ORGANIC LETTERS

2011
Vol. 13, No. 8
2026–2029

Enantioselective Direct Vinylogous Michael Addition of Functionalized Furanones to Nitroalkenes Catalyzed by an Axially Chiral Guanidine Base

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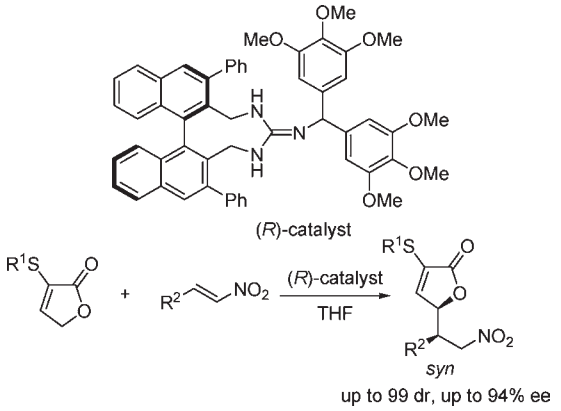
Received February 15, 2011

ABSTRACT



The highly *syn*-diastereo- and enantioselective direct vinylogous Michael addition of α-thio substituted furanones with conjugate nitroalkenes was demonstrated using an axially chiral guanidine base catalyst. The method provides facile access to enantioenriched α,γ-functionalized butenolides that can be further manipulated, thereby rendering them useful synthetic intermediates.

The modification of furanone derivatives at the γ-position, namely via vinylogous reactions, represents an attractive approach for the preparation of functionalized γ-butenolides,[1] which are commonly encountered motifs in natural products and biologically relevant molecules. Enantioselective catalysis of the direct vinylogous reaction of γ-butenolides and related compounds as pronucleophiles has received much attention because this method provides efficient access to optically active functionalized γ-butenolides in an atom economical manner.[1,2] Recently, Shibasaki,[3] and Trost[4] independently reported the chiral

(1) For reviews of vinylogous reactions, see: (a) Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. *Chem. Rev.* **2000**, *100*, 1929. (b) Bur, S. K.; Martin, S. F. *Tetrahedron* **2001**, *57*, 3221. (c) Denmark, S. E.; Heemstra, J. R., Jr.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 4682. (d) Casiraghi, G.; Zanardi, F.; Battistini, L.; Rassu, G. *Synlett* **2009**, 1525.

(2) For selected examples of enantioselective vinylogous Michael addition of 2-silyloxyfuranes as a preformed nucleophile. For chiral metal catalysis, see: (a) Kitajima, H.; Ito, K.; Katsuki, T. *Tetrahedron* **1997**, *53*, 17015. (b) Kitajima, H.; Ito, K.; Katsuki, T. *Synlett* **1997**, 568. (c) Nishikori, H.; Ito, K.; Katsuki, T. *Tetrahedron: Asymmetry* **1998**, *9*, 1165. (d) Desimoni, G.; Faita, G.; Filippone, S.; Mella, M.; Zamponi, M. G.; Zema, M. *Tetrahedron* **2001**, *57*, 10203. (e) Suga, H.; Kitamura, T.; Kakehi, A.; Baba, T. *Chem. Commun* **2004**, 1414. (f) Robichaud, J.; Tremblay, F. *Org. Lett.* **2006**, *8*, 597. (g) Yang, H.; Kim, S. *Synlett* **2008**, 555. For organocatalysis, see: (h) Brown, S. P.; Goodwin, N. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 1192. (i) Huang, Y.; Walji, A. M.; Larsen, C. H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 15051. (j) Simmons, B.; Walji, A. M.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 4349.

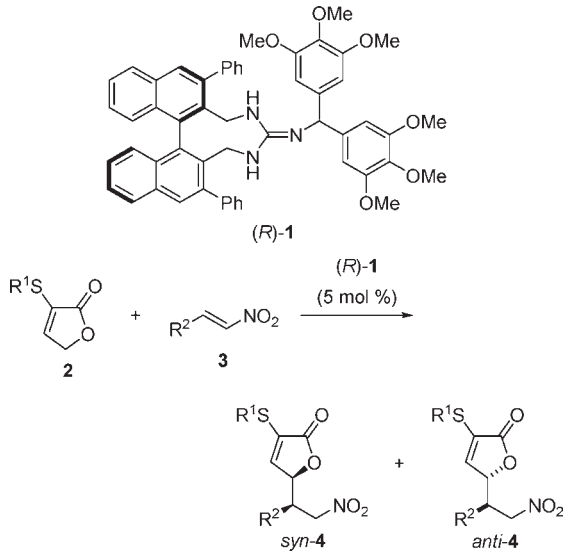
(3) Yamaguchi, A.; Matsunaga, S.; Shibasaki, M. *Org. Lett.* **2008**, *10*, 2319.

(4) Trost, B. M.; Hitce, J. *J. Am. Chem. Soc.* **2009**, *131*, 4572.

(5) For allylic alkylation, see: (a) Cui, H.-L.; Huang, J.-R.; Lei, J.; Wang, Z.-F.; Chen, S.; Wu, L.; Chen, Y.-C. *Org. Lett.* **2010**, *12*, 720. For vinylogous Michael reactions, see: (b) Zhang, Y.; Yu, C.; Ji, Y.; Wang, W. *Chem.—Asian J.* **2010**, *5*, 1303. (c) Wang, J.; Qi, C.; Ge, Z.; Cheng, T.; Li, R. *Chem. Commun.* **2010**, *46*, 2124. (d) Huang, H.; Yu, F.; Jin, Z.; Li, W.; Wu, W.; Liang, X.; Ye, J. *Chem. Commun.* **2010**, *46*, 5957. For vinylogous aldol reactions, see: (e) Yang, Y.; Zheng, K.; Zhao, J.; Shi, J.; Lin., L.; Liu, X.; Feng, X. *J. Org. Chem.* **2010**, *75*, 5382.

10.1021/ol200415u
Published on Web 03/18/2011

Scheme 1. Direct Vinylogous Michael Addition of α-Thio Substituted Furanones **2** to Conjugate Nitroalkenes **3** Catalyzed by Axially Chiral Guanidine Base **1**



metal complex-catalyzed direct vinylogous Mannich and Michael reactions of 2(5*H*)-furanone, respectively. Their pioneering studies stimulated intensive interest in the development of enantioselective direct functionalization of furanones[5] and related compounds[6] at the γ-position, and several excellent approaches have been accomplished using chiral metal catalysis[6a] and organocatalysis.[5,6b] Meanwhile, we have also developed a highly diastereo- and enantioselective direct vinylogous aldol reaction of (di)halofuranone derivatives with aromatic aldehydes using axially chiral guanidine **1** as a base catalyst.[7,8] During this investigation, we demonstrated that α-thio substituted furanone **2** served as an efficient vinylogous nucleophile.[7,9] This vinylogous reaction of **2** enables the enantioselective preparation of γ-butenolide derivatives adorned with multiple functional handles that can be further manipulated, thereby rendering them useful synthetic intermediates. In our ongoing studies of the utility of highly functionalized furanones such as α-thio substituted furanones **2**, we discovered and herein disclose a direct vinylogous Michael addition[10,11] of **2** to conjugate nitroalkenes **3** catalyzed by axially chiral guanidine base **1** that yields densely functionalized γ-butenolides **4** with high diastereo- and enantioselectivities (Scheme 1).

In our previous studies, furanone **2a** possessing a phenylthio group at the α-position was found to function as an efficient vinylogous pronucleophile in the vinylogous aldol reaction of benzaldehyde, providing the corresponding product in nearly optically pure form.[7] We therefore began our investigation with the reaction of furanone **2a** with β-nitrostyrene **3a**. The catalytic reaction using 5 mol % of guanidine **1** proceeded smoothly in THF at −40 °C to afford the vinylogous product **4aa** in good yield with high *syn*-diastereoselectivity (Table 1, entry 1); however the enantioselectivity was disappointing (43% ee). We therefore modified the substituent introduced at the sulfur atom of **2** to improve the enantioselectivity (entries 2 and 3). To our delight, introduction of an aliphatic group in place of the phenyl substituent on the sulfur atom led to an increase in enantioselectivity with retention of the high *syn*-diastereoselectivity, but the chemical yields were markedly dependent on the aliphatic substituents employed. The sterically demanding *tert*-butyl group exhibited a beneficial effect on both the chemical yield and the stereoselectivity (entry 3). Further screening of ethereal solvents revealed that chemical yields were also markedly affected by the solvent employed (entries 4−7). The use of an acyclic mono ether resulted in a significant decrease in the chemical yield accompanied by considerable formation of byproduct **5**, which resulted from overreaction of **4ca** with **3a** (entries 4−6). Acetone was also found to be inefficient for the present transformation (entry 8).[7,12] THF was most effective at facilitating the desired reaction, and the use of 2 equiv of furanone **2a** suppressed the unfavorable overreaction, giving rise to **4ca** in good yield with high diastereo- and enantioselectivity (entry 9).

(6) For a vinylogous Mannich reaction or Michael addition of α,β-unsaturated γ-butyrolactam, see: (a) Shepherd, N. E.; Tanabe, H.; Xu, Y.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 3666. (b) Feng, X.; Cui, H.-L.; Xu, S.; Wu, L.; Chen, Y.-C. *Chem.—Eur. J.* **2010**, *16*, 10309.

(7) Ube, H.; Shimada, N.; Terada, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 1858.

(8) For axially chiral guanidines as enantioselective catalysts, see: (a) Terada, M.; Ube, H.; Yaguchi, Y. *J. Am. Chem. Soc.* **2006**, *128*, 1454. (b) Terada, M.; Ikehara, T.; Ube, H. *J. Am. Chem. Soc.* **2007**, *129*, 14112. (c) Terada, M.; Nakano, M. *Heterocycles* **2008**, *76*, 1049. (d) Terada, M.; Nii, H. *Chem.—Eur. J.* **2011**, *17*, 1760. Also see:(e) Terada, M.; Nakano, M.; Ube, H. *J. Am. Chem. Soc.* **2006**, *128*, 16044. (f) Terada, M.; Tsushima, D.; Nakano, M. *Adv. Synth. Catal.* **2009**, *351*, 2817. (g) Nakano, M.; Terada, M. *Synlett* **2009**, 1670. (h) Ube, H.; Terada, M. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3895. (i) Terada, M. *J. Synth. Org. Chem. Jpn.* **2010**, *67*, 1159.

(9) For vinylogous aldol reaction of 3-(phenylthio)furan-2(5*H*)-one (**2a**) with aldehydes, see: Shirai, K.; Kumamoto, T.; Watanabe, M.; Kurihara, H. JP Patent 60 06678 [85 06678]; *Chem. Abstr.* **1985**, *102*, 220732e.

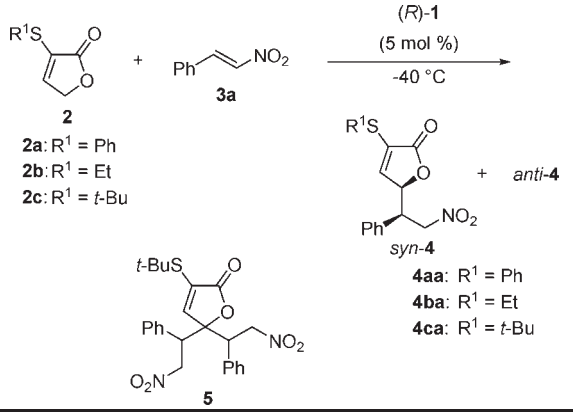
(10) For recent reviews of organocatalytic conjugate (Michael) additions, see: (a) Almaşi, D.; Alonso, D. A.; Nájera, C. *Tetrahedron: Asymmetry* **2007**, *18*, 299. (b) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701.

(11) For selected recent examples of enantioselective direct vinylogous conjugate (Michael) additions using organocatalysts. For alkylidene dicyanides, see: (a) Xue, D.; Chen, Y.-C.; Wang, Q.-W.; Cun, L.-F.; Zhu, J.; Deng, J.-G. *Org. Lett.* **2005**, *7*, 5293. (b) Poulsen, T. B.; Bell, M.; Jørgensen, K. A. *Org. Biomol. Chem.* **2006**, *4*, 63. (c) Xie, J.-W.; Yue, L.; Xue, D.; Ma, X.-L.; Chen, Y.-C.; Wu, Y.; Zhu, J.; Deng, J.-G. *Chem. Commun.* **2006**, 1563. (d) Jiang, L.; Zheng, H.-T.; Liu, T.-Y.; Yue, L.; Chen, Y.-C. *Tetrahedron* **2007**, *63*, 5123. (e) Alemán, J.; Jacobsen, C. B.; Frisch, K.; Overgaard, J.; Jørgensen, K. A. *Chem. Commun.* **2008**, 632. (f) Lu, J.; Liu, F.; Loh, T.-P. *Adv. Synth. Catal.* **2008**, *350*, 1781. (g) Lu, J.; Zhou, W.-J.; Liu, F.; Loh, T.-P. *Adv. Synth. Catal.* **2008**, *350*, 1796. (h) Lu, J.; Liu, F.; Zhou, W.-J.; Loh, T.-P. *Tetrahedron Lett.* **2008**, *49*, 5389. For enals, see: (i) Hong, B.-C.; Wu, M.-F.; Tseng, H.-C.; Liao, J.-H. *Org. Lett.* **2006**, *8*, 2217. (j) Bench, B. J.; Liu, C.; Evett, C. R.; Watanabe, C. M. H. *J. Org. Chem.* **2006**, *71*, 9458.

(12) In the direct vinylogous aldol reaction catalyzed by **1**, acetone was found to be an efficient solvent with respect to diastereo- and enantioselectivities. See ref 7.

(13) CCDC 811041 (**4cc**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Table 1. Enantioselective Direct Vinylogous Michael Addition of **2** to β-Nitrostyrene **3a** Catalyzed by Guanidine **1**[a]



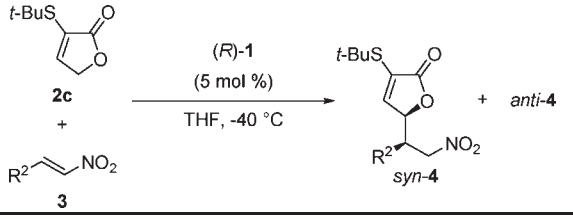
entry	2	solvent	t (h)	yield[b] (%)	*syn*/*anti*[c]	ee[d] (%)
1	**2a**	THF	2	78	90:10	43
2	**2b**	THF	20	7	90:10	91
3	**2c**	THF	20	72	98:2	94
4	**2c**	Et_2O	48	18	90:10	88
5	**2c**	TBME[e]	36	26	78:22	82
6	**2c**	CPME[f]	20	32	90:10	92
7	**2c**	DME[g]	32	67	95:5	82
8	**2c**	acetone	24	25	67:33	80
9	**2c**[h]	THF	16	81(76)[i]	98:2	94

[a] Unless otherwise noted, all reactions were carried out using 0.01 mmol of (*R*)-**1** (5 mol %), 0.30 mmol of **2** (1.5 equiv), and 0.20 mmol of **3a** in 4.0 mL of the indicated solvent at −40 °C. [b] NMR yield. [c] Diastereomeric ratio was determined by ^{1}H NMR analysis. [d] Enantiomeric excess was determined by chiral stationary phase column (Chiralpak AS-H) HPLC analysis for the major *syn*-isomers. [e] TBME: *tert*-Butyl methyl ether. [f] CPME: Cyclopentyl methyl ether. [g] DME: 1,2-Dimethoxyethane. [h] 0.40 mmol of **2c** (2.0 equiv) was employed. [i] Isolated yield after purification by gel permeation column chromatography.

With the optimal reaction conditions in hand, we further investigated the scope of the direct vinylogous Michael addition of **2c** to nitroalkenes **3**. As shown in Table 2, a variety of nitroalkenes **3** can be utilized in the present vinylogous reaction, affording the corresponding products **4** in moderate to good yields. Although introduction of electron-donating groups or *ortho*-substituents on the aromatic ring of the β-nitrostyrene derivatives retarded the reaction considerably and led to a slight reduction of enantioselectivities (entries 1, 5, and 6), excellent *syn*-diastereoselectivities were achieved irrespective of the electronic properties and steric demand of the aromatic ring. Nitroalkene **3h** possessing a heteroaromatic ring also served as a good Michael acceptor (entry 7). It is noteworthy that aliphatic substituted nitroalkenes, **3i** and **3j**, were also suitable substrates in the present catalytic reaction (entries 8 and 9), affording the *syn*-diastereomer exclusively with fairly good enantioselectivities, although a prolonged reaction time was required.

Finally, we demonstrated the potential of the present catalytic reaction through further elaboration of γ-butenolide product **4** by utilization of their multiple functionalities.

Table 2. Enantioselective Direct Vinylogous Michael Addition of **2c** to a Variety of Nitroalkenes **3** Catalyzed by Guanidine **1**[a]

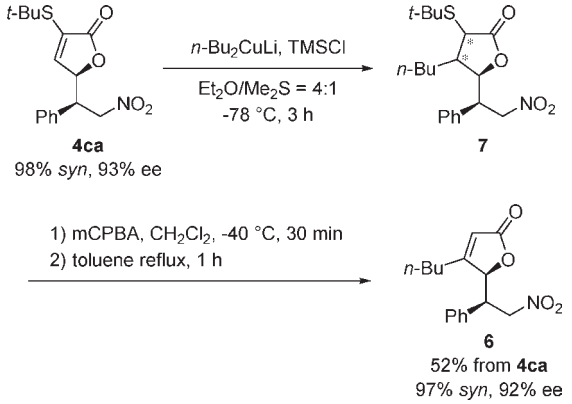


entry	3	4	t (h)	yield[b] (%)	*syn*/*anti*[c]	ee[d] (%)
1	**3b**: 4-$MeOC_6H_4$-	**4cb**	40	77	98:2	88
2	**3c**: 4-BrC_6H_4-	**4cc**[e]	16	65	98:2	94
3	**3d**: 4-ClC_6H_4-	**4cd**	16	63	98:2	93
4	**3e**: 3-BrC_6H_4-	**4ce**	40	60	99:1	94
5	**3f**: 2-$MeOC_6H_4$-	**4cf**	40	73	97:3	82
6	**3g**: 2-BrC_6H_4-	**4cg**	40	62	97:3	91
7	**3h**: thiophen-2-yl	**4ch**	40	75	98:2	88
8	**3i**: isobutyl	**4ci**	48	93	97:3	82
9	**3j**: cyclohexyl	**4cj**	48	61[f]	98:2	86

[a] Unless otherwise noted, all reactions were carried out using 0.01 mmol of (*R*)-**1** (5 mol %), 0.40 mmol of **2c** (2.0 equiv), and 0.20 mmol of **3** in 4.0 mL of THF at −40 °C. [b] Isolated yield. [c] Diastereomeric ratio was determined by ^{1}H NMR analysis. [d] Enantiomeric excess for the major *syn*-isomer was determined by chiral stationary phase column (Chiralpak AS-H) HPLC analysis. [e] The absolute stereochemistries of **4cc** were unambiguously determined to be 5*S*,1′*R* by X-ray crystallographic analysis.[13] [f] **3j** was recovered in 34%.

As illustrated in Scheme 2, vinylogous product **4ca** was readily transformed to β,γ-disubstituted butenolide **6** via standard chemical transformations. When treated with an organocuprate, **4ca** underwent a Michael addition to yield **7**, which was subsequently oxidized to the sulfoxide followed by

Scheme 2. Derivatization of Vinylogous Michael Product **4ca** to β,γ-Disubstituted Butenolide **6**



elimination under thermal conditions to provide **6** in an acceptable yield without considerable loss of stereoisomeric purities.

In conclusion, we have demonstrated that α-*tert*-butylthio substituted furanones can be utilized as efficient vinylogous pronucleophiles in the direct vinylogous Michael addition to conjugate nitroalkenes using an

axially chiral guanidine base catalyst. The method enables facile access to densely functionalized γ-butenolides in a highly *syn*-diastereo- and enantioselective manner. The synthetic potential of the present catalytic enantioselective reaction has also been demonstrated by further manipulation of α,γ-functionalized γ-butenolides by taking advantage of their multiple functionalities. Further studies of direct vinylogous transformations via activation of α-thio substituted furanones by chiral guanidine catalysts are underway in our laboratory.

Acknowledgment. This work was supported by JSPS for a Grant-in-Aid for Scientific Research (Grant No. 20245021). We also acknowledge Profs. T. Iwamoto and S. Ishida (Graduate School of Science, Tohoku University) for X-ray crystal structure determination of vinylogous Michael addition product *syn*-**4cc**.

Supporting Information Available. Experimental procedures, spectral data of products, and determination of stereochemistry of products. This material is available free of charge via Internet at http://pubs.acs.org.