Pergamon

Tetrahedron: Asymmetry Vol. 5, No. 9, pp. 1639-1642, 1994
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0957-4166/94 $7.00+0.00

0957-4166(94)00233-9

Enantiopure 1-Hydroxymethyl-2-dimethylaminomethylferrocene as Efficient Catalyst in the Enantioselective Addition of Diethylzinc to Aldehydes

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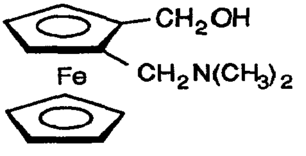
Abstract: A ferrocenyl amino alcohol possessing only planar chirality has been employed as a catalyst in the enantioselective alkylation of aldehydes with Et_2Zn. Seven chiral secondary alcohols in 64~83% e.e. have been prepared.

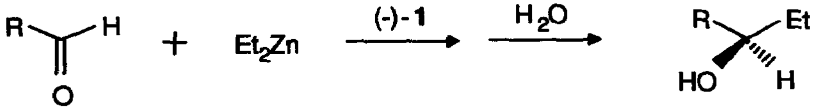
Asymmetric synthesis of enantiopure secondary alcohols by addition of organometallics to aldehydes, assisted by chiral reagents, is a challenging current endeavour.[1,2] Organozinc reagents are generally preferred because in non-polar solvents the uncatalysed reaction is slow and therefore the accelerating effect and the stereocontrol of the catalyst are more evident.[3-5] Fair to high degrees of enantiomeric excess have been observed. In general, the best results in terms of enantiomeric excess are obtained with arylaldehydes as well as with aliphatic aldehydes branched α to the carbonyl group, while the reaction with straight chain or β-branched substrates proceeds with less satisfactory stereoselectivities. A range of chiral catalysts have been used to assist the addition of dialkylzincs to aldehydes, among which several 1,2-substituted ferrocenyl amino alcohols, all possessing both planar and central chirality (the latter sometimes due to more than one stereogenic centre).[6-8] The role played by each of these elements of asymmetry is still a matter of debate. According to Schlögl *et al.*[8] centrochirality dominates in determining the sense of asymmetric induction, while metallocene (planar) chirality seems to be less important. On the other hand, the work of Butsugan *et al.*[6] indicates that the sense of induction depends on the planar chirality but not on the chirality of the alcohol moiety. Since the relative weight of planar and central chirality is of great consequence in the design of new catalysts, we have planned a study on the catalytic activity of appropriate ferrocenyl derivatives, beginning with molecules endowed with a single element of asymmetry, either a plane or a centre.

In this communication we report on the enantioselective addition of diethylzinc to aldehydes in the presence of the readily accessible enantiomers of the planochiral 1-hydroxymethyl-2-dimethylaminomethylferrocene, **1**, a very simple 1,2-substituted ferrocenyl derivative that is obtained in optically pure enantiomeric forms by enzyme-mediated kinetic resolution of the racemate.[9]



(-)-**1**

In order to examine the effect of the catalyst, the reaction of diethylzinc with various aldehydes (see scheme) has been investigated.



In a typical procedure diethylzinc (0.660 mmol, 0.6 mL of 1.1 M toluene solution) was added to a solution of aldehyde (0.330 mmol) and catalyst (0.033 mmol) in dry toluene (0.5 mL) degassed with argon. The whole mixture was stirred at room temperature and the progress of the reaction monitored by GC. The reaction was quenched by addition of sat. NH_4Cl solution, the organic phase was separated, and the aqueous phase extracted with diethyl ether. The organic layers were pooled, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was separated by column chromatography to give the corresponding *sec*-alcohols (Table 1). From the aqueous phase the catalyst was recovered unchanged (yield 95%) by addition of 1N NaOH to pH >8 and extraction with diethyl ether. The e.e. values of the products were determined as indicated in Table 1 and the absolute configurations deduced from the reported rotation data.

Table 1. Enantioselective addition of diethylzinc to aldehydes catalysed by 1

Entry	R-	Catalyst[a]	Time (h)	Yield of alcohol (%)[b]	e.e. (%)	Configuration
1	C_6H_5	(-)-1	3	94	82[c]	*R*
2	C_6H_5	(+)-1	3	92	80[c]	*S*
3	C_6H_5	(-)-1[d]	8	80	68[c]	*R*
4	C_6H_5	(-)-1[e]	3	83	68[c]	*R*
5	*p*-CH_3O-C_6H_4	(-)-1	8	84	76[f]	*R*
6	*p*-Cl-C_6H_4	(-)-1	3	98	78[f]	*R*
7	β-$C_{10}H_7$	(-)-1	3	92	78[f]	*R*
8	*c*-C_6H_{11}	(-)-1	8	91	83[g]	*R*
9	C_5H_{11}	(-)-1	4	92	64[g]	*R*
10	C_6H_{13}	(-)-1	4	91	70[g]	*R*

[a] The enantiomeric excess of the catalyst (>95%) was determined by ^1H NMR shift experiments using (*R*)-(9-anthryl)-2,2,2-trifluoroethanol (Pirkle's alcohol). [b] Determined by GC analysis of the reaction mixture. [c] Determined by HPLC analysis on Nucleodex β-PM chiral column. [d] 5% catalyst to benzaldehyde molar ratio. [e] Catalyst of 58% e.e. [f] Determined by GC analysis on achiral column (HP-5) of the corresponding methoxy(trifluoromethyl)phenylacetyl (MTPA) ester. [g] Determined by ^1H-NMR analysis of the corresponding acetate in the presence of Pirkle's alcohol.

As can be seen from Table 1, reaction of diethylzinc with benzaldehyde in the presence of 10% mol of (-)-(1*S*)-1-hydroxymethyl-2-dimethylaminomethylferrocene[10], (-)-**1**, resulted in a 94% yield of (*R*)-(+)-1-phenyl-1-propanol of 82% e.e. (entry 1). With the enantiomeric catalyst, (+)-**1**, the enantiomeric alcohol was obtained (entry 2). These results accord with the transition state models postulated by Corey and Hannon,[5] Hitsuno and Frèchet,[11] and Noyori and Kitamura,[1] all of which correctly predict the stereochemical course of the reaction. Reducing the catalyst to benzaldehyde ratio from 10% to 5% (entry 3) affected unfavourably the values of both the chemical yield and the enantiomeric excess of the product. The use of enantioenriched catalyst (predominant enantiomer (-)-**1**, 58% e.e., entry 4) resulted in a significant asymmetric amplification,[4] and (*R*)-(+)-1-phenyl-1-propanol with 68% e.e. was obtained. *Para*-substituted benzaldehydes bearing electronically different groups (entries 5 and 6) gave comparable selectivity according to the known steric, rather than electronic, origin of the stereoselectivity.[1] In addition, 2-naphthaldehyde and cyclohexanaldehyde were ethylated in good enantiomeric excess (entries 7 and 8). The reaction with unbranched aldehydes, hexanal and heptanal (entries 9 and 10), was also enantioselective, but somewhat less than the corresponding reaction with aromatic or α-branched aldehydes.

In summary, the present work provides the first example of 1,2-ferrocenyl derivative possessing only planar chirality, 1-hydroxymethyl-2-dimethylaminomethylferrocene, that can catalyse efficiently the enantioselective addition of diethylzinc to aldehydes.

Acknowledgment. Thanks are due to CNR Scheme "Progetto Finalizzato Chimica Fine e Secondaria" for financial support.

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(*Received in UK* 21 *June* 1994)