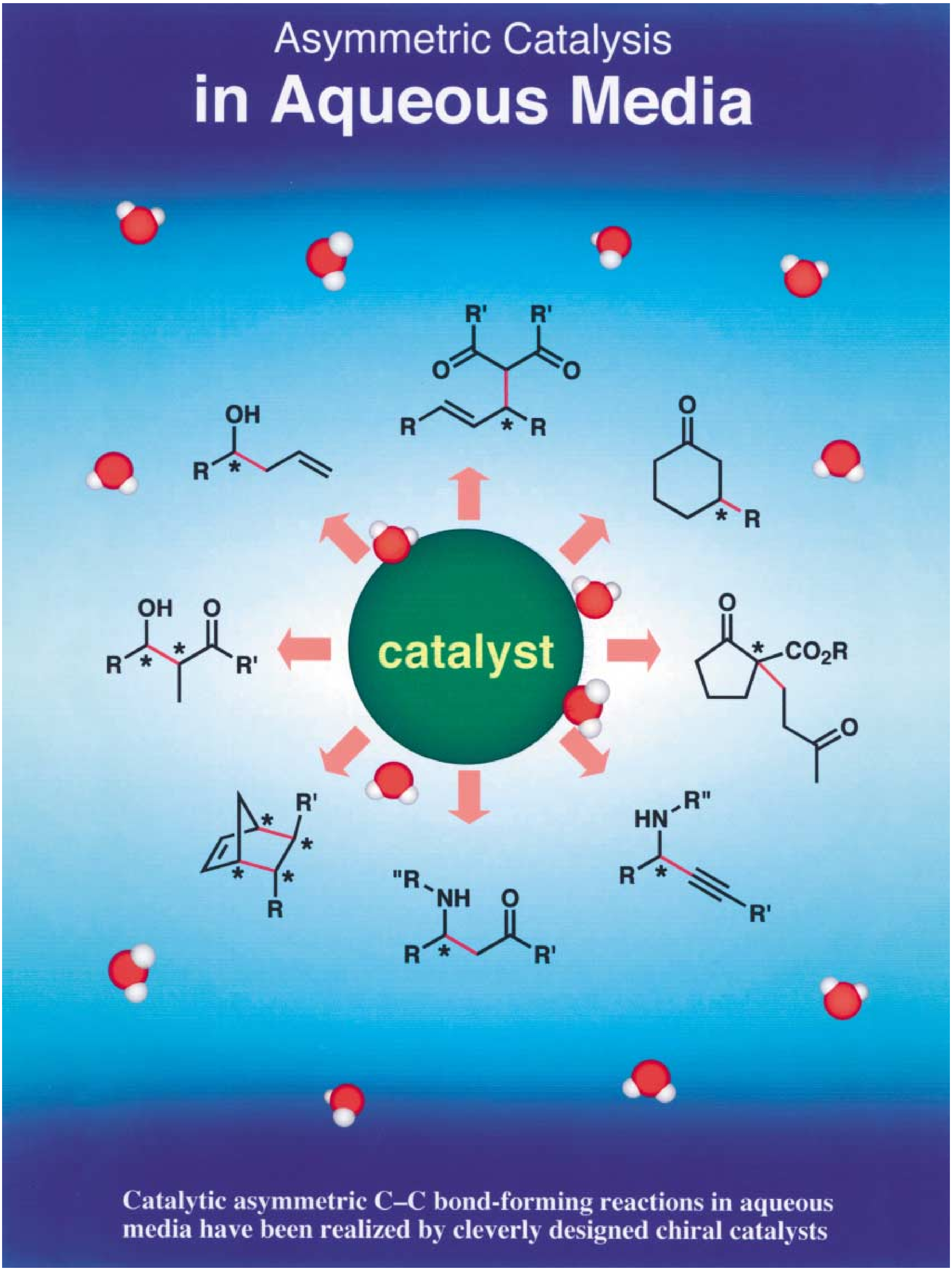

Asymmetric Catalysis in Aqueous Media

Catalytic asymmetric C–C bond-forming reactions in aqueous media have been realized by cleverly designed chiral catalysts

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Catalytic Asymmetric Carbon–Carbon Bond-Forming Reactions in Aqueous Media

Kei Manabe and Shū Kobayashi*[a]

Abstract: Use of water as a reaction solvent or co-solvent has received much attention in synthetic organic chemistry. Recently, successful examples of catalytic asymmetric carbon–carbon bond formation in aqueous media have been developed. Most of these examples show characteristic features that are realized only in the presence of water. The role of water in these reactions is also discussed here.

Keywords: aqueous media · asymmetric catalysis · enantioselectivity · Lewis acids · solvent effects · water

Introduction

Recently, use of water as a reaction solvent or co-solvent has received considerable attention in synthetic organic chemistry.[1] Organic reactions in aqueous media have several advantages compared with reactions under dry conditions, which are required in many conventional synthetic procedures. For example, it is necessary to dry solvents and substrates vigorously before use for many reactions in dry organic solvents, but for reactions in aqueous media, such drying is unnecessary. In addition, unique reactivity and selectivity that are not attained under dry conditions are often observed in aqueous reactions. Along these lines, reagents and catalysts that work well in aqueous media have been developed so far.

Research on catalytic asymmetric reactions has been one of the most important fields in modern organic chemistry, and many excellent catalysts have been developed.[2] On the other hand, development of catalytic asymmetric versions of the aqueous reactions, especially carbon–carbon bond-forming reactions, is still in a preliminary stage. Exceptions are asymmetric phase-transfer catalysis, many examples in which chiral ammonium or phosphonium as the catalyst in aqueous/organic biphasic systems have been reported,[3] and enzyme- (or catalytic antibody-) catalyzed reactions.[4] In the past five years, however, other catalytic asymmetric carbon–carbon bond-forming reactions with water as a solvent or co-solvent have appeared in the literature. These examples were realized by using unique catalytic systems designed for aqueous reactions, and demonstrate the significant role of water in affecting catalytic activity and efficiency. In this Concept, we summarize these reactions and disclose the concepts needed for development in this emerging field of importance. The examples of phase-transfer catalysis and enzyme-catalyzed reactions are not included here, and reactions that use catalytic or near stoichiometric amounts of water compared with the substrates used[5] are also beyond the subject of this Concept.

Discussion

Palladium-catalyzed allylic substitution: Palladium-catalyzed asymmetric carbon–carbon bond-forming reactions, especially allylic substitution reactions, have been intensively studied, and many excellent chiral ligands have been developed.[6] Recently, this type of reaction has been successfully carried out in aqueous media. In the search for efficient polymer-supported catalysts that work in water, Uozumi and co-workers have developed several polymer-supported chiral palladium catalysts.[7] For example, on the basis of their studies on new chiral ligand design, they developed polymer catalyst **1** and found that it catalyzed asymmetric allylic substitution in high yield and high enantioselectivity (Scheme 1). A key to the success of this catalyst is the use of polystyrene-poly(ethylene glycol) graft copolymer (PS-PEG) resin as a solid support. The amphiphilic nature of the resin is crucial for the efficient catalysis in water, probably because the hydrophobic PS matrix concentrates organic substrates around it and the hydrophilic PEG region interacts with the ionic species that must react with organic substrates. The authors also showed that catalyst **1** was easily recovered and reused.

Ohe, Uemura, and co-workers reported another example of asymmetric allylic substitution in aqueous media.[8] They developed a new chiral phosphinite ligand derived from D-

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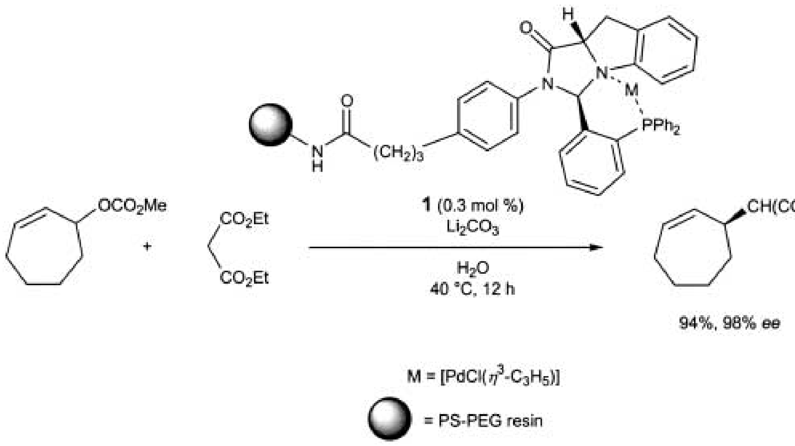
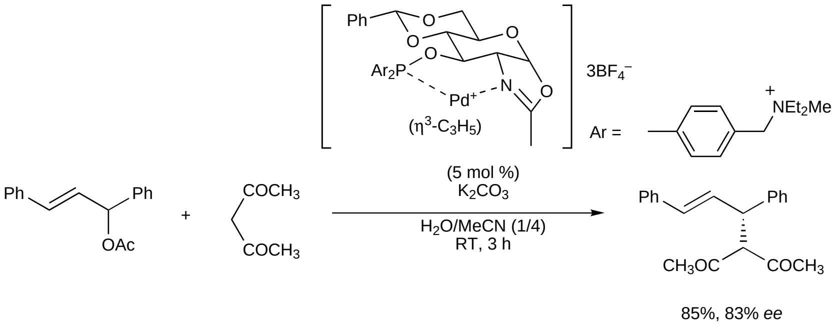


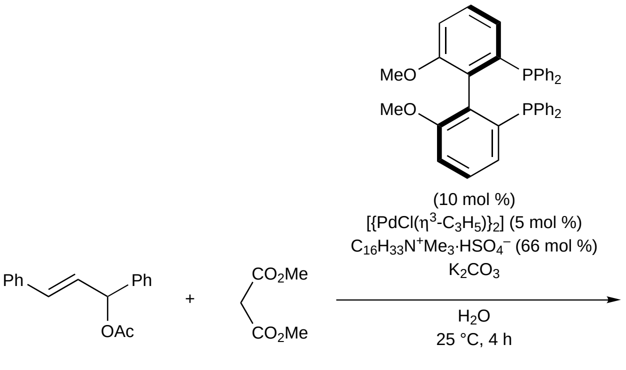
Scheme 1. Asymmetric allylic substitution catalyzed by polymer-supported palladium catalyst **1** in water.

glucosamine hydrochloride and used it for carbon–carbon bond-forming allylic substitution. Acetonitrile was used as a co-solvent, and good enantioselectivity was obtained as shown in Scheme 2.

Surfactants have been occasionally used in organic reactions in water, and several surfactant-type catalysts have been so far developed.[9] Sinou and co-workers found that asymmetric allylic substitution in water was improved with the aid of a surfactant. They tested various surfactants including anionic, cationic, zwitterionic, and nonionic ones; they found that the cationic one with hydrogen sulfate anion gave the best result (Scheme 3).[10]

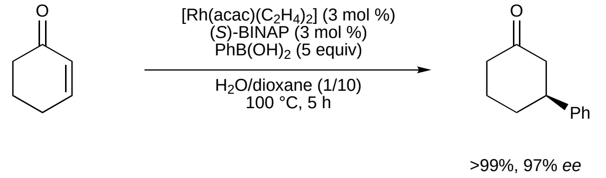


Scheme 2. Asymmetric allylic substitution in aqueous media.



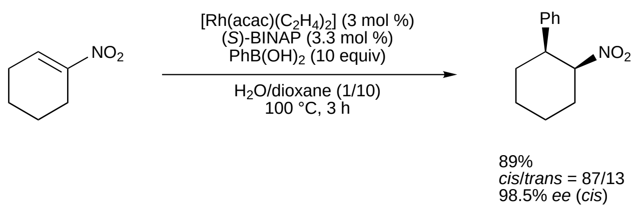
Scheme 3. Surfactant-aided asymmetric allylic substitution in water.

Rhodium-catalyzed 1,4-addition of boronic acids: 1,4-Addition of organometallic reagents to α,β-unsaturated carbonyl compounds constitutes a powerful tool in organic transformation. Recently, Miyaura and co-workers have developed rhodium-catalyzed 1,4-addition of aryl- or alkenylboronic acids to enones; they found that water as a co-solvent facilitates product formation.[11] An asymmetric version of the 1,4-addition in the presence of BINAP (BINAP = (1,1′-binaphthyl) as a chiral ligand has also been developed by Hayashi, Miyaura, and co-workers (Scheme 4).[12] In most cases, they used water/dioxane (1/10) as a solvent. Asymmetric 1,4-addition to α,β-unsaturated esters was also realized in aqueous dioxane.[13] The authors proposed a mechanism in which the rhodium enolate, formed by 1,4-addition of an organorhodium intermediate, was hydrolyzed to give the 1,4-addition product and a (hydroxo)rhodium species, which reacted with a boronic acid through transmetalation to complete the catalytic cycle. This mechanism was later confirmed by NMR studies, and on the basis of the mechanistic studies a more active catalyst, [{Rh(OH)(binap)}$_2$], was found and used for the reaction at lower temperature.[14] Hayashi and co-workers also reported that nitroalkenes could be used as substrates in the asymmetric 1,4-addition (Scheme 5).[15]



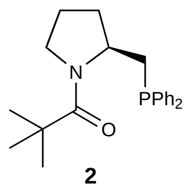
Scheme 4. Rhodium-catalyzed asymmetric 1,4-addition of arylboronic acids to enones in aqueous media.

In the course of their investigations on new chiral ligands, Tomioka and co-workers have



Scheme 5. Rhodium-catalyzed asymmetric 1,4-addition to nitroalkenes.

found that chiral amidomonophosphine **2** is an excellent ligand for the asymmetric 1,4-addition to enones in aqueous dioxane.[16]



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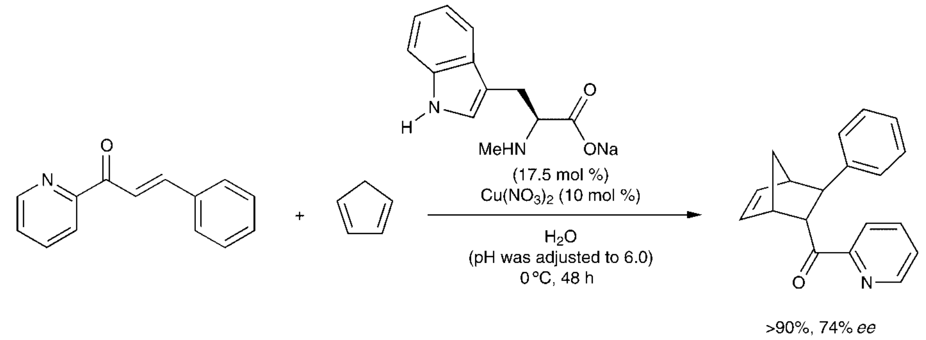
Lewis acid catalysis in aqueous media: Lewis-acid-catalyzed reactions are of great interest because of their unique reactivities and selectivities, and the mild reaction conditions used. While wide variety of reactions with Lewis acids have been developed, these Lewis acids are moisture sensitive and are easily decomposed or deactivated in the presence of even a small amount of water. In 1991, the first report on use of water-compatible Lewis acids, lanthanide triflates Ln(OTf)$_3$, in aqueous media was reported from our laboratory.[17] The most characteristic feature of Ln(OTf)$_3$ is that they are stable and can be used as Lewis acids in aqueous media even for acid-labile substrates, such as silyl enol ethers. After the first report, not only Ln(OTf)$_3$ (Ln = La, Ce, Pr, Nd, Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm, Yb, Lu), but also scandium (Sc) and yttrium (Y) triflates were shown to be water-compatible Lewis acids, and these rare-earth metal triflates, RE(OTf)$_3$, have been regarded as new types of Lewis acids.[18] Many useful reactions are catalyzed by RE(OTf)$_3$ in aqueous media. Only catalytic amounts of the triflates are enough to complete the reactions in almost all cases. Furthermore, RE(OTf)$_3$ can be recovered easily after reactions and reused without loss of activity. We have now clarified that some metal salts other than rare earth metals, such as Fe^{II}, Cu^{II}, Zn^{II}, Cd^{II}, and Pb^{II}, and possibly Mn^{II}, Co^{II}, Ni^{II}, Ag^{I}, and In^{III} (as chloride, perchlorate, or triflate salts), are also stable Lewis acids in water and work as catalysts. In addition, common characteristics, that is, a certain range of hydrolysis constants and a high order of exchange rate constants for substitution of inner-sphere water ligands (water exchange rate constant (WERC)), have been found among these water-compatible Lewis acids.[19]



Scheme 6. Catalytic asymmetric Diels–Alder reaction in water.

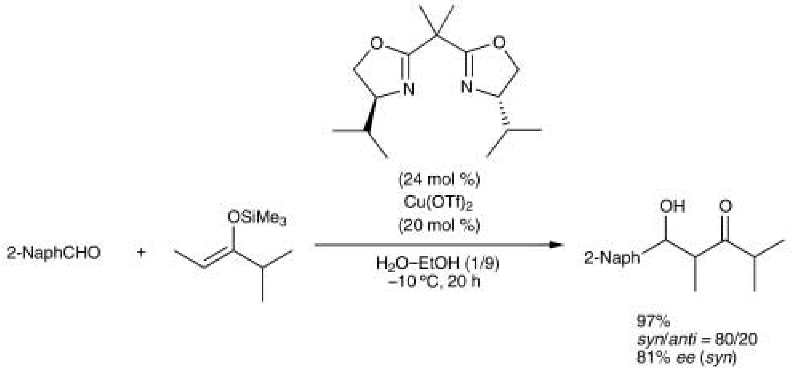
In spite of these advances in Lewis acid catalysis in aqueous media, chiral Lewis acid catalysts that work efficiently in aqueous media had not been reported, and development of such Lewis acids is regarded as one of the most challenging topics in organic synthesis.

Lewis-acid-catalyzed Diels–Alder reactions: Since the pioneering work by Breslow and co-workers on the beneficial effects of water on reaction rates,[20] Diels–Alder reactions have been one of the most intensively studied reactions in which water is used as a solvent. However, no catalytic asymmetric version had been realized until Engberts and co-workers disclosed a Lewis acid catalyst composed of a copper salt and an amino acid, especially *N*-methyltryptophan (abrine) (Scheme 6).[21] This is the first example of catalytic asymmetric carbon–carbon bond-forming reactions by using chiral Lewis acids in water. The pyridine part of the substrate is 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, have also beneficial effects on high rate and good enantioselectivity.

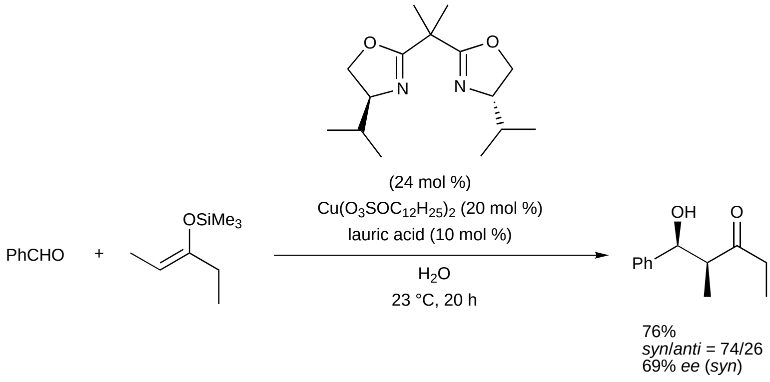
Lewis-acid-catalyzed aldol reactions: Lewis-acid-mediated addition of silyl enol ethers to aldehydes (Mukaiyama aldol reaction) is a useful method to construct β-hydroxy carbonyl compounds.[22] The finding that the aldol reactions were catalyzed by water-compatible Lewis acids prompted us to investigate catalytic asymmetric aldol reactions in aqueous media. However, our initial attempts to use combinations of these metal salts and chiral ligands failed.

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 the 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.

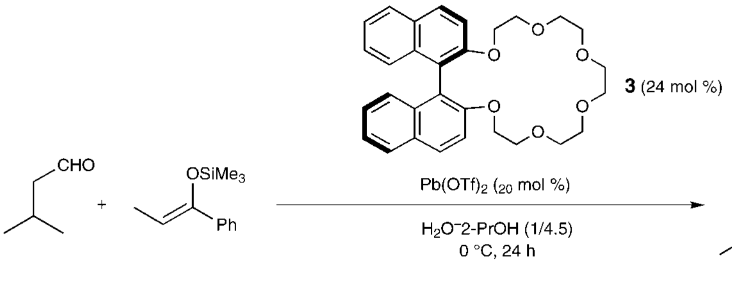
After many trials, we finally found good combinations of chiral ligands and the metal salts. Our first successful example was the use of chiral bis(oxazoline) ligands and copper triflate (Scheme 7).[23] Although this combination has been used in aldol reactions in dry organic solvents, it is useful only for bidentate-type aldehydes such as α-benzyloxyacetaldehyde.[24] On the other hand, our aqueous system can be applied to simple aldehydes such as benzaldehyde. Water as a co-solvent was found to play an important role in attaining high yields and enantioselectivity. Asymmetric aldol reactions in water without using organic co-solvents were also conducted with the aid of a Lewis-acid–surfactant-combined catalyst (Scheme 8).[25]



Scheme 7. Copper-catalyzed asymmetric aldol reaction in aqueous media.



Scheme 8. Copper-catalyzed asymmetric aldol reaction in water.



Scheme 9. Lead-catalyzed asymmetric aldol reaction in aqueous media.

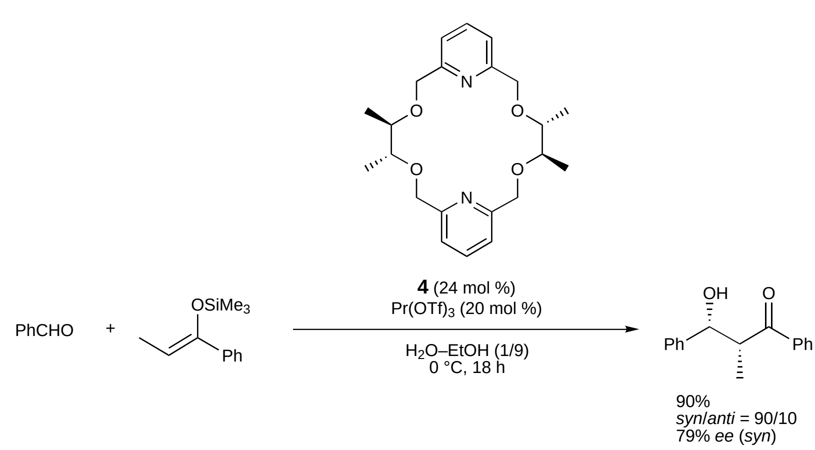
We have also developed another example of catalytic asymmetric aldol reactions in aqueous media using a combination of chiral crown ether **3**[26] and $Pb(OTf)_2$ (Scheme 9).[27] Since it is known that [18]crown-6 and the lead cation form a complex with a high binding constant in aqueous media, strong binding of **3** and the lead cation is expected and should be an important factor to attain high enantioselectivity.

Although lanthanide triflates are the first Lewis acids that were found to catalyze aldol reactions in aqueous media, it had been difficult to realize asymmetric versions of the reactions in such media. Recently, we have reported the first example of this type of reaction using chiral bis(pyridino)[18]-crown-6 (**4**)[28] (Scheme 10).[29] In this case, large lanthanide metals such as La, Ce, Pr, and Nd gave the aldol adduct with high diastereo- and enantioselectivities, showing that size-fitting between the crown ether and the metal cations is an important factor to attain high selectivity.

A study on the reaction profiles of the asymmetric aldol reactions catalyzed by $Pb(OTf)_2$ with **3** or $Pr(OTf)_3$ with **4** revealed that these crown-ether-type chiral ligands did not significantly reduce the activity of the metal triflates. This retention of the activity, even in the presence of the crown ethers containing oxygen and nitrogen atoms, is the key to realizing the asymmetric induction in these asymmetric aldol reactions in aqueous media. We think that use of chiral multidentate ligands, such as the crown ethers, is a versatile concept for Lewis-acid-catalyzed asymmetric reactions in aqueous media.

Mannich-type reactions: Lewis acid catalysts have also been developed for enantioselective addition reactions to imines. Among them, asymmetric Mannich-type reactions provide useful routes for the synthesis of optically active β-amino ketones or esters, which are versatile chiral building blocks for the preparation of many nitrogen-containing, biologically important compounds.[30]

Quite recently, we have developed the first example of catalytic asymmetric Mannich-type reactions in aqueous media (Scheme 11).[31] We chose

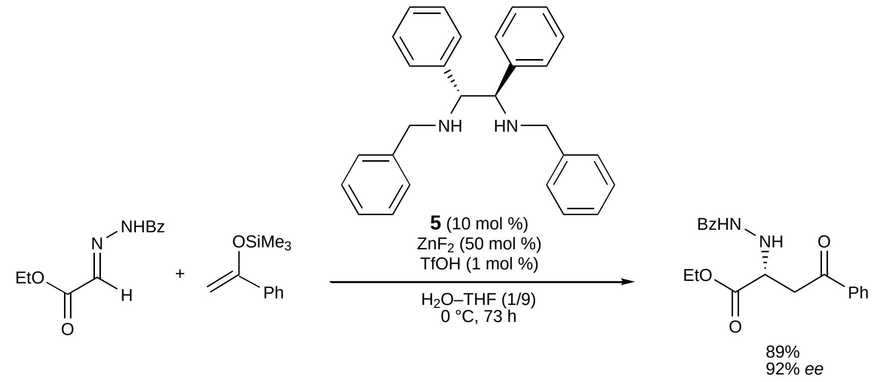


Scheme 10. Lanthanide-triflate-catalyzed asymmetric aldol reaction in aqueous media.

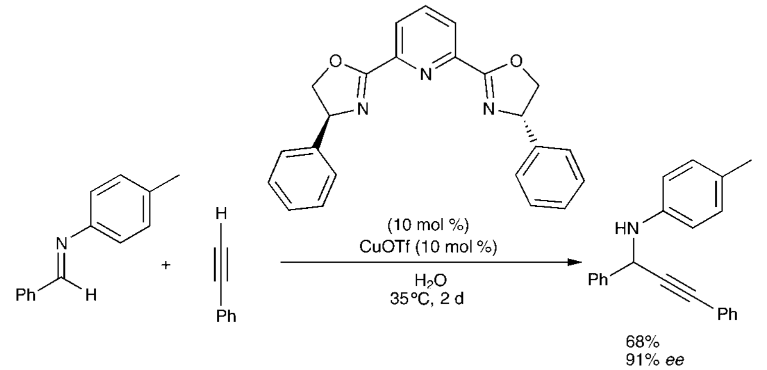
acylhydrazones as imine surrogates because they can be easily handled relative to imines.[32] It is surprising that only 10 mol% chiral ligand **5** is required in spite of the presence of 50 mol% zinc fluoride, suggesting that the ligand accelerates the zinc-fluoride-mediated Mannich-type reaction. In fact, contrary to the aldol reactions mentioned above, the yield of the Mannich adduct increases in the presence of the ligand. It is also unexpected that a small amount of triflic acid dramatically improves the yield of the Mannich adduct. Furthermore, the reaction did not proceed at all in THF without water, indicating that water plays an important role here.

Currently, we speculate that this reaction proceeds with double activation, in which Zn^{II} acts as a Lewis acid to activate the hydrazone and the fluoride anion acts as a Lewis base to attack the silicon atom of the silyl enol ether.

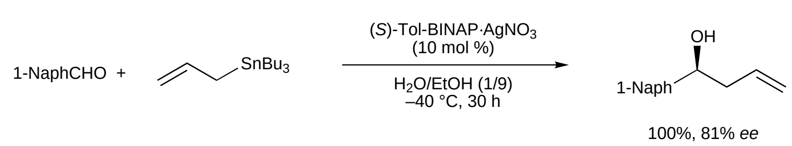
This asymmetric Mannich-type reaction was successfully applied to the synthesis of (1*R*,3*R*)-*N*-(3-hydroxy-1-hydroxymethyl-3-phenylpropyl)-dodecanamide (HPA-12),[33] which is the first compound of a specific inhibitor for sphingomyelin synthesis in mammalian cells and is expected to be of use as a drug that inhibits intracellular trafficking of sphingolipids.



Scheme 11. Catalytic asymmetric Mannich-type reaction in aqueous media.



Scheme 12. Catalytic asymmetric addition of alkynes to imines in water.

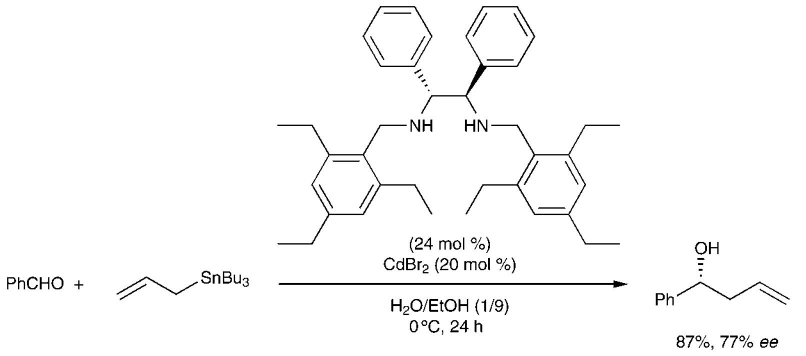


Scheme 13. Catalytic asymmetric allylation reaction in aqueous media.

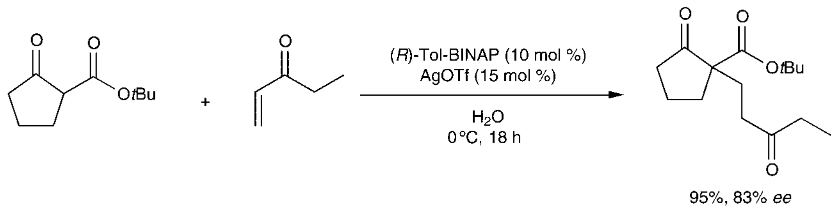
Addition of alkynes to imines: Quite recently, asymmetric addition of terminal alkynes to imines in water has been achieved by Li and Wei, who used a catalytic amount of CuOTf and a pybox ligand (Scheme 12).[34] The reaction also proceeds in toluene with high enantioselectivity. It should be mentioned that the atom efficiency of the reaction is 100%.

Allylation reactions: Asymmetric allylation reactions of carbonyl compounds with allylmetals have been a subject of extensive investigation.[35] Loh and Zhou reported asymmetric allylation in aqueous media using combinations of BINAP derivatives and silver salts,[36] which were originally developed by Yamamoto and coworkers in catalytic symmetric allylation in organic solvents.[37] In the case of the aqueous system, silver nitrate gave the best result (Scheme 13).

Ligand acceleration is a key factor to realize efficient asymmetric metal-catalyzed reactions. Previously, we found a unique system in which cadmium-catalyzed allylation of



Scheme 14. Ligand-accelerated asymmetric allylation reaction in aqueous media.



Scheme 15. Catalytic asymmetric Michael reaction in water.

carbonyl compounds with allyltributyltin was dramatically accelerated by several achiral ligands in aqueous media.[38] As an extension of this work, we have developed cadmium-catalyzed asymmetric allylation (Scheme 14).[39] Although the system has not yet optimized, this ligand-accelerated reaction may provide a new insight into designing efficient catalytic systems which work in aqueous media.

Lewis-acid-catalyzed Michael reactions: We have also shown that combinations of BINAP derivatives and silver salts were found to be good catalysts for asymmetric Michael reactions in water (Scheme 15).[40] It should be noted that the high selectivity was attained in water without using any organic co-solvents. The selectivity was dependent on the ratio of the ligand to the Ag salt, and the optimized ratio was found to be ligand/Ag salt = 1:1.5. A combination of a soft metal (silver) and a soft ligand (phosphine) is assumed to be a key for the high enantioselectivity, because this combination secures strong complexation in the presence of a large amount of a hard ligand (water).

Conclusion

In this Concept, we have summarized the recent advances in catalytic asymmetric catalysis in aqueous media. Although we concentrated on carbon–carbon bond-forming reactions here, asymmetric oxidation and reduction in aqueous media have also been developed.[41] Catalytic asymmetric reactions in aqueous media can be realized by cleverly designed catalysts, and we hope that this Concept provides useful ideas for creating new reaction systems.

In the use of aqueous media, there is an important advantage other than that stated in the Introduction. It is related to environmental issues. Reactions in aqueous media can potentially be applied to systems in which no organic solvents are used throughout the synthetic procedures. Therefore, these reaction systems reduce use of organic solvents, most of which are harmful both to humans and the environment. Although many problems still remain in realizing environmentally friendly chemical processes, the reactions shown here will contribute to the development of "green" asymmetric catalysis in the future.[42]

Acknowledgement

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