



Enantioselective addition of diethylzinc to benzaldehyde catalyzed by ferrocenic amino-alcohols combining centered and planar chiralities

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Abstract

Diastereomeric ferrocenic amino-alcohols combining three elements of chirality (one of which is a ferrocenic plane) are tested as catalysts in the alkylation of benzaldehyde with diethylzinc. Good to excellent yields and ees were obtained and show correlation between the metallocenic chirality and the configuration of the resulting 1-phenyl-1-propanol. © 1999 Elsevier Science Ltd. All rights reserved.

1. Introduction

The catalytic effect of amino-alcohols in the alkylation of benzaldehyde using diethylzinc is very well documented and many catalysts have been tested.¹ Such compounds are based on natural optically active products² or are purely synthetic.³ In this latter category, ferrocenic and benchrotrenic molecules represent the most effective examples.⁴

Dealing with the catalytic properties of ferrocenic amino-alcohols, three pairs of diastereomers have been tested by Watanabe⁵ (in which the centered chirality appears in an alpha position of the cyclopentadienyl moiety). This work shows evidence of the minor role played by the configurations of these alpha carbon centres. Bolm⁶ has recently published the case of an oxazoline (centered chirality in gamma position of the cyclopentadienyl moiety) for which modifying the planar chirality of the catalyst gives dramatic changes in the yield, enantiomeric excess and reaction time. The author explains this result

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using a concept developed by Togni⁷ who considered the different elements of chirality which act in a cooperative way or not. Except for the molecule described by Schlögl,⁸ one can note that for metallocenic amino-alcohols when maintaining the same planar chirality, the stereochemistry of the reduction of the carbonyl function was only slightly affected and a (p*R*)⁹-ferrocenyl 1- α -hydroxy, 2- α -amino led to (*R*)-1-phenyl-1-propanol.¹⁰ This fact is also observed by Nicolosi¹¹ in the case of the 1-hydroxymethyl-2-dimethylaminomethylferrocene for which an asymmetric amplification was also reported.

We describe herein the results obtained with 1,2-disubstituted ferrocenic amino-alcohols exhibiting two centered chiralities in alpha and beta positions of the hydroxylated side chain.

We recently reported an alternative strategy to control the planar chirality of ferrocenic amino-alcohols: 3-(2'-(*N,N*-dimethylamino)methylferrocenyl)-4-(4''-aryl)hexan-3-ols based on the highly diastereoselective alkylation of optically active 4-arylhexan-3-one by the lithiated *N,N*-dimethylaminomethylferrocene.¹²

Then, starting from optically active 2-aryl butanoic acids, this route allows the simultaneous preparation of two diastereomeric amino-alcohols with two stereogenic carbons and opposite metallocenic planar chirality. It was of interest to test them as catalysts. Fig. 1 illustrates the different examples of molecules tested.

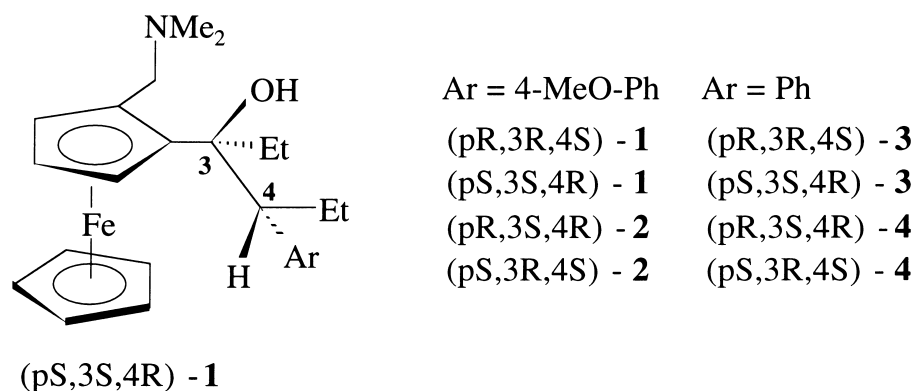


Figure 1.

2. Results and discussion

In a typical procedure diethylzinc (4 mmol, 4 mL of 1 M hexane solution) was added to a solution of benzaldehyde (0.11 mL, 1.1 mmol) and catalyst (0.05 mmol) in dry toluene (1.5 mL) under argon. The whole mixture was stirred at room temperature and the progress of the reaction followed by TLC. After 4 hours, the reaction was quenched by addition of saturated NH₄Cl solution. The organic phase was directly flash-chromatographed on silica gel first with pure pentane, then mixed with 10% ether. The catalyst was recovered unchanged eluting with ether.¹³ The ee values of the products were determined as indicated in Table 1.

Table 1 shows the main role played by the planar chirality and the lack of influence of the configurations of the carbons in the alpha and beta positions. These results match very well with those obtained by Watanabe.⁵ We did not observe asymmetry amplification for the 1-phenyl-1-propanol and the level of the ee is linearly dependent on the enantiomeric excess of the catalyst.

Table 1

compound	e.e. catal	mol ratio (cat./ald.%)	time	yield	$[\alpha]_D$ hexane	conf. ROH	e.e. *
(-)-(p <i>S</i> ,3 <i>S</i> ,4 <i>R</i>)- 1	92	1.7	4	96	-41	S	76
(+)-(p <i>R</i> ,3 <i>R</i> ,4 <i>S</i>)- 1	96	2.6	4	80	+43	R	94
(-)-(p <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)- 2	83	6	4	70	-39	S	82
(+)-(p <i>R</i> ,3 <i>R</i> ,4 <i>S</i>)- 3	98	2	4	78	+51	R	98
(+)-(p <i>R</i> ,3 <i>S</i> ,4 <i>R</i>)- 4	92	4.5	4	30	+47	R	92

Correlation of the planar chirality of our compounds with the 1-phenyl-1-propanol configuration obtained.

*Enantiomeric excesses were measured by chiral HPLC (Chiralcel OJ) for compounds **1**, and **2** or by GC (Chiralcel DEX-CB) for compounds **3** and **4**.

If we consider that the metallic moiety acts as a bulky group, comparison with a camphor analog derivative (DAIB)¹⁴ is possible taking into account the rigidity of the carbon skeleton of this type of molecule. This approach satisfactorily relates with the observed stereochemistry (Fig. 2).

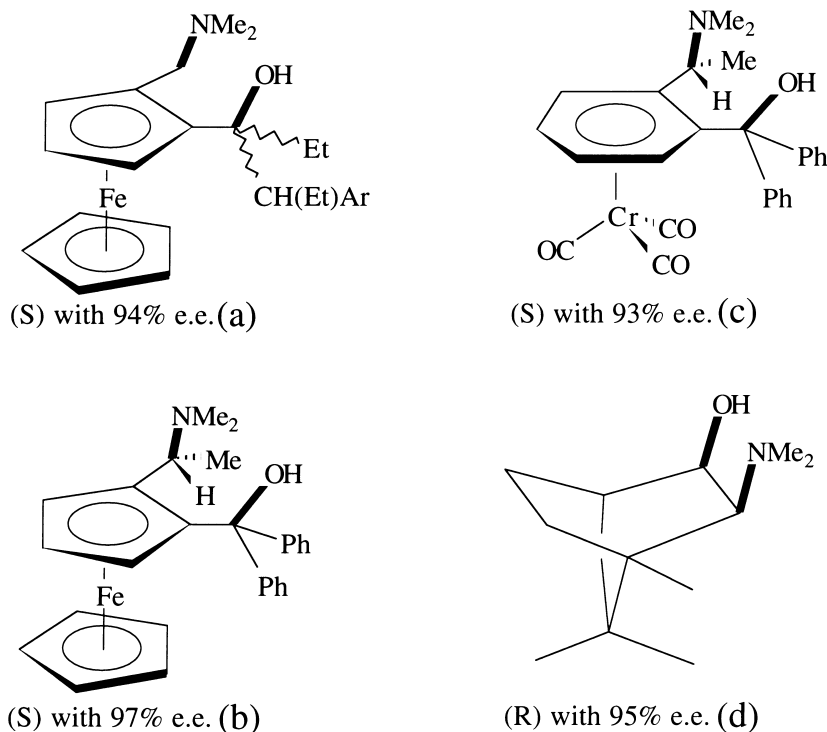


Figure 2.

This structural analogy also provides the evaluation of the difference between an *exo* and an *endo* position that leads to an inversion in the stereochemistry observed.^{15,16} To our knowledge, this analogy provides the best explanation for the behavior of the homoannularly bridged hydroxyaminoferrocene published by Schlögl.⁸

Fig. 3 illustrates the difference in the efficiency of our catalysts. Whereas compound (p*S*,3*S*,4*R*)-**1** showed catalytic activity with 0.4% mol, its diastereomeric analog (p*S*,3*R*,4*R*)-**2** required four times this concentration.

This difference could be related to the ability of **2** to exist in two conformations involving the formation of an hydrogen bond between the hydroxyl function with the amino group or with the iron atom. This

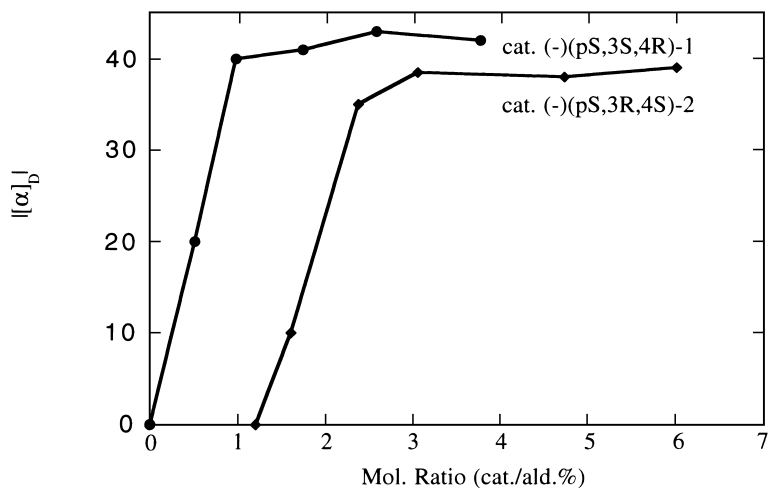


Figure 3.

ability has been fully characterized in solution as well as in the solid state.¹⁷ Some NMR experiments were performed to try to understand the different features observed for the diastereomeric (*pR*^{*},*3R*^{*},*4S*^{*})-**1** and (*pR*^{*},*3S*^{*},*4R*^{*})-**2** compounds.¹⁸

3. Conclusion

The diastereomeric ferrocenic amino-alcohols presented in this work proved to be very efficient catalysts for the alkylation of benzaldehyde with ethylzinc. A correlation between the planar chirality and the stereochemistry of the 1-phenyl-1-propanol obtained was found. The (*pR*,*3R*,*4S*) diastereomer was active at lower concentrations than the (*pR*,*3S*,*4R*) diastereomer due to conformational interactions.

4. General information

All reactions were carried out under an atmosphere of dry argon. Solvents were dried and distilled using standard techniques. Diethyl ether was distilled from sodium–benzophenone, toluene from sodium, pentane was treated with sulfuric acid and distilled on sodium. ¹H NMR spectra were recorded on a Bruker AM 250 instrument, using standard programmes for protons (299.9 MHz). Optical rotations were recorded on an America AA-10 polarimeter at a wavelength of 589 nm (sodium D line) using a 1.0 dm cell with a total volume of 1.3 mL. The enantiomeric excesses of 1-phenyl-1-propanol were determined by HPLC Kontron column (Chiralcel OJ eluent isopropanol–heptane 12% with a flow of 0.3 mL min⁻¹, detector at 254 nm) or by chiral CPG (Fisons/CarloErba) Chiralcel DEX-CB, 25 cm.

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13. The first method of hydrolysis we employed to perform the catalytic test (first with HCl 0.1N to extract the phenyl propanol, then neutralization with NaHCO₃ to extract the catalyst) had the consequence of altering the catalyst. We obtained in this way the very clean transformation of the (–)-(p*S*,3*S*,4*R*)-**1** into another enantiomerically pure amino-alcohol presumably (+)-(p*S*,3*S*,4*S*) as a consequence of a benzylic isomerization. This compound was previously observed and described as a minor product in the synthesis of **1** and **2** (see Ref. 12). This compound is also a catalyst but less efficient than **1** or **2** (a 3% molar ratio gives the (*S*)-phenyl propanol with 41% yield and in 52% ee).
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18. ¹H NMR spectra were recorded in different solvents — chloroform, acetone and methanol. At rt no changes were observed versus the concentration for each diastereomer in acetone and methanol. In chloroform, when the spectrum of **1** remained unchanged, that of compound **2** evolved with the concentration. Modifying the concentration from 3 to 180 mmol L^{–1} strongly affected the signals (broadening and shifting) corresponding to the (methylene and dimethyl) bond to the nitrogen atom, and the ferrocenyl protons. These results are consistent with the major feature of these molecules i.e. **1** exists as a single conformer with a strong intramolecular H-bond involving the amino and hydroxyl groups while **2** exhibits two main conformations due to the possible H-bonds for OH which can be either with Fe or with N(CH₃)₂. Then, with compound **1** the strong intramolecular bond controls the conformation and the molecule is not affected by the concentration variations. In contrast, for compound **2** the position and the rate of the equilibrium between the two possible conformations is under dilution control. Lowering the concentration in amino-alcohol **2** results in an increase of the concentration of the monomeric forms which renders operative the exchange between the two conformations. In 0.1 mol L^{–1} methanol solution, addition of ZnBr₂ results in dramatic changes for each diastereomer. Nevertheless these changes are significantly different for each of them. Focusing on the main changes for (p*R*^{*},3*R*^{*},4*S*^{*})-**1** in the range of concentration of ZnBr₂ from 0.01 to 1.00 mol L^{–1} a general deshielding is observed. The single signal belonging to the methyl groups of the dimethylamino function evolves to give two broad signals. This behavior could be the consequence of a strong chelating effect of the hydroxyl and amino groups on the Zn atom. In contrast with compound (p*R*^{*},3*S*^{*},4*R*^{*})-**2**, the most significant variations concern the protons borne by the ferrocene entity and those of the aminated branch. Thus, simultaneous modifications of the shape and chemical shift affect the methyl groups of the dimethylamino function and the protons of the substituted and unsubstituted cyclopentadienyl moieties. The splitting of the unsubstituted cyclopentadienyl accompanying the apparition of, at least, three signals corresponding to the methyl substituents borne by the nitrogen atom could be correlated to the existence of two conformers in slow equilibration process. Further additions of ZnBr₂ lead to the displacement to a unique conformer. This fact is indicated by the evolution of a single peak related to the cyclopentadienyl moiety.