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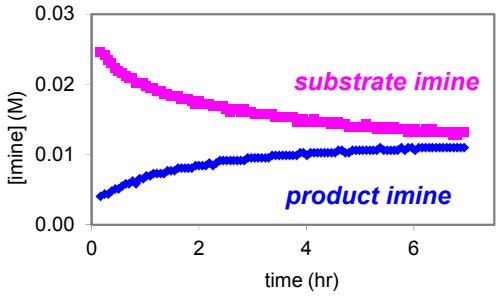

Identification of intermediates in the asymmetric conjugate addition of aldehdyes to nitro-olefins catalyzed by primary amine thioureas add mechanistic insight.

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COMMUNICATION

The Role of Reversibility in the Enantioselective Conjugate Addition of α, α- Disubstituted Aldehydes to Nitro-Olefins Catalyzed by Primary Amine Thioureas

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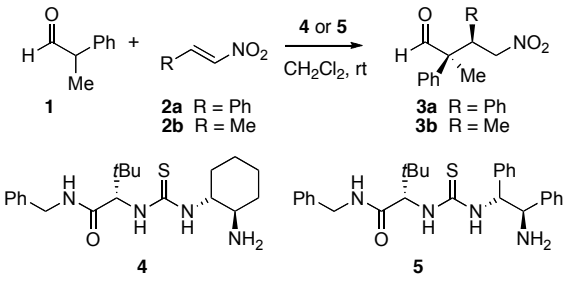
Kinetic and spectroscopic studies probing the conjugate addition of 2−phenylpropanal to nitro-olefins catalyzed by two different primary amine thiourea catalysts reveal the nature of the catalyst resting state and demonstrate that reversibility of the reaction is implicated in cases of low enantio- and diastereoselectivity.

Asymmetric organocatalytic approaches to the synthesis of α,α-disubstituted compounds such as amino acids, aldehydes, and alcohols has received attention in recent years because of the growing importance of quaternary stereocenters in pharmaceuticals.[1] Studies of the factors controlling stereoselectivity in these reactions remain rare. Understanding the establishment of a stereogenic center from enamine intermediates and the question of whether stereogenic integrity is preserved in reaction products that may themselves form enamines are critical issues in the development of such enantioselective organocatalytic reactions. For secondary amine catalysts, we recently demonstrated that kinetic *vs*. thermodynamic control of *E* vs. *Z* enamine formation in reversible enamine reactions is a key consideration in the design of selective catalytic solutions to this challenge.[2]

The successful use of NMR techniques[3] to probe the kinetics and structures of organocatalytic intermediates in our work in reactions catalyzed by secondary amines led us to turn to a similar approach in the study of primary amine thiourea catalysts developed by the groups of Tsogoeva[4] and Jacobsen[5] (Scheme 1). Hydrogen bonding interactionsare key to selectivity for the catalyst systems of the type shown in Scheme 1; these catalysts, which have been reviewed recently,[6,7] are thought to operate via cooperative, bifunctional mechanisms reminiscient of nascent enzymes and thus may offer important clues about the emergence of metabolic selectivity. In addition, these systems differ from secondary amine catalysts because the catalyst-aldehyde interaction should lead to stable imine rather than enamine intermediate species, meaning that interpretation of the role of *E/Z* enamine ratio may need to rely on circumstantial evidence.



Scheme 1. Conjugate addition of α-phenylpropanal to nitro-olefins using primary amine thiourea catalysts.

The reaction of Scheme 1 using catalysts such as **4** and **5** was reported by Jacobsen and coworkers,[5b] demonstrating that primary amine thiourea catalysts provided excellent enantio- and diastereoselectivities for a wide range of substrates in the conjugate addition of nitro-olefins to α,α-disubstituted aldehydes. Interestingly, however, lower selectivities were generally observed using catalyst **4** in that work when *trans*-β-nitrostyrene or substituted nitrostyrenes were employed as the electrophile, compared to aliphatic nitro-olefins. In particular, the reaction of aldehyde **1** with nitrostyrene **2a** only ca. 1:1 *syn:anti* diastereoselectivity and poor enantioselectivity (67% ee *syn*, 3% ee *anti*) using catalyst **4**, compared with ca. 9:1 d.r. and 97% ee in the same reaction using catalyst 5. Nitro-olefins other than **2a** afforded higher selectivities; for example, the reaction of **1** with **2b** using catalyst **4** gave 23:1 *syn:anti* diastereoselectivity and 99% ee (*syn*) These intriguing differences in outcome for different nitro-olefins and different catalysts led us to explore further mechanistic details of these

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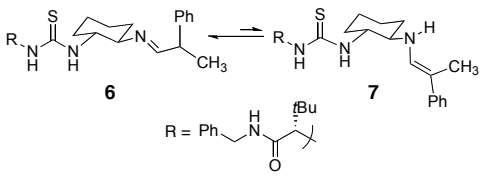
systems. We report here kinetic and spectroscopic findings that shed further light on the mechanism of the conjugate addition reaction of Scheme 1 and the nature of intermediates formed with primary amine urea catalysts. Our work implicates the degree of reversibility of the reaction as an important factor in the determination of selectivity.

Table 1 shows results for the reaction of Scheme 1 using catalysts **4** and **5** with *rac*-**1** and nitro-olefins **2a** and **2b**, confirming the selectivity trends observed in the study of Ref. 3. High ee and d.r. are obtained in all cases except the combination of catalyst **4** and nitro-olefin **2a**. Temporal monitoring of reaction profiles showed that reactions using catalyst **4** were consistently faster than reactions using catalyst **5**, and nitro-olefin **2b** reacted faster than **2a** using either catalyst. Reaction progress kinetic analysis employing "same excess" and "different excess" experimental protocols revealed that the reaction exhibits close to zero order kinetics in the concentration of both the aldehyde and nitro-olefin substrates and that the system exhibits mild catalyst inhibition (see Supporting Information). The observed reaction orders implicate the catalyst resting state as a species lying on the cycle after addition of both substrates to the catalyst. Inhibition suggests that the reaction product may bind reversibly to the catalyst.

Table 1. Results of the reaction of Scheme 1.

entry	catalyst	substrates	conversion at 60 min (%)	%ee (syn)	dr (*syn*:*anti*)
1	**4**	**2a**	26	66	1.2 : 1
2	**4**	**2b**	62	99	> 99 : 1
3	**5**	**2a**	8	99	> 99 : 1
4	**5**	**2b**	27	99	> 99 : 1

Probing the reaction of Scheme 1 by NMR spectroscopy allowed us to observe a number of features that support the kinetic results. Interaction between aldehyde **1** and catalyst **4** produces a species identified as the imine **6** (see Supporting Information). Failure to observe the enamine **7** suggests that equilibration between the two lies strongly towards **6**, as is expected for this primary amine catalyst (eq. 1).



(1)

Addition of nitrostyrene **2a** causes the imine **6** to disappear, shifting towards the buildup of one major and one minor intermediate species that exhibit coupling constants nearly identical to those of *syn*-**3a** and *anti*-**3a**, respectively (see Supporting Information). Quantitative formation of these species was accomplished in low temperature NMR experiments using equimolar amounts of **1**, **2a**, and **4** with molecular sieves added to suppress product hydrolysis from the catalyst. The major intermediate was identified as the product imine *syn*-**8a** by a combination of 2D NMR experiments as shown in Figure 1.[8] The minor species is suggested to be *anti*-**8a**, although its rigorous identification is more difficult. These kinetic and spectroscopic features, including the stability and kinetic viability of intermediates located downstream in the cycle from the stereo-determining addition of electrophile, are consistent with our observations for reactions of linear aldehydes with secondary amine catalysts such as diarylprolinol ethers.[9]

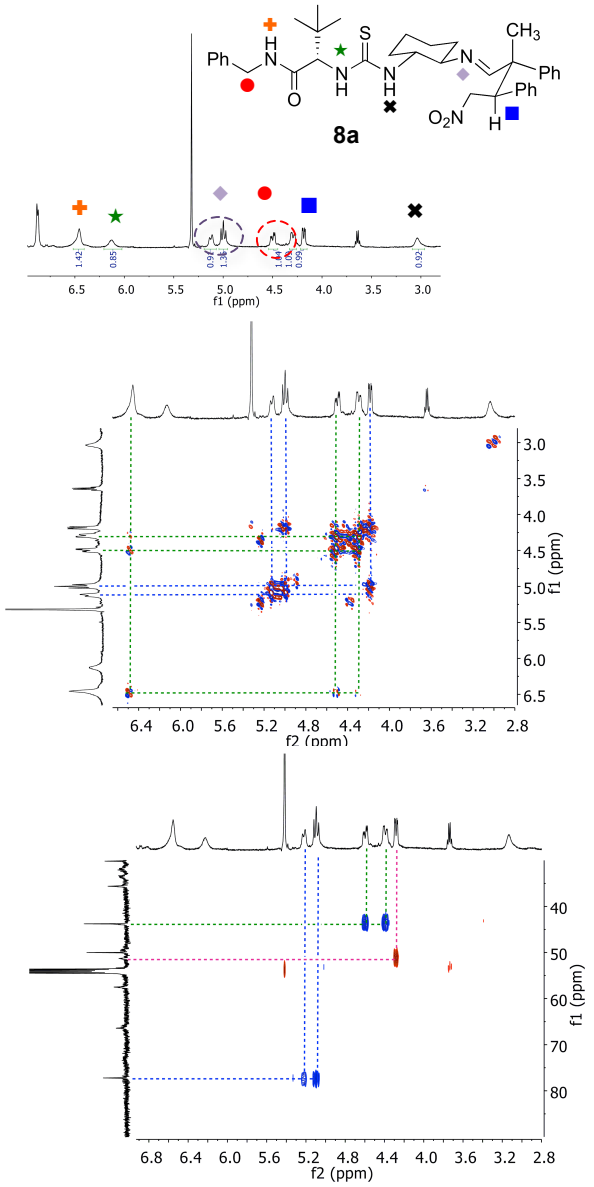


Figure 1. NMR identification of *syn*-8a from reaction of equimolar amounts of **1**, **2a**, and **4** (0.025 M) in CD_2Cl_2 at 0 ºC in the presence of 4Å molecular sieves. Top: ^{1}H-500 MHz spectrum; Middle: ^{1}H-^{1}H-COSY; Bottom:^{1}H-^{13}C HSQC.

If hydrolysis to product **3a** is a reversible process, a decreasing fraction of the free catalyst may be available to re-enter the catalyst cycle as the product imine builds up over the course of the reaction, providing a rationalization for the observed catalyst inhibition. The relative stability of the imine species formed from the aldehyde and the product, **6** and **8a**, respectively, was further probed by mixing catalyst **4** with equimolar concentrations of substrate aldehyde **1** and product aldehyde *syn*-**3a** (eq (2)). Figure 2 shows that immediately upon mixing with catalyst **4**, species **6** forms preferentially in a 6:1 ratio over **8a** and that over time the two species equilibrate to a nearly equal ratio. This implies that under reaction conditions, the

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relative proportion of the catalyst present as **8a** will increase over time as aldehyde **1** is depleted and product **3a** is formed.

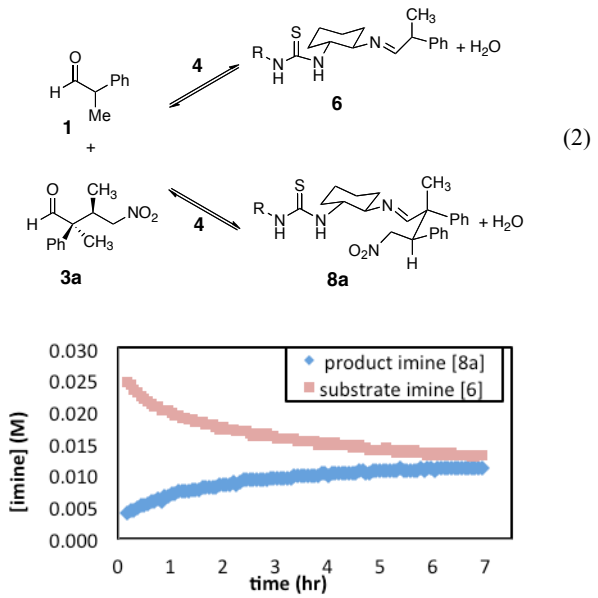
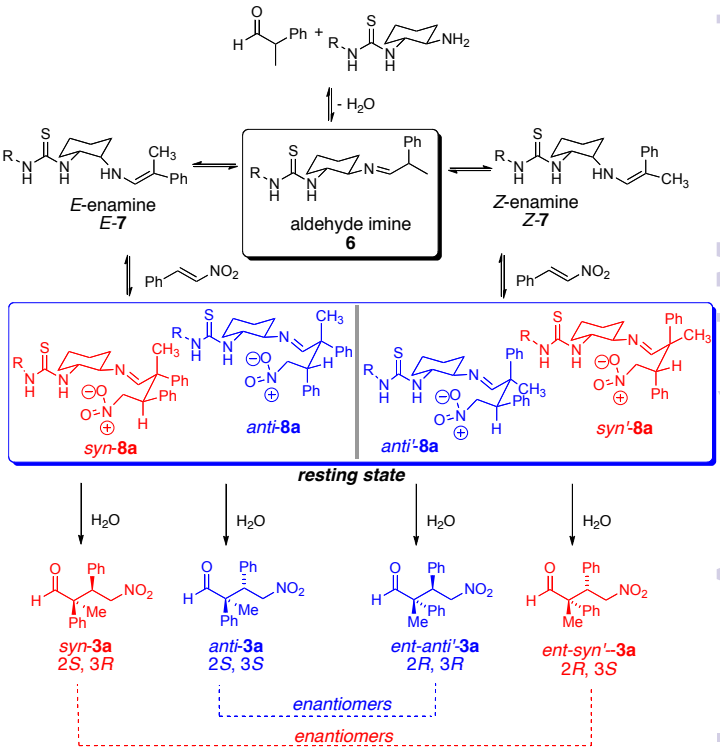


Figure 2. Temporal evolution of catalyst imine species **6** and **8a** resulting from competitive reaction of equimolar **1** and **3a** with catalyst **4** monitored by ^{1}H-NMR spectroscopy.

These results support a proposal that product imine **8a** is the resting state in the catalytic cycle shown in Scheme 2. Selectivity in this proposed scheme is determined at two levels: first, at the partitioning between *E*- and *Z* enamines **7** from imine **6**, and second, at the addition of the nitro-olefin to form imines leading to *syn* and *anti* reaction products. An interesting consequence is that while enantiomeric products arise from the first level of selectivity, both *ee* and *d.r.* may be affected by both selection levels. For example, it is theoretically possible for a reaction product of high *ee* to be obtained from poor *E*/*Z* enamine selectivity (e.g., *E*-**7** ≈ *Z*-**7**) coupled with high and inverse *syn/anti* selectivity at the second level (e.g., *syn*-**8a** >> *anti*-**8a** and *syn*'-**8a** << *anti'*-**8a)**. Factors affecting each selection level must be considered in interpreting results in such systems. In addition, the fact that the catalyst resting state lies *after* the first stereogenic bond-forming step suggests that recently raised mechanistic insights concerning the importance of bifurcation of a catalytic network following stable "downstream intermediates" may be a general phenomenon in organocatalysis.[9]

In recent studies of the conjugate addition of nitro-olefins to α,α-disubstituted aldehydes such as **1** using pyrrolidine-based secondary amine catalysts, we reported a selectivity phenomenon we termed "kinetic stereospecificity".[2] The catalyst preferentially forms the *E*-enamine with one enantiomer of aldehyde **1** and the *Z*-enamine from the other aldehyde enantiomer. Racemization of the aldehyde was not observed over the course of the reaction, and *ee* values in the conjugate addition reaction were successfully predicted on the basis of this kinetic stereospecificity between aldehyde enantiomer, aldehyde enamine, product enamine, and product diastereomer. In the current studies using thiourea catalysts, by contrast, complete racemization of **1** occurred in less than 15 minutes after mixing catalyst **4** separately with either *R*-**1** and *S*-**1**. Further, similar selectivity trends are observed in the reaction regardless of whether *rac*-**1**, with *R*-**1**, or *S*-**1** reacts with **2a** (see Supporting Information). This suggests that the selectivity at the first level in this thiourea system depends on the relative thermodynamic stability of *E*-**7** vs. *Z*-**7** and not on any kinetic "memory" related to the aldehyde-catalyst interaction.



Scheme 2. Proposed reaction network for the reaction of Scheme 1 using catalyst **4** and nitro-olefin **2a,** revealing the two levels of selection and the experimentally observed resting state **8a**. Observed intermediates are highlighted in boxes.

Reversibility may also be implicated in the lower selectivities that were observed for the reaction using **2a** and catalyst **4**. Temporal monitoring of selectivity shown in Figure 3 reveals that diastereoselectivity and enantioselectivity are high at the reaction's outset but that both erode rapidly with conversion. By contrast, both *d.r.* and *e.e.* remained constant for the reaction of **2a** carried out using catalyst **5** as well as in the reaction of **2b** with either catalyst.

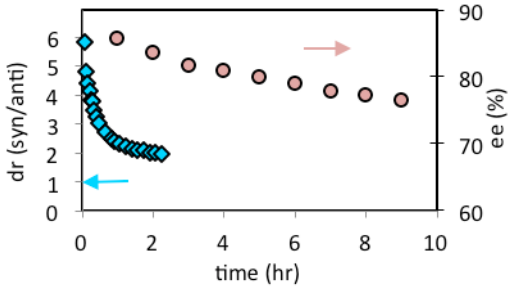


Figure 3. Temporal evolution of *syn/anti* ratio and *syn* ee for the reaction of Scheme 1 to form product **3a** using catalyst **4** (Table 1, entry 1).

A further question is whether reversibility in these reactions extends back through steps in the cycle past the product imine species **8a**, which might be tested by monitoring catalyst/product mixtures for

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the appearance of the nitro-olefin starting material over time. Figure 4 gives temporal profiles for experiments where catalysts **4** and **5** were mixed with either pure racemic *syn*-**3a** or pure racemic *anti*-**3a**. These results show that the reverse reaction proceeds slowly in all cases except the combination of catalyst **5** and the *anti*-**3a** product. Catalyst **5**, which Table 2 shows gives high ee and d.r. values, is unreactive both in the formation and decomposition of *anti*-**3a**. Initial rates of the reverse reaction are similar for the two catalysts.

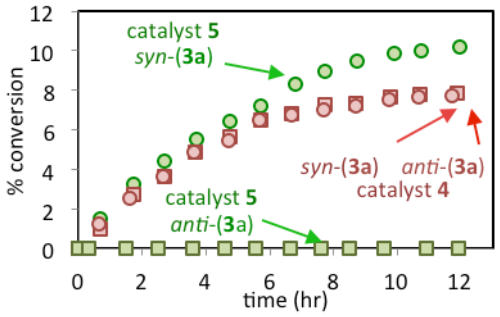


Figure 4. % Conversion of different diastereomers of reaction product *rac*-**3a** back to nitrostyrene starting material monitored by NMR spectroscopy using 0.15 M *rac*-**3a** as pure *syn* or pure *anti* with 0.03 M catalyst **4** or **5** as shown.

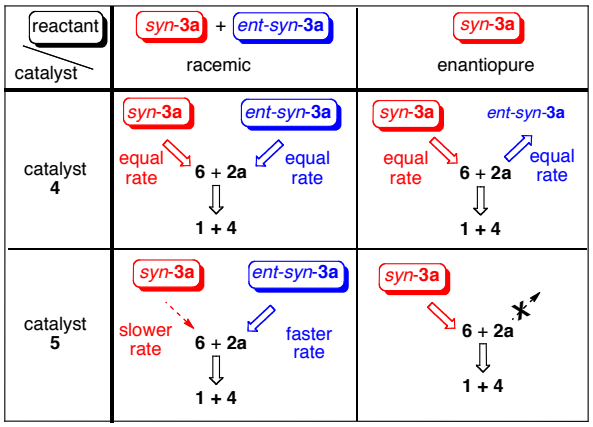
The results shown in Figure 4 lead to the question of the impact that this reversibility may have on selectivity. The reverse reaction carried out with *rac*-**3a** offers the possibility of a kinetic resolution. Table 2 shows the evolution of ee values of *syn*-**3a** in its reverse reaction with catalysts **4** and **5** starting from either racemic and enantiopure *syn*-**3a**. In the reaction of racemic **3a**, catalyst **4** is unselective while catalyst **5** exhibits a strong kinetic resolution, with the mismatched product reacting significantly faster than the matched product, giving a k_{rel} value of over 25. Consistent with these results, the *ee* of enantiopure *syn*-**3a** erodes only slightly in reaction with catalyst **5** and more significantly for catalyst **4**. *Anti*-**3a** is formed as a minor product for catalyst **4**, and is not observed with catalyst **5**. From these experimental results we may devise the qualitative network shown in Scheme 3. Catalyst **5** is more selective both in reacting the mismatched *ent-syn*-**3**a in the racemic mixture as well as in suppressing its formation from the enantiopure *syn*-**3a**.

Table 2. Evolution of *syn*-**3a** enantiomeric excess in the reverse reaction of Scheme 1 starting from both racemic and enantiopure product.[a]

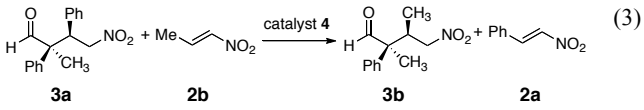
entry	catalyst	initial e.e. (%)	final e.e. (%) / conversion (%)
1	**4**	0	0 / 8
2	**4**	99	83 / 8
3	**5**	0	16 / 10
4	**5**	99	95 /18

[a]Reactions carried out in CD_2Cl_2 at ambient temperature using 0.3 M *syn*-**3a** and 0.03 M catalyst **4** or **5**. Values obtained after 24 hrs.

Interestingly, the reverse reaction carried out using racemic reaction product *syn*-**3b** showed no conversion back to starting materials when combined with either catalyst **4** or **5**. The ease with which molecules flow in both directions for the reaction of **2a** with catalyst **4**, compared with the lack of reversibility for reactions of **2b**, suggests that a smooth conversion from product **3a** to **3b** could occur when nitro-olefin **2b** and product **3a** are mixed with catalyst **4**, as shown in eq. (3). Figure 5 shows that this is indeed the case; indeed, comparison of Figs. 4 and 5 shows that the reverse reaction of **3a** proceeds four-fold faster in the presence of **2b**, which acts to drive the process irreversibly towards **3b**.



Scheme 3. Reverse reaction network for the reaction of Scheme 1 using catalyst **4** or **5** and either racemic or enantiopure reaction products **3a** as reactants (reactants shown in boxes). Relative rates are noted and the direction of the reactions are shown by the arrows.



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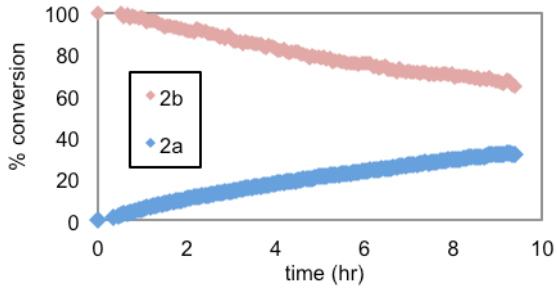

Figure 5. % Conversion of product *syn*-**3a** in the presence of nitro-olefin **2b** to nitrostyrene **2a** to product *syn*-**3b**, monitored by NMR spectroscopy using an equimolar mixture of 0.15 M each **3a** and **2b** with 0.03 M catalyst **4**.

In their studies of α,α-disubstituted aldehydes reacting with a range of differently substituted nitro-olefins, these systems, Jacobsen and coworkers[5b] showed that the highest diastereoselectivities were obtained for aryl-substituted aldehydes and that trans β-arene or heteroarene groups on the nitro-olefin gave lower diastereoselectivities. Their work pointed toward a cooperative role between the chiral diamine and the amino acid-derived functions groups of the catalyst. Our work suggests that lower selectivity is associated with the greater ease of reversibility found with phenyl compared to methyl substitution in the nitro-olefin substrate.

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Conclusions

Kinetic and spectroscopic investigations of the conjugate addition of α,α-disubstituted aldehydes to nitro-olefins using primary amine thiourea catalysts reveals that the resting state is a product imine species that undergoes reversible hydrolysis to form the reaction product. The reaction is subject to two selection levels, one in the formation of aldehyde enamine from imine, and another in the addition of the electrophile to form the second chiral center. In some substrate-catalyst combinations all steps in the reaction are found to be reversible while in others only the imine hydrolysis step is reversible. Differences in enantio- and diastereo-selectivity for different catalysts and nitro-olefin substrates is attributed to the degree of reversibility in each case. However, the underlying structural reasons for these differences in the degree of reversibility for different substrate/catalyst combinations cannot be addressed by kinetic studies alone and are the subject of ongoing investigation. The cooperative catalysis through which these reactions are thought to proceed may help to understand how enzyme-type efficiency and selectivity may have emerged from small molecule catalysis.

Notes and references

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[§]DGB gratefully acknowledges funding from the Simons Foundation Collaboration on the Origins of Life.

Electronic Supplementary Information (ESI) available: [details of reagents and procedures, kinetic plots, NMR spectroscopic data]. See DOI: 10.1039/c000000x/

1 a) S. Mukherjee, J.W. Yang, S. Hoffmann, and B. List, *Chem. Rev*., 2007, **107**, 5471; b) P. Melchiorre, M. Marigo, A. Carlone, and G. Bartoli, *Angew. Chemie Int. Ed*., 2008, **47**, 6138; c) S. Bertelsen and K.-J. Jørgensen, *Chem. Soc. Rev*., 2009, **38**, 2178; d) C. Palomo and A. Mielgo, *Angew. Chem. Int. Ed*., 2006, **45**, 7876; e) S. Sulzer-Mosse and A. Alexakis,. *Chem. Commun*., 2007, 3123.

2 Bures, J.; Armstrong, A.; Blackmond, D. G. *Chem Sci.,* 2012, **3**, 1273.

3 a) J. Schleucher, B. Schwoerer, R.K. Thauer and C. Griesinger, *J. Am. Chem. Soc*., 1995, ***117***, 2941; b) M.B. Schmid, K. Zeitler, and R.M. Gschwind, *Angew. Chemie Int. Ed.,* 2010, **49**, 4997; c) M.B. Schmid, K. Zeitler and R.M. Gschwind, *J. Am. Chem. Soc.* 2011, **133**, 7065; d) M.B. Schmid, K. Zeitler and R.M. Gschwind, *Chemical Science* 2011, **2**, 1793.

4 a) S. B. Tsogoeva, S. Wei, Chem. Commun., 2006, 1451; b) D. A. Yalalov, S. B. Tsogoeva and S. Schmatz, Adv. Synth. Catal., 2006, 348, 826.

5 a) H. Huang, E. N. Jacobsen, J. Am. Chem. Soc. 2006, **128**, 7170; b) M.P. Lalonde, Y. Chen and E.N. Jacobsen, *Angew Chemie Int Ed.,* 2006*,* **45**, 6366.

6 Reviews of primary amine thiourea catalysis: O. V. Serdyuk, C. M. Heckel, S. B.Tsogoeva, *Org. Biomol. Chem.* **2013**, *11* (41), 7051; b) P. Melchiorre, Angew. Chem., Int. Ed., 2012, 51, 9748.

7 Reviews thioureas (including tertiary amine thiourea derivatives): a) Connon, S. J. *Chem. Eur. J.* **2006**, *12*, 5418; b) Taylor, M.S., Jacobsen, E.N. *Angew. Chem Int Ed*. **2006**, *45*, 1520;; c) Schreiner, P. R. *Chem. Soc. Rev*. **2003**, *32*, 289; d) Takemoto, Y. *Org. Biomol. Chem*. **2005**, *3*, 4299.

8 A proposal for irreversible catalyst deactivation via formation of a cyclobutane species from the reaction of enamine **6** with nitro-olefin **2a** was suggested by Jacobsen and coworkers[3] on the basis of mass spectroscopic evidence. No NMR spectroscopic evidence for such a species is found in our studies, and in particular the lack of observation of a C-H proton on the cyclobutane ring connected to the NO_2 group argues its presence. We note, however, that the mass of the observed product imine **8a** is the same as the putative cyclobutane.

9 a) Bures, J.; Armstrong, A.; Blackmond, D. G. *J Am Chem Soc* **2011**, *133*, 8822; b) Bures, J.; Armstrong, A.; Blackmond, D. G. *J Am Chem Soc*. 2012, **134**, 6741.

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