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Synthesis and application of polymer-supported *N*-sulfonylated aminoalcohols as enantioselective catalysts

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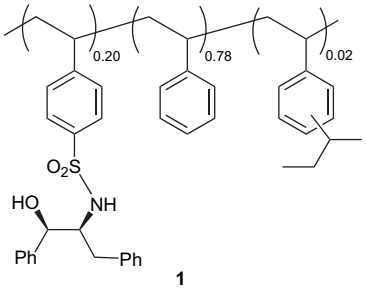
Abstract

Two novel cross-linked polystyrene-supported *N*-sulfonylated β-aminoalcohol resins **13** and **14** have been prepared from radical co-polymerizations of styrene, divinylbenzene, and styrenes bearing a *para*-substituent of *N*-sulfonylated aminoalcohol. Resins **13** and **14** were obtained in high yields of 85.8 and 84.7%, and were characterized by IR and solid state ^{13}C NMR spectroscopies. Elemental analyses reveal that 1 g of resin **13** contains 0.93 mmol bidentate *N*-sulfonylated β-aminoalcohol. The ligand content in tridentate resin **14** is calculated to be 0.95 mmol/g. The Ti(O-*i*-Pr)$_4$/**13** catalytic system works excellently in asymmetric $ZnEt_2$ additions to aldehydes affording secondary alcohols in ≥90% ee. Resin **13** can be reused 9 times without losing any activity, giving the product with enantioselectivities ≥87% ee. The Ti(O-*i*-Pr)$_4$/**14** system was used only once in asymmetric $AlEt_3$ additions to a variety of aldehydes affording secondary alcohols in good to excellent enantioselectivities from 73 to 92% ee.

Keywords: Polystyrene; *N*-Sulfonylated β-aminoalcohol; Titanium(IV) catalyst

1. Introduction

Asymmetric catalytic C–C bond formation reactions have been extensively studied in the past 10 years owing to their diversified applications to the synthesis of bioactive compounds [1], and many homogeneous catalytic systems were reported to furnish chiral products in excellent stereocontrols. Recently, transformations of homogeneous catalysts into recoverable heterogeneous catalytic systems have attracted considerable attention because of advantages of facilitated workup, easy recovery, and reusability of the recoverable catalysts. Polymer-supported catalysts, dendrimers, and inorganic material-supported catalysts are three major systems developed for this purpose [2], and it is found that the polymer-supported catalysts are in general superior to the latter two systems. In construction of C–C bonds, organozinc compounds are the most reliable reagents due to their mild reactivity and controllable characteristics for achieving excellent stereoselectivity. In cases of dialkylzinc additions to organic carbonyls, recoverable titanium catalysts of binaphthols (BINOLs) [3] or 2,2-dimethyl-α,α,α′,α′-tetraaryl-1,3-dioxolane-4,5-dimethanols (TADDOLs) [4] and zinc catalysts of BINOLs [5] or aminoalcohols [6] have been reported to afford chiral secondary alcohols in good to excellent enantioselectivities. In contrast, the polymer-supported *N*-sulfonylated amino acids or aminoalcohols served as good chiral auxiliaries or chiral ligands in a variety of asymmetric syntheses [7], including our system of polystyrene-supported *N*-sulfonylated aminoalcohol **1** which was used as a recoverable ligand in titanium-catalyzed asymmetric $ZnEt_2$ additions to aldehydes



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[8]. Resin **1** was reused 5 times furnishing the desired alcohol with enantioselectivities decreasing slightly from 92 to 86% ee.

To continue our efforts to develop heterogeneous and homogeneous catalytic systems [8,9], the aim of this study is to synthesize polymer-supported catalysts having better activity and reusability. We herein report two novel polymer-supported *N*-sulfonylated aminoalcohols **13** and **14** prepared from L-tyrosine instead of L-phenylalanine used in the synthesis of **1**. The heterogeneous Ti(O-*i*-Pr)$_4$/**13** system is an excellent recoverable catalyst in asymmetric diethylzinc additions to aldehydes and can be reused 9 times giving the product with enantioselectivities $\geq$87% ee. In contrast, the Ti(O-*i*-Pr)$_4$/**14** system was used only once in asymmetric triethylaluminum additions to aldehydes. This study demonstrates that the Ti(O-*i*-Pr)$_4$/**13** system having the *N*-sulfonylated aminoalcohol moieties farther away from the polymer backbone is a superior catalyst to the previously reported Ti(O-*i*-Pr)$_4$/**1** system.

2. Experimental

2.1. Materials

All solvents and aldehydes were dried or purified using standard methods. Diethylzinc (1.0 M solution in hexane) and triethylaluminum (0.9 M solution in hexane) were purchased from Aldrich and Fluka, respectively, and were used directly. Ti(O-*i*-Pr)$_4$ was freshly distilled prior to use. L-Tyrosine, 4-vinylbenzyl chloride, tosyl chloride, 2-hydroxy-3,5-dichlorobenzenesulfonyl chloride, and AIBN were purchased from Aldrich and used directly.

2.2. Measurements

All catalytic reactions were carried out under a dry nitrogen atmosphere. ^{1}H and ^{13}C NMR spectra were obtained on a Varian Mercury-400 spectrometer, and chemical shifts were measured relative to tetramethylsilane as an internal reference. Solid state ^{13}C NMR chemical shifts were obtained on a Bruker DSX400WB NMR spectrometer (100 MHz) and are referenced to the external tetramethylsilane. IR spectra were recorded on a Bruker EQUINOX 55 FTIR spectrometer. Melting points were taken on a Mel-Temp II instrument and are uncorrected. Elemental analyses were performed using a Heraeus CHN-OS-RAPID instrument. Enantiomeric excesses were determined by HPLC systems (Chiralcel-OD column) equipped with a UV detector while using the IPA/hexane solvent system as a mobile phase.

2.3. Synthesis of polymer-supported N-sulfonylated β-aminoalcohol resins

2.3.1. Benzyl (*S*)-3-(4-benzyloxyphenyl)-2-(dibenzylamino)propionate (*5*)

To a stirred suspension of L-tyrosine (30.0 g, 166 mmol) and K_2CO_3 (114 g, 825 mmol) in EtOH/water (300/120 mL) was added benzyl chloride (95.0 mL, 825 mmol) at room temperature. The resulting solution was heated under reflux for 12 h, and EtOH was removed to give a yellow solution. The solution was added to 150 mL water followed by extraction with EtOAc (150 mL × 3). The organic extracts were dried over $MgSO_4$ and the solvents were removed under reduced pressures. The resulting solution was distilled under reduced pressures to remove the benzyl chloride, affording the product as a yellow oil (85.2 g, 95.0%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46–6.82 (m, 24H, 5*Ph*), 5.22 (d, $J = 12.4$ Hz, 1H, PhCH_AH_BO), 5.12 (d, $J = 12.4$ Hz, 1H, PhCH_AH_BO), 5.06 (s, 2H, PhCH_2OAr), 3.91 (d, $J = 14.0$ Hz, 2H, PhCH_AH_BN), 3.65 (dd, $J = 7.6$, 8.0 Hz, 1H, *CH*N), 3.52 (d, $J = 14.0$ Hz, 2H, PhCH_AH_BN), 3.07 (dd, $J = 14.0$, 7.6 Hz, 1H, ArCH_AH_B), 2.94 (dd, $J = 14.0$, 8.0 Hz, 1H, ArCH_AH_B) ppm.

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 171.89, 157.12, 139.07, 137.00, 135.80, 130.19, 130.12, 128.48, 128.33, 128.31, 128.23, 128.04, 127.97, 127.66, 127.20, 126.73, 114.38, 69.67, 65.74, 62.34, 54.18, 34.56 ppm.

Anal. Calcd. for $C_{37}H_{35}NO_3$: C, 82.04; H, 6.51; N, 2.59%. Found: C, 81.62; H, 6.24; N, 2.10%.

2.3.2. (*S*)-3-(4-Benzyloxyphenyl)-2-(dibenzylamino)propan-1-ol (*6*)

To a suspension of $LiAlH_4$ (6.07 g, 160 mmol) in 150 mL THF, (*S*)-benzyl ester **5** (85.2 g, 157 mmol) in 100 mL THF was added dropwise under nitrogen at 0 °C. The mixture was reacted for 12 h and water (~50 mL) was added until no precipitate formed. Ether (200 mL) was added and the solution was filtered. The filtrate was evaporated under reduced pressures to remove the solvent and volatile materials. The benzyl alcohol formed in the reaction was distilled off completely under reduced pressures and the residue was recrystallized from a mixed solvent system of EtOAc/hexane (15/100 mL) to afford **6** as a white solid (63.3 g, 92.1%); m.p. 110–112 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43–6.88 (m, 19H, 4*Ph*), 5.04 (s, 2H, PhCH_2OAr), 3.92 (d, $J = 13.2$, 2H, PhCH_AH_BN), 3.49 (m, 3H, CH_AH_BOH and PhCH_AH_BN), 3.35 (s, br, 1H, *OH*), 3.04 (m, 3H, CH_AH_BOH, *CH*N and ArCH_AH_B), 2.38 (dd, $J = 13.6$, 10.0 Hz, 1H, ArCH_AH_B) ppm.

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 157.10, 139.01, 136.88, 131.27, 129.74, 128.79, 128.36, 128.33, 127.70, 127.21, 127.08, 114.80, 69.80, 60.71, 60.24, 53.07, 30.76 ppm.

Anal. Calcd. for $C_{30}H_{31}NO_2$: C, 82.35; H, 7.14; N, 3.20%. Found: C, 82.37; H, 6.99; N, 3.27%.

2.3.3. (*S*)-3-(4-Benzyloxyphenyl)-2-(dibenzylamino)propanal (*7*)

To a solution of **6** (30.0 g, 68.6 mmol) and NEt_3 (24.4 mL, 175 mmol) in 50 mL DMSO at 0 °C, pyridine–sulfur trioxide (25.4 g, 160 mmol) in 50 mL DMSO was added dropwise for 10 min. The resulting solution was warmed to room temperature and was allowed to react for 4 h. The reaction mixture was quenched with ice (100 g) and the mixture was extracted with EtOAc (100 mL × 3). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressures to give crude product **7** as a yellow oil which was used directly in next step of reaction.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.72 (s, 1H, *CH*O), 7.45–6.87 (m, 19H, 4*Ph*), 5.05 (s, 2H, PhCH_2OPh), 3.81 (d, $J = 13.6$ Hz, 2H, PhCH_AH_BN), 3.67 (d, $J = 13.6$ Hz, 2H, PhCH_AH_BN), 3.51 (dd, $J = 7.2$, 6.4 Hz, 1H, *CH*N), 3.08 (dd, $J = 14.0$, 7.2 Hz, 1H, ArCH_AH_B), 2.89 (dd, $J = 14.0$, 6.0 Hz, 1H, ArCH_AH_B) ppm.

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 202.12, 157.17, 138.80, 137.01, 131.15, 130.23, 128.62, 128.40, 128.24, 127.74, 127.26, 127.16, 114.74, 69.86, 68.39, 54.64, 29.20 ppm.

2.3.4. (1R,2S)-3-(4-Benzyloxyphenyl)-2-(dibenzylamino)-1-phenylpropan-1-ol hydrochloride (**8**)

To aldehyde **7** (68.6 mmol) in 60 mL THF was added PhMgBr (103 mmol in 60 mL THF) at 0 °C. The mixture was stirred for 12 h, and the resulting solution was hydrolyzed with saturated NH_4Cl solution (50 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (50 mL × 3). The combined organic phase was washed with brine (100 mL × 2) and dried over $MgSO_4$. After removing the solvent, the residue was diluted with ether (150 mL), and then 4 M HCl aqueous solution (30 mL) was added to afford a white precipitate. The precipitate was recrystallized from a mixed solvent of MeOH/EtOAc (5/100 mL) to give a white solid of **8** (26.1 g, 69.2%); m.p. 170–172 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 11.04 (s, br, 1H, *HCl*), 7.74–6.80 (m, 24H, 5*Ph*), 6.06 (s,1H, *OH*), 5.29 (d, $J = 10.4$ Hz, 1H, PhCH_AH_BN), 5.14 (s, 1H, Ph*CH*OH), 5.06 (s, 2H, PhCH_2OPh), 4.35 (m, 2H, PhCH_AH_BN), 3.99 (d, $J = 5.2$ Hz, 1H, PhCH_AH_BN), 3.43 (dd, $J = 12.4$, 8.8 Hz, 1H, *CH*N), 3.21 (dd, $J = 16.0$, 9.6 Hz, 1H, ArCH_AH_B), 2.96 (dd, $J = 15.6$, 3.6 Hz, 1H, ArCH_AH_B) ppm.

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 157.82, 140.46, 136.74, 131.89, 130.64, 129.91, 129.77, 129.33, 129.13, 128.59, 128.20, 128.03, 127.32, 127.11, 125.27, 115.44, 70.71, 70.08, 69.16, 56.16, 27.63 ppm.

Anal. Calcd. for $C_{36}H_{36}ClNO_2$: C, 78.60; H, 6.60; N, 2.55%. Found: C, 78.59; H, 6.84; N, 2.77%.

2.3.5. (1R,2S)-2-Amino-3-(4-hydroxyphenyl)-1-phenylpropan-1-ol hydrochloride (**9**)

To a solution of **8** (20.0 g, 36.4 mmol) in 80 mL methanol was added 4% $Pd(OH)_2$–C (0.80 g). The reaction vessel was connected to a hydrogen balloon, and the mixture was vigorously stirred under the hydrogen atmosphere for 48 h. The $Pd(OH)_2$–C catalyst was removed by filtration and washed with methanol. The filtrate was concentrated under reduced pressures to afford product **9** as a white solid (9.76 g, 95.8%); m.p. 212–214 °C.

A drop of NEt_3 was added to the $CDCl_3$ suspension of **9** to remove HCl from the compound to give a clear solution for NMR measurements.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41–6.70 (m, 9H, 2*Ph*), 4.65 (d, $J = 5.2$ Hz, 1H, Ph*CH*OH), 3.24 (m, 1H, *CH*N), 2.77 (dd, $J = 14.0$, 3.2 Hz, 1H, ArCH_AH_B), 2.29 (dd, $J = 14.0$, 10.4 Hz, 1H, ArCH_AH_B) ppm.

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 155.41, 142.07, 129.61, 128.79, 127.55, 126.69, 126.24, 115.35, 75.58, 57.79, 36.90 ppm.

Anal. Calcd. for $C_{15}H_{18}ClNO_2$: C, 64.40; H, 6.49; N, 5.01%. Found: C, 64.76; H, 6.63; N, 4.76%.

2.3.6. (1R,2S)-2-Amino-1-phenyl-3-(4-(4-vinylbenzyloxy)-phenyl)propan-1-ol (**10**)

Compound **9** (5.60 g, 20.0 mmol), sodium hydride (1.20 g, 50.0 mmol) and 60 mL DMF were placed in a 200 mL round-bottomed flask with stirring under a nitrogen atmosphere. After the evolution of hydrogen gas ceased, 4-vinylbenzyl chloride (2.82 mL, 20.0 mmol) was added and the resulting mixture was stirred at room temperature for 5 h. After removing DMF, the mixture was added to water (50 mL) and the solution was extracted with ethyl acetate (50 mL × 3). The combined organic extracts were dried over $MgSO_4$ and evaporated to dryness giving a pale yellow solid. The crude product was recrystallized from ethyl acetate (30 mL) to afford a white solid of **10** (5.58 g, 77.6%); m.p. 130–132 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43–6.88 (m, 13H, 3*Ph*), 6.72 (dd, $J = 17.6$, 11.2 Hz, 1H, CH_2CHAr), 5.76 (d, $J = 17.6$ Hz, 1H, CH_AH_BCHAr), 5.25 (d, $J = 11.2$ Hz, 1H, CH_AH_BCHAr), 5.01 (s, 2H, ArCH_2OAr), 4.72 (d, $J = 4.8$ Hz, 1H, Ph*CH*OH), 3.28 (m, 1H, *CH*N), 2.76 (dd, $J = 14.0$, 3.2 Hz, 1H, ArCH_AH_B), 2.33 (dd, $J = 14.0$, 10.8 Hz, 1H, ArCH_AH_B) ppm.

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 157.27, 141.38, 137.23, 136.55, 136.37, 131.35, 130.13, 128.30, 127.62, 127.56, 126.53, 126.35, 114.88, 114.04, 76.41, 69.71, 57.90, 37.39 ppm.

Anal. Calcd. for $C_{24}H_{25}NO_2$: C, 80.19; H, 7.01; N, 3.90%. Found: C, 80.11; H, 6.88; N, 3.90%.

2.3.7. (1R,2S)-2-(p-Toluenesulfonylamino)-1-phenyl-3-(4-(4-vinylbenzyloxy)phenyl)propan-1-ol (**11**)

Aminoalcohol **10** (2.16 g, 6.0 mmol), NEt_3 (4.18 mL, 30.0 mmol) and a catalytic amount of DMAP (10 mg) were added to 30 mL CH_2Cl_2 and the solution was cooled to 0 °C. Tosyl chloride (1.26 g, 6.6 mmol) in 30 mL CH_2Cl_2 was added dropwise to the above solution in 5 min. After the addition was complete, the solution was warmed to room temperature and reacted for 12 h. The resulting mixture was washed consecutively with 1.0 M HCl (30 mL), saturated $NaHCO_3$ (50 mL), and brine (50 mL). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressures to give a white solid. The crude product was recrystallized from CH_2Cl_2/hexane (10/20 mL) to afford a white solid of **11** (2.73 g, 88.6%); m.p. 132–134 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46–7.05 (m, 13H, 3*Ph*), 6.77–6.63 (m, 5H, CH_2CHAr and *Ph*), 5.77 (d, $J = 17.6$ Hz, 1H, CH_AH_BCHAr), 5.27 (d, $J = 10.4$ Hz, 1H, CH_AH_BCHAr), 5.05 (s, 1H, *NH*), 4.99 (s, 2H, ArCH_2OAr), 4.56 (d, $J = 7.2$ Hz, 1H, Ph*CH*OH), 3.58 (m, 1H, *CH*N), 2.95 (s, br, 1H, *OH*), 2.57 (dd, $J = 14.4$, 4.0 Hz, 1H, ArCH_AH_B), 2.43 (dd, $J = 14.4$, 10.0 Hz, 1H, ArCH_AH_B), 2.37 (s, 3H, CH_3) ppm.

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 157.35, 142.98, 140.15, 137.34, 136.42, 136.32, 129.93, 129.36, 129.12,

128.37, 127.62, 127.56, 126.85, 126.41, 126.18, 114.67, 114.15, 75.05, 69.59, 61.16, 33.43, 21.47 ppm.

Anal. Calcd. for $C_{31}H_{31}NO_4S$: C, 72.49; H, 6.08; N, 2.73%. Found: C, 72.32; H, 5.87; N, 2.45%.

2.3.8. (1R,2S)-2-(3,5-Dichloro-2-hydroxybenzenesulfonylamino)-1-phenyl-3-(4-(4-vinylbenzyloxy)phenyl)propan-1-ol (**12**)

Synthetic procedures are similar to that of **11**. The crude product was recrystallized from CH_2Cl_2/hexane (10/20 mL) to give a white solid of **12** (3.17 g, 90.4%); m.p. 58–60 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (s, br, 1H, Ar*OH*), 7.46–7.21 (m, 11H, 3*Ph*), 6.77–6.65 (m, 5H, CH_2CHAr and *Ph*), 5.77 (d, $J = 17.6$ Hz, 1H, CH_AH_BCHAr), 5.27 (d, $J = 11.2$ Hz, 1H, CH_AH_BCHAr), 5.19 (d, $J = 8.4$ Hz, 1H, Ph*CH*OH), 5.06 (d, $J = 3.6$ Hz, 1H, *NH*), 4.96 (dd, $J = 14.8$, 11.6 Hz, 2H, ArCH_AH_BOAr), 3.70 (m, 1H, *CH*N), 2.64 (dd, $J = 14.4$, 3.6 Hz, 1H, ArCH_AH_B), 2.50 (dd, $J = 14.4$, 10.4 Hz, 1H, ArCH_AH_B) ppm.

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 157.40, 148.59, 139.88, 137.47, 136.46, 134.07, 129.86, 128.66, 128.58, 128.20, 127.73, 126.46, 126.44, 126.01, 125.00, 123.87, 114.53, 114.14, 77.21, 75.78, 69.55, 62.14, 33.47 ppm.

Anal. Calcd. for $C_{30}H_{27}Cl_2NO_5S$: C, 61.64; H, 4.66; N, 2.40%. Found: C, 61.76; H, 4.57; N, 2.08%.

2.3.9. Polymer-supported bidentate N-sulfonylated β-aminoalcohol (**13**)

To a solution of *N*-sulfonylated aminoalcohol **11** (0.514 g, 1.00 mmol) and AIBN (0.010 g, 0.063 mmol) in 5 mL benzene were added styrene (0.45 mL, 3.9 mmol), divinylbenzene (0.014 mL, 0.10 mmol) and 40 mL water at room temperature. The temperature was raised to 80 °C and the solution was stirred vigorously for 48 h. The resulting polymer beads were filtered and washed consecutively with water (10 mL), methanol (10 mL), THF–methanol (5/5 mL), THF (10 mL), and methanol (10 mL). The polymer beads were dried under reduced pressures at 110 °C for 24 h to give resin **13** (0.80 g, 85.8%).

IR (KBr): $\nu = 3499$, 3340, 3047, 3026, 2921, 2849, 1948, 1805, 1605, 1508, 1450, 1415, 1324, 1256, 1155, 1092, 959, 807, 757, 701, 666, 547 cm^{-1}.

Solid state ^{13}C NMR (100.46 MHz): δ 157.97, 145.54, 128.45, 115.36, 77.31, 68.70, 63.52, 40.55, 33.10, 21.93 ppm.

Elemental analysis found: C, 78.79; H, 5.69; N, 1.30%. It is calculated to contain 0.93 mmol bidentate *N*-sulfonylated β-aminoalcohol in 1 g of resin **13**.

2.3.10. Polymer-supported tridentate N-sulfonylated β-aminoalcohol (**14**)

Synthetic procedures are similar to that of **13**. The polymer beads were dried under reduced pressures at 110 °C for 24 h to afford resin **14** (0.85 g, 84.7%).

IR (KBr): $\nu = 3538$, 3330, 3062, 3026, 2921, 2830, 1948, 1880, 1759, 1607, 1509, 1460, 1315, 1239, 1158, 1081, 869, 811, 757, 700, 612, 568 cm^{-1}.

Solid state ^{13}C NMR (100.46 MHz): δ 158.04, 145.77, 128.44, 117.19, 78.42, 67.96, 63.66, 40.55, 34.10 ppm.

Elemental analysis found: C, 71.34; H, 4.86; N, 1.33%. It is calculated that 1 g of resin **14** contains 0.95 mmol of chiral tridentate *N*-sulfonylated β-aminoalcohol ligand.

2.4. General procedure of catalytic reactions

2.4.1. General procedure of enantioselective addition of $ZnEt_2$ to aldehydes

Under a dry nitrogen atmosphere, resin **13** (0.05 mmol) and Ti(O-*i*-Pr)$_4$ (0.60 mmol) were mixed in dry dichloromethane (2 mL) at room temperature. After stirring the mixture for 1 h, a solution of $ZnEt_2$ (1.0 M in hexane, 0.75 mmol) was added at 0 °C. The mixture was stirred for 0.5 h and the resulting solution was treated with an aldehyde (0.50 mmol). The solution was allowed to react at 0 °C for 12 h and quenched with 1 M aqueous HCl (3 mL). The aqueous phase was extracted with ethyl acetate (3 × 10 mL). The combined organic phase was dried over $MgSO_4$, filtered, and concentrated. Chromatography of the residue on silica gel gave the chiral secondary alcohol. Enantiomeric purities of products were determined by HPLC.

2.4.2. General procedure of enantioselective addition of $AlEt_3$ to aldehydes

Under a dry nitrogen atmosphere, resin **14** (0.05 mmol) and Ti(O-*i*-Pr)$_4$ (1.40 mmol) were mixed in dry THF (2 mL) at room temperature. After stirring the mixture for 1 h, a solution of $AlEt_3$ (0.9 M in hexane, 1.25 mmol) was added at 0 °C. The mixture was stirred for 0.5 h and the resulting solution was treated with an aldehyde (0.50 mmol). The solution was allowed to react at 0 °C for 12 h and quenched with 1 M aqueous HCl (3 mL). The aqueous phase was extracted with ethyl acetate (3 × 10 mL). The combined organic phase was dried over $MgSO_4$, filtered, and concentrated. Chromatography of the residue on silica gel gave the secondary alcohol. Enantiomeric purities of products were determined by HPLC.

2.5. Reuse procedure

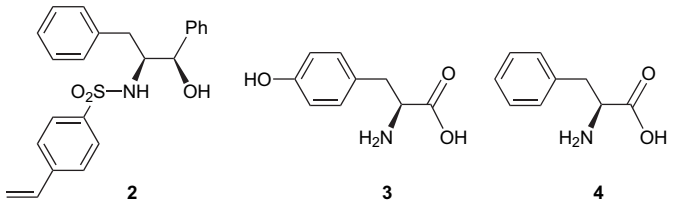
A U-shaped glassware with glass frit was used for the recycle use of recoverable titanium(IV) catalyst of resin **13**. The reaction mixture was stirred for 12 h at 0 °C and the product was then separated by filtration through the glass frit. The residual resin was washed with CH_2Cl_2 (2 × 2 mL) and was reused with additions of freshly distilled CH_2Cl_2 (2 mL) and 1.1 mol equiv. of Ti(O-*i*-Pr)$_4$ at 0 °C followed by $ZnEt_2$ and benzaldehyde.

3. Results and discussion

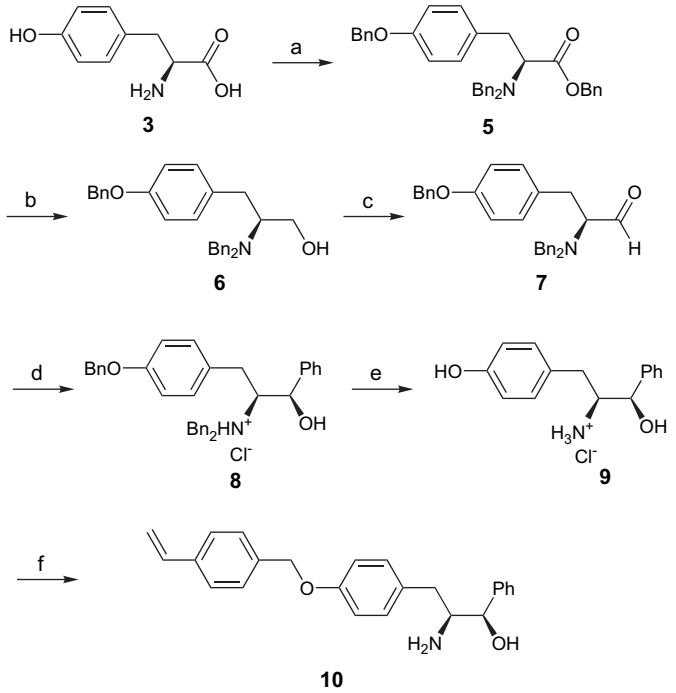
3.1. Synthesis of chiral N-sulfonylated aminoalcohols bearing a styrene moiety

Due to our recent interest in transformations of homogeneous *N*-sulfonylated aminoalcohols into heterogeneous

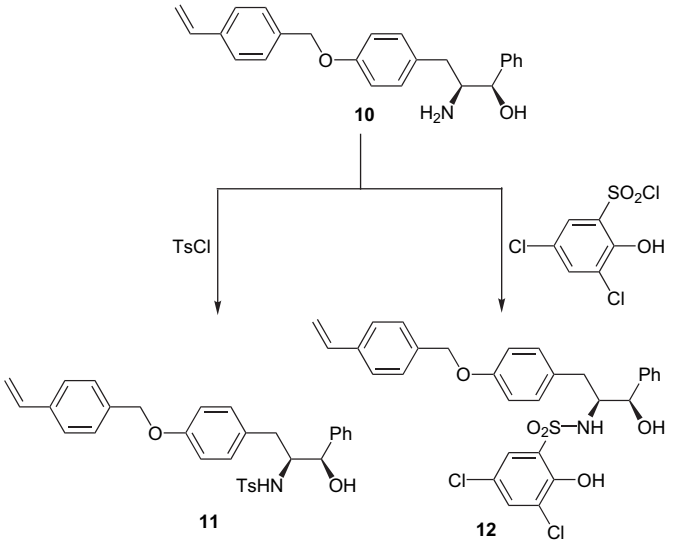
systems, we had previously reported the synthesis of cross-linked polystyrene-supported resin **1** from co-polymerization of styrene, divinylbenzene, and the aminoalcohol **2**. The polymer-supported *N*-sulfonylated aminoalcohol **1** shows similar reactivity and stereoselectivity to its homogeneous analogue in titanium-catalyzed asymmetric $ZnEt_2$ additions to aldehydes. Resin **1** can be reused 5 times affording the product in excellent to good enantioselectivities from 92% to 86%. The bidentate *N*-sulfonylated aminoalcohol moieties in resin **1** are close to the polymer backbone and it is speculated that the close proximity of *N*-sulfonylated aminoalcohols to the polymer backbone might affect the reusability of resin **1**. To verify our argument, L-tyrosine (**3**) is selected as a starting material for the synthesis of resins having *N*-sulfonylated aminoalcohol farther away from the polymer backbone. L-Tyrosine has an additional hydroxyl group at the *para*-position of the phenyl ring compared with L-phenylalanine (**4**) and this hydroxyl functional group is used for the synthesis of substituted styrene monomers containing *N*-sulfonylated aminoalcohol.



Based on literature procedures [9a,10] and with modifications, (1*R*,2*S*)-aminoalcohol **10** bearing the styrene moiety was prepared starting from **3** (Scheme 1). Though the synthesis



Scheme 1. Reagents and conditions: (a) BnCl, K_2CO_3, H_2O/EtOH, reflux; (b) $LiAlH_4$, THF, 0 °C–rt; (c) SO_3·py, NEt_3, DMSO, 0 °C–rt; (d) (1) PhMgBr, THF, 0 °C, (2) HCl; (e) $Pd(OH)_2$–C, H_2, MeOH, rt; (f) (1) NaH, DMF, 0 °C–rt, (2) 4-vinylbenzyl chloride, DMF, rt.

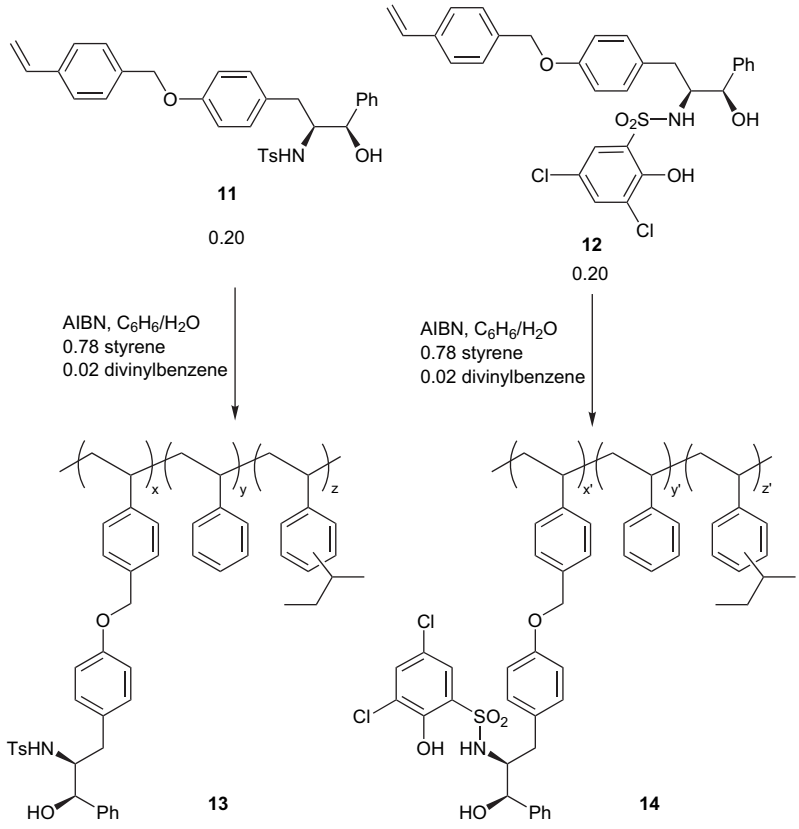


Scheme 2. Syntheses of **11** and **12**.

of **10** requires 6 steps, yield in each step is, in general, >90% except in steps (d) and (f) of 69.2% and 77.6%, respectively. The modified synthetic procedures reported in this study are remarkable and compound **10** was obtained in an excellent overall yield of 44.6% in 6 steps. Aminoalcohol **10** further reacted with tosyl chloride or 2-hydroxy-3,5-dichlorobenzene sulfonyl chloride to furnish both bidentate *N*-sulfonylated aminoalcohol **11** and tridentate *N*-sulfonylated aminoalcohol **12** (Scheme 2) in high yields of 88.6 and 90.4%, respectively.

3.2. Synthesis and characterization of polymer-supported N-sulfonylated aminoalcohols

Our previous study showed that resin **1** containing one *N*-sulfonylated aminoalcohol ligand in every 5 styrene units (i.e., aminoalcohol moieties attached to 20% styrene units) is the best performing recoverable ligand in titanium-catalyzed asymmetric diethylzinc additions to aldehydes. Similarly, *N*-sulfonylated aminoalcohol **11**, styrene and divinylbenzene in a ratio of 0.20/0.78/0.02 were co-polymerized with AIBN as an initiator under vigorous stirring at 80 °C for 48 h [11] to afford the cross-linked polystyrene-supported bidentate *N*-sulfonylated aminoalcohol **13** in 85.8% yield (Scheme 3). The cross-linked polystyrene resin **14** bearing tridentate *N*-sulfonylated aminoalcohols was obtained in 84.7% yield from co-polymerization of **12**, styrene and divinylbenzene in the same 0.20/0.78/0.02 ratio. These two resins were characterized by IR and solid state ^{13}C NMR spectroscopies. The IR spectra reveal characteristic broad O–H and N–H stretching peaks at 3499 and 3340 cm^{-1} belonging to the bidentate *N*-sulfonylated β-aminoalcohol group of resin **13** and at 3538 and 3330 cm^{-1} due to the tridentate *N*-sulfonylated β-aminoalcohol group of resin **14**. The vibrational peaks of polystyrene phenyl groups appear around 1600 and 1500 cm^{-1}. Solid state ^{13}C NMR peaks from 160 to 110 ppm are signals of polystyrene phenyl carbons. The ^{13}C signals at 77.31, 68.70, and 63.52 ppm for resin **13** and at 78.42, 67.96 and 63.66 ppm

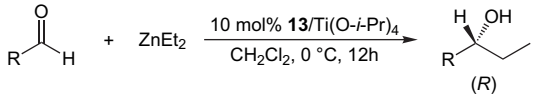


Scheme 3. Syntheses of polymer-supported *N*-sulfonylated β-aminoalcohols **13** and **14**.

for resin **14** are resonances of carbon atoms attached to the oxygen or nitrogen atoms of the *N*-sulfonylated β-aminoalcohol group. Since each attached *N*-sulfonylated β-aminoalcohol ligand contains one nitrogen atom, the ligand loading in the resin is based on the nitrogen content. Elemental analytical data show that the ligand content in resin **13** is 0.93 mmol/g, suggesting ligand loadings of ~15% styrene units. In resin **14**, the ligand content is 0.95 mmol/g, indicating ligand loadings of ~18% styrene units. Experimental ligand loadings in both resins are smaller than the initial 20% **11** or **12** used in polymerization reactions.

*3.3. Application of recoverable Ti(O-i-Pr)$_4$/**13** system to diethylzinc additions to aldehydes*

In this study, asymmetric $ZnEt_2$ addition reactions were first examined employing titanium catalysts of 10 mol% resin **13** (Eq. (1)) and results are listed in Table 1. The quantities of Ti(O-*i*-Pr)$_4$ were optimized (entries 1–4) and it was found that the system with 1.2 equiv. Ti(O-*i*-Pr)$_4$ gave the product in the best enantioselectivity of 96% ee (entry 3). Under the best reaction condition, four additional aromatic aldehydes were examined to furnish chiral alcohols in excellent enantioselectivities from 90 to 96% ee (entries 5–8). In addition to aromatic aldehydes, the aliphatic 3-phenylpropanal was also examined giving the product in an excellent 92% ee (entry 9). This study shows that the recoverable Ti(O-*i*-Pr)$_4$/**13** catalytic system has comparable reactivity and stereoselectivity with the homogeneous analogue in asymmetric Et_2Zn additions to aldehydes.



(1)

The reusability of resin **13** was conducted on the benzaldehyde substrate in a U-shaped fritted glassware. After each run of reaction, the solution in one arm of the U-shaped glassware

Table 1
$ZnEt_2$ addition to aldehydes catalyzed by *in situ*-formed titanium systems of 10 mol% resin **13**[a]

Entry	Aldehyde	Ti(O-*i*-Pr)$_4$[b] (equiv.)	Yield[c] (%)	ee[d] (%)
1	Benzaldehyde	0.8	97[e]	91
2	Benzaldehyde	1.0	98[e]	91
3	Benzaldehyde	1.2	96	96
4	Benzaldehyde	1.4	100[e]	73
5	1-Naphthaldehyde	1.2	95	90
6	2-Naphthaldehyde	1.2	99	93
7	3-Methoxybenzaldehyde	1.2	98	96
8	4-Chlorobenzaldehyde	1.2	97	94
9	3-Phenylpropanal	1.2	88	92

[a] Aldehyde/$ZnEt_2$ = 0.50/0.75; CH_2Cl_2, 2.0 mL.
[b] Ti(O-*i*-Pr)$_4$, equiv. relative to aldehyde.
[c] Isolated yields.
[d] The ee values were determined by HPLC using an OD column from Daicel.
[e] Yields were determined by ^{1}H NMR.

was filtered through the glass frit to another chamber, and the filtrate was transferred out for analysis. The resin that remained in the U-shape glassware was washed twice with 2 mL CH_2Cl_2, and the glassware was recharged with reagents and the solvent for next run of reaction. Resin **13** was reused 9 times without losing any activity. In each cycle, a quantitative yield of the secondary alcohol was obtained. Yet, enantioselectivities of the product in consecutive runs decrease slightly from 96, 94, 92, 92, 89, 88, 87, 88, to 89% ee. Though the activity of the residual resin remains the same, the product in a lower 72% ee was observed when the resin was used the tenth time. If the used resin was washed with 1 M HCl aqueous solution and dried under reduced pressures, the reaction employing this refreshed resin **13** gave the product in quantitative yield and 88% ee. This study clearly demonstrates that resin **13** is superior to resin **1** in both reactivity and reusability. For resin **1**, a longer reaction time of 16 h is required and the reusability is up to 5 times. Resin **13** has a longer spacing group between the polymer backbone and *N*-sulfonylated aminoalcohol and this difference might be a key factor of higher reactivity and better reusability of resin **13**.

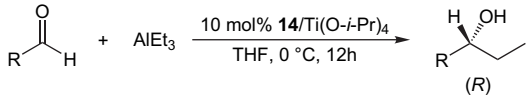
*3.4. Application of Ti(O-i-Pr)$_4$/**14** system to triethylaluminum additions to aldehydes*

In addition to dialkylzinc reagents, organoaluminum reagents [8,12] have also been employed in asymmetric addition reactions. Furthermore, arylaluminum compounds have been demonstrated to be highly efficient reagents in coupling reactions [13]. Since the homogeneous titanium catalyst of 10 mol% tridentate *N*-sulfonylated aminoalcohol is an excellent system in asymmetric $AlEt_3$ additions to aldehydes, a titanium system of 10 mol% tridentate resin **14** was also studied (Eq. (2)) and results are listed in Table 2. It is found that the Ti(O-*i*-Pr)$_4$/**14** system requires higher quantities of $AlEt_3$ at 2.5 equiv. and Ti(O-*i*-Pr)$_4$ at 2.8 equiv. in order to give products in satisfactory enantioselectivities (entries 1–4). In this study, $AlEt_3$ additions to a variety of aldehydes were examined affording chiral secondary alcohols in good to excellent stereoselectivities from 73–92% ee (entries 3 and 5–11). To our surprise, the reuse of resin **14** gave secondary alcohols in less than 50% ee, probably due to the high activity of the $AlEt_3$ reagent which poisoned resin **14**.

Table 2
$AlEt_3$ addition to aldehydes catalyzed by the *in situ*-formed titanium systems of 10 mol% resin **14**[a]

Entry	Aldehyde	Ti(O-*i*-Pr)$_4$[b] (equiv.)	Yield[c] (%)	ee[d] (%)
1	Benzaldehyde	1.8	92[e]	84
2	Benzaldehyde	2.4	96[e]	84
3	Benzaldehyde	2.8	95	92
4	Benzaldehyde	3.0	99[e]	85
5	1-Naphthaldehyde	2.8	89	88
6	2-Naphthaldehyde	2.8	94	84
7	2-Methoxybenzaldehyde	2.8	83	73
8	4-Methoxybenzaldehyde	2.8	95	87
9	4-Chlorobenzaldehyde	2.8	95	87
10	*trans*-Cinnamaldehyde	2.8	93	74
11	3-Phenylpropanal	2.8	70	80

[a] Aldehyde/$AlEt_3$ = 0.5/1.25; THF, 2.0 mL.
[b] Ti(O-*i*-Pr)$_4$, equiv. relative to aldehyde.
[c] Isolated yields.
[d] The ee values were determined by HPLC using an OD column from Daicel.
[e] Yields were determined by ^{1}H NMR.



(2)

4. Conclusions

In summary, novel polymer-supported bidentate *N*-sulfonylated β-aminoalcohol **13** and tridentate *N*-sulfonylated β-aminoalcohol **14** were prepared in high yields from radical polymerizations of styrene, divinylbenzene, and substituted styrene containing the chiral ligand. The Ti(O-*i*-Pr)$_4$/**13** system is an extremely superior recoverable catalyst in asymmetric $ZnEt_2$ additions to aldehydes. Resin **13** can be reused 9 times affording the product in quantitative yields with enantioselectivities ≥87%. The Ti(O-*i*-Pr)$_4$/**14** system is the first polymer-supported catalyst used in $AlEt_3$ additions to aldehydes, giving secondary alcohols in excellent yields and good to excellent enantioselectivities. Further studies of recoverable systems in asymmetric catalysis are currently underway.

Acknowledgment

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