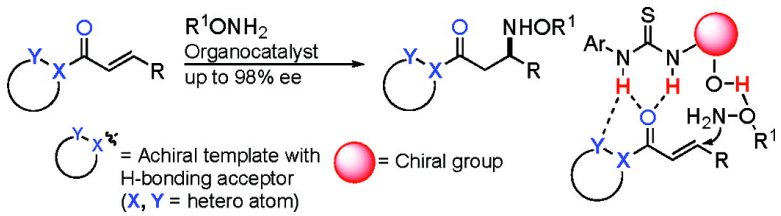
Communication

Organocatalysis in Conjugate Amine Additions. Synthesis of β-Amino Acid Derivatives

Mukund P. Sibi, and Kennosuke Itoh

J. Am. Chem. Soc., **2007**, 129 (26), 8064-8065• DOI: 10.1021/ja071739c • Publication Date (Web): 07 June 2007



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 24 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

J|A|C|S
COMMUNICATIONS

Published on Web 06/07/2007

Organocatalysis in Conjugate Amine Additions. Synthesis of β-Amino Acid Derivatives

Mukund P. Sibi* and Kennosuke Itoh

Department of Chemistry, North Dakota State University, Fargo, North Dakota 58105

Received March 12, 2007; E-mail: mukund.sibi@ndsu.edu

Organocatalysis is an area of intense investigation.[1] Spectacular advances have been made in the past decade using organocatalysts to prepare chiral building blocks. In this context, enamine and iminium ion intermediates derived from chiral amines as well as substrate and/or reagent activation through hydrogen bonds have been employed in enantioselective transformations.[2] In a majority of reactions of the latter class, a thiourea motif has played a key role.[3] Conjugate addition of nitrogen nucleophiles to unsaturated carboxylic acid derivatives provides rapid access to β-amino acids, an important class of compounds.[4] There are reported examples of conjugate nitrogen nucleophile addition using organocatalysts.[5] However, H-bond activation has played a limited role in enantioselective conjugate addition of heteroatom nucleophiles.[6] In continuation of our program on the synthesis of β-amino acids,[7] we have been interested in the development of simple and novel organocatalysts which in combination with appropriate acyclic systems would allow for the introduction of heteroatom nucleophiles (Scheme 1). This work describes a highly efficient conjugate hydroxylamine addition to enoates that proceed with high levels of enantioselectivity using a bifunctional organocatalyst.[8]

Our experiments began with the addition of *O*-benzylhydroxylamine to pyrazole crotonate **5a**, a template with properly positioned hydrogen bond acceptors for activation by the readily available chiral thiourea catalyst **6a**.[9] Reaction optimization involved variation of solvent, additive, and template.[10] Results from these experiments are shown in Table 1. A stoichiometric amount of the chiral thiourea was used in these experiments. Conjugate amine addition to **5a** in a variety of common organic solvents was slow, and the level of enantioselectivity was poor (entries 1−4). Non-hydrogen bonding solvents, such as methylene chloride, toluene, and trifluorotoluene, were better (entry 5−7). Of these solvents, the reaction in trifluorotoluene was the fastest, and the ee for the product was the highest (entry 7). The use of MS 4 Å as an additive led to improvements in chemical yields but not selectivity (compare entry 5 with 8; 6 with 9; 7 with 10). Cooling the reaction to 0 °C while using the optimal trifluorotoluene as a solvent led to a substantial improvement in selectivity (compare entry 10 with 11). The effect of the pyrazole substituent on reactivity and selectivity was evaluated (entries 12−15). Although the reactions were faster with templates **5b**−**d**, the levels of enantioselectivity were lower than that with **5a**.

Having a reasonable set of conditions at hand, we varied the organocatalyst to understand the importance of bifunctionality, stereochemistry, and structural rigidity on reactivity and selectivity in amine additions. These reactions were performed at room temperature with **5a** as the substrate, trifluorotoluene as the solvent, a stoichiometric amount of the chiral activator, and MS 4 Å as the additive. Results from these experiments are shown in Chart 1. The urea catalyst **6b** was less effective in comparison to the thiourea catalyst **6a** with respect to both reactivity and selectivity. Replacement of the bistrifluoromethylphenyl group (**6a**) with tetrafluorophenyl group (**6c**) led to improvement in chemical yield but the selectivity was much lower. The stereochemistry of the aminoindanol subunit had a significant impact with trans configured **6d** providing markedly lower selectivity than cis configured **6a**. The hydroxyl group on aminoindanol was important for reactivity and selectivity, as compound **6e** lacking the hydroxyl group gave modest yield and nearly racemic product. Reactions with ligands **6f**−**i** clearly demonstrated the requirement for rigidity of the ligand architecture.

We then evaluated the effect of catalyst loading and amine structure on reactivity and selectivity and these results are shown

Scheme 1

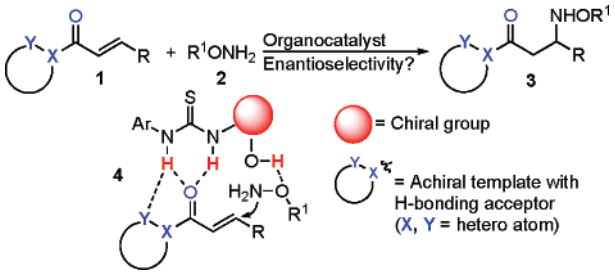
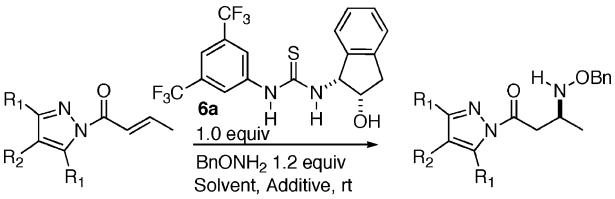


Table 1. Evaluation of Solvent and Templates in Conjugate Amine Additions[a]



5a R_1 = Me, R_2 = H
5b R_1 = Me, R_2 = Br
5c R_1 = Ph, R_2 = H
5d R_1 = Ph, R_2 = Br

7a R_1 = Me, R_2 = H
7b R_1 = Me, R_2 = Br
7c R_1 = Ph, R_2 = H
7d R_1 = Ph, R_2 = Br

entry	substrate	solvent	additive	product	time, h	% yield[b]	% ee[c]
1	**5a**	CH_3CN		**7a**	216	41	
2	**5a**	THF		**7a**	216	43	−4
3	**5a**	Et_2O		**7a**	216	58	10
4	**5a**	*t*-BuOH/THF		**7a**	168	61	0
5	**5a**	CH_2Cl_2		**7a**	192	61	43
6	**5a**	toluene		**7a**	192	68	54
7	**5a**	$CF_3C_6H_5$		**7a**	48	76	71
8	**5a**	CH_2Cl_2	MS 4 Å	**7a**	192	75	48
9	**5a**	toluene	MS 4 Å	**7a**	192	73	53
10	**5a**	$CF_3C_6H_5$	MS 4 Å	**7a**	24	75	71
11[d]	**5a**	$CF_3C_6H_5$	MS 4 Å	**7a**	72	82	87
12	**5b**	$CF_3C_6H_5$	MS 4 Å	**7b**	24	85	61
13	**5c**	$CF_3C_6H_5$		**7c**	24	76	42
14	**5c**	$CF_3C_6H_5$	MS 4 Å	**7c**	14	76	45
15	**5d**	$CF_3C_6H_5$	MS 4 Å	**7d**	12	72	31

[a] For details of the reaction conditions see Supporting Information. [b] Isolated yield. [c] Chiral HPLC analysis. [d] Reaction at 0 °C.

10.1021/ja071739c CCC: $37.00

Chart 1

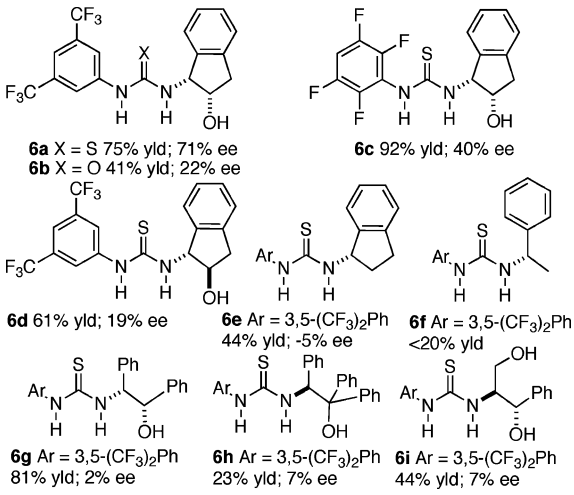
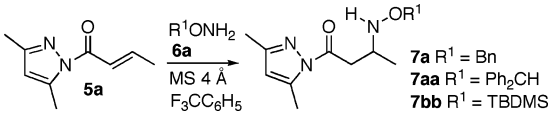


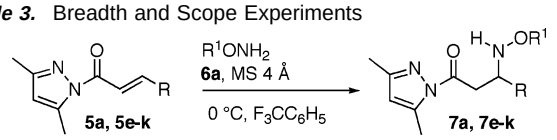
Table 2. Effect of Catalytic Loading and Nature of the Amine in Additions to **5a**



entry	amine R^1	mol % **6a**	time, h	product	% yield[a]	% ee[b]
1[c]	Bn	100	24	**7a**	75	71
2[c]	Bn	80	60	**7a**	80	71
3[c]	Bn	50	96	**7a**	78	70
4[c]	Bn	30	168	**7a**	63	71
5[d]	Ph_2CH	100	96	**7aa**	86	89
6[d]	TBDMS	100	120	**7bb**	82	94

[a] Isolated yield. [b] Chiral HPLC. [c] Reaction at room temperature. [d] Reaction at 0 °C.

Table 3. Breadth and Scope Experiments



entry	R	R^1	time, h	product	% yield[a]	% ee[b]
1	Me **5a**	Ph_2CH	96	**7aa**	86	89
2	CO_2Et **5e**	Ph_2CH	96	**7e**	50	94
3	CO_2Et **5e**	TBDMS	96	**7ee**	42	90
4	Et **5f**	Ph_2CH	168	**7f**	92	91
5	*n*-Pr **5g**	Ph_2CH	138	**7g**	84	88
6	*i*-Pr **5h**	Ph_2CH	216	**7h**	68	90
7	*c*−C_6H_{11} **5i**	Ph_2CH	288	**7i**	59	89
8[c]	CH_2OPMP **5j**	Ph_2CH	24	**7j**	98	98
9[d]	Ph **5k**	$PhCH_2$	72	**7k**	19	67

[a] Isolated yield. [b] Chiral HPLC. [c] Reaction run using 30 mol% of **6a**. [d] Reaction at room temperature.

in Table 2. Lowering the catalyst loading from 100 mol % to 30 mol % led to longer reaction times with no loss in enantioselectivity for the product (entries 1−4). Changing the O-substituent on the hydroxylamine from benzyl to benzhydryl to tert-butyldimethylsilyl gave the products in good selectivity (entries 5 and 6).

Substrate scope in conjugate additions has been evaluated and these results are shown in Table 3. Amine addition to crotonate **5a** was efficient yielding the product in high ee (entry 1). The fumarate **5e** gave the addition product in modest yield but very high selectivity (entries 2 and 3). Compounds with alkyl substituents on the β-carbon were competent substrates in the conjugate addition

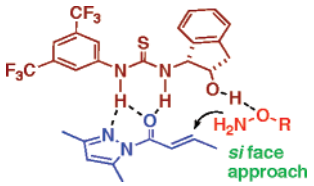


Figure 1. Stereochemical model.

affording the products with high enantioselectivity (entries 4−7). Compound **5j** gave the product in high yield and 98% ee, even when using 30 mol % of the thiourea catalyst (entry 8). Cinnamate **5i** was less reactive and gave the product in low yield and selectivity (entry 9). We have previously shown that the conjugate addition products can be readily converted to β-amino acids.[7] Overall, there is good substrate scope for the addition of amines to pyrazole derived enoates using a thiourea catalyst, providing access to a variety of β-amino acid derivatives in high selectivity.

A working model for the conjugate amine addition is shown in Figure 1. The model is consistent with the observed absolute stereochemistry for the conjugate addition product (*S*)-**7a** and the structural requirements for the chiral urea as shown in Chart 1. The differential reactivity with ligands **6a** and **6d** suggests that intramolecular delivery of the nucleophile is likely. Our results also indicate that the pyrazole template plays a crucial role in providing H-bond acceptor sites for better organization and hence higher levels of selectivity in these organocatalysis reactions.

Acknowledgment. We thank NSF (Grant CHE-0316203) for funding and L. Stanley and J. Zimmerman for helpful discussions.

Supporting Information Available: Characterization data for compounds **5**−**16** and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis*; Wiley-VCH: Weinheim, Germany, 2005. (b) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999.
(2) For recent reviews see: (a) Lelais, G.; MacMillan, D. W. C. *Aldrichimica Acta* **2006**, *39*, 79. (b) List, B. *Chem. Commun.* **2006**, 819. (c) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138.
(3) For reviews see; (a) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520. (b) Connon, S. J. *Chem.—Eur. J.* **2006**, *12*, 5419. (c) Takemoto, Y. *Org. Biomol. Chem.* **2005**, *3*, 4299.
(4) For recent reviews see: (a) Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991. (b) Xu, L.-W.; Xia, C.-G. *Eur. J. Org. Chem.* **2005**, 633.
(5) (a) Chen, Y. K.; Yoshida, M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 9328. (b) Ibrahem, I.; Rios, R.; Vesely, J.; Zhao, G-L.; Cordova, A. *Chem. Commun.* **2007**, 849. (c) Diner, P.; Nielsen, M.; Marigo, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 1983. (d) Li, H.; Wang, J.; Xie, H.; Zu, L.; Jiang, W.; Duesler, E. N.; Wang, W. *Org. Lett.* **2007**, *9*, 965. (e) Guerin, D. J.; Miller, S. J. *J. Am Chem. Soc.* **2002**, *124*, 2134. (f) Takasu, K.; Maiti, S.; Ihara, M. *Heterocycles* **2003**, *59*, 51. (g) Wang, J.; Li, H.; Zu, L.; Wang, W. *Org. Lett.* **2006**, *8*, 1391.
(6) For the addition of nonamine nucleophiles using organocatalysts see: (a) Li, B.-J.; Jiang, L.; Liu, M.; Chen, Y.-C.; Ding, L-S.; Wu, Y. *Synlett* **2005**, 603. (b) Wang, W.; Li, H.; Wang, J.; Zu, L. *J. Am. Chem. Soc.* **2006**, *128*, 10354.
(7) Sibi, M. P.; Shay, J. J.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc.* **1998**, *120*, 6615.
(8) For the use of amino indanol-derived thiourea in catalysis see: (a) Herrera, R. P.; Sgarzani, V.; Bernardi, L.; Ricci, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 6576. For examples of bifunctional organocatalysis see: (b) Wang, B.; Wu, F.; Wang, Y.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2007**, *129*, 768. (c) Inokuma, T.; Hoashi, Y.; Takemoto, Y *J. Am. Chem. Soc.* **2006**, *128*, 9413. (d) Yalalov, D. A.; Tsogoeva, S. B.; Schmatz, S. *Adv. Synth. Catal.* **2006**, *348*, 826. (e) McCooey, S. H.; Connon, S. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6367. (f) Huang, H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2006**, *128*, 7170. (g) Wang, J.; Li, H.; Zu, L.; Jiang, W.; Xie, H.; Duan, W.; Wang, W. *J. Am. Chem. Soc.* **2006**, *128*, 12652.
(9) See Supporting Information for conditions and experimental details.
(10) We have screened other templates in conjugate amine additions. For example, addition to oxazolidinone crotonate gave the addition product in low yield and selectivity. These results will be reported in a full account.

JA071739C