Synthesis of a new chiral auxiliary — Non-cross-linked polystyrene-supported oxazolidine-2-selone

Xiping He, Jia Li, Cuifen Lu, Zuxin Chen, and Guichun Yang

Abstract: A new chiral auxiliary, non-cross-linked polystyrene-supported oxazolidine-2-selone was synthesized using *N*-Boc-L-tyrosine ethyl ester as starting material. The structure of the target product was detected by IR, NMR, elemental analysis, and the spectrum result was consistent with the molecular structure.

Key words: non-cross-linked polystyrene, support, oxazoline-2-selone, chiral auxiliary.

Résumé : Faisant appel à l'ester éthylique de la *N*-Boc-L-tyrosine comme produit de départ, on a réalisé la synthèse d'un nouvel auxiliaire chiral, l'oxazolidine-2-sélone supportée par du polystyrène non réticulé. La structure du produit de synthèse a été confirmée par spectroscopies IR et RMN et par analyse élémentaire et les résultats spectraux sont en accord avec la structure moléculaire.

Mots-clés : polystyrène non réticulé, support, oxazoline-2-sélénone, auxiliaire chiral.

[Traduit par la Rédaction]

Introduction

Carbon–carbon bond-forming reactions involving asymmetric aldol reactions have emerged as powerful tools in organic synthesis. Chiral oxazolidine-2-selone was found to be an excellent auxiliary in asymmetric aldol reactions.[1–4] However, in most cases, the separation and purification of the chiral auxiliaries were troublesome. To recycle and reuse expensive chiral auxiliaries is a challenge in organic synthesis.

Insoluble polymer supports, such as Merrifield resin and Wang resin provided a simple procedure "filtration" for rapidly achieving the isolation of desired compounds or recovering expensive reagents or catalysts attached onto solid support for recycling.[5,6] But several shortcomings were shown because of nonlinear kinetic behavior, unequal distribution or access to the chemical reaction, and synthetic difficulties in transferring standard organic reactions to the solid phase. Soluble polymer supports have been studied as a way to overcome the problems of insoluble supports. Soluble polymer supports allow expeditious transfer of solution-based synthetic protocols, circumventing the extensive optimization process often required in heterogeneous reactions.[7,8] After the addition of an appropriate poor solvent, the polymer support can be precipitated and filtered, allowing its expeditious recovery.

Non-cross-linked polystyrene (NCPS) and functionalized NCPS show a more restrictive solubility profile because of their high stereoregular configuration of phenyl rings along the polymer main chain and the resulting tendency toward crystallization.[9,10] We theorized that this solubility versus recovery relationship of crystalline polymer — a well-known phenomenon in polymer chemistry — could lead to a better recovery yield of the polymer support when precipitated with a poor solvent.

Our group has undertaken a research program to develop novel chiral auxiliaries using NCPS as support.[11,12] In this article, we report the synthesis of a new NCPS-supported oxazolidine-2-selone chiral auxiliary from *N*-Boc-L-tyrosine ethyl ester (Scheme 1). Reagents and conditions: (a) K_2CO_3 (2.0 equiv), BnBr (1.2 equiv), DMF (dimethylformamide), 40 °C, 24 h; (b) $LiAlH_4$ (1.2 equiv), THF, 0 °C ~ RT (RT, room temperature), 18 h; (c) acetyl chloride (1.1 equiv), EtOAc–MeOH (1:2, *v*/*v*), 0 °C ~ RT, 24 h ; (d) DMF–DMA (dimethyl acetal) (1.1 equiv), TsOH (catalytic amount), N_2, toluene, reflux, 48 h; (e) 20% $Pd(OH)_2$ (catalytic amount), THF–MeOH (1:1, *v*/*v*), RT, 6 h; (f) K_2CO_3 (3.5 equiv), functionalized NCPS (**1**, 1.05 equiv), 40 °C, 24 h; and (g) Methyl lithium (1.2 equiv), hexamethyl disilylamine (1.15 equiv), Se (1.0 equiv), –78 °C ~ RT, 2 h.

Results and discussion

As shown in Scheme 1, NCPS-supported oxazolidine-2-selone was synthesized using *N*-Boc-L-tyrosine ethyl ester as the starting material. A benzylation reaction is used as the most common way to protect the hydroxy, therefore, *N*-Boc-L-tyrosine ethyl ester was first treated with BnBr to

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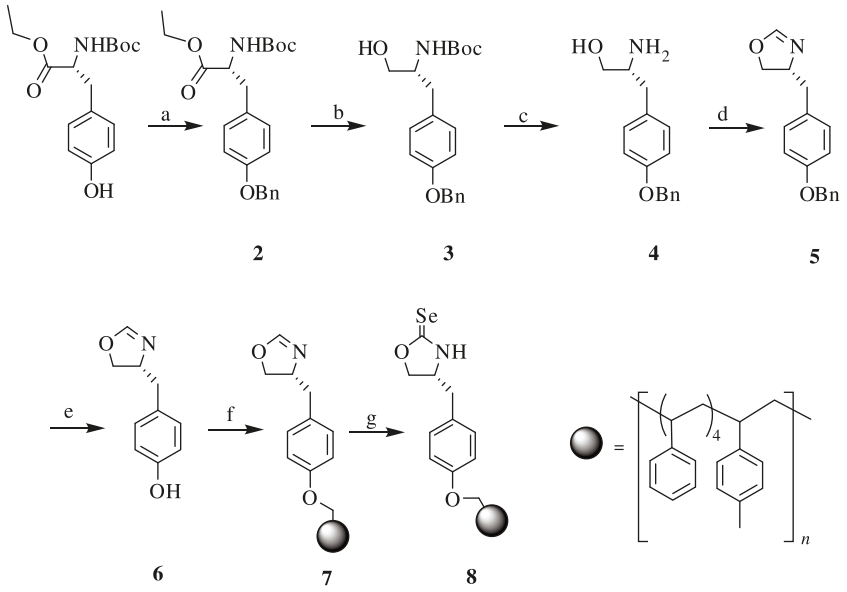
Scheme 1. Synthesis of non-cross-linked polystyrene (NCPS)-supported oxazolidine-2-selenone **8**.



2 **3** **4** **5** **6** **7** **8**

afford the benzylated product **2** in 80% yield. Then compound **2** was reduced by $LiAlH_4$ to obtain the alcohol **3** in 84% yield. Removal of the Boc group from **3** using acetyl chloride under MeOH–EtOAc obtained the amino alcohol **4** in 87% yield. Treating **4** with DMF–DMA produced the oxazoline **5** through a ring-closing reaction.[7] Removal of the benzyl group of **5** was carried out by 20% $Pd(OH)_2$ under H_2 to provide the chiral oxazoline **6** in 84% yield. Then **6** was linked to **1** to afford NCPS-supported oxazoline **7**. Compound **1** (Fig. 1) was prepared according to ref. 9, by copolymerizing 4-vinylbenzyl chloride and styrene in a ratio of 1:4. Finally, **7** was treated with selenium in the presence of lithium amide to obtain NCPS-supported oxazolidine-2-selone **8** in 75% yield. The structure of the chiral auxiliary **8** was detected by IR, NMR, elemental analysis, and the spectrum result was consistent with the molecular structure. This chiral auxiliary is soluble in typical organic solvents, such as $CHCl_3$, CH_2Cl_2, EtOAc, THF, DMF, and benzene, and insoluble in MeOH, EtOH, and H_2O, and this solubility versus recovery relationship of the crystalline polymer could lead to better recovery yield of the chiral auxiliary.

Conclusions

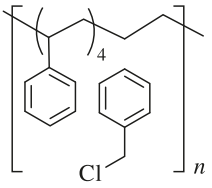
In conclusion, we have developed a new NCPS-supported oxazolidine-2-selone chiral auxiliary. This chiral auxiliary has potential value in asymmetric reactions such as high stereoselectivity and better recovery yield. Further application of this NCPS-supported oxazolidine-2-selone chiral auxiliary in aldol reactions is currently underway in our laboratory.

Experimental

General

All solvents were obtained from commercial sources and dried or purified by standard procedures before use. Melting points were measured on a WRS-1A digital melting point apparatus and uncorrected; optical rotations were measured

Fig. 1. Functionalized non-cross-linked polystyrene (NCPS).



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using a sodium D line on a WZZ-2B automatic polarimeter; IR spectra were recorded on a IR-spectrum one (PerkinElmer) spectrometer. NMR spectra were recorded on a Varian Unity INOVA 600 spectrometer in $CDCl_3$ using TMS as the internal standard; elemental analyses were done on a VarioEL III (Elementar, Germany) analyzer.

Synthesis of *N*-Boc-*O*-benzyl-L-tyrosine ethyl ester (2)

To a solution of *N*-Boc-L-tyrosine ethyl ester (8.64 g, 27.95 mmol) in dry DMF (50 mL) were added benzyl bromide (3.98 mL, 33.54 mmol), anhyd K_2CO_3 (7.71 g, 55.90 mmol), and 18-crown-6 (catalytic amount). Then the resulting mixture was stirred at 40 °C for 24 h. After evaporation of the solvent, the residue was dissolved in ethyl acetate (100 mL) and washed with brine (3 × 10 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated to afford a pale yellow solid. Recrystallization from EtOAc and petroleum ether (PE; 1:5, *v*/*v*) gave **2** (8.9 g, 80%); mp 63.2–63.7 °C. $[\alpha_D^{25}]$ = +16.2 (*c* 0.05, THF). IR (NaCl, cm^{-1}): 3371, 1716, 1611, 1584, 1511. ^1H NMR ($CDCl_3$, 600 MHz) δ: 7.43–7.27 (m, 5H), 7.05 (d, J = 7.8 Hz, 2H), 6.90 (d, J = 8.4 Hz, 2H), 5.04 (s, 2H), 4.96 (t, J = 7.8 Hz, 1H), 4.51 (s, 1H), 4.15 (dd, J_1 = 7.2 Hz, J_2 = 13.8 Hz, 2H), 3.03 (dd, J_1 = 6.0 Hz, J_2 = 11.4 Hz, 2H), 1.43 (s, 9H), 1.23 (t, J = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 172.1, 158.3, 155.6, 137.7, 131.0, 128.8, 128.6, 128.2, 127.7, 115.2, 80.5, 70.6, 61.3, 54.5, 37.4, 28.3, 14.3.

Synthesis of *N*-Boc-*O*-benzyl-L-tyrosinol (3)

To a solution of compound **2** (8.65 g, 21.65 mmol) in anhyd THF (50 mL), $LiAlH_4$ (0.96 g, 25.98 mmol) in THF (20 mL) was added dropwise at 0 °C. The mixture was allowed to stir at RT for 18 h before acidification to pH 6∼7 with 1 N HCl, and the insoluble solid was filtered. After evaporation of the solvent, the residue was dissolved in ethyl acetate (100 mL), washed with brine (3 × 10 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated to afford a white solid. Recrystallization from EtOAc and PE (1:3, *v*/*v*) gave **3** (6.2 g, 84%); mp 105.0–105.6 °C. $[\alpha_D^{25}]$ = –17.5 (*c* 0.02, THF). IR (NaCl, cm^{-1}): 3360, 2923, 1816, 1611, 1524, 694. ^1H NMR ($CDCl_3$, 600 MHz) δ: 7.43–7.26 (m, 5H), 7.12 (d, *J* = 8.4 Hz, 2H), 6.91 (d, *J* = 8.4 Hz, 2H), 6.05 (s, 2H), 5.03 (s, 2H), 3.81 (m, 1H), 3.63 (m, 1H), 3.58 (m, 1H), 2.77 (d, *J* = 7.2 Hz, 2H), 1.42 (s, 9H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 158.6, 156.5, 137.3, 130.1, 129.4, 128.5, 127.8, 115.6, 80.3, 70.5, 64.7, 60.3, 54.1, 37.5, 29.3.

Synthesis of *O*-benzyl-L-tyrosinol (4)

To a solution of compound **3** (5.6 g, 15.68 mmol) in mixed solvents of EtOAc (30 mL) and MeOH (60 mL) was added acetyl chloride (3.91 mL, 31.36 mmol) at 0 °C. After 30 min, the reaction mixture was stirred at RT for 24 h. NaOH (1.5 N) was added to counteract produced acids, then most of the solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (100 mL) and washed with brine (3 × 10 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated to afford a yellow solid. The crude product was further purified by column chromatography (MeOH–CH_2Cl_2, 1:20, *v*/*v*) to give **4** (3.5 g, 87%); mp 174.4–174.8 °C. $[\alpha_D^{25}]$ = –12.0 (*c* 0.04, CH_3OH). IR (NaCl, cm^{-1}): 3704, 3360, 3032, 1609, 1580, 748. ^1H NMR ($CDCl_3$, 600 MHz) δ: 7.45–7.35 (m, 5H), 7.19 (d, *J* = 8.4 Hz, 2H), 7.01 (d, *J* = 9.0 Hz, 2H), 5.13 (s, 2H), 3.74–3.55 (m, 2H), 3.47 (m, 1H), 2.89 (d, *J* = 6.6 Hz, 1H), 2.77 (t, *J* = 6.9 Hz, 1H), 1.85 (s, 3H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 157.3, 137.5, 131.1, 130.6(2C), 129.7, 128.3, 127.8, 115.6, 70.1, 66.2, 54.7, 40.1.

Synthesis of (4*S*)-4-(4′-benzyloxy)benzyl-4,5-dihydrooxazoline (5)

DMF–DMA (1.16 mL, 8.79 mmol) and TsOH (0.06 g) under N_2 were added to a solution of **4** (2.06 g, 8.0 mmol) in toluene (85 mL). The solution was refluxed for 48 h in a flask equipped with a Soxhlet extraction device containing 20 g of 4 Å molecular sieves under N_2. The reaction mixture was washed with 10% $NaHCO_3$ (30 mL) and brine (30 mL) and dried over Na_2SO_4. The residue was purified by flash column chromatography (EtOAc–PE–Et_3N, 1:4:1, *v*/*v*) to give **5** (1.71 g, 80%) as a white solid; mp 117.9–118.3 °C. IR (NaCl, cm^{-1}): 3035, 1630, 1513, 1114. ^1H NMR ($CDCl_3$, 600 MHz) δ: 8.10 (s, 1H), 7.30–7.42 (5H, m), 7.09 (d, *J* = 9.0 Hz, 2H), 6.91 (d, *J* = 9.0 Hz, 2H), 5.01 (s, 2H), 4.18 (t, *J* = 3.0 Hz, 1H), 3.70 (d, *J* = 7.2 Hz, 1H), 3.58 (dd, J_1 = 3.6 Hz, J_2 = 10.2 Hz, 1H), 2.82 (m, 2H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 161.8, 157.9, 137.2, 130.6, 130.4, 129.7, 128.8, 127.7, 115.3, 70.2, 63.8, 52.2, 36.2.

Synthesis of (4*S*)-4-(4′-*p*-hydroxy)benzyl-4,5-dihydrooxazoline (6)

Compound **5** (1.34 g, 5.0 mmol) was dissolved in THF (25 mL) and MeOH (25 mL), and 20% $Pd(OH)_2$ (0.27 g) was added, and the mixture was then stirred under H_2 at room temperature for 6 h. After filtration through Celite, washing with methanol and THF, and evaporation of the solvents, the residue was purified by flash column chromatography (EtOAc–PE–Et_3N, 1:2:1, *v*/*v*) to give **6** (0.74 g, 84%) as a white solid; mp 60.5–60.8 °C. $[\alpha_D^{20}]$ = –68.6 (*c* 0.04, MeOH). IR (NaCl, cm^{-1}): 3197, 1628, 1515, 1380, 1244. ^1H NMR ($CDCl_3$, 600 MHz) δ: 8.10 (s, 1H), 7.12 (d, *J* = 9.0 Hz, 2H), 6.89 (d, *J* = 9.0 Hz, 2H), 5.40 (s, 1H), 4.24 (t, *J* = 4.2 Hz, 1H), 3.84 (d, *J* = 8.4 Hz, 1H), 3.52 (dd, J_1 = 4.8 Hz, J_2 = 12.4 Hz, 1H), 2.64 (m, 2H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 160.4, 157.9, 130.6, 130.4, 115.3, 76.2, 70.2, 39.8.

Synthesis of NCPS-supported (4*S*)-4-substituted 4,5-dihydrooxazoline (7)

To a solution of compound **6** (0.66 g, 3.71 mmol) in DMF (30 mL) were added the functionalized NCPS **1** (2.20 g), anhyd K_2CO_3 (1.80 g, 13.0 mmol), and 18-crown-6 (catalytic amount). The resulting mixture was stirred at 40 °C for 24 h. Then most of the solvent was removed under reduced pressure. The viscous solution was dropped into cold EtOH (100 mL), and the precipitated solid was filtered and dried to afford polymer **7** (2.43 g, 85%). IR (NaCl, cm^{-1}): 3302, 1629, 1237, 699. ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 158.0, 155.0, 145.5, 130.4, 130.1, 128.2, 127.8, 125.9, 115.1, 70.8, 70.2, 66.9, 52.0, 41.0, 40.5. Elementary analysis for polymer **7**: C, 86.31%; H, 7.21%; N, 1.89%.

Synthesis of NCPS-supported (4*S*)-4-benzyloxyl oxazolidine-2-selenone (8)

Methyllithium (2.26 mL, 3.17 mmol) and hexamethyl disilylamine (0.63 mL, 3.04 mmol) were added to dry THF (15 mL) under N_2 at 0 °C. The solution was stirred for 10 min and then cooled to –78 °C. Compound **7** (1.50 g, 2.64 mmol) in dry THF (30 mL) was added dropwise to the solution and the mixture was stirred for 30 min at –78 °C. Se (0.24 g, 2.68 mmol) was added in batches, stirred for an additional 2 h at RT, and then the pH was adjusted to 4–5 by aq saturated citric acid. After filtrating through Celite, the filtrate was concentrated under reduced pressure. The viscous solution was dropped into cold EtOH (50 mL), and the precipitated solid was filtered and dried to afford polymer **8** (1.30 g, 75%). IR (NaCl, cm^{-1}): 3340, 1510, 1261, 698. ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 188.2, 158.1, 137.6, 136.4, 136.3, 130.1, 127.7, 127.1, 126.5, 126.3, 115.7, 114.2, 75.5, 68.8, 56.9, 52.2, 39.2. ^{77}Se NMR ($CDCl_3$, 150 MHz) δ: –319.80 (relative to (*R*)-4-benzyloxazolidine-2-selenone at –328.70). Elementary analysis for polymer **8**: C, 77.71%; H, 6.58%; N, 1.69%.

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