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Use of Bifunctional Ureas to Increase the Rate of Proline-Catalyzed α-Aminoxylations

Sarah L. Poe,[†] Andrew R. Bogdan,[†] Brian P. Mason,[†] Jeremy L. Steinbacher,[†] Suzanne M. Opalka,[†] and D. Tyler McQuade*,[‡]

Department of Chemistry and Chemical Biology, Cornell University, Ithaca, New York 14853, and Department of Chemistry and Biochemistry, Florida State University, Tallahassee, Florida 32306

mcquade@chem.fsu.edu

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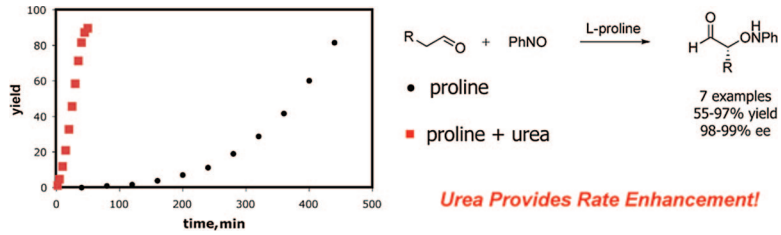

The rate of the proline-catalyzed α-aminoxylation of aldehydes is significantly increased in the presence of a bifunctional urea. Structure−activity relationship data indicate that both an amine and a urea are crucial for rate enhancement. The evidence presented herein suggests that this rate enhancement originates from the hydrogen bonding interaction between the bifunctional urea and an oxazolidinone intermediate to increase the rate of enamine formation. Proline derivatives that are incapable of forming oxazolidinones exhibit no rate enhancement in the presence of the bifunctional urea. The rate enhancement is general for a variety of aldehydes, and the faster reactions do not reduce yields or selectivities.

Introduction

The field of organocatalysis is comprised of many catalyst classes that enable an expanding range of selective transformations.[1] Though amine-based catalysts were some of the first organocatalysts to be explored, interest in them remains strong because they offer enamine, iminium ion, and SOMO mechanisms that provide a wide range of highly enantioselective reactions.[2] Proline alone, one of the most widely used organocatalysts, catalyzes transformations ranging from aldol condensations and Mannich reactions to Diels−Alder reactions, and many proline derivatives are also effective catalysts.[3] Though proline catalysis is quite versatile, limitations exist, including the need for high catalyst loadings and excess reagents, slow reaction rates, complex reaction kinetic profiles, and the use of unfavorable solvents.[4] These obstacles limit the application of proline-based catalysis, and a new strategy is required to exploit its full potential in both academic and industrial settings.

In the past five years, the proline-catalyzed α-aminoxylation of aldehydes and ketones with nitrosobenzene has received attention because it provides an effective route to α-hydroxy carbonyl species.[5] Initially reported in 2003 by the groups of both Zhong and MacMillan, this reaction was believed to proceed through a mechanism consistent with standard enamine catalysis, involving the formation of an enamine in a pre-equilibrium step followed by reaction with nitrosobenzene. However, subsequent work has revealed that α-aminoxylation exhibits unusual kinetic behavior that is not observed in typical

[†] Department of Chemistry and Chemical Biology, Cornell University.
[‡] Department of Chemistry and Biochemistry, Florida State University.

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(5) (a) Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 10808. (b) Zhong, G. *Angew. Chem.* **2003**, *115*, 4379; *Angew. Chem., Int. Ed.* **2003**, *42*, 4247. (c) Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Shoji, M. *Tetrahedron Lett.* **2003**, *44*, 8293. (d) List, B.; Hoang, L.; Martin, H. J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5839. (e) Córdova, A.; Sundén, H.; Bøegvig, A.; Johansson, M.; Himo, F. *Chem. Eur. J.* **2004**, *10*, 3673. (f) Hayashi, Y.; Yamaguchi, J.; Sumiya, T.; Shoji, M. *Angew. Chem.* **2004**, *116*, 1132; *Angew. Chem., Int. Ed.* **2004**, *43*, 1112. (g) Bøegvig, A.; Sundén, H.; Córdova, A. *Angew. Chem.* **2004**, *116*, 1129; *Angew. Chem., Int. Ed.* **2004**, *43*, 1109.

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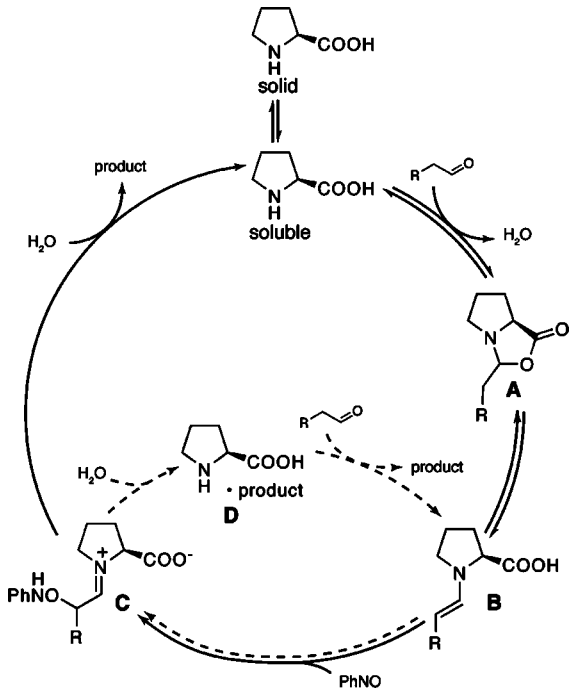
SCHEME 1. A Blackmond et al.-Inspired Catalytic Cycle for the α-Aminoxylation of Aldehydes[a]

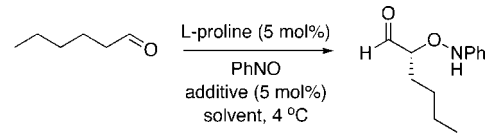


[a] Observed autoinduction is justified by the emergence of an alternate pathway (dashed lines) that is mediated by the product−proline complex **D**.

proline catalysis. Detailed studies by Blackmond and co-workers have shown that this reaction displays autoinduction that cannot be attributed to simple proline dissolution.[6] Instead, they propose a model in which a product−proline complex is formed and converted directly to the enamine, allowing for a faster pathway that circumvents free proline. In addition, independent work by Seebach et al. has addressed the oxazolidinone species that have been observed in proline-catalyzed reactions, and has shown evidence for their role as productive intermediates in enamine formation.[7] Taking this into account, we provide a modified version of the catalytic cycle put forth by Blackmond, which is proposed to proceed via rate-limiting enamine formation before entering a faster catalytic cycle in which exchange between the product−proline complex **D** and the enamine **B** becomes rate determining (Scheme 1).[6c,d]

Although the α-aminoxylation of aldehydes is much more rapid than other proline-catalyzed reactions, it does suffer from drawbacks such as byproduct formation and generally high catalyst loadings.[4a] Accelerating the rate-limiting enamine formation would result in a faster overall reaction and potentially mitigate or eliminate such problems. Furthermore, the reported optimal solvents for the α-aminoxylation of aldehydes are chloroform and DMSO, which are environmentally unfavorable. A faster reaction would enable the use of greener solvents that might otherwise provide a slow or unproductive reaction. In addition, perturbation of any of the steps along this complex reaction pathway may help to elucidate some of its mechanistic features. Inspired by the recent work that has successfully used additives such as amines, water, and diols to improve the proline-catalyzed aldol reaction,[8] we sought to identify an additive that could provide similar enhancements for the α-aminoxylation. If successful, it is possible that the rate enhancement might be extended to other proline-catalyzed reactions as well. We initially explored the use of bifunctional ureas in the α-aminoxylation of aldehydes due to the wide body of recent work suggesting that ureas activate carbonyl species by lowering the LUMO of the electrophile.[9] In addition to the potential for activating the aldehyde toward attack by proline, it has been shown that ureas with tethered Lewis bases can aid deprotonation, which would further enhance the formation of the activated enamine species.[10] Herein, we demonstrate that a bifunctional urea significantly increases the rate of α-aminoxylation while maintaining high yields and enantioselectivities, and we discuss the origin of the observed rate enhancement.

TABLE 1. α-Aminoxylation of Hexanal with Nitrosobenzene in the Presence of Various Additives



5a

entry	additive	solvent	time (min)	yield **5a**[a] (%)	ee (%)
1	no additive	$CHCl_3$	5	5	99
2	**1**, no proline	$CHCl_3$	5	NR	
3	**1**	$CHCl_3$	5	96	99
4	no additive	EtOAc	40	<1	98
5	**1**, no proline	EtOAc	40	NR	
6	**1**	EtOAc	40	81	98
7	**2**	EtOAc	40	3	98
8	**3**	EtOAc	40	2	<99
9	**4**	EtOAc	40	2	<99
10	**2** + **3**	EtOAc	40	7	<99

[a] Yields based on calibrated GC data.

Results and Discussion

Rate Enhancement and Structure−Activity Relationship Study. Bifunctional urea **1** was prepared from phenyl isocyanate and *N*,*N*-dimethylethylenediamine to obtain a compound consisting of both a urea and a tertiary amine. We examined the α-aminoxylation of hexanal in chloroform, shown by MacMillan[5a] to produce high yields and enantioselectivities, as well as in ethyl acetate, a solvent that is more environmentally benign but that has not yet been shown to be a suitable solvent for this reaction.[11] As seen in Table 1 (entries 1, 3 and 4, 6), the presence of urea **1** significantly increases the rate of

(6) Both the α-aminoxylation and α-amination of aldehydes have been found to exhibit autoinduction. See: (a) Mathew, S. P.; Iwamura, H.; Blackmond, D. G. *Angew. Chem.* **2004**, *116*, 3379; *Angew. Chem. Int. Ed*, **2004**, *43*, 3317. (b) Iwamura, H.; Mathew, S. P.; Blackmond, D. G. *J. Am. Chem. Soc.* **2004**, *126*, 11770. (c) Iwamura, H.; Wells, D. H., Jr.; Mathew, S. P.; Klussmann, M.; Armstrong, A.; Blackmond, D. G. *J. Am. Chem. Soc.* **2004**, *126*, 16312. (d) Mathew, S. P.; Klussmann, M.; Iwamura, H.; Wells, D. H.; Armstrong, A.; Blackmond, D. G. *Chem. Commun.* **2006**, 4291.

(7) Seebach, D.; Beck, A. K.; Badine, D. M.; Limbach, M.; Eschenmoser, A.; Treasurywala, A. M.; Hobi, R.; Prikoszovich, W.; Linder, B. *Helv. Chim. Acta* **2007**, *90*, 425.

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(10) (a) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672. (b) Berkessel, A.; Cleemann, F.; Mukherjee, S.; Müller, T. N.; Lex, J. *Angew. Chem.* **2005**, *117*, 817; *Angew. Chem. Int. Ed.* **2005**, *44*, 807. (c) Fuerst, D. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 8964.

(11) Rate enhancement in the presence of urea was observed in the following solvents: $CHCl_3$, EtOAc, DMSO, THF, toluene, acetonitrile, and DMF. We did not encounter a case in which no rate enhancement was observed.

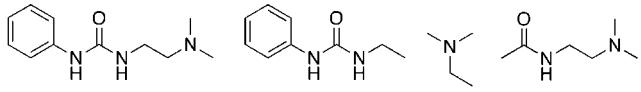
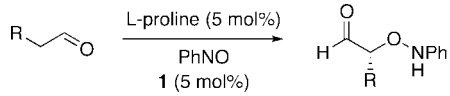


FIGURE 1. Additives used in the α-aminoxylation of hexanal.

TABLE 2. α-Aminoxylation of Aldehydes with Nitrosobenzene



entry	R	product	time (h)	yield[a] (%)	ee (%)
1	nBu	**5a**	2	96	99
2	Me	**5b**	3	90	98
3	iPr	**5c**	3.5	97	99
4	nHex	**5d**	5	84	99
5	CH_2Ph	**5e**	3.5	84	<99
6	Ph	**5f**	2	55	99
7	$CH_2CH{=}CH_2$	**5g**	2.5	75	99

[a] Due to the instability of the aldehyde, *O*-addition products were reduced to their corresponding 2-aminoxy alcohols prior to isolation.

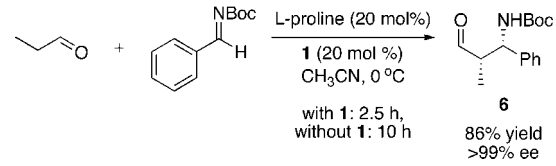
α-aminoxylation in both solvents. The effect of **1** is especially pronounced when the reaction is performed in ethyl acetate; though product **5a** was undetectable after 40 min for the proline-only case, the presence of urea **1** results in a yield of over 80% in the same amount of time. The acceleration that we observe for both solvents suggests that **1** enhances the rate-determining enamine formation.

To investigate the origin of the observed rate enhancement, we performed a structure−activity relationship study with a series of ureas, amines, and amides (Figure 1). When examined individually, each of these functional groups provided only modest rate enhancement (Table 1, entries 7−9). Furthermore, the combination of 1-ethyl-3-phenylurea (**2**) and *N*,*N*-dimethylethylamine (**3**, Table 1, entry 10) does not reproduce the rate enhancement that is observed with **1**, strongly suggesting that the proximity of the urea and amine is significant. Interestingly, although thioureas have been shown to be more effective hydrogen bond donors than their urea counterparts,[12] the thiourea analogue of **1** resulted in a slightly slower reaction than **1** (see the Supporting Information).

Scope. To show that the rate enhancement provided by bifunctional urea **1** does not come at the cost of degraded yields and enantioselectivities, we performed the α-aminoxylation on a range of aldehydes in ethyl acetate (Table 2).[13] The excellent to moderate yields and excellent enantioselectivities that were obtained with the proline−urea system are similar to those observed by others using proline only. Because the presence of urea increases the rate but does not alter yields or selectivities of this reaction, we suggest that it serves only to facilitate enamine formation and does not impact the selectivity-determining step. If the urea did influence the selectivity-determining step we would expect changes in the enantioselectivity and alterations in *O*- and *N*-selectivity.

Catalyst Loading. The increased reaction rates we observed with urea **1** prompted us to investigate the potential for decreased catalyst loadings. The solubility of proline in many organic solvents is low, and the conditions at the beginning of the reaction are saturating in proline. However, the α-aminoxylation reaction becomes homogeneous as the reaction proceeds, indicating that proline becomes soluble as the reaction progresses.[14] We looked at catalyst loadings of 0.5, 1.0, and 2.5 mol %, where [proline] = [urea], and compared the results with the proline-only controls. As expected, the rates of both the proline-only and proline−urea cases changed in response to changes in catalyst loading (Figure 2). In addition, all cases displayed significant rate enhancement when the urea was present, with the 2.5% and 1% catalyst loadings resulting in yields of 97% and 91%, respectively. As the loadings were progressively lowered and the reactions became slower, yields suffered as the oxidant began to decompose faster than it reacted with the enamine (Figure 2c). It should, however, be noted that none of the proline-only cases achieved yields above 50% due to this decomposition, highlighting the value of urea **1** in these reactions. The results seen in parts a and b of Figure 2 suggest the potential for additives such as **1** to enable reactions with even lower catalyst loadings, especially those that do not suffer from decomposition or byproduct formation.

SCHEME 2. Proline-Catalyzed Mannich Reaction between Propionaldehyde and Benzaldehyde *N*-Boc Imine



Extension to the Mannich Reaction. As suggested above, accelerating the rate of enamine formation may have implications for other proline-catalyzed reactions involving rate-determining enamine formation. When urea **1** was employed in the Mannich reaction between benzaldehyde *N*-Boc imine and propionaldehyde, a faster reaction was observed in comparison to the proline-only case while the yields and selectivities of product **6** were left unchanged (Scheme 2). A structure−activity relationship revealed that as for the α-aminoxylation, using urea **2** or amine **3** individually in place of **1** did not provide as great an enhancement, but in this case, the combination of **2** and **3** was able to reproduce the enhancement provided by **1** (see the Supporting Information). The reasons for this difference are currently unknown, but in any case, because urea **1** provides rate enhancement in this reaction as well as in the α-aminoxylation, it is possible that the increase in the rate of enamine formation may be general for other proline-catalyzed reactions.

Solubility Studies. We considered the possibility that the observed rate enhancement may be due to an increased solubility of proline in the presence of **1** rather than faster enamine formation. Indeed, Hayashi has shown that a more soluble proline derivative displays greater catalytic activity than proline in the α-aminoxylation of carbonyl species.[15] However, when proline and **1** were placed in ethyl acetate, no appreciable dissolution was observed after 48 h, and there was no distinguishable difference in dissolution between the proline−urea

(12) Bordwell, F. G.; Algrim, D. J.; Harrelson, J. A., Jr. *J. Am. Chem. Soc.* **1988**, *110*, 5903.

(13) We also observed rate enhancement in the α-aminoxylation of ketones.

(14) Interestingly, although proline fully dissolved during the course of the proline-only reactions, solid proline was still present even after 24 h in the proline−urea reactions.

(15) (a) Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Sumiya, T.; Urushima, T.; Shoji, M.; Hashizume, D.; Koshino, H. *Adv. Synth. Catal.* **2004**, *346*, 1435. (b) Aratake, S.; Itoh, T.; Okano, T.; Nagae, N.; Sumiya, T.; Shoji, M.; Hayashi, Y. *Chem. Eur. J.* **2007**, *13*, 10246. (c) Enders, D.; Chow, S. *Eur. J. Org. Chem.* **2006**, 4578. (d) Hong, B.-C.; Wu, M.-F.; Tseng, H.-C.; Huang, G.-F.; Su, C.-F.; Liao, J.-H. *J. Org. Chem.* **2007**, *72*, 8459. (e) Zhang, D.; Yuan, C. *Tetrahedron* **2008**, *64*, 2480.

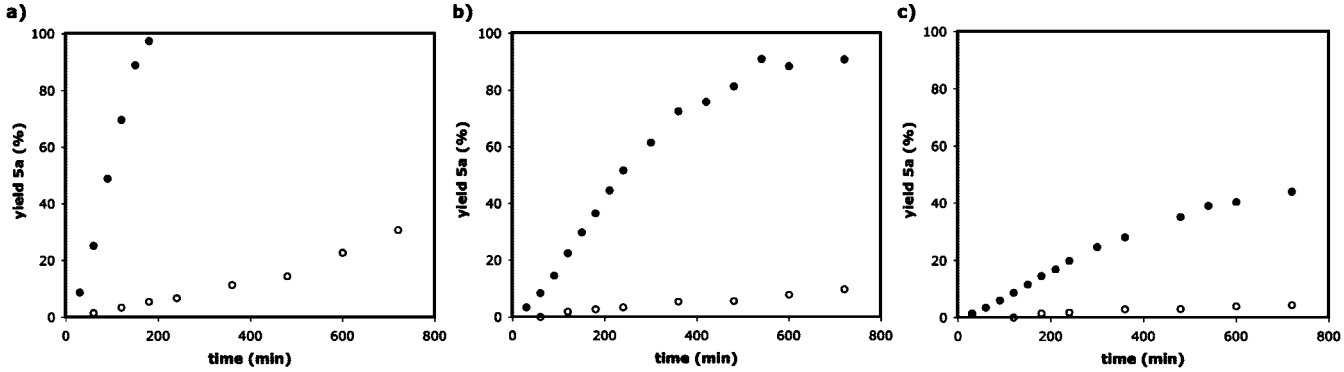


FIGURE 2. Reaction profiles for the α-aminoxylation of hexanal with (a) 2.5% proline, (b) 1% proline, and (c) 0.5% proline. Urea concentration varies as follows: [urea] = [proline] (●), no urea (○).

case and the proline-only control. We addressed this issue more quantitatively with a ^{1}H NMR experiment in which we assessed the solubility of proline in $CDCl_3$ by comparison against an internal standard (see the Supporting Information). Again, there was no difference in the extent of proline dissolution for the urea and nonurea cases; the observed solubility in both cases was approximately 0.0045 M, in agreement with previously reported results.[6c] These findings suggest that urea **1** does not directly solubilize proline but instead provides rate enhancement through a different mechanism.

Further evidence against the role of urea **1** in proline dissolution is provided by the persistence of rate enhancement by urea **1** even when catalyst dissolution cannot be a factor in the rate of α-aminoxylation. When oxazolidinone **7** (intermediate **A** in Scheme 1) was prepared from proline and hexanal[6b] and used as the catalyst, a significantly faster reaction is observed in the presence of **1** (Figure 3). It is interesting to note that as does the proline-only case, the reaction with oxazolidinone **7** alone exhibits autoinduction—although to a lesser extent—but that the addition of urea **1** eliminates this phenomenon completely (Figure 3, inset). The mechanistic implications of this observation are discussed below. Furthermore, rate enhancement by urea **1** is also observed when an insoluble solid-supported proline is used in place of free proline.[16] Because catalyst

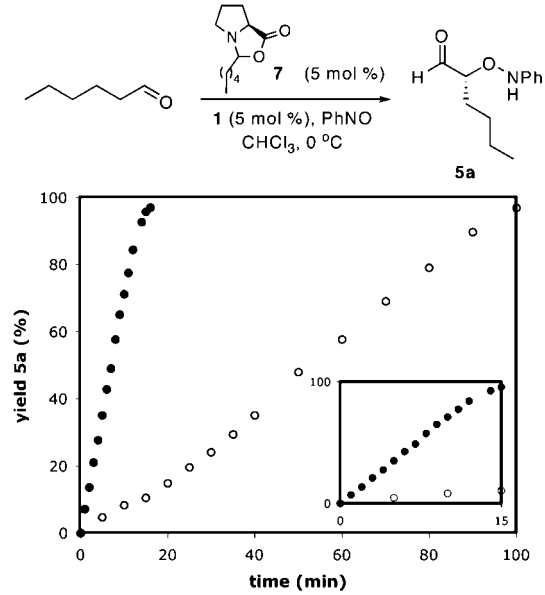


FIGURE 3. Oxazolidinone **7**-catalyzed α-aminoxylation of hexanal: with **1** (●) and without **1** (○).

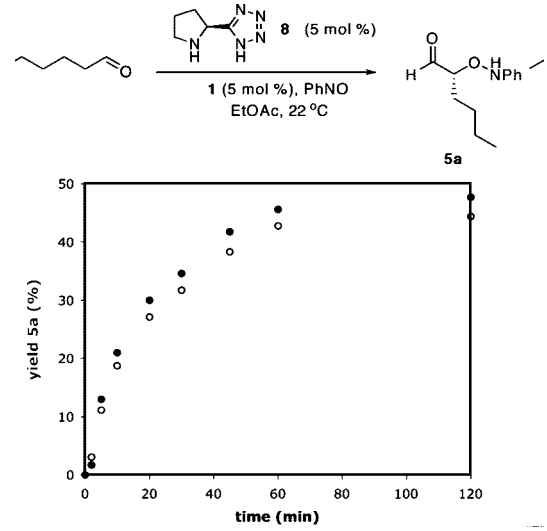


FIGURE 4. Pyrrolidine-tetrazole-catalyzed α-aminoxylation of hexanal: with **1** (●) and without **1** (○).

dissolution does not play a role in either of these reactions, it cannot be the reason for the rate enhancement imparted by **1**.

Origin of Rate Enhancement. While exploring the use of proline derivatives in this reaction, we observed that the presence of urea **1** did not enhance the rate of α-aminoxylation when pyrrolidine-tetrazole **8** was used as the catalyst (Figure 4).[17]

The absence of rate enhancement in this case is not consistent with a scenario involving the electrophile activation that has been implicated in other cases of urea catalysis,[9] because aldehyde activation by the urea would be expected to provide rate enhancement independent of pyrrolidine structure. A similar argument can be made against the activation of nitrosobenzene. Instead, this observation strongly suggests that the urea promotes enamine formation through a different mechanism. If oxazolidinones are indeed productive intermediates in the α-aminoxylation pathway, the rate enhancement that we observe may be due to interaction between the oxazolidinone and urea **1**. Specifically, this hydrogen bonding could enhance the oxazolidinone carboxylate's ability to act as a leaving group, resulting in faster enamine formation (Figure 5).

The results shown in Figure 4 also support our hypothesis; since the pyrrolidine-tetrazole cannot form an oxazolidinone

(16) Unpublished results.
(17) Momiyama, N.; Torii, H.; Saito, S.; Yamamoto, H. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5374.

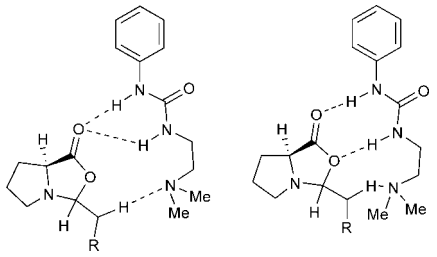


FIGURE 5. Two potential interactions between bifunctional urea **1** and oxazolidinone intermediate. (We thank one of the reviewers who suggested the right-hand structure.)

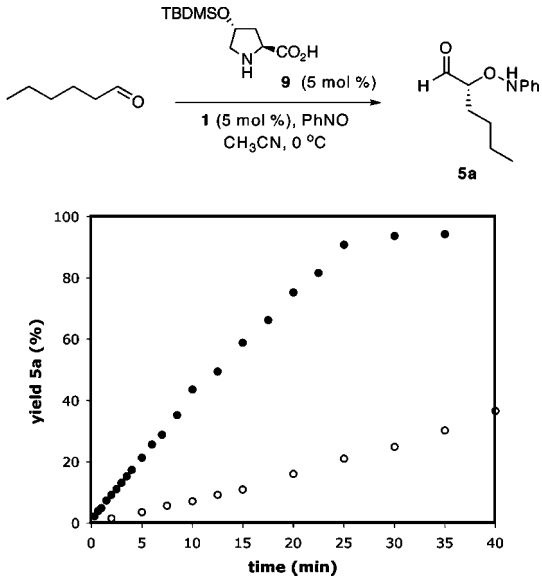


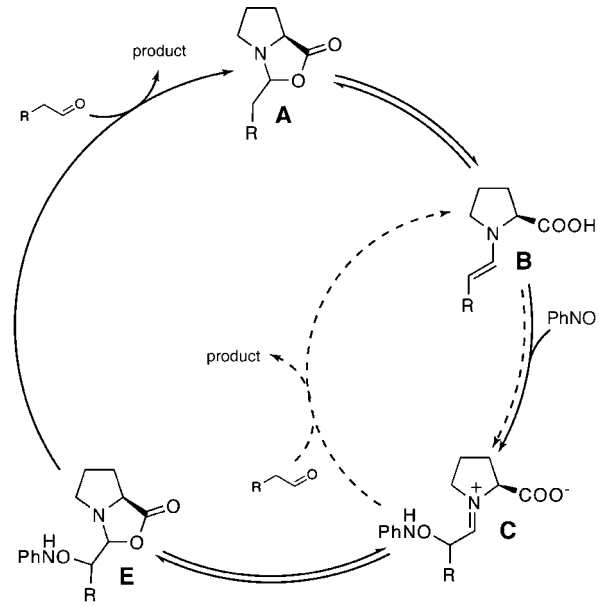
FIGURE 6. Soluble proline **9**-catalyzed α-aminoxylation of hexanal: with **1** (●) and without **1** (○).

species,[18] the urea cannot provide rate enhancement through the proposed mechanism. On the other hand, when carboxylate-containing siloxyproline **9**[19] was employed as the catalyst, rate enhancement was again observed upon the addition of urea **1** (Figure 6), again implicating the role of the oxazolidinone in the origin of rate enhancement.

To further explore this hypothesis, we looked at the influence the amine tether has on the rate of α-aminoxylation. Increasing the tether by one methylene resulted in a reaction that was twice as fast as with urea **1**, while altering the conformation with a 2,2-dimethylpropyl tether decreased the rate of reaction (see the Supporting Information). Further studies to probe these interactions are in progress, but these preliminary results suggest that the position and accessibility of the amine play an important role in the observed rate enhancement.

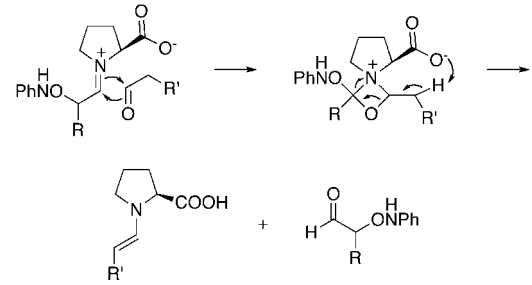
The results presented above certainly do not preclude the possibility for the participation of urea **1** in a step other than enamine formation. It is plausible that **1** instead accelerates a different step such as the proposed exchange between the product−proline complex and the enamine. However, the observation of rate enhancement in the proline-catalyzed Mannich reaction, which does not exhibit autoinduction, strongly suggests that the urea is involved in a step that takes

SCHEME 3. Proposed Catalytic Cycle for the α-Aminoxylation of Aldehydes Based on the Rate Enhancement Provided by Urea 1[a]



[a] The cycle contains an autoinductive pathway (dashed lines, without urea **1**) and a non-autoinductive pathway (solid lines, with urea **1**).

SCHEME 4. Proposed Mechanism for the Iminium−Enamine Exchange in the α-Aminoxylation Autoinductive Pathway



place prior to entering the autoinductive pathway. On the basis of this, we propose the catalytic cycle shown in Scheme 3, which is consistent with our results as well as those presented by others.[6,7] Because we observe the same behavior regardless of whether we start with free proline or with oxazolidinone **A** (water was not observed by ^{1}H NMR), we can simplify the pathway by eliminating both free proline and the water that is liberated from its condensation with the aldehyde.

Like Blackmond, we suggest the existence of two possible pathways in the α-aminoxylation catalytic cycle, with one (inner pathway) involving the transformation of a proline−product complex directly to the enamine. However, because no water is present to effect the release of product by hydrolysis, we propose that this complex is actually the iminium species **C** that is generated by the addition of nitrosobenzene to enamine **B**. Conversion of **C** to **B** with the concomitant release of product may proceed by the mechanism shown in Scheme 4. Though 2+2 cycloadditions are thermally unfavored for the formation of carbocycles, 2+2 cyclizations involving similar substrates have been

(18) Isart, C.; Burés, J.; Villarasa, J. *Tetrahedron Lett.* **2008**, *49*, 5414.

(19) **9** was prepared from *N*-Cbz-hydroxy-L -proline according to published procedures; see ref 11 and the following: Ohtake, H.; Imada, Y.; Murahashi, S.-I. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2737.

suggested previously.[20] In addition, preliminary calculations for such a transformation indicate a favorable ΔG^{o} (see the Supporting Information). Such a mechanism could explain why autoinduction is observed in some proline-catalyzed reactions but not in others, since the properties of the added electrophile should play a role in determining whether this exchange is possible. In cases for which it is not possible, reactions such as the Mannich would operate only through the outer pathway, where autoinduction is not possible.

In the context of this model, the explanation for the autoinduction that is observed in the proline-only case is the same as that previously proposed by Blackmond: the reaction proceeds slowly in the beginning due to slow enamine formation from the starting oxazolidinone **A** but becomes faster as the enamine is generated more rapidly through the inner cycle. On the other hand, when urea **1** is present, we propose that enamine formation is accelerated enough to allow the outer pathway to dominate. For this model to be valid, both the transformation from oxazolidinone **A** to enamine **B** as well as the oxazolidinone exchange between **E** and **A** along the outer pathway must be faster (when the urea is present) than the iminium−enamine conversion along the inner pathway. If not, the inner pathway would be expected to dominate and the autoinduction would persist. It is plausible that the transformation from **E** to **A** is fast, as oxazolidinone exchange has been shown to occur freely,[6c,18] and we propose that urea **1** accelerates the transformation from oxazolidinone **A** to enamine **B** enough so that the change from the inner to the outer pathway can occur. An argument can be made that the urea sufficiently accelerates the reaction that the exchange between iminium **C** and enamine **B** becomes rate-limiting, as has been proposed for the outer pathway.[6d] This would indeed eliminate autoinduction while allowing the reaction to proceed through the inner pathway. However, this would also result in the proline-only and proline−urea cases exhibiting the same rate. Even at its fastest, the proline-only reaction does not achieve the same rate as the proline−urea reaction, indicating that the latter proceeds via a different pathway. Also consistent with the model presented in Scheme 3 are the unchanged selectivities that we observe when urea **1** is present: since selectivity is determined during a step that is common to both pathways, the enantioselectivity should be the same regardless of which pathway is operative.

Conclusion

In summary, we have reported that the proline-catalyzed α-aminoxylation of aldehydes is enhanced by the presence of bifunctional urea **1**, which exhibits high reaction rates in a more benign solvent while still providing high enantioselectivities and yields. Our results suggest that **1** promotes enamine formation by interacting with the oxazolidinone intermediate, supporting the role of the oxazolidinone as a productive catalytic species. Our observation that urea **1** removes the autoinductive behavior typically seen in proline-catalyzed α-aminoxylations has allowed us to provide a model that is consistent with both the proline-only and proline−urea cases. We propose that the enhanced enamine formation that we observe will allow for the acceleration of other existing reactions as well as the realization of new reaction pathways.

(20) Richter, R.; Tucker, B.; Ulrich, H. *J. Org. Chem.* **1983**, *48*, 1694.

Experimental Section

Synthesis of 1-(2-(Dimethylamino)ethyl)-3-phenylurea (1). Phenyl isocyanate (1.08 mL, 10 mmol, 1 equiv) was added dropwise to a solution of *N*,*N*-dimethylethylenediamine (1.1 mL,10 mmol, 1 equiv) in $CHCl_3$ (10 mL) at room temperature and the reaction was stirred for 30 min. The solvent was removed in vacuo and the product was recrystallized from EtOAc to afford white crystals (1.8 g, 87%). ^{1}H NMR (300 Hz, $CDCl_3$) δ 7.35 (d, 2H), 7.22 (t, 2H), 6.97 (t, 1H), 6.36 (t, 1H), 3.30 (q, 2H), 2.42 (t, 2H), 2.12 (s, 3H); ^{13}C NMR (75 Hz, $CDCl_3$) δ 157.8, 139.9, 129.2, 122.7, 120.0, 60.1, 45.5, 38.7.

General Procedure for the α-Aminoxylation of Aldehydes. Nitrosobenzene (214 mg, 2.0 mmol, 1.0 equiv), (L)-proline (11.6 mg, 0.1 mmol, 0.05 equiv), and urea **1** (20.8 mg, 0.1 mmol, 0.05 equiv) were added to a 2 dram screw cap vial equipped with a stir bar. Ethyl acetate (4 mL) was added to the vial, upon which the reaction mixture turned green. The reaction mixture was submerged in an ice bath and stirred for 15 min. The appropriate aldehyde (6.0 mmol, 3.0 equiv) was added to the reaction mixture in one portion at 0 °C. The reaction mixture was continuously stirred at 0 °C until the reaction color changed from green to yellow and the reaction was determined to be complete by GC. The reaction was transferred to a suspension of sodium borohydride (300 mg, 8.0 mmol, 4.0 equiv) in ethanol (10 mL) at 0 °C. An additional 5 mL of ethanol was used to rinse the reaction vessel and added to the sodium borohydride suspension. After 20 min, the reaction mixture was poured into a separatory funnel containing 25 mL of saturated aqueous $NaHCO_3$ and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried with $MgSO_4$, filtered, and concentrated. The resulting residue was purified with column chromatography to afford the desired compounds. Enantioselectivities were determined by using chiral HPLC analysis.

Synthesis of Oxazolidinone 7. Preparation of oxazolidinone **7** was modified from the literature.[6b] Hexanal (123 μL, 1 mmol), proline (115.2 mg, 1 mmol), and 4 Å molecular sieves (139 mg) were stirred in $CDCl_3$ (5 mL) under an environment of N_2 for 14 h. Catalyst concentration was assessed by ^{1}H NMR, using mesitylene as an internal standard. Typical concentrations were 0.02−0.05 M.

Oxazolidinone 7-Catalyzed α-Aminoxylation of Hexanal. Urea **1** (10.4 mg, 0.05 mmol, 0.05 equiv), $CHCl_3$ (volume varied depending on the concentration of oxazolidinone **7**), and 4 Å molecular sieves (35 mg) were stirred at 0 °C for 10 min. Propionaldehyde (370 μL, 3 mmol, 3 equiv) was added, followed by a stock solution (1 mL) of nitrosobenzene (1 M) and mesitylene (0.1 M) in $CHCl_3$. Oxazolidinone **7** in $CDCl_3$ (volume varied depending on concentration) was added, and the reaction conversion was monitored by withdrawing aliquots from the reaction at different time intervals, diluting into ethyl acetate, and analyzing by GC with reference to mesitylene. The control reaction was performed in the same way but without urea **1**.

Pyrrolidine-tetrazole 8-Catalyzed α-Aminoxylation of Hexanal. Pyrrolidine-tetrazole **8** (7.0 mg, 0.05 mmol), urea **1** (10.4 mg, 0.05 mmol), and EtOAc (1 mL) were sonicated in a 1 dram screw cap vial. A stock solution (1 mL) of hexanal (3 M), nitrosobenzene (1 M), and mesitylene (0.1 M) in EtOAc was added and the reaction was rocked at 22 °C. Reaction conversion was monitored by withdrawing aliquots from the reaction at different time intervals, diluting into ethyl acetate, and analyzing by GC with reference to mesitylene. The control reaction was performed in the same way but without urea **1**.

Siloxyproline 9-Catalyzed α-Aminoxylation of Hexanal. Siloxyproline **9** (12.3 mg, 0.05 mmol, 0.05 equiv), urea **1** (10.4 mg, 0.05 mmol, 0.05 equiv), and acetonitrile (1 mL) were placed in a 1 dram screw cap and stirred at 0 °C for 15 min. A stock solution (1 mL) of nitrosobenzene (1 M) and mesitylene (0.1 M) in acetonitrile was added, followed by hexanal (370 μL, 3 mmol, 3 equiv) and the reaction was stirred at 0 °C. Reaction conversion

was monitored by withdrawing aliquots from the reaction at different time intervals, diluting into ethyl acetate, and analyzing by GC with reference to mesitylene. The control reaction was performed in the same way but without urea **1**.

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Supporting Information Available: Experimental methods, product characterization, and kinetic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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