A highly efficient and recoverable bi-cinchona alkaloid ligand for the catalytic asymmetric aminohydroxylation of olefins

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Abstract: A new freely recyclable bi-cinchona alkaloid ligand has been developed for the homogeneous catalytic asymmetric aminohydroxylation (AA) of olefins. It can be easily recovered by precipitation and reused for 5 times without any significant loss in its catalytic efficiency in AA reactions.

Keywords: asymmetric aminohydroxylation, recoverable and reusable ligand, bi-cinchona alkaloid.

INTRODUCTION

The Sharpless asymmetric aminohydroxylation (AA) reaction of olefins has rapidly become a very elegant method in the organic synthesis.1 It gives the possibility of enantioselectively introducing a 1,2-amino alcohol functionality, which is most important for the construction of biologically active compounds and chiral ligands from readily available alkenes.2 In spite of its great value in synthesis, the high cost of osmium and the ligands restrict its large-scale use in industry. Several attempts have been made to explore the possibility of recoverable and reusable ligands. One possible solution is to anchor the ligand on an insoluble polymer.3 Despite the advantage of easy separation, the use of insoluble polymer-supported ligands suffered from lowered catalytic activity and enantioselectivity.4 To combine the superiority of homogeneous catalysis with the easy separation of a ligand bound to a solid phase, cinchona alkaloid-type ligands were attached to PEG, a soluble polymer.5 However, for most of the reported PEG-bound cinchona alkaloid-derived ligands, the required mole ratio of ligand/olefin in AA reaction was high, up to 0.2:1, which was much more than that for the Sharpless free ligands, 1,4-bis(9-O-dihydroquinidinyl)phthalazine [(DHQD)_2PHAL] or 1,4-bis(9-O-dihydroquininyl)phthalazine [(DHQ)_2PHAL] (0.05:1).6 Hence, it is necessary to se-

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arch for an ideal ligand than cannot only be easily prepared but also be recovered and reused for several runs without any loss in its high catalytic activity.

In 2004 AA reactions of several olefins catalyzed by 1,4-bis(9-O-quininy1)phthalazine ([(QN)2PHAL] (A) were reported.7 Despite the fact that A was more economically preparable and offered a high level of activity and enantioselectivity, it was still difficult to recover. In order to improve the recyclability of the ligand, a highly polar residue was introduced into A and the recoverable ligand C was thus obtained (Scheme 1). On completion of the catalytic reaction, the product and ligand C could be extracted with CH2Cl2. Then C was recovered by precipitation with diethyl ether. The preparation of ligand C and its successful application in the AA reaction of olefins, is reported herein.

EXPERIMENTAL

1H and 13C-NMR spectra were recorded on a Bruker AV-400 spectrometer, with CDCl3 as the solvent. MS was performed on a Bruker APEX2 instrument. High preformance liquid chromatography (HPLC) was performed using an Agilent 1100 system interfaced to a HP 71 series computer workstation with a Daicel Chiracel OD-H, AD chiral column. Optical rotations were measured on a Perkin-Elmer 343 polarimeter. A was prepared according to published methods.8 All other solvents and chemicals were obtained from commercial sources and were used without further purification unless otherwise stated.

Scheme 1. The synthesis of ligand C.

The procedure for the preparation of B

A 100 mL three-necked round-bottom flask was charged with A (3.1 g, 4.0 mmol), 2,2'-azobisisobutyronitrile (AIBN) (0.26 g, 1.6 mmol), 2-mercaptoethanol (0.3 mL 4.2 mmol) and CHCl3 (20 mL) under nitrogen. The mixture was refluxed for 36 h, and then cooled to room temperature. H2O (20 mL) was added and the mixture was extracted with CHCl3 (3 × 30 mL). The combined organic layers were dried over anhydrous MgSO4 and concentrated under vacuum. The residue was purified by flash column chromatography (MeOH/Et2N, 5:1) to give B as a white solid (50 % yield). M.p. 126.5–8°C; 1H-NMR (400 MHz, CDCl3); δ 8.63 (2H, d, J = 3.6 Hz), 8.32 (2H, s), 8.00 (4H, d, J = 7.2Hz), 7.59 (2H, d, J = 2.0 Hz), 7.41 (2H, d, J = 4.8 Hz), 7.38 (1H, d, J = 8.8 Hz), 7.36 (1H, d, J = 9.2 Hz), 7.04 (2H, s), 5.02 (2H, d, J = 15.6 Hz), 3.92 (6H, s), 3.69 (2H, s), 3.49 (4H, s), 3.10 (4H, m), 2.46–2.70 (8H, m), 1.21–1.60 (14H, m). 13C-NMR (100 MHz, CDCl3); δ 157.76, 156.37, 147.33, 144.66, 141.84, 132.39, 131.53, 127.20, 122.80, 122.46, 121.96, 118.44, 114.42, 101.94, 60.22, 59.98, 58.01, 56.72, 55.77, 42.67, 41.19, 39.81, 35.32, 34.77, 29.67, 28.31, 27.85, 27.72,
The procedure for the preparation of the ligand C

B (1.7 g, 20 mmol), N-methylmorpholine (NMO) (0.7 g, 6 mmol), 20 ml THF and 8 ml t-BuOH were charged into a flask. A solution of OsO₄ in toluene (0.24 mL, 0.094 mmol) was added dropwise. The reaction mixture was stirred for 12 h at room temperature. Then NaHSO₃ (6 g) was added and the mixture was further stirred for 2 h. The mixture was then filtered. The filtrate was dried over anhydrous MgSO₄ and concentrated under vacuum. The residue was purified by flash column chromatography (MeOH/Et₃N, 5:1) to afford 1.32 g of C as a white solid (70 % yield). M.p. 164.5–6 °C; 1H-NMR (400 MHz, CDCl₃): δ 8.62 (2H, d, J = 4.4 Hz), 8.32 (2H, s), 7.97 (4H, d, J = 8.8 Hz), 7.57 (2H, s), 7.43 (2H, d, J = 4.4 Hz), 7.36 (2H, d, J = 8.8 Hz), 6.99 (2H, d, J = 6.0 Hz), 4.06 (4H, d, J = 5.2 Hz), 3.90 (6H, s), 3.47 (2H, m), 3.12 (4H, d, J = 4.4 Hz), 3.03 (4H, m), 2.80 (1H, d, J = 5.6 Hz), 2.71 (1H, m), 2.5 (2H, d, J = 12.8 Hz), 2.3 (2H, d, J = 12.8 Hz), 1.84–1.77 (16H, m); 13C-NMR (100 MHz, CDCl₃): δ 158.03, 157.79, 156.58, 155.59, 146.89, 146.69, 144.33, 144.08, 132.61, 132.29, 131.25, 131.06, 127.16, 126.06, 124.54, 121.95, 121.26, 117.44, 101.68, 101.42, 62.56, 58.75, 56.36, 55.58, 55.32, 55.12, 52.31, 52.04, 45.44, 42.53, 41.25, 40.19, 39.91, 39.64, 39.36, 39.08, 32.53, 29.21, 25.46, 24.84. HRMS (ESI): calcd. for C₅₀H₆₀N₆O₉S + H: 919.4059, found 919.4048.

Typical procedure for the asymmetric aminohydroxylation

A solution of benzyloxycarbonyl carbamate (0.469 g, 3.1 mmol) in n-PrOH (4 mL) was sequentially treated with 1.6 % (w/v) NaOH solution (7.5 mL) and freshly prepared t-BuOCl (0.35 mL, 3.05 mmol). After stirring for 5 min at room temperature (with the exception of 2-naphthol, entry 3 in Table I), K₂OsO₂(OH)₄ (0.0147 g, 0.04 mmol), olefin (1.0 mmol) and ligand C (0.0459 g, 0.05 mmol) in 3.5 mL of n-PrOH were added. The reaction mixture was stirred for 5–7 h, and then cooled at 0 °C. A saturated Na₂SO₃ solution (20 mL) was added to the mixture under stirring, which was continued for 15 min. The resulting mixture was extracted with CH₂Cl₂ (3 x 15 mL) and the combined organic layers were dried over anhydrous MgSO₄. After removal of the solvent, the residue was dissolved in CH₂Cl₂ (3 mL) and dry Et₂O (30 mL) was slowly added to the solution under vigorous stirring. The precipitate was collected by filtration, washed with cool Et₂O and dried under vacuum. The recovered ligand C was reused for the next reaction. Simultaneously, the filtrate was evaporated to give the crude product, which was further purified by column chromatography to afford the pure β-amino alcohol. A similar work-up was repeated four times with the recovered ligand being used. Each time, the amount of K₂OsO₂(OH)₄ needed was only 80 % of the first run.

RESULTS AND DISCUSSION

The ligand C can be easily synthesized from (QN)₂PHAL in two steps (Scheme 1). In order to obtain high yields of B, a suitable mole ratio of (QN)₂PHAL and 2-mercaptoethanol was crucial. It must be controlled to 1:1.05. Thereafter, the dihydroxylation of B can give the desired ligand C under the appropriate conditions. Both the intermediate B and the goal product C were novel compounds.

To test the catalytic activity of ligand C, the AA reactions of several olefins were studied using N-chlorocarbamate as the nitrogen source under conventional Sharpless conditions. All the reactions proceeded smoothly with 5 % of ligand C and provided the corresponding β-amino alcohol in moderate yields and high e.e.s. In particular, in addition to the wide scope of the substrate, which ranged from styrene to trans-cinnamate, the observed regioselectivity and enantioselectivity were all excellent. The results were summarized in Table I.

The recycling experiment of the AA reaction was conducted with styrene as the substrate. As expected, the ligand C could be easily recovered by simple pre-
cipitation on addition of diethyl ether. The result is shown in Table II. It is noteworthy that the mole ratio of ligand/olefin in this catalytic system was only 0.05:1, which is far lower than that of the PEG-bound cinchona alkaloid-derived ligands (0.2:1) \(^5\) and the insoluble polymer-supported ligand (0.1:1) \(^4\). After five cycles, the ligand C still kept its catalytic activity and enatioselectivity.

In the recycling reaction, 20 % osmium was also recovered because of its complexing with the ligand C, although leaching of the osmium was inevitable.

### TABLE I. Catalytic asymmetric aminohydroxylation of olefins with the ligand C\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Olefin</th>
<th>(t/\text{°C})</th>
<th>(t/\text{h})</th>
<th>Regioselectivity (\text{a:b})</th>
<th>Yield(^b)/%</th>
<th>e.e./%(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Olefin 1" /></td>
<td>r.t.</td>
<td>5</td>
<td>&gt;20:1</td>
<td>52</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2" alt="Olefin 2" /></td>
<td>r.t.</td>
<td>5</td>
<td>&gt;20:1</td>
<td>62</td>
<td>96</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3" alt="Olefin 3" /></td>
<td>0</td>
<td>6</td>
<td>&gt;20:1</td>
<td>63</td>
<td>98</td>
</tr>
<tr>
<td>4</td>
<td><img src="image4" alt="Olefin 4" /></td>
<td>r.t.</td>
<td>7</td>
<td>&gt;20:1</td>
<td>53</td>
<td>96</td>
</tr>
<tr>
<td>5</td>
<td><img src="image5" alt="Olefin 5" /></td>
<td>r.t.</td>
<td>6</td>
<td>&gt;20:1</td>
<td>48</td>
<td>98</td>
</tr>
</tbody>
</table>

\(^a\)All reactions were carried out with 1 mmol olefin, 4 mmol % \(\text{K}_2\text{OsO}_2(\text{OH})_4\) and 5 mmol % of ligand C in \(n\)-PrOH–H\(_2\)O (1:1) at 25 \(\text{°C}\), except entry 3 at 0 \(\text{°C}\). \(^b\)Isolated yield. \(^c\)The e.e. values were determined by HPLC analysis.

### TABLE II. Recovery and reuse of ligand C in the AA reactions of styrene\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Yield(^b)/%</th>
<th>e.e./%(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Run 1</td>
<td>48</td>
<td>93</td>
</tr>
<tr>
<td>Run 2</td>
<td>55</td>
<td>92</td>
</tr>
<tr>
<td>Run 3</td>
<td>54</td>
<td>95</td>
</tr>
<tr>
<td>Run 4</td>
<td>50</td>
<td>93</td>
</tr>
<tr>
<td>Run 5</td>
<td>52</td>
<td>94</td>
</tr>
</tbody>
</table>

\(^a\)Recycle experiments were conducted at room temperature in \(n\)-PrOH–H\(_2\)O (1:1); the mole ratio of olefin/ligand/\(\text{K}_2\text{OsO}_2(\text{OH})_4\) was 1/0.05/0.04. \(^b\)Isolated yield. \(^c\)Determined by chiral HPLC analysis.

### CONCLUSION

In summary, a novel, efficient and practical free bi-cinchona alkaloid ligand was synthesized by a simple procedure. This ligand in a low amount (5 mol %) exhibited good asymmetric induction and recyclability in homogeneous AA reactions. With styrene as substrate, C could be recovered and reused five times with-
out significant loss of catalytic activity and enantioselectivity. Moreover, when this ligand was applied in the sister reaction to AA, i.e., asymmetric dihydroxylation (AD), good results were also obtained. It is hoped that the utilization of the recoverable and reusable free ligand C in AA reactions might open up new perspectives for research on the AA system.

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REFERENCES