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A simple and effective soluble polymer-bound ligand for the asymmetric dihydroxylation of olefins: DHQD-PHAL-OPEG-OMe

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Abstract—The synthesis of a novel soluble polymer-bound ligand DHQD-PHAL-OPEG-OMe and its application in the catalytic asymmetric dihydroxylation (AD) reaction are described. 1,4-Dichlorophthalazine was used as the coupling reagent to connect dihydroquinidine and polyethylene glycol monomethyl ether (MW = 5000, Fluka) while providing an aromatic group at the 9-*O*-position of dihydroquinidine. Enantiomeric excesses for *trans*-disubstituted olefins in the AD reaction, with $K_3Fe(CN)_6$ as secondary oxidant, are up to 98%. © 2001 Elsevier Science Ltd. All rights reserved.

The osmium-catalyzed asymmetric dihydroxylation (AD) of olefins provides one of the most efficient methods for the preparation of chiral vicinal diols.[1] However, there are limitations to performing the catalytic AD reaction on a large scale due to the high cost of osmium and chiral ligands. To explore the possibility of the repetitive use of both components, insoluble polymer-supported ligands have been developed by several groups.[2] Despite the advantage of easy separation, the use of insoluble polymer-supported ligands suffered from lowered catalytic activity and enantioselectivity due to the restriction of the polymer matrix, which resulted in limited mobility and accessibility of the active sites and thus obstructed the ligand-accelerated catalytic (LAC) AD reaction.[3,4] To combine the advantages of homogeneous catalysis with the easy separation of a ligand bound to the solid phase, cinchona alkaloid-type ligands were anchored on a soluble polymer, polyethylene glycol monomethyl ether (HO-PEG-OMe), and showed similar activity and selectivity when compared to the corresponding free ligands in the AD reaction of olefins.[2] However, the PEG-bound mono-cinchona alkaloid ligand without an aromatic group at its 9-*O*-position showed low enantioselectivity (even the AD reaction of stilbene gave only 88% ee[3]), and the PEG-bound bis-cinchona alkaloid ligands required complicated synthetic manipulations.[5,6] According to structure–enantioselectivity relationship (SER) studies a bi- or tricyclic planar aromatic group at the 9-*O*-position of the alkaloid is necessary to achieve optimum enantioselectivity in the AD process.[7] Here we report the synthesis of a simple and effective soluble polymer-bound ligand **1**, with 1,4-dichlorophthalazine as the coupling reagent while providing an aromatic group at the 9-*O*-position of dihydroquinidine, and its successful use in the AD reaction of various olefins. We synthesized ligand **1** through two different approaches, both of which include only two steps (Scheme 1).[8] In approach A, the mono-substituted chlorophthalazine **2** was prepared according to the reported method.[5] Then **2** was heated with HO-PEG-OMe (MW = 5000) in dimethylsulfoxide in the presence of NaH to give ligand **1** (**2**/HO-PEG-OMe = 3/1, mol/mol). In approach B, a mixture of HO-PEG-OMe (MW = 5000), 1,4-dichlorophthalazine, KOH and K_2CO_3 in dry toluene was refluxed (1,4-dichlorophthalazine/HO-PEG-OMe = 3/1, mol/mol), with azeotropic removal of water, to give PEG-bound chlorophthalazine **3**. Then **3** was treated with dihydroquinidine in dry toluene (DHQD/**3** = 3/1, mol/mol), with butyllithium as base, to give ligand **1**.

Ligand **1** is completely soluble in a *tert*-butanol/water mixture (v/v = 1/1) allowing homogeneous AD reactions. The AD reaction results for the selected olefins are shown in Table 1. The features can be summarized as follows: (1) Ligand **1** produces considerably higher ees than polyethylene glycol dihydroquinidine glutarate

Keywords: polymer-bound ligand; asymmetric dihydroxylation; 1,4-dichlorophthalazine; dihydroquinidine; polyethylene glycol monomethyl ether.

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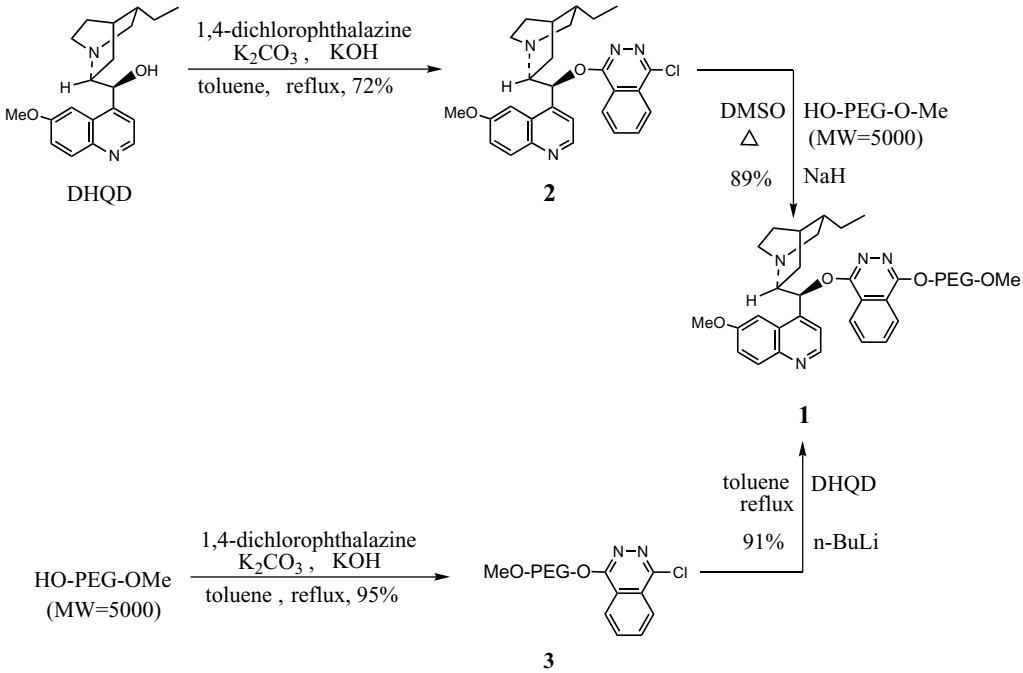
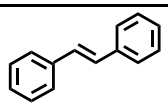
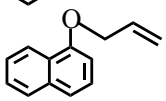
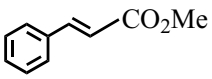
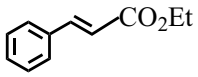


Scheme 1.

Table 1. Catalytic asymmetric dihydroxylation reactions using ligand **1**[a]

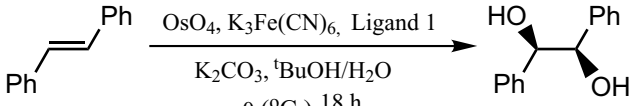
Entry	Olefin	T (°C)	t(h)	Yield(%)	ee(%)[b]
1		0	18	93[c]	98[c] (99[d], 88[e])
2		0	24	87	82 (98[d], 60[e])
3		0	24	89	79 (94[f])
4		0	24	92	90 (91[f])
5		r.t.	30	81	96
6		r.t.	30	83	93 (97[f])

[a]The molar ratio of olefin/OsO_4/ligand = 1/0.004/0.1. [b]The ee values were determined by HPLC analysis of the diols (see Ref. 10 for details). [c]The average value of five runs (see Table 2). [d]Results for a soluble polymer-bound ligand $(DHQD)_2PHAL$-PEG-OMe from Ref. 5. [e]Results for a soluble polymer-bound ligand polyethylene glycol dihydroquinidine glutarate from Ref. 3. [f]Results for a widely used free ligand $(DHQD)_2PHAL$ from Ref. 11.

for the same olefins tested. (2) Ligand **1** delivers much better enantioselectivity for *trans*-disubstituted olefins than for mono- and gem-disubstituted olefins, consistent with that reported for 9-*O*-aryl cinchona alkaloid ligands without a binding pocket.[9] (3) Interestingly, naphthyl allyl ether (entry 4 in Table 1) was transformed into the corresponding chiral diol in a very good yield and high ee, almost comparable to the results obtained with the widely used free ligand $(DHQD)_2PHAL$.[11] (4) When the reaction is finished, the ligand can be extracted with CH_2Cl_2 and precipitated by addition of diethyl ether. More than 95% of the ligand can be recovered by simple filtration. (5) The repeated use of the ligand showed almost unchanged ee values and yields (Table 2).

In conclusion, we have developed a simple and effective soluble polymer-bound ligand for the AD reaction.

Table 2. Reuse of ligand **1**



Run	Yield (%)	Ee (%)
1	92	99
2	94	96
3	90	98
4	93	97
5	94	98

This ether-bound ligand is more stable than ester-bound examples[2] under the standard aqueous basic (pH 12.2) AD reaction conditions with $K_3Fe(CN)_6$ as secondary oxidant. The recovery and repetitive use of the ligand is possible without significant loss of enantioselectivity and activity. Among the two synthetic approaches to ligand **1**, approach B is preferable for its high yield and convenience.

Typical procedure for asymmetric dihydroxylation reactions. $K_3Fe(CN)_6$ (0.980 g, 3.0 mmol), K_2CO_3 (0.410 g, 3.0 mmol), ligand **1** (0.55 g, 0.1 mmol), $K_2OsO_2(OH)_4$ (0.0015 g, 0.004 mmol) were dissolved in *tert*-butyl alcohol and water (5.5 mL of each) at room temperature. For *trans*-disubstituted olefins, $CH_3SO_2NH_2$ (95 mg, 1 mmol) was added. The solution was cooled to 0°C (with the exception of *trans*-methyl cinnamate and *trans*-ethyl cinnamate, see Table 1) and the olefin (1 mmol) was added. The mixture was stirred vigorously at 0°C for 18–24 h. Na_2SO_3 (1.0 g) was added and the mixture was stirred at room temperature for 30 min. CH_2Cl_2 was added to the reaction mixture, and after separation of the layers the aqueous phase was further extracted with CH_2Cl_2 (5 mL×3). If $CH_3SO_2NH_2$ was added, the combined organic layers were washed with 2 M NaOH. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated to about half volume. Diethyl ether (90 mL) was slowly added to the mixture under vigorous stirring conditions. The precipitate obtained was collected on a glass filter, washed with ethanol/diethyl ether, and dried in vacuo. The filtrate was evaporated to give the crude product, which was further purified by chromatography to afford the diol.

Acknowledgements

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8. **2**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.91 (t, J=7.2 Hz, 3H), 1.45–1.70 (m, 6H), 1.77 (m, 1H), 2.06 (m, 1H), 2.70–3.00 (m, 4H), 3.49–3.62 (m, 1H), 4.00 (s, 3H), 7.28 (d, J=7.3 Hz, 1H), 7.35 (dd, J=9.3 and 2.7 Hz, 1H), 7.48 (d, J=4.6 Hz, 1H), 7.64 (d, J=2.7 Hz, 1H), 7.95 (d, J=9.2 Hz, 1H), 7.99 (m, 3H), 8.13–8.21 (m, 1H), 8.33–8.41 (m, 1H), 8.67 (d, J=4.6 Hz, 1H); **3**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.2–3.9 (PEG peaks), 4.83 (s, 2H, -PHAL-O-CH_2-), 7.96 (m, 2H), 8.21 (m, 1H), 8.30 (m, 1H); **1**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.94 (t, J=7.0 Hz, 3H), 1.25–1.76 (m, 7H), 2.14 (m, 1H), 2.66–3.10 (m, 4H), 3.20–3.85 (PEG peaks), 4.00 (s, 3H), 4.82 (s, 2H, -PHAL-O-CH_2-), 7.28 (d, J=7.3 Hz, 1H), 7.35–7.45 (m, 2H), 7.63 (d, J=2.8 Hz, 1H), 7.85–8.00 (m, 3H), 8.16–8.25 (m, 1H), 8.27–8.33 (m, 1H), 8.62 (d, J=4.8 Hz, 1H).
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10. **Entry 1**: Chiralcel OJ, hexane/^{i}PrOH=4/1, flow rate=0.6 mL/min, t_R (min)=12.2 (major), 13.8 (minor); **entry 2**: Chiralcel OB-H, hexane/^{i}PrOH=9/1, flow rate=0.5 mL/min, t_R (min)=13.9 (major), 17.7 (minor); **entry 3**: Chiralcel OD, hexane/^{i}PrOH=40/1, flow rate=1.0 mL/min, t_R (min)=29.9 (major), 32.8 (minor); **entry 4**: Chiralcel OD, hexane/^{i}PrOH=19/1, flow rate=1.0 mL/min, t_R (min)=14.1 (minor), 20.6 (major); **entry 5**: Chiralcel OD, hexane/^{i}PrOH=4/1, flow rate=1.0 mL/min, t_R (min)=15.8 (major), 19.8 (minor); **entry 6**: Chiralcel AD, hexane/^{i}PrOH=9/1, flow rate=1.0 mL/min, t_R(min)=27.5 (major), 30.2 (minor).
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