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Tunable dendritic ligands of chiral 1,2-diamine and their application in asymmetric transfer hydrogenation

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Abstract—Tunable dendritic *N*-mono-sulfonyl ligands have been designed and synthesized via direct *N*-mono-sulfonylization of the chiral dendritic vicinal diamines and their ruthenium complexes demonstrated high catalytic and recyclable activities with comparable enantioselectivities to Noyori–Ikariya's TsDPEN-Ru in the asymmetric transfer hydrogenation of an extended range of substrates, such as ketones, keto esters, and olefins.

1. Introduction

The search for an ideal catalyst that combines the advantages of both homogeneous and heterogeneous catalysis is the center of many investigations into green chemistry. With this is mind, metallodendrimers are emerging as a promising class of compounds in transition-metal catalysis as demonstrated in the pioneering work by Knapen and Brunner in 1994.[1,2] This interest is due to the properties of dendrimers: high solubility, high concentration of easily accessible active sites, and easy separation by nanofiltration[3] or precipitation[4,5] under specific conditions. Fréchet dendrimers[6] have been extensively applied to immobilize homogeneous catalysts due to easy synthesis, characterization and purification, as well as their different solubility in polar solvent and nonpolar solvent, so they can be recovered by solvent precipitation.[4c–e,5] Moreover, many homogeneous catalysts based on Fréchet dendrimers demonstrated good catalytic activities and recyclable application with comparable selectivities to the parentally molecular catalysts.[7]

Chiral vicinal diamine and its derivatives have also increased considerably, especially in the field of catalytic asymmetric synthesis. Noyori et al. found that chiral *N*-tosyl-1,2-diphenylethylenediamine (TsDPEN) is a highly effective ligand for asymmetric transfer hydrogenation of simple ketones.[8] Recently, a series of chiral RSO_2–DPEN ligands[9–14] had been synthesized and found to be much effective for the reduction of other substrates, such as imines,[9] keto esters[10,11] and C=C double bonds,[12] as well as Michael addition.[13] In our previous work,[5] amino-functionalized dendritic ligands of chiral 1,2-diphenylethylenediamine (DPEN) with Fréchet polyether dendrons were synthesized and showed good recyclable catalytic activity and enantioselectivity in the transfer hydrogenation of aromatic ketone. However, these dendritic ligands could not be further modified on the amino groups or tuned,[12b] and are limited to the transfer hydrogenation of simple ketones and imines.[5b] In order to further research the application and influence of dendritic ligands on the asymmetric reactions, a novel series of dendritic ligands, **3a–d** functionalized at the benzene rings[15] of chiral DPEN have been synthesized from available enantiopure 1,2-*para*-methoxyphenyl ethylenediamine **1**,[16] which can be modified on the amino group NH_2 and used as chiral ligands to generate highly enantioselective catalysts for asymmetric transformation of a variety of substrates.[8–14] Herein, we report the synthesis of a series of mono-sulfonyl dendritic ligands, **4a–g** based on the dendritic ligands **3a–d** and the application in the asymmetric transfer hydrogenation of ketones, keto esters and C=C double bonds, as well as effects of the dendrimer wedges on the asymmetric transfer hydrogenation.[17]

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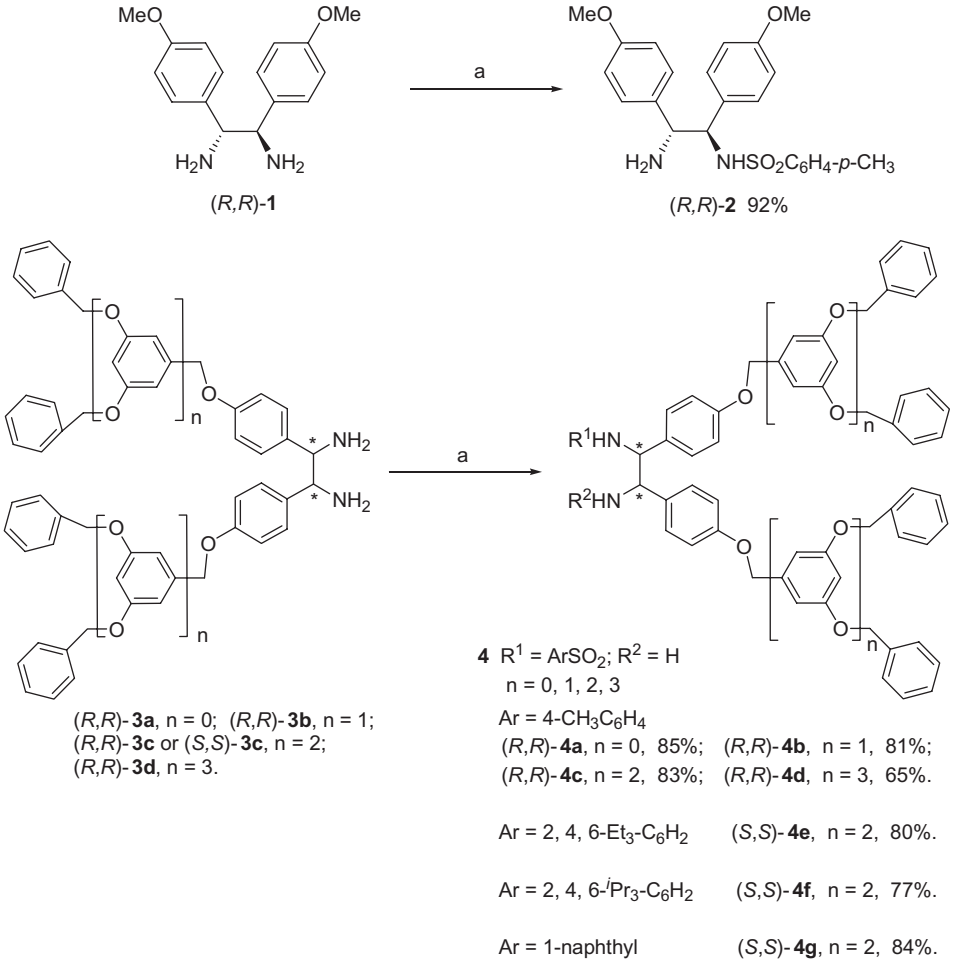
2. Results and discussion

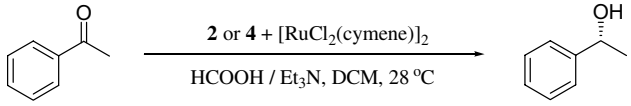
As shown in Scheme 1, the dendritic diamine ligands, (*R*,*R*)-**3a**–**d** and (*S*,*S*)-**3c** were modified by mono-sulfonamidation to give the dendritic *N*-arylsulfony diamine ligands, (*R*,*R*)-**4a**–**d** and (*S*,*S*)-**4e**–**g** in 65–85% yields. However, the synthesis of the *N*-(*N*,*N*-dialkylamino)-sulfamoyl diamine type ligands according to Mohar's procedure was unsuccessful.[11b] For comparison, a monomeric ligand, (*R*,*R*)-**2** was prepared by direct *N*-sulfonylization of (*R*,*R*)-**1** in 92% yield. All kinds of nondendritic ligands, (*R*,*R*)-**2** and dendritic ligands, (*R*,*R*)-**4a**–**d** and (*S*,*S*)-**4e**–**g** were characterized by NMR (^{1}H and ^{13}C), IR, and HRMS (ESI) or MALDI-TOF.[18,19]

An asymmetric transfer hydrogenation was studied using acetophenone **5** as the model substrate with the results summarized in Table 1.[20] Compared to the complexes of monomeric ligand, (*R*,*R*)-**2**, as well as TsDPEN, a slightly enhanced reactivity was observed for the dendritic catalysts, Ru[(*R*,*R*)-**4a**–**c**] with similar enantioselectivities (entries 3, 4, and 5 vs entries 1 and 2), which are more active than those dendritic catalysts derived from amino-functionalized vicinal diamine (the TOF values are less than 12).[5a] However, when the third generation catalyst, Ru[(*R*,*R*)-**4d**] was used, the reactivity had a notable drop in only 75% conversion (TOF value is 4.3) along with a slight decrease of enantioselectivity (entry 6) with the same reaction time. We presumed that the dendrons of Ru[(*R*,*R*)-**4d**] wrapped the catalytic site so tight that substrates could not easily access the active site of the catalyst.[16,17] The second generation catalyst, Ru[(*R*,*R*)-**4c**] can be recovered by precipitation with an addition of methanol after removed of DCM under reduced pressure[20] and reused four times with slightly higher enantioselectivities (entries 7–10 vs entry 5). Lower activities in the successive reactions in terms of the required reaction time and conversion rate were evaluated by ICP analysis, which showed that the catalyst had leached into the MeOH solution (about 10 mol % for each reuse). Interestingly, Ru[(*R*,*R*)-**4c**] was more active than the third generation catalyst derived from amino-functionalized vicinal diamine[5a] for the fifth use with 71.2% versus 52% conversions. Although the enantioselectivities of the second generation catalysts prepared from *N*-2,4,6-triethylphenylsulfonyl-1,2-diamine ligand, (*S*,*S*)-**4e**,[12] *N*-2,4,6-triisopropylphenylsulfony-1,2-diamine ligand, (*S*,*S*)-**4f**,[9b] and [RuCl$_2$(cymene)]$_2$ decreased (entries 14



Scheme 1. Synthesis of the chiral monomer **2** and the chiral dendritic ligands **4**. Reagents and conditions: (a) $ArSO_2Cl$ (1.05 equiv), DIPEA (1.3 equiv), DCM, 0 °C to rt.

Table 1. Asymmetric transfer hydrogenation of acetophenone using the (*R*,*R*)-**2**–Ru(II) and (*R*,*R*) or (*S*,*S*)-**4**–Ru(II) complexes[a]



5 **6**

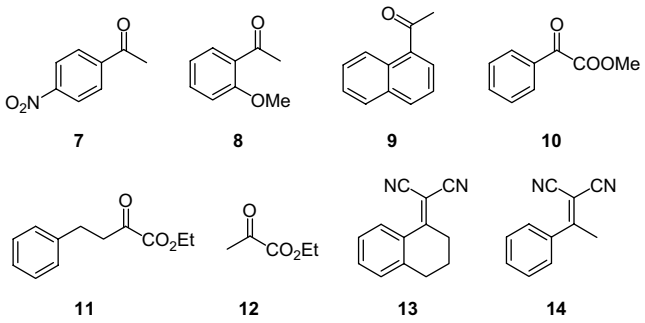
Entry	Ligand	Time (h)	Conversion[b] (%)	TOF[c] (h^{-1})	ee[d] (%)
1	(*R*,*R*)-TsDPEN	5	51	10.2	96.5
2	(*R*,*R*)-**2**	20	>99	12.8	96.3
3	(*R*,*R*)-**4a**	20	95	15.2	96.8
4	(*R*,*R*)-**4b**	20	>99	16.1	96.6
5	(*R*,*R*)-**4c**	20	97.1 (90.4)[e]	10.3 (13.2)[e]	96.1 (96.4)[e]
6	(*R*,*R*)-**4d**	20	75	4.3	94.6
7	(*R*,*R*)-**4c** (2nd use)[f]	21	95.4	nd	97.5
8	(*R*,*R*)-**4c** (3rd use)[f]	25	90.2	nd	97.2
9	(*R*,*R*)-**4c** (4th use)[f]	31	83.7	nd	97.5
10	(*R*,*R*)-**4c** (5th use)[f]	40	71.2	nd	97.0
11[g]	(*R*,*R*)-**4c**	13	>99	nd	90.1
12[g]	(*R*,*R*)-**4c** (2nd use)[f]	36	53	nd	91.1
13[h]	(*R*,*R*)-**4c**	96	97	nd	95.0
14[i]	(*S*,*S*)-**4e**	20	93.0 (73.4)[e]	14.7 (8.9)[e]	91.7 (89.5)[e]
15[i]	(*S*,*S*)-**4f**	20	91.7 (90.6)[e]	10.4 (9.3)[e]	92.8 (91.3)[e]
16[i]	(*S*,*S*)-**4g**	20	>99 (89.0)[e]	14.8 (15.9)[e]	96.3 (91.5)[e]

[a] (*R*)-Alcohol was obtained.
[b] Based on GC analysis.
[c] Average turn-over frequency calculated over the 5 h reaction time.
[d] Determined by GC on CP-Cyclodex B-236 M column.
[e] DMF as solvent, activation at 80 °C for 1 h.
[f] Recovered catalyst was used.
[g] Reaction at 40 °C.
[h] S/C = 500.
[i] (*S*)-Alcohol was obtained.

and 15), the second generation catalyst prepared from *N*-1-naphthylsulfonyl-1,2-diamine ligand, (*S*,*S*)-**4g**[9a] gave a high conversion with the same selectivity (entry 16). When DMF was used as solvent and the activated temperature increased to 80 °C for preparation of the second generation catalysts, a decrease in both conversion and enantioselectivity was observed (entries 5, 14–16).

For further exploring the distinctive characteristic of dendritic catalysts, several ketones, **7**–**9** were chosen as substrates (Table 2), because their low enantioselectivities were observed in the asymmetric transfer hydrogenation before.[8] In general, the conversions of **7** and **8** and the enantioselectivities of reduced products did not obviously change when using dendritic (*R*,*R*)-**4c** as a ligand compared to the monomeric ligand (*R*,*R*)-**2** and TsDPEN (entries 1–10). Reduction of **9** with (*R*,*R*)-**2** and dendritic ligands, (*R*,*R*)-**4c** gave better yields (>90%) than TsDPEN and much higher enantioselectivities (up to 95%) compared with that of the literature (entries 11–14).[8] We reasoned that the electronic effect of the electron-donating group at the *para*-site of the benzene ring of the diamine ligands in Ru(diamine) complexes can lead to a faster rate in this asymmetric transfer hydrogenation while the replacement of 1,3,5-trimethylbenzene with cymene for the η-arene ligand may lead to higher enantioselectivities (entry 12 vs 11). Although the dendritic ligands, (*S*,*S*)-**4e** and **4g** were found to reduce both reactivities and enantioselectivities in the asymmetric transfer hydrogenation of **7** and **8** (entries 4 and 5, 9 and 10), they can dramatically enhance the enantioselectivities to both 82% ee, from 64% ee for those *N*-tosyl-diamine ligands (entries 18 and 20 vs entry 17) in the asymmetric transfer hydrogenation of methyl benzoylformate **10**. The highest enantioselectivity (92.0% ee) was obtained by using (*S*,*S*)-**4f** as a ligand (entry 19). Those that showed an increase of enantioselectivities in the asymmetric reduction could be achieved by fine tuning of the coordinating amino group NH_2 of chiral 1,2-diamines. The ACE inhibitor intermediate, ethyl 2-hydroxy-4-phenylbutanoate was obtained with 78.6% ee by using (*R*,*R*)-**4c** as a ligand (entry 22). Good enantioselectivity (84.5% ee) was obtained in the reduction of ethyl 2-oxopropanoate **12** by using (*R*,*R*)-**4c** as a ligand (entry 27). However, the prochiral β-dicyanoolefins, **13** and **14** could be reduced by using Ru–(*S*,*S*)-**4e** as catalyst in high yields with 80% and 71% ee (entries 33 and 38), respectively, which can further form β-chiral acids by hydrolyzing the products.[12a]

Table 2. Asymmetric transfer hydrogenation of ketones and olefins using the (*R*,*R*)-**2**–Ru(II) and (*R*,*R*) or (*S*,*S*)-**4**–Ru(II) complexes[a]



7 **8** **9** **10**

11 **12** **13** **14**

Entry	Sub	Ligand	S/C	Time (h)	Yield[b] (%)	ee[c] (%) (Conf)[d]
1	**7**	TsDPEN	100	4.0	93	82.6 (*R*)
2	**7**	**2**	100	5.0	95	84.4 (*R*)
3	**7**	**4c**	100	5.0	94	87.4 (*R*)
4	**7**	**4e**	100	5.0	91	71.3 (*S*)
5	**7**	**4g**	100	5.0	95	87.6 (*S*)
6	**8**	TsDPEN	100	48	81	89.6 (*R*)
7	**8**	**2**	100	48	75	89.4 (*R*)
8	**8**	**4c**	100	48	80	87.0 (*R*)
9	**8**	**4e**	100	48	5[c]	51.4 (*S*)
10	**8**	**4g**	100	48	31	78.6 (*S*)
11	**9**	TsDPEN[e]	100	28	88	81.7 (*R*)
12	**9**	TsDPEN	100	28	80	95.1 (*R*)
13	**9**	**2**	100	28	95	95.0 (*R*)
14	**9**	**4c**	100	28	90	94.9 (*R*)
15	**10**	TsDPEN	100	2.5	81	65.0 (*S*)
16	**10**	**2**	100	2.5	82	64.4 (*S*)
17	**10**	**4c**	100	2.5	82	64.1 (*S*)
18	**10**	**4e**	100	2.5	80	81.7 (*R*)
19	**10**	**4f**	100	2.5	82	92.0 (*R*)
20	**10**	**4g**	100	2.5	82	82.0 (*R*)
21	**11**	TsDPEN	40	24	96	79.7 (*R*)
22	**11**	**4c**	40	24	94	78.6 (*R*)
23	**11**	**4e**	40	24	96	60.0 (*S*)
24	**11**	**4f**	40	24	94	69.0 (*S*)
25	**11**	**4g**	40	24	95	64.5 (*S*)
26	**12**	TsDPEN	40	24	100	86 (*R*)[11c]
27	**12**	**4c**	40	24	95	84.5 (*R*)
28	**12**	**4e**	40	24	94	79.3 (*S*)
29	**12**	**4f**	40	24	96	80.0 (*S*)
30	**12**	**4g**	40	24	97	77.0 (*S*)
31	**13**	TsDPEN[f]	100	4.5	98	60 (−)[g,h]
32	**13**	**4c**[f]	100	4.5	96	59 (−)[g,h]
33	**13**	**4e**[f]	100	4.5	97	80 (+)[g,h]
34	**13**	**4f**[f]	100	4.5	97	73 (+)[g,h]
35	**13**	**4g**[f]	100	4.5	94	76 (+)[g,h]
36	**14**	TsDPEN[f]	100	2.5	95	51 (*S*)[g]
37	**14**	**4c**[f]	100	2.5	82	49 (*S*)[g]
38	**14**	**4e**[f]	100	2.5	87	71 (*R*)[g]
39	**14**	**4f**[f]	100	2.5	83	33 (*R*)[g]
40	**14**	**4g**[f]	100	2.5	91	66 (*R*)[g]

[a] Reaction condition showed in Ref. 20 (S/C = 100), unless otherwise noted.
[b] Isolated yields.
[c] Determined by GC on CP-Cyclodex B-236 M column.
[d] Determined by comparison with rotation sign in available references or the retention times of standard compounds on GC or HPLC analyses.
[e] 1,3,5-Trimethylbenzene was used as a ligand according to the literature.[8]
[f] After activated at 60 °C for 1 h, the reaction was conducted at 28 °C in THF.
[g] Determined by HPLC on chiral OD column.
[h] Rotation sign.

3. Conclusion

In conclusion, a novel series of chiral dendritic *N*-monosulfonyl 1,2-diamine ligands based on the phenyl-functionalized 1,2-diamine have been designed and synthesized in high yields with their ruthenium complexes demonstrating higher reactivities when compared to the monomeric catalyst with the same enantioselectivities. Moreover, better recyclable activities of the second generation dendritic catalyst were observed when compared with the polymer-supported catalysts,[15b,d,e] as well as the dendritic catalysts derived from amino-functionalized vicinal diamine[5a] by using the formic acid–triethylamine azeotrope as the hydrogen source in the asymmetric transfer hydrogenation. It is notable that the phenyl-functionalized dendritic 1,2-diamine ligands can be selectively modified toward the development of 'fine-tuned' catalysts for the reduction of an extended range of substrates, such as aromatic ketones, keto esters, and olefins. A further interesting aspect of this study is that such ligands can serve as a chiral platform with which many types of reactions can be carried out.

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18. Full characterization of ligand (*R*,*R*)-**4d** as one representative: Mp 67–73 °C; $[\alpha]_D^{22} = +0.3$ (*c* 2.24, $CHCl_3$); IR (KBr), ν_{max}: 3492, 3449, 2871, 1596, 1450, 1157, 1050, 834, 737, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.41–7.30 (m, 82H), 7.00–6.94 (m, 6H), 6.74–6.57 (m,

46H), 5.12–4.89 (m, 60H), 4.26 (br s, 1H), 4.00 (br s, 1H), 2.26 (s, 3H) ppm; partial ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.2, 160.1, 160.0, 159.9, 139.2, 136.8, 128.6, 128.5, 128.0, 127.9, 127.8, 127.6, 127.1, 106.4, 101.6, 70.1, 70.0, 28.5 ppm. Element Analysis for $C_{231}H_{202}N_2O_{32}S$ Calcd: C, 77.65; H, 5.80; N, 0.77; S, 0.88. Found: C, 77.35; H, 5.70; N, 0.92; S 1.00.

19. MS data for the dendritic ligands: (*R*,*R*)-**4a** calcd for $C_{35}H_{35}N_2O_4S$, $[M+H]^+$: 579.2318, found 579.2312; (*R*,*R*)-**4b** calcd for $C_{63}H_{58}N_2NaO_8S$, $[M+Na]^+$: 1025.5267, found 1025.3811; (*R*,*R*)-**4c** calcd for $C_{119}H_{107}N_2O_{16}S$, $[M+H]^+$: 1851.7341, found 1851.7369; (*R*,*R*)-**4d** calcd for $C_{231}H_{202}N_2NaO_{32}S$, $[M+Na]^+$ (MALDI-TOF): 3570.4, found 3576; (*S*,*S*)-**4e** calcd for $C_{124}H_{116}N_2NaO_{16}S$, $[M+Na]^+$ (MALDI-TOF): 1943.8, found 1943.4; (*S*,*S*)-**4f** calcd for $C_{127}H_{122}N_2NaO_{16}S$, $[M+Na]^+$ (MALDI-TOF): 1985.8, found 1985.2; (*S*,*S*)-**4g** calcd for $C_{122}H_{106}N_2NaO_{16}S$, $[M+Na]^+$ (MALDI-TOF): 1909.7, found 1909.0.

20. General procedure: The catalyst (1 mol %) was prepared in situ by mixing 2 equiv of triethylamine, a dendritic ligand and $[RuCl_2(cymene)]_2$ (1.1:0.5 M ratio) in a solution of DCM (2 M related to acetophenone) for 1 h under argon at 28 °C. Then acetophenone and formic acid–triethylamine azeotrope (0.5 mL per mmol of ketone) were added and stirred at 28 °C.