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Asymmetric Michael/Cyclization Cascade Reaction of 3-Isothiocyanato Oxindoles and 3-Nitroindoles with Amino-Thiocarbamate Catalysts: Enantioselective Synthesis of Polycyclic Spirooxindoles

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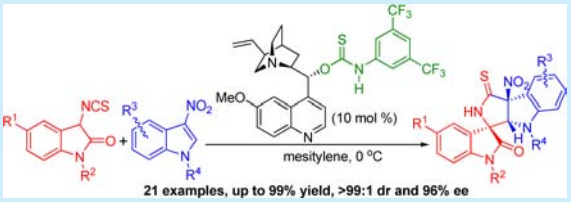
Supporting Information

ABSTRACT: An unprecedented organocatalytic asymmetric Michael/cyclization cascade reaction of 3-isothiocyanato oxindoles and 3-nitroindoles has been disclosed. A wide range of enantioenriched polycyclic spirooxindoles, containing three contiguous chiral centers with two of them having quaternary stereocenters, could be smoothly obtained with satisfactory results (up to 99% yield, >99:1 dr, and 96% ee). This method is very promising because the reaction is scalable, and the versatile transformations of the products into other spirocyclic oxindoles are also feasible.



Exploring efficient strategies for the construction heterocyclic compounds with rich structural diversity and complexity is a continuing challenge in synthetic chemistry. The spirooxindole skeletons in particular have captured tremendous attention among synthetic and medicinal chemists, due to their prevalence in a broad range of natural and unnatural biologically active products, as well as pharmaceutically important compounds.[1] Over the past several years, we have witnessed rapid progress in the development of creative methodologies for the generation of diverse spirooxindole molecules.[2] Specifically, numerous multifunctional polycyclic spirooxindoles, featuring structural complexity and well-defined three-dimensional architecture, have been demonstrated to correlate with a wide spectrum of biological properties and pharmacological activities (Figure 1).[3] Various synthetic methods for producing functionalized spirooxindole derivatives containing a polycyclic skeleton in asymmetric catalysis have been reported.[4] Despite the substantial advances made thus far, taking into account the importance of the natural-product-like spirocyclic oxindoles in pharmaceutical science and as promising candidates for drug discovery, the development of novel approaches for the efficient synthesis of polyfunctionalized spirooxindoles is in demand.

Since we initially employed 3-isothiocyanato oxindoles as nucleophiles in catalytic asymmetric synthesis,[5] many studies have documented the stereoselective construction of structurally diverse spirocyclic oxindoles using 3-isothiocyanato oxindoles as powerful and versatile precursors via cascade reaction.[6,7] Notably, 3-isothiocyanato oxindoles can easily undergo

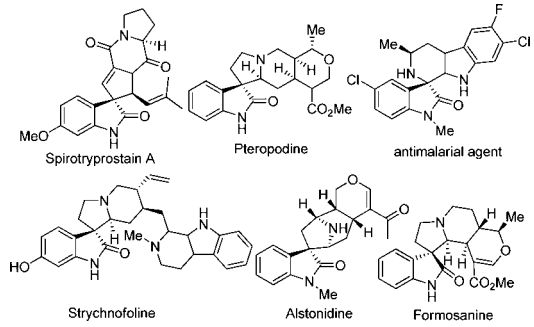


Figure 1. Biologically active compounds with polycyclic spirooxindole skeleton.

Michael/cyclization cascade reactions with some electron-deficient alkenes.[6] In addition, the indoles, bearing two electron-withdrawing substitutions at the N1- and C3-positon, have been recognized as a class of electron-deficient alkene reagents.[8] These indoles possess special reaction features; that is, they are readily attacked by nucleophiles at the C2-position and sequentially react with electrophiles at the C3-position (Scheme 1A). We noticed that 3-nitroindoles,[8] a class of potentially promising electrophilic alkenes, had barely been explored in the field of catalytic asymmetric synthesis.[9] In this context, as our continuous interest in developing new synthetic methods for the

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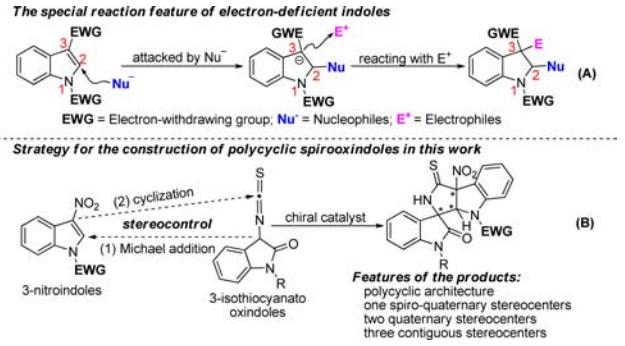
Scheme 1. (A) Special Reaction Feature of Electron-Deficient Indoles; (B) Strategy for the Construction of Polycyclic Spirooxindoles with 3-Isothiocyanato Oxindoles and 3-Nitroindoles

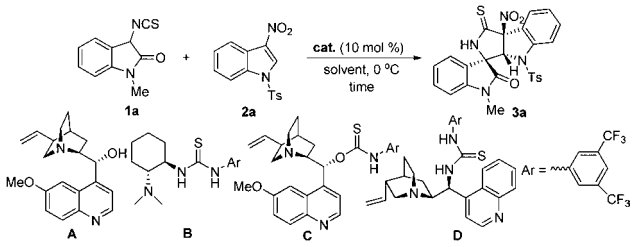


synthesis of spirocyclic oxindole compounds,[5,6a−f,10] we envisioned that a novel asymmetric Michael/cyclization cascade reaction between 3-isothiocyanato oxindoles and 3-nitroindoles should take place with an organocatalyst (Scheme 1B). If this strategy is realized, it will permit the rapid construction of a series of polycyclic spirooxindoles containing three contiguous chiral centers with two of them having quaternary stereocenters in a single step. Moreover, this work represents the first example of 3-nitroindoles used in an organocatalytic asymmetric cascade reaction.[11] Herein we wish to report our preliminary results on this subject.

To examine the feasibility of the proposed Michael/cyclization cascade reaction of 3-isothiocyanato oxindoles and 3-nitroindoles,[12] our investigation started with the screening of various chiral bifunctional organocatalysts **A**−**D**. As shown in Table 1, the reaction of **1a** and **2a** could proceed to completion within 1 h in mesitylene at 0 °C with 10 mol % **A**, furnishing the desired spirocyclic oxindole **3a** in 98% yield with a 76:24 diastereomeric ratio (dr) and 73% ee for the major diastereomer (entry 1). And then, **3a** could be smoothly obtained in 99% yield with 83% ee and 87% ee for the diastereoisomers using Takemoto's catalyst **B**, but the diastereoselectivity was very poor (entry 2). To our delight, a set of good results (99% yield, 97:3 dr, and 92% ee) could be obtained with amino-thiocarbamate catalyst **C** (entry 3). The 9-thiourea cinchona alkaloid **D** was inferior to catalyst **C** for the stereoselectivity (entry 4 vs 3). Afterward, changing the solvent from mesitylene to toluene gave comparable reactivity and stereoselectivity (entry 5), whereas dichloromethane and ethyl ether resulted in a dramatic decrease in yield and stereoselectivity (entries 6−7). After addition of molecular sieves (MS) as an additive, no improvement for the dr and ee was observed (entries 8−9). We were gratified to find that the ee value could be elevated to 96% by increasing the reaction concentration (entry 10). Unfortunately, changing the reaction temperature gave rise to a slightly lower ee value for the major diastereomer (entries 11−13). Ultimately, with 5 and 1 mol % **C** for the reaction, respectively, **3a** also could be obtained with good results (entries 14−15).

The scope of the cascade reaction was then investigated with catalyst **C** under the optimized conditions used in Table 1, entry 10. First, we focused on the examination of 3-nitroindole substrates by using 3-isothiocyanato oxindole **1a** as the donor. As summarized in Table 2, with electron-withdrawing or -donating substituents at the C5-position of 3-nitroindoles, reactions with **1a** presented very high reactivity and furnished the corresponding products in 94−99% yield with up to >99:1 dr and 95% ee

Table 1. Conditions Optimization[a]



entry	cat.	solvent	time (h)	yield (%)[b]	dr[c]	ee (%)[d]
1	**A**	mesitylene	1 h	98	76:24	73
2	**B**	mesitylene	1 h	99	51:49	83(87)[e]
3	**C**	mesitylene	2 h	99	97:3	92
4	**D**	mesitylene	2 h	97	41:59	74(82)[e]
5	**C**	toluene	2 h	99	96:4	90
6	**C**	CH_2Cl_2	4 h	87	87:13	70
7	**C**	Et_2O	4 h	85	70:30	44
8	**C**	mesitylene	2 h	99	98:2	92[f]
9	**C**	mesitylene	2 h	99	97:3	92[g]
10	**C**	mesitylene	2 h	99	98:2	96[h]
11	**C**	mesitylene	2 h	99	95:5	89[h,i]
12	**C**	mesitylene	4 h	99	97:3	93[h,j]
13	**C**	mesitylene	48 h	98	97:3	94[h,k]
14	**C**	mesitylene	3 h	98	98:2	95[h,l]
15	**C**	mesitylene	4 h	98	97:3	93[h,m]

[a]Unless noted, the reactions were carried out with **1a** (0.1 mmol), **2a** (0.1 mmol), and 10 mol % catalyst in 2.0 mL of solvent at 0 °C. [b]Yield of isolated product as a mixture of diastereoisomers. [c]Determined by chiral HPLC. [d]Ee of major diastereomer was determined by chiral HPLC analysis after the product reacting with CH_3I according to the reported procedure.[5] [e]The results in parentheses were the ee value for the minor diastereomer. [f]100 mg 4 Å MS were used. [g]100 mg 5 Å MS were used. [h]1.0 mL of solvent was used. [i]Run at room temperature. [j]Run at −10 °C. [k]Run at −40 °C, and 20 mol % catalyst was used. [l]5 mol % catalyst was used. [m]1 mol % catalyst was used.

(entries 1−4). Moreover, different substituents in the C4-, C6-, and C7-position also could give rise to very high reactivity and deliver the desired products with excellent results (entries 5−8). After the investigations on the varied sulfonyl protecting groups of the N1- in 3-nitroindoles, it was found that the sulfonyl protecting groups, such as Bs-, Ms-, and Ns-, had a dramatic effect on the diastereo- and enantioselectivity, while the reactivity seemed hardly affected (entries 9−11). Similarly, the *N*-acetylated and *N*-alkoxycarbonylated 3-nitroindoles generated the expected spirocyclic oxindoles **3m**−**p** in excellent yields with moderate to good dr and ee values (entries 12−15). On the other hand, a survey of 3-isothiocyanato oxindole substrates was also conducted. The reactions of 3-isothiocyanato oxindoles **1b**−**d**, bearing different *N*-protecting groups, with 3-nitroindole **2a** occurred with complete conversion after 2 h, giving good diastereoselectivities and moderate enentioselectivities (entries 16−18). These results revealed the steric hindrance of the N1-position of 3-isothiocyanato oxindoles was crucial to the stereocontrol ability of the chiral catalyst. Ultimately, regardless of the substitution on the 3-isothiocyanato oxindole aromatic ring, either an electron-withdrawing or -donating group, there is no significant influence on the reactivity and selectivity of the reaction (entries 19 and 20).

In order to examine the utility of the methodology, a gram scale experiment between **1a** and **2a** was carried out under the optimized conditions. As shown in Scheme 2, the reaction

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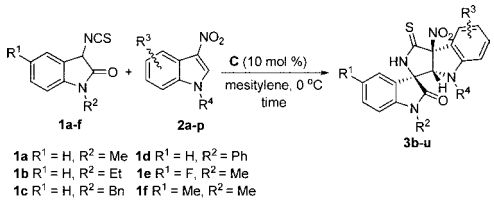
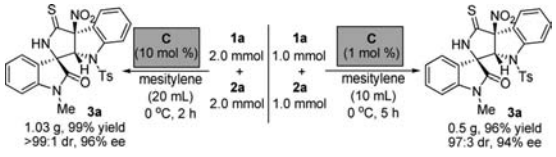
Table 2. Substrate Scope Examination[a]



	1	(R^3, R^4) 2	time (h)	3/yield (%)[b]	dr[c]	ee (%)[d]
1	1a	(5-Cl, Ts) (2b)	2	3b/99	>99:1	93
2	1a	(5-Br, Ts) (2c)	2	3c/98	>99:1	93
3	1a	(5-OMe, Ts) (2d)	7	3d/94	97:3	95
4	1a	(5-OBn, Ts) (2e)	8	3e/96	97:3	93
5	1a	(4-Cl, Ts) (2f)	4	3f/97	97:3	90
6	1a	(4-Br, Ts) (2g)	3	3g/98	>99:1	94
7	1a	(6-Cl, Ts) (2h)	2	3h/99	>99:1	93
8	1a	(7-Me, Ts) (2i)	4	3i/98	97:3	96
9	1a	(H, Bs) (2j)	2	3j/99	>99:1	95
10	1a	(H, Ms) (2k)	3	3k/97	77:23	31
11	1a	(H, Ns) (2l)	2	3l/98	91:9	72
12	1a	(H, Ac) (2m)	4	3m/96	50:50	80(67)[e]
13	1a	(H, Cbz) (2n)	2	3n/98	67:33	75
14	1a	(H, CO_2Et) (2o)	2	3o/98	66:34	83
15	1a	(H, Boc) (2p)	2	3p/99	55:45	77/72[e]
16	1b	2a	2	3q/90	84:16	40
17	1c	2a	2	3r/96	86:14	39
18	1d	2a	2	3s/97	79:21	36
19	1e	2a	2	3t/99	96:4	92
20	1f	2a	2	3u/99	>99:1	95

[a]Unless noted, the reactions were carried out with **1** (0.1 mmol), **2** (0.1 mmol), and 10 mol % **C** in 1.0 mL of mesitylene at 0 °C. [b]Yield of isolated product as a mixture of diastereoisomers. [c]Determined by ^{1}H NMR analysis of crude reaction mixture. [d]Ee of major diastereomer was determined by chiral HPLC analysis after the product reacting with CH_3I according to the reported procedure.[5] [e]The results in parentheses were the ee value for the minor diastereomer. Ts = Toluenesulfonyl; Bs = Benzenesulfonyl; Ms = Methanesulfonyl; Ns = 4-Nitrobenzenesulfonyl; Ac = Acetyl; Cbz = Carbobenzyloxyl; Boc = ^{t}Butyloxycarboryl.

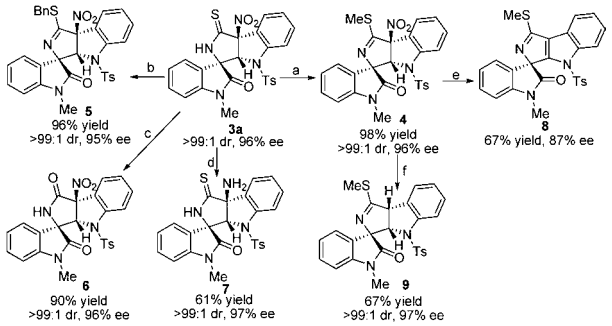
Scheme 2. Reaction of 1a and 2a on a Gram Scale



proceeded cleanly with 10 mol % **C** after 2 h and furnished **3a** in excellent results, which are similar to the results of the original reaction illustrated in Table 1, entry 10. Moreover, upon enlarging the scale of the original reaction by 10-fold, even in the presence of 1 mol % **C**, excellent results were still obtained. These observations reflected the present protocol was amenable to large scale production.

To further expand the potential of this methodology, versatile transformations of the product into some other structurally diverse spirocyclic oxindoles were performed (Scheme 3).[13] Product **3a** could be readily transformed into compound **4** with iodomethane and K_2CO_3 according to the reported procedure.[5] Similarly, reacting **3a** with benzyl bromide gave compound **5** bearing a benzylated thiolactam ring. Notably, **4** and **5** could be

Scheme 3. Transformations of the Product 3a to Other Polycyclic Spirocyclic Oxindoles[a]



[a]Conditions: (a) MeI, K_2CO_3, acetone, 0 °C, 12 h; (b) BnBr, K_2CO_3, acetone, 0 °C, 12 h; (c) H_2O_2, HCOOH, CH_2Cl_2, 0 °C to rt, 12 h; (d) Zn, TMSCl, EtOH, reflux, 4 h; (e) AcOH, H_2SO_4, 100 °C, 3 h; (f) $NaBH_4$, $NiCl_2$, MeOH, 24 h.

obtained in nearly quantitative yields and no changes happened in dr and ee values during the conversions. Compound **4** was converted to spirocyclic oxindole **8** containing a single spiro-stereocenter in 67% yield with 87% ee under strongly acidic conditions. Additionally, the nitro substituent in **4** could be eliminated by nickel boride reduction in MeOH, generating **9** in 67% yield with excellent stereoselectivity. Treatment of **3a** with a solution of 30% aqueous hydrogen peroxide and formic acid according to the reported method[5] gave compound **6** in 90% yield with >99:1 dr and 96% ee. After reduction by zinc powder and TMSCl, the nitro group in **3a** was transformed to an amine functionality, affording product **7** in 61% yield, without loss in stereoselectivity.[9]

The relative and absolute configuration of **4** was unequivocally established by X-ray analysis,[13] thus leading to the determination of the configuration of **3a**. The remaining configurations of other products were assigned on the assumption of a uniform mechanistic pathway. Based on previous studies on isothiocyanato oxindoles[6] and our experimental results, a plausible transition state model is also proposed to account for the observed enantioselectivity (see Supporting Information).

In conclusion, we have developed an efficient asymmetric Michael/cyclization cascade reaction of 3-isothiocyanato oxindoles and 3-nitroindoles for the construction of spirocyclic oxindoles using an amino-thiocarbamate catalyst. With the developed protocol, a wide range of enantioenriched polycyclic spirooxindoles, containing three contiguous chiral centers with two of them having quaternary stereocenters, could be smoothly obtained with satisfactory results (up to 99% yield, >99:1 dr, and 96% ee) under mild conditions. This method is very promising because the reaction is scalable and the versatile transformations of the products into other structurally diverse spirocyclic oxindoles were also feasible. Additionally, this methodology represents the first example regarding organocatalytic enantioselective reactions of 3-nitroindoles. Application of this methodology toward library synthesis and subsequent biological evaluation of its members are underway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, characterization data for new compounds, X-ray crystal structure and the CIF files of **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) For selected reviews, see: (a) Lin, H.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 36. (b) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209. (c) Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748. (d) Trost, B. M.; Brennan, M. K. *Synthesis* **2009**, 3003.

(2) For selected reviews, see: (a) Zhou, F.; Liu, Y.-L.; Zhou, J. *Adv. Synth. Catal.* **2010**, *352*, 1381. (b) Millemaggi, A.; Taylor, R. J. K. *Eur. J. Org. Chem.* **2010**, 4527. (c) Yu, J.; Shi, F.; Gong, L.-Z. *Acc. Chem. Res.* **2011**, *44*, 1156. (d) Klein, J. E. M. N.; Taylor, R. J. K. *Eur. J. Org. Chem.* **2011**, 6821. (e) Shen, K.; Liu, X.; Lin, L.; Feng, X. *Chem. Sci.* **2012**, *3*, 327. (f) Rios, R. *Chem. Soc. Rev.* **2012**, *41*, 1060. (g) Ball-Jones, N. R.; Badillo, J. J.; Franz, A. K. *Org. Biomol. Chem.* **2012**, *10*, 5165. (h) Singh, G. S.; Desta, Z. Y. *Chem. Rev.* **2012**, *112*, 6104. (i) Dalpozzo, R.; Bartoli, G.; Bencivenni, G. *Chem. Soc. Rev.* **2012**, *41*, 7247. (j) Franz, A. K.; Hanhan, N. V.; Ball-Jones, N. R. *ACS Catal.* **2013**, *3*, 540. (k) Hong, L.; Wang, R. *Adv. Synth. Catal.* **2013**, *355*, 1023. (l) Cheng, D.; Ishihara, Y.; Tan, B.; Barbas, C. F., III. *ACS Catal.* **2014**, *4*, 743.

(3) (a) Overman, L. E.; Rosen, M. D. *Angew. Chem., Int. Ed.* **2000**, *39*, 4596. (b) Dideberg, O.; Lamotte-Brasseur, J.; Dupont, L.; Campsteyn, H.; Vermeire, M.; Angenot, L. *Acta Crystallogr., Sect. B* **2008**, *105*, 3933. (c) Kumar, R. R.; Perumal, S.; Senthilkumar, P.; Yogeeswari, P.; Sriram, D. *J. Med. Chem.* **2008**, *51*, 5731. (d) Girgis, A. S. *Eur. J. Med. Chem.* **2009**, *44*, 91. (e) Vintonyak, V. V.; Warburg, K.; Kruse, H.; Grimme, S.; Hübel, K.; Rauh, D.; Waldmann, H. *Angew. Chem., Int. Ed.* **2010**, *49*, 5902. (f) Ali, M. A.; Ismail, R.; Choon, T. S.; Yoon, Y. K.; Wei, A. C.; Pandian, S.; Kumar, R. S.; Osman, H.; Manogaran, E. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 7064. (g) Antonchick, A. P.; Gerding-Reimers, C.; Catarinella, M.; Schürmann, M.; Preut, H.; Ziegler, S.; Rauh, D.; Waldmann, H. *Nat. Chem.* **2010**, *2*, 735.

(4) For selected examples, see: (a) Tan, B.; Candeias, N. R.; Barbas, C. F., III. *Nat. Chem.* **2011**, *3*, 473. (b) Tan, B.; Candeias, N. R.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2011**, *133*, 4672. (c) Tan, B.; Hernández-Torres, G.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2011**, *133*, 12354. (d) Awata, A.; Arai, T. *Chem.—Eur. J.* **2012**, *18*, 8278. (e) Cao, Z.-Y.; Wang, X.; Tan, C.; Zhao, X.-L.; Zhou, J.; Ding, K. *J. Am. Chem. Soc.* **2013**, *135*, 8197. (f) Sun, W.-S.; Zhu, G.-M.; Wu, C.-Y.; Li, G.-F.; Hong, L.; Wang, R. *Angew. Chem., Int. Ed.* **2013**, *52*, 8633. (g) Liu, Y.-L.; Wang, X.; Zhao, Y.-L.; Zhu, F.; Zeng, X.-P.; Chen, L.; Wang, C.-H.; Zhao, X.-L.; Zhou, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 13735. (h) Su, S.; Li, C.; Jia, X.; Li, J. *Chem.—Eur. J.* **2014**, *20*, 5905. (i) Mei, L.-Y.; Tang, X.-Y.; Shi, M. *Chem.—Eur. J.* **2014**, *20*, 13136. (j) Yin, X.-P.; Zeng, X.-P.; Liu, Y.-L.; Liao, F.-M.; Yu, J.-S.; Zhou, F.; Zhou, J. *Angew. Chem., Int. Ed.* **2014**, *53*, 13740. (k) Wang, Y.; Shi, F.; Yao, X.-X.; Sun, M.; Dong, L.; Tu, S.-J. *Chem.—Eur. J.* **2014**, *20*, 15047. (l) Cao, W.; Liu, X.; Guo, J.; Lin, L.; Feng, X. *Chem.—Eur. J.* **2015**, *21*, 1632.

(5) Chen, W.-B.; Wu, Z.-J.; Hu, J.; Cun, L.-F.; Zhang, X.-M.; Yuan, W.-C. *Org. Lett.* **2011**, *13*, 2472.

(6) For 3-isothiocyanato oxindoles in the synthesis of spirooxindole molecules, see: (a) Han, Y.-Y.; Chen, W.-B.; Han, W.-Y.; Wu, Z.-J.; Zhang, X.-M.; Yuan, W.-C. *Org. Lett.* **2012**, *14*, 490. (b) Chen, W.-B.; Han, W.-Y.; Han, Y.-Y.; Zhang, X.-M.; Yuan, W.-C. *Tetrahedron* **2013**, *69*, 5281. (c) Han, W.-Y.; Li, S.-W.; Wu, Z.-J.; Zhang, X.-M.; Yuan, W.-C. *Chem.—Eur. J.* **2013**, *19*, 5551. (d) Liu, X.-L.; Han, W.-Y.; Zhang, X.-M.; Yuan, W.-C. *Org. Lett.* **2013**, *15*, 1246. (e) Cui, B.-D.; Li, S.-W.; Zuo, J.; Wu, Z.-J.; Zhang, X.-M.; Yuan, W.-C. *Tetrahedron* **2014**, *70*, 1895. (f) Bai, M.; Cui, B.-D.; Zuo, J.; Zhao, J.-Q.; You, Y.; Chen, Y.-Z.; Xu, X.-Y.; Zhang, X.-M.; Yuan, W.-C. *Tetrahedron* **2015**, *71*, 949. (g) Kato, S.; Yoshino, T.; Shibasaki, M.; Kanai, M.; Matsnaga, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 7007. (h) Cao, Y.-M.; Shen, F.-F.; Zhang, F.-T.; Wang, R. *Chem.—Eur. J.* **2013**, *19*, 1184. (i) Wu, H.; Zhang, L.-L.; Tian, Z.-Q.; Huang, Y.-D.; Wang, Y.-M. *Chem.—Eur. J.* **2013**, *19*, 1747. (j) Chen, Q.; Liang, J.; Wang, S.; Wang, D.; Wang, R. *Chem. Commun.* **2013**, *49*, 1657. (k) Jiang, Y.; Pei, C.-K.; Du, D.; Li, X.-G.; He, Y.-N.; Shi, M. *Eur. J. Org. Chem.* **2013**, 7895. (l) Tan, F.; Cheng, H.-G.; Feng, B.; Zou, Y.-Q.; Duan, S.-W.; Chen, J.-R.; Xiao, W.-J. *Eur. J. Org. Chem.* **2013**, 2071. (m) Kato, S.; Kanai, M.; Matsunaga, S. *Chem.—Asian J.* **2013**, *8*, 1768. (n) Fu, Z.-K.; Pan, J.-Y.; Xu, D.-C.; Xie, J.-W. *RSC Adv.* **2014**, *4*, 51548. (o) Tan, F.; Lu, L.-Q.; Yang, Q.-Q.; Guo, W.; Bian, Q.; Chen, J.-R.; Xiao, W.-J. *Chem.—Eur. J.* **2014**, *20*, 3415. (p) Cai, H.; Zhou, Y.; Zhang, D.; Xu, J.; Liu, H. *Chem. Commun.* **2014**, *50*, 14771.

(7) For selected reviews on the cascade reaction, see: (a) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570. (b) Yu, X.; Wang, W. *Org. Biomol. Chem.* **2008**, *6*, 2037. (c) Alba, A.-N.; Companyó, X.; Viciano, M.; Rios, R. *Curr. Org. Chem.* **2009**, *13*, 1432. (d) Grondal, C.; Jeanty, M.; Enders, D. *Nat. Chem.* **2010**, *2*, 167. (e) Albrecht, L.; Jiang, H.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 8492. (f) Pellissier, H. *Adv. Synth. Catal.* **2012**, *354*, 237. (g) Volla, C. M. R.; Atodiresei, I.; Rueping, M. *Chem. Rev.* **2014**, *114*, 2390.

(8) For selected examples, see: (a) Gribble, G. W.; Pelkey, E. T.; Simon, W. M.; Trujillo, H. A. *Tetrahedron* **2000**, *56*, 10133. (b) Biolatto, B.; Kneeteman, M.; Paredes, E.; Mancini, P. M. E. *J. Org. Chem.* **2001**, *66*, 3906. (c) Roy, S.; Kishbaugh, T. L. S.; Jasinski, J. P.; Gribble, G. W. *Tetrahedron Lett.* **2007**, *48*, 1313. (d) Chataigner, I.; Piettre, S. R. *Org. Lett.* **2007**, *9*, 4159. (e) Gómez, M. V.; Aranda, A. I.; Moreno, A.; Cossío, F. P.; Cózar, A.; Díaz-Ortiz, Á.; Hoz, A.; Prieto, P. *Tetrahedron* **2009**, *65*, 5328. (f) Lee, S.; Diab, S.; Queval, P.; Sebban, M.; Chataigner, I.; Piettre, S. R. *Chem.—Eur. J.* **2013**, *19*, 7181.

(9) Awata, A.; Arai, T. *Angew. Chem., Int. Ed.* **2014**, *53*, 10462.

(10) For selected examples of our group, see: (a) Chen, W.-B.; Wu, Z.-J.; Pei, Q.-L.; Cun, L.-F.; Zhang, X.-M.; Yuan, W.-C. *Org. Lett.* **2010**, *12*, 3132. (b) Han, Y.-Y.; Han, W.-Y.; Hou, X.; Zhang, X.-M.; Yuan, W.-C. *Org. Lett.* **2012**, *14*, 4054. (c) Cui, B.-D.; Zuo, J.; Zhao, J.-Q.; Zhou, M.-Q.; Wu, Z.-J.; Zhang, X.-M.; Yuan, W.-C. *J. Org. Chem.* **2014**, *79*, 5305. (d) Cui, B.-D.; You, Y.; Zhao, J.-Q.; Zuo, J.; Wu, Z.-J.; Xu, X.-Y.; Zhang, X.-M.; Yuan, W.-C. *Chem. Commun.* **2015**, *51*, 757.

(11) To the best of our knowledge, ref 9 was the only report about the catalytic asymmetric cascade reaction of 3-nitroindoles with the PyBidine/Cu catalyst before this work.

(12) For the preparation of 3-nitroindoles, see: (a) Pelkey, E. T.; Gribble, G. W. *Synthesis* **1999**, 1117. (b) Nowrouzi, N.; Mehranpour, A. M.; Bashiri, E.; Shayan, Z. *Tetrahedron Lett.* **2012**, *53*, 4841.

(13) See the Supporting Information for more details.

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