A Convergent, Homochiral Bis(amino alcohol) for Obtaining High Enantioselectivity in the Addition of Diethylzinc to Aldehydes

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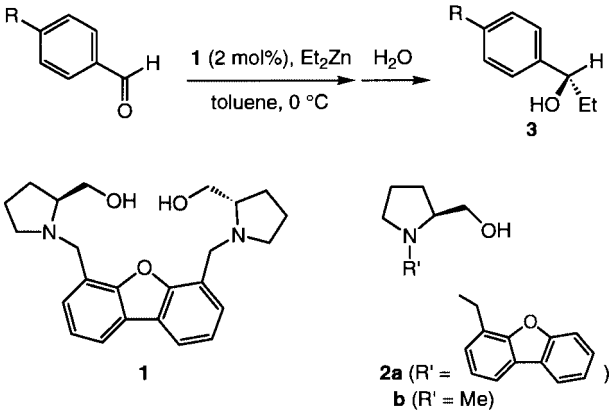
A new bimetallic approach using dibenzofuran derivative as a requisite spacer has been introduced to achieve high asymmetric induction in the addition of diethylzinc to aldehydes with otherwise ineffective amino alcohol residue.

Nucleophilic addition of organometallic reagents to carbonyl substrates constitutes one of the most fundamental, yet routinely employed operations in organic synthesis.[1] It has been well documented that addition of heteroatom containing chiral auxiliaries enhances the reactivity and also controls the stereochemical outcome in an absolute sense, making it attractive as a general method to create optically active alcohols.[2] In view of the increasing interest in the catalytic asymmetric induction in such carbon–carbon bond-forming reactions, enantioselective addition of dialkylzincs to aldehydes using chiral amino alcohols as catalysts emerged as an undisputed ideal and numerous studies have been made during last decade.[3] Despite the sophistication in terms of synthetic efficiency and mechanistic elucidation, the strategies of the previously known systems are largely fall into categories of either the search for highly effective chiral amino alcohols such as DAIB[4] or the synthesis of artificial chiral amino alcohols as exemplified by the series of pyrrolidinylmethanols.[5] Recently, design and appilcation of new chiral C_2-symmetric dimeric ligands have attracted much attention.[6] Herein we wish to report our own approach to this subject by the successful introduction of homochiral bis(amino alcohol) **1** as a catalytic promoter which in situ provides binucleic chiral alkylzinc species, allowing high asymmetric induction with otherwise ineffective amino alcohol residues.



We chose readily available (*S*)-prolinol as an amino alcohol and synthesized the convergent, homochiral bis(amino alcohol) **1** starting from dibenzofuran in a three-step sequence as shown in Scheme 1. Examination of the effectiveness of **1** as a chiral catalyst was conducted in the enantioselective addition of dialkylzinc to aldehydes. Treatment of benzaldehyde with diethylzinc (2.2 equiv) under the influence of **1** (5 mol%) in toluene at room temperature for 7 h gave rise to the corresponding alkylation product, 1-phenylpropanol (**3**, R = H) in 70% isolated yield, and the enantioselectivity was determined to be 75% ee (*S*) (Table 1, entry 1). In sharp contrast, however, the reaction with the mono(amino alcohol) derivative **2a** (10 mol%) under otherwise identical conditions resulted in a total loss of the enantiomeric excess [80%, 1.5% ee (*R*)] (entry 2), which seemed consistent with the report that simple *N*-methylprolinol (**2b**) failed to afford optically active alcohol in the ethylation of benzaldehyde with diethylzinc.[5]

Scheme 1.

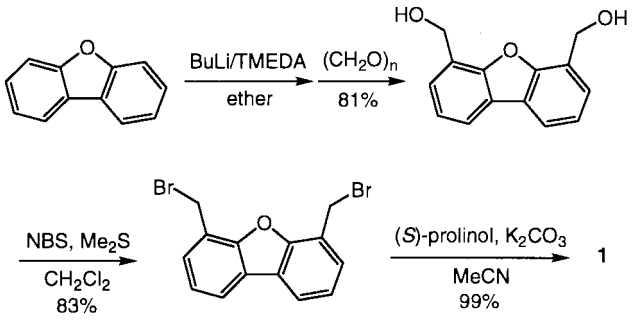


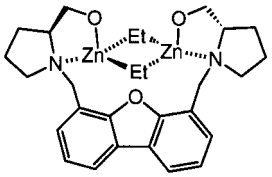
Table 1. Enantioselective addition of diethylzinc to aldehydes[a]

Entry	Aldehyde (R)	Catalyst	Condition (°C, h)	% Yield [b]	% ee [c] (config) [d]
1	H	**1**	r.t., 7	70	75 (*S*) [e]
2		**2a**	r.t., 7	80	1.5 (*R*) [f]
3		**1**	0, 48	84	88 (*S*)
4	Cl	**1**	0, 48	76	85 (*S*)
5	F	**1**	0, 48	70	90 (*S*)
6	Me	**1**	0, 48	66	83 (*S*)
7	Ph	**1**	0, 48	57	81 (*S*)

[a]Unless otherwise specified, the reaction was carried out in freshly distilled, degassed toluene with 2.2 equiv of Et_2Zn and 2 mol% of the (*S*)-prolinol-derived catalyst under the given reaction conditions. [b]Isolated yield. [c]Enantiomeric excess was determined by HPLC analysis using a chiral column (DAICEL Chiralcel OD) with hexane–2-propanol as solvent. [d]Absolute configuration was determined by comparison of the HPLC retention time with the authentic sample independently synthesized by the reported procedure.[5] [e]Use of 5 mol% of **1**. [f]With 10 mol% of catalyst.

Further optimization of the reaction conditions based on this finding eventually resulted in (*S*)-1-phenylpropanol being obtained in 88% ee and 84% isolated yield when the reaction was performed in the presence of 2 mol% of **1** as a catalyst in toluene at 0 °C for 48 h (entry 3). As also exemplified in Table 1, this catalytic condition is effective in the ethylation of various *para*-substituted benzaldehydes, leading to the production of the corresponding secondary alcohol **3** in 81–90% ee (entries 4–7).

Although the origin of the observed dramatic enhancement of the asymmetric induction is not yet clear, it is conceibable that one of the zincs of the in situ generated bimetallic species **4** acts as a Lewis acidic center, and the proximate ethyl group on the other zinc can be transferred by way of a preferable six-membered cyclic transition state (**5**) to give the corresponding secondary alcohol **3** with *S* configuration.[7] Another possibility is that **4** could capture the aldehyde carbonyl to form bidentate complex **6** prior to alkylation,[8] being responsible for high enantioselectivity in the subsequent ethyl transfer process. Precise elucidation of the reaction mechanism and actual reactive intermediate is our current research subject.



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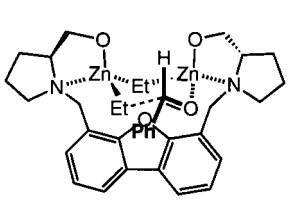

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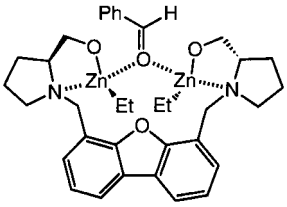

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Dedicated to Prof. Hideki Sakurai on the occasion of his 70th birthday.

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