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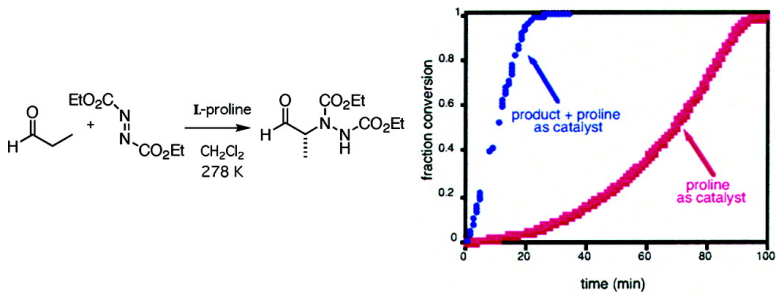

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In Situ Catalyst Improvement in the Proline-Mediated α-Amination of Aldehydes

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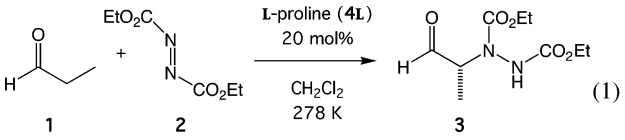
Since the discovery of the proline-catalyzed Robinson annulations in the 1970s[1] and the first intermolecular aldol reaction of List et al.[2] in 2000, metal-free catalytic methodologies for enantioselective formation of carbon−carbon and carbon−heteroatom bonds have expanded widely.[3] One feature that limits practical exploitation of proline catalysis, however, is the low efficiency of these transformations, with aldol reactions often requiring reaction times on the order of days to achieve a few turnovers.[4−6] Recent reports of carbon−heteroatom bond-forming reactions such as α-amination[7] and α-aminoxylation[8] are therefore mechanistically intriguing beyond their inherent synthetic utility because they are completed in high yield with turnover frequencies more than 2 orders of magnitude higher than analogous aldol reactions.

We recently addressed the subject of reaction rate in the α-aminoxylation of aldehydes via in situ monitoring of reaction progress as a function of time.[9] We report here the results of kinetic investigations of the α-amination of aldehydes (eq 1) revealing that, like the aminoxylation, this reaction exhibits autoinductive rate behavior and amplification of product ee. Further experiments highlight the role of product in the development of a highly efficient reaction process and offer suggestions for the design of catalysts of improved efficiency for such transformations. The unusual characteristics exhibited by these reactions also implicate amino acid catalysis in a rationalization of the origin of biological homochirality.



The reaction shown in eq 1 was carried out in a reaction microcalorimeter (Omnical) by injecting either **1** or **2** into a thermally equilibrated solution containing all other components.[10] Figure 1a reveals curvature in the temporal conversion profile that is characteristic of an accelerating rate. It was confirmed that the product **3** does not catalyze the reaction in the absence of proline. Autoinductive processes, in which the reaction product interacts with the original catalyst to form a more active catalyst, exhibit rate behavior such as that observed in Figure 1a.

To explore the influence of the reaction product on rate, experiments were carried out in which the isolated product, **3**, was added to the reaction. When **3** was simply mixed in a 1:1 ratio with L-proline at 278 K for 1 h prior to introduction of reactants, the reaction of eq 1 was notably faster than without pre-added product (Method A, Figure 1b). When a 1:1 mixture of proline and **3** was mixed in CH_2Cl_2 for 14 h in the presence of molecular sieves, filtered, and then used as a catalyst in the reaction of eq 1, the reaction rate was significantly higher than in the absence of added product (Method B, Figure 1c−f), with complete conversion being achieved in the time that the proline-catalyzed reaction

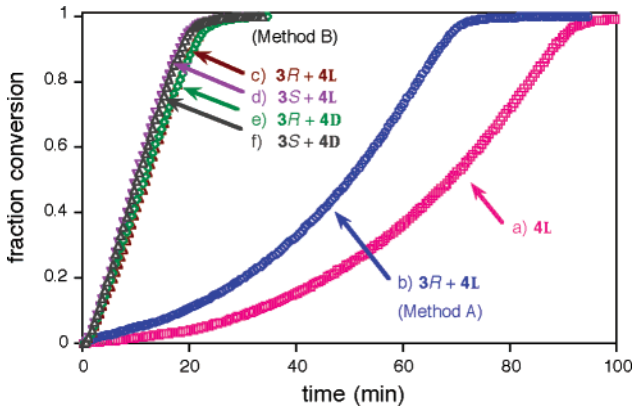


Figure 1. Fraction conversion vs time for the reactions in eq 1 carried out at 278 K with 0.60 M **2**, 2 equiv **1**, 20 mol % **4** used alone or mixed in a 1:1 ratio with product **3** using Method A (mixing for 1 h at 278 K) or Method B (mixing 14 h at 298 K with 4A molecular sieves then filtered. (a) **4** used alone. (b) Method A, **3***R* + **4**L. (c) Method B, **3***R* + **4**L. (d) Method B, **3***S* + **4**L. (e) Method B, **3***R* + **4**D. (f) Method B, **3***S* + **4**D. See Table 1.

Table 1. Enantiomeric Excess of Added Product **3** and Newly Formed Product **3** in Reactions as in Figure 1

proline 4D or 4L	% ee of added product **3**[a]	% ee of added **3** after Method B[c] pretreatment	ee of newly formed reaction product **3**	kinetic profile
4L	none	−	93 (*R*)	figure 1a
4L	93 (*R*)	n/a[b]	92 (*R*)	figure 1b
4L	93 (*R*)	1 (*R*)[c]	90 (*R*)	figure 1c
4L	93 (*S*)	6 (*S*)[c]	92 (*R*)	figure 1d
4D	93 (*R*)	1 (*R*)[c]	92 (*S*)	figure 1e
4D	93 (*S*)	3 (*S*)[c]	89 (*S*)	figure 1f

[a] Product isolated from **3**-proline mixture as the N-amino oxazolidinone after reduction and workup. [b] Method A: isolated reaction product **3** mixed with proline (1:1) in CH_2Cl_2 at 278 K for 1 h prior to introduction of reactants. [c] Method B: isolated reaction product mixed with proline (1:1) in CH_2Cl_2 at 298 K in the presence of molecular sieves for 14 h and then filtered prior to introduction of reactants.

reaches only 10% conversion. The observed rate enhancement was independent of both the enantiomer of **3** added and the enantiomer of proline employed.

While erosion of product ee has been noted in other reports of the α-amination of aldehydes,[7] we observed no decrease in the ee of **3** under standard reaction conditions at 278 K;[11] nor did the ee of **3** erode after refluxing in $CHCl_3$ for 1 h in the absence of proline. Racemization of **3** was noted, however, after extended ambient temperature treatment of **3** in the presence of proline and molecular sieves (Table 1) or after refluxing of **3** with proline in $CHCl_3$. Interestingly, Table 1 also shows that reactions carried out using catalysts modified by addition of **3***R* or **3***S* were directed by the stereochemistry of proline and not by that of the added product.

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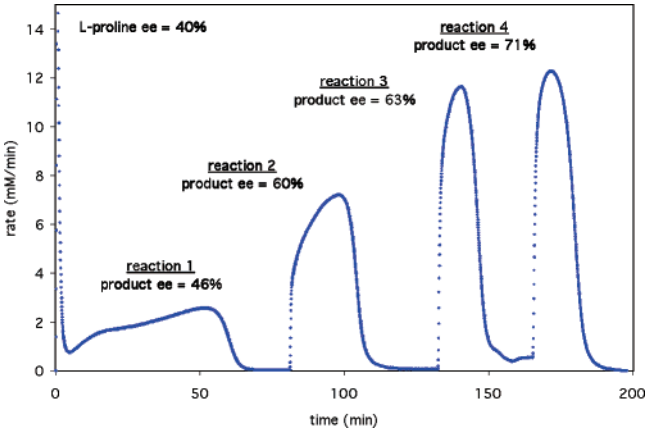
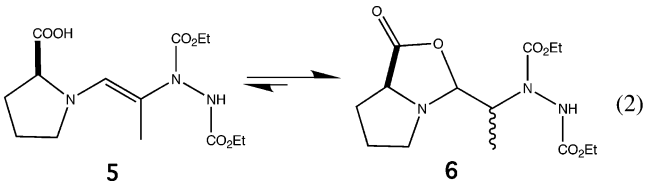


Figure 2. Reaction rate vs time for a one-pot, consecutive series of reactions of eq 1. carried out by adding fresh aliquots of **2** (0.41−0.46 mmol) to the reaction vial containing an excess of **1** (5.25 mmol, initial concentration 2.3 M), **4**L, (0.12 M, 40% ee) and the reaction product from each previous reaction.

Assignments of the ^{1}H and ^{13}C NMR spectra of the product−proline mixture in CD_2Cl_2 were assisted by H−H COSY, HMQC, and HMBC experiments and implicate formation of the oxazolidinone species **6**, ruling out a significant equilibrium concentration for the enamine **5** (see Supporting Information).[13] Mass spectroscopy showed an MH^+ peak for product **3** at mass 233, along with a peak at mass 286, consistent with the formation of **6** representing MH^+ minus CO_2.[12] List has suggested that under aldol reaction conditions oxazolidinones of ketones are preferentially formed in parasitic equilibria with their corresponding enamines, which are thought to be aldol reaction intermediates.[3c,13]



(2)

5 **6**

The concept of improved catalytic efficiency arising from the interaction of product **3** with proline suggests that species **6** may improve the efficiency of other proline-mediated transformations. Indeed, both the aminoxylation of propionaldehyde with nitrosobenzene and the direct aldol reaction of acetone and 2-chlorobenzaldehyde exhibit enhancements in reaction rate in the presence of this modified catalyst formed from proline and the amination reaction product **3** (see Supporting Information).[14]

The reaction of eq 1 carried out using mixtures of D- and L-proline showed that the reaction exhibited asymmetric amplification in product ee similar to the results obtained for the aminoxylation of **1** (see Supporting Information). Consecutive reactions carried out with a catalyst of 40% ee L-proline exhibited increasing rate and increasingly amplified product enantiomeric excess (Figure 2).

The nonlinear effect is consistent with a kinetic resolution of proline in the autoinductive process, similar to that invoked in the aminoxylation reaction in ref 9. In that case, the rate enhancement was attributed to the higher nucleophilicity of the analogous product−proline species compared to proline, but it is not clear that a similar rationale can be invoked in the present case. If not the active catalyst itself, species **6** may help to facilitate introduction of an increased concentration of an active catalytic species into the cycle.

The proposal that the efficiency of proline, the "universal asymmetric catalyst",[3b] can be improved by such modifications suggests potential design strategies that ultimately may yield new, highly efficient proline-based catalysis viable for practical exploitation. In addition, the observed features of an accelerating reaction rate coupled with amplification of enantiomeric excess provide the necessary and sufficient conditions for a chemical rationalization of the origin of biological homochirality.[15] Amino acids have recently been suggested as catalysts in molecular evolution from prebiotic building blocks;[16] our work demonstrates a means for achieving a critical component of a chemical rationalization of the origin of life.

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Supporting Information Available: Experimental procedures, description of NMR correlation experiments, plot conversion vs time for aminoxylation and aldol reactions using modified catalyst, and plot of product ee vs catalyst ee. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Under typical low-temperature reaction conditions, decomposition of **5** back to proline and product **3** must be slow, since racemization of **3** is not observed at 278 K on the time scale of the reaction.
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