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Enantioselective Construction of Spirooxindole Derivatives through [3+2] Annulation Catalyzed by a Bisthiourea as a Multiple-Hydrogen-Bond Donor

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Finding cost-effective and sustainable synthetic methods to reproduce the rich structural diversity and complexity of natural molecules has always captured the attention of chemists, especially in relation to biologically active compounds.[1] Particularly intriguing is the spirocyclic oxindole core, which is featured in a number of natural products, as well as medicinally relevant compounds.[2] The pharmaceutical value of these enantiomerically pure backbones have led to a demand for efficient methods for their asymmetric synthesis. Pioneered by the work of the groups of Overman[3] and Trost,[4] impressive advances have been documented for the stereoselective synthesis of spirocyclic oxindoles.[5,6] However, little effort so far has been focused on enantioselective approaches to the potentially bioactive isoxazolidine ring fused with an oxindole moiety.[7]

Bifunctional tertiary amine–thiourea catalysts have emerged as a powerful acid–base catalyst for asymmetric transformations.[8] In these strategies, the thiourea and tertiary amine groups act as a hydrogen-bond donor and acceptor, respectively, to catalyze the reactions (Figure 1a).[9] However, the bifunctional thiourea catalytic system still remains to be explored.[10] Chen and co-workers[11] have reported that the concerted hydrogen-bonding interaction of the two reactants with two thiourea functional groups might be responsible for the higher enantiocontrol in the Mannich-type reaction step (Figure 1b). Moreover, Barbas III and co-workers[12] used a bisthiourea catalyst as a hydrogen-bonding catalyst in the D–A reaction of 3-vinylindoles and methyleneindolinones (Figure 1b). It has been found that the multiple hydrogen-bonding interactions which exist in these reactions may have a profound influence on the enantioselectivity. Nevertheless, the exact catalytic mechanism and reaction scope still need more investigation. Considering our continuous interest in developing new enantioselective synthetic methods,[13] we describe herein an unusually efficient asymmetric [3+2] annulation, involving methyleneindolinones and nitrones, promoted by a bisthiourea catalyst as a multiple-hydrogen-bond donor, affording spiro[isoxazolidine-3,3′-oxindole] products with high enantio- and diastereoselectivities.

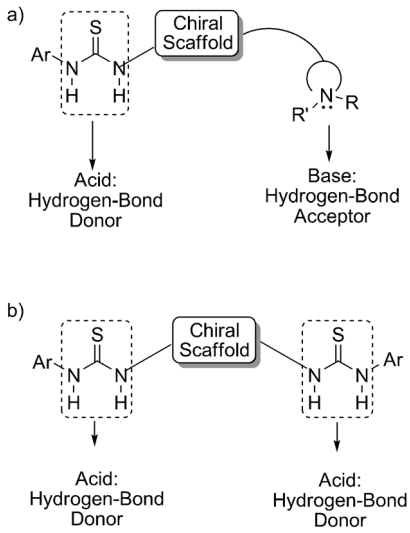

Figure 1. Different catalytic modes of bifunctional thioureas.

Initial experiments were carried out by using *N*-*tert*-butoxycarbonyl (*N*-Boc)-protected methyleneindolinone **1a** and nitrone **2a** as the starting materials in the presence of catalysts **I**–**IV** (20 mol%, Figure 2) in toluene at room temperature. Although the reactions proceeded smoothly, products with moderate d.r. and low *ee* were obtained (Table 1, entries 1–4). We realized that the catalysts **I**–**IV** could activate **1a** through hydrogen-bonding interactions,[14] but had no direct contact with 1,3-dipole **2a**, resulting in the poor enantiocontrol. Next, the reaction was attempted with catalysts **VI**–**VIII**. To our delight, the reactivity and enantioselectivity were dramatically improved (Table 1, entries 5 and 7). Bisthiourea catalyst **VI**, which can function as a multiple-hydrogen-bond donor, was the best catalyst for the reaction of hydrogen-bond acceptor substrates, like **1a** and **2a** (Fig-

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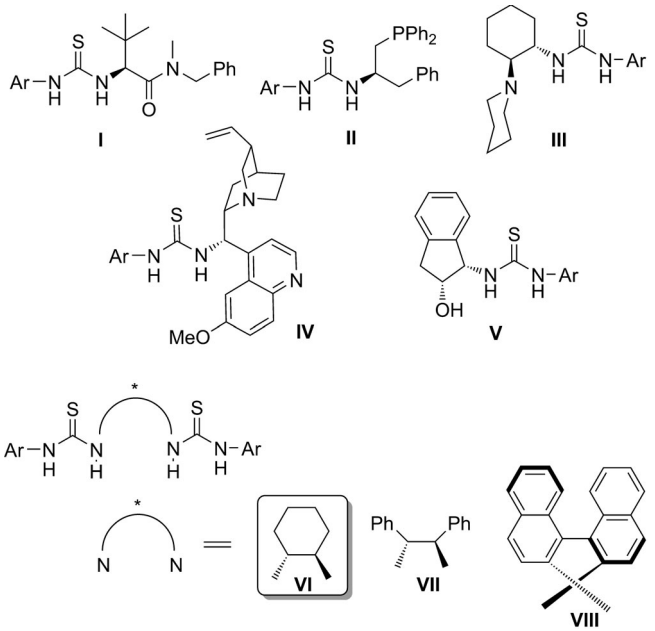
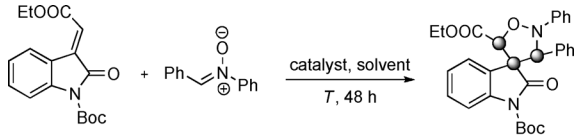


Figure 2. Screened catalysts (Ar = 3,5-$(CF_3)_2C_6H_3$).

Table 1. Optimization of the reaction conditions.[a]



Entry	Cat.	*T* [°C]	Solvent	Yield[b] [%]	d.r.[c]	*ee*[d] [%]
1	**I**	RT	toluene	52	78:22	28
2	**II**	RT	toluene	23	61:39	25
3	**III**	RT	toluene	38	73:27	9
4	**IV**	RT	toluene	40	65:35	8
5	**VI**	RT	toluene	73	80:20	60
6	**VII**	RT	toluene	43	66:34	10
7	**VIII**	RT	toluene	70	80:20	60
8	**V**	RT	toluene	45	70:27	11
9	**VI**	RT	CH_2Cl_2	61	63:37	15
10	**VI**	RT	petroleum ether	55	93:7	72
11	**VI**	RT	hexane	70	90:10	77
12	**VI**	RT	acetic ether	60	60:40	5
13	**VI**	RT	pentane	55	92:7	72
14	**VI**	−10	hexane	65	99:1	98
15	**VI**	−20	hexane	59	98:2	96

[a] The reactions were performed with **1a** (0.1 mmol) and **2a** (0.1 mmol) in the presence of the organocatalyst (20 mol%) in the solvent (1 mL). [b] Yield of the isolated product. [c] The d.r. was determined by ^{1}H NMR spectroscopic analysis. [d] The *ee* of the major diastereoisomer was determined by HPLC analysis.

ure 1b). Additionally, a poor *ee* value was obtained with catalyst **V**, which contains a free -OH group (Table 1, entry 8). These results indicate that the bisthiourea functionality in catalyst **VI** was essential.

Reactions catalyzed by **VI** were further optimized. The asymmetric induction was sensitive to solvent (Table 1, entries 5 and 9–13); of those tested, hexane provided the best diastereo– (90:10 d.r.) and enantioselectivity (77% *ee*; Table 1, entry 11). Other solvents, such as CH_2Cl_2, petroleum ether, acetic ether, and pentane, furnished the product in lower yields (Table 1, entries 9, 10, 12 and 13). Different reaction temperatures were attempted, and −10°C was found to be optimal (Table 1, entries 14 and 15). Optimal results were obtained for the reaction performed in hexane with 20 mol% of catalyst **VI** at −10°C (Table 1, entry 14).

Under the optimized conditions, the scope of the reaction was evaluated (Scheme 1). A wide range of methyleneindolinones were tolerated. Excellent enantio- and diastereoselectivities (up to 99% *ee* and 99:1 d.r.) were obtained. The enantioselectivities were slightly affected when the steric hindrance of substituents on the aromatic ring of methyleneindolinones was increased (Scheme 1, **3e**–**3g**). Further exploration of the substrate scope focused on the 1,3-dipolar nitrones (Scheme 1). The corresponding products were obtained in good yields and enantioselectivities (**3j**–**3q**). We have also tested *N*-methyl nitrone and the *N*-benzyl nitrone, however, the reactivity was poor. Halogen substituents (F, Cl, and Br, **3e**–**3o**) can also be successfully incorporated into the aromatic ring of the nitrone, which provides additional potential reaction sites for further synthetic transformations. The absolute configuration of the stereogenic centers of the product **3i** was confirmed by X-ray crystallographic analysis (Figure 3).[15]

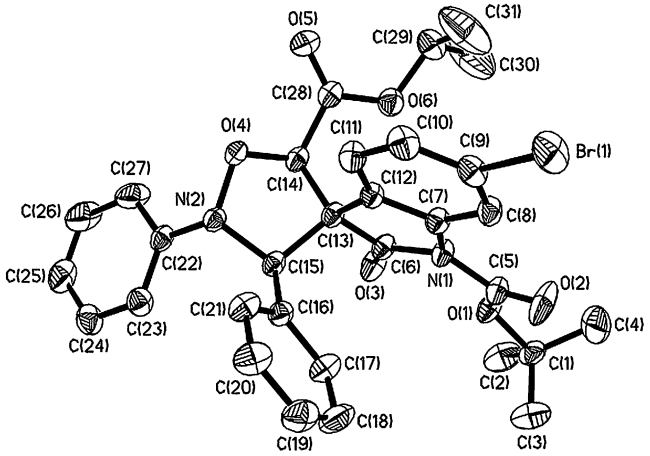
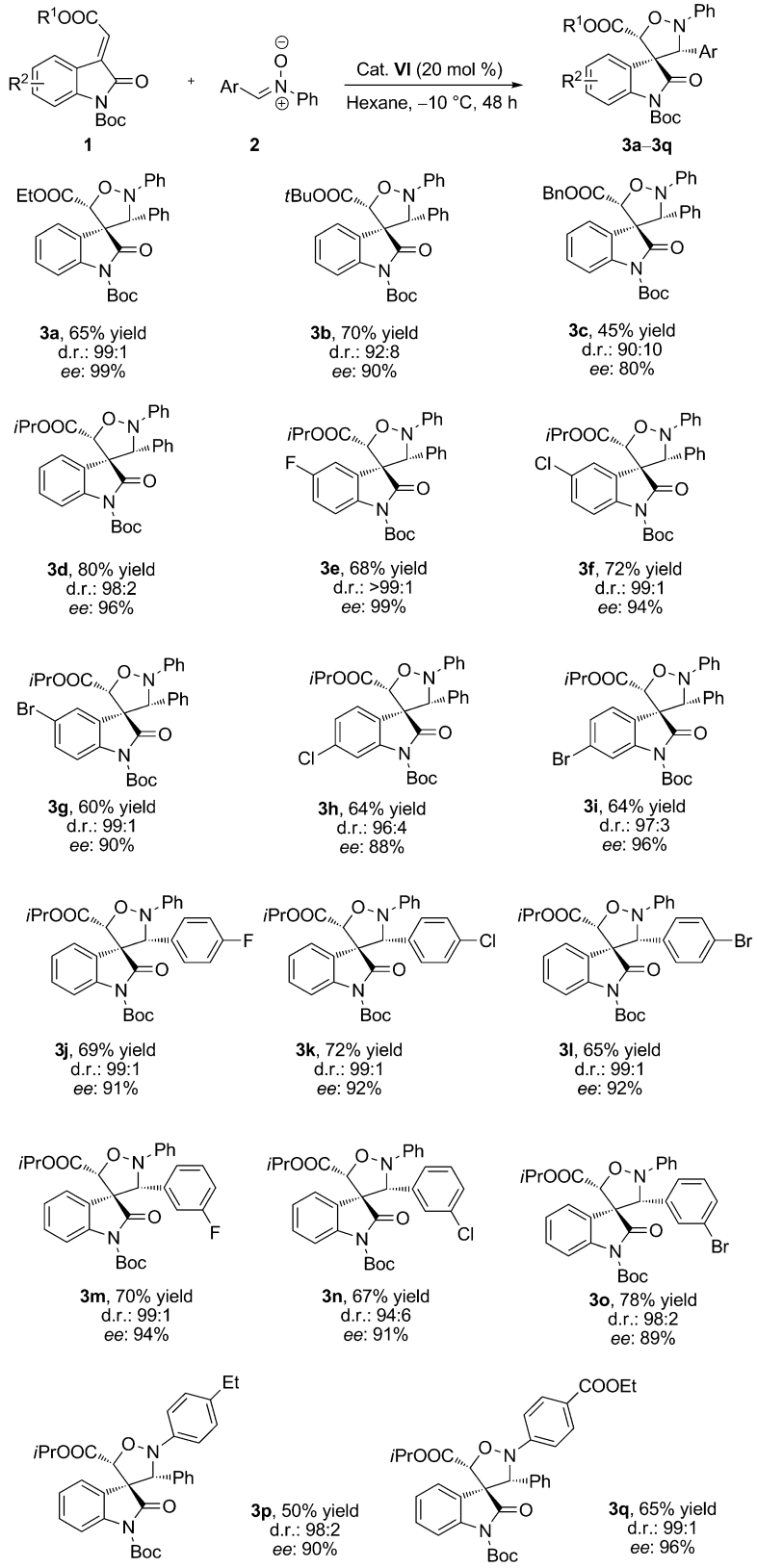


Figure 3. X-ray crystal structure of **3i**.

Under the standard conditions, the reaction was carried out on a gram scale (Scheme 2). Thus, 3 mmol of **1d** and **2a** in 15 mL of hexane gave 1.2 g of the desired product (75% yield, 95% *ee*, 98:2 d.r.), suggesting that this method is amenable to large scale production.

The effects of the *N*-methyleneoxindole protecting group were also taken into consideration. Under the standard conditions, only Boc-protected 3-methyleneoxindole derivatives provided the product stereoselectively, whereas the corresponding benzyl (Bn)- or Me-protected products were not detected (Figure 4a).[16] Further mechanistic studies were



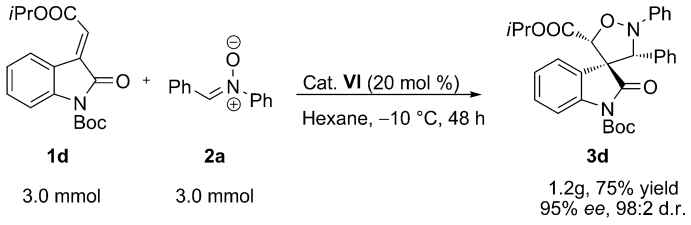
Scheme 1. Synthesis of spiro[isoxazolidine-3,3′-oxindole] derivatives. The reactions were performed with **1** (0.1 mmol) and **2** (0.1 mmol) in the presence of catalyst **VI** (20 mol %) in hexane (1 mL), the d.r. was determined by ^{1}H NMR spectroscopic analysis, and the *ee* of the major diastereoisomer was determined by HPLC analysis.

carried out with the help of MS and NMR spectroscopy. When catalyst **VI** was mixed with methyleneindolinone **1a** and 1,3-dipolar nitrone **2a**, a new species characterized by a base peak at $m/z = 1171.08$ was detected and assigned to be **VI**+**1a**+**2a** (Figure 4b). In ^{1}H and ^{13}C NMR experiments, the spectra gave strong evidence of catalyst interactions with both substrates (see the Supporting Information). On the basis of the aforementioned clues, we conclude that a synergistic interaction between the catalyst and the two reactants occurs, as shown in Figure 4c. The process was directed by multiple hydrogen-bonding interactions between the bisthiourea catalyst and the two substrates.

In summary, the [3+2] annulation of methyleneindolinone with nitrones has been developed as a highly convenient and practical approach to construct enantioenriched spiro[isoxazolidine-3,3′-oxindole] derivatives. The bisthiourea catalyst was used as a multiple-hydrogen-bond donor to simultaneously activate the two substrates. The products, with three contiguous stereocenters including one spiroquaternary stereocenter, are obtained in good yields with excellent enantio- and diastereoselectivity. This method would be suitable for large-scale chemical production because the reaction was scalable. We believe that these spiro[isoxazolidine-3,3′-oxindole] derivatives will provide promising candidates for chemical biology and drug discovery.

Experimental Section

General procedure: Methyleneindolinones **1** (0.1 mmol) and nitrones **2** (0.1 mmol) were dissolved in hexane (1.0 mL). When the mixture was cooled to −10 °C, catalyst **VI** (20 mol %) was added. After stirring



Scheme 2. Gram scale experiment.

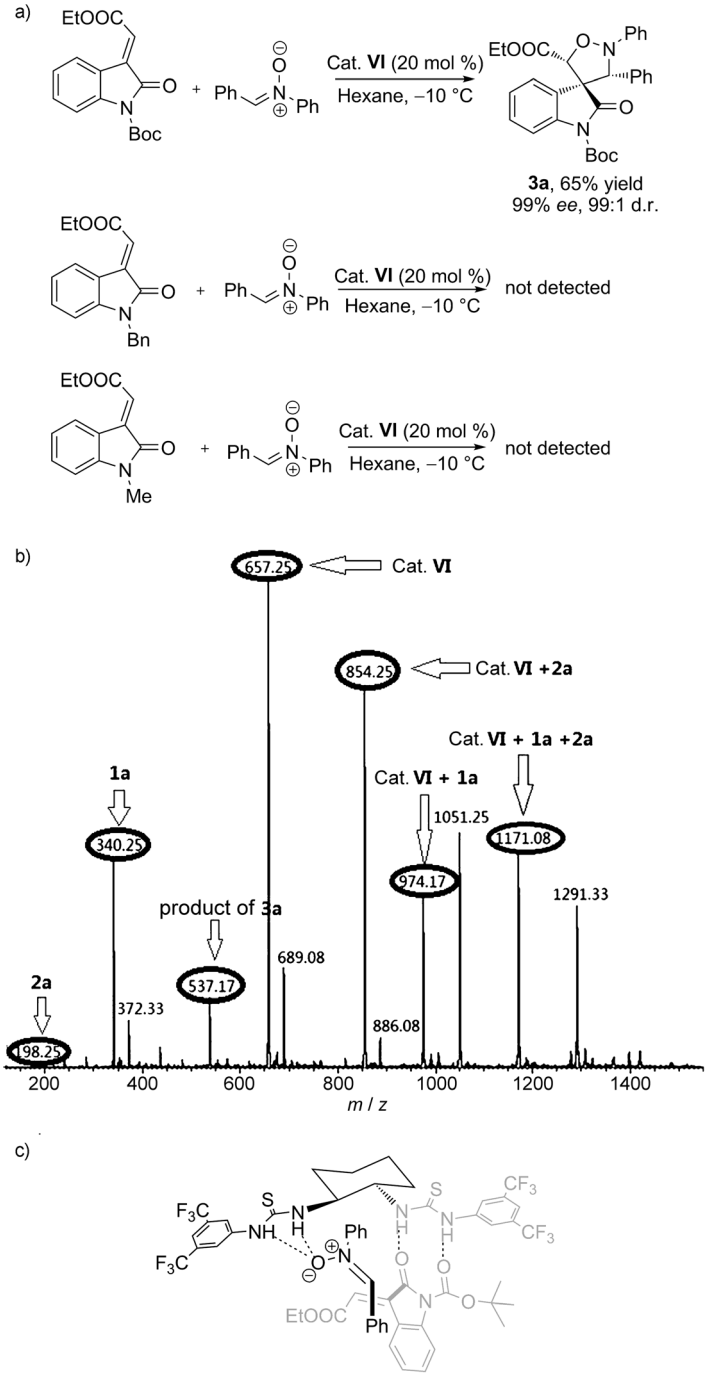


Figure 4. a) The effect of different *N*-methyleneoxindole protecting groups. b) The new species detected by MS (ESI) analysis of **1a** and **2a** after the addition of catalyst **VI**. c) Proposed mode of activation of the substrate/catalyst system.

for 48 h, the reaction mixture was directly subjected to flash column chromatography on silica gel (petroleum ether/ethyl acetate) to afford the corresponding pure products **3**. The diastereomeric ratio (d.r.) was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. HPLC analyses were performed on a chiral column (Daicel Chiralpak IA, AD-H column, Chromatography Interface 600 Series Link and Series 200 pump) with a Series 200 UV/Vis detector at 238 nm. The racemic simples for HPLC analysis were prepared in toluene at room temperature and catalyzed by the diphenylphosphate.

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[15] CCDC-886412 (**3i**) 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.
[16] We have also considered the *N*-carboxybenzyl (*N*-Cbz)- and *N*-fluorenylmethyloxycarbonyl (*N*-Fmoc)-protected methyleneindolinones. However, the latter substrate was not obtained. For *N*-Cbz-protected methyleneindolinones, only a trace of the product was obtained under the optimized conditions.

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