

Catalysis by Amino Acid-Derived Tetracoordinate Complexes: Enantioselective Addition of Dialkylzincs to Aliphatic and Aromatic Aldehydes

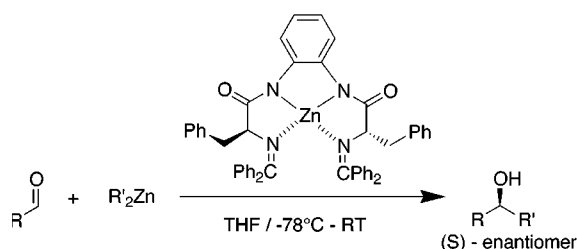
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ABSTRACT



Me₂Zn and Et₂Zn added to aromatic and aliphatic aldehydes in the presence of 3 mol % of 2. (*S*)-1-Phenylethanol (91% ee) and (*S*)-1-phenylpropanol (86% ee) were synthesized from benzaldehyde and (*S*)-1-furan-2-yl-1-propanol (86% ee) from 2-furaldehyde. Nonanal and 3-phenylpropanal provided (*S*)-3-undecanol (96% ee) and (*S*)-1-phenyl-3-pentanol (94% ee). A solid-phase variant was effective with reduced ee's (e.g., 86% ee → 79% ee) for (*S*)-1-phenylpropanol.

Long since the early pioneering work of McKenzie,¹ asymmetric synthesis has become one of the cornerstones of organic synthesis. While McKenzie used a chiral auxiliary (menthol) for his work, the ideal or aspirational enantioselective reaction would use a cheap, renewable source of chirality² and would require only catalytic amounts (e.g., multiplication of chirality).³ The addition of organozinc reagents⁴ to aldehydes in the presence of catalytic amounts of chiral ligands is among the most successful catalytic reactions of this type.⁵ Almost all the work with organozinc reagents has utilized chiral ligands possessing a β-amino alcohol moiety, which can bind zinc in a bidentate⁶ or

occasionally a tridentate manner.⁷ After a search of the literature, we could find no examples of tetradentate ligands used in the addition of organozinc reagents to aldehydes. As part of our efforts to develop a “universal ligand”, we were pleasantly surprised to find that a tetracoordinate zinc complex, formed from the amino acid-derived ligand system described previously,⁸ worked quite well as a catalyst for the addition of alkylzincs to both aromatic and aliphatic aldehydes.

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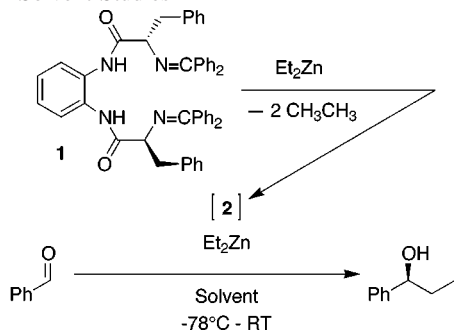
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The reaction of Et_2Zn with ArCHO and RCHO in the presence of chiral ligand **1** was evaluated.⁹ For these studies (Table 1) the reactive Zn^{II} complex **2** was formed in situ

Table 1. Solvent Studies



rxn	catalyst (mol %)	solvent	chemical yield ^a	enantiomeric excess ^b
1	1	THF	(61%)	82%
2	3	THF	85% (99%)	86%
3	3	PhCH_3	(99%)	6.3%
4	3	PhCH_3 / THF (2:1)	(96%)	63%

^a Isolated yields (yields in parentheses based on GC peak areas).

^b Determined by chiral GC: (*S*)-1-phenyl-propanol, Chiraldex β -PH (100 °C isotherm).

from Et_2Zn and ligand **1**. NMR studies showed that the zinc complex formed readily in d_8 -THF or d_8 -toluene. In THF one molecule of solvent appeared to coordinate axially to allow the zinc metal to adopt a square pyramidal geometry. The complex was stable in a dry, oxygen-free atmosphere. Complex formation was found to be complete after an hour at reflux. Once formed, the reaction mixture was cooled to -78°C and the aldehyde was added in a single portion. Using a syringe pump, an equimolar amount of Et_2Zn in THF was added and the reaction continued for 16 h at rt. Analysis of the product mixture was performed by capillary GC.

The C_2 -symmetric Zn^{II} -L-Phe-L-Phe complex **2** catalyzed the quantitative addition of Et_2Zn to PhCHO when 3–5 mol % of catalyst was used. THF was found to be the best solvent for the additions, but was not necessary for complex formation. With 1 mol % of catalyst the reaction proceeded but was incomplete after 16 h (rxn 1). EtZnI was not effective

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(9) Ligand **2** (219 mg, 0.3 mmol, 3 mol %) was azeotropically dried with PhCH_3 and then dissolved in 3 mL of THF. A 0.5 M solution of Et_2Zn in THF (0.64 mL, 0.32 mmol, 3.2 mol %) was added to **2** and heated to reflux for 1 h. After Zn insertion was complete, the reaction mixture was cooled to -78°C and $\text{PhCH}_2\text{CH}_2\text{CHO}$ (1.34 g, 10.0 mmol) was added in a single portion. More 0.5 M Et_2Zn solution in THF (26 mL, 13.0 mmol, 1.3 equiv) was then added dropwise, and the mixture was allowed to warm slowly to rt. After 16 h the reaction was quenched with 1 M HCl and worked up in the usual manner to provide (*S*)-1-phenyl-3-pentanol. A detailed protocol may be found in the Supporting Information.

as an alkyl donor. Only one ethyl group was transferred from Et_2Zn at an appreciable rate. The second ethyl group was transferred, but much more slowly. In every case the major isomer was the *S*-enantiomer, [(*S*)-(-)-1-phenyl-1-propanol] in 82–86% ee.

It is noteworthy that, contrary to reports of studies performed with bidentate “Soai-type” catalysts, the polar solvent THF enhanced the enantioselectivity of Et_2Zn additions (Table 1). When toluene was used (rxn 3), the reactions went to completion, but the ee’s dropped to 6%. Using a 2:1 mixture of toluene and THF decreased the ee’s to 63% (rxn 4).

Given these results, several aldehydes were screened using 3 mol % of the Zn^{II} -L-Phe-L-Phe complex **2** (Table 2). A

Table 2. Aromatic versus Aliphatic Substrates

Reaction scheme for Table 2: $\text{RCHO} + \text{Et}_2\text{Zn} \xrightarrow[\text{THF, } -78^\circ\text{C} \rightarrow \text{RT}]{\text{2 (3 mol \%)}} \text{RCH(OH)R'}$

rxn	R	R'	chemical yield ^a	enantiomeric excess ^b
5		CH_3	80% (92%)	91%
6		CH_3CH_2	30% (92%)	86%
7	PhCH_2CH_2	CH_3CH_2	27% ^c (81%)	94% ^c
8	$\text{CH}_3(\text{CH}_2)_7$	CH_3CH_2	51% ^d (99%)	96% ^d

^a Purified yields (yields in parentheses based on GC peak areas).

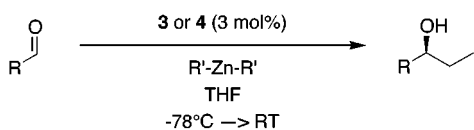
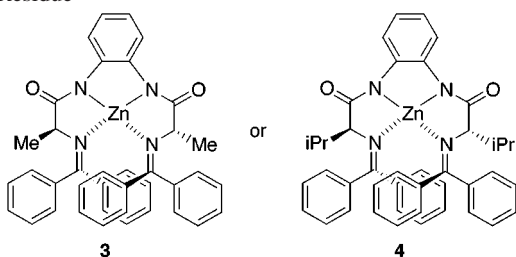
^b Determined by chiral GC: 1-phenylpropan-1-ol, Chiraldex β -PH (100 °C isotherm); 1-furylpropan-1-ol, Chiraldex γ -TA (60 °C isotherm); (*R*)-(-)-Mosher’s ester of 1-phenylpentan-3-ol and 3-undecanol, Chiraldex β -TA (140 °C isotherm). ^c Purified by flash, followed by sublimation. Observed $[\alpha]_D = +23.6^\circ$; literature $[\alpha]_D = +23.8^\circ$ (refs 10a and 10b). ^d Product purified by flash, followed by distillation. Observed $[\alpha]_D = +7.48^\circ$; literature $[\alpha]_D = +7.79^\circ$ (ref 10c).

slight increase in enantioselectivity was observed when dimethylzinc was substituted for diethylzinc in the addition to benzaldehyde (rxn 5 vs rxn 2). 2-Furaldehyde gave ee’s similar to those seen with benzaldehyde (rxn 6). Aliphatic aldehydes provided excellent ee’s with this catalyst. Addition to 3-phenylpropanal (rxn 7) yielded pure (*S*)-(+)-1-phenylpentan-3-ol (94% ee), following chromatography and sublimation. The optical rotation of the sublimed alcohol was $+23.6^\circ$ ($c = 1.56$; CHCl_3). Similarly, addition to nonanal (rxn 8) provided (*S*)-(+)-3-undecanol (96% ee) after chromatography and vacuum distillation. The optical rotation of the distilled alcohol was $+7.48^\circ$ ($c = 0.91$; ethanol).¹⁰ Both

of these reactions were run on a 1-g scale, and the enantiomeric purity of the each alcohol was confirmed by formation of the corresponding Mosher esters (^1H NMR and chiral GC). Despite the higher enantioselectivities observed with the aliphatic aldehydes, the reactions were complicated by significant formation ($\sim 50\%$ of the reaction mixture) of the corresponding aldol products.

Further studies with the L-Ala-L-Ala **3** and L-Val-L-Val **4** complexes have been performed (Table 3). As expected, the

Table 3. Enantioselectivity Depends on Steric Bulk of Amino Acid Residue



rxn	catalyst	substrate	product	chemical yield ^a	enantiomeric excess ^b
9	3	PhCHO		(86%)	19%
10	3	CH ₃ (CH ₂) ₇ CHO		(70%)	27%
11	4	PhCHO		(99%)	91%
12	4	CH ₃ (CH ₂) ₇ CHO		10% ^c (78%)	89%
13	4	Ph(CH ₂) ₂ CHO		12% ^c (50%)	92%

^a Isolated yields (yields in parentheses based on GC peak areas).

^b Determined by chiral GC: 1-phenylpropan-1-ol, Chiraldex β -PH (100 °C isotherm); (R)-(-)-Mosher's ester of 1-phenylpentan-3-ol and 3-undecanol, Chiraldex β -TA (140 °C isotherm). ^c Products were purified by flash chromatography, followed by sublimation (1-phenylpentan-3-ol) or distillation (3-undecanol).

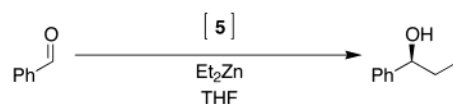
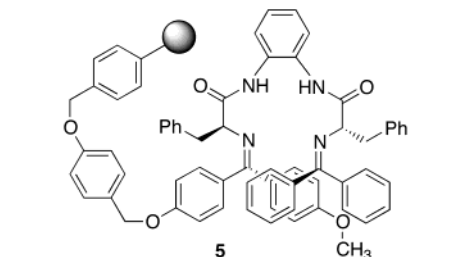
decreased bulk of the amino acid residues (L-Ala) on the catalyst caused a decrease in selectivity for both aromatic and aliphatic aldehydes (rxn 9 and 10). With increased steric demand (L-Val), enhanced stereoselection was observed with benzaldehyde (rxn 11). In contrast, the aliphatic aldehydes showed diminished enantioselectivity and reduced yields (rxn 12 and 13).

Optimization of a catalyst for particular applications will be facilitated by the use of solid-phase variants, which will

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permit simultaneous reactions to be run in parallel.¹¹ Preliminary results with the "Wang-supported L-Phe-L-Phe catalyst" **5** are shown in Table 4.¹² The Et₂Zn-activated resin

Table 4. Solid-Phase Ligand Functions As Catalyst with Only Slightly Reduced Enantioselectivities



rxn	temperature	chemical yield	enantiomeric excess
14	RT	98%	64%
15	RT	98%	68%
16a	RT (18 hrs)	73%	–
16b	30 °C (+ 5 hrs)	82%	75%
16c	40 °C (+24 h)	89%	79%

was then used multiple times without degradation of either the yields or the enantioselectivities (rxn 14 and 15).¹³ Overall, the yields were only slightly diminished relative to the solution-phase catalyst, and the ee's were lower. Since the ee seemed to increase upon reuse of the catalyst (rxn 15), it was assumed that Et₂Zn removed impurities that affected the enantioselection. Thus, for the next reaction (rxn 16) the L-Phe-L-Phe-bearing resin was "washed" with excess Et₂Zn prior to use. The conversion was monitored by GC as a function of time and temperature (rxn 16a–c). As expected,

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the rate of product formation increased with increasing time and temperature. Surprisingly, the ee's were enhanced as well. The explanation for this behavior may involve increased swelling of the polymer at higher temperatures, "uncoiling" of the polystyrene backbone, or other effects.¹⁴

Assuming that two zinc atoms are involved in alkyl transfer, the inner zinc is surrounded by electron-donating nitrogens, while the outer zinc is only solvated by exchangeable oxygens.¹⁵ Given the observed results, the mechanism may be related to the "ate" or "ate-like" mechanism proposed by Kitamura¹⁶ or may involve reversed roles for the two zinc

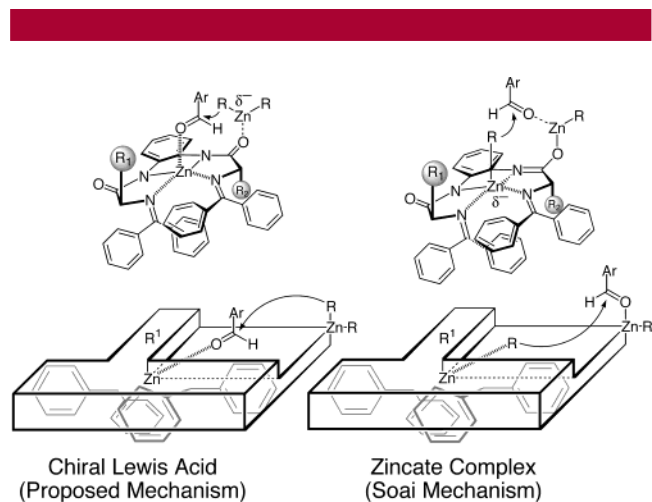


Figure 1. Possible mechanisms for the observed facial enantioselectivity.

atoms, with the "inner zinc" functioning as a chiral Lewis acid¹⁷ and the "outer zinc" functioning as the alkyl donor (Figure 1). The role of the THF is not clear. It may be required in order to effect alkyl transfer from Et₂Zn to the "inner zinc" (Soai mechanism) or may simply prevent aggregation. Obviously, further study will be required for a complete understanding of this new catalyst system.

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Supporting Information Available: Complete experimental procedures, spectral characterization of the ligands and intermediates (¹H NMR, ¹³C NMR, and IR), GC traces, and column conditions used. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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