Polyfunctional, Structurally Defined Catalysts for the Enantioselective Addition of Dialkylzinc Reagents to Aldehydes

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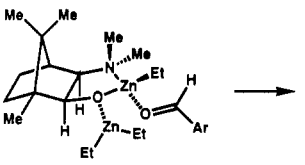
Summary: Two new chiral catalysts, **9** and **14**, have been developed for the enantioselective addition of dialkylzinc reagents to aromatic aldehydes, as exemplified by the reaction of benzaldehyde and diethylzinc in the presence of 10 mol % of **9** to form (*S*)-(−)-1-phenylpropanol (>95% yield, 94% enantioexcess). Catalysts **9** and **14** were prepared by the reaction of equimolar amounts of diethylzinc and diamino alcohols **7** and **8**, respectively. A short synthesis of **7** and **8** from ethyl (*S*)-*N*-(ethoxycarbonyl)pyroglutamate (**2**) via intermediates **3**–**6** is described.

The discovery that the relatively slow reaction of dialkylzinc reagents with aromatic aldehydes can be accelerated by chiral amino alcohols to produce secondary alcohols of modest enantiomeric purity[1] has stimulated a more detailed study of such reactions in a number of laboratories.[2,3] As a result several catalytic systems are now available which allow the synthesis of chiral secondary aryl alkyl carbinols from aromatic aldehydes with enantioselectivities on the order of 95/5.[2a,b,d,3] The catalysis and stereochemistry in such cases can be interpreted satisfactorily in terms of a six-membered cyclic transition state assembly,[3] for example **1**[3] for the Noyori system.[2a] This simple model has led to the rational design of a whole series of effective chiral catalysts which are lithium or zinc chelates derived from easily prepared chiral ligands that can be recovered from reaction mixtures with high efficiency.[3] We report herein on a new type of chiral catalyst for the dialkylzinc–aldehyde addition which has been characterized by X-ray crystallography and NMR spectroscopy, and which clearly functions by effecting polyfunctional catalysis within a six-membered cyclic transition-state assembly. This new family of catalysts is conformationally unambiguous, unchanged after reaction, and highly effective in enforcing enantiocontrol with benzaldehyde as a test case. They qualify as members of the chemical enzyme (chemzyme) class of synthetic reagents.[4] Such chemzymes function in a clear-cut mechanistic way to bring two reactants into proximity with mutual activation and a strong control of three-dimensional geometry which together lead to rapid reaction and high absolute stereoselectivity.[5]

The first new catalyst of this group was synthesized as follows. Ethyl (*S*)-*N*-(ethoxycarbonyl)pyroglutamate (**2**)[6]



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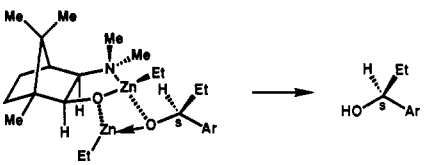
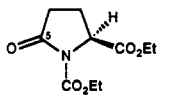


was treated sequentially with 1.3 equiv of diisobutylaluminum hydride (THF, −78 °C, 2 h) and half-saturated aqueous sodium potassium tartrate solution to give after extractive isolation (EtOAc) an oil (lactam reduction product) which after exposure to 0.1% *p*-$CH_3C_6H_4SO_3H$ in methanol at 23 °C and silica gel chromatography (SGC) furnished a mixture of **3** and the C(5) epimer as a clear oil (89%). Reaction of this diastereomeric mixture in CH_2Cl_2 with 1.4 equiv of trimethylsilyl cyanide and 0.1 equiv of stannic chloride[7] at −40 °C for 24 h produced after separation by SGC nitrile **4** (62%) and the C(5) epimer (31%), each as clear oils (SG-TLC R_f values 0.08 and 0.21, respectively, using 2:1 hexane–EtOAc). Reduction of **4** (1 atm of H_2 at 23 °C with W-II Raney nickel in methanol–formalin (14:1) for 16 h) provided amino ester **5** (81%, colorless oil), which was transformed into bis-amine alcohol **7** (87% overall), mp 71–72 °C, $[\alpha]^{23}_D$ −81.1° (*c* = 1.2, $CHCl_3$), by the sequence: (1) reaction with phenylmagnesium bromide in THF at 0 °C initially and then at 23 °C for 16 h to give tertiary alcohol **6** and (2) hydrolysis of **6** with 13.5% KOH in 4:1 methanol–water at 120 °C for 16 h. Reduction of **6** by lithium aluminum hydride afforded the bis-tertiary amine **8** cleanly. Both **7** and **8** function as catalysts for the ethylation of benzaldehyde by diethylzinc. The enantiomers of **7** and **8** are also available through the use of inexpensive (*R*)-glutamic acid as starting material.



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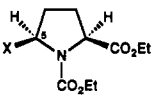
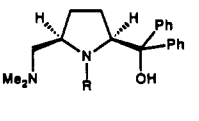
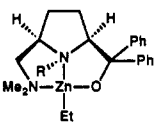


3 X = MeO
4 X = NC
5 X = Me_2NCH_2



6 R = CO_2Et
7 R = H
8 R = Me



9 R = H
14 R = Me

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(3) For previous results from this laboratory, see: Corey, E. J.; Hannon, F. J. *Tetrahedron Lett.* **1987**, *28*, 5233–5236; **1987**, *28*, 5237–5240.

(4) (a) Corey, E. J. *Proceedings of the 31st National Organic Symposium of the American Chemical Society*, June 1989, pp 1–14. (b) Corey, E. J. *The Chemist* **1989**, July/August 3–5. (c) Corey, E. J.; Imwinkelried, R.; Pikul, S.; Xiang, Y. B. *J. Am. Chem. Soc.* **1989**, *111*, 5493–5495.

(5) Of course, such chemical catalysts, while similar to enzymes in the above-named actions, lack the size- and shape-selecting binding sites of the much larger enzymic molecules.

(6) Rigo, B.; Lespagnol, C.; Pauly, M. *J. Heterocycl. Chem.* **1988**, *25*, 49–57.

(7) Asher, V.; Becu, C.; Anteunis, M. J. O.; Callens, R. *Tetrahedron Lett.* **1981**, *22*, 141–144.

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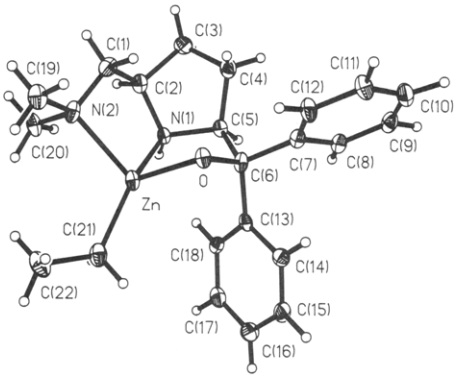
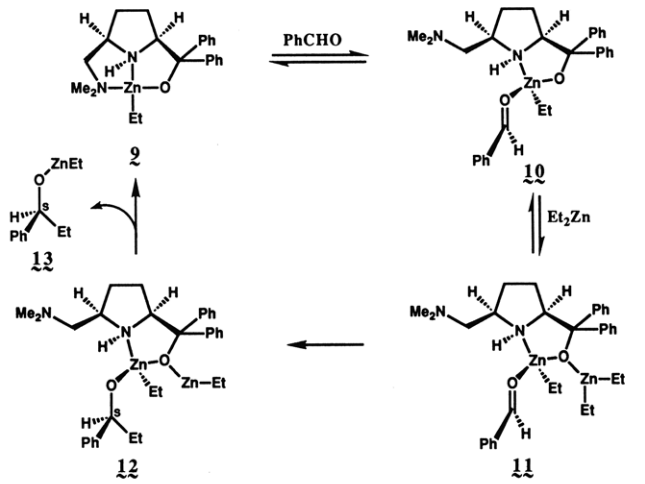


Figure 1. Molecular structure and labeling scheme for catalyst **9** ($C_{22}H_{30}ON_2Zn$). Selected bond lengths (Å): Zn–N(1) 2.153, Zn–N(2) 2.313, Zn–O 1.987, Zn–C(21) 1.993.

Reaction of a solution of **7** in toluene under argon with 1 equiv of diethylzinc at 50 °C for 20 min (1 equiv of C_2H_6 evolved) and cooling to 0 °C produced the crystalline complex **9**, which was recrystallized from toluene (under argon, cooling to −20 °C) to give crystals suitable for X-ray diffraction analysis. The ^{1}H NMR spectrum of the crystalline, air-sensitive product was indicative of structure **9** with both N-H and Zn-C_2H_5 protons apparent.[8] Structure **9** was clearly demonstrated for this product by single-crystal X-ray diffraction as shown in Figure 1.[9] The reaction of benzaldehyde with 1.2 equiv of diethylzinc in toluene solution (0.25 M in aldehyde) was strongly catalyzed by 10 mol % of the zinc complex **9**, used either as recrystallized material or freshly prepared in situ in toluene as described above. (*S*)-(−)-1-Phenylpropanol was obtained as the sole product in several experiments either at 0 °C for 16 h or at 23 °C for 4 h in 94–100% yield and 93–95% enantiomeric excess (ca. 97/3 enantioselectivity).[10] At the end of a reaction in C_6D_6 solution, catalyst **9** was found to remain unchanged in the reaction mixture by 500-MHz ^{1}H NMR analysis. No benzyl alcohol (a major product of any uncatalyzed reaction of diethylzinc and benzaldehyde) could be detected in the reaction mixture by ^{1}H NMR or gas chromatographic analyses. The chiral controller ligand, (2*S*,5*R*)-(−)-2-(hydroxydiphenylmethyl)-5-((dimethylamino)methyl)pyrrolidine (**7**), was recovered in >95% yield from the catalyzed diethylzinc–benzaldehyde reactions after aqueous workup.

Scheme I



There is no observable reaction between catalyst **9** and benzaldehyde (0.05 M each) in C_6D_6 at 23 °C over 19 h or more as determined by 500-MHz ^{1}H NMR analysis, clear evidence that the carbonyl addition reaction involves diethylzinc as well as aldehyde and catalyst **9**. Nonetheless, the ethyl group in the catalyst **9** is activated by the diethylzinc reagent to add to the aldehyde, as shown by an experiment in which benzaldehyde, 1 equiv of di-*n*-butylzinc, and 0.1 equiv of catalyst **9** underwent reaction to give a 10:1 mixture of (*S*)-(−)-1-phenylpentanol and (*S*)-(−)-1-phenylpropanol.

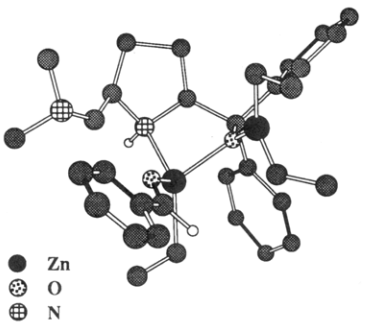
This information and additional data from the study of other catalysts of this family which is presented below point to the catalytic mechanism shown in Scheme I. The initial step, coordination of the aldehyde with the zinc atom of complex **9** to form **10**, is accompanied by replacement of the dimethylamino ligand to maintain the tetracoordinate status of zinc. Subsequent complexation of diethylzinc (a weak Lewis acid) with the nucleophilic oxygen of **10** leads to the termolecular assembly **11** from which transfer of an ethyl group from zinc to the nearby aldehyde carbonyl function can occur via a six-membered cyclic structure to form the complexed carbonyl adduct **12**. Elimination of zinc alkoxide from **12** produces the product, **13**, with regeneration of the catalyst **9**. In assembly **11** the aldehyde is coordinated to zinc through the sterically more accessible lone pair anti to phenyl and is arranged spatially to minimize steric repulsion with neighboring atoms. This preferred three-dimensional arrangement, shown more clearly in stereoformula **11a**, exposes the *si* face of the formyl carbon to the attacking ethyl group and leads to the *S*-configuration of the adduct **12**, in accord with the experimental result. The alternative three-dimensional arrangement of assembly **11** which leads to the carbonyl adduct of *R* absolute configuration is disfavored sterically because of repulsion between the aldehyde and the (dimethylamino)methyl substituent.

Evidence that the conversion of **11** to **12** is the rate-limiting step was provided by the experimental observation of the relative rates of reaction of benzaldehyde and its *p*-trifluoromethyl and *p*-methoxy derivatives, the relative reactivities being *p*-$CF_3C_6H_4CHO$ > C_6H_5CHO > *p*-$CH_3OC_6H_4CHO$. The reaction of *p*-(trifluoromethyl)-benzaldehyde with diethylzinc and **9** (10 mol %) under the conditions described above for benzaldehyde was complete in 3 h at 0 °C and gave cleanly (*S*)-1-(*p*-(trifluoromethyl)phenyl)propanol of 95.5% ee. The corresponding reaction of *p*-methoxybenzaldehyde required 18 h at 23 °C for 90% conversion to product, which was obtained in

(8) The following peaks were observed in the ^{1}H NMR spectrum of **9** (500 MHz, C_6D_6): δ 7.89 (b, 1 H, Ar), 7.53 (d, *J* = 7.53 Hz, 1 H, Ar), 7.23 (m, 4 H, Ar), 7.07 (m, 4 H, Ar), 4.11 (ddd, 1 H, *J* = 7.50, 9.80, 10.1 Hz, NC*H*CPh$_2$OZn), 2.49 (m, 1 H, NC*H*CH$_2$N(CH$_3$)$_2$), 2.42 (dd, *J* = 12.5, 12.4 Hz, 1 H, (CH$_3$)$_2$NC*H*$_2$), 1.86 (br s, 6 H, (C*H*$_3$)$_2$N), 1.64 (b, 1 H, N*H*), 1.32 (m, 1 H, pyrrolidine ring H), 1.18 (t, 5 H, ZnCH$_2$C*H*$_3$ + 1 pyrrolidine ring H + 1 (CH$_3$)$_2$NC*H*$_2$), 1.08 (m, 1 H, pyrrolidine ring H), 0.96 (m, 1 H, pyrrolidine ring H), −0.03 (m, 2 H, ZnC*H*$_2$CH$_3$).

(9) Empirical formula $C_{22}H_{30}O_2N_2Zn$, monoclinic, space group $P2_1$, *a* = 9.168 (5) Å, *b* = 10.392 (5) Å, *c* = 10.596 (6) Å, β = 104.69(5)°, *Z* = 2, *V* = 1003 Å, D_c = 1.34 g cm^{-3}, λ = 0.710 73 Å. Structure solved by direct methods (SHELTX-PLUS), *R*(F) = 0.0699, R_w(F) = 0.0708 for 4257 total reflections, 2627 with $F_o > 6.00\sigma(F_o)$. Largest Δ/σ for last cycle of refinement = 0.004. We are indebted to Jonathan Zerkowski for the collection of data for the X-ray study.

(10) The rotation of the (*S*)-(−)-1-phenylpropanol isolated in 94% yield from a typical experiment was $[\alpha]^{23}_D$ −42.2° (*c* = 0.95, $CHCl_3$); the enantiomeric purity was determined to be 95% ee by conversion to the menthyloxycarbonyl derivative (1-phenylpropanol, (−)-menthylchloroformate, DMAP, and pyridine in CH_2Cl_2), followed by capillary gas chromatographic analysis (DB1-30W column, 200 °C oven temperature; retention time of the major diastereomer, 9.43 min; minor diastereomer, 9.83 min) (See: Westley, J. W.; Halpern, B. *J. Org. Chem.* **1968**, *33*, 3978–3980). The same enantiomeric purity was also determined by HPLC analysis of the alcohol (Bakerbond DNBPG-ionic column, 0.25% 2-propanol in hexanes, 1.5 mL/min, 750 psi, 254 nm detector; retention time of (*S*)-(−)-1-phenylpropanol, 15.16 min; (*R*)-(+)-1-phenylpropanol, 15.87 min).



11a

only 83% ee mainly because of competing uncatalyzed reaction of the aldehyde and diethylzinc as demonstrated by a control experiment (*p*-$MeOC_6H_4CHO$, Et_2Zn, toluene, 23 °C, gas chromatographic analysis of rate).[11]

Cinnamaldehyde and diethylzinc in the presence of 10 mol % of **9** react rapidly to form (*S*)-(−)-(*E*)-1-phenylpent-1-en-3-ol, $[\alpha]^{23}_D$ −4.52° (*c* = 1.7, $CHCl_3$) (100% yield, 70% ee). The lower enantioselectivity in this case is partly due to the unusually fast rate of the competing uncatalyzed reaction, but may also be a consequence of nonstereospecific association of this aldehyde with the catalyst at both the oxygen lone pairs (i.e. cis and trans to the formyl hydrogen).

Although it is theoretically possible that the activation of benzaldehyde by catalyst **9** occurs as a consequence of hydrogen bond formation between the ammonium N-H unit of **9** and the aldehyde oxygen, this alternative is not supported by studies of catalyst **14** derived from the reaction of diethylzinc with the bis-tertiary amine alcohol **8**. The ^1H NMR spectrum of **14** resembles closely that of **9** except for the occurrence of an extra N-CH_3 peak and the absence of an N-H proton. Reaction of diethylzinc and benzaldehyde in the presence of 10 mol % of **14** affords (*S*)-(−)-1-phenylpropanol in 90% yield and 92% enantiomeric excess, and the catalyst remains unchanged at the end of the reaction as shown by ^1H NMR analysis. Thus, since the protic catalyst **9** and the aprotic catalyst **14** show virtually identical behavior, catalysis by **9** cannot depend on the presence of an electrophilic proton attached to nitrogen.

The effectiveness of catalysts **9** and **14** depends on their ability to remain monomeric, to coordinate to the aldehyde by internal ligand reorganization, to bind and activate diethylzinc, to bring the activated reactants into proximity, to enforce a three-dimensional preference for the transition-state assembly, and to regenerate themselves by forcing the dissociation of the reaction product. In such behavior there is a striking parallelism between these catalytic molecular robots and the much larger enzymic robots.[12]

Supplementary Material Available: Procedures and physical data for the synthesis of **3** to **9** and the reaction of benzaldehyde and diethylzinc with **7** as catalyst; X-ray data for the structure of **9** including atomic coordinates, anisotropic displacement parameters, idealized H atom coordinates, bond lengths and angles, and packing diagram (19 pages); observed and calculated structure factors for **9** (12 pages). Ordering information is given on any current masthead page.

(11) It is also possible that the lower enantioselectivity with *p*-methoxybenzaldehyde may be partly the result of other competing pathways such as one involving coordination of the aldehyde at the acyclic O-Zn-Et subunit in **9** and adduct formation directly from this structure. The exchange of the dimethylamino ligand for the OZnEt ligand at the central zinc of **10** is another possible source of lower stereoselectivity. Pivaldehyde which also reacts slowly with diethylzinc and 10 mol % of **7** (17% conversion after 60 h at 23 °C) also reacts with lowered enantioselectivity (69% ee).

(12) This research was assisted financially by grants from the National Science Foundation and the National Institutes of Health.

Synthesis of Cyclopentane-Fused Oxygen Heterocycles from the Intramolecular Reaction of Alkynes with Cyclopropylcarbene–Chromium Complexes

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Summary: The intramolecular reaction between cyclopropylcarbene–chromium complexes and alkynes has been examined. Oxygen heterocycles fused to five-membered rings were obtained from the reaction.

Recently, cyclopropylcarbene–chromium complexes have emerged as valuable reagents for organic synthesis, coupling with alkynes to give cyclopentenone derivatives in good to excellent yields.[1] Excellent regioselectivity was observed in the reaction of terminal alkynes with carbene complex **1**, but mixtures of **2** and **3** were usually obtained using unsymmetrically-substituted internal alkynes (Scheme I). One possible way to control the regioselectivity would be through an intramolecular version of the cycloaddition reaction (Scheme II); this approach has been used in the reaction of alkynes with arylcarbene–chromium complexes.[2] Thermolysis of an alkynylcarbene–chromium complex such as **4** in the presence of water should lead primarily to compound **5** if the chain length is reasonably small. Subsequent ring opening reactions could then provide cyclopentenone derivatives of well-defined regiochemistry. Herein we report preliminary results on the intramolecular version of the reaction in Scheme I.

In the first phase of this research, the reaction of acetylenic alcohols with the anhydride-like complex **8**[2] (generated in situ from complex **7** and acetyl chloride) was examined, which leads to the desired acetylenic carbene complexes in good yield. The reaction was very sensitive

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