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# Synthesis of non-cross-linked polystyrene supported (4*S*)-4-substituted-4,5-dihydrooxazoline

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From *N*-Boc L-tyrosine ethyl ester, we synthesised (4*S*)-4-[4-(4-vinylbenzyloxy)benzyl]-4,5- dihydrooxazoline, which was copolymerized with styrene to obtain non-cross-linked polystyrene supported 2-hydrogen oxazoline in 29.4% yield.

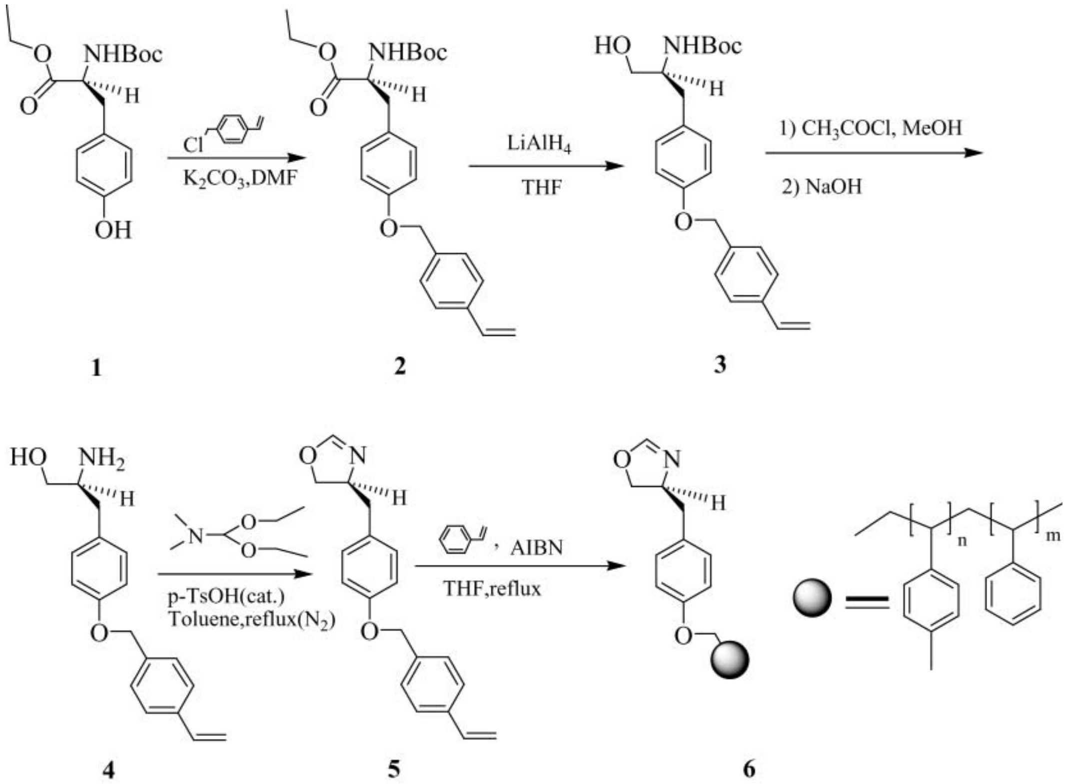
**Keywords**: non-cross-linked polystyrene, chiral ligand, support, 4-substituted-4,5-dihydrooxazoline

Chiral 4-substituted-4,5-dihydrooxazolines are important fragments of chiral auxiliaries,[1,2] or as key elements in numerous ligands for asymmetric catalysis.[3] However, their large-scale application is limited due to the difficult procedure which involves separation and recovery. In order to address this problem, chiral ligands were attached to insoluble polymer supports.[4–6] But there were several shortcomings because of non-linear kinetic behaviour, unequal distribution or access to the chemical reaction, and synthetic difficulties in transferring standard organic reactions to the solid phase. We have undertaken a research program to synthesise chiral auxiliaries by using non-cross-linked polystyrene (NCPS) as supports which combines the superiorities of insoluble polymer support with the advantages of classic liquid synthesis.[7–9] But to the best of our knowledge, there has been no report about chiral 4-substituted-4,5-dihydrooxazolines supported on a polymer. We now report how we synthesized NCPS supported (4*S*)-4-substituted-4,5-dihydrooxazoline through five steps from the material of *N*-Boc-L-tyrosine ethyl ester (Scheme 1).

## Experimental

Melting points were measured on a WRS-1A digital melting point apparatus and uncorrected; optical rotations were measured using the sodium D line with a WZZ-2B Automatic Polarimeter; IR spectra were recorded on a IR- spectrum one (PE) spectrometer; $^1$H NMR (600 MHz) and $^{13}$C NMR (150 MHz) spectra were recorded on a Varian Unity INOVA 600 spectrometer in $CDCl_3$ using TMS as internal standard; Elemental analyses were done on a VarioEL III (Germany) analyser; HRMS data were collected on Q-star Elite, ELI-LC-MS/MS (product from ABI, America).

*N-Boc-O-(4-vinylbenzyl)-L-tyrosine ethyl ester* (**2**): $K_2CO_3$ (7.40 g, 54 mmol), catalytic amounts of 18-crown-6 was added dropwise after stirring for 30 min under $N_2$, 4-vinylbenzyl chloride (4.3 mL, 30 mmol) in DMF (20 mL) to a solution of **1** (8.34 g, 27 mmol) in dry DMF (60 mL) to the reaction mixture, which was stirred at 40 °C for 24 h. The solvent was removed in vacuum and the residue diluted with water (30 mL) and ethyl acetate (50 mL). The aqueous layer was extracted with ethyl acetate (3 × 50 mL). The organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuum. The residue was purified by silica gel column chromatography (EtOAc/petroleum ether = 1/10) to give **2** as a milk white solid



**Scheme 1** Synthesis of NCPS supported (4*S*)-4-substituted-4,5-dihydrooxazoline.

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(9.48 g, 80%). M.p. 76.6–77.8 °C; $[\alpha]_D^{20}$ = +0.9 (c 0.09, THF); IR (NaCl): υ = 3377, 1740, 1716 $cm^{-1}$; $^1$HNMR ($CDCl_3$, 600 MHz): δ 1.23 (3H, t, *J* = 7.2 Hz, $CH_3$), 1.42 (9H, s, Boc), 3.02 (2H, q, *J* = 6.0 Hz, $ArCH_2$), 4.15 (2H, q, *J* = 6.6 Hz, $OCH_2$ ), 4.51 (1H, d, *J* = 7.2Hz, CHN), 4.97 (1H, d, *J* = 7.2 Hz, Boc-NH) 5.02 (2H, *s*, $ArCH_2O$), 5.25 (1H, d, *J* = 11.4 Hz, = $CH_2$), 5.75 (1H, d, *J* = 17.4 Hz, = $CH_2$), 6.73 (1H, dd, $J_1$ = 10.8 Hz, $J_2$ = 17.4 Hz, = CH), 6.88 (2H, d, *J* = 8.4 Hz, ArH), 7.04 (2H, d, *J* = 7.8 Hz, ArH), 7.37 (2H, d, *J* = 7.8 Hz, ArH) 7.42 (2H, d, *J* = 7.8 Hz, ArH); $^{13}$C NMR ($CDCl_3$, 150MHz): *δ* 14.1, 28.3(3C), 37.5, 54.5, 61.2, 69.7, 79.8, 114.0(2C),114.8, 126.4(2C), 127.6(2C), 128.3(2C), 130.3, 136.4, 136.5, 137.3, 155.1, 157.8, 171.9; HRMS: Calcd for $C_{25}H_{32}NO_5[M^+ + 1]$ 426.2280. Found 426.2283.

*N-Boc-O-(4-vinylbenzyl)-L-tyrosinol* (**3**): $LiAlH_4$ (0.41 g, 10.8 mmol) in THF (20 mL) was added to a stirred solution of **2** (5.93 g, 13.5 mmol) in dry THF (40 mL) at –20 °C. After stirring at room temperature for 12 h, the excess $LiAlH_4$ was carefully destroyed by the dropwise addition of 10% $H_2SO_4$. The solvent was removed under vacuum and the residue diluted with water (30 mL) and ethyl acetate (50 mL). The aqueous layer was extracted with ethyl acetate (3 × 50 mL). The organic phase was washed with brine, dried over $MgSO_4$, and concentrated in vacuum. The residue was purified by silica gel column chromatography (EtOAc/petroleum ether = 3/10) to give **3** as a white solid (3.88 g, 75%). M.p. 101.7–102.6 °C; $[\alpha]_D^{20}$ = –2.1 (c 0.26, THF); IR (NaCl): υ = 3359, 1686 $cm^{-1}$; $^1$HNMR ($CDCl_3$, 600 MHz): *δ* 1.40 (9H, s, Boc), 1.52 (1H, s, OH), 2.76 (2H , d, *J* = 7.2Hz, $ArCH_2$), 3.55 (1H, m, $CH_2$ O), 3.68 (1H, m, $CH_2O$), 3.80 (1H, br s, CH-N), 4.78 (1H, s, CHN), 5.02 (2H, s, $ArCH_2O$), 5.24 (1H, d, *J* = 11.4Hz, = $CH_2$), 5.75 (1H, d, *J* = 17.4Hz, = $CH_2$), 6.73 (1H, m, = CH), 6.89 (2H, d, *J* = 8.4Hz, ArH), 7.10 (2H, d, *J* = 8.4Hz, ArH), 7.37 (2H, d, *J* = 7.8Hz, ArH) 7.41 (2H, d, *J* = 8.4Hz, ArH); $^{13}$C NMR ($CDCl_3$, 150MHz): δ 28.3(3C), 36.7, 54, 65, 69.8, 79.5, 114.0, 115.0(2C), 126.4(2C), 127.6(2C), 130.0, 130.2(2C), 136.4(2C), 136.6, 137.3, 157.5; HRMS: Calcd for $C_{23}H_{30}NO_4[M^+ + 1]$ 384.2175. Found 384.2166.

*O-(4-vinylbenzyl)-L- tyrosinol* **4**: Acetyl chloride (1.48 mL, 20.8 mmol) in ethyl acetate (15 mL) was added dropwise to a solution of **3** (3.98 g, 10.4 mmol) in mixed solvents of ethyl acetate (15 mL) and methanol (60 mL) at 0 °C. After stirring for 30 min at 0 °C, the reaction mixture was warmed up to room temperature and stirred continually for 24 h. To the yellow mixture was added excess 1.5 M NaOH. The solvent was removed under vacuum and the residue diluted with water (30 mL) and ethyl acetate (50 mL). The aqueous layer was extracted with ethyl acetate (3 × 50 mL). The organic phase was washed with brine, dried over $MgSO_4$, and concentrated in vacuum. The residue was purified by silica gel column chromatography (MeOH /$CH_2Cl_2$ = 1/20) to give **4** as a white solid (2.50 g, 85%). M.p. 145.5–146.1 °C; $[\alpha]_D^{20}$ = –0.8 (c 0.12, MeOH); IR(NaCl): υ = 3334, 3271， 1509， 1176 $cm^{-1}$; $^1$HNMR ($CDCl_3$,600 MHz): *δ* 1.50 (2H, s, C–$NH_2$), 2.47 (1H, m, $ArCH_2$), 2.72 (1H, m, $ArCH_2$), 3.35 (1H, d, *J* = 3.6Hz, $CH_2O$), 3.49 (1H, s, OH), 3.61 (1H, m, $CH_2O$), 5.03 (2H, s, $ArCH_2O$), 5.26 (1H, d, *J* = 10.8Hz, = $CH_2$), 5.75 (1H, d, *J* = 18.0Hz, = $CH_2$), 6.71 (1H, dd, $J_1$ = 10.8Hz, $J_2$ = 18Hz, $CH_2$ = CH), 6.90 (2H, d, *J* = 7.8Hz, ArH), 7.09 (2H, d, *J* = 7.8Hz, ArH), 7.37 (2H, d, *J* = 7.8Hz, ArH) 7.41 (2H, d, *J* = 7.2Hz, ArH); $^{13}$C NMR($CDCl_3$, 150MHz): *δ* 41.9, 54.0, 68.5, 70.9, 114.3, 114.4(2C), 126.5(2C), 127.1(2C), 129.2(2C), 130.4, 136.2(2C), 140.3, 158.0; Elementary analysis Calcd for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47; N, 4.94. Found: C, 76.35; H, 7.43; N, 4.89%.

*(4S)- 4-[4-(4-vinylbenzyloxy)benzyl]-4,5-dihydrooxazoline* (**5**): DMF-DMA (1.02 mL, 7.7 mmol), and TsOH (50 mg) under $N_2$ were added to a solution of **4** (2.0 g, 7.01 mmol) in toluene (80 mL). The solution was refluxed for 48 h in a flask equipped with a Soxhlet extraction device containing 20 g 4A molecular sieves under $N_2$. The reaction mixture was washed with 10% $NaHCO_3$ (40 mL) and brine (40 mL), and dried over $Na_2SO_4$. The residue was purified by silica gel column chromatography (EtOAc/petroleum ether/triethylamine = 1/4/1) to give **5** as a white solid (1.48 g, 72%). M.p. 144.4–145.0 °C $[\alpha]_D^{20}$ = –4.3 (c 0.13, THF); IR(NaCl): υ = 3047, 1635, 1116 $cm^{-1}$; $^1$H NMR ($CDCl_3$, 600MHz): *δ* 2.88 (2H, m, $ArCH_2$), 3.54 (1H, m, $OCH_2$), 3.65 (1H, dd, $J_1$ = 3.6Hz, $J_2$ = 11.4 Hz, $OCH_2$), 5.03 (2H, s, $ArCH_2O$), 5.25 (1H, d, *J* = 10.8Hz, = $CH_2$), 5.75 (1H, d, *J* = 7.8Hz, = $CH_2$), 6.72 (1H, dd, $J_1$ = 10.8Hz, $J_2$ = 18.0 Hz, = CH), 6.91 (2H, d, *J* = 9.0Hz, ArH), 7.09 (2H, d, *J* = 9.0Hz, ArH), 7.38 (2H, d, *J* = 7.8Hz, ArH), 7.42 (2H, d, *J* = 8.4Hz, ArH) , 8.17 (1H, s, CH = N); $^{13}$CNMR($CDCl_3$, 150MHz): δ 46.4, 49.4, 69.8, 114.1, 115.2(2C), 126.4(2C), 127.7(2C), 128.7, 130.2, 130.4(2C), 136.4(2C), 136.5, 137.4, 160.5; Elementary analysis Calcd for Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.81; H, 6.54; N, 4.75%.

*NCPS supported (4S)-4-substituted-4,5- dihydrooxazoline* (**6**): Styrene (1.99 mL, 17.52 mmol) and AIBN (16 mg) under $N_2$ were added to a solution of **5** (1.28 g, 4.38 mmol) in THF (20 mL). The mixture was stirred at 70 °C for 4 days. Then most of the solvent was removed under reduced pressure. The residue was poured dropwise into a beaker of cold and stirring ethanol (50 mL) to precipitate white solid. The solid was filtrated and washed in ethanol (3 × 8 mL) to remove any micromolecules (TLC detecting) and dried in a vacuum to give polymer **6** (1.2 g, 80%). IR(NaCl): υ = 3302, 1671 $cm^{-1}$; $^1$HNMR ($CDCl_3$, 600MHz): *δ* 1.10–2.10 (bm, polymer-$CH_2$), 2.64 (2H, br s, $ArCH_2$), 3.47 (1H, s, $CH_2O$), 3.64 (1H, s, $CH_2$), 4.18 (1H, s, CH), 4.92 (2H, s, $ArCH_2O$), 6.50–7.25 (bm, polymer-ArH); $^{13}$C NMR ($CDCl_3$ 150 MHz): *δ* 23.0, 29.9, 32.0, 40.5, 52.0, 70.2, 110.0, 115.0, 125.9, 127.8, 128.2, 130.5, 145.5, 158.0; Elementary analysis Calcd for polymer **6**: C, 86.28; H,7.24; N, 1.97. Found: C, 85.95; H, 7.38; N, 2.08%. Compound **5** was copolymerised with styrene with the radio of 1/4, the theoretical structural unit of polymer **6** was composed of 1 mol **5** and 4 mol styrene, so the calculated analysis of polymer **6** was obtained by calculating the contents of C, H, N in the sum of 1 mol **5** and 4 mol styrene.

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