Dendritic BIPHEP: Synthesis and application in asymmetric hydrogenation of \( \beta \)-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 \( \beta \)-ketoesters were investigated. Ruthenium catalysts containing these dendrimer ligands were effective in the hydrogenation of \( \beta \)-ketoesters. It was found that the size of the dendritic wedges influenced the enantioselectivity significantly.

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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 \( \text{C}_2 \) 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 [5]. There are two general strategies for the design and synthesis of new efficient biaryl 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: \( \text{H}_8 \)-BINAP [5b] by Umetzu et al., \( \text{C}_2 \)-TunaPhos [5c] by Zhang et al., segphos [5d] by Saito et al., synphos [5e,5g] by Chan’s and de Gent’s groups, and recently difuorphos [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 1).

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 Frechet-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
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. \((\text{R})-(6,6'\text{-dihydroxybiphenyl-2,2'-dijl-bis(diphenylphosphine)}\) was synthesized according to the published method [5c].

NMR spectra were recorded on a BRUKER Model ADVANCE DPX 300 spectrometer (300 MHz \(^{1}\text{H}\) and 122 MHz \(^{31}\text{P}\)) using tetramethylsilane for \(^{1}\text{H}\) as an internal standard, 85% of \(\text{H}_{2}\text{PO}_{4}\) in D\(_2\text{O}\) for \(^{31}\text{P}\) as an external standard. All signals are reported in ppm unit. MALDI-TOF-MS were recorded on a Bruker Biflex spectrometer with \(\text{cyano-4-hydroxycinnamic acid (CCA)}\) 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 7302 chiral column (30m × 0.25 mm).

2.3. Synthesis of \((\text{R})-(6,6'\text{-dihydroxybiphenyl-2,2'-dijl-bis(diphenylphosphine oxide)}\) \((\text{R})-3\)

To a cool solution of \((\text{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 \((\text{R})-3\) as a white solid (0.95 g, yield 95%). \(^{1}\text{H}\) NMR (300 MHz, DCDCl\(_3\)): \(\delta 7.59–7.53 (m, 4H), 7.47–6.80 (m, 22H), 6.75–6.60 (m, 2H), 3.38 (s, br, 2H)\) HRMS calculated for C\(_{36}\text{H}_{28}\text{O}_{4}\text{P}_{2} 586.1463, found 587.1528 [M + 1]^{+}\).

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

A mixture of \((\text{R})-3 (0.34 mmol, 1.0 equiv), benzyl bromide (0.85 mmol, 2.5 equiv), K\(_2\text{CO}_{3}\) (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 CH₂Cl₂, and the aqueous layer was extracted twice with CH₂Cl₂. The combined organic layer was washed by brine and dried over anhydrous Na₂SO₄. 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; [α]₂⁰ = +48.8 (c 4.6, CH₂Cl₂). ¹H NMR (300 MHz, CDCl₃): 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 C₇₈H₆₄O₈P₂: 1191.8 [M + 1]+. Elemental analysis calculated (%) for C₁₃₄H₁₁₂O₁₆P₂: 2038.7, found 2039.9 [M + 1]+.

Compound (R)-7b: prepared according to the above procedure except that (R)-5b-NBu₃NEt₃-HSCl₂ = 1.5:60:50 (M/M) and the reaction time was 48 h to give (R)-7b as a white solid (90% yield). mp = 83–84 °C; [α]₂⁰ = –13.0 (c 2.0, CHCl₃). ¹H NMR (300 MHz, CDCl₃): δ 7.37–6.87 (m, 64H), 6.66–6.11 (m, 20H), 4.89 (s, 16H), 4.53–4.21 (m, 12H). ³¹P NMR (162 MHz, CDCl₃): δ = –13.22. MALDI-TOF Ms calculated for C₁₃₂H₁₁₀O₂₈ 2006.7, found 2008.5 [M + 1]+. Elemental analysis calculated (%) for C₁₃₂H₁₁₀O₂₈P₂: 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-NBu₃NEt₃-HSCl₂ = 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; [α]₂⁰ = +5.6 (c 2.0, CHCl₃). ¹H NMR (300 MHz, CDCl₃): δ 7.63–7.40 (m, 8H), 7.38–7.10 (m, 54H), 6.95–6.80 (m, 4H), 6.54–6.31 (m, 18H), 4.97–4.47 (m, 28H); MALDI-TOF Ms calculated for C₁₃₄H₁₁₀O₂₈P₂: 2303.4, found 2303.7 [M + 1]+. Elemental analysis calculated (%) for C₁₃₄H₁₁₀O₂₈P₂: 78.78, H 5.53, found: C 78.74, H 5.70.

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)Cl₂]₂ (5 mg, 0.01 mmol) and the dendritic BIPHEP (0.022 mmol). The tube was purged with N₂ 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 vacuum 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 CH₂Cl₂/ethanol (1:1, v/v) solvent. The autoclave was closed and pressurized with hydrogen to 45 atm. The mixture was stirred for 24 h at 60 °C. The autoclave was then cooled to room temperature and the H₂ 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 K₂CO₃ in acetone failed due to the competitive alkylation of diphenylphosphine groups. 2 was then oxidized by reacting with hydrogen peroxide to give phosphate 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) H₂O₂ (35%), CH₃OH, 2 h at r.t.; (b) 4, K₂CO₃, acetone, reflux; (c) NEt₃/NBu₃, HSiCl₃, toluene, reflux; (d) Benzyl bromide, K₂CO₃, acetone, reflux.

These dendritic BIPHEP ligands were characterized by ¹H, ³¹P NMR and mass spectra as well as elemental analyses. In the ³¹P 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)Cl₂]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 CH₂Cl₂-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 H₂ 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...
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(1e) 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).

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.

### References

5. For comprehensive reviews, see:
   (a) L. Pu, Chem. Rev. 98 (1998) 2045;
   (b) M. McCarthy, P.J. Guiry, Tetrahedron 57 (2001) 3809;
   (c) W. Tang, X. Zhang, Chem. Rev. 103 (2003) 3029;
6. (a) R. Noyori, Chemtech (1992) 360;
For recent examples on dendrimer catalysts, see:
(a) C.P. Casey, G.T. Whiteker, V. Mélville, L.M. Petrovich, J.A. Gavney,
(b) T. Umemura, X. Zhang, K. Matsumata, N. Sayo, H. Kumobyashi, T.
6223.
(d) T. Saito, T. Yokozawa, T. Ishizaki, T. Morit, N. Sayo, T. Miura, H.
(f) L. Qiu, J. Qi, C.C. Pai, S. Chan, Y.Z. Zhou, M.C.K. Chei, A.S.C.
(g) S.D. de Paule, S. Jedin, V. Ratovelomanana-Vidal, J.P. Genêt, N.
(i) S. Jedin, S.D. Paule, V. Ratovelomanana-Vidal, J.P. Genêt, N.
(j) L. Qiu, J. Wu, S. Chan, T.T. Au, Y.Q. Ji, B. Guo, C.C. Pai, Z.
(k) Y. Sun, X. Wan, M. Guo, D. Wang, X. Dong, Y. Fan, Z. Zhang,
(p) C. Müller, J.L. Ackerman, J.N.H. Reek, P.C.J. Kamer, R.W.N.M.
(q) M. Oge, M. Murata, T. Mizugaki, K. Ebitani, K. Kaneda, Adv.
(r) Y. Chen, T.F. Wu, L. Jiang, G.D. Hong, H. Liu, J.Y. Zhou, J.
3604.
(w) Y.C. Chen, T.F. Wu, J.G. Deng, H. Liu, Y.Z. Jiang, M.C.K. Choi,
(x) C. Francavilla, M.D. Drake, F.V. Bright, M.R. Dettly, J. Am.
3604.