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An Organocatalytic Michael–Michael Cascade for the Enantioselective Construction of Spirocyclopentane Bioxindoles: Control of Four Contiguous Stereocenters

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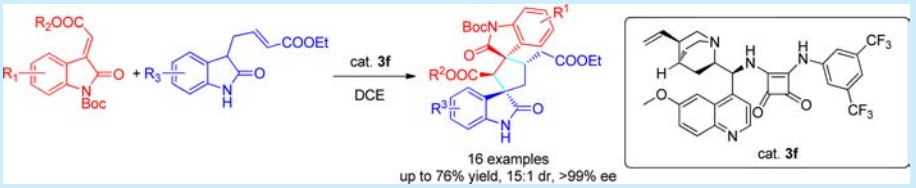
Supporting Information

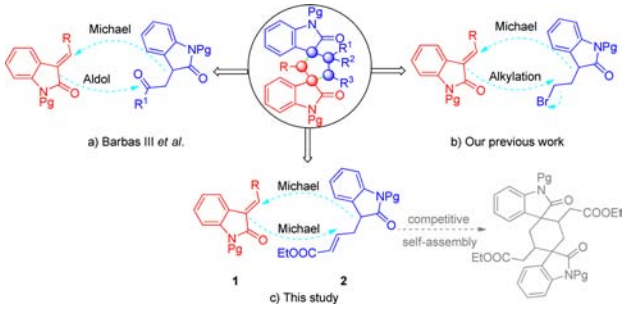


ABSTRACT: An organocatalytic Michael–Michael cascade for the enantioselective construction of spirocyclopentane bioxindoles was developed in moderate to good yield with good diastereoselectivities and excellent enantioselectivities. The straightforward process, catalyzed by a bifunctional chiral squaramide catalyst, serves as a powerful tool for the enantioselective construction of potentially biological bioxindoles with four contiguous chiral centers, of which two are spiro all-carbon quaternary centers on a single cyclopentane ring.

The spirooxindole core is a privileged heterocyclic ring system that is frequently encountered in a large family of natural products and biologically active molecules.[1−3] It has therefore drawn tremendous attention from synthetic[2] and medicinal chemists.[3] Among the spirooxindoles with various fusions, the spirocyclopentane oxindole framework has been one of the most important synthetic subjects[2,4−6] because of its occurrence in a family of natural products and potentially bioactive compounds.[1,5] Recently, a handful of organocatalytic asymmetric strategies have been developed for the construction of spirocyclopentane oxindoles in an enantioselective manner.[6] Moreover, as oxindole-based bispiro motifs have been featured in many medicinal compounds, some research groups, including ourselves, have devoted great efforts toward this end.[6a,b,7] However, the construction of spirocyclic bioxindoles is still viewed as a challenging task, which attributes to the simultaneous production of densely functionalized carbocycles with continuous multiple chiral centers and at least two all-carbon quaternary centers.[8] In this context, an alternative tactic for the stereoselective construction of structurally diverse bispirooxindoles is still demanding.

On the other hand, cascade reactions, which are in a way biomimetic, have been the subject of intense research in modern organic chemistry due to their experimentally simple yet extremely powerful synthetic efficiency for the construction of structural and stereochemical complexity for both natural and non-natural compounds.[9] The design of cascade reactions, which provide considerable complex specific targeted molecules, represents one of the significant challenges and hot-topics. Recently, asymmetric organocatalytic cascade reactions, relying on aminocatalysis and hydrogen bonding catalysis, have grown as a powerful tool for efficient and stereoselective construction of complex molecules, usually with multichiral centers, from readily available starting materials.[10] And it has provided an excellent platform for the construction of structural complex bioxindole scaffold.[6,7] In 2011, Barbas III et al. represented the seminal work of organocatalytic construction of spirocyclopentane bioxindoles with high stereocontrol by a Michael–aldol cascade reaction of activated methyleneindolinones[6a] (Scheme 1a). Our group subsequently developed a chiral squaramide catalyzed cascade Michael–alkylation reaction for the rapidly and efficiently enantioselective synthesis of spirocyclopentane bioxindoles[6b] (Scheme 1b). As a continuation of our program in the development of spirooxindole synthesis and cascade reactions,[6b,j,7a,11] we envisaged that

Scheme 1. Synthetic Cascade Approach to Spirocyclopentane Bioxindoles



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spirocyclopentane bioxindole skeletons possessing four contiguous stereocenters, of which two are spiro all-carbon quaternary centers, could be created via Michael−Michael cascade sequence between methyleneindolinones **1** and 3-substituted oxindoles **2** (Scheme 1c).

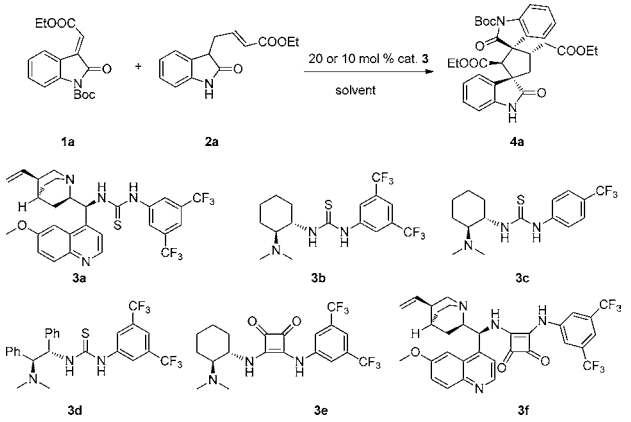
However, several challenging problems need to be addressed for this cascade reaction: (1) the depression of a background reaction of competitive self-assembly of 3-substituted oxindoles **2** (Scheme 1), (2) the efficient creation of highly sterically hindered densely functionalized cyclopentane possessing six substituents, and (3) the control of diastereo- and enantioselectivities, particularly in view of the simultaneous formation of four contiguous chiral centers, of which two are spiro all-carbon quaternary centers on the cyclopentane ring.

To testify our hypothesis, our experiment began with the reaction between methyleneindolinone **1a** and 3-substituted oxindole **2a** in CH_2Cl_2 at room temperature, using a bifunctional thiourea **3a** derived from quinidine as catalyst. Pleasingly, the proposed reaction proceeded smoothly in good conversion in 12 h, providing spirocyclopentane bioxindole **4a** as two diastereomers with 6:1 diastereoselctivity and 91% enantioselectivity (Table 1, entry 1). Encouraged by this promising result, we next examined a representative series of bifunctional H-bond donor catalysts, including chiral thioureas and squaramides derived from different privileged chiral scaffolds. The results exhibited that the catalysts probed displayed significantly different catalytic efficiency toward the process (Table 1, entries 1−6), and catalyst **3f**, a chiral squaramide derived from quinidine, was the most efficient catalyst in respect of both the conversion (90%) and selectivity (10:1 dr, 99% ee) of the reaction (Table 1, entry 6). Subsequent investigation on the solvent effect showed that the reaction medium played an important role in the reaction (Table 1, entries 6−12), and DCE gave the best results (91% conv, 13:1 dr, and 99% ee) (Table 1, entry 9). Thus, we chose **3f** as the catalyst and DCE as the optimal reaction solvent for the subsequent investigations.

With the optimized conditions in hand, we next investigated the generality of the cascade reaction orthogonally. Gratifyingly, various methyleneindolinones **1** with different substitution patterns, in terms of electronic properties, steric hindrances, and substitution positions, could participate in the cascade reaction smoothly in moderate to good yields (59−76%) with good to excellent selectivities (4:1−15:1 dr and 88 to >99% ee) in general, albeit with that electron-deficient group substituted substrates afforded slightly lower diastereo- and enantioselectivities (Table 2, entries 1−13). With regard to the 3-substituted oxindoles **2**, they all provided the corresponding adducts in good yields (69−76%), diastereoselectivities (10:1−15:1), and excellent enantioselectivities (98 to >99%) (Table 2, entries 14−16). It is worth noting that in all cases, both diastereoisomers of the products **4** could be easily separated by an ordinary column chromatography, which renders this organocatalytic cascade reaction a useful synthetic route to optically spirocyclopentane bioxindoles.

To determine the absolute configuration of the products, product **4n** was treated with TFA in CH_2Cl_2 at the room

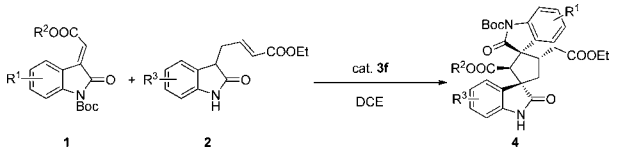
Table 1. Optimization of the Reaction Conditions[a]



entry	cat **3**	solvent	conversion (%)[b]	dr[b]	ee (%)[c]
1	**3a**	DCM	78	6:1	91
2	**3b**	DCM	90	5:1	93
3	**3c**	DCM	85	4:1	91
4	**3d**	DCM	40	2:1	80
5	**3e**[d]	DCM	91	7:1	84
6	**3f**[d]	DCM	90	10:1	99
7	**3f**[d]	THF	89	9:1	98
8	**3f**[d]	MTBE	68	4:1	87
9	**3f**[d]	DCE	91 (68)[e]	13:1	99
10	**3f**[d]	$CHCl_3$	50	4:1	99
11	**3f**[d]	toluene	45	3:1	90
12	**3f**[d]	Et_2O	30	2:1	78

[a]Unless otherwise specified, the reaction was carried out with **1a** (0.1 mmol), **2a** (0.11 mmol), catalyst **3** (0.02 mmol) in solvent (1.0 mL) at room temperature for 12 h. [b]Determined by ^{1}H NMR spectroscopy of the reaction crude mixture. [c]Determined by chiral HPLC on a Chiralcel IA column. [d]10 mol % cat **3** was used. [e]Isolated yield of the major diastereomer of **4a** was given in parentheses.

Table 2. Scope of the Reaction[a]



entry	R^1	R^2	R^3	product **4**	dr[b]	yield (%)[c]	ee (%)[d]
1	5-H	Et	H	**4a**	13:1	68	99
2	5-F	Et	H	**4b**	5:1	62	94
3	5-Cl	Et	H	**4c**	4:1	64	94
4	5-Br	Et	H	**4d**	4.5:1	61	91
5	5-Me	Et	H	**4e**	12:1	76	99
6	5-MeO	Et	H	**4f**	7:1	69	99
7	5-CF_3O	Et	H	**4g**	10:1	59	90
8	6-Cl	Et	H	**4h**	12:1	65	93
9	6-Br	Et	H	**4i**	7:1	68	90
10	7-Cl	Et	H	**4j**	15:1	59	88
11	7-Me	Et	H	**4k**	15:1	63	96
12	5-H	Me	H	**4l**	15:1	71	>99
13	5-H	*t*Bu	H	**4m**	13:1	69	99
14	5-H	Et	5-Br	**4n**	15:1	76	99
15	5-H	Et	5-Me	**4o**	10:1	69	98
16	5-H	Et	6-Cl	**4p**	15:1	76	>99

[a]Unless otherwise specified, the reaction was carried out with **1** (0.1 mmol), **2** (0.11 mmol), catalyst **3f** (0.01 mmol) in DCE (1.0 mL) at room temperature for 12 h. [b]Determined by ^{1}H NMR spectroscopy of the reaction crude mixture. [c]Isolated yield of the major diastereomer of **4**. [d]Determined by chiral HPLC on a Chiralcel IA column.

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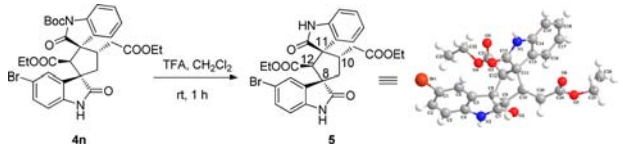
temperature providing the deprotected compound **5**. Suitable crystals of compound **5** were obtained, and the absolute configuration was determined as (C8*S*,C10*S*, C11*S*, C12*R*) unambiguously by X-ray single-crystal analysis (Scheme 2).

Scheme 2



In conclusion, we have developed a highly efficient asymmetric organocatalytic Michael−Michael cascade approach to the direct construction of densely functionalized spirocyclopentane bioxindoles. The straightforward process, catalyzed by a bifunctional chiral squaramide catalyst, serves as a powerful tool for the enantioselective construction of potentially biological bioxindoles possessing four contiguous chiral centers, of which two are spiro all-carbon quaternary centers.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, characterization data for new compounds, copies of NMR and HPLC spectra, and X-ray crystal structure. 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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