Asymmetric Amplification

Amplification of Enantiomeric Excess in a Proline-Mediated Reaction**

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The origin of homochirality has intrigued scientists ever since the biological importance of L-amino acids and D-sugars was first recognized. Although a theoretical basis for the evolution

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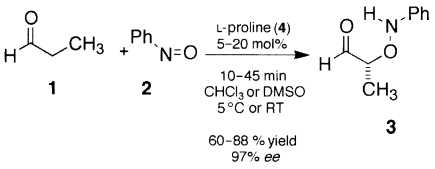
of high optical activity from a minute initial imbalance of enantiomers was suggested more than half a century ago,[1] experimental proof of such a concept eluded scientists until a remarkable report by Soai and co-workers in 1995.[2] The Soai reaction offered the first, and to date the only, example of an asymmetric autocatalytic reaction employing a catalyst with a very *low* enantiomeric excess and ultimately yielding the catalyst with a very *high* enantiomeric excess catalyst as product. While the Soai reaction serves as a mechanistic model[3] for the evolution of homochirality, the dialkylzinc chemistry involved in the reaction is unlikely to have been of importance in an aqueous prebiotic environment. Therefore speculation has continued concerning the types of transformations that might have been directly responsible for the development of high optical activity in biological systems. The area of amino acid catalysis may hold significant clues to the evolution of prebiotic chemistry. That prebiotic building blocks such as sugars can be formed asymmetrically from such reactions has recently led to speculation about the evolution of biological homochirality through such routes.[4] We report herein a proline-mediated reaction exhibiting an accelerating reaction rate and an amplified, temporally increasing enantiomeric excess of the product. Thus, catalysis with amino acids is implicated in an autoinductive, selectivity-enhancing process, providing the first general chemical strategy for the evolution of biological homochirality from a purely organic origin.

The growing field of asymmetric aminocatalysis[5] makes use of biomimetic strategies via enamine and iminium intermediate species common to class I aldolase and ketoacid decarboxylase enzymes. The proline-catalyzed intramolecular Hajos–Parrish–Eder–Sauer–Wiechert reaction was the first example employing a similar strategy in organic synthesis.[6,7] More recently, this approach has been successfully expanded by several groups, beginning with the first report by List, Barbas, and Lerner[8] which demonstrated the proline-catalyzed direct asymmetric intermolecular aldol reaction. A recent addition to this rapidly growing list of aminocatalytic transformations was offered by two independent and nearly simultaneous reports of the proline-catalyzed α-aminoxylation of aldehydes shown in Equation (1).[9,10] Both studies



(1)

noted good yields and high *ee* values with 5–20 mol % catalyst in reaction times measured on the order of tens of minutes. This finding was all the more notable given the dramatically lower activity of other proline-catalyzed reactions; for example, completion of the aldol reaction between acetone and isobutyraldehyde required 48 h at 30 mol % catalyst.[10] Most, recently the scope of this reaction was widened to include ketone substrates, which also exhibited rapid reaction times.[11]

Intrigued by these reports, which imply a fundamental mechanistic difference between the reaction shown in Equation (1) and other proline-catalyzed transformations, we undertook continuous monitoring of reaction progress by reaction calorimetry, a kinetic approach that we have developed over the past several years as a mechanistic probe of multistep reactions.[12,13] We observed, quite unexpectedly, that the rate of the reaction in Equation (1) *rose* steadily throughout the course of the reaction (Figure 1). A

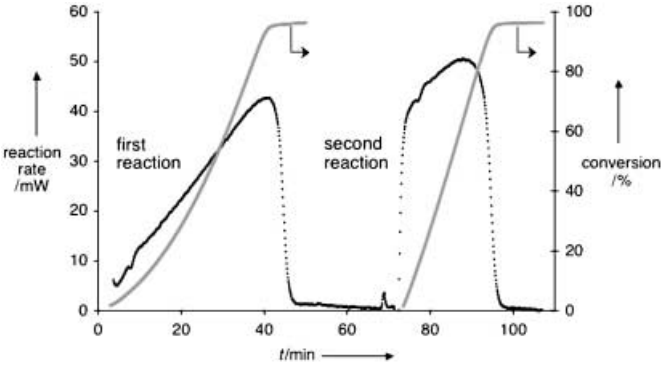


Figure 1. Reaction rate (filled black circles, corresponding to the left axis) and percent conversion (shaded grey line, corresponding to the right axis) versus time for a one-pot, two-consecutive-reaction sequence of the reaction shown in Equation (1) ($CHCl_3$ solvent, 278 K). Initial concentrations of aldehyde **1** and L-proline **4** were 2.07 and 0.07 M, respectively. First reaction: 0.26 M PhNO; second reaction: 0.24 M PhNO.

plot of conversion versus time accordingly showed the hyperbolic shape indicative of an accelerating reaction rate. This behavior suggests a process whereby the catalyst is improving over time, as in autocatalytic or autoinductive reactions, in which the reaction product either is itself a catalyst or promotes the formation of a more effective catalyst. Addition of the reaction product to fresh reagents gave no discernible heat flow signal, indicating that the effect is not due simply to an autocatalytic reaction. However, as shown in Figure 1, when a second dose of reagents was added to the crude reaction mixture containing the original proline catalyst and the product of the first reaction, the initial rate at the outset of this second reaction was as high as that at the end of the first. These experiments indicate that the rising rate is not due to substrate inhibition and suggest that the reaction is mediated by a proline-product adduct that forms over the course of the reaction and serves as an improved catalyst for the reaction. Enantioselective autoinductive reactions have been reported previously,[14,15] including the report by Danda et al.[14] of an organocatalytic hydrocyanation of a substituted benzaldehyde.

Amplification of the enantiomeric excess of the product is a key feature of a chemical rationalization of the evolution of biological homochirality. Considerable discussion has ensued over the past several years about whether proline-catalyzed reactions exhibit such nonlinear effects, since the Hajos–Parrish reaction was cited in the context of Kagan's mathematical models for nonlinear effects.[16] The more recent

observation by List and co-workers of a strictly linear relationship between the catalyst and the *ee* value of the product in both inter- and intramolecular aldol transformations,[17] however, has generally been taken to infer that amino acid catalysis is unlikely to be involved in processes resulting in amplification of enantiomeric excess.[18] We were intrigued to find, therefore, that when the reaction shown in Equation (1) was carried out with non-enantiopure proline, the enantiomeric excess of the product was *higher* than that expected for a linear relationship (Figure 2) and that enantiomeric excess *rose* over the course of the reaction (Figure 3).[19] Rate acceleration and continuous improvement of enantiomeric excess are requisite characteristics for chemical models of the evolution of homochirality from precursors of low optical activity.

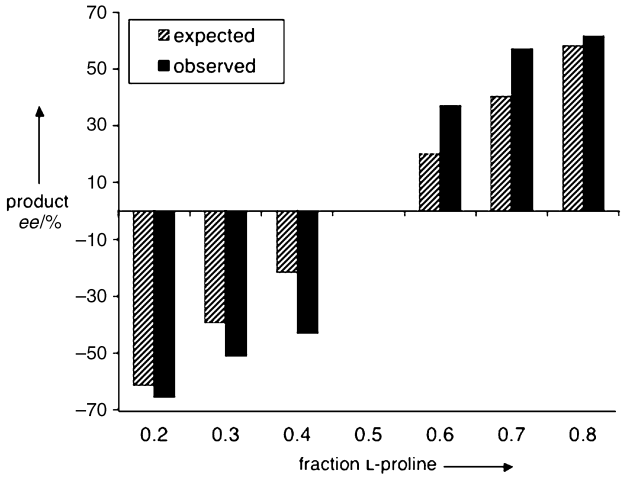


Figure 2. Final enantiomeric excess of the product as a function of the fraction of L-proline in the reaction shown in Equation (1) carried out using mixtures of D- and L-proline. Initial concentrations of aldehyde **1**, nitrosobenzene **2**, and total (L + D)-proline **4** were 2.07, 0.7, and 0.07 M, respectively ($CHCl_3$ solvent, 278 K). Conversions were greater than 90%.

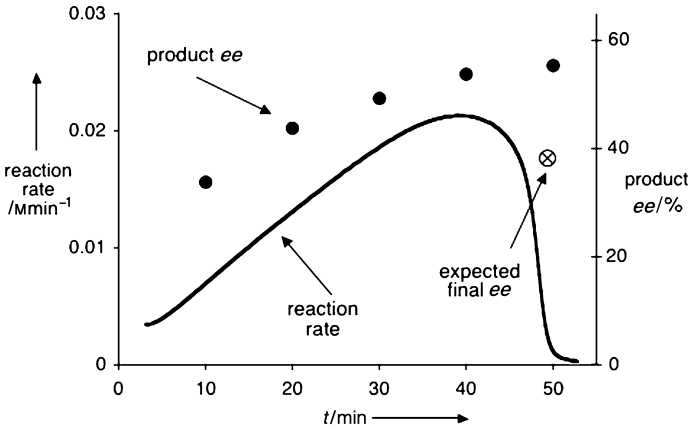
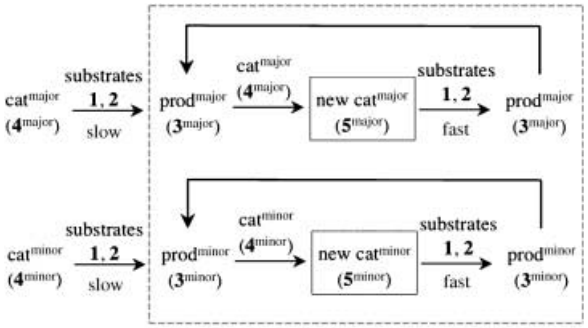


Figure 3. Reaction rate and enantiomeric excess of the product of the reaction of Scheme 1 carried out with a mixture of L- and D-proline with 40% *ee* (L). Reaction conditions: 278 K, total proline concentration (L + D): 0.071 M, nitrosobenzene: 0.70 M, propionaldehyde: 1.95 M.

Kagan and co-workers provided the first explanations of the phenomenon of nonlinear product enantioselectivity,[16] and variations on these models have been proposed for both catalytic[20,21] and autocatalytic reactions.[3] Scheme 1 outlines



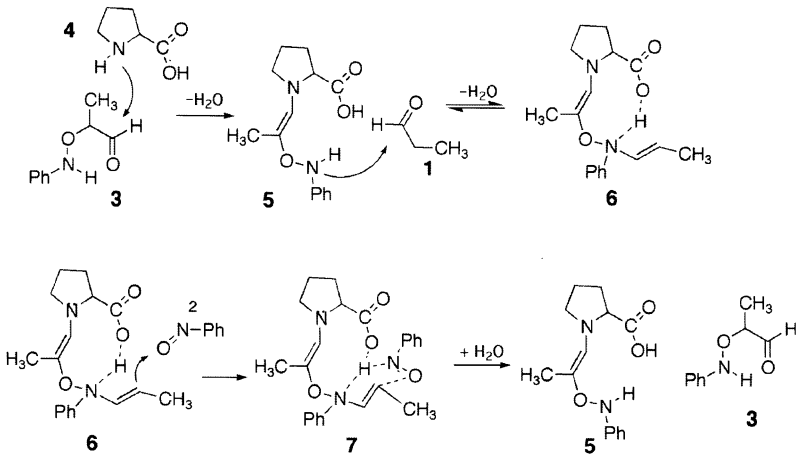
Scheme 1. General mechanism for the product-induced kinetic amplification of enantiomeric excess.

a general mechanism for a product-induced reaction in which both rate and selectivity improve over time for the case in which one enantiomer of the original catalyst **4** is present in excess concentration relative to the other (noted as the "major" and "minor" species, respectively). The first molecules of reaction product **3** are formed through the less-reactive pathways shown outside the dashed lines, after which the reaction is dominated by the manifold shown inside the dashed lines. Within this manifold, product **3** associates reversibly with the original catalyst **4** to form the new catalytic species **5**, which exhibits higher catalytic activity than **4**. As the concentration of **3** increases with increasing turnover, a larger fraction of both hands of the original catalyst **4** is driven toward further formation of **5**, resulting in increased reaction rate. If the mismatched catalyst-product "cross-reaction" rates ($\mathbf{3}^{maj}$–$\mathbf{4}^{min}$ and $\mathbf{4}^{maj}$–$\mathbf{3}^{min}$) are suppressed relative to those of the matched reaction, the enantiomeric excess of the improved catalyst **5** will be higher than that of **4** and will increase over time. Accordingly, the enantiomeric excess of the product **3** will increase over time and will be amplified relative to that of the original catalyst **4**.

The process described in Scheme 1 is kinetic. The enantiomeric excess of the product **3** will rise until the formation of new catalyst **5** has reached equilibrium, after which the *ee* value will slowly erode back to the linear relationship. In agreement with this, we found that reactions carried out with lower concentrations of proline, which take longer to reach completion, exhibited milder ultimate asymmetric amplification. However, it is important to note that such erosion of enantiomeric excess is predicted only for a *closed* system such as that occurring in reaction vials in the laboratory. In an *open* system, in which catalyst and product fluxes can exist across the system boundaries,[22] the chemical propagation mechanism described in Scheme 1 would permit enantiomeric excess to continue to rise. Kinetic amplification of enantiomeric excess as observed in the present studies could be sustained, requiring only that

the process of equilibration between the original catalyst **4** and the product **3** to form the improved catalyst **5** is slower than the **5**-catalyzed formation of product **3** from substrates.

We may now relate the model shown in Scheme 1 to the chemistry of the reaction in Equation (1) to suggest a structure for the improved catalyst **5** and to rationalize its higher activity. The key to the effectiveness of this system lies in the fact that the reaction product **3** is multifunctional; it is both an aldehyde and an amine. Scheme 2 suggests that



Scheme 2. Proposed mechanism for product induction in the reaction shown in [Eq. (1)].

proline **4** may attack the carbonyl group of the reaction product **3** to form the new catalyst **5**. This reaction is virtually irreversible on the reaction timescale, since product racemization was not observed. This species **5** is a special amine bearing an α-oxygen atom with lone pairs of electrons. The "alpha effect"[23] describes the unexpectedly high activity of such a nitrogen nucleophile, thought to be due in part to stabilization of the transition state by the lone pair on the oxygen α to the nucleophilic atom. Thus **5** may be a highly efficient competitor to proline for nucleophilic attack on propionaldehyde, forming a new enamine, **6**. This enamine may be competent to attack PhNO, forming a transition state such as **7** by interaction with the carboxylic acid proton as a Brønsted acid cocatalyst. This leads to the formation of product **3** and regeneration of the improved catalyst **5**.

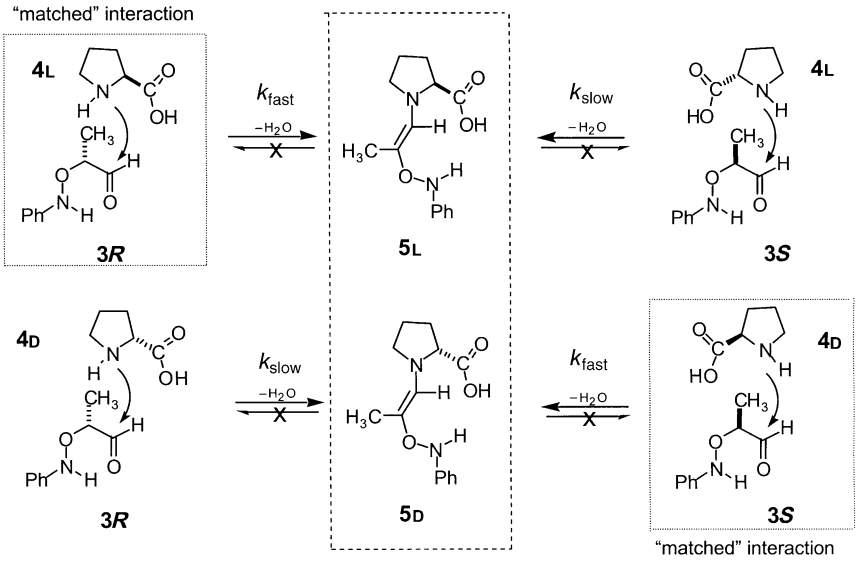
The observed asymmetric amplification is rationalized as a kinetic resolution of the proline in the reaction with product **3** to form **5**, as shown in Scheme 3. The "matched" reactions **4**L–**3*R*** and **4**D–**3*S*** dominate the enantiopure cases. If we assume that the *E* enamine is the stable product from either the "matched" or "mismatched" interaction, we can see that this competitive process alters the enantiomeric excess of species **5** relative to that of the original proline **4**. This case is more complex than in a simple first-order kinetic resolution because the selectivity factor k_{rel} will be a function of the temporally changing product concentration, as shown in Equation (2):

$$\frac{d[\mathbf{4_L}]}{d[\mathbf{4_D}]} = k_{rel}\,\frac{[\mathbf{4_L}]}{[\mathbf{4_D}]} \quad k_{rel} = \frac{k_{fast}[\mathbf{3}\boldsymbol{R}] + k_{slow}[\mathbf{3}\boldsymbol{S}]}{k_{fast}[\mathbf{3}\boldsymbol{S}] + k_{slow}[\mathbf{3}\boldsymbol{R}]} \tag{2}$$

We observed that extended room temperature preequilibration of proline with excess propionaldehyde in $CHCl_3$ produces a clear solution, as compared to the cloudy suspension normally observed after mixing for shorter times or at lower temperatures. The reaction exhibits considerably lower activity following this preequilibration, resulting in less than 10% conversion into **3** after 1 h[13] and giving linear behavior in product enantioselectivity. This suggests that new catalyst **5** cannot form as readily when the concentration of free proline is low, and under such conditions the initial reaction is directed toward the slower proline-catalyzed pathway.

The product **3** may also be capable of condensing with itself, and, in fact, it has been suggested that the products of this reaction exist in oligomeric form.[10] Preliminary ^{1}H NMR studies of the crude reaction product mixture reveal complex spectra.[13] In the case of reactions carried out with non-enantiopure **4**, the formation of higher-order species could further skew the enantiomeric excess of the improved catalyst species **5** relative to **4**, resulting in either enhancement or suppression of the nonlinear effect, depending on the relative rates at which different species react in such condensation reactions.

The nucleophilic nitrogen atom of product **3** might also attack propionaldehyde directly. Since the reaction was found not to be autocatalytic, the enamine thus formed cannot be



Scheme 3. Proposed kinetic resolution in the formation of **5** through the interaction of proline **4** with the reaction product **3**.

competent to react with **2** to form a further molecule of product **3**; the lack of a Brønsted acid function as an intramolecular cocatalyst may compromise its effectiveness.[24] This argument leads naturally to speculation about the potential for truly autocatalytic systems based on similar chemistry. For example, reactions of aldehydic or keto acids with a nitrogen-containing electrophile might yield an amine nucleophile capable of reproducing itself. Investigations along these lines are ongoing in our laboratories.

The experimental observation of an unexpectedly high, accelerating reaction rate and an amplified, temporally increasing enantiomeric excess of product in the proline-mediated aminoxylation of aldehydes is consistent with a mechanistic model for a selectivity-enhancing autoinductive process as given in Schemes 1–3. This represents the first example of a purely organic reaction exhibiting characteristics that are key to a chemical rationalization of the evolution of biological homochirality. A full kinetic model of these experimental results will be published separately.

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