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Chiral induction controlled by aggregation of organometallics: trifluoromethylated aminoalcohols for chiral ligands in Et_2Zn alkylation of benzaldehyde†

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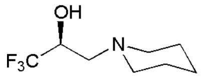
Chiral induction in the reaction of Et_2Zn with PhCHO by fluorinated chiral amino alcohols was correlated to the extent of aggregation of Et_2Zn species, which was estimated by manometric study.

The asymmetric alkylation of benzaldehyde by diethylzinc has been used for assessing the chiral induction ability of optically active ligands, although the mechanism is complex and has not yet been completely clarified.[1] The complex feature of the reaction has sometimes been attributed to the aggregation of zinc species associated with the ligands.[2] This aggregation of the zinc species sometimes promoted the enantio amplification phenomena.[2,3] To date, detailed kinetic studies on the reaction suggest that the active catalyst species among such zinc species might be a monomeric zinc species associated with the chiral ligands.[2,4]

In the course of our study on the development of trifluoromethylated chiral ligands in asymmetric organic synthesis, we found that the fluorinated chiral amino alcohols promote the unexpectedly higher aggregation of the diethylzinc species, the extent of which correlated well to the asymmetric induction in the reaction with benzaldehyde.

A detailed comparison of the reaction with fluorinated ligands, **1** and **2**,[5] to nonfluorinated ligands, **3** and **4**,[6] showed us the peculiar concentration effects of fluorinated ligands on chiral induction. Fig. 1 illustrates the correlation between the optical purity of the product and the relative amount of the ligands **1**–**4**. Of note is the fact that the larger the amount of the fluorinated ligand **1**, used even up to 50 mol%, the higher the optical purity of the products attained in the reactions. However, the larger the amount of the fluorinated ligand **2**, the lower the optical purity of the products. In contrast, the reaction of nonfluorinated ligands **3** and **4** reached their highest plateau of enantioselectivity within 5 mol%.[7]



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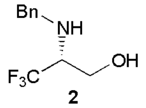

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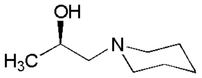

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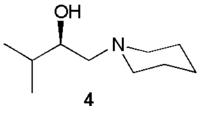

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The conventional mechanistic studies for enantioselective alkylation by Et_2Zn suggest participation of the monomeric zinc species as the sole reactive species.[2,4] The mechanism would predict the rather small effect of the ligand concentration to the enantiomeric excess of the product. In fact, the nonfluorinated ligands **3** and **4** showed small relative concentration effects on the ee's of the products. However, the fluorinated ligands **1** and **2** showed considerably larger positive and negative concentration effects. Such concentration effects of the fluorinated ligands on the ee implies the possible participation of some aggregated species for this asymmetric alkylation with fluorinated ligands. The negative concentration effect by ligand **2** is especially peculiar and noteworthy.[7c,8]

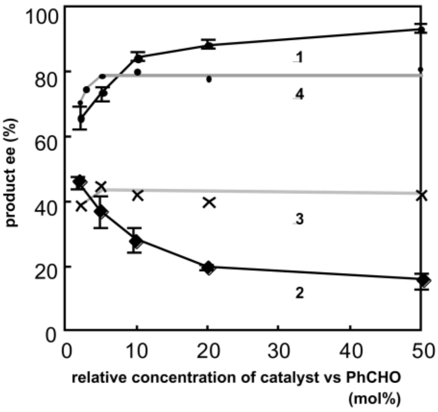

Fig. 1 Effect of relative concentration in asymmetric ethylation of benzaldehyde by diethylzinc catalyzed by **1**–**4**. $[Et_2Zn]_0 = 0.63$ M, $[PhCHO]_0 = 0.31$ M, 0 °C—rt, 48 h, in hexane.

The absolute concentration effect of ligand **1** was consistent with the result of the relative concentration effect above. When the reacting solution was diluted to $[Et_2Zn]_0 = 0.14$ M with 10 mol% of ligand **1**, the chiral induction was depressed to 70% ee; when, the solution was concentrated to $[Et_2Zn]_0 = 1.0$ M, the chiral induction was raised to 93% ee.

The extents of the aggregation of the Zn species in hexane solutions with ligands were directly estimated by solvent vapor pressure measurements.[9] The correlations between the degree of the aggregation of the zinc species, and the $[R]/[S]$ ratios of products under the same conditions, are illustrated in Fig. 2.

An appreciable correlation between these two factors was found; the correlation coefficient for the ligand **1** was $r^2 = 0.99$, and that for **2** was $r^2 = 0.98$.

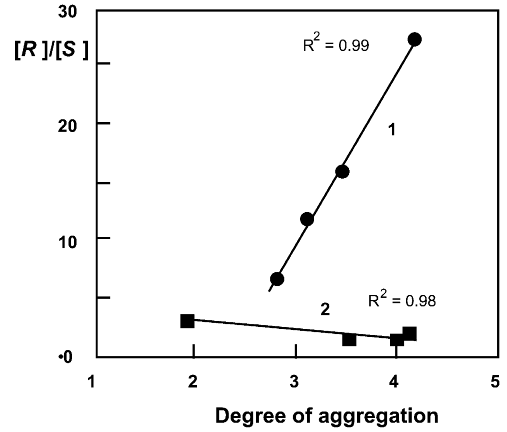

Fig. 2 The correlation between $[R]/[S]$ ratio of the product and degree of aggregation of Et_2Zn with chiral ligands **1** and **2**.

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† Electronic supplementary information (ESI) available: experimental details. See http://www.rsc.org/suppdata/cc/b2/b201238c/

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To date, several reports have implied such correlation between the aggregation of organometallic species and their reactivity. Addition of MeOH was reported to enhance both the ee and yield of the product in the reaction of Ph_2Zn with Naph-CO-CH_3, catalyzed by the chiral DAIB ligand.[10] In addition, a correlation between the degree of aggregation of the 'EtMgBr' species and product distributions (addition *vs.* reduction) in the Grignard reaction of benzophenone was reported. That is, an aggregated 'EtMgBr' species, such as that in ethyl ether or that in THF with addition of a small amount of water, favoured addition, and the monomeric reagent in THF favoured Meerwein-Ponndorf-Verley type reduction.[9,11] More recently, the contribution of the dimeric species in autocatalytic dialkylzinc additions was reported;[12] here, the possible participation of the tricoordinated Zn species, not the fully coordinated Zn species, was suggested.

Although the details of the mechanism should be solved, the fluorinated ligands may not be associated to the Zn metal center so strongly as the nonfluorinated ones, due to the strong electron-withdrawing effect induced by the trifluoromethyl groups. Thus, tentatively, there would be some chance of the three coordinated Zn species being generated from the highly aggregated Zn species.

The present results give us some information on the characteristics, properties, and utilization of the fluorinated ligands, as well as on a role of the aggregation of organometallics.[13,14] Further studies on the applicability of this new class of fluorinated ligands to other enantioselective reactions are in progress.

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