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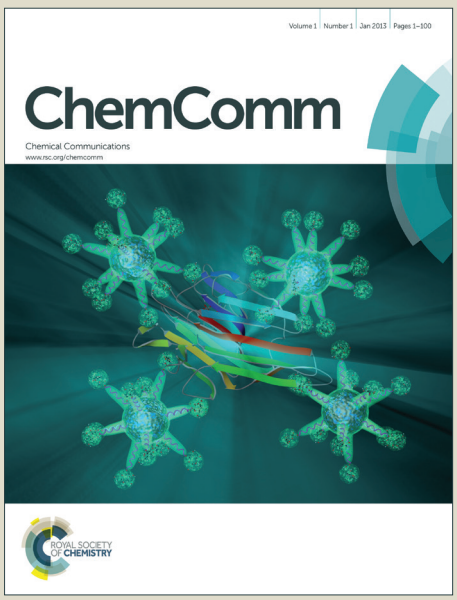

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A Mannich/Cyclization Cascade Process for the Asymmetric Synthesis of Spirocyclic Thioimidazolidine-oxindoles

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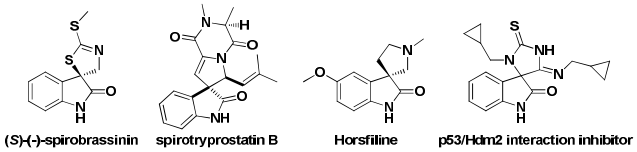
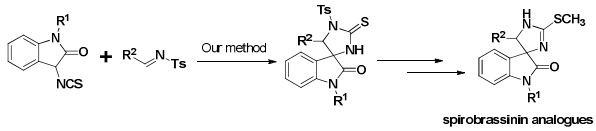
An asymmetric cascade Mannich/cyclization reaction between 3-isothiocyanato oxindoles and sulfimides using a commercially available organocatalyst has been developed. A wide range of structurally diverse spiro[imidazolidine-4,3'-oxindole] derivatives were obtained with good yields (up to 92%) and excellent enantioselectivities (up to 99% ee).

The oxindole framework bearing a spirocyclic quaternary stereocenter at the C3 position has drawn significant attention from researchers worldwide in medicinal chemistry and organic chemistry because it occurs in numerous natural alkaloids and synthetic biologically active compounds,[1] such as spirobrassinin, spirotryprostatin B, horsfiline, and an inhibitor of p53/Hdm2 interaction (Scheme 1). A variety of methodologies for asymmetric synthesis of spirooxindoles with organo- or transition-metal catalysts have been developed in recent years,[1,2] especially for building spirooxindoles bearing an all-carbon quaternary stereocenter at the C-3' position of the oxindole[3,4] Whereas, methods for the asymmetric synthesis of spirooxindoles bearing a nitrogen atom at the C3'-position are still limited.[5] In view of their pharmacologic activities, further studies for synthesizing chiral spirooxindole cores bearing a nitrogen atom at the C3'-position are highly desirable.



Scheme 1 Examples of quaternary carbon-bearing spirooxindoles

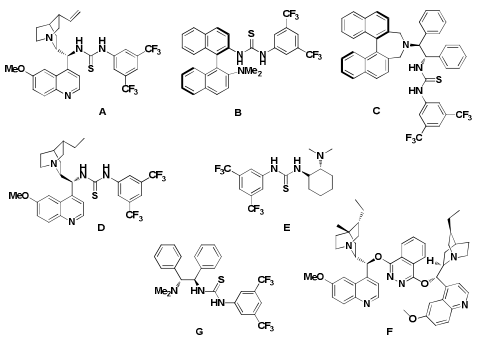
Using 3-isothiocyanato-oxindoles as nucleophiles to react with electron-deficient reagents including aldehydes[6a,b], ketones[6c,d], Michael acceptors[7] and imines[6d,8] is an efficient one-step method to access spirooxindoles. Wang and Yuan have extended the utility of such compounds to the asymmetric construction of spirooxindoles through Michael additions[7a~c] and aldol reactions[6a,c,d]. However, the intermolecular enantioselective Mannich reactions of isothiocyanates to imides is still a challenge in organic synthesis. To the best of our knowledge, Kato and co-workers reported the only example on the asymmetric Mannich reactions of isothiocyanato-oxindoles using a Sr(II)-Schiff base complex catalyst, in which metal Sr was necessary as a ligand for the Schiff base.[8]



Scheme 2 A new pathway to construct spirobrassinin derivatives

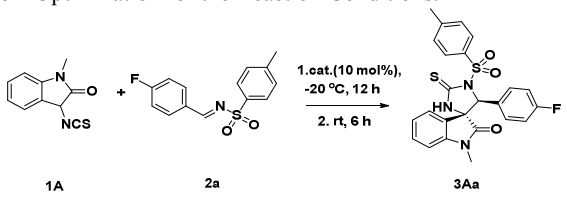
In our previous researches, we have developed two highly efficient organocatalyzed methods for the asymmetric synthesis of spiro-oxindoles as part of the construction of natural product-like library for further activity research.[9] Herein, we have established another highly efficient asymmetric Mannich reaction strategy to construct different spiro-oxindoles, which could smoothly be converted into a novel series of spirobrassinin imidazolidine analogues (Scheme 2).

To establish the optimal experimental conditions for the synthesis of spirocyclic thioimidazolidineoxindoles, we chose 3-isothiocyanato oxindole **1A** and imide **2a** as the model substrates, and the results are summarized in Table 1. Initially, several organocatalysts were screened in THF at -20 °C to evaluate their ability for the reaction (Scheme 3, and Table 1, entries 1~7). It was found that



Scheme 3 Screened catalysts for the Mannich reaction

Table 1 Optimization for the Reaction Conditions.[a]



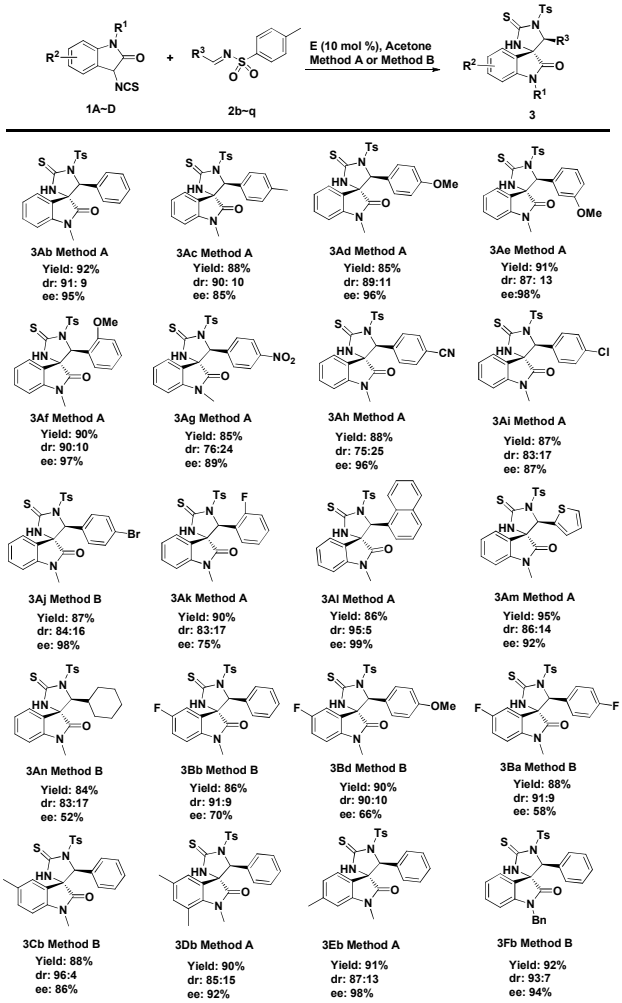
Entry	Catalyst	Additive	Solvent	Yield[b] (%)	dr[c]	ee[d] (%)
1	A	-	THF	89	72:28	98[e]
2	B	-	THF	72	-	7[e]
3	C	-	THF	89	-	3[e]
4	D	-	THF	90	-	-43[e]
5	E	-	THF	88	89:11	98[e]
6	F	-	THF	92	-	49[e]
7	G	-	THF	88	-	-7[e]
8	E	-	DCE	63	66:34	>99[f]
9	E	-	$CHCl_3$	41	71:29	>99[f]
10	E	-	Toluene	73	41:59	>99[f]
11	E	-	Acetone	90	87:13	98
12	E	-	MeOH	94	70:30	98
13	E	-	DMSO	85	53:47	>99
14	E	-	EtOH	85	73:27	98
15	E	*p*-CNC_6H_4COOH	Acetone	90	83:17	>99
16	E	*p*-$MeC_6H_4SO_3H$	Acetone	83	68:32	>99
18	E	TMSCl	Acetone	40	87:13	>99
19	E	LiCl	Acetone	75	76:24	>99
20	E	EtONa	Acetone	66	88:12	>99

[a] Unless noted, the reaction was carried out with **1A** (0.2 mmol), **2a** (0.3 mmol), catalyst, additive and 4 Å molecular sieves in specified solvent (2.5 mL) at -20 °C for 12 h, then at rt for another 6 h. [b] Isolated yield. [c] Determined by ^{1}H-NMR analysis of the product after purification *via* flash chromatography. [d] Determined by chiral HPLC. [e] -20 °C, 12 h, then warm to rt 12 h. [f] -20 °C, 12 h, then warm to rt 24 h.

both catalysts **A** and **E** gave the target products **3Aa** in good yield and enantioselectivity, and better diastereoselectivity was obtained with catalyst **E** (89:11 dr of **E** *vs.* 72:28 dr of **A**). Therefore, we chose catalyst **E** as the optimal catalyst for further investigation (Table 1, entry 5). Then different solvents were further screened, and the results demonstrated that the reactivities in nonpolar solvents were inferior to those in polar solvents (Table 1, entries 8-14). In polar solvents, the starting materials were completely converted into **3A**a when the reaction mixture were stirred at -20 °C for 12 h followed by another 6 h at room temperature. While in nonpolar solvents the reactants were not exhausted even with prolonging reaction time to 24 h. In consideration of the yield, enantioselectivity and diastereoselectivity of the desired product, acetone was the best solvent for this transformation. Subsequently, investigation of different additives in acetone revealed that *para*-cyanobenzoic acid as an additive improved the enantioselectivity with little decrease of diastereoselectivity (Table 1, entries 15~20). Whereas in some other cases, it was found that the additive was not so necessary. Overall the optimal reaction conditions were as follows: the starting material **1A** (0.2 mmol) in 2.5 mL of acetone was treated with **2a** (0.3 mmol) in the presence of 10 mol% of catalyst **E** and/or 10 mol% of *para*-cyanobenzoic acid as an additive at -20 °C for 12 h, followed by another 6 h at room temperature (Table 1, entries 11 and 15).

With the optimal conditions in hand, we have investigated the functional group tolerance by probing changes in the substituted 3-isothiocyanatoindolin-2-ones (**1A-D**) and imines (**2b-q**). As shown in Scheme 4, various substituted 3-isothiocyanatoindolin-2-ones (**1A-D**) and imides (**2b-q**) were tolerant in this transformation, and afforded the desired products (**3Ab-Db**) with good enantioselectivities and diastereoselectivities in excellent yields. The type of substituents on the benzene ring of sulfimides slightly affected the yields, enantioselectivities and diastereoselectivities. Good results were obtained when electron-donating groups (**3Ac~Af**), electron-withdrawing groups (**3Ag-Ah**) and halogen substituents (**3Ai-Aj**) were positioned on the benzene ring (the R^3 group of sulfimides). The sterically hindered substrates bearing *ortho*-methoxyl group also can obtain **3Af** in 90% yield with 90:10 dr and 97% ee, while the introduction of a fluorine atom at the *ortho*-position resulted in a slight decrease in the ee value (**3Ak**). Further studies demonstrated that naphthaldimine (**3Al**) and 2-thenaldimine (**3Am**) were tolerated in this reaction, with 95:5 dr, 99% ee in 86% yield and with 86:14 dr, 92% ee in 95% yield respectively. However, treatment of cyclohexan-ealdimine with 3-isothiocyanatoindolin-2-ones afforded **3An** with 52% ee.

Scheme 4 Asymmetric Mannich Reaction of 3-Isothiocyanates and Sulfimides[a]



[a] Reaction conditions: **1** (0.2 mmol) , **2** (0.3mmol) and 4 Å molecular sieves in acetone (2.5 mL), method A or method B. The isolated yields were given after column chromatography. The dr values were determined by ^{1}H-NMR analysis. The ee values were determined by chiral HPLC analysis. Method A: with 10 mol % of *p*-CNC_6H_4COOH as additive, -20 °C, 12 h, then warm to rt, 6 h. Method B: without additive, -20 °C, 24 h, then warm to rt, 6 h.

Modification of the 3-isothiocyanatoindolin-2-ones scaffold was also tolerated. Although introduction of fluorine at the C-5 position of the oxindole scaffold had a negative effect on enantioselectivity, with ee values of only 58-70% (**3Bb**, **3Bd** and **3Ba**), replacement of the fluorine atom with a methyl group increased the ee value to 86% and improved the diastereoselectivity (**3Cb**). Isothiocyanates with methyl substituent in other position (**3Db** and **3Eb**) also proved to be amenable to this procedure, with high yields and ee values. Furthermore, *N*-benzyl protected oxindole **1F** offered offered **3Fb** in 92% yield with 93:7 dr and 94% ee. To determine the absolute configurations of the target products, we have recrystallized representative compound **3Aj** in MeOH solvent and determined the structure with single crystal X-ray analysis (Figure 1, and see Supporting information for details).

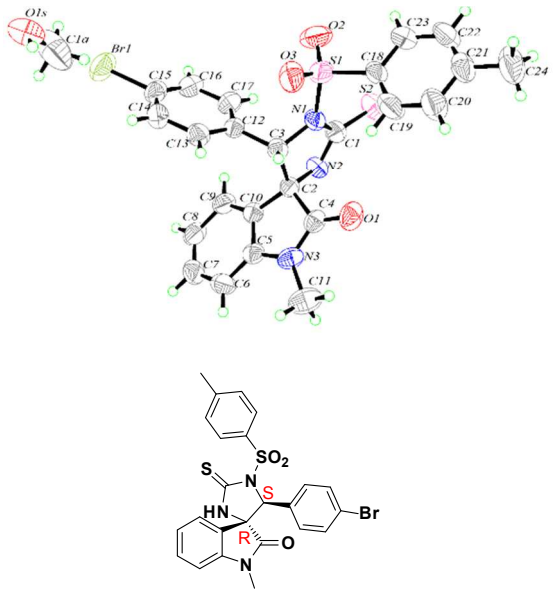
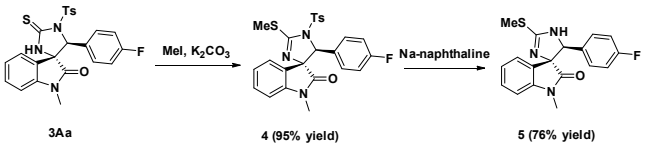


Figure 1 X-ray crystallographic structure ant its absolute configuration of **3Aj**

Furthermore, the target products were easily transformed into spirobrassinin imidazolidine analogues. For example, the product **3Aa** could be smoothly converted into the 2-methylthio-imidazolidine (**4**) according to a reported procedure,[10] which was further desulfonylated by treatment with sodium naphthalenide in DME to afford the spirobrassinin derivative **5** in 76% yield (Scheme 5).[11]



Scheme 5 Transformation of **3Aa** into spirobrassinin derivative

In summary, we have successfully developed an asymmetric cascade Mannich/cyclization reaction of 3-isothiocyanato oxindoles with imines using a bifunctionalthiourea-tertiary amine as catalyst. This process provided efficient access to spiro[imidazolidine-4,3'-oxindole] bearing two stereocenters in up to 92% yield, 96:4 dr and >99% ee. We believe that the availability of these compounds will provide promising candidates for chemical biology and drug discovery.

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Notes and references

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[c] The authors contributed equally to the work.

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