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Chiral Amplification Based on Enantioselective Dual-Phase Distribution of a Scalemic Bisoxazolidine Catalyst

Shuanglong Liu and Christian Wolf*

Department of Chemistry, Georgetown University, Washington, DC 20057
cw27@georgetown.edu

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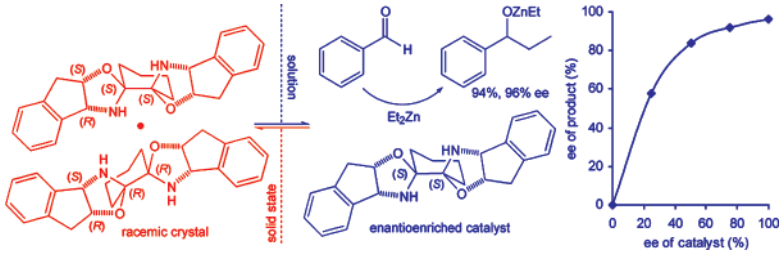
ABSTRACT



A readily available bisoxazolidine ligand was found to catalyze the asymmetric alkylation of aldehydes with Et_2Zn and less reactive Me_2Zn, providing high yields and ee's in both reactions. The bisoxazolidine-catalyzed alkylations and alkynylation of benzaldehyde show a positive nonlinear effect that cannot be accounted for by Kagan's ML_n model. The chiral amplification originates from selective phase distribution favoring enrichment of the major enantiomer of the scalemic catalyst in solution.

The enantioselective alkylation of aldehydes with organozinc reagents has emerged as one of the most extensively studied carbon−carbon bond formations.[1] This reaction produces chiral secondary alcohols, which are popular synthetic building blocks,[2] and it is commonly used to test the potential of new chiral ligand designs and high-throughput screening methods.[3] Numerous amino alcohols,[4] diols,[5] and diamine derivatives[6] that effectively catalyze the asymmetric addition of diethylzinc to aldehydes are known. However, few examples of reactions with dimethylzinc have been reported, which can be partly attributed to its inherently low reactivity.[7]

We have recently introduced bisoxazolidine **1** and demonstrated the use of this new class of C_2-symmetric catalysts for asymmetric alkynylation of aldehydes.[8] The bisoxazolidine ligand can be prepared in a single step from *cis*-1-amino-2-indanol and 1,2-cyclohexanedione in the presence of catalytic amounts of formic acid and is readily available in both enantiomeric forms (Scheme 1). Comparison with mono-oxazolidines revealed that the *N*,*O*-diketal structure is crucial for both catalytic activity and enantioselectivity. We now report that bisoxazolidine **1** catalyzes the asymmetric reaction of aldehydes with both Et_2Zn and Me_2Zn. Importantly, we found that the addition of saturated organozinc and alkynylzinc reagents to benzaldehyde in the presence of this catalyst proceeds with a positive nonlinear

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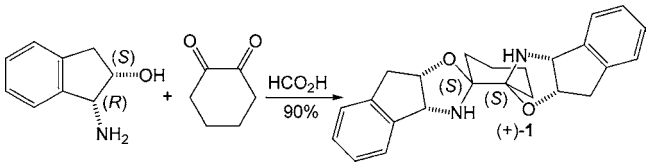
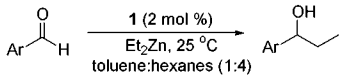
Scheme 1. Synthesis of Bisoxazolidine (+)-**1** from (1*R*,2*S*)-Aminoindanol and 1,2-Cyclohexanedione

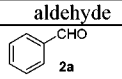
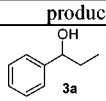
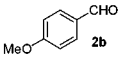
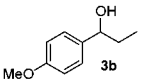
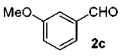
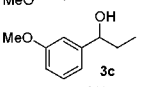
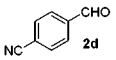
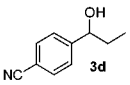
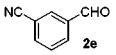
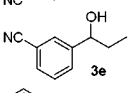
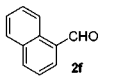
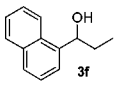
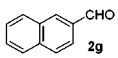
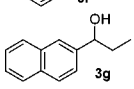
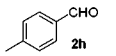
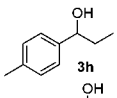
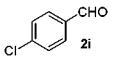
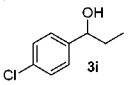
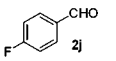
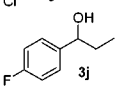
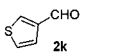
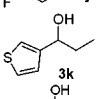
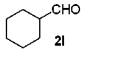


effect that originates from an unexpected solid−liquid phase behavior which cannot be accounted for by Kagan's ML_n model.

Encouraged by the high yields and enantiomeric excess of propargylic alcohols obtained by bisoxazolidine-catalyzed alkynylation of aldehydes, we decided to employ **1** in the reaction of diethylzinc with several aldehydes (Table 1).

Table 1. Bisoxazolidine-Catalyzed Asymmetric Addition of Et_2Zn to Aldehydes.



entry	aldehyde	product	yield (%)[a]	ee (%)
1			99	96[b]
2			99	96[c]
3			92	91[b]
4			91	90[b]
5			96	92[b]
6			87	78[b]
7			92	91[b]
8			99	86[c]
9			97	86[b]
10			95	94[b]
11			99	71[b]
12			92	90[c]

[a] Isolated yields. [b] Determined by HPLC on Chiralcel OD, OB-H, and Chiralpak AD. [c] Determined by GC on octakis(6-*O*-methyl-2,3-di-*O*-pentyl)-γ-cyclodextrin.

Optimization of catalyst loading and solvents showed that the reaction proceeds in the presence of 2 mol % of bisoxazolidine **1** using hexanes and toluene (4:1 v/v) as solvent at room temperature. This procedure is suitable to aldehydes bearing electron-donating and -withdrawing substituents, and the corresponding chiral alcohols were isolated in up to 99% yield and 96% ee (entries 2−11).

Despite the excellent results generally obtained with Et_2Zn, this reaction often proceeds with unsatisfactory yield and enantioselectivity when Me_2Zn is used.[9] Significant progress has been achieved with chiral chromium,[10] titanium,[11] and osmium[12] complexes, but the development of a methylation method that resembles the high yield, enantioselectivity, and operational simplicity of ligand-catalyzed Et_2Zn addition is still desirable. We were pleased to find that the use of 5 mol % of **1** in apolar solvents provides a viable alternative when aromatic aldehydes are employed (Figure 1). Our

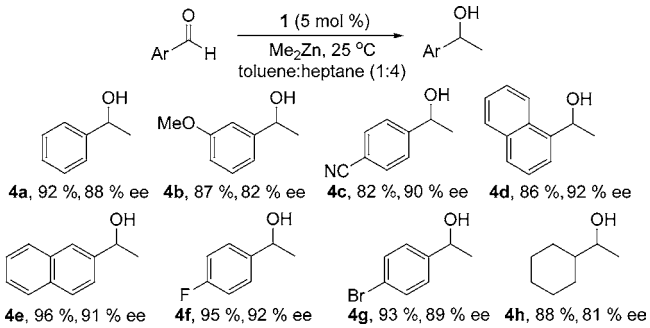


Figure 1. Structures of chiral alcohols obtained by bisoxazolidine-catalyzed addition of Me_2Zn to aldehydes.

method affords 1-phenylethanol, **4a**, in 92% yield and 88% ee, and similar results were obtained with other aromatic aldehydes. Bisoxazolidine-catalyzed ethylation and methylation of cyclohexanecarboxaldehyde, **21**, furnished alcohols **3l** and **4h** in high yields and ee's, but alkylation of linear aldehydes showed only moderate enantioselectivity (entry 12 in Table 1, Figure 1, and Supporting Information).

Following the seminal work from Oguni's and Noyori's groups, many examples of positive deviations from a linear relationship between the enantiopurity of chiral amino alcohols or other precatalysts and the enantiomeric excess of 1-arylpropanols obtained by asymmetric addition of

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(10) Cozzi, P. G.; Kotrusz, P. *J. Am. Chem. Soc*. **2006**, *128*, 4940−4941.

(11) (a) Knochel, P.; Almena Perea, J. J.; Jones, P. *Tetrahedron* **1998**, *54*, 8275−8319. (b) Blay, G.; Fernandez, I.; Hernandez-Olmos, V.; Marco-Aleixandre, A.; Pedro, J. R. *Tetrahedron: Asymmetry* **2005**, *16*, 1953−1958.

(12) Muniz, K. *Tetrahedron Lett.* **2003**, *44*, 3547−3549.

diethylzinc to aromatic aldehydes have been reported.[7,13] This positive nonlinear effect (NLE) has been explained by predominant formation of thermodynamically favored, heterochiral zinc complexes in solution. The organozinc adduct of the minor enantiomer is thus trapped in a catalytically inactive form while the surplus of the organozinc adduct of the major enantiomer is available to catalyze the reaction. Because heterochiral recognition and association generates an enantiomerically enriched or enantiopure monomeric catalytic species, the enantiomeric excess of the reaction product can exceed the ee of the precatalyst employed.[14] Positive and negative nonlinear effects have been observed in a variety of asymmetric reactions and are generally explained with Kagan's ML_n model, which is based on the assumption that a scalemic catalyst is in equilibrium with homochiral and heterochiral adducts exhibiting different catalytic activity.[15]

Analysis of the enantioselective alkylation of benzaldehyde with diethylzinc in the presence of scalemic mixtures of **1** revealed a positive nonlinear effect (Figure 2). For example,

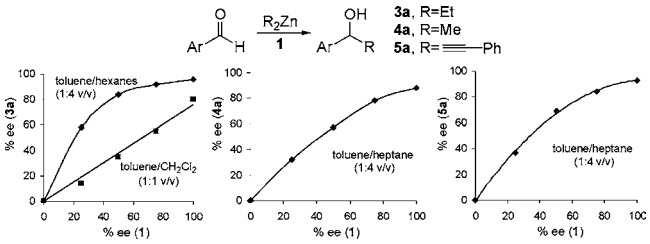
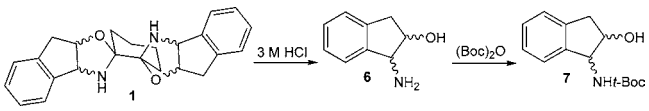


Figure 2. Nonlinear effects in the bisoxazolidine-catalyzed enantioselective ethylation, methylation, and alkynylation of benzaldehyde with organozinc reagents (from left to right). See the Supporting Information for reaction conditions.

1-phenylpropanol is obtained in 94% yield and 96% ee in the presence of 2 mol % of **1** having 50% ee. During our studies, we noticed that the solubility of the ligand significantly decreases as the enantiopurity of the bisoxazolidine is reduced. When scalemic **1** was used, the catalyst could not be fully dissolved, and we suspected that this might account for the NLE observed. We found that the solubility of enantiopure **1** in toluene and hexanes (1:4 v/v) is 10.5 mg/mL, whereas only 1.4 mg/mL of racemic **1** dissolves in the same solvent mixture. To prove our hypothesis, we stirred a mixture containing (+)-**1** in 50% ee in toluene and hexanes (1:4 v/v) for 12 h. The precipitate was isolated, and the enantiomeric composition of **1** in the solid state and in solution was determined.

Unfortunately, screening of several HPLC columns did not provide a chromatographic method for direct enantioseparation of **1**. We therefore decided to subject the bisoxazolidine mixtures to hydrolysis and derivatization to afford *N*-*t*-Boc-aminoindanol **7**, which can be resolved by chiral HPLC on Chiralcel OD (Scheme 2). Gravimetric and

Scheme 2. Hydrolysis and Derivatization of Ligand **1** for Chiral HPLC Analysis



chromatographic analysis showed that the crystalline material was almost racemic and corresponded to 47% of the originally used bisoxazolidine. By contrast, the supernatant contained the remaining 53% of **1** in 89% ee.[16] The same results were obtained when the experiment was conducted in the presence of 150 equiv of diethylzinc. Upon mixing of solutions containing a large excess of Et_2Zn and either enantiopure (+)-**1** or (-)-**1** to afford 50% ee, a precipitate formed which contained nearly racemic **1** (4.5% ee) but no trace of Et_2Zn. NMR analysis of mixtures of **1** and Me_2Zn revealed that complexation occurs without concomitant deprotonation. This shows that **1** is not a precatalyst and unlike amino alcohols does not require 1 equiv of R_2Zn to form a catalytically active species.[17] Accordingly, alkylation of **2a** proceeds with high yield and enantioselectivity when equimolar amounts of **1** and Et_2Zn are used; see the Supporting Information.

Apparently, the positive nonlinear effect observed in the bisoxazolidine-catalyzed reaction between benzaldehyde and diethylzinc is a result of the inherently low solubility of *racemic* **1** in apolar organic solvents. This unexpected solid−liquid phase behavior of scalemic **1** selectively increases the purity of the major enantiomer in solution and gives rise to a positive NLE that cannot be described by Kagan's ML_n model.[18] In our case, chiral amplification originates from thermodynamically controlled crystallization of racemic **1**, whereas the enantiomeric surplus remains in solution and is available for asymmetric catalysis (Scheme 3). As expected, no NLE was observed when the reaction was carried out in toluene and dichloromethane (1:1 v/v) because racemic **1** is soluble in this solvent mixture (Figure 2).

To date, only a few examples of enantioenrichment of chiral catalysts and chiral amplification based on solid−

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(16) The ee of the precipitate was determined as 6%. We found that the ee of the solid formed decreases further when the precipitate is washed more thoroughly, but less material is recovered in these cases.

(17) Organozinc reagents have been reported to not deprotonate secondary amino groups. See ref 4c.

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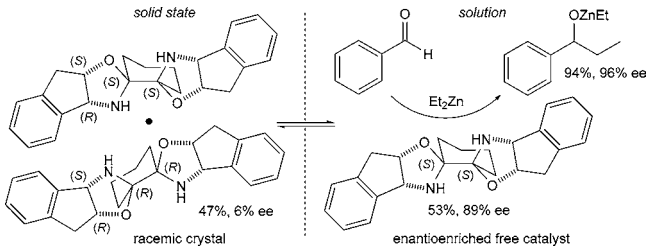
Scheme 3. Enantioenrichment and Solid−Liquid Phase Behavior of Scalemic **1** Resulting in a Positive Nonlinear Effect



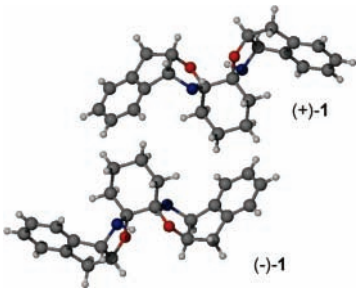


Figure 3. Single-crystal structure of racemic **1**.

solution equilibration have been reported.[19] Bolm et al. observed precipitation of a heterochiral meso zinc complex upon treatment of a bipyridine-derived precatalyst exhibiting 50% ee with 5 equiv of diethylzinc.[20] A small amount of the major enantiomer was found to be enriched to 84% ee in solution while the precipitate contained 74% of the ligand in 44% ee. Importantly, the enantioenrichment of bisoxazolidine **1** does not require the presence of a reagent or chiral additive, and we therefore anticipated that the unique solid−liquid-phase behavior of scalemic **1** would also afford a positive NLE in other reactions. In fact, precipitation of racemic ligand resulting in chiral amplification was observed when scalemic mixtures of bisoxazolidine **1** were applied in the methylation and alkynylation of benzaldehyde following a previously reported procedure (Figure 2 and Supporting Information).[8]

Slow evaporation of a diluted solution of (+)-**1** exhibiting 50% ee in toluene and hexanes produced a single-crystal suitable to X-ray diffraction; see the Supporting Information for details. In accordance with our findings that racemic **1** is significantly less soluble than the enantiopure form, crystallographic analysis confirmed formation of racemic single crystals while conglomerates were not observed (Figure 3). The melting point ranges of enantiopure and racemic **1** were determined as 135−137 °C and 208−210 °C, respectively. Noteworthy, many attempts to grow a single crystal from a solution of enantiopure **1** in toluene and hexanes were unsuccessful, while racemic crystals were easily prepared from scalemic mixtures in the same solvents. It is quite possible that enantioenrichment of chiral catalysts and nonlinear effects due to formation of a thermodynamically favored racemic crystal lattice is a common phenomenon when asymmetric reactions are carried out in biphasic systems. Our studies coincided with Blackmond's recent findings that enantioenrichment of proteinogenic amino acids and chiral amplification observed in proline-mediated aldol-type reactions are directly related to the phase behavior of the catalyst and may explain the evolution of biomolecular homochirality in Nature.[21] A clear distinction between nonlinear effects that originate from a physical phase behavior similar to that of bisoxazolidine **1** and chiral amplification that can be explained by Kagan's ML_n model is important, in particular, when NLEs are used as mechanistic probes.[22]

In conclusion, bisoxazolidine **1** has been successfully applied in the catalytic asymmetric alkylation of aldehydes with organozinc reagents. The high yield, enantioselectivity, and operational simplicity generally encountered in nucleophilic additions of Et_2Zn to aromatic aldehydes has been extended to less reactive Me_2Zn. The bisoxazolidine-catalyzed alkylation and alkynylation of benzaldehyde studied show a positive nonlinear effect that is not related to the reaction mechanism but a result of a dual-phase behavior favoring enrichment of the major enantiomer of scalemic **1** in solution. This enantioselective phase distribution does not require the presence of any additives, and stereochemical and crystallographic analysis confirmed that the chiral amplification originates from crystallization of racemic **1**. These observations cannot be accounted for by Kagan's model, and it is possible that our results have important implications for the interpretation of nonlinear effects obtained with other catalytic systems.

Supporting Information Available: Synthetic procedures, NLE analysis, X-ray diffraction data and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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