A Practical and Simple Method of Recycling Catalyst in Asymmetric Aminohydroxylation of Olefins

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Received November 25, 2005

Key Words : Monomeric cinchona alkaloid ligand, Asymmetric aminohydroxylation, Recycle, Chiral β-aminoalcohol

The Os-catalyzed asymmetric aminohydroxylation (AA) of olefins provides a straightforward method for the enantioselective synthesis of a wide variety of protected vicinal aminoalcohols.1-4 The resulting chiral β-aminoalcohols group is the most abundant structural element in many biologically active molecules as well as the starting point in the design of many chiral ligands.5-7 Although AA reaction servers as a powerful method for the synthesis of a variety of products, its application has still been limited because of the high cost of osmium and chiral ligand. In order to explore the possibility of the repetitive use of ligand and/or osmium, several attempts to immobilize this catalytic system have been made. Nandan group8 prepared highly crosslinked copolymers between ethylene glycol dimethacrylate (90 mol%) and a bis(quininyl)pyridazine derivative (10 mol%). This insoluble ligand was then used in AA reaction of various olefins in 52-65% yields and 34-54% ees. Up to now, many insoluble polymer-supported ligands have been successfully reused in AA reaction.8-11 Yang first reported an immobilized soluble PEG-bound bis-cinchona alkaloid ligand which could be recovered and reused in homogeneous AA reactions. Excellent yields and ees were obtained in homogeneous system.12 In most reported recycling methods, osmium component was hardly recovered and sometimes synthesis route of the polymer-supported ligands were complicated. Here we report a recyclable monomeric ligand 1 and its application in homogeneous AA reaction. In addition, poly(ethylene glycol) (PEG, MW 400) linked with the special encapsulating effect on osmium was successfully applied in AD reaction.13 Enlightened by this, we applied PEG in AA reaction for the recovery of osmium and achieved an amazing result that about 50% amount of osmium component could be efficiently recycled through very simple method.

Results and Discussion

According to the similar synthesis method,14 ligand 1 was prepared by simple three-step reaction (Scheme 1). 3,6-Dichloropyridazine reacted with quinine in presence of NaH in DMF to give compound 2 (80% yield), which was heated with 2-mercaptoethanol in the presence of 2,2'-azobisisobutyronitrile (AIBN) in CHCl3 to give the sulfide 3 (66% yield). Compound 3 was then oxidized to the desired sulfone 1 using a mixture of OsO4/N-methylmorpholine N-oxide (NMO) in THF/t-BuOH (3:1) at room temperature (79% yield).

Ligand 1 was applied in the homogeneous AA reactions under conventional Sharpless conditions using benzoyloxycarbonyl carbamate as the oxidant-nitrogen source. The results were summarized in Table 1.

As can be seen from Table 1, all of the six selected olefins

![Scheme 1. The synthesis route of ligand 1.](image-url)
were transformed to β-aminoalcohols in moderate yields. Lindig 1 delivered excellent enantioselectivity for the reaction of trans-cinnamate (Table 1, entries 4 and 5).

Just like the soluble polymer-supported ligands, the monomeric ligand 1 was completely insoluble in diethyl ether and could be recovered in 80% according to the reported recycling method. But the osmium was lost. Therefore, we developed a new approach to immobilize osmium by utilizing the encapsulation ability of PEG. Then we investigated the effect of PEG and different amount of PEG on the reactivity and immobilization. Five AA reactions were performed on a 1 mmol scale with addition of 1.0-2.0 mL PEG in reaction medium. The results in Table 3 showed that no significant decrease in activity and enantioselectivity was observed within the first four recycles using the forementioned recycle method.

In summary, we have prepared recoverable ligand 1 by simple synthesis with cheap starting materials and applied this monomeric ligand in the homogeneous asymmetric aminohydroxylation. With addition of PEG in reaction medium, the monomeric ligand and half amount of osmium can be easily recycled for at least four times without significant decrease of its activity and enantioselectivity. In addition, the Cbz-protected group is easily cleaved by one-step catalytic hydrogenation reaction in presence of 10%Pd/C and H2 to give the free aminoalcohols. It may improve the possibility of utilizing AA reaction to prepare aminoalcohols in scale.

![Diagram of AA reaction of iso-Propyl trans-cinnamate using ligand 1 and OsO4 in PEG](Image)

### Table 2. The effects of the amounts of PEG on the reactivity and immobilization ability

<table>
<thead>
<tr>
<th>Amount of PEG (mL)</th>
<th>Yield (A+B) (%)</th>
<th>%ee (A)</th>
<th>Immobilized Os (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>70</td>
<td>96</td>
<td>9.5</td>
</tr>
<tr>
<td>1.0</td>
<td>67</td>
<td>95</td>
<td>43.2</td>
</tr>
<tr>
<td>1.5</td>
<td>68</td>
<td>95</td>
<td>49.7</td>
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<td>2.0</td>
<td>65</td>
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<td>50.3</td>
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<tr>
<td>2.5</td>
<td>61</td>
<td>93</td>
<td>50.1</td>
</tr>
</tbody>
</table>

*The reactions were carried out on a 1 mmol scale with addition of different amount of PEG. *Isolated yields by column chromatograph. *Determined by chiral HPLC analysis. *Determined by ICP-AES analysis.

### Table 3. AA reaction of iso-Propyl trans-cinnamate reusing ligand 1 and OsO4 in PEG

<table>
<thead>
<tr>
<th>Entry</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yield (A+B) (%)</td>
<td>70</td>
<td>67</td>
<td>71</td>
<td>69</td>
<td>63</td>
<td>57</td>
</tr>
<tr>
<td>%ee (A)</td>
<td>96</td>
<td>93</td>
<td>96</td>
<td>97</td>
<td>98</td>
<td>94</td>
</tr>
</tbody>
</table>

*Recycle experiments were carried out on a 1 mmol reaction scale of olefin using 10 mmol% of ligand 1 and 2 mmol% of K2OsO2(OH)4 (4 mmol in the first run). *Isolated yields by column chromatograph. *Determined by chiral HPLC analysis.
Experimental Section

NMR spectra were recorded on a Bruker AV-400 spectrometer. High performance liquid chromatography (HPLC) was performed by Agilent 1100 interfaced to a HP 71 series computer workstation with Daicel Chiralcel OD-H, AD chiral column.

Preparation of compound 2. Under nitrogen, a 100 mL three-necked flask was charged with quinine (5.2 g, 16.0 mmol), 3,6-dichloropyridazine (1.20 g, 8.0 mmol), NaH (1.9 g, 80 mmol) and distilled DMF (30 mL). The mixture was stirred at 60 °C until TLC indicated that quinine had disappeared. The mixture was cooled to room temperature, filtered and concentrated. The residue was recrystallized with ethyl acetate to give white powder (4.46 g, 80% yield). m.p. 123-125 °C; IR (cm⁻¹): 3418.83, 3073.40, 2934.51, 2865.66, 1621.41, 1509.83, 1434.68, 1261.53, 1027.94, 991.66. 1H NMR (400 MHz, CDCl3): δ 1.50-1.81 (m, 10H), 2.21-2.26 (m, 4H, ArH), 2.57-2.64 (m, 4H, NCH2), 3.02-3.09 (m, 4H, NCH2), 3.12-3.19 (m, 4H, ArH), 3.63-3.66 (m, 4H, ArH), 4.80 (s, 2H, CH), 7.00 (s, 2H, ArH), 7.19-7.22 (m, 2H, ArH), 7.26 (s, 2H, ArH), 7.30 (s, 2H, ArH), 7.34-7.36 (m, 2H, ArH), 7.40 (s, 2H, ArH), 7.41-7.43 (m, 2H, ArH), 7.45 (s, 2H, ArH). 13C NMR (100 MHz, CDCl3): δ 56.42, 55.77, 42.56, 39.60, 27.57, 23.59, 16.96.

Preparation of compound 3. A solution of compound 2 (3.63 g, 5.0 mmol), 2-mercaptetanol (3.63 g, 50 mmol), and distilled DMF (30 mL) was prepared and consequently refluxed for 12 h. Then the reaction liquid was washed with brine (20 mL × 2), dried over anhydrous MgSO4 and evaporated to give crude product, which was further purified by column chromatography (hexen/EtOAc, 4:1) to provide protected aminoalcohol. Then benzyloxycarbonyl carbamate (469 mg, 3.05 mmol) was added to regenerate the reaction conditions. After stirring for 5 min at room temperature, a solution of ligand 1 (80 mg, 0.1 mmol in 3.5 mL of n-PrOH) and iso-Propropyl trans-cinnamate (190 mg, 1.0 mmol) was added followed by K2OsO2(OH)4 (14.7 mg, 0.04 mmol) and PEG-400 (1.5 mL). The reaction mixture was stirred until starting material disappeared by TLC analysis. n-PrOH was then removed under reduced pressure and the water layer was extracted with Et2O (20 mL × 2). Either layer was dried over anhydrous MgSO4 and evaporated to give the crude product, which was purified by silica gel chromatography (hexen/EtOAc, 4:1) to provide protected β-aminoalcohol. Then benzoyloxycarbonyl carbamate (469 mg, 3.1 mmol in n-PrOH (7 mL), the proper amount of NaOH (approximately 60 mg, pH = 11), t-butylhydroperoxide (0.35 mL, 3.05 mmol) and K2OsO2(OH)4 (7 mg, 0.02 mmol) were added to regenerate the reaction conditions. iso-Propropyl trans-cinnamate (190 mg, 1.0 mmol) was then added. Similar work-up and purification was repeated for 5 times.

Acknowledgments. We thank the National Natural Science Foundation of China (NSFC) for financial support (Nos.: 20272082, 20572131).

References