Diastereoselective Synthesis of Thieno[3′,2′:4,5]cyclopenta[1,2-*d*][1,3]-oxazolines − New Ligands for the Copper-Catalyzed Asymmetric Conjugate Addition of Diethylzinc to Enones

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Several new ligands featuring a rigid three ring skeleton have been prepared for the first time following a modular approach. Chirality has been introduced by use of an oxazoline moiety fused with a cyclopenta[*b*]thiophene backbone. The efficiency and stereochemical impact of these ligands on the copper-catalyzed enantioselective addition of Et_2Zn to chalcone was examined and enantiomeric excesses up to 79% were achieved using the ligand (*R*,*R*)-**16** substituted with a methyl group at the cyclopenta moiety. Computational and ESI-mass spectral studies show that these new compounds behave as monodentate ligands towards Cu^+.

Introduction

The preparation of new and efficient enantiopure ligands providing a chiral environment to metals active in asymmetric catalysis is currently a major concern in modern organic chemistry.

The beneficial effect of a sulfur chelation on the level of asymmetric induction for bidentate ligands and catalysts has been widely reported. Chiral thioether-containing ligands in combination with N chelation sites have been successfully tested and a number of asymmetric catalytic C−C bond forming reactions ranging from Pd-catalyzed allylic substitutions[1] to additions to aldehydes[2] and conjugate additions,[3] have been reported so far.

Combination of the efficiency of oxazoline moieties and the use of sulfur as an auxiliary donor in metal-catalyzed reactions has also motivated the preparation of various S−N ligands.[4] On the other hand, hybrid ligands incorporating the thiophene moiety have been largely overlooked although there are reports of thiophene functioning as either an η^1 or η^5 ligand[5] and regarding its capability of promoting electron tuning at the chelating site.[6] In a quite recent paper, the preparation of a number of formally tridentate oxazoline ligands with additional thiophene and thioethers donor groups was reported. In that case, the ligand was bidentate with oxazoline-N and thioether-S atoms coordinating to the copper atom whereas thiophene did not coordinate.[7] However, in the absence of such a competition the role played by the thiophene moiety as a ligand towards Pd, has been clearly established. Recently, catalysts where the sulfur is part of a strong π-donor structure incorporating the oxazoline system and either thienyl (**I**)[8] or dibenzothiophene (**II**)[9] (Figure 1) backbones as auxiliary binding sites, have been successfully applied to Pd-catalyzed allylic substitution reactions.

On the basis of the results observed to date, we assumed that the sulfur atom of the thiophene and dibenzothiophene backbones probably participate in the stabilization of the sterically-favoured Pd complex.

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Results and Discussion

Ligand Synthesis

The oxazoline scaffold is common both in natural products[10] and in ligands for asymmetric catalysis.[11] Consequently, the synthesis of oxazolines has generated intense interest among organic chemists.[12] Based upon our pre-

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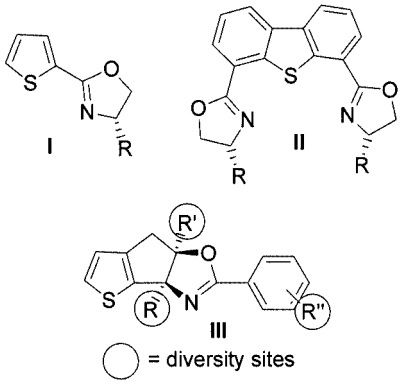
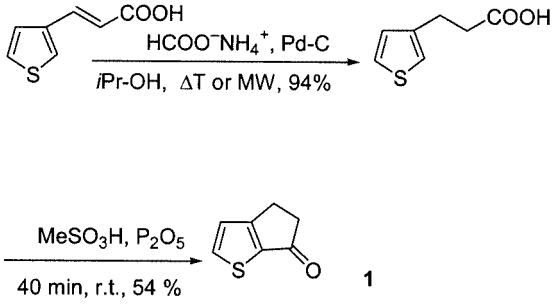


Figure 1. Representative thiophene-oxazoline ligands



Scheme 1

vious work in the area of sulfur-based ligands,[13] and in an effort to explore new ligand templates for catalytic enantioselective reactions, we have targeted the previously unknown thieno-containing oxazoline **III** . This paper reports the synthesis of **III** with some structural variants and the preliminary results of their application as ligands for Cu^{I} in homogeneous stereoselective Michael addition reactions.

The molecular architecture of **III** contains several noteworthy features: (i) the unprecedented backbone of three fused five-membered rings allows for a rigid conformation of the molecular scaffold and should favour the preferential formation in solution of a single well defined complex with the metal, (ii) variation of the ligand structural motif is convenient since the polycyclic skeleton allows a variety of synthetic transformations, and (iii) the structure of the new ligand mimics that of the thia-analogue of the enantiomerically pure 1-amino-2-indanol, a key component of indinavir a potent inhibitor of HIV protease.[14]

The synthetic plan to the thieno-oxazoline **III** reveals that its direct precursor, the previously unreported thienyl-amino-indanol can be synthesized in a rather simple way using as a key core unit the known 4,5-dihydro-6*H*-cyclopenta[*b*]thiophen-6-one (**1**). A modification of the previously reported methodology[15] required replacement of the sodium amalgam reduction of the double bond of the 3-(3-thienyl)-acrylic acid with the more methodologically simple, environmentally friendly and high yielding (94%) catalytic hydrogen transfer, performed with classical heating or under microwave irradiation. The resulting 3-thienylpropionic acid was subjected to intramolecular cyclization to give **1** in 54% yield.

Apart from substitutions in the phenyl ring of **III** and following the concept that molecules with modular architectures are highly desirable since they facilitate the optimization of the ligand features,[16] the projected synthesis was also aimed at modification of the ligand at the carbocyclic ring, using **1** as a common key unit.

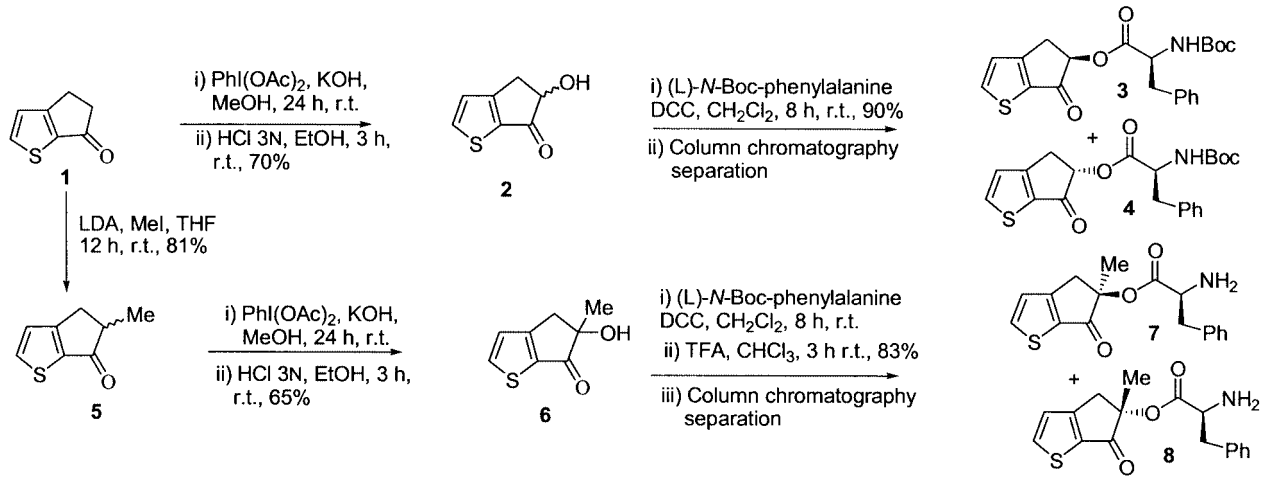
The α-hydroxylation of **1** for preparation of the desired amino alcohol was achieved (Scheme 2) using the Moriarty reaction,[17] which afforded **2** in 70% yield. Resolution of the racemic mixture of **2** was performed by treatment with L-*N*-Boc-phenylalanine followed by column chromatographic separation of the two diastereomers **3** and **4**.

The absolute configuration of the stereogenic centre at C-5 in the 4,5-dihydro-6*H*-cyclopenta[*b*]thiophen-6-one moiety of **4**, was determined to be (*S*) by a single crystal X-ray structural analysis. It follows that the absolute configuration of the corresponding stereogenic centre in **3** is (*R*).

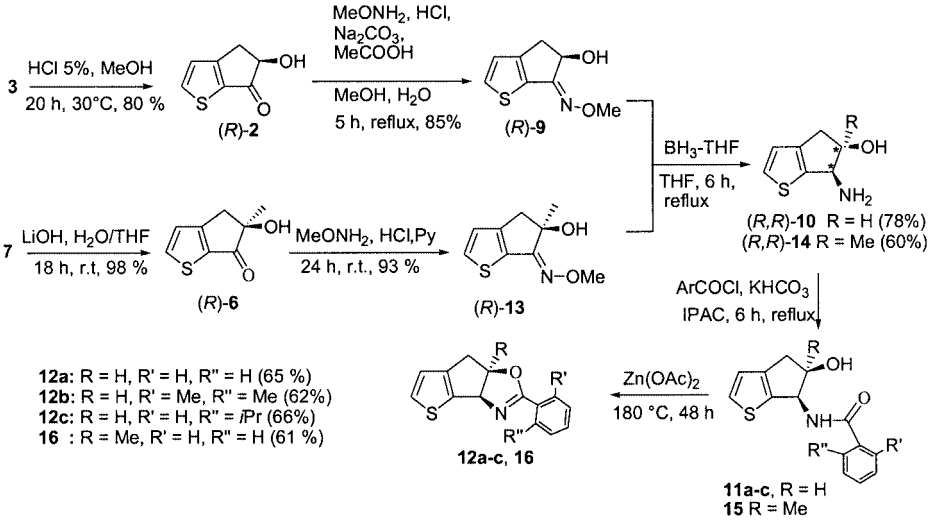
Analogously, the 5-methyl-substituted derivative was synthesized starting from **1**. Formation of the lithium enolate by addition of LDA followed by quenching with MeI[18] led to formation of 4,5-dihydro-5-methyl-6*H*-cyclopenta[*b*]thiophen-6-one (**5**). This compound was subjected to the Moriarty reaction leading to the α-hydroxy derivative **6** in 65% yield. Resolution by column chromatography of the racemic mixture of the two diastereomers obtained by treatment of **6** with L-*N*-Boc-phenylalanine became viable only after removal of the *N*-Boc protection at the amino group, using TFA. The configuration of **7** at C-5 was established to be (*R*) by single crystal X-ray analysis. The absolute configuration of the corresponding stereogenic centre in **8** thus follows to be (*S*).

Subsequently, our synthetic plan addressed the preparation of the amino alcohols and relied on installation of the amino functionality. From hydrolysis of **3** with 5% HCl, enantiomerically pure (*R*)-**2**[19] was obtained, which was converted into the corresponding α-hydroxy methyloxime (*R*)-**9** by treatment with methoxyamine hydrochloride in 85% yield (Scheme 3) and exclusively in the *anti* configuration, as supported by NOE experiments. Reduction of the *anti* oxime ether with borane-tetrahydrofuran complex,[20] resulted in *cis*-1,2-amino alcohol (*R*,*R*)-**10** stereoselectively (selectivity 97:3) in 78% isolated yield. By a similar sequence, the enantiopure amino alcohol (*R*,*R*)-**14** was obtained in 60% yield from **6**, the only minor variation being the use of basic conditions in the hydrolytic step. The *cis*/*trans* ratio for **14** was 98:2 according to NMR analysis.

The oxazolines **12a**−**c** and **16** were prepared by cyclic dehydration of the carboxamides **11a**−**c** and **15**[21] obtained from the corresponding carboxylic acids and enantiomerically pure 2-amino alcohols **10** and **14**. This very common method for oxazoline synthesis can be achieved by converting the hydroxy group into a good nucleofuge,[22] or by exploiting its nucleophilic activity towards the electrophilic amide[23] with this latter option resulting in full retention of configuration. Starting from the available *cis* amino al-



Scheme 2



Scheme 3

cohols **10** and **14**, a synthetic route was planned, based on those reported previously. Cyclization of the intermediate carboxyamides **11a**−**c** and **15** promoted by Zn acetate occurs (Scheme 3) with complete stereochemical integrity of the carbon−oxygen bond at C-5 giving rise to the *cis*-oxazoline systems **12a**−**c**, and **16** in fairly good yields.

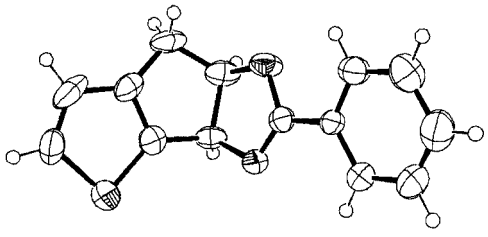
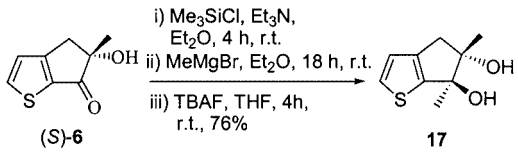
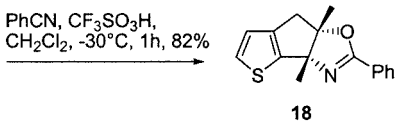


Figure 2. ORTEP drawing of **12a**

This choice was dictated by the observation that conformationally constrained amino alcohols like aminoindanol do not afford the *trans*-oxazoline and that this derivative can be obtained with some deal of difficulty even from the more conformationally flexible *cis*-2-aminocyclohexanol. For this reason, routes starting from the *cis* amino alcohols and implying an inversion of configuration,[24] were neglected. A further structural variation was attempted by replacement of the residual hydrogen at position 6 of the cyclopenta[*b*]thiophene scaffold with a methyl group. Attempts to obtain the dimethylated target compound through the intermediacy of a thia-analogue of the 1-amino-2-indanol according to the previously reported procedure failed. The reluctancy of the oxime ether **13** to undergo nucleophilic addition with a variety of organometallic reagents for introduction of the methyl group at C-6, can be explained by the well established lower electrophilicity of oximes compared to that of the corresponding carbonyl compounds[25] and, at least in part, by the steric crowding around this position. Instead, starting from the α-hydroxy ketone **6** after protection of the OH function, addition of

MeMgBr occurred smoothly followed by TBAF desilylation to afford the diastereomerically pure *trans* 1,2-diol **17** in 76% overall yield (Scheme 4).



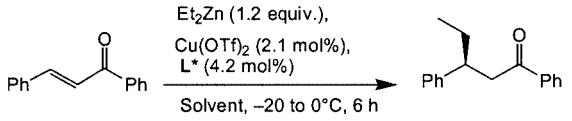


Scheme 4

The final step of this sequence, the assembly of the oxazoline moiety, was accomplished by use of a recently reported procedure.[26] Exposure of **17** to the action of benzonitrile in the presence of triflic acid led to the formation of the *cis*-oxazoline derivative **18** in 82% yield. Remarkably, in this reaction the OH functionality at C-6 plays the role of a nucleofuge group and the formation of the new C−N bond occurs with inversion of configuration, as required.

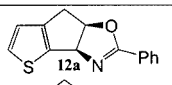
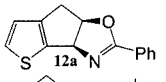
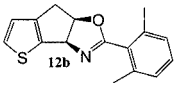
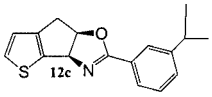
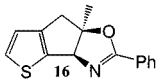
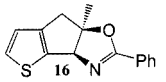
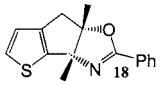
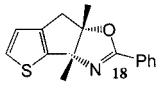
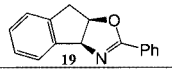
Conjugate Additions

Conjugate addition reactions of organometallic reagents to enones are among the most widely used methods for carbon−carbon bond formation in organic synthesis.[27] A number of chiral stoichiometric reagents have been reported during the last few years which allow enantioselective additions,[28] although the development of chiral catalysts has been less rapid. The copper-catalyzed, chiral-ligand-accelerated 1,4-addition of organozinc reagents is of great importance in this rapidly expanding field. In particular, chiral phosphites,[29] phosphoramidites[30] and other chiral P,N ligands[31] have been used in additions to cyclic enones giving good enantioselectivities. On the other hand, while few non-phosphorylated hybrid ligands containing thioether and chiral nitrogen-based moieties have been already applied to these reactions,[32] the use of catalysts incorporating an oxazoline system and a thienyl backbone in the copper-catalyzed conjugate addition of Et_2Zn to enones is unprecedented. With the set of ligands **12a**−**c**, **16** and **18** in hand, we evaluated their performance in comparison with that of the already known[33] 2-phenyl-8,8a-dihydro-3a*H*-indeno[1,2-*d*][1,3]oxazole (**19**) in the reaction of diethylzinc with chalcone, selected to determine optimal reaction conditions (Table 1). The catalytic system was generated in situ by addition of a two fold excess of the corresponding ligand to a solution of $Cu(OTf)_2$ followed by addition of diethylzinc. Reactions were carried out in either toluene or diethyl ether at −20 °C, giving only the 1,4 adducts in satisfactory yields in all cases.



Scheme 5

Table 1. Cu-catalyzed enantioselective 1,4-conjugate addition of Et_2Zn to chalcone

Entry	L*	Solvent	Yield (%)	*ee* (%)	Config.
1		toluene	61	51	*S*
2		Et_2O	51	53	*S*
3		toluene	58	47	*S*
4		toluene	55	43	*S*
5		toluene	58	70	*R*
6		Et_2O	49	79	*R*
7		toluene	58	58	*R*
8		Et_2O	40	65	*R*
9		Et_2O	50	32	*S*

All the ligands studied gave good enantioselectivities. In most of the cases examined, changing the solvent from toluene to ether led to some improvement in the enantioselectivity (compare Entries 7 and 8).[34] During the preliminary screening it was found that the catalysts prepared in situ from $Cu(OTf)_2$ were more active than those prepared from CuOTf and gave slightly higher enantiomeric excesses. On the other hand, substituents in the phenyl ring of the ligands had only a negligible influence on the outcome of the reaction. This lack of response left only modification of the cyclopenta[*b*]thiophene group as the major variable. A significant improvement in the enantioselectivity (79% *ee*) with respect to that obtained in the case of the parent compound **12a** (53%, Entry 2), was achieved by using ligand **16**, which contains a methyl group at position 5. The presence of an additional methyl group at position 6 (ligand **18**), in close proximity to the oxazoline nitrogen (a favoured site for the metal chelation), had a detrimental effect (Entry 8, 65% *ee*).

It is evident from this that there is no straightforward relationship between the structure of the ligands (e.g. their

steric requirements) and the enantioselectivities observed in the conjugate addition. A delicate balance seems to exist between the increasing steric hindrance at the chelation site and the efficacy of the stereogenic center in affecting the enantioselectivity. Finally the cyclopenta[*b*]thiophene-derived ligands were consistently superior in terms of enantioselectivity with respect to **19**, derived from *cis*-aminoindanol.

We were intrigued by the question of whether copper(I) involved in this process needs to reside in the chiral environment bridging both the oxazoline and the thiophene moieties. Therefore, a computational investigation was carried out[35] at the DFT level on the **12a**/Cu^{+1} complex. The computational study dealing with the structure elucidation of ligand **12a** coordinated to copper(I) reveals that the complex is a 2:1 adduct where the metal is coordinated by only two of the four donor atoms, namely the oxazoline N atoms. A schematic representation of the two lowest energy conformations of this complex is given in Figure 3. The two structures are almost degenerate, the energy difference being only 0.5 kcal·mol^{-1}. The less stable conformation m_2 is characterized by an S···S distance of 4.406 Å (7.736 Å in m_1). Even if this distance is rather large, it probably causes a weak interaction between the S lone pairs that makes m_2 slightly less stable than m_1. The thiophene moieties themselves, of both ligands, do not seem to have any close contact to Cu. This weak propensity for the thiophene S atom to establish an effective η^1-type interaction with Cu, which contrasts with the efficacy of the coordination of this metal with the softer thioether S-atom, has been reported previously.[7] However, we feel that the presence of an inherently electron-rich thiophene ring in ligands for asymmetric catalysis might modulate electronic availability at the chelation site, as has already reported.[6] In this case, the oxazoline nitrogen might have higher electron density and this might account for the better performance of ligand **12a** with respect to **19**, in line with previous results.[36]

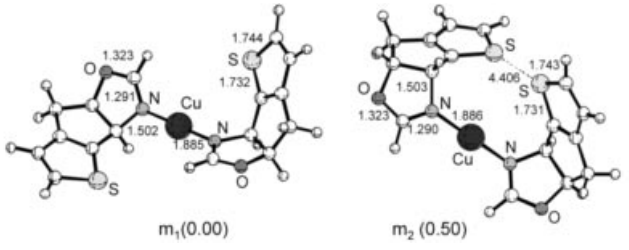


Figure 3. Schematic representation of the two lowest energy conformations m_1 and m_2 of the **12a**/Cu^{+1} complex. Relative energies (kcal·mol^{-1}) are reported in parenthesis. Bond lengths are in Angstrøms

The assumption that the catalytic species is an ML_2-type complex formed by 2 mol of the ligand per Cu atom and, therefore, that these N,S ligands are bound to the metal by the oxazoline-N atoms is supported experimentally by the ESI mass spectrum of the Cu^{+1}-ligand complex (see Exp. Sect.).

The results described herein show that the new thienocyclopenta-oxazoline ligands provide one of the few examples of successful copper-catalyzed enantioselective conjugate addition of dialkylzinc reagents using nonphosphorylated sulfur-containing ligands. The *ee* values of **16** are superior to those obtained for the same reaction with the previous S,N ligands and very close to the best values available for P,N ligands. Although this class of ligands has hardly been explored for asymmetric synthesis, the results look promising since further variations in the ligand structure can be projected. The optimization of the structure of this type of sulfur containing ligand is currently in progress and extension to other asymmetric transformations will be investigated.

Experimental Section

General Remarks: Melting points were determined with a Büchi melting point apparatus and are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded using $CDCl_3$ solutions at 300 and 75.46 MHz, respectively, with a Varian Gemini 300. Chemical shifts (δ) are reported in ppm relative to $CHCl_3$ (δ = 7.26 for ^1H and δ = 77.0 for ^{13}C). *J* values are given in Hz. ^{13}C NMR spectral assignments were made by DEPT experiments. IR spectra were recorded on a Perkin−Elmer model 257 grating spectrometer. Mass spectra were obtained using a VG 7070-E spectrometer at an ionizing voltage of 70 eV. $[\alpha]_{20}^{D}$ values were determined with a Perkin−Elmer Polarimeter 341. The originality of all the compounds was checked by a CAS-on-line structure search. Reactions were conducted in oven-dried (120 °C) glassware under a positive Ar atmosphere. Transfer of anhydrous solvents or mixtures was accomplished with oven-dried syringes/septum techniques. THF was distilled from sodium/benzophenone just prior to use and stored under Ar. Et_2O was distilled from phosphorus pentoxide twice. CH_2Cl_2 was passed through basic alumina and distilled from CaH_2 prior to use. Other solvents were purified by standard procedures. Light petroleum ether refers to the fraction with bp 40−60 °C. The reactions were monitored by TLC performed on silica gel plates (Baker-flex IB2-F). Column chromatography was performed on Merck silica gel 60 (70−230 mesh). Preparative thick layer chromatography was carried out on glass plates using a 1 mm layer of Merck silica gel 60 Pf 254. All chemicals were used as obtained or purified by distillation as required. Iodobenzene diacetate was recrystallized twice from 5 M acetic acid.

4,5-Dihydro-6*H*-cyclopenta[*b*]thiophen-6-one (1): Pd−C (6.6 g, 10 wt%) and ammonium formate (13.7 g, 218 mmol) were added to a solution of 3-(3-thienyl)acrylic acid (11.2 g, 73 mmol) in *i*PrOH (250 mL). After 6 h at 90 °C, the mixture was filtered through celite and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/Et_2O, 1:1) affording 10.6 g of 3-(3-thienyl)propanoic acid as a white solid (94%). Experimental data are in accordance with ref.[37]. Alternatively the reaction could also be run on up to 20 mmol scale under microwave irradiation in a monomode reactor (Synthwave 402 Prolabo focused MW 2.45 GHz) for 20 minutes at 75 W giving the same yield after work up.

3-(3-Thienyl)propanoic acid (10.6 g, 68.2 mmol) was added to a solution of phosphorus pentoxide (54.2 g, 381.6 mmol) in methanesulfonic acid (362 mL). The mixture was stirred at room temperature for 40 min. The dark red solution was poured onto ice

(530 g) and extracted with CH_2Cl_2 (4 × 200 mL). The combined organic extracts were washed with 5% NaOH (200 mL), 1 N HCl (200 mL) and brine (200 mL), dried with $MgSO_4$, filtered and concentrated. The solid was purified by column chromatography (petroleum ether/Et_2O, 1:1) to provide **2** as a white solid (5.08 g, 54%). Experimental data are in accordance with ref.[37].

(±) 5-Hydroxy-4,5-dihydro-6*H*-cyclopenta[*b*]thiophen-6-one (2): A solution of KOH (5.54 g, 98.7 mmol) in MeOH (50 mL) was added dropwise to **1** (4.54 g, 32.9 mmol) at 0 °C. After stirring at 0 °C for 15 min, iodobenzene diacetate (15.9 g, 49.4 mmol) was added and the mixture was stirred for 24 h at room temperature. Water was added and the mixture was extracted with diethyl ether, dried with $MgSO_4$ and concentrated under reduced pressure. The solution was dissolved in EtOH (43 mL) and 3 N HCl (32.9 mL) was added. After 4 h at room temperature the crude was concentrated and extracted with EtOAc. The combined organic phases were washed with $NaHCO_3$, brine, dried with $MgSO_4$, filtered and concentrated. The product was purified by column chromatography on silica gel (petroleum ether/EtOAc, 2:1) to give **2** (3.55 g, 70%) as a thick yellow oil. ^{1}H NMR: δ = 2.79 (dd, *J* = 3.5, 16.8 Hz, 1 H, CH_2), 3.24 (dd, *J* = 6.7, 16.8 Hz, 1 H, CH_2), 3.51 (br. s, 1 H, OH), 4.62 (dd, *J* = 3.5, 6.7 Hz, 1 H, CH), 6.94 (d, *J* = 4.8 Hz, 1 H, ArCH), 7.87 (d, *J* = 4.8 Hz, 1 H, ArCH) ppm. ^{13}C NMR: δ = 40.40 (CH_2), 77.16 (CH), 124.99 (ArCH), 137.04 (ArC), 143.30(ArCH), 166.21(ArC), 201.19 (C=O) ppm. EI-MS: *m*/*z* = 154 [M^+] .

Resolution of Racemic 2: A solution of *N*-Boc-L-phenylalanine (2.98 g, 11.21 mmol) in CH_2Cl_2 (27 mL) was cooled to 0 °C. *N*,*N*-Dicyclohexylcarbodiimide (2.31 g, 11.2 mmol) was added in several portions and a white precipitate quickly formed. After 10 min **3** (1.15 g, 7.47 mmol) dissolved in CH_2Cl_2 (18 mL) was added followed by DMAP (0.046 g, 0.37 mmol). The mixture was stirred at room temperature for 8 h. After addition of water (15 mL), the organic phase was extracted with diethyl ether and dried with $MgSO_4$. The residue was purified by column chromatography on silica gel (petroleum ether/Et_2O, 1:1) to afford 1.35 g of each diastereoisomer (90% overall yield).

(5*R*,2*S*)-6-Oxo-5,6-dihydro-4*H*-cyclopenta[*b*]thien-5-yl 2-[(*tert*-Butoxycarbonyl)amino]-3-phenylpropanoate (3): Thick colorless oil. $[\alpha]_D^{20}$ = −4.0 (*c* = 0.25, $CHCl_3$). ^{1}H NMR: δ = 1.27 (s, 9 H, CH_3), 2.71 (dd, *J* = 2.9, 17.2 Hz, 1 H, CH_2), 2.94−3.10 (m, 2 H, CH_2), 3.37 (dd, *J* = 7.0, 17.2 Hz, 1 H, CH_2), 4.52−4.59 (m, 1 H, CH), 4.86 (br. d, *J* = 7.1 Hz, 1 H, NH), 5.44−5.47 (m, 1 H, CH), 6.93 (d, *J* = 4.8 Hz, 1 H, ArCH), 7.06−7.21 (m, 5 H, ArCH), 7.87 (d, *J* = 4.8 Hz, 1 H, ArCH) ppm. ^{13}C NMR ($CDCl_3$): δ = 28.54 ($3CH_3$), 31.82 (CH_2), 38.51 (CH_2), 54.77 (CH), 78.30 (CH), 80.27 (C), 124.32 (ArCH), 127.32 (ArCH), 128.82 (2ArCH), 129.70 (2ArCH), 136.22 (ArC), 136.40 (ArC), 142.22 (ArCH), 155.30 (ArC), 164.10 (C=O), 171.50 (C=O), 190.65 (C=O) ppm.

(5*S*,2*S*)-6-Oxo-5,6-dihydro-4*H*-cyclopenta[*b*]thien-5-yl 2-[(*tert*-Butoxycarbonyl)amino]-3-phenylpropanoate (4): White solid. M.p. 106.8−107.5 °C. $[\alpha]_D^{20}$= −15 (*c* = 0.25, $CHCl_3$). ^{1}H NMR: δ = 1.29 (s, 9 H, CH_3), 2.81 (dd, *J* = 3.4, 17.1 Hz, 1 H, CH_2), 2.98−3.14 (m, 2 H, CH_2), 3.43 (dd, *J* = 7.1, 17.1 Hz, 1 H, CH_2), 4.51−4.57 (m, 1 H, CH), 4.85 (br. d, *J* = 8.3 Hz, 1 H, NH), 5.60 (dd, *J* = 3.4, 7.1 Hz, 1 H, CH), 6.95 (d, *J* = 5.0 Hz, 1 H, ArCH), 7.09−7.23 (m, 5 H, ArCH), 7.88 (d, *J* = 5.0 Hz, 1 H, ArCH) ppm. ^{13}C NMR ($CDCl_3$): δ = 28.50 ($3CH_3$), 32.05 (CH_2), 38.16 (CH_2), 54.54 (CH), 77.87 (CH), 80.28 (C), 124.37 (ArCH), 127.32 (ArCH), 128.83 (2ArCH), 129.86 (2ArCH), 135.96 (ArC), 138.43 (ArC), 142.34 (ArCH), 155.41 (ArC), 164.50 (C=O), 171.59 (C=O), 190.88 (C=O) ppm. $C_{21}H_{23}NO_5S$ (401.5): calcd. C 62.82, H 5.77, N 3.49; found C 62.80, H 5.74, N 3.43. CCDC = 237742.

(5*R*)-Hydroxy-4,5-dihydro-6*H*-cyclopenta[*b*]thiophen-6-one [(+)-(2)]: HCl 5% in MeOH (27 mL) was added to **3** (0.36 g, 0.9 mmol), and then stirred for 20 h at 30 °C. The crude was extracted with EtOAc, dried with $MgSO_4$, filtered and concentrated. Column chromatography on silica gel (petroleum ether/EtOAc, 2:1) afforded (+)-**2** (0.11 g, 80%) as a thick colorless oil. $[\alpha]_D^{20}$ = +31 (*c* = 0.2, $CHCl_3$). For the other diastereoisomer (**4**), the same procedure gave (*S*)-(−)-**2**. Thick colorless oil. $[\alpha]_D^{20}$ = −31 (*c* = 0.2, $CHCl_3$).

(5*R*)-Hydroxy-4,5-dihydro-6*H*-cyclopenta[*b*]thiophen-6-one *O*-Methyloxime (9): $MeONH_2$· HCl (0.14 g, 1.65 mmol) and Na_2CO_3 (0.12 g, 1.13 mmol) were added to a solution of **(+)-2** (0.23 g, 1.5 mmol) in MeOH (1 mL) and H_2O (3 mL) and CH_3COOH was added dropwise until pH = 4.5. The mixture was refluxed and stirred for 5 h; then water was added. The organic phase was extracted with $CHCl_3$ and dried with $MgSO_4$. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc, 3:1) to afford 0.23 g (1.28 mmol, 85%) of **9**. White solid. M.p. 81.5−82.6 °C. $[\alpha]_D^{20}$ = −10.5 (*c* = 1.5, $CHCl_3$). IR (CCl_4): nu (tilde) = 3597.8, 3030.4, 2936.5, 1590 (C=N) cm^{-1}. ^{1}H NMR: δ = 2.76 (dd, *J* = 2.5, 16.7 Hz, 1 H, CH_2), 2.88 (br. s, 1 H, OH), 3.24 (dd, *J* = 6.8, 16.7 Hz, 1 H, CH_2), 3.90 (s, 3 H, OCH_3), 5.18 (dd, *J* = 2.5, 6.8 Hz, 1 H, CH), 6.80 (d, *J* = 5.0 Hz, 1 H, ArCH), 7.51 (d, *J* = 5.0 Hz, 1 H, ArCH) ppm. ^{13}C NMR: δ = 36.23 (CH_2), 62.24 (CH_3), 75.16 (CH), 122.62 (ArCH), 131.89 (ArC), 136.82 (ArCH), 153.02 (ArC), 157.07 (C) ppm. EI-MS [M^+]: 183. $C_8H_9NO_2S$ (183.2): calcd. C 52.44, H 4.95, N 7.64; found C 52.41, H 4.97, N 7.62.

(5*R*)-6-Amino-5,6-dihydro-4*H*-cyclopenta[*b*]thiophen-5-ol: A solution of BH_3· THF (1.0 M solution in THF 10.5 mL, 10.5 mmol) was added dropwise to a solution of **9** (0.64 g, 3.5 mmol) in freshly distilled THF (3.5 mL) at 0 °C. The mixture was refluxed for 6 h. Upon cooling, the mixture was extracted with Et_2O, the aqueous layer made alkaline with NH_4OH to pH=9 and then extracted twice with EtOAc. The organic layer was dried with $MgSO_4$, filtered and concentrated. ^{1}H NMR analysis of the crude showed a *cis*/*trans* ratio of 97:3. Separation by column chromatography on silica gel (chloroform/methanol, 5:1) gave the two separated isomers in a 78% overall yield.

***cis*-(5*R*,6*R*)-6-Amino-5,6-dihydro-4*H*-cyclopenta[*b*]thiophen-5-ol (10):** Thick colorless oil. $[\alpha]_D^{20}$ = −55 (*c* = 0.2, MeOH). IR (CCl_4): $\tilde{\nu}$ = 3419.2, 2923.4, 1611.0 cm^{-1}. ^{1}H NMR: δ = 2.11 (br. s, 3 H, OH, NH_2), 2.53 (dd, *J* = 5.8, 15.6 Hz, 1 H, CH_2), 2.94 (dd, *J* = 6.8, 15.6 Hz, 1 H, CH_2), 4.22 (d, *J* = 6.3 Hz, 1 H, C*H*−N), 4.50−4.56 (m, 1 H, C*H*−O), 6.69 (d, *J* = 5.0 Hz, 1 H, ArCH), 7.15 (d, *J* = 5.0 Hz, 1 H, ArCH) ppm. ^{13}C NMR: δ = 35.74 (CH_2), 53.71 (CH), 74.93 (CH), 121.71 (ArCH), 127.83 (ArCH), 141.64 (ArC), 141.96 (ArC) ppm. EI-MS: (*m*/*z*) = 155 [M^+]. C_7H_9NOS (155.2): calcd. C 54.17, H 5.84, N 9.02, found C 54.15, H 5.83, N 9.01.
***trans*-(5*R*,6*S*)-6-Amino-5,6-dihydro-4*H*-cyclopenta[*b*]thiophen-5-ol:** Thick colourless oil. $[\alpha]_D^{20}$ = −7 (*c* = 0.2, MeOH). ^{1}H NMR δ = 2.30 (bs, 3 H, OH + NH_2, 2.53 (dd, *J* = 6.3, 14.9 Hz, 1 H, CH_2), 3.06 (dd, *J* = 7.7, 14.9 Hz, 1 H, CH_2), 4.12 (d, *J* = 5.0 Hz, 1 H, C*H*−N), 4.22−4.38 (m, 1 H, C*H*−O), 6.68 (d, *J* = 5.0 Hz, 1 H, ArCH), 7.13 (d, *J* = 5.0 Hz, 1 H, ArCH) ppm. ^{13}C NMR δ = 37.47 (CH_2), 55.57 (CH), 74.93 (CH), 123.83 (ArCH), 130.21 (ArCH), 143.07 (ArC), 143.52 (ArC) ppm. C_7H_9NOS (155.2): calcd. 54.17, H 5.84, N 9.02, found C 54.20, H 5.86, N 9.04.

General Procedure for the Synthesis of Amides 11a−c: To a solution of **10** (0.26 g, 1.7 mmol) in IPAC (6 mL) at 65 °C was added an aqueous solution of potassium hydrogen carbonate (1.5 M, 1.4 mL). The mixture was maintained at 65−70 °C and acetyl chloride (1.5

equiv.) was added dropwise. The mixture was stirred for 2.5 h at 80 °C. After cooling, water was added and the mixture was extracted with EtOAc, dried with $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc, 3:1) to afford the amides **11a−c**.

***N*-[(5*R*,6*R*)-5-Hydroxy-5,6-dihydro-4*H*-cyclopenta[*b*]thiophen-6-yl]-benzenecarboxamide (11a):** Yield 78%. White solid. M.p. 153−154 °C. $[\alpha]_D^{20}$ = +76 (*c* = 0.3, MeOH). IR (CCl_4: $\tilde{\nu}$ = 1654.8, 2992.5, 3283, 3438.3 cm^{-1}. EI-MS: *m*/*z* = 259 [M^+]. ^1H NMR: δ = 3.05 (dd, *J* = 4.5, 15.6 Hz, 1 H, CH_2), 3.42 (dd, *J* = 6.6, 15.6 Hz, 1 H, CH_2), 5.90−6.05 (m, 1 H, CH), 6.12−6.21 (m, 1 H, CH), 6.60 (bs, 1 H, NH), 6.85 (d, *J* = 4.8 Hz, 1 H, ArCH), 7.30−7.70 (m, 3 H, ArCH), 7.90−8.15 (m, 3 H, ArCH) ppm. ^{13}C NMR: δ = 35.17 (CH_2), 53.51 (CH), 75.17 (CH), 126.31 (ArCH), 127.58 (ArCH), 128.93 (ArCH), 130.22 (ArCH), 130.79 (ArCH), 133.33 (ArC), 139.09 (ArC), 143.15 (ArC), 168.02 (C=O) ppm. EI-MS: *m*/*z* = 259 [M^+].

***N*-[(5*R*,6*R*)-5-Hydroxy-5,6-dihydro-4*H*-cyclopenta[*b*]thiophen-6-yl]-2,6-dimethylbenzenecarboxamide (11b):** Yield 76%. White solid. M.p. 148−150.3 °C. $[\alpha]_D^{20}$ = +74.5 (*c* = 0.3, MeOH). ^1H NMR: δ = 2.30 (s, 6 H, CH_3), 2.75 (dd, *J* = 4.5, 15.6 Hz, 1 H, CH_2), 3.12 (dd, *J* = 6.6, 15.6 Hz, 1 H, CH_2), 4.95−5.00 (m, 1 H, CH), 5.41−5.54 (m, 1 H, CH), 6.25 (br. d, 1 H, NH), 6.75 (d, *J* = 4.8 Hz, 1 H, ArCH), 6.92−7.15 (m, 3 H, ArCH), 7.22 (d, *J* = 4.8 Hz, 1 H, ArCH) ppm. ^{13}C NMR: δ = 20.49 (CH_3), 36.29 (CH_2), 53.64 (CH), 76.20 (CH), 126.00−146.35 (ArC + ArCH), 169.22 (C=O) ppm. EI-MS: *m*/*z* = 287 [M^+].

***N*-[(5*R*,6*R*)-5-Hydroxy-5,6-dihydro-4*H*-cyclopenta[*b*]thien-6-yl]-2-isopropylbenzamide (11c):** Yield 77%. White solid. M.p. 154−155 °C. $[\alpha]_D^{20}$ = +72.1, (*c* = 0.3, MeOH). ^1H NMR: δ = 1.25 (d, *J* = 6 Hz, 6 H, Me_2), 2.12−2.14 (m, 2 H, CH_2, C*H*Me_2), 3.37 (br. s, 1 H, OH), 3.46−3.55 (m, 1 H, CH_2), 4.95−5.0 (m, 1 H, CH), 5.13−5.17 (m, 1 H, CH), 6.12 (br. d, 1 H, NH), 6.85 (d, *J* = 4.8 Hz, 1 H, ArCH), 7.10 (d, *J* = 4.8 Hz, 1 H, ArCH), 7.27−7.31 (m, 4 H, ArCH) ppm. ^{13}C NMR: δ = 24.11 (Me_2), 34.19 (C*H*Me_2), 37.76 (CH_2), 54.14 (CH), 74.29 (CH), 126.00−146.35 (ArC, ArCH), 169.51 (C=O). EI-MS: *m*/*z* = 301 [M^+].

General Procedure for the Synthesis of Oxazoles 12a−c: $Zn(OAc)_2$ (1.3 g, 6.7 mmol), which prior to use was dried under vacuum (10^{-2} Torr) for 3−4 h at 160−170 °C and then powdered, was added to the respective amide (0.7 mmol). The mixture was stirred at 180 °C for 48 h then cooled and water added. The organic layer was extracted with EtOAc, dried with $MgSO_4$, filtered and concentrated. Purification by column chromatography (petroleum ether/EtOAc, 3:1) gave the oxazoles **12a−c**.

(3a*R*,7a*R*)-2-Phenyl-7,7a-dihydro-3a*H*-thieno[3′,2′:4,5]cyclopenta-[1,2-*d*][1,3]oxazole (12a): Yield 65%. White solid. M.p. 128−130 °C. $[\alpha]_D^{20}$ = −186 (*c* = 0.3, $CHCl_3$). IR (CCl_4): nu (tilde) = 1646.1, 2923.4, 2958.5 cm^{-1}. ^1H NMR (C_6D_6): δ = 2.48 (dd, *J* = 6.7, 16.7 Hz, 1 H, CH_2), 2.64 (d, *J* = 16.7 Hz, 1 H, CH_2), 4.84 (dd, *J* = 6.8, 13.2 Hz, 1 H, C*H*−O), 5.20 (d, *J* = 6.8 Hz, 1 H, C*H*−N), 6.71 (d, *J* = 5.1 Hz, 1 H, ArCH), 6.84−6.89 (m, 5 H, ArCH), 7.98 (d, *J* = 5.1 Hz, 1 H, ArCH) ppm. ^{13}C NMR (C_6D_6): δ = 35.84 (CH_2), 73.36 (CH), 88.58 (CH), 122.10 (ArCH), 127.95 (ArC), 128.26 (ArCH), 128.42 (2ArCH), 131.09 (2ArCH), 131.45 (ArCH), 142.00 (ArC), 142.81 (ArC), 164.45 (C=N) ppm. EI-MS: *m*/*z* = 241 [M^+]. $C_{14}H_{11}NOS$ (241.3): calcd. C 69.68, H 4.59, N 5.80; found C 69.66, H 4.56, N 5.81. CCDC = 237740.

(3a*R*,7a*R*)-2-(2,6-Dimethylphenyl)-7,7a-dihydro-3a*H*-thieno-[3′,2′:4,5]cyclopenta[1,2-*d*][1,3]oxazole (12b): Yield 62%. Thick colorless oil. $[\alpha]_D^{20}$ = −131 (*c* = 0.3,$CHCl_3$). ^1H NMR (C_6D_6): δ = 2.09 (s, 3 H, CH_3), 3.04 (d, *J* = 16.2 Hz, 1 H, CH_2), 3.24 (dd, *J* = 7.5, 16.2 Hz, 1 H, CH_2), 5.41 (dd, *J* = 1.6, 7.5 Hz, 1 H, C*H*−O), 5.91 (d, *J* = 7.5 Hz, 1 H, C*H*−N), 6.82 (d, *J* = 5.0 Hz, 1 H, ArCH), 6.92 (d, *J* = 7.5 Hz, 2 H, ArCH), 7.07−7.12 (m, 1 H, ArCH), 7.40 (d, *J* = 5.0 Hz, 1 H, ArCH) ppm. ^{13}C NMR (C_6D_6,): δ = 20.01 (2Me), 32.18 (CH_2), 74.46 (CH), 84.33 (CH), 121.13−145.43 (ArC + ArCH), 163.09 (C=N) ppm. EI-MS: *m*/*z* = 269 [M^+].

(3a*R*,7a*R*)-2-(2-Isopropylphenyl)-7,7a-dihydro-3a*H*-thieno-[3′,2′:4,5]cyclopenta[1,2-*d*][1,3]oxazole (12c): Yield 66%. Thick colorless oil. $[\alpha]_D^{20}$ = −127 (*c* = 0.1,$CHCl_3$). ^1H NMR ($CDCl_3$): δ = 1.17 (d, *J* = 6.8 Hz, 6 H, Me_2), 2.88−2.98 (m, 1 H, C*H*Me_2), 3.13 (d, *J* = 16.9 Hz, 1 H, CH_2), 3.30 (dd, *J* = 5.7, 16.9 Hz, 1 H, CH_2), 5.67−5.78 (m, 1 H, C*H*−O), 6.80 (d, *J* = 5.0 Hz, 1 H, C*H*−N), 7.24 (d, *J* = 8.6 Hz, 2 H, ArCH), 7.36 (d, *J* = 5.0 Hz, 1 H, ArCH), 7.86 (m, 3 H, ArCH) ppm. ^{13}C NMR ($CDCl_3$): δ = 23.97 ($2CH_3$), 34.38 (CH), 36.08 (CH_2), 73.36 (CH), 88.62 (CH), 122.30 (ArCH), 125.52 (ArC), 126.60 (2ArCH), 128.71 (2ArCH), 131.19 (ArCH), 142.44 (ArC), 142.96 (ArC), 152.90 (ArC), 164.68 (C=N) ppm. EI-MS: *m*/*z* = 283 [M^+].

5-Methyl-4,5-dihydro-6*H*-cyclopenta[*b*]thiophen-6-one (5): A solution of **1** (1.9 g, 13.7 mmol) in THF (10 mL) was added dropwise to a stirred solution of LDA (9 mL, 1.5 M, in THF, 13.7 mmol) in THF (40 mL), at −78 °C and stirred for 30 min. MeI (0.83 g, 1.9 mL, 13.7 mmol) was added and the solution was stirred at room temperature for 12 h. A solution of NH_4Cl (10 mL) was added and the mixture was extracted with Et_2O (3 × 50 mL), dried with $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/Et_2O, 2:1) to give **5** (1.7 g, 81%) as a colorless oil. ^1H NMR: δ = 1.34 (d, *J* = 7.7 Hz, 3 H, CH_3), 2.61 (dd, *J* = 3.0, 17.1 Hz, 1 H, CH_2), 3.01−3.05 (m, 1 H, CH), 3.28 (dd, *J* = 6.9, 17.1 Hz, 1 H, CH_2), 7.03 (d, *J* = 4.7 Hz, 1 H, ArCH), 7.91 (d, *J* = 4.7 Hz, 1 H, ArCH) ppm. ^{13}C NMR: δ = 17.0 (CH_3), 32.9 (CH), 47.5 (CH_2), 124.1 (ArCH), 140.2 (ArC), 140.7 (ArCH), 167.2 (ArC), 200.3 (C=O) ppm. EI-MS: *m*/*z* = 152 [M^+].

(±) 5-Hydroxy-5-methyl-4,5-dihydro-6*H*-cyclopenta[*b*]thiophen-6-one (6): A solution of KOH (5.54 g, 98.7 mmol) in MeOH (50 mL) was added dropwise to **5** (5.00 g, 32.9 mmol) at 0 °C. After stirring at 0 °C for 15 min, iodobenzene diacetate (15.9 g, 49.4 mmol) was added. After 24 h of stirring at room temperature water was added, the mixture extracted with diethyl ether, dried with $MgSO_4$ and concentrated under reduced pressure. The mixture was then dissolved in EtOH (43 mL) and 3 N HCl (32.9 mL) was added. After 2.5 h at room temperature the solvent was concentrated and the solution extracted with EtOAc. The combined organic phases were washed with $NaHCO_3$, brine, dried with $MgSO_4$, filtered and concentrated. The solid was purified by column chromatography (petroleum ether/Et_2O, 2:1) to give **6** as a white solid (3.63 g, 65%). M.p. 74.8−76.2 °C. ^1H NMR: δ = 1.37 (s, 3 H, CH_3), 3.02 (s, 2 H, CH_2), 6.28 (d, *J* = 4.4 Hz, 1 H, ArCH), 7.74 (d, *J* = 4.4 Hz, 1 H, ArCH) ppm. ^{13}C NMR: δ = 26.24 (CH_3), 40.56 (CH_2), 82.61 (C), 124.49 (ArCH), 136.99 (ArC), 142.37(ArCH), 165.11(ArC), 198.99 (C=O) ppm. EI-MS: *m*/*z* = 168 [M^+]. $C_8H_8O_2S$ (168.2): calcd. C 57.12, H 4.79; found C 57.10, H 4.77.

Resolution of Racemic 6: (2*S*)-5-Methyl-6-oxo-5,6-dihydro-4*H*-cyclopenta[*b*]thien-5-yl 2-Amino-3-phenylpropanoate (7) and (8): A solution of N-Boc-L-phenylalanine (6.1 g, 22.8 mmol) in CH_2Cl_2 (55 mL) was cooled to 0 °C. *N*,*N*-dicyclohexylcarbodiimide (4.7 g, 22.8 mmol) was added in several portions and a white precipitate formed quickly. After 10 min **6** (2.5 g, 15.2 mmol) dissolved in

CH_2Cl_2 (36.5 mL) and DMAP (0.092 g, 0.76 mmol) were added. The mixture was stirred at room temperature for 8 h. After addition of water (80 mL), the organic phase was extracted with diethyl ether and dried with $MgSO_4$. The residue was purified as a mixture of the two diastereoisomers by column chromatography on silica gel (petroleum ether/EtOAc, 3:1) to afford 6.3 g (98%) of the desired product. CF_3COOH (12 mL, 155.3 mmol) was added dropwise to a solution of the two diastereoisomers (6.3 g, 15.1 mmol) in $CHCl_3$ (48 mL). After 3.5 h the solution was concentrated to dryness, the residue diluted with $CHCl_3$ (45 mL) and washed twice with 15% NH_4OH, then brine, and dried with $MgSO_4$. After evaporation of the solvents, the residue was purified by column chromatography on silica gel (Et_2O/MeOH, 30:1), to give 1.98 g of each diastereoisomer (overall yield 83% from **6**).

(*R*,*S*)-7: White solid. M.p. 110.6−111.4 °C. $[\alpha]_D^{20}$ = +28 (*c* = 0.2, MeOH). ^1H NMR (CD_3OD): δ = 1.39 (s, 3 H, CH_3), 2.74−3.35 (m, 4 H, $2CH_2$), 3.60 (dd, *J* = 6.5, 12.9 Hz, 1 H, CH), 7.02 (d, *J* = 4.8 Hz, 1 H, ArCH), 7.07−7.21 (m, 5 H, ArCH), 8.07 (d, *J* = 4.8 Hz, 1 H, ArCH) ppm. ^{13}C NMR: (CD_3OD): δ = 22.90 (CH_3), 37.96 (CH_2), 40.27 (CH_2), 55.09 (CH), 86.92 (C), 124.45 (ArCH), 126.69(ArCH), 128.36 (2ArCH), 129.57 (2ArCH), 137.04 (ArC), 141.80 (ArCH), 163.42 (ArC), 173.56 (ArC), 194.76 (C=O) ppm. $C_{17}H_{17}NO_3S$ (315.4): calcd. C 64.74, H 5.43, N 4.44; found C 64.75, H 5.45, N 4.46. CCDC = 237741.

(*S*,*S*)-8: Yellow solid. M.p. 114.1−116.4 °C. $[\alpha]_D^{20}$ = +47 (*c* = 0.2, MeOH). ^1H NMR (CD_3OD): δ = 1.31 (s, 3 H, CH_3), 2.86−3.08 (m, 4 H, $2CH_2$), 3.61−3.67 (dd, *J* = 7.0, 14.0 Hz, 1 H, CH), 6.99 (d, *J* = 4.7 Hz, 1 H, ArCH), 7.08−7.23 (m, 5 H, ArCH), 8.08 (d, *J* = 4.7 Hz, 1 H, ArCH) ppm. ^{13}C NMR (CD_3OD): δ = 22.82 (CH_3), 37.83 (CH_2), 40.14 (CH_2), 54.85 (CH), 86.88 (C), 124.46 (ArCH), 126.74 (ArCH), 128.38 (2ArCH), 129.36 (2ArCH), 137.20 (ArC), 141.78 (ArCH), 163.35 (ArC), 173.8 (ArC), 194.72 (C=O) ppm. EI-MS: *m*/*z* = 315 [M^+].

(*R*)-5-Hydroxy-5-methyl-4,5-dihydro-6*H*-cyclopenta[*b*]thiophen-6-one [(−)-(6)]: $LiOH{\cdot}H_2O$ (6.15 g, 146 mmol) was added to a solution of **7** (1.80 g, 5.70 mmol) in THF (172 mL) and H_2O (290 mL). After 18 h at room temperature, the mixture was reduced in volume so that most of the THF was removed, then extracted with EtOAc (3 × 100 mL), dried with $MgSO_4$, filtered and concentrated. The crude was purified by column chromatography on silica gel (Et_2O/petroleum ether, 1:1) to afford 0.94 g (5.59 mmol, 98%) of (−)-**6** as a thick colorless oil. $[\alpha]_D^{20}$ = +55 (*c* = 0.2, $CHCl_3$). For the other diastereoisomer **8** the same procedure gave (*S*)-**6**. Thick colorless oil. $[\alpha]_D^{20}$ = −55 (*c* = 0.2, $CHCl_3$).

(*R*)-5-Hydroxy-5-methyl-4,5-dihydro-6*H*-cyclopenta[*b*]thiophen-6-one *O*-Methyloxime (13): $MeONH_2{\cdot}HCl$ (0.4 g, 4.78 mmol) was added to (0.67 g, 3.98 mmol) of **6** in pyridine (20 mL). After 24 h at room temperature the mixture was concentrated to remove the pyridine. Water was added, and the solution was extracted with EtOAc (2 × 40 mL). The combined organic phases were dried with $MgSO_4$, filtered, concentrated and purified by column chromatography on silica gel (petroleum ether/Et_2O, 2:1) to afford 0.73 g (3.7 mmol, 93%) of **13** as a yellow solid. M.p.: 101−102.6 °C. $[\alpha]_D^{20}$ = −15.1 (*c* = 0.5, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 1.57 (s, 3 H, CH_3), 3.01 (dd, *J* = 7.4, 16.9 Hz, 2 H, CH_2), 3.93 (s, 3 H, OCH_3), 6.82 (d, *J* = 4.9 Hz, 1 H, ArCH), 7.56 (d, *J* = 4.9 Hz, 1 H, ArCH) ppm. ^{13}C NMR ($CDCl_3$): δ = 28.58 (CH_3), 43.88 (CH_2), 62.42 (CH_3), 82.43 (C), 122.89 (ArCH), 130.91 (ArC), 136.95 (ArCH), 151.86 (ArC), 159.22 (C) ppm. EI-MS: *m*/*z* = 197 [M^+].

(*R*,*R*)-6-Amino-5-methyl-5,6-dihydro-4*H*-cyclopenta[*b*]thiophen-5-ol (14): A solution of $BH_3{\cdot}THF$ (1.0 M solution in THF 11.2 mL, 11.2 mmol) was added dropwise to a solution of **13** (0.73 g, 3.7 mmol) in freshly distilled THF (3.7 mL) at 0 °C. The mixture was heated at reflux for 6 h. Upon cooling, the mixture was extracted with Et_2O, the aqueous layer was made alkaline with NH_4OH to pH = 9, and then extracted with EtOAc twice. The organic layer was dried with $MgSO_4$, filtered and concentrated. ^1H NMR analysis of the crude product showed a *cis*/*trans* ratio of 98:2. Separation by column chromatography on silica gel (chloroform/methanol, 5:1) gave *cis* and *trans*-**14** (0.38 g) with an overall yield of 60%. ***trans* Isomer:** Thick yellow oil. ^1H NMR ($CDCl_3$): δ = 1.38 (s, 3 H, CH_3), 1.80 (br. s, 3 H, OH+NH_2), 2.80 (dd, *J* = 15.9, 20.9 Hz, 2 H, CH_2), 3.98 (s, 1 H, CH), 6.75 (d, *J* = 5.0 Hz, 1 H, ArCH), 7.19 (d, *J* = 5.0 Hz, 1 H, ArCH) ppm. EI-MS: *m*/*z* = 169 [M^+]. ***cis* Isomer:** White solid. M.p. 146.3−147.8 °C. $[\alpha]_D^{20}$ = +10 (*c* = 0.1, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 1.35 (s, 3 H, CH_3), 1.79 (br. s, 3 H, OH+NH_2), 2.83 (dd, *J* = 15.9, 20.9 Hz, 2 H, CH_2), 4.16 (s, 1 H, CH), 6.77 (d, *J* = 5.0 Hz, 1 H, ArCH), 7.21 (d, *J* = 5.0 Hz, 1 H, ArCH) ppm. ^{13}C NMR ($CDCl_3$): δ = 22.98 (CH_3), 42.94 (CH_2), 64.96 (CH), 87.16 (C), 122.92 (ArCH), 128.55 (ArCH), 142.58 (ArC), 144.18 (ArC) ppm. EI-MS: *m*/*z* = 169 [M^+].

(*R*,*R*)-*N*-[(-5-Hydroxy-5-methyl-5,6-dihydro-4*H*-cyclopenta[*b*]thien-6-yl]benzamide (15): An aqueous solution of potassium hydrogen carbonate (1.5 M, 1.2 mL) was added to a solution of *cis*-**14** (0.25 g, 1.5 mmol) in IPAC (5.3 mL) at 65 °C. The mixture was maintained at 65−70 °C and benzoyl chloride (0.28 mL, 2.2 mmol) was added dropwise. The mixture was stirred for 3 h at 80 °C. After cooling, water was added and the mixture was extracted with EtOAc, dried with $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether/Et_2O, 3:1) to afford 0.36 g (88%) of **(15)** as a white solid. M.p. 168.6−170.1 °C. $[\alpha]_D^{20}$ = −43 (*c* = 0.23, $CHCl_3$). IR (CCl_4): nu (tilde) = 1694, 3435 cm^{-1}. ^1H NMR (CD_3OD): δ = 1.29 (s, 3 H, CH_3), 2.72 (d, *J* = 15.7 Hz, 2 H, CH_2), 2.91 (d, *J* = 15.7 Hz, 1 H, CH), 5.35 (br. s, 1 H, OH), 6.70 (d, *J* = 4.9 Hz, 1 H, ArCH), 7.18−7.39 (m, 4 H, ArCH), 7.65−7.69 (m, 2 H, ArCH), 8.17 (br. s, 1 H, NH) ppm. ^{13}C NMR (CD_3OD): δ = 23.48 (CH_3), 43.08 (CH_2), 62.03 (CH), 87.20 (C), 122.50 (ArCH), 127.40 (2ArCH), 128.38 (2ArCH), 130.01 (ArCH), 131.65 (ArCH), 134.59 (ArC), 139.49 (ArC), 146.03 (ArC), 169.23 (C) ppm.. EI-MS: *m*/*z* = 273 [M^+].

(*R*,*R*)-7a-Methyl-2-phenyl-7,7a-dihydro-3a*H*-thieno-[3′,2′:4,5]cyclopenta[1,2-*d*][1,3]oxazole (16): $Zn(OAc)_2$ (1.3 g, 6.7 mmol) which had been dried before use (under vacuum at 10^{-2} Torr and 160−170 °C for 3−4 h) and then powdered, was added to **15** (0.15 g, 0.6 mmol). The mixture was stirred for 48 h at 170 °C cooled, and water was added. The organic layer was extracted with EtOAc, dried with $MgSO_4$, filtered and concentrated. Purification by column chromatography on silica gel (petroleum ether/EtOAc, 3:1) gave **16** (0.094 g, 61%) as a yellow oil. $[\alpha]_D^{20}$ = +163.7 (*c* = 0.5, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 1.65 (s, 3 H, CH_3), 2.98 (d, *J* = 16.7 Hz, 1 H, CH_2), 3.27 (d, *J* = 16.7 Hz, 1 H, CH_2), 5.19 (s, 1 H, CH), 6.73 (d, *J* = 5.0 Hz, 1 H, ArCH), 7.25−7.40 (m, 4 H, ArCH), 7.86−7.90 (m, 2 H, ArCH) ppm. ^{13}C NMR ($CDCl_3$,): δ = 25.46 (CH_3), 41.88 (CH_2), 78.37 (CH), 98.36 (C), 122.11 (ArCH), 128.15 (2ArCH), 128.27 (2ArCH), 130.65(ArCH), 131.26 (ArCH), 134.30 (ArC), 141.44 (ArC), 142.27 (ArC), 163.94 (C=N) ppm. EI-MS: *m*/*z* = 255 [M^+].$C_{15}H_{13}NOS$ (255.3): calcd. C 70.56, H 5.13, N 5.49; found C 70.54, H 5.11, N 5.48.

(*R*,*S*)-5,6-Dimethyl-5,6-dihydro-4*H*-cyclopenta[*b*]thiophene-5,6-diol (17): Et_3N (3.5 mL, 25.28 mmol) was added to a solution of **(*S*)-6** (0.53 g, 3.16 mmol, $[\alpha]_D^{20}$ =-55; *c* = 0.2, $CHCl_3$) in Et_2O (3.2 mL). Me_3SiCl (3.2 mL, 25.28 mmol) was added dropwise at 0 °C, and

the mixture was stirred for 4 h at room temperature. $NaHCO_3$ was added and after extraction with Et_2O (3 × 10 mL) the crude was dried with $MgSO_4$, filtered and concentrated. The protected ketone was used in the next step without any further purification. ^1H NMR (C_6D_6): δ = 0.1 (s, 9 H, CH_3), 1.18 (s, 3 H, CH_3), 2.48 (d, J = 17.1 Hz, 1 H, CH_2), 2.70 (d, J = 17.1 Hz, 1 H, CH_2), 6.19 (d, J = 4.7 Hz, 1 H, ArCH), 6.85 (d, J = 4.7 Hz, 1 H, ArCH) ppm.

MeMgBr (3 M solution in Et_2O, 5.3 mL, 15.8 mmol) was added dropwise to a solution of crude silyl ether (3.16 mmol) in dry Et_2O (6.2 mL) at −30 °C. After 18 h at room temperature, $NaHCO_3$ was added. The crude was extracted with Et_2O (3 × 10 mL), dried with $MgSO_4$, filtered, concentrated, and used in the next reaction without any further purification. ^1H NMR (C_6D_6): δ = 0.1 (s, 9 H, CH_3), 1.18 (s, 3 H, CH_3), 1.35 (s, 3 H, CH_3), 2.51 (s, 2 H, CH_2), 6.38 (d, J = 4.8 Hz, 1 H, ArCH), 6.72 (d, J = 4.8 Hz, 1 H, ArCH) ppm.

TBAF (1 M solution in THF, 3.8 mL, 3.8 mmol) was added dropwise to a solution of crude alcohol (3.16 mmol) in THF (3.16 mL) at room temperature. After 4 h, NH_4Cl was added and the mixture was extracted with EtOAc (3 × 10 mL). The organic phase was washed twice with water, dried with $MgSO_4$, filtered and concentrated. The crude was purified by column chromatography on silica gel (CH_2Cl_2/Et_2O, 5:1) to afford (0.44 g, 2.40 mmol) of the diol **17** in a 76% overall yield starting from (*S*)-**6**. White solid. M.p. 162−163 °C. $[\alpha]_D^{20}$ = +21 (c = 0.1, MeOH). ^1H NMR (C_6D_6): δ = 1.10 (s, 3 H, CH_3), 1.26 (s, 3 H, CH_3), 2.47 (d, J = 17.4 Hz, 1 H, CH_2), 3.03 (d, J = 17.4 Hz, 1 H, CH_2), 6.35 (d, J = 5.0 Hz, 1 H, ArCH), 6.71 (d, J = 5.0 Hz, 1 H, ArCH) ppm. ^{13}C NMR (C_6D_6,): δ = 21.19 (CH_3), 21.84 (CH_3), 42.43 (CH_2), 82.68 (C), 87.86 (C), 122.50 (ArCH), 128.38 (ArCH), 143.08 (ArC), 147.33 (ArC) ppm. $C_9H_{12}O_2S$ (184.3): calcd. C 58.67, H 6.56; found C 58.66, H 6.55.

(*S*,*S*)-3a,7a-Dimethyl-2-phenyl-7,7a-dihydro-3a*H*-thieno-[[3′,2′:4,5]cyclopenta1,2-*d*][1,3]oxazole (18): PhCN (0.09 mL, 0.91 mmol) was added to a solution of **17** (0.15 g, 0.82 mmol) in CH_2Cl_2 (1.6 mL). The mixture was cooled to −30 °C, CF_3SO_3H (0.22 mL, 2.46 mmol) was added dropwise and stirring was continued at this temperature for 1 h. After addition of $NaHCO_3$, the mixture was extracted with EtOAc (3 × 10 mL), dried with $MgSO_4$, filtered and concentrated. The crude was purified by column chromatography on silica gel (petroleum ether/Et_2O, 3:1) to afford 0.18 g (82%) of the oxazole **18**. White solid. M.p. 124.1−125.3 °C. $[\alpha]_D^{20}$ = +122 (c = 0.3, MeOH). ^1H NMR (C_6D_6): δ = 1.46 (s, 3 H, CH_3), 1.53 (s, 3 H, CH_3), 2.91 (d, J = 16.8 Hz, 1 H, CH_2), 3.24 (d, J = 16.8 Hz, 1 H, CH_2), 6.68 (d, J = 5.2 Hz, 1 H, ArCH), 7.13−7.23 (m, 5 H, ArCH), 7.90 (d, J = 5.2 Hz, 1 H, ArCH) ppm. ^{13}C NMR (C_6D_6,): δ = 21.84 (CH_3), 23.15 (CH_3), 42.10 (CH_2), 80.99 (C), 99.62 (C), 122.17 (ArCH), 124.47 (2ArCH), 127.8 (2ArCH), 128.45 (ArC), 129.69 (ArCH), 130.99 (ArCH), 139.49 (ArC), 148.31 (ArC), 161.71 (C=N) ppm. EI-MS: m/z = 269 [M^+].$C_{16}H_{15}NOS$ (269.4): calcd. C 71.34, H 5.61, N 5.20; found C 71.32, H 5.60, N 5.19.

Preparation of the Complex Cu(OTf)$_2$-(12): In a 10-mL flame-dried flask, a solution of $Cu(OTf)_2$ (4 mg, 0.0105 mmol, 2.1 mol %) and the chiral ligand (0.005 g, 0.042 mmol, 4.2 mol %) in dry toluene (1 mL) was stirred at room temperature under argon for 1 h. The solvent was removed in vacuo and the residue obtained was analyzed by ESI-MS: m/z = 844 [Cu + 2OTf$^-$ + 2L], 694 [M^+ − TFO$^-$], 545 [M^+ − 2TFO$^-$], 305 [M^+ − 2TFO$^-$ − L].

General Procedure for Copper-Catalyzed Conjugate Addition of Et$_2$Zn to Chalcone: In a 10-mL flame-dried flask, a solution of $Cu(OTf)_2$ (4 mg, 0.0105 mmol, 2.1 mol %) and the chiral ligand (0.042 mmol, 4.2 mol %) in dry solvent (1 mL) was stirred at room temperature under argon. After 1 h, chalcone (104 mg, 0.5 mmol) was added. The solution was then cooled to −20 °C and $ZnEt_2$ (0.6 mmol, 0.6 mL of a 1 M solution in hexane) was added dropwise. The mixture was stirred while the temperature was allowed to rise from −20° to 0 °C over 6 h. The reaction was quenched with 1 N HCl (5 mL) and the aqueous layer was extracted twice with EtOAc (2 × 5 mL). The combined organic extracts were dried (Na_2SO_4), filtered and the solvents evaporated. Purification by column chromatography on silica gel (EtOAc/light petroleum, 1:20), yielded 40−61% of product as a colorless oil that solidified on standing. The enantiomeric excess was determined by HPLC analysis on a Daicel Chiralcel OD column at λ = 254 nm; flow rate 0.30 mL/Min; eluent: hexane/*i*PrOH, 99.75:0.25, t_S = *70.30 min*, t_R = *74.92 min*

Computational Details: All the DFT computations reported here were performed using the Gaussian 98[35] series of programs using the nonlocal hybrid Becke's three-parameter exchange functional[38a,38b] (denoted as B3LYP). This functional has been demonstrated as being capable of providing a reliable description (structure and energy) of transition metal complexes and potential surfaces associated with catalytic processes.[38c−38f] For the metal cation (Cu^{+1}), we used the energy-adjusted pseudopotential basis set proposed by Preuss and coworkers[38g] (sdd pseudopotentials in the Gaussian 98 formalism). All the remaining atoms were described by the DZVP basis set, which is a Local Spin Density (LSD)-optimized basis set of double-zeta quality.[38h] This basis set, which includes polarization functions, is suitable for description of the interactions between the metal, the sulfur and nitrogen lone-pairs and the π system. The geometry of the various critical points has been fully optimized with the gradient method available in Gaussian 98. A computation of the harmonic vibrational frequencies was carried out to determine the nature of each critical point.

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