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Asymmetric Construction of Spiro[thiopyranoindole-benzoisothiazole] Scaffold via a Formal [3 + 3] Spiroannulation

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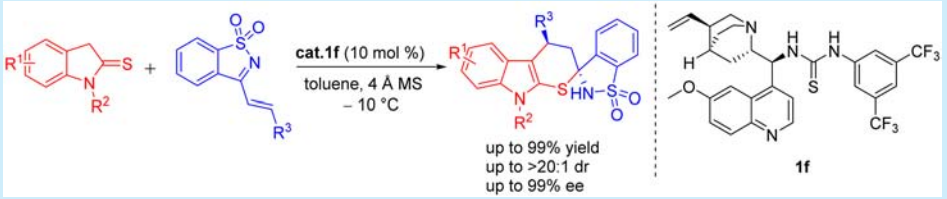
Supporting Information



ABSTRACT: An enantioselective formal thio[3 + 3] spiroannulation reaction of indoline-2-thiones to 1-azadienes has been developed by the use of a quinine-derived bifunctional tertiary amine-thiourea catalyst, which furnished a series of optically active spiro[thiopyranoindole-benzoisothiazole] heterocycles with a spiro quaternary C–N/C–S stereogenic centers in high yields with good to excellent diastereo- and enantioselectivities.

The construction of chiral molecular complexity around a biologically relevant framework has played a critical role in the discovery and development of novel drugs. In reverse, stimulation to drug innovation is also of great significance for both the improvement of health care and the progress of target-oriented organic synthesis.[1] 3,4-Dihydro-2*H*-thiopyran and indoline scaffolds are important cores of a large family of alkaloids and medicinally relevant compounds. Correspondingly, some sulfur containing natural heterocycle products **A**–**C**[2] show very interesting biological activities, such as antiatherosclerosis, antipsoriatic, antiviral, and antifungal activity (Figure 1).[3] Indole derivatives containing spiro- or heterocyclic

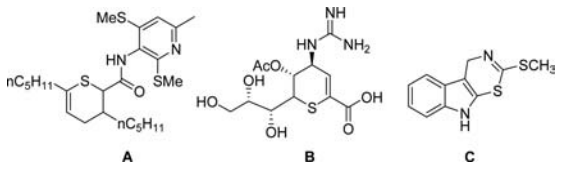


Figure 1. Some sulfur bearing natural heterocycle products.

subunits are featured in a number of naturally occurring products as well as biologically, pharmaceutically, and medically active molecules.[4] Just recently, our group has reported the asymmetric synthesis of enantioenriched thiopyranoindole-annulated heterocycles via the organocatalytic formal [3 + 3] cascade process between indoline-2-thiones and 2-benzylidene-malononitrile.[5] Furthermore, the development of an efficient approach for the enantioselective synthesis of spiro[thiopyrano-indole-benzoisothiazole] scaffolds combined with multiple privileged motifs are synthetically valuable and pharmaceutically desirable.

Asymmetric organocatalytic cascade reactions have served as a powerful tool for the quick construction of complex molecules with multiple stereogenic centers.[6] In the past decade, asymmetric organocatalytic cascade reactions, relying on aminocatalysis and hydrogen bonding catalysis, have grown as a hot research area for efficient and stereoselective construction of complex molecules, usually with multichiral centers, from readily available starting materials.[7] 3-Styryl-1,2-benzoisothiazole-1,1-dioxides, one type of cyclic 1-azadienes, serve as good reactants in domino [4 + 2], [3 + 3], and [5 + 3] reactions for the construction of chiral heterocyclic scaffolds.[8] In 2013, Chen and co-workers reported the first asymmetric catalytic inverse-electron-demand aza-Diels–Alder reaction with interrupted cyclic 2,5-dienones and electron-deficient 1-azadienes under the catalysis of chiral amines derived from quinine or quinidine.[9] Recently, the same group developed an asymmetric formal [3 + 3] cycloaddition process with diversely structured aliphatic ketones and electron-deficient cyclic 1-azadienes by cascade enamine–enamine catalysis of a cinchona-based primary amine, affording spirocyclic architectures in excellent diastereo- and enantioselectivity.[10] Herein, an enantioselective formal thio[3 + 3] spiroannulation process of indoline-2-thiones to 1-azadienes was documented to construct highly functionalized spiro[thiopyranoindole-benzoisothiazole] heterocycles containing spiro quaternary C–N/C–S stereogenic centers, which was driven by a cinchona alkaloid derived chiral bifunctional tertiary amine-thiourea catalyst.

Initially, we investigated the reaction of indoline-2-thiones **2a** and 1-azadienes **3a** catalyzed by a catalyst $(DHQD)_2PHAL$ (**1a**) in toluene at rt; the cascade process proceeded smoothly

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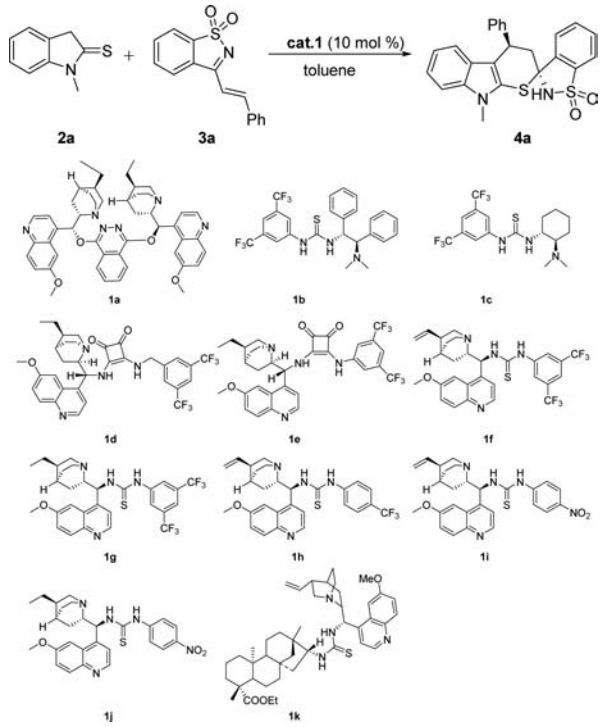
to furnish the desired spirocyclic product **4a** in a satisfying 94% yield and >20:1 diastereoselectivity, but only 9% ee was observed for this transformation (Table 1, entry 1). When

Table 1. Optimization of Organocatalysts[a]



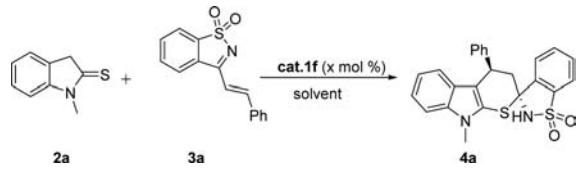
entry	cat.	time (h)	yield (%)[b]	dr[c]	ee (%)[d]
1	**1a**	30	94	>20:1	9
2	**1b**	24	95	>20:1	−37
3	**1c**	24	92	>20:1	−38
4	**1d**	25	98	>20:1	26
5	**1e**	25	95	>20:1	30
6	**1f**	24	95	>20:1	78
7	**1g**	24	96	>20:1	75
8	**1h**	20	94	>20:1	52
9	**1i**	20	95	>20:1	54
10	**1j**	20	95	>20:1	50
11	**1k**	24	94	>20:1	26

[a]The reactions were performed in the presence of 10 mol % of catalysts with **2a** (0.1 mmol), **3a** (0.15 mmol) in toluene (2 mL) at rt. [b]Yield of isolated products. [c]Determined by ^{1}H NMR spectra. [d]Determined by chiral HPLC analysis.

(1*R*,2*R*)-1,2-diphenylethane-1,2-diamine (*DPEN*) and (1*R*,2*R*)-1,2-cyclohexanediamine (CHDA) derived bifunctional thiourea−tertiary amine catalyst **1b** or **1c** was employed, the reaction afforded the desired product **4a** in 95% or 92% yield with 37% or 38% ee, respectively (Table 1, entries 2 and 3). Encouraged by those promising results, we next examined a series of bifunctional H-bond donor catalysts, including chiral squaramides **1d** and **1e** and bifunctional tertiary amine-thioureas **1f**−**1k** derived from different privileged chiral scaffolds. The catalytic results showed that the catalysts probed displayed significantly different catalytic reactivity and enantioselectivity toward the formal [3 + 3] cascade process (Table 1, entries 4−11). Among them, the catalyst **1f**, a chiral quinine-derived bifunctional tertiary amine−thiourea catalyst, was proven to be efficient for this transformation, which provided the desired product **4a** in 95% yield, >20:1 dr, and 78% ee (Table 1, entry 6).

Subsequently, some common solvents such as THF, Et_2O, CH_2Cl_2, toluene, PhCl, xylene, and mesitylene were tested, and it was disclosed that toluene still is the optimal reaction medium (Table 1, entry 6 vs Table 2, entries 1−6). By

Table 2. Optimization of the Reaction Conditions[a]



entry	solvent	temp (°C)	time (h)	yield (%)[b]	dr[c]	ee (%)[d]
1	THF	25	20	93	>20:1	10
2	Et_2O	25	25	95	>20:1	44
3	CH_2Cl_2	25	20	90	>20:1	70
4	PhCl	25	24	94	>20:1	72
5	xylene	25	24	94	>20:1	74
6	mesitylene	25	24	93	>20:1	70
7	toluene	0	26	95	>20:1	80
8[e]	toluene	0	26	95	>20:1	92
9[e]	toluene	−10	30	95	>20:1	94
10[e]	toluene	−15	34	96	>20:1	94
11[e,f]	toluene	−10	30	96	>20:1	94
12[e,g]	toluene	−10	30	93	>20:1	90
13[e,f,h]	toluene	−10	40	91	>20:1	92

[a]Unless otherwise specified, the reaction was carried out with **2a** (0.1 mmol), **3a** (0.15 mmol), catalyst **1f** (0.01 mmol) in solvent (2.0 mL). [b]Isolated yield. [c]Determined by ^{1}H NMR spectra. [d]Determined by chiral HPLC. [e]4 Å MS (50 mg) was added. [f]0.1 M. [g]0.15 M. [h]5 mol % catalyst.

decreasing the reaction temperature from rt to 0 °C, the desired product was obtained in 95% yield, >20:1 dr, and 80% ee (Table 2, entry 7). While 4 Å MS was introduced, 92% ee was observed (Table 1, entry 8), which indicates that slightly alkaline 4 Å MS is favorable to the improvement in enantioselective control. Then, the influences of reaction temperature, reactant concentration, and catalytic loading were examined (Table 2, entries 9−13). Finally, the optimized reaction conditions were established as follows: in toluene at −10 °C, with a substrate concentration of 0.1 M in the presence of 10 mol % catalyst **1f** and 50 mg of 4 Å MS as the additives (Table 2, entry 11).

With the optimized reaction conditions in hand, the formal [3 + 3] cycloaddition reaction of indoline-2-thiones **2a** to 1-azadienes **3a**−**3w** was investigated for the substrate scope. As shown in Table 3, 1-azadienes **3a**−**3w** bearing both electron-donating and -withdrawing substituents on phenyl groups were all tolerated, and the corresponding reactions proceeded smoothly to afford the desired products **4a**−**4w** in 82−98% yields with 76−99% ee's, respectively (Table 3, entries 1−23). For 1-azadienes **3b**−**3i** bearing substituents (−F, −Cl, −Br, $-NO_2$, −Me, −OMe) at *o*- and *m*-positions of the phenyl rings, their electronic and steric properties had regular influence on the enantioselectivity of the corresponding reactions. Apparently, the substrates with electron-withdrawing substituents (−F,-NO_2) on the phenyl rings give products **4b** and **4h** with higher enantioselectivities (Table 3, entries 2 and 8). In addition, for 1-azadienes **3j**−**3s** bearing both monosubstituents

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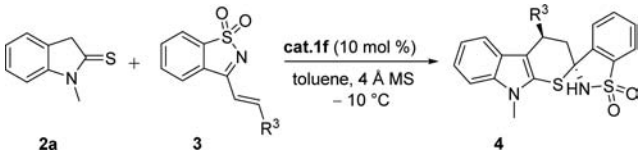
Table 3. Substrate Scope on 1-Azadienes 3a−3w[a]



2a 3 4

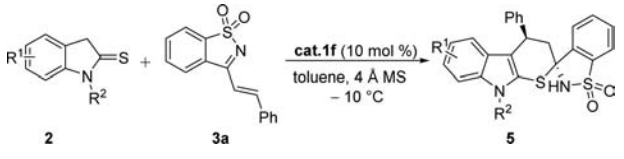
entry	3, R^3	time (h)	4	yield (%)[b]	dr[c]	ee (%)[d]
1	**3a**, C_6H_5	30	**4a**	96	>20:1	94
2	**3b**, 2-F-C_6H_4	40	**4b**	98	>20:1	99
3	**3c**, 2-Cl-C_6H_4	40	**4c**	95	>20:1	92
4	**3d**, 2-Br-C_6H_4	40	**4d**	98	>20:1	82
5[e]	**3e**, 2-OCH_3-C_6H_4	40	**4e**	95	>20:1	84
6	**3f**, 3-Cl-C_6H_4	35	**4f**	95	>20:1	88
7	**3g**, 3-Br-C_6H_4	40	**4g**	93	>20:1	93
8	**3h**, 3-NO_2-C_6H_4	40	**4h**	96	>20:1	97
9[e]	**3i**, 3-CH_3-C_6H_4	40	**4i**	94	>20:1	90
10	**3j**, 4-F-C_6H_4	40	**4j**	98	>20:1	92
11	**3k**, 4-Cl-C_6H_4	30	**4k**	96	>20:1	92
12	**3l**, 4-Br-C_6H_4	30	**4l**	98	>20:1	93
13	**3m**, 4-NO_2-C_6H_4	40	**4m**	92	>20:1	84
14	**3n**, 4-CN-C_6H_4	40	**4n**	96	>20:1	92
15	**3o**, 4-CH_3-C_6H_4	30	**4o**	94	>20:1	91
16	**3p**, 4-OCH_3-C_6H_4	40	**4p**	96	>20:1	87
17[e]	**3q**, 4-*i*Pr-C_6H_4	40	**4q**	82	>20:1	81
18	**3r**, 2,4-2Cl-C_6H_3	40	**4r**	95	>20:1	84
19[e]	**3s**, 2,4-2MeO-C_6H_3	40	**4s**	90	>20:1	95
20	**3t**, 1-naphthyl	40	**4t**	93	>20:1	78
21	**3u**, 2-naphthyl	40	**4u**	96	>20:1	86
22	**3v**, 2-thienyl	40	**4v**	93	>20:1	86
23	**3w**, *E*-PhCH=CH	40	**4w**	94	>20:1	76

[a]Unless noted otherwise, the same reaction conditions as those for entry 11 in Table 2. [b]Isolated yield. [c]Determined by ^{1}H NMR spectra. [d]Determined by chiral HPLC. [e]The reaction was conducted in CH_2Cl_2.

(−F, −Cl, −Br, −CN, −NO_2, −Me, −iPr, −OMe) at the *p*-position and disubstituents (−2Cl, −2OMe) at the *o*-, *p*-positions of the phenyl rings, the effect of the electronic and steric properties seemed to be intriguing, although all reactions led to their desired products **4j**−**4s** in 82−98% yields with 81−95% ee's (Table 3, entries 10−19). Furthermore, the substrates **3t**−**3w** containing fused aromatic, cinnamic, and heterocyclic systems such as the thienyl group were also well tolerated, which afforded the desired products **4t**−**4w** in 93−96% yields with 76−86% ee's, respectively (Table 2, entries 20−23).

The structural variations of substrates **2** were also investigated under otherwise identical reaction conditions, and the catalytic results are summarized in Table 4. On one hand, the influence of the *N*-protecting groups of indoline-2-thiones was first investigated. When the *N*-unsubstituted indoline-2-thiones **2b** was employed, the desired product **5b** was obtained in 88% yield with 99% ee (Table 4, entry 1). For the substrates of *N*-ethyl, *N*-benzyl, *N*-phenyl, *N*-allyl substituted indoline-2-thiones **2c**−**2f**, all the reactions furnished the expected products **5c**−**5f** in 98−99% yields, >20:1 dr and 94−98% ee's, respectively (Table 4, entries 2−5). On the other hand, it was pleasingly disclosed that various indoline-2-thiones **2** with different substituents (−F, −Cl, −Br, −I, −Me) could smoothly participate in the cascade reaction, which provided the desired products **5g**−**5o** in 90−98% yields, >20:1 dr, and 72−96% ee's. Obviously, for the reactions involving substrate

Table 4. Substrate Scope on Indoline-2-thiones 2b−2o[a]



2 3a 5

entry	2/R^1, R^2	time (h)	5	yield (%)[b]	dr[c]	ee (%)[d]
1	**2b**/H, H	40	**5b**	88	>20:1	99
2	**2c**/H, Et	35	**5c**	98	>20:1	96
3	**2d**/H, Bn	35	**5d**	99	>20:1	94
4	**2e**/H, Ph	35	**5e**	99	>20:1	98
5	**2f**/H, Allyl	40	**5f**	98	>20:1	94
6[e]	**2g**/5-Br, CH_3	40	**5g**	92	>20:1	74
7	**2h**/5-F, CH_3	40	**5h**	95	>20:1	90
8[e]	**2i**/5-I, CH_3	40	**5i**	91	>20:1	72
9	**2j**/6-Br, CH_3	40	**5j**	96	>20:1	90
10	**2k**/6-Cl, CH_3	40	**5k**	98	>20:1	94
11	**2l**/7-F, CH_3	40	**5l**	96	>20:1	82
12	**2m**/7-Cl, CH_3	40	**5m**	95	>20:1	92
13	**2n**/5-CH_3, CH_3	40	**5n**	90	>20:1	82
14	**2o**/5,7-2CH_3, CH_3	40	**5o**	92	>20:1	96

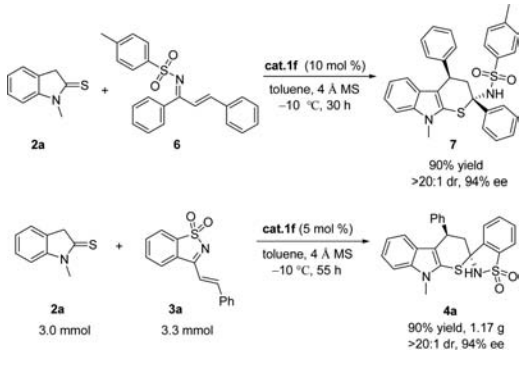
[a]Unless noted otherwise, the same reaction conditions as those for entry 11 in Table 2. [b]Isolated yield. [c]Determined by ^{1}H NMR spectra. [d]Determined by chiral HPLC. [e]The reaction was conducted in CH_2Cl_2.

5g or **5i**, the −Br or −I substituent at the 5-position of the indoline-2-thione backbone had a detrimental effect on the enantioselectivity (Table 4, entries 6 and 8). Furthermore, the relative and absolute configurations of the desired products were analogously assigned by X-ray analysis of **4a** and **4f**′ derived from **4f**,[11] as well as the nuclear Overhauser effect (NOE) analyses of compound **4f** (see the Supporting Information for the details).

In addition, acyclic *N*-tosyl-1-azadiene **6** was also employed as an alterable reaction partner in the cascade formal [3 + 3] cycloaddition reaction, which furnished the desired product **7** in 90% yield with >20:1 dr and 94% ee. To demonstrate the potential utility of this methodology, a gram-scale synthesis of **4a** was carried out in the presence of a 5 mol % catalyst loading, which afforded the desired product **4a** in 90% yield with >20:1 dr and 94% ee (Scheme 1).

In conclusion, we have developed a highly efficient asymmetric organocatalytic formal [3 + 3] cycloaddition reaction in the presence of a quinine-derived bifunctional

Scheme 1. Further Investigation of the Potential of the Reaction



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tertiary amine-thiourea catalyst, in which a series of densely functionalized spiro[thiopyranoindole-benzoisothiazole] heterocycle compounds were obtained in high yields with good to excellent diastereo- and enantioselectivities. This straightforward process serves as a powerful tool for the enantioselective construction of spiro[thiopyranoindole-benzoisothiazole] heterocycle derivatives possessing a spiro quaternary stereogenic center of C−N/C−S bonds. The unique structure of these products might be attractive for potential drug discovery. Further studies on the scope and synthetic applications of this reaction are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01951.

Experimental details, compound characterization (PDF)
X-ray crystallographic data for **4a** (CIF)
X-ray crystallographic data for **4f′** (CIF)

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Notes

The authors declare no competing financial interest.

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