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Synthesis of C_2-symmetrical 1,1′-disubstituted ferrocenyl amino alcohols and use in catalytic asymmetric addition of diethylzinc to benzaldehyde

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Abstract

Optically active C_2-symmetrical 1,1′-disubstituted ferrocenyl amino alcohols have been used as chiral catalysts in the asymmetric addition of diethylzinc to benzaldehyde. 1-Phenylpropanol has been obtained in up to 83% enantiomeric excess.

1. Introduction

Stereoselective addition of organometallic reagents to carbonyl compounds is one of the most efficient methods for generating optically active alcohols.[1] Among the possible reactions, catalytic enantioselective addition of dialkylzinc has attracted much attention.[2] Thus, a wide variety of chiral catalysts, i.e., amino alcohols,[3] diamines[4] and diols[5] have been used successfully to promote this enantioselective alkylation. Among them, 1,2-disubstituted ferrocenyl amino alcohols possessing either a planar and a central chirality[6] or only a planar chirality[7] have shown good enantioselectivities. Note that chiral C_2-symmetrical amino alcohols have been less studied.[8] Also, to our knowledge, the involvement of C_2-symmetrical 1,1′-disubstituted chiral ferrocenyl amino alcohols has not been reported so far.

We have previously described the synthesis and successful application in catalysis of chiral ferrocenyl amino alcohols.[9] Hence, we set out to extend this study and to explore the chemistry of C_2-symmetrical ferrocenyl amino alcohols. In this paper, we describe the synthesis and use as catalysts

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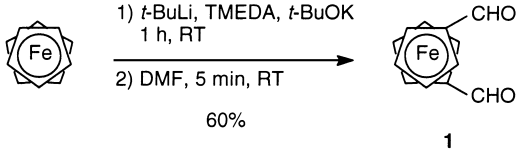
for the enantioselective addition of diethylzinc to benzaldehyde of a series of new chiral C_2-symmetrical 1,1′-disubstituted ferrocenyl amino alcohols.

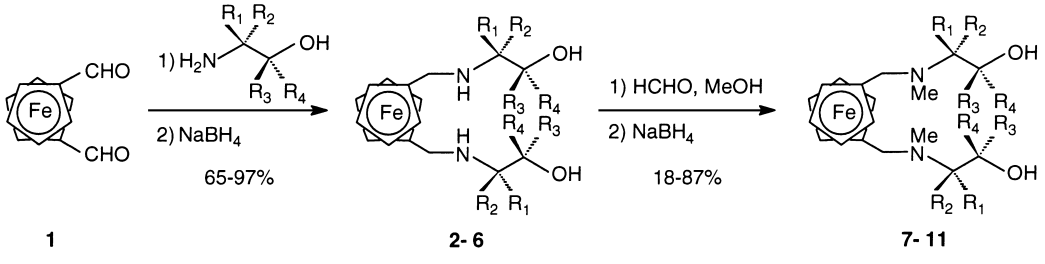
2. Results and discussion

We first established a novel easy methodology for the synthesis of ferrocene-1,1′-dicarboxaldehyde **1** based, in part, on conditions reported by Mueller-Westerhoff (Scheme 1).[10] Thus, the lithiation of ferrocene in the presence of *t*-BuLi, TMEDA and *t*-BuOK at room temperature for 1 h in diethyl ether followed by the addition of DMF at room temperature for 5 min led to complex **1** in 60% yield after work-up.



Scheme 1.

The ferrocenyl amino alcohols **7**–**11** were then obtained in three steps as depicted in Scheme 2. First, ferrocene-1,1′-dicarboxaldehyde **1** was reacted in THF in the presence of neutral Al_2O_3[11] with commercially available (*S*)-valinol, (*R*)-phenylglycinol, (*S*)-isoleucinol, (1*R*,2*S*)-norephedrine and (*S*)-2-amino-1,1-diphenyl-1-propanol giving the corresponding imines. Then, a reduction, carried out on the crude reaction mixtures, with sodium borohydride in methanol provided the amino alcohols **2**–**6** in 65–97% overall yield after work-up. Enantiomerically pure ferrocenes **7**–**11** were finally obtained by *N*-methylation of the amino function of **2**–**6** (Table 1).[12–16]

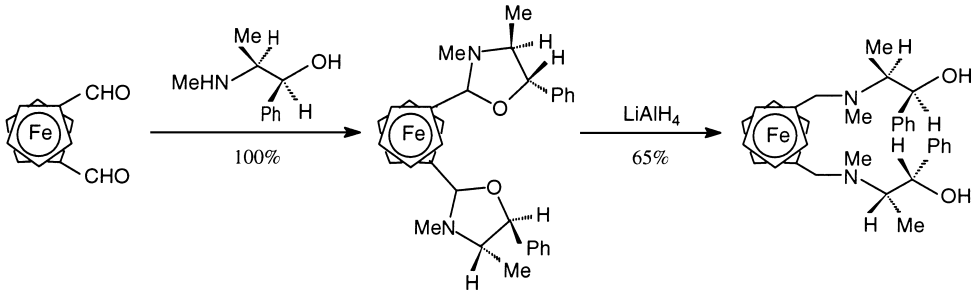


Scheme 2.

Next, the reaction between commercial pseudoephedrine and ferrocene-1,1′-dicarboxaldehyde **1** led quantitatively to the oxazolidine **12**. A reduction performed with an excess of $LiAlH_4$ in refluxing THF afforded the amino alcohol **13** in 65% chemical yield (Scheme 3).[18]

Table 1
Synthesis of chiral ferrocenyl amino alcohols **2**–**11**

R_1	R_2	R_3	R_4	Product	Yield (%)	Product	Yield (%)
iPro	H	H	H	**2**	65	**7**	66
H	Ph	H	H	**3**	97	**8**	78
iBu	H	H	H	**4**	80	**9**	87
Me	H	H	Ph	**5**	75	**10**	82
Me	H	Ph	Ph	**6**	79	**11**	18[17]



1 **12** **13**

Scheme 3.

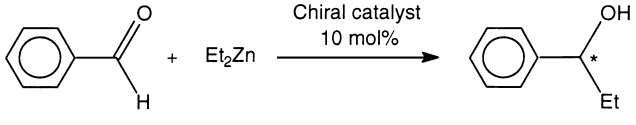
Table 2

Enantioselective addition of diethylzinc to benzaldehyde in the presence of chiral catalysts **2**, **7**–**11** and **13**[a]

Entry	Catalyst	Yield[b] (%)	ee[c] (%)	configuration[d]
1	**2**	74	15	*R*
2	**7**[e]	97	35	*R*
3	**7**	94	47	*R*
4	**8**	76	37	*S*
5	**9**	96	24	*S*
6	**10**	98	70	*R*
7	**11**	100	83	*R*
8	**13**	94	64	*S*

[a] The reactions were performed in dry toluene during 43 h under nitrogen with 10 mol% catalyst using benzaldehyde and diethylzinc in a ½ ratio at room temperature. [b] Determined by ^{1}H NMR, the by-products or the other products being benzyl alcohol and unreacted benzaldehyde. [c] Determined by GC analysis on FS-Cyclodex β-I/P (30 m x0.24). [d] Determined from the comparison fo the sign of the specific rotation with the literature data. [e] Using 5 mol% catalyst.

The reaction of diethylzinc with benzaldehyde was then investigated in the presence of 10 mol% of catalysts **2**, **7**–**11** and **13** at room temperature and the results are summarized in Table 2 (Scheme 4).



Scheme 4.

As can be seen, 1-phenylpropanol was obtained in high yield and in 15 to 83% enantiomeric excesses. When reducing the amount of catalyst, a significant decrease of the ee was observed. For example, when 10 mol% of amino alcohol **7** was used, (*R*)-1-phenylpropanol was obtained in 47% ee (entry 3), whereas reducing the catalyst to 5 mol% led to an erosion of the ee to 35% (entry 2). The presence of an NH moiety as is the case for **2** was detrimental to the ee (entry 3 versus 1) and slightly detrimental to the activity.

As expected, the sense of the asymmetric induction and the degrees of enantioselectivities are highly dependent on the structure of the catalyst.

More importantly, we can conclude that the steric hindrance near the hydroxyl moiety was crucial for a further enhancement of the enantioselectivity. Thus, without noticeably changing the environment of the N–Me, when going from a primary alcohol **7** to a diphenyl substituted tertiary alcohol **11** a drastic increase from 47 to 83% ee was obtained (entries 3 and 7). In the latter complex, the carbon atom bearing the hydroxyl group is not stereogenic and the sense of enantioselectivity is determined by the absolute configuration of the stereogenic carbon adjacent to the nitrogen. Moreover, the overall sense of induction is controlled in the first instance by the absolute configuration of the hydroxy terminus. Thus, a reversal of the configuration of that particular carbon led to opposite alcohols after catalysis (entry 8 versus 6) with comparable levels of induction (64% versus 70%).

Surprisingly, an unexpected reversal of configuration was observed even without changing the chirality of the catalyst (entry 5 versus 3).

3. Summary

This study provides the first example of chiral 1,1′-disubstituted ferrocene assisted catalysis. The extension of this study to the synthesis of 1,2-disubstituted ferrocenyl amino alcohols and their application in the asymmetric catalysis are under progress.

Acknowledgements

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12. For **7**: $[\alpha]_D^{20}$=−18.9 (*c* 0.32, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.84 (d, *J*=6.7 Hz, 6H, CHC*H*$_3$), 1.03 (d, *J*=6.7 Hz, 6H, CHC*H*$_3$), 1.84 (m, 2H, C*H*(CH_3)$_2$), 2.25 (s, 6H, NCH_3), 2.43 (m, 2H, NC*H*CH_2OH), 3.16 (dd, *J*=10.3 Hz, 2H, C*H*$_2$OH), 3.50 (d, *J*=13.0 Hz, 2H, FcC*H*$_2$N), 3.51 (dd, *J*=10.3 and 5.0 Hz, 2H, C*H*$_2$OH), 3.64 (d, *J*=13.0 Hz, 2H, FcC*H*$_2$N), 4.09 (m, 8H, C_5H_4).
13. For **8**: $[\alpha]_D^{20}$=−72.6 (*c* 0.25, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 2.09 (s, 6H, NCH_3), 3.19 (d, *J*=12.9 Hz, 2H, FcC*H*$_2$NMe), 3.45 (d, *J*=12.9 Hz, 2H, FcC*H*$_2$NMe), 3.65 (dd, *J*=10.3 and 4.9 Hz, 2H, C*H*$_2$OH), 3.76 (dd, *J*=9.2 and 4.9 Hz, 2H, C*H*$_2$OH), 3.93 (dd, *J*=10.3 and 9.2 Hz, 2H, NC*H*Ph), 4.07 (m, 8H, C_5H_4), 7.2 (m, 4H, Ph), 7.35 (m, 6H, Ph); MS, m/e 512 (M^+).
14. For **9**: $[\alpha]_D^{20}$=+28.4 (*c* 0.98, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.90 (d, *J*=7.0 Hz, 6H, (C*H*$_3$)$_2$CH), 0.92 (d, *J*=7.0 Hz, 6H, (C*H*$_3$)$_2$CH), 0.98–1.50 (m, 6H, (CH_3)$_2$C*H*), 2.12 (s, 6H, NCH_3), 2.80 (m, 2H, NC*H*CH_2OH), 3.17–3.50 (m, 8H, FcC*H*$_2$N+C*H*$_2$OH), 4.08 (m, 8H, C_5H_4).
15. For **10**: $[\alpha]_D^{20}$=+28 (*c* 0.14, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.82 (d, *J*=6.8 Hz, 6H, CHC*H*$_3$), 2.15 (s, 6H, NCH_3), 2.82 (m, 2H, C*H*CH_3), 3.46 (m, 4H, FcC*H*$_2$N), 4.1 (m, 8H, C_5H_4), 4.84 (d, *J*=4.2 Hz, 2H, C*H*Ph), 7.3 (m, 10H, Ph).
16. For **11**: $[\alpha]_D^{20}$=+12.2 (*c* 1.23, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.08 (d, *J*=7.1 Hz, 6H, CHC*H*$_3$), 1.91 (s, 6H, NCH_3), 2.98 (d, *J*=12.7 Hz, 2H, FcC*H*$_2$N), 3.13 (d, *J*=12.7 Hz, 2H, FcC*H*$_2$N), 3.64 (q, *J*=7.1 Hz, 2H, NC*H*CH_3), 4.01 (m, 8H, C_5H_4), 7.35 (m, 20H, Ph).
17. During the methylation step, an intermediate stable oxazolidine was produced which had to be reduced by $LiAlH_4$ and further purified by column chromatography and recrystallisation leading to an overall low yield.
18. For **13**: $[\alpha]_D^{20}$=+86.2 (*c* 0.28, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.73 (d, *J*=6.6 Hz, 6H, CHC*H*$_3$), 2.20 (s, 6H, NCH_3), 2.70 (qd, *J*=9.7 and 6.6 Hz, 2H, NC*H*CH_3), 3.34 (d, *J*=12.8 Hz, 2H, FcC*H*$_2$N), 3.56 (d, *J*=12.8 Hz, 2H, FcC*H*$_2$N), 4.17 (m, 8H, C_5H_4), 4.21 (d, *J*=9.7 Hz, 2H, C*H*–Ph), 7.28 (m, 10H, C_6H_5).