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Asymmetric Hydrogenation in the Core of Dendrimers

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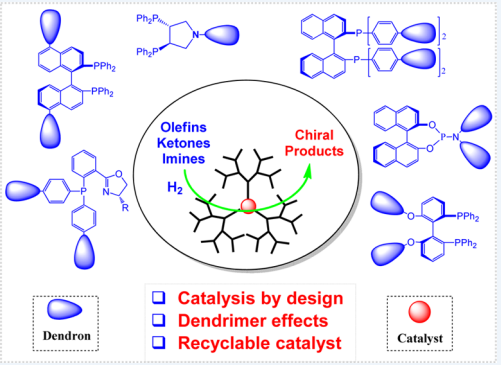
CONSPECTUS: The transition metal complexes containing chiral phosphorus ligands are the most widely and successfully used catalysts in asymmetric hydrogenation of unsaturated compounds. However, a major problem associated with these homogeneous catalytic systems is the separation and recycling of the often expensive and easily oxidized chiral catalysts. In addition, many hydrogenation reactions still lack efficient chiral catalysts, and the stereoselectivities in many hydrogenation reactions are substrate-dependent. Therefore, the development of highly effective and recyclable chiral phosphorus catalysts is highly desirable.



Over the past few decades, a number of chiral catalysts have been successfully anchored onto different supports, such as cross-linked polymeric resins and inorganic materials. However, most of the classical supported chiral catalysts suffered from inferior catalytic properties to their homogeneous counterparts due to poor accessibility, random anchoring, and disturbed geometry of the active sites in the solid matrix. To overcome this drawback, dendrimers, which have well-defined and globular macromolecular architectures serve as a promising type of soluble catalyst support. The catalytic sites are generally located at the core or on the periphery of the dendrimer, and the resulting dendritic catalysts are designable. Incorporation of a chiral catalyst into a sterically demanding dendrimer will create a specific microenvironment around the catalytic site and thus influence the catalytic performance of the metal center, like an enzyme does.

In this Account, we survey the development of core-functionalized chiral dendritic phosphorus ligands for asymmetric hydrogenation mainly by our research group. Several series of chiral dendritic phosphorus ligands, including diphosphines, monodentate phosphoramidites, and P,N-ligands, have been synthesized by attaching the corresponding chiral phosphorus units into the core or the focal point of Fréchet-type dendrons. Their transition metal (Ru, Rh, or Ir) complexes have been applied in the asymmetric hydrogenation of prochiral olefins and ketones, as well as some challenging imine-type substrates. All reactions were carried out in a homogeneous manner, and the structure−property relationships in some cases were established. The sterically demanding dendritic wedges were found to play important roles in catalytic properties, and better catalytic activities or enantioselectivities or both than those obtained from the corresponding monomeric catalysts were achieved in most cases. In addition, the dendritic catalysts could be readily recycled by means of solvent precipitation, water- or temperature-induced two-phase separation. Our study has thus demonstrated that dendrimer catalysis could combine the advantages of both classical heterogeneous and homogeneous catalysis.

1. INTRODUCTION

The quest for new chiral ligands and their transition metal catalysts with improved reactivity, stereoselectivity, and recyclability is a major effort in the study of asymmetric catalysis. In particular, chiral phosphorus ligands such as chiral diphosphines, P,N-ligands, and monodentate phosphorus ligands have attracted great attention over the past decades.[1−5] Their transition metal complexes have proven to be excellent homogeneous catalysts in various asymmetric hydrogenation reactions.[6] However, a major problem associated with these catalytic systems is the separation and recycling of the often expensive and easily oxidized chiral catalysts.[7] To overcome this drawback, chiral molecular catalysts have been immobilized on solid materials via chemical bonding or physical adsorption. Despite the successes achieved in the recycling of catalysts, these supported catalysts often suffer from inferior catalytic properties to their homogeneous counterparts due to poor accessibility, random anchoring, and disturbed geometry of the active sites in the solid matrix. Under these circumstances, alternative options for catalyst recycling competing with classical heterogeneous catalysis are highly desired.[8]

Recently, soluble linear polymers and dendrimers have proven to be promising alternatives to solid materials as catalyst supports.[9,10] The unique feature of such soluble immobilized catalysts is that the reactions are carried out in a homogeneous manner (one-phase catalysis), and the catalysts can be recycled at the end of reaction by using a solvent precipitation method (two-phase separation). In the case of linear polymer-supported catalysts, metal complexes of chiral phosphorus ligands can be

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attached onto the terminus, pendant, or main chain of the polymer backbone (Figure 1a).[9] However, the flexibility of a linear polymer may result in low activity or stereoselectivity due to its mutual entangling or self-twisting. Moreover, the catalytic sites of the catalysts are randomly oriented among the support. In contrast, supported catalysts based on dendrimers have well-defined and monodispersed structures.[10−12] Generally, the catalytic sites are incorporated at the core or the periphery of dendrimers (Figure 1b).[11] These dendritic catalysts can be rationally designed, and their catalytic properties can thus be fine-tuned through the systematic adjustment of their structure, size, shape, and solubility. In addition, dendritic catalysts with large size and globular shape facilitate their separation and reuse from the reaction mixture.[13] Therefore, dendrimer catalysis may fill the gap between classical heterogeneous and homogeneous catalysis and combine the advantages of both of them. Since the pioneering work reported by van Koten and co-workers,[10] significant progress has been achieved in this field over the past two decades.[11−21] To date, a number of chiral dendritic catalysts have also been reported.[7,18,19] Most of them showed high catalytic activity or enantioselectivity in various asymmetric reactions, which are comparable to, or in some cases better than,[20,21] those of the parent small molecular catalysts. In this Account, we hope to describe the recent progress in the development of core-functionalized chiral dendritic phosphorus ligands for asymmetric hydrogenation.

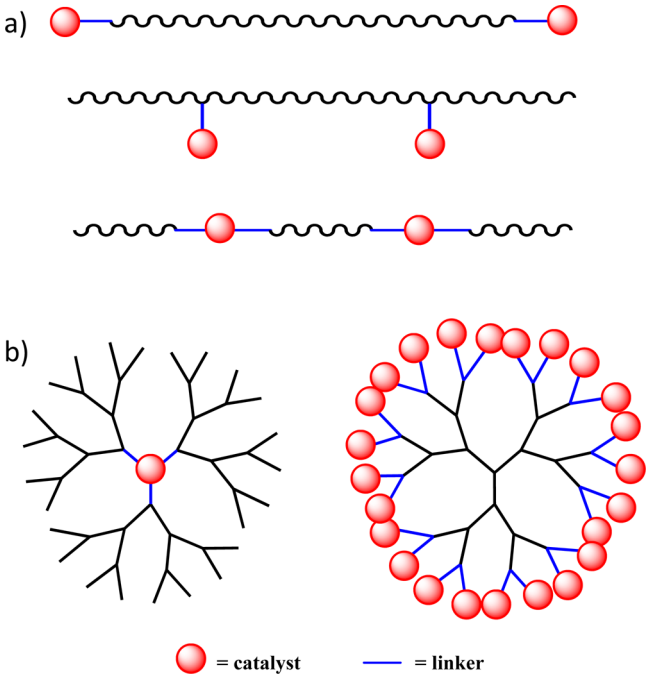

Figure 1. Soluble supported chiral catalysts based on (a) linear polymers and (b) dendrimers.

The very first attempt to carry out asymmetric hydrogenation using a chiral dendrimer ligand was reported by the Brunner group in 1995.[22] They designed and synthesized an expanded chelate ligand, in which an achiral diphosphine core was surrounded by chiral dendritic substituents. Its Rh-complex was applied in the asymmetric hydrogenation of acetamidocinnamic acid but with poor enantioselectivity (2% ee). Most recently, Parquette and co-workers reported tropos diphosphinite ligands bearing dynamically folded chiral dendrons. Excellent asymmetric induction inside the dendritic catalysts was realized in the Rh-catalyzed asymmetric hydrogenation.[23]

On the other hand, chiral phosphines could be attached onto the periphery of dendrimers with high catalyst loading. In 1998, Togni and co-workers reported the first example of dendrimers bearing chiral ferrocenyl diphosphine as the end groups.[24] Their Rh complexes showed excellent enantioselectivity in the asymmetric hydrogenation of dimethyl itaconate, which are only slightly lower than that obtained with small molecular catalyst. Other important contributions to this field were made by Gade and co-workers. They have developed series of dendrimers bearing chiral diphosphines on the periphery for asymmetric hydrogenation since 2002.[25,26]

Before we started our research on chiral dendritic phosphorus ligands for asymmetric hydrogenation, only the Brunner group and the Togni group as described above had reported their work in this field.[22,24] Different from Brunner's chiral dendrimer ligands, our chiral dendrimers were synthesized by incorporating chiral phosphorus ligands at the core of achiral dendritic supports. The purpose of this Account is to report our efforts in the design and synthesis of such dendritic ligands bearing chiral phosphorus units at the core and their applications in transition-metal-catalyzed asymmetric hydrogenation, with emphasis on the importance of dendritic wedges in achieving better catalytic performance and more convenient catalyst recycling.

2. CHIRAL PHOSPHINE-CORED DENDRITIC LIGANDS FOR ASYMMETRIC HYDROGENATION: DENDRITIC EFFECTS ON CATALYTIC ACTIVITY

Incorporation of a chiral catalyst into a sterically demanding dendrimer will create a specific microenvironment around the catalytic site and thus influence the catalytic performance of the metal center like an enzyme does. For the reactions involving a catalyst deactivation process caused by the formation of inactive multimetallic species, the site-isolation effect of the resulting dendritic microenvironment can improve the catalytic activity by suppressing the catalyst deactivation pathway. In addition, for amphiphilic dendritic catalysts, substrate accumulation near the catalytic site may occur, which offers the opportunity to improve catalytic activity. More importantly, the core-functionalized dendritic catalysts often show low activity, particularly for high generation catalysts, which is possibly due to the retarded mass transfer relating to the steric hindrance around the catalytic center. On the other hand, this steric hindrance may also influence the conformation of the cored catalytic unit and thus tune the selectivity of catalyst. These possible dendritic effects together with the structure−activity relationships have been systematically studied in the asymmetric hydrogenation using chiral phosphine-cored dendritic ligands.

2.1. Dendritic BINAP

As the most versatile and effective diphosphine ligand widely utilized in asymmetric hydrogenation, BINAP was first selected as the model ligand for the development of chiral phosphine-cored dendritic ligands. In 2000, we reported the first example of a dendritic ligand bearing chiral diphosphine at the core for asymmetric hydrogenation (Scheme 1).[27] Fréchet-type dendrons were introduced into the 5,5′-positions of BINAP through amide linkers. In contrast to the classical supported catalysts, these dendritic ligands could be easily characterized by using NMR spectroscopy and mass spectrometry. The resulting core-functionalized dendritic ligands were then applied in the Ru-catalyzed asymmetric hydrogenation of 2-(4-isobutylphenyl)

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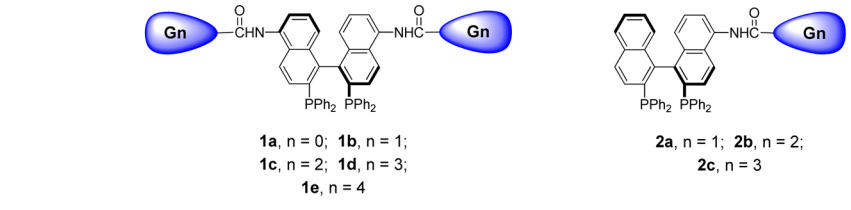
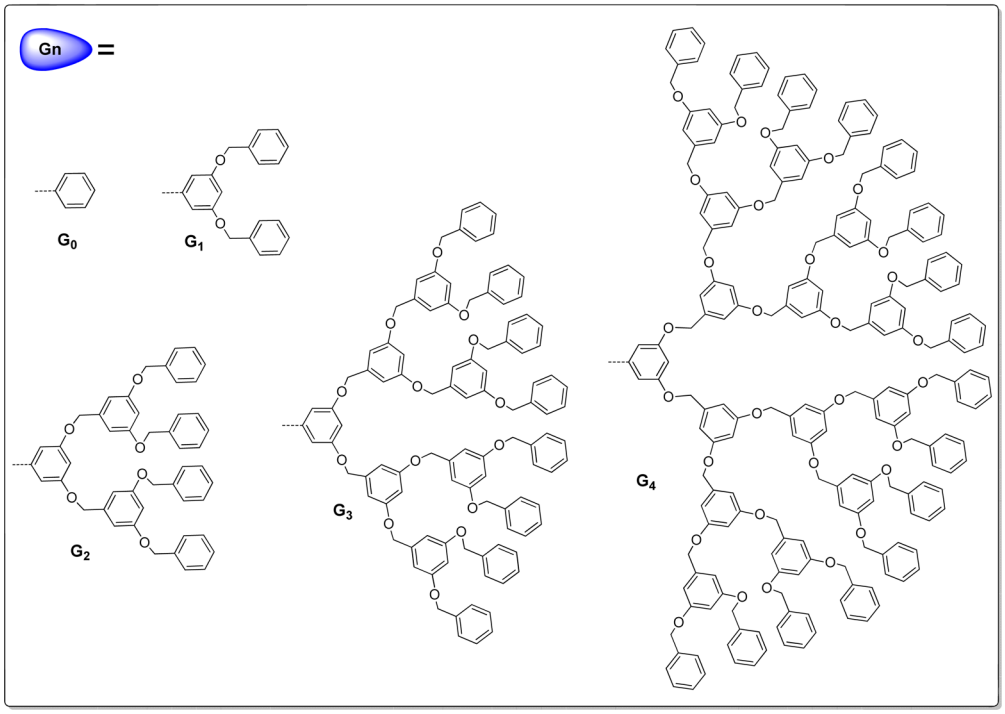
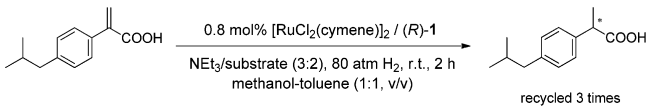
Scheme 1. Structures of Dendritic BINAP Ligands





acrylic acid, showing slightly higher enantioselectivities than BINAP. Unexpectedly, the reactivity increased when higher generation catalysts were used, and this size effect was most pronounced when size moved from generation 2 to 3 (Figure 2).



Ligand	conv. (%)	ee (%)
(*S*)-BINAP	10.2	89.8 (*S*)
(*R*)-**1b**	10.4	91.8 (*R*)
(*R*)-**1c**	13.2	92.6 (*R*)
(*R*)-**1d**	34.3	91.6 (*R*)

Figure 2. Asymmetric hydrogenation of 2-(4-isobutylphenyl)acrylic acid using dendritic BINAP ligands.

In addition, the second-generation catalyst could be recycled at least three times by methanol precipitation with similar activities and enantioselectivities.

To study the structure−activity relationships and understand the observed dendritic effect on activity, the monomeric BINAP ligand **1a** and monosubstituted dendritic BINAP ligands **2a−c** were also synthesized.[28,29] The time course curves of the dendritic catalysts were determined for the same reaction (Figure 3). It was found that the disubstituted dendritic ligands showed distinct positive dendritic generation effect on the reaction rate, and such rate enhancement became more significant when the solvent was changed from toluene/methanol to neat toluene. In contrast, the dendritic size effect for the monosubstituted dendritic ligands was not observed. These results indicated that the microenvironment created by the two bulky dendritic wedges played an important role in promoting the catalytic activity. This microenvironment effect was also observed in the Rh-catalyzed asymmetric hydrogenation of acetamidocinnamic acid in dichloromethane,[29] which is not a good solvent for this polar substrate. As shown in Figure 4, in the presence of high generation dendritic ligand (*R*)-**1e**, complete conversions could be achieved, and the reaction mixture turned into a homogeneous solution. The substrate accumulation in the relatively polar microenvironment of dendrimer near the catalytic site might be the main reason for the rate enhancement. Interestingly, similar reaction rate enhancement was also observed with (*S*)-BINAP as ligand in the presence of the third generation dendron G_3-COOMe, which do not contain the catalytically active center, indicating the noncovalent encapsulation of BINAP by the dendron molecules (entry 3 in Figure 4).

These dendritic ligands were also effective in the Ru-catalyzed asymmetric hydrogenation of simple aryl ketones.[30] One class of the best catalysts for simple ketone hydrogenation are the $RuCl_2$[(diphosphine)(1,2-diamine)] complexes, which were initially reported by Noyori.[31] The dendritic Ru-complexes were prepared in situ by using a two-step procedure, and the bulky nature of dendritic wedges did not influence the coordination of DPEN ligand with ruthenium. Similar to the Noyori's catalytic system, the match of chirality between the

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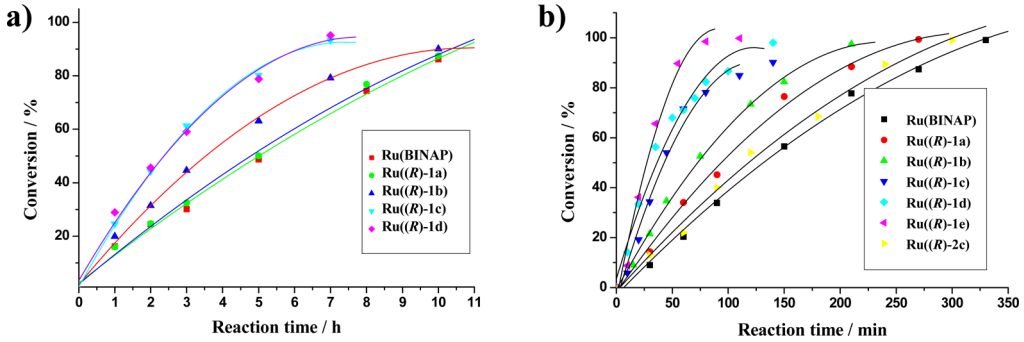
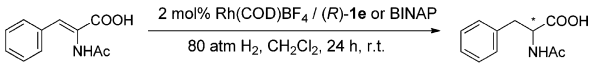


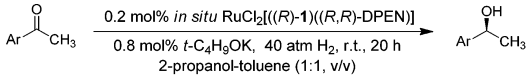
Figure 3. Comparison of activity in asymmetric hydrogenation of 2-(4-isobutylphenyl)acrylic acid using dendritic BINAP ligands: (a) toluene/methanol (1:1, v/v); (b) neat toluene.



Ligand	conv. (%)	ee (%)
(*R*)-BINAP	< 5	24 (*S*)
(*R*)-**1e**	> 95	65 (*S*)
(*S*)-BINAP + **G$_3$-COOMe** (1:1 mole ratio)	> 95	25 (*R*)

Figure 4. Asymmetric hydrogenation of acetamidocinnamic acid using dendritic BINAP ligands.

dendritic BINAP and DPEN is important for achieving high enantioselectivity. Good to high enantioselectivities for several simple aryl ketones were achieved (Figure 5). In addition, the



Ligand	ee (%)		
			
(*R*)-**1a**/(*R*,*R*)-DPEN	78	96	95
(*R*)-**1b**/(*R*,*R*)-DPEN	78	95	92
(*R*)-**1c**/(*R*,*R*)-DPEN	75	95	94
(*R*)-**1d**/(*R*,*R*)-DPEN	75	95	94
(*R*)-**1e**/(*R*,*R*)-DPEN	74	93	92
(*R*)-**1d**/(*S*,*S*)-DPEN	50	—[a]	—[a]
(*R*)-BINAP/(*R*,*R*)-DPEN	80	—[a]	—[a]
(*R*)-BINAP/(*S*,*S*)-DPEN	30	—[a]	—[a]

[a]The experiment was not carried out.

Figure 5. Asymmetric hydrogenation of simple aryl ketones using dendritic BINAP ligands.

third-generation catalyst could be recycled by methanol precipitation and reused 2 times without obvious loss of enantioselectivity.

Despite considerable progress made in the asymmetric hydrogenation of olefins, ketones, and imines, the asymmetric hydrogenation of heteroaromatic compounds remains a major challenge.[32] To facilitate catalyst recycling and reduce catalyst loading, we applied the BINAP-functionalized dendritic ligands in the Ir-catalyzed asymmetric hydrogenation of quinolines.[33] In sharp contrast to the small diphosphine ligands, the dendritic catalysts were highly effective even at an extremely high substrate/catalyst ratio with the maintenance of high enantioselectivity (Figure 6). The maximum initial TOF and TON reached 3450 h^{-1} and 43000, respectively, which are the highest ones obtained so far for this transformation. In addition, the catalytic activity gradually increased with the increasing of dendrimer generation. This strong dendritic effect might be due to the encapsulation of iridium center by the crowded dendritic wedges, reducing the catalyst dimerization.[34] Hydrogenation of various 2-alkyl quinolines was realized by using dendritic ligand (*S*)-**1c**, affording the chiral 1,2,3,4-tetrahydroquinolines with high enantioselectivities. The catalyst could be recycled at least 6 times by *n*-hexane precipitation with similar enantioselectivities but at the expense of relatively low activities.

2.2. Dendritic PHOX

Chiral P,N-ligands, for example, chiral phosphinooxazoline (PHOX) derivatives, have proven to be excellent ligands for the Ir-catalyzed asymmetric hydrogenation of simple alkenes and imines.[4] However, this catalytic system often suffers from a catalyst deactivation process during the hydrogenation, due to the formation of inactive trinuclear iridium species.[35] To date, less study on the immobilization of Ir(PHOX)-type catalysts has been reported.[36] To overcome this drawback, we incorporated a chiral PHOX ligand into the core of dendrimers (Scheme 2).[37] These dendritic ligands were prepared in good to excellent yields by attaching Fréchet dendrons onto the two P-phenyl rings. Their catalytic properties were then evaluated in the asymmetric hydrogenation of 2,4-diaryl-1,5-benzodiazepine derivatives. Although the reduced products represent an important class of chiral heterocycles with pharmacological activity, highly stereoselective reduction of such substrates remains a challenge.[38] Gratifyingly, these dendritic Ir-catalysts exhibited considerable enhancement in activity (Figure 7). In addition, excellent enantioselectivities and good diastereoselectivities, which comparable to those obtained with the small parent catalyst, were achieved by using a dendritic Ir/**3c** catalyst(Figure 8). The mass spectrometric analysis of the dendritic catalyst showed distinct behavior in comparison with the parent catalyst, no dimer species were found after reaction with hydrogen. This result suggested that the metal center was stabilized by the dendritic site isolation effect. Notably, a decreased activity was observed for the third-generation dendritic catalyst, which might be due to the retarded mass transfer. The easy separation and recyclability of the dendritic catalyst were also demonstrated with the solvent (*n*-hexane) precipitation method.

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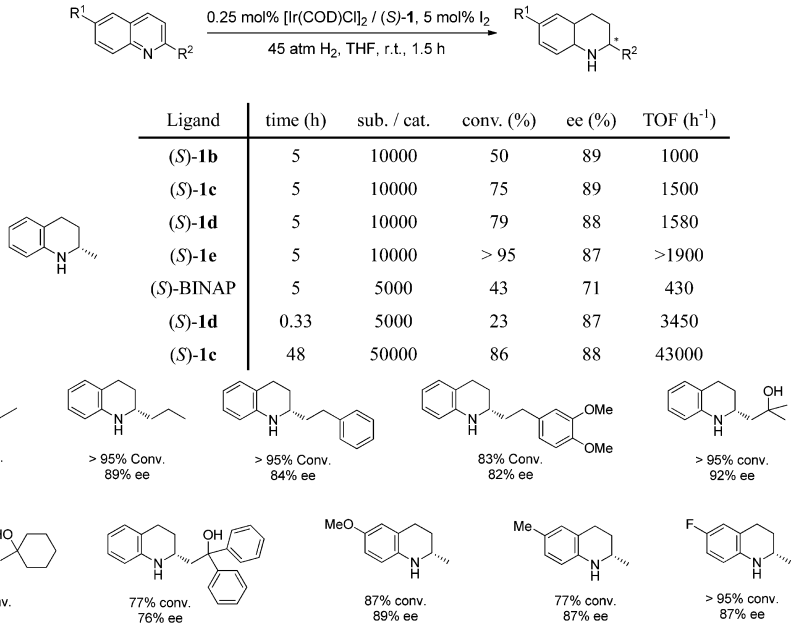
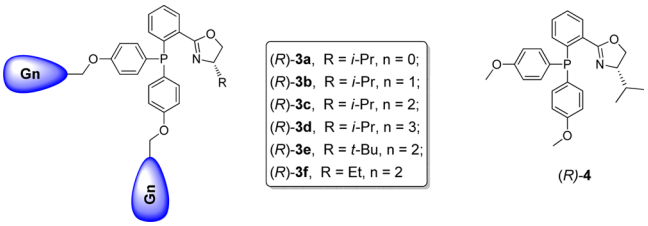


Ligand	time (h)	sub. / cat.	conv. (%)	ee (%)	TOF (h^{-1})
(*S*)-**1b**	5	10000	50	89	1000
(*S*)-**1c**	5	10000	75	89	1500
(*S*)-**1d**	5	10000	79	88	1580
(*S*)-**1e**	5	10000	> 95	87	>1900
(*S*)-BINAP	5	5000	43	71	430
(*S*)-**1d**	0.33	5000	23	87	3450
(*S*)-**1c**	48	50000	86	88	43000

Figure 6. Asymmetric hydrogenation of quinolines using dendritic BINAP ligands.

Scheme 2. Structures of Dendritic PHOX Ligands



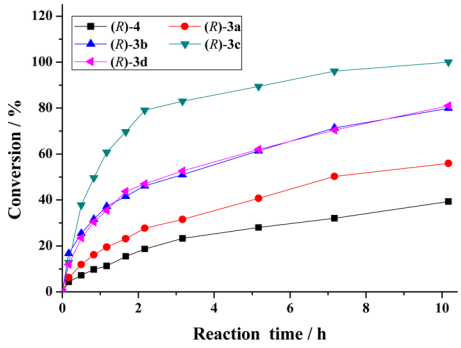


Figure 7. Time course curves of hydrogenation of diaryl-1,5-benzodiazepines.

2.3. Dendritic PyrPhos

For the core-functionalized dendritic catalysts, interesting dendritic effects on reactivity have been observed. Obviously, these novel dendritic effects were related to dendrimer generation. However, it is not very clear how the primary structure of dendrimer biases its conformation and consequently influences its catalytic properties. In order to systematically study the structure−property relationships, we synthesized two series of dendritic diphosphine ligands, (*R*,*R*)-**5** and (*R*,*R*)-**6**, by attaching PyrPhos at the focal point of the normal and backfolded Fréchet-type dendrons through an amide linker, respectively (Scheme 3).[39] Their Rh-complexes were then applied in the hydrogenation of α-acetamido cinnamic acid. These dendritic catalysts exhibited a remarkable generation effect on catalytic activity. In contrast to the dendritic BINAP, the rate of the reaction decreased when higher generation catalysts were utilized. The time course curves showed that the catalyst almost lost its activity going from generation 3 to 4 (Figure 9a). In addition, the diphosphine ligands bearing backfolded dendrons gave lower rates compared with those obtained with the normal dendrons (Figure 9b). This behavior was consistent with the more effective encapsulation of the active core by the more sterically demanding backfolded dendrons. Thus, the relationship between the dendrimer primary structure and its catalytic properties was established, which is beneficial to the understanding of the observed dendritic effects and to the design of new dendritic catalysts in the future.

3. CHIRAL DENDRITIC PHOSPHORUS LIGANDS WITH TUNABLE STRUCTURES FOR ASYMMETRIC HYDROGENATION: DENDRITIC EFFECTS ON ENANTIOSELECTIVITY

Although many effective chiral phosphorus ligands have been synthesized and used in transition-metal-catalyzed asymmetric hydrogenation, the stereoselectivities in many reactions are substrate-dependent, and many reactions still lack efficient chiral catalysts. The tuning of chiral ligand to make it a perfect match with metal center as well as substrate is critically important for achieving efficient asymmetric catalysis. Therefore, it is highly desirable to develop tunable chiral phosphorus ligands. By attaching the well-defined dendrons onto suitable positions of chiral phosphorus ligands, we have developed several series of tunable chiral dendritic phosphorus ligands, which enable us not only to fine-tune catalytic properties but also to facilitate catalyst recycling.

3.1. Dendritic BIPHEP

Chiral diphosphine ligands based on biaryl groups, such as BINAP and MeO−BIPHEP, have been developed and have shown excellent catalytic properties in asymmetric hydrogenation. The dihedral angles of such phosphorus ligands have proven to exert very important influence on the catalytic performance. Several chiral diphosphine ligands with tunable bite angles have been reported.[40] In 2006, we developed another new

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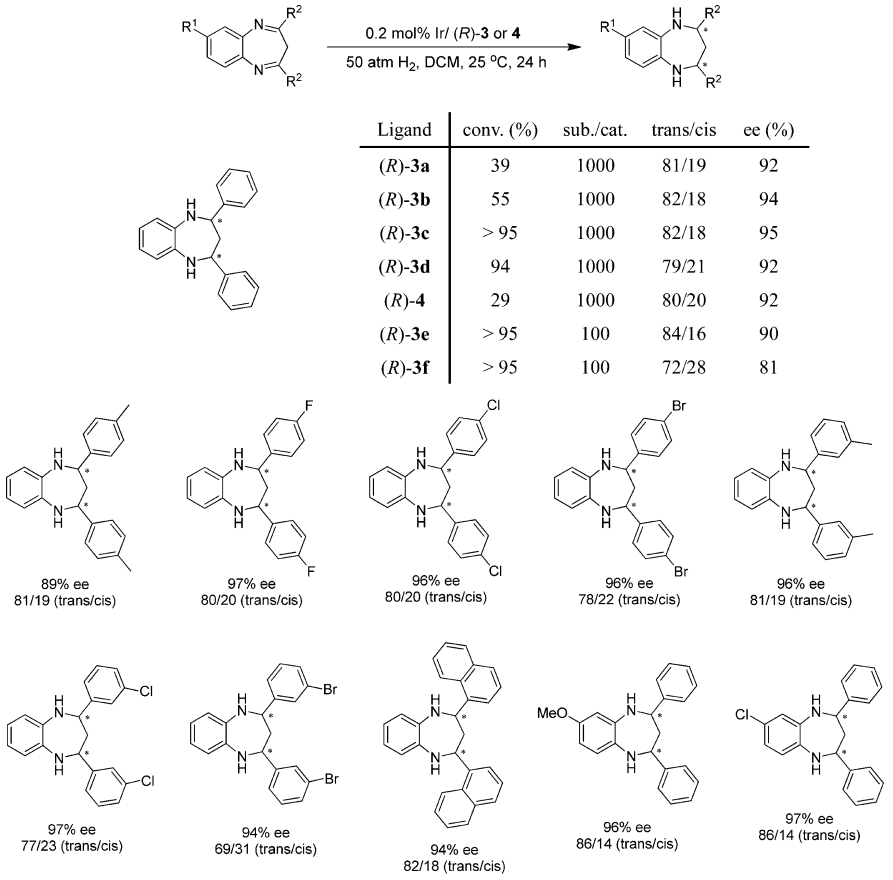
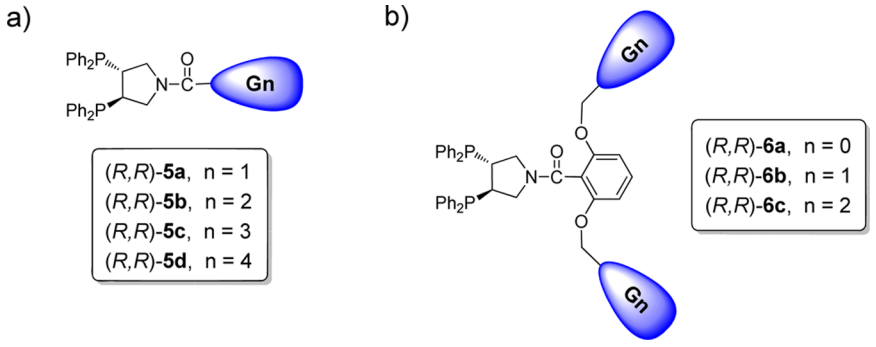


Figure 8. Asymmetric hydrogenation of diaryl-1,5-benzodiazepines using dendritic PHOX ligands.

Scheme 3. Chiral Dendritic PyrPhos Ligands with normal (a) and Backfolded (b) Dendritic Wedges



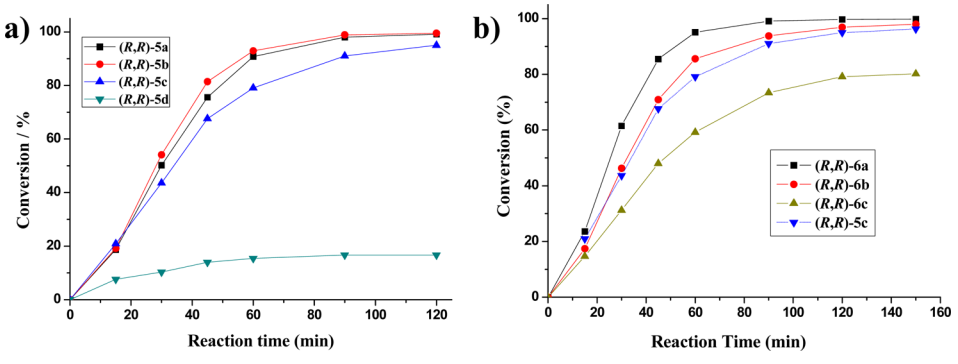


Figure 9. Time course curves of hydrogenation of α-acetamido cinnamic acid using normal (a) and backfolded (b) dendritic PyrPhos ligands.

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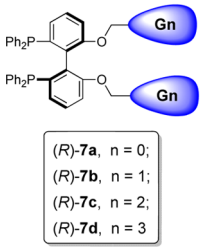
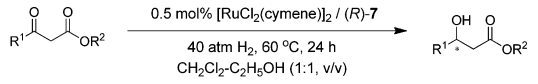


Ligand	dihedral angle (°)
(*R*)-**7a**	88.6
(*R*)-**7b**	94.2
(*R*)-**7c**	95.4
(*R*)-**7d**	116.2

Figure 10. Structures of dendritic BIPHEP ligands and calculated dihedral angles of the biphenyl unit.



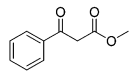
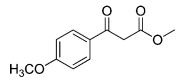
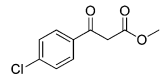
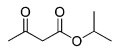
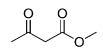
substrate	ee (%) (*R*)-**7a**	(*R*)-**7b**	(*R*)-**7c**	(*R*)-**7d**
	93.1	92.0	86.6	91.3
	84.9	81.1	77.9	79.6
	88.0	85.0	80.1	80.9
	98.2	94.1	89.1	88.4
	94.1	94.1	88.0	88.5

Figure 11. Asymmetric hydrogenation of β-ketoesters using dendritic BIPHEP ligands.

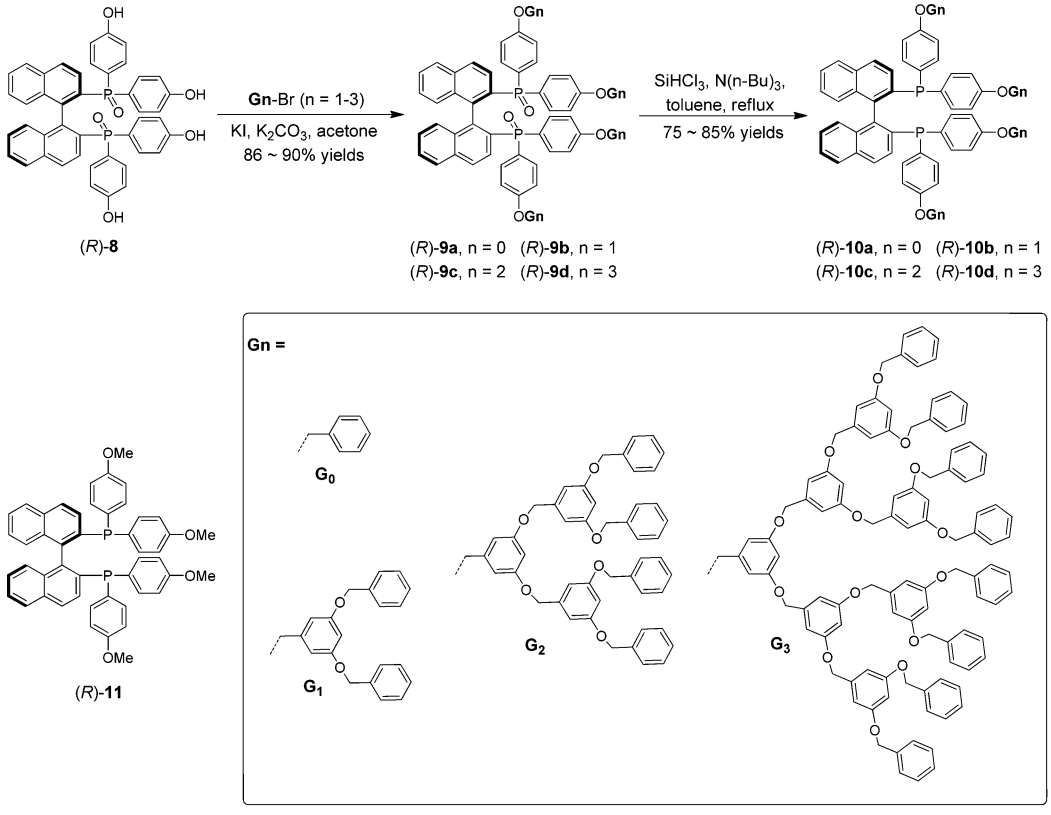
strategy for designing tunable BIPHEP-type ligands via replacing the methoxyl groups at the 6,6′-positions of the biphenyl backbone by different generation dendrons (Figure 10).[41] Their Ru complexes were then applied in the asymmetric hydrogenation of β-ketoesters. These dendritic catalysts exhibited similar activity, but the enantioselectivity varied significantly from generation 1 to 2 (Figure 11). To further understand this size effect, computational calculation of dihedral angles of the two-phenyl rings was performed by using the semiempirical AM1 method. It was found that the dendritic ligands have larger dihedral angles than the model ligand, in accordance with the common understanding that the atropoisomeric biaryl phosphines with narrow dihedral angles usually give high enantioselectivities in such reactions.

3.2. Dendritic BINAP

Most chiral diphosphine ligands involve a chiral scaffold bearing two diphenylphosphine chelating units. The chiral information is transferred from the chiral skeleton to the metal center via the chiral array of the four P-phenyl rings.[42] Generally, modification to the four P-phenyl rings by introducing different substituents can fine-tune the chiral pocket of the catalyst. Alternatively, we developed another general method for modifying such chiral biaryl diphosphine ligands by attaching sterically demanding dendrons onto the four P-phenyl rings. By choosing BINAP as the model ligand, a new class of tunable dendritic BINAP ligands was prepared in very good yields by the method illustrated in Scheme 4.[43]

The introduction of bulky dendritic wedges did not influence the coordination of ruthenium with the phosphorus atoms as demonstrated by the results of ^{31}P NMR spectroscopy. β-Ketoesters were first chosen as standard substrates to evaluate the efficiency of these dendritic Ru-catalysts, as well as to

Scheme 4. Synthesis and Molecular Structures of Tunable Dendritic BINAP Ligands



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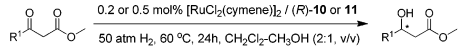
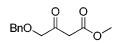
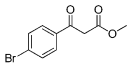
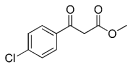
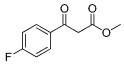
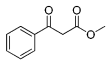
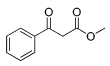
establish the structure−property relationships. Interestingly, remarkable dendritic effect on enantioselectivity was verified in the asymmetric hydrogenation of both alkyl and aryl β-ketoesters (Figure 12). Excellent enantioselectivities were obtained by using



Substrate	conv. (%); ee (%)				
	(*R*)-**11**	(*R*)-**10a**	(*R*)-**10b**	(*R*)-**10c**	(*R*)-**10d**
	>95; 84	>95; 66	>95; 44	>95; 92	>95; 97
	>95; 83	>95; 67	>95; 54	>95; 95	>95; 97
	>95; 82	>95; 69	>95; 42	>95; 92	67; 92
	>95; 82	>95; 64	>95; 50	67; 93	33; 94
	>95; 80	>95; 62	>95; 41	75; 91 >95; 92[a]	36; 94 >95; 95[a]
	>95; 92[b]	>95; 91[b]	>95; 91[b]	>95; 91[b]	80; 91[b]

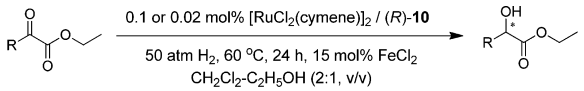
[a] 5 mol% $TsOH·H_2O$ was added as additive. [b] Dendritic Ru/**1** catalysts were used.

Figure 12. Asymmetric hydrogenation of β-ketoesters using dendritic BINAP ligands.

high generation catalysts, which were obviously superior to the corresponding small catalysts. The lowest ee values were observed with the first-generation dendritic catalyst. Notably, relatively low activity was observed for the second- and third-generation catalysts. In addition, the unusual size effect on enantioselectivity was not observed for similar Ru complexes bearing dendritic wedges at the 5,5′-positions of the binaphthyl backbone (Scheme 1). These results suggested that the sterically demanding dendritic wedges attached on the P atoms could fine-tune the chiral pocket of the catalyst. Furthermore, the second-generation catalyst could be reused at least 7 times with similar enantioselectivity but gradually decreased reactivity.

These tunable dendritic BINAP ligands were also applied in the Ru-catalyzed asymmetric hydrogenation of α-ketoesters and the less studied α-ketoamides.[6] Quite similar dendritic effects were also observed in both cases, and high enantioselectivities were observed with the second- and third-generation dendritic catalysts (Figure 13 and 14). When the second-generation ligand (*R*)-**10c** was used, various aryl α-keto esters were smoothly hydrogenated to give chiral α-hydroxyl esters with high enantioselectivities. Notably, hydrogenation of ethyl 2-oxo-2-phenylacetate under very low catalyst loading (0.01 mol %) proceeded smoothly with full conversion and 91% ee. In the case of α-ketoamides, various alkyl and aryl α-keto amides bearing different substituents on the *N*-atom were smoothly hydrogenated by using (*R*)-**10c**. High enantioselectivities for alkyl α-ketoamides were obtained, which represent the highest enantioselectivities for such substrates.

To understand these unusual dendritic generation effects, theoretical calculation of the dendritic Ru complexes was carried out by using the semiempirical PM6 method. Unlike the dendritic BIPHEP ligands described above, the dihedral angles of the two naphthalene rings of BINAP were not changed with increasing generation. Instead, the calculation results indicated that the increasing steric repulsion of the dendritic wedges might influence the chiral array of the four P-phenyl groups and consequently modulate the enantioselectivity. In contrast, similar conformational changes were not observed for the similar Ru-complexes bearing dendritic wedges at the 5,5′-positions of the binaphthyl backbone (Scheme 1). These results are consistent with the experiment results.



Ligand	sub./cat.	conv. (%)	ee (%)
(*R*)-**10a**	1000	> 95	70
(*R*)-**10b**	1000	> 95	59
(*R*)-**10c**	1000	> 95	93
(*R*)-**10d**	1000	> 95	95
(*R*)-**11**	1000	> 95	84
(*R*)-**10c**	5000	> 95	93
(*R*)-**10c**	10000	> 95	91

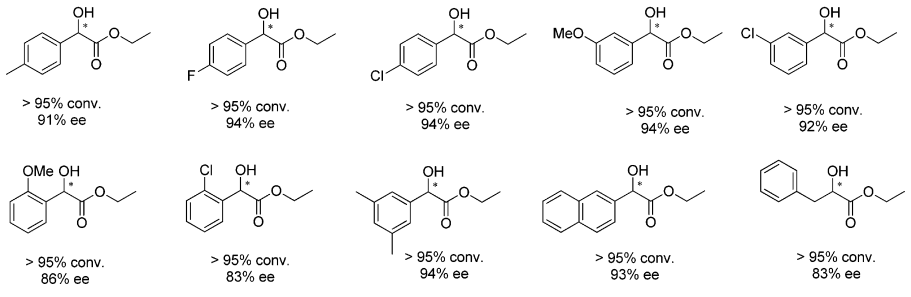


Figure 13. Asymmetric hydrogenation of α-ketoesters using dendritic BINAP ligands.

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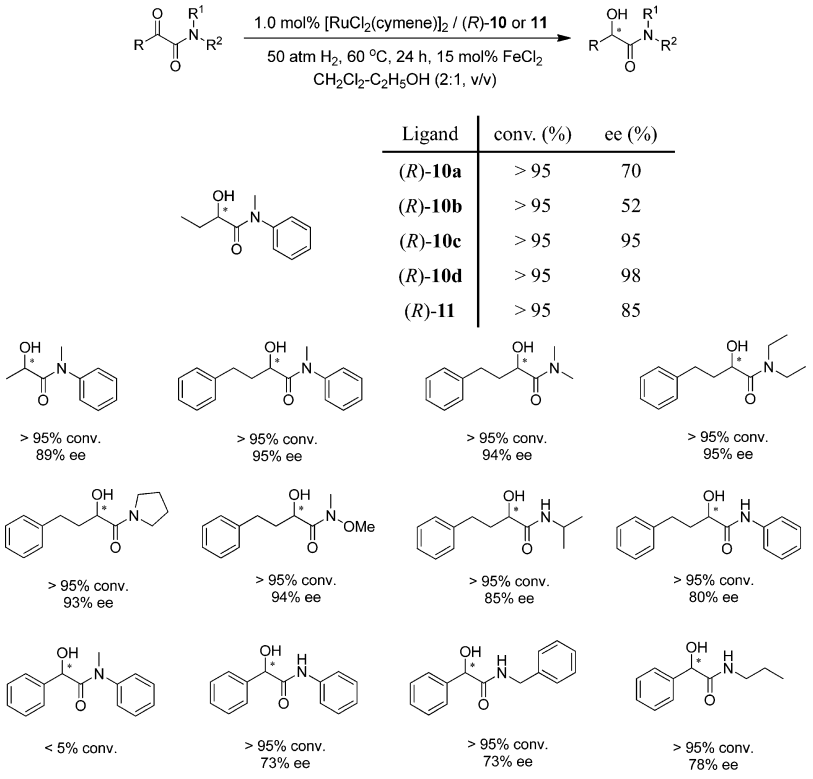
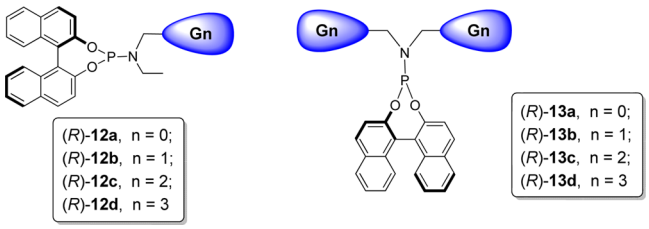


Figure 14. Asymmetric hydrogenation of α-ketoamides using dendritic BINAP ligands.

3.3. Dendritic MonoPhos

Chiral monodentate phosphorus ligands, such as monophosphoramidites and monophosphites, have proven to be capable of inducing excellent enantioselectivity in the asymmetric hydrogenation.[5] The first chiral dendritic phosphoramidite ligand was reported by Reek and co-workers.[44] They attached the third-generation carbosilane dendrons onto the axially chiral dicarbazole skeleton through an amide linker. The resulting dendritic ligand was found to be effective in the Rh-catalyzed asymmetric hydrogenation of methyl 2-acetamidocinnamate with high enantioselectivity. By choosing the privileged monodentate MonoPhos as the model ligand, we prepared two series of dendritic MonoPhos readily by replacing one or two methyl groups on the N-atom with the Fréchet-type dendritic wedges (Scheme 5).[45,46] This modular synthetic strategy was also used for the synthesis of other phosphoramidite ligands from different chiral diols. The Rh-complexes of ligands (*R*)-**12** bearing one dendritic wedge were first applied in the asymmetric hydrogenation of α-dehydroamino acid esters and dimethyl itaconate. Excellent enantioselectivities were achieved for both substrates, which are slightly higher or comparable to those obtained from small MonoPhos derivatives. In addition, encapsulation of the metal center into the bulky dendritic structure could suppress, to some extent, the decomposition of Rh-catalyst caused by the hydrolysis in protic solvents.

Scheme 5. Structures of Dendritic MonoPhos Ligands Bearing (a) One Dendritic and (b) Two Dendritic Wedges



The easy availability and modular structure of monodentate phosphoramidites allow the fine-tuning of the catalyst to find more effective ligands. The substituents on the *N*-atom were found to play an important role on enantioselectivity, and large groups on the *N*-atom often resulted in low asymmetric induction. To investigate the effect of sterically demanding dendritic wedges on the catalytic properties and to establish the structure−property relationships, the dendritic MonoPhos ligands bearing two dendritic wedges on the *N*-atom were applied in the Rh-catalyzed asymmetric hydrogenation of α-dehydroamino acid derivatives and enamides.[46] An unprecedented enhancement of enantioselectivity was observed in both cases (Figures 15 and 16). The second- and third-generation dendritic catalysts gave excellent enantioselectivities, which are obviously higher than those obtained from the small MonoPhos derivative. To understand this unusual dendritic effect, ^{31}P NMR spectroscopy of all these dendritic Rh-complexes was examined. The chemical shifts were found to be very similar, suggesting that the sterically demanding dendritic wedges did not influence the coordination of rhodium with the phosphorus atom. The increasing steric repulsion between dendritic wedges might influence the chiral pocket of the catalyst where the hydrogenation reaction occurs. On the other hand, negative dendrimer generation effect on catalytic activity (entry 1 in Figure 15) was noticed, which is plausibly due to the encapsulation of the catalytic site by the dendritic wedges. In addition, the second-generation catalyst was quantitatively precipitated by the addition of *n*-hexane and reused at least five times with similar enantioselectivities before the fifth run.

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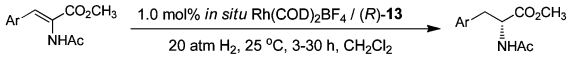
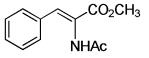
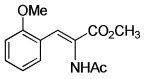
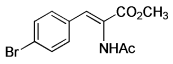
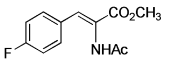
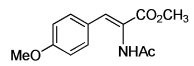
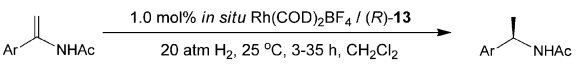


Substrate	*ee* (%)			
	(*R*)-**13a**	(*R*)-**13b**	(*R*)-**13c**	(*R*)-**13d**
	92 (3 h)[a]	91 (3 h)[a]	99 (12 h)[a]	98 (30 h)[a]
	83	93	99	94
	94	97	98	95
	92	93	97	97
	92	95	94	97

[a] Data in bracket is reaction time for achieving 100% conversions.

Figure 15. Asymmetric hydrogenation of α-dehydroamino acid esters catalyzed by dendritic Rh/**13** catalysts.



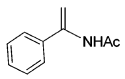
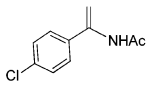
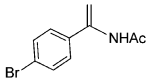
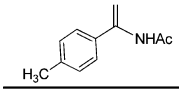
Substrate	*ee* (%)			
	(*R*)-**13a**	(*R*)-**13b**	(*R*)-**13c**	(*R*)-**13d**
	60	78	86	90
	60	71	78	94
	61	73	78	94
	47	60	78	92

Figure 16. Asymmetric hydrogenation of enamides catalyzed by dendritic Rh/**13** catalysts.

4. CHIRAL DENDRITIC DIPHOSPHINE LIGANDS WITH CORE–SHELL STRUCTURES FOR ASYMMETRIC HYDROGENATION: FACILITATING CATALYST RECYCLING

By taking advantage of the unique features of dendrimer, such as globular and nanoscale molecular size and tunable solubility in different organic solvents, the dendritic catalysts can be recycled by means of nanofiltration, solvent precipitation, or two-phase separation.[13] In the case of core-functionalized dendrimers, their solubility can be easily modified by end-group modification, and thus the solvent precipitation method has often been used for the recycling of such dendritic catalysts. However, this method often requires the use of a relatively large amount of organic solvents and sometimes still suffers from difficulties in the separation of the precipitated dendritic catalysts. From the viewpoint of practical application, it is highly desirable to develop new recyclable catalytic systems with readily available dendrimer catalysts, particularly low generation dendritic catalysts.

On the basis of special properties of some solvent pairs, such as *n*-hexane/ethanol, which are completely miscible but show phase separation with the addition of a little water, a novel system of "one-phase catalysis and two-phase separation" was developed using dendritic catalysts with core–shell structures (Figure 17).[47] Two series of BINAP-cored dendrimers bearing alkyl chains on the periphery were designed and synthesized (Figure 18).[47,48] These nonpolar chiral dendritic ligands preferred to dissolve in nonpolar *n*-hexane. The number and length of the alkyl chains had a remarkable effect on the partition coefficients in the *n*-hexane/ethanol–water biphasic system (Figure 18). Their Ru-complexes were then applied in the asymmetric hydrogenation of 2-arylacrylic acids in *n*-hexane/ethanol under homogeneous conditions. Enantioselectivities comparable to that of BINAP itself were achieved. Upon completion of the hydrogenation, a small amount of water (2.5% v/v) was added to the reaction mixture, which immediately induced phase separation. The hexane layer mainly containing the dendritic catalyst Ru/(*R*)-**16** was separated and directly reused in the next round of reaction, with almost the same activity and enantioselectivity (Figure 19). This strategy as a general method has been applied to other catalytic systems.[49,50]

This type of dendritic BINAP ligand has also been applied in thermotropic catalytic systems, in which the catalyst could be recycled by simply cooling or heating the reaction mixture. However, in most cases, this method requires the use of fluorous catalysts and perfluorocarbon solvents.[51] The first-generation dendritic Ru/**15e** catalyst showed temperature-dependent solubility in 1,4-dioxane/ethanol mixture and was applied in the asymmetric hydrogenation of β-ketoesters.[48] The reaction was carried out in ethanol/1,4-dioxane (3:1, v/v) at 60 °C under homogeneous conditions, giving chiral products with slightly higher enantioselectivities compared with that with Ru(BINAP). Upon completion of the reaction, the catalyst could be recovered by cooling the reaction mixture and reused three times with similar enantioselectivity (Scheme 6).

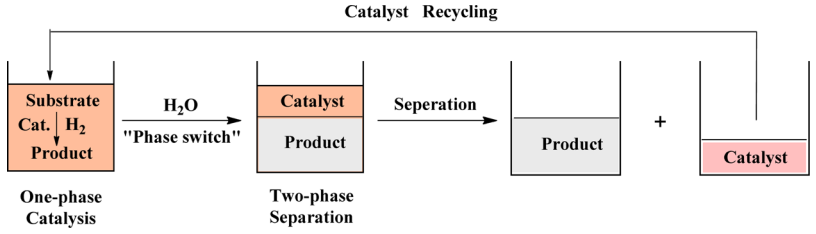


Figure 17. Illustration of the effective and recyclable catalyst system.

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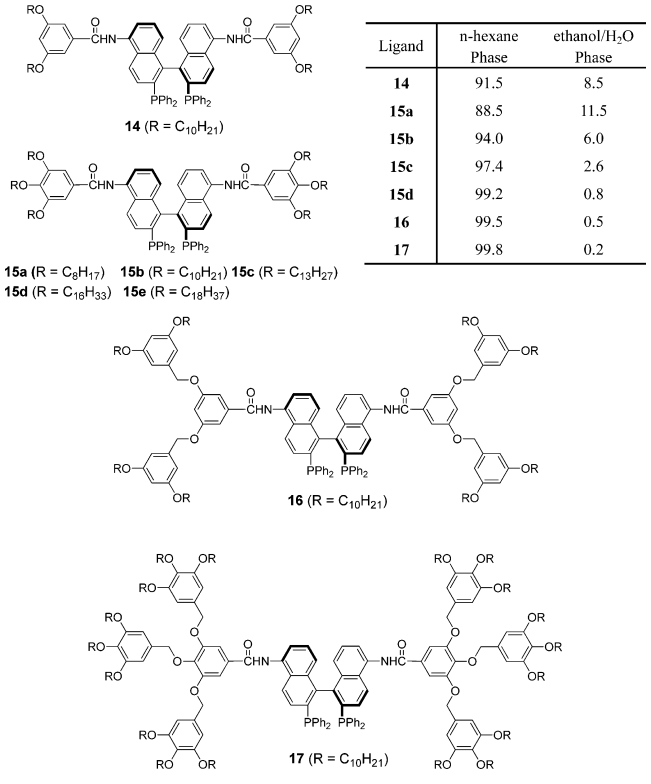
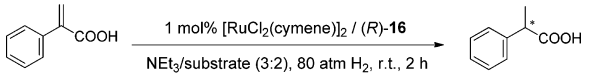


Ligand	n-hexane Phase	ethanol/H_2O Phase
14	91.5	8.5
15a	88.5	11.5
15b	94.0	6.0
15c	97.4	2.6
15d	99.2	0.8
16	99.5	0.5
17	99.8	0.2

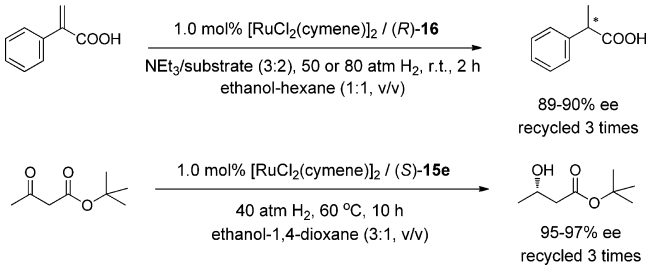
Figure 18. Chiral dendritic BINAP ligands with core−shell structures and partition coefficients in *n*-hexane/ethanol (2.5% H_2O) biphasic system.



Entry	conv. (%)	ee (%)[a]
Run 1	94	90
Run 2	93	90
Run 3	93	89
Run 4	91	89

Figure 19. Catalyst recycling in the hydrogenation of 2-phenylacrylic acid with Ru/(*R*)-**16** catalyst.

Scheme 6. Asymmetric Hydrogenation of 2-Arylacrylic Acid and *β*-Ketoester Using Dendritic BINAP Ligands with Core−Shell Structures



5. CONCLUSIONS AND OUTLOOK

Several series of chiral dendritic phosphorus ligands including diphosphines, monodentate phosphoramidites, and P,N-ligands have been synthesized by attaching the corresponding chiral phosphorus units into the core or the focal point of Fréchet-type dendrons. Most of their transition metal (Ru, Rh, or Ir) complexes were found to be effective catalysts for the asymmetric hydrogenation of prochiral olefins and ketones, as well as some challenging imine-type substrates. The dendritic catalyst could be readily recycled by means of solvent precipitation, water- or temperature-induced two-phase separation. Importantly, in most cases, the dendritic wedges played important roles in catalytic activity, enantioselectivity, or both. First, they provided a unique microenvironment around the metal center to stabilize the catalyst by suppressing the formation of inactive dimeric or trimeric metal species. Second, they served as a new tool for systematically fine-tuning the conformation of chiral catalysts. Third, as a new type of well-defined supports with highly branched structures, they could facilitate the recycling of the often expensive chiral phosphorus catalysts. In particular cases, unusual dendritic positive effects have been observed, including remarkable enhancement of activity and enantioselectivity.

Meanwhile, we can see that the number and types of chiral phosphorus dendritic ligands are very limited. The main problem is the difficulty in synthesizing these easily oxidized and complicated macromolecules. The development of new methods (such as "click" and noncovalent strategies) for the synthesis of such dendritic ligands and the use of easily available hyperbranched polymers as alternative catalyst supports are expected to be the focus for further research in this area. In addition, efforts in elucidating the nature of the observed dendritic effects will form part of the future studies, which are likely to be beneficial for the rational design of new dendritic catalysts for asymmetric hydrogenation.

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Notes

The authors declare no competing financial interest.

Biographies

Yan-Mei He received her B.S. (in 1990) and M.S. (in 1993) degrees from the College of Chemistry and Molecular Engineering in Peking University, China. She joined the Institute of Chemistry, Chinese Academy of Sciences, as an assistant professor in 2003, working in the group of Dr. Qing-Hua Fan. Currently, she is a senior engineer (associate professor level) in the CAS Key Laboratory of Molecular Recognition and Function. Her research interests focus on asymmetric catalysis and functional dendrimers.

Yu Feng was born in 1982. He received his B.S. degree from Xiangtan University in 2005 and Ph.D. degree from the Institute of Chemistry, Chinese Academy of Sciences, in 2010 under the supervision of Professor Qing-Hua Fan. He is now an associate professor in the CAS Key Laboratory of Molecular Recognition and Function. His research interests include synthesis and application of functional dendrimers, supramolecular catalysis, and functional organogels.

Qing-Hua Fan was born in 1966. He received his B.S. degree from Xiangtan University in 1989 and M.S. degree from the Institute of Chemistry, Chinese Academy of Sciences (ICCAS), in 1992. Then he worked in the laboratory of silicon polymers and related advanced functional materials. In 1995, he moved to The Hong Kong Polytechnic University as a Ph.D. student under the direction of Professor Albert S. C. Chan. After obtaining his Ph.D. degree in 1998, he came back to ICCAS as an associate professor and a research group leader and became

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full professor in 2003. His research interests include asymmetric catalysis, environmentally benign catalytic reactions, and synthesis and application of functional dendrimers.

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■ DEDICATION

Dedicated to Prof. Li-Xin Dai on the occasion of his 90th birthday.

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