Novel Dendritic Ligands of Chiral 1,2-Diamine and Their Application in Asymmetric Hydrogenation of Simple Aryl Ketones

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Abstract: Novel dendritic chiral vicinal diamine ligands have been synthesized and a series of dendritic Ru(BINAP)(diamine) catalysts were developed for asymmetric hydrogenation of a variety of simple aryl ketones in good catalytic activity and high enantioselectivity, as well as facile catalyst recycling. An increase of enantioselectivities was obtained by using the dendritic catalysts compared with Noyori catalysts under the same conditions in the case of several substrates. Meanwhile, a remarkable structural effect on catalytic activity and enantioselectivity, as well as reuse was observed.

Key words: chiral 1,2-diamine, dendritic ligand, ruthenium complex, asymmetric hydrogenation

As a result of their unique architecture and structural as well as functional versatility, dendrimers have generated considerable interest in numerous areas of physical sciences, engineering, as well as the biological sciences.[1,2] One intensively studied application has been in the area of catalysis where metallodendritic compounds appear as a novel generation of catalysts that have catalytic properties of homogeneous catalysts but may be easily separated after use.[3] This feature is essential for high reaction efficiency, economical and environmental reasons.

Optically active 1,2-diphenylethylenediamine (DPEN), (*R*,*R*)-**1** is one of the most important chiral ligands.[4] Noyori and coworkers[5,4d] found that ruthenium(II) dichloride(diphosphine)(DPEN) complexes are effective catalysts for asymmetric hydrogenation of ketones.[6] Recently, polymer-supported and heterogenized ligands of Noyori catalysts have been reported for the asymmetric hydrogenation of ketones.[7,8] To the best of our knowledge, however, dendrimer-supported DPEN had not been reported before this research was launched. Herein we report the synthesis of the dendritic ligands, (*S*,*S*)-**7a–d** based on the functionalization of the benzene rings[9] and the application in the asymmetric hydrogenation of simple aryl ketones. Moreover, the dendritic ligands, (*S*,*S*)-**7a–d** can be served as a chiral scaffold on which many types of dendritic chiral catalysts could be easily built.[4,10]

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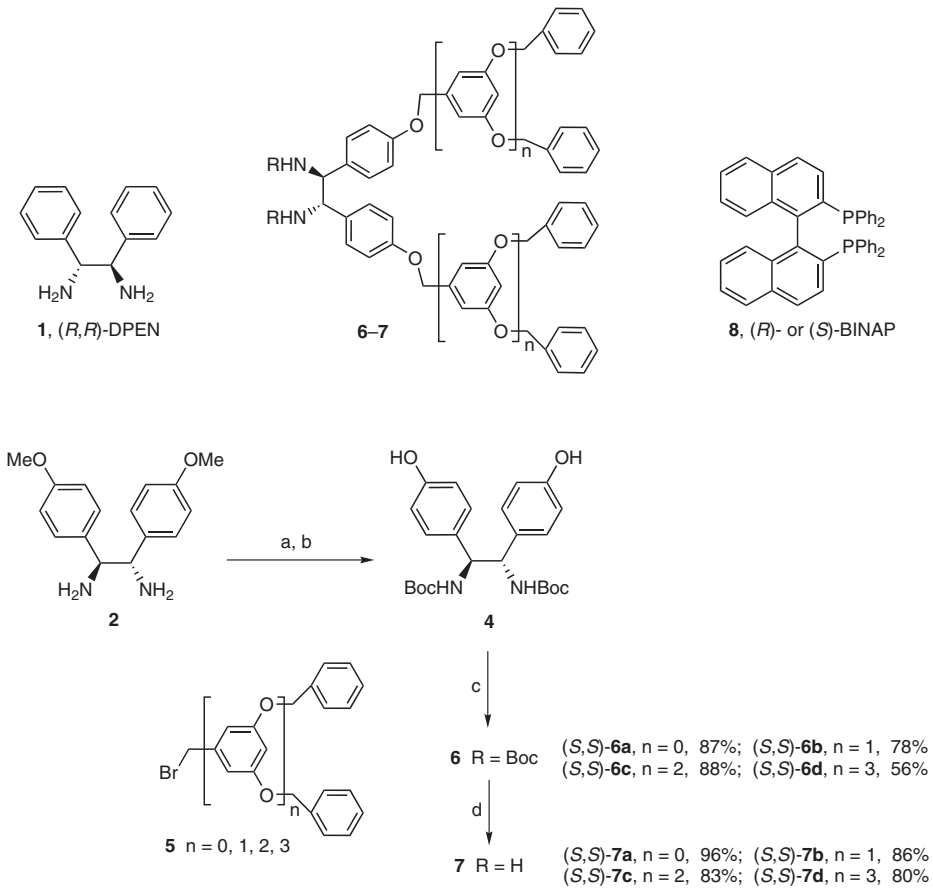
As shown in Scheme 1, the synthesis of dendritic diamine ligands, (*S*,*S*)-**7a–d** were achieved by direct deprotection of (*S*,*S*)-**6a–d** in 80–96% yields, which were prepared in a straightforward manner by the coupling of (*S*,*S*)-**4** with the corresponding dendritic bromides **5** in the presence of K_2CO_3 and 18-crown-6 in 56–88% yields. (*S*,*S*)-**4** was obtained by deprotection of methoxyl group and the following Boc protection with 86% yield in two steps from (*S*,*S*)-**2**.[11] All kinds of dendritic ligands, (*S*,*S*)-**7a–d** were characterized by NMR (^{1}H and ^{13}C), IR, and HRMS (ESI) or MALDI–TOF.[12]

In the recent years, the design and synthesis of effective enantioselective catalysts for hydrogenation of simple ketones have been attracting much attention, and various strategies have been introduced.[13] Among all the chiral catalysts reported today, the ternary catalyst system of Ru–chiral diphosphine–chiral diamine–KOH,[5a] has been found to be the most effective catalysts for the asymmetric hydrogenation of simple ketones lacking a secondary coordinating functional group. To investigate the efficiency of **7a–d** in the asymmetric hydrogenation, we first needed to prepare the ternary system (Ru–chiral diphosphine–chiral diamine–KOH). The ruthenium catalysts were prepared in situ according to the Noyori protocol.[5c] For example, the second generation dendritic pre-catalyst was prepared by reacting the (*S*)-BINAP (**8**) with $[RuCl_2(benzene)]_2$ at 100 °C in DMF for 10 minutes, followed by treatment with 1.0 equivalent of dendritic diamine ligand, (*S*,*S*)-**7c** at room temperature for 10 hours. The resulting dendritic catalyst showed a predominant ^{31}P NMR signal at δ = 47.3 ppm, which was very close to the small molecular complex (δ = 47.4 ppm).[5c] The ruthenium complexes of other dendritic diamine ligands, **7a**, **7b** and **7d** and the mono ligand, (*S*,*S*)-**2** were also prepared with the similar method and used in the catalytic reactions without further purification.

Our initial efforts were aimed at probing the asymmetric induction of these catalysts using 1-acetonaphthone (**9**) as a typical substrate. In most cases 2-propanol is the choice of solvent for the asymmetric hydrogenation of ketones with the ternary catalyst system. Because the dendritic catalysts are insoluble in neat 2-propanol and more soluble in toluene, mixed solvents with toluene were first selected. Although slightly higher enantioselectivity was



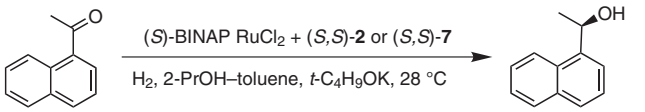
Scheme 1 *Reagents and conditions*: a) (i) 1 N BBr_3, CH_2Cl_2, 48 h; (ii) 2 N NaOH, pH = 7–8; b) Boc_2O (2.2 equiv), DIPEA (3.0 equiv), THF, 0 °C to r.t., 86% (two steps); c) **5**, K_2CO_3 (2.5 equiv), 18-crown-6 (0.2 equiv), acetone, reflux; d) TFA, CH_2Cl_2, r.t.

achieved in the mixture of 2-propanol and THF for the hydrogenation of **9** with **7c** as ligand (Table 1, entry 11 vs. entries 5 and 10), only 79% ee was obtained for the hydrogenation of acetophenone (**11**) compared with 82% ee in 2-propanol–toluene (Table 2, entry 3). The 1:1 ratio of 2-propanol and toluene is the best choice, because increase and decrease of the ratio lowed both conversion and enantioselectivity of the asymmetric hydrogenation due to the solubility of the dendritic catalyst (Table 1, entry 5 vs. entries 7 and 8). Pure toluene retarded the reaction (entry 9). As expected, the mismatching dendritic catalyst gave poor enantioselectivity (9% ee, entry 6). The enantioselectivities of the first and second generation dendritic catalysts are comparable to the enantioselectivities of both monomeric and Noyori catalysts (entries 1–5). However, the third generation catalyst gave lower enantioselectivity (84%) and significantly decreased conversion (45%) under the same conditions (entry 12) even at higher temperature (50 °C, 51% conversion and 88% ee, entry 13). The sudden loss of the reaction activity of the third generation dendritic catalyst might be thus attributed to the change in dendrimer conformation, i.e., from an extended to a more globular structure as the steric requirements of the dendritic branches increase. Therefore, the globular structure of the dendrimer resulted in encapsulation of the active species by the dendrimer, which consequently influenced the diffusion of the substrate into the catalytically active core of the dendritic catalyst. This phenomenon had been observed by other groups.[14] When the hydrogen pressure was increased to 70 atm, remained enantioselectivity (94% ee) was obtained with complete conversion in 20 hours (entry 14). This shows that higher pressure is favorable for the substrate easily to traverse the third dendritic catalyst's globular shell.

With these results in hand, the asymmetric hydrogenation was extended to other ketone substrates (**11**–**18**) by using the new dendrimer-based catalytic system. As shown in Table 2, the dendritic catalysts gave remained even higher enantioselectivities compared with both monomeric and Noyori catalysts for the hydrogenation of aryl ketones under same conditions. For hydrogenation of **11** catalyzed by dendritic catalysts, (*S*)-**8**–Ru–(*S*,*S*)-**7c** gave the best result (82% ee), which is comparable to the enantioselectivities of both monomeric and Noyori catalysts (entries 1–3). Although the monomeric catalyst afforded lower enantioselectivities than Noyori catalyst for the hydrogenation of **12** and **17** (entry 5 vs. 6 and entry 25 vs. 26), the same or higher enantioselectivities were obtained with the dendritic catalysts (entries 7, 27 and 28). It is notable that hydrogenation of ketones **14** and **18** gave higher enantioselectivities with the dendritic ligands and the monomeric ligand (*S*,*S*)-**2** than with (*R*,*R*)-**1** (entries 13–16, and 29–32). These results showed that the electronic ef-

fect of the electron-donating methoxyl group at the *para* site of the benzene ring might lead to higher enantioselectivities.

Table 1 Hydrogenation of 1-Acetonaphthone Using the in situ Dendritic Ru-BINAP Catalysts[a]

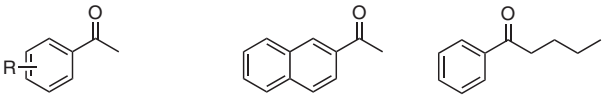


9 **10**

Entry	Ligand	Solvents (v/v)	Conversion (%)[b]	ee (%)[b]
1	(*R*)-**8**/(*R*,*R*)-**1**	2-PrOH–toluene (1:1)	>99	95[c]
2	(*S*)-**8**/(*S*,*S*)-**2**	2-PrOH–toluene (1:1)	>99	95
3	(*S*)-**8**/(*S*,*S*)-**7a**	2-PrOH–toluene (1:1)	>99	96
4	(*S*)-**8**/(*S*,*S*)-**7b**	2-PrOH–toluene (1:1)	>99	94
5	(*S*)-**8**/(*S*,*S*)-**7c**	2-PrOH–toluene (1:1)	>99	95
6	(*R*)-**8**/(*S*,*S*)-**7c**	2-PrOH–toluene (1:1)	>99	9[c]
7	(*S*)-**8**/(*S*,*S*)-**7c**	2-PrOH–toluene (2:1)	41	90
8	(*S*)-**8**/(*S*,*S*)-**7c**	2-PrOH–toluene (1:2)	63	92
9	(*S*)-**8**/(*S*,*S*)-**7c**	toluene	9	87
10	(*S*)-**8**/(*S*,*S*)-**7c**	2-PrOH–CH_2Cl_2 (1:1)	>99	93
11	(*S*)-**8**/(*S*,*S*)-**7c**	2-PrOH–THF (1:1)	>99	96
12	(*S*)-**8**/(*S*,*S*)-**7d**	2-PrOH–toluene (4:5)	45	84
13	(*S*)-**8**/(*S*,*S*)-**7d**[d]	2-PrOH–toluene (4:5)	51	88
14	(*S*)-**8**/(*S*,*S*)-**7d**[e]	2-PrOH–toluene (4:5)	>99	94

[a] Unless otherwise stated, reaction was carried out at 28 °C by using 0.6 mmol of ketones in 4 mL of solvents for 20 h; 1-acetonaphthone:BINAP:Ru:dendritic diamine:*t*-BuOK = 500:1.1:1:1:6 (molar ratio); H_2 pressure = 40 atm.
[b] Determined by GC on CP-Cyclodex B-236 M column.
[c] The absolute configuration of the product is *S*-form.
[d] Reaction was carried out at 50 °C for 20 h.
[e] H_2 pressure is 70 atm.

Table 2 Hydrogenation of Aryl Ketones Using the in situ Dendritic Ru-BINAP Catalysts[a]

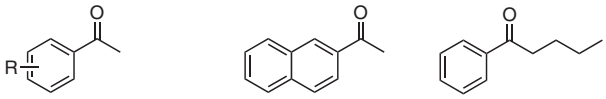


11: R = H
12: R = *o*-Me
13: R = *o*-OMe
14: R = *m*-OMe
15: R = *p*-OMe
16: R = *p*-Br

17 **18**

Entry	Substrate	Ligand	ee (%)[b]
1	**11**	(*R*)-**8**/(*R*,*R*)-**1**	83[c]
2	**11**	(*S*)-**8**/(*S*,*S*)-**2**	83
3	**11**	(*S*)-**8**/(*S*,*S*)-**7c**	82
4	**11**	(*S*)-**8**/(*S*,*S*)-**7d**[d]	77
5	**12**	(*R*)-**8**/(*R*,*R*)-**1**[e]	94[c]
6	**12**	(*S*)-**8**/(*S*,*S*)-**2**[e]	91
7	**12**	(*S*)-**8**/(*S*,*S*)-**7a**[e]	94
8	**12**	(*S*)-**8**/(*S*,*S*)-**7d**[d,e]	89
9	**13**	(*R*)-**8**/(*R*,*R*)-**1**[f]	73[c]
10	**13**	(*S*)-**8**/(*S*,*S*)-**2**[f]	72
11	**13**	(*S*)-**8**/(*S*,*S*)-**7b**[f]	76
12	**13**	(*S*)-**8**/(*S*,*S*)-**7d**[d,f]	73
13	**14**	(*R*)-**8**/(*R*,*R*)-**1**	76[c]
14	**14**	(*S*)-**8**/(*S*,*S*)-**2**	87
15	**14**	(*S*)-**8**/(*S*,*S*)-**7a**	87
16	**14**	(*S*)-**8**/(*S*,*S*)-**7d**[d]	85
17	**15**	(*R*)-**8**/(*R*,*R*)-**1**	84[c]
18	**15**	(*S*)-**8**/(*S*,*S*)-**2**	83
19	**15**	(*S*)-**8**/(*S*,*S*)-**7c**	84
20	**15**	(*S*)-**8**/(*S*,*S*)-**7d**[d]	83
21	**16**	(*R*)-**8**/(*R*,*R*)-**1**	59[c]
22	**16**	(*S*)-**8**/(*S*,*S*)-**2**	59
23	**16**	(*S*)-**8**/(*S*,*S*)-**7b**	62
24	**16**	(*S*)-**8**/(*S*,*S*)-**7d**[d]	60
25	**17**	(*R*)-**8**/(*R*,*R*)-**1**	74[c]
26	**17**	(*S*)-**8**/(*S*,*S*)-**2**	72
27	**17**	(*S*)-**8**/(*S*,*S*)-**7c**	76
28	**17**	(*S*)-**8**/(*S*,*S*)-**7d**[d]	77
29	**18**	(*R*)-**8**/(*R*,*R*)-**1**	81[c]
30	**18**	(*S*)-**8**/(*S*,*S*)-**2**	88

Table 2 Hydrogenation of Aryl Ketones Using the in situ Dendritic Ru-BINAP Catalysts[a] (continued)



11: R = H
12: R = *o*-Me
13: R = *o*-OMe
14: R = *m*-OMe
15: R = *p*-OMe
16: R = *p*-Br

17 **18**

Entry	Substrate	Ligand	ee (%)[b]
31	**18**	(*S*)-**8**/(*S*,*S*)-**7c**	86
32	**18**	(*S*)-**8**/(*S*,*S*)-**7d**[d]	88

[a] Unless otherwise stated, reaction was carried out at 28 °C by using 0.6 mmol of ketones in 4 mL 2-PrOH–toluene (v/v, 1:1); aryl ketone:BINAP:Ru:dendritic diamine:*t*-C_4H_9OK = 500:1.1:1:1:6 (molar ratio); H_2 pressure = 40 atm. All catalytic reactions reached 100% conversions in 20 h.
[b] Determined by GC on CP-Cyclodex B-236 M column. Unless otherwise stated, the absolute configuration of the product is *R*-form.
[c] The absolute configuration of the product is *S*-form.
[d] Reaction was completed with 2-PrOH–toluene (v/v, 4:5) as solvent at 70 atm of H_2 pressure.
[e] Reaction was carried out at 50 °C.
[f] Reaction was completed in 48 h at 70 atm of H_2 pressure.

An important feature of the design of soluble dendrimer-based catalyst is easy and reliable separation of the chiral catalyst. The high generations of the dendritic catalysts are expected to achieve quantitative recovery of catalyst from the reaction mixtures based on large molecular size and different solubility in various organic solvents. In this study, the second and the third generation catalysts were used to carry out the recycling experiment. Upon the completion of the reaction, methanol was added to the reaction mixture and the catalyst was precipitated and recovered via centrifugation. The recovered catalyst was reused for at least two cycles with remained enantioselectivity. In three consecutive runs, the following enantioselectivities were observed: 95%, 94%, 94% by using the second generation catalyst and 94%, 93%, 94% by using the third generation catalyst with complete conversions. ICP analysis showed that less than 3.6 mol%, 0.7 mol% of ruthenium of the second and the third generation catalysts had leached into the MeOH solution, respectively. Thus, we refer that larger dendrimer has robust protection for the stability of the catalyst complex, which had been observed in bis (μ-oxo)dicopper species[15] and binuclear (μ-O)(μ-$OAc)_2$diiron(III) complexes[16] toward oxidative self-decomposition.

In conclusion, a series of chiral dendritic ligands based on the phenyl-functionalized 1,2-diamine have been synthesized for the first time and the dendritic Ru(BINAP)(diamine) catalysts showed to be a recoverable and highly effective dendritic catalyst system for asymmetric hydrogenation of simple aryl ketones. A remarkable structural effect on catalytic activity as well as reuse was observed. It is notable that an increase of enantioselectivities was obtained for several substrates by using the dendritic catalysts compared with Noyori catalyst under same conditions, but a light decrease had been reported with the polymer-supported catalyst[8a] as well as the dendritic BINAP catalyst.[7f] These results demonstrated that the use of soluble dendrimer-based catalysts might combine the advantages of homogeneous and heterogeneous catalysis. In this work, we also found that the electronic properties of the benzene ring of DPEN greatly affect the enantioselectivity and this will provide a guiding concept for us to design novel catalytic system for the asymmetric hydrogenation.[17] A further interesting aspect of this study is that such ligands can be served as a chiral platform on which many types of chiral dendritic catalysts could be easily built. Our attention will now turn to this chemistry and results will be reported in due course.

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Ligand (*S,S*)-**7a**: *m/z* calcd for $C_{28}H_{28}N_2O_2$: 424.2151; found: 424.1915.
Ligand (*S,S*)-**7b**: *m/z* calcd for $C_{56}H_{54}KN_2O_6$ [M + K + 2 H]: 889.3619; found: 889.4199; $C_{56}H_{50}NO_6$ [M – NH_2]: 832.3638; found: 832.3673.
Ligand (*S,S*)-**7c**: *m/z* calcd for $C_{112}H_{101}N_2NaO_{14}$ [M + Na + H] (MALDI–TOF): 1719.7; found: 1720.1.
Ligand (*S,S*)-**7d**: *m/z* calcd for $C_{224}H_{203}N_2NaO_{30}$ [M + Na + 7 H] (MALDI–TOF): 3423.4: found: 3423.4.

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