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Mechanistic Rationalization of Organocatalyzed Conjugate Addition of Linear Aldehydes to Nitro-olefins

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Supporting Information

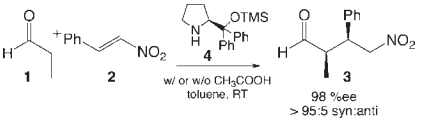
ABSTRACT: Kinetic studies of the conjugate addition of propanal to nitrostyrene catalyzed by diarylprolinol ethers reveal that formation of the product iminium species is rate-determining and is promoted by both the reaction product and acid additives. The beneficial role of a dominant cyclobutane intermediate in maintaining high stereoselectivity is highlighted. This mechanistic understanding led to the design of highly productive reaction protocols.

Stereoselective organocatalyzed conjugate addition has become a benchmark reaction for assessing the performance of new catalysts and in the development of cascade reaction sequences for the synthesis of complex molecules from simple building blocks.[1] The reaction of preformed enamines in stoichiometric Michael additions to nitro-oelfins was studied exhaustively by Seebach[2] in the 1980s, and that work inspired the development of amine-catalyzed versions of stereoselective conjugate addition (Scheme 1). Hayashi reported the Michael addition of aldehydes to nitroalkenes catalyzed by diarylprolinol ethers such as **4** with high enantio- and diastereoselectivity and good substrate scope.[3,4] Since then a number of reports have appeared of stereoselective conjugate additions using a variety of catalysts and substrates.[5,6] The mechanism of the catalytic reaction has not been well-studied, and most groups have relied on analogy to the stoichiometric reactions and on information gained from other examples of enamine catalysis, in particular the proline-mediated aldol reaction, to design organocatalyzed conjugate addition reactions. For example, acid additives are widely reported to influence rate and diastereoselectivity, being suggested variously to enhance the enamine formation step or the product iminium hydrolysis.

We report here detailed kinetic and structural studies revealing several novel mechanistic features of the conjugate addition reaction catalyzed by diarylprolinol ethers shown in Scheme 1. Clarification of the rate-determining step, the catalyst resting state, and the role of acid in the cycle allows us to develop one of the most efficient conjugate addition reactions reported to date. The beneficial role of an apparently "parasitic" catalytic intermediate in maintaining high stereoselectivity is revealed.

Our initial investigations of the reaction in Scheme 1 monitored by reaction calorimetry[7] revealed the unusual kinetic behavior shown in Figure 1 (presented as reaction heat flow vs time, where heat flow is directly proportional to reaction rate). The reaction commences with a rapid rate spike (Figure 1, left inset), corresponding closely to one turnover of the catalytic cycle.[7] This initial rate

Scheme 1. Conjugate Addition Catalyzed by Diarylprolinol Ethers



regime is followed by a much slower but accelerating rate (Figure 1, right inset). This behavior is reminiscent of the product-induced rates we observed in proline-catalyzed aminoxylation and α-amination reactions, where we have shown that the reaction product as well as protic additives can accelerate the rate.[8] Further kinetic experiments by NMR spectroscopy confirm that rate is accelerated by addition of either the reaction product **3** or acetic acid (Figure 2, presented as product concentration vs time). In the absence of additives, the accelerating rate, signified by the sigmoidal shape of the product concentration curves of Figure 2, is unaffected by changes in the initial concentration of either substrate **1** or **2**, indicating that the intrinsic kinetics of the cycle is zero order in both substrate concentrations.

Figure 2 shows that for reactions with added acid or reaction product, temporal conversion profiles are no longer sigmoidal but become linear. The reaction rate is directly proportional to the concentration of added acid up to 1 equiv compared to catalyst **4**, after which it exhibits saturation behavior, as shown in Figure 3. Product enantioselectivity (98% ee) is constant over the course of the reaction and is unaffected by changes in substrate concentrations or by the addition of acid or reaction product.[7] The syn/anti ratio remains constant at >95:5 over the course of the reaction until very high conversion, in both the presence and absence of added acid (Figure 4a). However, this ratio deteriorates when the reaction product remains in the presence of the catalyst after completion of the reaction, equilibrating to 60:40 syn/anti overnight. Acid accelerates this post-reaction erosion of diastereoselectivity (Figure 4b).

The observation of zero-order kinetics in both [**1**] and [**2**] implies that the rate-determining step occurs in the cycle after addition of both substrates and that the resting state of the catalyst contains both substrates. The correlation between the initial spike in reaction heat flow and catalyst concentration suggests an initial rapid buildup to a steady-state catalyst resting state that occupies the major part of the total catalyst concentration. Consideration of the generally accepted mechanism of enamine-based organocatalysis[1] shows that these observations rule out

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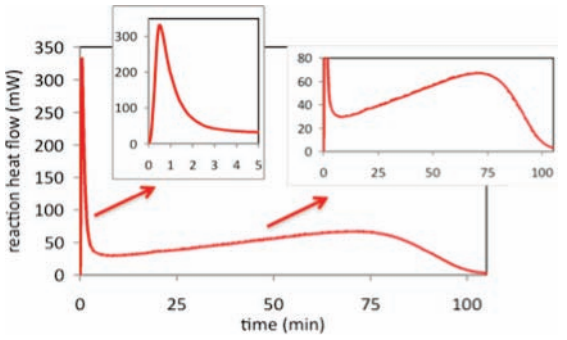


Figure 1. Temporal reaction rate in the reaction in Scheme 1 with initial concentrations $[\mathbf{1}]_0 = 1.7$ M, $[\mathbf{2}]_0 = 1.5$ M, and $[\mathbf{4}] = 0.1$ M monitored by reaction calorimetry, showing an initial spike in rate (left inset) and the subsequent accelerating rate profile (right inset).

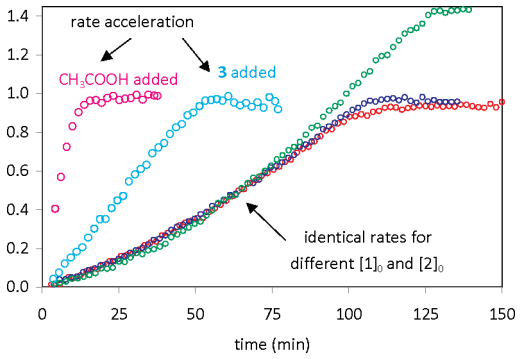


Figure 2. Temporal concentration of product **3** in the reaction in Scheme 1 monitored by ^{1}H NMR spectroscopy. Red circles: $[\mathbf{1}]_0 = 1.2$ M, $[\mathbf{2}]_0 = 1.0$ M. Blue circles: $[\mathbf{1}]_0 = 1.7$ M, $[\mathbf{2}]_0 = 1.0$ M. Green circles: $[\mathbf{1}]_0 = 1.7$ M, $[\mathbf{2}]_0 = 1.5$ M. Turquoise circles: same as red circles, with 0.5 M **3** added. Pink circles: same as red circles, with 0.1 M CH_3COOH added. Catalyst loading is $[\mathbf{4}] = 0.1$ M in all cases.

enamine formation as the rate-determining step but could be consistent with rate-determining hydrolysis of the product iminium species. However, experiments adding water to the reaction show that rate is neither accelerated nor substantially slowed in the presence of water, meaning that hydrolysis to form the product is unlikely to be rate-determining.[7]

We turned to further detailed NMR studies to probe the nature of the resting state of the catalyst. Carrying out the reaction with an excess of catalyst and in the presence of molecular sieves allows us to capture the catalytic species without interference from the cycle turnover. We identified the major species present as the cyclobutane **5** shown in Scheme 2 via 2D NMR experiments (HSQC, HMBC, COSY, and NOESY).[7]

Attempts to isolate **5** were unsuccessful, in agreement with previous work, where isolation of similar cyclobutanes was possible only for those with multiple bulky substituents.[10] However, in situ monitoring of reactions by NMR spectroscopy allowed us to follow the temporal evolution of **5** as well as the free catalyst **4** and a species identified as the product enamine **6**. A minor amount (<5%) of a deactivated catalyst species **7**, formed from conjugate addition of **4** to the nitro-olefin, is also observed.[7] Figure 5 shows these temporal concentration profiles for the reaction in the absence of added acid. Dominance of the cyclobutane intermediate **5** persists until full consumption of the limiting

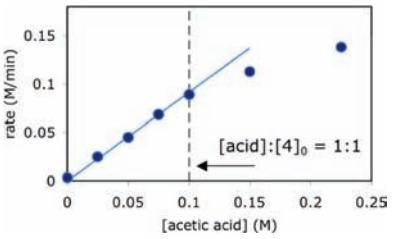


Figure 3. Effect of added acid concentration on reaction rate for the reaction in Scheme 1 with $[\mathbf{1}] = 1.2$ M, $[\mathbf{2}] = 1.0$ M, and $[\mathbf{4}] = 0.1$ M. Rate measured from reaction calorimetric profiles at 20% conversion.

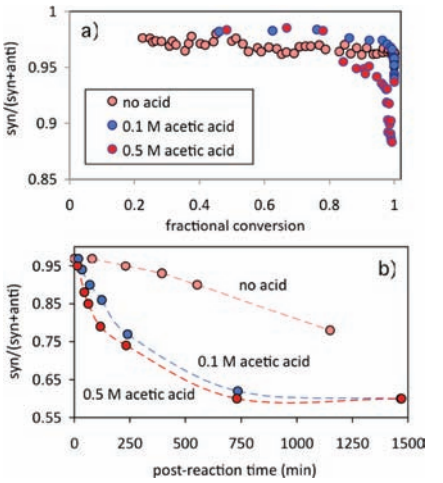
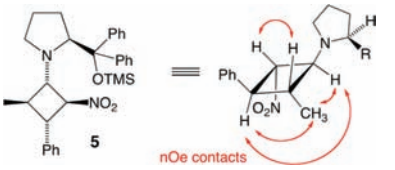


Figure 4. Syn/anti selectivity in the Michael reaction in Scheme 1 under the conditions given in Figure 2 and acetic acid concentrations as shown, as a function of (a) fraction conversion *during* reaction and (b) time *after* reaction completion.

Scheme 2. ^{1}H NOESY Identification of Species 5



reactant, at which time the resting state shifts to the product enamine **6**. Reaction in the presence of acid inverts the ratio of free catalyst **4** to product enamine **6** at the end of the reaction from 1:10 to 10:1.[7] Under acidic conditions **4** is present in protonated form after reaction completion.

With these findings we are able to propose the reaction mechanism shown in Scheme 3. The rapid initial buildup of intermediate **5** as the resting state was observed by in situ reaction calorimetric monitoring, shown in Figure 1, reaching the maximum concentration prior to acquisition of the first NMR spectrum in Figure 5. Cyclobutane **5** may exist as an off-cycle reservoir that sequesters the catalyst under reaction turnover. Alternatively, a route directly from cyclobutane **5** that bypasses **9** might be envisioned.[11] The lower stability of product enamine **6** compared to **5** prevents it from accumulating until after the limiting substrate has been fully consumed and **5** begins to decay, as shown in Figure 5. Added acid enhances the reaction rate by promoting the irreversible protonation step, thus

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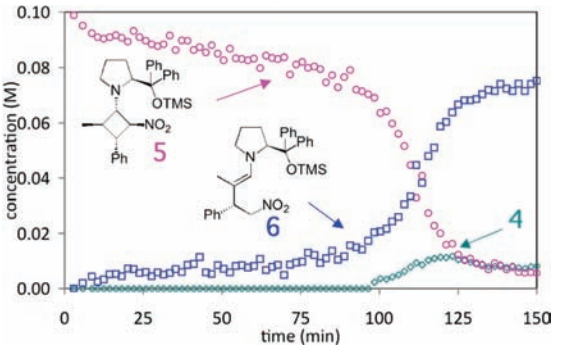
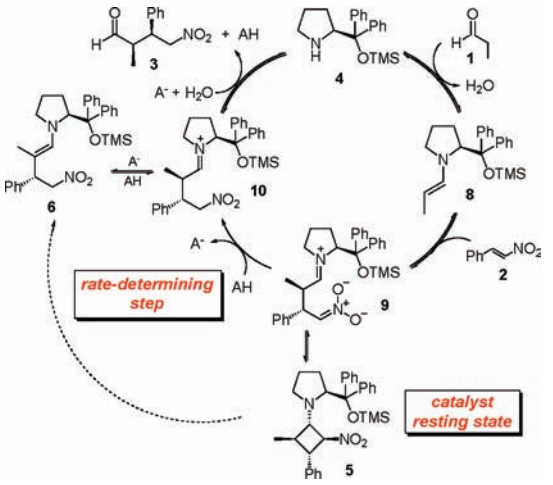


Figure 5. Temporal evolution of catalytic species in the reaction in Scheme 1, monitored by ^{1}H NMR spectroscopy. Data are taken from the reaction with no added acid, shown in red circles in Figure 2, with $[\mathbf{1}]_0$ = 1.2 M, $[\mathbf{2}]_0$ = 1.0 M, and $[\mathbf{4}]_0$ = 0.1 M. **4** is the free catalyst (open green diamonds), **5** is the cyclobutane intermediate (open magenta circles), and **6** is the product enamine (open blue squares).

Scheme 3. Proposed Catalytic Cycle

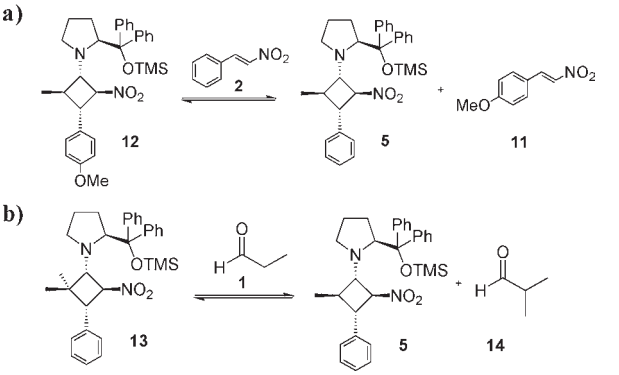


drawing species **5** out of the resting state. In the absence of added acid, the initially slow turnover increases as the temporally increasing concentration of the acidic nitro reaction product promotes its formation, leading to the temporally increasing rate shown in Figures 1 and 2. We found that addition of simple nitroalkanes also accelerates the rate, while added NEt_3 decreases the rate.[7]

Cyclic species similar to **5** and cyclic nitronates have been reported in stoichiometric reactions with enamines.[10,12,13] Seebach and co-workers carried out extensive studies of stoichiometric additions of prolinol methyl ether-derived enamines to nitro-olefins and alkylidene malonates, including detailed stereochemical investigations.[2] Michael addition of the enamine to the nitroalkene results in a zwitterionic species that may undergo either *O*-alkylation or, as in the present case with nitrostyrene, *C*-alkylation to form the cyclobutane **5**.[10b]

To our knowledge, the only published proposal of a cyclobutane species such as **5** in a *catalytic* conjugate addition system was made by Jacobsen and co-workers in reactions of α,α-disubstituted aldehydes catalyzed by primary amine thiourea catalysts, where a putative cyclobutane species was suggested to form irreversibly off-cycle and was implicated in catalyst deactivation.[14] In the present case for catalyst **4** and linear aldehydes, however, the data in Figure 5

Scheme 4. Crossover between Cyclobutane Species: (a) Upon Addition of Nitro-olefin 2 to Cyclobutane 12 To Give 5 and 11 and (b) Upon Addition of Aldehyde 1 during Reaction of 14 and 2, Showing a Shift from 13 to 5[7]



show that cyclobutane **5** converts with ease to the product enamine **6**, even in the absence of added acid, after the limiting substrate is fully reacted. The near closure of a mass balance on catalyst intermediates observed in Figure 5 indicates that irreversible deactivation of the catalyst is minimal in this system.

Confirmation that intermediate **5** is not an irreversible sink for the catalyst but remains reversibly linked to the catalytic cycle is given by several different crossover experiments. NMR studies show that the cyclobutane species **12** formed from *p*-OMe *trans*-nitrostyrene **11** equilibrates with cyclobutane **5** in the presence of **2** (Scheme 4), even as the total concentration of cyclobutane species remains constant.[7] Similarly, upon addition of linear aldehyde **1** to the reaction mixture of disubstituted aldehyde **14** and **2**, a shift from cyclobutane **13** to **5** is observed. Reaction turnover is significantly slower for α,α-disubstituted aldehydes, and hence the appearance of **5** can only be accounted for by reverse reaction of **13**. These results demonstrate not only that cyclobutane formation from catalyst **4** is reversible but also that both enamine formation and addition of enamines to nitro-olefins are reversible steps for systems with catalyst **4**.

These results highlight an important consequence of species **5** acting as the reversibly formed catalyst resting state: all steps within the cycle preceding formation of **5** are equilibrated to accommodate the hold-up in the cycle. Thus, the first irreversible step within the cycle is the protonation of **9** and is, by definition, rate-determining for a cycle under steady-state conditions.[15] This conclusion might be unexpected in light of what is known about other enamine-based reaction mechanisms: for example, in reactions of **1** with electrophiles where no reversible reservoir subsequent to the electrophile addition exists, enamine formation is rate-determining for highly reactive electrophiles such as azodicarboxylates,[8] and both enamine formation and the subsequent electrophile addition are irreversible.

Intermediates that may exist outside—but linked reversibly to—a catalytic cycle have been characterized as "parasitic",[1a] but in the case of this Michael addition, the reservoir species **5** plays a critical role beneficial to stereoselection. The dominance of **5** suppresses erosion of diastereoselectivity during reaction turnover by preventing an accumulation of iminium **10** and therefore of product enamine **6** during reaction. Erosion of diastereoselectivity is a consequence of conditions where the catalyst is not fully sequestered as species **5**, e.g., after reaction turnover is complete, as shown in Figure 5. The unexplained variability in diastereoselectivities that may be noted in

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literature reports[7] for this reaction could in fact be due to a lack of precise control of reaction end point time for sampling, and lower reported values may reflect post-reaction isomerization rather than intrinsic catalyst selectivity.

The dominance and reversibility of species **5** also helps to rationalize the success that the reaction in Scheme 1 using catalyst **4** has enjoyed in applications involving cascade reactions. This reaction was first employed by Enders in an elegant triple organocatalytic (enamine-iminium-enamine) cascade sequence,[16] and it has been featured—always as the *first* cycle—in many subsequent reports of cascade sequences. Our work suggests that the dominance of **5** allows the cycle to proceed without significant competition for the catalyst from the subsequent reactions. For example, we were unable to detect any interaction between **4** and cinnamaldehyde, the substrate for the second reaction in Enders's cascade, in the presence of **5**. As turnover in this first cycle of the cascade nears completion and **5** decays, the potential for erosion of product diastereoselectivity is avoided because the product and catalyst are irreversibly drawn into subsequent cycles. Because this catalytic cycle monopolizes the catalyst fully, however, such conjugate additions must be placed at the beginning of the cascade, as indeed is the case in all reported examples. Our work provides the mechanistic rationale for this empirically derived protocol.

A critical concern for practical application of organocatalytic reactions is productivity. The development of reaction protocols that employ high reagent concentrations (low solvent volumes) and low catalyst loadings is a key challenge. In many enamine-based catalyst/reaction combinations that exhibit positive order substrate kinetics, however, highly concentrated reaction mixtures result in higher rates and a concomitant increase in evolved heat in the early stages of the reaction, rendering such desired process intensification unfeasible. In the present case, we reasoned that the observed zero-order kinetic profiles make operation under highly concentrated conditions practical. Indeed, we demonstrated that the reaction proceeds smoothly in the absence of solvent by dissolving solid **2** into neat **1** (1.4 equiv) with 2.5 mol % catalyst **4** and a 1:1 ratio of **4** and acetic acid, with quantitative yield achieved in 10 min.[7] Lower catalyst loadings have been demonstrated previously in this Michael reaction using **4** as well as other catalysts; for example, Wennemers[6b] obtained high yields using as low as 0.1 mol % of a tripeptide catalyst, but typical reaction conditions employed in that work required 48 h reaction time and used ca. 10 volumes of solvent for each volume of product formed. Our protocol provides an unprecedented example of practical and scaleable process intensification in organocatalysis, derived from mechanistic understanding.

In summary, detailed kinetic and structural analysis allows a comprehensive picture of the mechanism of Michael additions of aldehydes to nitroolefins catalyzed by diarylprolinol ethers, identifying the rate-determining step and the role of acid additives in the cycle. This work reveals the role of a key intermediate in the maintenance of high stereoselectivity. The concept that a seemingly "parasitic" catalytic species could have a beneficial influence on selectivity is novel, and its generality is currently under investigation in our laboratories. This mechanistic understanding allowed design of highly efficient reaction protocols and may inspire further catalyst and reaction design.

■ ASSOCIATED CONTENT

Supporting Information. Experimental details, kinetic studies, and structural identification of catalytic species. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) If this route is competitive with protonation of **9**, this places **5** on the cycle and provides an explanation for the much lower reactivity of α,α-disubstituted aldehydes, for which such a route is unavailable. Experimental data presently available cannot distinguish between these possibilities.

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