EurJOC European Journal of Organic Chemistry

SHORT COMMUNICATION

DOI: 10.1002/ejoc.201300081

Highly Enantioselective Organocatalytic Michael Addition/Cyclization Cascade Reaction of Ylideneoxindoles with Isothiocyanato Oxindoles: A Formal [3+2] Cycloaddition Approach to Optically Active Bispirooxindole Derivatives

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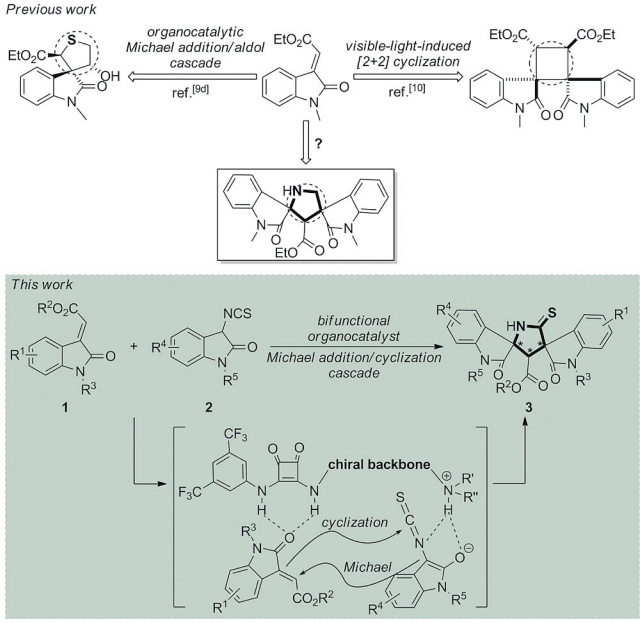
Keywords: Asymmetric synthesis / Organocatalysis / Michael addition / Domino reactions / Cascade reaction / Cyclization / Spiro compounds

A formal [3+2] cycloaddition involving the organocatalytic asymmetric Michael addition/cyclization cascade reaction of ylideneoxindoles with isothiocyanato oxindoles was developed. This method allows efficient and rapid synthesis of highly functionalized bispirooxindole products bearing three contiguous stereogenic centers with two quaternary stereocenters in almost quantitative yields with extremely high enantio- and diastereoselectivities.

Introduction

Spirooxindole frameworks are commonly found in natural products and bioactive and pharmaceutically relevant compounds.[1] As a result, structure variation of this "privileged" pharmacophore has received much attention over the last decade. A variety of three-,[2] four-,[3] five-,[4] and six-membered[5] carbo- and heterocyclic ring systems were successfully incorporated at the C3 position of the oxindolic architecture as a result of the possible application of these scaffolds in medicinal chemistry or in the synthesis of complex heterocycles. In particular, extensive research effort has been devoted to the asymmetric construction of spirooxindoles.[6] In this context, the bispirooxindole scaffold has recently attracted considerable interest because of its unique structure and stereochemical diversity.[6k,6q,6r] However, only limited examples have been reported to date, probably because of the challenges associated with the assembly of the highly sterically congested spirocyclic moiety and multiple stereogenic centers. For example, the Barbas group has pioneered an organocatalytic Michael addition/aldol cascade reaction between 3-substituted oxindoles and methyleneindolinones,[6k] whereas Wang and co-workers have documented an alternative chiral squaramide-catalyzed Michael addition/alkylation cascade reaction of finely designed 3-substituted oxindoles and methyleneindolinones.[6q] These reactions afforded the corresponding spirocyclopentane bioxindoles in good yields with moderate to excellent stereoselectivity. Despite advances, to the best of our knowledge, the catalytic enantioselective synthesis of bispirooxindoles connected by pyrrolidinyl motif has rarely been documented.

Recently, 3-isothiocyanato oxindole has become a robust and versatile synthon in the construction of complex targets,[6h,7] and it has also been used in a diastereoselective synthesis of structurally diverse bispirooxindole derivatives



Scheme 1. Reaction design: organocatalytic asymmetric Michael addition/cyclization cascade reaction of ylideneoxindoles with isothiocyanato oxindoles.

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201300081.

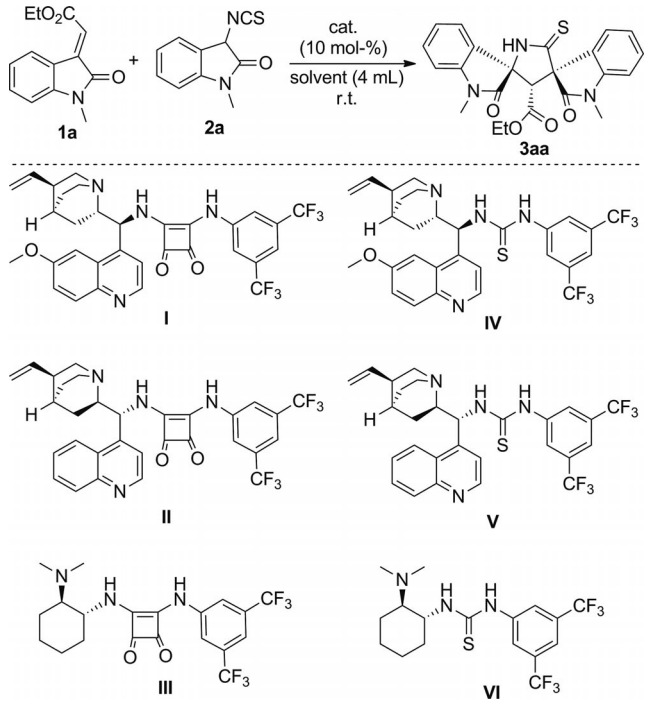
through Michael addition/aldol and Michael addition/Mannich reactions with isatins/isatinimines.[8] As part of our ongoing research efforts toward the synthesis of biologically important heterocycles,[9] we developed two types of cyclization reactions of 3-ylideneoxindoles **1** to establish the spirooxindole motif: 1) organocatalytic Michael addition/aldol cascade[9d] and 2) visible-light-induced [2+2] cycloaddition (Scheme 1).[10] The corresponding spirooxindole tetrahydrothiophene and bispirooxindole cyclobutane derivatives were obtained with excellent stereoselectivities. In this communication, we disclose highly efficient squaramide-catalyzed Michael addition/cyclization cascade reactions of 3-ylideneoxindoles **1** with 3-isothiocyanato oxindoles **2**. This formal [3+2] cycloaddition reaction provides highly functionalized bispirooxindole derivatives in extremely high chemical yield, diastereoselectivity, and enantioselectivity with very low catalyst loading (Scheme 1).[11]

Results and Discussion

We selected (*E*)-ethyl 2-(1-methyl-2-oxoindolin-3-ylidene)acetate (**1a**) and 3-isothiocyanato oxindole (**2a**) as the model substrates to examine the possibility of the designed asymmetric Michael addition/cyclization sequence. A series of common bifunctional squaramide and thiourea organocatalysts were screened at 10 mol-% loading at room temperature. Representative results are summarized in Table 1. To our delight, the reaction worked very well and afforded desired bispirooxindole product **3aa** in 95% isolated yield with extremely high stereoselectivity (>99%*ee* and >95:5 *dr*[12]) in the presence of quinine-derived catalyst **I** within only 2 min (Table 1, entry 1). Chiral squaramide organocatalysts **II** and **III**[13] can also catalyze this transformation efficiently, albeit with slightly longer reaction time (Table 1, entries 2 and 3 vs. entry 1; 20 vs. 2 min). The use of amine–thiourea catalysts **IV**–**VI**[14] also gave the desired products in high yields with high diastereoselectivities, but with decreased enantioselectivities (Table 1, entries 4–6). With optimal catalyst **I** identified, we continued to screen solvents and other reaction parameters. It was found that the reaction media had little influence on the reaction efficiency, except toluene (Table 1, entries 7–10); CH_2Cl_2 proved to be the best choice. Further investigation of the reaction conditions including concentration of the substrate and catalyst loading resulted in optimal reaction conditions: **1a** (1 equiv.), **2a** (1.05 equiv.) **I** (1 mol-%), CH_2Cl_2 (4.0 mL per 0.2 mmol of **1a**), room temperature (99% yield, >99%*ee*, >95:5 *dr*; Table 1, entry 13). Importantly, the enantiomer of **3aa** could also be readily accessed by simply changing quinine-derived squaramide **I** to its quinidine analogue under identical conditions (91% yield, –95%*ee*, >95:5 *dr*).[15]

We evaluated the generality of this methodology under the optimized conditions. As illustrated in Table 2, the reaction showed excellent functional group tolerance, and a variety of bispirooxindole products were obtained in high yields (up to 99% yield) with excellent enantio- and diastereoselectivities (up to >99%*ee*, >95:5 *dr*). For example, incorporation of one or more substituents on the aromatic ring of 3-ylideneoxindole moiety **1** had little effect on the efficiency and stereochemical outcome of this cyclization reaction. Moreover, both electron-withdrawing and electron-donating substituents at different positions in **1** were tolerated, providing the corresponding cycloadducts in high yields with great stereoselectivities. Notably, the reaction with sterically hindered 4-bromo-substituted 3-ylideneoxindole **1j** gave rise to corresponding product **3ja** in 98%

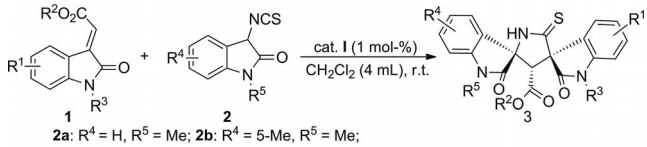
Table 1. Optimization of the asymmetric synthesis of bispirooxindole product **3aa**.[a]



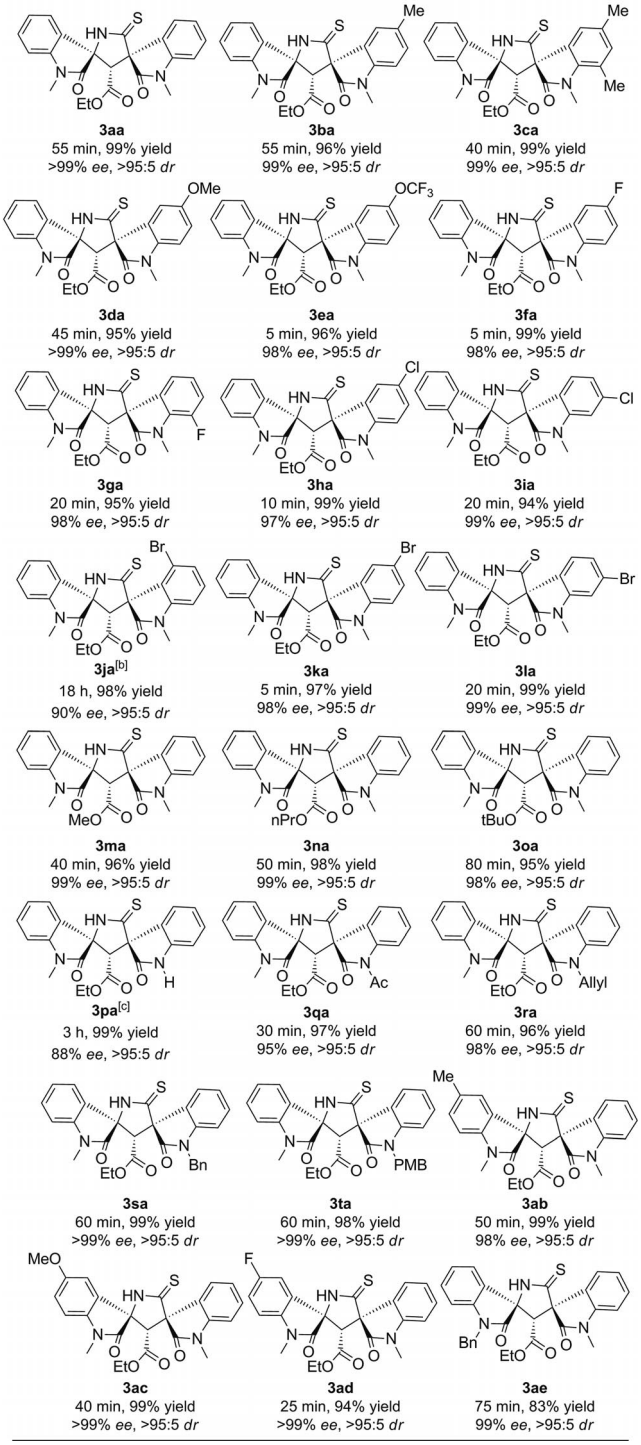
Entry	Cat.	Solvent	*t* [min]	Yield [%][b]	*ee* [%][c]	*dr*[d]
1	**I**	CH_2Cl_2	2	95	>99	>95:5
2	**II**	CH_2Cl_2	20	96	–95	>95:5
3	**III**	CH_2Cl_2	20	98	–93	>95:5
4	**IV**	CH_2Cl_2	60	98	87	>95:5
5	**V**	CH_2Cl_2	60	84	–85	>95:5
6	**VI**	CH_2Cl_2	60	93	–81	>95:5
7	**I**	$CHCl_3$	10	94	94	>95:5
8	**I**	PhMe	2	99	79	>95:5
9	**I**	THF	2	99	94	>95:5
10	**I**	CH_3CN	5	99	94	>95:5
11[e]	**I**	CH_2Cl_2	10	94	>99	>95:5
12[f]	**I**	CH_2Cl_2	10	95	99	>95:5
13[g]	**I**	CH_2Cl_2	55	99	>99	>95:5
14[h]	**I**	CH_2Cl_2	120	97	>99	>95:5

[a] Reaction conditions: **1a** (0.20 mmol), **2a** (0.21 mmol), cat. (10 mol-%) in solvent (4 mL) at room temperature. [b] Yield of isolated product after chromatography. [c] Determined by HPLC analysis on a chiral stationary phase. [d] Determined by analysis of the crude reaction mixture by ^1H NMR spectroscopy. [e] CH_2Cl_2 (8 mL) was used. [f] Performed with a catalyst loading of 5 mol-%. [g] Performed with a catalyst loading of 1 mol-%. [h] Performed with a catalyst loading of 0.5 mol-%.

Table 2. Substrate scope of the asymmetric Michael addition/cyclization sequence for the synthesis of bispirooxindole derivatives.[a]



2a: R^4 = H, R^5 = Me; **2b**: R^4 = 5-Me, R^5 = Me;
2c: R^4 = 5-OMe, R^5 = Me; **2d**: R^4 = 5-F, R^5 = Me; **2e**: R^4 = H, R^5 = Bn



[a] Unless otherwise noted, the reaction was carried out with 3-ylideneoxindole **1** (0.2 mmol), 3-isothiocyanato oxindole **2** (0.21 mmol), and cat. **I** (1 mol-%) in CH_2Cl_2 (4 mL) at room temperature. [b] The reaction was conducted at –60 °C. [c] The reaction was conducted at –25 °C.

yield with 90% *ee* and >95:5 *dr*. In addition, excellent results were achieved by changing the ester moiety or the protecting group on the N atom. The cascade process with N-free substrate **1p** was performed, and the reaction afforded **3pa** in 99% yield with 88% *ee* and >95:5 *dr*. To further validate the compatibility of this strategy, we then investigated the scope of 3-isothiocyanato oxindoles **2**. It was found that incorporation of various functional groups to the aromatic ring of **2** could be realized, affording products **3ab**–**ad** in a highly stereoselective fashion. In addition, benzyl-protected substrate **2e** also participated in this reaction to give corresponding product **3ae** in good yield (83% yield) with excellent enantio- and diastereoselectivity (99% *ee*; >95:5 *dr*).

The absolute configuration of **3aa** was determined to be (8*S*,11*R*,12*S*) by X-ray crystallographic analysis (Figure 1).[16] To demonstrate the synthetic utility of this Michael addition/cyclization cascade reaction, a gram-scale reaction was carried out with a catalyst loading of 0.5 mol-%. To our delight, bispirooxindole compound **3aa** was obtained in 98% yield with 98% *ee* and >95:5 *dr* within 3 h, highlighting the potential of the current reaction in the synthesis of bispirooxindole-containing natural products and medicinal reagents (Scheme 2).

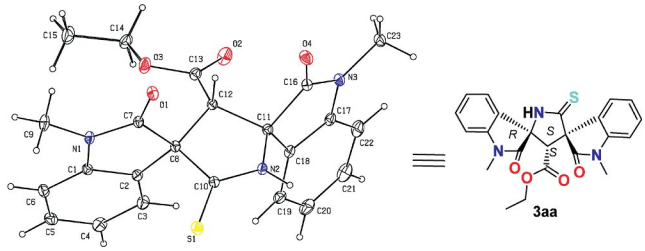
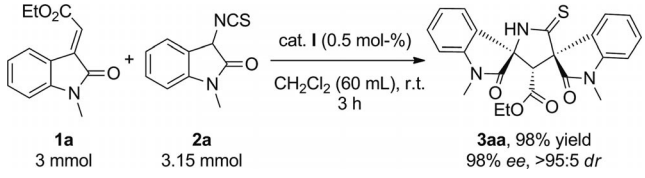
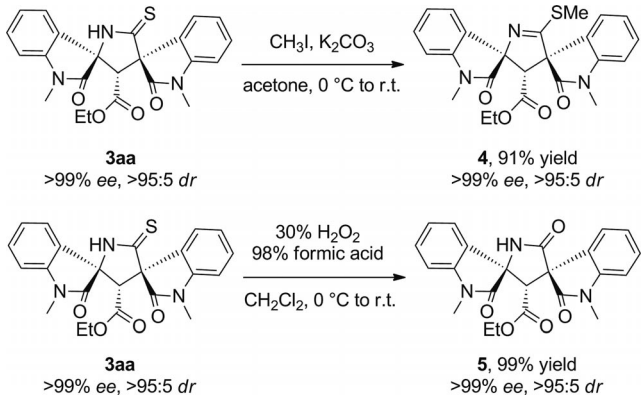


Figure 1. X-ray crystal structure of compound **3aa**.



Scheme 2. Gram-scale synthesis of **3aa**.

More importantly, these bispirooxindolic compounds can be easily converted into other important building blocks and valuable complex targets. As shown in Scheme 3, treatment of **3aa** with CH_3I under basic conditions gave product **4**[6f,8] in 91% yield with >99% *ee* and >95:5 *dr*. Furthermore, the oxidation of bispirooxindole **3aa** with 30% aqueous H_2O_2 and 98% formic acid efficiently generated corresponding lactam **5** (99% yield, >99% *ee*, >95:5 *dr*).[6g,6h,8] Note that no loss of the diastereo- or enantioselectivity was observed.



Scheme 3. Synthetic transformations of product **3aa**.

Conclusions

In conclusion, we have developed a practical and highly efficient Michael addition/cyclization cascade reaction, a formal [3+2] cycloaddition, for the rapid construction of bispirooxindole skeletons in very high chemical yields with excellent enantio- and diastereoselectivities. The mild reaction conditions, low catalyst loading, short reaction time, and high tolerance of functional groups make this strategy an attractive method for the construction of bispirooxindole-containing natural products and pharmaceutically important drug leads. Further applications of this transformation to synthesize other important complex heterocycles are currently in progress.

Experimental Section

Typical Procedure: 3-Ylideneoxindole **1a** (46 mg, 0.20 mmol), 3-isothiocyanato **2a** (43 mg, 0.21 mmol), and cat. **I** (1.26 mg, 1 mol-%) were dissolved in CH_2Cl_2 (4 mL). The resulting solution was stirred at room temperature until the reaction was complete, as monitored by TLC (Note: The reaction was usually complete when the color of the mixture changed from red to colorless around 55 min). The crude reaction mixture was directly purified by flash column chromatography (petroleum ether/ethyl acetate = 3:1 to 1:1) to afford **3aa** as a white solid in 99% yield with >99% *ee* and >95:5 *dr*.

Supporting Information (see footnote on the first page of this article): General experimental methods and characterization data.

Acknowledgments

We are grateful to the National Natural Science Foundation of China (NSFC) (grant numbers 21072069, 21002036, 21232003, and 21202053) for support of this research.

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[13] For a recent review, see: a) J. Alemán, A. Parra, H. Jiang, K. A. Jørgensen, *Chem. Eur. J.* **2011**, *17*, 6890–6899; for selected examples, see: b) Y. Zhu, J. P. Malerich, V. H. Rawal, *Angew. Chem.* **2010**, *122*, 157–160; *Angew. Chem. Int. Ed.* **2010**, *49*, 153–156; c) D.-Q. Xu, Y.-F. Wang, W. Zhang, S.-P. Luo, A.-G. Zhong, A.-B. Xia, Z.-Y. Xu, *Chem. Eur. J.* **2010**, *16*, 4177–4180; d) Y.-F. Wang, W. Zhang, S.-P. Luo, G.-C. Zhang, A.-B. Xia, X.-S. Xu, D.-Q. Xu, *Eur. J. Org. Chem.* **2010**, 4981–4985; e) V. Amendola, G. Bergamaschi, M. Boiocchi, L. Fabbrizzi, M. Milani, *Chem. Eur. J.* **2010**, *16*, 4368–4380; f) W. Yang, D.-M. Du, *Org. Lett.* **2010**, *12*, 5450–5453; g) L. Dai, H.-J. Yang, F. Chen, *Eur. J. Org. Chem.* **2011**, 5071–5076.

[14] For selected examples, see: a) B. Vakulya, S. Varga, A. Csámpai, T. Soós, *Org. Lett.* **2005**, *7*, 1967–1969; b) H. Jiang, M. W. Paixão, D. Monge, K. A. Jørgensen, *J. Am. Chem. Soc.* **2010**, *132*, 2775–2783; c) V. Marcos, J. Alemán, J. L. G. Ruano, F. Marini, M. Tiecco, *Org. Lett.* **2011**, *13*, 3052–3055; d) M. Moccia, F. Fini, M. Scagnetti, M. F. A. Adamo, *Angew. Chem.* **2011**, *123*, 7025–7027; *Angew. Chem. Int. Ed.* **2011**, *50*, 6893–6895.

[15] See the Supporting Information for details.

[16] The structure of compound **3aa** was determined by X-ray analysis. CCDC-908920 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.

Received: January 16, 2013
Published Online: February 8, 2013

