various anilines are performed under microwave heating, and the reactions are thermally accelerated in the presence of only 0.5 mol % of catalyst. Mannich products with up to 98% ee are obtained after a short reaction time. *In situ* reduction of the resulting ketones affords *N*-aryl amino alcohols in up to 86% yield (Scheme 1.48) [93].



Scheme 1.48.

Chiral organocatalyzed aldol reaction, Michael-type reaction, and Diels–Alder reaction have been applied to microwave-assisted reactions [94]. In all cases, the reaction times are dramatically shortened. The most successful example in terms of enantioselectivity was bipyrrolidine-catalyzed Michael-type reaction. Compared with conventional heating (Conditions B), it is clear that microwave heating accelerates the reaction without loss of diastereo- and enantioselectivities (Scheme 1.49).



Scheme 1.49.

## 1.5. CONCLUSION/PERSPECTIVE

Catalytic asymmetric synthesis in nonconventional media/conditions has been surveyed. While chiral catalysts have been developed in conventional organic solvents, nonconventional media/conditions are important not only from a scientific aspect but also from an economical point of view. Since many elegant *in vitro* reactions are carried out in an aqueous environment in our bodies, catalytic symmetric reactions in water under *in vitro* conditions are being studied to clarify and understand their mechanisms. Further, water is inexpensive and the most environmentally friendly solvent. On the other hand, recovery and reuse of catalysts in asymmetric reactions is extremely important especially in industry, since most chiral catalysts are expensive. Immobilization of chiral catalysts in nonconventional media such as fluorinated solvents, SCFs, and ILs can meet such purposes.

Several new device systems have also been developed for truly efficient organic synthesis, and they also apply to catalytic asymmetric synthesis. Microwave-assisted reactions are such examples. While reaction times are shortened dramatically from days to even seconds, the high temperature generally required leads to lower selectivities.

Alternative promising nonconventional devices include microchannel reactors with small channels, which are micrometer sized in width and depth, and are solvent-free systems. Although preliminary examples for applying catalytic asymmetric synthesis under such conditions have been reported, further investigation is necessary.

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