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Origins of Asymmetric Amplification in Autocatalytic Alkylzinc Additions

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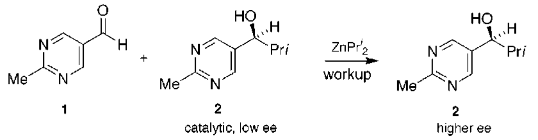
Some time ago it was suggested by Frank[1] and by Calvin[2] that amplification of enantiomeric excess could be feasible in an autocatalytic process.[3] An experimental demonstration of this concept remained elusive, however, until the remarkable results of the group of Soai in 1995.[4] The reaction of aldehyde **1** with ZnPr$^{i}_{2}$ catalyzed by the reaction product **2** led to a significant enhancement of enantiomeric excess in newly formed **2**. Imbalances as low as 0.05% ee, created from racemic mixtures by photolysis using circularly polarized light, were used to initiate autocatalytic reactions resulting in products up to 85% ee. However, no mechanistic information about this intriguing autocatalytic system has been reported.



We report here on kinetic studies of the autocatalytic reaction shown above which provide a simple and consistent explanation for the observed asymmetric amplification. Reactions at ambient temperature were continuously monitored in a reaction microcalorimeter (Omnical CRC90) as previously described.[5−7] The heat-flow profile obtained in such an experiment provides a direct measure of the reaction rate as a function of time.

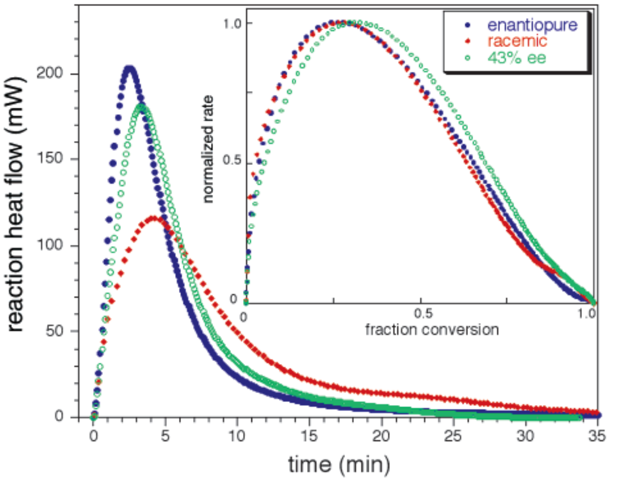


Figure 1. Reaction heat flow as a function of time for the reaction shown in Scheme 1 using 10 mol % catalyst **2** of differing enantiomeric excess: 97% ee$_{cat}$ (blue ●), 43% ee$_{cat}$ (green ○), and 0% ee$_{cat}$ (red ◆). Inset: reaction rate normalized by the maximum value, plotted against fraction conversion of the substrate **1** (same symbols as in main figure).

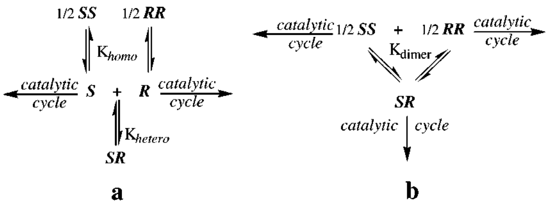


Figure 2. Proposed mechanisms for asymmetric alkylation of aldehydes.

Figure 1 shows heat flow versus time for three reactions with different initial enantiomeric excesses of the catalyst **2**. The reactions demonstrate classic autocatalytic behavior, with the rate rising to a maximum as the catalyst concentration increases and then falling off over time as the reactant concentrations are depleted. The difference in rates observed in the three reactions in Figure 1 implies that the effective concentration of active catalyst is a function of catalyst ee, consistent with a mechanism incorporating a suppression of the role of the minor enantiomer in catalysis.

In the inset to Figure 1, the same data are plotted versus fraction conversion of **1** after normalizing the rate by its maximum value in each case. This leads to a striking observation: the data for the nearly enantiopure and the *rac*-**2** catalysts are *superimposable* throughout the reaction, while the data for 43% ee **2** is offset. This implies that the reaction rates in the enantiopure and racemic cases are proportional to one another, and in fact the rate for the racemic catalyst remains approximately *half* that of the enantiopure catalyst.

The mechanism elucidated by Noyori and co-workers for asymmetric alkylzinc additions to aldehydes[8] describes a monomeric catalyst species in equilibrium with unreactive heterochiral ***SR*** and homochiral ***SS*** and ***RR*** dimers, with equilibrium constants K_{hetero} and K_{homo} respectively (Figure 2a).[9] Asymmetric amplification results when the monomers are preferentially disposed toward formation of ***SR*** ($K_{\mathrm{hetero}} > 2K_{\mathrm{homo}}$). A constant rate ratio of 0.5 for racemic versus enantiopure catalysts over the course of the autocatalytic reactions can only be observed for nonselective formation of the heterochiral and homochiral dimers with $K_{\mathrm{hetero}} = 2K_{\mathrm{homo}}$. Yet this is the very condition which *precludes* amplification of the autocatalyst enantiomeric excess.

This paradox become explicable if the model is modified to allow dimer species themselves to be the active catalysts, as in the simplest case of Kagan's ML$_n$ models, in which a single equilibrium constant, K_{dimer}, describes the fast interconversion of

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(6) McMillan, C. R. Part II, Thesis, Oxford University, June 2000. **1** (0.18 M) was injected into a solution of **2** (0.2−10 mol %) preequilibrated with 0.2 M ZnPr$^{i}_{2}$ in toluene at 298 K. A reaction rate datum point was collected every 6 s.

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(9) K_{homo} and K_{hetero} with dimerization as the forward reaction.

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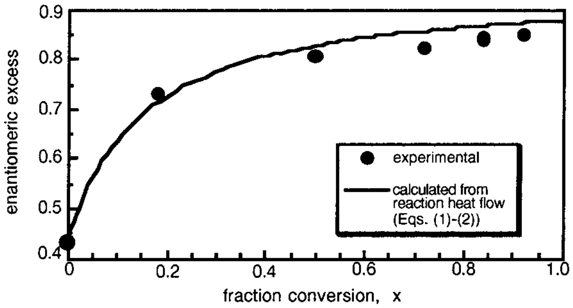


Figure 3. Enantiomeric excess as a function of fraction conversion, *x*, using catalyst **2** with 43% ee. (●) Data; (−) calculated from heat flow.

the dimers during their formation (Figure 2b).[10] Modification for the case of autocatalysis gives eq 1 for reaction rate and eq 2 describing the change in catalyst (product) ee with conversion of substrate. The ratio of rates for enantiopure and racemic catalysts remains constant over the course of the reaction ($\beta = 1$ for racemic and remains approximately zero for enantiopure catalysts in reactions giving high ee product). For catalysts with intermediate ee values, the rate compared to enantiopure catalyst changes with conversion (in these cases, β is a continuously changing function of the catalyst ee).

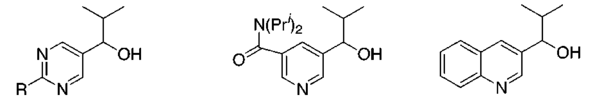
$$\text{rate} = k\cdot[1]\cdot[\mathrm{Pr}^{\mathrm{i}}_2\mathrm{Zn}]\cdot[2]\cdot\left(\frac{1+g\beta}{1+\beta}\right) \tag{1}$$

$$g = \frac{\text{activity of } [\boldsymbol{SR}]}{\text{activity of } [\boldsymbol{RR}]} \quad \beta = \frac{[\boldsymbol{SR}]}{[\boldsymbol{RR}] + [\boldsymbol{SS}]} \quad K = \frac{([\boldsymbol{SR}])^2}{([\boldsymbol{RR}])([\boldsymbol{SS}])}$$

$$\mathrm{ee}_{\mathrm{d}x} = \frac{[\boldsymbol{RR}] - [\boldsymbol{SS}]}{[\boldsymbol{RR}] + [\boldsymbol{SS}] + g[\boldsymbol{SR}]} \quad \mathrm{ee}_{x+\mathrm{d}x} = \frac{\mathrm{ee}_x[\mathbf{2}] + \mathrm{ee}_{\mathrm{d}x}\frac{\mathrm{d}x}{2}[\mathbf{1}]_0}{[\mathbf{2}] + \frac{\mathrm{d}x}{2}[\mathbf{1}]_0} \tag{2}$$

This modified ML_2 model[11] applied simultaneously to the reaction rate data from all three runs in Figure 1 gave an excellent fit for parameters describing a statistical distribution of dimers ($K_{\mathrm{dimer}} = 4$) and an inactive heterochiral dimer.[12] Figure 3 shows the experimental enantioselectivity as a function of conversion for the 43% ee catalyst compared to that calculated from the fit of the reaction rate data according to eqs 1 and 2. The excellent agreement from data obtained independently offers further support for the kinetic model. Such significant amplification of enantioselectivity with no disposition toward a heterochiral dimer may have implications for spontaneous asymmetric synthesis.

All of the examples of autocatalysis discovered by Soai and coworkers involve rigid γ-amino alcohols as catalysts. Reactions of the corresponding aldehydes with ZnPr^i_2 were carried out at 0 °C, compared to our experiments at ambient temperature. Efficiency varies, with the most spectacular levels of amplification obtained from the 4-alkynylpyrimidine **4** or its close relatives (Figure 4). All of these results are in accord with the dimeric

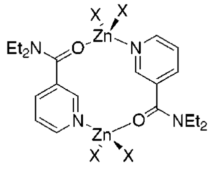


3 R = H [5 - 55] *(4a)*
4 R =C≡—Bu^t [5.5 - 69.6] *(4e)*
5 [56 - 85] *(4c)*
6 [8.9 - 55.8] *(4d)*

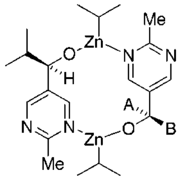
Figure 4. Examples of asymmetric amplification from ref 4. Numbers in brackets give initial and final catalyst ee values for reactions at 273 K with 20 mol % catalyst in toluene.

catalyst model reported here if it is recognized that a slight increase in selectivity toward racemic dimer formation as temperature is lowered can lead to markedly enhanced asymmetric amplification.[13] It should also be noted that this system displays condition-dependent complexities. Contribution from a slow but significant background reaction triggering racemic autocatalysis may be minimized only by employing higher catalyst concentrations.[14]

The rigid nature of the secondary alcohol products precludes mononuclear chelation in the corresponding zinc alkoxide, and predicates the system toward formation of the postulated dimers. Supportive evidence for their feasibility comes from the X-ray crystal structure of ZnX_2 complexes of diethylnicotinamide **7a** and **7b**.[15] The macrocyclic bimetallic chelate of **8** derived from alcohol **2** exhibits an homologous arrangement, with formally tricoordinate zinc.[16] Preliminary ^{1}H NMR studies on these are consistent both with the existence of dimeric Zn alkoxides and a lack of selectivity in association, exhibited in the Ar−CH_3 signal.[17]



7a, X = Cl,
7b, X = SCN



***(S,S)*-8** A = H, B = Pr^i
***(R,S)*-8** A = Pr^i, B = H

In summary, a simple dimeric catalyst model explains the broad features of asymmetric autocatalysis quite strikingly. The two Zn atoms in compound **8** are nicely disposed toward bimetallic N,O-coordination of aldehyde **1**,[10a] providing a template for attack of ZnPr^i_2. The required stereospecificity of this process is under active investigation.

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[11] k = third-order rate constant; $\mathrm{ee}_{\mathrm{d}x}$ = ee for a differential element of conversion dx; $\mathrm{ee}_{x+\mathrm{d}x}$ = cumulative ee at fraction conversion x; $[\mathbf{1}]_0$ = initial substrate concentration.

[12] In Scheme 2, $K_{\mathrm{dimer}} = 4$ corresponds to the ratio $K_{\mathrm{hetero}}/K_{\mathrm{homo}} = 2$.

[13] The best examples of amplification in ref 4 for catalyst **2** may be fitted by an ML_2 model with $K_{\mathrm{dimer}} = 16$, corresponding to doubling of $K_{\mathrm{hetero}}/K_{\mathrm{homo}}$ to 4.

[14] Final ee values for reactions at 298 K using 97% ee **2** as catalyst at 1.0, 4.9, and 9.4 mol % were 90.4, 91.0, and 93.2%, respectively.

[15] Davies, G.; El-Toukhy, A.; Onan, K. D.; Veidis, M.; *Inorg. Chim. Acta* 1984, **84**, 41; Bigoli, F.; Braibanti, A.; Pellinghelli, M. A.; Tiripiccio, A. *Acta Crystallogr., Sect. B.* 1973, **29**, 2708.

[16] The dimers characterized in the Oguni−Noyori case are tetracoordinate with additional Zn−O bonding, and presumed to be inert.

[17] ^{1}H NMR spectra were recorded in at 500 MHz by adding a 10-fold deficiency of compound **1** to ZnPr^i_2, ca. 0.16 M in toluene. For *rac*-1, δ 8.43 br CHAr, 4.27 br CHO, (2.59, 2.56) ArCCH_3 (1:1); for 87% ee. (*R*)-1, d 8.45 CHAr, 4.27 br CHO, 2.56 ArCCH_3. Gridnev, I. D. Claridge, T. D. W. Unpublished work.