Chiral Zinc Amides as the Catalysts for the Enantioselective Addition of Diethylzinc to Aldehydes†

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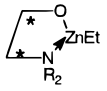
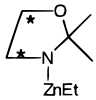
Asymmetric C−C bond forming reactions are of prime importance in modern synthetic organic chemistry. Among the several advances made in this area, the ligand-accelerated alkylation of carbonyl compounds has generated considerable interest during the past decade.[1] After the discovery by Oguni and Omi that various additives catalyze the addition of dialkylzinc reagents to aldehydes,[2] there has been a rapid growth of research aimed at this reaction.[3] Much of these efforts has been directed toward the design of new chiral ligands, the majority of them being *β*-amino alcohols. It has been well established that the corresponding zinc alkoxides **1** catalyze the addition with varying degree of efficiency, the most successful to date being DAIB[4a] and DBNE.[4b] In this communication we report a conceptually different catalytic system *viz*. zinc amides of oxazolidines (**2**).

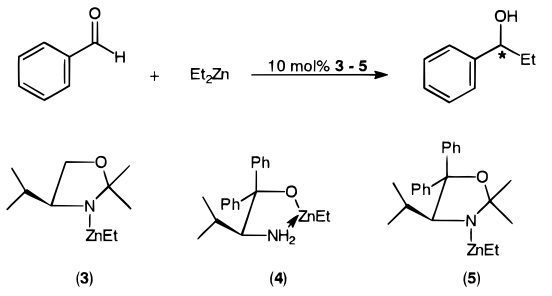


(**1**)



(**2**)

Since the enantioselective addition of dialkylzinc reagents to aldehyde is known to involve a chiral zinc alkoxide with a coordinatively unsaturated tricoordinated center, we anticipated that a zinc amide with dicoordinated zinc should be a better Lewis acid. Our postulate indeed turned out to be correct when we examined the catalysis by three different types of zinc species (**3**−**5**).



(**3**) (*R* product, 38% *ee*)

(**4**) (*S* product, < 5% *ee*)

(**5**) (*S* product, 100% *ee*)

At the outset, we decided on (*S*)-valinol and its derivatives as the potential ligands. All the model studies were done using diethylzinc as the nucleophile and benzaldehyde as the carbonyl substrate. It was found that whereas valinol itself catalyzes the reaction very slowly (48 h at 25 °C), the corresponding acetonide is a more effective ligand (12 h at 25 °C). A dramatic change in the catalytic efficiency was realized when we examined sterically more demanding (*S*)-α,α-diphenylvalinol derivatives. The zinc alkoxide **4** derived from the amino alcohol[5] provided a slow reaction rate (incomplete in 12 h at 25 °C) with poor enantioselectivity (<5% ee).[6] On the other hand, the zinc amide derived from the corresponding oxazolidine led to a very fast reaction (4 h at 0 °C) and a total stereocontrol (100% ee) for the addition reaction.

Table 1. Enantioselective Addition of Diethylzinc to Benzaldehyde Catalyzed by 5

entry	**5**, mol %	temp, °C	solvent	Et_2Zn, equiv	% ee[a]
1	10	25	toluene	1.2	99
2	10	0	toluene	1.2	99
3	10	0	toluene	2	100
4	5	0	toluene	2	96
5	10	0	Et_2O−toluene	2	93
6	10	25	THF−toluene	2	*b*

[a] Estimated by HPLC analysis on CHIRACEL-OD column. [b] Incomplete reaction.

The alkylation proceeds even faster at room temperature (over in <1 h) without a significant loss of stereoselectivity. Reducing the catalyst concentration to 5 mol % provided 96% ee for (*S*)-1-phenylpropanol. Among the various solvents examined, toluene proved to be the best. As expected, coordinating solvents (Et_2O, THF) lowered the reaction rate as well as selectivity (Table 1). It was gratifying to note that the oxazolidine ring remains intact during the course of the reaction.[7]

We could not experimentally establish whether the second diethylzinc coordinates to the nitrogen or oxygen atom. However, indirect but convincing evidence was provided by the stereochemical outcome from the catalyst **3** and **5**. It was found that the product has *R* configuration from **3** and *S* from **5**. We propose that diethylzinc, being a softer Lewis acid, coordinates to the oxygen atom of the oxazolidine **3**. However in the case of **5**, the steric environment around the oxygen atom forces the diethylzinc molecule to chelate exclusively to the nitrogen atom. Here the stereochemical outcome of the reaction is determined by the disposition of the substituents at the nitrogen atom which becomes chiral. At this stage we are unable to provide a precise model that explains and predicts the stereochemical outcome of this catalytic system. An empirical presentation that depicts the activation of aldehyde by zinc amide followed by the transfer of ethyl group from diethylzinc, is as shown in Figure 1.

Finally we used this methodology for the enantioselective alkylation of various aldehydes. As evident from Table 2, all the aldehydes, including those with *ortho* substituents, were alkylated smoothly. Both *β*-naphthaldehyde and the recalcitrant α-naphthaldehyde were alkylated with 100 and 96% ee, respectively. However aliphatic aldehydes did not provide good enantioselectivity (e.g. entry 7). In all the cases examined, (*S*)-diphenylvalinol ligand consistently provided product with *S* configuration.

† Dedicated to Prof. H. C. Brown on the occasion of his 85th birthday.

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(5) Prepared by stirring the amino alcohol with a toluene solution of diethylzinc at room temperature for 10−15 min.

(6) A similar outcome for this reaction has been reported earlier, see: Delair, P.; Einhorn, C.; Einhorn, J.; Luche, J. L. *Tetrahedron* **1995**, *51*, 165.

(7) The ligand is recovered quantitatively as its hydrochloride after the workup. Incidentally, the observation ruled out any possibility of the corresponding acyclic imine-alkoxide as the intermediate.

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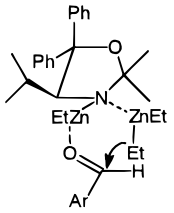

Figure 1.

Table 2. Enantioselective Addition of Diethylzinc to Aldehydes Catalyzed by 5[a]

entry	aldehyde	time, h	% yield	config.	% ee
1	benzaldehyde	4	85	*S*	100[b]
2	*p*-chlorobenzaldehyde	3	86	*S*	100[b]
3	*o*-tolualdehyde	4	75	*S*	97[c]
4	*p*-tolualdehyde	4	79	*S*	98[c]
5	α-naphthaldehyde	8	74	*S*	96[b]
6	*β*-naphthaldehyde	4	81	*S*	100[b]
7	cyclohexanecarboxaldehyde	8	50	*S*	43[d]

[a] All the reactions were conducted at 0 °C using 10 mol % catalyst and 2 equiv of Et_2Zn. [b] Estimated by HPLC analysis on CHIRACEL-OD column. [c] By comparison with the reported maximum specific rotation, see Experimental Section. [d] Incomplete reaction.

In conclusion, we have demonstrated that *β*-amino alcohols, which are otherwise poor ligands for the addition of dialkylzinc reagents to aldehydes, can be turned to efficient chiral catalytic systems through the zinc amides of the corresponding oxazolidines. To the best of our knowledge, this is the first such demonstration. Since a large number of amino alcohols are easily accessible and several structural modifications through these oxazolidines are possible, one should be able to tune the catalytic system to a wide variety of aldehydic substrates. Furthermore, other applications of such chiral zinc amides can be expected.

Experimental Section

All the reactions were performed under dry argon atmosphere. Diethylzinc was purchased from Aldrich and diluted to a 2 M solution in anhydrous toluene. All the aldehydes were freshly distilled prior to use. The reactions were monitored by TLC using silica gel 60 F_{254} precoated plates, and the products were purified by "flash column chromatography" using silica gel 60 (40−60 um). ^{1}H NMR spectra were recorded at 200 MHz with TMS as the internal standard. ^{13}C NMR spectra were recorded at 50 MHz with $CDCl_3$ ($\delta = 77$) as the reference. Chiral HPLC analysis was carried out on a Chiracel-OD column using 2-propanol−hexane as the eluent.

2,2-Dimethyl-4-isopropyl-1,3-oxazolidine[8] and (*S*)-(−)-α,α-diphenylvalinol[9] were prepared as described in the literature.

Preparation of the Zinc Amides 3 and 5. A solution of appropriate oxazolidine (10 mM) was treated with diethylzinc (10 mM). The formation of **3** gradually takes place at room temperature while **5** is formed on heating to 80 °C. A brisk evolution of 1 equiv of ethane takes place within 15−30 min. The resulting solutions of the zinc amides can be stored; however, it is more convenient to prepare and use them *in situ* as described below.

(*S*)-(−)-2,2-Dimethyl-5,5-diphenyl-4-isopropyl-1,3-oxazolidine. A solution of (*S*)-α,α-diphenylvalinol (1.27 g, 5 mM) in acetone (10 mL) was stirred at room temperature for 16 h. Evaporation of excess acetone provided the oxazolidine as a thick viscous mass. An analytically pure sample was obtained by short column chromatography on deactivated neutral alumina. The remainder crude oxazolidine was stored and used conveniently as a 1 M solution in toluene: $[\alpha]_D$ −118 (*c* 1.1 $CHCl_3$); ^{1}H NMR δ 7.15−7.55 (m, 10H), 4.00 (d, $J = 4.8$ Hz, 1H), 1.8 (m, 1H), 1.75 (s, 3H), 1.25 (s, 3H), 1.1 (d, $J = 6.8$ Hz, 3H), 0.5 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR δ 148.0, 144.0, 127.9, 127.5, 127.4, 127.0, 126.8, 126.7, 94.1, 88.2, 71.9, 28.4, 27.7, 26.7, 23.1, 17.7; MS *m*/*z* 296 (M + 1), 113 (base peak). Anal. Calcd for $C_{20}H_{25}ON$: C, 81.30; H, 8.53; N, 4.74. Found: C, 81.28; H, 8.51; N, 4.79.

Enantioselective Addition of Diethylzinc to Aldehydes. The following procedure for benzaldehyde is representative. To the oxazolidine (0.5 mM, 0.5 mL of 1 M solution in toluene) was added diethylzinc (10 mM, 5 mL of 2 M solution in toluene), and the reaction mixture was stirred at 80 °C for 30 min. The resulting solution of zinc amide **5** was cooled to 0 °C, and benzaldehyde (0.53 mL, 5 mM) was added. The resulting yellow solution was stirred at 0 °C until the coloration disappeared and TLC indicated complete absence of benzaldehyde (approximately 4 h). The reaction mixture was then cautiously quenched with MeOH (2 mL) followed by 3 N HCl (5 mL) and then diluted with ether (20 mL). After stirring vigorously for 5 min, the precipitated oxazolidine hydrochloride (quantitative yield) was filtered and washed with ether (10 mL). The combined organic portion was washed with water followed by brine and dried over anhydrous Na_2SO_4. The residue obtained after evaporation of the solvent was purified by "flash column chromatography" followed by Kugelrohr distillation to obtain pure (*S*)-(−)-1-phenyl-1-propanol: $[\alpha]_D$ −46.70 (*c* 5.1, $CHCl_3$) [lit.[10] −45.45 (*c* 5.15, $CHCl_3$)]; ^{1}H NMR δ 1.00 (t, $J = 6.9$ Hz, 3H), 1.85 (m, 2H), 2.90 (bs, OH), 4.60 (t, $J = 6.9$ Hz, 1H), 7.20−7.50 (m, 5H).

(*S*)-(−)-1-(*p*-Chlorophenyl)-1-propanol: $[\alpha]_D$ −28.30 (*c* 5.2, benzene) [lit.[11] +28.00 (*c* 5, benzene) for *R*-isomer]; ^{1}H NMR δ 0.90 (t, $J = 6.8$ Hz, 3H), 1.75 (m, 2H), 2.25 (bs, OH), 4.55 (t, $J = 6.8$ Hz, 1H), 7.20−7.30 (m, 4H).

(*S*)-(−)-1-(*o*-Toluyl)-1-propanol: $[\alpha]_D$ −56.18 (*c* 4, benzene) [lit.[12] −57.51 (*c* 4, benzene)]; ^{1}H NMR δ 1.00 (t, $J = 7.2$ Hz, 3H), 1.75 (m, 2H), 2.2 (bs, OH), 2.35 (s, 3H), 4.85 (t, $J = 7.2$, 1H), 7.10−7.50 (m, 4H).

(*S*)-(−)-1-(*p*-Toluyl)-1-propanol: $[\alpha]_D$ −37.31 (*c* 5, benzene) [lit.[12] −34.87 (*c* 4, benzene) for 92% ee]; ^{1}H NMR δ 0.90 (t, $J = 6.8$ Hz, 3H), 1.75 (m, 2H), 2.25 (bs, OH), 2.35 (s, 3H), 4.55 (t, $J = 6.8$ Hz, 1H), 7.10−7.30 (m, 4H).

(*S*)-(−)-1-(α-Naphthyl)-1-propanol: $[\alpha]_D$ −50.53 (*c* 2.5, $CHCl_3$) [lit.[11] +55.60 (c 2.4, $CHCl_3$) for *R*-isomer]; ^{1}H NMR δ 1.00 (t, $J = 7.4$ Hz, 3H), 2.00 (m, 2H), 2.30 (bs, OH), 5.40 (t, $J = 7.2$ Hz), 7.35−8.25 (m, 7H).

(*S*)-(−)-1-(*β*-Naphthyl)-1-propanol: $[\alpha]_D$ −28.24 (*c* 3.4, benzene) [lit.[13] −26.60 (*c* 3.35, benzene)]; ^{1}H NMR δ 0.90 (t, $J = 7.3$ Hz, 3H), 1.85 (m, 2H), 2.20 (bs, OH), 4.75 (t, $J = 6.6$ Hz, 1H), 7.40−7.60 (m, 2H), 7.70−8.00 (m, 2H).

(*S*)-(−)-1-(Cyclohexyl)-1-propanol: $[\alpha]_D$ −3.50 (neat) [lit.[14] −8.10 (neat)].

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