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Chiral ferrocenyl amino alcohols as analogues of norephedrine catalysts for enantioselective addition of diethylzinc to benzaldehyde

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Abstract

Optically active ferrocenyl amino alcohols have been prepared from commercially available L-alaninol and L-leucinol. They have been used in catalytic amounts as chiral ligands in the addition of diethylzinc to benzaldehyde. 1-Phenylpropanol has thus been obtained in up to 95% enantiomeric excess.

Keywords: ferrocenyl amino alcohols; diethylzinc; enantioselective alkylation.

Asymmetric metal catalysis constitutes one of the most efficient methods to obtain enantiopure chiral coumpounds.[1] In particular, increasing interest has been devoted to the study of enantioselective addition of diethylzinc to aldehydes in the presence of chiral auxiliaries.[2] Among them, the chiral amino alcohols derived from ephedrine[3] and norephedrine[4] have been shown to be suitable chiral catalysts for such transformations. Furthermore, various chiral ferrocenyl derivatives exhibiting either a central chirality in the side chain,[5] or a planar chirality on the substituted ferrocene moiety[6] or a combination of both,[7] have also proven to be highly enantioselective catalysts.

Following our interest for the application of ferrocenyl-type catalysts to enantioselective alkylations,[8] we focused our attention on the stereoselective synthesis of a novel class of chiral ferrocenyl amino alcohols and their application in enantioselective addition of diethylzinc to benzaldehyde.[9]

The natural L-alaninol **1a** and L-leucinol **1b** have been reacted with an excess of benzyl bromide in the presence of K_2CO_3 leading, respectively, to the protected amino alcohols **2a** and **2b** in 83% isolated yield (Scheme 1). The *N*,*N*-dibenzylamino alcohols **2a**–**b** were then transformed quantitatively to the amino aldehydes **3a**–**b** by a Swern oxidation.

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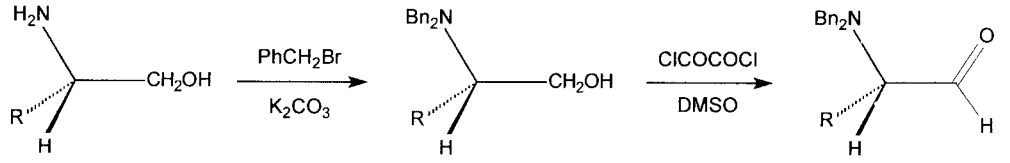
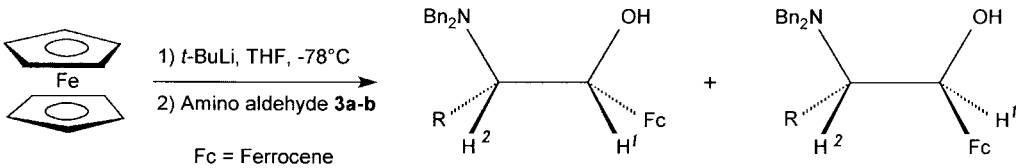


1a R = CH_3 **2a** **3a**
1b R = $CH_2CH(CH_3)_2$ **2b** **3b**

Scheme 1.

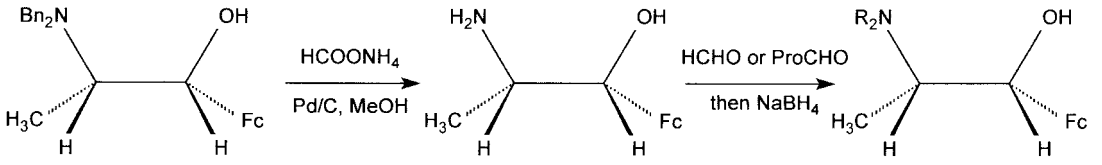
Addition of ferrocenyllithium, which was prepared by reaction of *t*-BuLi with ferrocene in THF at –78°C onto the amino aldehydes **3a** and **3b**, provided a mixture of diastereomers **4a**/**5a** and **4b**/**5b** in 61 and 55% overall yield, respectively (Scheme 2).[10] In agreement with the literature,[11] the '*erythro*' isomer was the major amino alcohol obtained: **4a**:**5a** = 92:8 and **4b**:**5b** = 79:21. The ratios were determined by HPLC on the crude isolated product and both diastereomers were separated by silica gel column chromatography. The coupling constant values $J_{1,2}$ (Scheme 2) allowed to establish the stereochemistry of each diastereomer (**4a**: $J_{1,2} = 6$ Hz; **5a**: $J_{1,2} = 9.5$ Hz; **4b**: $J_{1,2} = 4$ Hz; **5b**: $J_{1,2} = 9$ Hz).



R = CH_3 **4a** **5a**
R = $CH_2CH(CH_3)_2$ **4b** **5b**

Scheme 2.

The hydrogenolysis of the ferrocenylamino alcohol **4a** was next carried out in the presence of Pd/C/$HCOONH_4$ in methanol providing **6** in 60% isolated yield. Then the reaction of **6** with an excess of formaldehyde followed by the reduction with $NaBH_4$ led to the bismethylated derivative **7** in 45% yield.[12] Unfortunately, the direct butylation of **6** with an excess of butyl iodide in the presence of potassium carbonate led only to a monosubstitution of the amino group. Thus, the *N*,*N*-dibutylamino alcohol **8** was obtained by two consecutive reactions of propanal on **6** followed by the reduction with $NaBH_4$ in 36% global yield (Scheme 3).[13] The amino alcohols **7**



4a **6**
R = CH_3 **7**
R = Bu **8**

Scheme 3.

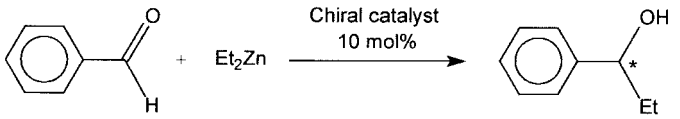
and **8** could be prepared directly from **1a** following the same procedure as for **2a**. Nevertheless, the route through **2a** is of higher synthetic value because the primary amine **6** obtained after hydrogenolysis can be variously mono or bialkylated.

The catalytic efficiency of the amino alcohols **4–5** and **7–8** was evaluated in the addition of diethylzinc to benzaldehyde and the results are summarised in Table 1 (Scheme 4). The reaction was carried out in toluene at 20°C in the presence of 10 mol% of catalyst using benzaldehyde and diethylzinc in a 1:2 ratio.

Table 1
Addition of diethylzinc to benzaldehyde in the presence of chiral catalysts **4**, **5**, **7** and **8**

Entry	Catalyst	Time (h)	Yield [a] (%)	ee [b] (%)	configuration [c]
1	**4a**	17	97	90	*R*
2	**4b**	22	95	66	*R*
3	**5a**	5	96	73	*S*
4	**5b**	6	99	53	*S*
5	**7**	2	100	94	*R*
6	**7** [d]	3.5	98	94	*R*
7	**7** [e]	5.5	100	94	*R*
8	**8**	1	100	95	*R*

[a] Determined by ^{1}H NMR, the by products or the other products being benzyl alcohol and unreacted benzaldehyde. [b] Determined by GC analysis on FS-Cyclodex β-I/P (30mx0.24). [c] Determined from the comparison of the sign of the specific rotation with the literature data. [d] using 5 mol% catalyst. [e] The reaction was carried out at 0°C.



Scheme 4.

The above chiral ferrocenyl amino alcohols catalyse efficiently the addition of diethylzinc to benzaldehyde and afforded 1-phenyl-1-propanol in high yields (> 95%) and in moderate to high enantiomeric excesses (53 to 95%). The results show that the enantioselectivity of the reaction is very sensitive to the structure of the chiral catalyst. It appeared clearly that the sense of chirality induced by the catalyst is controlled essentially by the chirality of the benzylic alcohol stereocentre. For example, (*R*)-1-phenylpropanol was obtained in 90% ee in the presence of **4a** (entry 1), whereas the opposite (*S*)-1-phenylpropanol was produced with the diastereomer **5a** (73% ee) (entry 3). The same type of reversal of the sense of enantioselectivity with respect to the configuration of the alcohol moiety of the catalyst was observed when using the chiral catalyst derived from ephedrine and pseudo ephedrine.[3b] The enhancement of the bulkiness on the carbon bearing the amino function induces a decrease of the enantioselectivity (compare entries 1 versus 2 and 3 versus 4). Interestingly, the substituents on the N atom only slightly influence the selectivity of the transformation, the highest ee being obtained with butyl (compare entries 1, 5 and 8).

A lowering of the temperature had no effect on the selectivity of the reaction. Indeed, carrying out the reaction at either room temperature or 0°C led to 94% ee (entries 6 and 7). Most interestingly, the replacement of the phenyl group of *N*-alkylated ephedrine[3a] and norephedrine[4b] by ferrocenyl moiety provided the most enantioselective catalyst of the series. In particular, the gain in ee brought about by such coordination is 30% for the *N*,*N*-dimethylated amino alcohol. In a similar manner, Jones reported on the properties of the *N*,*N*-dialkylnorephedrine.[14] A beneficial effect has been reported for the enantioselectivity of the asymmetric alkylation of benzaldehyde in complexing the phenyl group of the above amino alcohols by a $Cr(CO)_3$ unit. In addition to the higher ee, this class of ligands is more efficient. For example, 1-phenylpropanol was obtained after only 1 h in the presence of ligand **7** at room temperature against 16 h for the (–)-*N*-methylephedrine.[3d]

In summary, the new ferrocenyl-modified norephedrines can be easily synthesised. When applied as catalysts in the addition of diethylzinc to benzaldehyde, they provided the corresponding alcohol with high ee. These new amino alcohols are currently evaluated in other reactions. Results will be reported in due date.

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10. For **4a**: $[\alpha]_D^{20} = +14$ (*c* 0.542, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.11 (d, $J = 6.5$ Hz, 3H), 2.85 (qd, $J = 6$ and 6.5 Hz, 1H), 3.37 (d, $J = 14$ Hz, 2H), 3.68 (d, $J = 14$ Hz, 2H), 4.08 (m, 1H), 4.14–4.17 (m, 3H), 4.16 (s, 5H), 4.39 (d, $J = 6$ Hz, 1H), 7.18–7.39 (m, 10H). For **4b**: $[\alpha]_D^{20} = -141$ (1.74, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.72 (d,

$J = 6.5$ Hz, 3H), 0.88 (d, $J = 6.5$ Hz, 3H), 1.28–1.37 (m, 1H), 1.50 (m, 1H), 1.73 (m, 1H), 2.79 (ddd, $J = 4$, 6.5 and 6.5 Hz, 1H), 3.48 (d, $J = 13.5$ Hz, 2H), 3.56 (d, $J = 13.5$ Hz, 2H), 4.04 (m, 1H), 4.09 (m, 1H), 4.13 (m, 1H), 4.17 (s, 5H), 4.31 (m, 1H), 4.61 (d, $J = 4$ Hz, 1H), 7.23–7.31 (m, 10H). For **5a**: $[\alpha]_D^{20} = -20$ (0.925, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): 0.91 (d, $J = 6.5$ Hz, 3H), 2.52 (qd, $J = 6.5$ and 9.5 Hz, 1H), 3.32 (d, $J = 13.5$ Hz, 2H), 3.86 (d, $J = 13.5$ Hz, 2H), 4.00 (m, 1H), 4.03 (m, 2H), 4.10 (m, 1H), 4.15 (d, $J = 9.5$ Hz, 1H), 4.18 (s, 5H), 7.22–7.32 (m, 10H). For **5b**: $[\alpha]_D^{20} = -120$ (0.75, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): 0.58 (d, $J = 6.5$ Hz, 3H), 0.69 (d, $J = 6.5$ Hz, 3H), 0.98–1.13 (m, 2H), 1.39 (m, 1H), 2.43 (ddd, $J = 4.5$, 6 and 9 Hz, 1H), 3.45 (d, $J = 13.5$ Hz, 2H), 3.87 (d, $J = 13.5$ Hz, 2H), 4.05 (m, 3H), 4.13 (m, 1H), 4.16 (d, $J = 9.0$ Hz, 1H), 4.21 (s, 5H), 7.21–7.39 (m, 10H).

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12. For **7**: $[\alpha]_D^{20} = +7$ (0.45, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): 0.88 (d, $J = 7$ Hz, 3H), 2.26 (s, 6H), 2.44 (qd, $J = 7$ and 6.5 Hz, 1H), 4.12 (m, 3H), 4.19 (s, 5H), 4.31 (m, 1H), 4.58 (d, $J = 4$ Hz, 1H).
13. For **8**: $[\alpha]_D^{20} = +31$ (0.35, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): 0.86 (t, $J = 7$ Hz, 6H), 0.89 (d, $J = 7$ Hz, 3H), 1.16–1.38 (m, 8H), 2.20–2.28 (m, 4H), 2.86 (qd, $J =$ 5.5 and 7 Hz, 1H), 4.06 (m, 1H), 4.11 (m, 2H), 4.11 (m, 2H), 4.19 (s, 5H), 4.26 (m, 2H), 4.35 (d, $J = 5.5$ Hz, 1H).
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