

Module 7 Reactions in Nonconventional Conditions

Lecture 25 Reactions in Nonconventional Conditions I

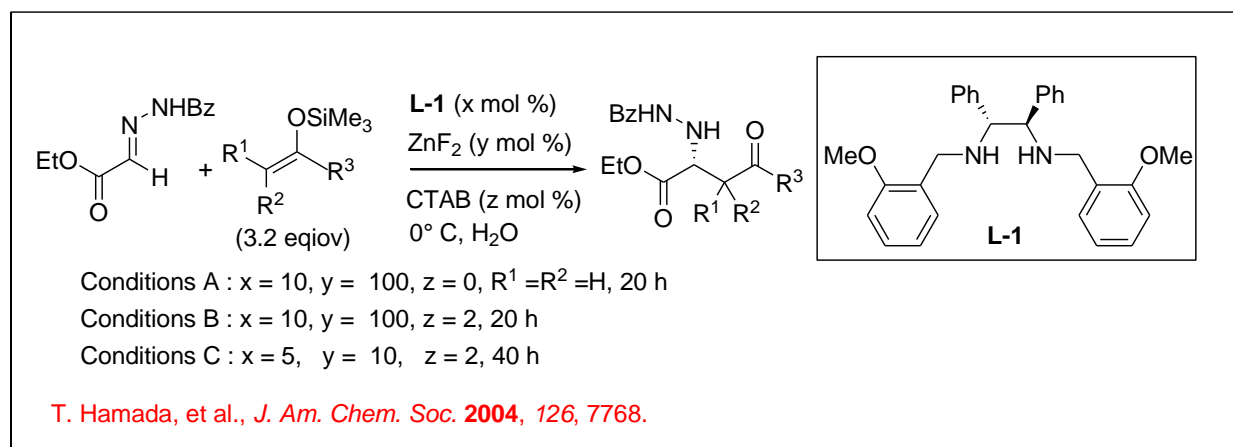
Many of the organic solvents are volatile, flammable, sometimes explosive and have damaging effect to human health or on the environment. Thus, effort has been made to use nonconventional solvents which are not only attractive from economical aspects, they can provide advantages of recovery and recyclability of the catalysts. The section covers the use of water, fluorous solvents, supercritical fluids and ionic liquids as nonconventional solvents.

7.1 Reactions in water

The use of water as a reaction medium for organic synthesis has attracted much interest in recent years. Because water is the most abundant liquid on the planet, cheap, readily available, non-toxic and non-flammable. This lecture covers some of the recent developments in asymmetric catalysis that have been performed in water as reaction medium.

7.1.1 Mannich Reaction

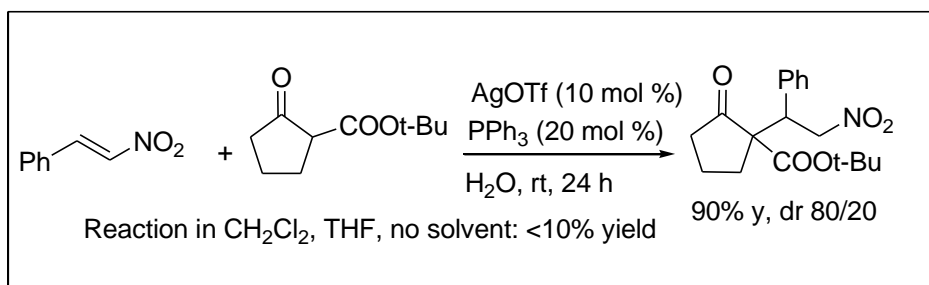
Mannich reaction affords useful route for the synthesis of β -amino ketones and esters that serve as building blocks for the construction of nitrogen containing compounds. The asymmetric version of the reaction has been shown from α -hydrazono ester and silicon enoate using chiral ZnF_2 -**L-1** complex in aqueous medium (Scheme 1). The reaction proceeds without any organic solvents or additives and the presence of cetyltrimethyl ammonium bromide (CTAB) is necessary to accelerate the reaction.



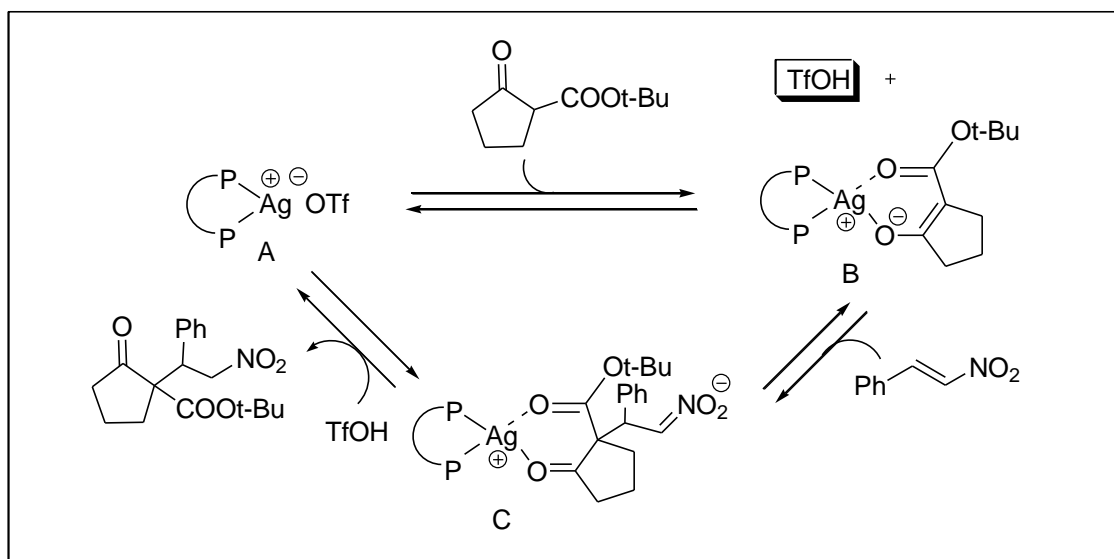
Scheme 1

7.1.2 Michel Reaction

Michel addition of β -ketoesters to nitroalkenes using AgOTf-PPh_3 proceeds efficiently in water but not in organic solvents (Scheme 2). Regarding the mechanism, the reaction in water becomes heterogeneous, and the metal enolate stays in organic phase, while TfOH is excluded into water phase because of the difference between their hydrophobicity (Scheme 3). Thus, the metal enolate B does not have the contact with TfOH , and the reverse reaction from B to A is suppressed. In contrast, in normal organic solvent, the reaction mixture becomes homogeneous and the reverse reaction from B to A is fast.

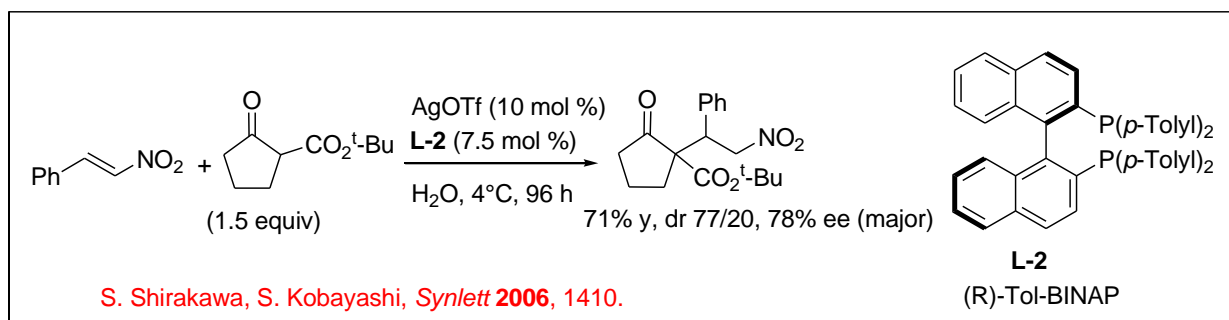


Scheme 2



Scheme 3

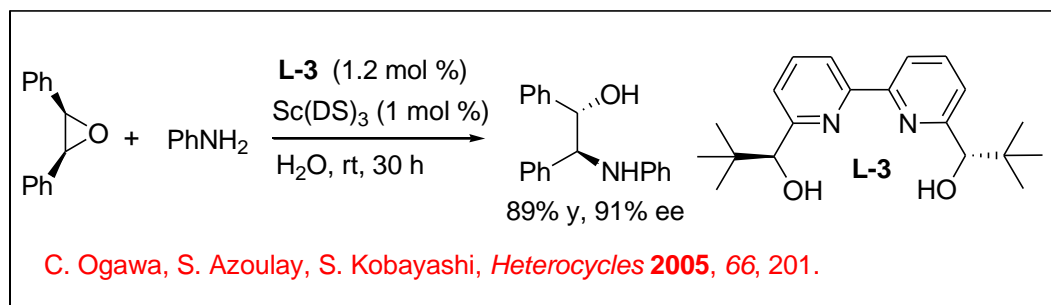
This reaction has been applied for the asymmetric version employing **L-2** as chiral source to afford the target products with up to 78% ee (Scheme 4).



Scheme 4

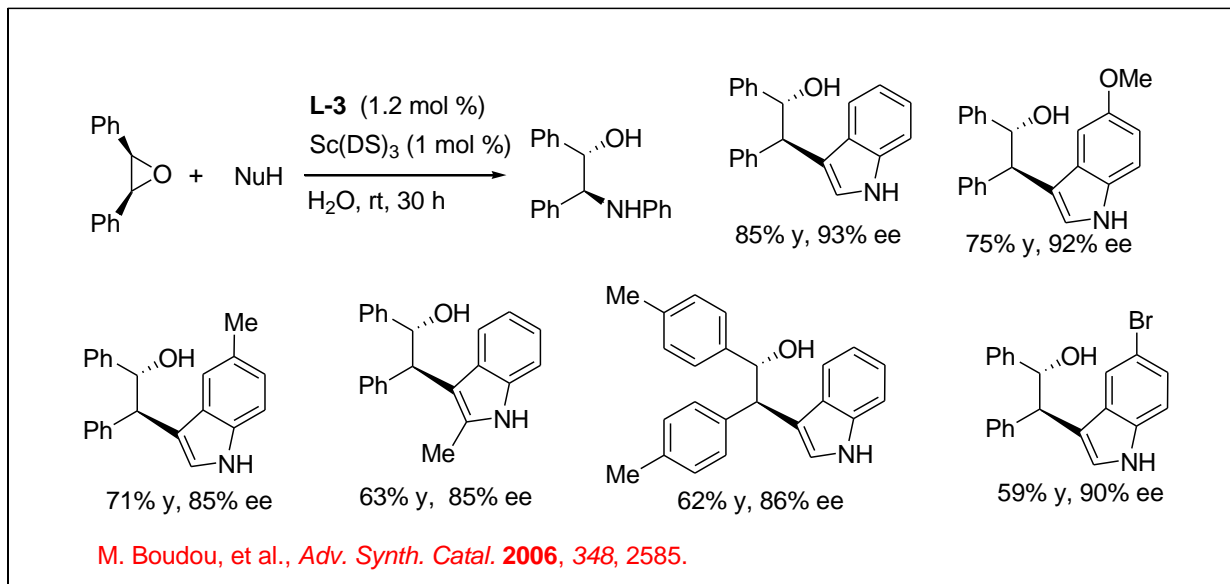
7.1.3 Desymmetrization of Epoxides

This reaction condition has been subsequently used for the asymmetric desymmetrization of epoxides with nitrogen nucleophiles using **L-3** as chiral source (Scheme 5). The reaction proceeds with high enantioselectivity and no diol formation has been observed.

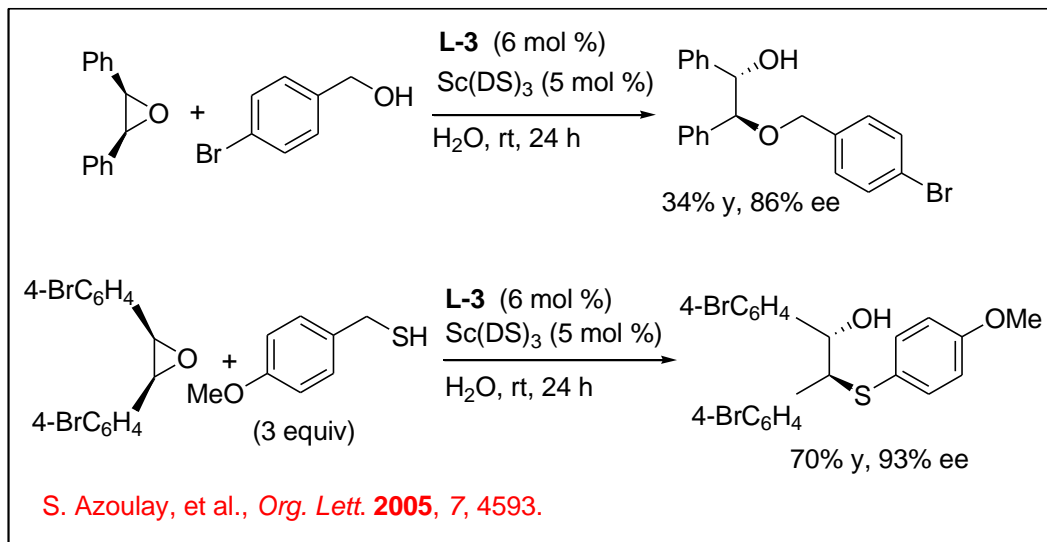


Scheme 5

The asymmetric desymmetrization of the epoxides is also successful with indoles, alcohols and thiols with high enantioselectivities (Schemes 6 and 7).



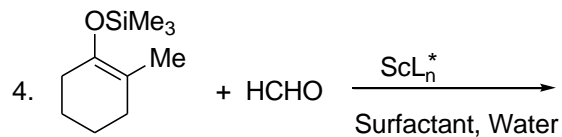
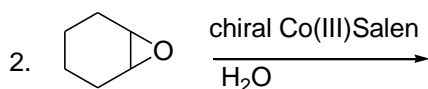
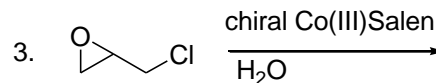
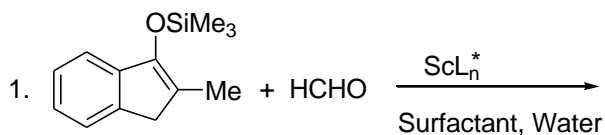
Scheme 6



Scheme 7

Problems

A. Complete the following reactions.



B. Describe chiral Fe, Ti and Co-catalyzed asymmetric oxidations in water medium.

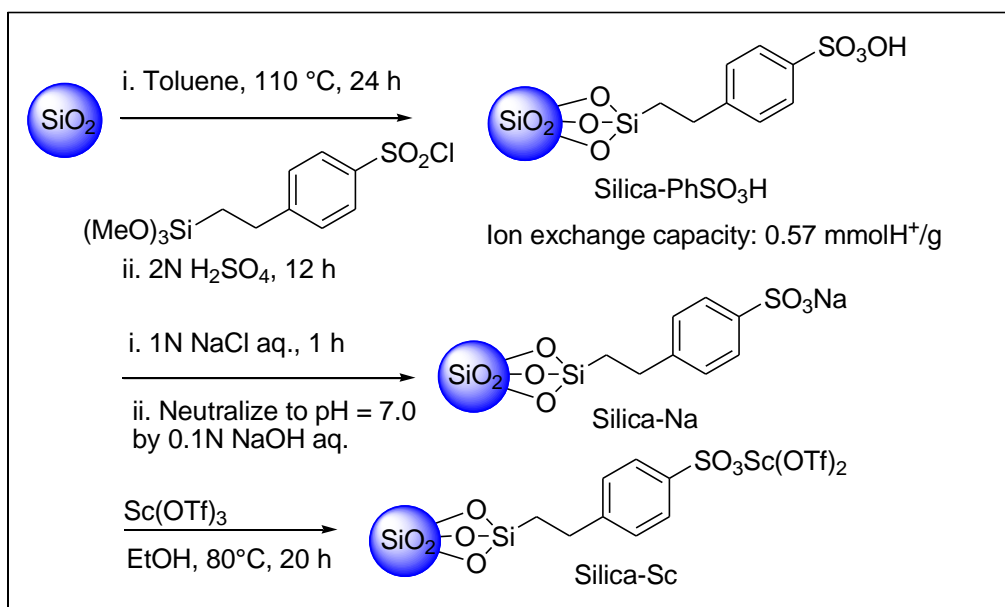
Reference/Text Book

1. I. Ojima, *Catalytic Asymmetric Synthesis*, 3rd ed., Wiley, New Jersey, 2010.
2. M. B. Smith, *Organic Synthesis*, 2nd edition, McGraw Hill, New Delhi, 2004.

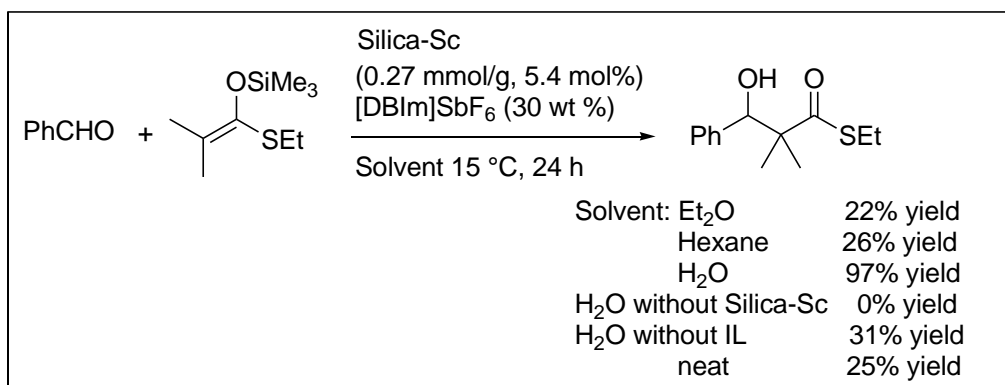
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7.1.4 Aldol Reaction

Silica gel-supported scandium (Silica-Sc) with ionic liquid, [DBIm]SbF₆, is a heterogeneous catalytic system works efficiently in Mukaiyama aldol reaction in water (Schemes 1 and 2). The reaction proceeds efficiently in water medium compared to that in organic solvents, without solvent or in the absence of ionic liquid (IL).

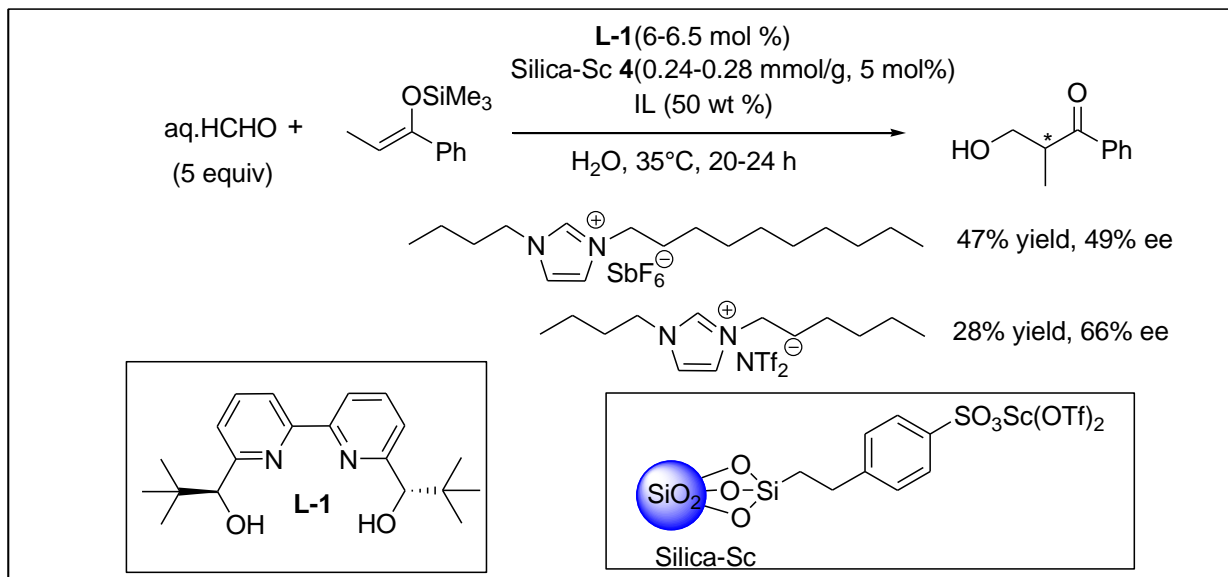


Scheme 1



Scheme 2

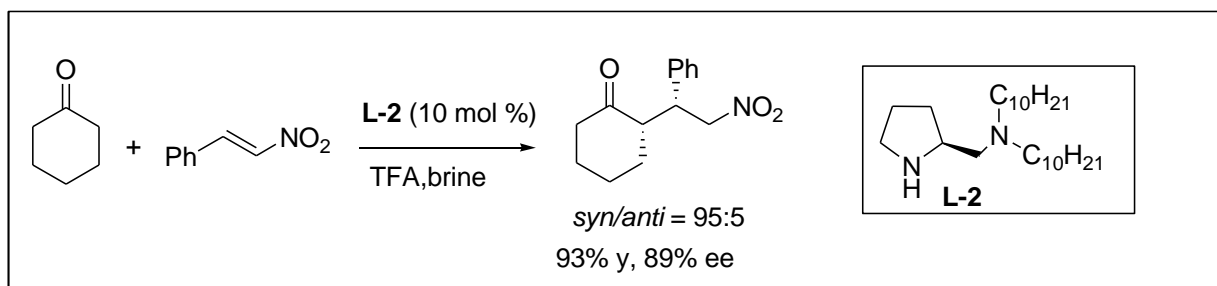
Asymmetric version of the reaction has been subsequently developed employing **L-1** as chiral source with moderate enantioselectivity (Scheme 3).



Scheme 3

7.1.5 Michael Reaction

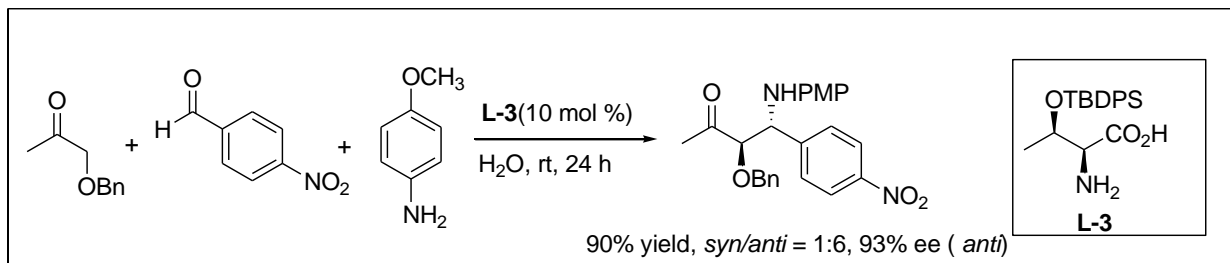
Asymmetric Michael reaction of ketones with α -nitrostyrene has been studied using proline derivative **L-2** in brine with good enantioselectivity (Scheme 4).



Scheme 4

7.1.6 Mannich Reaction

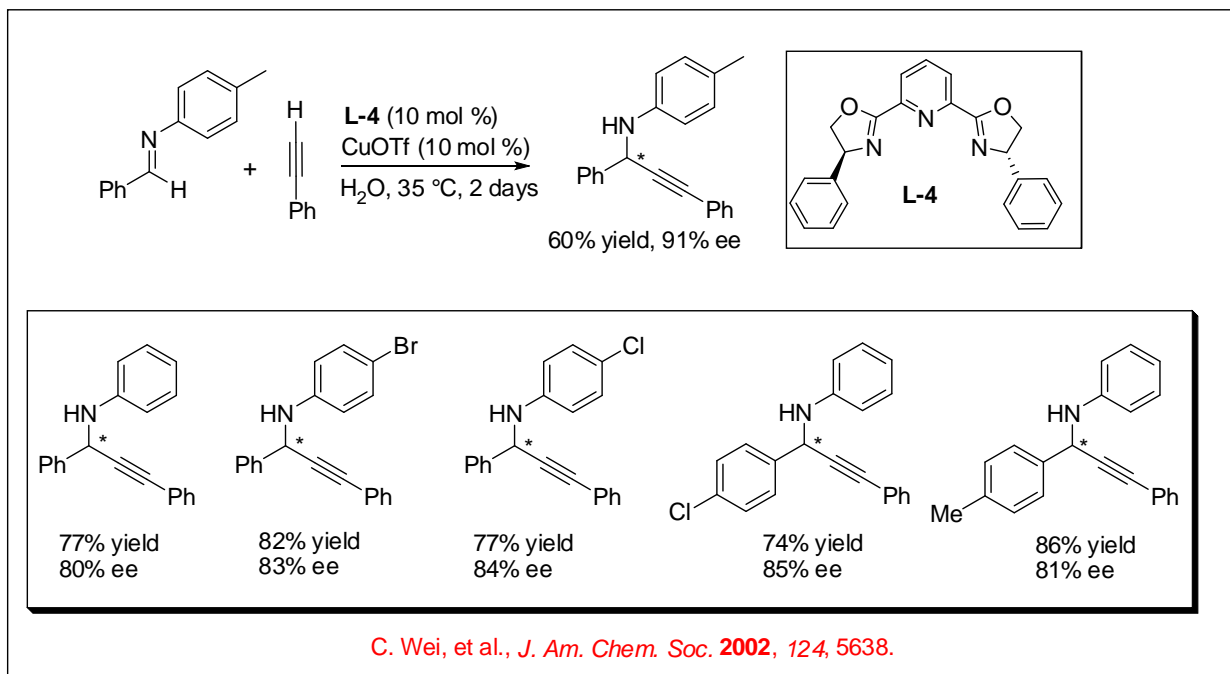
Asymmetric Mannich reaction of aryl aldehydes, aryl amines and aliphatic ketones occurs in water in the presence of threonine derivative **L-3** with excellent diastereoselectivity (Scheme 5).



Scheme 5

7.1.7 Addition Reactions of Alkynes

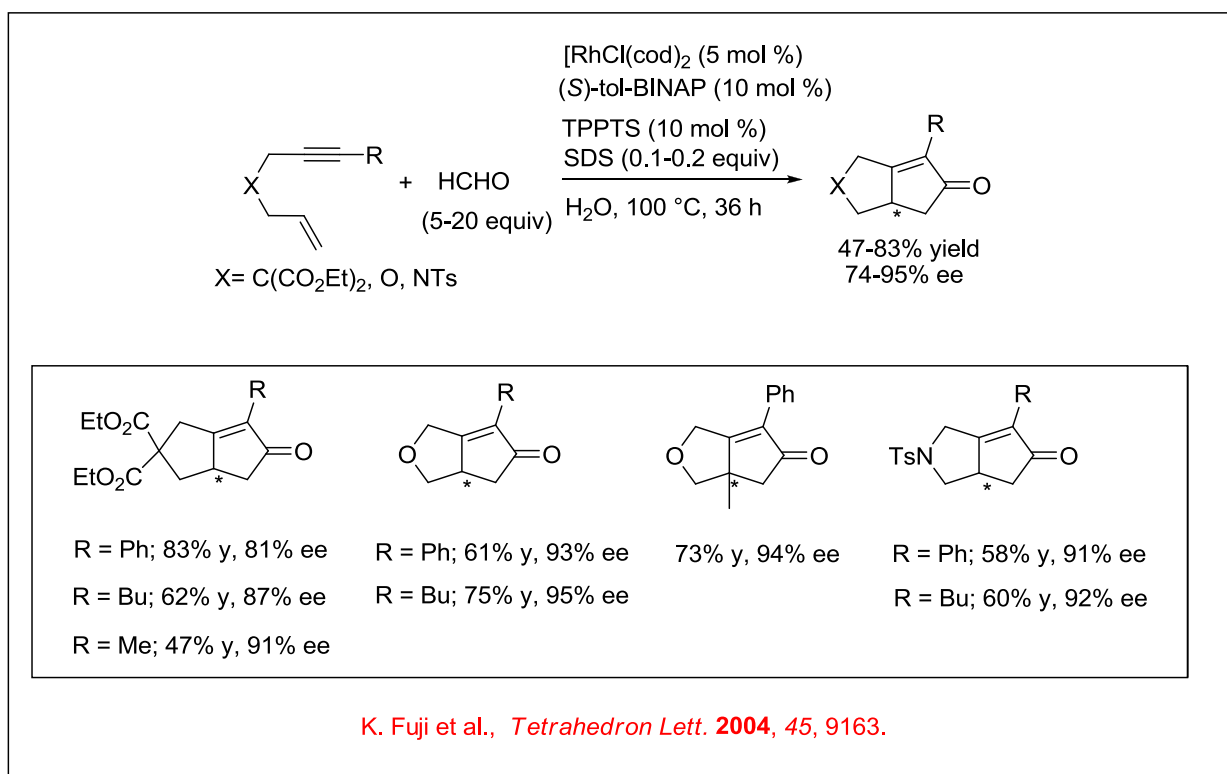
Propargylamines are important synthetic intermediates for the synthesis of nitrogen containing compounds in organic synthesis. The direct alkyne-imine addition can be accomplished employing chiral CuOTf-**L-4** complex (Scheme 6). The method is simple and affords a diverse range of propargylic amines with high enantioselectivity.



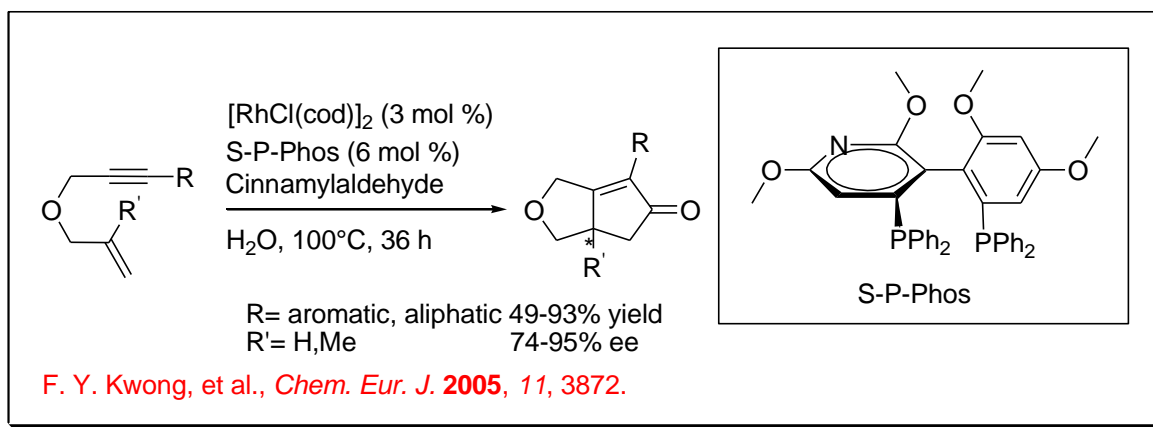
Scheme 6

7.1.8 Pauson-Khand Reaction

Asymmetric Pauson-Khand reaction can be performed using chiral Rh complexes in water. The complex derived from $[\text{RhCl}(\text{cod})]_2$ and (S)-tol-BINAP has been found to be effective for the Pauson-Khand reaction employing HCHO as CO source with good enantioselectivity (Scheme 7). Chiral rhodium complex derived from $[\text{RhCl}(\text{cod})]_2$ and S-P-Phos has also been used for the Pauson-Khand reaction with similar enantioselectivity (Scheme 8).



Scheme 7



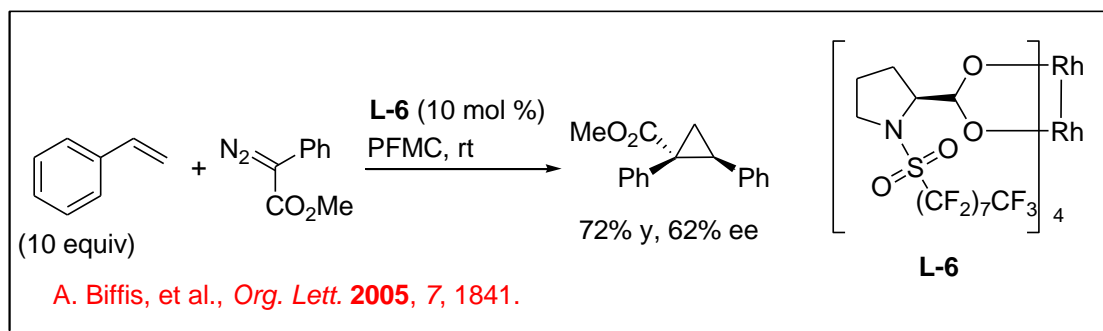
Scheme 8

7.2 Reactions in Fluorous Solvents

Fluorous solvents having suitable boiling and melting points can be used as solvent. Importantly, the fluorous solvents are different from the corresponding hydrocarbons and form two layers with conventional organic solvents. Thus, some catalysts can be immobilized in fluorous solvents in biphasic system and can be recovered and recycled. In addition, in some combination, the fluorous and organic solvents on heating are miscible at elevated temperature leading to a homogeneous mixture, which, after the reaction, on cooling to room temperature lead to the formation of a biphasic system. The products stay in organic phase and the catalysts move to fluorous phase that can be recovered and recycled.

7.2.1 Cyclopropanation

Fluorous complex tetrakis-dirhodium(II)-(S)-N-(n-perfluorooctylsulfonyl)pollinate **L-6** exhibits good chemo- and diastereoselectivity in cyclopropanation of styrene (Scheme 9). The advantage of the protocol is that the catalyst can be separated from the reaction mixture and recycled.



Scheme 9

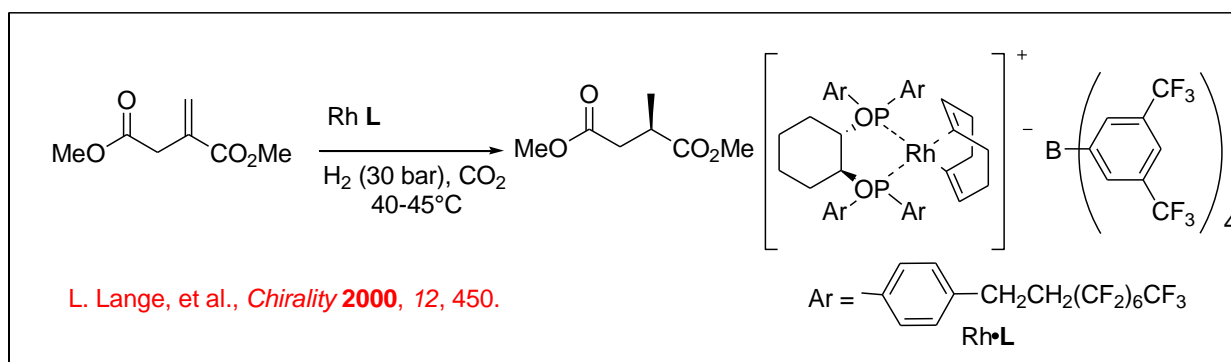
7.3 Reactions in Supercritical Fluids (SCFs)

SCF is a substance above its critical temperature (T_c) and pressure (P_c), but below the pressure condensation leads to a solid. At the critical point, high temperature and pressure, the substance can exist both as a vapor and a liquid in equilibrium. Thus, in a closed system, as both the temperature and pressure increase, the liquid becomes less dense due to thermal expansion, and the gas becomes dense as the pressure rises. Thus, the densities of both the phases converge until they become identical at the critical point. At this point, both the phases become indistinguishable and SCF is formed. In such SCF, a high reactivity and selectivity are sometime observed.

Supercritical carbon dioxide ($scCO_2$) offers the advantages that simple depressurization leads to removal of the residual $scCO_2$, and thus, no hazardous solvent is produced, providing effective route for the separation of the products. Thus the synthesis of organic compounds can be accomplished under solvent-free conditions that find wide applications in pharmaceutical, food and cosmetic industries.

7.3.1 Hydrogenation of Alkenes

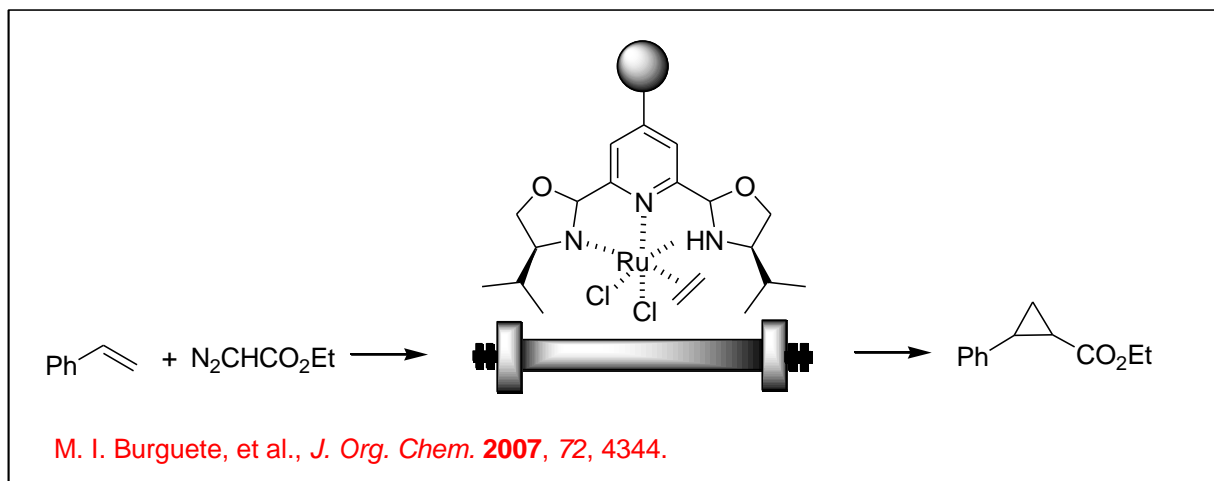
Asymmetric hydrogenation of alkenes can be carried out in $scCO_2$ using chiral Rh complex with good enantioselectivity (Scheme 10). The catalyst is dissolved in $scCO_2$ during the reaction making the process homogeneous.



Scheme 10

7.3.2 Cyclopropanation

The continuous flow of scCO₂ has been used for the asymmetric cyclopropanation using an immobilized chiral Ru complex (Scheme 11). The reaction has been reported 7.7 fold more efficient compared to that within dichloromethane solvent. In addition, easy product separation and environmental friendliness makes the process more attractive.

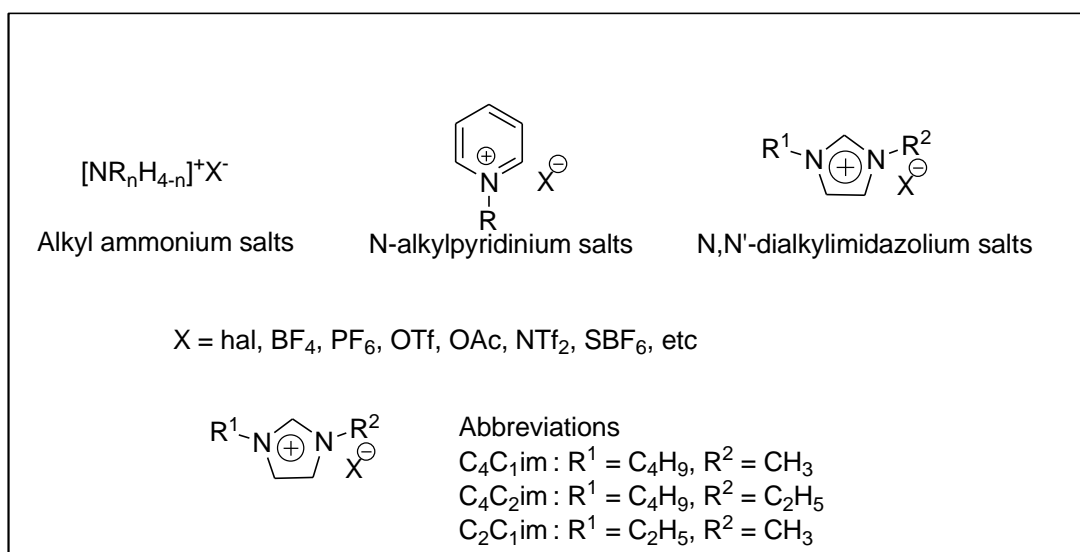


Scheme 11

7.4 Reactions in Ionic Liquid (IL)

Ionic liquids are composed of ions having melting points below 100 °C. They are nonvolatile and facilitate the recovery and recyclability of the catalysts.

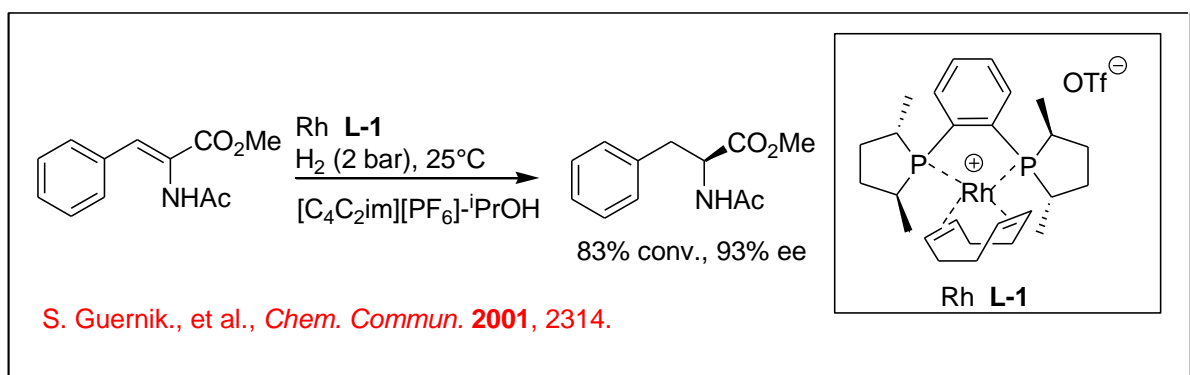
Scheme 12 presents some of the typical ILs.



Scheme 12

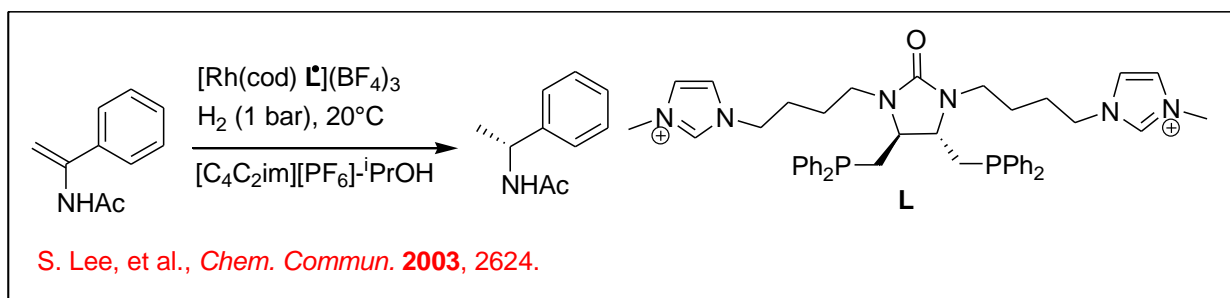
7.4.1 Hydrogenation of Alkenes

Asymmetric hydrogenation of alkenes using molecular hydrogen as hydrogen source is one of the useful chemical transformation. For example, the chiral rhodium complex Rh **L-1** catalyses the hydrogenation of α -acetoamide cinnamic acid and related enamides with high enantioselectivity in IL $[\text{C}_4\text{C}_2\text{im}][\text{PF}_6]$. The catalyst can be reused and IL can suppress the catalyst aging in some cases.



Scheme 13

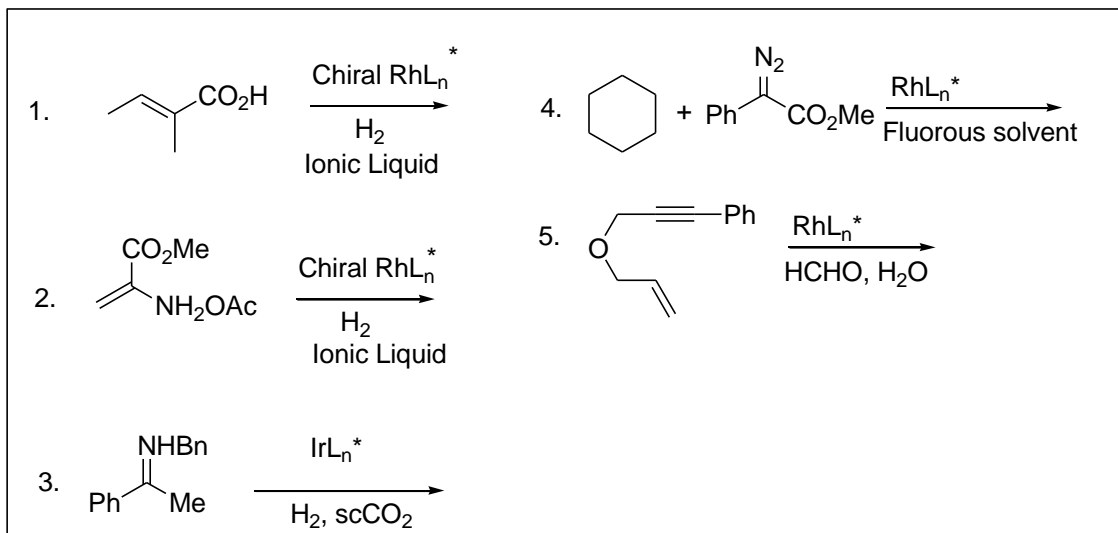
The modified rhodium complex bearing chiral diphosphine with imidazolium moieties has been used as effective catalyst for hydrogen reaction in IL (Scheme 14). The catalyst can be recovered and recycled without loss of activity and selectivity.



Scheme 14

Problems

C. Write the major product for the following reactions.



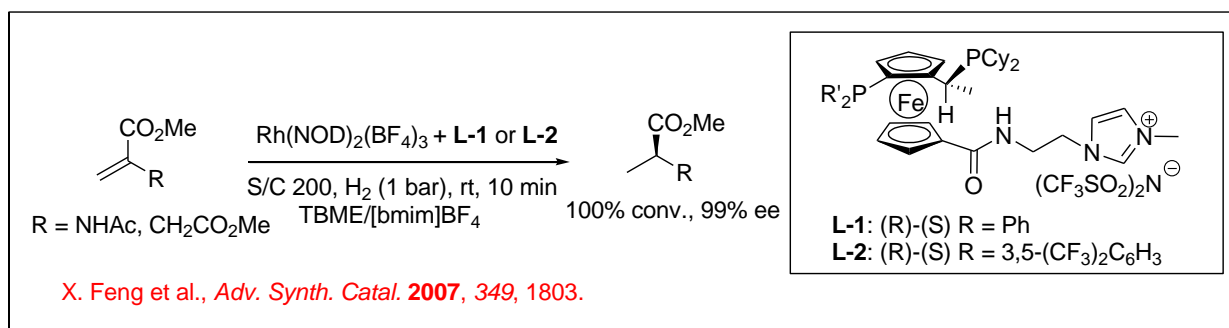
Reference/Text Book

3. I. Ojima, *Catalytic Asymmetric Synthesis*, 3rd ed., Wiley, New Jersey, 2010.
4. M. B. Smith, *Organic Synthesis*, 2nd edition, McGraw Hill, New Delhi, 2004.

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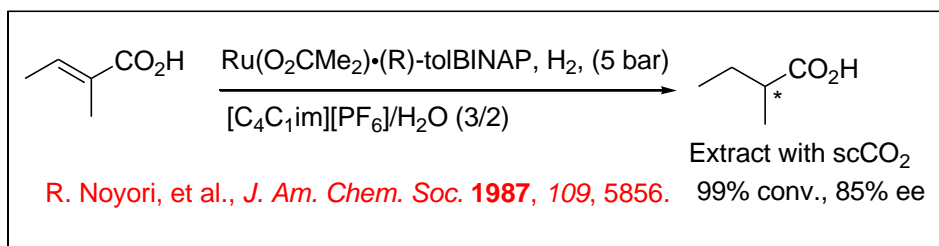
7.4.1 Hydrogenation of Alkenes

The asymmetric hydrogenation of methyl acetamidiacrylate can be accomplished in biphasic cosolvent/IL combination in the presence of chiral rhodium complex bearing Josephose with imidazolium tag in *tert*-butyl methyl ether/[bmim]BF₄ (Scheme 1). The presence of imidazolium tag in the Josephose ligand enhances the affinity of the Rh complex for the IL and suppresses the catalyst leaching. The catalyst can be recycled without loss of activity.



Scheme 1

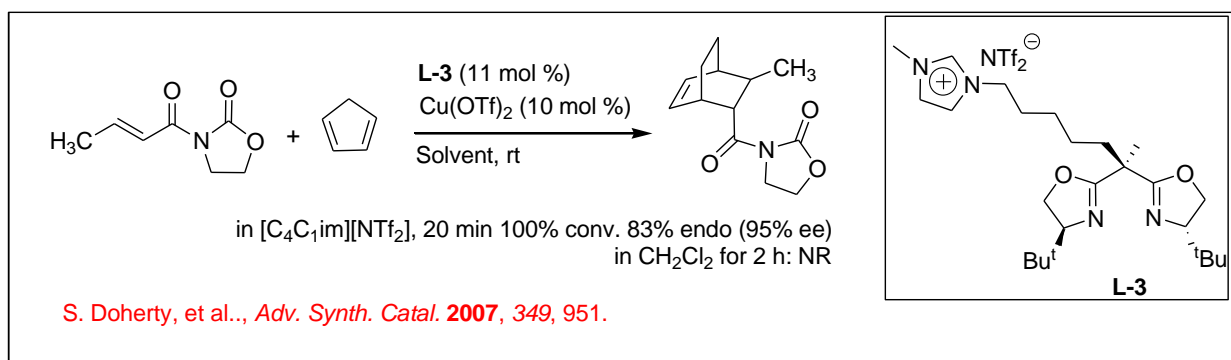
The hydrogenation of tiglic acid has been successful using Ru-BINAP in [bimm]PF₆/H₂O with good enantioselectivity (Scheme 2). The enantioselectivity depends on the pressure of the reaction. At high pressure the presence of water increases the enantioselectivity, but low pressure show no effect.



Scheme 2

7.4.2 Diels-Alder Reaction

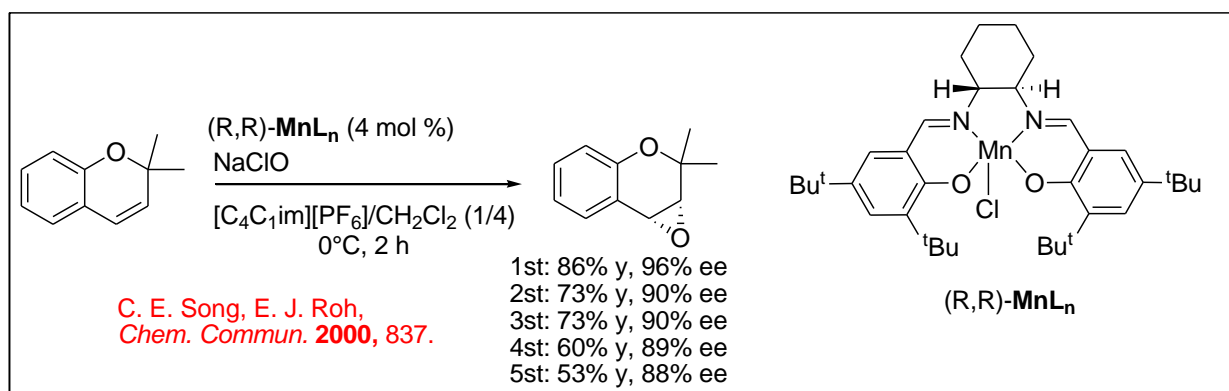
Copper(II) bisoxazoline complex having imidazolium tag can catalyze the Diels-Alder reaction of *N*-crotonyloxazolidinones with cyclopentadienes in [C₄C₁im][NTf₂] (Scheme 3). The catalyst can be recovered and recycled without loss of activity and enantioselectivity at least 10 times. The presence of imidazolium tag to bisoxazoline considerably enhances the recovery and reuse of the catalyst from the IL.



Scheme 3

7.4.3 Epoxidation

The epoxidation of alkenes using chiral Mn(III) salen has been successful in a mixture of [C₄C₁im][PF₆]/CH₂Cl₂ (Scheme 4). Since IL is solidified at 0 °C, the reaction requires CH₂Cl₂ to form homogeneous solution. The catalyst and IL can be recycled with slight drop in the enantioselectivity.

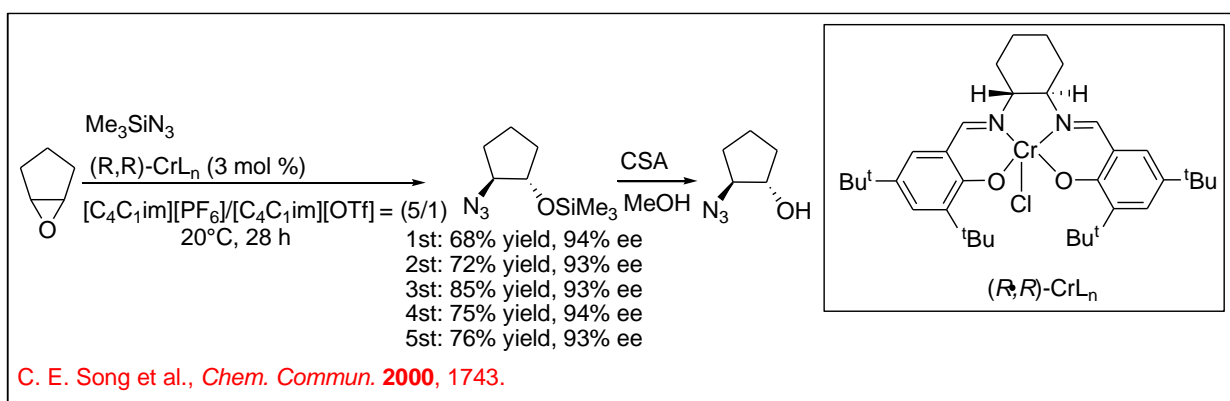


Scheme 4

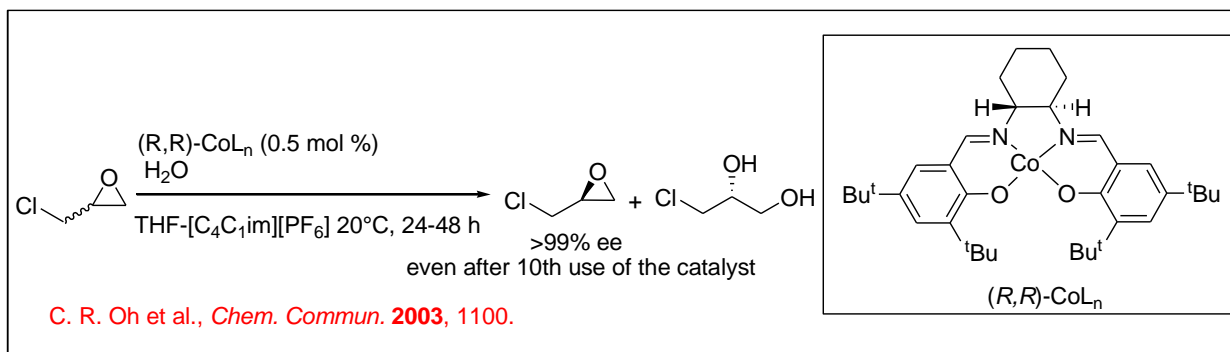
The ring opening of epoxides with TMSN_3 can be pursued using chiral Cr(III)salen complex in $[\text{C}_4\text{C}_1\text{im}][\text{OTf}]$ and $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$ at ambient temperature (Scheme 5). The catalyst can be recycled up to five times without loss of activity.

7.4.4 Epoxide Opening

Hydrolytic resolution of racemic epoxides is effective using chiral Co(II)salen complex in THF and $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$ with excellent enantioselectivity (Scheme 6). In this reaction, Co(II) is oxidized to Co(III) catalyzes the reaction. The catalyst can be recycled 10 times without loss of activity and selectivity.



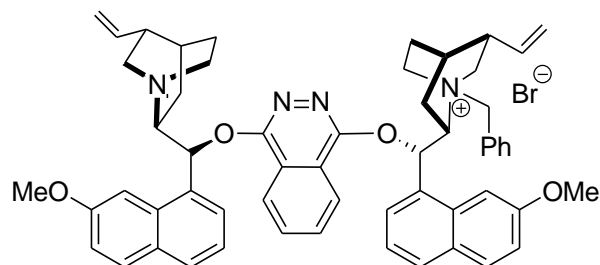
Scheme 5



Scheme 6

7.4.5 Dihydroxylation Reaction

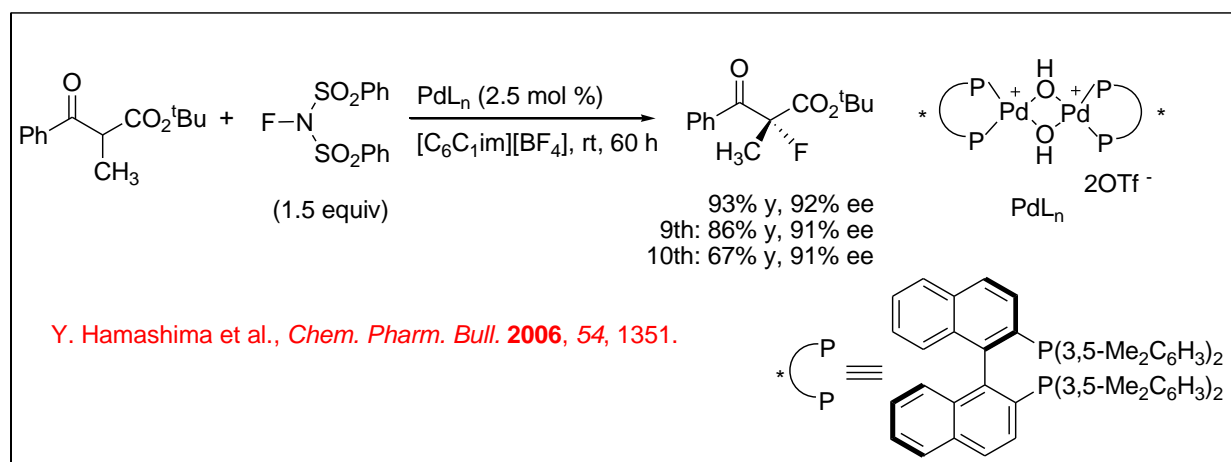
The asymmetric dihydroxylation of *trans*-stilbene has been done using OsO₄ (1.5 mol%) and **L-3** (2 mol%) in the presence of *N*-methylmorpholine *N*-oxide (NMO) (2.6 mol%) and [C₄C₁im][PF₆] (2 mL) in acetone-water (v/v, 10/1) at 0 °C. The catalyst can be recovered in IL and recycled up to three times without significant loss of activity and with a small amount of OsO₄ leaching from the IL to organic phase.



L- 27

7.4.6 Fluorination

Fluorination of β-ketoester can be accomplished employing chiral Pd-BINAP in [C₄C₁im][BF₄]. (Scheme 7). The reaction proceeds smoothly with good enantioselectivity and the catalyst can be recycled up to 10 times without slight loss of activity.

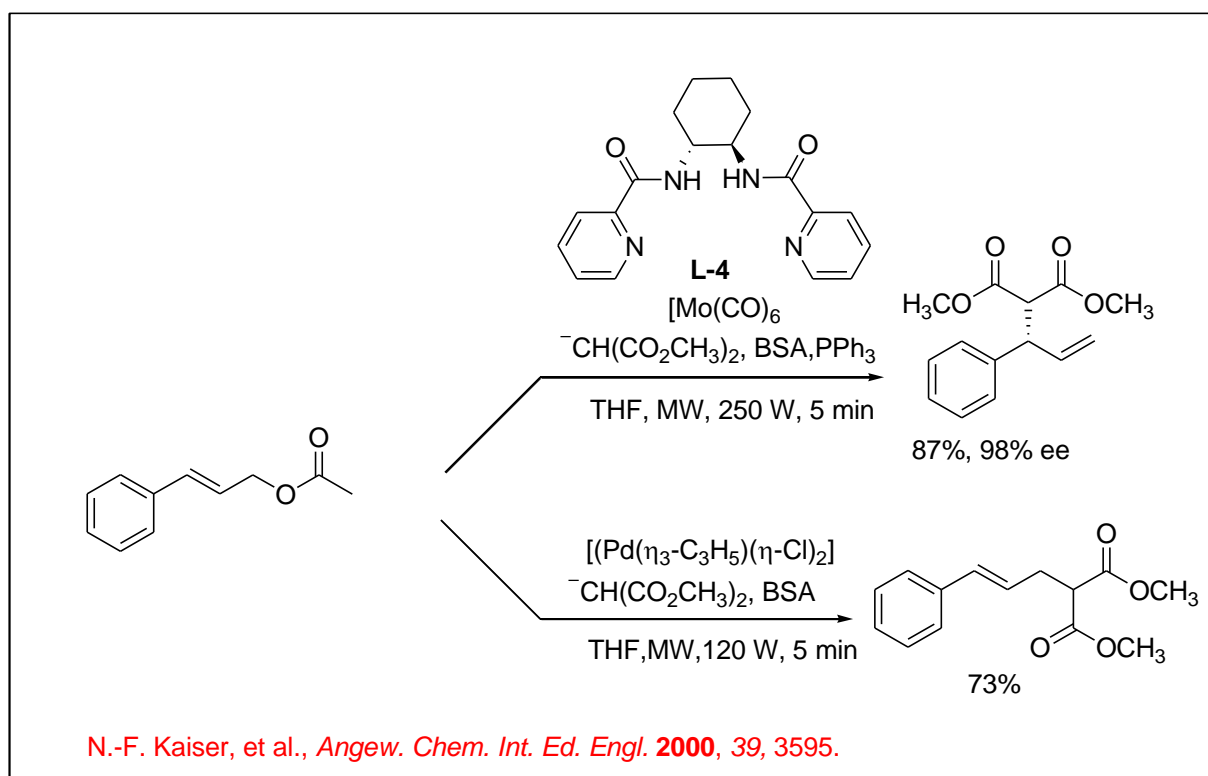


Scheme 7

7.5 Microwave-Assisted Reactions

The use of microwave irradiation can reduce the reaction time compared to the conventional heating. Thus, sometimes, the side reactions can be minimized with increase of the product yield. Thus, microwave assisted organic synthesis has been widely accepted in academia as well as pharmaceutical industries.

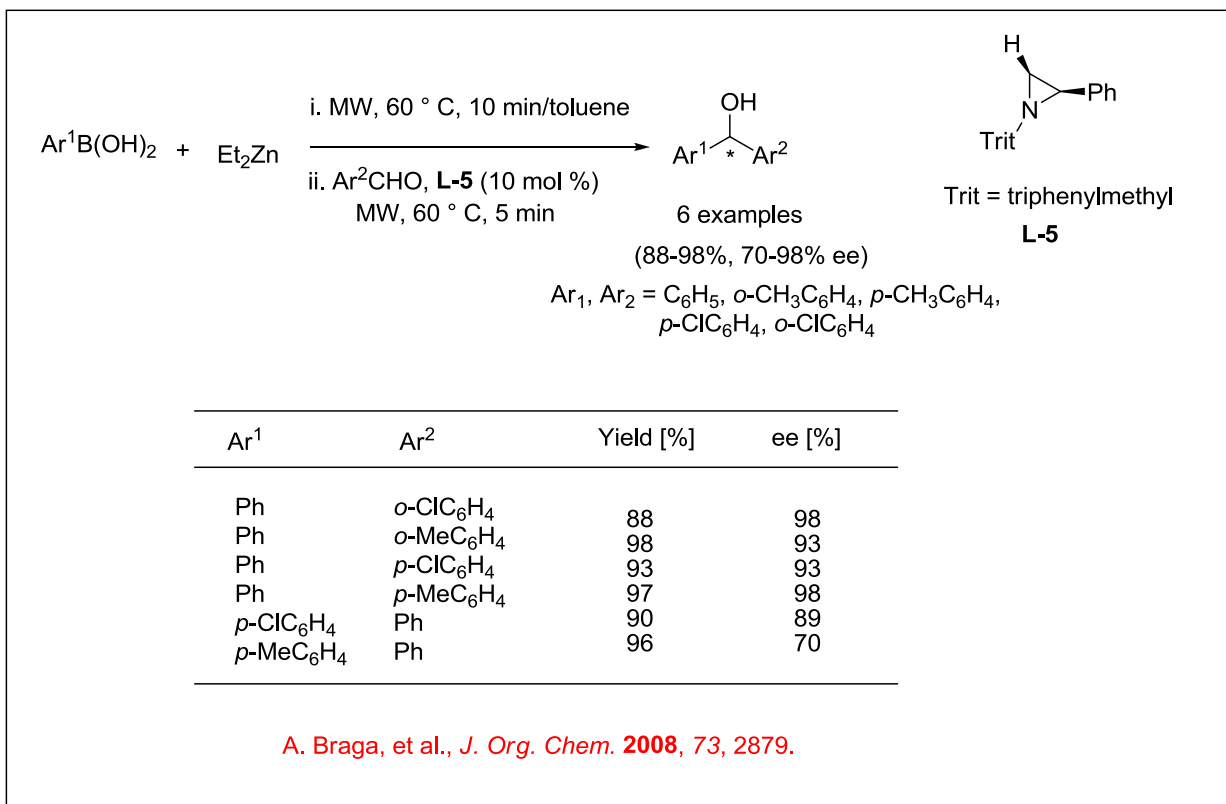
Asymmetric allylic alkylation can be effective using chiral molybdenum complex under microwave irradiation in THF (Scheme 8). For example, crotonate reacts with dimethyl malonate with high enantioselectivity. Under these conditions, palladium based system gives different regioisomer.



Scheme 8

Microwave irradiation has also been found to be effective for the arylation of aromatic aldehydes with high enantioselectivity (Scheme 9). For example, the reaction of arylboronic acid with aryl aldehydes in the presence of diethylzinc and aziridine based ligand **L5** gives arylated product with up to 98% ee. The

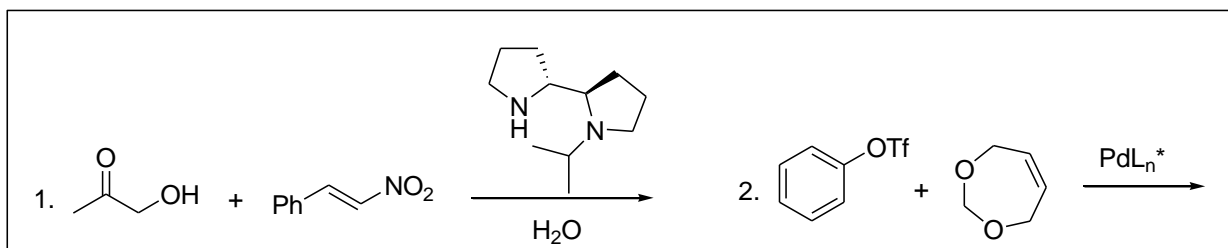
reaction time can be decreased from 1 h to 15 min by changing conventional heating to microwave irradiation.



Scheme 9

Problems

- A. Provide some examples for asymmetric Heck reaction in water.
- B. Describe asymmetric organocatalysis in water.
- C. Complete the following reactions.



Reference/Text Book

5. I. Ojima, *Catalytic Asymmetric Synthesis*, 3rd ed., Wiley, New Jersey, 2010.
6. M. B. Smith, *Organic Synthesis*, 2nd edition, McGraw Hill, New Delhi, 2004.