J|A|C|S COMMUNICATIONS

Published on Web 10/14/2009

Enantioselective Intramolecular Michael Addition of Nitronates onto Conjugated Esters: Access to Cyclic γ-Amino Acids with up to Three Stereocenters

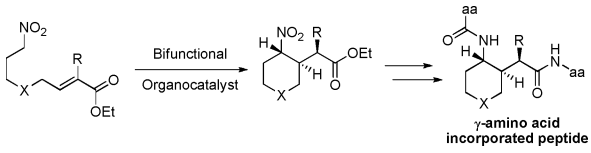
William J. Nodes,[†] David R. Nutt,[‡] Ann M. Chippindale,[‡,§] and Alexander J. A. Cobb*[,†]

School of Pharmacy and Department of Chemistry, University of Reading, Whiteknights, Reading, Berks RG6 6AD, U.K.

Received August 25, 2009; E-mail: a.j.a.cobb@reading.ac.uk

The asymmetric Michael reaction is one of the most powerful carbon−carbon bond-forming reactions available to the organic chemist and remains an important challenge within organic synthesis.[1] Since the start of the new millenium, much work has focused on asymmetric *organocatalytic* processes.[2] In most cases, the Michael acceptor is almost always a conjugated enone, enal, or nitroalkene variant.[3] Very few examples of other Michael acceptors exist,[4] in particular the conjugated ester, which is surprising given its synthetic utility. Within our laboratory, we were particularly drawn to the use of nitronates in the intramolecular Michael addition to conjugated esters as an entry to cyclically constrained γ-amino acids (Scheme 1).

Scheme 1. Catalytic Synthesis of γ-Amino Acids: Concept

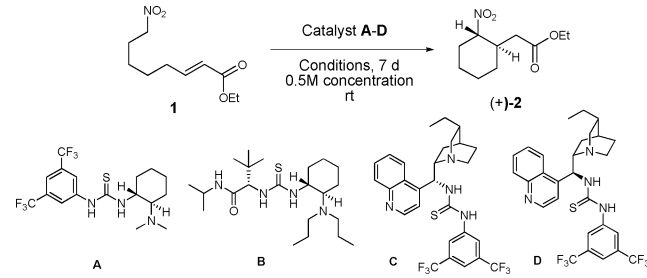


Unnatural peptides (foldamers) incorporating such unusual amino acids have recently received much attention because of their interesting folding properties.[5] Furthermore, these compounds represent analogues of γ-aminobutyric acid (GABA) and are therefore of biological significance.[6] However, neither the enantiomerically pure synthesis of γ-amino acids[7] nor the synthesis of cyclically constrained variants has been widely reported. We envisioned that our route would address this by utilizing the intramolecular Michael addition of a nitronate to a conjugated ester. Importantly, with this procedure, *up to three contiguous stereocenters* can be constructed in one step. Furthermore, the presence of a nitro group can allow it to act as a masked amine during subsequent peptide synthesis.[7] However, to the best of our knowledge, to date no asymmetric methods, organocatalytic or otherwise, exist for closing a nitronate onto a conjugated ester.[8]

On the basis of previous studies using nitronates as nucleophiles,[9] we decided to investigate the potential of chiral bifunctional organocatalysts in this process and thus screened a range of thiourea catalysts (Table 1). Using catalyst **A**, we were delighted to obtain cyclized product **2** in an acceptable yield and with excellent enantioselectivity. A subsequent catalyst screen showed that under these conditions, bifunctional cinchona catalysts **C** and **D** gave superior enantioselectivities (Table 1, entries 3 and 4). Interestingly, the use of hydroquinidine-derived catalyst **D** gives the *oppositely* configured product to hydroquinine-derived catalyst **C** in almost identical yield, diastereoselectivity, and enantioselectivity.

Ultimately, reaction in acetonitrile was shown to give the best balance among yield, diastereoselectivity, and enantioselectivity (Table 1, entry 9). Although increased catalyst loading did improve the results in terms of reaction time, it gave a lower yield and, interestingly, a lower dr. It is thought that longer reaction times allow the system to equilibrate to the thermodynamically more stable trans system. We tested this hypothesis by re-exposing compound (+)**-2** with an initial dr of 5.7:1 to catalyst **C** in $CDCl_3$ at room temperature. After 3 days, the dr was 6.1:1, and after 6 days, the dr had improved to 6.4:1. However, increases in temperature, use of additives, and increased concentration deteriorated either the diastereoselectivity or enantioselectivity of the process.

Table 1. Development of Bifunctional Organocatalytic Intramolecular Michael Addition



entry	solvent	catalyst (mol %)	yield (%)	dr[a]	ee (%)[b,c]
1	DCE	**A** (10)	78	4:1	90
2	DCE	**B** (10)	11	1:1	4
3	DCE	**C** (10)	79	4:1	92
4	DCE	**D** (10)	77	4:1	94[d]
5	THF	**C** (10)	67	>19:1	95
6	C_6H_6	**C** (10)	71	2:1	96
7	CH_2Cl_2	**C** (10)	83	>19:1	95
8	H_2O	**C** (10)	51	9:1	95
9	MeCN	**C** (10)	87	>19:1	95
10	MeCN	**C** (20)[e]	81	9:1	96
11	MeCN	**C** (30)[e]	81	9:1	96

[a] Determined by ^{1}H NMR spectroscopy. [b] Determined by HPLC analysis on the corresponding benzyl ester. [c] Absolute stereochemistry was determined by Nef Reaction on the product and comparison of the optical rotation with literature values (see the Supporting Information). [d] The opposite enantiomer was observed. [e] Reaction was complete after 2 days.

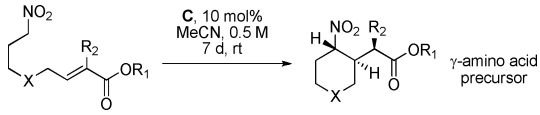
A variety of substrates were screened using the optimized conditions (Table 1, entry 9). Pleasingly, the enantioselectivities of the reaction process remained very good, as did the diastereoselectivities (Table 2). Of particular interest were the systems leading to three asymmetric centers (entries 4−6 and 9), which gave excellent enantioselectivities and impressive diastereoselectivities. The relative configurations were determined by ^{1}H NMR analysis of the corresponding lactams and, in the case of **5**, X-ray crystallography (see the Supporting Information). Interestingly, in the racemic reaction, whereby the precursor to compound **5** was simply exposed to cesium fluoride, the C1′ *epimer* was obtained in a 6:1 diastereomeric ratio.

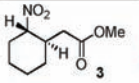
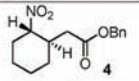
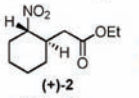
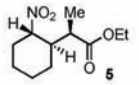
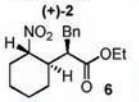
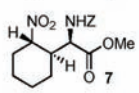
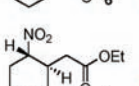
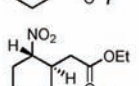
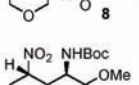
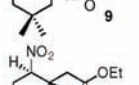
In all cases except entry 8, reactions were stopped after 7 days to allow for completion and equilibration to the trans product. However, compounds **5**, **6**, and **10** were produced more slowly and had not

[†] School of Pharmacy.
[‡] Department of Chemistry.
[§] X-ray crystallographer.

10.1021/ja9070915 CCC: $40.75 © 2009 American Chemical Society

Table 2. Substrate Scope for Intramolecular Michael Addition[a]



entry	product	yield, dr, ee	entry	product	yield, dr, ee
1	 **3**	57% yield, 4:1 dr 96% ee	2	 **4**	66% yield 4:1 dr 98% ee
3	 **(+)-2**	87% yield >19:1 dr 96% ee	4	 **5**	50% yield >19:6:1 dr 94% ee
5[c]	 **6**	52% yield >19:4:1 dr >99% ee	6[c]	 **7**	65% yield 2:1:<1 dr 95% ee
7	 **8**	69% yield >19:1 dr 92% ee	8[d]	 **9**	76% yield >19:1 dr 96% ee
9[c]	 **10**	11% yield 3:1:<1 >99% ee	10	 **(-)-2**	20% yield 7:3 dr 38% ee (from (*Z*)-substrate)

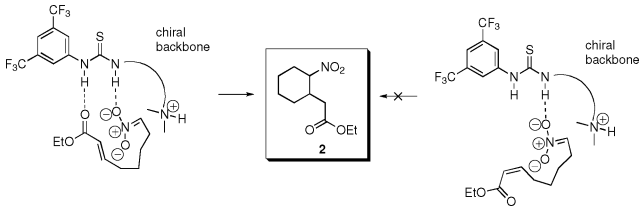
[a] Determined by ^{1}H NMR spectroscopy. [b] Determined by HPLC analysis. [c] Absolute configuration was assigned by analogy to compounds **2** and **5**. [d] Reaction was complete after 2 days.

reached completion, accounting for the moderate yields, but the enantioselectivity of each remained excellent.

Finally, *Z* esters were also utilized within this methodology. Interestingly, these reactions did not proceed efficiently, and only the simple *Z* substrate of **1** partially worked to produce compound **2** with the *opposite* absolute configuration and decreased diastereoselectivity and enantioselectivity (Table 2, entry 10).

We propose that the thiourea needs to coordinate to both the nitronate and the ester in order to activate the system and allow the reaction to proceed. This can only occur effectively with the *E* ester, as the geometry of the *Z* ester prevents such an interaction from occurring (Scheme 2). This may also account for the lower diastereoselectivity and enantioselectivity with the *Z* ester.

Scheme 2. Proposed Explanation for *Z* Ester Nonreactivity



Ab initio electronic structure calculations indicate that the *E*/*Z* configuration of the double bond indeed facilitates or prevents the thiourea moiety from interacting simultaneously with the nitro and ester groups (Figure 1).

In order to demonstrate the utility of these compounds in the synthesis of peptides, we performed N- and C-terminal derivatizations. Reduction of the nitro group of compound **2** and subsequent DCC coupling to *N*-Boc-L-valine gave dipeptide precursor **11** with no loss of enantiopurity nor any observable lactam formation (Scheme 3a). The acid of product **5** was coupled with MeO-L-valine at the C-terminus, also with no loss of enantiopurity (Scheme 3b), giving dipeptide precursor **12**.

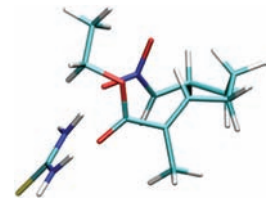
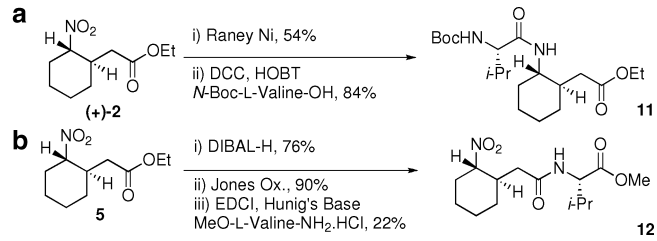


Figure 1. Optimized structure of a simplified thiourea interacting with the deprotonated precursor of **5**, as obtained at the B3LYP/3-21G level of theory with the GAMESS-UK program.[10]

Scheme 3. N- and C-Terminal Derivatizations



In conclusion, we have shown the first use of bifunctional organocatalysis in the intramolecular Michael addition of nitronates to conjugated esters. We have also demonstrated its utility in peptide chemistry, and further mechanistic investigations of the reaction are underway in our laboratories.

Acknowledgment. Financial support was provided by the EPSRC (to W.J.N.).

Supporting Information Available: Experimental procedures, characterization data, and CIF and PDB files. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, U.K, 1992.
(2) For selected reviews, see: (a) Special issue on asymmetric organocatalysis: *Acc. Chem. Res.* **2004**, *37*, 487. (b) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138. (c) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701. (d) Almaşi, D.; Alonso, D. A.; Nájera, C. *Tetrahedron: Asymmetry* **2007**, *18*, 299.
(3) For selected examples, see ref 2 and: (a) Chen, Y. K.; Yoshida, M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 9328. (b) Lu, H.-H.; Wang, X.-F.; Yao, C.-J.; Zhang, J.-M.; Wu, H.; Xiao, W.-J. *Chem. Commun.* **2009**, 4251. (c) Rabalakos, C.; Wulff, W. D. *J. Am. Chem. Soc.* **2008**, *130*, 13524.
(4) Vinyl sulfones and phosphonates have recently emerged as Michael acceptors in organocatalytic processes. See ref 2 and, for example: Sulzer-Mossé, S.; Alexakis, A.; Mareda, J.; Bollot, G.; Bernardinelli, G.; Filinchuk, Y. *Chem.—Eur. J.* **2009**, *15*, 3204.
(5) (a) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173. (b) Horne, W. S.; Gellman, S. H. *Acc. Chem. Res.* **2008**, *41*, 1399. (c) Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219. (d) Seebach, D.; Hook, D. F.; Glättli, A. *Biopolymers* **2006**, *84*, 23. (e) Hill, D. J.; Mio, M. J.; Prince, R. B.; Hughes, T. S.; Moore, J. S. *Chem. Rev.* **2001**, *101*, 3893.
(6) Abdel-Halim, H.; Hanrahan, J. R.; Hibbs, D. E.; Johnston, G. A. R.; Chebib, M. *Chem. Biol. Drug Des.* **2008**, *71*, 306.
(7) For an organocatalytic example, see: Chi, Y.; Guo, L.; Kopf, N. A.; Gellman, S. H. *J. Am. Chem. Soc.* **2008**, *130*, 5608.
(8) Nonasymmetric examples exist. For examples, see: (a) Jousse, C.; Mainguy, D.; Desmaële, D. *Tetrahedron Lett.* **1998**, *39*, 1349. (b) Marsh, G. P.; Parsons, P. J.; McCarthy, C.; Corniquet, X. G. *Org. Lett.* **2007**, *9*, 2613.
(9) For examples, see: (a) Marcelli, T.; van der Haas, R. N. S.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 929. (b) Okino, T.; Nakamura, S.; Furukawa, T.; Takemoto, Y. *Org. Lett.* **2004**, *6*, 625. For recent reviews of bifunctional organocatalysts, see: (c) Connon, S. J. *Chem. Commun.* **2008**, 2499. (d) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520.
(10) Guest, M. F.; Bush, I. J.; van Dam, H. J. J.; Sherwood, P.; Thomas, J. M. H.; van Lenthe, J. H.; Havenith, R. W. A.; Kendrick, J. *Mol. Phys.* **2005**, *103*, 719.

JA9070915