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Enantioselective Construction of Polyfunctionalized Spiroannulated Dihydrothiophenes via a Formal Thio [3+2] Cyclization

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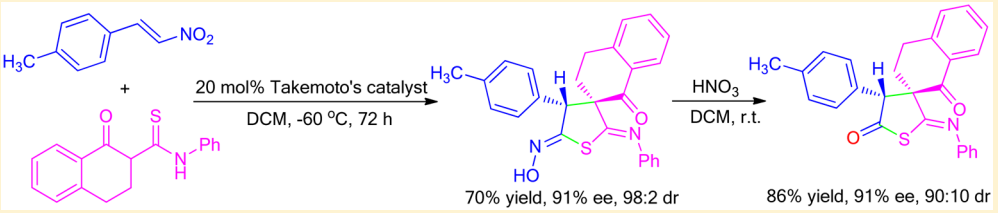
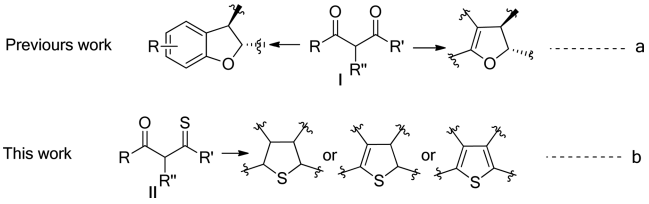
Supporting Information



ABSTRACT: A formal thio [3+2] cyclization catalyzed by Takemoto's organocatalyst has been reported for the construction of optically active spiroannulated dihydrothiophenes in high yields with excellent regio-, chemo-, diastereo-, and enantioselectivities.

Thiophenes are unique sulfur-containing heterocycles that have attracted particular attention due to their special place as building blocks in natural products, pharmaceutical agents, and materials. In particular, optically active and polyfunctionalized thiophenes are of considerable interest as they possess a wide range of biological properties (Figure 1), such as essential coenzyme biotin with important biological functions,[1] leukotriene antagonists,[2] potential inhibitors of HIV,[3] antitumor natural products,[4] and human A3 adenosine receptor ligands.[5] In addition, the chiral thiophenes could serve as building blocks for new chiral ligands in asymmetric metal catalysis[6] and chiral organocatalyst[7] as well as in natural product synthesis. Because of the importance of applications of chiral thiophenes in these areas, the stereoselective synthesis of chiral dihydrothiophenes and tetrahydrothiophenes with high atomic efficiency and, more importantly, good feasibility to assemble various substitution patterns has become a very hot topic in current research efforts.[8]

In addition, spirocyclic compounds are recognized as important precursors for the easy access of a variety of cyclic products by a rearrangement reaction due to their steric strain associated with the quaternary carbon.[9] Development of novel synthetic methods for the construction of new spirocyclic compounds represents a major challenge in synthetic, organic, and medicinal chemistry.[10] Surprisingly, practical and efficient approaches, especially catalytic asymmetric variants to assemble spiroannulated dihydrothiophenes, have rarely been reported.[11] In addition, organocatalytic asymmetric reactions have been used as an efficient tool for the synthesis of enantiopure molecules under mild, environmentally benign conditions over the past few decades.[12] Meanwhile, domino reactions have served as a powerful tool for the rapid and efficient assembly of complex structures from simple starting materials with minimized waste production.[13] Herein, we present such an advance and its direct application in an atom-economical synthesis of spiroannulated dihydrothiophenes based on the development of a new organocatalytic enantioselective formal thio [3+2] cyclization of thioamides to (*E*)-*α*-nitrostyrenes. Notably, the designed reactions are highly regio-, chemo-, diastereo-, and enantioselective, which simultaneously give the desired multifunctional products with two vicinal chiral carbon centers.



In the course of our investigations on the use of 1,3-dicarbonyl compounds **I** in organic synthesis, the 1,3-dicarbonyl compounds **I** turned out to be highly reactive and versatile, and many *O*-containing heterocycles have been prepared from 1,3-dicarbonyl compounds **I** in our group (eq a).[14] Encouraged by the successful results described above, we conceived that *S*-heterocycles (e.g., thiophenes, dihydrothiophenes, and tetrahydrothiophenes) could be synthesized from 1,3-dicarbonyl compounds **II** containing a carbonyl and thiocarbonyl group (eq b). The substrate thioamide **3a** containing a carbonyl and thiocarbonyl group, which has been proven to be highly reactive, was prepared by the reaction of 2-tetralone with sodium hydride and isothiocyanatobenzene.[15a−d] We envisioned that the organocatalysts **1a−i** (Figure 2) would be efficient for the domino formal thio [3+2]

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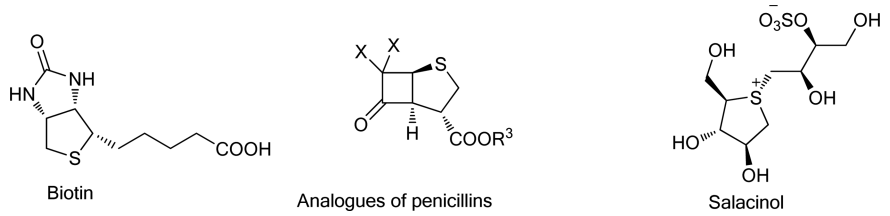


Figure 1. Some representative examples of biologically active compounds that contain a thiophene ring.

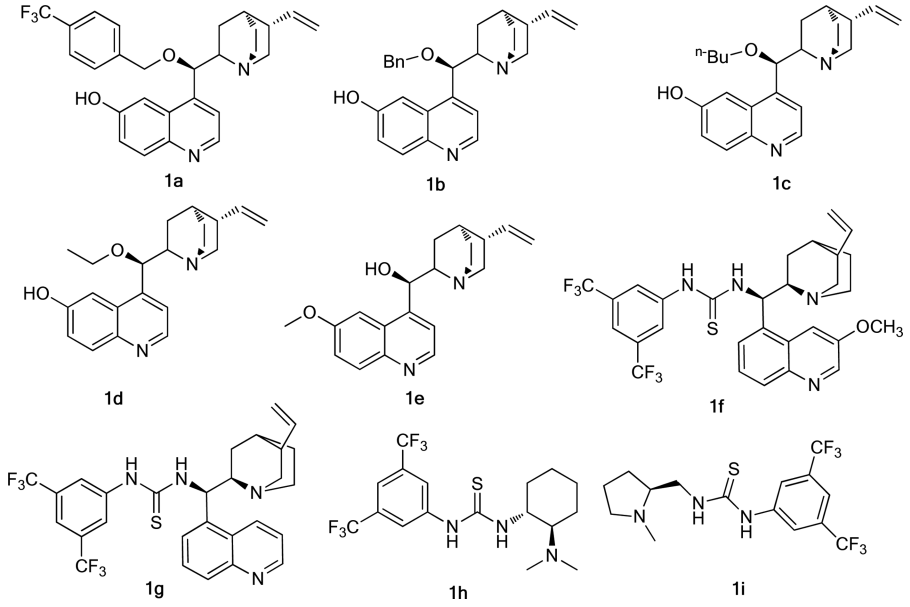
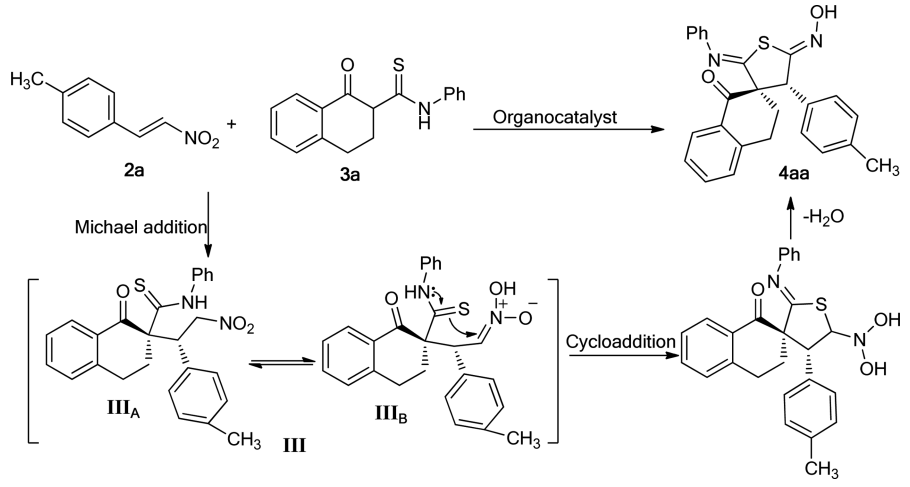


Figure 2. Structure of Organocatalysts **1a–i**.

Scheme 1. Organocatalytic Enantioselective Formal [3+2] Cyclization of Thioamide 3a to (*E*)-α-Nitrostyrene 2a



cyclization of thioamide **3a** with (*E*)-α-nitrostyrene **2a** to afford chiral polyfunctionalized spiroannulated dihydrothiophene **4aa** (Scheme 1). The key step of the above reaction is the Michael addition of **2a** to **3a**, yielding saturated nitroalkane **III**, which may exist in a tautomeric form ($\mathbf{III_A}$ or $\mathbf{III_B}$). Subsequently, the nucleophilic attack of the sulfur atom on the α-carbon atom resulted in its attachment to a nitro group and elimination of a water molecule to afford spirotetrahydrothiophene **4aa**.[15e]

Table 1 shows some screening results for the reaction of **2a** with **3a**. Initially, quinine **1a** was investigated as the organocatalyst for the thio [3+2] cyclization. The reaction proceeded smoothly, and chiral **4aa** was formed in a moderate yield with good diastereoselectivity but poor enantioselectivity (Table 1, entry 1). Subsequently, organocatalysts **1b–g**, which are readily available from natural cinchona alkaloids, also exhibited high catalytic activity when the thio [3+2] cyclization was carried out at 25 °C for 24 h (entries 2–7). Similar results were achieved when the thio [3+2] cyclization was catalyzed by quinine **1e** and its derivatives **1b–d** (entries 2–5). Bifunctional thioureas **1f–i** appeared to be efficient organocatalysts for the asymmetric additions of nucleophiles to (*E*)-α-nitrostyrenes.[16] As such, we envisioned that bifunctional organocatalysts **1f–i**

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Table 1. Catalyst Screening[a]

entry	cat.	yield (%)[b]	dr[c]	ee (%)[d]
1	**1a**	55	87:13	11
2	**1b**	65	90:10	40
3	**1c**	68	81:19	41
4	**1d**	60	89:11	43
5	**1e**	58	90:10	43
6	**1f**	55	55:45	0
7	**1g**	51	65:35	25
8	**1h**	71	93:7	46
9	**1i**	60	78:22	40
10[e]	**1c**	63	92:8	48
11[e]	**1d**	62	92:8	50
12[e]	**1h**	69	95:5	74
13[e]	**1i**	45	90:10	54

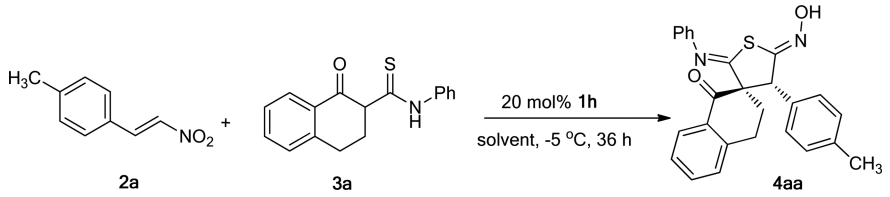
[a]Unless otherwise noted, reactions performed with 0.12 mmol of **2a**, 0.1 mmol of **3a**, 20 mol % catalyst in 1 mL of DCM at 25 °C for 24 h. [b]Isolated yield. [c]Determined by ^{1}H NMR analysis. [d]Determined by chiral HPLC analysis. [e]At −5 °C for 36 h.

would be efficient for the thio [3+2] cyclization of thioamide **3a** with (*E*)-*α*-nitrostyrene **2a**. The domino reaction proceeded smoothly when the reaction was carried out in the presence of organocatalyst **1f**, and product **4aa** was obtained in moderate yield, and the diastereoselectivity and enantioselectivity were very poor (entry 7). To our surprise, Takemoto's catalyst **1h** proved to be superior to other catalysts in this cascade reaction, and product **4aa** was obtained with good diastereoselectivity and moderate enantioselectivity (Table 1, entry 8). By lowering the temperature to −5 °C, the enantioselectivity was dramatically increased when the reaction was catalyzed by Takemoto's catalyst **1h** (entry 12), and the reaction time should be extended. Thus, catalyst **1h** was chosen for further optimization of solvents and temperature (Table 2).

Most commonly used solvents are compatible with our asymmetric conditions and afforded good yields (55−68%) with excellent to good diastereoselectivities (up to 96:4) and varied enantioselectivities (Table 2, entries 1−6). When the reaction was carried out in chlorinated solvents, such as DCM and $CHCl_3$, excellent diastereoselectivities and good enantioselectivities were obtained (entries 1 and 6). The reaction in polar solvents, such as THF and ether, afforded **4aa** with somewhat lower enantioselectivities (entries 2 and 3). When the reaction was carried out in hydrocarbon solvents, product **4aa** was isolated in almost unchanged yields and slightly decreased enantioselectivities (entries 4 and 5). Thus, solvent DCM was chosen as the candidate solvent for further screening of temperature. By lowing the temperature to −60 °C, we got an excellent enantioselectivity (92% ee) and diastereoselectivity (98:2) in the presence of **1h**; the reaction time should be extended (entry 9). The ee was dramatically decreased when the catalyst loading was reduced to 10 mol %. On the basis of the above screening, the optimal reaction conditions (1.2 equiv **2a** and 1.0 equiv **3a** in DCM with 20 mol % catalyst **1h** at −60 °C) were established.

With the optimal reaction conditions determined, the scope of the present organocatalytic asymmetric the thio [3+2] cyclization using catalyst **1h** was extended to various thioamides **3** and (*E*)-*α*-nitrostyrenes **2**. As shown in Table 3, this new methodology not only provides facile access to a range of multisubstituted spiroannulated dihydrothiophenes but also serves as a facile approach for the preparation of a range of substituted tricycles bearing adjacent quaternary and tertiary stereocenters in excellent enantiomeric excesses and diastereoselectivities. The **1h**-promoted thio [3+2] cyclization process takes place with a variety of (*E*)-*α*-nitrostyrene Michael acceptors, which possess neutral, electron-donating and -withdrawing groups in the phenyl ring (Table 3, entries 1−10). It appears that the substituents' electronic and steric natures has minimal impact on efficiency, enantioselectivity, and diastereoselectivity of the thio [3+2] cyclization. Not only aromatic groups but also heteroaromatic groups, such as furyl, could be successfully employed to afford product **4ma** with excellent diastereoselectivity, although the enantioselectivity decreased (Table 3, entry 12). (*E*)-*α*-Nitrostyrenes with substituents at

Table 2. Screening Studies of Organocatalytic Thio [3+2] Cyclization of Thioamide 3a to (*E*)-*α*-Nitrostyrene 2a[a]



2a 3a 4aa

entry	sol.	yield (%)[b]	dr[c]	ee (%)[d]
1	DCM	68	96:4	74
2	THF	65	93:7	32
3	diethyl ether	54	89:11	62
4	toluene	55	92:8	68
5	hexane	57	92:8	52
6	$CHCl_3$	65	94:6	66
7[e]	DCM	69	97:3	83
8[f]	DCM	66	97:3	87
9[g]	DCM	70	98:2	91
10[h]	DCM	64	98:2	90
11[I]	DCM	50	97:3	78

[a]Unless otherwise noted, reactions performed with 0.12 mmol of **2a**, 0.1 mmol of **3a**, 20 mol % **1h** in 1 mL of solvent at −5 °C for 36 h. [b]Isolated yield. [c]Determined by ^{1}H NMR analysis. [d]Determined by chiral HPLC analysis. [e]At −30 °C for 48 h. [f]At −50 °C for 60 h. [g]At −60 °C for 72 h. [h]At −70 °C for 96 h. [I]10 mol % **1h**, at −60 °C for 72 h.

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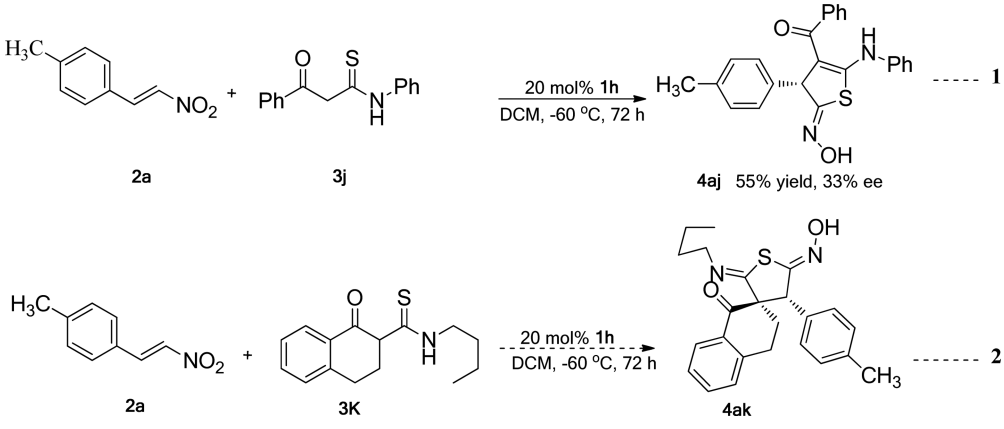
Table 3. Asymmetric Thio [3+2] Cyclization of Thioamides 3 to (*E*)-α-Nitrostyrenes 2[a]

entry	Ar^1 (2)	R^1 Ar^2 (3)	yield% (4)[b]	dr[c]	ee (%)[d]
1	*p*-$CH_3C_6H_4$(**2a**)	H C_6H_5(**3a**)	70 (**4aa**)	98:2	91
2	*p*-$MeOC_6H_4$(**2b**)	H C_6H_5(**3a**)	55(**4ba**)	97:3	80
3	*m*-$MeOC_6H_4$(**2c**)	H C_6H_5(**3a**)	60 (**4ca**)	99:1	88
4	*o*-$MeOC_6H_4$(**2d**)	H C_6H_5(**3a**)	76 (**4da**)	98:2	80
5	*p*-ClC_6H_4 (**2e**)	H C_6H_5(**3a**)	78 (**4ea**)	98:2	93
6	*m*-ClC_6H_4 (**2f**)	H C_6H_5(**3a**)	70 (**4fa**)	96:4	91
7	*o*-ClC_6H_4(**2h**)	H C_6H_5(**3a**)	64(**4ha**)	98:2	88
8	*p*-Br C_6H_4 (**2i**)	H C_6H_5(**3a**)	75(**4ia**)	99:1	92
9	C_6H_5 (**2j**)	H C_6H_5(**3a**)	70(**4ja**)	99:1	93
10	*p*-$NO_2C_6H_4$ (**2k**)	H C_6H_5(**3a**)	60(**4ka**)	97:3	92
11	*β*-naphthyl(**2l**)	H C_6H_5(**3a**)	55(**4la**)	99:1	94
12	2-furanyl(**2m**)	H C_6H_5(**3a**)	65(**4ma**)	92:8	79
13	*p*-$CH_3C_6H_5$(**2a**)	6-MeO C_6H_5(**3b**)	65(**4ab**)	99:1	92
14	*p*-$CH_3C_6H_4$(**2a**)	H *p*-$CH_3C_6H_5$(**3c**)	70(**4ac**)	98:2	90
15	*p*-$CH_3C_6H_4$(**2a**)	H *p*-ClC_6H_5(**3d**)	50(**4ad**)	97:3	84
16	*p*-$CH_3C_6H_4$(**2a**)	H *m*-ClC_6H_5(**3e**)	78 (**4ae**)	99:1	92
17	*p*-$CH_3C_6H_4$(**2a**)	H *o*-ClC_6H_5(**3f**)	75(**4af**)	99:1	90
18	*p*-$CH_3C_6H_4$(**2a**)	H *m*-$MeOC_6H_5$(**3g**)	58(**4ag**)	99:1	88
19	*p*-$CH_3C_6H_4$(**2a**)	H *o*-$MeOC_6H_5$(**3h**)	75(**4ah**)	99:1	92
20	*p*-$CH_3C_6H_4$(**2a**)	H *β*-naphthyl (**3i**)	68(**4ai**)	99:1	82

[a]Unless otherwise noted, reactions performed with 0.12 mmol of **2**, 0.1 mmol of **3**, 20 mol % **1h**, in 1 mL of DCM at −60 °C for 72 h. [b]Isolated yield. [c]Determined by ^{1}H NMR analysis. [d]Determined by chiral HPLC analysis.

Scheme 2. Synthesis of Chiral Monocyclic 2,3-Dihydrothiophene



the ortho position afford multifunctionalized spiroannulated dihydrothiophenes with slightly inferior diastereoselectivities (Table 3, entries 4 and 7). To extend the scope of the thio [3+2] cyclization further, various thioamides **3b−i** were utilized as Michael donors in the reaction with (*E*)-α-nitrostyrenes in the presence of **1h** (Table 3, entries 13−20). The electronic nature of a substituent on the aromatic moiety of **3** has little effect on efficiency, enantioselectivity, or diastereoselectivity of the thio [3+2] cyclization with our organocatalytic protocol. Thioamides **3**, which possess electron-donating and -withdrawing groups in the phenyl ring, afforded products **4** in good yields with high enantioselectivities and diastereoselectivities. However, poor ee was obtained in the reaction of linear thioamide **3j** with (*E*)-α-nitrostyrene **2a**, and 2,3-dihydrothiophene **4aj** was obtained with 33% ee in the thio [3+2] cyclization (Scheme 2, eq 1). However, no desired product was obtained in the reaction of thioamide **3k** with (*E*)-α-nitrostyrene **2a**, and the reaction still remains to be explored (Scheme 2, eq 2). The absolute configuration of the polyfunctionalized spiroannulated dihydrothiophenes is confirmed by single-crystal X-ray analysis of representative enantiopure **4ae** that bears a chlorine atom. As shown in Figure S4, it is composed of a (*Z, R, S, Z*) configuration.

Having established the catalytic asymmetric thio [3+2] cyclization methodology of thioamides **3** and (*E*)-α-nitrostyrenes **2**, the synthetic utilities of these chiral polyfunctionalized spiroannulated dihydrothiophenes were further explored (Scheme 3). The oxime group of spiroannulated dihydrothiophene **4aa** could be converted to a carbonyl group in the presence of nitric acid at room temperature. Product **5aa** was

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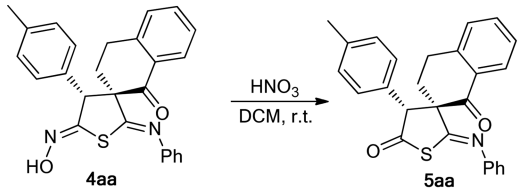
Scheme 3. Selective Transformation of Chiral Polyfunctionalized Spiroannulated Dihydrothiophenes



92% ee, 98:2 dr

86% yield, 91% ee, 90:10 dr

obtained with excellent enantioselectivity and high yields, but the diastereoselectivity was decreased. The possible reason for the decreased diastereoselectivity was that an enolization reaction of **5aa** occurred under the strong acid reaction conditions (please see the Supporting Information).

In summary, we have successfully demonstrated an efficient and highly enantioselective thio [3+2] cyclization of thioamides **3** to (*E*)-α-nitrostyrenes **2** with excellent regio-, chemo-, diastereo-, and enantioselectivities by employing Takemoto's catalyst as the organocatalyst. This novel methodology provides facile access to various enantioenriched multifunctional polyfunctionalized spiroannulated dihydrothiophenes with two vicinal chiral carbon centers including an adjacent quaternary and a tertiary stereocenter. Notably, the oxime group of spiroannulated dihydrothiophenes could be cleanly converted to ketones without affecting the enantioselectivities in the presence of nitric acid.

EXPERIMENTAL SECTION

General Methods. NMR spectra were recorded with tetramethylsilane as the internal standard. TLC was performed on glass-backed silica plates. Column chromatography was performed using silica gel (150−200 mesh) eluting with ethyl acetate and petroleum ether. ^{1}H NMR spectra were recorded at 600 or 400 MHz, and ^{13}C NMR spectra were recorded at 150 or 75 MHz. Chemical shifts (δ) are reported in ppm downfield from $CDCl_3$ (δ = 7.26 ppm) or DMSO (δ = 2.50 ppm) for ^{1}H NMR and relative to the central $CDCl_3$ resonance (δ = 77.0 ppm) or DMSO resonance (δ = 39.5 ppm) for ^{13}C NMR spectroscopy. Coupling constants (*J*) are given in Hz. ESI-HRMS spectrometer was measured with a Finnigan LCQ^{DECA} ion trap mass spectrometer. Optical rotations were measured at 589 nm at 25 °C in a 1 dm cell, and specific rotations are given in 10^{-1} deg cm^2 g^{-1}. Enantiomeric excess was determined by HPLC analysis using Chiralpak column (4.6 mm*250 mm, 5 μm).

1. General Procedure for Synthesis of Thioamides ***3****.* [15] To a vigorously stirred suspension of sodium hydride (50 mmol) in 90 mL of dry DMF at −10 °C was slowly added 2-tetralone (7.30 g, 50 mmol) over a period of 1 h so that the temperature did not exceed 0 °C. After the gas was evolved, a solution of the appropriate aryl isothiocyanate (50 mmol) in 10 mL of dry DMF was added dropwise. The mixture was stirred for 3 h at −10 °C, left in a fridge overnight, then added slowly to 50 mL of 1 M HCl and acidified with 2 M HCl. After 3 h, most of the water−DMF solution was decanted. The oily residue was dissolved in CH_2Cl_2, washed twice with 1 M HCl and water, then evaporated and purified by flash chromatography on silica gel using CH_2Cl_2 as eluent. Crude **3** was treated with Et_2O, cooled in a fridge, and collected by filtration. The crude **3** was then dissolved in MeCN at 50 °C and treated with 50 mL of 2 M HCl for hydrolysis of imine side products. After evaporation of the solvent, the product was purified again by flash chromatography on silica gel using CH_2Cl_2 as eluent and crystallized from Et_2O.

3a: the spectra are in accordance with the literature;[15] 6.88 g, 49% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.69 (s, 1H), 8.07 (t, *J* = 7.0 Hz, 1H), 7.78 (t, *J* = 8.8 Hz, 2H), 7.55 (td, *J* = 7.5, 1.1 Hz, 1H), 7.42 (t, *J* = 7.9 Hz, 2H), 7.35 (dd, *J* = 13.1, 5.6 Hz, 1H), 7.31−7.27 (m, 2H), 3.81 (q, *J* = 10.3, 4.9 Hz, 1H), 3.28 (dt, *J* = 16.8, 4.7 Hz, 1H), 3.11−3.04 (m, 1H), 2.87−2.81 (m, 1H), 2.80−2.72 (m, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 198.0, 197.4, 144.7, 138.9, 134.5, 132.0, 128.9 (d, *J* = 2.2 Hz), 128.0, 126.9 (d, *J* = 11.8 Hz), 123.9, 59.6, 29.8, 28.5.

3b: the spectra are in accordance with the literature;[15] 6.4 g, 41% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.85 (s, 1H), 8.03 (d, *J* = 8.8 Hz, 1H), 7.78 (d, *J* = 7.8 Hz, 2H), 7.39 (t, *J* = 7.8 Hz, 2H), 7.26 (t, *J* = 7.4 Hz, 1H), 6.85 (dd, *J* = 8.8, 2.3 Hz, 1H), 6.70 (d, *J* = 1.9 Hz, 1H), 3.88 (s, 3H), 3.74 (q, *J* = 8.5, 6.1 Hz, 1H), 3.24 (dt, *J* = 16.7, 4.9 Hz, 1H), 3.03−2.96 (m, 1H), 2.80−2.74 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 198.00 (s), 195.9, 164.5, 147.5, 139.0, 130.6, 128.8, 126.7, 125.4, 123.8, 113.8, 112.4, 59.1, 55.6, 29.6, 28.8.

3c: the spectra are in accordance with the literature;[15] 7.8 g, 53% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.47 (s, 1H), 8.02 (d, *J* = 7.8 Hz, 1H), 7.59 (d, *J* = 8.9 Hz, 2H), 7.52−7.47 (m, 1H), 7.30 (q, *J* = 16.9, 8.4 Hz, 2H), 7.24 (d, *J* = 7.7 Hz, 1H), 6.88 (d, *J* = 8.9 Hz, 1H), 3.79 (s, 3H), 3.76 (q, *J* = 9.5, 4.3 Hz, 1H), 3.21 (dt, *J* = 16.7, 4.6 Hz, 1H), 3.07−2.98 (m, 1H), 2.79−2.66 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 198.0, 197.2, 158.1, 144.7, 134.4, 132.0 (d, *J* = 10.3 Hz), 128.9, 128.0, 126.9, 125.6, 114.3, 114.0, 59.6, 55.5, 29.8, 28.5.

2. General Procedure for the Asymmetric Thio [3+2] Cyclization of Thioamides ***3*** *to (E)-α-Nitrostyrenes* ***2****.* A mixture of **2a** (20.0 mg, 0.12 mmol), **3a** (28.0 mg, 0.12 mmol), and **1h** (8.2 mg, 0.02 mmol) was stirred in DCM (1 mL) at −60 °C under N_2 for 72 h. Then, flash chromatography on silica gel (10% ethyl acetate/petroleum ether) gave **4aa** as a white solid (30 mg, 70% yield).

*(2S,2′Z,4′R,5′Z)-5′-(Hydroxyimino)-2′-(phenylimino)-4′-(p-tolyl)-3,4,4′,5′-tetrahydro-1H,2′H-spiro[naphthalene-2,3′-thiophen]-1-one (****4aa****).* Thirty milligrams, 70% yield, mp 221−223 °C. IR (KBr): υ_{max} 3426, 1655, 1616, 829, 759 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.31−8.28 (m, 1H), 8.07 (d, *J* = 7.9 Hz, 1H), 7.41 (m, *J* = 7.5, 1.3 Hz, 1H), 7.31 (t, *J* = 7.9 Hz, 2H), 7.25−7.21 (m, 2H), 7.15−7.11 (m, 2H), 7.08 (d, *J* = 8.0 Hz, 2H), 6.87−6.84 (m, 2H), 5.37 (s, 1H), 3.31 (ddd, *J* = 16.4, 11.9, 4.2 Hz, 1H), 2.85 (dt, *J* = 16.7, 4.1 Hz, 1H), 2.44 (dt, *J* = 13.8, 4.2 Hz, 1H), 2.27 (s, 3H), 2.14−2.08 (m, 1H). ^{13}C NMR (151 MHz, CDCl3) δ 194.0, 167.2, 156.6, 150.5, 143.8, 137.9, 133.7, 132.2, 130.8, 130.4, 129.2, 128.6, 128.3, 126.8, 125.4, 119.8, 64.9, 53.9, 29.3, 25.6, 21.1. ESI-HRMS: calcd for $C_{26}H_{22}N_2O_2S$+H 427.1470, found 427.1494. $[\alpha]^{25}_D$ −52.0 (*c* 0.5, CHCl3); 91% ee. The enantiomeric ratio was determined by HPLC on Chiralpak AD column (25% 2-propanol/hexane, 1 mL/min); t_{major} = 20.942 min, t_{minor} = 7.953 min.

*(2S,2′Z,4′R,5′Z)-5′-(Hydroxyimino)-4′-(4-methoxyphenyl)-2′-(phenylimino)-3,4,4′,5′-tetrahydro-1H,2′H-spiro[naphthalene-2,3′-thiophen]-1-one (****4ba****).* Twenty-five milligrams, 55% yield, mp 205−207 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.61 (s, 1H), 7.94 (d, *J* = 7.7 Hz, 1H), 7.55 (t, *J* = 7.3 Hz, 1H), 7.38 (t, *J* = 7.9 Hz, 3H), 7.29 (q, *J* = 12.6, 8.3 Hz, 3H), 7.18 (t, *J* = 7.4 Hz, 1H), 6.88 (q, *J* = 14.6, 8.1 Hz, 4H), 5.17 (s, 1H), 3.71 (s, 3H), 3.23−3.09 (m, 1H), 2.91 (d, *J* = 17.1 Hz, 1H), 2.48−2.41 (m, 1H), 1.95 (d, *J* = 10.1 Hz, 1H). ^{13}C NMR (151 MHz, DMSO) δ 194.4, 169.3, 159.2, 152.8, 150.8, 144.5, 134.6, 131.8, 129.9, 129.5, 127.9, 127.4, 127.1, 125.8, 119.9, 114.0, 64.7, 55.5, 53.3, 29.2, 25.2. ESI-HRMS: calcd for $C_{26}H_{22}N_2O_3S$+H 443.1429, found 443.1452. $[\alpha]^{25}_D$ −28.0 (*c* 0.5, $CHCl_3$); 80% ee. The enantiomeric ratio was determined by HPLC on Chiralpak AD column (25% 2-propanol/hexane, 1 mL/min); t_{major} = 26.602 min, t_{minor} = 9.914 min.

*(2S,2′Z,4′R,5′Z)-5′-(Hydroxyimino)-4′-(3-methoxyphenyl)-2′-(phenylimino)-3,4,4′,5′-tetrahydro-1H,2′H-spiro[naphthalene-2,3′-thiophen]-1-one (****4ca****).* Twenty-eight milligrams, 60% yield, mp 219−222 °C. IR (KBr): υ_{max} 3390, 1655, 1622, 1122, 1177, 869, 753 cm^{-1}. ^{1}H NMR (600 MHz, DMSO) δ 11.66 (s, 1H), 7.97 (d, *J* = 7.9 Hz, 1H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.41−7.37 (m, 3H), 7.32 (d, *J* = 7.7 Hz, 1H), 7.28 (t, *J* = 7.4 Hz, 1H), 7.20 (t, *J* = 7.4 Hz, 1H), 6.96−6.91 (m, 2H), 6.88 (t, *J* = 8.9 Hz, 3H), 5.15 (s, 1H), 3.73 (s, 3H), 3.22−3.14 (m, 1H), 2.93 (d, *J* = 17.1 Hz, 1H), 2.47 (dd, *J* = 9.5, 4.5 Hz, 1H), 2.02−1.97 (m, 1H). ^{13}C NMR (151 MHz, DMSO) δ 194.5, 169.4, 159.3, 152.6, 150.9, 144.5, 137.2, 134.6, 131.6, 130.0, 129.8, 129.5, 127.9, 127.4, 125.9, 122.5, 119.8, 116.7, 113.2, 64.7, 55.5, 53.7, 29.3, 25.3. ESI-HRMS: calcd for $C_{26}H_{22}N_2O_3S$+H 443.1429, found 443.1475. $[\alpha]^{25}_D$ −30.0 (*c* 0.5, $CHCl_3$); 88% ee. The enantiomeric

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ratio was determined by HPLC on Chiralpak AD column (25% 2-propanol/hexane, 1 mL/min); t_{major} = 19.019 min, t_{minor} = 9.050 min.

*(2S,2′Z,4′R,5′Z)-5′-(Hydroxyimino)-4′-(2-methoxyphenyl)-2′-(phenylimino)-3,4,4′,5′-tetrahydro-1H,2′H-spiro[naphthalene-2,3′-thiophen]-1-one (**4da**).* Thirty-five milligrams, 76% yield, mp 202−205 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.48 (s, 1H), 7.97 (d, J = 7.8 Hz, 1H), 7.58 (t, J = 7.4 Hz, 1H), 7.41 (q, J = 7.7 Hz, 3H), 7.34−7.24 (m, 3H), 7.20 (t, J = 7.4 Hz, 1H), 7.05 (d, J = 8.2 Hz, 1H), 6.99 (t, J = 7.4 Hz, 1H), 6.91 (d, J = 7.5 Hz, 2H), 5.16 (s, 1H), 3.70 (s, 3H), 3.14 (dt, J = 11.4, 5.4 Hz, 1H), 2.76−2.67 (m, 1H), 2.58−2.52 (m, 1H), 2.00−1.95 (m, 1H). ^{13}C NMR (151 MHz, DMSO) δ 195.5, 171.0, 157.0, 154.3, 151.3, 144.3, 134.7, 130.6, 130.0, 129.7, 129.4, 128.2, 127.4, 126.0, 125.7, 121.1, 119.8, 112.4, 63.9, 56.0, 29.0, 25.1. ESI-HRMS: calcd for $C_{26}H_{22}N_2O_3S$+H 443.1429, found 443.1419. $[\alpha]^{25}_D$ +108.0 (c 0.5, CHCl3); 80% ee. The enantiomeric ratio was determined by HPLC on Chiralpak AD column (10% 2-propanol/hexane, 1 mL/min); t_{major} = 29.895 min, t_{minor} = 18.141 min.

*(2S,2′Z,4′R,5′Z)-4′-(4-Chlorophenyl)-5′-(hydroxyimino)-2′-(phenylimino)-3,4,4′,5′-tetrahydro-1H,2′H-spiro[naphthalene-2,3′-thiophen]-1-one (**4ea**).* Thirty-six milligrams, 78% yield, mp 227−230 °C. IR (KBr): υ_{max} 3445, 1661, 1625, 1091, 759, 848, 695 cm^{-1}. ^{1}H NMR (600 MHz, DMSO) δ 11.75 (s, 1H), 7.96 (d, J = 7.8 Hz, 1H), 7.53 (t, J = 7.3 Hz, 1H), 7.40 (s, 4H), 7.38−7.34 (m, 3H), 7.29 (d, J = 7.4 Hz, 1H), 7.17 (t, J = 7.1 Hz, 1H), 6.86 (d, J = 6.7 Hz, 2H), 5.31 (s, 1H), 3.20 (t, J = 13.6 Hz, 1H), 2.91 (d, J = 16.8 Hz, 1H), 2.48−2.41 (m, 1H), 1.93 (t, J = 12.2 Hz, 1H). ^{13}C NMR (151 MHz, DMSO) δ 194.1, 168.7, 152.2, 150.7, 144.5, 134.6, 134.2, 133.1, 132.6, 131.8, 129.9, 129.5, 128.6, 127.9, 127.3, 125.9, 119.9, 64.7, 53.1, 29.3, 25.3. ESI-HRMS: calcd for $C_{25}H_{19}N_2O_2SCl$+H 447.0934, found 447.0925. $[\alpha]^{25}_D$ −96.0 (c 0.5, CHCl3); − 93% ee. The enantiomeric ratio was determined by HPLC on Chiralpak AD column (25% 2-propanol/hexane, 1 mL/min); t_{major} = 18.887 min, t_{minor} = 7.716 min.

*(2S,2′Z,4′R,5′Z)-4′-(3-Chlorophenyl)-5′-(hydroxyimino)-2′-(phenylimino)-3,4,4′,5′-tetrahydro-1H,2′H-spiro[naphthalene-2,3′-thiophen]-1-one (**4fa**).* Thirty-two milligrams, 70% yield, mp 220−223 °C. ^{1}H NMR (600 MHz, DMSO) δ 11.67 (s, 1H), 7.85 (d, J = 7.9 Hz, 1H), 7.43 (t, J = 7.4 Hz, 1H), 7.33 (s, 1H), 7.26 (dd, J = 13.2, 9.1 Hz, 5H), 7.24−7.20 (m, 1H), 7.19 (d, J = 7.7 Hz, 1H), 7.07 (t, J = 7.4 Hz, 1H), 6.74 (d, J = 7.8 Hz, 2H), 5.22 (s, 1H), 3.12−3.04 (m, 1H), 2.83−2.79 (m, 1H), 2.37−2.33 (m, 1H), 1.85−1.78 (m, 1H). ^{13}C NMR (151 MHz, DMSO) δ 194.0, 168.6, 152.0, 150.7, 144.5, 137.7, 134.6, 133.1, 131.8, 130.6, 130.0, 129.5, 128.9, 128.4, 127.9, 127.4, 125.9, 124.7, 119.9, 64.7, 53.1, 29.3, 25.3. ESI-HRMS: calcd for $C_{25}H_{19}N_2O_2SCl$+H 447.0934, found 447.0927. $[\alpha]^{25}_D$ −52.0 (c 0.5, CHCl3); 91% ee. The enantiomeric ratio was determined by HPLC on Chiralpak AD column (25% 2-propanol/hexane, 1 mL/min); t_{major} = 11.884 min, t_{minor} = 7.323 min.

*(2S,2′Z,4′R,5′Z)-4′-(2-Chlorophenyl)-5′-(hydroxyimino)-2′-(phenylimino)-3,4,4′,5′-tetrahydro-1H,2′H-spiro[naphthalene-2,3′-thiophen]-1-one (**4ha**).* Thirty milligrams, 64% yield, mp 218−220 °C. ^{1}H NMR (600 MHz, DMSO) δ 11.67 (s, 1H), 7.96 (d, J = 7.9 Hz, 1H), 7.61 (t, J = 7.4 Hz, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.45−7.40 (m, 6H), 7.34 (d, J = 7.8 Hz, 1H), 7.22 (t, J = 7.3 Hz, 1H), 6.94 (d, J = 7.6 Hz, 2H), 5.29 (s, 1H), 3.25−3.16 (m, 1H), 2.77−2.69 (m, 1H), 2.61−2.55 (m, 1H), 2.10−2.02 (m, 1H). ^{13}C NMR (151 MHz, DMSO) δ 194.9, 169.8, 151.1, 144.2, 139.1, 135.1, 133.6, 132.5, 130.2, 130.1, 129.5, 128.9, 128.3, 127.6, 125.9, 124.7, 119.8, 63.9, 49.3, 29.0, 25.1. ESI-HRMS: calcd for $C_{25}H_{19}N_2O_2SCl$+H 447.0934, found 447.0925. $[\alpha]^{25}_D$ +130.0 (c 0.5, CHCl3); 88% ee. The enantiomeric ratio was determined by HPLC on Chiralpak AD column (8% 2-propanol/hexane, 1 mL/min); t_{major} = 52.093 min, t_{minor} = 37.379 min.

*(2S,2′Z,4′R,5′Z)-4′-(4-Bromophenyl)-5′-(hydroxyimino)-2′-(phenylimino)-3,4,4′,5′-tetrahydro-1H,2′H-spiro[naphthalene-2,3′-thiophen]-1-one (**4ia**).* Thirty-eight milligrams, 75% yield, mp 223−225 °C. ^{1}H NMR (600 MHz, DMSO) δ 11.70 (s, 1H), 7.96 (d, J = 7.8 Hz, 1H), 7.56 (d, J = 8.3 Hz, 3H), 7.42−7.28 (m, 6H), 7.19 (t, J = 7.3 Hz, 1H), 6.86 (d, J = 7.7 Hz, 2H), 5.28 (s, 1H), 3.20 (t, J = 12.0 Hz, 1H), 2.92 (d, J = 17.1 Hz, 1H), 2.47−2.42 (m, 1H), 1.97−1.89 (m, 1H). ^{13}C NMR (151 MHz, DMSO) δ 193.8, 168.3, 152.0, 150.6, 144.0, 134.1, 132.7, 132.0, 131.3, 129.5, 129.1, 127.9, 127.0, 125.6, 121.7, 119.7, 64.7, 53.2, 29.2, 25.4. ESI-HRMS: calcd for $C_{25}H_{19}N_2O_2BrS$+H 491.0429, found 491.0419. $[\alpha]^{25}_D$ −50.0 (c 0.5, CHCl3); 92% ee. The enantiomeric ratio was determined by HPLC on Chiralpak AD column (25% 2-propanol/hexane, 1 mL/min); t_{major} = 22.536 min, t_{minor} = 8.160 min.

*(2S,2′Z,4′R,5′Z)-5′-(Hydroxyimino)-4′-phenyl-2′-(phenylimino)-3,4,4′,5′-tetrahydro-1H,2′H-spiro[naphthalene-2,3′-thiophen]-1-one (**4ja**).* Thirty milligrams, 70% yield, mp 211−213 °C. ^{1}H NMR (600 MHz, DMSO) δ 11.67 (s, 1H), 7.96 (d, J = 7.4 Hz, 1H), 7.56−7.49 (m, 1H), 7.41−7.33 (m, 7H), 7.29 (s, 2H), 7.18 (d, J = 4.5 Hz, 1H), 6.87 (d, J = 6.9 Hz, 2H), 5.22 (s, 1H), 3.22−3.12 (m, 1H), 2.95−2.86 (m, 1H), 2.49−2.42 (m, 1H), 2.00−1.92 (m, 1H). ^{13}C NMR (151 MHz, DMSO) δ 194.3, 169.2, 152.6, 150.8, 144.5, 135.5, 134.6, 131.7, 130.6, 130.0, 129.5, 128.7, 128.3, 127.9, 127.4, 125.9, 119.9, 64.7, 53.9, 29.3, 25.3. ESI-HRMS: calcd for $C_{25}H_{20}N_2O_2S$+H 413.1324, found 413.1315. $[\alpha]^{25}_D$ −46.0 (c 0.5, CHCl3); 93% ee. The enantiomeric ratio was determined by HPLC on Chiralpak AD column (25% 2-propanol/hexane, 1 mL/min); t_{major} = 20.443 min, t_{minor} = 7.964 min.

*(2S,2′Z,4′R,5′Z)-5′-(Hydroxyimino)-4′-(4-nitrophenyl)-2′-(phenylimino)-3,4,4′,5′-tetrahydro-1H,2′H-spiro[naphthalene-2,3′-thiophen]-1-one (**4ka**).* Twenty-eight milligrams, 60% yield, mp 248−250 °C. ^{1}H NMR (600 MHz, DMSO) δ 11.72 (s, 1H), 8.15 (d, J = 8.8 Hz, 2H), 7.89 (dd, J = 7.9, 1.0 Hz, 1H), 7.60 (d, J = 8.8 Hz, 2H), 7.50−7.46 (m, 1H), 7.33−7.29 (m, 2H), 7.24 (d, J = 7.7 Hz, 1H), 7.12 (t, J = 7.4 Hz, 1H), 6.83−6.77 (m, 2H), 5.42 (s, 1H), 3.19−3.12 (m, 1H), 2.86 (dt, J = 16.9, 4.1 Hz, 1H), 2.41 (dd, J = 9.0, 4.8 Hz, 1H), 1.85 (ddd, J = 13.9, 11.6, 4.4 Hz, 1H).^{13}C NMR (151 MHz, DMSO) δ 193.8, 168.2, 151.8, 150.6, 147.5, 144.5, 143.0, 134.6, 132.2, 131.8, 129.9, 129.5, 128.0, 127.3, 126.0, 123.6, 119.9, 64.9, 53.2, 29.4, 25.4. ESI-HRMS: calcd for $C_{25}H_{19}N_3O_4S$+H 458.1175, found 458.1158. $[\alpha]^{25}_D$ −52.0 (c 0.5, CHCl3); 92% ee. The enantiomeric ratio was determined by HPLC on Chiralpak AD column (25% 2-propanol/hexane, 1 mL/min); t_{major} = 25.934 min, t_{minor} = 10.925 min.

*(2S,2′Z,4′S,5′Z)-4′-(Furan-2-yl)-5′-(hydroxyimino)-2′-(phenylimino)-3,4,4′,5′-tetrahydro-1H,2′H-spiro[naphthalene-2,3′-thiophen]-1-one (**4ma**).* Twenty-seven milligrams, 65% yield, mp 166−168 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.12 (d, J = 7.8 Hz, 1H), 7.46 (t, J = 7.2 Hz, 1H), 7.35 (s, 1H), 7.31 (t, J = 7.5 Hz, 3H), 7.20 (d, J = 7.6 Hz, 1H), 7.13 (t, J = 7.4 Hz, 1H), 6.84 (d, J = 7.7 Hz, 2H), 6.42 (d, J = 3.0 Hz, 1H), 6.31 (s, 1H), 5.53 (s, 1H), 3.35 (ddd, J = 16.3, 12.1, 4.0 Hz, 1H), 2.95−2.86 (m, 1H), 2.51 (dt, J = 14.1, 4.1 Hz, 1H), 2.11−2.03 (m, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 193.5, 166.1, 153.9, 150.3, 147.9, 143.9, 142.9, 133.8, 132.0, 129.2, 128.7, 128.4, 126.9, 125.5, 119.7, 111.1, 110.5, 64.6, 48.4, 29.4, 25.5. ESI-HRMS: calcd for $C_{23}H_{18}N_2O_3S$+H 403.1116, found 403.1107. $[\alpha]^{25}_D$ +34.0 (c 0.5, CHCl3); 79% ee. The enantiomeric ratio was determined by HPLC on Chiralpak AD column (25% 2-propanol/hexane, 1 mL/min); t_{major} = 16.305 min, t_{minor} = 8.274 min.

*(2S,2′Z,4′R,5′Z)-5′-(Hydroxyimino)-4′-(naphthalen-2-yl)-2′-(phenylimino)-3,4,4′,5′-tetrahydro-1H,2′H-spiro[naphthalene-2,3′-thiophen]-1-one (**4la**).* Twenty-six milligrams, 55% yield, mp 210−213 °C. ^{1}H NMR (600 MHz, DMSO) δ 11.63 (s, 1H, 7.84 (d, J = 7.9 Hz, 1H, 7.79 (s, 1H), 7.74 (d, J = 8.5 Hz, 2H), 7.38 (d, J = 8.5 Hz, 1H), 7.34 (s, 3H), 7.25 (t, J = 7.1 Hz, 2H), 7.18 (t, J = 7.5 Hz, 1H), 7.09 (d, J = 7.6 Hz, 1H), 7.03 (t, J = 7.3 Hz, 1H), 6.76 (d, J = 7.8 Hz, 2H), 5.32 (s, 1H), 3.03 (t, J = 12.2 Hz, 1H), 2.75 (d, J = 17.0 Hz, 1H), 2.40 (d, J = 14.0 Hz, 1H), 1.89−1.84 (m, 1H). ^{13}C NMR (151 MHz, DMSO) δ 194.3, 169.1, 152.7, 150.9, 144.5, 134.5, 133.1 (d, J = 17.8 Hz), 132.8, 131.8, 129.9 (d, J = 7.9 Hz), 129.5, 128.3 (d, J = 6.5 Hz), 128.0, 127.3, 126.8, 125.9,119.9, 65.0, 54.0, 29.5, 25.3. ESI-HRMS: calcd for $C_{29}H_{22}N_2O_2S$+H 463.1480, found 463.1468. $[\alpha]^{25}_D$ −86.0 (c 0.5, CHCl3); 94% ee. The enantiomeric ratio was determined by HPLC on Chiralpak AD column (25% 2-propanol/hexane, 1 mL/min); t_{major} = 21.910 min, t_{minor} = 11.895 min.

*(2S,2′Z,4′R,5′Z)-5′-(Hydroxyimino)-6-methoxy-2′-(phenylimino)-4′-(p-tolyl)-3,4,4′,5′-tetrahydro-1H,2′H-spiro[naphthalene-2,3′-thiophen]-1-one (**4ab**).* Thirty-one milligrams, 65% yield, mp 210−213 °C. ^{1}H NMR (600 MHz, DMSO) δ 11.48 (s, 1H), 7.77 (d, J = 8.8 Hz, 1H), 7.23 (t, J = 7.8 Hz, 2H), 7.09 (d, J = 8.0 Hz, 2H), 7.02 (t, J = 7.4 Hz, 1H), 6.98 (d, J = 8.0 Hz, 2H), 6.76−6.69 (m, 3H), 6.65 (d, J = 2.2 Hz, 1H), 5.01 (s, 1H), 3.63 (s, 3H), 3.02−2.94 (m, 1H), 2.70 (dd, J =

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12.5, 4.7 Hz, 1H), 2.25 (dt, J = 13.5, 4.4 Hz, 1H), 2.08 (s, 3H), 1.82−1.74 (m, 1H). ^{13}C NMR (151 MHz, DMSO) δ 192.8, 169.5, 164.1, 152.9, 150.9, 147.1, 137.5, 132.6, 130.5, 129.9, 129.2, 125.8, 125.3, 119.9, 114.4, 112.9, 64.5, 56.0, 53.8, 29.3, 25.6, 21.1. ESI-HRMS: calcd for $C_{27}H_{24}N_2O_3S$+H 457.1586, found 457.1573. $[\alpha]^{25}_D$ +100 (c 0.5, CHCl3); −92% ee. The enantiomeric ratio was determined by HPLC on Chiralpak AD column (25% 2-propanol/hexane, 1 mL/min); t_{major} = 81.738 min, t_{minor} = 18.387 min.

(2S,2′Z,4′R,5′Z)-5′-(Hydroxyimino)-4′-(p-tolyl)-2′-(p-tolylimino)-3,4,4′,5′-tetrahydro-1H,2′H-spiro[naphthalene-2,3′-thiophen]-1-one (**4ac**). Thirty-two milligrams, 70% yield, mp 210−213 °C. IR (KBr): υ_{max} 3420, 1661, 1625, 845, 750 cm^{-1}. ^{1}H NMR (600 MHz, DMSO) δ 11.23 (s, 1H), 7.55 (d, J = 7.8 Hz, 1H), 7.11 (s, 1H), 6.87 (d, J = 7.7 Hz, 1H), 6.83 (d, J = 7.9 Hz, 2H), 6.72 (d, J = 8.0 Hz, 2H), 6.56−6.52 (m, 2H), 6.45 (d, J = 8.8 Hz, 2H), 4.75 (s, 1H), 3.03 (s, 3H), 2.76−2.69 (m, 1H), 2.47 (dt, J = 16.7, 4.2 Hz, 1H), 2.02 (dt, J = 13.8, 4.4 Hz, 1H), 1.83 (s, 3H), 1.57−1.51 (m, 1H). ^{13}C NMR (151 MHz, DMSO) δ 194.5, 168.1, 157.4, 153.0, 144.5, 143.8, 137.5, 134.5, 132.4, 131.8, 130.5, 129.5, 129.2, 127.9, 127.3, 121.5, 115.0, 64.8, 55.7, 29.3, 25.3, 21.1. ESI-HRMS: calcd for $C_{27}H_{24}N_2O_2S$+H 441.1637, found 441.1643. $[\alpha]^{25}_D$ 80.0 (c 0.5, $CHCl_3$); −90% ee. The enantiomeric ratio was determined by HPLC on Chiralpak AD column (25% 2-propanol/hexane, 1 mL/min); t_{major} = 24.791 min, t_{minor} = 9.800 min.

(2S,2′Z,4′R,5′Z)-2′-((4-Chlorophenyl)imino)-5′-(hydroxyimino)-4′-(p-tolyl)-3,4,4′,5′-tetrahydro-1H,2′H-spiro[naphthalene-2,3′-thiophen]-1-one (**4ad**). Thirty-two milligrams, 50% yield, mp 231−233 °C. ^{1}H NMR (600 MHz, DMSO) δ 11.69 (s, 1H), 7.95 (d, J = 7.9 Hz, 1H), 7.55 (t, J = 7.4 Hz, 1H), 7.37 (t, J = 7.6 Hz, 1H), 7.30 (d, J = 7.6 Hz, 1H), 7.23 (t, J = 7.8 Hz, 4H), 7.14 (d, J = 7.5 Hz, 2H), 6.94−6.90 (m, 1H), 5.17 (s, 1H), 3.15 (t, J = 11.9 Hz, 1H), 2.90 (d, J = 17.1 Hz, 1H), 2.44 (d, J = 13.9 Hz, 1H), 2.25 (s, 3H), 1.99−1.93 (m, 1H).^{13}C NMR (151 MHz, DMSO) δ 194.4, 170.1, 159.3, 152.5, 147.1, 144.5, 137.6, 134.6, 132.4, 131.7, 130.4, 129.5, 129.2, 127.9, 127.4, 121.9 (d, J = 8.4 Hz), 116.7, 116.6, 64.8, 53.6, 29.2, 25.2, 21.1. ESI-HRMS: calcd for $C_{26}H_{21}N_2O_2SCl$+H 461.1091, found 461.1064. $[\alpha]^{25}_D$ −48.0 (c 0.5, CHCl3); 84% ee. The enantiomeric ratio was determined by HPLC on Chiralpak AD column (25% 2-propanol/hexane, 1 mL/min); t_{major} = 17.322 min, t_{minor} = 7.495 min.

(2S,2′Z,4′R,5′Z)-2′-((3-Chlorophenyl)imino)-5′-(hydroxyimino)-4′-(p-tolyl)-3,4,4′,5′-tetrahydro-1H,2′H-spiro[naphthalene-2,3′-thiophen]-1-one (**4ae**). Thirty-seven milligrams, 78% yield, mp 228−230 °C. ^{1}H NMR (600 MHz, DMSO) δ 11.68 (s, 1H), 7.96 (d, J = 7.9 Hz, 1H), 7.52 (dd, J = 9.3, 5.3 Hz, 1H), 7.41−7.39 (m, 1H), 7.35 (t, J = 7.5 Hz, 1H), 7.28 (d, J = 7.5 Hz, 1H), 7.25−7.21 (m, 2H), 7.13 (d, J = 8.0 Hz, 2H), 6.97−6.93 (m, 1H), 6.84 (d, J = 7.9 Hz, 1H), 5.21 (s, 1H), 3.22−3.14 (m, 1H), 2.89 (dt, J = 16.8, 4.5 Hz, 1H), 2.46 (dt, J = 13.8, 4.6 Hz, 1H), 2.26 (s, 3H), 2.02−1.95 (m, 1H). ^{13}C NMR (151 MHz, DMSO) δ 194.1, 171.1, 152.2 (d, J = 17.0 Hz), 144.4, 137.5, 134.5, 134.3, 132.2, 131.7, 131.6, 130.4, 129.4, 129.2, 127.9, 127.2, 125.5, 119.8, 118.6, 64.8, 53.7, 29.2, 25.3, 21.1. ESI-HRMS: calcd for $C_{26}H_{21}N_2O_2SCl$+H 461.1091, found 461.1085. $[\alpha]^{25}_D$ −20.0 (c 0.5, CHCl3); −92% ee. The enantiomeric ratio was determined by HPLC on Chiralpak AD column (25% 2-propanol/hexane, 1 mL/min); t_{major} = 17.311 min, t_{minor} = 6.704 min.

(2S,2′Z,4′R,5′Z)-2′-((2-Chlorophenyl)imino)-5′-(hydroxyimino)-4′-(p-tolyl)-3,4,4′,5′-tetrahydro-1H,2′H-spiro[naphthalene-2,3′-thiophen]-1-one (**4af**). Thirty-six milligrams, 75% yield, mp 213−216 °C. ^{1}H NMR (600 MHz, DMSO) δ 11.62 (s, 1H), 7.87 (d, J = 7.9 Hz, 1H), 7.49−7.40 (m, 2H), 7.28 (t, J = 7.6 Hz, 2H), 7.20 (dd, J = 14.3, 7.9 Hz, 3H), 7.11 (t, J = 7.7 Hz, 1H), 7.06 (d, J = 7.9 Hz, 2H), 6.86 (dd, J = 7.9, 1.3 Hz, 1H), 5.13 (s, 1H), 3.29−3.21 (m, 1H), 2.81 (dt, J = 16.8, 4.5 Hz, 1H), 2.37 (dt, J = 13.9, 4.7 Hz, 1H), 2.16 (s, 3H), 1.95−1.90 (m, 1H). ^{13}C NMR (151 MHz, DMSO) δ 194.0, 172.6, 152.3, 147.8, 144.6, 137.6, 134.6, 132.5, 131.5, 130.5, 130.3, 129.5, 129.3, 128.9, 128.0, 127.3, 127.1, 123.8, 121.0, 64.7, 54.2, 29.1, 25.1, 21.1. ESI-HRMS: calcd for $C_{26}H_{21}N_2O_2SCl$+H 461.1091, found 461.1081. $[\alpha]^{25}_D$ +140 (c 0.5, CHCl3); 90% ee. The enantiomeric ratio was determined by HPLC on Chiralpak AD column (25% 2-propanol/hexane, 1 mL/min); t_{major} = 22.988 min, t_{minor} = 7.736 min.

(2S,2′Z,4′R,5′Z)-5′-Hydroxyimino)-2′-((3-methoxyphenyl)imino)-4′-(p-tolyl)-3,4,4′,5′-tetrahydro-1H,2′H-spiro[naphthalene-2,3′-thiophen]-1-one (**4ag**). Twenty-seven milligrams, 58% yield, mp 188−191 °C. IR (KBr): υ_{max} 3426, 1665, 1622, 1238, 1143, 835, 765, 698 cm^{-1}. ^{1}H NMR (600 MHz, DMSO) δ 11.62 (s, 1H), 7.94 (d, J = 7.9 Hz, 1H), 7.54 (t, J = 7.4 Hz, 1H), 7.36 (t, J = 7.5 Hz, 1H), 7.29 (t, J = 7.8 Hz, 2H), 7.23 (d, J = 7.9 Hz, 2H), 7.14 (d, J = 7.8 Hz, 2H), 6.75 (d, J = 8.2 Hz, 1H), 6.43 (d, J = 7.8 Hz, 1H), 6.38 (s, 1H), 5.17 (s, 1H), 3.74 (s, 3H), 3.19−3.11 (m, 1H), 2.89 (d, J = 17.2 Hz, 1H), 2.44 (dd, J = 9.5, 4.6 Hz, 1H), 2.24 (s, 3H), 1.97−1.91 (m, 1H). ^{13}C NMR (151 MHz, DMSO) δ 194.4, 169.4, 160.5, 152.7, 152.1, 144.5, 137.5, 134.6, 132.3, 131.8, 130.9, 130.5, 129.5, 129.2, 127.9, 127.3, 111.9, 111.6, 105.4, 64.7, 55.7, 53.6, 29.3, 25.3, 21.1. ESI-HRMS: calcd for $C_{27}H_{24}N_2O_3S$+H 457.1586, found 457.1576. $[\alpha]^{25}_D$ −80.0 (c 0.5, CHCl3); 88% ee. The enantiomeric ratio was determined by HPLC on Chiralpak AD column (25% 2-propanol/hexane, 1 mL/min); t_{major} = 22.733 min, t_{minor} = 8.555 min.

(2S,2′Z,4′R,5′Z)-5′-(Hydroxyimino)-2′-((2-methoxyphenyl)imino)-4′-(p-tolyl)-3,4,4′,5′-tetrahydro-1H,2′H-spiro[naphthalene-2,3′-thiophen]-1-one (**4ah**). Thirty-six milligrams, 75% yield, mp 190−193 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.63 (s, 1H), 7.95 (d, J = 7.7 Hz, 1H), 7.55 (t, J = 7.3 Hz, 1H), 7.36 (t, J = 7.5 Hz, 1H), 7.29 (t, J = 6.5 Hz, 2H), 7.24 (d, J = 8.0 Hz, 2H), 7.14 (d, J = 7.9 Hz, 2H), 6.76 (d, J = 8.2 Hz, 1H), 6.44 (d, J = 7.8 Hz, 1H), 6.39 (s, 1H), 5.18 (s, 1H), 3.75 (s, 3H), 3.22−3.11 (m, 1H), 2.94−2.85 (m, 1H), 2.44 (dd, J = 9.5, 4.6 Hz, 1H), 2.25 (s, 3H), 1.94 (dd, J = 17.4, 7.2 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 194.3, 169.4, 160.5, 152.7, 152.1, 144.5, 137.5, 134.6, 132.3, 131.7, 130.9, 130.5, 129.5, 129.2, 127.9, 127.3, 111.9, 111.6, 105.4, 64.7, 55.7, 53.6, 29.3, 25.2, 21.1. ESI-HRMS: calcd for $C_{27}H_{24}N_2O_3S$+H 457.1586, found 457.1578. $[\alpha]^{25}_D$ −88.0 (c 0.5, CHCl3); 92% ee. The enantiomeric ratio was determined by HPLC on Chiralpak AD column (25% 2-propanol/hexane, 1 mL/min); t_{major} = 22.779 min, t_{minor} = 8.598 min.

(R,Z)-(5-(Hydroxyimino)-2-(phenylamino)-4-(p-tolyl)-4,5-dihydrothiophen-3-yl)(phenyl)methanone (**4aj**). Twenty-three milligrams, 55% yield, mp 150−153 °C. ^{1}H NMR (600 MHz, DMSO) δ 12.79 (s, 1H), 11.68 (s, 1H), 7.50−7.43 (m, 4H), 7.35−7.29 (m, 4H), 7.25 (t, J = 7.4 Hz, 2H), 6.90 (d, J = 7.9 Hz, 2H), 6.79 (d, J = 7.8 Hz, 2H), 5.49 (s, 1H), 2.15 (s, 3H). ^{13}C NMR (150 MHz, DMSO) δ 189.0, 162.6, 153.7, 141.6, 139.8 (d, J = 7.0 Hz), 136.1, 130.1 (d, J = 12.1 Hz), 129.2, 128.3, 127.2, 126.8 (d, J = 18.4 Hz), 123.4, 106.6, 53.0, 21.1. ESI-HRMS: calcd for $C_{24}H_{20}N_2O_2S$+H 401.1324, found 401.1324. $[\alpha]^{25}_D$ +18.0 (c 0.5, CHCl3); 33% ee. The enantiomeric ratio was determined by HPLC on Chiralpak AD column (25% 2-propanol/hexane, 1 mL/min); t_{major} = 13.840 min, t_{minor} = 23.509 min.

(2S,2′Z,4′R,5′Z)-5′-(Hydroxyimino)-2′-(naphthalen-2-ylimino)-4′-(p-tolyl)-3,4,4′,5′-tetrahydro-1H,2′H-spiro[naphthalene-2,3′-thiophen]-1-one (**4ai**). Thirty-four milligrams, 68% yield, mp 120−123 °C. ^{1}H NMR (600 MHz, DMSO) δ 11.62 (s, 1H), 8.04 (d, J = 7.8 Hz, 1H), 7.94 (d, J = 7.9 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.55 (t, J = 7.0 Hz, 3H), 7.53−7.48 (m, 2H), 7.38 (t, J = 7.2 Hz, 1H), 7.32 (d, J = 7.4 Hz, 1H), 7.27 (d, J = 7.6 Hz, 2H), 7.15 (d, J = 7.1 Hz, 2H), 7.04 (d, J = 7.2 Hz, 1H), 5.19 (s, 1H), 3.30−3.22 (m, 1H), 2.96 (d, J = 17.0 Hz, 1H), 2.55 (d, J = 14.0 Hz, 1H), 2.26 (s, 3H), 2.06 (t, J = 10.1 Hz, 1H). ^{13}C NMR (151 MHz, DMSO) δ 194.9, 170.6, 152.8, 147.0, 144.5, 137.6, 134.7, 134.1, 132.7, 131.7, 130.3, 129.6, 129.3, 128.5, 128.0, 127.5, 127.2, 126.7, 126.4, 125.9, 125.8, 122.8, 114.68, 65.1, 53.6, 29.2, 25.4, 21.1. ESI-HRMS: calcd for $C_{30}H_{24}N_2O_2S$+H 477.1637, found 477.1622. $[\alpha]^{25}_D$ −106.0 (c 0.5, $CHCl_3$); 82% ee. The enantiomeric ratio was determined by HPLC on Chiralpak AD column (25% 2-propanol/hexane, 1 mL/min); t_{major} = 29.007 min, t_{minor} = 8.372 min.

(2S,4′R,Z)-2′-(Phenylimino)-4′-(p-tolyl)-3,4-dihydro-1H,2′H-spiro-[naphthalene-2,3′-thiophene]-1,5′(4′H)-dione (**5aa**). Sixty-six milligrams, 80% yield, mp 161−164 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.04 (d, J = 7.5 Hz, 1H), 7.58 (t, J = 10.7, 4.1 Hz, 1H), 7.47 (t, J = 7.8 Hz, 2H), 7.42 (t, J = 7.5 Hz, 1H), 7.28 (t, J = 7.4 Hz, 1H), 7.25−7.19 (m, 3H), 7.17 (d, J = 8.1 Hz, 2H), 7.14−7.09 (m, 2H), 5.14 (s, 1H), 2.96−2.78 (m, 3H), 2.35 (s, 3H), 2.24−2.19 (m, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 195.5, 166.6, 150.2, 142.3, 140.3, 135.9, 134.5, 130.3, 130.0, 129.8 (d, J = 10.0 Hz), 129.3 (d, J = 13.6 Hz), 128.7, 127.5, 126.4, 119.7, 66.9, 55.5, 29.6, 25.0, 21.2. ESI-HRMS: calcd for

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$C_{26}H_{21}NO_2S$+H 412.1371, found 412.1373. $[\alpha]^{25}_D$ +242.0 (*c* 0.5, $CHCl_3$); −92% ee. The enantiomeric ratio was determined by HPLC on Chiralpak AD column (2% 2-propanol/hexane, 1 mL/min); t_{major} = 20.271 min, t_{minor} = 15.195 min.

Crystal Data for **4ae**. $C_{26}H_{21}ClN_2O_2S$ (460.96) (CCDC number: 1405299), monoclinic, $P2_1$; a = 10.0744(3) Å, α = 90.00°; b = 10.4491(3) Å, β = 95.102(2)°; c = 21.6791(6) Å, γ = 90.00°; U = 2273.08(11) Å^3; Z = 4; T = 296(2) K; absorption coefficient 0.286 mm^{-1}; reflections collected = 83234, unique = 10421 [R(int) = 0.0413]; refinement by full-matrix least-squares on F^2, data/restraints/parameters 10421/1/650; goodness-of-fit on F^2 = 1.071; final R indices [I > 2 sigma(I)], R1 = 0.0393, wR2 = 0.0867; R indices (all data), R1 = 0.0487, wR2 = 0.0924; largest diff. peak and hole 0.328 and −0.043 e Å^{-3}.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01357.

^{1}H NMR and ^{13}C NMR spectra for all new compounds (PDF)

X-ray structural data for **4ae** (CIF)

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Notes

The authors declare no competing financial interest.

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