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TETRAHEDRON: *ASYMMETRY*

Synthesis of the novel chiral 1,3-amino alcohol 8-*N*,*N*-bis(ferrocenylmethyl)amino-menthol and its use as catalyst in the enantioselective addition of diethylzinc to aldehydes

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Abstract—Optically active 8-*N*,*N*-bis(ferrocenylmethyl)aminomenthol **5**, obtained by condensation of (−)-aminomenthol with ferrocenecarboxaldehyde followed by *N*-alkylation with (ferrocenylmethyl)trimethylammonium iodide and further reduction, was found to catalyze (5 mol%) the enantioselective ethylation of aromatic, aliphatic and organometallic aldehydes to secondary alcohols with high enantioselectivities (up to 95%) at room temperature. © 2002 Elsevier Science Ltd. All rights reserved.

Catalytic asymmetric carbon–carbon bond formation is one of the most active research areas in organic synthesis. In this field, the asymmetric addition of diethylzinc (Et_2Zn) to aldehydes has attracted much attention.[1] These reactions require a compound coordinating the metal ion to enhance the nucleophilicity of the organometallic reagent, since the uncoordinated organozinc species is virtually unreactive to the aldehyde. Due to the enhanced reactivity of the complexed reagent, even a catalytic amount of the ligand can be used. A variety of chiral catalysts such as chiral diols,[2] β-amino alcohols,[3] diamines[4] and amino thiols[5] have been developed for this reaction, which shows excellent enantioselection for both aromatic and aliphatic substrates.

In this context, ferrocenylamino alcohols were reported to have the ability to catalyze the asymmetric addition of dialkylzinc reagents to aldehydes.[1b,6] Among them, ferrocene derivatives possessing either planar and central chirality[7] or only planar chirality[8] induced high enantioselectivities, while ferrocenylamino alcohols possessing only central chirality[9] were found to provide modest degrees of induction. Despite the approaches used, the design and development of a cost-effective catalyst, lowering the concentration and/or recovering the catalyst and facilitating work-up procedures are still challenging endeavors.

The synthesis of our ligands was accomplished in high yields starting from the commercially available ferrocenecarboxaldehyde and (−)-8-aminomenthol **1** (5*c*-methyl-2*t*-(1-methyl-1-aminoethyl)-cyclohexan-1*r*-ol), easily prepared from (+)-pulegone.[10] Condensation of ferrocenecarboxaldehyde with (−)-8-aminomenthol **1** leads to the chiral 2-ferrocenyl-octahydro-1,3-benzoxazine[11] **2** in 98% yield as a single diastereomer, with equatorial orientation of the ferrocenyl substituent as revealed by the X-ray structure[12] (Fig. 1). *N*-Alkylation of **2** was achieved by reaction with (ferrocenylmethyl) trimethyl ammonium iodide[13] or benzyl bromide in refluxing acetonitrile in the presence of potassium carbonate to give **3a** and **3b** in 98 and 92% yields, respectively. Compounds **3** underwent ring opening of the 1,3-oxazine ring either by the action of methylmagnesium bromide at room temperature[14] to give **4** in 86–92% yields or with DIBAL-H in toluene at 0°C to afford[15] **5** in 93% yield (Scheme 1).

With these ligands in hand, we first examined the enantioselective addition of diethylzinc to benzaldehyde, taken as a benchmark reaction, in the presence of 5 mol% of the chiral ligands **3**–**5** in toluene at room temperature. Compounds **3**–**5** proved ineffective catalysts for the ethylation of benzaldehyde even after extended reaction times. With the expectation that an additive would alter the nature of the zinc species in

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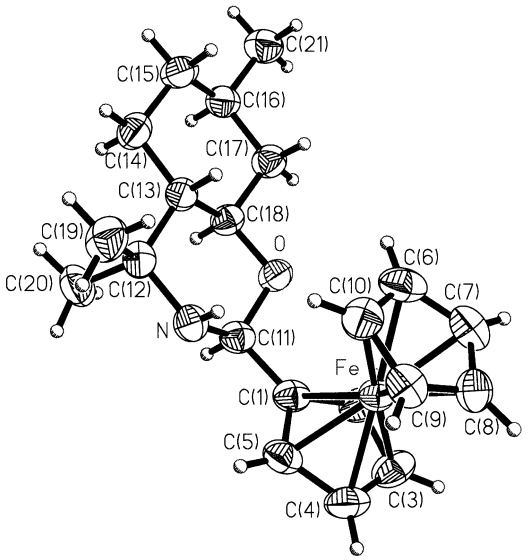


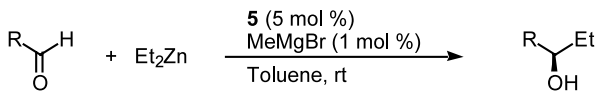
Figure 1. ORTEP drawing of compound **2**.

solution, we pre-treated the catalysts with methylmagnesium bromide. We were pleased to discover that pretreatment of the catalysts **3** and **4** with 1 mol% of methylmagnesium bromide afforded (*S*)-1-phenyl-1-propanol in excellent yield (93%) although with moderate e.e. (50%). Taking into account the fact that the yield and e.e. in both reactions are identical and the fact that **3** is converted into **4** by the action of methylmagnesium bromide, we think that the active species as catalyst in both reactions is derived from the ligand **4**. However, when the enantiopure amino alcohol **5** was used, the result was very promising and optically active 1-phenyl-1-propanol was obtained in 87% yield and 95% e.e., with preferred formation of the (*S*)-isomer.

This finding prompted us to evaluate the catalytic capability of the new catalyst with other aldehydes. The results showed that the chiral amino alcohol **5** was efficient in this asymmetric reaction, giving reasonable enantioselection for aromatic, aliphatic and organometallic substrates[16] (Scheme 2). As can be seen in Table 1, the yields of the alcohols were in the range 70–90% with e.e.s of 60–95%.

The chiral ligand **5** was recovered in excellent yield (ca. 94%) from the reaction mixture by silica gel chromatography and re-used without any loss of enantiomeric purity of the product.

It has been established that in the presence of methanol, the related ligand, 3-*exo*(dimethylamino)-isoborneol serves as an effective chiral catalyst for the addition of diethylzinc to a variety of aryl–alkyl and diaryl ketones.[17] In this context, the addition of



Scheme 2.

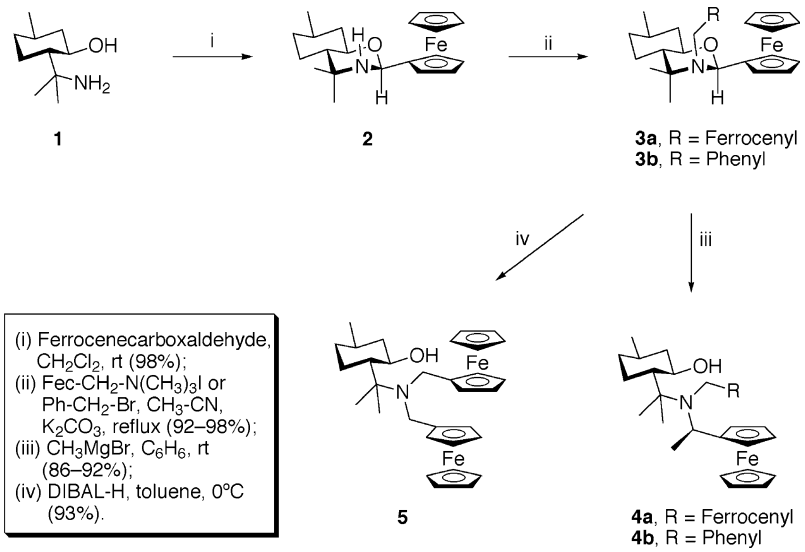
Table 1. Enantioselective addition of diethylzinc to aldehydes in the presence of chiral catalysts **5**

Entry	Aldehyde	Yield[a,b] (%)	E.e. (%)[b]	Configuration[c]
1	Ph-CHO	87	95	*S*
2	*p*-$MeOC_6H_4CHO$	65	71	*S*
3	*p*-ClC_6H_4CHO	76	95	*S*
4	$C_6H_5CH=CHCHO$	78	90	*R*
5	$CH_3CH=CHCHO$	70	68	*S*
6	$CH_3(CH_2)_4CHO$	73	77	*S*
7	FecCHO	90	73	*R*

[a] Yields of isolated products. The reactions were performed in dry toluene during 20 h under nitrogen with 5 mol% catalyst using aldehyde and diethylzinc in 1:2 ratio at room temperature.

[b] Determined by HPLC on Cyclobond I 2000, Astec (eluent hexane/isopropanol 90/10, flow rate 0.7 mL/min).

[c] Determined from the comparison of the sign of the specific rotation with the literature data.



Scheme 1.

diethylzinc to benzaldehyde in the presence of 5 mol% of the ligand **5** and 1.5 equiv. of methanol provided (*S*)-1-phenyl-1-propanol in 85% yield albeit in 40% e.e.

In summary, we have clearly demonstrated that the enantiopure ferrocene–substituted 1,3-amino alcohol **5** can act as an efficient promoter in the enantioselective addition of diethylzinc to a range of aldehydes. The main distinctive feature of this ligand is represented by an economical and simple asymmetric synthesis, involving cheap starting materials, which combine to give a more complex compound without side products.

Acknowledgements

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11. **Spectral data for compound 2**: $[\alpha]_D^{20} = -28.0$ (*c* 1.5, $CHCl_3$), mp 105–7°C, IR (Nujol), 3318, 3094, 3073, 1209, 1145, 1107, 1059, 1011, 926, 830, 776. MS (GC-EI), 368 (M^++1, 28), 367 (M^+, 100), 301 (6), 255 (23), 254 (47), 214 (45), 213 (89), 199 (17), 186 (77), 121 (45). ^{1}H NMR ($CDCl_3$, 300 MHz): 5.06 (s br, 1H; H2), 4.32–4.29 (m, 1H; H2′/H5′), 4.28–4.25 (m, 1H; H2′/H5′), 4.15 (s, 5H; Cp), 4.10–4.05 (m, 2H; H3′/H4′), 3.50 (ddd, 1H, $^3J = 10.8$, $^3J = 9.6$ Hz, $^3J = 4.2$ Hz; H8a), 1.97 (dddd, 1H, $^2J = 12.3$ Hz, $^3J = 5.4$ Hz, $^3J = 3.9$ Hz, $^3J = 1.8$ Hz; $H8_{eq}$), 1.78–1.62 (m, 2H; $H6_{ec}$, $H5_{eq}$), 1.56–1.44 (m, 1H; H7), 1.13 (s, 3H; Me_{ax}-C4)), 1.11 (s, 3H; Me_{eq}-C4)), 0.94 (s, 3H, $^3J = 6.6$ Hz; Me-C7), 1.20–0.80 (m, 4H; H4a, $H5_{ax}$, $H6_{ax}$, $H8_{ax}$). The N-H proton was not observed. ^{13}C NMR ($CDCl_3$, 75 MHz): 89.61 (C1′), 80.42 (C2), 74.86 (C8a), 68.70 (Cp), 67.45 (CH:Fc), 67.39 (CH:Fc), 66.60 (CH:Fc), 66.51 (CH:Fc), 51.86 (C4a), 51.28 (C4), 41.87 (C8), 35.10 (C6), 31.39 (C7), 30.06 (Me_{eq}-C4), 25.58 (C5), 22.30 (Me-C7), 19.78 (Me_{ax}-C4).

12. **X-Ray data for compound 2**. The crystal was mounted with glue and transferred to the diffractometer (Siemens P4). The structures were solved by the heavy atom method and refined anisotropically on F^2 (program SHELX-93). Crystal data: $C_{21}H_{29}FeNO$, $M=367.30$, orthorhombic, Space group $P2_12_12_1$, $a=8.508$ (2), $b=13.680$ (6), $c=15.876$ Å, $V=1847.9$, $Z=4$ (11) Å^3, $T=298$ K, $\mu=0.823$ mm^{-1}, reflections collected 11922, independent refections 3240 ($R_{int}=0.0288$), data/restraints/parameter = 3240/210/224, goodness of fit on $F^2=1.081$, $R_1=0.0170$ [$I>2\sigma(I)$] and $wR_2=0.0460$ (for all data). The absolute structure parameter is −0.012 (9). For compound **2** unit cell parameters were determined from a least-squares fit of 75 accurately centered reflections ($11.6<2\theta<25.0$). Maximun $\Delta/\sigma=0.003$, maximun $\Delta\rho=0.120$ e Å^{-3}. Hydrogen atoms were included using the rigid method for the methyl group and the others the riding method, except the amine H, which was free. CCDC 178737.
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15. **Spectral data for compound 5**: $[\alpha]_D^{20}=+66.3$ (*c* 1.1, $CHCl_3$), mp 157–160°C, IR (Nujol), 3351, 1604, 1562, 1408, 1107, 1001, 831, 725. MS (EI), 567 (M^+, 2), 369 (20), 215 (12), 200 (32), 199 (100), 186 (14), 121 (55). ^{1}H NMR ($CDCl_3$, 300 MHz): 4.64–4.46 (m, 2H; Fc), 4.12 (s, 5H; Cp), 3.97 (s, 5H; Cp), 3.84–3.58 (m, 6H; Fc), 3.48 (td, 1H, $^3J=9.9$, $^3J=3.6$ Hz; H1), 3.16–3.04 (m, 4H; 2×CH_2Fc), 1.94 (dm, 1H, $^2J=11.7$ Hz; H6$_{eq}$), 1.88–1.04 (m, 8H), 0.98 (s, 6H; 2×Me), 0.91 (s, 3H; Me-C5). ^{13}C NMR ($CDCl_3$, 75 MHz): 72.16 (C1′), 70.27 (CH:Fc), 68.32 (Cp), 67.02 (CH:Fc), 61.27 (M_2CN), 47.76 (C), 47.23 (CH_2Fc), 45.38 (CH_2Fc), 44.73 (C6), 35.09 (C4), 30.77 (C5), 25.81 (C3), 22.01 (Me), 21.52 (Me), 19.99 (Me).
16. **General experimental procedure**: To a degassed solution of amino alcohol **5** (0.226 g, 0.4 mmol, 5 mol%) in dry toluene (20 mL), methylmagnesium bromide in diethyl ether (3 M, 33 μL, 0.1 mmol, 1 mol%) was injected by syringe under N_2-atmosphere at room temperature. The resulting solution was stirred for 30 min, a solution of diethylzinc in toluene (1.0 M, 16 mL, 16 mmol) was then injected by syringe, ensuring that the tip of the needle was below the surface of the solution. The mixture was stirred at room temperature for 45 min and a solution of the appropriate aldehyde (8 mmol) in dry toluene (3 mL) was added. The reaction was monitored by GC–MS and when no more traces of the aldehyde were detected (20 h) the reaction was quenched by slow addition of aqueous NH_4Cl solution (15%, 20 mL). The precipitated solid was separated by filtration, air-dried and chromatographed on a silica gel column (dichloromethane/hexanes 1:1) to give **5** in almost quantitative yield. The filtrate was extracted with diethyl ether (2×15 mL) and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude product was purified by bulb-to-bulb distillation or flash column chromatography (EtOAc/hexanes 1:4) to give the corresponding optically active secondary alcohol. Chemical integrity was checked by ^{1}H NMR, the enantiomeric excess was determined by enantioselective HPLC.
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