# Asymmetric Synthesis of (*S*)-metoprolol *via* Sharpless Asymmetric Dihydroxylation Induced by A Recoverable Polymer Ligand QN-AQN-OPEG-OMe

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**Abstract:** The catalytic asymmetric dihydroxylation (AD) discovered by Sharpless, a Nobel Prize winner in 2001, has rapidly become an invaluable synthetic tool in the possibility of converting prochiral olefins to chiral vicinal diols. After our long-running investigation of optimized methodology for the production of stereo-defined diols based on the AD reaction, an efficient and environmentally friendly approach for the synthesis of (*S*)-metoprolol *via* AD reaction was reported. The synthetic route proceeded in four-step reactions of nucleophilic substitution, AD reaction, cyclization, and nucleophilic ring opening. The key step, AD reaction, proceeded effectively in homogeneous catalysis by using a soluble polymer chiral ligand QN-AQN-OPEG-OMe, which can be easily separated from the reaction system and reused at least four times while maintaining its high catalytic activity and enantioselectivity. This protocol has been demonstrated to produce kilogram quantities of (*S*)-metoprolol on scale.

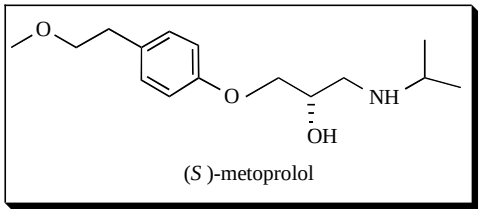
**Keywords:** Asymmetric dihydroxylation, asymmetric synthesis, polymer ligand, recoverable, (*S*)-metoprolol.

## INTRODUCTION

Stereoselectivity is an important factor in pharmacology [1]. In the past the pharmacopoeia was dominated by racemates, but since the 1980s advanced synthesis techniques have allowed the preparation of pure enantiomers in significant quantities. Presently, chiral drugs are currently in high demand, therefore, advances have been remarkable in chiral molecule preparation and isolation, including resolution techniques, biological processes, and biocatalysis, beginning from a chiral pool and proceeding through catalytic asymmetric synthesis.

Beta-adrenergic blocking agents are administered for the treatment of cardiovascular diseases (e.g. angina, hypertension, and heart failure), and are also prescribed to manage childhood and adolescent disorders including dysrhythmias, behavioral disorders, migraine headaches, and anxiety [2]. As a selective beta-blocker, metoprolol is an effective one in clinical treatment. The biological activity of (*S*)-metoprolol (Scheme **1**) is much higher than that of the corresponding enantiomer. Enantiomers of metoprolol are usually prepared from a chiral pool [3-5]. The catalytic asymmetric syntheses of metoprolol by using a La-Li-BINOL complex or 1,4-bis(9-O-quinidinyl)phthalazine catalyst have been reported, but both of the chiral ligands could not be recovered [6, 7].

The development of new ligands for use as chiral catalysts has resulted in products with steadily increasing enantiomeric purity in the catalytic asymmetric synthesis. Novel




(*S* )-metoprolol

**Scheme 1.** Chemical structures of (*S*)-metoprolol.

techniques for recovering chiral catalysts from the product mixture are also being rapidly developed [8, 9]. From a viewpoint of efficiency in organic synthesis, polymer-supported chiral catalysts are extremely useful to asymmetric reaction mainly due to they can be easily separated from the reaction mixture and reused [10-13]. In addition, because homogeneous catalyst has been found to be more efficient in asymmetric synthesis than the heterogeneous one, the immobilization of homogeneous reagents and catalysts is of great interest. The soluble polymer polyethylene glycol monomethyl ether (HO-PEGOMe) was used for bounding chiral ligand to promote homogeneous catalysis [14-17]. Therefore, a combination of the two methodologies would provide a useful tool for efficient asymmetric synthesis of metoprolol.

Our group has carried out in a long-running investigation of optimized methodology for the production of stereo-defined diols and $\beta$-amino alcohols based on the AD reaction [18]. During this study, we observed that up to 99% ee chiral vicinal diols were obtained by the AD reaction in the presence of a soluble polymer-anchored cinchona alkaloid ligand QN-AQN-OPEG-OMe. After the AD reaction, this ligand was recovered by simple filtration and reused in four succes-

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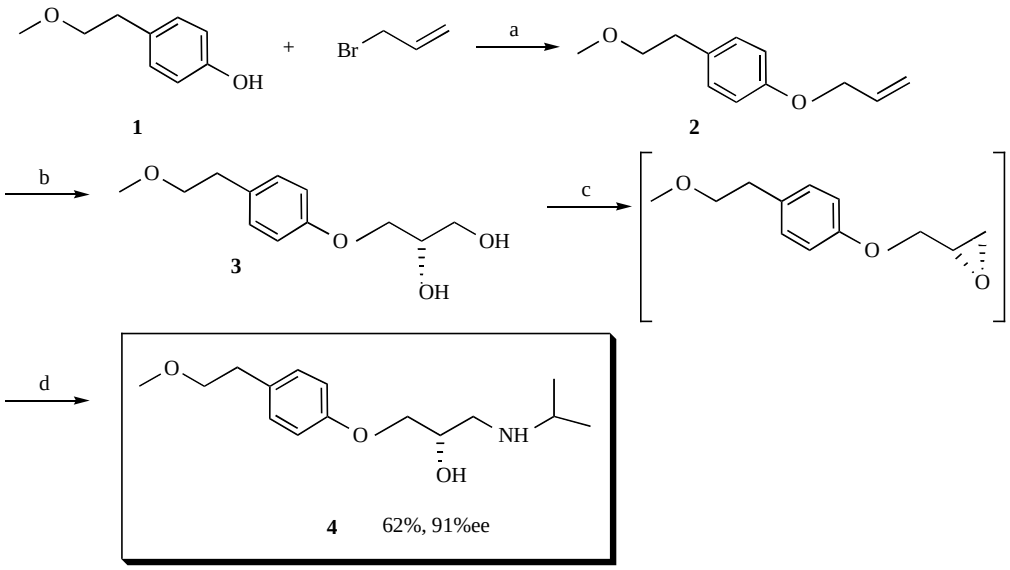


Reagents and conditions: a. $K_2CO_3$, PEG-1000, acetone; b. $K_2OsO_2(OH)_4$, QN-AQN-OPEG-OMe, $K_3Fe(CN)_6$-$K_2CO_3$, $^t$BuOH/$H_2O$ (1/1, *V*/*V*); c. $MeC(OMe)_3$, PPTS, AcBr, $K_2CO_3$; d. $H_2O$, $^i$PrNH$_2$.

**Scheme 2.** Synthetic route of (*S*)-metoprolol.

sive cycles with high enantioselectivity and catalytic activity [19].

Herein, the full details of preparing of (*S*)-metoprolol *via* the AD reaction catalyzed by using the recoverable polymer ligand QN-AQN-OPEG-OMe are reported.

## RESULTS AND DISCUSSION

Scheme **2** shows the simple four-step synthesis of (*S*)-metoprolol (**4**). In the first step, allyl bromide was nucleophilically substituted to 3-[4-(2-methoxyethyl) phenoxy] propylene (**1**) in the presence of $K_2CO_3$ in dry acetone to give **2** (87% chemical yield).

Ligand QN-AQN-OPEG-OMe was characterized by an anthraquinone core between anchored PEG-OMe and the 9-O-position of quinine. It was synthesized in two simple step. Primarily, 1,4-difluoroanthraquinone was reacted with HO-OPEG-OMe (FW=5000) by mono-substituted nucleophilically in the presence of KOH and $K_2CO_3$ in dry toluene, with concurrent azeotropic removal of water, to give intermediate F-AQN-OPEG-OMe in 88% yield. Then, ligand was available in 96% yield by reaction of F-AQN-OPEG-OMe with quinine utilizing butyllithium as base [19]. Next, in a $^t$BuOH/$H_2O$ (1/1, *V*/*V*) system, by using three equivalents of $K_3Fe(CN)_6$ and three equivalents of $K_2CO_3$ as co-oxidants, 0.4 mol% $K_2OsO_2(OH)_4$, and 10 mol% QN-AQN-OPEG-OMe at 0°C, **2** was converted to vicinal diol **3** *via* AD reaction. During the reaction, QN-AQN-OPEG-OMe was expected to complex with $OsO_4$ in situ to form the chiral catalyst. In addition, as QN-AQN-OPEG-OMe was completely soluble, it accelerated the homogenous catalysis to achieve a high chemical yield and optical purity. When the reaction concluded, QN-AQN-OPEG-OMe can be extracted by using $CH_2Cl_2$ and precipitated by the addition of diethyl ether. More than 95% of the ligand can be recovered by simple filtration. The efficiency of ligand recovery was validated by using the same procedure. After four cycles, the chemical yield and optical purity of **3** remained almost unchanged if 40% of the initial amount of $K_2OsO_2(OH)_4$ was added before every recylcling reaction.

With **3** (96% ee) in hand, it is possible to conduct the epoxidation of the vicinal hydroxy groups to the corresponding 1,2-epoxypropanes in the presence of trimethyl orthoacetate, PPTS, acetyl bromide, and $K_2CO_3$. Subsequently, a nucleophilic ring- opening reaction involving isopropylamine was carried out to produce **4** (overall chemical yield 62%, 91% ee).

The overall route was of low cost and has been utilized to manufacture (*S*)-metoprolol on large scales. following the above mentioned procedures, starting with **1**, scale was increased to 10, 100 and 1000 respectively. Yields and ee for this scale up are reported in Fig. (**1**). (*S*)-metoprolol **4** was produced in high chemical yield and enantioselectivity on kilogram scale, polymer ligand QN-AQN-OPEG-OMe being reusued for four cycles.

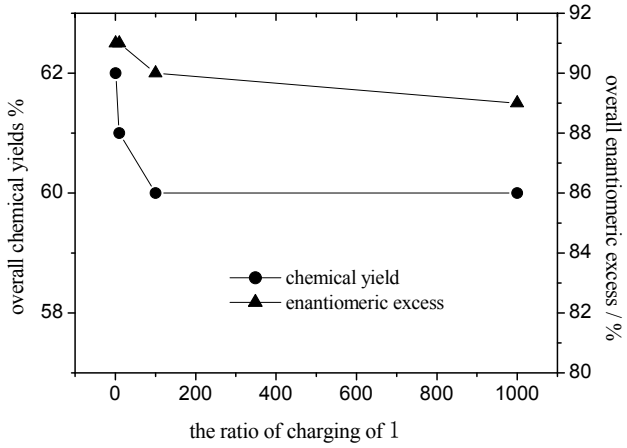


**Fig. (1).** Overall chemical yield and enantiomeric excess of producing (*S*)-metoprolol on large scales.

## CONCLUSIONS

An efficient and environmental friendly route for the preparation of (*S*)-metoprolol was developed. The synthetic route proceeded in four steps: nucleophilic substitution, AD reaction, cyclization, and nucleophilic ring opening. High yield and purity were achieved in the homogeneous catalytic AD reaction by using a soluble polymer chiral ligand QN-AQN-OPEG-OMe, which can be easily separated from the reaction system and reused for at least five times while maintaining its high catalytic activity and enantioselectivity. This protocol has been demonstrated to produce (*S*)-metoprolol on large scale. Further applications of this methodology for the synthesis of (*S*)- bisoprolol are currently under the way.

## EXPERIMENTAL

### Preparation of Aryl Allyl Ether 2

A flame-dried one-neck round-bottom flask was charged with 6.08 g (0.04 mol) 3-[4-(2-methoxyethyl) phenoxy] propylene (**1**), 27.64 g (0.2 mol) of $K_2CO_3$, 0.40 g PEG-1000, 24.20 g (0.2 mol) allyl bromide, and 40 mL anhydrous acetone, The reaction mixture was then refluxed for 5 h. Excess of allyl bromide and acetone was removed by distillation. The residue was dissolved in 40 mL of 2 M NaOH (aq.) and stirred for 20 min. The organic layers were dried over anhydrous sodium sulfate. The crude product was purified by using silica gel column chromatography (Hex/EtOAc), chemical yielding **2** (6.68g, 87%).

**2** $^1$H NMR （$CD_3COCD_3$:$\delta$ 2.74-2.83(m ,2H), 3.27(s, 3H), 3.48-3.53(t,2H, $J$ = 7 Hz), 4.52-4.55 (m, 2H), 5.21-5.25 (dd,1H, $J_1$ = 1.6 Hz, $J_2$ = 1.6 Hz), 5.37-5.43 (dd,1H, $J_1$ = 1.7 Hz, $J_2$ = 1.7 Hz), 6.02-6.07(m, 1H), 6.84-6.87(dd, 2H, $J_1$ = 2.2 Hz, $J_2$ = 2.1 Hz), 7.13-7.16 (dd, 2H, $J_1$ = 2.1 Hz, $J_2$ = 2.1 Hz).

### Preparation of Diol 3

The following reactants, 16.50 g (3 mmol) QN-AQN-OPEG-OMe, 29.70 g (0.09 mol) $K_3Fe(CN)_6$, 12.6g (0.09 mol) $K_2CO_3$, and 42 mg (0.11 mmol) $K_2O_SO_2(OH)_4$ were stirred vigorously in 300 mL $^t$BuOH-$H_2O$ (1:1, *v*/*v*) at 0 °C. Then, 5.76 g (0.03mol) **2** was added dropwise over 30 min and the mixture was stirred for 17 h. After TLC analysis confirmed the absence of the starting material, 24 g $Na_2SO_3$ was added and the mixture was stirred at room temperature for another 2 h. After the addition of 600 mL of $CH_2Cl_2$, the organic phase was separated and the aqueous phase was extracted by using $CH_2Cl_2$ (450 mL×3). The combined organic phases were dried over anhydrous $MgSO_4$ and concentrated to about 450 mL. Diethyl ether (3.0 L) was slowly added to the mixture with vigorously stirring. The obtained precipitate was collected on a glass filter, and washed with cold absolute EtOH/diethyl ether (1:3) and then dried over $P_2O_5$ in vacuo for recycling. More than 15.96 g of ligand was obtained from this procedure (97% recovery). The filtrate was evaporated to give the crude product, which was purified by using flash chromatography (Hex/EtOAc) to furnish diol **3** (6.37g, 94%, 96% ee).

**3** HPLC (Chiralcel OD, Hex/ $^i$PrOH =3:1; 0.6 mL/min), $t_R$(min)= 12.8 (major), 15.9(minor). $[\alpha]_D^{22}$=+ 8.2°(*c* 1.0, MeOH); $^1$H NMR($CDCl_3$): $\delta$ 2.69 (br, 2H), 2.81-2.84 (t,2H, $J$ = 7.6 Hz), 3.34-3.36 (s, 3H), 3.55-3.58 (t,2H, $J$ = 7.6 Hz), 3.75-3.71(m ,1H), 3.83-3.84 (dd, 1H, $J_1$ = 3.6 Hz, $J_2$ = 3.6 Hz), 4.00-4.01 (d,2H, $J$ = 4 Hz), 4.06-4.10 (s,1H), 6.83-6.85 (d, 2H, $J$= 8.4 Hz), 7.12-7.15 (d,2H, $J$ = 8.4 Hz).$^{13}$C NMR($CDCl_3$, 100 MHz): δ 34.8, 58.2, 68.6, 69.9, 73.3, 76.2, 76.6, 76.8, 113.9, 129.4, 131.2,156.4. MS:$[M+H]^+$ 226.1.

### Preparation of (*S*)-Metoprolol 4

For this reaction, 5.65 g (0.025 mol) of **3** was dissolved in $CH_2Cl_2$ (85 mL). Then, 74.6 mg PPTS and 3.65 mL trimethyl orthoacetate were added and the resulting solution was stirred at room temperature for 20 min. The solvent was removed under reduced pressure and the residue was dissolved in $CH_2Cl_2$ (50.0 mL). Under vigorous stirring, 2.20 mL acetyl bromide was added dropwise (over 6 min) and the resulting solution was stirred at room temperature for 30 min. After vacuum evaporation of the volatiles, the product (a yellow oil) was dissolved in MeOH (85 mL). Then, 4.48 g of anhydrous $K_2CO_3$ was added. The resulting solution was stirred at room temperature for 1.5 h and then was poured into a saturated $NH_4Cl$ solution (25.0 mL). The aqueous layer was extracted with $CH_2Cl_2$ (50.0 mL×3) and the combined organic phases were dried over anhydrous $Na_2SO_4$. The solvent was removed under reduced pressure and the crude product was obtained by using silica gel flash column chromatography (EtOAc / haxane, 1:3 to 1:2). Then, 37.3 mL isopropylamine and 2.0 mL $H_2O$ were added and the resulting solution was refluxed for 1.5 h. The solvent was removed under reduced pressure and the resulting oil was purified by using silica gel flash column chromatography (acetone/EtOAc /$Et_3N$, 6:6:1) to give **4** (5.08 g, 76%, 91% ee).

**4** HPLC (Chiralcel OD-H, Hex /$^i$PrOH / $Et_3N$ =6:6:1; 0.5 mL/min), $t_R$(min)= 28.3 (major), 31.5(minor). $[\alpha]_D^{22}$ =–8.78$^o$ (*c* 10.0, $CHCl_3$). $^1$H NMR($CDCl_3$, 400MHz): $\delta$ 1.08 (6H, d, *J*=6.2Hz), 2.31(2H, bs), 2.81- 2.91 (2H, m), 2.85 (2H, m), 3.36(3H, s), 3.57 (2H, t, *J*=7.1 Hz), 3.91 (2H, m), 4.01 (lH, m), 6.86 (2H, d, *J*=8.2Hz), 7.14 (2H,d, *J*=8.2Hz). $^{13}$C NMR($CDCl_3$, 100MHz): $\delta$ 22.7, 35.1, 48.85, 49.4, 58.5, 68.3, 70.6, 73.1, 76.7, 77.0, 77.4, 114.3, 129.7, 131.2, 157.0. MS(FAB): $[M+1]^+$ 268.1.

### Recycling of AD Reaction by Using Chiral Ligand QN-AQN-OPEG-OMe

The recycling experiment of the AD reaction was conducted using **2** as the substrate. The recovered ligand was used in the next run without purification. The first run was carried out with 29.70 g (0.09 mol) $K_3Fe(CN)_6$, 12.60 g (0.09 mol) $K_2CO_3$, 55.27 mg (0.15 mmol) $K_2OsO_2(OH)_4$, and 5.76 g (0.03mol) of **2** to give **3** in 92% chemical yield, with 95% ee. After the reaction, 15.32 g of the ligand was recovered (96% recovery). The second run was carried out with all of the recovered ligand, 29.70 g (0.09 mol) of $K_3Fe(CN)_6$, 12.6g (0.09 mol) of $K_2CO_3$, 70.00 mg (0.19 mmol) of $K_2OsO_2(OH)_4$, and 5.76 g (0.03mol) of **2** to give **3** in 95% chemical yield and 94% ee, after which 14.71 g of the ligand

was recovered (96% recovery). The third run was carried out with all of the recovered ligand, 29.70 g (0.09 mol) of $K_3Fe(CN)_6$, 12.6 g (0.09 mol) of $K_2CO_3$, 84.74 mg (0.23 mmol) of $K_2OsO_2(OH)_4$, and 5.76 g (0.03mol) of **2** to give **3** in 91% chemical yield and 95% ee. Following this step, 14.12 g of the ligand was recovered (96% recovery). The fourth run was carried out with 14.12 g of the recovered ligand, 29.70 g (0.09 mol) of $K_3Fe(CN)_6$, 12.6 g (0.09 mol) of $K_2CO_3$, 99.48 mg (0.27 mmol) of $K_2OsO_2(OH)_4$, and 5.76 g (0.03mol) of **2** to deliver **3** in 92% chemical yield and 93% ee, with 13.41 g of the ligand recovered (95% recovery).

## SUPPLEMENTARY MATERIAL

Supplementary material is available on the publishers Web site along with the published article.

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## CONFLICT OF INTEREST

Declared none.

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