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Dendritic BIPHEP: Synthesis and application in asymmetric hydrogenation of β-ketoesters

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Abstract

A series of new chiral dendritic BIPHEP ligands have been prepared and their applications in the Ru-catalyzed asymmetric hydrogenation of β-ketoesters were investigated. Ruthenium catalysts containing these dendrimer ligands were effective in the hydrogenation of β-ketoesters. It was found that the size of the dendritic wedges influenced the enantioselectivity significantly.

Keywords: Dendritic ligand; Chiral diphosphine; Ruthenium complex; Asymmetric hydrogenation

1. Introduction

Homogeneous asymmetric catalysis is one of the most important developments in modern chemistry over the past several decades [1]. Binaphthyl or biphenyl and other biaryl groups have often been used as chiral scaffolds to produce an excellent asymmetric environment [2]. Many effective C_2 symmetric chiral diphosphines such as BINAP [1a,2d,3] and more recently MeO-BIPHEP [4] have been developed and shown excellent results, especially in the field of ruthenium-mediated asymmetric hydrogenation [1a]. Subtle changes in geometric, steric, and/or electronic properties of chiral ligands can lead to dramatic variations of reactivity and enantioselectivity. The dihedral angles of the biaryl phosphine ligands have also proven to exert very important influence on the catalytic activity and/or enantioselectivity [5]. There are two general strategies for the design and synthesis of new efficient biary phosphine ligands with unusual stereoelectronic profiles, i.e. different dihedral angles. The first strategy is to replace the phenyl phosphorus substituents by bulkier aromatics, such as *p*-Tol-BINAP [6], DTBM-segphos [5d]. The second strategy focuses on the steric design of the biaryl core: H_8-BINAP [5b] by Umera et al., C_n-TunaPhos [5c] by Zhang et al., segphos [5d] by Saito et al., synphos [5e,5g] by Chan's and de Genêt's groups, and recently difluorphos [5i] by Jeulin et al. and a bridged biphenyl phosphine ligand possessing additional chiral centers on the linking unit of the biphenyl groups [5j] by Qiu et al. (Scheme 1) have been specially targeted because they display a tunable or unusual dihedral angles. Most of them have been proven excellent ligands in asymmetric hydrogenation reactions. Herein, we report another new strategy for designing tunable BIPHEP-type ligands via replacing the methoxyl substituents at the 6,6′-positions of the biphenyl backbone by different generation dendrimers (Scheme 2).

The use of organometallic dendrimers in homogeneous catalysis is an important frontier of research in recent years [7]. Because of the well-defined molecular architecture of dendrimers, it is possible to fine-tune their catalytic properties through the systematic adjustment of their structure, size, shape, and solubility [8]. Recently, we have developed two types of chiral dendritic ligands for asymmetric catalysis through the incorporation of BINAP [9] and BINOL [10] into the core of the Fréchet-type dendrimers, respectively. In both cases, it was found that the size of the dendritic wedges influenced the reactivity and/or the enantioselectivity of the dendritic catalysts. As an extension of our previous study on chiral dendrimer catalysts [9–11], we herein report the synthesis of chiral dendritic

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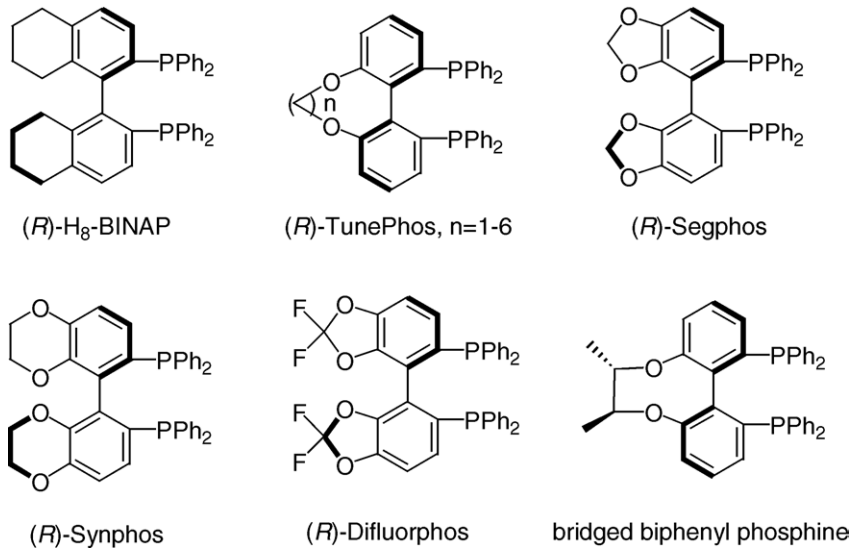


Scheme 1. Some atropoisomeric diphosphine ligands.

BIPHEP ligands and their application in the Ru-catalyzed asymmetric hydrogenation of β-ketoesters. It was found that the size of the dendritic wedges influenced the enantioselectivity significantly.

2. Experimental

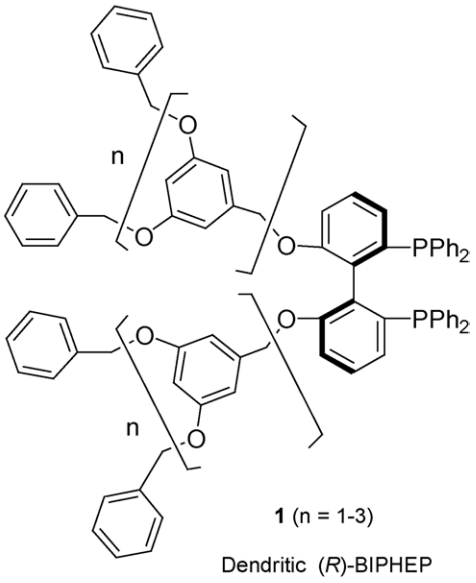
2.1. General remarks

All experiments were carried out under a nitrogen atmosphere by using standard Schlenk-type techniques, or performing in a glovebox.

2.2. Materials and equipment

All solvents were dried using standard, published methods and were distilled under nitrogen atmosphere before use. Except as specified, commercial reagents were used as received without further purification. (*R*)-(6,6′-dihydroxybiphenyl-2,2′-diyl)-bis(diphenylphosphine) **2** was synthesized according to the published method [5c].

NMR spectra were recorded on a BRUKER Model AVDANCE DPX 300 spectrometer (300 MHz ^{1}H and 122 MHz ^{31}P) using tetramethylsilane for ^{1}H as an internal standard, 85% of H_3PO_4 in D_2O for ^{31}P as an external standard. All signals are reported in ppm unit. MALDI-TOF-MS were recorded on a Bruker Biflex β spectrometer with α-cyano-4-hydroxycinnamic acid (CCA) as a matrix. Elemental analysis was performed with a Carlo Erba 1106 Elemental Analyzer. Optical rotations were measured with AA-10R automatic polarimeter. For high-pressure hydrogenation, 50 ml stainless autoclave equipped with a glass liner was used. The ee values were determined by GC using a WARIAN CP 7502 chiral column (30 m × 0.25 mm).



Scheme 2. Structure of dendritic (*R*)-BIPHEP.

2.3. Synthesis of (R)-(6,6′-dihydroxybiphenyl-2,2′-diyl)-bis(diphenylphosphine oxide) (R)-3

To a cool solution of (*R*)-**2** (1.0 g, 1.7 mmol) in methanol (20 ml) was added 0.2 ml of hydrogen peroxide (35% aqueous solution). The reaction mixture was stirred for 2 h at room temperature. After completion of the reaction indicated by TLC, the reaction mixture was poured into 50 ml water to precipitate the product (*R*)-**3** as a white solid (0.95 g, yield 95%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59–7.53 (m, 4H), 7.47–6.80 (m, 22H), 6.75–6.60 (m, 2H), 3.38 (s, br, 2H); HRMS calculated for $C_{36}H_{28}O_4P_2$ 586.1463, found 587.1528 $[M + 1]^+$.

2.4. General procedure for the synthesis of the dendritic BIPHEP oxides (R)-6 and (R)-5a–5c

A mixture of (*R*)-**3** (0.34 mmol, 1.0 equiv), benzyl bromide (0.85 mmol, 2.5 equiv), K_2CO_3 (14.3 mmol, 42 equiv) in acetone (20 ml) was stirred at refluxing temperature for 48 h. After most of the acetone was removed under reduced pressure, the residue

was partitioned between water and CH_2Cl_2, and the aqueous layer was extracted twice with CH_2C1_2. The combined organic layer was washed by brine and dried over anhydrous Na_2SO_4. The solvent was removed and the crude product was further purified by flash chromatography on silica gel to give (*R*)-**6** as a white solid (yield 50%). mp = 123–124 °C; $[\alpha]_D^{22}$ = +44.8 (*c* 4.6, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61–7.48 (m, 8H), 7.36–7.06 (m, 20H), 6.96–6.82 (m, 6H), 6.68 (d, *J* = 7.2 Hz, 2H), 4.74–4.37 (m, 4H); HRMS calculated for $C_{50}H_{40}O_4P_2$ 766.2402, found 767.2472 $[M+1]^+$.

Compound (*R*)-**5a**: a white solid, 55% yield. mp = 94–95 °C; $[\alpha]_D^{22}$ = +24.9 (*c* 1.8, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49–6.70 (m, 46H), 6.41–5.87 (m, 6H), 4.64–4.37 (m, 12H); MALDI-TOF Ms calculated for $C_{78}H_{64}O_8P_2$ 1190.4, found 1191.8 $[M+1]^+$. Elemental analysis calculated (%) for $C_{78}H_{64}O_8P_2$: C 78.64, H 5.42, found: C 79.12, H 5.41.

Compound (*R*)-**5b**: a white foam, 60% yield. mp = 91–92 °C; $[\alpha]_D^{22}$ = +14.4 (*c* 1.4, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63–7.40 (m, 8H), 7.38–7.10 (m, 54H), 6.95–6.80 (m, 4H), 6.54–6.13 (m, 18H), 4.97–4.47 (m, 28H); MALDI-TOF Ms calculated for $C_{134}H_{112}O_{16}P_2$ 2038.7, found 2039.9 $[M+1]^+$. Elemental analysis calculated (%) for $C_{134}H_{112}O_{16}P_2$: C 78.88, H 5.53, found: C 78.74, H 5.70.

Compound (*R*)-**5c**: a white foam, 60% yield. mp = 84–85 °C; $[\alpha]_D^{22}$ = +7.2 (*c* 5.0, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60–7.00 (m, 106H), 6.80–6.19 (m, 42H), 4.91–4.40 (m, 60H); MALDI-TOF Ms calculated for $C_{246}H_{208}O_{32}P_2$ 3735.4, found 3736.7 $[M+1]^+$. Elemental analysis calculated (%) for $C_{246}H_{208}O_{32}P_2$: C 79.04, H 5.61, found: C 78.91, H 5.40.

2.5. General procedure for the synthesis of the dendritic BIPHEP ligand (R)-7 and (R)-1a–1c

A mixture of (*R*)-**6** (0.65 mmol, 1 equiv), *n*-Bu_3N (2 mmol, 3 equiv), NEt_3 (23 mmol, 35 equiv), $HSiCl_3$ (20 mmol, 30 equiv) and freshly distilled toluene (80 ml) was stirred at refluxing temperature for 24 h under nitrogen atmosphere. After cooling to room temperature, 30% aqueous NaOH (100 ml) was added carefully to the mixture and the suspension was further stirred at 60–70 °C for 30 min. The organic layer was separated, washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was further purified by flash column chromatography on silica gel to give (*R*)-**7** as a white solid (76% yield). mp = 177–178 °C; $[\alpha]_D^{20}$ = −23.0 (*c* 2.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28–6.55 (m, 36H), 4.42–4.65 (m, 4H); ^{31}P NMR (162 MHz, $CDCl_3$): δ −13.19; HRMS calculated for $C_{50}H_{40}O_2P_2$ 734.2504, found 735.2564 $[M+1]^+$.

Compound (*R*)-**1a**: prepared according to the above procedure except that (*R*)-**5a**:NBu_3:NEt_3:$HSiCl_3$ = 1:5:50:45 (M/M) and the reaction time was 48 h to give (*R*)-**1a** as a white solid (84% yield). mp = 83–85 °C; $[\alpha]_D^{20}$ = −37.4 (*c* 2.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31–7.07 (m, 38H), 6.96 (t, *J* = 7.37 Hz, 4H), 6.78–6.75 (m, 4H), 6.40 (s, 2H), 6.26 (s, 4H), 4.66–4.29 (m, 12H); ^{31}P NMR (162 MHz, $CDCl_3$): δ −13.19. MALDI-TOF Ms calculated for $C_{78}H_{64}O_6P_2$ 1158.4, found 1159.7 $[M+1]^+$. Elemental analysis calculated (%) for $C_{78}H_{64}O_6P_2$: C 80.81, H 5.56, found: C 80.52, H 5.58.

Compound (*R*)-**1b**: prepared according to the above procedure except that (*R*)-**5b**:NBu_3:NEt_3:$HSiCl_3$ = 1:5:60:50 (M/M) and the reaction time was 48 h to give (*R*)-**1b** as a white solid (90% yield). mp = 83–84 °C; $[\alpha]_D^{20}$ = −13.0 (*c* 2.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37–6.87 (m, 64H), 6.66–6.11 (m, 20H), 4.89 (s, 16H), 4.53–4.21 (m, 12H); ^{31}P NMR (162 MHz, $CDCl_3$): δ −13.22; MALDI-TOF Ms calculated for $C_{134}H_{112}O_{14}P_2$ 2006.7, found 2008.5 $[M+1]^+$. Elemental analysis calculated (%) for $C_{134}H_{112}O_{14}P_2$: C 80.14, H 5.62, found: C 80.59, H 5.64.

Compound (*R*)-**1c**: prepared according to the above general procedure except that (*R*)-**5c**:NBu_3:NEt_3:$HSiCl_3$ = 1:60:60:100 (M/M) and the reaction time was 96 h to give (*R*)-**1c** as a white solid (90% yield). mp = 81–83 °C; $[\alpha]_D^{20}$ = +5.6 (*c* 2.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36–6.89 (m, 104H), 6.68–6.11 (m, 44H), 4.90–4.70 (m, 48H), 4.48–4.16 (m, 12H); ^{31}P NMR (162 MHz, $CDCl_3$): δ −13.40; MALDI-TOF Ms calculated for $C_{246}H_{208}O_{30}P_2$ 3703.4, found 3706.5 $[M+1]^+$. Elemental analysis calculated (%) for $C_{246}H_{208}O_{30}P_2$: C 79.72, H 5.66, found: C 79.56, H 5.55.

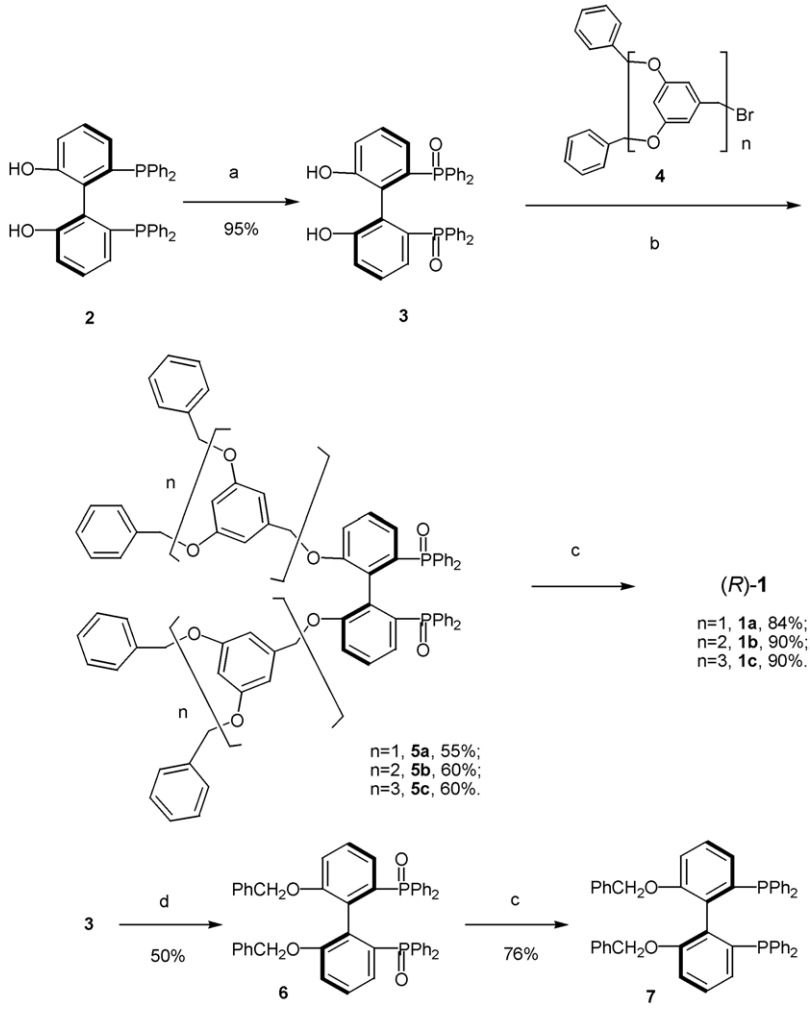
2.6. General procedure for the asymmetric hydrogenation of β-ketoesters

Preparation of Ru(BIPHEP)-type catalysts[14]: To a 5-ml Schlenk tube were added $[Ru(benzene)Cl_2]_2$ (5 mg, 0.01 mmol) and the dendritic BIPHEP (0.022 mmol). The tube was purged with N_2 three times before addition of freshly distilled and degassed DMF (1 ml). The resulting mixture was heated at 100 °C for 10 min. After the mixture was cooled to 50 °C, the solvent was removed under vaccum to give the catalysts.

Asymmetric hydrogenation: A 10-ml glass-lined stainless autoclave with a magnetic stirring bar was charged with 2.4 mmol of substrate, 0.012 mmol the dendritic Ru(BIPHEP) catalyst and 2 ml of CH_2Cl_2/ethanol (1:1, v/v) solvent. The autoclave was closed and pressurized with hydrogen to 40 atm. The mixture was stirred for 24 h at 60 °C. The autoclave was then cooled to room temperature and the H_2 was carefully released. The solvent was removed and most of the dendritic catalyst was precipitated by addition of methanol. The residue was passed through a short silica gel column and concentrated to dryness to give the products.

3. Results and discussions

We chose MeO-BIPHEP as the starting compound to make the dendritic BIPHEP ligands **1** (**1a**–**1c**) (Scheme 3). Enantiomerically pure MeO-BIPHEP was prepared according to the published procedures [4] and demethylated to provide HO-BIPHEP **2** in high yield [5c]. Fréchet's polyether dendrons **4** were chosen as the building blocks due to their inertness to catalytic reaction [12]. However, the direct coupling reaction of **2** with dendrons **4** in the presence of excess anhydrous K_2CO_3 in acetone failed due to the competitive alkylation of diphenylphosphine groups. **2** was then oxidized by reacting with hydrogen peroxide to give phosphine oxide **3** in high yield. The coupling of **3** with **4** was successfully carried out using acetone as the



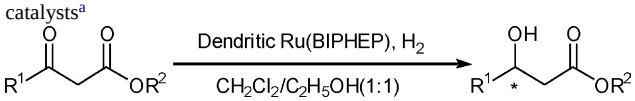
Scheme 3. Synthesis of dendritic BIPHEP. *Reagents and conditions*: (a) H_2O_2 (35%), CH_3OH, 2 h at r.t.; (b) **4**, K_2CO_3, acetone, reflux; (c) NEt_3/NBu_3, $HSiCl_3$, toluene, reflux; (d) Benzyl bromide, K_2CO_3, acetone, reflux.

solvent and anhydrous K_2CO_3 as the base, giving the dendritic BIPHEP dioxide **5a** ($n = 1$), **5b** ($n = 2$) and **5c** ($n = 3$) in moderate yields. Reduction of the phosphine oxides were performed with a mixture of toluene/NEt_3/$HSiCl_3$ to afford **1a**–**1c** in 84, 90 and 90% yields, respectively. In the case of higher generation dendrimer **5c**, large excess of amines and $HSiCl_3$, and longer reaction time were required in order to achieve complete conversion. For comparison, a model compound of small molecule **7** was also synthesized using the same method as described above. It was noted that the high generation dendritic ligands (**1b** and **1c**) gave higher yields as compared with the model ligand **7**. This could be ascribed to the dendritic wedges, which facilitate the separation of the reduced product from the reaction mixtures.

These dendritic BIPHEP ligands were characterized by ^1H, ^{31}P NMR and mass spectra as well as elemental analyses. In the ^{31}P NMR spectra, all dendrimer ligands gave very similar chemical shifts, which were in close agreement to that of MeO-BIPHEP. The structures of **1** were further confirmed by MS spectra analyses. The MALDI TOF MS spectra of **1a**, **1b** and **1c** showed the $[M + 1]^+$ ions as 1159.7, 2008.5 and 3706.5, respectively. These results clearly demonstrated the formation of monodispersed dendritic BIPHEP.

In order to evaluate the catalytic efficiency of these new dendritic ligands and the influence of the dendritic wedges on the enantioselectivity of a given reaction, the well-studied asymmetric hydrogenation of β-ketoesters was selected as the standard reactions. This choice is due to the following factors: (1) Ru–MeO–BIPHEP type complexes are excellent catalysts for this asymmetric transformation [13]; (2) The dihedral angles of several kinds of biaryl diphosphine ligands have been proven to influence the catalytic activity and/or enantioselectivity of this type reactions [5]. The Ru-catalyst was prepared by mixing $[Ru(benzene)Cl_2]_2$ and the proper dendrimer ligand in situ in hot DMF [14]. All complexes were tested for the catalytic asymmetric hydrogenation of various ketoesters. A CH_2Cl_2–ethanol mixture was chosen as the solvent because the dendritic catalysts are insoluble in neat ethanol. The reaction was carried out under 40 atm of H_2 pressure at 60 °C for 24 h. For comparison, the model ligand **7** was performed under the same reaction conditions. The experimental results were summarized in Table 1. While all dendritic catalysts showed

Table 1
Asymmetric hydrogenation of β-ketoester catalyzed by dendritic Ru(BIPHEP) catalysts[a]



Entry	Substrate	Ligand	ee (%)[b]
1	R^1 = Ph, R^2 = CH_3	(*R*)-**7**	93.1
2	R^1 = Ph, R^2 = CH_3	(*R*)-**1a**	92.0
3	R^1 = Ph, R^2 = CH_3	(*R*)-**1b**	86.6
4	R^1 = Ph, R^2 = CH_3	(*R*)-**1c**	91.3
5	R^1 = *p*-CH_3O-Ph, R^2 = CH_3	(*R*)-**7**	84.9
6	R^1 = *p*-CH_3O-Ph, R^2 = CH_3	(*R*)-**1a**	81.1
7	R^1 = *p*-CH_3O-Ph, R^2 = CH_3	(*R*)-**1b**	77.9
8	R^1 = *p*-CH_3O-Ph, R^2 = CH_3	(*R*)-**1c**	79.6
9	R^1 = *p*-Cl-Ph, R^2 = CH_3	(*R*)-**7**	88.0
10	R^1 = *p*-Cl-Ph, R^2 = CH_3	(*R*)-**1a**	85.0
11	R^1 = *p*-Cl-Ph, R^2 = CH_3	(*R*)-**1b**	80.1
12	R^1 = *p*-Cl-Ph, R^2 = CH_3	(*R*)-**1c**	80.9
13	R^1 = CH_3, R^2 = $C(CH_3)_3$	(*R*)-**7**	98.2
14	R^1 = CH_3, R^2 = $C(CH_3)_3$	(*R*)-**1a**	94.1
15	R^1 = CH_3, R^2 = $C(CH_3)_3$	(*R*)-**1b**	89.1
16	R^1 = CH_3, R^2 = $C(CH_3)_3$	(*R*)-**1c**	88.4
17	R^1 = R^2 = CH_3	(*R*)-**7**	94.1
18	R^1 = R^2 = CH_3	(*R*)-**1a**	94.1
19	R^1 = R^2 = CH_3	(*R*)-**1b**	88.0
20	R^1 = R^2 = CH_3	(*R*)-**1c**	88.5

[a] Reactions were carried out at 60 °C using 2.4 mmol of substrate in 2 ml C_2H_5OH/CH_2Cl_2 (1/1, v/v); substrate:catalyst = 200:1 (M/M); H_2 = 40 atm; 100% conversion were obtained in 24 h.
[b] ee Values were determined by GC with a chiral column.

similar reactivity, the enantioselectivity varied dramatically with increase in generation from 1 to 3. For example, methyl 3-oxo-3-phenylpropanoate (entries 1–4) was reduced with ca. 93.1% ee using the model small molecule Ru(**7**) catalyst. The enantioselectivity decreased to 92.0% ee with the first generation Ru(**1a**) catalyst and reached a minimum of 86.6% ee with the second generation Ru(**1b**) catalyst. Unexpectedly, with further increase of generation to 3, enantioselectivity increased slightly to 91.3% ee. This result indicated that similar catalytically active Ru-complex of Ru(**1c**) was formed under the reaction conditions despite the bulky dendritic substituents. This general trend is true for all other substrates listed in Table 1 (entries 5–20). The profound size effect is probably due to the steric bulk of the dendritic wedges, which are expected to increase the dihedral angle of the two-phenyl rings in the Ru-BIPHEP complex, and thus influence the selectivity of the catalysts. Similar size effects have been observed in the dendritic Ru(BINAP) catalyzed asymmetric hydrogenation of unsaturated carboxylic acids [9] and in the dendritic bisoxazoline-Cu catalyzed diels-alder reactions [8b].

In order to further understand the dendrimer effect on catalytic properties, the molecular geometries of the dendritic ligands were fully optimized by the semi-empirical AM1 (Austin Model 1) Hamiltonian [15] as implemented in the AMPAC quantum chemical package [16]. The calculated dihedral angles of chiral diphosphine ligands are listed in Table 2. As expected, the dendritic ligands **1a**–**1c** had larger dihedral angles than the model ligand **7** as well as BINAP and MeO-BIPHEP [5c]. It has been

Table 2
Calculated dihedral angles of chiral diphosphine ligands

Ligand	(*R*)-**7**	(*R*)-**1a**	(*R*)-**1b**	(*R*)-**1c**
Dihedral angle (°)	88.6	94.2	95.4	116.2

previously demonstrated that the atropoisomeric biaryl phosphine ligands with narrow dihedral angles usually gave high enantioselectivity in the Ru-catalyzed asymmetric hydrogenation of β-ketoester [5]. Therefore, the decrease in enantioselectivity with increased generation of the dendrimer catalyst could be ascribed to the large dihedral angles.

4. Conclusions

In conclusion, a series of dendritic chiral diphosphines with tunable dihedral angles have been synthesized for the first time and used for Ru-catalyzed asymmetric hydrogenation of β-ketoesters. These dendritic catalysts exhibit very good catalytic activities while the enantioselectivities changed dramatically. This result demonstrates that the dihedral angles of BIPHEP-type diphosphine ligands can be fine-tuned through the systematic adjustment of the size of the dendritic wedges, which consequently influence the stereoselectivity of the catalytic reaction. Future work on applications of these dendritic ligands will focus on achieving other transition metal-catalyzed enantioselective reactions where large dihedral angles are needed [17].

Acknowledgements

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