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Dendritic catalysts for asymmetric transfer hydrogenation based (1*S*,2*R*)-norephedrine derived ligands

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Abstract—Two series of novel dendritic ligands based on (1*S*,2*R*)-norephedrine have been designed and synthesized, and incorporated into Ru(II) complexes as catalysts for asymmetric transfer hydrogenation. Some dendritic catalysts demonstrated dendritic acceleration effects as well as high catalytic activity and good enantioselectivity.

1. Introduction

Dendrimers are highly branched macromolecules with precisely defined molecular structures on the nanoscale size. Since pioneering works in 1994,[1] the chemistry of dendritic catalysts has been attracting increasing attention, as they may aid the recycling utilization simply by using the supra-filtration or solvent precipitation method and in some cases, they have demonstrated some positive dendritic effects such as reaction acceleration, catalyst stabilization, etc.[2] Although a large number of dendritic catalysts have been described to date,[3,4] few reports on asymmetric catalytic reactions have appeared,[4] and even less on the asymmetric transfer hydrogenation of ketones for producing chiral secondary alcohols,[5] important intermediates for the construction of many significant optical compounds. To our knowledge, the best catalysts for asymmetric transfer hydrogenation reported to date are ruthenium(II) complexes with chiral monoarylsulfonylated diamines or β-amino alcohol ligands.[6,7] In a previous report, we disclosed the synthesis of dendritic analogues of TsDPEN and the application of their Ru(II) complexes in the asymmetric transfer hydrogenation of acetophenone.[5a] Although high enantioselectivity was observed, catalytic efficiency (i.e. the turn-over frequency, TOF) of these dendritic catalysts was fairly low and the reaction time was long for high conversion. Since the ruthenium(II) complex of *N*-benzyl-(1*S*,2*R*)-norephedrine gave good results for the transfer hydrogenation of ketones in terms of both enantioselectivity and catalytic activity,[7] the latter being among the highest yet reported for Ru(II)-catalyzed transfer hydrogenation owing to the ligand acceleration effect,[6,7] we have recently designed and synthesized novel (1*S*,2*R*)-norephedrine-bearing dendritic catalysts, studied their catalytic activities in transfer hydrogenation. Herein we report the results.

2. Results and discussion

First, the polyether dendrimers with peripheral benzyl groups were chosen to investigate the transfer hydrogenation, owing to their inertness. The polyether dendritic wedges **10**–**12** with benzylic bromo groups located at the focal point were synthesized by the convergent-growth approach introduced by Hawker and Fréchet.[8] The simple chiral monomer **1** and the novel dendritic ligands **2**–**4** were synthesized by *N*-alkylation of (1*S*,2*R*)-norephedrine with the corresponding monomer bromide **9** and wedges **10**–**12**, respectively, using K_2CO_3 as a base promoter (Scheme 1).

These ligands were purified by column chromatography on silica gel and characterized by ^1H, ^{13}C NMR, ESI-HRMS and IR spectroscopies. All analytical results were consistent with the proposed structures.

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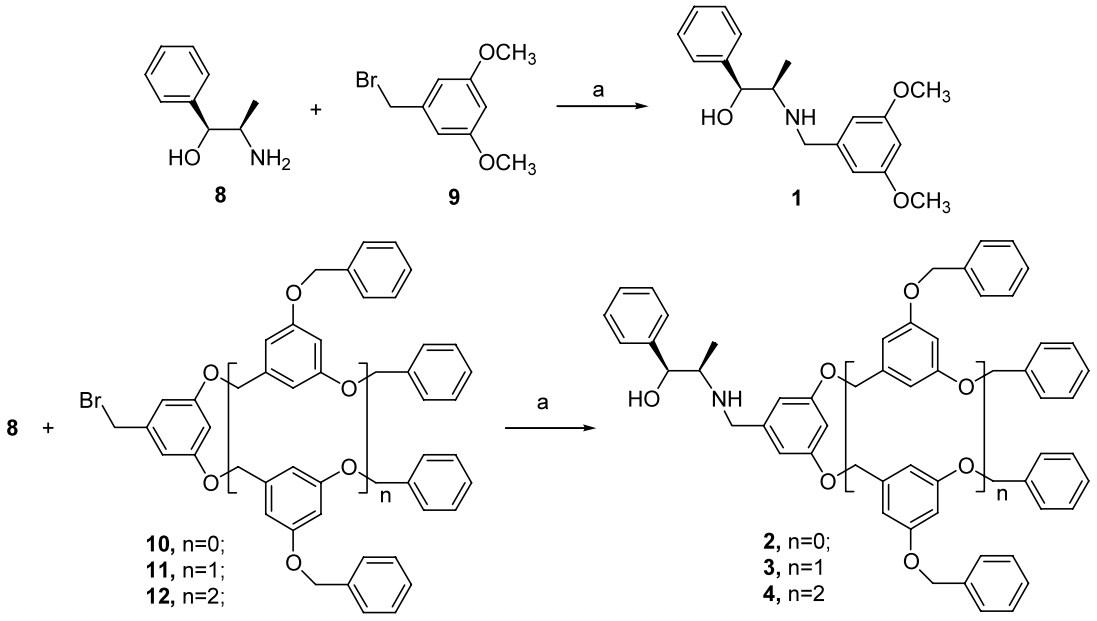
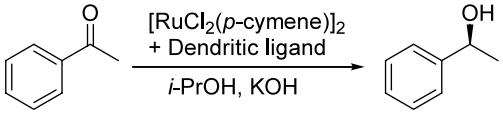


Scheme 1. Synthesis of the chiral monomer **1** and the chiral dendritic ligands **2**–**4**. *Reagents and conditions*: a. K_2CO_3, CH_3CN, reflux, yield: 60–82%.

Acetophenone was used as the model substrate and the catalysts were generated in situ by refluxing $[RuCl_2(p\text{-cymene})]_2$ and corresponding ligands in *i*-PrOH for 1 h. Asymmetric transfer hydrogenation reactions were studied in a general procedure and the results were summarized in Table 1.

In comparison with the monomer catalyst Ru-**1**, an enhancement of reactivity and a nearly maintained enantioselectivity were observed for the first generation dendritic catalyst Ru-**2** (entries 1 and 4). However, the second and third generation dendritic catalysts Ru-**3**, Ru-**4** gave the decreased reactivity and enantioselectiv-

Table 1. Dendritic (1*S*,2*R*)-norephedrine–Ru(II) complexes Ru-**n** catalysed asymmetric transfer hydrogenation of acetophenone[a]



Entry	Ligand	Time (h)	Conv. (%)[b]	Ee (%)[c]	TOF[d]
1	1	2	70	93	48
2	1[e]	2	63	87	34
3	1[f]	2	43	91	24
4	2	2	88	92	65
5	3	2	70	84	–
6	3[e]	2	82	90	59
7	4	6	15	58	–
8	4[f]	2	63	88	40
9	4[f]	4	86	89	–
10	4[f]	25	93	88	
11	5	2	75	92	57
12	6	2	90	93	79
13	7	7	51	82	–
14	7[e]	2	80	89	41
15	7[e]	25	93	89	–

[a] The reactions were carried out at 25°C using 0.4 mmol of acetophenone in 4 mL *i*-PrOH with Ru:ligand:base:substrate = 1:2.5:5:100.
[b] Based on GC analysis.
[c] Determined by GC with a CP-Chirasil-DEX CB column (25 m×0.32 mm) and the configuration *S* was determined by the retention time.
[d] Average TOFs were calculated over the 0.5 h reaction time.
[e] Extra 1 mL CH_2Cl_2 was added.
[f] Extra 2 mL CH_2Cl_2 was added.

ity (entries 5 and 7), possibly due to their poor solubility in *i*-PrOH. This presumption was confirmed by the fact that a great enhancement of reactivity and enantioselectivity (entries 6 and 8) was observed when adding 1 and 2 mL of CH_2Cl_2 as cosolvent to the Ru-**3** and Ru-**4** systems, respectively, to improve the solubility. It is particularly noteworthy that some dendritic effects were observed in our investigation. For example, the second generation dendritic catalyst Ru-**3**, when added with 1 mL CH_2Cl_2 could accelerate the reaction and maintain the enantioselectivity well compared with Ru-**1** (entries 2 and 6). In addition to the high generation dendritic catalyst Ru-**4**, ee values were still maintained when prolonging the reaction time 2 h up to 4–25 h (entries 8–10). This phenomenon demonstrates a different property over the homogenous catalysis with simple chiral ligands, where the ee values generally decrease with prolonged reaction times because of the reversibility of the transfer hydrogenation in *i*-PrOH.[6]

Because the poor solubilities of the above dendritic ligands in *i*-PrOH decrease the activity and enantioselectivity greatly, we designed and synthesized another series of dendritic ligands **5**–**7** with 2-methoxyethyl groups, instead of benzyl groups, on the periphery with the hope that improved solubility could lead to enhanced activity and enantioselectivity. Thus, the dendritic wedges **13**–**15** were firstly synthesized through a modified route developed by Nierengarten,[9] and then the corresponding chiral dendritic ligands **5**–**7** were synthesized as indicated in Scheme 2, and characterized by various spectroscopic methods.

The catalytic activity and enantioselectivity in transfer hydrogenations were successively tested using the chiral dendritic catalysts Ru-**5** to Ru-**7** made from the dendritic ligands **5**–**7**, and the results were summarized in Table 1 (entries 11–15). It could be seen that, in comparison with the monomer catalyst Ru-**1**, the first and second generation dendritic catalysts Ru-**5** and Ru-**6** maintained the enantioselectivity well and the dendritic acceleration effect was also observed. In particular, the second generation catalyst Ru-**6** gave high enantioselectivity (93% ee) as well as the catalytic activity (90% yield after 2 h, 79 TOF). These results have supported our presumption for the dendrimer structure design. However, the third generation dendritic catalyst Ru-**7** displayed poor solubility in *i*-PrOH, and thus the catalytic activity and enantioselectivity were not good (entry 13). By adding 1 mL CH_2Cl_2 to the reaction system of Ru-**7**, good catalytic activity and enantioselectivity were still obtained (entry 14). Moreover, the phenomenon of reversibility inhibition was observed too and the ee value was maintained with prolonged reaction time (entry 15).

3. Conclusion

In summary, two series of novel chiral dendritic ligands with the peripheral benzyl and 2-methoxyethyl groups, respectively, based on the same chiral core (1*S*,2*R*)-norephedrine, were designed and synthesized. They were incorporated into Ru(II) complexes as catalysts for asymmetric transfer hydrogenation of acetophenone. Some dendritic catalysts demonstrated dendritic acceleration effect as well as high catalytic activity and good enantioselectivity (e.g. to Ru-**6**, up to 90% yield after 2 h, 79 TOF and 93% ee). Moreover, for the high generation dendritic catalysts, the phenomenon of inhibition of the reaction reversibility was also observed.

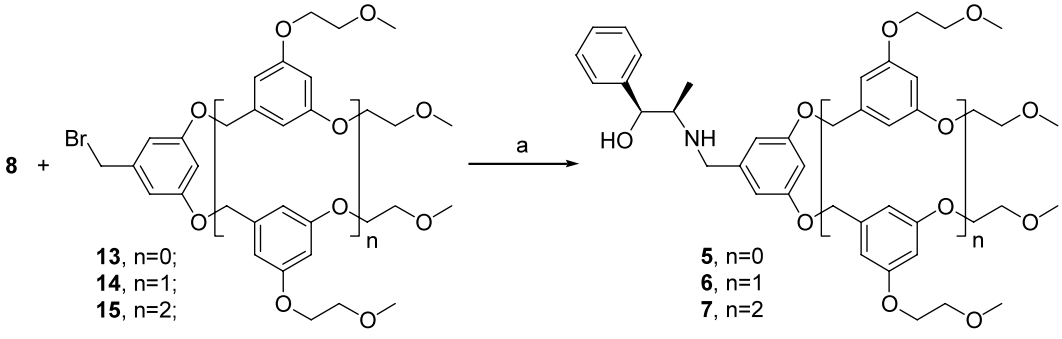
4. Experimental

4.1. General

Acetophenone was distilled from $KMnO_4$ and propan-2-ol was distilled from CaH_2. All other reagents and chemicals were reagent grade and were used as received from commercial suppliers. Melting points were determined in open capillaries and were uncorrected. ^1H and ^{13}C NMR spectra were recorded on Bruker (300 MHz or 400 MHz) with TMS as internal standard. HRMS data were measured with ESI techniques (Bruker Apex II). Enantiomeric ratios were determined by GC with a CP-Chirasil-DEX CB column (25 m×0.32 mm) on Varian CP-3800.

4.2. General procedure for the preparation of ligands 1–7

(1*S*,2*R*)-Norephedrine (181 mg, 1.20 mmol), the bromide (1.00 mmol), and K_2CO_3 (207 mg, 1.50 mmol)



Scheme 2. Synthesis of the chiral dendritic ligands **5**–**7**. *Reagents and conditions*: a. K_2CO_3, CH_3CN, reflux, yield: 50–80%.

were mixed with 40 mL acetonitrile. The resulting mixture was then heated under reflux for 1–2 days with vigorous stirring and the acetonitrile was removed under reduced pressure. The residue was diluted with CH_2Cl_2 (50 mL), washed with water and brine. After drying over anhydrous Na_2SO_4 and concentration, the crude product was purified by column chromatography on silica gel using mixture eluent of CH_2Cl_2 and CH_3OH (50:1–30:1, v/v) to provide ligands **1**–**7**.

4.2.1. (1*S*,2*R*)-*N*-(3,5-Dimethoxy)benzyl-2-amino-1-phenyl-1-propanol 1. Yield: 63%; $[\alpha]_D^{23}=-14.0$ (*c* 0.2, acetone); ^{1}H NMR (300 MHz, $CDC1_3$) δ 0.89 (d, $J=6.6$ Hz, 3H), 2.98–3.02 (m, 1H), 3.81 (s, 6H), 3.83 (s, 2H), 4.80 (d, $J=3.9$ Hz, 1H), 6.40 (t, $J=2.4$ Hz, 1H), 6.51 (d, $J=2.4$ Hz, 2H), 7.26–7.35 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4, 51.2, 55.2, 57.6, 73.1, 99.0, 105.9, 126.0, 127.0, 128.0, 141.3, 142.3, 160.9; IR (Film) 3355, 3060, 2934, 2837, 1599, 1461, 1429, 1319, 1203, 1154, 1064 cm^{-1}; ESI-HRMS calcd for $C_{18}H_{23}NO_3$+H$^+$ 302.1751, found 302.1755.

4.2.2. (1*S*,2*R*)-*N*-(3,5-Dibenzyloxy)benzyl-2-amino-1-phenyl-1-propanol 2. Yield: 60%; mp 78–79°C; $[\alpha]_D^{23}=-8.2$ (*c* 0.5, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (d, $J=6.5$ Hz, 3H), 2.97–3.02 (m, 1H), 3.83 (s, 2H), 4.78 (d, $J=3.9$ Hz, 1H), 5.06 (s, 4H), 6.55 (t, $J=2.2$ Hz, 1H), 6.60 (d, $J=2.2$ Hz, 2H), 7.31–7.46 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.5, 51.5, 57.6, 70.0, 73.0, 100.7, 107.1, 126.0, 127.0, 127.5, 127.9, 128.0, 128.5, 136.8, 141.1, 142.4, 160.0; IR (Film) 3370, 3063, 3030, 2972, 2927, 2870, 1597, 1451, 1377, 1340, 1293, 1205, 1155, 1056 cm^{-1}; ESI-HRMS calcd for $C_{30}H_{31}NO_3$+H$^+$ 454.2377, found 454.2375.

4.2.3. (1*S*,2*R*)-*N*-[3,5-Di(3,5-dibenzyloxy)benzyloxy]-benzyl-2-amino-1-phenyl-1-propanol 3. Yield: 82%; mp 71–73°C; $[\alpha]_D^{23}=-4.1$ (*c* 0.5, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (d, $J=6.5$ Hz, 3H), 2.98–3.01 (m, 1H), 3.83 (s, 2H), 4.78 (d, $J=3.7$ Hz, 1H), 4.99 (s, 4H), 5.05 (s, 8H), 6.52 (s, 1H), 6.59 (d, $J=0.5$ Hz, 4H), 6.71(d, $J=1.9$ Hz, 4H), 7.25–7.44 (m, 25H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.2, 51.8, 58.3, 70.6, 70.7, 73.7, 101.4, 102.2, 107.0, 107.8, 126.7, 127.7, 128.2, 128.6, 128.7, 129.2, 137.4, 139.9, 141.9, 143.1, 160.6, 160.8; IR (Film) 3406, 3202, 3030, 2925, 2871, 1599, 1452, 1376, 1337, 1298, 1210, 1153, 1053 cm^{-1}; ESI-HRMS, calcd for $C_{58}H_{55}NO_7$+H$^+$ 878.4046, found 878.4046.

4.2.4. (1*S*,2*R*)-*N*-[3,5-Di[3,5-di(3,5-dibenzyloxy)-benzyloxy]benzyloxy]benzyl-2-amino-1-phenyl-1-propanol 4. Yield: 65%; mp 51–54°C; $[\alpha]_D^{23}=+2.0$ (*c* 0.6, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (d, $J=6.4$ Hz, 3H), 2.98–3.01 (m, 1H), 3.84 (s, 2H), 4.80 (s, 1H), 5.01 (s, 12H), 5.06 (s, 16H), 6.60–6.63 (m, 9H), 6.71–6.74 (m, 12H), 7.32–7.47 (m, 45H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.6, 51.2, 57.6, 69.9, 70.0, 73.1, 100.6, 101.5, 106.3, 107.1, 126.0, 127.0, 127.5, 127.9, 128.5, 136.7, 139.2, 139.3, 141.2, 142.4, 160.0, 160.1; IR (Film) 3433, 3062, 3031, 2916, 2870, 1595, 1496, 1449, 1374, 1341,1321, 1295, 1211, 1155 cm^{-1}; ESI-HRMS, calcd for $C_{114}H_{103}NO_{15}$+H$^+$ 1727.7479, found 1727.7395.

4.2.5. (1*S*,2*R*)-*N*-[3,5-Di(2-methoxyethoxy)]benzyl-2-amino-1-phenyl-1-propanol 5. Yield: 50%; $[\alpha]_D^{23}=-7.9$ (*c* 0.6, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (d, $J=6.5$ Hz, 3H), 2.98–3.01 (m, 1H), 3.46 (s, 6H), 3.75 (t, $J=4.5$ Hz, 4H), 3.81 (s, 2H), 4.11 (t, $J=4.6$ Hz, 4H), 4.78 (d, $J=3.9$ Hz, 1H), 6.45 (t, $J=2.0$ Hz, 1H), 6.57 (d, $J=2.2$ Hz, 2H), 7.25–7.36 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 50.9, 57.7, 59.1, 67.2, 70.9, 72.7, 100.4, 107.0, 126.0, 127.0, 128.0, 141.0, 141.1, 160.0; IR (Film) 3370, 3030, 2925, 2883, 1596, 1450, 1367, 1346, 1319, 1297, 1240, 1200, 1172, 1126, 1080, 1034 cm^{-1}; ESI-HRMS, calcd for $C_{22}H_{31}NO_5$+H$^+$ 390.2275, found 390.2276.

4.2.6. (1*S*,2*R*)-*N*-[3,5-Di[3,5-di(2-methoxyethoxy)]-benzyloxy]benzyl-2-amino-1-phenyl-1-propanol 6. Yield: 80%; $[\alpha]_D^{23}=+3.5$ (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (d, $J=6.5$ Hz, 3H), 2.96-2.98 (m, 1H), 3.45 (s, 12H), 3.74 (t, $J=4.6$ Hz, 8H), 3.82 (s, 2H), 4.11 (t, $J=4.6$ Hz, 8H), 4.77 (d, $J=3.7$ Hz, 1H), 4.97 (s, 4H), 6.48–6.49 (m, 3H), 6.56 (2H, d, $J=2.1$ Hz), 6.62 (d, $J=2.2$ Hz, 4H), 7.25–7.34 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.3, 49.7, 57.9, 59.0, 67.2, 69.8, 70.8, 71.8, 101.1, 102.2, 105.9, 106.1, 108.0, 125.8, 127.1, 128.1, 136.7 139.0, 140.5, 159.9, 160.0; IR (Film) 3440, 2929, 2880, 1598, 1449, 1369, 1322, 1296, 1241, 1173, 1125, 1069 cm^{-1}; ESI-HRMS, calcd for $C_{42}H_{55}NO_{11}$+H$^+$ 750.3848, found 750.3850.

4.2.7. (1*S*,2*R*)-*N*-[3,5-Di[3,5-di[3,5-di(2-methoxyethoxy)]benzyloxy]benzyloxy]benzyl-2-amino-1-phenyl-1-propanol 7. Yield: 68%; $[\alpha]_D^{23}=+2.0$ (*c* 1.5, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (d, $J=6.5$ Hz, 3H), 2.97–3.00 (m, 1H), 3.44 (s, 24H), 3.73 (t, $J=4.5$ Hz, 16H), 3.82 (s, 2H), 4.09 (t, $J=4.5$ Hz, 16H), 4.78 (d, $J=3.7$ Hz, 1H), 4.97 (s, 12H), 6.48 (s, 3H), 6.54 (s, 3H), 6.59–6.62 (m, 12H), 6.68 (d, $J=1.5$ Hz, 3H), 7.31 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 51.2, 57.6, 59.1, 67.2, 69.9, 70.8, 73.1, 100.6, 101.0, 101.5, 106.0, 106.3, 107.0, 126.0, 127.0, 128.0, 139.0, 139.2, 141.2, 142.5, 160.0; IR (Film) 3456, 2926, 2880, 1710, 1596, 1449, 1369, 1344, 1322, 1297, 1172, 1126, 1068, 1037 cm^{-1}; ESI-HRMS, calcd for $C_{82}H_{103}NO_{23}$+H$^+$ 1470.6994, found 1470.6967.

4.3. Typical procedure for the asymmetric transfer hydrogenation

$[RuCl_2(p\text{-cymene})]_2$ (0.002 mmol) and dendritic ligand (0.010 mmol) were heated in dry *i*-PrOH (1 mL) at 80°C for 1 h under argon. After cooling the mixture to room temperature, *i*-PrOH (2.8 mL), CH_2Cl_2 (as pointed out in Table 1) and KOH (0.2 mL, 0.1 M in *i*-PrOH) were added and the resulting solution was stirred for 0.5 h before acetophenone (0.4 mmol) was added. The reaction was allowed to react at 25°C under argon for a predetermined time. The solvent was removed under reduced pressure and the residue passed a flash chromatography (washing with Et_2O). The ee value and conversion were then determined by chiral GC on CP-Chirasil-DEX CB column (25 m×0.32 mm).

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