JOC The Journal of Organic Chemistry

Article

Access to spirocyclic benzothiophenones with multiple stereocenters via an organocatalytic cascade reaction

Bed#ich Formánek, Ji#í Tauchman, Ivana Císa#ová, and Jan Vesely

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.0c00882 • Publication Date (Web): 01 Jun 2020

Just Accepted

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Access to spirocyclic benzothiophenones with multiple stereocenters via an organocatalytic cascade reaction

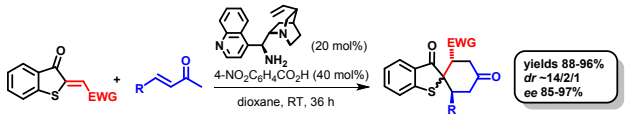
Bedřich Formánek,† Jiří Tauchman,† Ivana Císařová,‡ Jan Veselý*†

† Department of Organic Chemistry, Faculty of Science, Charles University, Hlavova 2030/8, 128 43, Prague 2, Czech Republic

E-mail: jan.vesely@natur.cuni.cz

‡ Department of Inorganic Chemistry, Faculty of Science, Charles University, Hlavova 2030/8, 128 43, Prague 2, Czech Republic

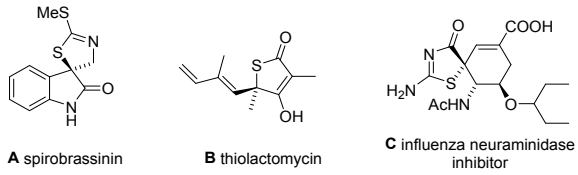
Supporting Information Placeholder



The present report describes an organocatalytic cascade reaction between 2-alkylidene benzo[b]thiophenone derivatives and enones in the presence of Cinchona alkaloid amine. Spirobenzothiophenonic cyclohexane derivatives containing three stereocenters were prepared via one-step synthesis in yields ranging from 88 to 96% and in enantioselectivities (ee) ranging from 85 to 97%, with diastereoselectivities of approximately 14/2/1. Therefore, this method provides an efficient route for the synthesis of a new class of optically active 2-spirobenzothiophenones.

INTRODUCTION

Sulfur-containing heterocycles are common structural motifs occurring in compounds with interesting physiochemical properties and with various biological and pharmacological activities.[1] Interestingly, more than one third of the twenty best-selling small molecule pharmaceuticals in 2018 contained a sulfur atom in their structural motifs.[2] In addition, sulfur-bearing full-substituted carbon stereocenters stand out as prominent structural fragments in natural products, bioactive compounds and drugs. Such motifs (Figure 1) can be found in plant metabolites, such as spirobrassinin **A** (anticancer activity)[3] and thiolactomycin **B** (antibacterial activity)[4], and in men-made molecules, such as spirolactam **C** (antiviral agent)[5].



A spirobrassinin **B** thiolactomycin **C** influenza neuraminidase inhibitor

Figure 1. Selected examples of biologically relevant compounds.

Noticeably, the biological activities of these compounds may be significantly affected by their optical purity. Thus, efficient enantioselective methods must be developed to construct structurally diverse, sulfur-bearing tetrasubstituted carbon stereocenters. In general, the preparation of quaternary carbon stereocenters is a challenging task considering the reduced reactivity of their sterically demanding precursors and the limited enantiocontrol of the newly formed stereocenters due to the lowered steric dissimilarities of non-hydrogen substituents on the prochiral carbon. In addition, the strong coordinating and adsorptive properties of sulfur species may cause additional difficulties by disrupting the catalytic process.[6]

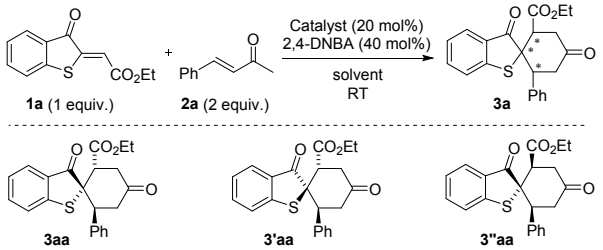
Nevertheless, these difficulties can be overcome through asymmetric organocatalysis. Over the past decade, several organocatalytic methods have been developed to construct various sulfur-containing heterocycles with a tetrasubstitued chiral carbon.[7] Since the pioneering work by Córdova et al.[8] based on the sulfa-Michael addition-initiated construction of tetrahydrothioxanthones, various enantioselective sulfa-Michael additions have been developed using electron-deficient alkenes, such as enones[9a,b], dienones[9c], acrylates[9d] and unsaturated amides[9e]. Other valuable protocols for the synthesis of enantiomerically enriched, sulfur-bearing full-substituted carbon stereocenters include Mannich reactions of thiols into ketimines[10] and electrophilic sulfenylation reactions of α-branched aldehydes, β-keto esters, nitroacetates, oxindols, benzofuran-2(3*H*)-ones, and oxazolones.[7,11] An alternative organocatalytic strategy for the preparation of such enantiomerically enriched compounds containing a sulfur-bearing full-substituted stereogenic center is based on the stereoselective formation of C-C or C-N bonds using prochiral sulfur-based substrates, such as α-sulfenylated acrylates and enals, rhodanines, 3-thiooxindoles, and thiazolones.[7,12] Yet, only a few reports on organocatalytic reactions on benzo[*b*]thiophene derivatives have been published to date[13]. Considering the above and our interest in the enantioselective preparation of heterocycles with full-substituted stereogenic center bearing sulfur atom, we aimed to use an enantioselective double Michael cascade reaction of benzo[*b*]thiophenone derivatives[14] with less reactive enones to prepare such stereocenters.

RESULTS AND DISCUSSION

At the outset, we chose alkylidene-benzothiophenone derivative **1a** as a suitable Michael acceptor and (*E*)-4-phenylbut-3-en-2-one (**2a**) as a donor for our model cascade reaction catalyzed by a primary amine derived from cinchonidine (**I**). In line with previous results[15,16], the acid

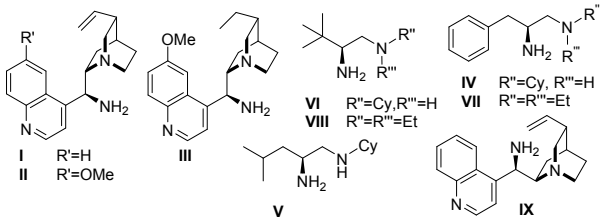
additive was required to obtain the desired product in a high yield. As expected, the cyclization reaction proceeded successfully in toluene, providing spiroproduct **3a** in a high yield with moderate enantioselectivity of the main diastereomer (**3aa**), albeit with poor diastereoselectivity (entry 1, Table 1). Nevertheless, when screening various solvents, the yield remained mostly unchanged (60-92%, entry 1-7, Table 1), whereas the reaction rate and stereochemical outcome were notably affected, with a significantly slower conversion of starting alkylidene derivative **1a** in chlorinated and polar protic solvents (entries 2 and 4, Table 1). Moreover, compound **3a** was obtained with low diastereo- and enantiocontrol in both solvent systems.

Table 1. Screening of the chiral tertiary amine catalyst and optimization studies.



Entry	Catalyst	Solvent	Time [d]	Yield [%][a]	3aa/3´aa/3´´aa[b]	*ee* [%][c]
1	I	toluene	4	85	10.8/15.0/1	72
2	I	$CHCl_3$	7	60	7.4/5.4/1	85
3	I	DMF	4	82	7.7/3.4/1	88
4	I	MeOH	7	76	2.5/2.8/1	79
5	I	MTBE	4	86	12.8/5.6/1	87
6	I	THF	3	92	7.6/2.3/1	93
7	I	1,4-dioxane	4	86	13.4/4.0/1	96
8	II	1,4-dioxane	2	95	20.2/6.3/1	93
9	III	1,4-dioxane	2	93	31.1/12.2/1	93
10	IV	1,4-dioxane	7	63	76.5/10.2/1	77
11	V	1,4-dioxane	7	61	58.2/7.5/1	83
12	VI	1,4-dioxane	7	74	60.5/7.4/1	74
13	VII	1,4-dioxane	7	38	15.9/3.4/1	54
14	VIII	1,4-dioxane	7	20	8.8/3.0/1	35
15[d]	I	1,4-dioxane	1.5	96	25.4/3.1/1	95

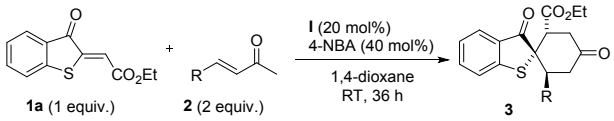
[a] Isolated overall yield of diastereomers **3aa**, **3'aa**, **3''aa** after column chromatography. [b] Determined by ^{1}H NMR analysis of crude mixture. [c] *Ee* of diastereomer **3aa** determined by HPLC analysis. [d] 4-$NO_2C_6H_4CO_2H$ was used as an additive.



Model reactions performed in ethereal and dipolar aprotic solvents afforded product **3a** in shortened reaction times with improved diastereoselectivity (entries 3, 5-6). Among the solvents tested, 1,4-dioxane provided **3a** with the highest stereoselectivity (*dr* 13/4/1). Thus, we continued our evaluation of various primary aminocatalysts **I-III** in dioxane using 2,4-dinitrobenzoic acid as an additive. In the presence of quinine-derived amine derivative **II**, the starting materials were fully converted in reduced times while increasing the yield of spirocompound **3a**. However, the diastereoselectivity of the reaction and the enantiomeric purity of the main diastereomer **3aa** decreased slightly. To modify the catalytic centers in terms of electronic and steric properties, we used diamines **IV-VIII**, readily available from the amino acids.[17] Unfortunately, none of the aminocatalysts tested afforded yields of **3a** comparable to the yield determined when using organocatalyst **I**. Full conversion of **1a** was not reached even after prolonged reaction times (entries 10-14). Subsequently, we assess the effects of acid additives, additive-to-amine **I** ratio, reactant ratio, catalyst loading and temperature on our reaction (for details, please, see SI). In summary, in the presence of 4-nitrobenzoic acid as an additive, we prepared spirobenzothiophenone derivative **3a** in a virtually quantitative yield, with high diastereoselectivity and enantioselectivity (entry 15, Table 1). Notably, the major diastereomer **3aa** can be easily isolated by column chromatography.

After completing the optimization tests, we focused our attention on finding the scope and limitations of the method developed in this study. Gratifyingly, the reaction proceeded smoothly with various enones (**2a-h**) bearing an aromatic moiety (Table 2). Both electron-withdrawing and electron-donating groups can be present on the aromatic ring without affecting the efficiency of the method. In addition, enones bearing an heteroaromatic ring (**2i-1j**) also led to satisfactory results (entries 9-10). In most cases, the diastereoselectivity of the reaction and the enantiomeric purity of the isolated spirocompounds **3aa**-**3aj** remained high. A slight decrease in stereoselectivity was observed only when introducing the substituent in the *ortho* position of the aryl moiety (entry 5).

Table 2. Screening of various enone derivatives in organocatalytic reaction.



Entry	R	Product	Yield [%][a]	*dr* [%][b]	*ee* [%][c]
1	Ph	**3aa**	71 (96)	25.4/3.1/1	95
2	2-naphthyl	**3ab**	65 (96)	11.4/1.5/.1	95
3	4-$NO_2C_6H_4$	**3ac**	63 (96)	16.8/2.2/1	86
4	3-$NO_2C_6H_4$	**3ad**	52 (92)	9.6/1.9/1	92
5	2-NO_2Ph	**3ae**	47 (96)	26.5/7.4/1	86
6	4-$CF_3C_6H_4$	**3af**	63 (95)	10.1/2.1/1	90
7	4-BrC_6H_4	**3ag**	62 (96)	13.8/1.9/1	93
8	4-$CH_3C_6H_4$	**3ah**	75 (95)	12.7/1.2/1	96
9	2-thienyl	**3ai**	69 (93)	9.6/1.3/1	95
10	5-benzo[*b*]thiophenyl	**3aj**	55 (94)	5.5/1.1/1	95
11[d]	Ph	*ent*-**3aa**	54 (92)	11.0/1.5/1	-87

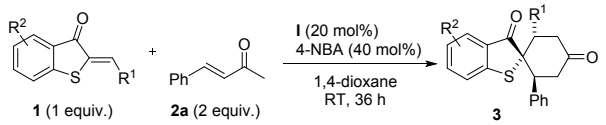
[a] Isolated yield of main diastereomer (overall yield of all diastereomers) after column chromatography. [b] Determined by ^{1}H NMR analysis of crude mixture. [c] *Ee* of major diastereomer determined by HPLC analysis. [d] Catalyst **IX** was used.

Similarily, the presence of the EWG group in the *para* position on the aromatic ring caused a small drop in the enantioselectivity of the reaction (entries 3,6). Importantly, access to the opposite enantiomer of spirocompounds **3** is allowed when using pseudoenantiomeric catalyst **IX**, for

exemple, with enone **2a**, observing only a slight decrease in the enantiocontrol of the reaction (entry 11).

Then, we examined benzothiophenones with different alkylidene moieties under optimized conditions (Table 3). The presence of EWG on the alkylidene moiety (R^1) was necessary to drive the reaction to completion. When alkylidenes bearing an aryl group (**1b-1c**) were mixed with **2a**, the reaction did not proceed. The result was also affected by the low solubility of substrate **1c** in dioxane. Nevertheless, when changing the solvent system to DMF, trace amounts of **3ca** were detected as a result. Conversely, the best results were found when a cyano group was attached to the alkylidene, most likely due to its strong electron-deficient character. High diastereo- and enantioselectivity levels were also observed with benzothiophenone derivatives bearing a modified ester moiety (entries 4-6). Similarily, the position of substitution on the aromatic benzothiophenone ring (R^2) only had a limited effect on the efficiency of the reaction (entries 9-12). In all cases, the level of stereocontrol was high, except when introducing an electron-withdrawing substituent in 5-position (entry 8), which caused a marked decrease in diastereoselectivity.

Table 3. Reaction scope of organocatalytic cyclization between alkylidenes **1** and enones **2**.



1 (1 equiv.) **2a** (2 equiv.) **3**

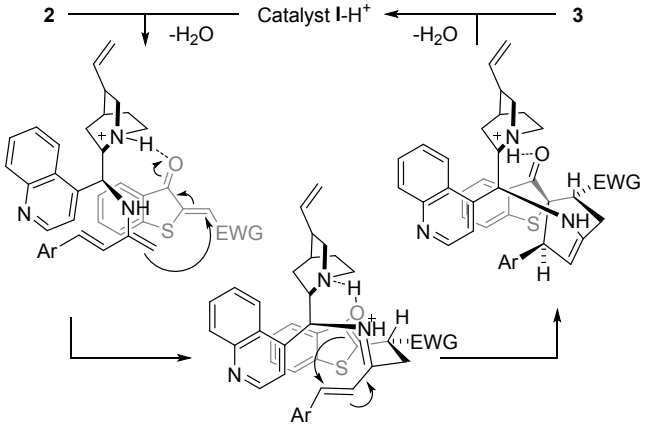
Entry	R^1	R^2	Product	Yield [%][a]	*dr* [%][b]	*ee* [%][c]
1	Ph	H	**3ba**	n.r.	n.d.	n.d.
2	4-$NO_2C_6H_4$	H	**3ca**	<5	n.d.	n.d.
3	PhCO	H	**3da**	36 (90)	22.8/3.4/1	85
4	CO_2Me	H	**3ea**	68 (90)	44.9/4.1/1	95
5	CO_2Et	H	**3aa**	71 (96)	25.4/3.1/1	95
6	CO_2allyl	H	**3fa**	57 (96)	14.6/2.0/1	95
7	CN	H	**3ga**	57 (96)	16.7/1/0	97
8	CO_2Et	5-Br	**3ha**	36 (96)	1.3/1.3/1	92
9	CO_2Et	5-Me	**3ia**	48 (96)	10.1/2.0/1	92
10	CO_2Et	4-Me	**3ja**	70 (88)	10.1/1.8/1	90
11	CO_2Et	6-Me	**3ka**	73 (96)	17.3/2.3/1	95
12	CO_2Et	7-Me	**3la**	51 (94)	9.4/1.6/1	96
13[d]	CO_2Me	H	**3ea**	63 (93)	42.6/3.8/1	94

[a] Isolated yield of main diastereomer (overall yield of all diastereomers) after column chromatography. [b] Determined by ^{1}H NMR analysis of crude mixture. [c] *Ee* of major diastereomer determined by HPLC analysis. [d] 1 g scale experiment (4.54 mmol of **1e**).

To ascertain the absolute configuration of spirobenzothiophenones **3**, we performed single-crystal X-ray diffraction analysis of compound **3ag**. All stereogenic centers, including the spiroatom, have an (*S*)-configuration (for details, please, see SI). That observation is in line with the generally accepted mechanism of organocatalytic double Michael addition cascade reaction of nitrogen- and oxygen-containing analogs.[15,16] In a proposed bifunctional mode of activation, the enamine generated from enone and primary amine attacks electron-deficient β-carbon of **1**. The presence of protonated quinuclidine moiety is crucial for the stereochemical outcome due to hydrogen bonding. The following Michael addition of generated enol to iminium ion leads to formation of enamine intermediate affording the major diastereoisomer **3** after hydrolysis (Scheme 1).

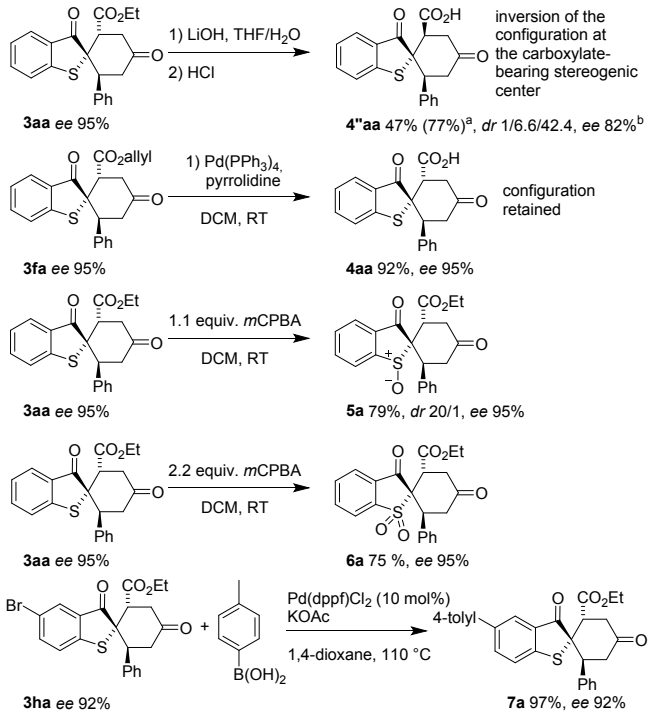
Subsequently, we assessed the usability of spirocompounds **3** on the following set of transformations (Scheme 2). When compound **3aa** was treated with lithium hydroxide, under standard saponification conditions, we observed epimerization

Scheme 1. Proposed reaction mechanism.



at the carbon center adjacent to the ethylcarboxylate group, followed by hydrolysis, affording the acid **4''aa** in a good yield. To avoid epimerization, we used a metal-catalyzed deesterification procedure for allyl ester **3fa**, preparing the corresponding acid **4aa** in a high yield with an enantiomeric excess equal to the starting material. Spirocompounds **3** can be easily transformed into the corresponding sulfoxides **5**. For example, compound **3aa** was converted by treatment with 1.1 equivalent of *m*CPBA into the diastereomerically pure sulfoxide **5a**. A higher excess of *m*CPBA and a prolonged reaction time led to desired sulfone **6a** without decreasing the optical purity.

Scheme 2. Further transformations of spirocyclohexanone derivatives.



[a] Overall yield of all diastereomers after column chromatography. [b] *Ee* of major diastereomer determined by HPLC analysis.

Furthermore, Suzuki coupling between bromoderivative **3ha** and tolylboronic acid proceeded well, with no deactivation of the Pd catalyst by the sulfur-bearing starting molecule. The desired product (**7a**) was obtained in high yield and enantiopurity (*ee* 92%).

In summary, we have developed an organocatalytic cascade reaction of benzothiophenone derivatives with enones catalyzed by a *Cinchona* alkaloid amine derivative. The corresponding spirocompounds were afforded in virtually quantitative yields, and the main diastereomers were obtained in high yields and with an excellent degree of enantiomeric purity. Moreover, we demonstrated that enantiomerically enriched benzothiophenones can be used in various transformations, thereby leading to chiral molecules with a high potential for applications in medicinal chemistry.

EXPERIMENTAL SECTION

Chemicals and solvents were either purchased from commercial suppliers or purified using standard techniques. For thin-layer chromatography (TLC), silica gel plates Merck 60 F254 were used, visualizing the compounds by irradiation with UV light and/or by treatment with a solution of phosphomolybdenic acid (25 g), $Ce(SO_4)_2 \cdot H_2O$ (10 g), conc. H_2SO_4 (60 mL) and H_2O (940 mL) followed by heating or treatment with a solution of ninhydrin (2 g), AcOH (5 mL) and 96% EtOH (1000 mL) followed by heating. Flash chromatography was performed using silica gel Silicycle - Siliaflash® P 60 (particle size 40–63 μm, pore diameter 60 Å).

^{1}H, ^{13}C, ^{19}F NMR spectra were measured on FT-NMR spectrometers Bruker AVANCE III 600 MHz or Bruker AVANCE III HD 400. Chemical shifts are given in ppm relative to tetramethylsilane and coupling constants *J* are given in Hz. The spectra were recorded in $CDCl_3$ as solvent at 25°C and served as internal standards (δ_{CDCl3} = 7.26 ppm) for ^{1}H NMR and (δ_{CDCl3} = 77.0 ppm) for ^{13}C NMR, trifluoroacetic acid was used as external standard for ^{19}F NMR. IR spectra were recorded on a Thermo Nicolet AVATAR 370 FT-IR spectrometer with KBr tablets of the compounds using the DRIFT method. Melting points were measured using a Büchi Melting Point B-545 apparatus. All melting points were measured in an open glass capillary, and all values are uncorrected. Chiral HPLC was performed using a LC20AD Shimadzu liquid chromatograph with SPD-M20A diode array detector with IA, IB and IC Daicel Chiralpak® columns. High-resolution mass spectroscopic data were acquired using ESI (TOF analyzer) at the Laboratory of mass spectrometry, Faculty of Science, Department of Chemistry, Charles University.

General procedure for the synthesis of the aminoamide catalyst (GP1)

Following a slightly modified procedure[18], DCC was slowly added (0.87 g, 4.2 mmol) in dry DCM (4 mL) to a solution of *N*-Boc-protected aminoacid (4.0 mmol) in dry DCM (6 mL) at 0 °C. After stirring for 30 min, the corresponding amine (4.0 mmol), in dry DCM (2 mL), was added portionwise (10 portions, 1h). Then, the solution was stirred for another 1 h at room temperature. The resulting white solid was filtered and washed with DCM, and the organics were combined and concentrated under reduced pressure. Column chromatography of the residue on silica gel (DCM/acetone/NH_4OH: 100/0/0 → 100/5/1) furnished *N*-Boc-protected aminoamide, which was used directly in next step.

CH_3COCl was added (1 mL) dropwise to the solution of *N*-Boc-protected aminoamide in dry MeOH (0.5M) at 0°C. The solution was refluxed for 1 h, then cooled to room temperature. The solvent was evaporated under reduced pressure, adding DCM (12 mL) and H_2O (8 mL), and the pH value was adjusted to 12 with saturated K_2CO_3. The organic phase was separated, and the aqueous phase was extracted with DCM (2 × 8 mL). The organics were combined, dried (Na_2SO_4) and concentrated under reduced pressure. Filtration through a pad of silica gel (5 cm layer, DCM/MeOH/NH_4OH: 100/1/1) furnished the corresponding aminoamide, which was used as such in the following step (GP2).

(*S*)-2-Amino-*N*-cyclohexyl-3-phenylpropanamide (IV')

The title compound was synthesized according to the general procedure GP1. Analytically pure product was obtained after column chromatography on silica gel (50 g, DCM/MeOH/NH_4OH: 100/1/1). Off-white powder, yield 483 mg (49% after two steps), **m.p.** 99 °C. $[\alpha]_D$ = +26.6° (c 1.0; 96% EtOH). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33 – 7.29 (m, 2H), 7.25 – 7.21 (m, 3H), 7.06 (d, *J* = 7.3 Hz, 1H), 3.80 – 3.70 (m, 1H), 3.56 (dd, *J* = 9.1, 4.3 Hz, 1H), 3.23 (dd, *J* = 13.7, 4.2 Hz, 1H), 2.70 (dd, *J* = 13.7, 9.1 Hz, 1H), 1.87 – 1.83 (m, 2H), 1.68 (dt, *J* = 13.1, 3.7 Hz, 2H), 1.59 (dt, *J* = 12.7, 3.9 Hz, 1H), 1.42 – 1.31 (m, 2H), 1.29 (s, 2H), 1.21 – 1.06 (m, 3H) ppm. **^{13}C{^{1}H}NMR** (101 MHz, $CDCl_3$) δ 173.0, 138.0, 129.30 (2C), 128.6 (2C), 126.7, 56.4, 47.5, 41.1, 33.1, 33.0, 25.5, 24.8 (2C) ppm. **IR** (KBr): *ν* = 3297, 3061, 3034, 2938, 2851, 1548, 1449, 1251, 1240, 1150, 1093, 866 cm^{-1}. **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{15}H_{23}N_2O^+$ 247.1805; found 247.1803.

General procedure for synthesis of diamine catalysts (GP2)

Following a slightly modified procedure[18], $LiAlH_4$ was added (114 mg, 3.0 mmol) portionwise to a solution of aminoamide (1.0 mmol) in dry THF (0.2M) at 0°C. Then, the solution was refluxed overnight. After cooling to room temperature, a saturated aqueous solution of Na_2SO_4 was added dropwise until gas evolution ceased. The resulting solid was filtered and washed with THF several times. The organics were combined, dried (Na_2SO_4) and concentrated under reduced pressure. Column chromatography of the residue on silica gel (EtOAc/MeOH/NH_4OH: 100/0/0 → 90/10/0 → 90/10/1) furnished the diamine catalyst.

The catalysts **I-III**, **IX** were prepared using known procedures, and their spectral data matched previously published data.[19]

(*S*)-*N*^{1}-Cyclohexyl-3-phenylpropane-1,2-diamine (IV)
The title compound was synthesized according to the general procedure GP2. Yellow oil, yield 109 mg (47%). Our physical and spectroscopic data corroborated previously published materials.[18]

(*S*)-*N*^{1}-Cyclohexyl-4-methylpentane-1,2-diamine (V)
The title compound was synthesized according to the general procedure GP2. Yellow oil, yield 131 mg (66%). $[\alpha]_D$ = +13.5° (c 1.0; 96% EtOH). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.85 – 2.79 (m, 1H), 2.66 (dd, *J* = 11.5, 3.6 Hz, 1H), 2.41 – 2.34 (m, 1H), 2.30 (dd, *J* = 11.5, 8.9 Hz, 1H), 1.88 – 1.85 (m, 2H), 1.75 – 1.67 (m, 3H), 1.61 – 1.58 (m, 1H), 1.42 – 1.38 (m, 3H), 1.29 – 1.12 (m, 5H), 1.10 – 1.01 (m, 2H), 0.90 (dd, *J* = 12.1, 6.6 Hz, 6H) ppm. **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 57.0, 54.2, 49.2, 45.9, 33.9, 33.6, 26.2, 25.08, 25.06, 24.7, 23.5, 22.0 ppm. **IR** (KBr): *v* = 3309, 2938, 2860, 2597, 2352, 1583, 1431, 1344, 1305, 1180, 890 cm^{-1}. **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{12}H_{27}N_2^+$ 199.2169; found = 199.2168.

(*S*)-*N*^{1}-Cyclohexyl-3,3-dimethylbutane-1,2-diamine (VI)
The title compound was synthesized according to the general procedure GP2. Yellow oil, yield 40 mg (20 % after three steps). Our physical and spectroscopic data corroborated previously published materials.[17]

(*S*)-*N*^{1},*N*^{1}-Diethyl-3-phenylpropane-1,2-diamine (VII)
The title compound was synthesized according to the general procedure GP2. Yellow oil, yield 60 mg (29% after three steps). Our physical and spectroscopic data corroborated previously published materials.[18]

(*S*)-*N*^{1},*N*^{1}-Diethyl-3,3-dimethylbutane-1,2-diamine (VIII)
The title compound was synthesized according to the general procedure GP2. Yellow oil, yield 21 mg (12% after three steps). Our physical and spectroscopic data corroborated previously published materials.[20]

General procedure for the synthesis of alkylidene-benzo[b]thiophenones (GP3)
a) Following a slightly modified procedure[13a], the corresponding Wittig reagent (2.0 mmol) was added to a solution of benzo[*b*]thiophene-2,3-dione (2.0 mmol) in toluene (10 mL) at room temperature and stirred overnight. The organics were concentrated under reduced pressure. Column chromatography of the residue on silica gel (hexanes/EtOAc or hexanes/toluene) furnished the corresponding 2-alkylidene-benzo[*b*]thiophenones.
b) Following a slightly modified procedure[21], a solution of *n*-BuLi (2.5M in hexanes, 2.0 mmol) was added dropwise to a solution of phosphonium salt (2.2 mmol) in dry THF (80 mL) at room temperature and stirred for 30 min under argon atmosphere. Then, benzo[*b*]thiophene-2,3-dione (2.0 mmol) was added at one portion and sirred overnight. The organics were concentrated under reduced pressure. Column chromatography of the residue on silica gel (hexanes/EtOAc or hexanes/toluene) furnished the corresponding 2-alkylidene-benzo[*b*]thiophenones.

Ethyl (*Z*)-2-(3-oxobenzo[*b*]thiophen-2(3*H*)-ylidene)acetate (1a)
The title compound was synthesized according to the general procedure GP3-a. Orange powder, yield 117 mg (25%). Our physical and spectroscopic data corroborated previously published materials.[13a]

(*Z*)-2-Benzylidenebenzo[*b*]thiophen-3(2*H*)-one (1b)
The title compound was synthesized according to the general procedure GP3-b. Yellow powder, yield 248 mg (52%). Our physical and spectroscopic data corroborated previously published materials.[22]

(*Z*)-2-(4-Nitrobenzylidene)benzo[*b*]thiophen-3(2*H*)-one (1c)
The title compound was synthesized according to general procedure GP3-b. Instead of column chromatography, residue was suspended in 96% EtOH (5 mL), filtered on sintered funnel and washed with Et_2O (5 mL). Orange-yellow powder, yield 238 mg (42%). Our physical and spectroscopic data corroborated previously published material.[23]

(*Z*)-2-(2-Oxo-2-phenylethylidene)benzo[*b*]thiophen-3(2*H*)-one (1d)
The title compound was synthesized according to general procedure GP3-b. Orange powder, yield 53 mg (10%). Our physical and spectroscopic data corroborated previously published materials.[13a]

Methyl (*Z*)-2-(3-oxobenzo[*b*]thiophen-2(3*H*)-ylidene)acetate (1e)
The title compound was synthesized according to general procedure GP3-a. Yellow powder, yield 238 mg (54%). Our physical and spectroscopic data corroborated previously published materials.[13a]

Allyl (*Z*)-2-(3-oxobenzo[*b*]thiophen-2(3*H*)-ylidene)acetate (1f)
The title compound was synthesized according to the general procedure GP3-b. Yellow powder, yield 365 mg, (74%). **m.p.** 101 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.7 Hz, 1H), 7.60 (td, *J* = 7.8, 1.3 Hz, 1H), 7.45 – 7.43 (m, 1H), 7.29 (t, *J* = 7.5 Hz, 1H), 7.05 (s, 1H), 5.99 (ddt, *J* = 17.2, 10.4, 5.8 Hz, 1H), 5.40 (dd, *J* = 17.2, 1.5 Hz, 1H), 5.30 (dd, *J* = 10.4, 1.3 Hz, 1H), 4.76 (dt, *J* = 5.8, 1.4 Hz, 2H) ppm. **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 188.3, 165.8, 147.5, 147.4, 136.6, 131.5, 129.2, 127.2, 126.2, 124.2, 118.9, 118.0, 66.1 ppm. **IR** (KBr): *v* = 1682, 1607, 1589, 1464, 1359, 1311, 1281, 1222, 1177, 1069, 1027, 991, 955, 940, 848, 737 cm^{-1}. **HRMS** (ESI) m/z: $[M+Na]^+$ calcd for $C_{13}H_{10}O_3NaS^+$ 269.0243; found 269.0240.

(*Z*)-2-(3-Oxobenzo[*b*]thiophen-2(3*H*)-ylidene)acetonitrile (1g)
The title compound was synthesized according to the general procedure GP3-a. Yellow-brown powder, yield 161 mg (43%) (separated from 2-(2-oxobenzo[*b*]thiophen-3(2*H*)-ylidene)acetonitrile). **m.p.** 167 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.89 (dd, *J* = 7.7, 0.7 Hz, 1H), 7.67 (td, *J* = 7.9, 1.4 Hz, 1H), 7.47 (d, *J* = 7.9 Hz, 1H), 7.35 (td, *J* = 7.6, 0.9 Hz, 1H), 6.54 (s, 1H) ppm. **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 185.4, 152.2, 144.1, 137.3, 129.0, 128.0, 126.8, 124.4, 115.7, 97.9 ppm. **IR** (KBr): *v* = 3034, 2217, 1691, 1589, 1568, 1458, 1311, 1287, 1228, 1069, 1024, 842, 740 cm^{-1}. **HRMS** (ESI) m/z: $[M+Na]^+$ calcd for $C_{10}H_5ONNaS^+$ 209.9984; found 209.9982.

Ethyl (*Z*)-2-(5-bromo-3-oxobenzo[*b*]thiophen-2(3*H*)-ylidene)acetate (1h)
Following a slightly modified procedure[24], a solution of DBU (2.38 g, 15.7 mmol) in benzene (5 mL) was added dropwise to a stirred solution of 4-bromobenzenethiol (2.84 g, 15.0 mmol) and ethyl bromoacetate (2.61 g, 15.7 mmol) in benzene (5 mL) under argon atmosphere and stirred for 2 h at reflux. The reaction mixture was filtered through a sintered funnel, and the solid residue was washed with benzene (2 × 5 mL). The organics were concentrated under reduced pressure. Kugelrohr distillation (200°C, 3 mbar) of the crude mixture furnished a transparent oil, 3.86 g.

Following a slightly modified procedure[25], the oil was dissolved in THF (15 mL), adding a solution of NaOH (1.80 g, 45.0 mmol) in H_2O (13 mL), and the reaction mixture was vigorously stirred at room temperature overnight. Then, the mixture was poured into H_2O (50 mL) and acidified by adding 1M HCl. The precipitated solid was filtered, washed with H_2O (2 × 10 mL) and dried in desiccator (silica gel) to yield 2-((4-bromophenyl)thio)acetic acid, white plates, 3.35 g.

Following a slightly modified procedure[26], the crude thioacetic acid derivative (1.24 g) was treated with $SOCl_2$ (2 mL, excess) and heated to reflux for 1 h under argon atmosphere. $SOCl_2$ was evaporated under reduced pressure. The residue was dissolved in DCM (10 mL) and $AlCl_3$ (0.80 g, 6 mmol) was added in one portion at 0°C and stirred for 1 h under argon atmosphere at room temperature. Subsequently, after adding crushed ice and then water (10 mL), the resulting solution was extracted with DCM (3 × 10 ml). The organics were combined, washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Crude 5-bromobenzo[*b*]thiophen-3(*2*H)-one was dissolved in benzene (30 mL), subsequently adding a solution of ethyl glyoxalate (50% w/w in toluene, 2 mL, excess), and then piperidine (2 drops). The reaction mixture was stirred for 2 h at room temperature. To the mixture, EtOAc (10 mL) was added, and the organic phase was washed with 1M HCl (10 mL), H_2O (10 mL), $Na_2S_2O_3$ (aq. 5% w/w, 10 mL), brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography of the residue on silica gel (hexanes/EtOAc) furnished the title compound.

Yellow-brown powder, yield 1.50 g, (32% after five steps). **m.p.** 142 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 2.0 Hz, 1H), 7.69 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.33 (d, *J* = 8.3 Hz, 1H), 7.02 (s, 1H), 4.33 (q, *J* = 7.1 Hz, 2H), 1.36 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 187.2, 166.0, 146.5, 146.4, 139.0, 130.9, 129.8, 125.5, 119.9, 119.3, 61.8, 14.2 ppm. **IR** (KBr): *ν* = 3085, 2977, 1691, 1607, 1580, 1559, 1449, 1410, 1362, 1317, 1257, 1198, 1081, 1027, 896, 827, 773 cm^{-1}. **HRMS** (ESI) m/z: $[M+Na]^+$ calcd for $C_{12}H_9O_3BrNaS^+$ 334.9348; found 334.9344.

Ethyl (*Z*)-2-(5-methyl-3-oxobenzo[*b*]thiophen-2(3*H*)-ylidene)acetate (1i)

The title compound was synthesized according to general procedure GP3-a. Orange powder, yield 99 mg (20%). Our physical and spectroscopic data corroborated previously published materials.[13a]

Ethyl (*Z*)-2-(4-methyl-3-oxobenzo[*b*]thiophen-2(3*H*)-ylidene)acetate (1j)

The title compound was synthesized according to the general procedure GP3-a. Orange powder, yield 84 mg (17%). **m.p.** 118 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42 (t, *J* = 7.6 Hz, 1H), 7.25 (d, *J* = 7.2 Hz, 1H), 7.03 (d, *J* = 7.5 Hz, 1H), 6.94 (s, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 2.66 (s, 3H), 1.36 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 189.1, 166.4, 148.2, 147.4, 142.7, 135.5, 128.6, 126.7, 121.7, 117.5, 61.5, 19.0, 14.2 ppm. **IR** (KBr): *ν* = 2977, 1700, 1679, 1607, 1577, 1380, 1362, 1305, 1257, 1222, 1195, 1177, 1027, 872, 851 cm^{-1}. **HRMS** (ESI) m/z: $[M+Na]^+$ calcd for $C_{13}H_{12}O_3NaS^+$ 271.0399; found 271.0397.

Ethyl (*Z*)-2-(6-methyl-3-oxobenzo[*b*]thiophen-2(3*H*)-ylidene)acetate (1k)

The title compound was synthesized according to the general procedure GP3-a. Additionally, the product was recrystallized from 96% EtOH/$CHCl_3$ (2/1, v/v). Orange powder, yield 159 mg (32%). **m.p.** 149 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.9 Hz, 1H), 7.23 (s, 1H), 7.06 (d, *J* = 7.9 Hz, 1H), 6.98 (s, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 2.42 (s, 3H), 1.35 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 187.7, 166.2, 148.4, 147.9, 147.5, 127.3, 127.1, 126.9, 124.5, 118.1, 61.5, 22.2, 14.2 ppm. **IR** (KBr): *ν* = 2980, 1700, 1685, 1598, 1571, 1404, 1371, 1362, 1308, 1281, 1234, 1186, 1072, 1024, 857 cm^{-1}. **HRMS** (ESI) m/z: $[M+Na]^+$ calcd for $C_{13}H_{12}O_3NaS^+$ 271.0399; found 271.0397.

Ethyl (*Z*)-2-(7-methyl-3-oxobenzo[*b*]thiophen-2(3*H*)-ylidene)acetate (1l)

The title compound was synthesized according to the general procedure GP3-a. Bright yellow powder, yield 293 mg (59%). Our physical and spectroscopic data corroborated previously published material.[13a]

General procedure for synthesis of enones (GP4)

Following a slightly modified procedure[27], morpholinium trifluoroacetate (1.0 mmol, 201 mg) was added to a solution of corresponding aldehyde (5.0 mmol) in acetone (12.5 mL). The reaction mixture was refluxed until reaching full conversion (monitored by TLC, 1–2 d). The reaction mixture was carefully concentrated (bumping) under reduced pressure, subsequently adding EtOAc (10 mL) and a saturated $NaHCO_3$ solution (20 mL). The organic phase was separated, and the aqueous phase was extracted with EtOAc (2 × 10 mL). The organics were combined, dried (Na_2SO_4) and concentrated under reduced pressure. Column chromatography of the residue on silica gel (hexanes/EtOAc) furnished enones.

(*E*)-4-(Naphthalen-2-yl)but-3-en-2-one (2b)

The title compound was synthesized according to the general procedure GP4. White solid, yield 461 mg (47%). Our physical and spectroscopic data corroborated previously published materials.[27]

(*E*)-4-(4-Nitrophenyl)but-3-en-2-one (2c)

The title compound was synthesized according to the general procedure GP4. Yellow powder, yield 516 mg (54%). Our physical and spectroscopic data corroborated previously published materials.[27]

(*E*)-4-(3-Nitrophenyl)but-3-en-2-one (2d)

The title compound was synthesized according to the general procedure GP4. Yellowish powder, yield 440 mg (46%). **m.p.** 97 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.39 (t, *J* = 1.9 Hz, 1H), 8.23 (ddd, *J* = 8.2, 2.2, 1.0 Hz, 1H), 7.85 –7.84 (m, 1H), 7.59 (t, *J* = 8.0 Hz, 1H), 7.54 (d, *J* = 16.3 Hz, 1H), 6.82 (d, *J* = 16.3 Hz, 1H), 2.41 (s, 3H) ppm. **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 197.5, 148.7, 140.1, 136.2, 133.7, 130.0, 129.3, 124.6, 122.5, 28.0 ppm. **IR** (KBr): *ν* = 3076, 1670, 1527, 1353, 1296, 1266, 1216, 1108, 1012, 979, 815 cm^{-1}. **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{10}H_{10}NO_3^+$ 192.0655; found 192.0654.

(*E*)-4-(2-Nitrophenyl)but-3-en-2-one (2e)

The title compound was synthesized according to general procedure GP4. Brownish powder, yield 287 mg (30%). Our physical and spectroscopic data corroborated previously published material.[28]

(*E*)-4-(4-(trifluoromethyl)phenyl)but-3-en-2-one (2f)

The title compound was synthesized according to the general procedure GP4. White powder, yield 728 mg (68%). Our physical and spectroscopic data corroborated previously published materials.[27]

(*E*)-4-(4-Bromophenyl)but-3-en-2-one (2g)

The title compound was synthesized according to the general procedure GP4. White powder, yield 574 mg (51%). Our physical

and spectroscopic data corroborated previously published materials.[29]

(*E*)-4-(4-Tolyl)but-3-en-2-one (2h)
The title compound was synthesized according to the general procedure GP4. Yellow powder, yield 489 mg (61%). Our physical and spectroscopic data corroborated previously published materials.[29]

(*E*)-4-(Thiophen-2-yl)but-3-en-2-on (2i)
The title compound was synthesized according to the general procedure GP4. Yellow wax, yield 449 mg (59%). Our physical and spectroscopic data corroborated previously published materials.[27]

(*E*)-4-(Benzo[*b*]thiophen-5-yl)but-3-en-2-one (2j)
Following a slightly modified procedure[30], a solution of *i*PrMgCl·LiCl (1.3M in THF, 27 mL, 35 mmol) was added dropwise to an oven dried flask with a stirred solution of 5-bromobenzo[*b*]thiophene (2.131 g, 10 mmol) in dry THF (55 mL) at 25 °C under argon atmosphere. The resulting reaction mixture was stirred at the same temperature for 20 h. Then, freshly distilled dry DMF (6.0 mL, 77 mmol) was added dropwise. After 30 min, the mixture was cooled to 0°C, adding water (90 mL) and then 1M HCl until dissolving all solids. The resulting solution was extracted with EtOAc (3 × 50 ml). The organics were combined, washed with brine (50 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography of the residue on silica gel (hexanes/EtOAc) furnished benzo[*b*]thiophene-5-carbaldehyde, yellow solid, 560 mg, which was used as such. The title compound was synthesized according to the general procedure GP4. Yellowish solid, yield 682 mg (96%). Our physical and spectroscopic data corroborated previously published materials.[31]

General procedure for organocatalytic reaction (GP5)
The corresponding enone **2** (0.20 mmol, 2.0 equiv.) was added to a homogeneous solution of catalyst **I** (5.9 mg, 0.02 mmol, 0.2 equiv.) and 4-nitrobenzoic acid (6.7 mg, 0.04 mmol, 0.4 equiv.) in 1,4-dioxane (0.5 mL). The mixture was stirred for 10 minutes at room temperature. Then, the corresponding alkylidene compound **1** (0.10 mmol, 1.0 equiv.) was added to the reaction mixture. The reaction was stirred for the indicated time. After completing the reaction (monitored on TLC), the solvent was evaporated under reduced pressure. Column chromatography of the residue on silica gel (hexanes/EtOAc) furnished corresponding spiro compounds **3**. Racemates for chiral HPLC analysis were prepared according to a similar method using the catalyst 9-amino(9-deoxy)*epi*-cinchonidine (**I**) (2.9 mg, 0.01 mmol, 0.1 equiv.) and its pseudoenantiomer 9-amino(9-deoxy)*epi*-cinchonine (**IX**) (2.9 mg, 0.01 mmol, 0.1 equiv.).

Ethyl (2*S*,2'*S*,6'*S*)-3,4'-dioxo-6'-phenyl-3*H*-spiro[benzo[*b*]thiophene-2,1'-cyclohexane]-2'-carboxylate (3aa)
The title compound was synthesized according to the general procedure GP5 (reaction time: 36 hours), affording the product as a 25.4/3.1/1 diastereomeric mixture, with a yield of 37 mg (96%). The major diastereomer, a yellowish wax, was separated with a yield of 27 mg (71%), 95% *ee* (IA column, *n*-heptane:*i*-PrOH = 80:20; t_R = 8.5 (minor.), 9.2 (major.) min), $[\alpha]_D$ = -40.3° (c 0.62; $CHCl_3$). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.2 Hz, 1H), 7.40 (td, *J* = 7.7, 1.3 Hz, 1H), 7.17 – 7.14 (m, 3H), 7.12 – 7.07 (m, 4H), 4.16 – 4.04 (m, 3H), 3.60 (t, *J* = 6.5 Hz, 1H), 3.58 – 3.49 (m, 2H), 2.75 – 2.67 (m, 2H), 1.07 (t, *J* = 7.2 Hz, 3H) ppm. **^{13}C{^{1}H} NMR** (151 MHz, $CDCl_3$) δ 207.4, 201.7, 171.2, 150.7, 136.8, 135.7, 130.9, 129.2 (2C), 127.8 (2C), 127.7, 126.6, 124.9, 123.4, 65.0, 61.6, 48.0, 47.3, 43.2, 39.4, 13.7 ppm. **IR** (KBr): *v* = 3072, 2982, 1725, 1684, 1587, 1496, 1450, 1413, 1374, 1281, 1184, 1150, 918, 891, 870, 743 cm^{-1}. **HRMS** (ESI) m/z: $[M+Na]^+$ calcd for $C_{22}H_{20}O_4NaS^+$ 403.0975; found 403.0977.

Ethyl (2*R*,2'*R*,6'*R*)-3,4'-dioxo-6'-phenyl-3*H*-spiro[benzo[*b*]thiophene-2,1'-cyclohexane]-2'-carboxylate (*ent*-3aa)

The title compound was synthesized according to general procedure GP5 with catalyst **IX** (reaction time: 36 hours), affording the product as a diastereomeric mixture 11.0/1.5/1, yield 35 mg (92%). The major diastereomer, a yellowish wax, was separated with a yield of 21 mg (54%) and 87% *ee* (IA column, *n*-heptane:*i*-PrOH = 80:20; t_R = 8.5 (major.), 9.2 (minor.) min), $[\alpha]_D$ = +37.6° (c 0.93; $CHCl_3$). The other recorded spectral data corroborated previously reported values for compound **3aa**.

Ethyl (2*S*,2'*S*,6'*S*)-6'-(naphthalen-2-yl)-3,4'-dioxo-3*H*-spiro[benzo[*b*]thiophene-2,1'-cyclohexane]-2'-carboxylate (3ab)
The title compound was synthesized according to general procedure GP5 (reaction time: 36 hours), affording the product as a 11.4/1.5/1 diastereomeric mixture, with a yield of 41 mg (96%). The major diastereomer, a off-white foam, was separated with a yield of 28 mg (65%) and 95% *ee* (IA column, *n*-heptane:*i*-PrOH = 80:20; t_R = 11.1 (minor.), 16.6 (major.) min), $[\alpha]_D$ = -40.5° (c 0.58; $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.72 – 7.67 (m, 2H), 7.63 – 7.58 (m, 3H), 7.41 – 7.36 (m, 2H), 7.34 – 7.30 (m, 1H), 7.29 – 7.27 (m, 1H), 7.11 (d, *J* = 8.1 Hz, 1H), 7.04 – 7.00 (m, 1H), 4.31 (dd, *J* = 11.8, 4.7 Hz, 1H), 4.20 – 4.08 (m, 2H), 3.72 (dd, *J* = 15.3, 11.6 Hz, 1H), 3.63 – 3.56 (m, 2H), 2.79 – 2.72 (m, 2H), 1.12 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 207.3, 201.9, 171.4, 150.8, 135.8, 134.6, 132.8, 132.6, 130.8, 128.6, 127.9, 127.4, 127.4, 127.1, 126.6, 126.0, 125.9, 124.9, 123.5, 65.0, 61.6, 48.0, 47.7, 43.5, 39.5, 13.8 ppm. **IR** (KBr): *v* = 3055, 2977, 2929, 1739, 1718, 1691, 1592, 1452, 1401, 1284, 1266, 1240, 1219, 1189, 1111, 1021, 863, 740 cm^{-1}. **HRMS** (ESI) m/z: $[M+Na]^+$ calcd for $C_{26}H_{22}O_4NaS^+$ 453.1131; found 453.1132.

Ethyl (2*S*,2'*S*,6'*S*)-6'-(4-nitrophenyl)-3,4'-dioxo-3*H*-spiro[benzo[*b*]thiophene-2,1'-cyclohexane]-2'-carboxylate (3ac)
The title compound was synthesized according to the general procedure GP5 (reaction time: 36 hours), affording the product as a 16.8/2.2/1 diastereomeric mixture, with a yield of 41 mg (96%). The major diastereomer, a yellowish wax, was separated with a yield of 27 mg (63%) and 86% *ee* (IC column, *n*-heptane:*i*-PrOH = 80:20; t_R = 47.5 (major.), 55.4 (minor.) min), $[\alpha]_D$ = -27.3° (c 0.11; $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.8 Hz, 2H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.46 – 7.41 (m, 1H), 7.37 (d, *J* = 8.8 Hz, 2H), 7.16 (d, *J* = 7.9 Hz, 1H), 7.14 – 7.11 (m, 1H), 4.35 (dd, *J* = 12.5, 4.6 Hz, 1H), 4.21 – 4.09 (m, 2H), 3.68 – 3.51 (m, 3H), 2.72 (ddd, *J* = 15.6, 5.1, 1.6 Hz, 1H), 2.64 (ddd, *J* = 15.2, 4.6, 1.6 Hz, 1H), 1.14 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 206.0, 201.5, 171.4, 150.6, 147.3, 144.3, 136.4, 130.5, 130.3 (2C), 126.8, 125.4, 123.6, 122.9 (2C), 64.1, 61.9, 47.8, 47.2, 42.5, 39.3, 13.8 ppm. **IR** (KBr): *v* = 3079, 2980, 2929, 1724, 1679, 1586, 1518, 1449, 1347, 1278, 1219, 1186, 1150, 1111, 1066, 1015, 857, 755 cm^{-1}. **HRMS** (ESI) m/z: $[M+Na]^+$ calcd for $C_{22}H_{19}O_6NNaS^+$ 448.0822; found 448.0825.

Ethyl (2*S*,2'*S*,6'*S*)-6'-(3-nitrophenyl)-3,4'-dioxo-3*H*-spiro[benzo[*b*]thiophene-2,1'-cyclohexane]-2'-carboxylate (3ad)

The title compound was synthesized according to the general procedure GP5 (reaction time: 36 hours), affording the product as a 9.6/1.9/1 diastereomeric mixture, with a yield of 39 mg (92%). The major diastereomer, a yellow wax, was separated with a yield of 22 mg (52%) and 92% *ee* (IA column, *n*-heptane:*i*-PrOH = 80:20; t_R = 14.5 (minor.), 16.5 (major.) min), $[\alpha]_D$ = -19.0° (c 0.53; $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.94 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.62 (d, *J* = 8.8 Hz, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 1H), 7.29 (t, *J* = 7.9 Hz, 1H), 7.14 (d, *J* = 8.1 Hz, 1H), 7.09 (t, *J* = 7.5 Hz, 1H), 4.36 (dd, *J* = 12.7, 4.6 Hz, 1H), 4.23 – 4.10 (m, 2H), 3.70 – 3.60 (m, 2H), 3.54 – 3.51 (m, 1H), 2.72 (ddd, *J* = 15.8, 5.1, 1.7 Hz, 1H), 2.65 (ddd, *J* = 15.2, 4.6, 1.7 Hz, 1H), 1.16 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 206.1, 201.6, 171.5, 150.6, 147.4, 138.9, 136.3, 135.2, 130.7, 128.7, 126.8, 125.3, 124.4, 123.5, 122.8, 64.1, 61.9, 47.7, 47.1, 42.4, 39.4, 13.8 ppm. **IR** (KBr): *ν* = 3076, 2983, 2935, 1724, 1679, 1586, 1527, 1449, 1347, 1308, 1278, 1222, 1189, 1147, 1099, 1018, 905, 806, 746 cm^{-1}. **HRMS** (ESI) m/z: $[M+Na]^+$ calcd for $C_{22}H_{19}O_6NNaS^+$ 448.0826; found 448.0825.

Ethyl (2*S*,2'*S*,6'*S*)-6'-(2-nitrophenyl)-3,4'-dioxo-3*H*-spiro[benzo[*b*]thiophene-2,1'-cyclohexane]-2'-carboxylate (3ae)

The title compound was synthesized according to the general procedure GP5 (reaction time: 36 hours), affording the product as a 26.5/7.4/1 diastereomeric mixture, with a yield of 41 mg (96%). The major diastereomer, yellowish wax, was separated with a yield of 20 mg (47%) and 86% *ee* (IA column, *n*-heptane:*i*-PrOH = 80:20; t_R = 15.9 (minor.), 19.5 (major.) min), $[\alpha]_D$ = +141.4° (c 0.49; $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.72 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.64 – 7.62 (m, 1H), 7.47 – 7.43 (m, 1H), 7.39 – 7.35 (m, 1H), 7.31 – 7.25 (m, 2H), 7.21 (d, *J* = 7.9 Hz, 1H), 7.16 – 7.12 (m, 1H), 5.17 (dd, *J* = 10.3, 5.2 Hz, 1H), 4.16 – 4.08 (m, 2H), 3.55 – 3.43 (m, 3H), 2.84 – 2.74 (m, 2H), 1.10 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 206.2, 201.6, 170.5, 150.7, 150.3, 136.1, 132.2, 131.9, 130.8, 129.4, 128.5, 126.7, 125.3, 124.7, 123.7, 64.5, 62.0, 47.4, 42.7, 40.8, 39.7, 13.7 ppm. **IR** (KBr): *ν* = 3085, 2989, 2926, 1718, 1679, 1583, 1530, 1446, 1353, 1278, 1222, 1180, 1156, 1138, 1015, 851, 756 cm^{-1}. **HRMS** (ESI) m/z: $[M+Na]^+$ calcd for $C_{22}H_{19}O_6NNaS^+$ 448.0825; found 448.0825.

Ethyl (2*S*,2'*S*,6'*S*)-3,4'-dioxo-6'-(4-(trifluoromethyl)phenyl)-3*H*-spiro[benzo[*b*]thiophene-2,1'-cyclohexane]-2'-carboxylate (3af)

The title compound was synthesized according to the general procedure GP5 (reaction time: 36 hours), affording the product as a 10.1/2.1/1 diastereomeric mixture, with a yield of 43 mg (95%). The major diastereomer, a white foam, was separated with a yield of 28 mg (63%) and 90% *ee* (IA column, *n*-heptane:*i*-PrOH = 90:10; t_R = 14.8 (major.), 17.5 (minor.) min), $[\alpha]_D$ = -27.5° (c 0.46; $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 7.8 Hz, 1H), 7.45 – 7.41 (m, 1H), 7.37 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.3 Hz, 2H), 7.17 (d, *J* = 7.9 Hz, 1H), 7.11 (t, *J* = 7.5 Hz, 1H), 4.23 (dd, *J* = 12.2, 4.6 Hz, 1H), 4.20 – 4.07 (m, 2H), 3.64 – 3.53 (m, 3H), 2.75 – 2.69 (m, 1H), 2.66 (dd, *J* = 15.3, 4.6 Hz, 1H), 1.12 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 206.6, 201.6, 171.4, 150.6, 141.0, 136.1, 130.7, 129.9 (q, *J* = 32.3 Hz, 1C), 129.7 (2C), 126.8, 125.2, 124.7 (q, *J* = 3.8 Hz, 2C), 123.8 (q, *J* = 272.7 Hz, 1C), 123.6, 64.5, 61.7, 47.6, 47.5, 42.8, 39.4, 13.8 ppm. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.75 (s, 3F) ppm. **IR** (KBr): *ν* = 3064, 2956, 2920, 1730, 1682, 1586, 1452, 1419, 1329, 1281, 1171, 1126, 1069, 1018, 833, 767 cm^{-1}. **HRMS** (ESI) m/z: $[M+Na]^+$ calcd for $C_{23}H_{19}O_4F_3NaS^+$ 471.0844; found 471.0848.

Ethyl (2*S*,2'*S*,6'*S*)-2'-(4-bromophenyl)-3,4'-dioxo-3*H*-spiro[benzo[*b*]thiophene-2,1'-cyclohexane]-6'-carboxylate (3ag)

The title compound was synthesized according to the general procedure GP5 (reaction time: 36 hours), affording the product as a 13.8/1.9/1 diastereomeric mixture, with a yield of 44 mg (96%). The major diastereomer, a yellowish wax, was separated with a yield of 29 mg (62%) and 93% *ee* (IB column, *n*-heptane:*i*-PrOH = 80:20; t_R = 9.4 (major.), 10.8 (minor.) min), $[\alpha]_D$ = -32.2° (c 0.45; $CHCl_3$). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.61 (d, *J* = 7.7 Hz, 1H), 7.45 – 7.42 (m, 1H), 7.23 (d, *J* = 8.5 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 7.04 (d, *J* = 8.5 Hz, 2H), 4.15 – 4.08 (m, 3H), 3.57 – 3.50 (m, 3H), 2.72 – 2.67 (m, 1H), 2.63 (ddd, *J* = 15.4, 4.6, 1.3 Hz, 1H), 1.09 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C{^{1}H} NMR** (151 MHz, $CDCl_3$) δ 206.9, 201.7, 171.3, 150.7, 136.1, 135.9, 130.9 (2C+2C *overlapped*), 130.7, 126.7, 125.1, 123.5, 121.7, 64.6, 61.7, 47.5, 47.1, 43.0, 39.3, 13.8 ppm. **IR** (KBr): ν = 3067, 2989, 2905, 1727, 1673, 1583, 1485, 1446, 1332, 1281, 1216, 1186, 1150, 1009, 869, 824 cm^{-1}. **HRMS** (ESI) m/z: $[M+Na]^+$ calcd for $C_{22}H_{19}O_4BrNaS^+$ 481.0080; found 481.0081.

Ethyl (2*S*,2'*S*,6'*S*)-3,4'-dioxo-6'-(*p*-tolyl)-3*H*-spiro[benzo[*b*]thiophene-2,1'-cyclohexane]-2'-carboxylate (3ah)

The title compound was synthesized according to the general procedure GP5 (reaction time: 36 hours), affording the product as a 12.7/1.2/1 diastereomeric mixture, with a yield of 38 mg (95%). The major diastereomer, an off-white wax, was separated with a yield of 30 mg (75%) and 96% *ee* (IC column, *n*-heptane:*i*-PrOH = 80:20; t_R = 18.1 (minor.), 22.0 (major.) min), $[\alpha]_D$ = -34.0° (c 0.53; $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 9.2 Hz, 1H), 7.44 – 7.41 (m, 1H), 7.20 (d, *J* = 8.1 Hz, 1H), 7.13 – 7.09 (m, 1H), 7.01 (d, *J* = 8.2 Hz, 2H), 6.93 (d, *J* = 7.7 Hz, 2H), 4.15 – 4.05 (m, 2H), 4.01 (dd, *J* = 11.4, 5.2 Hz, 1H), 3.62 – 3.58 (m, 1H), 3.54 – 3.45 (m, 2H), 2.75 – 2.68 (m, 2H), 2.19 (s, 3H), 1.07 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 207.6, 201.7, 171.2, 150.7, 137.3, 135.7, 134.0, 130.9, 129.1 (2C), 128.6 (2C), 126.7, 124.9, 123.5, 65.2, 61.5, 47.8, 47.2, 43.6, 39.6, 20.9, 13.7 ppm. **IR** (KBr): *ν* = 3058, 2980, 2929, 1718, 1679, 1586, 1512, 1449, 1308, 1281, 1216, 1189, 1150, 1060, 1024, 869, 737 cm^{-1}. **HRMS** (ESI) m/z: $[M+Na]^+$ calcd for $C_{23}H_{22}O_4NaS^+$ 417.1131; found 417.1132.

Ethyl (2*R*,2'*S*,6'*S*)-3,4'-dioxo-6'-(thiophen-2-yl)-3*H*-spiro[benzo[*b*]thiophene-2,1'-cyclohexane]-2'-carboxylate (3ai)

The title compound was synthesized according to the general procedure GP5 (reaction time: 36 hours), affording the product as a 9.6/1.3/1 diastereomeric mixture, with a yield of 36 mg (93%). The major diastereomer, a yellow wax, was separated with a yield of 27 mg (69%) and 95% *ee* (IC column, *n*-heptane:*i*-PrOH = 80:20; t_R = 18.5 (minor.), 21.4 (major.) min), $[\alpha]_D$ = -20.8° (c 0.51; $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.64 (dd, *J* = 7.8, 0.7 Hz, 1H), 7.49 – 7.45 (m, 1H), 7.27 – 7.25 (m, 1H), 7.14 (t, *J* = 7.5 Hz, 1H), 7.02 (dd, *J* = 5.1, 1.2 Hz, 1H), 6.85 – 6.84 (m, 1H), 6.77 (dd, *J* = 5.1, 3.5 Hz, 1H), 4.43 (dd, *J* = 11.5, 4.9 Hz, 1H), 4.18 – 4.06 (m, 2H), 3.60 – 3.47 (m, 3H), 2.81 (ddd, *J* = 15.3, 4.9, 1.5 Hz, 1H), 2.68 (ddd, *J* = 15.8, 6.1, 1.5 Hz, 1H), 1.11 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 206.3, 201.5, 171.3, 150.9, 139.8, 135.9, 130.7, 126.9, 126.9, 126.2, 125.1, 124.7, 123.6, 64.7, 61.7, 47.6, 44.7, 43.4, 39.3, 13.8 ppm. **IR** (KBr): *ν* = 3064, 2980, 2929, 1721, 1682, 1583, 1446, 1371, 1332, 1284, 1192, 1120, 1063, 1021, 878, 740 cm^{-1}. **HRMS** (ESI) m/z: $[M+Na]^+$ calcd for $C_{20}H_{18}O_4NaS_2^+$ 409.0539; found 409.0541.

Ethyl (2*S*,2'*S*,6'*S*)-2'-(benzo[b]thiophen-5-yl)-3,4'-dioxo-3*H*-spiro[benzo[*b*]thiophene-2,1'-cyclohexane]-6'-carboxylate (3aj)

The title compound was synthesized according to the general procedure GP5 (reaction time: 36 hours), affording the product as a 5.5/1.1/1 diastereomeric mixture, with a yield of 41 mg (94%). The major diastereomer, a yellow wax, was separated with a yield of 24 mg (55%) and 95% *ee* (IC column, *n*-heptane:*i*-PrOH = 80:20; t_R = 23.6 (minor.), 26.1 (major.) min), $[\alpha]_D$ = -56.4° (c 1.14; $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.62 – 7.60 (m, 3H), 7.38 – 7.34 (m, 2H), 7.21 (d, *J* = 4.6 Hz, 1H), 7.14 (d, *J* = 8.1 Hz, 2H), 7.05 (t, *J* = 7.5 Hz, 1H), 4.24 (dd, *J* = 11.7, 4.6 Hz, 1H), 4.18 – 4.06 (m, 2H), 3.69 – 3.53 (m, 3H), 2.74 (dd, *J* = 16.1, 5.2 Hz, 2H), 1.10 (t, *J* = 7.2 Hz, 3H) ppm. **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 207.4, 201.9, 171.4, 150.8, 139.2, 139.0, 135.8, 133.3, 130.8, 126.7, 126.6, 125.6, 124.9, 124.3, 123.8, 123.5, 121.8, 65.2, 61.6, 47.8, 47.6, 43.7, 39.5, 13.8 ppm. **IR** (KBr): *v* = 3067, 2977, 2926, 1724, 1682, 1586, 1449, 1419, 1371, 1278, 1213, 1183, 1156, 1051, 1018, 899, 815, 740, 704 cm^{-1}. **HRMS** (ESI) m/z: $[M+Na]^+$ calcd for $C_{24}H_{20}O_4NaS_2^+$ 459.0693; found 459.0695.

(2*S*,2'*S*,6'*S*)-2'-Benzoyl-6'-phenyl-3*H*-spiro[benzo[*b*]thiophene-2,1'-cyclohexane]-3,4'-dione (3da)

The title compound was synthesized according to the general procedure GP5 (reaction time: 36 hours), affording the product as a 22.8/3.4/1 diastereomeric mixture, with a yield of 37 mg (90%). The major diastereomer, a yellow-orange wax, was separated with a yield of 15 mg (36%) and 85% *ee* (IA column, *n*-heptane:*i*-PrOH = 80:20; t_R = 10.1 (major.), 12.3 (minor.) min), $[\alpha]_D$ = -110.7° (c 0.28; $CHCl_3$). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.88 (d, *J* = 7.0 Hz, 2H), 7.64 (d, *J* = 7.8 Hz, 1H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.8 Hz, 2H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.25 (d, *J* = 6.9 Hz, 2H), 7.10 – 7.03 (m, 5H), 4.54 (dd, *J* = 13.0, 4.8 Hz, 1H), 4.43 (dd, *J* = 7.5, 2.8 Hz, 1H), 3.84 – 3.75 (m, 2H), 2.68 (dd, *J* = 14.9, 2.9 Hz, 1H), 2.56 (d, *J* = 15.3 Hz, 1H) ppm. **^{13}C{^{1}H} NMR** (151 MHz, $CDCl_3$) δ 207.1, 203.0, 199.9, 151.4, 137.0, 135.9, 135.4, 133.9, 131.1, 129.5 (2C), 128.9 (4C), 127.6 (3C), 126.6, 124.8, 123.5, 64.6, 48.0, 47.5, 43.0, 39.5 ppm. **IR** (KBr): *v* = 3058, 3028, 2956, 2920, 1718, 1676, 1586, 1449, 1308, 1278, 1222, 1201, 1180, 1078, 1006, 985, 758 cm^{-1}. **HRMS** (ESI) m/z: $[M+Na]^+$ calcd for $C_{26}H_{20}O_3NaS^+$ 435.1025; found 435.1026.

Methyl (2*S*,2'*S*,6'*S*)-3,4'-dioxo-6'-phenyl-3*H*-spiro[benzo[*b*]thiophene-2,1'-cyclohexane]-2'-carboxylate (3ea)

The title compound was synthesized according to the general procedure GP5 (reaction time: 36 hours), affording the product as a 44.9/4.1/1 diastereomeric mixture, with a yield of 33 mg (90%). The major diastereomer, a yellow wax, was separated with a yield of 25 mg (68%) and 95% *ee* (IA column, *n*-heptane:*i*-PrOH = 90:10; t_R = 12.1 (minor.), 14.5 (major.) min), $[\alpha]_D$ = -33.6° (c 0.60; $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 7.8 Hz, 1H), 7.42 – 7.38 (m, 1H), 7.17 – 7.07 (m, 7H), 4.12 (dd, *J* = 11.8, 4.7 Hz, 1H), 3.66 (s, 3H), 3.62 – 3.53 (m, 3H), 2.75 – 2.66 (m, 2H) ppm. **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 207.3, 201.8, 172.0, 150.7, 136.9, 135.8, 130.8, 129.3 (2C), 127.8 (2C), 127.7, 126.7, 124.9, 123.5, 64.8, 52.4, 47.9, 47.5, 43.2, 39.5 ppm. **IR** (KBr): *v* = 3094, 3058, 3025, 2956, 2905, 1721, 1676, 1586, 1446, 1428, 1362, 1284, 1204, 1174, 1153, 1054, 994, 887 cm^{-1}. **HRMS** (ESI) m/z: $[M+Na]^+$ calcd for $C_{21}H_{18}O_4NaS^+$ = 389.0818; found 389.0820.

Allyl (2*S*,2'*S*,6'*S*)-3,4'-dioxo-6'-phenyl-3*H*-spiro[benzo[*b*]thiophene-2,1'-cyclohexane]-2'-carboxylate (3fa)

The title compound was synthesized according to the general procedure GP5 (reaction time: 36 hours), affording the product as a 14.6/2.0/1 diastereomeric mixture, with a yield of 38 mg (96%). The major diastereomer, a yellowish wax, was separated with a yield of 22 mg (57%) and 95% *ee* (IA column, *n*-heptane:*i*-PrOH = 90:10; t_R = 12.0 (minor.), 14.1 (major.) min), $[\alpha]_D$ = -35.8° (c 0.69; $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.8 Hz, 1H), 7.42 – 7.38 (m, 1H), 7.18 – 7.07 (m, 7H), 5.77 – 5.67 (m, 1H), 5.22 (dd, *J* = 17.2, 1.4 Hz, 1H), 5.16 (dd, *J* = 10.4, 1.2 Hz, 1H), 4.55 (dt, *J* = 5.9, 1.3 Hz, 2H), 4.09 (dd, *J* = 11.8, 4.7 Hz, 1H), 3.65 – 3.52 (m, 3H), 2.77 – 2.67 (m, 2H) ppm. **^{13}C{^{1}H} NMR** (151 MHz, $CDCl_3$) δ 207.3, 201.7, 171.1, 150.7, 136.8, 135.8, 131.0, 130.9, 129.3 (2C), 127.8 (2C), 127.7, 126.7, 124.9, 123.5, 119.2, 66.2, 64.9, 48.0, 47.5, 43.2, 39.5 ppm. **IR** (KBr): *v* = 3061, 3025, 2956, 2920, 1718, 1679, 1586, 1449, 1422, 1332, 1308, 1284, 1263, 1216, 1177, 1150, 1075, 988, 934, 761 cm^{-1}. **HRMS** (ESI) m/z: $[M+Na]^+$ calcd for $C_{23}H_{20}O_4NaS^+$ 415.0975; found 415.0975.

(2*S*,2'*S*,6'*S*)-3,4'-Dioxo-6'-phenyl-3*H*-spiro[benzo[*b*]thiophene-2,1'-cyclohexane]-2'-carbonitrile (3ga)

The title compound was synthesized according to the general procedure GP5 (reaction time: 36 hours), affording the product as a 16.7/1/0 diastereomeric mixture, with a yield of 32 mg (96%). The major diastereomer, a yellow foam, was separated with a yield of 19 mg (57%) and 97% *ee* (IC column, *n*-heptane:*i*-PrOH = 60:40; t_R = 17.5 (major.), 26.0 (minor.) min), $[\alpha]_D$ = +10.3° (c 0.44; $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.69 – 7.67 (m, 1H), 7.49 – 7.45 (m, 1H), 7.21 – 7.10 (m, 7H), 3.85 (dd, *J* = 11.7, 5.0 Hz, 1H), 3.71 – 3.59 (m, 3H), 2.82 – 2.75 (m, 2H) ppm. **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 203.7, 200.3, 150.1, 136.7, 136.2, 130.6, 128.8 (2C), 128.2, 128.1 (2C), 127.0, 125.6, 123.8, 118.2, 64.1, 48.8, 43.2, 39.6, 36.8 ppm. **IR** (KBr): *v* = 3061, 3025, 2926, 2241, 1715, 1682, 1586, 1449, 1407, 1329, 1311, 1278, 1219, 1156, 1081, 1018, 967, 887, 758 cm^{-1}. **HRMS** (ESI) m/z: $[M+Na]^+$ calcd for $C_{20}H_{15}O_2NNaS^+$ 356.0716; found 356.0717.

Ethyl (2*S*,2'*S*,6'*S*)-5-bromo-3,4'-dioxo-6'-phenyl-3*H*-spiro[benzo[*b*]thiophene-2,1'-cyclohexane]-2'-carboxylate (3ha)

The title compound was synthesized according to the general procedure GP5 (reaction time: 36 hours), affording the product as a 1.3/1.3/1 diastereomeric mixture, with a yield of 44 mg (96%). The major diastereomer, an off-white foam, was separated with a yield of 17 mg (36%) and 92% *ee* (IA column, *n*-heptane:*i*-PrOH = 80:20; t_R = 8.6 (major.), 9.6 (minor.) min), $[\alpha]_D$ = -8.8° (c 0.46; $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 2.0 Hz, 1H), 7.50 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.16 – 7.10 (m, 5H), 7.07 (d, *J* = 8.4 Hz, 1H), 4.15 – 4.08 (m, 2H), 4.05 (dd, *J* = 11.4, 4.8 Hz, 1H), 3.60 (t, *J* = 6.5 Hz, 1H), 3.54 – 3.46 (m, 2H), 2.75 – 2.68 (m, 2H), 1.11 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 207.0, 200.4, 171.1, 149.5, 138.4, 136.5, 132.5, 129.22, 129.18 (2C), 128.0 (2C), 127.9, 124.9, 118.5, 66.1, 61.7, 48.1, 47.2, 43.2, 39.5, 13.8 ppm. **IR** (KBr): *v* = 3064, 2977, 2926, 1721, 1676, 1583, 1446, 1407, 1368, 1290, 1251, 1195, 1144, 1084, 1018, 872, 701 cm^{-1}. **HRMS** (ESI) m/z: $[M+Na]^+$ calcd for $C_{22}H_{19}O_4BrNaS^+$ 481.0076; found 481.0080.

Ethyl (2*S*,2'*S*,6'*S*)-5-methyl-3,4'-dioxo-6'-phenyl-3*H*-spiro[benzo[*b*]thiophene-2,1'-cyclohexane]-2'-carboxylate (3ia)

The title compound was synthesized according to the general procedure GP5 (reaction time: 36 hours), affording the product as a 10.1/2.0/1 diastereomeric mixture, with a yield of 38 mg (96%). The major diastereomer, a yellowish wax, was separated with a yield of 19 mg (48%) and 92% *ee* (IA column, *n*-heptane:*i*-PrOH = 80:20; t_R = 16.2 (major.), 17.2 (minor.) min), $[\alpha]_D$ = -22.1°

(c 0.91; $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42 (s, 1H), 7.23 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.14 – 7.09 (m, 5H), 7.07 (d, *J* = 8.1 Hz, 1H), 4.16 – 4.04 (m, 3H), 3.60 – 3.47 (m, 3H), 2.74 – 2.68 (m, 2H), 2.28 (s, 3H), 1.09 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 207.5, 201.7, 171.3, 147.7, 137.1, 137.1, 134.9, 131.0, 129.3 (2C), 127.8 (2C), 127.6, 126.6, 123.2, 65.3, 61.5, 48.0, 47.4, 43.4, 39.5, 20.7, 13.8 ppm. **IR** (KBr): *ν* = 3061, 3031, 2977, 2926, 1724, 1682, 1601, 1562, 1470, 1413, 1371, 1275, 1186, 1144, 1090, 1048, 1024, 818, 755 cm^{-1}. **HRMS** (ESI) m/z: $[M+Na]^+$ calcd for $C_{23}H_{22}O_4NaS^+$ 417.1132; found 417.1131.

Ethyl (2*S*,2'*S*,6'*S*)-4-methyl-3,4'-dioxo-6'-phenyl-3*H*-spiro[benzo[*b*]thiophene-2,1'-cyclohexane]-2'-carboxylate (3ja)

The title compound was synthesized according to the general procedure GP5 (reaction time: 36 hours), affording the product as a 10.1/1.8/1 diastereomeric mixture, with a yield of 35 mg (88%). The major diastereomer, a yellow wax, was separated with a yield of 28 mg (70%) and 90% *ee* (IA column, *n*-heptane:*i*-PrOH = 80:20; t_R = 7.3 (minor.), 7.7 (major.) min), **$[\alpha]_D$** = -4.2° (c 1.32; $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.22 (t, *J* = 7.6 Hz, 1H), 7.15 – 7.07 (m, 5H), 6.99 (d, *J* = 7.9 Hz, 1H), 6.81 (d, *J* = 7.4 Hz, 1H), 4.13 – 3.97 (m, 2H), 3.99 (dd, *J* = 11.7, 4.6 Hz, 1H), 3.67 (dd, *J* = 7.7, 5.9 Hz, 1H), 3.55 – 3.45 (m, 2H), 2.76 – 2.65 (m, 2H), 2.50 (s, 3H), 1.04 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 207.7, 202.5, 171.2, 151.3, 141.7, 136.8, 134.6, 129.1 (2C), 128.0, 127.7 (2C), 127.6, 127.1, 121.0, 64.0, 61.4, 48.4, 47.2, 42.9, 39.5, 19.1, 13.7 ppm. **IR** (KBr): *ν* = 3061, 3031, 2977, 2923, 1718, 1676, 1586, 1571, 1461, 1413, 1374, 1293, 1260, 1228, 1180, 1147, 1051, 1015, 857, 773 cm^{-1}. **HRMS** (ESI) m/z: $[M+Na]^+$ calcd for $C_{23}H_{22}O_4NaS^+$ 417.1131; found 417.1128.

Ethyl (2*S*,2'*S*,6'*S*)-6-methyl-3,4'-dioxo-6'-phenyl-3*H*-spiro[benzo[*b*]thiophene-2,1'-cyclohexane]-2'-carboxylate (3ka)

The title compound was synthesized according to the general procedure GP5 (reaction time: 36 hours), affording the product as a 17.3/2.3/1 diastereomeric mixture, with a yield of 38 mg (96%). The major diastereomer, a yellow wax, was separated with a yield of 29 mg (73%) and 95% *ee* (IA column, *n*-heptane:*i*-PrOH = 80:20; t_R = 8.2 (minor.), 9.8 (major.) min), **$[\alpha]_D$** = -39.9° (c 1.36; $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.0 Hz, 1H), 7.17 – 7.09 (m, 5H), 6.96 (s, 1H), 6.89 (d, *J* = 8.0 Hz, 1H), 4.17 – 4.05 (m, 3H), 3.63 – 3.50 (m, 3H), 2.73 – 2.64 (m, 2H), 2.30 (s, 3H), 1.10 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 207.5, 201.2, 171.4, 151.1, 147.4, 137.1, 129.3 (2C), 128.7, 127.8 (2C), 127.6, 126.4, 126.4, 123.6, 65.0, 61.5, 47.9, 47.6, 43.3, 39.4, 22.0, 13.8 ppm. **IR** (KBr): *ν* = 3058, 3031, 2977, 2923, 1730, 1676, 1595, 1452, 1404, 1371, 1278, 1222, 1180, 1150, 1030, 887, 770, 701 cm^{-1}. **HRMS** (ESI) m/z: $[M+Na]^+$ calcd for $C_{23}H_{22}O_4NaS^+$ 417.1131; found 417.1127.

Ethyl (2*S*,2'*S*,6'*S*)-7-methyl-3,4'-dioxo-6'-phenyl-3*H*-spiro[benzo[*b*]thiophene-2,1'-cyclohexane]-2'-carboxylate (3la)

The title compound was synthesized according to the general procedure GP5 (reaction time: 36 hours), affording the product as a 9.4/1.6/1 diastereomeric mixture, with a yield of 37 mg (94%). The major diastereomer, a yellowish wax, was separated with a yield of 20 mg (51%) and 96% *ee* (IB column, *n*-heptane:*i*-PrOH = 80:20; t_R = 7.0 (minor.), 8.5 (major.) min), **$[\alpha]_D$** = -45.7° (c 0.99; $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 7.2 Hz, 1H), 7.22 (d, *J* = 7.3 Hz, 1H), 7.15 – 7.07 (m, 5H), 7.02 (t, *J* = 7.5 Hz, 1H), 4.18 – 4.05 (m, 3H), 3.61 – 3.51 (m, 3H), 2.76 – 2.68 (m, 2H), 2.18 (s, 3H), 1.08 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 207.5, 202.1, 171.3, 150.5, 136.9, 135.8, 132.7, 130.8, 129.2 (2C), 127.7 (2C), 127.6, 125.2, 124.1, 65.2, 61.5, 48.1, 47.3, 43.3, 39.6, 18.5, 13.7 ppm. **IR** (KBr): *ν* = 3067, 2974, 2920, 1721, 1679, 1571, 1473, 1452, 1407, 1269, 1180, 1150, 1048, 767 cm^{-1}. **HRMS** (ESI) m/z: $[M+Na]^+$ calcd for $C_{23}H_{22}O_4NaS^+$ 417.1135; found 417.1131.

Large scale synthesis of 3ea

The enone **2a** (1.324 g, 9.08 mmol) was added to a homogeneous solution of catalyst **I** (0.261 g, 0.91 mmol) and 4-nitrobenzoic acid (0.302 g, 1.82 mmol) in 1,4-dioxane (22.5 mL). The mixture was stirred for 10 minutes at room temperature. Then, the alkylidene derivative **1e** (1.008 g, 4.54 mmol) was added to the reaction mixture. The reaction was stirred for the indicated time. After completing the reaction (monitored on TLC), the solvent was evaporated under reduced pressure. Column chromatography of the residue on silica gel (hexanes/EtOAc) affording the product **3ea** as a 42.6/3.8/1 diastereomeric mixture, with a yield of 1.560 g (93%). The major diastereomer, a yellow wax, was separated with a yield of 1.057 g (63%) and 94% *ee*.

Physical and spectroscopic data corroborated with above mentioned experiment in small scale.

(2*S*,2'*R*,6'*S*)-3,4'-Dioxo-6'-phenyl-3*H*-spiro[benzo[*b*]thiophene-2,1'-cyclohexane]-2'-carboxylic acid (4''aa)

Following a slightly modified procedure[32], a solution of $LiOH{\cdot}nH_2O$ (105 mg, 2.50 mmol) in H_2O (1 mL) was added dropwise to a stirred solution of **3aa** (38.0 mg, 0.10 mmol) in THF (1 mL) at 0°C. The reaction mixture was vigorously stirred at room temperature until no starting material was present (monitored by TLC, approximately 2 h). Then, EtOAc (5 mL) and 1M HCl (4 mL) were added, and the aqueous phase was saturated with solid NaCl and extracted with EtOAc (3 × 5 ml). The organics were combined, dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography of the residue on silica gel (DCM/MeOH/AcOH: 200/2/1) furnished product as a 1.0/6.6/42.4 diastereomeric mixture, with a yield of 27 mg (77%). The major diastereomer of acid **4''aa**, a white wax, was separated with a yield of 17 mg (47%) and 82% *ee* (for HPLC analysis, the product was treated with an excess of a diethylether solution of diazomethane and compared with a diastereomeric mixture of methyl ester **3ea**; IA column, *n*-heptane:*i*-PrOH = 90:10; t_R = 25.4 (major.), 31.7 (minor.) min), **$[\alpha]_D$** = +25.8° (c 0.16; $CHCl_3$). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.6 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.19 – 7.15 (m, 3H), 7.02 – 6.96 (m, 4H), 3.91 – 3.89 (m, 1H), 3.64 (dd, *J* = 14.3, 3.1 Hz, 1H), 3.12 (t, *J* = 14.7 Hz, 1H), 3.02 – 3.00 (m, 1H), 2.79 (t, *J* = 14.7 Hz, 1H), 2.61 (d, *J* = 14.7 Hz, 1H) ppm. **^{13}C{^{1}H} NMR** (151 MHz, $CDCl_3$) δ 205.6, 201.6, 172.7, 149.9, 135.0, 134.9, 131.9, 128.8 (2C), 128.0, 127.5 (2C), 126.4, 125.0, 123.5, 68.5, 49.9, 49.3, 44.7, 41.0 ppm. **IR** (KBr): *ν* = 3159, 3058, 3028, 2956, 2920, 2851, 1739, 1705, 1586, 1446, 1365, 1308, 1284, 1225, 1195, 1132, 1066, 890, 842 cm^{-1}. **HRMS** (ESI) m/z: $[M+Na]^+$ calcd for $C_{20}H_{16}O_4NaS^+$ 375.0662; found 375.0663.

(2*S*,2'*S*,6'*S*)-3,4'-Dioxo-6'-phenyl-3*H*-spiro[benzo[*b*]thiophene-2,1'-cyclohexane]-2'-carboxylic acid (4aa)

Following a slightly modified procedure[33], pyrrolidine (7.5 mg, 0.105 mmol) was added dropwise to a stirred solution of **3fa** (39.2 mg, 0.10 mmol), Ph_3P (1.3 mg, 0.005 mmol) and $Pd(Ph_3P)_4$ (2.9 mg, 0.0025 mmol) in DCM (0.5 mL) at 0°C. The reaction mixture was stirred at room temperature until no starting material was present (monitored by TLC, approx. 1 h). Then, 1M HCl (4 mL) was added, and the organic phase was separated. The aqueous phase was extracted with EtOAc (3 × 5 ml), and the organics were combined, dried ($MgSO_4$) and concentrated under

reduced pressure. Column chromatography of the residue on silica gel (DCM/MeOH/AcOH: 200/2/1) furnished compound **4aa**, an off-white wax, with a yield of 32 mg (92%) and 95% *ee* (for HPLC analysis **4aa** was treated with an excess of a diethylether solution of diazomethane and compared with methyl ester **3ea**; IA column, *n*-heptane:*i*-PrOH = 90:10; t_R = 12.1 (minor.), 14.5 (major.) min), $[\alpha]_D$ = -30.3° (c 0.50; $CHCl_3$). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.62 (d, *J* = 7.7 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.17 – 7.14 (m, 3H), 7.13 – 7.08 (m, 4H), 4.11 (dd, *J* = 11.7, 4.7 Hz, 1H), 3.65 – 3.58 (m, 3H), 2.76 (dd, *J* = 15.5, 4.9 Hz, 1H), 2.70 (dd, *J* = 15.3, 4.5 Hz, 1H) ppm. **^{13}C{^{1}H} NMR** (151 MHz, $CDCl_3$) δ 207.6, 201.7, 175.1, 150.7, 136.8, 135.9, 130.8, 129.3 (2C), 127.8 (2C), 127.8, 126.8, 125.0, 123.6, 64.3, 47.9, 47.4, 43.2, 39.4 ppm. **IR** (KBr): *ν* = 3162, 3058, 3031, 2920, 2848, 1718, 1682, 1586, 1449, 1410, 1359, 1308, 1275, 1219, 1186, 1147, 1120, 1075, 890 cm^{-1}. **HRMS** (ESI) m/z: $[M+Na]^+$ calcd for $C_{20}H_{16}O_4NaS^+$ 375.0662; found 375.0664.

Ethyl (2*S*,2'*S*,6'*S*)-3,4'-dioxo-6'-phenyl-3*H*-spiro[benzo[*b*]thiophene-2,1'-cyclohexane]-2'-carboxylate 1-oxide (5a)

*m*CPBA (77% w/w, 24.6 mg, 0.11 mmol) was added to a stirred solution of **3aa** (38.0 mg, 0.10 mmol) in DCM (2 mL) at room temperature. The reaction mixture was stirred at the same temperature until no starting material was present (monitored by TLC, for approximately 1 h). Then, DCM (5 mL) was added, and the organic phase was washed with saturated $NaHCO_3$ (2 × 5 ml), dried (Na_2SO_4) and concentrated under reduced pressure. Column chromatography of the residue on silica gel (hexanes/EtOAc: 2/1 → 1/1) furnished compound **5a**, a white wax, with a yield of 31 mg (79%) and 95% *ee* (the racemic mixture for HPLC analysis was prepared under the same conditions from the racemate of compound **3aa**; our attempts to prepare (by oxidation of **3aa** with H_2O_2 in AcOH) an equimolar mixture of sulfoxide diastereomers (contrary configurations on sulfur atom) gave inconsistent results due to the instability of the second diastereomer on silica gel or chiral stationary phase; IA column, *n*-heptane:*i*-PrOH = 70:30; t_R = 11.7 (minor.), 18.0 (major.) min), $[\alpha]_D$ = +59.4° (c 0.35; $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.6 Hz, 1H), 7.63 (dd, *J* = 6.4, 1.3 Hz, 2H), 7.58 – 7.54 (m, 1H), 7.03 – 6.96 (m, 5H), 4.97 (dd, *J* = 13.3, 4.6 Hz, 1H), 4.31 – 4.18 (m, 2H), 3.86 (dd, *J* = 15.3, 7.9 Hz, 1H), 3.53 (dd, *J* = 7.8, 2.6 Hz, 1H), 3.40 (dd, *J* = 14.7, 13.2 Hz, 1H), 2.84 (dt, *J* = 15.4, 2.2 Hz, 1H), 2.65 (ddd, *J* = 14.7, 4.6, 1.8 Hz, 1H), 1.28 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 206.9, 200.5, 172.7, 149.9, 136.5, 135.7, 134.7, 132.8, 128.44 (2C), 128.39 (2C), 128.3, 127.4, 126.0, 72.8, 61.9, 44.3, 43.5, 42.9, 40.6, 13.9 ppm. **IR** (KBr): *ν* = 3061, 3031, 2977, 2932, 1724, 1697, 1586, 1452, 1371, 1329, 1275, 1225, 1186, 1147, 1066, 1042, 979, 872, 758 cm^{-1}. **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{22}H_{21}O_5S^+$ 397.1104; found 397.1111.

Ethyl (2*S*,2'*S*,6'*S*)-3,4'-dioxo-6'-phenyl-3*H*-spiro[benzo[*b*]thiophene-2,1'-cyclohexane]-2'-carboxylate 1,1-dioxide (6a)

*m*CPBA (77% w/w, 49.3 mg, 0.22 mmol) was added to a stirred solution of **3aa** (38.0 mg, 0.10 mmol) in DCM (2 mL) at room temperature. The reaction mixture was stirred at the same temperature until no sulfoxide **5a** was present (monitored by TLC, approx. 30 h). Then, DCM (5 mL) was added, and the organic phase was washed with saturated $NaHCO_3$ (2 × 5 ml), dried (Na_2SO_4) and concentrated under reduced pressure. Column chromatography of the residue on silica gel (hexanes/EtOAc: 2/1) furnished compound **6a**, a transparent wax, with a yield of 31 mg (75%) and 95% *ee* (IA column, *n*-heptane:*i*-PrOH = 70:30; t_R = 13.4 (minor.), 18.4 (major.) min), $[\alpha]_D$ = -106.7° (c 0.30; $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.94 – 7.92 (m, 1H), 7.88 – 7.84 (m, 2H), 7.75 – 7.71 (m, 1H), 7.16 – 7.15 (m, 3H), 7.03 – 7.00 (m, 2H), 4.38 (dd, *J* = 7.8, 5.8 Hz, 1H), 4.04 (q, *J* = 7.1 Hz, 2H), 3.98 (dd, *J* = 11.0, 5.2 Hz, 1H), 3.46 (dd, *J* = 17.0, 5.2 Hz, 1H), 3.17 (dd, *J* = 16.0, 5.8 Hz, 1H), 3.08 (dd, *J* = 17.1, 11.0 Hz, 1H), 3.04 (dd, *J* = 16.0, 7.7 Hz, 1H), 0.99 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 206.4, 190.9, 169.7, 144.5, 137.0, 136.7, 134.2, 132.3, 129.4 (2C), 128.3 (2C), 128.0, 124.4, 121.6, 70.0, 62.0, 44.4, 44.3, 43.7, 39.2, 13.4 ppm. **IR** (KBr): *ν* = 3064, 3028, 2980, 2923, 1727, 1583, 1455, 1419, 1305, 1225, 1186, 1153, 1018, 884, 764 cm^{-1}. **HRMS** (ESI) m/z: $[M+Na]^+$ calcd for $C_{22}H_{20}O_6NaS^+$ 435.0873; found 435.0877.

Ethyl (2*S*,2'*S*,6'*S*)-3,4'-dioxo-6'-phenyl-5-(*p*-tolyl)-3*H*-spiro[benzo[*b*]thiophene-2,1'-cyclohexane]-2'-carboxylate (7a)

p-Tolyl boronic acid (8.2 mg, 0.06 mmol), **3ha** (23.0 mg, 0.05 mmol), [1,1′-bis(diphenylphosphino)ferrocene]dichloro palladium(II) (3.7 mg, 0.005 mmol), and anhydrous KOAc (19.6 mg, 0.20 mmol) were added to a flame-dried Schlenk flask under a stream of argon, dissolved in dry 1,4-dioxane (0.5 mL). The mixture was carefully degassed in three vacuum-argon cycles. The reaction mixture was stirred at 110°C under argon atmosphere overnight. Then, the reaction mixture was filtered through a plug of cotton wool. The organic phase was concentrated under reduced pressure. Column chromatography of the residue on silica gel (hexanes/EtOAc: 10/1) furnished compound **7a**, a white solid, with a yield of 23 mg (97%) and 92% *ee* (IA column, *n*-heptane:*i*-PrOH = 80:20; t_R = 12.1 (major.), 14.5 (minor.) min), $[\alpha]_D$ = +30.0° (c 0.20; $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 1.3 Hz, 1H), 7.67 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.43 (d, *J* = 8.2 Hz, 2H), 7.25 – 7.23 (m, 3H), 7.18 – 7.09 (m, 5H), 4.18 – 4.06 (m, 3H), 3.66 – 3.50 (m, 3H), 2.77 – 2.71 (m, 2H), 2.39 (s, 3H), 1.10 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 207.5, 201.7, 171.3, 149.3, 138.3, 137.8, 137.0, 136.2, 134.6, 131.5, 129.7 (2C), 129.3 (2C), 127.9 (2C), 127.8, 126.6 (2C), 124.4, 123.8, 65.8, 61.6, 48.2, 47.4, 43.4, 39.6, 21.1, 13.8 ppm. **IR** (KBr): *ν* = 3031, 2977, 2920, 1730, 1700, 1682, 1598, 1464, 1422, 1374, 1263, 1189, 1144, 1093, 1024, 911, 812, 749 cm^{-1}. **HRMS** (ESI) m/z: $[M+Na]^+$ calcd for $C_{29}H_{26}O_4NaS^+$ 493.1444; found 493.1441.

ASSOCIATED CONTENT

Supporting Information

Spectral data for all prepared compounds with copies of the ^{1}H NMR, ^{13}C NMR and ^{19}F NMR and HPLC chromatograms are available online from http://xxxxxxxxxx.
CIF file for compound **3ag**. (CIF)

Accession codes

CCDC 1978776 contains the supplementary crystallographic data of this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

AUTHOR INFORMATION

Corresponding Author

* E-mail: jan.vesely@natur.cuni.cz

ORCID

Jan Veselý: orcid.org/0000-0001-5198-8950

Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

Jan Veselý gratefully acknowledges the Czech Science Foundation (No 20-29336S) for the financial support. Bedřich Formánek thanks the Charles University Grant Agency (No 393615) for the financial support. We also thank Dr. Simona Petrželová and Jan Ulč for the NMR service provided, Dr. Martin Štícha for his MS analysis and Dr. Carlos V. Melo for proofreading the manuscript.

REFERENCES

(1) (a) Nudelman, A. *The Chemistry of Optically Active Sulfur Compounds*; Gordon and Breach: New York, 1984. (b) Damani, L. A. *Sulphur-Containing Drugs and Related Organic Compounds*; Wiley: NewYork, 1989. (c) Liu, H.; Jiang, X. Transfer of Sulfur: From Simple to Diverse *Chem.−Asian J.* **2013**, *8*, 2546−2563. (d) Feng, M.; Tang, B.; Liang, S.; Jiang, X. Sulfur Containing Scaffolds in Drugs: Synthesis and Application in Medicinal Chemistr *Curr. Top. Med. Chem.* **2016**, *16*, 1200−1216.

(2) Urquhart, L. Top drugs and companies by sales in 2018 *Nat. Rev. Drug Discov.* **2019**, *18*, 245.

(3) (a) Pedras, M. S. C.; Hossain, M.; Sarwar, M. G.; Montaut, S. Determination of the enantiomeric purity of the phytoalexins spirobrassinins by 1H NMR using chiral solvation *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5469−5471. (b) Suchý, M.; Kutschy, P.; Monde, K.; Goto, H.; Harada, N.; Takasugi, M.; Dzurilla, M.; Balentová, E. Synthesis, Absolute Configuration, and Enantiomeric Enrichment of a Cruciferous Oxindole Phytoalexin, (S)-(−)-Spirobrassinin, and Its Oxazoline Analog *J. Org. Chem.* **2001**, *66*, 3940−3947.

(4) (a) Nishida, I.; Kawaguchi, A.; Yamada, M. Effect of thiolactomycin on the individual enzymes of the fatty acid synthase system in Escherichia coli *J. Biochem.* **1986**, *99*,1447−1454. (b) Slayden, R. A.; Lee, R. E.; Armour, J. W.; Cooper, A.M.; Orme, I. M.; Brennan, P. J.; Besra, G. S. Antimycobacterial action of thiolactomycin: an inhibitor of fatty acid and mycolic acid synthesis *Antimicrob. Agents Ch.* **1996**, *40*, 2813−2819. (c) Heath, R. J.; White, S. W.; Rock, C. O. Lipid biosynthesis as a target for antibacterial agents *Prog. Lipid Res.* **2001**, *40*, 467−497. (d) Campbell, J. W.; Cronan, J. E. Bacterial fatty acid biosynthesis: Targets for antibacterial drug discovery *Annu. Rev. Microbiol.* **2001**, *55*, 305−332.

(5) Mohan, S.; Kerry, P. S.; Bance, N.; Niikura, M.; Pinto, B. M. Serendipitous Discovery of a Potent Influenza Virus A Neuraminidase Inhibitor *Angew. Chem., Int. Ed.* **2014**, *53*, 1076−1080.

(6) (a) Hegedus, L. L.; McCabe, R. W. *Catalyst Poisoning*; MarcelDekker: New York, 1984. (b) Hutton, A. T. *Comprehensive Coordination Chemistry*; Wilkinson, G., Gillard, R. D., McCleverty, J.A., Eds.; Pergamon: Oxford, U.K., 1984; 5, 1151.

(7) For recent review, see: Yu, J.-S.; Huang, H.-M.; Ding, P.-G.; Hu, X.-S.; Zhou, F.; Zhou, J. Catalytic Enantioselective Construction of Sulfur-Containing Tetrasubstituted Carbon Stereocenters *ACS Catal.* **2016**, *6*, 5319−5344 and references therein.

(8) Rios, R.; Sundén, H.; Ibrahem, I.; Zhao, G.-L.; Córdova, A. A one-pot organocatalytic asymmetric entry to tetrahydrothioxanthenones *Tetrahedron Lett.* **2006**, *47*, 8679−8682.

(9) (a) Su, Y.; Ling, J.-B.; Zhang, S.; Xu, P.-F. Organocatalytic Cascade Sulfa-Michael/Aldol Reaction of β,β-Disubstituted Enones: Enantioselective Synthesis of Tetrahydrothiophenes with a Trifluoromethylated Quaternary Center *J. Org. Chem.* **2013**, *78*, 11053−11058. (b) Chen, J.; Meng, S.; Wang, L.; Tang, H.; Huang, Y. Highly enantioselective sulfa-Michael addition reactions using N-heterocyclic carbene as a non-covalent organocatalyst *Chem. Sci.* **2015**, *6*, 4184−4189. (c) Tian, X.; Liu, Y.; Melchiorre, P. Aminocatalytic Enantioselective 1,6 Additions of Alkyl Thiols to Cyclic Dienones: Vinylogous Iminium Ion Activation *Angew. Chem., Int. Ed.* **2012**, *51*, 6439−6442. (d) Lu, H.-H.; Zhang, F.-G.; Meng, X.-G.; Duan, S.-W.; Xiao, W.-J. Enantioselective Michael Reactions of β,β-Disubstituted Nitroalkenes: A New Approach to $\beta^{2,2}$-Amino Acids with Hetero-Quaternary Stereocenters *Org. Lett.* **2009**, *11*, 3946−3949. (e) Chen, W.; Jing, Z.; Chin, K. F.; Qiao, B.; Zhao, Y.; Yan, L.; Tan, C.-H.; Jiang, Z. Catalytic asymmetric conjugate addition of mercaptans to β-substituted-β-trifluoromethyl oxazolidinone enoates: Access to chiral trifluoromethylated tertiary thioethers and thiols *Adv. Synth. Catal.* **2014**, *356*, 1292−1300.

(10) (a) Nakamura, S.; Takahashi, S.; Nakane, D.; Masuda, H. Organocatalytic Enantioselective Addition of Thiols to Ketimines Derived from Isatins *Org. Lett.* **2015**, *17*, 106−109. (b) Beceño, C.; Chauhan, P.; Rembiak, A.; Wang, A.; Enders, D. Bronsted Acid-Catalyzed Enantioselective Synthesis of Isatin-Derived N,S-Acetals *Adv. Synth. Catal.* **2015**, *357*, 672−676.

(11) For selected works, see: (a) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. Enantioselective organo-catalyzed α sulfenylation of aldehydes *Angew. Chem., Int. Ed.* **2005**, *44*, 794−797. (b) Lin, A.; Fang, L.; Zhu, X.; Zhu, C.; Cheng, Y. Organocatalytic Enantioselective Sulfenylation of β-Keto Phosphonates: A Convenient Approach to Construct Hetero-Quaternary Stereocenters *Adv. Synth. Catal.* **2011**, *353*, 545−549. (c) Shirakawa, S.; Tokuda, T.; Kasai, A.; Maruoka, K. Design of Chiral Bifunctional Quaternary Phosphonium Bromide Catalysts Possessing an Amide Moiety *Org. Lett.* **2013**, *15*, 3350−3353. (d) Huang, L.; Li, J.; Zhao, Y.; Ye, X.; Liu, Y.; Yan, L.; Tan, C.-H.; Liu, H.; Jiang, Z. Chiral Bicyclic Guanidine-Catalyzed Enantioselective Sulfenylation of Oxindoles and Benzofuran-2(3H)-ones *J. Org. Chem.* **2015**, *80*, 8933−8941.

(12) For selected works, see: (a) Fujiwara, Y.; Fu, G. C. Application of a New Chiral Phosphepine to the Catalytic Asymmetric Synthesis of Highly Functionalized Cyclopentenes That Bear an Array of Heteroatom-Substituted Quaternary Stereocenters *J. Am. Chem. Soc.* **2011**, *133*, 12293−12297. (b) Sakakura, A.; Yamada, H.; Ishihara, K. Enantioselective Diels-Alder Reaction of α-(Acylthio)acroleins: A New Entry to Sulfur-Containing Chiral Quaternary Carbons *Org. Lett.* **2012**, *14*, 2972−2975. (c) Wu, W.; Huang, H.; Yuan, X.; Zhu, K.; Ye, J. Asymmetric construction of spirocyclohexanonerhodanines catalyzed by simple diamine derived from chiral tert-leucine *Chem. Commun.* **2012**, *48*, 9180−9182. (d) Géant, P.-Y.; Urban, M.; Remeš, M.; Císařová, I.; Veselý, J. Enantioselective organocatalytic synthesis of sulfur-containing spirocyclic compounds *Eur. J. Org. Chem.* **2013**, *2013*, 7979−7988. (e) Zhou, F.; Zeng, X.-P.; Wang, C.; Zhao, X.-L.; Zhou, J. Organocatalytic asymmetric synthesis of 3,3-disubstituted oxindoles featuring two heteroatoms at the C3 position *Chem. Commun.* **2013**, *49*, 2022−2024. (f) Gao, W.-M.; Yu, J.-S.; Zhao, Y.-L.; Liu, Y.-L.; Zhou, F.; Wu, H.- H.; Zhou, J. Highly enantioselective Michael addition of 3-arylthio- and 3-(alkylthio)oxindoles to nitroolefins catalyzed by a simple cinchona alkaloid derived phosphoramide *Chem. Commun.* **2014**, *50*, 15179−15182. (g) Diosdado, S.; Etxabe, J.; Izquierdo, J.; Landa, A.; Mielgo, A.; Olaizola, I.; López, R.; Palomo, C. Catalytic Enantioselective Synthesis of Tertiary Thiols From 5H-Thiazol-4-ones and Nitroolefins: Bifunctional Ureidopeptide-Based Bronsted Base Catalysis *Angew. Chem., Int. Ed.* **2013**, *52*, 11846−11851. (h) Badiola, E.; Fiser, B.; Gómez-Bengoa, E.; Mielgo, A.; Olaizola, I.; Urruzuno, I.; García, J. M.; Odriozola, J. M.; Razkin, J.; Oiarbide, M.; Palomo, C. Enantioselective Construction of Tetrasubstituted Stereogenic Carbons through Bronsted Base Catalyzed Michael

Reactions: α'-Hydroxy Enones as Key Enoate Equivalent *J. Am. Chem. Soc.* **2014**, *136*, 17869−17881. (i) Wang, T.; Yu, Z.; Hoon, D. L.; Huang, K.-W.; Lan, Y.; Lu, Y. Highly enantioselective construction of tertiary thioethers and alcohols via phosphine-catalyzed asymmetric γ-addition reactions of 5H-thiazol-4-ones and 5H-oxazol-4-ones: scope and mechanistic understandings *Chem. Sci.* **2015**, *6*, 4912−4922.

(13) (a) Skrzynska, A.; Albrecht, A.; Albrecht, L. Aminocatalytic Strategy for the Synthesis of Optically Active Benzothiophene Derivatives *Adv. Synth. Catal.* **2016**, *358*, 2838−2844. (b) Saktura, M.; Joachim, B.; Grzelak, P.; Albrecht, L. Aromatizative Inverse-Electron-Demand Hetero-Diels-Alder Reaction in the Synthesis of Benzothiophene Derivatives *Eur. J. Org. Chem.* **2019**, *39*, 6592−6596.

(14) Selected examples demonstrating reactivity of such derivatives: (a) Zhang, Y.; Yu, A.; Jia, J.; Ma, S.; Li, K.; Wei, Y.; Meng, X. NaH promoted [4+3] annulation of crotonate-derived sulfur ylides with thioaurones: synthesis of 2,5-dihydrobenzo[4,5]thieno[3,2-b]oxepines *Chem. Commun.* **2017**, *53*, 10672-10675. (b) Jia, J.; Yu, A.; Ma, S.; Zhang, Y.; Li, K.; Meng, X. Solvent-Controlled Switchable Domino Reactions of MBH Carbonate: Synthesis of Benzothiophene Fused α-Pyran, 2,3-Dihydrooxepine, and Oxatricyclodecene Derivatives *Org. Lett.* **2017**, *19*, 6084-6087. (c) Li, K.; Yu, A.; Meng, X. Synthesis of Dibenzothiophene and 1,4-Dihydrodibenzothiophene Derivatives via Allylic Phosphonium Salt Initiated Domino Reactions *Org. Lett.* **2018**, *20*, 1106-1109. (d) Ding, W.; Yu, A.; Zhang, L.; Meng, X. Construction of Eight-Membered Cyclic Diaryl Sulfides via Domino Reaction of Arynes with Thioaurone Analogues and DFT Study on the Reaction Mechanism *Org. Lett.* **2019**, *21*, 9014-9018.

(15) Melchiorre, P. Cinchona-based Primary Amine Catalysis in the Asymmetric Functionalization of Carbonyl Compounds *Angew. Chem., Int. Ed.* **2012**, *51*, 9748-9770 and references therein.

(16) (a) Bencivenni, G.; Wu, L.-Y.; Mazzanti, A.; Giannichi, B.; Pesciaioli, F.; Song, M.-P.; Bartoli, G.; Melchiorre, P. Targeting Structural and Stereochemical Complexity by Organocascade Catalysis: Construction of Spirocyclic Oxindoles Having Multiple Stereocenters *Angew. Chem., Int. Ed.* **2009**, *48*, 7200−7203. (b) Cassani, C.; Tian, X.; Escudero-Adan, E. C.; Melchiorre, P. Multiple approaches to enantiopure spirocyclic benzofuranones using organocatalytic cascade reactions *Chem. Commun.* **2011**, *47*, 233−235. (c) Madhusudhan R., G.; Ko, C.-T.; Hsieh, K.-H.; Lee, C.-J.; Das, U.; Lin, W. Expanding the Scope of Primary Amine Catalysis: Stereoselective Synthesis of Indandione-Fused 2,6-Disubstituted trans-Spirocyclohexanones *J. Org. Chem.* **2016**, *81*, 2420-2431.

(17) Yu, F.; Hu, H.; Gu, X.; Ye, J. Asymmetric Michael Addition of Substituted Rhodanines to α,β-Unsaturated Ketones Catalyzed by Bulky Primary Amines *Org. Lett.* **2012**, *14*, 2038−2041.

(18) Li, J.; Luo, S.; Cheng, J.-P. Chiral Primary-Tertiary Diamine Catalysts Derived From Natural Amino Acids for syn-Aldol Reactions of Hydroxy Ketones *J. Org. Chem.* **2009**, *74*, 1747−1750.

(19) Vakulya, B.; Varga, S.; Csampai, A.; Soos, T. Highly enantioselective conjugate addition of nitromethane to chalcones using bifunctional cinchona organocatalysts *Org. Lett.* **2005**, *7*, 1967−1969.

(20) Hu, S.-S.; Zhang, L.; Li, J.-Y.; Luo, S.-Z.; Cheng, J.-P. Chiral Primary Amine Catalyzed Asymmetric Direct Cross-Aldol Reaction of Acetaldehyde *Eur. J. Org. Chem.* **2011**, *18*, 3347−3352.

(21) Huang, A.; Kodanko, J. J.; Overman, L. E. Chiral Primary Amine Catalyzed Asymmetric Direct Cross-Aldol Reaction of Acetaldehyde *J. Am. Chem. Soc.* **2004**, *126*, 14043−14053.

(22) Zheng, G.; Ma, X.; Liu, Y.; Dong, B.; Wang, M. Iodine-Catalyzed Intramolecular Oxidative Thiolation of Vinylic Carbon-Hydrogen Bonds via Tandem Iodocyclization and Dehydroiodination: Construction of 2-Methylene-3-thiophenones *Adv. Synth. Catal.* **2014**, *356*, 743−748.

(23) Nguyen, T. B.; Retailleau, P. Cooperative Activating Effect of Tertiary Amine/DMSO on Elemental Sulfur: Direct Access to Thioaurones from 2'-Nitrochalcones under Mild Conditions *Org. Lett.* **2018**, *20*, 186−189.

(24) Ono, N.; Miyake, H.; Saito, T.; Kaji, A. A convenient synthesis of sulfides, formaldehyde dithioacetals, and chloromethyl sulfides *Synthesis* **1980**, *11*, 952−953.

(25) Nittoli, T.; Curran, K.; Insaf, S.; DiGrandi, M.; Orlowski, M.; Chopra, R.; Agarwal, A.; Howe, A. Y. M.; Prashad, A.; Floyd, M. B.; Johnson, B.; Sutherland, A.; Wheless, K.; Feld, B.; O'Connell, J.; Mansour, T. S.; Bloom, J. Identification of Anthranilic Acid Derivatives as a Novel Class of Allosteric Inhibitors of Hepatitis C NS5B Polymerase *J. Med. Chem.* **2007**, *50*, 2108−2116.

(26) Eggers, K.; Fyles, T. M.; Montoya-Pelaez, P. J. Synthesis and Characterization of Photo-Switchable Lipids Containing Hemi-Thioindigo Chromophores *J. Org. Chem.* **2001**, *66*, 2966−2977.

(27) Zumbansen, K.; Döhring, A.; List, B. Morpholinium Trifluoroacetate-Catalyzed Aldol Condensation of Acetone with both Aromatic and Aliphatic Aldehydes *Adv. Synth. Catal.* **2010**, *352*, 1135−1138.

(28) Solin, N.; Han, L.; Che, S.; Terasaki, O. An amphoteric mesoporous silica catalyzed aldol reaction *Catal. Commun.* **2009**, *10*, 1386−1389.

(29) Stern, T.; Rückbrod, S.; Czekelius, C.; Donner, C.; Brunner, H. A Selective and Benign Synthesis of Functionalized Benzalacetones via Mizoroki-Heck Reaction Using Aryldiazonium Salts *Adv. Synth. Catal.* **2010**, *352*, 1983−1992.

(30) Kuo, G.-H.; Player, M. R.; Yang, S.-M.; Zhang, Y.-M.; Huang, H. Preparation of benzothiophene derivatives as GPR40 agonists for the treatment of type II diabetes WO 2016057731 A1, 2016.

(31) Ho, J.-H.; Ho, T.-I. Substituent dependent photochemical rearrangements of halostyrylheterocycles in acid media *Tetrahedron Lett.* **2003**, *44*, 4669−4672.

(32) Gilbert, J. C.; Selliah, R. D. Enantioselective synthesis of (-)-trichodiene *J. Org. Chem.* **1993**, *58*, 6255−6265.

(33) Deziel, R. Mild palladium(0)-catalyzed deprotection of allyl esters. A useful application in the synthesis of carbapenems and other β-lactam derivatives *Tetrahedron Lett.* **1987**, *28*, 4371−4372.