Enantioselective Alkylation of Aldehydes with Diethylzinc Catalyzed by C_2-Symmetric Ligands

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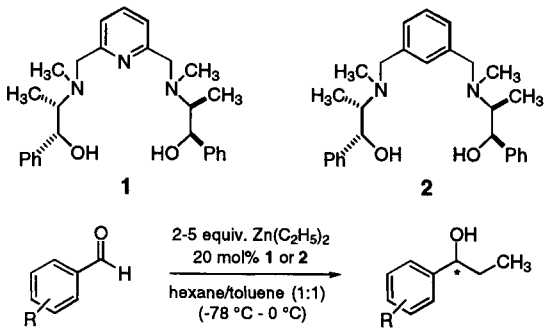
Dedicated to Professor E.J. Corey in celebration of his career achievements and his many contributions to the field of organic chemistry

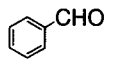
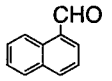
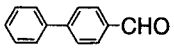
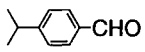
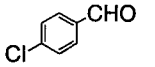
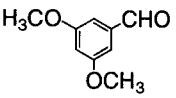
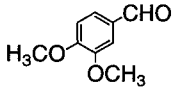
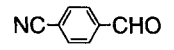
Abstract: The C_2-symmetric pyridine **1**, incorporating two units of (-)-ephedrine, is an effective catalyst for the enantioselective reactions of diethylzinc with a series of aromatic aldehydes. The propanol products possess the S-configuration. This result is a significant reversal of stereochemistry based upon literature precedents and our direct comparisons with reactions catalyzed by the corresponding C_2-symmetric xylene **2**.

Recent studies of the nucleophilic addition of dialkylzinc reagents to the aldehyde carbonyl unit have stimulated a renewal of interests in opportunities in this arena of organometallic chemistry.[1] Noyori and coworkers have recorded impressive advances for the enantioselective addition of diethylzinc to aromatic aldehydes as catalyzed by chiral 3-*exo*-(dimethylamino)isoborneol.[2] While dialkylzincs are linear, unreactive species, coordination with donor ligands provide formation of pseudo tetrahedral complexes of zinc displaying greater nucleophilic behavior. Reports by Corey,[3] Bolm,[4] Soai,[5] Ohno,[6] Oppolzer,[7] and others[8] have documented the utility of a variety of optically active amino alcohols, diamines, and pyridine derivatives as chiral auxiliaries to promote the enantiofacial reaction of organozinc intermediates. Herein we describe a comparison of the C_2-symmetric auxiliaries **1** and **2** as effective chiral catalysts for the enantiocontrolled addition of diethylzinc. Our studies show a dramatic reversal of product stereoselectivity which may have important implications for a mechanistic understanding and the design of bimetallic reagents for asymmetric synthesis.



The reactions of diethylzinc occur through the intermediacy of bimetallic complexes in which a chiral organozinc is formed upon coordination with donor ligands to achieve nucleophilic capacity. A second metal center may function as a chiral Lewis acid for activation of aldehyde substrate. The notion of a bimetallic mechanism has been documented in detail by *ab initio* calculations.[9] Such assumptions have led us to compare chiral **1** and **2** as C_2-symmetric catalysts based upon incorporation of two units of (-)-(1R,2S)-ephedrine. Results are presented in the Table. Isolated yields of purified 1-aryl-1-propanols generally ranged from 72% to 90%, and enantioselectivities were determined from proton NMR analyses upon conversion to the corresponding MTPA esters.[10] For comparison, the reactions of the Table were conducted under identical conditions of solvent, concentration and catalyst load (20 mol%). However, the pyridine **1** afforded a more reactive species with completion of our reactions at low temperatures (ranging from -70 °C to -50 °C). Catalyst **2** provided slow addition at 0 °C over 48 hours, and was not effective at lower temperatures.[11] The pyridine **1** uniformly produced products of higher optical purity, and reactions at the level of 5 mol% catalyst were equally enantioselective.

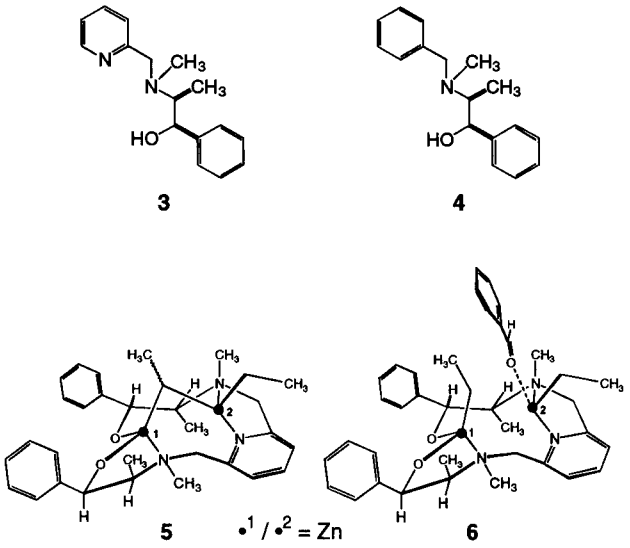
Table. Enantioselective Addition of Diethylzinc

Entry	Substrate	Ligand	Yield	%ee[b]	Stereo.	$[\alpha]_D^{23\,°C}$ (mg/mL $CHCl_3$)
1		1	82%	90	S	-32.5 ° (1.5)
		2	72%	76	R	+35.9 ° (7.3)
2		1	86%	87	S	-55.2 ° (8.0)
		2	80%	74	R	+45.5 ° (8.0)
3		1	80%	85	S	-29.2 ° (10.0)
		2	58%	75	R	+26.9 ° (5.0)
4		1	49%[a]	85	S	-27.8 ° (5.9)
		2	55%	75	R	+25.6 ° (9.3)
5		1	79%	78	S	-26.1 ° (18.5)
		2	90%	71	R	+26.8 ° (10.0)
6		1	78%	85	S	-20.4 ° (8.0)
		2	82%	75	R	+24.1 ° (6.0)
7		1	77%[a]	72	S	-27.3 ° (0.5)
		2	87%	71	R	+26.1 ° (10.0)
8		1	90%	65	S	-26.9 ° (7.5)
		2	87%	69	R	+23.2 ° (11.0)

[a]Yield based on recovered aldehyde. [b]Determined from the corresponding MTPA esters by ^1H NMR (500 MHz). Typical reaction conditions: All reactions were carried out under argon atmosphere with 20 mol% catalyst in the presence of 5 fold excess diethylzinc in 1:1 (toluene/hexane) at -70 °C to -50 °C (catalyst **1**), 0 °C (catalyst **2**) for 48h

The most notable feature of our comparison is the production of the (S)-1-aryl-1-propanols for reactions involving **1**. Numerous reports suggest that asymmetry adjacent to the secondary alcohol is the primary steric influence in determining enantiofacial attack.[12] However, our results show an unprecedented reversal of alkylation stereochemistry for catalysts sharing a common asymmetry.[13] Selected substrates of the Table have also been used for comparison reactions involving the aminoalcohols **3** and **4** at 0 °C to 23 °C. These chiral catalysts lead predominantly to the (R)-propanols as in the case of **2**. We speculate that the behavior of **1** may involve formation of bimetallic chelate **5** with a bridging ethyl group as a consequence of the proximity of the zinc centers. Proton NMR experiments have provided evidence for the formation of a soluble dialkoxyzinc species with loss of two molecules of ethane upon reaction of **1** with a single equivalent of diethylzinc. Transfer of ethyl affords a nucleophilic zincate **6** with a neighboring Lewis acid site for aldehyde activation. A minimization of steric factors and a favorable trajectory for carbonyl addition, with internal reagent delivery, yields the (S)-1-arylpropan-1-ols. In the absence of the pyridine nitrogen, catalyst **2** follows the anticipated reaction course to the (R)-1-arylpropan-1-ols.[9]

In summary, we have shown that C_2 symmetric ligands possessing two coordination sites provide for enantioselective



reactions. Further studies will examine aspects of our mechanistic concerns.

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11. During the final stages of this work, a study of diethylzinc alkylation using enantiomeric **2** (derived from (+)-(1R,2S)-ephedrine) appeared. Our observations for **2** are in general agreement. Andrés, J.M.; Martinez, M.M.; Pedrosa, R.; Pérez-Encabo, A. *Tetrahedron: Asymmetry* **1994**, *5*, 67.
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