Enantioselective addition of diethylzinc to ferrocene carbaldehyde - reaction outcome by using natural compound based catalysts

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Dedicated to Acad. Dimitar Ivanov on the occasion of his 120th birth anniversary

The efficiency of the alkaloids quinine, cinchonine, cinchonidine and ephedrine, the aminoalcohols prolinol, and alaninol, as well as the aminoacids proline, and phenylalanine as catalysts for the enantioselective addition of diethylzinc to ferrocene carbaldehyde and benzaldehyde has been studied. The addition reactions proceeded with acceptable yields and low to moderate enantioselectivities. The side products ferrocenyl methanol and 1-ferrocenyl-1-propanone, observed during the additions to ferrocene carbaldehyde were isolated and characterized.

Key words: diethylzinc, addition to aldehydes, natural products

INTRODUCTION

The synthesis of chiral aminoalcohols, first reported by Oguni and Omi [1-3], to catalyze enantioselectively the addition of diorganozinc compounds to aldehydes, still attracts considerable interest due to the utility of the secondary alcohols formed by this reaction [1-7]. Over the past decades a large number of aminoalcohols has been synthesized and tested as ligands [1-9]. One of the most potent aminoalcohols used as a catalyst is the dimethylamino-isoborneol investigated by Noyori [10-16]. For the synthesis of aminoalcohols natural sources of chirality (e.g. terpenoids, aminoacids, alkaloids) are generally used. In many cases catalysts based on naturally occurring aminoalcohols have been applied as such or aminoalcohols have been obtained after minor modifications. The cinchona alkaloids quinine, quinidine, cinchonine and cinchonidine have been used directly [17,18] or after simple chemical transformations [19,20] as efficient catalyst for enantioselective addition of diethylzinc to aldehydes. In similar manner ephedrine and norephedrine derivatives have been obtained and used in catalytic diethylzinc addition reactions [21-25]. On the other hand various strategies have been developed for the synthesis of structurally diverse aminoalcohols which are suitable ligands for different catalytic applications [4-9]. Among them are the 1,2-substituted ferrocenyl aminoalcohols of type C (Fig. 1; E = -CH(R1)OH) and other derivatives that possess chirality plane and have proven to be very useful for asymmetric catalysis [26-29].

Key compounds for synthesis of planar chiral 1,2-disubstituted ferrocenes are the chiral alkyl- (or aryl-) ferrocenyl methanols obtained either by asymmetric reduction of alkyl- (or aryl-) ferrocenyl ketones [26-29] or through enantioselective addition of dialkylzinc compounds to ferrocene carbaldehyde (Fig. 1). After the enantioselective addition of e.g. diethylzinc (2) to ferrocene carbaldehyde (1), catalyzed by suitable chiral ligand, the resulting 1-ferrocenyl-1-propanol (3) can be easily trans-
formed to dialkylamino derivative A with retention of the configuration. Compounds of type A undergo highly diastereoselective ortho-lithiation (up to 96% de) with butyllithium reagents due to the directed ortho-metallation caused by the dialkylamino group attached to the stereogenic center. The reaction of the lithiated ferrocene B with suitable electrophiles (e.g. aldehydes, ketones) leads to the formation of planar chiral amino-alcohols or other aminoalkylferrocenyl derivatives of type C bearing various functionalities [26-29].

The aim of the present work is to evaluate the ability of some alkaloids (quinine, cinchonine, cinchonidine, ephedrine), aminoalcohols obtained from aminoacids (prolinol, alaninol) and aminoacids (proline, phenylalanine), (see Fig. 2), to catalyze enantioselectively the addition of diethylzinc to ferrocene carbaldehyde.

Fig. 2. Chiral natural compounds and derivatives applied as catalysts for enantioselective addition of diethylzinc to ferrocene carbaldehyde.

**EXPERIMENTAL**

**General**

All reactions were carried out in flame-dried Schlenk flasks under argon atmosphere. Hexane was distilled over Na[Et₄Al]. Thin layer chromatography (TLC) was performed on aluminum sheets pre-coated with silica gel 60 F₂₅₄ (Merck). Flash column chromatography was carried out using silica gel 60 (230-400 mesh, Merck). Optical rotations ([α]D) were measured on a Perkin Elmer 241 polarimeter. The NMR spectra were recorded in CDCl₃ on a Bruker DRX 250 (250.13 MHz for ¹H NMR, 62.9 MHz for ¹³C NMR) spectrometer with TMS as the internal standard for chemical shifts (δ, ppm). ¹H and ¹³C NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), integration, and identification. EI-MS (70eV) were recorded on a Hewlett Packard 6890/5973 and reported as fragmentation in m/z with relative intensities (%) in parentheses.

**General procedure for enantioselective addition of diethylzinc to carbaldehydes**

To a solution of the corresponding ligand 6-13 (3 mol %) in hexane or toluene (20 ml) Et₂Zn (2.1 mmol, 1M solution in hexane) was added dropwise at 0°C under Ar atmosphere. The mixture was stirred for 30 min at 0°C and then the corresponding aldehyde (1.40 mmol) was added at -20°C. The reaction mixture was stirred at 20°C (in 2 cases at 60°C) and monitored by TLC (petroleum ether/Et₂O = 1:1) until the aldehyde was consumed or no further consumption was observed. The mixture was quenched (aq. NH₄Cl), extracted with Et₂O, and dried (Na₂SO₄). After evaporation of the solvent, the crude product was purified by column chromatography (petroleum ether/Et₂O = 5:1).

**General procedure for enantioselective addition of diethylzinc to carbaldehydes in the presence of Ti(O-iPr)₄**

To a suspension of the ligands 6, 10 and 12 (0.57 mmol, 20 mol %) in toluene (8 ml), Ti(O-iPr)₄ (0.58 mmol) was added at 20°C under Ar atmosphere. The reaction mixture was stirred at 20°C for 1.5 h and then benzaldehyde (14) (2.83 mmol) and Ti(O-iPr)₄ (3.40 mmol) were added. After 1 h the mixture was cooled to -20°C and Et₂Zn (5.66 mmol, 1M solution in hexane) was added. It was stirred at -20°C until completion of the reaction (monitored by TLC). The mixture was quenched (aq. NH₄Cl), filtered through a pad of Celite, extracted with Et₂O, and dried (Na₂SO₄). After evaporation of the solvent, the crude product was purified by column chromatography (petroleum ether/Et₂O = 10:1).

**Data of 1-ferrocenylpropan-1-ol (3):** ¹H NMR: 4.27-4.14 (m, 10H, C₃H₅, C₄H₆, CH), 1.99 (br. s, 1H, OH), 1.76-1.61 (m, 2H, CH₂), 0.95 (t, J = 7.5
The enantioselectivity of the aldehyde reduction catalyzed by ferrocenyl methanol (4) was not complete in several cases. It was, however, remarkable to observe the formation of significant amounts of ferrocenyl methanol (4) as side products. The formation of 4 and 5 could be explained with the assumption [47] that redox Cannizaro like reaction between 1 and 3 occurs leading to oxidation of 3 to the ketone 5 and reduction of 1 to the alcohol 4. It is noteworthy to mention that in a paper of Noyori [11] the formation of 1-phenyl-1-propanone has been described beside the 1-phenyl-1-propanol formation in the course of the addition of diethylzinc to benzaldehyde, however without any discussion. The primary alcohol 4 could also be a result of reduction of the aldehyde 1 through β-hydrogen transfer from the ethyl-group of the diethylzinc reagent.

The addition reactions catalyzed by ligands 6-13 provided acceptable yields of 1-ferrocenylpropan-1-ol (3). The ratios of unreacted 1, product 3 and side-products 4, and 5, determined by NMR experiments and the quantities of isolated products are introduced in Table 1. Considering the composition of the compounds observed after performing the reactions it can be concluded that the conversion of the starting aldehyde 1 is very good despite of the prolonged reaction time. Enhancement of the reaction temperature to 60°C shortened significantly the reaction time (Table 1, entry 1 vs 2 and 7 vs 8), however the enantioselectivity was lowered.

The best enantioselectivities were observed with quinine (6) and prolinol (10), however the values were significantly lower in comparison with some literature data [19,20,48,49]. The insufficient degree of enantioselectivity in case of ligands 7, 8, 9 and 11 was also surprising if compared with reported results [17,18,50,51]. The enantioselectivity realized with proline (entry 10) was low and it could not be enhanced attempting to block the carboxy group through reaction with n-BuLi (entry 11) prior to performing the catalytic addition of diethylzinc. In the case of phenylalanine (entry 12) there is no enantioselectivity at all.

For the purpose of comparison ligands 6, 10 and 12 furnishing promising enantioselectivities were tested in the addition reaction of diethylzinc to benzaldehyde (Table 2). The reaction catalyzed by ligand 6 provided very good yields whereas in all other cases the yields were moderate. The observed prolonged reaction times could be shortened by applying titanium tetraisopropoxid (Ti(O-iPr)_4)
as promoter, however without affecting the enantioselectivity (Table 2, entry 1 vs. 2). Ligand 10 provided comparable results compared with those obtained with aldehyde 1.

![Diagram of reaction]

**Table 2.** Enantioselective addition of Et₂Zn to benzaldehyde (14) catalyzed by chiral ligands (L*) 6, 10 and 12.

<table>
<thead>
<tr>
<th>Entry</th>
<th>L*</th>
<th>Reaction Temp.</th>
<th>Reaction Time [h]</th>
<th>Composition [%]</th>
<th>ee [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>20°C</td>
<td>101</td>
<td>28 61 7 1</td>
<td>27 (S)</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>60°Cb</td>
<td>7</td>
<td>16 50 7 4</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>20°C</td>
<td>164</td>
<td>4 72 7 8</td>
<td>9 (S)</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>20°C</td>
<td>183</td>
<td>6 66 7 4</td>
<td>1 (R)</td>
</tr>
<tr>
<td>5</td>
<td>9</td>
<td>20°C</td>
<td>67</td>
<td>2 53 9 2</td>
<td>34 (R)</td>
</tr>
<tr>
<td>6</td>
<td>10</td>
<td>20°C</td>
<td>191</td>
<td>8 52 7 traces</td>
<td>50 (R)</td>
</tr>
<tr>
<td>7</td>
<td>10</td>
<td>60°Cb</td>
<td>24</td>
<td>14 27 10 5</td>
<td>5 (S)</td>
</tr>
<tr>
<td>8</td>
<td>11</td>
<td>10</td>
<td>138</td>
<td>10 60 7 2</td>
<td>18 (S)</td>
</tr>
<tr>
<td>9</td>
<td>12</td>
<td>10</td>
<td>193</td>
<td>4 67 10 6</td>
<td>11 (S)</td>
</tr>
<tr>
<td>11</td>
<td>12/n-BuLi³</td>
<td>20°C</td>
<td>193</td>
<td>5 8 10 10</td>
<td>0</td>
</tr>
</tbody>
</table>

These entries were determined by polarimetry based on the maximum values for the specific rotations of (S)-(-)-15 ([α]D²⁰ = -47 (c 2.2, hexane) for 98% ee [52]).

**REFERENCES**


**CONCLUSION**

Comparative study has been performed to evaluate the efficiency of the alkaloids quinine, cinchonine, cinchonidine, ephedrine, the aminoalcohols prolinol, and alaninol, and the aminocoids proline, and phenylalanine as catalysts for the enantioselective addition of diethylzinc to ferrocene carbaldehyde. The important intermediate 1-ferrocenyl-1-propanol has been obtained in moderate enantioselectivity besides ferrocenyl methanol and 1-ferrocenyl-1-propanone as side products. The efficiency of the natural products studied as enantioselective catalysts was not sufficient for additions of diethylzinc to ferrocene carbaldehyde and also to benzaldehyde.
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ЕНАНТИОСЕЛЕКТИВНО ПРИСЪЕДИНЯВАНЕ НА ДИЕТИЛЦИНК КЪМ ФЕРОЦЕНКАРБАЛДЕХИД – РЕЗУЛТАТИ ОТ ИЗПОЛЗВАНЕ НА ПРИРОДНИ СЪЕДИНЕНИЯ КАТО КАТАЛИЗАТОРИ

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(Резюме)

Изучена е ефективността на алкалоидите хинин, цинхонин, цинхонидин и ефедрин, на аминоалкохолите пролинол и аланинол, както и на аминокиселините пролин и фенилаланин за енантиоселективно присъединяване на диетилцинк към фероценкарбалдехид и бензалдехид. Присъединителните реакции протичат с приемливи добиви и ниски до умерени енантиоселективности. При присъединителните реакции към фероценкарбалдехид се наблюдават страничните продукти фероценил метанол и 1-фероценил-1-пропанон, които са изолирани и охарактеризирани.