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Enantioselective Construction of Functionalized Thiopyrano-Indole Annulated Heterocycles via a Formal Thio [3 + 3]-Cyclization

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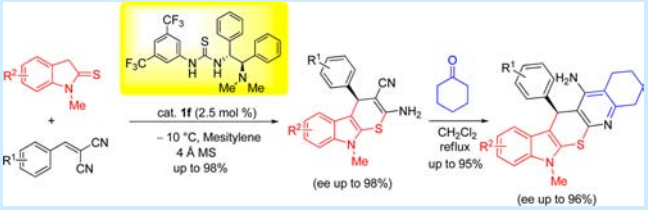
Supporting Information

ABSTRACT: A formal thio [3 + 3]-cyclization catalyzed by a *DPEN*-derived chiral thiourea has been reported for the construction of optically active thiopyrano-indole annulated heterocyclic compounds in high yields with excellent enantioselectivities. The high reactivity between indoline-2-thione (keto-S) and 2-benzylidenemalononitrile has also been supported by density functional theory (DFT) calculations.

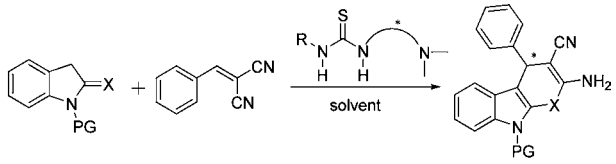


Organosulfur compounds play important roles in biological and medicinal chemistry.[1] Among the various classes of organic sulfur compounds, thiopyran and fused-thiopyran derivatives have drawn considerable interest, due to their structural motifs being widely present in many drugs that have the effects of analgesic, anticancer,[2] antihyperplasia,[3] anti-inflammatory,[4] antibacterials,[5] and antipsychotic[6] activities. However, to date, the asymmetric catalytic approaches to construct these privileged sulfur-containing heterocycles in enantiomerically pure form are still surprisingly rare.

In view of advantages offered by organocatalysis such as robustness, nontoxicity, low cost, ready manipulation, and easy availability, the research field of asymmetric organocatalytic domino reactions explosively grew and was intensively studied in the past decade in both academia and industry. It has also been demonstrated that organo-catalyzed asymmetric cascade reactions have been endowed with broad synthetic utilities and extremely powerful synthetic efficiency for the construction of structural and stereochemical complexity for both natural and non-natural compounds.[7] Accordingly, some valuable optically active sulfur-containing heterocyclic compounds, such as 3,4-dihydro-2*H*-thiopyrans,[8] 3,6-dihydro-2*H*-thiopyrans,[9] tetrahydrothiophenes,[10] thiochromenes, and thiochromans,[11] were synthesized by corresponding organocatalytic Michael–aldol, hetero-Diels–Alder, and Michael–Michael cascade reactions. To the best of our knowledge, there is no report on a direct catalytic asymmetric method for the synthesis of optically active thiopyranoindole-annulated heterocyclic compounds using readily available reagents. Being interested in their important biologically activities of thiopyranoindole-annulated heterocyclic compounds,[12] we herein have reported an organocatalytic [3 + 3]-cascade reaction to access enantiomerically enriched thiopyrano[2,3-*b*]indole-3-carbonitriles and their derivatives in high yields with excellent ee.

We initially attempted to construct pyranoindole-annulated compounds via an organocatalytic [3 + 3]-cascade reaction between indolin-2-ones **2** and 2-benzylidenemalononitrile **4** (Scheme 1). However, a series of acid–base bifunctional organocatalysts (Scheme S1 in Supporting Information (SI)) were proven to be ineffective for the reaction. In view of thiols being stronger acids than alcohols, thioenols of indoline-2-thiones **3** are also expected to be more acidic than their oxygen analogues of **2**.[13] Subsequently, we turned our attention to the transformation of indoline-2-thiones **3** with 2-benzylidenemalononitriles **4**, expecting to achieve optically active thiopyranoindole-annulated heterocyclic compounds. Fortunately, when a bifunctional thiourea **1a** derived from quinine was used as a catalyst in a 10 mol % catalyst loading, the proposed reaction proceeded smoothly to provide optically active thiopyrano[2,3-*b*]indole-3-carbonitrile in 95% yield with 63% ee at rt in toluene (Table S1, entry 1). Encouraged by this promising result, some representative bifunctional H-bonding donor catalysts **1b**–**1h** were further investigated for this transformation (please see Table S1 in the SI). To our delight, (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine (*DPEN*) derived bifunctional thiourea–tertiary amine catalyst **1f** was found to be the most efficient catalyst for this reaction in mesitylene, which provided the desired product **5a** in 95% yield with 82% ee (Table 1, entry 1).

Scheme 1. Organocatalytic [3 + 3]-Cascade Transformation



2a (X = O, PG = H); **2b** (PG = Me); **2c** (PG = Bn)
2d (PG = Ph); **2e** (PG = allyl)

No desired products

3a (X = S, PG = H); **3aa** (PG = Me); **3b** (PG = Et)
3c (PG = Bn)

High reactivity
High enantioselectivity

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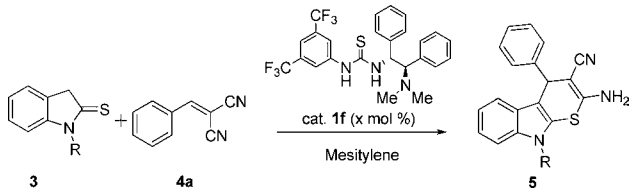
Table 1. Optimization of the Reaction Conditions[a]



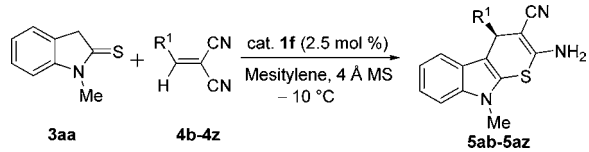
entry	3, R	x (mol %)	time (h)	5	yield (%)[b]	ee (%)[c]
1	**3a**, H	10	0.5	**5a**	95	82
2	**3b**, Et	10	2	**5b**	94	91
3	**3c**, Bn	10	3.5	**5c**	92	85
4	**3d**, Ph	10	5	**5d**	95	66
5	**3e**, Allyl	10	5	**5e**	98	68
6	**3aa**, CH_3	10	1	**5aa**	95	91
7	**3aa**, CH_3	5	2	**5aa**	96	91
8	**3aa**, CH_3	2.5	3	**5aa**	95	91
9	**3aa**, CH_3	1	6	**5aa**	96	84
10[d]	**3aa**, CH_3	2.5	2	**5aa**	95	93
11[d,e]	**3aa**, CH_3	2.5	6	**5aa**	94	93
12[d,f]	**3aa**, CH_3	2.5	15	**5aa**	95	96
13[d,g]	**3aa**, CH_3	2.5	23	**5aa**	94	96

[a]Unless otherwise noted, all reactions were carried out with **3** (0.1 mmol), **4a** (0.12 mmol, 1.2 equiv) in mesitylene (2 mL). [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]4 Å MS (50 mg) was added. [e]At 0 °C. [f]At −10 °C. [g]At −20 °C.

The reaction conditions were further optimized by examination of the effects of *N*-subtituents, reaction temperature, additives, and catalyst loadings, and the results are shown in Table 1. The effect of *N*-subtituents on indoline-2-thiones **3**, such as Me, Et, Bn, Ph, and allyl protecting groups, was first examined in the presence of 10 mol % of **1f** in mesitylene at rt (Table 1, entries 1−6). For the substrate indoline-2-thione **3aa** bearing a methyl group, the desired product **5aa** was obtained in 95% yield with 91% ee within 1 h (Table 1, entry 6). To our delight, the enantioselectivity could be further improved to 96% ee by the addition of activated 4 Å molecular sieves at −10 °C in mesitylene, even when the catalyst loading was lowered to 2.5 mol % (Table 1, entry 12).

With the optimal reaction conditions in hand, we next examined the substrate scope for the synthesis of various optically active thiopyranoindole-annulated heterocyclic compounds, and the results are summarized in Table 2. In general, all the reactions proceeded smoothly to afford the desired products in good yields with excellent enantioselectivities. For the 2-benzylidenemalononitrile derivatives **4b**−**4t** bearing both electron-withdrawing and -donating groups on the phenyl rings, all the reactions provided the corresponding desired products **5ab**−**5at** in 88−98% yields with 87−97% ee (Table 2, entries 1−19). Furthermore, the substrates **4u**−**4x** containing fused aromatic, cinnamic, and heterocyclic systems such as furanyl and thienyl were also well tolerated for this reaction, which afforded the desired products **5au**−**5ax** in 90−96% yields with 88−96% ee (Table 2, entries 20−24). In addition, two substrates **4y** and **4z** bearing aliphatic substituents were examined and gave rise to the products in 95% and 96% yields with ee's of 77% and 73%, respectively (Table 2, entries 25 and 26). Finally, we were fortunate to obtain single crystals of compound **5ai**, which allows for an unambiguous assignation of the absolute configuration of the carbon stereocenter by X-ray crystallographic analysis (Figure S1 in SI).[14]

Table 2. Substrate Scope[a]

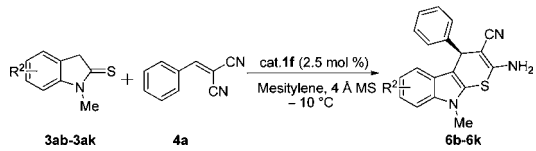


entry	4, R^1	time (h)	5	yield (%)[b]	ee (%)[c]
1	**4b**, 2-FPh	15	**5ab**	95	96
2	**4c**, 2-ClPh	20	**5ac**	91	90
3	**4d**, 3-ClPh	15	**5ad**	98	97
4	**4e**, 3-BrPh	15	**5ae**	97	89
5	**4f**, 3-NO_2Ph	15	**5af**	94	97
6	**4g**, 4-FPh	15	**5ag**	95	96
7	**4h**, 4-ClPh	15	**5ah**	93	96
8	**4i**, 4-BrPh	15	**5ai**	96	95
9	**4j**, 4-NO_2Ph	15	**5aj**	94	96
10	**4k**, 4-CNPh	15	**5ak**	94	94
11	**4l**, 4-CF_3Ph	15	**5al**	98	95
12	**4m**, 2-OCH_3Ph	20	**5am**	88	92
13	**4n**, 3-CH_3Ph	15	**5an**	96	97
14	**4o**, 4-OCH_3Ph	15	**5ao**	96	90
15	**4p**, 4-CH_3Ph	30	**5ap**	95	87
16	**4q**, 4-isopropylPh	20	**5aq**	96	95
17	**4r**, 2,4-di-ClPh	20	**5ar**	95	88
18[d]	**4s**, 2,4-di-OCH_3Ph	20	**5as**	96	87
19	**4t**, 3,5-di-OCH_3Ph	20	**5at**	95	98
20	**4u**, 2-naphthyl	20	**5au**	96	96
21	**4v**, 2-thienyl	20	**5av**	96	93
22	**4w**, 2-furyl	20	**5aw**	90	88
23[d]	**4x**, *E*-PhCH=CH	30	**5ax**	91	93
24[d]	**4y**, isopropyl	30	**5ay**	95	77
25[d]	**4z**, *n*-butyl	30	**5az**	96	73

[a]Unless otherwise noted, the same reaction conditions as those of entry 12 in Table 1. [b]Isolated yield. [c]Chiral HPLC analysis. [d]The reaction was carried out with **3aa** (0.1 mmol), **4** (0.12 mmol, 1.2 equiv), cat. **1f** (10 mol %) at 0 °C.

The structural variations of substrates **3** were also investigated under otherwise identical conditions (Table 3). It was proven that the indoline-2-thiones **3ab**−**3aj** bearing electron-with-

Table 3. Substrate Scope[a]



entry	3a, R^2	time (h)	6	yield (%)[b]	ee (%)[c]
1	**3ab**, 5-Br	15	**6b**	96	91
2	**3ac**, 5-F	15	**6c**	98	95
3	**3ad**, 5-I	20	**6d**	96	94
4	**3ae**, 6-Br	15	**6e**	96	92
5	**3af**, 6-Cl	15	**6f**	96	93
6	**3ag**, 7-F	20	**6g**	98	94
7	**3ah**, 7-Cl	15	**6h**	96	90
8	**3ai**, 5-CH_3	20	**6i**	98	96
9	**3aj**, 5,7-di-CH_3	20	**6j**	94	95
10	**3ak**, 4-Br	30	**6k**	81	54

[a]Unless otherwise noted, the same reaction conditions as those of entry 12 in Table 1. [b]Isolated yield. [c]Chiral HPLC analysis.

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drawing or -donating groups on the 5-, 6-, and 7-positions were well tolerated for this transformation, which furnished the corresponding products **6b**−**6j** in 94−98% yields with 90−96% ee (Table 3, entries 1−9). For the reaction involving the substrate **3ak**, the −Br substituent at the 4-position of the indoline-2-thione backbone seems to have a detrimental effect on both the reactivity and enantioselectivity (Table 3, entry 10).

In consideration of both amino and cyano being versatile functional groups, a further structural conversion was conducted by treatment of several thiopyrano[2,3-*b*]indole-3-carbonitriles **5** and acetic anhydride or cyclohexanone. The enantiomerically active compounds **7** and **8** were obtained in 62−95% yields with 92−96% ee, respectively (Figure 1).[15]

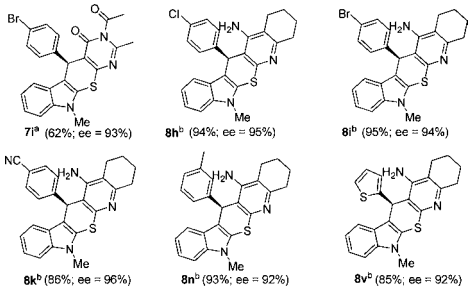

Figure 1. Derivatives of thiopyrano[2,3-*b*]indole-3-carbonitriles. [a] Ac_2O, pyridine, 80 °C, 6 h. [b] Cyclohexanone, $AlCl_3$, CH_2Cl_2, 80 °C, 12 h.

In order to explain the opposite reactivity of indoline-2-thiones **3** (keto-S) and indolin-2-ones **2** (keto-O) with 2-benzylidenemalononitrile **4a**, we carried out density functional theory (DFT) calculations. According to the proposed transition-state model by previous studies,[16] the two reactants indoline-2-thione **3aa** (or keto-O **2b**) and **4a** are activated simultaneously by the bifunctional thiourea catalyst **1f** as shown in Figure 2 at the

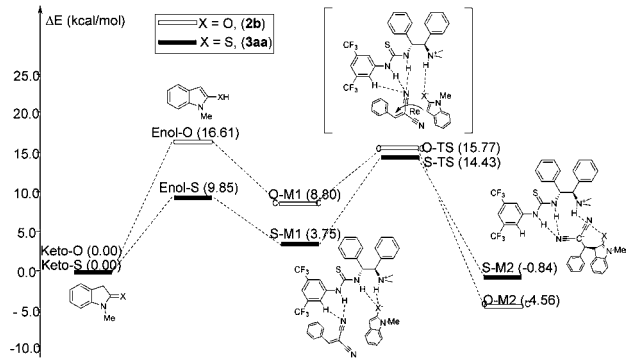

Figure 2. Energy profile corresponding to the *R*-configuration of the desired product.

B3LYP/6-311++G(d,p) level using the CPCM solvent model. First, the ketone type of nucleophile **3aa** (or keto-O **2b**) was transformed to the enol type, increasing the energies to 9.85 and 16.61 kcal/mol, respectively. Apparently, the enolization of the indolin-2-one **2b** is much more difficult than that of indoline-2-thione **3aa**. Therefore, the enolic nucleophile can readily protonate the catalyst with respect to Pápai and Wang's work.[17] After the protonation step, the C−C bond formation step takes place through the formation of a multiple H-bonded complex and the enantioselectivity of the reaction is governed by the binding mode of both substrates to the bifunctional thiourea catalyst **1f**.

The improved favorability of S-M1 (3.75 kcal/mol) as compared to O-M1 (8.80 kcal/mol) is in line with the experimental observation of higher reactivity of keto-S. In other words, when the two reactants coordinate with the catalyst **1f** by multiple hydrogen bonds, complex S-M1 is more stable than O-M1. Transition states for the C−C bond formation step are also depicted in Figure 2. Accordingly, the energy barrier of the formation of a C−C bond is 1.34 kcal/mol lower for indoline-2-thione **3aa** compared to indoline-2-one **2b**. All these results suggest that 2-benzylidenemalononitrile prefers to react with indoline-2-thione (S-M1) energetically for the C−C bond formation.

In conclusion, we have developed a highly efficient asymmetric organocatalytic cascade thio−Michael−cyclization reaction for the preparation of structurally important thiopyranoindole-annulated heterocyclic compounds. The high reactivity between indoline-2-thione **3aa** (keto-S) and 2-benzylidenemalononitrile **4a** has also been supported by the density functional theory (DFT) calculations. Further exploration involving these reagents in practical synthesis is under investigation in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, compound characterization, and X-ray crystallographic data (CIF) for **5ai**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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