Modular chiral dendritic monodentate phosphoramidite ligands for Rh(II)-catalyzed asymmetric hydrogenation: unprecedented enhancement of enantioselectivity†

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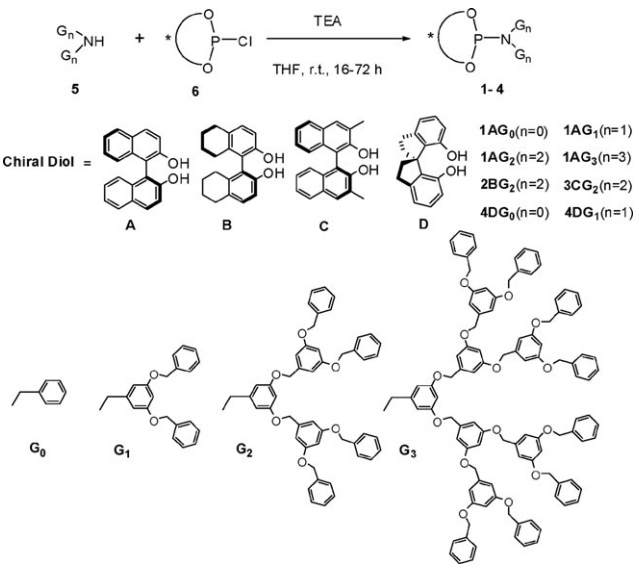
Modular chiral dendrimers with monodentate phosphoramidite ligands located at the core were synthesized and applied in the Rh-catalyzed asymmetric hydrogenations, afforded unprecedented enhancement of enantioselectivity.

The search for ideal chiral catalysts which combine the advantages of both homogeneous and heterogeneous catalysis is the center of many present investigations on the transition metal catalyzed asymmetric synthesis.[1,2] Due to the well-defined and tunable molecular architectures as well as nano-scale size, metallodendrimers have been emerging as a promising class of catalysts as demonstrated in the pioneering work by van Koten in 1994.[3] So far, a number of organometallic dendrimers with catalytic sites at the core or at the periphery have been reported.[4] Among them, however, examples of positive dendrimer effect, in which the dendrimer played an active role in enhancing catalytic reactivity and/or selectivity, are still limited.[5–8] For asymmetric catalysts, subtle conformational changes may significantly influence their enantioselectivity because the catalytic reaction is governed by small increments of free enthalpy of activation.[9] Thus, attachment of chiral catalyst onto the well-defined dendrimer framework is expected to provide a unique tool for fine-tuning catalytic performance through adjusting their microenvironment. To the best of our knowledge, however, only two groups reported successful study which afforded obviously better enantioselectivity with higher generation dendritic catalysts.[7b,c] Most recently, we have reported dendrimers with a chiral diphosphine unit, BINAP (2,2′-bis(diphenylphosphino)-1,1′-binaphthyl) at their core, and found that the iridium catalysts with these dendritic BINAP exhibited significantly higher catalytic activity than the parent Ir-catalyst.[8e] As an extension of our research,[8] here we report a new kind of chiral dendrimers with a monodentate phosphoramidite at the core, which consist of structurally tunable chiral backbone and sterically demanding polyether dendritic wedges.

Monodentate chiral phosphorus ligands have recently attracted considerable attention because of their excellent performance, relatively simple synthesis and good stability.[10] To achieve facile catalyst separation, monodentate phosphorus ligands and/or their metallic complexes have been successfully immobilized onto organic or inorganic supports *via* chemical bonds or noncovalent interactions.[11] Chiral dendritic monodentate phosphoramidite ligands were also developed recently by us and Reek's group,[12] but evident dendrimer effects were not observed and the recycling of catalyst was not explored. In this present study, we synthesized a new kind of modular chiral dendritic monodentate phosphoramidite ligands through substitution of the dimethylamino moiety by the Fréchet-type dendritic wedges and applied them in the Rh-catalyzed asymmetric hydrogenation of α-dehydroamino acid esters and enamides. Unprecedented positive dendrimer effect on enantioselectivity was observed in both catalytic reactions for the first time.

The synthesis of chiral dendritic monodentate phosphoramidite ligands **1–4** is outlined in Scheme 1. Fréchet-type dendrimer was chosen as the support due to its inertness to



Scheme 1 The synthesis of modular chiral dendritic monodentate phosphoramidite ligands (**1–4**).

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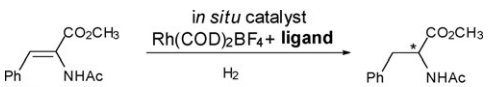
reaction,[13] and dendrons **5** (**5G$_0$**–**5G$_3$**) bearing a secondary amine group located at the focal point were firstly synthesized by using the convergent method. Then, the chiral chlorophosphite **6A**, which was generated *in situ* from phosphorus trichloride and (*S*)-BINOL (**A**) in the presence of triethylamine,[14] reacted with dendrons **5** to give the zeroth to third generation dendritic ligands **1** (**1AG$_n$**, n = 0–3) in moderate yields, respectively, as air-stable white powders after purification by flash column chromatography. To demonstrate the modularity and facility of this method, the other dendritic ligands (**2–4**) were also synthesized by reacting **5** with chlorophosphite **6** (**6B–6D**) generated from the corresponding chiral diols (**B–D**), respectively. All these dendritic ligands were well characterized by ^{1}H, ^{13}C and ^{31}P NMR spectroscopy as well as MALDI-TOF mass spectrometry. All results are consistent with the compounds synthesized.

With these dendritic ligands in hand, the rhodium catalysts were prepared *in situ* by reacting 2 equiv. of the appropriate dendrimer ligands with [Rh(COD)$_2$]BF$_4$ in dichloromethane at room temperature. Then, the hydrogenation of methyl 2-acetamidocinnamate (**7a**) as the model substrate was first performed using 1 mol% Rh/**1AG$_2$** catalyst in different solvents (Table 1, entries 1–3). It was found that dichloromethane was the best choice in terms of conversion and enantioselectivity. Both the reaction rate and enantioselectivity were increased when the hydrogen pressure was increased (entries 3–6). The ratio of ligand to metal has obvious influence on the enantioselectivity or the reaction rate. Unlike the parent catalyst MonoPhos,[10g] the dendritic catalyst afforded much lower enantioselectivity with a **1AG$_2$**/Rh ratio of 1 (entry 7). In contrast, similar enantioselectivity but low conversion were observed when the ratio of **1AG$_2$**/Rh was increased from 2 to 3 (entry 8 *vs.* 3).

Table 1 Condition optimization for the Rh-catalyzed asymmetric hydrogenation of methyl 2-acetamido cinnamate (**7a**)[a]



Entry	Ligand	Solvent	t/h	H_2/atm	ee[b] (%)
1	**1AG$_2$**	THF	12	20	77 (*R*)
2	**1AG$_2$**	EA	12	20	94 (*R*)
3	**1AG$_2$**	CH_2Cl_2	12	20	99 (*R*)
4	**1AG$_2$**	CH_2Cl_2	24	1	94 (*R*)
5	**1AG$_2$**	CH_2Cl_2	24	5	98 (*R*)
6	**1AG$_2$**	CH_2Cl_2	12	50	99 (*R*)
7[c]	**1AG$_2$**	CH_2Cl_2	12	20	93 (*R*)
8[d]	**1AG$_2$**	CH_2Cl_2	24	20	99 (*R*)
9	**1AG$_0$**	CH_2Cl_2	3	20	92 (*R*)
10	**1AG$_1$**	CH_2Cl_2	3	20	91 (*R*)
11	**1AG$_3$**	CH_2Cl_2	30	20	98 (*R*)
12	**2BG$_2$**	CH_2Cl_2	12	20	95 (*R*)
13	**3CG$_2$**	CH_2Cl_2	12	20	31 (*R*)
14	**4DG$_0$**	CH_2Cl_2	3	20	92 (*S*)
15	**4DG$_1$**	CH_2Cl_2	3	20	94 (*R*)[e]

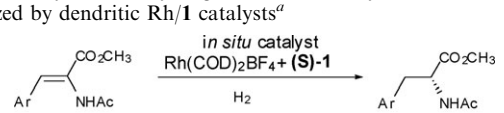
[a] *Reaction conditions*: 0.094 mmol of **7a** in 1.5 mL solvent, ligand/Rh = 2.2 (mol/mol), substrate/catalyst = 100 (mol/mol), 25 °C. [b] 100% conversions were achieved in all cases except for entries 2 (28%), 8 (24%) and 13 (49%). The *ee* values of the reduced products were determined by GC analysis with chiral column. [c] (*S*)-**1AG$_2$**/Rh = 1.0 (mol/mol). [d] (*S*)-**1AG$_2$**/Rh = 3.0 (mol/mol). [e] (*R*)-**4DG$_1$** was used.

Next, we investigated the effect of dendrimer generation on the catalyst performance (Table 1). In sharp contrast to the small monodentate phosphoramidite ligands,[10g,h,14] in which large groups on the nitrogen atom of the ligand led to poor enantioselectivity, the second- and third-generation dendrimer ligands **1AG$_2$** and **1AG$_3$** bearing sterically demanding groups on the nitrogen atom gave excellent enantioselectivities (entries 3 and 11). However, the reason of this enhancement in enantioselectivity by introduction of large dendritic wedges is not clear at present time.[15] On the other hand, these bulk dendrimer ligands afforded low reaction rate, which was probably due to the encapsulation of the catalytically active center by the dendritic wedges.[8c] In addition, the enantioselectivity induced by H8-BINOL-derived dendrimer ligand **2BG$_2$** was found to be slightly lower than that obtained with **1AG$_2$** (entry 12 *vs.* 3). Much lower enantioselectivity was observed with dendrimer ligand **3CG$_2$** derived from 3,3-dimethyl-BINOL (entry 13). The dendrimer ligands **4DG$_0$** and **4DG$_1$** bearing 1,1′-spirobiindane backbone gave the same or slightly higher enantioselectivity as compared to ligands **1AG$_0$** and **1AG$_1$** (entry 14 *vs.* 9, and entry 15 *vs.* 10).

To further demonstrate the unique positive dendritic effect on enantioselectivity, other α-dehydroamino acid esters (**7b–7e**) and enamides (**9a–9d**) were hydrogenated by using dendritic ligands **1** (**1AG$_n$**, n = 0–3). Generally, excellent enantioselectivities were achieved by using the catalysts with high-generation dendrimers. For example, among these dendrimer catalysts, Rh/**1AG$_2$** or/and Rh/**1AG$_3$** gave the best enantioselectivities in the asymmetric hydrogenation of substrates (**7b–7e**) (Table 2). Similarly, in the cases of the hydrogenation of enamides (**9a–9d**), it was found that the enantioselectivity increased significantly with increasing dendrimer generation (Table 3).

Another important feature of dendrimer catalysts is the easy and reliable separation of the chiral catalysts.[16] To investigate the recyclability of the dendritic catalysts in this study, the Rh/**1AG$_2$**-catalyzed asymmetric hydrogenation of **7a** was chosen as the standard reaction. Upon the completion of the reaction, the catalyst was quantitatively precipitated by the addition of hexane and reused at least five times with similar enantioselectivities before run 5 (Table 4).

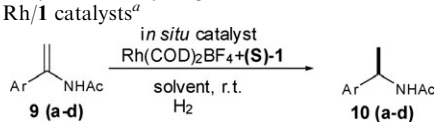
Table 2 Asymmetric hydrogenation of α-dehydroamino acid esters catalyzed by dendritic Rh/**1** catalysts[a]



		ee (%)[b]			
Entry	Ar	**1AG$_0$**	**1AG$_1$**	**1AG$_2$**	**1AG$_3$**
1	2-MeOC$_6$H$_4$ (**7b**)	83	93	99	94
2	4-BrC$_6$H$_4$(**7c**)	94	97	98	95
3	4-FC$_6$H$_4$ (**7d**)	92	93	97	97
4	4-MeOC$_6$H$_4$ (**7e**)	92	95	94	97

[a] *Reaction conditions*: 0.094 mmol of **7** in 1.5 mL CH_2Cl_2, (*S*)-**1**/Rh = 2.2 (mol/mol), substrate/catalyst = 100 (mol/mol), 20 atm H_2, 25 °C, 3–30 h. [b] Determined by GC analysis with chiral column. In all cases, 100% conversions were observed.

Table 3 Asymmetric hydrogenation of enamides catalyzed by dendritic Rh/**1** catalysts[a]



		ee (%)[b]			
Entry	Ar	**1AG$_0$**	**1AG$_1$**	**1AG$_2$**	**1AG$_3$**
1	C_6H_5 (**9a**)	60	78	86	90
2	4-ClC_6H_4 (**9b**)	60	71	78	94
3	4-BrC_6H_4 (**9c**)	61	73	78	94
4	4-MeC_6H_4 (**9d**)	47	60	78	92

[a] *Reaction conditions*: 0.094 mmol of **9** in 1.5 mL CH_2Cl_2, (*S*)-**1**/Rh = 2.2 (mol/mol), substrate/catalyst = 100 (mol/mol), 20 atm H_2, 25 °C, 3–35 h. [b] Determined by GC analysis with chiral column. In all cases, 100% conversions were observed.

Table 4 Catalyst recycling in the asymmetric hydrogenation of **7a** catalyzed by dendritic Rh/**1AG$_2$** catalyst[a]

Cycle	Run 1	Run 2	Run 3	Run 4	Run 5
Conv. (%)	100	100	100	100	100
ee (%)	98	98	98	98	91

[a] See Table 1.

In summary, we have demonstrated for the first time the importance of the dendritic wedges on enantioselectivity in the Rh-catalyzed asymmetric hydrogenation of functionalized olefins, such as α-dehydroamino acid derivatives and enamides. Higher enantioselectivities were achieved as the dendritic wedges on the N-atom of the phosphoramidite ligand became bigger. Such dendritic enhancement of enantioselectivity is rarely observed in the field of dendrimer chemistry.[7b,c] Current work is aiming at the detailed insight of the nature of this strong dendrimer effect and the exploration of these dendritic monodentate phosphoramidites in other asymmetric reactions.

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