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Enamine Catalysis with Low Catalyst Loadings - High Efficiency via Kinetic Studies

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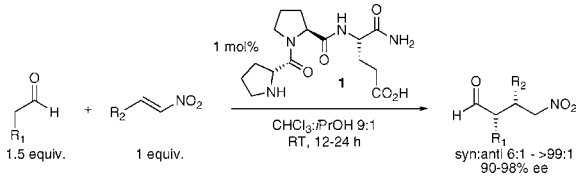
Enamine catalysis with chiral secondary amines of low molecular weight has become a versatile method to activate aldehydes and ketones for reactions with different electrophiles.[1] A multitude of different amine-based catalysts has been introduced over the past decade that provide the products in high stereoselectivities.[1] The understanding of the kinetics and rate determining steps in enamine catalysis is, however, still limited.[2,3] Better insight into the catalytic cycle could in particular be useful to address a major challenge in enamine catalysis: typically high catalyst loadings (10−20 mol %) are necessary to obtain the products in good yields and stereoselectivities.[1] Only a few examples have been presented where enamine catalysis is possible utilizing 1 mol % or less of the catalyst.[4−6] Herein we describe how kinetic studies provided insight into the catalytic cycle of peptide catalyzed conjugate addition reactions and allowed for reducing the catalyst loading by a factor of 10 to as little as 0.1 mol %.

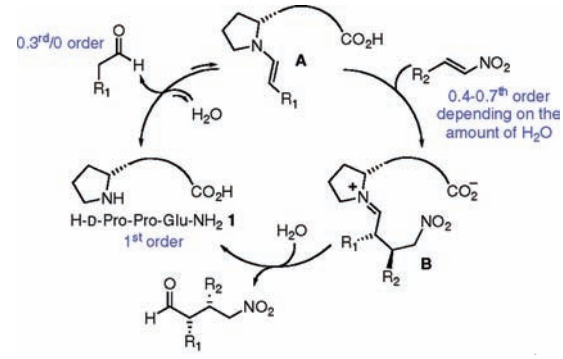
Previously we introduced peptides of the type H-Pro-Pro-Xaa-NH_2 as highly active and stereoselective catalysts for enamine catalysis (Xaa = amino acid with a carboxylic acid in the side chain).[5,6] For example, in the presence of 1 mol % of peptide H-D-Pro-Pro-Glu-NH_2 **1** a broad range of different aldehydes and nitroolefins react readily with each other to provide synthetically useful γ-nitroaldehydes in excellent yields and stereoselectivities (Scheme 1).[6] In contrast to many other examples in enamine catalysis, essentially no side products form, no catalyst deactivation takes place, and no additives are necessary for effective catalysis.[7] Thus, these peptide catalyzed conjugate addition reactions are ideal models to gain insight into the rate determining steps within enamine catalysis.

Scheme 1. Conjugate Addition Reactions Catalyzed by Peptide **1**



The proposed generally accepted catalytic cycle of this reaction involves enamine formation (A) followed by reaction with the nitroolefin and hydrolysis of the resulting imine (B) (Scheme 2).[3,8] To analyze which of these steps is rate determining, we performed kinetic studies utilizing *in situ* IR spectroscopy as a noninvasive method to monitor the reaction progress.[9,10] The 1,4-addition reaction between butanal and nitrostyrene catalyzed by 1 mol % of **1** was utilized as the model reaction. Reaction orders of the catalyst, aldehyde, and nitroolefin were determined by performing at least five reactions in which only the concentration of the component in question was varied.[11] The slope of the straight line within a log/log plot of the initial reaction rates versus the concentrations of the component in question provided then the reaction order of the varied reaction component.[10,11] These experiments revealed as expected a first order dependence of the reaction on catalyst **1**. Interestingly, for the aldehyde a 0.3 order dependence was observed at low aldehyde concentrations

Scheme 2. Catalytic Cycle Proposed for Conjugate Addition Reactions of Aldehydes to Nitroolefins Catalyzed by Peptide **1**



that turned into a zero order dependence at higher concentrations (Figure 1a, green line). This demonstrates that a steady state is reached at a certain concentration of the aldehyde and suggests that the reaction of the catalyst with the aldehyde to form the enamine is not rate limiting. Attempts to detect the enamine were not successful suggesting that the equilibrium is far on the side of the catalyst and the aldehyde. Varying the amount of water present in the reaction mixture had a significant effect on the overall rate of the reaction.[12] When the reaction was performed with dried solvents and reagents, product formation was much faster.[13] Conversely, addition of water (10 mol %) slowed the reaction down (Figure 1b). These observations are most likely due to the influence of water on the enamine formation step. In fact, under "dry conditions",[13] the steady state was reached already at a lower aldehyde concentration (Figure 1a, red). In contrast, in the presence of 10 mol % of water, no steady state was observed even at higher concentrations of the aldehyde (Figure 1a, blue). The dependence of the reaction on the nitroolefin was not influenced by the concentration of the aldehyde, and the rate orders are identical under steady state and nonsteady state conditions.[10] In contrast, the rate order of the nitroolefin depends on the amount of water. With dried solvents and reagents, a 0.4 order dependence of the reaction on the nitroolefin was observed, whereas 0.5 and 0.7 order dependences on the nitroolefin were observed under standard conditions and with 10 mol % of water, respectively. These results demonstrate that both the C−C bond formation step and the hydrolysis of the iminium ion are rate limiting for the reaction.

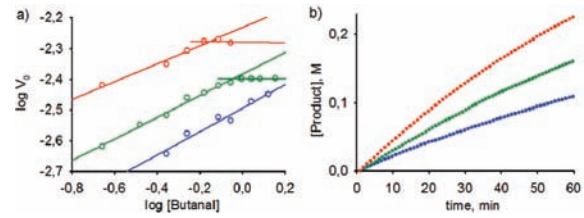


Figure 1. Influence of water on (a) the rate order of the aldehyde and (b) product formation (standard conditions, green line; "dry" conditions,[13] red line; and 10 mol % excess of water, blue line).

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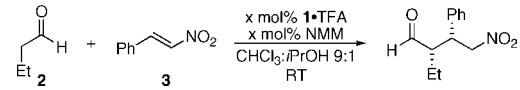
Table 1. Conjugate Addition Reactions between *n*-Butanal and Nitrostyrene Catalyzed by Peptide **1** under Different Conditions



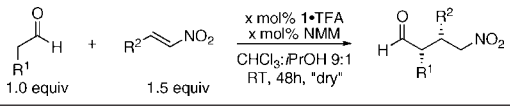
entry	mol % **1**	ratio **2:3**	cond[a]	time (h)	conv[b] (%)	syn/anti[b]	ee[c] (%)
1	1	1.5:1	std	16	quant.	98:2	97
2	1	1:1.5	std	7	>95	98:2	97
3	1	1.5:1	dry	4	>95	97:3	97
4	1	1:1.5	dry	3	>95	97:3	97
5	1	1:1.2	dry	5	>95	95:5	97
6	1	1:1.5	dry, 0 °C	20	>95	>99:1	98
7	0.1	1:1.5	dry	48	~90	94:6	97

[a] Under "dry conditions" anhydrous reagents and solvents were used whereas regular solvents and reagents were utilized under "standard (std) conditions". [b] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [c] Determined by chiral phase HPLC analysis.

These insights into the kinetics of the conjugate addition reaction provided a guide for improving the reaction conditions. Clearly a reduction of the water amount accelerates the reaction (Figure 1b). In addition, the fact that the nitroolefin and not the aldehyde is involved in the rate limiting step suggests that an excess of nitrolefin with respect to the aldehyde should lead to a faster reaction. Indeed, when the conjugate addition reaction was performed utilizing 1.5 equiv of nitrostyrene and 1.0 equiv of butanal, the γ-nitroaldehyde was obtained within a significantly shorter time compared to the originally used conditions utilizing an excess of the aldehyde (Table 1, entries 1 and 2). Combined with the use of dried solvents and reagents, the original reaction time of 16 h was reduced to 3 h (Table 1, entry 4). Under those conditions, the γ-nitroaldehyde was isolated with the same high enantioselectivity and only slightly reduced diastereoselectivity utilizing 1 mol % of the peptidic catalyst. Essentially perfect stereoselectivities were obtained when the reaction was performed at reduced temperature (Table 1, entry 6). Most remarkably, under these improved reaction conditions a catalyst loading of as little as 0.1 mol % is still sufficient for excellent catalytic activity and stereoselectivity within 48 h (Table 1, entry 7).

These low catalyst loadings proved to be broadly applicable. A wide range of aldehyde and nitroolefin combinations react in the presence of 0.1 mol % of peptide H-D-Pro-Pro-Glu-NH_2 **1** readily to γ-nitroaldehydes (Table 2). All products were isolated in high to excellent yields and stereoselectivities. Only the less reactive substrates required a slightly higher quantity of the catalyst (0.2 and 0.4 mol %, respectively) to allow for high product yields (Table 2, entries 2, 5, 9, and 10).

Table 2. Conjugate addition reactions between aldehydes and nitroolefins catalyzed by peptide **1**



entry	R^1	R^2	mol %	yield[a] (%)	syn/anti[b]	ee[c] (%)
1	Et	Ph	0.1	87	94:6	97
2	Me	Ph	0.2	92	95:5	96
3	*n*Pr	Ph	0.1	98	95:5	96
4	Bn	Ph	0.1	87	94:6	98
5	*i*Pr	Ph	0.4	93	95:5	94
6	Et	C_6H_3-2,4-Cl_2	0.1	95	95:5	96
7	Et	C_6H_4-2-CF_3	0.1	96	97:3	97
8	Bn	C_6H_4-2-CF_3	0.1	92	98:2	99
9	Et	C_6H_4-4-OMe	0.4	96	93:7	95
10	Et	$CH_2CH(CH_3)_2$	0.2	92	91:9	98

[a] Isolated yield. [b] Determined by ^{1}H NMR spectroscopic analysis of the crude material. [c] Determined by chiral phase HPLC analysis.

In conclusion, kinetic studies provided insight into the rate determining step of peptide catalyzed conjugate addition reactions between aldehydes and nitroolefins. They revealed that not enamine formation but both the reaction of the enamine with the electrophile and hydrolysis of the resulting imine are rate limiting. These findings allowed for reducing the catalyst loading by a factor of 10 to as little as 0.1 mol % for a broad range of substrates. This is the lowest catalyst loading achieved so far in enamine catalysis with organocatalysts of low molecular weight. The work also highlights the value of mechanistic insight based on kinetic studies for optimizing organocatalytic reactions.

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Supporting Information Available: Experimental details on the kinetic studies and presented compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For a recent review see: Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471–5569.
(2) For kinetic studies on enamine catalysis, see: (a) Zotova, N.; Broadbelt, L. J.; Armstrong, A.; Blackmond, D. G. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3934–3937. (b) Nozière, B.; Córdova, A. *J. Phys. Chem. A* **2008**, *112*, 2827–2837. (c) Halland, N.; Lie, M. A.; Kjaersgaard, A.; Marigo, M.; Schiøtt, B.; Jørgensen, K. A. *Chem.—Eur. J.* **2005**, *11*, 7083–7090. (d) Erkkilä, A.; Pihko, P. M. *Eur. J. Org. Chem.* **2007**, 4205–4216. (e) Zotova, N.; Franzke, A.; Armstrong, A.; Blackmond, D. G. *J. Am. Chem. Soc.* **2007**, *129*, 15100–15101. (f) Iwamura, H.; Wells, D. H.; Mathew, S. P.; Klussmann, M.; Armstrong, A.; Blackmond, D. G. *J. Am. Chem. Soc.* **2004**, *126*, 16312–16313. (g) Iwamura, H.; Mathew, S. P.; Blackmond, D. G. *J. Am. Chem. Soc.* **2004**, *126*, 11770–11771. (h) Mathew, S. P.; Iwamura, H.; Blackmond, D. G. *Angew. Chem., Int. Ed.* **2004**, *43*, 3317–3321. (i) Nyberg, A. I.; Usano, A.; Pihko, P. M. *Synlett* **2004**, *11*, 1891.
(3) For the generally accepted mechanism of enamine catalysis see ref 1 and: (a) Clemente, F. R.; Houk, K. N. *Angew. Chem., Int. Ed.* **2004**, *43*, 5766–5768. (b) List, B.; Hoang, L.; Martin, H. J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5839–5842. (c) Bahmanyar, S.; Houk, K. N.; Martin, H. J.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 2475–2479. For an alternative proposal see: Seebach, D.; Beck, A. K.; Badine, D. M.; Limbach, M.; Eschenmoser, A.; Treasurywala, A. M.; Hobi, R. *Helv. Chim. Acta* **2007**, *90*, 425–471.
(4) (a) Lombardo, M.; Easwar, S.; Pasi, F.; Trombini, C. *Adv. Synth. Catal.* **2009**, *351*, 276–282. (b) Vishnumaya, M. R.; Singh, V. D. *J. Org. Chem.* **2009**, *74*, 4289–4297. (c) Jia, Y. N.; Wu, F. C.; Ma, X.; Zhu, G. J.; Da, C. S. *Tetrahedron Lett.* **2009**, *50*, 3059–3062. (d) Zhu, S.; Yu, S.; Ma, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 545–548. (e) Maya, V.; Raj, M.; Singh, V. K. *Org. Lett.* **2007**, *9*, 2593–2595. (f) Kano, T.; Tokuda, O.; Maruoka, K. *Tetrahedron Lett.* **2006**, *47*, 7423–7426. (g) Mitsumori, S.; Zhang, H.; Cheong, P. H. Y.; Houk, K. N.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 1040–1041. (h) Rodríguez, B.; Bolm, C. *J. Org. Chem.* **2006**, *71*, 2888–2891. (i) Kano, T.; Tamaguchi, Y.; Tokuda, O.; Maruoka, K. *J. Am. Chem. Soc.* **2005**, *127*, 16408–16409. (j) Marigo, M.; Fielenbach, D.; Braunton, A.; Kjoersgaard, A.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3703–3706. (k) Dahlin, N.; Bøgevig, A.; Adolfsson, H. *Adv. Synth. Catal.* **2004**, *346*, 1101–1105.
(5) (a) Krattiger, P.; Kovàsy, R.; Revell, J. D.; Ivan, S.; Wennemers, H. *Org. Lett.* **2005**, *7*, 1101–1103. (b) Revell, J. D.; Gantenbein, D.; Krattiger, P.; Wennemers, H. *Biopolymers (Pept. Sci.)* **2006**, *84*, 105–113.
(6) (a) Wiesner, M.; Revell, J. D.; Wennemers, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 1871–1874. (b) Wiesner, M.; Revell, J. D.; Tonazzi, S.; Wennemers, H. *J. Am. Chem. Soc.* **2008**, *130*, 5610–5611. (c) Wiesner, M.; Neuburger, M.; Wennemers, H. *Chem.—Eur. J.* **2009**, DOI: 10.1002/chem.200901021.
(7) Reactions catalyzed by peptide **1** proceed equally as well in the presence or absence of salts such as TFA•NMM; see ref 6c for details.
(8) For an initial report and proposed mechanism of this 1,4-addition reaction, see: Betancort, J. M.; Barbas, C. F., III. *Org. Lett.* **2001**, *3*, 3737–3740.
(9) Cabot, R.; Lledo, A.; Reves, M.; Riera, A.; Verdaguer, X. *Organometallics* **2007**, *26*, 1134–1142.
(10) For experimental details see Supporting Information.
(11) (a) Birk, J. P. *J. Chem. Educ.* **1976**, *53*, 704–707. (b) Casado, J.; López-Quintela, M. A.; Lorenzo-Barral, F. M. *J. Chem. Educ.* **1986**, *63*, 450.
(12) For other kinetic studies on the influence of water on enamine catalysis see ref 2e−2i.
(13) "Dry" conditions refer to the use of dried solvents, reagents, and glassware. Water generated in the course of the reaction is allowed to be present and is in fact crucial. Reactions performed in the presence of molecular sieves do not allow for product formation.

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