Substrate Dependence of Nonlinear Effects: Mechanistic Probe and Practical Applications

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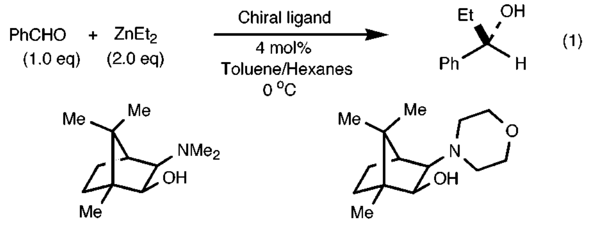
Enantioselective catalysis has witnessed explosive growth in the last two decades as it has become the most versatile and efficient method for the preparation of molecules of high enantiomeric excess.[1] Of the numerous contributions that have shaped our understanding of catalytic asymmetric reactions, few have had such a profound impact as the experimental and theoretical description of nonlinear effects by Kagan and co-workers.[2−5] Before this seminal work,[2] it was generally believed that a strictly linear correlation existed between the ee of the catalyst and the ee of the product. However, Kagan demonstrated that this assumption was not valid[2] and many systems have since been shown to exhibit nonlinear behavior.[3,4]

The consequences of strong positive nonlinear effects are remarkable.[3,4,6−8] For example, Noyori used the DAIB ligand (eq 1) of only 15% ee in the asymmetric addition of alkyl groups to aldehydes from which a product of 95% ee was generated. When enantiopure DAIB was used in this reaction, the product was generated in 98% ee.[9] Soai has demonstrated that ligands with very low ee, or even traces of chiral material, can be used in an autocatalytic asymmetric process to generate product in high ee.[10−13] The only drawback to using partially resolved catalysts exhibiting strong positive nonlinear behavior such as DAIB in production of enantioenriched material is that they display a lower overall rate than when they are enantiomerically pure.[7]



DAIB (1) **MIB (2)**

Because nonlinear effects are so easily detected,[3] many asymmetric catalysts have now been tested. However, we are unaware of studies of nonlinear effects that focus on the substrate dependency of this behavior. The substrate dependency of nonlinear effects has important implications for two primary reasons: (1) in the optimization of asymmetric processes it is beneficial to determine the ee of the ligand necessary to obtain a product of the desired ee and (2) substrate dependency of nonlinear effects can be used to probe the mechanism of asymmetric reactions. In this Communication we present a study of the substrate dependency of nonlinear effects using the MIB ligand of Nugent (eq 1).[14] This ligand is closely related to the DAIB ligand **1** that has been extensively studied by Noyori and co-workers.[9,15−18] We find that simply modifying the electronic properties of benzaldehyde derivatives results in a change in the product ee (ee_p) of over 30% in the asymmetric addition (eq 1) with 10% ee of MIB. This effect is even more pronounced with aliphatic aldehydes. Equally important, the current model for the mechanism of the asymmetric addition reaction (eq 1) with DAIB is not consistent with the observed substrate dependency of the nonlinear effect with MIB.

We chose to employ the MIB ligand because of its ease of synthesis and its stability on long-term storage.[14] Asymmetric addition reactions (eq 1) were conducted using 4 mol % MIB of 10, 20, and 100% ee of the ligand at 0 °C (Table 1). These additions were performed by combining the ligand and aldehyde followed by addition of the diethylzinc over 1 min (Method A). Under these conditions, no precipitate formed over the course of the reaction (Table 1). Reactions were also performed at room temperature by mixing the ligand and diethylzinc (Method B, Supporting Information). After 1 h the aldehyde was added and the reactions were sampled between 10 and 20% conversion except for *m*-trifluoromethyl benzaldehyde which was 96% complete after 2 min (Table S2, Supporting Information). No precipitate was present at these conversions; however, solid did form in some reactions at later times. Importantly, both methods exhibited the same trend in nonlinear behavior. A plot of the ee of the MIB ligand versus the ee_p for the reaction conducted at 0 °C clearly shows that nonlinear effects are substrate dependent in this system (Figure 1). The data in Figure 1 demonstrate that benzaldehyde derivatives with electron-donating substituents exhibit *greater nonlinear behavior than analogues with electron-withdrawing substituents*. Changing substrates form *p*-methylbenzaldehyde to *o*-methylbenzaldehyde resulted in no change in the nonlinear behavior (compare entries 2 and 7, Table 1). However, 2,4,6-trimethylbenzaldehyde exhibited a markedly smaller nonlinear effect (entry 8). Aliphatic aldehydes were found to show greater variation in nonlinear behavior than aromatic aldehydes (Table 1). The linear chain nonal gave a stronger nonlinear effect than cyclohexanecarboxaldehyde. Increasing the steric hindrance around the carbonyl carbon leads to a decrease in the nonlinear effect (entries 8 and 10).

Variation of the substituent on benzaldehyde also affects the overall rate using nonenantiopure MIB in eq 1. With 10% ee MIB, the reaction of the *m*-(trifluoromethyl)benzaldehyde was complete in under 30 min while the *p*-methoxybenzaldehyde was only 23% complete after 2 h. The higher overall rate with electron-withdrawing aldehydes is consistent with the proposed rate determining addition of the alkyl group to the carbonyl.[16] Control experiments were conducted to estimate the rate of the background

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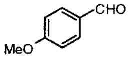
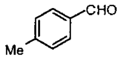
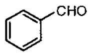
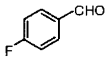
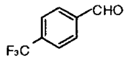
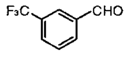
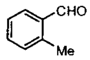
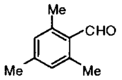
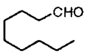
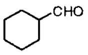
Table 1. Product ee's with 10, 20, and 100% ee MIB Determined by Using Method A[h]

Entry	Aldehyde	MIB of 10% ee[a]	MIB of 20% ee[a]	MIB of 100% ee[a]
1		94.5[b]	96.9	98.4
2		92.2	95.9	98.9
3		89.1	95.1	98.0
4		87.2	94.9	98.3
5		71.3	82.6	97.3
6		62.1	80.9	97.8
7		94.1	96.4	98.6
8		51.3[c]	77.0[d]	94.1[e]
9		79.3	87.6	91.3
10		40.0[f]	48.6[g]	99.8

[a] ee measured after completion of the reaction, except where otherwise stated. [b] 92% conversion after 23 h. [c] 14% conversion after 96 h. [d] 33% conversion after 96 h. [e] 40% conversion after 24 h. [f] 94% conversion after 24 h. [g] 94% conversion after 16 h. [h] Data for Method B are given in the Supporting Information.

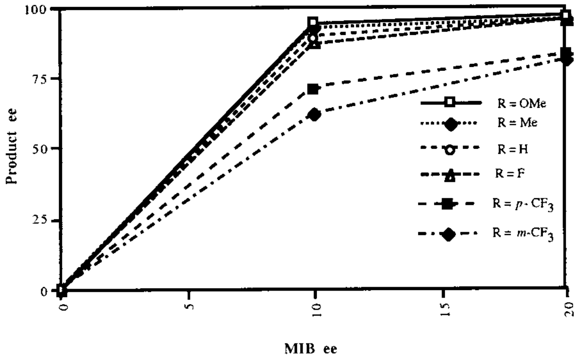
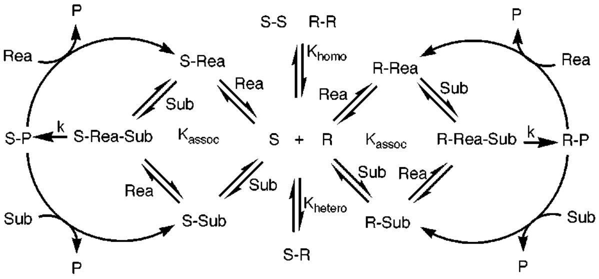


Figure 1. Ee of product vs ee of MIB for substituted benzaldehyde derivatives.

reaction, that is the reaction that takes place without the participation of the chiral ligand. Reaction of benzaldehyde in eq 1 without the amino alcohol ligand exhibited 3% conversion after 24 h. The more reactive *p*-trifluoromethyl derivative was 3% complete in 2 h and 22% complete after 24 h. These results indicate that the background reaction is significantly slower than the ligand accelerated pathway.[19]

Because of the similarity of the MIB and the DAIB ligands, it is reasonable to assume that the reaction mechanisms in eq 1 are the same.[20] The proposed mechanism for the asymmetric addition

Scheme 1. The Noyori Mechanism[a]



[a] See Supporting Information for structures.

reaction using DAIB is shown in Scheme 1. Using Noyori's abbreviations, S and R are ligand adducts (L_S)Zn(Et) and (L_R)Zn(Et), Sub is the aldehyde substrate, Rea is the reagent $ZnEt_2$, and P is the product. Noyori and co-workers have shown that the nonlinear effects in the DAIB system arise from a reservoir effect. Convincing evidence has been presented that the active catalysts are derived from the monomeric species (L_S)Zn(Et) and (L_R)Zn(Et) and that the resting states for the catalyst are the heterochiral and homochiral dimers (S−R, S−S, and R−R in Scheme 1). The heterochiral dimer has been shown to be significantly more stable than the homochiral dimers.[16] It is proposed that the monomers (L)Zn(Et) bind aldehyde and $ZnEt_2$ to give $ZnEt_2$·(L)(Et)Zn-Sub. This complex reacts irreversibly to give the alkoxide product.

When nonenantiopure ligand is employed, the ee$_p$ is dependent on the concentrations of the aldehyde and diethylzinc and the equilibrium constants K_{homo}, K_{hetero}, and K_{assoc} (Scheme 1). Of these equilibrium constants, K_{homo} and K_{hetero} are independent of the substrate and only K_{assoc} will be affected by the binding strength of the aldehyde. Aldehydes that bind more strongly will increase the concentration of the $ZnEt_2$·(L)(Et)Zn-Sub at the expense of the dimers. This model predicts that aldehydes that bind more tightly will result in a decrease in ee$_p$. In the extreme case of very high K_{assoc}, where only monomers are formed, there will be no nonlinear effects. This model of the mechanism is inconsistent with the observed substrate dependency of the nonlinear effects measured here in which more tightly binding substrates exhibit *greater* nonlinear behavior. We are currently investigating whether the data can be explained by reaction of aldehydes with the diastereomeric homo- and heterochiral dimers through different pathways.

In conclusion, we have shown that nonlinear effects are substrate dependent. This observation has important ramifications in the practical application of nonenantiopure ligands to synthesis of products with high enantiomeric excess. We have also demonstrated that investigation of substrate-dependent nonlinear effects has the potential to provide important information about equilibria that control ee$_p$. We are currently attempting to modify the Noyori model to fit the previously reported mechanistic data as well as the data reported here. These investigations will be reported in due course.

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Supporting Information Available: Experimental conditions and results of addition reactions at 0 (Table S1) and 23 °C (Table S2) (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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