Organic LETTERS

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

Catalytic Asymmetric Mannich/Cyclization of 2-Isothiocyanato-1-indanones: An Approach to the Synthesis of Bispirocyclic Indanone−Thioimidazolidine−Oxindoles

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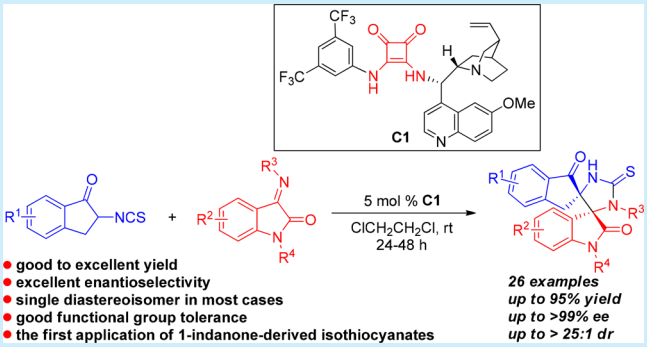
Supporting Information

ABSTRACT: This study demonstrates that novel isothiocyanates derived from 1-indanones are useful building blocks in heteroannulation reactions with isatinimines. This convenient Mannich/cyclization cascade reaction serves as a powerful tool for the enantioselective construction of bispirocyclic indanone−thioimidazolidine−oxindoles bearing two adjacent spiro-quaternary stereocenters in good to excellent yields with excellent diastereo- and enantioselectivities. Versatile transformations of the products into other potential bioactive bispirocyclic heterocycles have also been demonstrated.



Indanones have played an important role in the development of catalytic asymmetric synthesis; in particular, 1-indanone-derived cyclic β-ketoesters are the most commonly used substrates to verify the asymmetric substitution reaction strategies.[1] However, the reactions of 1-indanone-derivatives as nucleophilic reagents are limited.[2] To the best of our knowledge, the use of 1-indanone-derived nucleophilic cascade reagents to trigger the asymmetric cascade reactions have not been realized until now.

On the other hand, the important heterocyclic skeleton of spirooxindole is the core framework of many natural products and bioactive molecules.[3] Among them, spirooxindoles containing two adjacent spiro-quaternary stereocenters and 1-indanone units have shown considerable bioactivities, such as antitumor, cholinesterase, or acetylcholinesterase (AChE) inhibitory activities (Figure 1).[4] In this context, the spiroindanone-oxindole architecture present in the biologically relevant spirooxindole derivatives is worth noticing. Accordingly, the development of efficient methods for the asymmetric synthesis of spiroindanone−oxindoles could be important in the future design and discovery of medicinally significant compounds.

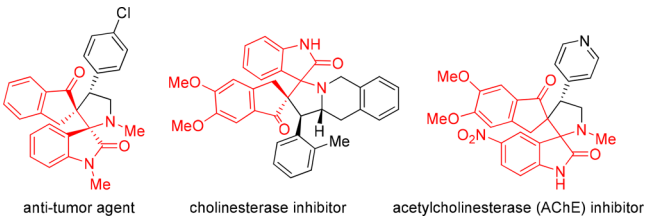


Figure 1. Examples of biologically active spiroindanone−oxindoles.

In contemporary organic synthetic chemistry, domino or cascade reactions have become a new tool in total synthesis[5] and one of the most effective ways to synthesize heterocyclic structural architectures.[6] In particular, organocatalytic domino or cascade reactions have become powerful strategies for the buildup of chemical and stereochemical diversity with multiple stereocenters from simple and readily available starting materials.[7] In this process, the design and synthesis of cascade reagents with high reactivity and high selectivity is one of the most critical steps. Over the past years, various cascade reagents for the preparation of chiral compounds with multiple stereocenters have been introduced. Among them, isothiocyanates bearing an electron-withdrawing moiety in the α-position have proved to be particularly efficient cascade reagents for the asymmetric synthesis of heterocyclic compounds.

After Seidel et al.'s pioneering application of isothiocyanates derived from oxazolidinones in organocatalysis,[8] isocyanoacetates have become irreplaceable building blocks for the synthesis of numerous important classes of nitrogen heterocyclic compound by the organocatalyzed asymmetric [3 + 2] cycloadditions with electrophiles. Ever since the report by Yuan et al. in 2011,[9] 3-isothiocyanato oxindoles have become extremely efficient and versatile cascade reagents for the enantioselective synthesis of spirooxindoles.[10] We envisoned that 2-isothiocyanato 1-indanones might also be used as cascade reagents. To verify the viability of this concept, we successfully synthesized and explored the readily accessible 1-indanone-derived isothiocyanates (Scheme 1a).

Received: May 2, 2018

DOI: 10.1021/acs.orglett.8b01389
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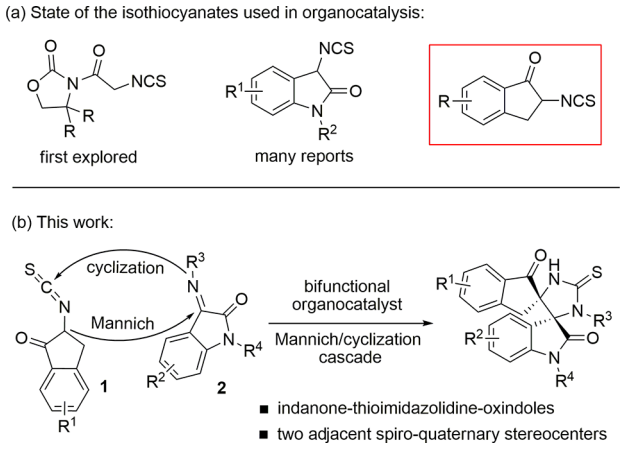
Scheme 1. Isothiocyanate Strategy in the Organocatalyzed Asymmetric Synthesis of Heterocycles and the Synthetic Objectives of Our Study



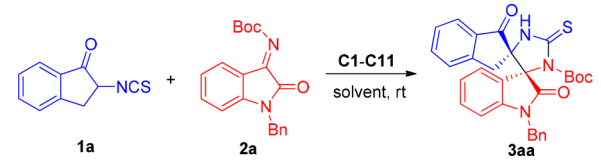
Given the biological and chemical importance of spiroindanone−oxindoles and their analogues, the task of developing a new approach to this class of compounds was undertaken. Herein, we present an efficient strategy for the enantioselective construction of bispirocyclic indanone−thioimidazolidine−oxindoles (Scheme 1b) bearing two adjacent spiro-quaternary stereocenters through a squaramide-catalyzed cascade Mannich/cyclization reaction between 2-isothiocyanato-1-indanone **1** and isatinimine **2**.

We first performed the reaction of 2-isothiocyanato-2,3-dihydro-1*H*-inden-1-one **1a** with *N*-Boc isatinimine **2a**. To our delight, in the presence of 5 mol % of squaramide **C1** derived from quinine, the cascade Mannich/cyclization reaction was completed in CH_2Cl_2 at room temperature in 12 h and afforded the desired product **3aa** in 87% yield with excellent diastereoselectivity and enantioselectivity (>25:1 dr, > 99% ee) (Table 1, entry 1). With the above excellent result in hand, we evaluated a small library of organocatalysts (Figure 2) for this cascade process (Table 1, entries 1−11). Some squaramide catalysts **C1**−**C9** derived from cinchona alkaloid and (1*S*,2*S*)-(+)-1,2-diaminocyclohexane were screened (Table 1, entries 2−9). The opposite enantiomer of the product **3aa** was obtained with lower enantioselectivity when quinidine-derived squaramides **C3** or **C4** were used as catalysts (Table 1, entries 3 and 4).

In addition, as a comparison of the used squaramides, the corresponding quinine-derived thiourea **C10** was also evaluated (Table 1, entry 10). There was a slight decline in yield and enantioselectivity. There was a significant drop in yield and enantioselectivity when quinine **C11** used as the catalyst (Table 1, entry 11). As shown in the Table 1, the squaramide **C1** derived from quinine still proved to be the most efficient catalyst with respect to the yield and enantioselectivity of this cascade reaction.

To improve the reaction efficiency, further optimization was carried out using squaramide **C1** as the catalyst. The effects of solvent, reaction temperature, and catalyst loading amount were investigated (Table 1, entries 12−19). Solvent effects play important roles in the reactions (Table 1, entries 12−16). The results show that $ClCH_2CH_2Cl$ was the best solvent with respect to both yield and enantioselectivity. However, the results of the reaction did not improve when the temperature was lowered to 0 °C (Table 1, entry 17). Subsequently, the

Table 1. Screening of Organocatalysts and Optimization of Reaction Conditions[a]



1a 2a 3aa

entry	solvent	cat.	yield[b] (%)	dr[c] (%)	ee[d] (%)
1	CH_2Cl_2	**C1**	87	>25:1	>99
2	CH_2Cl_2	**C2**	76	>25:1	>99
3	CH_2Cl_2	**C3**	83	>25:1	−95
4	CH_2Cl_2	**C4**	72	>25:1	−95
5	CH_2Cl_2	**C5**	69	>25:1	99
6	CH_2Cl_2	**C6**	79	>25:1	99
7	CH_2Cl_2	**C7**	76	>25:1	>99
8	CH_2Cl_2	**C8**	84	>25:1	85
9	CH_2Cl_2	**C9**	90	>25:1	85
10	CH_2Cl_2	**C10**	84	>25:1	98
11	CH_2Cl_2	**C11**	68	>25:1	52
12	$CHCl_3$	**C1**	80	>25:1	99
13	$ClCH_2CH_2Cl$	**C1**	92	>25:1	>99
14	PhMe	**C1**	79	>25:1	96
15	THF	**C1**	80	>25:1	98
16	MeCN	**C1**	79	>25:1	95
17[e]	$ClCH_2CH_2Cl$	**C1**	87	>25:1	99
18[f]	$ClCH_2CH_2Cl$	**C1**	92	>25:1	99
19[g]	$ClCH_2CH_2Cl$	**C1**	64	>25:1	99

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.11 mmol), catalyst (5 mol %) in 0.5 mL of solvent were stirred at room temperature for 12 h. [b]Isolated yield. [c]Determined by ^{1}H NMR. [d]Determined by chiral HPLC analysis. [e]The reaction was performed at 0 °C. [f]10 mol % of catalyst was used. [g]2.5 mol % of catalyst was used.

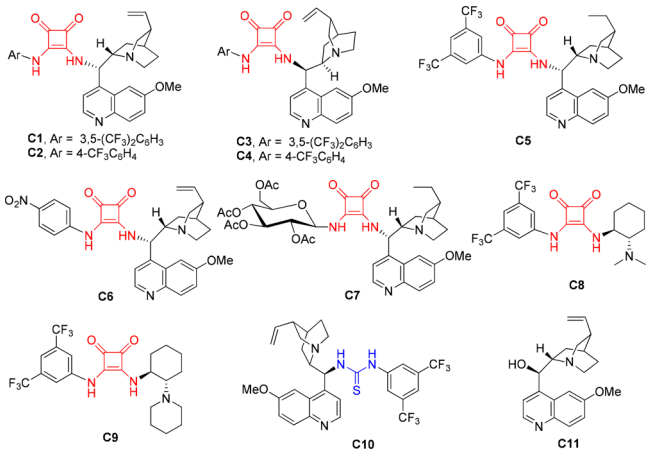


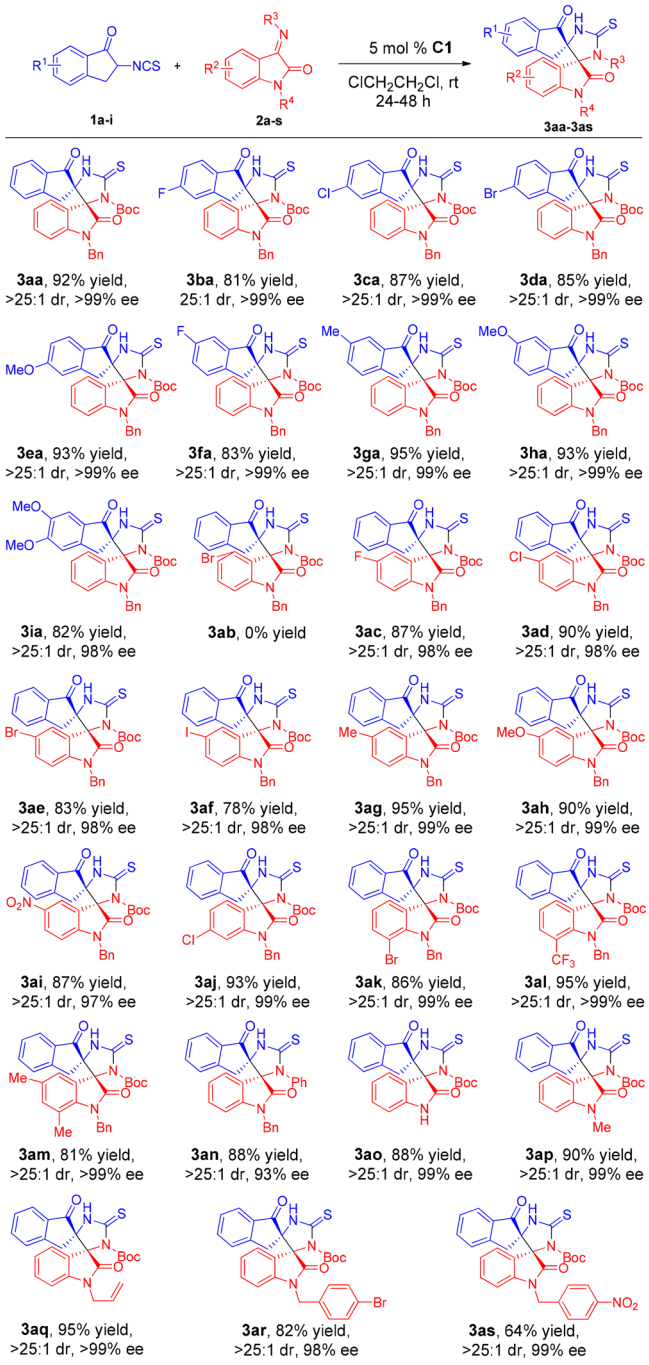
Figure 2. Screened organocatalysts.

effect of catalyst loading amount was tested. An increase in catalyst loading amount did not further improve the reaction results (Table 1, entry 18). When the catalyst loading amount was reduced to 2.5 mol %, the yield of **3aa** significantly declined (Table 1, entry 19). Thus, we use a 5 mol % catalyst loading.

Following this optimization of the reaction conditions, the substrate scope of this enantioselective squaramide-catalyzed Mannich/cyclization cascade reaction was examined for the synthesis of bispirocyclic indanone−thioimidazolidine−oxindoles **3**. The results are shown in Scheme 2. Initially, structural

DOI: 10.1021/acs.orglett.8b01389
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 2. Substrate Scope[a]



[a]Reaction conditions: **1** (0.1 mmol), **2** (0.11 mmol), and catalyst **C1** (5 mol %) in $ClCH_2CH_2Cl$ (0.5 mL) were stirred at rt for 24−48 h. The dr of products were determined by ^1H NMR. The ee values of products were determined by HPLC.

variations were made on the 2-isothiocyanato-1-indanones **1**. We found that the substrates with electron-withdrawing substituents such as F, Cl, and Br and electron-donating substituents such as Me and MeO all could react smoothly with **2a** to afford the corresponding products (**3ba**−**ia**) in high yields with excellent enantioselectivities. Compared with electron-withdrawing substituents, electron-donating substituents on the aromatic rings of 1-indanones improved the reaction yield. However, the positions of the substituted group on the aromatic rings of 1-indanones had little influence on this cascade process (**3ba**, **3fa**, **3ea**, and **3ha**). It is worth mentioning that nearly a single diastereoisomer of the product was obtained. Then a variety of isatinimines were tested. When 4-substituted isatinimines were reacted with **1a**, no obvious reaction product was observed, which may be due to large steric hindrance. Subsequently, various 5-substituted, 6-substituted, 7-substituted, and 5,7-disubstituted *N*-Boc-isatinimines were examined. All these substrates smoothly underwent this cascade Mannich/cyclization reaction to afford the desired spirooxindoles (**3ac**−**am**). In addition, we also tested a *N*-Ph-isatinimine, which gave the corresponding product **3an** with a dramatic decline of enantioselectivity.

Subsequently, the influence of the *N*-protecting group of the isatinimines on the reaction results was investigated. The *N*-unprotected, *N*-methyl-, and *N*-allylisatinimines all could give the corresponding products (**3ao**−**aq**) with comparable excellent yields and stereoselectivities to *N*-benzylisatinimine. Finally, we tried two isatinimines with *p*-bromobenzyl and *p*-nitrobenzyl *N*-protecting groups, which afforded their corresponding products in lower yields than *N*-benzylisatinimine (**3ar** and **3as**).

The absolute configuration of the type of product was elucidated by single-crystal X-ray diffraction analysis of **3ia** as (2′*S*,3″*R*) (Figure 3), and the configurations of other products were assigned by analogy.

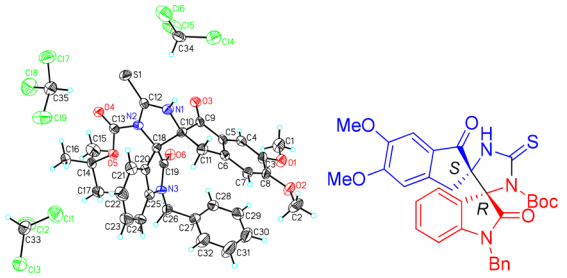
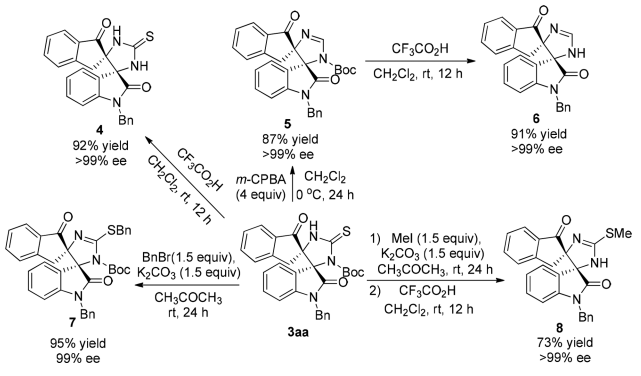


Figure 3. X-ray structure of **3ia** (inclusion of $CHC1_3$ molecules).

Remarkably, the derivatization of the major diastereomer of **3aa** into other structurally diverse spiroindanone-oxindoles, such as compounds **4**−**8** bearing two adjacent spiro-quaternary stereocenters, could be smoothly realized (for details, see the Supporting Information). As illustrated in Scheme 3, the Boc group of **3aa** could be easily removed with CF_3CO_2H, affording the corresponding product **4**. In addition, the thioimidazolidine moiety of **3aa** also could be smoothly converted into an imidazolidine ring with *m*-CPBA, which led

Scheme 3. Further Investigation of Transformation of 3aa



DOI: 10.1021/acs.orglett.8b01389
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to compound **5**,[11] which is another class of heterocycles now available for future biological investigation. The Boc group of **4** could also be easily removed with CF_3CO_2H to afford compound **6**. In addition, the thioimidazolidine moiety of **3aa** also could be smoothly converted into a 2-(alkylthio)-imidazolidine ring as in compounds **7** and **8**, which resulted in the formation of another family of bispirocyclic indanone−thioimidazolidine−oxindole analogues.

To further highlight the synthetic value of this methodology, a large-scale experiment was conducted under the optimized conditions (for details, see the Supporting Information). The cascade reaction of **1a** and **2a** on a gram scale performed well, and the product was obtained in slightly decreased yield (82%) with the same excellent diastereo- and enantioselectivity (>25:1 dr, > 99% ee).

In conclusion, we have synthesized a new type of 1-indanone-derived isothiocyanate cascade reagent and successfully applied these in the enantioselective squaramide-catalyzed cascade Mannich/cyclization reaction for the construction of bispirocyclic indanone−thioimidazolidine−oxindoles bearing two adjacent spiro-quaternary stereocenters in good to excellent yields (up to 95%) with excellent diastereo- and enantioselectivities (up to >25:1 dr, > 99% ee). In addition, the practicality of this methodology has been demonstrated by the synthetic transformations and the resulting novel heterocycles.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01389.

Experimental details, ^1H and ^{13}C spectra of new compounds, and HPLC chromatograms (PDF)

Accession Codes

CCDC 1839384 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for financial support from the National Postdoctoral Program for Innovative Talents of China (No. BX201700030) and the Project funded by China Postdoctoral Science Foundation (No. 2017M620630). We also thank the Analysis & Testing Center of the Beijing Institute of Technology.

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