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Reversal of Stereochemistry in Diethylzinc Addition to Aldehydes by a Simple Change of the Backbone Substituent in L-Serine Derived Ligands

Mukund P. Sibi,* Jian-xie Chen, and Gregory R. Cook*

Center for Main Group Chemistry, Department of Chemistry, North Dakota State University
Fargo, ND 58105-5516

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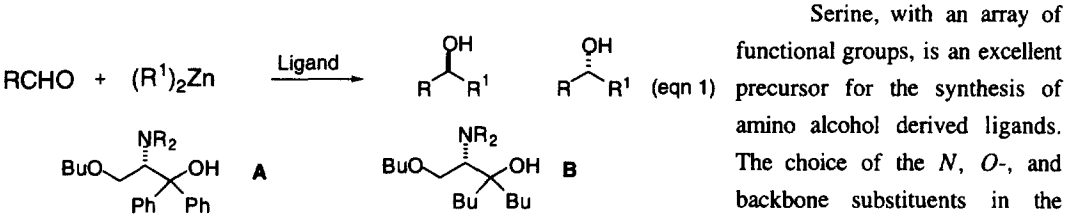
Abstract: A change in the backbone substituent from phenyl to butyl group in L-serine-derived ligands provides a simple way to prepare enantiomeric products in diethylzinc addition to aldehydes.

Keywords: Enantioselective Addition; Serine; Diethylzinc

Development of new ligands for the enantioselective addition of zinc reagents to carbonyl compounds is an area of intense scrutiny.[1] A large number of simple,[2] complex,[3] and polymeric ligands[4] have been developed for the selective addition of zinc reagents to aldehydes. Good to very high levels of selectivity have been reported for this transformation.[5] The preparation of enantiomeric series of products in this transformation generally requires the use of ligands of opposite configuration. A substantial improvement in this strategy would be the ability to design ligands from the same chiral starting material, make simple modifications, and obtain products of opposite configuration. This would obviate the need for the availability of both enantiomeric series of the ligands which at times could be difficult. A few authors have noted the formation of enantiomeric products by modification of ligand while maintaining the same configuration.[6] In the majority of these cases the levels of selectivity for one and/or both enantiomers have not been very high. We have evaluated protected 2-amino-1,3-propanediols derived from L-serine,[7] which provide enantiomeric products with good selectivity by replacement of phenyl groups (**A**) with butyl groups (**B**) and these details are the focus of this letter (eqn 1).



Serine, with an array of functional groups, is an excellent precursor for the synthesis of amino alcohol derived ligands. The choice of the *N*, *O*-, and backbone substituents in the ligands were guided by precedents in the literature and allowed us to examine the effect of the following structural features on selectivity: the number and nature of the substituent(s) on the nitrogen,[8] an aryl or alkyl group on the carbon backbone,[9] and an ether substituent on the additional donor atom. Serine methyl ester served as the starting

e-mail: sibi@plains.nodak.edu; Fax: 701-231-8831; grcook@plains.nodak.edu; Fax: 701-231-8831

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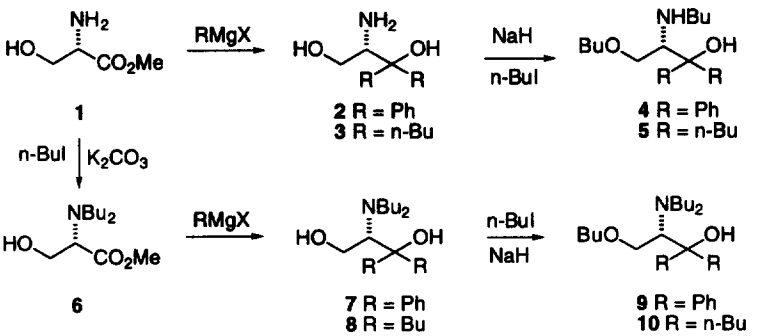
Scheme 1



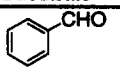
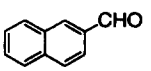
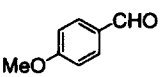
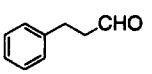
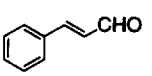
material for the preparation of all of the ligands used in this study (Scheme 1). The methodology for the synthesis of the ligands was straightforward and utilized standard reactions and *N*-, and *O*-alkylation protocols. Individual steps in the synthesis of the ligands have not been optimized.[10]

Benzaldehyde was chosen as the reference substrate for our investigation. The following standard reaction conditions were initially employed to screen the efficiency of the ligands: addition of the aldehyde (1 eq) to a toluene solution of diethylzinc (2 eqs) and 5 mol% of the ligand at room temperature in the presence or absence of *n*-BuLi as an additive. The results from these experiments are tabulated in table. Interesting trends emerge. The primary amino alcohols **2** and **3** were inefficient in terms of both chemical yield as well as enantioselectivity[1] (entries 1 and 2).[11] Changing the primary amino group in **2** and **3** to a secondary one as well the protection of the primary alcohol as an ether, as in **4** and **5**, led to improvement in chemical yield as well as selectivity (compare entry 1 with 3 and 2 with 4). Ligand **4**, with a phenyl group on the backbone, showed a higher level of selectivity than **5**, with a butyl group on the backbone. But more interestingly, the sense of stereoinduction were opposite with the two ligands. Thus, ligands with the same configuration but differing in substitution on the carbon backbone gave enantiomeric products.

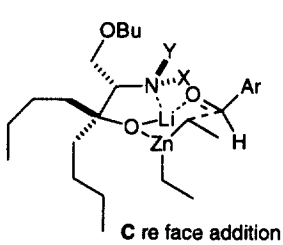
It has been noted in the literature that use of the lithium alkoxide of the ligand (prepared by treatment of the ligand with an equivalent of *n*-BuLi) at times leads to enhancement in selectivity compared to the parent alcohol.[12] To explore this additive effect, lithium alkoxides of **4** and **5** were examined in the addition reaction. This was indeed fruitful as evidenced by a substantial increase in selectivity for **4** from 66% to 83% (compare entry 3 with 5). In contrast, there was no improvement with **5**. The additive however did not affect the sense of stereoinduction.

The next series of ligands examined were the tertiary amine alcohols **9** and **10**. Introduction of an additional butyl group on the nitrogen in **4** was detrimental in the phenyl series (ligand **9**) to the enantioselectivity (entry 7). On the other hand, a similar change in the butyl series (**5** to **10**) gave higher selectivity (entry 8). Use of the lithium alkoxides led to a large increase in selectivity for **10** (entry 10) whereas no improvement was seen for **9** (entry 9). Introduction of the additional *N*-alkyl group in the phenyl series (**4** to **9**) led to a crossover (compare entry 3 with 7) in product configuration. In contrast, a similar change in the butyl series (**5** to **10**) did not result in any crossover (compare entry 4 with 8). A brief optimization with **4** and **10** by lowering the temperature to 0 °C, doubling the amount of BuLi or diethylzinc, or higher catalytic loading (20 mol%) did not improve the enantioselectivity. We have investigated diethylzinc addition to a few other representative aldehydes using 5 mol% of the ligand. In all cases, the two ligands, **4** and **10**, gave products of opposite configuration in respectable yields and moderate to good enantioselectivity (entries 11-18).

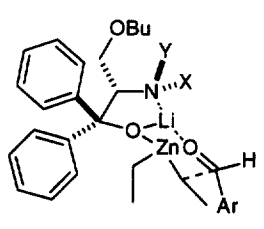
Table. Addition of Diethylzinc to Aldehydes. Effect of Ligand.[a]

Entry	Substrate	Ligand	n-BuLi	Yield (%)[b]	ee(%) (config)[c]
1		**2** (5%)	-	37	10 (S)
2		**3** (5%)	-	39	12 (S)
3		**4** (5%)	-	94	66 (S)
4		**5** (5%)	-	80	28 (R)
5		**4** (5%)	5%	95	83 (S)
6		**5** (5%)	5%	88	26 (R)
7		**9** (5%)	-	91	26 (R)
8		**10** (5%)	-	89	69 (R)
9		**9** (5%)	5%	95	33 (R)
10		**10** (5%)	5%	92	79 (R)
11		**4** (5%)	5%	89	76 (S)
12		**10** (5%)	5%	90	78 (R)
13		**4** (5%)	5%	84	73 (S)
14		**10** (5%)	5%	88	74 (R)
15		**4** (5%)	5%	87	70 (S)
16		**10** (5%)	5%	85	69 (R)
17		**4** (5%)	5%	86[d]	66 (S)
18		**10** (5%)	5%	82[d]	60 (R)

[a] A ratio of 1:2 of aldehyde:DEZ was used in all experiments. [b] Isolated yields. [c] EE's were determined by HPLC analysis. The product configuration was determined by comparison of its sign of rotation to known compounds. [d] The aldehyde was added at –40 °C and the reaction mixture warmed to 0 °C.



C re face addition



D si face addition

The chiral ligand-mediated addition of dialkylzinc to aldehydes is a well-studied reaction and several models accounting for the level of selectivity and the sense of stereoinduction have been proposed.[13] Two chair-like transition states **C** and **D**, which take into consideration the need for a lithium alkoxide (a strong Lewis acid), explains our results. In this model, the primary determinant of product configuration is the interaction of the *N*-substituent (X and Y) with the CH_2OBu group with reinforcement by the α-substituents (Bu groups in **C** and Ph in **D**). This in turn dictates the approach and coordination of the aldehyde to the lithium atom. In reactions with ligands **5**, **9**, and **10**, model **C** is operative. Ligand **10** containing flexible α,α-dibutyl groups reinforce the effect of the *N*-butyl substituents (X = Y = Bu, model **C**) creating a more crowded bottom face of the metallocycle. This allows for the coordination of the aldehyde from the top face and a *re* face ethyl addition accounts for the observed product configuration. In contrast, the conformationally more restricted phenyl groups in **9** lead to lower selectivity

because they are less effective in enhancing the steric interactions. Model **D** is operative when secondary amine ligand **4** is used. In this complex, the coordination of the aldehyde to the Lewis acid occurs on the less hindered bottom face (X = H, Y = Bu) and *si* face ethyl addition accounts for the product configuration. The marginal preference for **C** with **5** is difficult to explain. The change in product configuration on going from **4** to **10** i.e. a secondary amino alcohol to tertiary amino alcohol is similar to that observed by Soai.[8] Experiments are underway to refine our proposed models, and to probe the role of the additional donor oxygen,[7] the bulk of the nitrogen substituents, fluorinated backbone substituents, and examination of other aliphatic and aromatic aldehydes as substrates with various zinc reagents.

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