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Development of homogeneous and heterogeneous asymmetric catalysts for practical enantioselective reactions*

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Abstract: Two strategies for the development of practical asymmetric catalysis have been discussed in this article. The first part of this article focuses on the design and screening of highly efficient and enantioselective chiral catalysts for asymmetric hydrogenation reactions employing combinatorial approach. The second part presents a conceptually new strategy (i.e., "self-supporting" approach) for the immobilization of homogeneous catalysts through assembly of chiral multitopic ligands and metal ions without using any support. The success of this strategy will be exemplified in heterogeneous asymmetric carbonyl-ene, sulfoxidation, and epoxidation, as well as in asymmetric hydrogenation reactions.

Keywords: chiral; asymmetric catalysis; homogeneous; heterogeneous; hydrogenation; oxidation; C–C bond formation.

INTRODUCTION

Asymmetric catalysis of organic reactions to provide enantiomerically enriched products is of central importance to modern synthetic and pharmaceutical chemistry [1]. To achieve maximum chiral multiplication, chemists must create efficient catalytic systems that permit precise discrimination among enantiotopic atoms, groups, or faces in achiral molecules. The candidates for these enantioselective catalysts are often metal complexes bearing chiral and nonracemic organic ligands, often in enantiopure form. Therefore, tuning the catalyst to achieve the perfect match among chiral ligand, metallic ion, substrate, and so on is a key point for achieving the maximum chiral multiplication. In our previous account paper [2a–b], we demonstrated the power of the combinatorial approach in the discovery of novel chiral catalyst systems, particularly for the development of highly efficient, enantioselective, and practical catalysts for asymmetric reactions. In the first part of this article, two new examples will be given to demonstrate our effort on the development of homogeneous chiral catalysts for practical enantioselective hydrogenation [3–4].

Homogeneous asymmetric catalysis has the advantages of high enantioselectivity and catalytic activity in a variety of asymmetric transformations under mild reaction conditions [1]. Despite these facts, some of its drawbacks, such as the difficulties associated with recovery and the reuse of expensive chiral catalysts, and the product contamination caused by metal leaching significantly limited its practical applications. Therefore, immobilization of homogeneous chiral catalysts for asymmetric catal-

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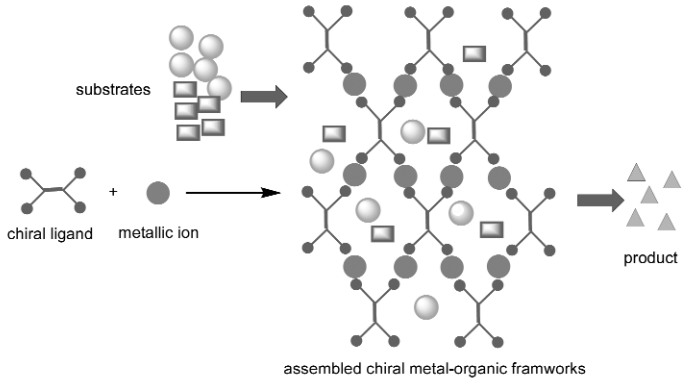
ysis has attracted a great deal of recent interests as one of the most promising solution to these problems [5]. Very recently, we and other research groups independently developed a new strategy, i.e., "self-supporting" approach (Scheme 1), for immobilization of homogeneous catalysts [6]. With this strategy, the heterogeneous chiral catalysts were generated by the combination of multitopic chiral ligands with metallic ions without using any supports. The second part of this article will highlight the stories [7–10].

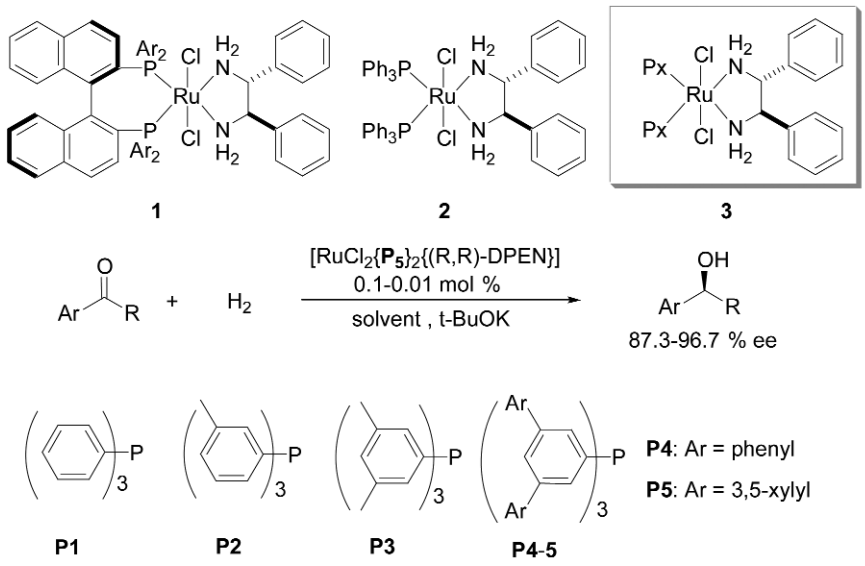


Scheme 1

BULKY ACHIRAL TRIARYLPHOSPHINES MIMIC BINAP IN Ru(II)-CATALYZED ASYMMETRIC HYDROGENATION OF KETONES

The research was inspired by Noyori's early discovery on the use of complex [$RuCl_2${**P1**}$_2${(*R*,*R*)-DPEN}] (**2**) (**P1** = Ph_3P) as the catalyst for asymmetric hydrogenation of 1-acetonaphthone, affording 1-(1-naphthyl)ethanol with a moderate (75 %) ee value [11a]. As an effort toward the development of truly practical catalysts for enantioselective hydrogenation of ketones, we tried to employ a combinatorial approach to search for more effective achiral ligands through random screening of a variety of simple triarylphosphanes (**Px**) including commercially available or easily prepared triarylphosphine derivatives (Scheme 2) [3]. It was serendipitously found that the catalyst composed of tri(3-tolyl)phosphine (**P2**) or tri(3,5-xylyl)phosphine (**P3**) ligand demonstrated the improved enantioselectivities (77.4 and 87.0 % ee, respectively) in comparison with that obtained with the catalyst containing triphenylphosphine (76.7 % ee) in the catalysis of hydrogenation of acetophenone. It is obvious that the introduction of 3,5-dimethyl groups in the triphenylphosphine ligand allows the *P*-aryl rings approach to the (*R*,*R*)-DPEN moiety more closely because of steric repulsion between two monophosphine ligands. Such a structural change in the catalyst precursor will inevitably increase the impact of monophosphine ligands on the asymmetric induction of its Ru(I) complexes in the hydrogenation on the basis of Noyori's nonclassical six-membered pericyclic mechanism [11b].

Based on the understanding of the impact of steric hindrance of the achiral triarylphosphine ligands on the enantioselection of the hydrogenation, we then designed sterically more bulky achiral monophosphine ligands **P4** and **P5** for the construction of Ru catalysts in combination with (*R*,*R*)-DPEN in order to further improve the enantioselectivity of the catalysis. As expected, the complexes generated with **P4** and **P5** indeed showed enhanced enantioselectivities in the model reaction under the same experimental conditions, affording 88.8 and 89.0 % ee of 1-phenylethanol, respectively. In the catalysis with complex **3** containing **P5**, *n*PrOH was found to be the best choice of the solvent among several alcohols examined, and up to 95.5 % ee of 1-phenylethanol could be attained with >99 % conversion. Under the optimized conditions, a variety of aromatic and heteroaromatic ketones were hydrogenated under the catalysis of [$RuCl_2${**P5**}$_2${(*R*,*R*)-DPEN}], 87.3–96.3 % ee of the secondary alco-



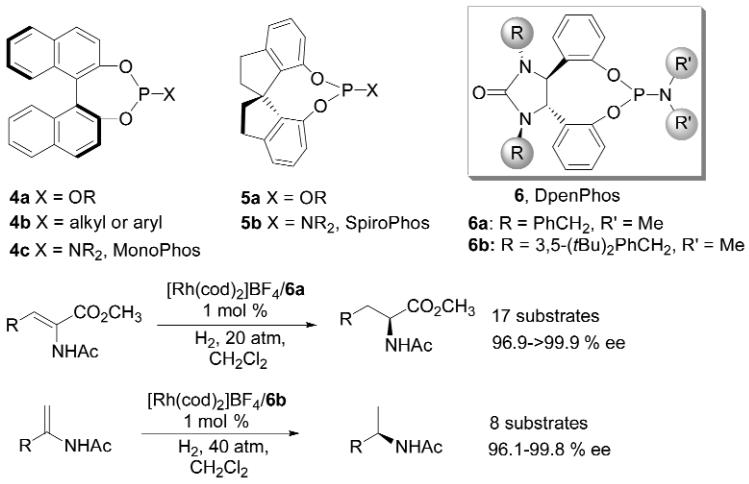
Scheme 2

hols could be obtained with quantitative conversion of the ketones. Although the enantioselectivies of the reactions using the present catalyst system have not yet been to the perfect stage, the results obtained from this work will definitely stimulate further research to develop practical catalysts for enantioselective hydrogenation of ketones using simple and cheap achiral monodentate phosphine ligands. This is particularly important for industrial application of asymmetric catalysis due to the fact of expensive chiral diphosphine ligands.

NEW TYPE OF MODULAR MONODENTATE PHOSPHORAMIDITE LIGANDS FOR Rh-CATALYZED ENANTIOSELECTIVE HYDROGENATION

The tuning of the catalyst to make a perfect match among chiral ligands, metallic ion, as well as substrate, and so on is the key issue for achieving highly efficient and enantioselective catalysis of asymmetric reactions, in which the adjustment of the steric and electronic modifications in chiral ligands plays a central role [1]. Therefore, the development of structurally tunable ligands is highly desirable for ligand and catalyst diversity. Inspired by the pioneering works of Feringa, de Vries, Reetz, Pringle, and others [12] on the successful use of monodentate phosphorus ligands (**4**–**5**) in asymmetric hydrogenations, a new class of monodentate phosphoramidite ligands (**6**, DpenPhos) has been developed on the basis of a modular concept for Rh(I)-catalyzed asymmetric hydrogenations of a variety of olefin derivatives (Scheme 3) [4]. It was found that the enantioselectivities for the hydrogenation of dehydroamino acid and enamide derivatives could be dramatically enhanced with the change of R from the smallest proton to 3,5-di*tert*butylbenzyl group. On the other hand, the increase of the steric hindrance of substituents at phosphorus atom of the ligands (R') proved to be unfavorable for the enantioselectivity of the reactions. All these results clearly indicated that dual steric tuning of both R and R' groups in the monodentate DpenPhos ligands was critically important for achieving maximum asymmetric induction in Rh(I)-catalyzed hydrogenations.

Under the optimized reaction conditions, various dehydro-α-amino acid derivatives could be hydrogenated with the catalysis of Rh/(*R*,*R*)-**6a**, affording the corresponding α-amino acid derivatives with extremely high ee values (96.9–>99.9 %). For the hydrogenation of enamide substrates, the catalyst composed of monodentate ligand (*R*,*R*)-**6b** was particularly effective. A variety of α-arylenamides



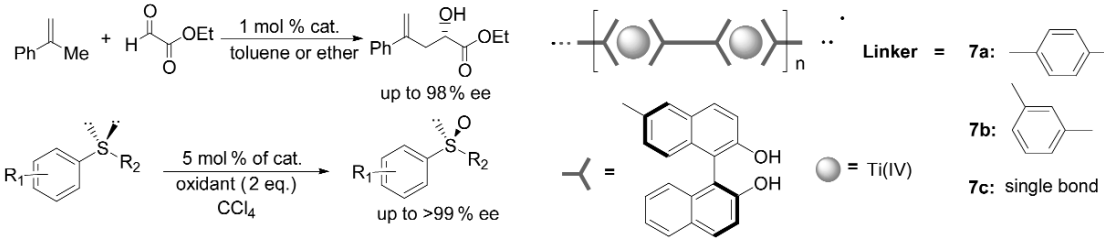
Scheme 3

has been hydrogenated to afford the corresponding α-arylamine derivatives quantitatively with excellent enantioselectivity (96.1–99.8 %). Moreover, both the catalysts Rh/(*R*,*R*)-**6a** and Rh/(*R*,*R*)-**6b** were also effective for the hydrogenation of dimethyl itaconate to give corresponding hydrogenated product in quantitative yield with 97.2–99 %. [4].

SELF-SUPPORTED HETEROGENEOUS Ti CATALYSTS FOR ENANTIOSELECTIVE CARBONYL-ENE AND SULFOXIDATION REACTIONS

Recent extensive research on the design and the synthesis of metal-organic frameworks has led to the rapid increase in the discovery of such metal-organic assemblies [13]. The use of nonchiral metal-organic assemblies as the catalysts for organic reactions were demonstrated by Fujita's and Aoyama's groups in cyanosilylation and Diels–Alder reactions in 1994 and 1998, respectively [14]. Accordingly, the design and synthesis of chiral metal-organic frameworks or polymers might provide a new strategy for asymmetric heterogeneous catalysis, because the chiral bridging ligand can spontaneously form a chiral environment inside the cavities of the materials or on the surface of the solids for enantioselective control of the reaction and the metal ion acts as the catalytically active center [6].

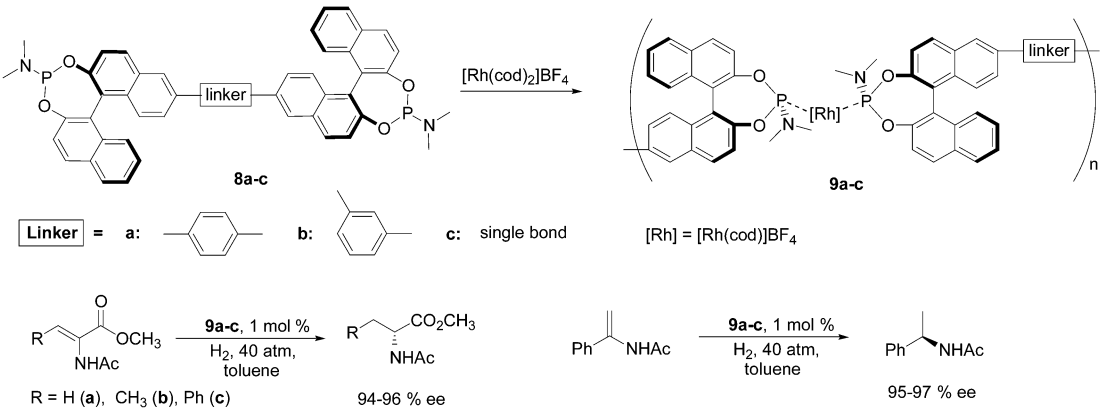
Sasai [6b] and our group [6c,7] independently reported a new strategy for heterogenization of chiral Ti complexes by in situ assembly of bridged multitopic BINOL ligands with $Ti(OiPr)_4$ without using any support, and the assembled heterogeneous catalysts (**7a**, **7c**) were found to demonstrate excellent enantioselectivity in both carbonyl-ene reaction of α-methylstyrene with ethyl glyoxylate (up to 98 % ee) and oxidation of sulfides (up to >99 % ee) (Scheme 4). The spacers between two BINOL units of the ligands in the assembled catalysts showed significant impact on the enantioselectivity of carbonyl-ene reaction, which demonstrated the importance of the supramolecular structures of the assemblies on their catalytic behaviors. In the catalysis of sulfoxidation, the self-supported heterogeneous Ti catalysts were found to be highly stable and could be readily recycled and reused for over one month (at least eight cycles) without significant loss of activity and enantioselectivity (up to >99.9 % ee). Sasai and coworker also reported that the heterogeneous Al-bridged polymers prepared by the reaction of $LiAlH_4$ with bis-BINOL ligands were found to be efficient catalysts for enantioselective Michael addition of dibenzyl malonate to 2-cyclohexenone, affording the corresponding adduct with the results (88 % yield, 96 % ee) comparable to those obtained with a homogeneous catalyst (100 % yield, 97 % ee) [6b].



Scheme 4

SELF-SUPPORTED MonoPhos/Rh(I) CATALYSTS FOR ENANTIOSELECTIVE HYDROGENATIONS

The "self-supported" MonoPhos/Rh(I) [12b] catalysts (**9a–c**) were prepared by the reaction of bis-MonoPhos ligands (**8a–c**) with Rh(I) ion on the basis of molecular assembling through coordination in dichloromethane (Scheme 5) [8]. The application of the self-supported Rh(II) catalysts in the asymmetric hydrogenation of some representative substrates, including β-aryl or alkyl substituted dehydro-α-amino acid and enamide derivatives, afforded a variety of enantioenriched amino acid and secondary amine derivatives with high yields and enantioselectivities, which are comparable to the cases of homogeneous catalysis at the same level of catalyst loading. Particularly, the self-supported catalysts demonstrated improved enantioselectivity (95–97 % ee) in the hydrogenation of enamide derivative in comparison with the cases using MonoPhos/Rh homogeneous catalyst (87 % ee). The heterogeneous nature of the catalysis was confirmed by the facts of inactivity of the supernatants of these self-supported catalysts. The inductively coupled plasma (ICP) spectroscopy analysis indicated that no detectable Rh has leached into the organic solution and the concentration of phosphor in organic phase was less than 3 ppm for each round of hydrogenation, which further confirmed the heterogeneous nature of the present systems. The catalysts could be readily recycled and reused for at least 7 runs without significant loss of activity and enantioselectivity [8].

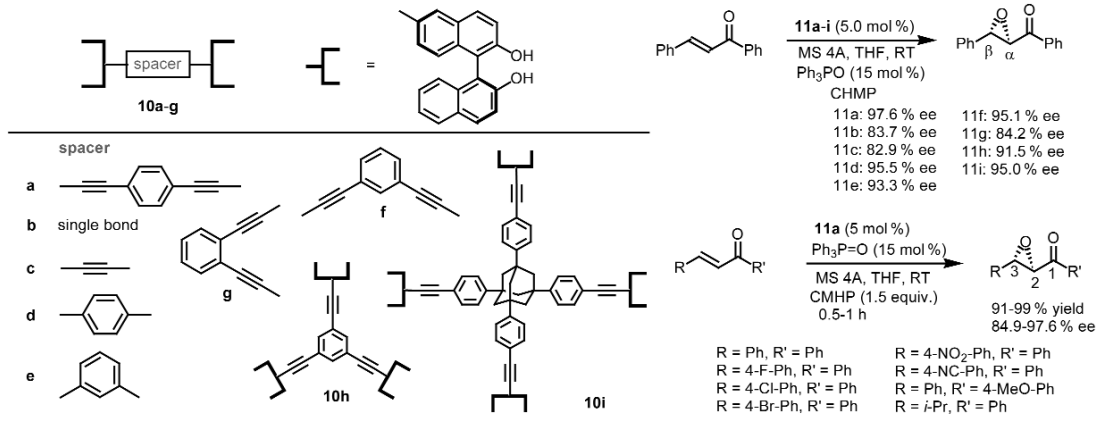


Scheme 5

HETEROGENIZATION OF SHIBASAKI'S BINOL/La(III) CATALYST FOR ENANTIOSELECTIVE EPOXIDATION OF α,β-UNSATURATED KETONES USING MULTITOPIC BINOL LIGANDS: THE IMPACT OF BRIDGING SPACERS

In the use of self-supporting strategy for heterogenization of homogeneous chiral catalysts, the stereochemical characteristics of the multitopic ligands should have significant impact in principle on the microstructures of the resulting homochiral metal-organic polymers, and thus may exert a profound influence on the enantioselectivity and activity of the catalysis in a given reaction. Such effect of bridging spacers of the multitopic ligands has been exemplified in the heterogenization of Shibasaki's La catalyst [15] for the enantioselective catalysis of epoxidation of α,β-unsaturated ketones [9].

As shown in Scheme 6, four types of multitopic ligands (**10a–i**) containing different bridging linkers, including linear (**a–d**), bent (**e–g**), trigonal-planar (**h**), and tetrahedral (**i**) spacers, were designed and synthesized to investigate the impact of spatial arrangement of chiral units ((*S*)-BINOL) on the catalytic properties of their assemblies with La metallic ion. The application of the heterogenized catalysts **11a–i**, generated from the reactions of multitopic ligands **10a–i** and La(O*i*Pr)$_3$, in the epoxidation of chalcone, indeed demonstrated dramatic influence of spacer structures on the enantioselectivity of the catalysis. The ligands with larger extension angles and longer linkage spacers usually demonstrated higher activity and enantioselectivity. Given the modular nature of the multitopic ligands, it can be envisioned that both the reactivity and enantioselectivity may be fine-tuned by judicious choice of the spacer part of the ligands. Under the optimized reaction conditions, the heterogeneous catalysis of the enantioselective epoxidation of a variety of α,β-unsaturated ketones was then investigated. The reactions proceeded efficiently to give corresponding epoxides in excellent yields (91–99 %) and high enantioselectivities (84.9–97.6 % ee). The remarkable advantage of the present self-supported heterogeneous catalysts over their homogeneous counterparts was exemplified by the facile recovery and recycle of **11a** in the catalysis of epoxidation of chalcone (at least 6 cycles without significant loss of enantioselectivity and activity). Moreover, the La leaching in each cycle during the recycling of the catalyst was determined to be less than 0.4 ppm by ICP. The heterogeneous nature of the above catalyst system could be further confirmed by the fact that the supernatant of **11a** in THF had no catalytic activity under the same experimental conditions.

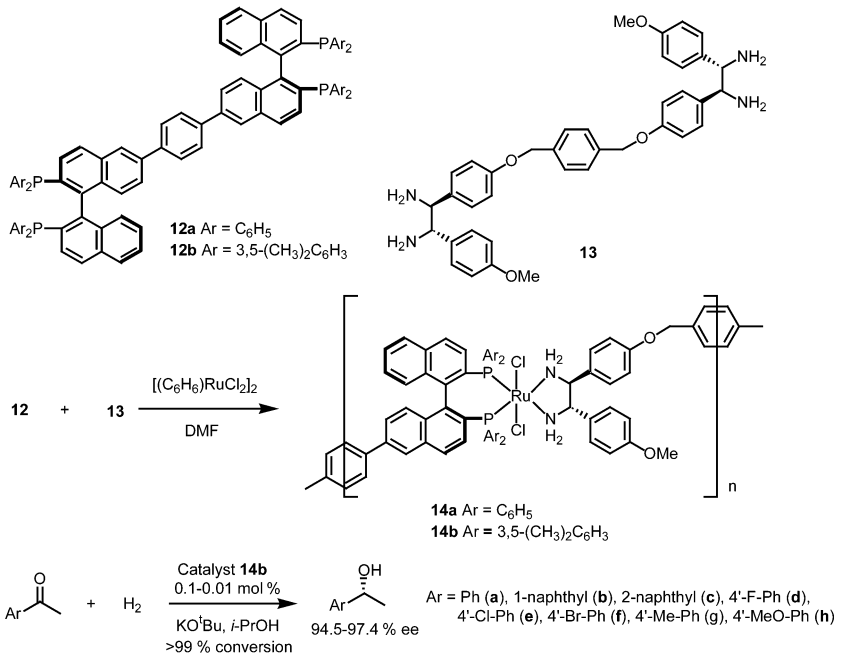


Scheme 6

PROGRAMMED ASSEMBLY OF TWO DIFFERENT LIGANDS WITH METALLIC IONS: GENERATION OF SELF-SUPPORTED NOYORI-TYPE CATALYSTS FOR HETEROGENEOUS ASYMMETRIC HYDROGENATION OF KETONES

As mentioned above, the heterogenization of the chiral catalysts using self-supporting strategy by homo-combination of multitopic chiral ligands with metallic ions is very convenient. On the other hand, the major challenge to the assembly of chiral catalyst by hetero-combination of different multitopic chiral ligands with metal ions is that a complex multi-species system would be formed when the three reacting components were mixed together. Thus, selective formation of a hetero-ligands complex would require that the structural and coordination information stored in the ligands and metallic ion, respectively, to be sufficiently strong to dictate their coordination organization and thus direct the assembly process in a programmed way. In this respect, the structural feature of Noyori's catalyst [11], $[RuCl_2\{(R)\text{-BINAP}\}\{(R,R)\text{-DPEN}\}]$ (BINAP: 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl; DPEN: 1,2-diphenylethylenediamine), can provide an excellent opportunity for generation of self-supported catalysts by this approach.

As shown in Scheme 7, the bridged BINAP **12** and the diamine **13** were designed to possess a 1,4-phenylene and a 1,4-phenylene-bis-methoxy linkers, which were assembled at 6-position of the corresponding 1,1'-binaphthyl backbone or at 4'-position of (*S*,*S*)-DPEN derivative, respectively, in order to avoid the intramolecular interaction of two chiral units [10]. The self-supported catalysts (**14a**–**b**) were prepared by reacting bridged BINAP ligands (**12a**–**b**) with $[(C_6H_6)RuCl_2]_2$ in DMF at 100 °C, followed by the treatment of the resulting reddish brown solution with 1 equiv of bridged DPEN **13** at room temperature. The application of the self-supported catalyst **14** in the catalysis of the hydrogenation of acetophenone indicated that catalyst **14b** was highly efficient and enantioselective, affording 1-phenylethanol in quantitative yield with 97.4 % ee, which is slightly higher than those obtained with its homogeneous counterparts (95.5–96.4 %). Moreover, acetophenone could also be hydrogenated at a reduced catalyst loading (0.01 mol % of **14b**) to give the corresponding secondary alcohol with complete conversion and 95.2 % ee. The TOF under this circumstance is calculated to be ~500 h^{-1}, illustrating the high activity of the assembled solid catalyst. When the supernatant of catalyst **14b** in 2-propanol was used as catalyst, the hydrogenation of acetophenone did not occur at all. Furthermore, the catalyst **14b** was used to catalyze the hydrogenation of a series of aromatic ketones, affording the corresponding secondary alcohols with excellent enantioselectivities. The self-supported catalyst **14b** could be reused for seven cycles of hydrogenation without obvious loss of enantioselectivities and catalytic activities [10].



Scheme 7

CONCLUSION

Two strategies for the development of practical asymmetric catalysis have been discussed in this article. The first part focused on the design and screen of highly efficient and enantioselective chiral catalysts for asymmetric hydrogenations employing combinatorial approach. The second part presented a conceptually new strategy (i.e., "self-supporting" approach) for the immobilization of homogeneous catalysts through self-assembly of chiral multitopic ligands and metal ions without using any support. The success of this strategy has been demonstrated in heterogeneous asymmetric carbonyl-ene, sulfoxidation, and epoxidation, as well as in asymmetric hydrogenation reactions. We hope that the strategies described in this account will stimulate further research on the development of practical asymmetric catalysts for enantioselective reactions.

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