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CHIRAL CATALYSTS FOR THE ENANTIOSELECTIVE ADDITION OF ORGANOMETALLIC REAGENTS TO ALDEHYDES

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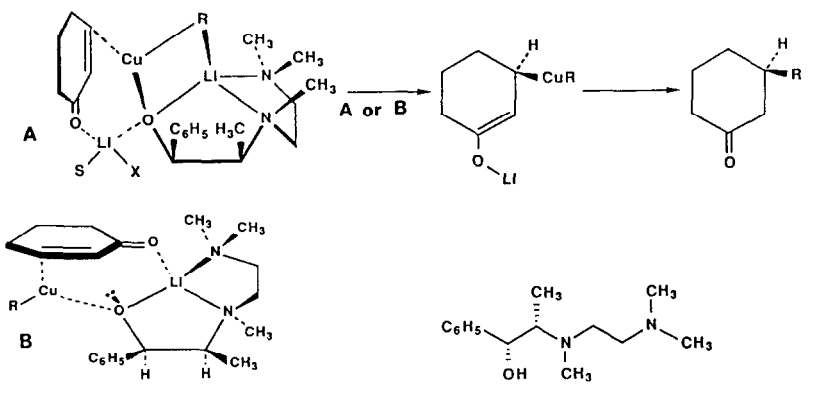
Summary: A mechanistic model for the enantioselective addition of diethylzinc to benzaldehyde with chiral tridentate lithium complexes as catalysts correctly predicts the observed direction of enantioselectivity which occurs at levels of 85-95% ee.

A recent paper from these laboratories described two rationally designed and effective chiral catalysts for the enantioselective conjugate addition of organocopper reagents to α,β-enones.[1] Thus, the lithium salt derived from **1** (available in one step from (1*R*, 2*S*)-(-)-ephedrine) brings together 2-cyclohexenone and an organocopper reagent to generate selectively the product shown (e.g. for R=C_2H_5 as the *R*(+) form in 92% ee). The two most reasonable modes of assembly of the reactants and catalyst, A and B, both predict the same product enantiomer and, consequently, no decision between these possibilities has been made.[1] In parallel with these studies we have investigated a similar approach to the catalytic, enantioselective 1,2-addition of organometallic reagents to aldehydes. This paper describes some of the results and insights emerging from this project using four different catalysts and organozinc reagents. Organozinc reagents are the simplest to study because the rates of the uncatalyzed (i.e. spontaneous) reactions with aldehydes are low and catalytic effects can be large.[2] Fair to excellent enantioselectivities have been reported previously[2,3] using various chiral ligands, organometallic reagents and aldehydes.

As in our previous work,[1] the design of potential catalysts was guided by mechanistic considerations and, particularly, the idea that the assembly **2**, containing a rigid chiral catalyst and the reactants, may provide the required low-energy pathway. The specific ligand **3** (oil), $[\alpha]^{23}_{D}$-33.6°, (c=0.9 in $CHCl_3$) was synthesized from



1

N-benzyloxycarbonyl-*(S)*-proline and (1*S*, 2*R*)-(+)-ephedrine by amide formation (dicyclohexylcarbodiimide in CH_2Cl_2 at 0°) and subsequent reduction of the amide by lithium aluminum hydride in tetrahydrofuran (THF). Reaction of **3** in toluene with 1 equiv of *n*-butyllithium in hexane generated a soluble, chelated lithium salt of **3** which was found to be an effective catalyst for the reaction of organozinc reagents with benzaldehyde as a test aldehyde. Thus, reaction of benzaldehyde (1 equiv) and diethylzinc (1.2 equiv of commercial reagent) in toluene or 15:1 ether-toluene in the presence of 0.1 equiv of the lithium salt of **3** at 0°C for 7 h produced *S*-(-)-1-phenylpropanol of 95% ee (68%) along with unreacted aldehyde (22%) and benzyl alcohol (10%).[4] It was observed that at lower temperatures larger amounts of benzyl alcohol are formed. Reduction of benzaldehyde to benzyl alcohol was found to occur in the absence of catalyst at a rate comparable to that observed in the presence of the lithium salt of **3**. This non-catalyzed reaction probably occurs by internal β-hydrogen transfer in a 1:1 complex of benzaldehyde and diethylzinc (6-membered cyclic transition state). In addition the lack of complete reaction of aldehyde, even at long reaction times, provides clear evidence that alkoxide reaction products (as their zinc salts in the reaction mixture) retard the catalyzed reaction, presumably by complexation with the catalyst.

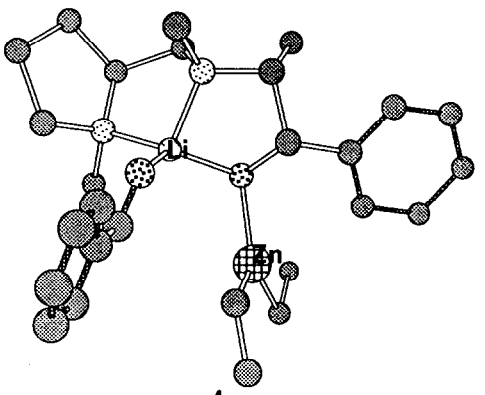
We formulate the catalyzed reaction as proceeding by complexation of benzaldehyde and diethylzinc with the lithium salt of **3** as shown in **4**, which predicts unambiguously preferential transfer of ethyl to the *si* face of the formyl group to form the *S*-(-)-secondary alcohol, as observed. Molecular models of **4** (in which the terminal 5-rings are *anti* about the central 5-ring) show this structure to be sterically much more favorable for catalysis than the alternative **5** (in which the terminal 5-rings are *syn* about the central 5-ring). Computer generated drawings of **4** and **5** are shown herein.[5] Assembly **5** clearly cannot be on the major pathway since it predicts the wrong enantiomeric product.

The reaction of di-*n*-butylzinc (distilled) with benzaldehyde in the presence of 0.1 equiv of the lithium salt of **3** in toluene was also enantioselective (68% yield of *(S)*-(-)-1-phenylpentanol of 84% ee), but somewhat less so than the corresponding reaction with diethylzinc. The use of organozinc preparations containing halide ions or RZnHal results in much lower enantioselectivity. Two other aldehydes, cinnamaldehyde and cyclohexane carboxaldehyde were also submitted to reaction with diethylzinc in toluene in the presence of 0.1 equiv of the lithium salt of **3** and were found to be converted to *(S)*-carbinols of 69% and 60% ee, respectively.

Chiral ligand **6**, a diastereomer of **3**, was synthesized as described above for **3** except for the use of (1*S*, 2*S*)-(+)-pseudoephedrine as the amino alcohol component. Ligand **6**, $[\alpha]^{23}_D$ + 18° (c=1.83 in $CHCl_3$), was converted to the toluene-soluble chelated lithium alkoxide (1 equiv of n-BuLi in toluene). Use of this chelate (0.1 equiv) to catalyze the reaction of benzaldehyde (1 equiv) and diethylzinc (1.1 equiv) in toluene at 0°C for 7 h resulted in an 85% yield of *S*-(-)-1-phenylpropanol of 85% ee along with 5% of benzyl alcohol and 10% of unreacted benzaldehyde.

The lithium chelate of **1** (0.1 equiv) in toluene solution catalyzed the reaction of benzaldehyde (1 equiv) and diethylzinc in toluene at 23°C over 14 h to give 81% of *R*-(+)-1-phenylpropanol of 90% ee together with 10% of benzyl alcohol and 11% of benzaldehyde. Our mechanistic model (**7**) correctly predicts the observed stereochemical course of this carbonyl addition reaction.

Ligand **8**, the diastereomer of **1** derived from the reaction of (1*S*, 2*S*)-(+)-pseudoephedrine and 2-chloroethyldimethylamine, was also transformed into a toluene-soluble lithium chelate. Reaction of this lithium salt (0.1 equiv), benzaldehyde (1 equiv) and diethylzinc (1.1) equiv) in toluene at 23°C for 14 h produced *S*-(-)-1-phenylpropanol (69% yield, 91% ee) in addition to benzyl alcohol and recovered benzaldehyde. Assembly **9**,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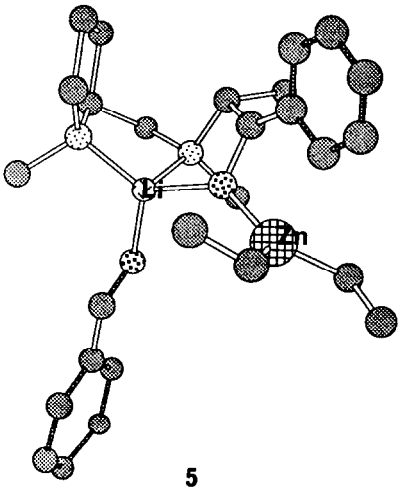
Zn

4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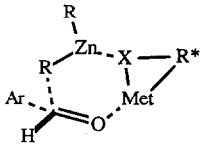
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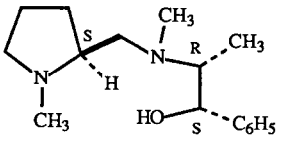
R*
R
Ar
Met
O
H

2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HO
S
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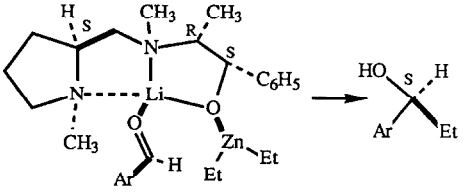
3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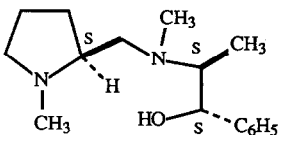
Et

4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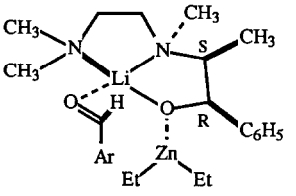
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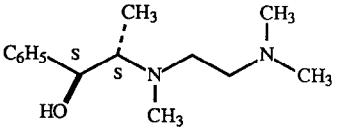
7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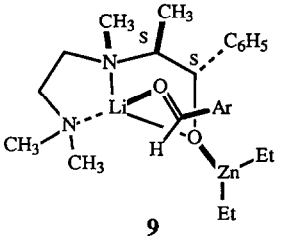
CH3

8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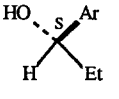
9


HO
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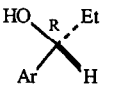
HO
R
Et
Ar
H

expected to be the most favorable for reaction, correctly predicts selective formation of the observed *S*-(-)-enantiomer.

The results described above may be summarized as follows:

Ligand	Precursor	Predominant Enantiomer, % ee
3	(1*S*, 2*R*)-ephedrine	*S*(-), 95
6	(1*S*, 2*S*)-ψ-ephedrine	*S*(-), 85
1	(1*R*, 2*S*)-ephedrine	*R*(+), 90
8	(1*S*, 2*S*)-ψ-ephedrine	*S*(-), 91

It is apparent that the chirality of the benzylic alcohol stereocenter of the catalyst correlates with the chirality of the predominant enantiomer, in accord with the mechanistic hypothesis which guided this work. The following paper describes our results with an entirely different set of chiral zinc chelates as catalysts for the reaction of diethylzinc and benzaldehyde. These are also in accord with our mechanistic model.[6,7]

REFERENCES AND NOTES

1. E. J. Corey, R. Naef, and F. J. Hannon, *J. Am. Chem. Soc.*, **108**, 7114 (1986).
2. (a) N. Oguni, T. Omi, Y. Yamamoto, and A. Nakamura, *Chem. Letters,* 841 (1983); (b) N. Oguni and T. Omi, *Tetrahedron Letters,* **25**, 2823 (1984); (c) M. Kitamura, S. Suga, K. Kawai, and R. Noyori, *J. Am. Chem. Soc.,* **108**, 6071 (1986); (d) K. Soai, A. Ookawa, K. Ogawa, and T. Kaba, *J. Chem. Soc. Chem. Comm.,* 467 (1987).
3. For reviews of much previous work see (a) T. Mukaiyama and M. Asami in "Topics in Current Chemistry," Vol. 127, Springer-Verlag, Berlin, 1985, p. 133; (b) G. Solladié in "Asymmetric Synthesis," Vol. 2, Academic Press, New York, 1983, p. 157; (c) J. W. ApSimon and T. L. Collier, *Tetrahedron*, **42**, 5157 (1986).
4. Yields were measured by gas chromatographic (GC) analysis; isolated yields were slightly lower. Enantiomeric excess (ee) values were determined by capillary GC analysis of the menthyloxycarbonyl derivatives of secondary alcohol products according to J. W. Westley and B. Halpern, *J. Org. Chem.*, **33**, 3978 (1968). The optical rotations of the isolated products were also measured.
5. These drawings were made using a program written for Macintosh PC's by Mr. Stewart Rubenstein of these laboratories ("Chem 3-D," available from Cambridge Scientific Computing, Inc., P. O. Box 2123, Cambridge, MA 02238).
6. The following experimental procedure is illustrative. A solution of 69.2 mg of **3** (0.264 mmole, 0.1 equiv) in 10 ml of dry ether at -78°C was treated with 0.1 ml of *n*-butyllithium (2.48 *M* hexane solution, 0.248 mmole, 0.1 equiv) under an argon atmosphere. The solution was stirred for 10 min, then 0.265 ml of benzaldehyde (2.61 mmole, 1 equiv) and 2.90 ml of diethylzinc (1 *M* toluene solution, 2.90 mmole, 1.1 equiv) were added. The reaction mixture was warmed to 0°C and stirred for 8 h at 0°C, at which time no further conversion to product was observed by TLC analysis. The mixture was poured into 20 ml of saturated aqueous NH_4Cl and extracted with two 35-ml portions of ether. The combined extracts were washed with 1 *N* HCl, dried with $MgSO_4$ and concentrated at 40°C (23 Torr). Capillary GC analysis[4] of the product mixture showed 68% yield of 1-phenypropanol, 22% of benzaldehyde and 10% of benzyl alcohol. Chromatography on silica gel (7:3 hexanes-ether) afforded 183.3 mg of 1-phenylpropanol, (52%), $[\alpha]^{23}_D$-46.2° (*c*=1.83, $CHCl_3$), 95% ee by capillary GC analysis of the menthyloxycarbonyl derivatives (DBI 30 W column, 170°C oven temperature). The catalytic ligand **3** was recovered from the aqueous portion of the work up in >95% yield following basification with solid NaOH, saturation with NaCl and extraction with ethyl acetate.
7. This research was assisted financially by a grant from the National Science Foundation.

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