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# Synthesis of Chiral N-Ferrocenylmethylaminoalcohols and their Application in Enantioselective Addition of Diethylzinc to Aldehydes

Jian Feng GE[1, 2], Zong Xuan SHEN[1], Ya Wen ZHANG[1]*

[1] Department of Chemistry and Chemical Engineering, Suzhou University, Suzhou 215006
[2] Department of Material and Engineering, Suzhou University, Suzhou 215006

**Abstract:** Three chiral N-ferrocenylmethylaminoalcohols were synthesized from readily available natural *L*-valine, leucine and phenylanine, and used as chiral ligands in the enantioselective addition of diethylzinc to aldehydes.

**Keywords:** N-Ferrocenylmethylaminoalcohol, asymmetric synthesis, enantioselective addition, diethylzinc

Catalytic asymmetric carbon-carbon bond formation is one of the most active research areas in organic synthesis. In this field, the application of chiral ligands in enantioselective addition of diethylzinc to aldehydes has attracted much attention. Various ligands such as chiral amino alcohols[1], amino thiols[2], piperazines[3], quaternary ammonium salts[4], 1, 2-diols[5], oxazaborolidines[6] and transition metal complex with chiral ligands[7] have been reported. In recent years, much effort has been made to study chiral ligands with ferrocenyl group because of the inherent nature of their planar chirality[8]. In this letter, we wish to report the synthesis of three chiral ferrocenylmethyl aminoalcohols from readily available natural L-valine, leucine and phenylalanine, and their application to enantioselective addition of diethylzinc to aldehydes.

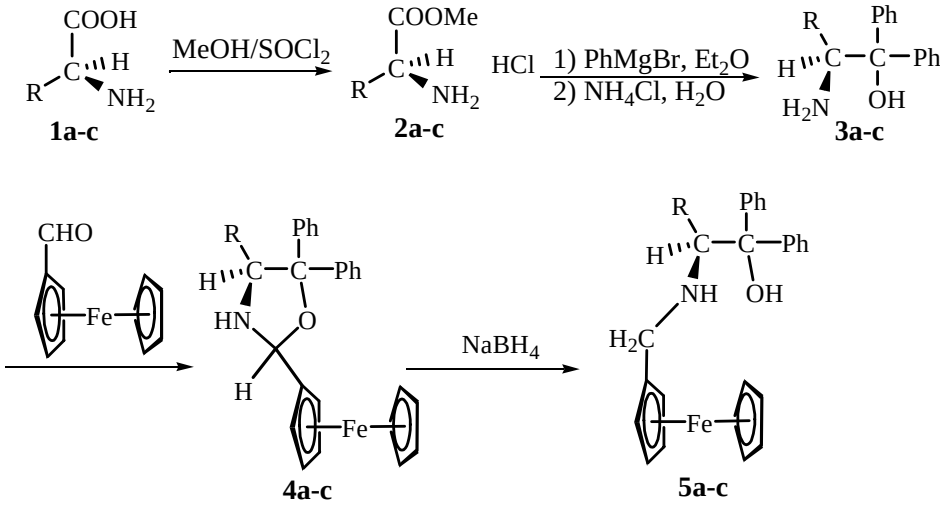
## Results and Discussion

The synthetic route is shown in **Scheme 1**. The methyl ester of amino acid **2a-c** was synthesized by esterifying the corresponding amino acid **1a-c** with methanol-thionyl chloride. Treating **2a-c** with excess of phenyl magnesium bromide gave the chiral amino alcohol **3a-c**. The N, O-acetal **4a-c** was obtained by stirring **3a-c** and equal molar amount of ferrocenecarboxaldehyde in methylene chloride at room temperature, the diastereomeric mixture of **4a-c** was reduced with $NaBH_4$ in EtOH to obtain *N*-ferrocenylmethylaminoalcohol **5a-c**.

The results of enantioselective addition of diethylzinc to aldehydes promoted by chiral ligands **5a-c** are shown in **Table 1**.

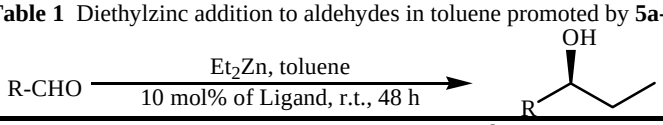
* E-mail: zhangyw@suda.edu.cn.

**Scheme 1** Synthesis of N-ferrocenylmethylaminoalcohols from Amino Acids




**a**: R= $(CH_3)_2CH$; **b**: R= $(CH_3)_2CHCH_2$; **c**: R=$PhCH_2$

**Table 1** Diethylzinc addition to aldehydes in toluene promoted by **5a-c**




| Entry | Ligand | R- | Yield (%)[a] | *ee* (%) | Config.[c] |
|---|---|---|---|---|---|
| 1 | **5a** | $C_6H_5$- | 92 | 68[b] | *S* |
| 2 | **5a**[d] | $C_6H_5$- | 94 | 45[b] | *S* |
| 3 | **5b** | $C_6H_5$- | 96 | 83[b] | *S* |
| 4 | **5c** | $C_6H_5$- | 77 | 75[b] | *S* |
| 5 | **5b** | *m*-$ClC_6H_4$- | 96 | 94[c] | *S* |
| 6 | **5b** | *p*-$CH_3OC_6H_4$- | 66 | 86[c] | *S* |
| 7 | **5b** | $C_6H_5CH$=CH- | 97 | 89[c] | *S* |
| 8 | **5c** | *m*-$ClC_6H_4$- | 95 | 92[c] | *S* |
| 9 | **5c** | *p*-$CH_3OC_6H_4$- | 87 | 81[c] | *S* |
| 10 | **5c** | $C_6H_5CH$=CH- | 58 | 87[c] | *S* |

[a] Isolated yields; [b] Determined by HPLC analysis using a chiral OD column; [c] Based on the reported specific rotations in reference[1]; [d] Solvent: *n*-Hexane

## Experimental

Melting points were measured in capillaries and uncorrected. Optical rotations were measured at 589 nm ( Na D line ) on a WZZ-1 polarimeter. $^1$H NMR spectra were recorded at 400 MHz, chemical shifts (δ) were reported in parts per million (ppm) relative to tetramethylsilane (TMS); A Varian Inova-400 was used. Infrared spectra were recorded on Niclet Avatar 360 FT-IR.

*General procedure for synthesis of chiral N-ferrocenylmethylaminoalcohols 5a-c:*

A mixture of aminoalcohol **3a-c** (7.4 mmol), ferrocenecarboxaldehyde (1.6 g, 7.4 mmol) and methylene chloride (40 mL) was stirred at room temperature for two days. After methylene chloride was removed under reduced pressure, the residue was filtrated through a pad of silica gel eluting with a solvent of petroleum ether/ethyl acetate (V:V=8:1). After the solvent was removed under reduced pressure, the residue was refluxed with ethyl ether and filtrated to obtain brown solid **4a-c**. The diastereomers of **4a-c** (3 mmol), 95% ethyl alcohol (25 mL), THF (25 mL) and $NaBH_4$ (18 mmol) was stirred overnight at room temperature. The solvent was removed under reduced pressure, the residue was stirred in an ice-water bath and 100 mL saturated aqueous solution of ammonium chloride was added cautiously, then the mixture was extracted with methylene chloride (3×30 mL). The combined extracts were washed with water, dried over magnesium sulfate, concentrated to dryness and recrystallized from methylene chloride / *n*-hexane to give yellow crystals of **5a-c**.

**5a**: Yield 61%. m.p. 172~173°C, $[\alpha]_D^{22}$ -37.8 (*c* 1.0, $CHCl_3$). Anal. calcd for $C_{28}H_{31}FeNO$: (%) C 74.17, H 6.89, N 3.09; Found C 74.06, H 6.82, N 3.06. IR (KBr, $cm^{-1}$): 3347, 3215 (NH, OH). $^1$H NMR ($CDCl_3$/TMS, δ ppm): 0.70 (d, 3H, *J*=6.4Hz, C***H***$_3$), 0.98 (d, 3H, *J*=6.4 Hz, C***H***$_3$), 1.33 (bs, 1H, N***H***), 1.99~2.06 (m, 1H, C***H***), 3.00 (d, 1H, *J*=12.8 Hz, FcCH***H***), 3.17 (d, 1H, *J*=12.8 Hz, FcCH***H***), 3.59 (s, 1H, C***H***), 3.99~4.08 (m, 9H, $C_5$***H***$_4$Fe$C_5$***H***$_5$), 5.27 (s, 1H, O***H***), 7.14~7.73 (m, 10H, 2×$C_6$***H***$_5$).

**5b**: Yield 77%. m.p. 138~140°C, $[\alpha]_D^{22}$ -28.2 (*c* 0.6, $CHCl_3$). Anal. calcd for $C_{29}H_{33}FeNO$: (%) C 74.52, H 7.12, N 3.00; Found C 74.74, H 7.11, N 2.97. IR (KBr, $cm^{-1}$): 3373, 3084 (NH, OH). $^1$H NMR ($CDCl_3$/TMS, δ ppm): 0.83 (d, 3H, *J*=5.7 Hz, C***H***$_3$), 0.85 (d, 3H, *J*=7.1 Hz, C***H***$_3$), 1.12~1.58 (m, 4H, $(CH_3)_2$C***H***C***H***$_2$, N***H***), 2.93 (d, 1H, *J*=12.7 Hz, FcCH***H***), 3.12 (d, 1H, *J*=12.7 Hz, FcCH***H***), 3.68 (d, 1H, *J*=8.5 Hz, NC***H***), 3.94~4.05 (m, 9H, $C_5$***H***$_4$Fe$C_5$***H***$_5$), 4.79 (s, 1H, O***H***), 7.16~7.70 (m, 10H, 2×$C_6$***H***$_5$).

**5c**: Yield 67%. m.p. 195~196°C, $[\alpha]_D^{22}$ -41.1 (*c* 0.4, $CHCl_3$). Anal. calcd for $C_{32}H_{31}FeNO$: (%) C 76.65, H 6.23, N 2.79; Found C 76.43, H 6.13, N 2.74. IR (KBr, $cm^{-1}$): 3425, 3319 (NH, OH). $^1$H NMR ($CDCl_3$/TMS, δ ppm): 1.34 (bs, 1H, N***H***), 2.35~2.96 (m, 4H, 2×C***H***$_2$), 3.65 (s, 1H, NC***H***), 3.72~4.05 (m, 9H, $C_5$***H***$_4$Fe$C_5$***H***$_5$), 5.00 (s, 1H, O***H***), 7.17~7.77 (m, 15H, 3×$C_6$***H***$_5$).

*Typical procedure for the addition of diethylzinc to aldehydes promted by **5a-c:***

A solution of 0.2 mmol of chiral ligand in 20 mL of dry toluene was cooled to 0 $^o$C and diethylzinc (0.5 mL, 4.8 mmol) was added under nitrogen atmosphere. After 20 min, 2 mmol of aldehyde was added while stirring. The reaction mixture was gradually warmed to room temperature and stirred for 48 h. The reaction was quenched by addition of 10 mL of 10% hydrochloric acid at 0 $^o$C, then the layers were separated and the aqueous layer was extracted with diethyl ether. The combined organic layers were washed with saturated $NaHCO_3$ and NaCl solutions successively before drying over anhydrous $Na_2SO_4$. After the solvent was removed under reduced pressure, the residue was purified by column chromatography (ethyl acetate: petroleum ether= 1:10) and distilled in vacuum to afford

the optically active secondary alcohol.

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