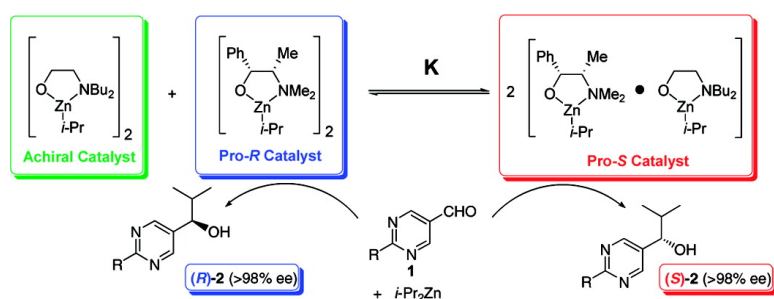Communication

Mechanistic Insights in the Reversal of Enantioselectivity of Chiral Catalysts by Achiral Catalysts in Asymmetric Autocatalysis

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Mechanistic Insights in the Reversal of Enantioselectivity of Chiral Catalysts by Achiral Catalysts in Asymmetric Autocatalysis

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During our further studies on asymmetric autocatalysis,[1] reactions in which the chiral product acts as a chiral catalyst for its own production, we reported that some autocatalytic reactions, for example, the addition of diisopropylzinc to 2-*tert*-butylethynyl-pyrimidine-5-carbaldehyde **1**, occur with an amplification of enantiomeric excess (ee) of the catalyst/product, so that the final product has a higher ee than the initial catalyst.

On the other hand, we recently reported that achiral amino alcohols reverse the enantioselectivity of chiral amino alcohols during this autocatalytic reaction.[2] Thus, in association with asymmetric autocatalysis, the two possible absolute configurations of the pyrimidyl alkanol **2** can be obtained with high enantiomeric excess from a unique chiral catalyst. Typically, (1*R*,2*S*)-dimethyl-norephedrine (DMNE **3**) affords (*R*)-alcohol **2**, whereas (*S*)-alcohol **2** is obtained by using a mixture of (1*R*,2*S*)-DMNE and achiral *N,N*-dibutylaminoethanol (DBAE **4**), both enantiomers being formed with >98% ee with the same source of chirality (Scheme 1).

Scheme 1
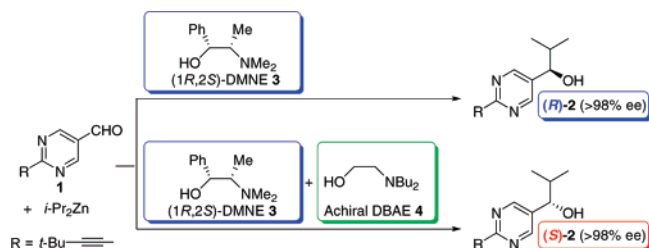
We initially interpreted this reversal as a consequence of interactions between the two catalysts, which form a catalytically active aggregate promoting the formation of the opposite enantiomer.[2a] However, it was recently proposed theoretically that in the hypothesis of a mutual inhibition of the chiral catalyst by the product of major configuration, and in association with asymmetric auto-catalysis, a reversal of enantioselectivity may also occur.[2b] Because both scenarios would imply important mechanistic insights either in the β-amino alcohol-catalyzed addition of dialkyzincs to alde-hydes or in the asymmetric autocatalysis, we here report kinetic and enantioselectivity studies of the reaction that permit evaluation of the validity of the two models and lead to structural and quantitative information about the complex responsible for the reversal of enantioselectivity.

Kinetic studies of the addition of diisopropylzinc to aldehyde **1** catalyzed whether by enantiopure DMNE **3** or achiral DBAE **4** were first performed, with various loadings of catalyst. Toluene, in which the reactions are homogeneous, was chosen as a solvent,

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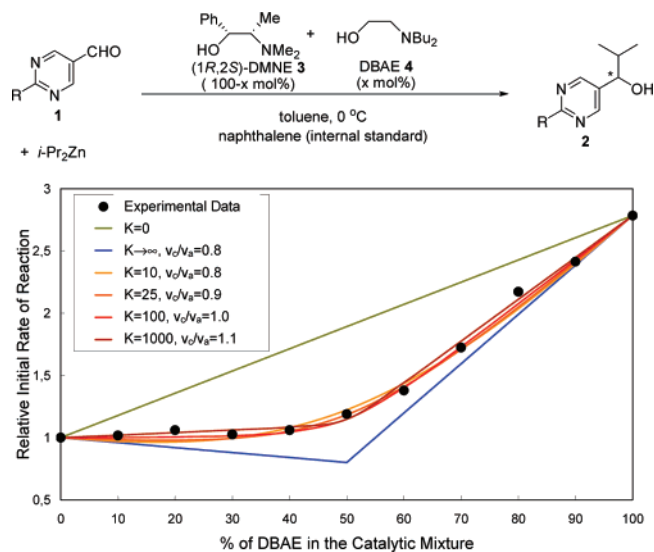
Figure 1. Evolution of the relative initial rate of catalysis with the composition of the catalytic mixture of enantiopure DMNE and achiral DBAE (total amount of catalysts: 100 mol %).

and the yields of the reactions were measured every 30 s in the first 5 min by HPLC by using naphthalene as an internal standard.

Although three possible processes (noncatalyzed, autocatalyzed, and amino alcohol-catalyzed formation of **2**) may contribute to the formation of the product, the first two were shown to be negligible during the first moments of the reaction, due to an incubation period before asymmetric autocatalysis starts.[3a] It appeared that the reaction is, under these conditions, first order in amino alcohol and that achiral DBAE **4** is about 2.7 times more active than chiral DMNE **3** ($v_b = 2.7v_a$).

Then additional kinetic studies of the reaction catalyzed by mixtures of chiral DMNE and achiral DBAE in various proportions were performed in toluene at 0 °C to get some information about the interactions between the two catalysts. The total amount of amino alcohols (100 mol % in order to minimize experimental errors) was kept constant. Again, only the first moments of the reaction, before asymmetric autocatalysis occurs, were taken in account, and the measured initial reaction rate corresponds to the cocatalysts activity. The variation of the initial reaction rate with the composition of the catalytic mixture (plots in Figure 1) shows a strong nonlinearity. The initial rate of the reaction is roughly the same as that for the DMNE-catalyzed reaction when the amount of DBAE is lower than the amount of chiral DMNE and increases progressively when the concentration in DBAE exceeds the concentration in chiral catalyst. It is worth noting that, in this system, the presence of the achiral catalyst fastens the reaction, contrary to related studies.[4]
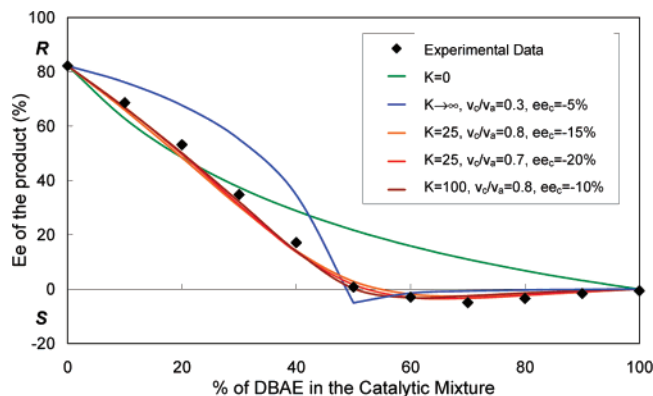
Figure 2. Evolution of the initial enantiomeric excess of the product with the composition of the catalytic mixture of enantiopure DMNE and achiral DBAE (total amount of catalysts: 100 mol %).

The enantiomeric excesses of the obtained products (before asymmetric amplification occurs) were also measured after purification and depend on the catalytic mixture as shown in Figure 2 (plots). Again, a sharp nonlinearity was observed, partially due to the interactions between the two catalysts. The enantiomeric excess of the product decreases almost linearly from 82% to 1% ee (R configuration) from a 0:100 to 50:50 ratio of ligands (DBAE/DMNE). When the amount in DBAE exceeds the amount of chiral DMNE (ratio > 50:50), (S)-alkanol **2** is formed with a low but significant enantiomeric excess (up to 5% ee). This observation indicates that the high enantiomeric excess obtained at the end of the reaction is mainly due to asymmetric autocatalysis. However, it should be noted that the reversal occurs even *before* asymmetric autocatalysis occurs, showing that the reversal phenomenon is probably due to an interaction between the two catalysts, as shown in Scheme 2.[5]

Scheme 2. Possible Interpretation of Enantioselectivity Reversal
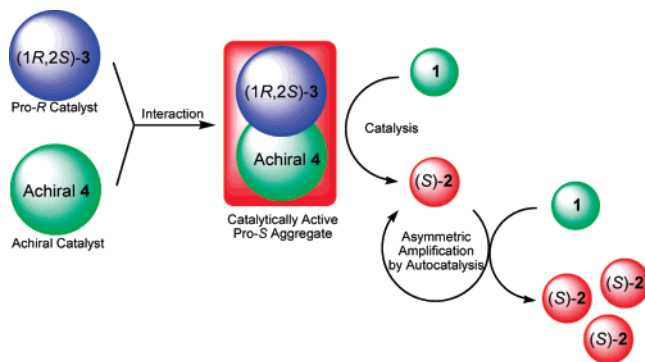
Thus, at equimolar amounts of the two catalysts a critical change in behavior is observed in both rate and enantioselectivity. Zinc amino alkoxides issued from β-amino alcohols are known for their propensity to form aggregates, particularly dimers.[6] Active catalysts are yet considered to be monomeric, and dimeric species or higher aggregates only act as a reservoir.[6b,d,7] However, this postulate is not consistent with the observed reversal of enantioselectivity. Considering a possible interaction between the two catalysts, these changes at equimolar amounts of ligands strongly support the formation of a catalytically active aggregate bearing the same molarity of the two ligands, the simpler one being a dimeric complex. Considering their structural similarities, we postulated that the dimeric forms of DMNE **3** and DBAE **4** catalyze the reaction as well. Thus a Kagan-type equilibrium[8] between three dimeric catalytic species was considered, two being chiral (**A** and **C**) and

Scheme 3. Dimeric Catalytic Species Model
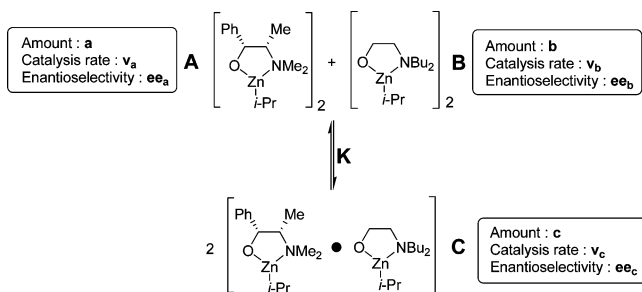
one achiral (**B**), whose respective proportions a, c, and b are linked by an association constant K (Scheme 3). Each of these dimeric complexes is considered to catalyze the reaction with the respective rate v_a, v_b, and v_c and enantioselectivity ee_a, ee_b, and ee_c.

The initial rates v_a and v_b of the pure DMNE-catalyzed reaction (respectively DBAE-catalyzed) being known, the initial rate v of the reaction catalyzed by mixtures of the two catalysts can be calculated for various values of K and v_c.[9] The best-fitting simulations were obtained with the hypothesis of a good propensity to form the heterodimer **C** ($K \approx 10-1000$) and by considering that the mixed aggregate has a similar catalytic activity to that of dimeric DMNE ($v_c \approx 0.8-1.1\ v_a$) (curves in Figure 1).

On the other hand, the enantiomeric excess of the product varies with the composition of the catalytic mixture as a function of the catalytic properties of the mixed aggregate **C** (v_c and ee_c) and its occurrence (K).[10] The observed reversal of enantioselectivity implies that the heterodimer **C** promotes the formation of the opposite enantiomer to the one produced by the homodimer **A** ($ee_c < 0$), and it has also to be considered to have sufficient catalytic activity ($v_c \approx v_a$) to fit the partial linearity from a 100:0 to 50:50 ratio of ligands (DMNE/DBAE). The curves shown in Figure 2 greatly correlate with the experimental data and were obtained with the following hypotheses: (1) heteroassociation is slightly favored versus homoassociation of the ligands ($K \approx 25-100$), (2) the mixed aggregate is a little less active than the homochiral dimer ($v_c \approx 0.7-0.8\ v_a$), and (3) the mixed aggregate yields (S)-**2** with moderate enantioselectivity ($ee_c \approx 10-20\%$ for S configuration).

Thus, the present kinetic and enantioselectivity studies are very consistent with the formation of dimeric catalytic species. Simulation of the observed nonlinearity in the rate of the reaction provides quantitative information about the catalytic properties of the mixed aggregate responsible for the reversal of enantioselectivity. The simulation of enantioselectivity provides an independent means of confirming and refining the estimated parameters and greatly corroborates the validity of the postulated model.[11]

To support our model,[12] we also performed some *ab initio* molecular orbital calculations on structurally close species. The total energies of the most stable conformers of monomeric and dimeric isopropylzinc alkoxides issued from (1R,2S)-DMNE **3** and N,N-dimethylaminoethanol (DMAE **5**) were calculated at the B3LYP/6-31G* level. The three dimeric species show an *anti* 5/4/5 tricyclic skeleton, in agreement with previous studies.[6,13] The formations of the dimeric zinc alkoxide of DMNE **A** and of the dimeric zinc alkoxide of DMAE (taken as a model of aggregate **B**) from their monomeric forms were shown to be exothermic by 125.8 and 153.3 kJ/mol of dimer, respectively. Moreover, the formation of the heterodimer **C′** (shown in Figure 3) from the homodimers is exothermic by 11.9 kJ/mol of heterodimer, consistent with the quite high value of K estimated from our experiments.

In the dimeric heterocomplex **C′**, the chirality present in the chiral ligand imposes a preferential conformation to the achiral moiety, probably for both steric and electronic reasons. It can be rationalized
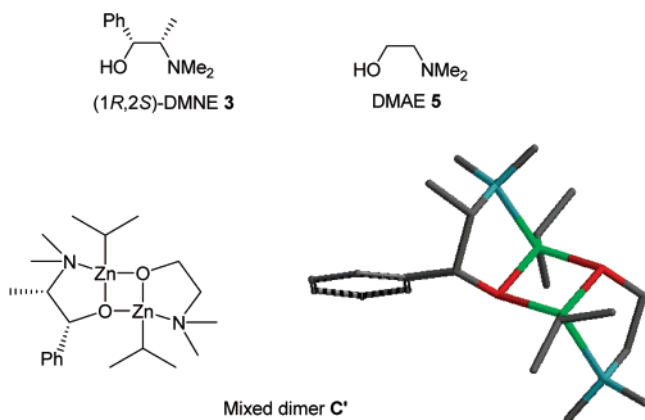
Figure 3. Calculated structure of heterodimer **C′** resulting from the aggregation of isopropylzinc alkoxides of (1*R*,2*S*)-DMNE **3** and DMAE **5** (red, oxygen; gray, carbon; green, zinc; blue, nitrogen; hydrogen atoms are not shown for clarity).

by a parallel with a number of studies showing that heterochiral dimers are often more stable than homochiral dimers.[6,13]

Thus, in the present work we have demonstrated that the reversal of the sense of enantioselectivity is due to the preferential formation of a catalytically active chiral heterodinuclear aggregate derived from zinc alkoxides of chiral and achiral ligands possessing the same functionalities and similar activities,[14,15] and that the subsequent asymmetric autocatalysis with significant asymmetric amplification affords pyrimidylalkanol with high ee. Furthermore, the fact that polynuclear zinc β-amino alkoxides are catalytically active brings some new mechanistic insights into the amino alcohol-catalyzed addition of dialkyzincs to aldehydes and may have implications in the origin of nonlinear effects in these reactions.

Supporting Information Available: Typical experimental procedure, kinetic studies, exhaustive simulations, and computational details. This information is available free of charge via the Internet at http://pubs.acs.org.

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(9) The rate v of the reaction was calculated from the following equation: $v = a*v_a + b*v_b + c*v_c$, with $K = c^2/ab$. Representative simulations are shown in the Supporting Information.

(10) The enantiomeric excess ee of the product was calculated from the following equation: ee $= (a*v_a*ee_a + c*v_c*ee_c)/(a*v_a + b*v_b + c*v_c)$. Representative simulations are shown in the Supporting Information.

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JA077156K