CHIRALITY 22:347–354 (2010)

Enantioselective Addition of Phenylacetylene to Aldehydes Catalyzed by Polymer-Supported Titanium(IV) Complexes of β-Hydroxy Amides

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ABSTRACT A series of polymer-supported chiral β-hydroxy amides and C_2-symmetric β-hydroxy amides have been synthesized and successfully used for the enantioselective addition of phenylacetylene to aldehydes. High yields (up to 93%) and enantioselectivities (up to 92% ee) were achieved by using polymer-supported chiral β-hydroxy amide **4b**. The resin **4b** is reused four times, giving the product with enantioselectivity 80% ee. Fortunately, it is found that this heterogonous system is suitable not only for aromatic aldehydes but also aliphatic aldehyde. *Chirality 22:347–354, 2010.*

KEY WORDS: enantioselective addition; polymer-supported catalyst; titanium tetraisopropoxide; diethylzinc; β-hydroxy amide

INTRODUCTION

Optically active propargyl alcohols are important building blocks for the synthesis of many organic compounds.[1] Recently, the catalytic enantioselective addition of terminal alkynes to aldehydes has generated a tremendous amount of interest.[2–11] Since the first efficient asymmetric alkynes addition to aldehydes was demonstrated by Soai[12] using (1*S*,2*R*)-*N*,*N*-dibutylnorephedrine, many chiral ligands, such as *N*-methylephedrine,[13–15] BINOL and its derivatives,[5,10,16–21] and sulfonamides[22,23] have been used successfully in this reaction. Other chiral ligands, such as amino alcohols,[24,25] oxazoline,[26–27] and imino alcohol,[28] have also been reported to catalyze this reaction.

Polymer-supported chiral ligands as one of the most important heterogeneous ligands have been used successfully in a lot of reactions.[29–31] In recent years, many groups reported the synthesis of new polymer-supported chiral ligands and their applications in asymmetric hydrogen transfer reaction,[32–37] cyclopropanation,[38,39] Aldol reaction,[40,41] Diels-Alder reaction,[42] Michael addition,[43,44] and sulfonation reaction.[45] The asymmetric alkylation of carbonyl groups is one of the most important methods to built C—C bond. There have been many reports about these asymmetric reactions catalyzed by polymer-supported chiral ligands such as asymmetric silylcyanation,[46] allylation,[47,48] and addition of dialkylzinc to aldehydes and ketones.[49–54] However, there have been far fewer examples about the enantioselective alkynylation of aldehydes catalyzed by polymer-supported chiral ligands. Until recently, Degni et al.[50] reported the use of polymer-supported *L*-prolinol diverved catalysts for this addition. However, the good enantioselectiviy (91% ee) but poor yield (45%) was obtained by using equivalent amount of chiral ligands. Abdi and coworkers[55] reported the enantioselective addition of phenylacetylene to aldehydes catalyzed by polymeric Zn(salen) complex. Only 72% ee value was obtained for this reaction.

Recently, our group has developed a new β-hydroxy amide chiral ligand **a** and C_2-symmetric β-hydroxy amide **b**, and successfully introduced them into the asymmetric addition of phenacetylene to aldehydes to afford excellent enantioselectivities.[56,57] With our continuing efforts toward the development of recyclable ligands,[58] we synthesized a series of polymer-supported chiral β-hydroxy amides and C_2-symmetric β-hydroxy amides and successfully used them for the enantioselective addition of phenylacetylene to aldehydes. High yields (up to 93%) and enantioselectivities (up to 92%) were achieved by using polymer-supported chiral β-hydroxy amide **4b** (Fig. 1).

EXPERIMENTAL SECTION

Melting points were determined using X-4 melting point apparatus and were uncorrected. Optical rotations were measured with Perkin-Elmer 341 polarimeter. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian Mercury-400 MHz spectrometer with TMS as an internal standard. The solid state ^{13}C NMR experiment was performed on Bruker AV400 WB solid-state NMR instrument at 100 MHz. IR spectra were obtained on Nicollet NEXUS 670 FT-IR spectrometer. HRMS data were measured with ESI techniques (Bruker Apex II). Elemental analyses were

Contract grant sponsor: National Natural Science Foundation of China; Contract grant numbers: 20702022, 20621091, 2057203
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Received for publication 6 January 2009; Accepted 28 March 2009
DOI: 10.1002/chir.20749
Published online 18 June 2009 in Wiley InterScience (www.interscience.wiley.com).

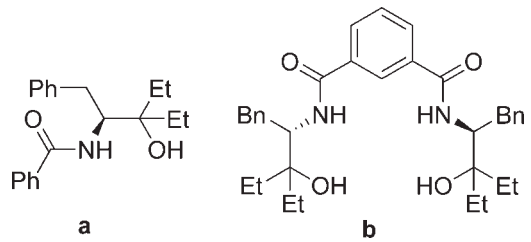


Fig. 1. β-Hydroxy amide ligands.

performed on Elementar vario EL. Enantiomeric excess values were determined by HPLC with Chiralcel OD-H column. All catalytic reactions were carried out under nitrogen atmosphere. *L*-Tyrosine and *L*-phenylalanine was purchased form Alfa Aesar. Merrifild resin and 1-(chloromethyl)-4-vinylbenzene was purchased from Acros. Diethylzinc (1 M solution in CH_2Cl_2),[59] 5-hydroxybenzene-1,3-dioyl dichloride,[60,61] and 4-((*S*)-2-amino-3-ethyl-3-hydroxypentyl) phenol (**1**)[62] were synthesized according to the literature methods, respectively. Dichloromethane was freshly distilled from phosphorous pentoxide. Toluene, hexane, and THF were freshly distilled from a deep-blue solution of sodium-benzophenone under nitrogen. Ti(O-*i*-Pr)$_4$ was distilled under nitrogen prior to use.

Synthesis of (S)*-1-(4-(4-Vinylbenzyloxy) phenyl)-2-amino-3-ethylpentan-3-ol (2)*

Under nitrogen, amino alcohol **1** (5.57 mmol) and dry DMF (18 ml) were placed in a 100-ml round-bottomed flask. Sodium hydride (0.14 g) was added slowly with stirring. After the completely emission of hydrogen gas, 1-(chloromethyl)-4-vinylbenzene (0.824 ml) was added dropwise and the resulting mixture was stirred at room temperature for 12 h under nitrogen. Water was added and the mixture was extracted with ethyl acetate (3 × 30 ml). The organic layer was combined and washed sequentially with water (30 ml), brine (3 × 30 ml), and dried over anhydrous $MgSO_4$. After column chromatography (PE/EA = 1/3), compound **2** was obtained as white solid (yield 40%); m.p. 72–73°C. $[\alpha]_D^{20} = -26^\circ$ (c = 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92–0.97 (m, 6H), 1.41–1.67 (m, 4H), 2.25 (dd, *J* = 11.6, 14.0 Hz, 1H), 2.91 (d, *J* = 12.0 Hz, 1H), 5.04 (s, 2H), 5.26 (d, *J* = 10.8 Hz, 1H), 5.76 (d, *J* = 17.6 Hz, 1H), 6.72 (dd, *J* = 10.8, 17.6 Hz, 1H), 6.92 (d, *J* = 8.4 Hz, 2H), 7.10 (d, *J* = 8.4 Hz, 2H), 7.38–7.44 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 7.56, 26.40, 27.74, 36.95, 57.18, 69.57, 74.18, 113.88, 114.87, 126.22, 127.47, 129.89, 132.13, 136.26, 136.46, 137.09, 157.18. IR (KBr): 3341, 3186, 2965, 2936, 2878, 1608, 1152, 1387, 1293, 1245, 1004, 907, 797 cm^{-1}.

Synthesis of N*-((*S*)-1-(4-(4-Vinylbenzyloxy) phenyl)-3-ethyl-3-hydroxypentan-2-yl)benzamide (3)*

A solution of benzoyl chloride (3.3 mmol) in CH_2Cl_2 (10 ml) was added to a solution of amino alcohol **2** (3 mmol) and Et_3N (3.3 mmol) in CH_2Cl_2 (10 ml) at 0°C. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was washed with 1 M HCl (2 × 10 ml), saturated aqueous $NaHCO_3$ (3 × 10 ml), and brine (3 × 10 ml). The organic layer was dried over anhydrous $MgSO_4$, concentrated under reduced pressure, and the residue was recrystallized from ethyl acetate/hexane to afford the desired monomer **3** (yield 82%); m.p. 180–181°C. $[\alpha]_D^{20} = -115^o$ (c 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90–0.99 (m, 6H), 1.54–1.77 (m, 4H), 2.80 (dd, *J* = 10.8, 14.4 Hz, 1H), 3.08 (dd, *J* = 3.4, 14.2 Hz, 1H), 4.25–4.31 (m, 1H), 4.97 (s, 2H), 5.25 (d, *J* = 10.8 Hz, 1H), 5.75 (d, *J* = 17.6 Hz, 1H), 6.23 (d, *J* = 8.8 Hz, 1H), 6.71 (dd, *J* = 11.2, 17.6 Hz, 1H), 6.85 (d, *J* = 8.4 Hz, 2H), 7.13 (d, *J* = 8.8 Hz, 2H), 7.28–7.46 (m, 7H), 7.53 (d, *J* = 8.4, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 7.92, 8.28, 28.11, 28.43, 29.93, 34.54, 57.01, 69.94, 114.21, 115.13, 126.58, 127.06, 127.86, 128.66, 130.34, 131.39, 131.49, 134.98, 136.69, 136.85, 137.45, 157.53, 168.32. IR (KBr): 3487, 3355, 2958, 2878, 1633, 1536, 1513, 1240, 1017, 827, 692 cm^{-1}. HRMS (ESI): exact mass calcd for $C_{29}H_{33}NO_3$ $(M+H)^+$: 444.2533, found: 444.2536.

Synthesis of Merrifield Resin-Supported Chiral Ligand 6

Compound **5** was prepared in similar procedures as described for amino alcohol **2** and was wash sequentially with CH_2Cl_2, MeOH, MeOH/H_2O, acetone, MeOH, and CH_2Cl_2, and dried under vacuum at 50°C to afford **5** as yellowish powder. Chiral ligand **6** was prepared in similar procedures as described for **3** and was wash sequentially with CH_2Cl_2, MeOH, MeOH/H_2O, acetone, MeOH, and CH_2Cl_2, and dried under vacuum at 50°C to afford **6** as yellowish powder. IR (KBr): 3427, 3025, 2927, 1638, 1511, 1242, 1177, 1018, 820, 701 cm^{-1}. Anal. found: C, 81.4; H, 6.68; N, 1.76.

Synthesis of C_2-Symmetric Monomer 7

Monomer **7** was prepared in similar procedures as described for **3** and was purified by column chromatograph (PE/EA = 1/1) as white solid (yield 81%); m.p. 103–104°C. $[\alpha]_D^{20} = -113^\circ$ (c = 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86–0.97 (m, 12H), 1.51–1.75 (m, 8H), 2.46 (br, 2H), 2.78 (dd, *J* = 10.8, 14.2 Hz, 2H), 3.07 (dd, *J* = 3.8, 14.2 Hz, 2H), 4.28–4.34 (m, 2H), 4.93 (s, 4H), 5.24 (d, *J* = 12.0 Hz, 2H), 5.73 (d, *J* = 18.4 Hz, 2H), 6.30 (d, *J* = 8.8 Hz, 2H), 6.69 (dd, *J* = 10.8, 17.6 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 4H), 7.12 (d, *J* = 8.8 Hz, 4H), 7.27–7.38 (m, 9H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.75 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 7.61, 7.89, 27.48, 27.91, 34.15, 56.41, 69.47, 76.88, 113.86, 114.58, 125.04, 126.17, 127.56, 128.84, 129.40, 130.04, 131.10, 134.78, 136.29, 137.03, 157.10, 167.80. IR (KBr): 3410, 2967, 2938, 1643, 1512, 1242, 1176, 1015, 987, 827 cm^{-1}. HRMS (ESI): exact mass calcd for $C_{52}H_{60}N_2O_6$ $(M+H)^+$: 809.4524, found: 809.4533.

Synthesis of C_2-Symmetric Compound 10

Compound **10** was prepared in similar procedures as described for **3** and was purified by column chromatograph (PE/EA = 2/1) as white solid (yield 66%); m.p. 82–83°C. $[\alpha]_D^{20} = +35^\circ$ (c = 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.13–3.26 (m, 4H), 3.73 (s, 6H), 4.97–5.00 (m,

2H), 7.15–7.36 (m, 15H), 7.43 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 37.49, 52.36, 54.18, 116.55, 117.81, 126.94, 128.45, 129.01, 134.80, 135.89, 157.20, 166.73, 172.40. IR (KBr): 3335, 3030, 2953, 1741, 1647, 1529, 1438, 1219, 750, 700 cm^{-1}.

Synthesis of C_2-Symmetric Compound 11

Compound **11** was prepared in similar procedures as described for amino alcohol **2** and was purified by column chromatograph (PE/EA = 1.5/1) as white solid (yield 46%); m.p. 102–103°C. $[\alpha]_D^{20} = +51°$ (c = 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.17–3.31 (m, 4H), 4.76 (s, 6H), 5.03–5.08 (m, 4H), 5.27 (d, J = 11.2 Hz, 1H), 5.77 (d, J = 17.6 Hz, 1H), 6.72 (dd, J = 10.8, 17.6 Hz, 1H), 6.70–6.76 (br, 2H), 7.13–7.46 (m, 16H), 7.59 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 37.59, 52.29, 53.89, 69.86, 114.09, 116.70, 117.30, 126.29, 127.00, 127.73, 128.47, 129.04, 135.37, 135.91, 136.20, 137.37, 158.71, 166.05, 172.17. IR (KBr): 3247, 3030, 2951, 1744, 1645, 1532, 1438, 1360, 1215, 1034, 828, 747, 700 cm^{-1}.

Synthesis of C_2-Symmetric Monomer 12

A solution of **11** (1.84 mmol) in THF (10 ml) was added to a solution of EtMgBr (18.4 mmol) in THF at 0°C. The reaction mixture was allowed to warm to room temperature and stirred overnight. The saturated aqueous solution of ammonium chloride was added dropwisely to the mixture under 0°C. The reaction mixture was then extracted with ethyl acetate (3 × 30 ml), and the organic layer was washed with saturated aqueous $NaHCO_3$ (3 × 10 ml), and brine (3 × 10 ml). The organic layer was dried over anhydrous $MgSO_4$, concentrated under reduced pressure, and the residue was purified by column chromatograph to afford the desired monomer **12** (yield 89%); m.p. 137–138°C. $[\alpha]_D^{20} = -98°$ (c = 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.79–0.88 (m, 12H), 1.49–1.77 (m, 8H), 2.51 (br, 2H), 2.75–2.86 (m, 2H), 3.09–3.19 (m, 2H), 4.32–4.39 (m, 2H), 4.82–5.00 (m, 2H), 5.28 (d, J = 11.2 Hz, 1H), 5.78 (d, J = 17.6 Hz, 1H), 6.28 (br, 2H), 6.73 (dd, J = 10.8, 17.6 Hz, 1H), 7.12–7.43 (m, 17H). ^{13}H NMR (100 MHz, $CDCl_3$): δ 8.03, 8.17, 27.81, 28.38, 29.92, 35.46, 56.76, 70.17, 77.25, 114.59, 116.27, 117.42, 126.50, 126.69, 127.43, 128.22, 128.58, 128.92, 129.40, 135.72, 136.59, 137.86, 139.12, 167.25. IR (KBr): 3416, 3281, 2967, 2938, 1744, 1644, 1533, 1356, 1137, 1035, 827, 745, 698 cm^{-1}. HRMS (ESI): exact mass calcd for $C_{43}H_{52}N_2O_5$ $(M+Na)^+$: 699.3768, found: 699.3765.

General Procedure for Synthesis of Polymer-Supported Chiral Ligands 4a-b, 8a-b, and 13

The synthesis of polymer-supported chiral ligands **4a** as the sample: Under nitrogen atmosphere, compound **3** (2 mmol), styrene (7.8 mmol), divinyl benzene (0.2 mmol) and AIBN (0.125 mmol) were solved in THF (4 ml). H_2O (20 ml) was added to the mixture and stirred at room temperature for 1 h. Then the mixture was reflux for 48 h under N_2 to afford white solid. The solid was washed sequentially with H_2O, THF, acetone, MeOH, and CH_2Cl_2. After dried under vacuum at 60°C for 48 h, the solid was crashed and collected (<100 mesh) to afford the product as white solid powder.

4a: ^{13}C Solid State NMR (100 MHz): δ 9, 27, 40, 77, 128, 145, 180, 194, 228. IR (KBr): 3425, 3025, 2923, 1640, 1512, 1449, 1241, 1176, 1020, 819, 759, 698, 539 cm^{-1}. Anal. found: C, 82.80; H, 6.90; N, 1.67.

4b: IR (KBr): 3428, 3025, 2921, 1637, 1512, 1449, 1240, 1177, 1024, 820, 757, 698, 538 cm^{-1}. Anal. found: C, 85.72; H, 7.78; N, 1.12.

8a: IR (KBr): 3426, 3025, 2924, 1653, 1511, 1451, 1241, 1017, 819, 760, 700 cm^{-1}. Anal. found: C, 81.74; H, 6.84; N, 1.74.

8b: IR (KBr): 3429, 3025, 2921, 1661, 1603, 1511, 1493, 1450, 1241, 1026, 756, 698 cm^{-1}. Anal. found: C, 87.35; H, 6.71; N, 0.76.

13: IR (KBr): 3416, 3351, 3025, 2924, 1647, 1594, 1514, 1450, 1347, 1135, 1032, 751, 698, 540 cm^{-1}. Anal. found: C, 81.27; H, 6.87; N, 2.17.

General Procedure for Asymmetric Addition of Phenylacetylene to Aldehydes

Under dry nitrogen, the polymer-supported ligand (0.04 mmol) and Ti(O-*i*-Pr)$_4$ (0.14 mmol) were mixed in solvent (1.0 ml) at room temperature and stirred for 1 h. Then a solution of diethylzinc (0.6 mmol, 1.0 M in CH_2Cl_2) was added. After the mixture was stirred at room temperature for 2 h, phenylacetylene (0.6 mmol) was added and stirred for another 1 h. The solution was treated with aldehyde (0.2 mmol). After the reaction was completed (TLC), the reaction solution was cooled to 0°C and quenched by 0.5 M aqueous HCl. The mixture was extracted with diethyl ether (3 × 10 ml), washed with brine (3 × 15 ml), dried with anhydrous Na_2SO_4, and concentrated under vacuum. The crude product was purified by column chromatography (silica gel, PE : EA = 8:1) to give the propargyl alcohol.

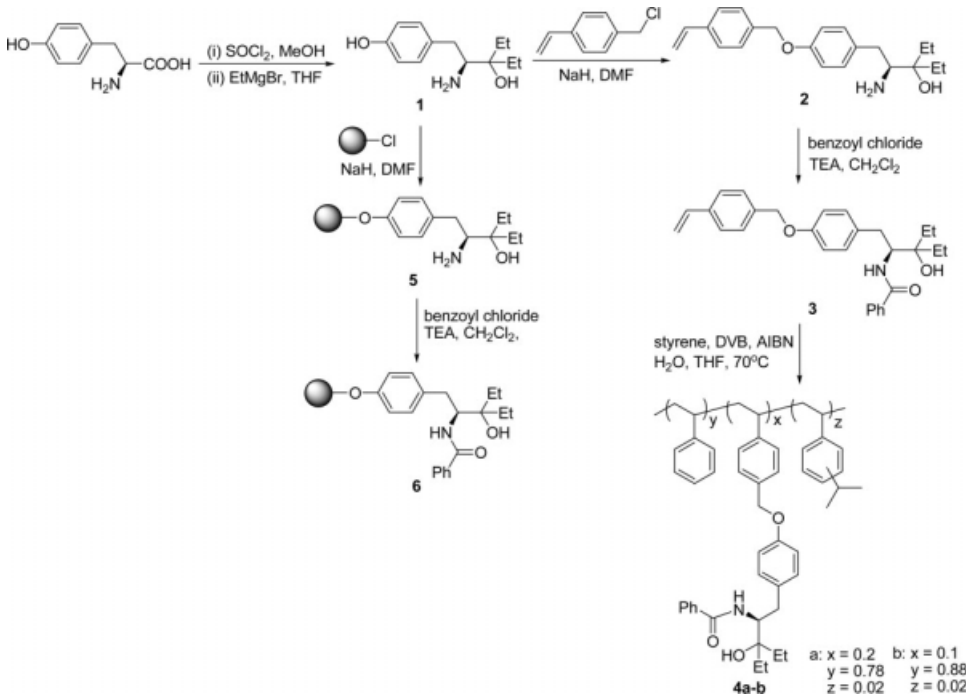
General Procedure for Restoration of Polymer-Supported Ligand 4b

After one catalytic cycle, the polymer-supported ligand **4b** was washed sequentially with 1 M HCl (30 ml), MeOH (30 ml), mixture of MeOH and CH_2Cl_2 (1:1, 30 ml) and CH_2Cl_2 (30 ml), then dried under vacuum at 50°C for 18 h before reuse.

RESULTS AND DISCUSSION

Synthesis of Polymer-Supported β-Hydroxy Amides

Generally, there are two methods to synthesis polymer-supported chiral ligands: (a) directly grafted the chiral ligands onto the surface of Merrifield resin; (b) derivation of the chiral ligands with terminal olefinic link, and copolymerization of the ligands with other monomers to form the polymer-supported chiral ligands. In this article, both methods were introduced to synthesize polymer-supported β-hydroxy amides. As shown in scheme 1, amino alcohol **1** was synthesized from *L*-tyrosine. Compound **1** coupled with 1-(chloromethyl)-4-vinylbenzene to form compound **2**. The reaction of **2** with benzoyl chloride yielded monomer **3**. Polymer-supported amino alcohols **4a-b** were

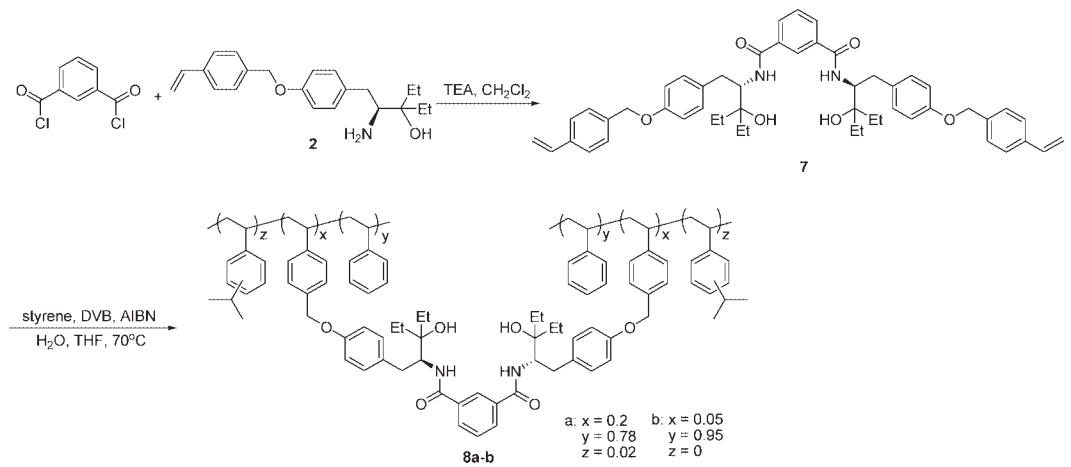


Scheme 1. Synthesis of polymer-supported chiral ligands **4a-b** and **6**.

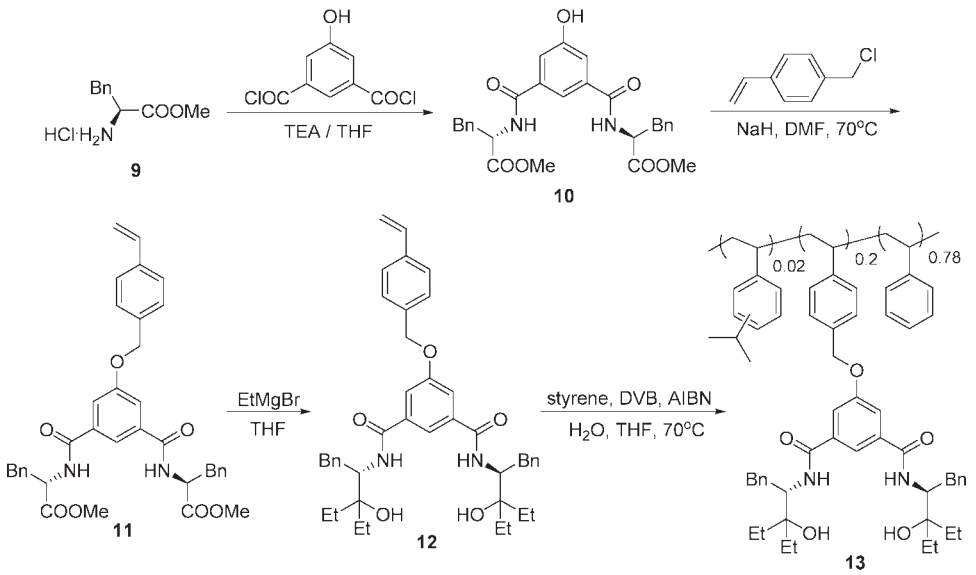
synthesized through copolymerization of monomer **3** with styrene and divinyl benzene. Compound **1** was directly grafted onto Merrifield resin to form polymer-supported amino alcohol **5**. Reaction of polymer-supported **5** with benzoyl chloride yielded the polymer-supported β-hydroxy amide **6**. The amount of chiral ligand grafted onto polymers was calculated from elemental analysis of nitrogen.

C_2-Symmetric β-hydroxy amide **b** performed good catalytic reactivity in the enantioselective addition of phenylacetylene to aldehydes. Herein, we successfully designed and synthesized polymer-supported C_2-symmetric β-hydroxy amides in order to further improve the ee value. As shown in scheme 2, monomer **7** was obtained through the reaction of **2** and isophthaloyl dichloride. By using the same method with **4**, polymer-supported ligands **8a-b** were obtained with different cross linking and the amount of monomers.

There is another strategy to synthesize polymer-supported C_2-symmetric β-hydroxy amide as shown in scheme 3. *L*-Phenylalanine derived compound **9** reacted with 5-hydroxybenzene-1,3-dioyl dichloride to yield C_2-symmetric **10**. Compound **10** coupled with 1-(chloromethyl)-4-vinylbenzene to form compound **11**. Monomer **12** was obtained by the reaction of **11** with EtMgBr at ambient temperature. C_2-Symmetric β-hydroxy amide **13** was synthesized by the same copolymerization of polymer-supported ligand **4a**.



Scheme 2. Synthesis of polymer-supported chiral ligands **8a-b**.



Scheme 3. Synthesis of polymer-supported chiral ligand **13**.

Enantioselective Addition of Phenylacetylene to Aldehyde Catalyzed by Polymer-Supported Titanium(IV) Complexes of β-Hydroxy Amides

First, monomer **3** was chosen as model ligand to catalyze the enantioselective addition of phenylacetylene to benzaldehyde, 1,3-diphenylprop-2-yn-1-ol was obtained in 85% yield, and 89% ee (Table 1, Entry 1). To elucidate effects of ligand loadings, catalytic system of **4a** having the 20% ligand loading was then examined. The results showed that the yield and ee value of propargyl alcohol were raised sharply with increasing the amount of Ti(O-*i*-Pr)$_4$. Further increasing the amount of Ti(O-*i*-Pr)$_4$ resulted in a slightly decrease in ee value, whereas, the reaction yield decreased deeply (Table 1, Entries 2–6). The best ee value 86% was obtained with Ti(O-*i*-Pr)$_4$/ligand of 3.5/1 (Table 1, Entry 3). Four solvents were examined and toluene was found to be the best choice (Table 1, Entries **3**, 7-9). Improving the amount of the chiral ligand from 20% to 30% caused the increasing of ee value (88% ee) (Table 1, Entries **3** and 10). For the catalytic system of the resin **4b** containing 10% ligand loading, the product was obtained in high yield (85%) with a slight increase in enantioselectivity (87% ee) (Table 1, Entry 11). The titanium complex of 20 mol % resin **6** was examined to afford propargyl alcohol in only 58% yield and 49% ee (Table 1, Entry 12). The low yield and ee is attributed to interferences of close proximities of active catalytic metal centers in the resin **6** having 98% ligand loading. This study reveal that the immobilized catalytic system of **4b** with 10% ligand loading is superior to the catalytic systems of resins **4a** and **6** having higher ligand loadings of 20% and 98%, respectively.

The C_2-symmetric monomers and corresponding polymer-supported ligands were also used in the enantioselective addition of phenylacetylene to benzaldehyde. Monomer **7** has good catalytic reactivity (Table 2, Entry 1), whereas the polymer-supported **8a** and **8b** have poor or

TABLE 1. Asymmetric addition of phenylacetylene to benzaldehyde catalyzed by ligands 3, 4a-b, and 6[a]

Entry	Ligand (mol %)	Ti(O^{i}Pr)$_4$/Ligand	Solvent	Yield (%)[b]	ee (%)[c] (Config.)
1	**3** (20)	3/1	Toluene	85	89 (*R*)
2	**4a** (20)	3/1	Toluene	50	77
3	**4a** (20)	3.5/1	Toluene	73	86
4	**4a** (20)	4/1	Toluene	83	85
5	**4a** (20)	5/1	Toluene	76	83
6	**4a** (20)	6/1	Toluene	56	83
7	**4a** (20)	3.5/1	THF	49	43
8	**4a** (20)	3.5/1	CH_2Cl_2	56	86
9	**4a** (20)	3.5/1	Hexane	54	86
10	**4a** (30)	3.5/1	Toluene	80	88
11	**4b** (20)	3.5/1	Toluene	85	87
12	**6** (20)	3.5/1	Toluene	58	49

[a]$ZnEt_2$/Phenylacetylene/PhCHO = 0.6/0.6/0.2 mmol. Reaction temperature: rt. Reaction time: 18 h.
[b]Isolated yields.
[c]Determined by HPLC with Chiralcel OD-H column.

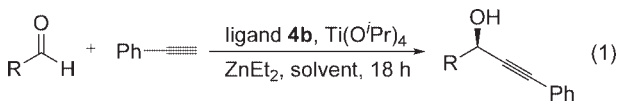
TABLE 2. Asymmetric addition of phenylacetylene to benzaldehyde catalyzed by ligands 7, 8a-b, and 13[a]

Entry	Ligand (mol %)	$Ti(O^iPr)_4$/ Ligand	Yield (%)[b]	ee (%)[c] (Config.)
1	**7** (10)	3/1	93	92 (*R*)
2	**8a** (10)	3.5/1	66	50
3	**8b** (10)	3.5/1	83	78
4	**13** (10)	3.5/1	80	74

[a]Reaction temperature: rt. Reaction time: 18 h.
[b]Isolated yields.
[c]Determined by HPLC with Chiralcel OD-H column.

moderate catalytic activities (Table 2, Entries 2 and 3). It may be caused by the higher mechanical robustness of **8a–b** than **4**, and less swelling capacity. Another C_2-symmetric chiral ligand **13** also have moderate enantioselectivities (Table 2, Entry 4).

Compared with the catalytic activities of different polymer-supported ligands, ligand **4b** was chose as the best suitable ligands. Generalities of the heterogeneous catalytic system of resin **4b** were then examined on a variety of aldehydes. As the results summarized in Table 3, the desired propargyl alcohols in excellent isolated yields from 84 to 93% with good enantioselectivities from 86 to 92% were achieved. The best enantioselectivity of 92% ee was obtained for the alkynylation of 4-chlorobenzaldehyde (Table 3, Entry 4). Furthermore, it was worthy to be noticed that this heterogeneous catalytic system was also suitable for the aliphatic aldehyde and good enantioselectivity from 80 to 83% were obtained (Table 3, Entries 7–9).



Reusability of Polymer-Supported Chiral Ligand 4b

Reuse experiments of the immobilized catalytic system of **4b**/Ti(O-*i*-Pr)$_4$ were conducted with benzaldehyde as the substrate. After the restore procedure, ligand **4b** was used for the next cycle. The resin **4b** was reused four times to afford 1,3-diphenylprop-2-yn-1-ol in high yields. However, enantioselectivities decrease slightly from 87, 85, 82, to 80% ee.

TABLE 3. Asymmetric addition of phenylacetylene to aldehydes catalyzed by ligand 4b[a]

Entry	Aldehyde	Yield (%)[b]	ee (%)[c] (Config.)
1	benzaldehyde	85	87 (*R*)
2	2-chlorobenzaldehyde	84	86 (*R*)
3	3-chlorobenzaldehyde	87	89 (*R*)
4	4-chlorobenzaldehyde	89	92 (*R*)
5	4-tolualdehyde	89	90 (*R*)
6	2-naphthaldehyde	93	88 (*R*)
7	*n*-butyraldehyde	85	83 (*R*)
8	3-methylbutanal	81	82 (*R*)
9	cyclohexanecarbaldehyde	82	80 (*R*)

[a]Ligand **4b**/Ti(O-*i*-Pr)$_4$/$ZnEt_2$/Phenylacetylene/Aldehyde = 0.04/0.14/0.6/0.6/0.2 mmol. Reaction temperature: rt. Reaction time: 18 h.
[b]Isolated yields.
[c]Determined by HPLC with Chiralcel OD-H column.

CONCLUSION

In conclusion, a series of polymer-supported chiral β-hydroxy amides and C_2-symmetric β-hydroxy amides have been synthesized and successfully used for the enantioselective addition of phenylacetylene to aldehydes. High yields (up to 93%) and enantioselectivities (up to 92%) were achieved by using polymer-supported chiral β-hydroxy amide **4b**. The resin **4b** is reused four times, giving the product with enantioselectivity 80% ee. Fortunately, it is found that this heterogeneous system is suitable not only for aromatic aldehydes but also aliphatic aldehyde.

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