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Mechanistic investigation into the addition of diethylzinc to aromatic aldehydes catalyzed by chiral *o*-hydroxyaryldiazaphosphonamides

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Abstract

A mechanistic investigation into the addition of diethylzinc to aromatic aldehydes catalyzed by chiral *o*-hydroxyaryldiazaphosphonamides is described. A positive non-linear effect has been encountered and the X-ray structure of catalyst *anti*-**1** has been realized.

Keywords: *o*-hydroxyaryldiazaphosphonamide; non-linear effect; diethylzinc; enantioselective alkylation; aromatic aldehyde.

Among the numerous methods existing available for C–C bond formation, the enantioselective alkylation of aldehydes appears to be one of the most useful.[1] Thus, a great deal of attention has been focused on the addition of organozinc compounds to aldehydes in presence of various chiral ligands[2] as catalysts such as chiral β-aminoalcohols[3] and their parent compounds (such as aminothiols,[4] diamines,[5] diaminodiols[6] or diols[7]). Recently, we have described the synthesis of chiral *o*-hydroxyarylphosphine oxides,[8] a new family of catalysts in the enantioselective addition of diethylzinc to various aromatic aldehydes leading to the expected alcohols in enantiomeric excesses (ee) up to 98%.[9] Although various mechanistic studies have been reported for this reaction, these assumptions deal only with the use of aminoalcohols as catalytic chiral promoters. In the context of our studies, we report herein some mechanistic considerations using chiral *o*-hydroxyaryldiazaphosphonamides as catalysts.

Among a wide variety of organophosphorous compounds, diastereomers **1** and **2** appeared to be two of the most efficient catalysts in the enantioselective addition of diethylzinc to benzaldehyde. Two pertinent results are summarized in Table 1.

In order to explain the high observed enantioselectivity, numerous experiments have been achieved. First of all, the structure of **1**, established by X-ray structure analysis, clearly shows that the molecule had been described with the correct absolute configuration (*S*).[11] Moreover, it clearly appears that whatever the stereochemistry at the phosphorus atom, only (*R*)-1-phenyl propanol was formed as the

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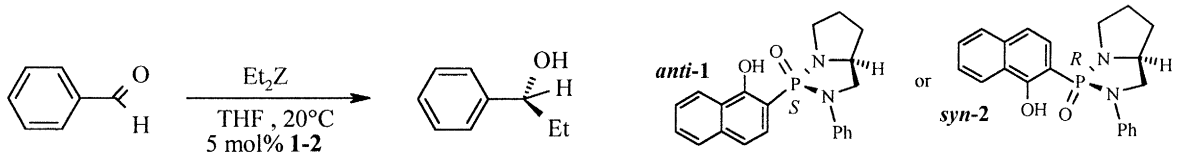
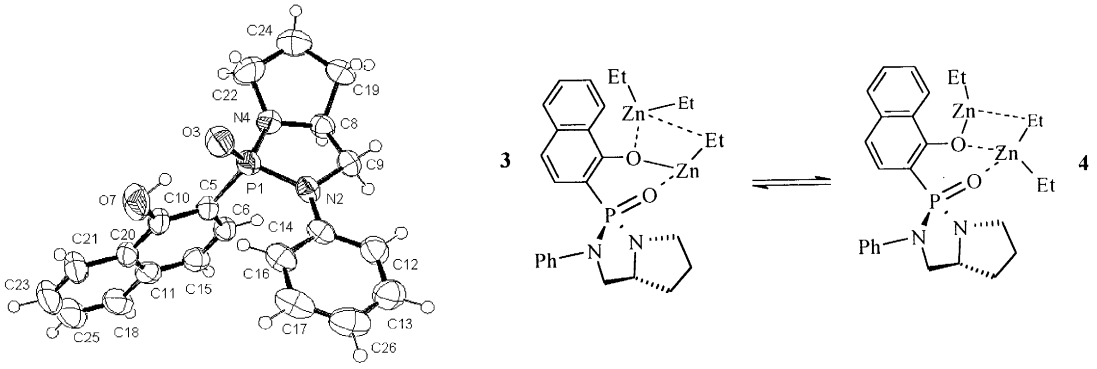
Table 1
Addition of Et_2Zn to PhCHO in presence of 5 mol% of **1**–**2**.



Entry[a]	Catalyst	Conversion (%)[b]	Ee (%)[b]
1	**1**	100	98 (*R*)
2	**2**	100	92 (*R*)

[a] Experiment performed at 1 mmol scale. [b] Conversion and ee determined by HPLC analysis on a Daicel Chiralcel OD-H column at λ = 254 nm, eluent : hexane/*i*-PrOH = 90/10, flow rate 0.9 mL/min.

major enantiomer. ^{31}P NMR analysis of ligand **1a** exhibits a signal at 33.2 ppm. Addition of one equivalent of Et_2Zn revealed several signals due to the formation of numerous complexes. Addition at room temperature or −78°C of two equivalents of Et_2Zn led to a single signal at 35.8 ppm, illustrating that the species **3** or **4** probably exist both in equilibrium as a dinuclear complex according to previously reported results with β-aminoalcohols (Scheme 1).[12]



Scheme 1.

In this area, the addition of dialkylzinc reagents to aldehydes facilitated by aminoalcohols as bidentate ligands is generally accepted to generate dimeric species. Thus, in order to substantiate this assumption, we made use of non-linear effects to identify a higher order molecularity of the catalyst. The results obtained in the presence of 5 mol% of **1** clearly demonstrate a positive non-linear effect and support the hypothesis of the involvement of structures with more than one *o*-hydroxyaryldiazaphosphonamide molecule (Fig. 1).

These data fit very well with Kagan's two-ligand model assuming a stastistical distribution of the enantiomeric ligands.[13] Although the actual active species in this reaction are unclear, a plausible mechanism may be envisioned involving a ML_2 statistical distribution model or a reservoir effect. Thus, assuming the mechanism proposed by Noyori et al., we can suppose that this positive non-linear effect

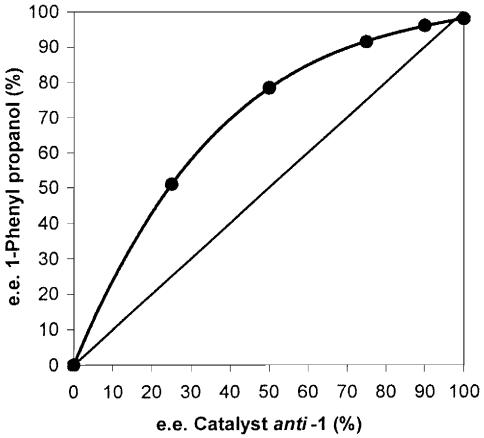
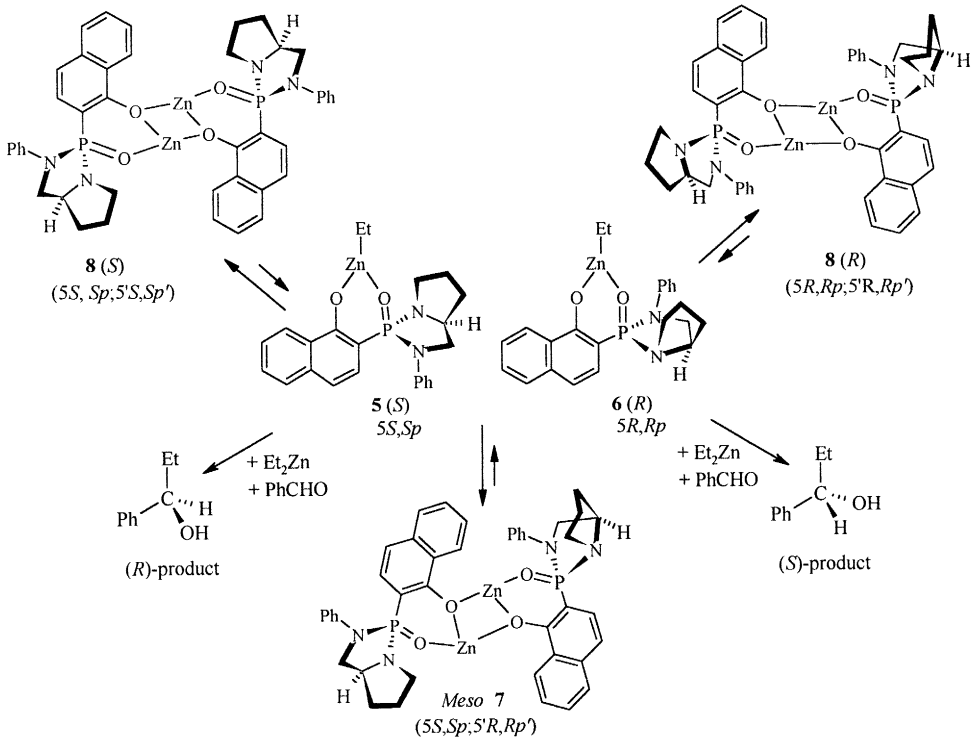


Fig. 1.

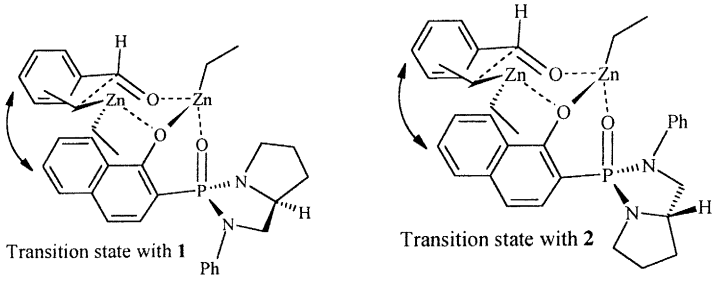
was a result of autoassociation of the chiral reagent formed by the reaction between **1** and the organozinc compound (Scheme 2).[14]



Scheme 2.

Thus, when a mixture of (−)- and (+)-**1** was used, two types of dimeric species were formed: homochiral **8**-(*S*) and **8**-(*R*) and heterochiral **7**. The enantiomeric monomers **5**-(*S*) and **6**-(*R*) are the active catalysts in this reaction and each one produces predominantly one enantiomer of phenyl propanol. In this alkylation with diethylzinc, it is logical to conclude that if dimers are formed the heterochiral that retains the minor enantiomer of the catalyst should be less implicated in the reaction, leaving the homochiral-enriched dimer free to operate as the active agent or its precursor. On the basis of all our experiments,

a six-membered transition state could be proposed predicting the stereochemistry encountered using indifferently **1** or **2** as catalysts. Thus, the predominant formation of (*R*)-1-phenyl propanol in the two cases could be explained by an attack of an ethyl moiety on the *Re* face of the carbonyl group of benzaldehyde (Scheme 3).



Scheme 3.

In this paper, we have studied the mechanism of addition of diethylzinc to benzaldehyde catalyzed by a new class of chiral compounds: the *o*-hydroxyaryldiazaphosphonamides. Our investigations have suggested a possible mechanistic pathway implying monomeric and dimeric species both in equilibrium. Further investigations of their catalytic ability are still in progress.

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10. General procedure for asymmetric addition of diethylzinc to benzaldehyde: In a 25 mL two necked round bottomed flask was successively introduced under an argon atmosphere at 0°C, 4.72×10^{-5} mol of ligand (5 mol respect to substrate) in 5

mL of freshly distilled THF, 100 mg of benzaldehyde (9.43×10^{-4} mol) and 2 equiv. of Et_2Zn (1.1 M in hexane solution). The reaction mixture was allowed to warm up and stirred at room temperature for 48 h. After quenching by the addition of 3 mL of saturated NH_4Cl solution, the aqueous layer was extracted with 3×10 mL of diethyl ether. The combined organic layers were dried over $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The residue was purified by flash chromatography on a silica gel column (eluent: diethylether:pentane 50:50) to afford the corresponding pure 1-phenyl propanol.

11. X-Ray structure analysis of **1**: A plate white monocrystal of $C_{21}H_{21}N_2O_2P$, obtained by recrystallization in ethyl acetate, with approximate dimensions 0.4×0.4×0.3 mm was mounted on a glass capillary. All the measurements were made on a Rigaku diffractometer with Mo-Kα radiation. Cell constants and the orientation matrix for data collection were obtained from a least-squares refinement using setting angles of 30 reflections in the range range θ=1–25°, which corresponded to a monoclinic cell with the dimensions: *a*=8.0696(3), *b*=10.1959(5), *c*=11.7395(5) Å. For *Z*=2 and *M*=364.38, ρ_{calcd}=1.33 g cm^{-3}. The space group was determined to be $P2_1$ from the systemic absences. A total of 1724 reflections were collected at *T*=298 K. The standards were measured after every 120 reflections. Among the first 200 pairs of reflections, the signs of the corresponding calculated differences, establishing that the molecule is described with the correct absolute configuration *S*. *CCDC138892.*
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