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Enantioselective Synthesis of Spirooxindole Enols: Regioselective and Asymmetric [3+2] Cyclization of 3-Isothiocyanato Oxindoles with Dibenzylidene Ketones

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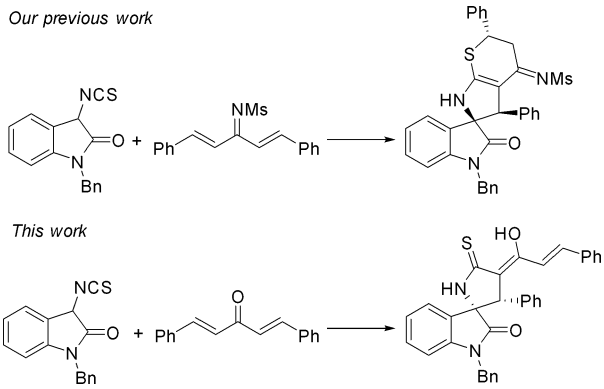
A novel cinchona-alkaloid-derived organocatalyst has been developed to catalyze the asymmetric regioselective [3+2] cycloaddition of 3-isothiocyanato oxindoles with dibenzylidene ketones. A series of spirooxindole enols could be obtained in high yields with good-to-excellent diastereo- and enantioselectivities.

Spirocyclic oxindoles, which are presented as significant structural motifs in many natural products and biologically active compounds,[1] allured many synthetic and medicinal chemists for the rapid and stereoselective construction of their structures. Accordingly, great efforts have been devoted to the novel and efficient protocol for the asymmetric generation of this series of compounds, and several novel synthetic methods have been explored recently.[2]

In 2011, 3-isothiocyanato oxindoles were first used for the construction of spirooxindole cores by Yuan and co-workers.[3] They reported a direct catalytic asymmetric intermolecular aldol reaction of 3-isothiocyanato oxindoles to simple ketones with bifunctional thiourea–tertiary amine as the catalyst. Since their pioneering work, a variety of spirooxindoles with a nitrogen atom at the C3′ position of the oxindole unit have been synthesized,[4] through the reaction of 3-isothiocyanato oxindoles with different electron-deficient unsaturated bonds, such as C=O, C=N, C=C, N=N, and C≡C.[5] For example, Kanai and Matsunaga developed an asymmetric Mannich-type reaction of isothiocyanato oxindoles with imines catalyzed by a Sr/Schiff-base complex;[5a] Xiao and co-workers exhibited a $Zn(OTf)_2$-catalyzed Michael addition/cyclization reaction between 3-isothiocyanato oxindoles and 3-nitro-2*H*-chromenes.[5k]

Based on these elegant studies and our recent research on cinchona-alkaloid-derived organocatalysts to catalyze the asymmetric cycloaddition of 3-isothiocyanato oxindoles in the preparation diverse spirocyclic oxindoles,[6] we started the exploration of regio- and enantioselective[7] cycloaddition between 3-isothiocyanato oxindoles and those compounds containing two or three electron-deficient unsaturated bonds. Previously, we reported the construction of spirocyclic oxindoles through the regio- and stereoselective [3+2]/[4+2] cascade reaction of 3-isothiocyanato oxindole with α,β-unsaturated imines (Scheme 1, our previous work).[6e] In this paper, we wish to report the enantioselective synthesis of spirooxindole enols through the regioselective and asymmetric [3+2] cyclization of 3-isothiocyanato oxindoles with dibenzylidene ketones[8] (Scheme 1, this work).



Scheme 1. Our previous work and this work for the preparation of spirooxindole enol.

We first investigated the reaction by using 1-benzyl-3-isothiocyanato oxindole **1a** (0.2 mmol, 1.0 equiv) and (1*E*,4*E*)-1,5-diphenylpenta-1,4-dien-3-one **2a** (0.25 mmol, 1.0 equiv) as the model substrates. Several cinchona-alkaloid-derived catalysts[9] were screened in tetrahydrofuran (THF) at room temperature to improve the reaction outcomes (Figure 1). As shown in Table 1, catalyst **Q-7** gave the better reaction outcome, affording enol **3aa** in 93% isolated yield with 88% *ee* (Table 1, entries 1–8) (see Table S1 in the Supporting Information for the preparation of racemate **3aa**). Upon optimization of the reaction conditions, by carrying out the reaction in different solvents, we found that, in toluene, this reaction gave the desired product **3aa** with the best *ee* value (Table 1, entries 9–11). However, a small amount of S-containing heterocyclic spiroox-

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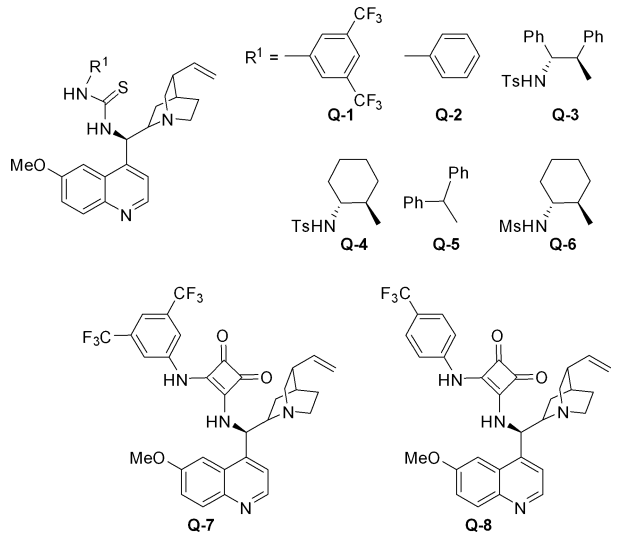
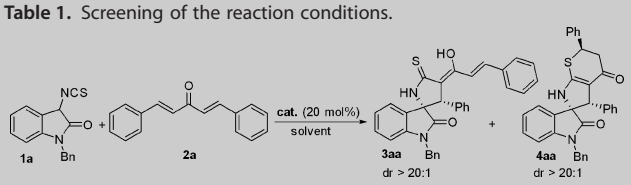


Figure 1. Multifunctional organocatalysts derived from cinchona alkaloids.

Table 1. Screening of the reaction conditions.



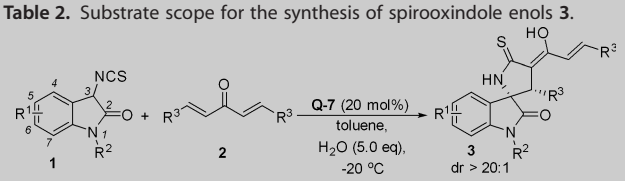
Entry[a]	Cat.	Solvent	3aa Yield [%][b]	3aa *ee* [%][c]	4aa Yield[b]	4aa *ee* [%][c]
1	**Q-1**	THF	91	52	trace	–
2	**Q-2**	THF	92	23	trace	–
3	**Q-3**	THF	89	45	trace	–
4	**Q-4**	THF	91	3	trace	–
5	**Q-5**	THF	88	32	trace	–
6	**Q-6**	THF	92	35	trace	–
7	**Q-7**	THF	93	83	trace	–
8	**Q-8**	THF	90	75	trace	–
9	**Q-7**	CH_3CN	83	12	trace	–
10	**Q-7**	DCM	58	51	33	53
11	**Q-7**	toluene	63	90	31	90
12[d]	**Q-7**	toluene	92	88	trace	–
13[d,e]	**Q-7**	toluene	92	90	trace	–
14[d,f]	**Q-7**	toluene	91	91	trace	–

[a] Reaction was carried out with **1a** (0.20 mmol), **2a** (0.25 mmol), and cat. (20 mol%) in 4.0 mL solvent at room temperature for 12 h. [b] Isolated yield. [c] Determined by chiral HPLC. [d] H_2O (1.0 mmol) was added. [e] Reaction was carried out at 0 °C for 12 h. [f] Reaction was carried out at −20 °C for 24 h.

indole derivative **4aa** was also obtained when dichloromethane (DCM) or toluene was used as solvent (Table 1, entries 10 and 11). The addition of H_2O promoted the generation of enol by suppressing the formation of **4aa**, thereby giving **3aa** in higher yield (Table 1, entry 12). Lowering the reaction temperature improved the enantioselectivity of product **3aa** (Table 1, entries 12–14).[10] When the reaction was carried out in toluene at −20 °C with H_2O (1.0 mmol for 0.2 mmol **1a**) for 24 h, **3aa** was obtained in 91% isolated yield along with 91% *ee*, which served as the best reaction conditions for this transformation (Table 1, entry 14).

After the optimal reaction conditions were established, we surveyed the substrate scope of this asymmetric cyclization reaction by using various 3-isothiocyanato oxindoles **1** with a variety of dibenzylidene ketones **2**, and the results are summarized in Table 2. By changing the phenyl group of dibenzylidene ketone **2**, all of the reactions proceeded efficiently, giving the corresponding products **3aa**–**3ag** in high yields (87–95% yield) and good-to-excellent enantioselectivities (86–96% *ee*, Table 2, entries 1–7). As can be seen, electron-withdrawing groups at the benzene ring of dibenzylidene ketones **2** provided the desired products in higher *ee* values, whereas the electron-donating ones gave the products in higher yields. As for **2g**, bearing a sterically bulky substituent at the *para* position of the benzene ring, the corresponding cycloadduct **3ag** was given in 95% yield with 86% *ee*. For different 3-isothiocyanato oxindoles **1**, the reaction also proceeded smoothly to give the desired products **3ba**–**3fa** in high yields and excellent enantioselectivities (90–93% yield, 90–94% *ee*, Table 2, entries 8–12). Their absolute configurations were confirmed as the (*S,S*)-configuration by using vibrational circular dichroism (VCD) spectroscopy to analyze **3ba**.[11]

Table 2. Substrate scope for the synthesis of spirooxindole enols **3**.

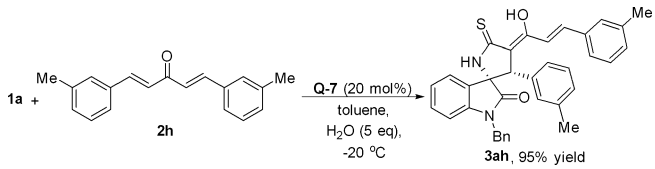


Entry[a]	1: R^1, R^2	2: R^3	3 Yield [%][b]	3 *ee* [%][c]
1	**1a**: H, Bn	**2a**: H	**3aa**: 91	91
2	**1a**: H, Bn	**2b**: *p*-F	**3ab**: 87	96
3	**1a**: H, Bn	**2c**: *p*-Cl	**3ac**: 89	93
4	**1a**: H, Bn	**2d**: *p*-Br	**3ad**: 89	92
5	**1a**: H, Bn	**2e**: *p*-Me	**3ae**: 93	90
6	**1a**: H, Bn	**2f**: *p*-MeO	**3af**: 95	89
7	**1a**: H, Bn	**2g**: *p*-*t*Bu	**3ag**: 95	86
8	**1b**: 5-Me, Bn	**2a**: H	**3ba**: 93	92
9	**1c**: 5-OMe, Bn	**2a**: H	**3ca**: 92	94
10	**1d**: 6-OMe, Bn	**2a**: H	**3da**: 92	91
11	**1e**: H, Me	**2a**: H	**3ea**: 91	92
12	**1f**: H, 3,5-dimethylbenzyl	**2a**: H	**3fa**: 92	90

[a] Reaction was carried out with H_2O (1.0 mmol), **1** (0.20 mmol), **2** (0.25 mmol), and **Q-7** (20 mol%) in 4.0 mL toluene at −20 °C for 24 h. [b] Isolated yield. [c] Determined by chiral HPLC.

(1*E*,4*E*)-1,5-Di-m-tolylpenta-1,4-dien-3-one **2h** has also been used as the substrate. Owning to the steric hindrance of the methyl groups at the *meta* position of the benzene ring, the free rotation of the benzene ring was blocked, giving the cycloadduct **3ah** as a pair of inseparable diastereomeric rotamers with a 1:1 ratio in 95% total yield (Scheme 2). We could not determine its *ee* value at the present stage.

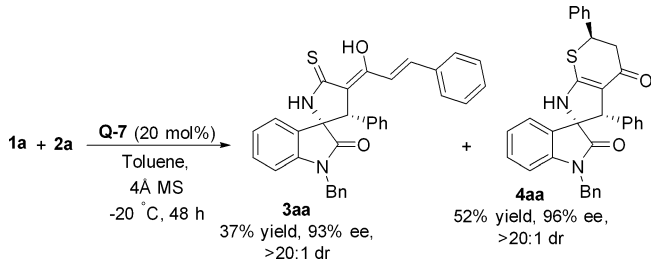
On the other hand, with the addition of 4 Å molecular sieves (50 mg for 0.2 mmol **1a**), the generation of enol **3aa** was par-



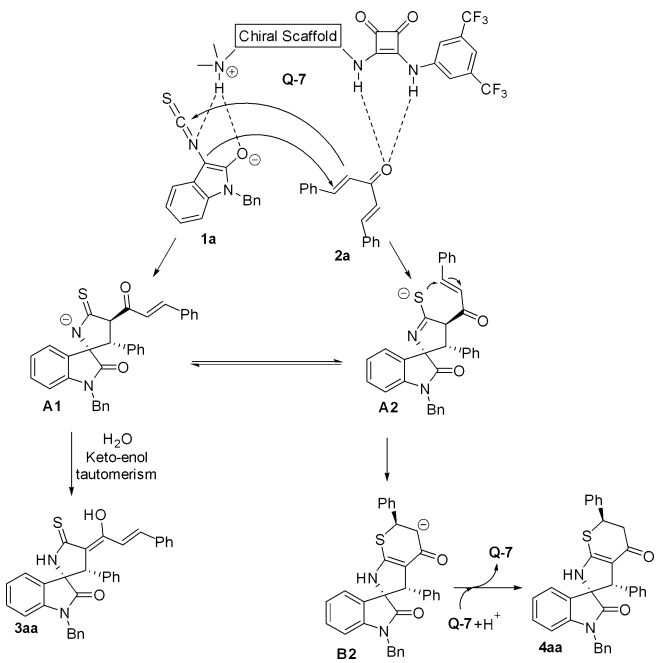
Scheme 2. The reaction of **1a** with **2h**.

tially inhibited, and **4aa** could then be isolated in 52% yield along with 96% *ee* and >20:1 d.r. at −20 °C in toluene (Scheme 3).

In Scheme 4, we proposed a plausible reaction mechanism according to previous work[5] and our own findings.[6] The organocatalyst **Q-7** interacts with **2a** through its hydrogen-bonding donor site and abstracts one proton from **1a** with its amino base site. After an intermolecular Michael addition/cyclization, intermediate **A1** or **A2** is generated. These two intermediates are in equilibrium, owing to the double-bond migration. Intermediate **A1** undergoes protonation in the presence of H_2O and the keto-enol tautomerism affords the enol **3aa**. Although the generation of enol **3aa** is inhibited in the absence of H_2O, intermediate **A2** can undergo a further intramolecular Michael addition/cyclization and subsequent protonation to give the corresponding product **4aa**.



Scheme 3. Synthesis of **4aa**.



Scheme 4. Proposed reaction mechanism.

In summary, we have developed a novel cinchona-alkaloid-derived organocatalyst to catalyze asymmetric regioselective [3+2] cycloaddition of 3-isothiocyanato oxindoles with dibenzylidene ketones, giving a series of spirooxindole enols in high yields along with good-to-excellent diastereo- and enantioselectivities. The reactivities of dibenzylidene ketone, which contains two electron-deficient C=C bonds and a C=O bond, with 3-isothiocyanato oxindoles have been investigated and their regioselectivities have been explored. Upon suppressing the formation of a S-containing heterocyclic spirooxindole derivative via a [3+2]/[4+2] cascade reaction of three reactive sites in 3-isothiocyanato oxindole with dibenzylidene ketone by adding water, spirooxindole enols can be obtained exclusively. Efforts to apply this methodology to synthesize biologically active compounds ongoing.

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Keywords: [3+2] cyclization · asymmetric organocatalysis · regioselectivity · stereoselectivity · spirooxindole enols

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[10] For the detail of reaction condition screening, see Tables S1 and S2 in the Supporting Information.

[11] For the configuration of compound **3ba**, see its X-ray crystal structure in Figure S1 in the Supporting Information, and its absolute configuration has been assigned as the (*S*,*S*)-configuration by vibrational circular dichroism (VCD) spectroscopy (see Figure S2–S4 for the details).

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