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Highly Stereoselective Alkylation Through Asymmetric Intramolecular Autoactivation; Synthesis and Use of a New Chiral Ligand

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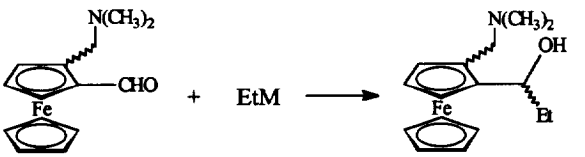
Abstract: The ethylation of 2-(*N*,*N*-dimethylaminomethyl)ferrocenylcarboxaldehyde **1** without a catalyst is stereospecific and occurs with high rates, yields and diastereoselectivities through an intramolecular asymmetric autoactivation. This reaction allowed the synthesis of the enantiopure (+)-(*S*,1*S*)-{2-(*N*,*N*-dimethyl-aminomethyl)ferrocenyl}-1-propanol **2** by applying this result to the enantiomerically pure aldehyde **1**. This new chiral auxiliary acted as a catalyst during the ethylation of benzaldehyde with diethylzinc. Copyright © 1996 Published by Elsevier Science Ltd

The synthesis of enantiomerically pure molecules is of great interest in organic chemistry. As such, the access to chiral alcohols has received special attention. An efficient method to prepare optically active secondary alcohols consists in carrying out the asymmetric alkylation of aldehydes with an organometallic reagent in the presence of a catalytic amount of a chiral auxiliary,[1] particularly aminoalcohols.[1d-i] Several aldehydes have been alkylated according to this procedure with high enantioselectivity.[1d-i] In some examples, the synthesis of the chiral alcohols has been achieved by asymmetric autocatalysis[2] or autoinduction[3] in the presence of R_2Zn. For example, when used as a chiral catalyst in the addition of diisopropylzinc to pyridine-3-carboxaldehyde, the optically active 2-methyl-1-(3-pyridyl)propanol (20 mol%, 86% *ee*) generates itself in good yield with 35% of enantiomeric excess.[2a] A range of ferrocene derivatives has also been shown to take part in enantioselective alkylations either as the catalyst[4] or as the substrate i.e. the aldehyde[5] or both.[6] More particularly, the ortho disubstituted ferrocene derivatives, whose optical properties are due to the ferrocene planar chirality, are often used because of their easy synthesis.[7] In fact, they are generally synthesized through a diastereoselective ortho-lithiation followed by an electrophilic attack. We are conducting a study of complexes of chromium[1i,8a-b] and substituted ferrocenes[8c] with a planar chirality. We attempted to extend our research to the addition of dialkylzinc for ferrocenyl aminoalcohols. Ferrocenylaminophosphines have been described as chiral auxiliaries in asymmetric homogeneous catalysis.[9]

In this paper, we report on the application of intramolecular asymmetric autoactivation in the stereoselective alkylation of 2-(*N*,*N*-dimethylaminomethyl)ferrocenylcarboxaldehyde **1** with organometallic reagents.

Ferrocenyl aldehyde **1** was first reacted with EtLi[10] at 20°C in diethylether without catalyst for one minute. The resulting ferrocenylaminoalcohol was produced in ca. 95% as a mixture of two diastereomers (1*S*1'*S*,1*R*1'*R*)-**2** and (1*S*1'*R*,1*R*1'*S*)-**2**[11] in 90.5/9.5 relative ratio (81% *de*) as assayed by ^{1}H NMR (Table 1, entry 1) (Scheme 1).

Scheme 1:



racemic-**1** (1*S*1'*S*,1*R*1'*R*)-**2** and (1*S*1'*R*,1*R*1'*S*)-**2**

Table 1: Stereoselective addition of ethylmetallic reagents to **1** through intramolecular autoactivation.[10]

Entry	EtM	Solvent	T (°C)	Time (min)	(1*S*1'*S*,1*R*1'*R*)-**2** / (1*S*1'*R*,1*R*1'*S*)-**2** ratio	Yield of alcohol (%) [a]	% *de* [a]
1	EtLi	ether	20	1	90.5/9.5	95	81
2	EtMgBr	ether	reflux	15[b]	97/3	91	94
3	Et_2Zn	toluene	20	1	>99/1	98	>98

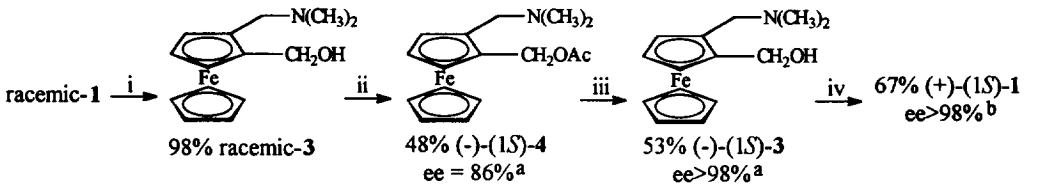
[a] Determined by ^{1}H NMR.[12] [b] Corresponds to the time of injection; the hydrolysis occured immediately after.

To find the configurations within the major diastereomers, we conducted a study analogous to that reported previously by Bau et *al.*[13] Then, aldehyde **1** was treated again without a catalyst with ethylmagnesium bromide in diethylether for 15 minutes leading to the same mixture of diastereomers in 91% yield and 94% *de* (Table 1, entry 2). Finally, an analogous reaction with Et_2Zn in toluene for one minute led to the previous mixture of diastereomers in 98% yield and >98% *de*.

It is noteworthy that these three reactions, carried out without any catalyst are very fast when compared with what is usually observed in stereoselective alkylations, i.e. from hours to several days.[5,6] The yields and *de*'s are also very high.

It is well recognized that there is neither asymmetric induction nor enhancement of rates without a catalyst. Moreover, without any activation Et_2Zn is rather unreactive due to its linear non polar geometry.[1d,14] Such an activation is realized through coordinatively unsaturated bent structure. According to this criteria, we can conclude that an autoactivation takes place through participation of the nitrogen atom and is responsible for the observed rates and selectivities. In fact, the nitrogen atom is located close to the aldehyde and is able to activate Et_2Zn. This is a new example of stereocontrol provided only by the planar chirality.[4d]

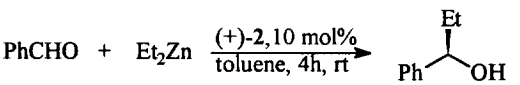
We then tried to synthesize enantiomerically pure aminoalcohol **2**. In fact, because of the high stereoselectivity obtained during the addition of Et_2Zn (Table 1, entry 3), enantiomerically pure **2** is expected in reactions conducted with enantiopure **1**. However, we first needed to carry out the resolution of racemic **1**. The route chosen includes a lipase promoted kinetic resolution according to Nicolosi's procedure,[15] which made such resolution normally difficult to achieve, very convenient (Scheme 2).



Scheme 2: *Reagents:* i) $NaBH_4$; ii) CCL, *t*-BuOMe, vinylacetate; iii) CCL, *t*-BuOMe, BuOH; iv) MnO_2.
[a] Determined by chiral HPLC analysis using CHIRALCEL OD (250 x 4.6 mm).[16] [b] Determined by ^1H NMR analysis using 1 equivalent of Pirckle's alcohol.

Thus, racemic **1** was first reduced in presence of $NaBH_4$ giving the corresponding aminoalcohol **3** in 98% yield after work up. Then, a transesterification of racemic **3** with vinylacetate catalysed by *Candida Cylindracea Lipase* (CCL) proceeded smoothly until an equilibrium was reached. Complex (-)-(1*S*)-**4** was subsequently isolated in 48% and 86% *ee*. The deacylation of (-)-(1*S*)-**4** was also undertaken through a transesterification process catalysed by CCL with BuOH leading to optically pure (-)-(1*S*)-**3** (*ee* >98%) in 53% isolated yield. Finally, an oxydation conducted with MnO_2 gave (+)-(1*S*)-**1** in 67% yield after work up (>98% *ee*). Enantiopure (+)-(1*S*,1'*S*)-**2** was obtained, as expected, through stereospecific alkylation of (+)-(1*S*)-**1** with Et_2Zn.

Scheme 3:



We then attempted to estimate the ability of such a chiral ferrocenylaminoalcohol (+)-(1*S*,1'*S*)-**2** to catalyze the addition of diethylzinc to benzaldehyde. Thus, benzaldehyde was reacted with diethylzinc in presence of 10 mol% of (+)-(1*S*,1'*S*)-**2** in toluene at room temperature for 4 hours. (+)-(1*R*)-1-phenyl-1-propanol was produced in 80 % yield and 62 % *ee* (Scheme 3). Benzaldehyde was also reduced in the reaction conditions as benzylic alcohol was isolated in 7% yield and 13% of unreacted aldehyde was recovered. As the enantioselectivity is greatly dependent on the bulkiness of the substituents near the C-O and the C-N bonds of the catalyst, it was not surprising to obtain only 62% of *ee* for the above general reaction.[1]

In summary, the alkylation of **1** with ethylmetallic reagents has been carried out without involving any external catalyst. The alkylation proceeded at high rates and with high diastereoselectivities. An asymmetric intramolecular autoactivation is thought to be responsible for such capabilities. Moreover, we synthesized enantiopure 2-(*N,N*-dimethylaminomethyl)ferrocenylcarboxaldehyde (+)-(1*S*,1'*S*)-**1**. Finally, the aminoalcohol proved to be a good catalyst for the addition of Et_2Zn to benzaldehyde. The extension of this study to the synthesis and to the application of new ferrocenylaminoalcohols is under progress.

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10. The solvents were dried over sodium and distilled. EtLi was prepared *in situ* by action of lithium with EtBr; EtMgBr was prepared *in situ* by action of magnesium with EtBr; Et_2Zn is commercial.
11. All the relative configurations of the aromatic rings of the chiral ferrocenes were determined according to the nomenclature of Cahn, Ingold and Prelog extended to planar chiralities by Schlögl: Schlögl, K. *Topics in Stereochemistry*, **1967**, *1*, 39-91. The denomination "1*S*" or "1*R*" refers to the sp^3 chirality and the "1'*S*" or "1'*R*" one refers to the planar chirality.
12. ^{1}H NMR of the major diastereoisomer of **2** (300 MHz; in $CDCl_3$): δ 4.65 (dd: J = 3.7 and 9.1Hz; 1H; CH-O); 4.19 (m; 1H; C_5H_3); 4.11-4.01 (m; 2H; C_5H_3); 4.04 (s; 5H; C_5H_5); 3.90 (d: J = 12.4Hz; 1H; CH_2N); 2.75 (d: J = 12.4Hz; 1H; CH_2N); 2.15 (s; 6H; $N(CH_3)_2$); 1.95 (m; 1H; $\underline{CH_2}Me$); 1.73 (m; 1H; $\underline{CH_2}Me$); 1.19 (t: J = 7.4Hz; 3H; CH_3). ^{1}H NMR of the minor diastereoisomer of **2** (300 MHz; in $CDCl_3$): δ 4.20 (dd: J = 6.4 and 9.7Hz; 1H; CH-O); 4.15 (s; 5H; C_5H_5); 4.04 (m; 3H; C_5H_3); 3.86 (d: J = 12.6Hz; 1H; CH_2N); 2.77 (d: J = 12.6Hz; 1H; CH_2N); 2.15 (s; 6H; $N(CH_3)_2$); 1.95 (m; 1H; $\underline{CH_2}Me$); 1.83 (m; 1H; $\underline{CH_2}Me$); 1.12 (t: J = 7.4Hz; 3H; CH_3).
13. The condensation of the 2-(*N,N*-dimethylaminomethyl)ferrocenyllithium to propanal was achieved and led to the 2 racemic diastereomers of **2** (ratio: 57/43). The relative configurations of the major one could be determined according to Bau's results and studies;[7a] the major product is the one which is stabilized by an hydrogen bond between the nitrogen and the oxygen atoms, favoured by the spatial disposition of the substituents. So the major diastereomer has (1*S*1'*S*,1*R*1'*R*) as absolute configuration. In fact, an ^{1}H NMR study showed that this diastereomer corresponds to the major one obtained by ethylation of the aldehyde **1** with the three ethylmetallic reagents[12] (Scheme 1).
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16. For **2**: eluent 2% 2-propanol in hexane; for **3**: eluent 2% 2-propanol in hexane; for **4**: eluent 1% 2-propanol in hexane. Flow: 1ml/min; UV detector (254nm).

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