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The effect of conformational equilibrium on the enantioselectivity of catalysts: a quantitative relationship for the evaluation, design, and prediction of chiral ligands in the addition of diethylzinc to benzaldehydes

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ABSTRACT

A kinetic system correlating the enantioselectivity with a catalyst's conformational equilibrium, as a theoretical basis for the evaluation, design, and prediction of chiral ligand, is described for the addition of diethylzinc to benzaldehyde, and more importantly, a quantitative relationship between the conformations and the enantioselectivity is derived from this catalytic asymmetric kinetic system, which interprets that the observed enantioselectivity is not a weighted average of the enantioselectivity of the individual conformers.

1. Introduction

Over the past few decades, tremendous effort has been devoted to the design and synthesis of efficient chiral ligands and catalysts that are capable of affording high enantioselectivity and reactivity in asymmetric catalysis. Despite this great achievement, the methods for developing new chiral ligands and catalysts have not changed greatly. So far, designing ligands and catalysts has mainly depended on intuitive and empirical rather than rational approaches. The main reason for the clear lack of progress may be an absence of guiding principles and general rules for chiral catalyst design, as Holz et al. have lamented;[1] '...in spite of literally thousands of chiral ligands that have been reported in the past, there is no unique rationale for the efficiency of all catalysts not even for those that have been applied in the same reaction. Therefore the design of new catalysts is based on trial and error.' This comment reflects the state-of-the-art in the design of ligands and catalysts.

In our prior report, we observed that a necessary relationship existed between the free ligand's relative conformational populations and the observed enantioselectivity in the asymmetric addition of diethylzinc to benzaldehyde,[2] that is, variation in the relative amounts of the conformational isomers in equilibrium led to an alteration in the measured enantioselectivity. In addition, we found that enantioselectivity increased with an increase in the relative proportions of the desired conformation that showed the highest levels of enantioselectivity. This phenomenon was further demonstrated by subsequent theoretical calculations. The synthesis and evaluation of new chiral ligands in the asymmetric addition of organozincs to aldehydes revealed that this relationship could guide an accurate design of highly enantioselective ligands, or a rational improvement of existing ligands just by our knowledge of conformational design.[3] Based on this principle, we reported the logical design of a pair of chiral diastereomeric ligands, which showed nearly the same excellent enantioselectivity in the asymmetric addition of diethylzinc to aldehydes from a single common chiral source.[4]

It is well-known that subtle structural changes of chiral ligands and catalysts can often result in a dramatic variation of the enantioselectivity and reactivity. This phenomenon implies that the redistributions of the conformational equilibrium can often cause significant alterations in the catalytic performance because small modifications of structures of chiral ligands and catalysts can often lead to conformational variations, that is, redistribution of the conformational equilibrium of the chiral ligands and catalysts.[5]

In order to provide a theoretical support for our previous investigations on the relationship between the conformation and the enantioselectivity,[2,4] we herein report a kinetic system that correlates the enantioselectivity in the addition of diethylzinc to benzaldehydes with the catalyst's conformation. This would represent a step in the direction of providing a general theoretical basis for chiral catalyst design, evaluation, and prediction.

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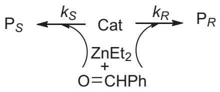
2. Results and discussion

The previous kinetic investigation by Noyori et al. indicated that under catalytic conditions, the asymmetric addition of diethylzinc to benzaldehyde is first order with respective to chiral ligand or catalyst (Cat).[6] Therefore, the reaction rate (d[P]/dt) is dependent on the catalyst concentration but is unaffected by the concentration of the dialkylzinc reagent and the benzaldehyde substrate, that is d[P]/dt = k[Cat].

For the sake of understanding, we first considered the simplest type of chiral catalyst that exists only as a single conformation (or rigid backbone catalyst). To exemplify the effect of a catalyst (Cat) with a single conformation on the enantioselectivity in the asymmetric addition of diethylzinc to benzaldehydes, a kinetic system in a catalytic cycle is shown in Scheme 1, where k_R and k_S are the rate constants for the formation of a pair of enantiomeric products P_R and P_S, respectively. The expression for the enantioselectivity (ee value) is easily derived from this kinetic system.



Scheme 1. The asymmetric reaction kinetic system of a catalyst.

In terms of Scheme 1, we considered the following mathematical derivation. The rates of the (*R*)- and (*S*)-enantiomers in a catalytic cycle are illustrated in Eqs. 1 and 2, respectively.

$$d[P_S]/dt = k_S[\mathrm{Cat}] \tag{1}$$

$$d[P_R]/dt = k_R[\mathrm{Cat}] \tag{2}$$

Similarly, the overall rate of the catalyzed reaction may be expressed by Eq. 3, where k refers to the total rate constant of the catalyzed reaction.

$$d[P]/dt = k[\mathrm{Cat}] \tag{3}$$

The expression of the entire rate of product formation is shown in Eq. 4.

$$d[P]/dt = d[P_S]/dt + d[P_R]/dt \tag{4}$$

Substituting Eqs. 1–3 into Eq. 4, and solving for k, we obtain Eq. 5.

$$k = k_R + k_S \tag{5}$$

Dividing Eq. 1 by Eq. 2, and integrating, we get Eq. 6. Eq. 7 follows directly.

$$[P_S]/[P_R] = k_S/k_R \tag{6}$$

$$[P_S] = [P_R]\,\frac{k_S}{k_R} \tag{7}$$

Substituting Eq. 7 into Eq. 8 (the definition of ee), and using Eq. 5, we receive Eq. 9.

$$\mathrm{ee} = \frac{[P_R] - [P_S]}{[P_R] + [P_S]} \tag{8}$$

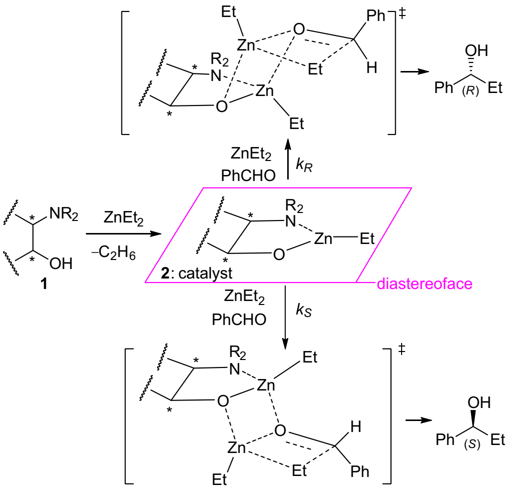
where P_R is the major enantiomer of the catalyzed reaction, and P_S is the minor enantiomer.

$$\mathrm{ee} = \frac{k_R - k_S}{k_R + k_S} = \frac{k_R - k_S}{k} \tag{9}$$

As shown by Eq. 9, the observed enantioselectivity is a ratio of rate constant difference and the sum in the formation of both enantiomers. Eq. 9 reflects not only the degree of chiral induction, but also the reactivity of the catalyzed reaction because the ee value is directly proportional to the difference ($k_R - k_S$) in the reaction rate constants, and the sum ($k_R + k_S$) of rate constants indicates the reactivity of the catalyzed reaction.

A chiral catalyst, in terms of catalytic performance such as selectivity and reactivity, is expected to exhibit the highest level of enantioselectivity and the fastest reaction rate. Ideally, at a limiting case, $k_S = 0$, ee = 100%, and $k_R \to \infty$.

Noyori et al. have studied the mechanism of this reaction extensively, both theoretically and experimentally.[7] The asymmetric catalyst is believed to be a five-membered zinc aminoalkoxide **2** (Scheme 2), which is a bifunctional catalyst. Complex **2** acts as a Lewis acid to activate the carbonyl substrates and also as a Lewis base to activate diethylzinc reagents. Both the aldehyde and diethylzinc can coordinate to either face of the five-membered chelate ring to give a pair of (*R*)- or (*S*)-enantiomers with the rate constants k_R and k_S, respectively. The relative magnitudes of the rate constants k_R and k_S mainly depend on the 1,2- and 1,3-nonbonded interactions between the groups on α- and β-carbon atoms and the incoming substrate and reagent during the coordination process. The less hindered face of the five-membered zinc ring shows a faster rate. Therefore, the difference ($k_R - k_S$) between the rate constants k_R and k_S reflects the diastereofacial differentiation of the five-membered zinc cycle. The large difference in the diastereofaces results in high enantioselectivity because the ee value of the reaction is directly proportional to the difference ($k_R - k_S$) in the reaction rate constants of the (*R*)- and (*S*)-enantiomer formation.



Scheme 2. Mechanism of the addition of diethylzinc to benzaldehyde catalyzed by a β-aminoalcohol.

Since the parameters in Eq. 9 are generally, although not invariably, unknown for a catalyzed reaction, Eq. 9 can be used to qualitatively assess the catalytic performance of different chiral catalysts. For example, chiral ligands **3** and **5** are diastereomers with a rigid backbone (Scheme 3).[8] At first glance, it is difficult to determine the relative magnitudes of the enantioselectivity and reactivity. On the basis of the above analyses, in addition to Eq. 9, it is easy to predict the catalytic performance of diastereomers **3** and **5**.

Upon binding of **3** and **5** to zinc chiral catalysts **4** and **6**, respectively, with rigid structures are formed. Since **4** and **6**, respectively, have a sterically equivalent k_S face leading to the equal transition state with respect to the five-membered zinc ring, the relative magnitude of their rate constants is equal at this k_S side, i.e. $k_{4S} = k_{6S}$, whereas they differ in reactivity at the k_R side because