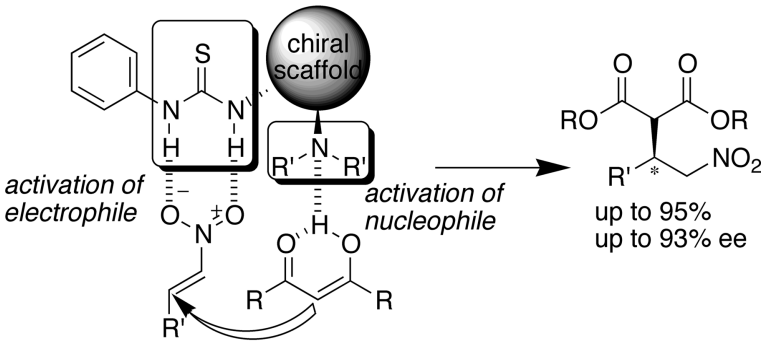
Communication

Enantioselective Michael Reaction of Malonates to Nitroolefins Catalyzed by Bifunctional Organocatalysts

Tomotaka Okino, Yasutaka Hoashi, and Yoshiji Takemoto

J. Am. Chem. Soc., **2003**, 125 (42), 12672-12673• DOI: 10.1021/ja036972z • Publication Date (Web): 30 September 2003



More About This Article

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

- Supporting Information
- Links to the 30 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 09/30/2003

Enantioselective Michael Reaction of Malonates to Nitroolefins Catalyzed by Bifunctional Organocatalysts

Tomotaka Okino, Yasutaka Hoashi, and Yoshiji Takemoto*

Graduate School of Pharmaceutical Sciences, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-8501, Japan

Received June 30, 2003; E-mail: takemoto@pharm.kyoto-u.ac.jp

One of the important Michael additions in organic chemistry is the addition of nucleophiles to nitroolefins due to their multiple reactivity and the valuable synthetic building blocks that are created.[1] Various enantioselective reactions have been reported by employing stoichiometric amounts of enantiopure additives.[2] Although the catalytic asymmetric versions of this reaction were achieved, most required metal catalysts or strict reaction conditions.[3−7] L-Proline derivatives have catalyzed the stereoselective addition of carbonyl compounds to nitroolefins, but only with moderate enantioselectivites.[8]

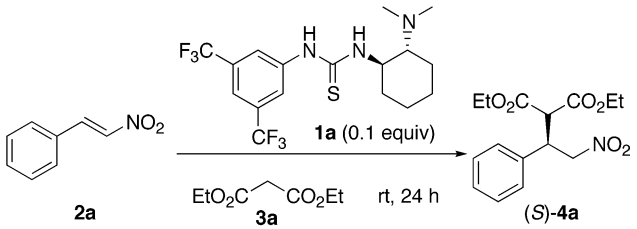
Urea derivatives act as acid catalysts[9,10] in only a few reactions compared to the enantioselective reactions catalyzed by L-proline,[11] chiral Lewis bases,[12] and phase-transfer catalysts.[13] Furthermore, chiral urea and thiourea derivatives have only catalyzed enantioselective, nucleophilic additions of HCN and ketene silyl acetals to imines.[10f−h] Herein a highly enantioselective Michael reaction of malonates to nitroolefins is reported using novel metal-free chiral bifunctional organocatalysts.

We previously reported that thiourea catalyzed the nucleophilic addition of TMSCN and ketene silyl acetals to nitrones and aldehydes.[10a] Unlike imines, aldehydes, and nitrones, nitroolefins have two oxygen atoms, which potentially can be activated by the acidic hydrogens of thiourea.[14,15] We anticipated that introduction of an additional basic, nucleophile-activating group in the thiourea catalyst might facilitate a synergistic interaction between the functional groups and thereby lead to an efficient catalyst for the Michael reaction. In other words, the nitroolefin and the nucleophile are simultaneously activated. Moreover, chiral thiourea catalysts with these functional groups on a chiral scaffold should yield the addition products with excellent enantioselectivity. This type of bifunctional catalyst has yet to be reported.[16]

The reaction conditions were optimized with thiourea **1a**, which has (*R*,*R*)-1,2-cyclohexyldiamine as a chiral scaffold. The reaction of *trans*-*β*-nitrostylene **2a** with diethyl malonate **3a** in the presence of 10 mol % of **1a** in methanol afforded the desired Michael adduct **4a** in 33% yield and 29% ee (Table 1, entry 1). Since methanol and **1a** competitively activate **2a**, the enantioselectivity of **4a** might be poor. Therefore, other solvents were examined. As expected, polar solvents (THF, MeCN), which reduced the activity of **1a**, resulted in poor yields of **4a** (entries 2, 3). In contrast, **1a** in nonpolar solvents (CH_2Cl_2, toluene) efficiently promoted the reaction with **2a** in moderate yields of **4a** with excellent enantioselectivities (entries 4, 5). In addition, using 2 equiv of **3a** improved the yield of **4a** (86%, 93% ee, entry 6).

Next, the effects of the thiourea catalysts were investigated (Table 2). **2a** and **3a** reacted very slowly in the presence of TEA and chiral amine **1b** without a thiourea moiety to give a poor yield and enantioselectivity of **4a** (entries 1, 2). Although combining thiourea **1c** and TEA enhanced the reaction rate, only a moderate chemical yield of **4a** was achieved (entry 3). *These results indicate that for a high yield and selectivity the catalyst should possess both a thiourea and tertiary amino group within the molecule.* In addition, these results reveal that substituents (R^1 and R^2) in the amino groups of **1d** and **1e** have a significant effect on the reaction rate, but only marginally affect the enantioselectivity of **4a** (entries 4, 5). In contrast, replacing 3,5-bis(trifluoromethyl)phenyl group of **1a** with

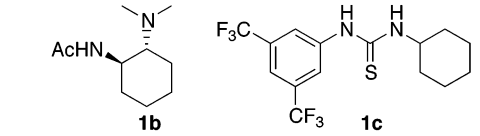
Table 1. Results for Optimal Reaction Conditions

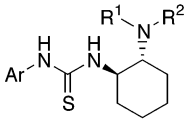


entry	solvent	**3a** (equiv)	% yield[b]	% ee[c,d]
1	MeOH	1	33	29
2	MeCN	1	47	75
3	THF	1	29	88
4	CH_2Cl_2	1	53	90
5	toluene	1	60	92
6	toluene	2	86	93

[a] The reaction was conducted with **1a** (0.1 equiv), **3a** (1−2 equiv), and several solvents at room temperature. [b] Isolated yield. [c] Enantiomeric excess was determined by HPLC analysis of **4a** using a chiral column. [d] Absolute configuration was determined by comparing the specific rotation of **4a** with that of literature data.[6]

Table 2. Optimization of Thioureas





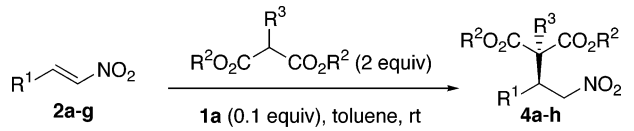
1d; Ar = 3,5-$(CF_3)_2C_6H_3$, R^1, R^2 = *o*-$(CH_2)_2C_6H_4$
1e; Ar = 3,5-$(CF_3)_2C_6H_3$, R^1 = Me, R^2 = ^{i}Pr
1f; Ar = Ph, R^1 = R^2 = Me
1g; Ar = 2-(MeO)C_6H_4, R^1 = Me

entry	additive	time (h)	% yield[b]	% ee[c,d]
1	TEA	24	17	−
2	**1b**	24	14	35
3	TEA+**1c**	24	57	−
4	**1d**	48	29	91
5	**1e**	48	76	87
6	**1f**	48	58	80
7	**1g**	48	40	52

[a] The reaction was conducted with **3a** (2 equiv) and toluene in the presence of various additives (0.1 equiv) at room temperature. [b] Isolated yield. [c] Enantiomeric excess was determined by HPLC analysis of **4a** using a chiral column. [d] Absolute configuration was determined by comparing the specific rotation of **4a** with that of literature data.[6]

10.1021/ja036972z CCC: $25.00

Table 3. Michael Addition of Malonates to Nitroolefins Catalyzed by Thiourea



entry	R^1	R^2	R^3	adduct	time (h)	% yield[b]	% ee[c] (config.)[d]
1	Ph	Et	H	**4a**	24	86	93 (*S*)
2	2,6-$(MeO)_2$Ph	Et	H	**4b**	72	87	93 (*S*)
3	4-F−Ph	Et	H	**4c**	12	87	92 (*S*)
4	1-naphthyl	Et	H	**4d**	24	95	92 (−)[e]
5	2-thienyl	Et	H	**4e**	48	74	90 (−)[e]
6	pentyl	Et	H	**4f**	48	78	81 (*S*)
7	^{i}Bu	Et	H	**4g**	48	88	81 (*S*)
8	Ph	Me	Me	**4h**	36	82	93 (−)[e]

[a] The reaction was conducted with nitroolefins (1 equiv), nucleophiles (2 equiv), and toluene at room temperature. [b] Isolated yield. [c] Enantiomeric excess was determined by HPLC analysis of **4** using a chiral column. [d] Absolute configuration was determined by comparing the specific rotation of **4** with that of literature data.[6] [e] Not determined.

other aryl groups, such as phenyl and 2-methoxyphenyl, decreased the enantioselectivity due to a weak hydrogen-bonding ability (entries 6, 7). It is noteworthy that the stereoselectivity diminished in the order of **1a** > **1f** > **1g**, which corresponds to the decrease in the N−H acidity of the thiourea compounds.

Table 3 summarizes the results using different nitroolefins. Excellent enantioselectivities (92−93% ee) were obtained when the nitroolefin substituents were aryl group (entries 1−5), while alkyl substituents at β-position slightly decreased the enantioselectivity (81% ee) (entries 6, 7). Previously, several examples of catalytic enantioselective Michael reactions of 2-alkyl malonates to nitroolefin have been reported, but the selectivities were low.[6a,7] This reaction was used to construct a quaternary carbon center. 2-Methylmalonate was reacted with **2a** under the same reaction conditions to yield the desired product **4h** with a high enantioselectivity (entry 8).

Besides these investigations, this Michael reaction was examined without solvent. Reacting **2a** with **3a** in the presence of **1a** (**2a**:**3a**:**1a** = 1:2:0.05) afforded **4a** with a good enantioselectivity (88% ee, 83% yield) within 12 h.

In summary, thiourea catalyst **1a** worked well as a bifunctional organocatalyst that promoted the Michael reaction of malonates to various nitroolefins with high enantioselectivities. The reaction was also successful without solvent. Further studies are currently investigating enantioselective Michael reactions of other nucleophiles to nitroolefins and developing polymer-supported catalysts.

Acknowledgment. This work was supported by grants from the NOVARTIS Foundation (Japan) for the promotion of Science and Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology.

Supporting Information Available: Experimental procedures and spectroscopic data for the products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For a review see: Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877−1894.

(2) (a) Johnson, T. A.; Jang, D. O.; Slafer, B. W.; Curtis, M. D.; Beak, P. *J. Am. Chem. Soc.* **2002**, *124*, 11689−11698. (b) Schäfer, H.; Seebach, D. *Tetrahedron* **1995**, *51*, 2305−2324. (c) Juaristi, E.; Beck, A. K.; Hansen, J.; Matt, T.; Mukhopadhyay, T.; Simson, M.; Seebach, D. *Synthesis* **1993**, 1271−1290. (d) Kobayashi, N.; Iwai, K. *J. Org. Chem.* **1981**, *46*, 1823−1828.

(3) Luchaco-Cullis, C. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 8192−8193.

(4) Hayashi, T. *Synlett* **2001**, 879−887.

(5) (a) Duursma, A.; Minnaard, A. J.; Feringa, B. L. *Tetrahedron* **2002**, *58*, 5773−5778. (b) Alexakis, A.; Benhaim, C.; Rosset, S.; Humam, M. *J. Am. Chem. Soc.* **2002**, *124*, 5262−5263. (c) Rimkus, A.; Sewald, N. *Org. Lett.* **2003**, *5*, 79−80.

(6) (a) Barnes, D. M.; Ji, J.; Fickes, M. G.; Fitzgerald, M. A.; King, S. A.; Morton, H. E.; Plagge, F. A.; Preskill, M.; Wagaw, S. H.; Wittenberger, S. J.; Zhang, J. *J. Am. Chem. Soc.* **2002**, *124*, 13097−13105. (b) Ji, J.; Barnes, D. M.; Zhang, J.; King, S. A.; Wittenberger, S. J.; Morton, H. E. *J. Am. Chem. Soc.* **1999**, *121*, 10215−10216.

(7) Brunner, H.; Kimel, B. *Monatsh. Chem.* **1996**, *127*, 1063−1072.

(8) (a) Andrey, O.; Alexakis, A.; Bernardinelli, G. *Org. Lett.* **2003**, *5*, 2559−2561. (b) Enders, D.; Seki, A. *Synlett* **2002**, 26−28. (c) List, B.; Pojarliev, P.; Martin, H. J. *Org. Lett.* **2001**, *3*, 2423−2425. (d) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2001**, *123*, 5260−5267.

(9) For a review see: Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726−3748.

(10) (a) Okino, T.; Hoashi, Y.; Takemoto, Y. *Tetrahedron Lett.* **2003**, *44*, 2817−2821. (b) Curran, D. P.; Kuo, L. H. *J. Org. Chem.* **1994**, *59*, 3259−3261. (c) Curran, D. P.; Kuo, L. H. *Tetrahedron Lett.* **1995**, *37*, 6647−6650. (d) Schreiner, P. R.; Wittkopp, A. *Org. Lett.* **2002**, *4*, 217−220. (e) Wittkopp, A.; Schreiner, P. R. *Chem. Eur. J.* **2003**, *9*, 407−414. (f) Vachal, P.; Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 867−870. (g) Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 10012−10014. (h) Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964−12965.

(11) (a) Cordova, A.; Notz, W.; Zhong, G.; Betancort, J. M.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2002**, *124*, 1842−1843. (b) Cordova, A.; Watanabe, S.; Tanaka, F.; Notz, W.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2002**, *124*, 1866−1867. (c) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798−6799.

(12) (a) Kobayashi, S.; Nishio, K. *Tetrahedron Lett.* **1993**, *34*, 3453−3456. (b) Denmark, S. E.; Wynn, T. *J. Am. Chem. Soc.* **2001**, *123*, 6199−6200. (c) Nakajima, M.; Saito, M.; Shiro, M.; Hashimoto, S. *J. Am. Chem. Soc.* **1998**, *120*, 6419−6420.

(13) (a) Okino, T.; Takemoto, Y. *Org. Lett.* **2001**, *3*, 1515−1517. (b) Dolling, U. H.; Davis, P.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1984**, *106*, 446−447. (c) O'Donnell, M. J.; Bennett, W. D.; Wu, S. *J. Am. Chem. Soc.* **1989**, *111*, 2353−2355. (d) Nelson, A. *Angew. Chem., Int. Ed.* **1999**, *38*, 1583−1585. (e) Ooi, T.; Takahashi, M.; Doda, K.; Maruoka, K. *J. Am. Chem. Soc.* **2002**, *124*, 7640−7641. (f) Kita, T.; Georgieva, A.; Hashimoto, Y.; Nakata, T.; Nagasawa, K. *Angew. Chem., Int. Ed.* **2002**, *41*, 2832−2834. (g) Ishikawa, T.; Araki, Y.; Kumamoto, T.; Seki, H.; Fukuda, K.; Isobe, T. *Chem. Commun.* **2001**, 245−246.

(14) (a) Etter, M. C.; Urbañczyk-Lipkowska, Z.; Zia-Ebrahimi, M.; Panunto, T. W. *J. Am. Chem. Soc.* **1990**, *112*, 8415−8426. (b) Kelly, T. R.; Kim, M. H. *J. Am. Chem. Soc.* **1994**, *116*, 7072−7080. (c) Linton, B. R.; Goodman, M. S.; Hamilton, A. D. *Chem. Eur. J.* **2000**, *6*, 2449−2455.

(15) ^{1}H NMR titration of a toluene-d_8 solution of *trans*-β-nitrostylene or diethyl malonate with catalyst **1a** resulted in no significant change of their resonances, since both of them might interact with **1a** very weakly.

(16) For a review of metallic bifunctional catalyst see: (a) Gröger, H. *Chem. Eur. J.* **2001**, *7*, 5246−5251. (b) Shibasaki, M.; Sasai, H.; Arai, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1236−1256.

JA036972Z