SHORT PAPER

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The synthesis of amphiphilic chiral dendritic 1,1′-bi-2-naphthol derivatives and their application as amphiphiles in aqueous asymmetric hydrogenation†

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Six new amphiphilic chiral dendritic BINOLs were synthesised via coupling reactions of optically active BINOL and the Frèchet-type poly(aryl ether) dendrons with peripheral oligo(ethyleneglycol) groups, and were used as amphiphiles for promoting the asymmetric hydrogenation of 2-[*p*-(2-methylpropyl)- phenyl]acrylic acid in an aqueous media.

Keywords: amphiphilic chiral dendritic 1,1′-bi-2-naphthol derivatives

Dendrimers are highly branched macromolecules that have a spherical structure featuring a densely packed-exterior and a largely-meshed interior which may act as a "cavity". Because of these unique properties, dendrimers are considered as a new type of supramolecular host.[1] The encapsulation of guest molecules into the dendritic box and shape-selective release of the encapsulated guests was first reported by Meijer.[2] Among the dendrimers reported to date, the amphiphilic dendrimers as unimolecular amphiphiles, have been extensively studied. This type of dendrimer is able to encapsulate guest molecules and could be used as very effective extractants in liquid–liquid extractions,[3] supports in drug delivery,[4] microreactors in catalysis[5] and as chemical sensors in molecular recognition.[6] In order to prepare chiral supramolecular hosts, chiral dendrimers are required. However, very few dendritic chiral host molecules, in particular water-soluble amphiphilic chiral dendrimers, have been described.[6, 7] In this work, chiral 1,1′-binaphthol (BINOL), which has an excellent ability for chiral recognition in asymmetric catalysis,[8] was chosen as model chiral motif for the design and synthesis of novel amphiphilic chiral dendrimers.

In connection with our interest in aqueous asymmetric catalysis, the use of these chiral amphiphilic dendrimers for asymmetric hydrogenation in aqueous media, was also examined. It is well known that the aqueous asymmetric catalysis is one of the most important developments in modern chemistry over the past three decades due to its environmentally benign nature.[9] Aqueous asymmetric hydrogenation has been well established. However, it required modification of chiral phosphine ligands to obtain water-soluble chiral catalysts.[10] Recently, Oehme *et al*. reported another approach by using the concept of "micelle catalysis".[11] The amphiphilic and even the non-amphiphilic ligands could be used for asymmetric hydrogenation in aqueous media. In some cases, a remarkable enhancement of activity and enantioselectivity with the addition of surfactants was achieved. This was attributed to the formation of micelles.[12] However, micelles could be formed at a surfactant concentration that is higher than the critical micellar concentration (CMC). Therefore, it is expected that an amphiphilic dendrimer, a unimolecular micelle, would have distinct advantages over conventional micelles in aqueous asymmetric catalysis. To our knowledge, no examples of using chiral amphiphilic dendrimer in aqueous asymmetric hydrogenation have been reported.

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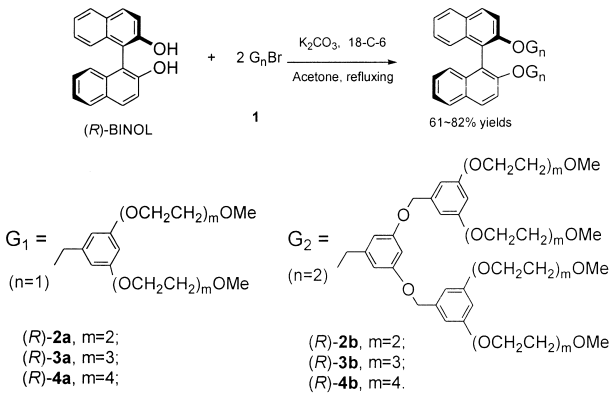
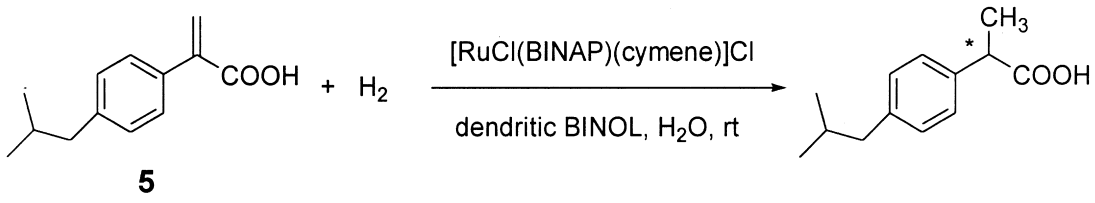
The axially chiral dendrimers were synthesised according to the strategy for the synthesis of the dendritic wedges introduced by Fréchet, using (*R*)-BINOL as the core molecule.[13, 14] The synthetic routes for compounds **2–4** are outlined in Scheme 1. Firstly, the Fréchet-type poly(aryl ether) dendrons with oligo(ethyleneglycol) surface groups were synthesised according to the published methods.[15] The coupling of corresponding dendritic benzyl bromide **1** with BINOL was successfully carried out using potassium carbonate as the base, acetone as the solvent and 18-crown-6 as phase-transfer catalyst to afford compounds **2–4** in moderate yields. Due to the water solubility of these dendrimers, aqueous work-up procedures were avoided throughout the synthesis. For comparison purposes, the second-generation dendrimers, dendritic (S)-**4b** and dendritic racemic BINOL rac-**4b**, were also synthesised using the same method.



Scheme 1
Synthesis of amphiphilic chiral dendritic BINOLs.

All of these dendritic BINOL derivatives give well-resolved ^{1}H NMR spectra consistent with their structures. The ^{1}H NMR spectra also indicate that these dendritic BINOLs maintain a C_2 symmetry in solution. The results of MALDI mass spectra of these dendritic BINOLs match the calculated value. These results clearly demonstrated the formation of monodispersed dendritic BINOLs. The specific optical rotation $[\alpha]_D^{20}$ decreased with the increase in the dendritic generation. However, the molar rotation was almost identical regardless of the generation, which showed that the dendritic wedges attached to the binaphthyl core do not lead to major chiral amplification.

Table 1 Effect of amphiphilic chiral dendritic BINOLs on aqueous asymmetric hydrogenation of **5** catalysed by Ru-BINAP catalyst



5

Entry	BINOLs	Concentration/m M	[a] BINOLs/**5**	[b] TOF/h	e.e./%
1	—	0	0	0.6	41.3
2	(*R*)-**4b**	1.0 $\times10^{-3}$	1 : 24.5	0.9	60.1
3	(*R*)-**4b**	2.0 $\times10^{-3}$	1 : 12.2	1.4	61.4
4	(*R*)-**4b**	3.0 $\times10^{-3}$	1 : 8.1	2.2	63.5
5	(*R*)-**4b**	6.0 $\times10^{-3}$	1 : 4.1	3.2	67.5
6	(*R*)-**4a**	6.0 $\times10^{-3}$	1 : 4.1	1.5	62.1
7	(*R*)-**3b**	2.0 $\times10^{-3}$	1 : 12.2	2.2	61.0
8	(*R*)-**2b**	2.0 $\times10^{-3}$	1 : 12.2	5.0	67.3
9	(*S*)-**4b**	2.0 $\times10^{-3}$	1 : 12.2	1.6	65.6
10	rac-**4b**	2.0 $\times10^{-3}$	1 : 12.2	1.3	62.0

[a] BINOLs/**5** was the mol ratio of dendritic BINOL to **5**. [b] Turnover frequency, average TOFs calculated over the quoted reaction time.

With these chiral amphiphilic dendritic BINOL host molecules in hand, we chose the asymmetric hydrogenation of 2-[*p*-(2-methylpropyl)phenyl]acrylic acid (**5**) as the model reaction for comparing their performances. This choice was based on the fact that the Ru–BINAP-type catalysts were effective in the asymmetric hydrogenation of 2-arylacrylic acids and the reduced products represented an important class of anti-inflammatory drugs.[16] The catalytic results are summarised in Table 1. Several conclusions can be drawn from these results: (1) addition of the new amphiphilic chiral dendritic BINOLs significantly improved the enantioselectivity and the reaction rate of the aqueous hydrogenation (entry 1 *vs* 2); (2) higher concentration of the amphiphilic dendrimer afforded higher reaction rates with similar enantiomeric excess (entries 2–5). (3) Under same concentration, the reaction rate increased with the increase of generation of the dendritic host with similar enantioselectivity (entry 5 *vs* 6); (4) The dendrimer with a longer peripheral oligo(ethyleneglycol) groups gave a lower reaction rate and similar enantioselectivity (entries 3, 7 and 8); and (5) comparison of entries 3, 9 and 10 indicated that asymmetric induction was mainly governed by the Ru-BINAP catalyst.

Experimental

The ^{1}H-NMR was recorded on a Brucker DM 300 spectrometer in $CDCl_3$ with TMS as internal standard. MALDI-TOF mass spectra were obtained on an Instrum III spectrometer with α-cyano-4-hydroxycinnamic acid (CCA) as a matrix. Optical rotations were measured with AA-10R automatic polarimeter. Commercial reagents were used as received without further purification.

A typical procedure for synthesis of chiral dendritic BINOLs: A mixture of the first generation of Frechet-type dendritic benzyl bromide G_1Br(m=2) with peripheral diethyleneglycol chains (172.1mg, 0.41mmol), (*R*)-BINOL (40.2mg, 0.14mmol), K_2CO_3 (0.73g, 5.3mmol) and 18-crown-6 (7.3mg, 0.03mmol) in dry acetone (5ml) was heated under reflux under nitrogen with vigorous stirring for 24h. The reaction mixture was allowed to cool to room temperature and the salts were removed by filtration. The solvent was evaporated and the residue was subjected to column chromatography, eluting with 1:1 petroleum ether/ethyl acetate gradient gradually increasing to ethyl acetate, then with 10:1 ethyl acetate/methanol gradually increasing to 3:1 ethyl acetate/methanol to give (*R*)-**2a** as a yellow oil (157.2 mg, 73.6%). $[\alpha]_D^{20}$ = +12.0 (c =4.18, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.87 (d, 2H, *J*=9.0Hz), 7.79 (d, 2H, *J*=9.0Hz), 7.37 (d, 2H, *J*=9.0Hz), 7.20–7.14 (m, 6H), 6.18 (s, 2H), 6.02 (s, 4H), 4.91 (s, 4H), 3.66–3.60 (m, 24H), 3.49 (t, 8H, *J*=4.1Hz), 3.32 (s, 12H); MALDI-TOF-MS *m*/*z*: 961.43 $[M+Na]^+$, 977.40 [M+K]+, Calcd: 938.455 [M].

(*R*)-**2b**: yield 61.2%; $[\alpha]_D^{20}$ = + 6.48 (c = 4.63, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.93 (d, 2H, *J*=9.0Hz), 7.80 (d, 2H, *J*=8.9Hz), 7.48 (d, 2H, *J*=9.0Hz), 7.29–7.23 (m, 6H), 6.51(s, 8H), 6.45 (s, 4H), 6.31(s, 2H), 6.14(s, 4H), 5.00(s, 4H), 4.51 (s, 8H), 4.11 (t, 16H, *J*=4.5Hz), 3.85 (t, 16H, *J*=4.6Hz), 3.70 (t, 16H, *J*=4.9Hz), 3.57 (t, 16H, *J*=4.8Hz), 3.38 (s, 24H); MALDI-TOF-MS *m*/*z*: 1858.21 $[M+Na]^+$, 1874.16 $[M+K]^+$, Calcd: 1834.88 [M].

(*R*)-**3a**: yield 73.0%; $[\alpha]_D^{20}$ = + 21.2 (c = 4.68, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.85 (d, 2H, *J*=9.0Hz), 7.75 (d, 2H, *J*=9.0Hz), 7.36 (d, 2H, *J*=9.1Hz), 7.15–7.09 (m, 6H), 6.16 (s, 2H), 6.00 (s, 4H), 4.89 (s, 4H), 3.59–3.50 (m, 40H), 3.47 (t, 8H, *J*=4.9Hz), 3.29 (s, 12H); MALDI-TOF-MS *m*/*z*: 1137.85 $[M+Na]^+$, 1153.83 $[M+K]^+$, Calcd: 1114.55 [M].

(*R*)-**3b**: yield 66.1%; $[\alpha]_D^{20}$ = + 11.2 (c = 4.64, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$), d: 7.93 (d, 2H, *J*=9.0Hz), 7.79 (d, 2H, *J*=9.0Hz), 7.48 (d, 2H, *J*=9.1Hz), 7.25–7.19 (m, 6H), 6.51 (s, 8H), 6.45 (s, 4H), 6.32 (s, 2H), 6.15 (s, 4H), 5.01 (s, 4H), 4.52 (s, 8H), 4.10 (t, 16H, *J*=4.2Hz), 3.84 (t, 16H, *J*=4.5Hz), 3.75–3.68 (m, 48H), 3.54 (t, 16H, *J*=4.1Hz), 3.37 (s, 24H); MALDI-TOF-MS *m*/*z*: 2210.74 $[M+Na]^+$, 2226.74 $[M+K]^+$, Calcd: 2187.59 [M].

(*R*)-**4a**: yield 82.6%; $[\alpha]_D^{20}$ = + 22.0 (c = 4.01, CH_2Cl_2); ^{1}HNMR (300 MHz, $CDCl_3$), δ: 7.95 (d, 2H, *J*=9.0Hz), 7.86 (d, 2H, *J*=9.0Hz), 7.45 (d, 2H, *J*=9.0Hz), 7.27–7.22 (m, 6H), 6.24 (s, 2H), 6.08 (s, 4H), 4.98 (s, 4H), 3.72–3.63 (m, 56H), 3.54 (t, 8H, *J*=4.8Hz), 3.37 (s, 12H); MALDI-TOF-MS *m*/*z*: 1313.48 $[M+Na]^+$, 1329.43 $[M+K]^+$, Calcd: 1290.60 [M].

(*R*)-**4b**: yield 76.1%; $[\alpha]_D^{20}$ = + 11.4 (c =3.71, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.93 (d, 2H, *J*=9.0Hz), 7.79 (d, 2H, *J*=9.0Hz), 7.48 (d, 2H, *J*=9.1Hz), 7.29–7.25 (m, 6H), 6.51 (s, 8H), 6.46 (s, 4H), 6.31 (s, 2H), 6.14 (s, 4H), 5.00 (s, 4H), 4.51 (s, 8H), 4.10 (t, 16H, *J*=4.2Hz), 3.85 (t, 16H, *J*=4.6Hz) 3.69 (m, 80H), 3.53 (t, 16H, *J*=4.0Hz), 3.35 (s, 24H); MALDI-TOF-MS *m*/*z*: 2562.58 $[M+Na]^+$, 2578.78 $[M+K]^+$, Calcd: 2539.30 [M].

Asymmetric hydrogenation: In a typical experiment the 50-ml glass-lined stainless autoclave with a magnetic stirring bar was charged with 0.05mmol of **5**, 0.001 mmol of [RuCl(BINAP)(cymene)]Cl, suitable amount of (*R*)-**4b**, 0.1 mmol of NEt_3 and 2 ml of H_2O. The autoclave was then pressurised with H_2 to 50 atmos. The mixture was stirred with a magnetic stirrer under the H2 pressure at 24–30°C for 5h. After the H_2 was vented, the final mixture was extracted with ethyl acetate (3×5 ml) and dried over magnesium sulfate. Enantioselectivity excesses were measured by GC (with a Chrompack Chirasil-dex (25m×0.25mm)) after the reduced product was transformed into the corresponding methyl ester.

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