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Squaramide-Catalyzed Enantioselective Cascade Approach to Bispirooxindoles with Multiple Stereocenters

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Abstract: A bifunctional squaramide-catalyzed Michael/Michael cascade reaction for the construction of spirotetrahydrofuran bispirooxindoles was developed. The products were obtained in moderate to excellent yields with excellent diastereo- and enantioselectivities (up to >20:1 *dr*, >99% *ee*). This straightforward process serves as a powerful method for the enantioselective construction of potentially bioactive bispirooxindoles in which two of the four contiguous chiral centers are spiro all-carbon quaternary centers on a single tetrahydrofuran ring. Meanwhile, the synthetic practicality of this methodology was illustrated by performing the reaction on a gram-scale with the same efficiency and stereoselectivity.

Keywords: asymmetric catalysis; Michael addition; organocatalysis; spirooxindoles; squaramides

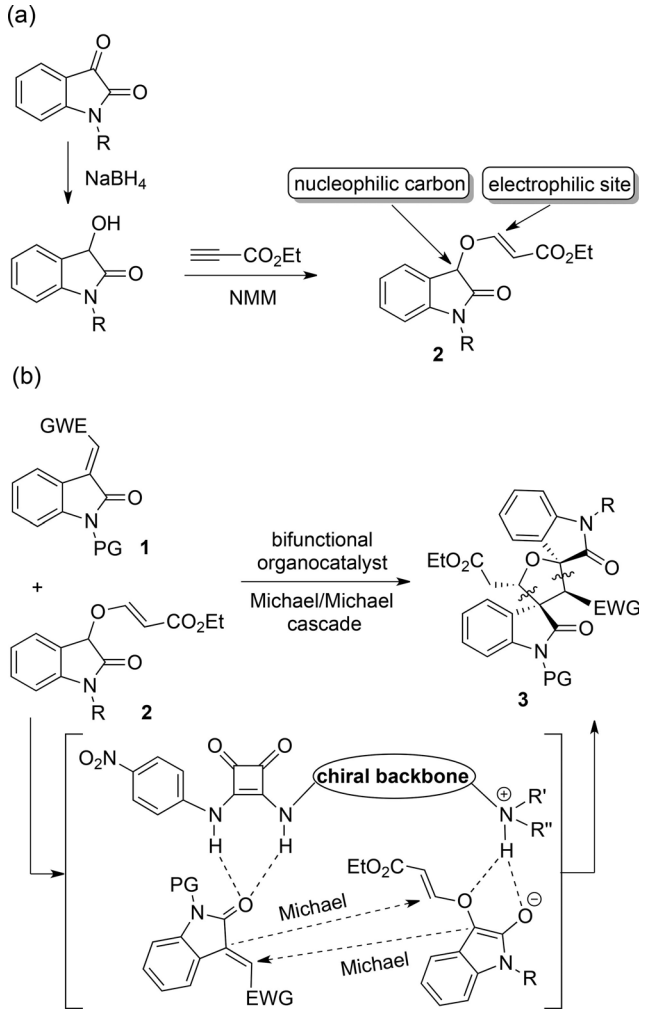
Introduction

Obtaining optically pure compounds with potential biological activity is a major challenge in drug discovery. To meet the ever increasing demand for privileged scaffolds in medicinal chemistry and chemical biology, organic chemists must attempt to synthesize optically active complex compounds having significant structural diversity from simple and readily available materials in an efficient and operationally simple procedure.[1] The spirooxindoles with a spiro center at the 3-position of the oxindole ring, often containing multiple stereocenters, are considered as privileged molecular structures associated with potent pharmaceutical properties.[2]

The pioneering researches by the groups of List, MacMillan, and Jørgensen[3] on organocatalytic domino/cascade reactions have opened a new range of opportunities for the efficient asymmetric synthesis of complex molecular structures bearing several contiguous stereocenters in operationally simple procedures.[4] In fact, organocatalytic cascade reactions have already been employed in the enantioselective synthesis of various spirooxindoles.[5] The leading construction of bispirooxindoles in a cascade reaction was reported by Tan, Barbas III and co-workers in 2011.[6] However, the asymmetric synthesis of bispirooxindoles is still recognized as a challenging task since it is difficult to produce densely functionalized carbocycles with multiple contiguous stereocenters and at least two all-carbon quaternary centers.[7] In this context, the development of more flexible synthetic strategies for the stereoselective construction of structurally diverse bispirooxindoles is still needed. Herein, we attempted to develop an organocatalyzed asymmetric cascade approach to constructing bispirooxindole frameworks.

On the other hand, 3-hydroxy-2-oxindoles, which are easily derived from isatin by simple reduction, have been used as nucleophiles in the asymmetric catalytic synthesis of 3-substituted 3-hydroxyoxindoles.[8] We envisioned that a kind of new cascade reagent **2** bearing an active nucleophilic carbon and an electrophilic site may be derived from isatin in two simple steps (Scheme 1a). The electron induction of the oxygen atom connected to the 3-position of the oxindole ring in compound **2** was expected to increase the nucleophilicity of the oxindole C-3.

Appropriate reaction conditions were thus investigated to avoid the competitive self-assembly of 3-substituted oxindole cascade reagents **2** in the presence of NMM. The cascade reagents were successfully synthesized afterwards. To evaluate the reactivity of these newly designed 3-substituted oxindole cascade reagents, we have designed a squaramide-catalyzed[9] cascade Michael/Michael reaction using these donor-



Scheme 1. New cascade reagents – design and proposed strategy towards bispirooxindoles. EWG = electron-withdrawing group, PG = protecting group.

Michael acceptor reagents with 3-olefinic oxindoles to construct the complex bispirooxindoles. It is notable that a highly functionalized bispirooxindole-tetrahydrofuran scaffold with four contiguous stereogenic centers, of which two are spiro all-carbon quaternary centers on a single tetrahydrofuran ring, can be constructed in a simple operation under mild reaction (Scheme 1b).

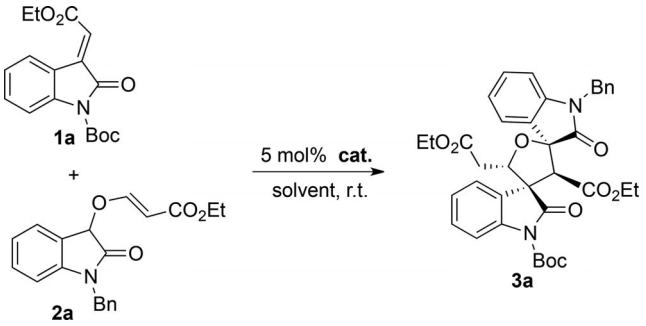
For this proposed reaction, however, two potential challenges have to be addressed. One is the construction of highly sterically hindered and densely functionalized tetrahydrofuran possessing six substituents and bearing four contiguous stereogenic centers including two spiro-stereocenters. The other is the control of diastereo- and enantioselectivity of this cascade reaction in one operation.

Results and Discussion

To test the feasibility of this proposed reaction, we chose the readily available isatin-derived enoate **1a** and the 3-substituted oxindole **2a** as the model substrates to carry out the screening of organocatalysts for this cascade process (Table 1).

To our delight, in the presence of 5 mol% squaramide **I** derived from quinine, the cascade Michael/Michael addition was completed in toluene at room

Table 1. Screening of organocatalysts and optimization of reaction conditions for asymmetric synthesis of bispirooxindole **3a**.[a]



Entry	Solvent	Catalyst	Yield[b] [%]	*dr*[c]	*ee*[d] [%]
1	PhMe	**I**	51	>20:1	90
2	PhMe	**II**	48	>20:1	93
3	PhMe	**III**	54	>20:1	93
4	PhMe	**IV**	57	>20:1	94
5	PhMe	**V**	49	>20:1	−94
6	PhMe	**VI**	46	>20:1	−93
7	PhMe	**VII**	61	>20:1	66
8	PhMe	**VIII**	59	>20:1	89
9	PhMe	**IX**	49	>20:1	36
10	CH_2Cl_2	**IV**	51	>20:1	87
11	$CHCl_3$	**IV**	48	>20:1	85
12	xylene	**IV**	46	>20:1	91
13	THF	**IV**	66	>20:1	92
14	Et_2O	**IV**	63	>20:1	89
15	1,4-dioxane	**IV**	43	>20:1	91
16	MeCN	**IV**	26	>20:1	85
17[e]	THF	**IV**	62	>20:1	92
18[f]	THF	**IV**	68	>20:1	93
19[g]	THF	**IV**	57	>20:1	93
20[f,h]	THF	**IV**	72	>20:1	94
21[f,i]	THF	**IV**	75	>20:1	95

[a] *Reaction conditions:* **1a** (0.17 mmol), **2a** (0.15 mmol), catalyst (5 mol%) in 0.75 mL solvent at room temperature for 5 h.
[b] Isolated yield.
[c] Determined by ^{1}H NMR.
[d] Determined by HPLC analysis.
[e] 10 mol% catalyst were used.
[f] 2.5 mol% catalyst was used.
[g] 1.0 mol% catalyst were used.
[h] The reaction was performed at 0 °C for 20 h.
[i] The reaction was performed at −10 °C for 30 h.

temperature in 3 h, and afforded the desired product **3a** in 51% yield (>20:1 *dr*, 90% *ee*) (Table 1, entry 1). It should be noted that this reaction performed completely within 3 h and the by-products are also generated at the same time. Besides the main spot of the product **3a**, several fuzzy spots that may be other isomers can be observed on TLC detection. We are as yet not able to isolate and identify the by-products. With the above result in hand, we evaluated a small library of organocatalysts (Figure 1) for this cascade reaction.

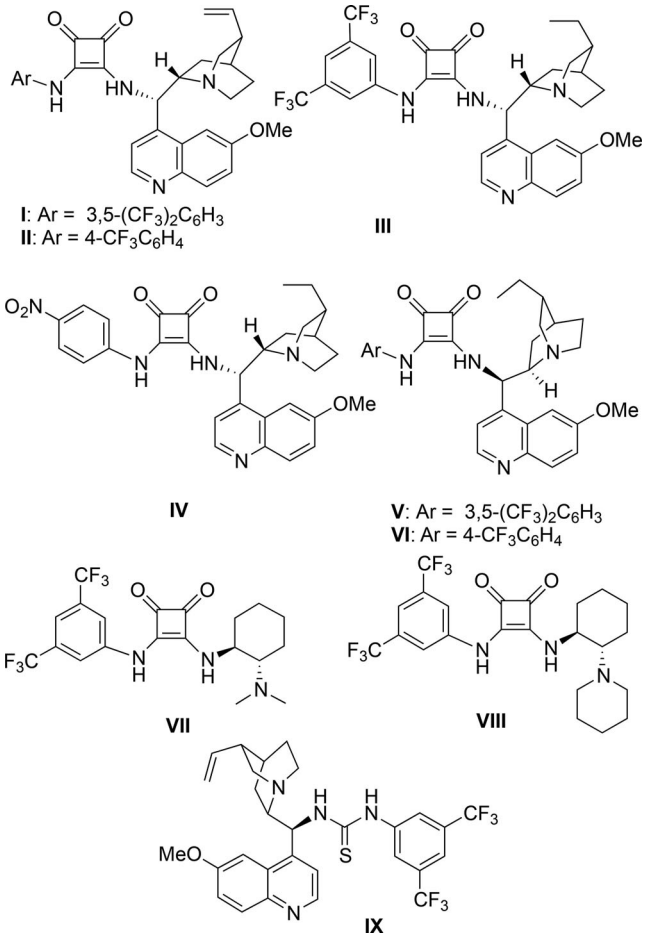
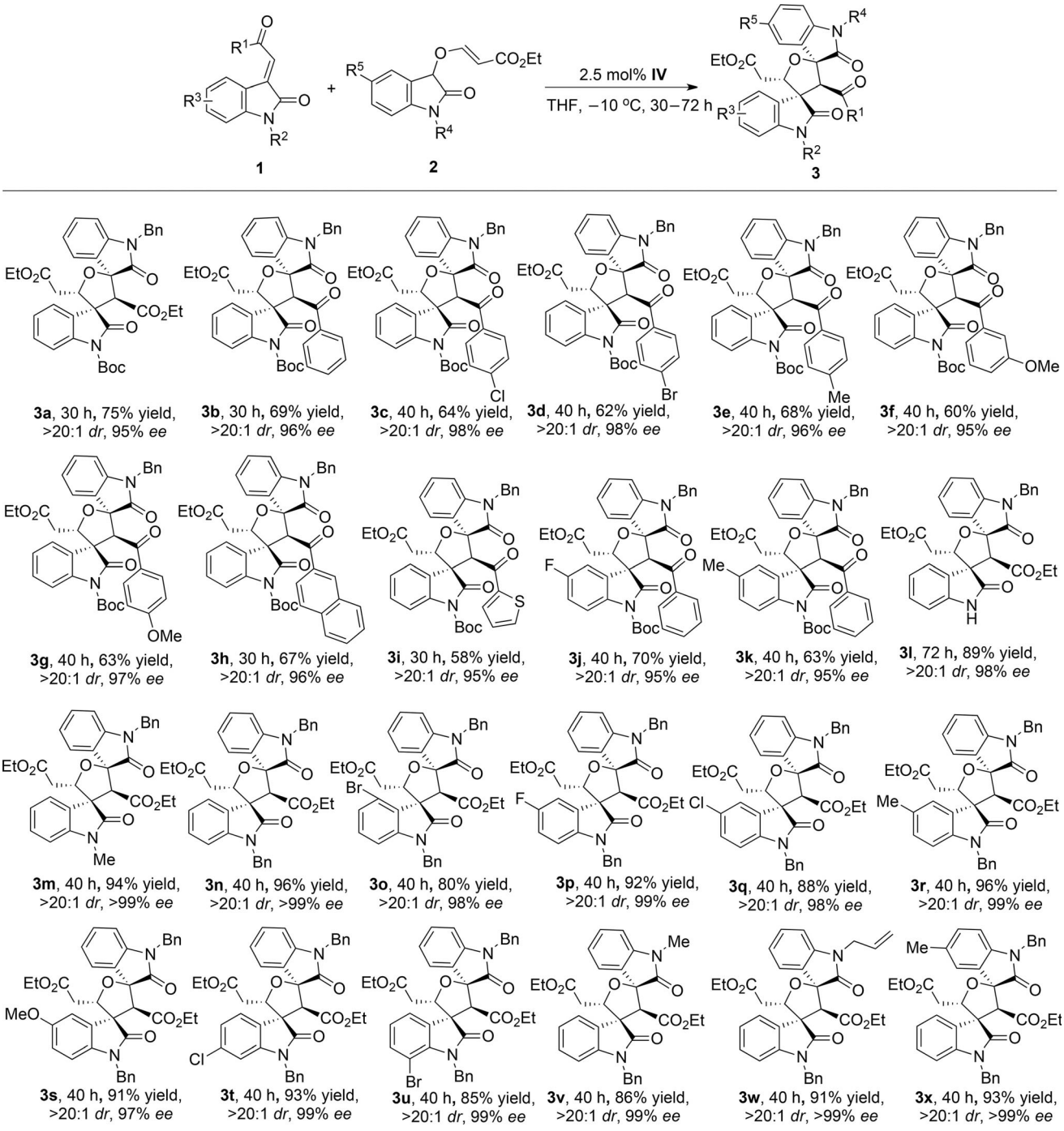


Figure 1. Squaramide and thiourea organocatalysts.

Encouraged by this promising result, we next examined a series of bifunctional H-bond squaramide catalysts derived from different privileged chiral scaffolds (Table 1, entries 2–8). The results demonstrate that the chiral squaramide catalysts displayed different catalytic efficiencies in this reaction, and squaramide **IV** derived from hydroquinine was proved to be the most efficient catalyst with respect to both the yield (57%) and the stereoselectivity (>20:1 *dr*, 94% *ee*) of the reaction (Table 1, entry 4). In addition, for comparison with the used squaramides, the corresponding quinine-derived thiourea **IX** was also evaluated (Table 1, entry 9). Unfortunately, no further improvement was observed.

In order to improve the yield and stereoselectivity of the reaction, further optimization was carried out using squaramide **IV** as the catalyst. We investigated the effect of solvent, catalyst loading and temperature to define the optimal reaction conditions (Table 1, entries 10–21). Subsequent investigations on solvent effect showed that the reaction medium played an important role in this reaction (Table 1, entries 10–16), and THF gave the best overall results (66% yield, >20:1 *dr*, and 92% *ee*) (Table 1, entry 13). Subsequently, the catalyst loading of reaction was evaluated (Table 1, entries 17–19). We found that a better result was obtained when reducing the catalyst loading to 2.5 mol% (Table 1, entry 18). Additionally, it is necessary to note that the temperature exerted a remarkable effect on the reaction outcome. The yield and enantioselectivity of the reaction were all improved when lowering the temperature to 0 °C (Table 1, entry 20). When the temperature was lowered to −10 °C, we were glad to find that the result has been slightly improved (Table 1, entry 21). Considering the reaction time, we stopped lowering the temperature.

With the optimized reaction conditions in hand, we then explored the generality of the reaction. The results are shown in Scheme 2. Initially, structural variations were made on the 3-olefinic oxindoles **1**. A variety of 3-olefinic oxindoles bearing aromatic enones were tested, and all these substrates could undergo the cascade Michael/Michael reaction smoothly to afford the desired spirooxindoles **3b–i**. The presence of either electron-withdrawing (**3c** and **3d**) or electron-donating groups (**3e–g**) on the aromatic rings of 3-olefinic oxindoles is well tolerated, which indicates that the electronic nature of the substituents on the aromatic rings has little influence on this cascade reaction. The position of the substituent on the aromatic ring of aromatic enone also has little effect on the stereoselectivity (**3f** and **3g**). Additionally, a heterocyclic substrate was also amenable to this cascade reaction and afforded the corresponding product **3i**. We have also examined a 3-olefinic oxindole bearing an aliphatic enone. It reacted smoothly with **2a** with a high conversion rate, but the reaction did not afford any separable compounds. The *N*-Boc (*tert*-butyloxycarbonyl)-3-olefinic oxindoles with electron-withdrawing or electron-donating groups could give the corresponding products (**3j** and **3k**) smoothly. Furthermore, we examined the effects of the *N*-protecting group of the oxindole. When reacting with **2a**, the *N*-unprotected, *N*-methyl and *N*-benzyl 3-olefinic oxindoles show lower reactivity than that of *N*-Boc (*tert*-butyloxy carbonyl), and these substrates could give the corresponding products (**3l–n**) with significantly improved yields and enantioselectivities. Among them, the *N*-



Scheme 2. Substrate scope; *reaction conditions:* **1** (0.17 mmol), **2** (0.15 mmol), and catalyst **IV** (2.5 mol%) in 0.75 mL THF were stirred at −10 °C. The diastereoselectivities (*dr*) of the products were determined by ^{1}H NMR. The *ee* values of the products were determined by HPLC.

benzyl 3-olefinic oxindole gave the best results (96% yield, >20:1 *dr* and >99% *ee*). We observed that there is only one desired product each of **3l–n** and no detectable by-products by TLC detection.

Then, various *N*-benzyl 3-olefinic oxindoles were further tested, and all these substrates could undergo the cascade Michael/Michael reaction smoothly to afford the desired bispirooxindoles (**3o–u**). Similarly, the presence of either electron-withdrawing (**3o**, **3p**, **3q** and **3u**) or electron-donating groups (**3r** and **3s**) on the aromatic rings of the 3-olefinic oxindoles is well tolerated, which indicates that the electronic nature of the substituents on the aromatic rings has little influence on this cascade reaction. Moreover, we also

tried to use chalcone as the substrate. Unfortunately, no reaction was observed, this may be due to the relatively low reactivity of chalcone.

However, the position of the substituent on the aromatic ring of the 3-olefinic oxindoles has an obvious effect on the yield. The yields of the corresponding products given by 4-substituted (**3o**) or 7-substituted (**3u**) 3-olefinic oxindoles were relatively lower than those from 5-substituted 3-olefinic oxindoles. It was subsequently found that two other cascade reagents with different *N*-protection groups (methyl or allyl) also gave positive results in this cascade reaction (**3v** and **3w**). Finally, we also examined one 5-substituted donor-Michael acceptor reagent for this cascade process and the corresponding product **3x** was also obtained with excellent yield and stereoselectivity.

The absolute configuration of the product was elucidated by single crystal X-ray diffraction analysis of **3d**.[10] The absolute configuration of **3d** was determined as (3*S*,3′*S*,4′*S*,5′*S*) (Figure 2), and the configurations of the other products were assigned by analogy.

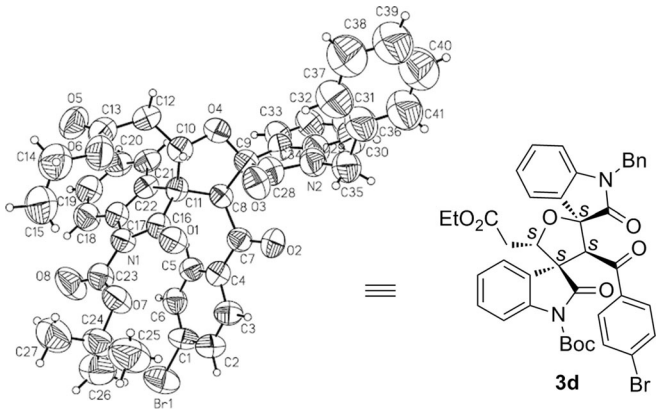
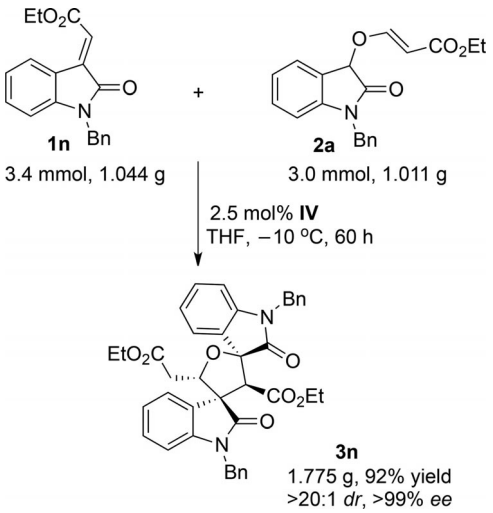


Figure 2. X-ray crystal structure of **3d**.

To illustrate the preparative utility of this asymmetric cascade Michael/Michael reaction, a gram-scale reaction was also conducted under the same conditions (Scheme 3). Compared with 0.15 mmol scale, the bispirooxindole **3n** was obtained in slightly decreased yield (92%) with the same excellent diastereoselectivity (>20:1 *dr*) and enantioselectivity (>99% *ee*).

The DBU-catalyzed reaction for the synthesis of racemic product **3** with excellent diastereoselectivity implies that the diastereoselectivity of this cascade reaction is the typical result of a substrate-controlled reaction. According to the absolute configuration of reaction product **3a**, we propose a tandem reaction mechanism (Scheme 4). 3-Olefinic oxindole **1a** is assumed to be activated and oriented by the hydrogen bonds of the squaramide, meanwhile the tertiary nitrogen of the hydroquinine provides suitable basicity to enhance the nucleophilicity of 3-substituted oxindole **2a**. Initially, the anion of **2a** attacks **1a** from the *Si*-face *via* transition state **A**, which undergoes the first intramolecular Michael addition and gives intermediate **B**. Then, a second intramolecular Michael addition caused by the generated 3-alkyl-indolin-2-one anion attacking the enoate from the *Re*-face forms the transition state **C**, which delivers the product **3a** and regenerates the bifunctional catalyst **IV** after a protonation process.



Scheme 3. Gram-scale synthesis of **3n**.

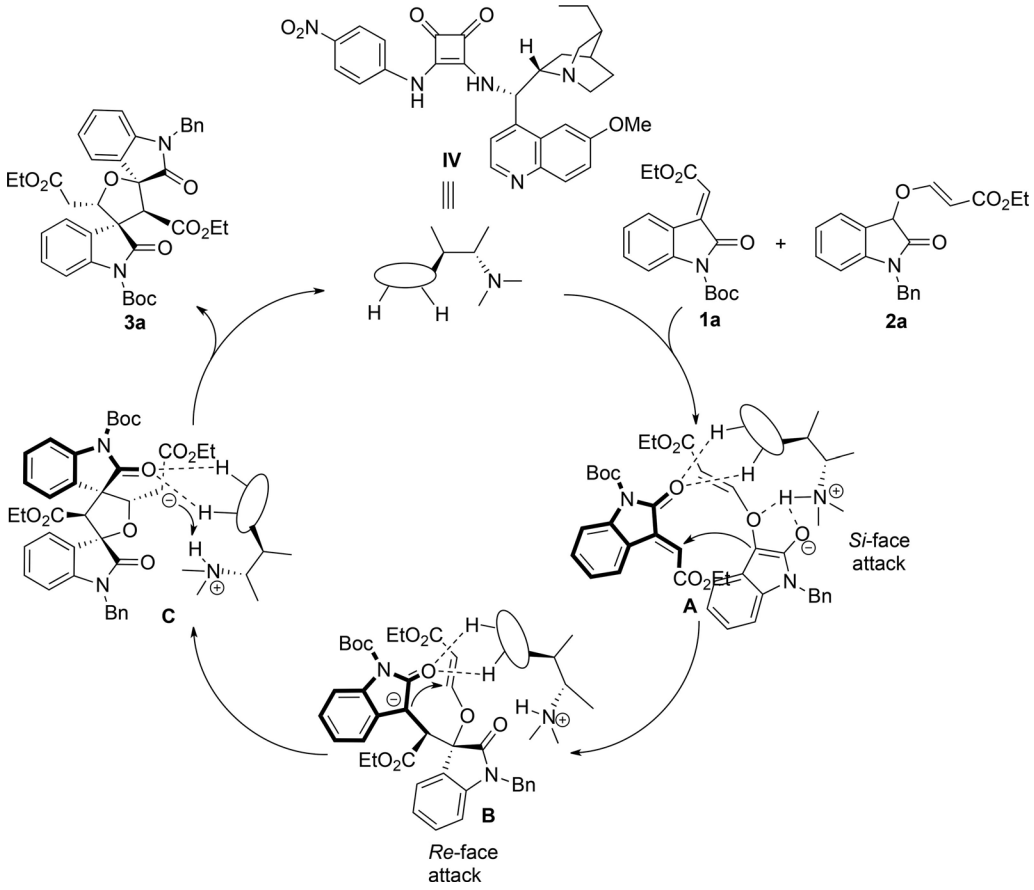
Conclusions

In conclusion, we have synthesized a new type of cascade reagent, and successfully applied it in the asymmetric cascade Michael/Michael reaction as a donor-Michael acceptor substrate for the construction of spirotetrahydrofuran bispirooxindoles. The corresponding products were obtained in moderate to excellent yield (up to 96%) with excellent diastereo- and enantioselectivities (up to >20:1 *dr*, 99% *ee*). This straightforward cascade process, catalyzed by a bifunctional chiral squaramide catalyst, serves as a powerful method for the enantioselective construction of potentially bioactive bispirooxindoles with four contiguous sterocenters, of which two are spiro all-carbon quaternary centers on a single tetrahydrofuran ring. Meanwhile, this cascade sequence can be scaled up with the same efficiency and stereoselectivity.

Experimental Section

General Procedure for the Synthesis of the Racemates of 3

To a dried small bottle were added **2** (0.05 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.8 mg, 0.005 mmol,



Scheme 4. Proposed reaction mechanism.

0.1 equiv.) and THF (0.25 mL). The mixture was stirred at room temperature for 15 min, and **1** (0.06 mmol) was then added. After stirring at room temperature for 12 h, the reaction mixture was concentrated and directly purified by silica gel column chromatography to afford the racemates of **3**.

General Procedure for Squaramide-Catalyzed Enantioselective Cascade Michael/Michael Reaction

To a dried small bottle were added **2** (0.15 mmol) and catalyst **IV** (2.0 mg, 0.00375 mmol, 2.5 mol%) in THF (0.75 mL). The mixture was stirred at −10 °C for 15 min, and **1** (0.17 mmol) was then added. After stirring at −10 °C for 30–72 h, compound **2** was completely consumed as detected by TLC analysis (petroleum ether/EtOAc 2:1). After that, the reaction mixture was concentrated and directly purified by silica gel column chromatography to afford the desired product **3**.

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[10] CCDC 1483994 (for **3d**) 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.

8 Squaramide-Catalyzed Enantioselective Cascade Approach to Bispirooxindoles with Multiple Stereocenters

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