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A highly efficient and practical new PEG-bound bi-cinchona alkaloid ligand for the catalytic asymmetric aminohydroxylation of alkenes

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Abstract—A new recyclable PEG-bound bi-cinchona alkaloid ligand has been developed for homogeneous catalytic asymmetric aminohydroxylation; it can be easily recovered by precipitation and reused more than five times without any significant loss in its catalytic efficiency.

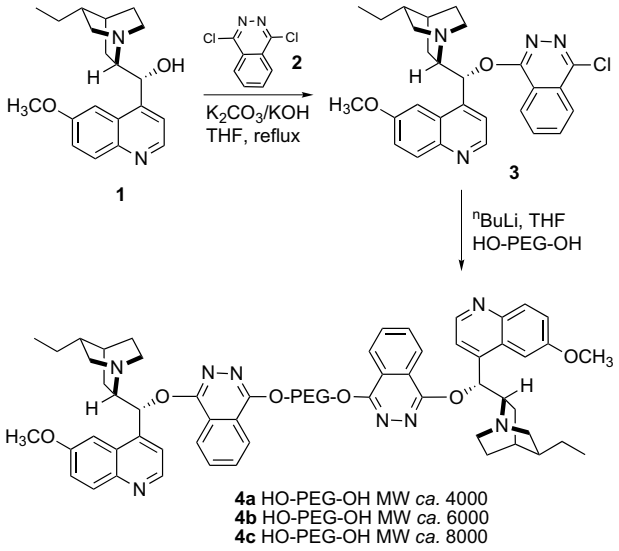
1. Introduction

The Sharpless asymmetric aminohydroxylation (AA) reaction is one of the most efficient methods for the preparation of chiral vicinal aminoalcohols.[1] It offers the advantages of direct addition of the two heteroatom substitutes to an olefin with excellent enantioselectivities in good yields. The catalytic system based on cinchona alkaloids, $K_2OsO_2(OH)_4$ and various nitrogen sources has received a great deal of interest.[1,2] However, the toxicity and high cost of osmium tetroxide and cinchona alkaloids has limited its application on a large scale. To address these drawbacks, efforts have been made for developing immobilized catalysts which may provide an efficient recycling and subsequent reuse.[3] Although the use of solid-supported catalysts in the asymmetric dihydroxylation (AD) has gained much attention,[4] only a few examples of polymer-supported chiral catalysts used in the heterogeneous AA have been reported to date.[5]

Herein, we report our recent development of a novel soluble PEG-bound bi-cinchona alkaloid ligand for the enantioselective AA reaction. To the best of our knowledge, this is the first example of an immobilized chiral catalyst for the homogeneous AA reaction.

2. Results and discussion

Poly(ethylene glycol) (HO–PEG–OH) is very useful as a soluble support for catalyst immobilization.[6] The new PEG-bound bi-cinchona alkaloid ligand **4** was designed to contain two DHQ–PHAL structures linked with PEG (Scheme 1). Unlike other immobilized cinchona alkaloid ligands that contain only one catalytic site, this ligand can have two catalytic sites (DHQ–PHAL) on each



Scheme 1.

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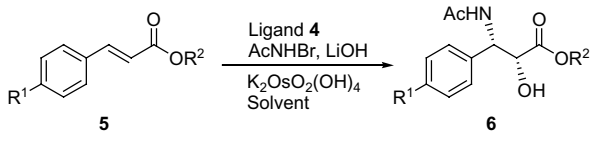
molecule. We envisioned that the introduction of two DHQ–PHAL structures could potentially increase the efficiency of the ligand for asymmetric catalysis. Also, the soluble polymer backbone (PEG) would provide easily accessible reaction sites in solution. Thus, the combination features of more catalytic sites and the higher solubility of this polymer-supported ligand might make it comparable to the corresponding nonimmobilized ligand $(DHQ)_2PHAL$.

The synthesis of the ligand is shown in Scheme 1. The mono-substituted chlorophthalazine **3** was prepared by coupling of dihydroquinine **1** with 1 equiv of 1,4-dichlorophthalazine **2**. The reaction of the obtained *mono*-substituted chlorophthalazine **3** (2.5 equiv) with poly(ethylene glycol) (1 equiv) in THF in the presence of ^{n}BuLi followed by precipitation from ethyl ether afforded **4** as a white solid in good yield. Poly(ethylene glycol) with different molecular weights (MW ca. 4000, 6000, and 8000) was used in the preparation.[7] As we expected, the obtained ligands **4a**, **4b**, and **4c** were all soluble in ^{t}BuOH, acetone and other common organic solvents such as $CHCl_3$ and THF.

We have studied the AA reaction of *trans*-cinnamate derivatives with $K_2OsO_2(OH)_4$ using AcNHBr as the nitrogen source under conventional Sharpless conditions (Scheme 2) with the results summarized in Table 1. The reaction proceeded smoothly with 20 mol% of ligand to afford **6** in good yield and enantioselectivity. Less satisfactory results were obtained with a reduced amount of ligand loading (5 and 10 mol%) (compare entries 5 and 6 with 7). When the reaction was carried out with 10 mol% of ligand, a much lower yield was observed although the enantioselectivity still remained high (entries 6 and 7). In studies on the effects of the R^2 group (R^2 = Me, Et, ^{i}Pr, Bn), *iso*-propyl was found to be the best, leading to greatly improved regioselectivity (>20:1) and enantioselectivity (97%) (entries 1, 2, 7, and 8). To examine the effect of changing the molecular weight of poly(ethylene glycol), we investigated ligands **4a**,**b**, and **4c** in the reaction of **5c**. As shown in entries 3, 4 and 7, similar chemical yields (85–93%) and ees (95–97%) were observed, suggesting that changing the molecular weight of PEG did not have any apparent influence on the asymmetric induction of the reaction.[8] With the optimized conditions, other *iso*-propyl *trans*-cinnamate derivatives containing electron-donating or electron-withdrawing substituents at the *para*-position were successfully employed with very good enantiomeric excesses (91–97%) being achieved (entries 9–11).



a R^1 = H, R^2 = Me
b R^1 = H, R^2 = Et
c R^1 = H, R^2 = ^{i}Pr
d R^1 = H, R^2 = Bn
e R^1 = CH_3, R^2 = ^{i}Pr
f R^1 = OCH_3, R^2 = ^{i}Pr
g R^1 = NO_2, R^2 = ^{i}Pr

Scheme 2.

The polymeric ligand could be easily recovered by simple precipitation (ether), filtration, washing, and drying after the catalytic reaction. To further test the efficiency of the recovered catalyst, we reused it in the aminohydroxylation of *iso*-propyl *trans*-cinnamate with the reaction results summarized in Table 2. As can be seen, the recovered catalyst can be recycled more than five times without any significant loss of its activity. Excellent yields and enantioselectivities were also observed in all five runs under the same reaction conditions. It is interesting to note that excellent enantioselectivities can also be achieved by using a somewhat lower amount (2.8 mol%) of the expensive osmium oxidant in the recycling process; however, the reaction takes a longer time and gives a slightly lower yield. Thus, the C-13 Taxol side chain precursor **6** (R^1 = H) could be prepared in a single step in a large scale with high enantioselectivities and yields but low costs by using the recyclable immobilized bi-cinchona alkaloid ligand **4**.

Table 1. The homogeneous asymmetric AA reaction using PEG-bound bi-cinchona alkaloid ligand **4**[a]

Entry	Substrate	Solvent[b]	Ligand	Time (h)	Yield (%)	Regioselectivity (%)[c]	Ee (%)[d]
1	**5a**	Acetone–H_2O	**4c**	12	75	~10:1	74
2	**5b**	^{t}BuOH–H_2O	**4c**	12	80	>20:1	84
3	**5c**	^{t}BuOH–H_2O	**4a**	12	85	>20:1	97
4	**5c**	^{t}BuOH–H_2O	**4b**	12	90	>20:1	95
5	**5c**	^{t}BuOH–H_2O	**4c**[e]	14	45	>20:1	76
6	**5c**	^{t}BuOH–H_2O	**4c**[f]	14	60	>20:1	98
7	**5c**	^{t}BuOH–H_2O	**4c**	12	93	>20:1	97
8	**5d**	Acetone–H_2O	**4c**	14	85	~10:1	79
9	**5e**	^{t}BuOH–H_2O	**4c**	12	75	>20:1	91
10	**5f**	^{t}BuOH–H_2O	**4c**	12	86	>20:1	99
11	**5g**	^{t}BuOH–H_2O	**4c**	18	65	>20:1	97

[a] $K_2OsO_2(OH)_4$ (4 mol%), polymeric ligand **4** (20 mol%), AcNHBr (1 equiv), and $LiOH{\cdot}H_2O$ (1 equiv) were used unless otherwise noted.
[b] In the cases of substrates **5a** and **5d**, acetone–H_2O was used due to their solubility.
[c] Determined by ^{1}H NMR spectroscopy.
[d] Determined by chiral HPLC analysis on a chiralcel AD column (detected at 254 nm).
[e] Compound **4c** (5 mol%) was used.
[f] Compound **4c** (10 mol%) was used.

Table 2. The asymmetric aminohydroxylation of isopropyl *trans*-cinnamate with recycled PEG-bound bi-cinchona alkaloid ligand **4c** in the homogeneous phase[a]

Run	Time (h)	Yield (%)	Ee (%)[b]
1	15	90	99
2	18	92	99
3	20	91	97
4	18	84	98
5	14	88	95

[a] Reaction performed on a 3.3 mmol (630 mg) scale at 5 °C using 4 mol% of $K_2Os_2O_2(OH)_4$, 20 mol % of polymeric ligand **4c**, AcNHBr (3.3 mmol) and $LiOH{\cdot}H_2O$ (3.3 mmol) in ^{t}BuOH–H_2O (1:1).

[b] Determined by chiral HPLC analysis on a chiralcel AD column (detected at 254 nm; eluent: *n*-hexane/*iso*-propyl alcohol = 80:20 (V/V)).

To compare the catalyst efficiency with that of the known MeO-PEG supported *mono*-DHQ–PHAL[4i], we prepared the MeO-PEG-bound cinchona alkaloid ligand and investigated its use in the AA reaction of *iso*-propyl *trans*-cinnamate under the same conditions. In the similar five runs, the corresponding enantiomeric excesses of 97%, 92%, 92%, 85%, and 70% were observed, respectively. These results suggested better catalyst efficiency of our PEG-bound bi-cinchona alkaloid ligand in this reaction.

3. Conclusion

In summary, we have developed an efficient and practical new PEG-bound bi-cinchona alkaloid ligand and demonstrated its successful application in the homogeneous asymmetric aminohydroxylation of *trans*-cinnamate derivatives. The immobilized soluble catalyst can be readily prepared and easily recovered after the reaction. In addition, the recovered catalyst could be further reused more than five times without any significant loss of its activity. This has greatly improved the possibility of the potential use of this AA reaction in industry in near future.

4. Experimental

4.1. Preparation of mono-substituted chlorophthalazine 3[4f,j]

Under nitrogen, to a 250 mL flame-dried three-necked round bottom flask was added dihydroquinine (3.26 g, 10 mmol), 1,4-dichlorophthalazine (2.00 g, 15 mmol), K_2CO_3 (4.14 g, 30 mmol), and freshly distilled THF (50 mL). After the reaction was refluxed for 5 h, KOH (0.58 g, 10 mmol) was added and the mixture refluxed for another 18 h. The reaction was cooled to room temperature and diluted with water (50 mL) and CH_2Cl_2 (100 mL). The organic layer was separated and the water layer extracted with CH_2Cl_2 (30 mL × 3). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The crude product was purified by chromatography on silica gel (petroleum/ethyl acetate/methanol 8:2:1) to give pure **3** as a white solid (3.58 g, 73%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.87 (t, $J = 7.2$ Hz, 3H), 1.25–1.60 (m, 5H), 1.77–1.93 (m, 4H), 2.46 (m, 1H), 2.73 (m, 1H), 3.13 (m, 1H), 3.32 (m, 1H), 3.57 (m, 1H), 4.02 (s, 3H), 7.37 (dd, $J_1 = 2.7$ Hz, $J_2 = 8.7$ Hz, 1H), 7.44 (d, $J = 4.5$ Hz, 1H), 7.66 (d, $J = 2.4$ Hz, 1H), 7.98–8.04 (m, 3H), 8.19–8.22 (m, 1H), 8.39–8.42 (m, 1H), 8.65 (d, $J = 4.5$ Hz, 1H); EIMS (*m*/*z*, %): 488 (M^+), 309 (100%).

4.2. Preparation of new PEG-bound bi-cinchona alkaloid ligand 4

Under nitrogen, to a solution of poly(ethylene glycol) (2 mmol, MW ca. 4000, 6000, or 8000) in freshly distilled THF (50 mL) in a 100 mL flame-dried three necked flask at 0 °C was added ^{n}BuLi (2.4 mL, 2.5 M in hexane). After the addition, the mixture was allowed to warm to room temperature and stirred for 1 h. *Mono*-substituted chlorophthalazine **3** (2.44 g, 5.0 mmol) was then added and the reaction mixture heated to reflux for 18 h. After cooling to room temperature, water (10 mL) was carefully added to the reaction. The organic layer was separated and the water layer extracted with CH_2Cl_2 (30 mL × 3). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was dissolved with the minimum amount of CH_2Cl_2 and diethyl ether (200 mL) then added. The obtained precipitate was collected by filtration and washed with cold diethyl ether/ethanol (3:1) several times. These dissolution and precipitation procedures were repeated two more times to give ligand **4** as a white solid (ca. 68–75% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.85 (t, $J = 7.3$ Hz, 6H), 1.25–1.80 (m, 14H), 2.17 (s, 2H), 2.43 (m, 2H), 2.67 (m, 2H), 2.87 (m, 2H), 3.12 (m, 2H), 3.30–3.90 (PEG peaks), 4.00 (s, 6H), 4.67 (m, 4H, DHQ–PHAL–OCH_2–), 7.18 (s, 2H), 7.34–7.48 (m, 4H), 7.62 (s, 2H), 7.86–7.94 (m, 4H), 7.99 (d, $J = 9.2$ Hz, 2H), 8.19 (d, $J = 7.7$ Hz, 2H), 8.33 (d, $J = 7.9$ Hz, 2H), 8.63 (d, $J = 4.3$ Hz, 2H). GPC analysis for ligand **4a** (PEG MW ca. 4000): Mn 4575, Mw 4739, Mp 4911, PDI 1.04.

4.3. General procedure of the homogeneous asymmetric AA reaction using PEG-bound bi-cinchona alkaloid ligand 4

To a 50 mL flask charged with 5 mL of aqueous solution of $LiOH{\cdot}H_2O$ (42.8 mg, 1.0 mmol) was added $K_2OsO_2(OH)_4$ (14.7 mg, 0.04 mmol, 4 mol %). The mixture was stirred for 30 min to dissolve; ^{t}BuOH (10 mL) and ligand **4** (20 mol %) were then added. The resulting mixture was stirred for 30–40 min at room temperature to give a clear solution. Water (5 mL) was subsequently added and the reaction cooled to 5 °C; *trans*-cinnamate derivatives (1.0 mmol) was added followed by the addition of fresh AcNHBr (158 mg, 1.0 mmol) in one portion. The reaction was stirred at 5 °C and monitored by TLC. After completion, the reaction mixture was treated with Na_2SO_3 (0.5 g) and stirred for 30 min at room temperature after which CH_2Cl_2 was added. The organic layer was separated and the water layer extracted with CH_2Cl_2 for three times. The combined organic extracts were washed with brine and dried over Na_2SO_4. After

evaporation of the solvent, the residue was dissolved with the minimum amount of CH_2Cl_2; diethyl ether (~100 mL) was added to precipitate the immobilized catalyst. The obtained precipitate was collected by filtration and washed with diethyl ether several times. After drying under vacuum, the obtained solid could be reused in subsequent reactions (more than 90% of the ligand can be recovered). The filtrate was concentrated and purified by chromatography on silica gel (petroleum/ethyl acetate 1:1) to give the product.

4.4. Determination of the enantiomeric excess

The enantiomeric excess was determined by HPLC analysis using a chiralcel AD column with *n*-hexane/*iso*-propyl alcohol (80:20 or 90:10) as eluent (flow rate 1.0 mL/min, UV detected at 254 nm). Racemic products were prepared for comparison.

Acknowledgements

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8. Based on the availability of the different molecular weights of poly(ethylene glycol) in our lab, ligand **4c** prepared from PEG_{8000} was the most commonly used in this study.