ORGANIC
LETTERS

2011
Vol. 13, No. 16
4300–4303

Kinetic Profiling of Prolinate-Catalyzed α-Amination of Aldehydes

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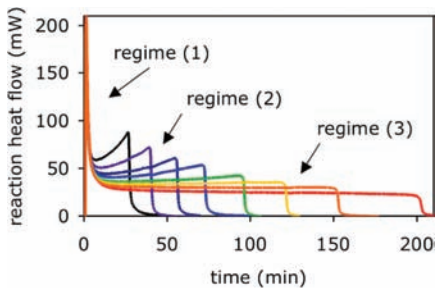
Received June 17, 2011



Deconvolution of the role of off-cycle species from the desired catalytic cycle leads to an optimized protocol for the prolinate-catalyzed amination of aldehydes. The scope of complex reaction networks will be greatly broadened by understanding ancillary rate processes that influence the productive catalytic pathway.

Catalyst–substrate interactions that occur off the productive pathway form what have been termed “parasitic species,”[1] although recent work has suggested that the role of such intermediates can be more complex and not exclusively deleterious to the active catalytic cycle.[2] When the catalyst is removed irreversibly from the cycle via such interactions, the result can be sluggish rates and low yields, as has been shown for proline-catalyzed aldol reactions.[3] Alternatively, a reversible off-cycle interaction may in fact protect the system from irreversible deactivation, as has been shown for Pd-catalyzed Heck[4a] and amination[4b] reactions. Off-cycle reservoirs of catalytic intermediates may be common in cases where the catalyst is capable of reacting directly with more than one of the substrates, presenting a potential complication when the sequence of reactivity is critical to the outcome, such as in cascade reactions. The interplay between key species on and off the catalytic cycle may result in unexpected reactivity patterns, and therefore the scope of complex reaction networks will be greatly broadened by understanding ancillary rate processes that influence the productive catalytic pathway.

We recently reported an intriguing reversal in product enantioselectivity in the proline-mediated α-amination of aldehydes (Scheme 1) when the reaction is carried out in the presence of a catalytic amount of organic base or with prolinate salts.[5] In addition to the reversal in enantioselectivity, we observed an unusual and complex kinetic profile that could not be rationalized by simple consideration of the generally accepted catalytic cycle. We report here further detailed studies that implicate the formation of off-cycle reservoir species, and we demonstrate how deconvolution of productive and unproductive reaction processes can lead to the design of a significantly more efficient reaction protocol.

Detailed kinetic study of the reaction of Scheme 1 catalyzed by **4b** reveals the curious behavior shown in Figure 1. The reaction exhibits three distinctly different temporal kinetic profiles, including (1) an initial regime of high but

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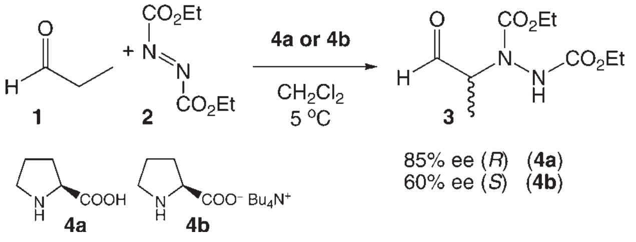
10.1021/ol201639z

Scheme 1. Proline or Prolinate Catalyzed Amination

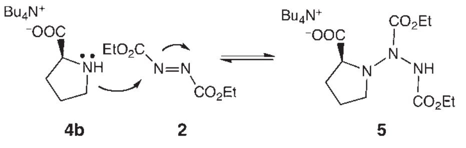


rapidly decreasing rate; (2) a regime of temporally increasing rate; and (3) a regime where rate does not change with time. These studies using reaction calorimetry have been confirmed by FTIR spectroscopic monitoring of the reaction.[6] All reactions showed the reversal of product enantioselectivity for **4b** compared to **4a** as we reported previously.

Figure 1 shows that the initial high rate regime prevails for approximately two turnovers before the rate rapidly decays by a factor of 4. For reactions starting with higher concentrations of **2**, this regime gives way to an extended period of zero-order kinetics lasting until full consumption of the limiting substrate, at which point the rate returns abruptly to zero. Reactions with lower initial [**2**] exhibit a kinetic regime where rate *increases* with time, even as substrate concentration is depleted, again abruptly decaying to zero upon full consumption of substrate **2**. At intermediate initial concentrations of **2**, all three kinetic regimes are apparent in a single experiment.

Figure 2 extracts data from the experiments in Figure 1 to construct conventional kinetic plots where the rate dependence of each substrate is evaluated at a constant value of the other. These plots suggest that the overall zero-order dependence observed in the reaction progress curves in Figure 1 represents a balance between a positive order in [**1**] and an apparent *negative* order in [**2**].

We found that a severe suppression of the amination rate occurs upon premixing the catalyst **4b** with **2**, and increased mixing time correlates with increased rate suppression. NMR, FTIR, and MS-ESI studies implicate formation of a triazane complex **5** from a Michael-type addition of the prolinate to **2** (eq 1).[6] Precedent for such reactions dates back more than half a century.[7] Although we were unable to isolate **5**, addition of **1** and **2** to the solution containing the species we identify as **5** demonstrated its competence as a (pre)catalyst to form product **3**, providing support for the reversibility of the reaction shown in eq 1. Such a species was not observed to form between **2** and proline.



(1)

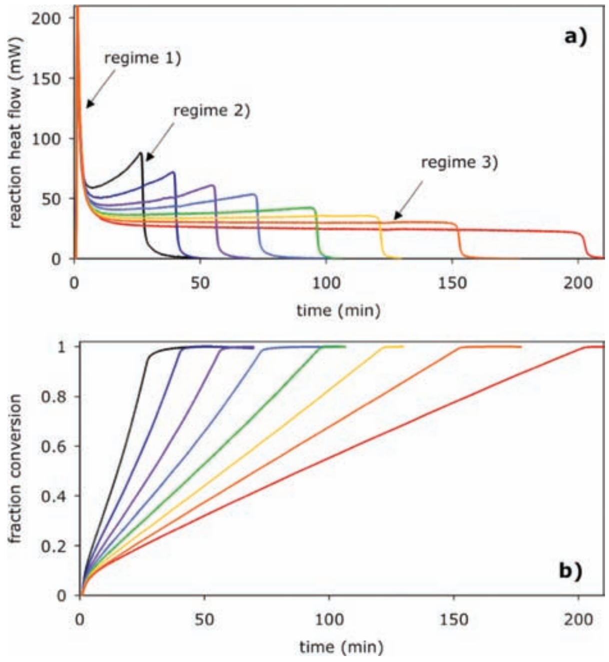


Figure 1. Reaction progress as a function of time monitored by reaction calorimetry, showing reaction rate as heat flow (top) and converted to fraction conversion to product (bottom) for the reaction of Scheme 1. Reaction carried out at 5 °C in $CHCl_3$ using 0.035 M catalyst **4b** with initial concentrations [**1**] = 1.5 M and $[\mathbf{2}]_0$ increasing from left to right: 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, and 1.1 M. Product enantioselectivity is 50−56% ee (*S*).

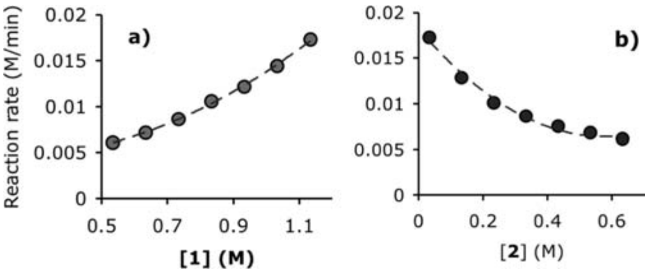


Figure 2. Reaction rate vs concentration from Regime 3 of the series of reactions of Figure 1; (a) dependence of rate on [**1**] with [**2**] constant at 0.03 M; (b) dependence of rate on [**2**] with [**1**] constant at 1.13 M.

Further support for the suggestion of **5** as an off-cycle reservoir species comes from recent work by Mayr, who studied in detail the formation and reactivity of similar triazane species from azodicarboxylates and amines.[8] They isolated the *i*Pr and *t*Bu triazanes formed from the corresponding azodicarboxylates and pyrrolidine but reported no conversion for the R = Et form. Although we were

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[6] See Supporting Information for details.

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unable to isolate the product of the reaction between pyrrolidine and **2**, monitoring by NMR showed quantitative conversion to a species identified as the Et-triazane, by comparison to spectra of the isolated *i*Pr-triazane.[6] Previous work has shown that while *i*Pr and *t*Bu triazanes are isolable, the Et and Bn forms are prone to decomposition.[7c,d] The relative reactivities of the azodicarboxylates toward amines do, however, appear to follow their relative reactivity toward enamines and phosphines.[9]

These off-cycle processes may help to rationalize the three distinct rate regimes observed in this reaction. The intrinsic reaction kinetics of the cycle are manifested in the high initial rate. The formation of **5** is implicated in the rapid decrease in this initial rate, which occurs as a large fraction of the active catalyst is rapidly siphoned away from the productive catalytic cycle. The stability of **5** rationalizes the anomalous negative reaction order in [**2**] shown in Figure 2, because the concentration of **4b** within the catalytic cycle decreases with increasing [**2**]. The rate acceleration observed at the end of the reaction, where conditions of low [**2**] and high [**1**] prevail, occurs as a larger fraction of **4b** is released from the off-cycle reservoir and becomes available to the cycle. Similar anomalous kinetics have been observed in Pd-catalyzed amination reactions due to an off-cycle reservoir.[4b]

Kinetic simulations reveal that all of the features of the unusual kinetic profiles shown in Figure 1 may be accurately reproduced with the simple set of elementary steps given in eqs 2–4, containing the equilibrium constant, K_{eq}, for reversible formation of **5**, and the rate constant for enamine formation, $k_{r.d.s.}$, as the only adjustable parameters (Figure 3). The simulation demonstrates the buildup of **5** early in the reaction, predicting that as much as 80% of the catalyst **4b** is siphoned off the cycle in the form of species **5** under conditions of high [**2**] (Figure 4). Throughout the course of the reaction, **5** remains the dominant intermediate.

$$\mathbf{2} + \mathbf{4b} \overset{K_{eq}}{\rightleftarrows} \mathbf{5} \tag{2}$$

$$\mathbf{1} + \mathbf{4b} \xrightarrow{K_{r.d.s.}} \text{enamine} + H_2O \tag{3}$$

$$\text{enamine} + \mathbf{2} + H_2O \rightarrow \mathbf{3} + \mathbf{4b} \tag{4}$$

The simulations confirm previous findings that the rate-determining step within the cycle is formation of the enamine.[10] The intrinsic reaction is first-order in [**1**], which participates in the rate-determining step, and zero-order in [**2**], which enters the cycle after the rate-determining step. Thus the deceptively complex experimental rate profiles are revealed to arise from the simple one-step intrinsic kinetics of the catalytic cycle coupled with an off-cycle reservoir equilibrium.

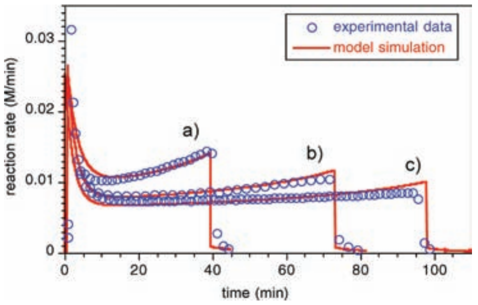

Figure 3. Comparison of experimental (open circles) and simulated (solid lines) reaction rate profiles as a function of time for the mechanism of eqs 2–4 using 0.035 M catalyst **4b** and initial concentrations [**1**] = 1.5 M and (a) [**2**] = 0.4 M; (b) [**2**] = 0.7 M; and (c) [**2**] = 0.8 M. Best fit of eqs 2–4 to the data obtained with $K_{-eq} = 42\ M^{-1}$ and $k_{r.d.s.} = 0.5\ M^{-1}$/min; rate constant for the (kinetically not meaningful) product formation step set at an arbitrarily high value ($10^{12}\ M^{-2}$/min). Kinetic modeling carried out using Copasi (**CO**mplex **PA**thway **SI**mulator) v. 4.5.[9]

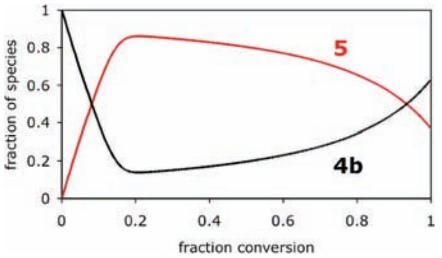

Figure 4. Partitioning of catalytic species over the course of the reaction predicted from the simulation of the reaction under the conditions shown in Figure 3c.

Understanding the role of the off-cycle reservoir leads to suggestions for optimizing the reaction's productivity by seeking ways to minimize the buildup of species **5**. One approach aims to retain the catalyst within the cycle by maintaining high concentrations of **1** and low concentrations of **2**, thereby decreasing the driving force for formation of **5** and preventing its accumulation by allowing more effective competition from the desired amination reaction. An experimental protocol was devised with a slow addition of **2** over time to a vial containing aldehyde **1** and catalyst **4b**. Figure 5 shows that under optimized "semibatch" operation, the rate of addition of **2** is roughly equal to its rate of conversion to product for more than 50% conversion, which prevents a buildup of **2**, and therefore of **5**, in the system. The reaction is complete within 25 min, or a factor of 8 times faster than the standard protocol mixing all reactants simultaneously. A turnover frequency of 1.25 min^{-1} is achieved under these conditions.

A second approach for improved productivity focuses on increasing the free catalyst concentration by catalyzing the decomposition of **5** back to **2** and **4b**. The effect of acid

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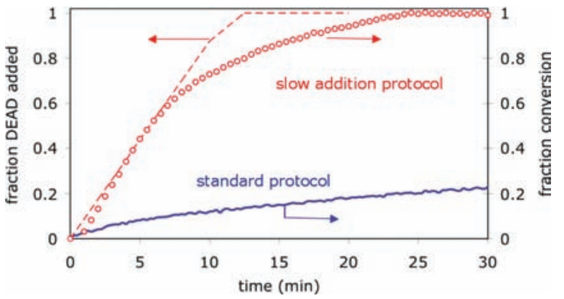
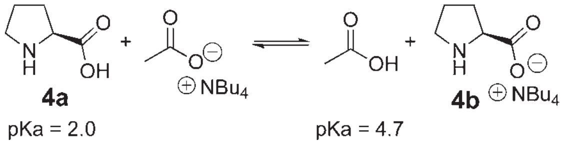


Figure 5. Fraction conversion to product (right axis) for reactions carried out at 5 °C in $CHCl_3$ using 0.035 M catalyst **4b** and [**1**] = 1.5 M; [**2**] = 1.1 M. Open circles: addition of DEAD at 0.035 mL/min for 10.5 min, 0.02 mL/min for 2 min.

on the decomposition of triazanes to azodicarboxylate esters has been reported.[10a] Figure 6 shows that addition of acetic acid to catalyst **4b** results in a much more rapid reaction compared to the standard protocol. The addition of acid serves two purposes: first, acid increases the rate of decomposition of **5**; and second, acid increases the rate of enamine formation, as has previously been demonstrated.[10b] Figure 6 also shows that a rate acceleration identical to that observed with acetic acid added to catalyst **4b** is achieved by combining the N^+Bu_4 salt of acetic acid with proline **4a**, an in situ preparation of the catalyst that effectively streamlines the reaction protocol (eq 5). Such an in situ catalyst preparation protocol may prove to be important both in screening studies and in practical applications because it avoids the need to isolate the hygroscopic prolinate salts. Product enantioselectivity using **4b** in the absence and presence of 1 equiv of acetic acid was 66% (*S*) and 62% (*S*), respectively.



(5)

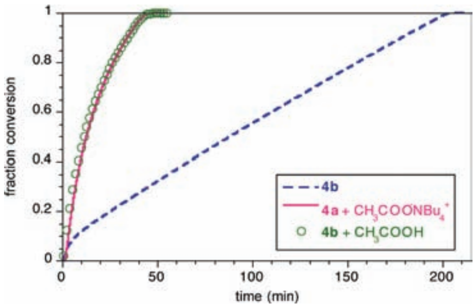


Figure 6. Fraction conversion to product for reactions using 0.035 M catalyst and [**1**] = 1.5 M; [**2**] = 1.1 M. Open circles: **4b** with 1 equiv of acetic acid added with respect to the catalyst; Solid line: **4a** with 1 equiv of the N^+Bu_4 salt of acetic acid added with respect to the catalyst. Dashed line: standard reaction protocol.

In summary, an optimized reaction protocol that increases productivity by 8-fold was developed through deconvolution of the role of off-cycle species from the desired catalytic cycle for the prolinate-catalyzed amination of aldehydes. Proline may be converted to prolinate by simple in situ acid–base manipulations, with concomitant reversal in the sense of product stereochemistry. The development of efficient and selective reaction protocols based on this mechanistic understanding will enhance the application of these reactions in complex cascade and multicomponent reaction networks.

Acknowledgment. Funding from the EPSRC and The Scripps Research Institute and preliminary kinetic studies by Dr. Antonio Moran (IC), and helpful discussions with Matthew Hughes, are gratefully acknowledged.

Supporting Information Available. General experimental procedures and details of the kinetic measurements. This material is available free of charge via the Internet at http://pubs.acs.org.