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

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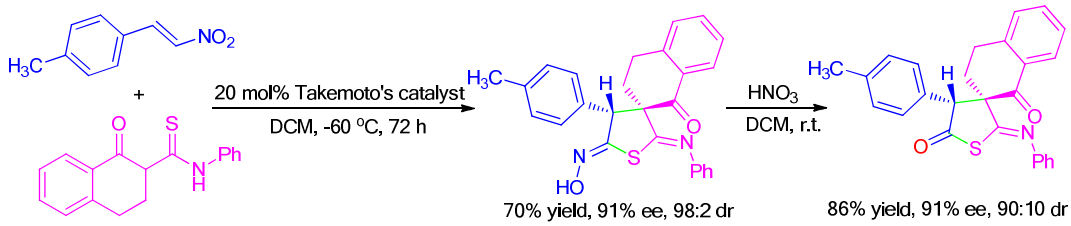
Abstract A formal thio [3 + 2]-cyclization catalyzed by Takemoto's organocatalyst has been reported for the construction of optically active spiroannulated dihydrothiophenes in high yields with excellent regio-, chemo-, diastereo- and enantioselectivities.



Keywords: Dihydrothiophenes, Organocatalysis , 1,3-Dicarbonyl Compounds, Nitrostyrenes, Thioamides

Thiophenes are unique sulfur-containing heterocycles and attracted particular attention due to their special place as building blocks in natural products, pharmaceutical agents and materials. Especially, 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 product[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. Due to the importance of applications of chiral thiophenes in the above-mentioned 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 the current research efforts.[8]

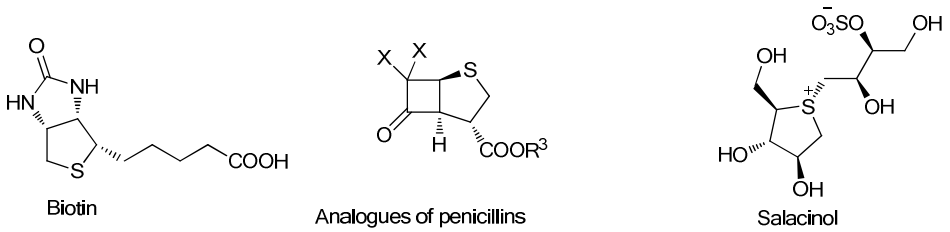
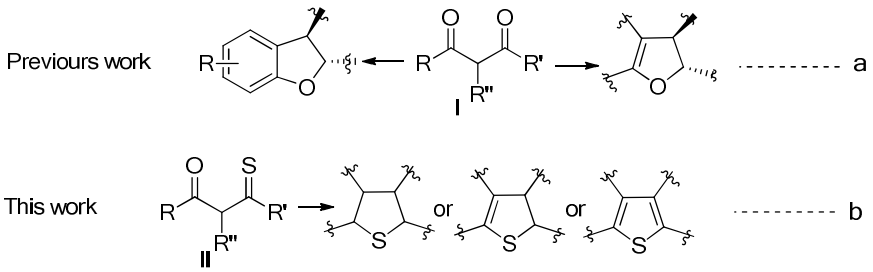


Figure 1 Some Representative Examples of Biologically Active Compounds Which Contain a Thiophene Ring

In addition, spirocyclic compounds are recognized as important precursors for the easy access of a variety of cyclic products by 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 decades.[12] Meanwhile, domino reactions have been 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.

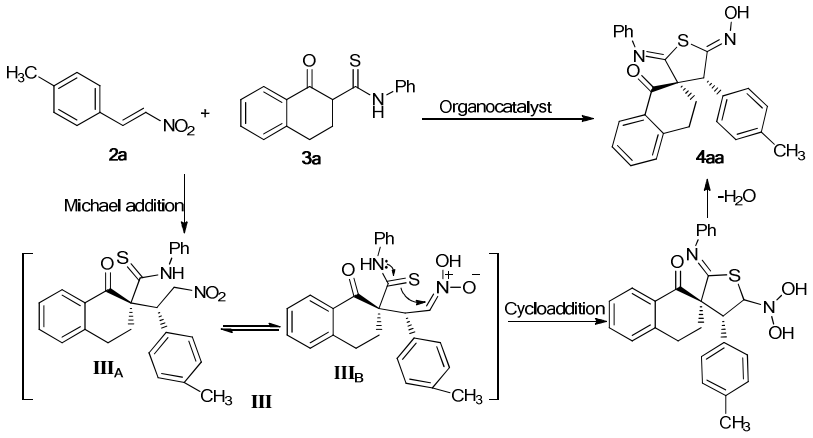


In the course of our investigations on the use of 1,3-dicarbonyl compounds **I** in organic synthesis, the 1,3-dicarbonyl compounds **I** turned out to be highly reactive and versatile, and many *O*-containing heterocycles have been prepared from

1,3-dicarbonyl compounds **I** in our group (Eq. a).[14] Encouraged by the successful results mentioned 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 proved 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]-cyclization of thioamide **3a** with (*E*)-α-nitrostyrene **2a** to afford the chiral polyfunctionalized spiroannulated dihydrothiophene **4aa** (**Scheme 1**). The key step of the above reaction is the Michael addition of **2a** to **3a** yielding the 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 attached to a nitro group and eliminated a water molecule 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, while the enantioselectivity was poor (Table 1, entry 1). Subsequently, organocatalysts **1b-g,** which are readily available from natural cinchona alkaloids, also exhibited a high catalytic activity when the thio[3+2]-cyclization was carried out at 25 ^{o}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** 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 the product **4aa** was obtained in a moderate yield, while the diastereoselectivity and enantioselectivity were very poor (entry 7). To our surprise, Takemoto's catalyst **1h** was proved to be superior to other catalysts in this cascade reaction**,** and the product **4aa** was obtained with good diastereoselectivity and moderate enantioselectivity (Table 1, entry 8). By lowering the temperature to -5 ^{o}C, the enantioselectivity was dramatically increased when the reaction was catalyzed by Takemoto's catalyst **1h** (entry 12), while the reaction time should be extended. Thus, catalyst **1h** was

chosen for further optimization of solvents and temperature (Table 2).



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

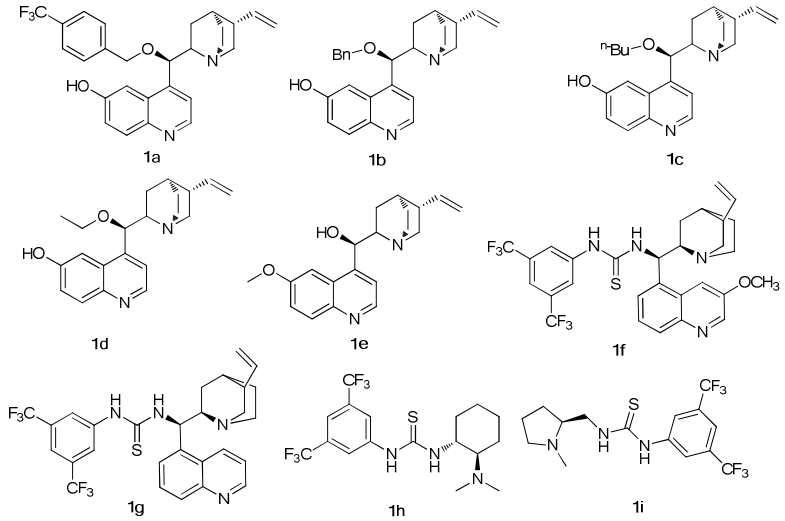


Figure 2 Structure of Organocatalysts 1a-i

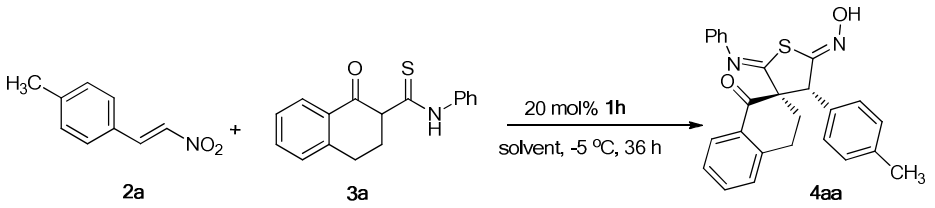
TABLE 1 Catalyst Screening [a)]

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 DCM at 25 °C for 24 h. [b)] Isolated yield. [c)] Determined by chiral HPLC analysis. [d)] Determined by chiral HPLC analysis. [e)] At -5 °C for 36 h.

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). Then solvent DCM was chosen as candidate solvent for further screening of temperature. By lowing the temperature to -60 ^oC, we got an excellent enantioselectivity (92% ee) and diastereoselectivity (98:2) in the presence of **1h** while the reaction time should be extended (entry 9). The ee was dramatically decreased when the catalyst loading was reduced to 10 mol%. Based on 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 ^oC) were established.

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



2a 3a 4aa

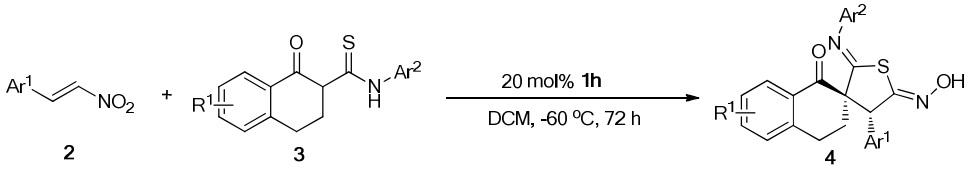
Entry	Sol.	Yield (%)[b)]	Dr [c)]	Ee (%)[d)]
1	DCM	68	96:4	74
2	THF	65	93:7	32
3	Diethyl ether	54	89:11	62
4	Toluene	55	92:8	68
5	Hexane	57	92:8	52
6	$CHCl_3$	65	94:6	66
7[e)]	DCM	69	97:3	83
8[f)]	DCM	66	97:3	87
9[g)]	DCM	70	98:2	91
10[h)]	DCM	64	98:2	90
11[i)]	DCM	50	97:3	78

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

With the optimal reaction conditions in hand, 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 a 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 the thio[3+2]-cyclizations process takes place with a variety of (*E*)-α-nitrostyrene Michael acceptors, which possess neutral, electron-donating, electron-withdrawing groups in the phenyl ring (Table 3, entries 1-10). It appeared that substituents' electronic and steric nature has minimal impact on efficiency, enantioselectivity, and diastereoselectivity of the thio [3+2]-cyclization. Not only aromatic groups but also heteroaromatic group such as furyl could be successfully employed to afford product **4ma** with excellent diastereoselectivity, while the enantioselectivity decreased (Table 3, entry 12). (*E*)-α-Nitrostyrenes with substituents on the ortho position afford multi-functionalized 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 effects on efficiency, enantioselectivity, and diastereoselectivity of the thio [3+2]-cyclization with our organocatalytic protocol. Thioamides **3,** which possess electron-donating, electron-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 confirmed by single-crystal X-ray analysis of representative enantiopure **4ae** that bears a chlorine atom. As shown in Figure 3, it composes of (*Z, R, S, Z)* configuration (See Supporting information).

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

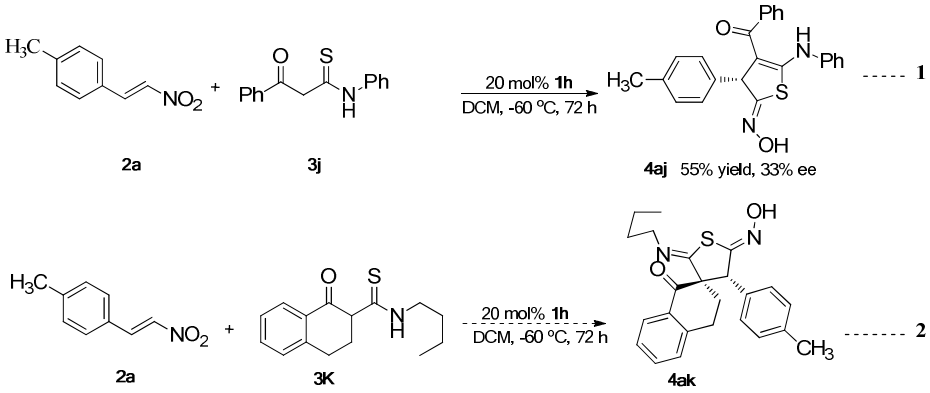


2 3 4

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

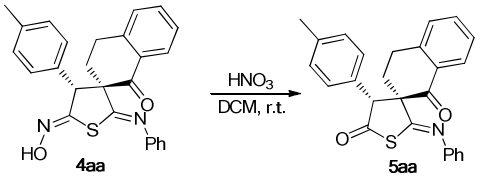
2	*p*-MeOC$_6$H$_4$(**2b**)	H	C$_6$H$_5$(**3a**)	55(**4ba**)	97:3	80
3	*m*-MeOC$_6$H$_4$(**2c**)	H	C$_6$H$_5$(**3a**)	60 (**4ca**)	99:1	88
4	*o*-MeOC$_6$H$_4$(**2d**)	H	C$_6$H$_5$(**3a**)	76 (**4da**)	98:2	80
5	*p*-ClC$_6$H$_4$ (**2e**)	H	C$_6$H$_5$(**3a**)	78 (**4ea**)	98:2	93
6	*m*-ClC$_6$H$_4$ (**2f**)	H	C$_6$H$_5$(**3a**)	70 (**4fa**)	96:4	91
7	*o*-ClC$_6$H$_4$(2h)	H	C$_6$H$_5$(**3a**)	64(**4ha**)	98:2	88
8	*p*-Br C$_6$H$_4$ (**2i**)	H	C$_6$H$_5$(**3a**)	75(**4ia**)	99:1	92
9	C$_6$H$_5$ (**2j**)	H	C$_6$H$_5$(**3a**)	70(**4ja**)	99:1	93
10	*p*-NO$_2$C$_6$H$_4$ (**2k**)	H	C$_6$H$_5$(**3a**)	60(**4ka**)	97:3	92
11	*β*-naphthyl(**2l**)	H	C$_6$H$_5$(**3a**)	55(**4la**)	99:1	94
12	*2*-furanyl(**2m**)	H	C$_6$H$_5$(**3a**)	65(**4ma**)	92:8	79
13	*p*-CH$_3$C$_6$H$_5$(**2a**)	*6*-MeO	C$_6$H$_5$(**3b**)	65(**4ab**)	99:1	92
14	*p*-CH$_3$C$_6$H$_4$(**2a**)	H	*p*-CH$_3$C$_6$H$_5$(**3c**)	70(**4ac**)	98:2	90
15	*p*-CH$_3$C$_6$H$_4$(**2a**)	H	*p*-ClC$_6$H$_5$(**3d**)	50(**4ad**)	97:3	84
16	*p*-CH$_3$C$_6$H$_4$(**2a**)	H	*m*-ClC$_6$H$_5$(**3e**)	78 (**4ae**)	99:1	92
17	*p*-CH$_3$C$_6$H$_4$(**2a**)	H	*o*-ClC$_6$H$_5$(**3f**)	75(**4af**)	99:1	90
18	*p*-CH$_3$C$_6$H$_4$(**2a**)	H	*m*-MeOC$_6$H$_5$(**3g**)	58(**4ag**)	99:1	88
19	*p*-CH$_3$C$_6$H$_4$(**2a**)	H	*o*-MeOC$_6$H$_5$(**3h**)	75(**4ah**)	99:1	92
20	*p*-CH$_3$C$_6$H$_4$(**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 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

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 carbonyl group in the presence of nitric acid at room temperature. The product **5aa** was obtained with excellent enantioselectivity and high yields, while the diastereoselectivity was decreased. The possible reason for the decreased diastereoselectivity was that an enolization reaction of **5aa** was happened under the strong acid reaction conditions (Please see Supporting Information).



Scheme 3 Selective Transformation of Chiral Polyfunctionalized Spiroannulated Dihydrothiophenes

In summary, we have successfully demonstrated an efficient and highly enantioselective thio[3+2]-cyclizations 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 a 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 the 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 MHz or 400MHz, and ^{13}C NMR spectra were recorded at 150 MHz 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 were determined by HPLC analysis using Chiralpak column (4.6mm*250mm, 5μm).

1. General procedure for synthesis of thioamides 3. [15] To a vigorously stirred suspension of sodium hydride (50 mmol) in 90 mL dry DMF at -10 ^{o}C, 2-tetralone (7.30 g, 50 mmol) was added slowly, over a period of 1 h, so the temperature did not exceed 0 ^{o}C. After the gas was evolved, a solution of the appropriate aryl isothiocyanate (50 mmol) in 10 mL 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 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. The crude **3** was treated with Et_2O, cooled in a fridge, and collected by filtration. The crude **3** was dissolved in MeCN at 50 °C and treated with 50 mL 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 accord 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 accord with the literature.6.4 g, 41% yield; [15] 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 accord 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 1 h 8.2 mg (0.02 mmol) was stirred in DCM (1 mL) at -60 ^{o}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**).* 30 mg, 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**).* 25 mg, 55% yield, 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**).* 28 mg, 60% yield, 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 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**).* 35 mg, 76% yield, 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**).* 36 mg, 78% yield. 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**)*. 32 mg, 70% yield, 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**)*. 30 mg, 64% yield, mp 218 - 220°C. 1H 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**)*. 38 mg, 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**).* 30 mg, 70% yield, 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**).* 28 mg, 60% yield, 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**).* 27 mg, 65% yield, 166 - 168°C. 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**)*. 26 mg, 55% yield, 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**)*. 31 mg, 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* = 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**)*. 32 mg, 70% yield, 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, CHCl3); -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**)*. 32 mg, 50% yield, 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**)***.** 37 mg, 78% yield, 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**).* 36 mg, 75% yield, 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**).* 27 mg, 58% yield, 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**).* 36 mg, 75% yield, 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**)*. 23 mg, 55% yield, 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**)*. 34 mg, 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**).* 66 mg, 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 $C_{26}H_{21}NO_2S$+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 4**ae** $C_{26}H_{21}ClN_2O_2S$ (460.96), (CCDC number: 1405299) monoclinic**,** $P2_1$, a = 10.0744(3)Å, alpha = 90.00 deg. b = 10.4491(3) Å, beta = 95.102(2) deg. c = 21.6791(6) Å, gamma = 90.00 deg. *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>2sigma(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 -0.043e.Å^{-3}.

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Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra for all new compounds and X-ray structural data for 4**ae** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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