Tetrahedron Letters,Vol.28,No.44,pp 5237-5240,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

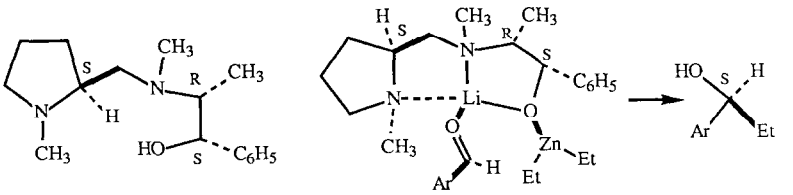
ZINC COMPLEXES OF CHIRAL PHENOLS AS CATALYSTS FOR ENANTIOSELECTIVE ADDITION OF ORGANOZINC REAGENTS TO ALDEHYDES

E. J. Corey and Francis J. Hannon

Department of Chemistry, Harvard University, Cambridge, Massachusetts, 02138

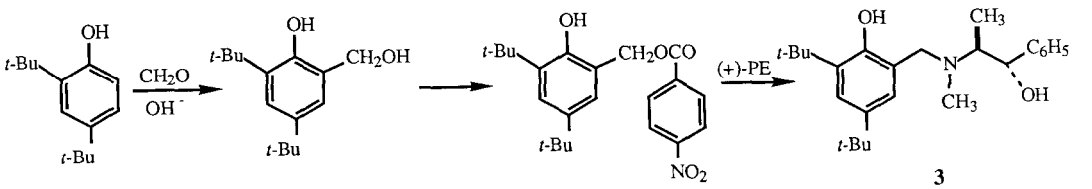
Summary: A class of zinc (II) chelates with chiral tertiary amino phenolic alcohols serve as effective catalysts for the enantioselective addition of diethylzinc to aromatic aldehydes with predictable absolute stereochemistry.

The preceding paper in this journal summarizes the results of an investigation on the application of rationally designed chiral lithium chelates as catalysts for the enantioselective addition of organozinc reagents to aldehydes.[1] For example, the lithium chelate from chiral diamino alcohol **1** catalyzes the addition of diethylzinc to benzaldehyde in accord with the mechanistic concept represented by expression **2** to give *S*-(-)-1-phenylpropanol with 95% enantiomeric excess (ee) in 68% yield (along with 22% of recovered aldehyde and 10% of benzyl alcohol, produced by a non-catalyzed, competing reduction). As a logical extension of this work we have studied the use of tridentate neutral zinc (II) complexes as catalysts for the same reaction. Zinc (II) was chosen as the catalytic metal ion since it was thought likely to show higher Lewis acid affinity than lithium for the aldehyde reaction component. Each of the three chiral complexing agents selected for initial evaluation contained one tertiary amino function and two hydroxylic groups positioned so as to form a neutral tridentate zinc chelate. In order to achieve differentiation between the pair of oxido anions, one was in the form of alkoxide and the other as a much less basic and also sterically shielded phenoxide oxygen.



1 **2**

Ligand **3** was synthesized from 2,4-di-*t*-butylphenol and (1*S*, 2*S*)-(+)-pseudoephedrine ((+)-PE) by the following simple but effective process. Reaction of **3** with diethylzinc[2] (1 equiv) at 85°C for 30 min in toluene



3

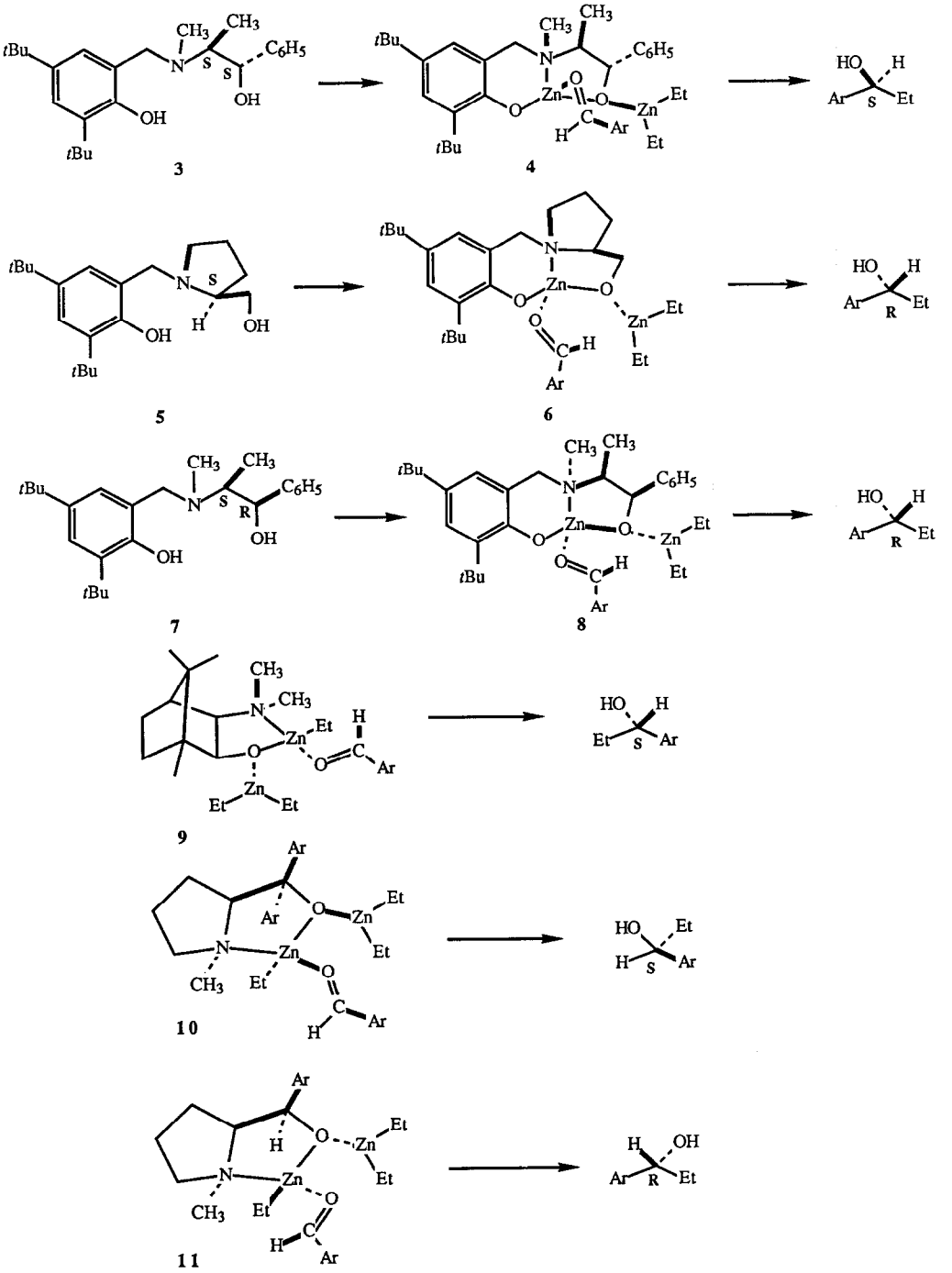
produced a clear solution containing the chelated zinc complex of **3**. To this solution was added 10 equiv of diethylzinc and 7.5 equiv of benzaldehyde. After an 8 h reaction period at 23°C, gas chromatographic (GC) analysis indicated nearly complete formation of 1-phenylpropanol (93%) with *ca.* 5.5% of unreacted benzaldehyde remaining and *ca.* 1.5% of benzyl alcohol (the product of uncatalyzed β-hydrogen transfer from diethylzinc[1]). Isolation of 1-phenylpropanol, conversion to the menthyloxycarbonyl derivative, and GC analysis according to a standard procedure,[1,3] revealed that *(S)*-(-)-1-phenylpropanol was selectively formed in this experiment in 85.8% enantiomeric excess (ee). This stereochemical result accords with the mechanistic model discussed in the foregoing paper[1] and the expectation that the catalyzed reaction would occur by assembly of catalyst, aldehyde, and zinc reagent as shown in **4**, which predicts correctly the predominant *S*-configuration of product. The reaction of benzaldehyde and diethylzinc under catalysis by the zinc complex of **3** proceded similarly in ether-toluene solution to form *(S)*-(-)-1-phenylpropanol of 87.2% ee.

Ligand **5** was synthesized by the same approach used for **3** from 2,4-di-*t*-butyl-6-*p*-nitrobenzoyloxymethylphenol and *(S)*-2-hydroxymethylpyrrolidine (*(S)*-prolinol). Amino diol **5** was converted into the corresponding zinc complex by heating with 1 equiv of diethylzinc in toluene for 30 min at 85°C. Reaction of benzaldehyde (7.5 equiv) with diethylzinc (10 equiv) in the presence of 1 equiv of chiral zinc complex of **5** (23°C, 12 h) afforded *(R)*-(+)-1-phenylpropanol in 93% yield and 70% ee. The stereochemistry of this reaction agrees with mechanistic expectations that the predominant enantiomer would be generated from the three component complex represented by **6.**

Reaction of (1*R*, 2*S*)-(-)-ephedrine with 2,4-di-*t*-butyl-6-*p*-nitrobenzoyloxymethylphenol produced chiral amino diol **7** which was converted to the zinc complex by reaction with 1 equiv of diethylzinc in toluene at 85°C for 30 min. Catalytic reaction of this complex (1 equiv) diethylzinc (10 equiv) and benzaldehyde (7.5 equiv) at −78°C initially and then at 23°C for 12 h resulted in a 91% yield of *(R)*-(+)-1-phenylpropanol of 75.3% ee, 8% of unreacted benzaldehyde and *ca.* 1% of benzyl alcohol. This result also accords with the mechanistic model for the reaction and the predicted mode of assembly shown in **8**.

In each of these catalytic reactions involving the zinc complexes of **3**, **5**, and **7**, it was noted that the reaction becomes very slow when conversion to product reaches *ca.* 80% and that small amounts of unreacted benzaldehyde remain even at long reaction times in the presence of excess diethylzinc. It appears likely that the zinc alkoxide produced in the reaction can inhibit further reaction by complexing at the catalytic zinc site (in competition with unreacted aldehyde). Preliminary studies indicate that it is possible to remove this inhibition, and these results will be reported in due course. The methodology reported herein is of practical value since the chiral ligands are easily synthesized from inexpensive materials and are quantitatively recoverable from the organozinc reactions, and the reactions themselves are homogeneous and simple to carry out. Of equal importance is the fact that all of the experiments with the zinc complexes of **3**, **5**, and **7** as tests of the underlying mechanistic concepts fully support our model.

Further details on the synthesis of the chiral ligand **3** are as follows. 2,4-Di-*t*-butylphenol, formaldehyde (1.2 equiv) and As_2O_3 catalyst (0.3 mole %) were allowed to react in 20% aqueous potassium hydroxide solution at 23°C for 48 h to give after isolation of product and recrystallization from hexane 2,4-di-*t*-butyl-6-hydroxymethylphenol,[4] mp 96-97°C in 58% yield. Reaction of this product with 1.2 equiv of *p*-nitrobenzoyl chloride and 2 equiv of pyridine in methylene chloride at 23°C for 3 h and subsequent recrystallization of the crude product from methylene chloride afforded 98% yield of 2,4-di-*t*-butyl-6-*p*-nitrobenzoyloxymethylphenol, mp 128-


3
4
5
6
7
8
9
10
11

135°C (dec). This phenol and (1*S*, 2*S*)-(+)-pseudoephedrine (2 equiv) were heated together at reflux in tetrahydrofuran solution for 3 h to yield after extractive isolation and chromatography on silica gel 77% of amino diol **3**, $[\alpha]^{23}_D$ + 72.2° (c=1.36 in $CHCl_3$), as a colorless oil.[5]

Other recent studies on the use of tertiary amino alcohols as catalysts for the reaction of aldehydes with diethylzinc have shown interesting enantioselectivities[6-9] which can now be rationalized on the basis of both the model and the results described in this and the foregoing paper.[1] Thus, (-)-3-*exo*-(dimethylamino)isoborneol affords predominately *(S)*-(-)-1-phenylpropanol, probably via complex **9**.[7] (2'*S*)-(+)-Diphenyl(1'-methylpyrrolidin-2'-yl)methanol catalyzes preferentially the formation of *(S)*-(-)-1-phenylpropanol, probably via complex **10**, whereas (1*R*, 2'*S*)-(-)-phenyl(1'-methylpyrrolidin-2'-yl)methanol as catalyst leads to a predominance of *(R)*-(+)-1-phenylpropanol, probably via **11**.[10]

REFERENCES AND NOTES

1. E. J. Corey and F. J. Hannon, *Tetrahedron Letters*, preceding paper.
2. Reactions of diethylzinc were conducted under an inert atmosphere.
3. J. W. Westley and B. Halpern, *J. Org. Chem.*, **33**, 3978 (1968).
4. M. Karhu, *J. Chem. Soc. Perkin I*, 1661 (1979).
5. Similar procedures were employed for the syntheses of **5**, $[\alpha]^{23}_D$ - 10.2° (c=1.06 in $CHCl_3$), and **7**, $[\alpha]^{23}_D$ + 6.23° (c=1.06 in $CHCl_3$).
6. N. Oguni and T. Omi, *Tetrahedron Letters*, **25**, 2823 (1984).
7. M. Kitamura, S. Suga, K. Kawai, and R. Noyori, *J. Am. Chem. Soc.*, **108**, 6071 (1986).
8. K. Soai, A. Ookawa, K. Ogawa, and T. Kaba, *J. Chem. Soc. Chem. Comm.*, 467 (1987).
9. P. A. Chalanor and S. A. Renuka Perera, *Tetrahedron Letters*, **28**, 3013 (1987).

10. This research was assisted financially by a grant from the National Science Foundation.

(Received in USA 16 July 1987)