ORGANIC LETTERS
2009
Vol. 11, No. 7
1583−1586

Highly Enantioselective Synthesis of Nitrocyclopropanes via Organocatalytic Conjugate Addition of Bromomalonate to α,β-Unsaturated Nitroalkenes

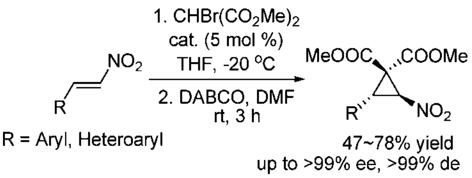
Yi-ning Xuan, Shao-zhen Nie, Li-ting Dong, Jun-min Zhang, and Ming Yan*

Industrial Institute of Fine Chemicals and Synthetic Drugs, School of Pharmaceutical Sciences, Sun Yat-sen University, Guangzhou 510006, China

yanming@mail.sysu.edu.cn

Received February 2, 2009

ABSTRACT



Highly enantioselective synthesis of nitrocyclopropanes was achieved via the organocatalytic conjugate addition of dimethyl bromomalonate to nitroalkenes and the consequent intramolecular cyclopropanation. 6′-Demethyl quinine was found to be the efficient catalyst. Excellent enantioselectivities, diastereoselectivities, and good yields were obtained for a variety of aryl or heteroaryl nitroethylenes.

Chiral cyclopropanes are important structural motifs in a great number of drugs and natural products.[1] In addition, chiral cyclopropanes are useful synthetic intermediates in organic synthesis.[2] The high strain of the cyclopropane ring makes them susceptible to ring opening reaction with many nucleophilic reagents. Great efforts have been made to develop efficient synthetic methods of chiral cyclopropanes.[3] Nitrocyclopropanes are a class of special cyclopropane compounds, which are presented in some natural products such as the peptidolactone hormaomycin[4] and are also used as the precursor of the broad-spectrum antibiotic Trovafloxacin.[5] Furthermore, nitrocyclopropanes can be converted into a wide range of useful compounds.[6] The asymmetric synthesis of nitrocyclopropanes had been developed via the reaction of nitroalkyl carbenes with alkenes.[7] Asymmetric conjugate addition and consequent intramolecular alkylation are extremely powerful and general methods for the synthesis of chiral cyclopropanes.[3a,8] In recent years, asymmetric organocatalysis has emerged as a powerful tool for the

---

(1) For the reviews of cyclopropanes as the structure motif in drugs and natural products, see: (a) Donaldson, W. A. *Tetrahedron* **2001**, *57*, 8589. (b) Faust, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 2251. (c) Wessjohann, L. A.; Brandt, W.; Thiemann, T. *Chem. Rev.* **2003**, *103*, 1625.

(2) For the reviews of cyclopropanes as useful synthetic intermediates, see: (a) Wong, H. N. C.; Hon, M. Y.; Tse, C. W.; Yip, Y. C.; Tanitroalkeneo, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165. (b) Reissig, H. U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151.

(3) For the reviews of asymmetric synthesis of cyclopropanes, see: (a) Pellissier, H. *Tetrahedron* **2008**, *64*, 7041. (b) Lebel, H.; Marcoux, J. F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977. (c) Hartley, R. C.; Caldwell, S. T. *J. Chem. Soc., Perkin Trans. 1* **2000**, 477.

(4) (a) Zlatopolskiy, B. D.; Loscha, K.; Alvermann, P.; Kozhushkov, S. I.; Nikolaev, S. V.; Zeeck, A.; de Meijere, A. *Chem. Eur. J.* **2004**, *10*, 4708. (b) Zindel, J.; de Meijere, A. *J. Org. Chem.* **1995**, *60*, 2968. (c) Andres, N.; Wolf, H.; Zaehner, H.; Roessner, E.; Zeeck, A.; Koenig, W. A.; Sinnwell, V. *Helv. Chim. Acta* **1989**, *72*, 426.

(5) (a) Gootz, T. D.; Brighty, K. E. *Med. Res. Rev.* **1996**, *16*, 433. (b) Brighty, K. E.; Castaldi, M. J. *Synlett* **1996**, 1097.

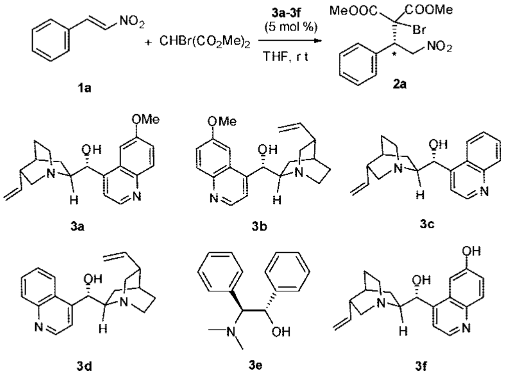
(6) For the reactions of nitrocyclopropanes, see: (a) Lifchits, O.; Alberico, D.; Zakharian, I.; Charette, A. B. *J. Org. Chem.* **2008**, *73*, 6838. (b) Wurz, R. P.; Charette, A. B. *J. Org. Chem.* **2004**, *69*, 1262. (c) Larionov, O. V.; Savel'eva, T. F.; Kochetkov, K. A.; Ikonnokov, N. S.; Kozhushkov, S. I.; Yufit, D. S.; Howard, J. A. K.; Khrustalev, V. N.; Belokon, Y. N.; de Meijere, A. *Eur. J. Org. Chem.* **2003**, 869. (d) Hubner, J.; Liebscher, J.; Patzel, M. *Tetrahedron* **2002**, *58*, 10485. (e) Cao, W.; Erden, I.; Keeffe, J. R. *Angew. Chem., Int. Ed.* **1995**, *34*, 1091. (f) Zindel, J.; Zeeck, A.; Konig, W. A.; de Meijere, A. *Tetrahedron Lett.* **1993**, *34*, 1917. (g) Baer, H. H.; Williams, U.; Radatus, B. *Carbohydr. Res.* **1988**, *174*, 291. (h) Seebach, D.; Haener, R.; Vettiger, T. *Helv. Chim. Acta* **1987**, *70*, 1507.

10.1021/ol900227j CCC: $40.75

synthesis of valuable chiral compounds.[9] Conjugate addition of 1-bromonitroalkanes to unsaturated aldehydes[10] and ketones[11] catalyzed by chiral amines was developed by us and other research groups. The corresponding nitrocyclopropanes were obtained in good yields and with excellent enantioselectivities. On the other hand, the asymmetric synthesis of nitrocyclopropanes via the addition of chloromalonates to nitroalkenes was also reported by Connon and co-workers in 2006.[12] The reaction provided the nitrocyclopropanes in moderate yield and with low enantioselectivity using cinchona alkaloid derived thioureas as the catalysts. Very recently, Fan and co-workers reported the asymmetric synthesis of nitrocyclopropanes via oxidative cyclization of the Michael adducts of nitroalkenes with malonates.[13] Good enantioselectivities were achieved using a chiral thiourea catalyst derived from cyclohexanediamine. Cinchona alkaoids are highly useful organocatalysts for a large number of asymmetric transformations.[14] Among the various derivatives of cinchona alkaoids, 6′-demethyl cinchona alkaoids (cupreines and cupreidines) showed great advantages in a variety of reactions. These catalysts feature simultaneous activation of both nucleophile and electrophile.[15] Deng and co-workers reported a highly enantioselective addition of malonates to nitroalkenes catalyzed by 6′-demethyl cinchona alkaoids.[16] The reaction was also catalyzed by cinchona alkaloid based urea and thiourea organocatalysts with excellent enantioselectivities.[17] Herein we report a highly enantioselective conjugate addition of dimethyl bromomalonate to nitroalkenes catalyzed by 6′-demethyl quinine. The consequent intramolecular cyclopropanation provided nitrocyclopropanes in good yields and with excellent enantioselectivities.

The reaction of dimethyl bromomalonate and β-nitrostyrene was studied using cinchona alkaloids and its derivatives as the catalysts (Scheme 1). Natural cinchona alkaloids **3a**−**3d** were inefficient, and no reaction occurred after 48 h at room temperature. Chiral amino alcohol **3e** also did not show any catalytic activity. In contrast, 6′-demethyl quinine **3f** afforded the adduct in good yield and with excellent enantioselectivity. The product **2a** was deposited from the reaction solution and easily separated by the centrifuge. The result confirms the importance of free phenolic hydroxyl group for the catalytic activity of cinchona alkaloids. The similar phenomenon was also observed by Deng and co-workers.[16]

Scheme 1. Catalytic Addition of Dimethyl Bromomalonate to β-Nitrostyrene



Encouraged by the preliminary result, further optimization of reaction conditions was carried out and the results are summarized in Table 1. Lower reaction temperature significantly improved the yield, probably due to reduced side reactions. In addition, the enantioselectivity could be improved furthermore. Over 99% ee and excellent chemical yield were achieved at −20 °C (Table 1, entry 3). The decrease of catalyst loading resulted in lower chemical yield, but the enantioselectivity of the reaction was not influenced (Table 1, entries 3−5).

Table 1. Optimization of Reaction Conditions[a]

entry	*t* (°C)	**3f** (mol %)	yield (%)[b]	ee (%)[c]
1	rt	5	81	98
2	0	5	90	98
3	−20	5	95	>99
4	−20	2	88	99
5	−20	1	80	99

[a] Reactions were carried out for 24 h with **1a** (0.5 mmol), dimethyl bromomalonate (0.55 mmol), **3f** (0.025 mmol) in THF (0.5 mL). [b] Isolated yield. [c] Enantiomeric excess values were determined by chiral HPLC after transformation to **4a**.

The intramolecular cyclopropanation of the product **2a** was further studied. A number of bases and solvents were

---

(7) Asymmetric synthesis of nitrocyclopropanes via the reaction of nitroalkyl carbenes with alkenes, see: (a) Zhu, S.; Perman, J. A.; Zhang, X. P. *Angew. Chem., Int. Ed.* **2008**, *47*, 8460. (b) Moreau, B.; Charette, A. B. *J. Am. Chem. Soc.* **2005**, *127*, 18014. (c) Charette, A. B.; Wurz, R. P. *J. Mol. Catal. A* **2003**, *196*, 83. (d) Wurz, R. P.; Charette, A. B. *Org. Lett.* **2003**, *5*, 2327.

(8) (a) Ibrahem, I.; Zhao, G. L.; Rios, R.; Vesely, J.; Sunden, H.; Dziedzic, P.; Cordova, A. *Chem. Eur. J.* **2008**, *14*, 7867. (b) Xie, H.; Zu, L.; Li, H.; Wang, J.; Wang, W. *J. Am. Chem. Soc.* **2007**, *129*, 10886.

(9) For the general reviews on asymmetric organocatalysis, see: (a) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701. (b) Guillena, G.; Najera, C.; Ramon, D. J. *Tetrahedron: Asymmetry* **2007**, *18*, 2249. (c) Dalko, P. I. *Enantioselective Organocatalysis*; Wiley-VCH: Weinheim, Germany, 2007. (d) The special issue devoted to “Asymmetric Organocatalysis”: List, B. *Chem. Rev.* **2007**, *107*, 5413. (e) Yu, X. H.; Wang, W. *Chem. Asian J.* **2008**, *3*, 516.

(10) (a) Zhang, J. M.; Hu, Z. P.; Dong, L. T.; Xuan, Y. N.; Yan, M. *Tetrahedron: Asymmetry* **2009**, in press. (b) Vesely, J.; Zhao, G. L.; Bartoszewicz, A.; Cordova, A. *Tetrahedron Lett.* **2008**, *49*, 4209.

(11) (a) Lv, j.; Zhang, J. M.; Lin, Z.; Wang, Y. M. *Chem. Eur. J.* **2009**, *15*, 972. (b) Hansen, H. M.; Longbottom, D. A.; Ley, S. V. *Chem. Commun.* **2006**, 4838.

(12) McCooey, S. H.; McCabe, T.; Connon, S. J. *J. Org. Chem.* **2006**, *71*, 7494.

(13) Fan, R. H.; Ye, Y.; Li, W. X.; Wang, L. F. *Adv. Synth. Catal.* **2008**, *350*, 2488.

(14) For the review of cinchona alkaloids as organocatalysts, see: Tian, S. K.; Chen, Y.; Hang, J.; Tang, L.; McDaid, P.; Deng, L. *Acc. Chem. Res.* **2004**, *37*, 621.

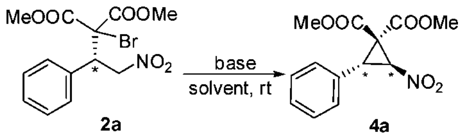
(15) Marcelli, T.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 7496.

(16) Li, H.; Wang, Y.; Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2004**, *126*, 9906.

(17) (a) Connon, S. J. *Chem. Commun.* **2008**, 2499. (b) McCooey, S. H.; Connon, S. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6367. (c) Ye, J. X.; Dixon, D. J.; Hynes, P. S. *Chem. Commun.* **2005**, 4481.

examined. The experiment results are listed in Table 2. The choice of the appropriate base and solvent was important for the success of the transformation. The combination of DABCO and DMF provided nitrocyclopropane **4a** in good yield (Table 2, entry 7). The relative configuration of **4a** was determined to be *trans* based on NOE analysis. No *cis*-isomer was observed by NMR analysis.

Table 2. Effect of Bases and Solvents on the Intramolecular Cyclopropanation of **2a**[a]



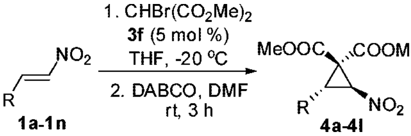
entry	solvent	base	time (h)	yield (%)[b]
1	DCM	Et_3N	120	trace
2	DMF	K_2CO_3	120	–
3	THF	Et_3N	72	trace
4	THF	DABCO	38	32
5	MeOH	DABCO	3	–
6	EtOAc	DABCO	3	trace
7	DMF	DABCO	3	82
8	DMSO	DABCO	2	64
9	NMP[c]	DABCO	3	79

[a] Reactions were carried out at room temperature with **2a** (0.1 mmol), base (0.105 mmol) and solvent (1 mL). [b] Isolated yield. Only *trans*-isomer was observed. >99% ee values were obtained in all cases. [c] *N*-Methylpyrrolidin-2-one.

The asymmetric conjugate addition of dimethyl bromomalonate to a number of nitroalkenes catalyzed by **3f** and consequent intramolecular cyclopropanation were studied. The results are summarized in Table 3. Various substituted β-phenyl nitroethylenes provided nitrocyclopropanes in good yields and with excellent enantioselectivities (Table 3, entries 1–9). The *ortho*-, *meta*-, and *para*-substituents on the phenyl ring were tolerated very well. The electronic property of the substituent seemed to have a slight effect on the yield and enantioselectivity. The reaction of β-naphthyl nitroethylene required extended reaction time and provided the nitrocyclopropane product with moderate enantioselectivity (Table 3, entry 10). The result could be ascribed to the bigger steric hindrance of the naphthyl group. β-Heteroaryl nitroethylenes provided nitrocyclopropanes with excellent enantioselectivities, however, in low to moderate chemical yields (Table 3, entries 11 and 12). β-Alkyl nitroethylenes were also examined, but no conjugate adducts were observed.

A single crystal of nitrocyclopropane **4h** was obtained. The absolute configuration of **4h** was determined as (2*S*,3*R*)-dimethyl 2-nitro-3-(4-nitrophenyl)cyclopropane-1,1-dicarboxylate by X-ray diffraction analysis (Figure 1).[18] Analogously, the other nitrocyclopropane products were proposed to have the same absolute configurations.

Table 3. Synthesis of Chiral Nitrocyclopropanes from a Variety of Nitroalkenes[a]



entry	R	time (h)[b]	product, yield (%)[c]	ee (%)[d]
1[e]	Ph, **1a**	24	**4a**, 78	>99
2	4-Cl-C_6H_4, **1b**	24	**4b**, 69	96
3	2-Cl-C_6H_4, **1c**	34	**4c**, 70	97
4[e]	3-Cl-C_6H_4, **1d**	24	**4d**, 72	>99
5	4-Br-C_6H_4, **1e**	24	**4e**, 68	94
6[f]	4-Me-C_6H_4, **1f**	66	**4f**, 63	97
7[f]	4-MeO-C_6H_4, **1g**	72	**4g**, 67	94
8	4-NO_2-C_6H_4, **1h**	12	**4h**, 58	96
9	2-NO_2-C_6H_4, **1i**	66	**4i**, 73	95
10	1-naphthyl, **1j**	94	**4j**, 75	75
11	2-thienyl, **1k**	24	**4k**, 69	98
12	2-furyl, **1l**	24	**4l**, 47	99
13	pentyl, **1m**	48	–	–
14	cyclohexyl, **1n**	48	–	–

[a] Asymmetric conjugate additions were carried out with **1** (0.5 mmol), dimethyl bromomalonate (0.55 mmol), **3f** (0.025 mmol) in THF (0.5 mL). Unless otherwise stated, adducts **2** were separated by flash column chromatography. The intramolecular cyclopropanations were carried out with **2** (0.1 mmol) and DABCO (0.105 mmol) in DMF (1 mL). [b] The reaction time of the first step. [c] The combined yield of two steps. Only *trans*-isomer was observed. [d] Determined by chiral HPLC. [e] Adducts of the first reaction were separated by centrifugation. [f] The first step was conducted in THF (1 mL) due to low solubility of the substrate.

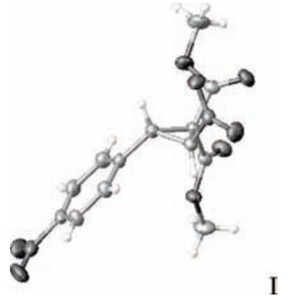


Figure 1. X-ray structure of **4h**.

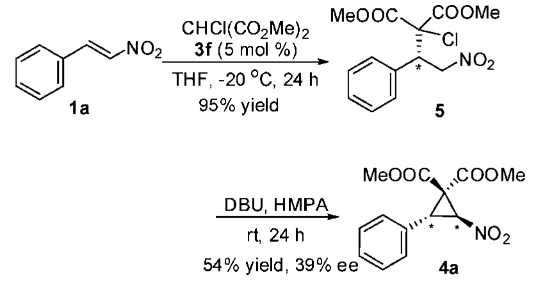
The asymmetric conjugate addition of dimethyl chloromalonate to β-nitrostyrene and the consequent intramolecular cyclopropanation were also studied (Scheme 2). The conjugate addition was achieved in good yield, but the intramolecular cyclopropanation of adduct **5** was found to be more difficult than cyclopropanation of **2a**. Only a trace amount of **4a** was observed after 48 h with the DABCO/DMF system. The DBU/HMPA system adopted by Connon and co-workers[12] provided **4a** in better yield, but the enantioselectivity was rather poor (39% ee).

In summary, we have developed a convenient and efficient method for the asymmetric synthesis of nitrocyclopropanes via the organocatalytic conjugate addition of dimethyl bro-

---

(18) CCDC 718886 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.

Scheme 2. Asymmetric Cyclopropanation of β-Nitrostyrene with Dimethyl Chloromomalonate



momalonate to nitroalkenes and the consequent intramolecular cyclopropanation. Excellent enantioselectivities, diastereoselectivities, and good chemical yields were achieved. The readily available catalyst and the simple procedure make the method attractive for the practical synthesis of chiral nitrocyclopropanes. Further applications of the nitrocyclopropane products in organic synthesis are currently under investigation.

Acknowledgment. We thank the National Natural Science Foundation of China (No. 20772160), NCET plan of the Ministry of Education of China, Guangzhou Bureau of Science and Technology for the financial support of this study. We also thank Professor Xiao-peng Hu for performing the X-ray diffraction analysis.

Supporting Information Available: Experimental procedures, NMR spectra, and HPLC chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.

OL900227J