ORGANIC LETTERS

2012
Vol. 14, No. 1
134–137

Synthesis of Highly Functionalized Chiral 3,3′-Disubstituted Oxindoles via an Organocatalytic Enantioselective Michael Addition of Nitroalkanes to Indolylidenecyanoacetates

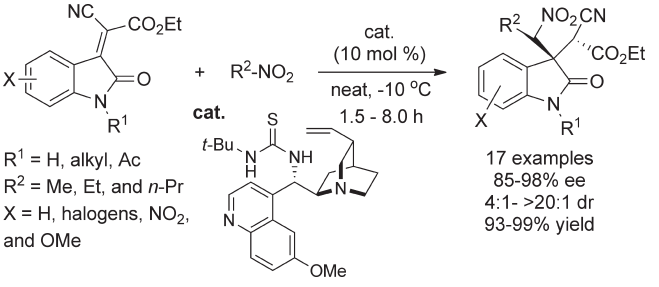
Lu Liu,[†] Deyan Wu,[†] Shu Zheng,[†] Tengfei Li,[†] Xiangmin Li,[†] Sinan Wang,[†] Jian Li,[†] Hao Li,*[,†] and Wei Wang*[,†,‡]

Department of Pharmaceutical Science, School of Pharmacy, East China University of Science & Technology, Shanghai 200237, People's Republic of China, and Department of Chemistry and Chemical Biology, University of New Mexico, Albuquerque, New Mexico 87131-0001, United States

lieehao@hotmail.com; wwang@unm.edu

Received October 30, 2011

ABSTRACT



An efficient bifunctional cinchona alkaloid derived thiourea-promoted enantioselective conjugate addition of nitroalkanes to indolylidenecyanoacetates has been developed under neat conditions. The process leads to synthetically interesting densely functionalized 3,3′-disubstituted oxindoles with creation of up to three stereogenic centers.

Given the broad spectrum of attractive biological properties of oxindole alkaloids,[1] their structures have been a driving force for developing new synthetic reactions. Notably, a number of elegant synthetic strategies have been developed recently, particularly organocatalyzed asymmetric versions.[2] Despite the significant advances made, an organocatalytic enantioselective conjugate addition of nitroalkanes to oxindole-derived Michael acceptors has not been reported to our knowledge.[3−5] The rich chemistry of the resulting nitro-containing products[6] enabled facile elaboration to structures of interest, important aspects in diversity-oriented synthesis (DOS).[7]

In continuation of our efforts to create structurally diverse oxindole compounds with potentially interesting biological properties[8] and with a view to fashioning the quaternary stereogenic center[9] of a large array of oxindole natural products,[1] we envisioned studying the reaction shown in Scheme 1. The successful realization of a catalytic asymmetric process would enable the generation of 3,3′-disubstituted oxindoles bearing three versatile nitro-, nitrile, and ester functionalities, which could allow convenient synthetic elaboration.[1] Moreover, up to three stereogenic centers including one full carbon quaternary chiral center could be potentially created in this operation.

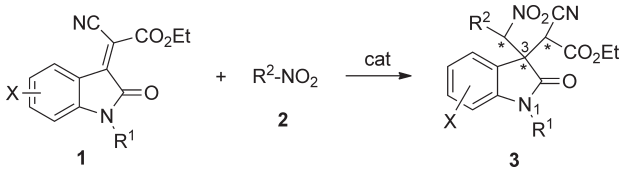
In this paper, we disclose a new, efficient organocatalytic enantioselective Michael addition of nitroalkanes to

[†] East China University of Science & Technology.
[‡] University of New Mexico.

(1) For reviews of oxindole alkaloids, see: (a) Badillo, J. J.; Hanhan, N. V.; Franz, A. K. *Curr. Opin. Drug Discovery Disc.* **2010**, *13*, 758. (b) Peddibhotla, S. *Curr. Bioact. Compd.* **2009**, *5*, 20. (c) Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748. (d) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209.

10.1021/ol202931e
Published on Web 12/12/2011

Scheme 1. Organocatalytic Enantioselective Michael Addition of Nitroalkanes to α,β-Unsaturated Cyanoacetate Oxindoles



indolylidenecyanoacetates to generate 3,3′-disubstituted chiral oxindoles in high yield and with good to high enantioselectivity (85−98% ee) and good to high dr (1:4 to >20:1 dr ratio) under neat conditions. Furthermore, as demonstrated, the adducts can be readily transformed to chiral spiro-oxindoles as potential CRTH2 (DP2) receptor antagonists.[10]

In the initial study, a variety of bifunctional amine thiourea catalysts (10 mol %)[11,12] were screened for the proposed catalytic enantioselective Michael addition of nitromethane **2a** to indolylidene-cyanoacetate **1a** without a solvent (Table 1). We found that the reaction proceeded smoothly to afford the desired product **3a** in high yields (92−99%, entries 1−8) with moderate dr, but the enantioselectivities varied. Among the catalysts probed, catalyst **IV**[13] gave the highest ee value (77% ee, entry 4). Therefore, it was selected for further optimization of the reaction conditions. It appeared that when the reaction was carried out in a solvent, regardless of polarity (entries 4 and 9−16), they were detrimental to the enantioselectivity and longer reaction times were required. Lowering the reaction temperature improved the enantioselectivity and diastereoselectivity significantly, while still preserving high yields and short reaction times (entries 17−19).

Having established an optimal reaction protocol, we next probed a variety of indolylidenecyanoacetates (**1**) with nitroalkanes (**2**) to determine the scope of the **IV**-catalyzed enantioselective Michael addition transformation (Table 2). We found that the process served as a general approach to enantioenriched 3,3′-disubstituted oxindoles **3** with a significant structural variation. Notably, in all cases, the processes proceeded efficiently (1.5−8 h) in high yield (93−99%) and with good to high enantioselectivity (85−98% ee) and diastereoselectivity (4:1 to >20:1 dr). It appeared that the electronic effect was limited. The benzene ring of **1** bearing electron-neutral (entry 1), electron-withdrawing (entries 2−6), electron-donating groups (entry 7) gave 85−98% ee and diastereoselectivity (9:1 to >20:1). Nevertheless, it was found that derivatization of the nitrogen moiety in **1** (entries 8−15) had an influence on the diastereoselectivity of products; in general, the dr was decreased while the reaction yields and enantioselectivities were affected marginally. Finally, we also probed the structural features of nitroalkanes that included nitroethane and -propane (entries 16 and 17) as Michael donors for the conjugate addition reaction. They smoothly underwent the reaction with high efficiency, and three stereogentic centers were generated.

(2) (a) For a review, see: Zhou, F.; Liu, Y.-L.; Zhou, J. *Adv. Synth. Catal.* **2010**, *352*, 1381. For recent selected examples, see: (b) Chauhan, P.; Chimni, S. S. *Chem.—Eur. J.* **2010**, *16*, 7709. (c) Wang, X.-N.; Zhang, Y.-Y.; Ye, S. *Adv. Synth. Catal.* **2010**, *352*, 1892. (d) Guo, Q.; Bhanushali, M.; Zhao, C.-G. *Angew. Chem., Int. Ed.* **2010**, *49*, 9460. (e) Bui, T.; Candeias, N. R.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2010**, *132*, 5574. (f) Li, X.; Luo, S.; Cheng, J.-P. *Chem.—Eur. J.* **2011**, *16*, 14290. (g) Guang, X.-Y.; Wei, Y.; Shi, M. *Chem.—Eur. J.* **2010**, *16*, 13617. (h) Aikawa, K.; Mimura, S.; Numata, Y.; Mikami, K. *Eur. J. Org. Chem.* **2011**, 62. (i) Zheng, K.; Yin, C.; Liu, X.; Lin, L.; Feng, X. *Angew. Chem., Int. Ed.* **2011**, *50*, 2573. (j) Zhang, Z.; Zheng, W.; Antilla, J. C. *Angew. Chem., Int. Ed.* **2011**, *50*, 1135. (k) Jiang, X.; Cao, Y.; Wang, Y.; Liu, L.; Shen, F.; Wang, R. *J. Am. Chem. Soc.* **2010**, *132*, 15328. (l) Zhao, M.-X.; Tang, W.-H.; Chen, M.-X.; Wei, D.-K.; Dai, T.-L.; Shi, M. *Eur. J. Org. Chem.* **2011**, 6078. (m) Allous, I.; Comesse, S.; Sanselme, M.; Daich, A. *Eur. J. Org. Chem.* **2011**, 5303. (n) Peng, J.; Huang, X.; Jiang, L.; Cui, H.-L.; Chen, Y.-C. *Org. Lett.* **2011**, *13*, 4584. (o) Duan, S.-W.; Lu, H.-H.; Zhang, F.-G.; Xuan, J.; Chen, J.-R.; Xiao, W.-J. *Synthesis* **2011**, 1847. (p) Lee, H. J.; Kang, S. H.; Kim, D. Y. *Synlett* **2011**, 1559. (q) Zhong, F.; Han, X.; Wang, Y.; Lu, Y.-X. *Angew. Chem., Int. Ed.* **2011**, *50*, 7837. (r) Alluri, S.; Feng, H.; Livings, M.; Samp, L.; Biswas, D.; Lam, T. W.; Lobkovsky, E.; Ganguly, A. K. *Tetrahedron Lett.* **2011**, *52*, 3945. (s) Tan, B.; Candeias, N. R.; Barbas, C. F., III. *Nature Chem.* **2011**, *3*, 473. (t) Liu, X.-L.; Wu, Z.-J.; Du, X.-L.; Zhang, X.-M.; Yuan, W.-C. *J. Org. Chem.* **2011**, *76*, 4008. (u) Freund, M. H.; Tsogoeva, S. B. *Synlett* **2011**, 503. (v) Liu, Z.; Gu, P.; Shi, M.; McDowell, P.; Li, G. *Org. Lett.* **2011**, *13*, 2314. (w) Singh, A.; Roth, G. P. *Org. Lett.* **2011**, *13*, 2118. (x) Hande, S. M.; Nakajima, M.; Kamisaki, H.; Tsukano, C.; Takemoto, Y. *Org. Lett.* **2011**, *13*, 1828. (y) Pesciaioli, F.; Righi, P.; Mazzanti, A.; Bartoli, G.; Bencivenni, G. *Chem.—Eur. J.* **2011**, *17*, 2842. (z) Zheng, W.; Zhang, Z.; Kaplan, M. J.; Antilla, J. C. *J. Am. Chem. Soc.* **2011**, *133*, 3339. (aa) Ding, M.; Zhou, F.; Liu, C.-H.; Wang, Y.-L.; Zhao, X.-L.; Zhou, J. *Chem. Sci.* **2011**, *2*, 2035.

(3) For a recent review, see: Córdova, A. *Catalytic Asymmetric Conjugate Addition Reactions*; Wiley-VCH: Weinheim, 2010.

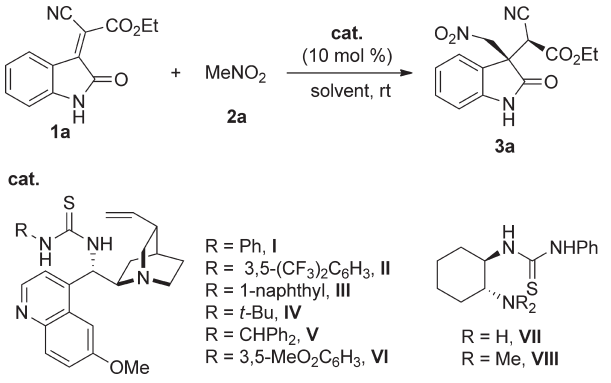
(4) For recent reviews of organocatalytic conjugate addition reactions, see: (a) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, *2007*, 1701. (b) Almaşi, D.; Alonso, D. A.; Nájera, C. *Tetrahedron: Asymmetry* **2007**, *18*, 299. Recent selected examples of conjugate addition of nitroalkanes,: enals as Michael acceptors: (c) Ghosh, S. K.; Zheng, Z.; Ni, B. *Adv. Synth. Catal.* **2010**, *352*, 2378. (d) Maltsev, O. V.; Kucherenko, A. S.; Beletskaya, I. P.; Tartakovsky, V. A.; Zlotin, S. G. *Eur. J. Org. Chem.* **2010**, 2927. (e) Mager, I.; Zeitler, K. *Org. Lett.* **2010**, *12*, 1480. (f) Zhang, J.-M.; Lou, C.-L.; Hu, Z.-P.; Yan, M. *ARKIVOC* **2009**, 362. (g) Wang, Y.; Li, P.; Liang, X.; Zhang, T. Y.; Ye, J. *Chem. Commun.* **2008**, 1232. (h) Gotoh, H.; Ishikawa, H.; Hayashi, Y. *Org. Lett.* **2007**, *9*, 5307. Enones: (i) Kwiatkowski, P.; Dudzinski, K.; Lyzwa, D. *Org. Lett.* **2011**, *13*, 3624. (j) Manzano, R.; Andres, J. M.; Álvarez, R.; Muruzabal, M. D.; de Lera, A. R.; Pedrosa, R. *Chem.—Eur. J.* **2011**, *17*, 5931. (k) Yang, W.; Du, D.-M. *Org. Lett.* **2010**, *12*, 5450. (l) Yang, Y.-Q.; Chen, X.-K.; Xiao, H.; Liu, W.; Zhao, G. *Chem. Commun.* **2010**, *46*, 4130. (m) Lu, H.-H.; Wang, X.-F.; Yao, C.-J.; Zhang, J.-M.; Wu, H.; Xiao, W.-J. *Chem. Commun.* **2009**, 4251. (n) Pansare, S. V.; Lingampally, R. *Org. Biomol. Chem.* **2009**, *7*, 319. (o) Malmgren, M.; Granander, J.; Amedjkouh, M. *Tetrahedron: Asymmetry* **2008**, *19*, 1934. (p) Ballini, R.; Barboni, L.; Castrica, L.; Fringuelli, F.; Lanari, D.; Pizzo, F.; Vaccaro, L. *Adv. Synth. Catal.* **2008**, *350*, 1218. (q) Li, P.; Wang, Y.; Liang, X.; Ye, J. *Chem. Commun.* **2008**, 3302. (r) Vakulya, B.; Varga, S.; Soos, T. *J. Org. Chem.* **2008**, *73*, 3475. (s) Linton, B. R.; Reutershan, M. H.; Aderman, C. M.; Richardson, E. A.; Brownell, K. R.; Ashley, C. W.; Evans, C. A.; Miller, S. J. *Tetrahedron Lett.* **2007**, *48*, 1993. Nitroolefins: (t) Dong, X.-Q.; Teng, H.-L.; Wang, C.-J. *Org. Lett.* **2009**, *11*, 1265. (u) Rabalakos, C.; Wulff, W. D. *J. Am. Chem. Soc.* **2008**, *130*, 13524. (v) Yang, X.; Zhou, X.; Lin, L.; Chang, L.; Liu, X.; Feng, X. *Angew. Chem., Int. Ed.* **2008**, *47*, 7079. Sulfones: (w) Zhu, Q.; Lu, Y.-X. *Org. Lett.* **2009**, *11*, 1721. Esters: (x) Ooi, T.; Fujioka, S.; Maruoka, K. *J. Am. Chem. Soc.* **2004**, *126*, 11790.

(5) Studies from our group: (a) Mei, K.; Jin, M.; Zhang, S.-L.; Li, P.; Liu, W.-J.; Chen, X.-B.; Xue, F.; Duan, W.-H.; Wang, W. *Org. Lett.* **2009**, *11*, 2864. (b) Zu, L.; Xie, H.; Li, H.; Wang, J.; Wang, W. *Adv. Synth. Catal.* **2007**, *349*, 2660. (c) Wang, J.; Li, H.; Zu, L.; Jiang, W.; Wang, W. *Adv. Synth. Catal.* **2006**, *348*, 2047. (d) Wang, J.; Li, H.; Zu, L.; Jiang, W.; Xie, H.; Duan, W.-H.; Wang, W. *J. Am. Chem. Soc.* **2006**, *128*, 12652.

(6) Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877.

(7) (a) Galloway, W. R. J. D.; Isidro-Llobet, A.; Spring, D. R. *Nature Commun.* **2010**, *1*, Gal1/1–Gal1/13. (b) Nielsen, T. E.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 48.

Table 1. Optimization of Reaction Conditions[a]

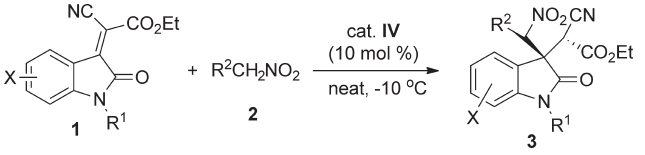


entry	cat.	solvent	time (h)	% yield[b]	% ee[c]	dr[d]
1	**I**	neat	1/3	93	69	2:1
2	**II**	neat	0.5	92	69	2:1
3	**III**	neat	1/3	90	62	3:1
4	**IV**	neat	5/6	99	77	3:1
5	**V**	neat	5/6	95	75	3:1
6	**VI**	neat	3	90	70	2:1
7	**VII**	neat	2	93	46	2:1
8	**VIII**	neat	0.5	94	60	2:1
9	**IV**	CH_2Cl_2	7	96	70	3:1
10	**IV**	DMF	14	95	28	3:1
11	**IV**	THF	24	94	52	3:1
12	**IV**	toluene	3.5	96	62	3:1
13	**IV**	MeCN	8	95	72	3:1
14	**IV**	EtOAc	6	92	65	4:1
15	**IV**	dioxane	6	91	48	3:1
16	**IV**	MeOH	8	90	51	3:1
17[e]	**IV**	neat	2.5	97	82	9:1
18[f]	**IV**	neat	3.5	99	87	9:1
19[g]	**IV**	neat	7	98	88	9:1
20[h]	**IV**	neat	40	95	87	9:1

[a] Reaction conditions: unless specified, a mixture of **1a** (121 mg, 0.5 mmol) and a catalyst (0.05 mmol) in nitromethane (1.0 mL) was stirred at rt for a specified time. After concentration in vacuo, the residue was purified by silica gel chromatography, eluting with EtOAc and hexanes (1/2 v/v ratio). [b] Isolated yield. [c] Determined by chiral HPLC (Chiralpak AD-H). [d] Determined by ^{1}H NMR [e] Reaction carried out at 0 °C. [f] Reaction carried out at −10 °C. [g] Reaction carried out at −25 °C. [h] 5 mol % of catalyst used.

The Michael adducts **3** hold great potential in DOS and therapeutic agent development. Toward this end, we showed that, for example, product **3b** could be readily transformed into a spirooxindole **4** (Scheme 2). Selective reduction of the nitro group by ferrous sulfate to an amine was followed by spontaneous lactamization to give product **4** in 85% yield whose diastereoselectivity was improved (dr >20:1). It is noteworthy that the racemic spirooxindoles have been reported as CRTH2 (DP2) receptor antagonists of potential usefor the treatment of allergic inflammatory diseases.[10] The asymmetric method reported here could be employed for the preparation of the

Table 2. Generality of **IV**-Catalyzed Conjugate Addition of Nitroalkanes **2** to Indolylidenecyanoacetates **1**[a]



entry	X, R^1, R^2, **3**	time (h)	% yield[b]	% ee[c]	dr[d]
1	H, H, H, **3a**	3.5	99	87	9:1
2	5-Br, H, H, **3b**	3	95	98	12:1
3	5-Cl, H, H, **3c**	3	94	85	>20:1
4	7-Cl, H, H, **3d**	5	96	85	>20:1
5	5-NO_2, H, H, **3e**	1.5	94	92	12:1
6	5-I, H, H, **3f**	3	95	89	11:1
7	5-MeO, H, H, **3g**	2	93	85	>20:1
8	H, CH_2CO_2Me, H, **3h**	4	95	88	4:1[f]
9	H, Me, H, **3i**	4	96	97	6:1[g]
10	H, Ac, H, **3j**	6	94	96	6:1[h]
11	5-Br, Me, H, **3k**	6	98	92	8:1
12	5-Br, CH_2CO_2Me, H, **3l**	6	97	85	10:1
13	5-Br, Bn, H, **3m**	8	97	85	4:1
14	5-I, Me, H, **3n**	6	94	91	10:1
15	5-OMe, Me, H, **3o**	4	95	90	>20:1
16[e]	H, H, Me, **3p**	3	95	88	7:1[i]
17[e]	H H, Et, **3q**	3	97	97	6:1[j]

[a] Reaction conditions: unless specified, see footnote *a* in Table 1. [b] Isolated yields. [c] Determined by chiral HPLC analysis (Chiralpak AD-H or AS-H). [d] Determined by ^{1}H NMR. [e] Major isomer with *R*-configuration determined by NOESY (see the Supporting Information for details). [f] 14% ee for minor isomer. [g] 84% ee for minor isomer. [h] 73% ee for minor isomer. [i] 25% ee for minor isomer. [j] 98% ee for minor isomer.

(8) For studies of organocatalyzed synthesis of oxindoles from our laboratory, see: (a) Liu, L.; Zhang, S.; Xue, F.; Lou, G.; Zhang, H.; Ma, S.; Duan, W.; Wang, W. *Chem.—Eur. J.* **2011**, *17*, 7791. (b) Deng, J.; Zhang, S.-L.; Ding, P.; Jiang, H.-L.; Wang, W. *Adv. Synth. Catal.* **2010**, *352*, 833. (c) Xue, F.; Zhang, S.-L.; Liu, L.; Duan, W.-H.; Wang, W. *Chem. Asian. J.* **2009**, *4*, 1664.

(9) For recent reviews of catalytic asymmetric synthesis of quaternary stereogenic centers, see: (a) Bella, M.; Gasperi, T. *Synthesis* **2009**, 1583. (b) Riant, O.; Hannedouche, J. *Org. Biomol. Chem.* **2007**, *5*, 873. (c) Christoffers, J.; Baro, A. *Adv. Synth. Catal.* **2005**, *347*, 1473. (d) Peterson, E. A.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 11943. (e) Ramon, D. J.; Yus, M. *Curr. Org. Chem.* **2004**, *8*, 149.

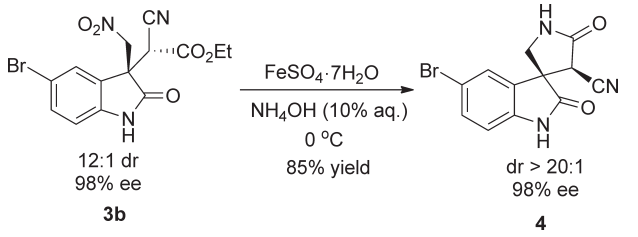
(10) Crosignani, S.; Page, P.; Missotten, M.; Colovray, V.; Cleva, C.; Arrighi, J. F.; Atherall, J.; Macritchie, J.; Martin, T.; Humbert, Y.; Gaudet, M.; Pupowicz, D.; Maio, M.; Pittet, P.-A.; Golzio, L.; Giachetti, C.; Rocha, C.; Bernardinelli, G.; Filinchuk, Y.; Scheer, A.; Schwarz, M. K.; Chollet, A. *J. Med. Chem.* **2008**, *51*, 2227.

(11) For recent reviews of bifunctional (thio)ureas catalysis, see: (a) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999. (b) Connon, S. J. *Chem.—Eur. J.* **2006**, *12*, 5419. (c) Marcelli, T.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 7496. (d) Colby, E. A.; Mennen, S. M.; Xu, Y.; Miller, S. J. *Chem. Rev.* **2007**, *107*, 5759. (e) List, B. *Chem. Rev.* **2007**, *107*, 5413. (f) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713. (g) Yu, X.-H.; Wang, W. *Org. Biomol. Chem.* **2008**, *6*, 2037. (h) Zhang, Z.; Schreiner, P. R. *Chem. Soc. Rev.* **2009**, *38*, 1187. (i) Takemoto, Y. *Chem. Pharm. Bull.* **2010**, *58*, 593.

(12) For leading references, see: (a) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901. (b) Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672. (c) Li, H.; Wang, Y.; Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2004**, *126*, 9906. (d) Vakulya, B.; Varga, S.; Csampai, A.; Soós, T. *Org. Lett.* **2005**, *7*, 1967. (e) Wang, J.; Li, H.; Yu, X.-H.; Zu, L.-S.; Wang, W. *Org. Lett.* **2005**, *7*, 4293. (f) Marcelli, T.; van der Haas, R. N. S.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 929.

(13) Huuskonen, J.; Rissanen, K.; Koskinen, A. M. P. *Eur. J. Org. Chem.* **2009**, 1340.

Scheme 2. Synthesis of Spirooxindole via Reduction-Lactamization Cascade



enantiomers for biological studies. The absolute configuration of product **3b** was determined by the single-crystal X-ray analysis of compound **4** (Figure 1).[14]

In summary, we have developed a new enantioselective Michael addition of nitroalkanes to indolylidenecyanoacetates, catalyzed by a bifunctional cinchona alkaloid thiourea **IV** under neat, mild reaction conditions. Notably, up to three stereogenic centers and one quaternary chiral center are generated in good to high enantio- and diastereoselectvity. The reaction provides alternative access to synthetically and biologically interesting, structurally diverse, enantioenriched 3,3′-disubstituted oxindoles.

(14) See the Supporting Information for the CIF. The structure of the compound derived from molecule **4** was determined by X-ray crystal analysis. CCDC-851133 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk and see the Supporting Information.

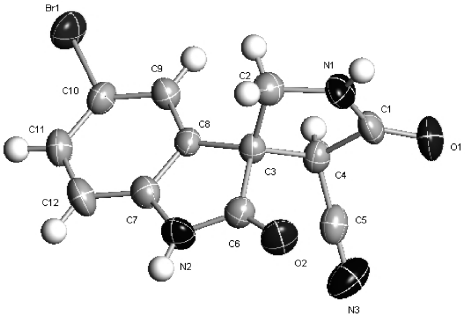


Figure 1. X-ray structure of compound **4**.

Efforts toward application of the densely functionalized Michael adducts in DOS and expanding the strategy for new organic transformations are being pursued in our laboratory.

Acknowledgment. This research is financially supported by East China University of Science & Technology and the China 111 Project (Grant No. B07023).

Supporting Information Available. ^{1}H and ^{13}C NMR and HRMS data and experimental procedures and characterization of the products **3** and **4**. X-ray data for compound **4** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.