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Cyclopenta[*b*]thiophene-alkyloxazolines: new nitrogen–sulfur hybrid ligands and their use in asymmetric palladium-catalyzed allylic alkylation

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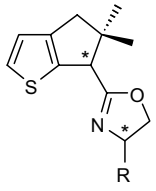
Abstract—New chiral nitrogen and sulfur containing hybrid ligands have been prepared and fully characterized. Their structure includes cyclopenta[*b*]tiophene and oxazoline moieties as sources of chirality. Their catalytic activity has been tested successfully in the Pd-allylic alkylation leading to enantioselectivities of up to 74% ee.

1. Introduction

The search for new ligands in asymmetric catalysis is a field of continuing interest. To facilitate practical applications, new ligands should be easy to prepare from simple and easily accessible starting materials. In this context the use of nitrogen and sulfur containing ligands is growing. Recent reports have shown that these compounds are suitable for many types of catalysis.[1] Among chiral moieties containing nitrogen, oxazolines have several advantages as sources of chirality, the principal being that they are readily accessible from homochiral amino alcohols and have proven to be effective catalysts in a variety of reactions.[2] The use of a second different heteroatom binding site to induce electronic bias in the intermediate catalyst–substrate complex has been reported so far, often with sulfur being used for this purpose. Whereas the thioeter moiety has been frequently used,[3] thiophene has only occasionally been employed,[4] although there are reports of thiophene functioning as either η^1 or η^5 ligands.[5] High stability and fairly good accessibility from the chiral pool, highlight some beneficial aspects of ligands based on sulfur and nitrogen when compared with phosphines. Furthermore the thiophene–oxazoline combination in ligands for asymmetric catalysis has for the most part been largely overlooked.[6]



CPTO$_X$

Figure 1.

Herein we report the synthesis of novel bidentate ligands (Fig. 1) with two stereogenic centres with an oxazoline moiety linked to a rigid cyclopenta[*b*]thiophene,5,6,-dihydro backbone in which the sulfur atom is part of a strong π-donor structure.

The first promising results with these chiral ligands for the enantioselective palladium-catalyzed allylic substitution are also described.

2. Synthesis of the ligands

The different cyclopenta[*b*]thiophene-alkyloxazolines (CPTOx's) have been synthesized following classical

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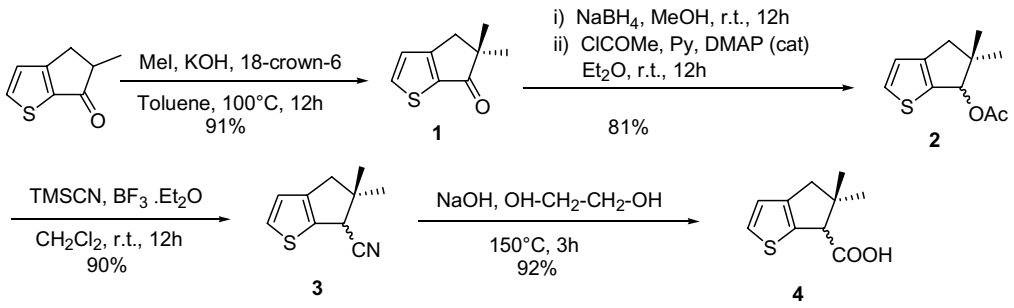
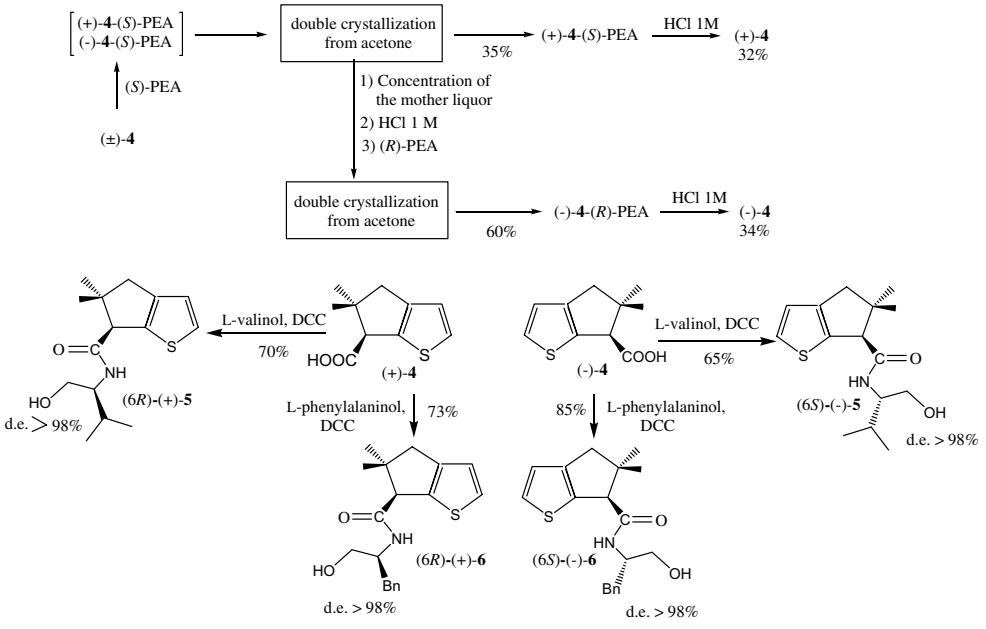


Scheme 1.

synthetic procedures for oxazolines. The 5-methyl-4,5-dihydro-4H-cyclopenta[*b*]thiophen-6-one was prepared using the one-pot reaction developed by Meth-Cohn and Gronowitz.[7] Under treatment of this ketone with MeI and KOH in the presence of catalytic amounts of 18-crown-ether the 5,5 dimethyl derivative **1** was isolated in 91% yield. For the synthesis of racemic carboxylic acid *rac*-**4**, **1** was readily converted as shown in Scheme 1 via $NaBH_4$ reduction into the corresponding alcohol. At this stage the acetylated derivative **2** was transformed into the nitrile **3** by treatment with Me_3SiCN under activation of $BF_3{\cdot}Et_2O$.

Hydrolysis with NaOH in ethylene glycol[8] finally afforded *rac*-**4** in 67% overall yield from **1**.

We next examined (Scheme 2) the resolution of *rac*-**4** using phenethylamine as a chiral amine. Crystallization and successive recrystallization of a diastereomeric salt mixture of *rac*-**4** with (*S*)-(−)-α-phenethylamine [(*S*)-PEA] from acetone, afforded the (+)-**4**-(*S*)-PEA salt as a white solid in 35% yield. By treatment with 1 M HCl followed by dilution with water and extraction with Et_2O after solvent evaporation, the enantiomerically enriched free acid (+)-**4** was obtained in 32% overall yield from *rac*-**4**. Concentration under reduced pressure of the mother liquor followed by treatment with 1 M HCl, gave (−)-enriched **4**, which was converted into the (−)-**4**-(*R*)-PEA salt by treatment with (*R*)-(−)-α-phenethylamine [(*R*)-PEA]. Crystallization and successive recrystallization from acetone gave the diastereomerically enriched salt in 60% yield, from which, upon treatment with 1 M HCl, enantiomerically enriched (−)-**4** was obtained in 34% yield from *rac*-**4**. From the filtrate, *rac*-**4** was recovered with no chemical deterioration nor significant loss and could thus be used in the next resolution. The two enantiomerically enriched compounds (+)-**4** and (−)-**4** were then transformed into the corresponding amides (+)-**5** and (−)-**5** by a reaction with (2*S*)-(−)-2-amino-2-isopropyl-ethan-1-ol (L-valinol). On the same grounds the reaction of (+)-**4** and (−)-**4** with (*S*)-(−)-2-amino-3-phenyl-1-propanol (L-phenylalaninol) led to hydroxyamides (+)-**6** and (−)-**6**. In no one case did racemization occur during the reaction using DCC in CH_2Cl_2 at rt. The diastereomeric excesses detected on the crude amides were found to be



Scheme 2.

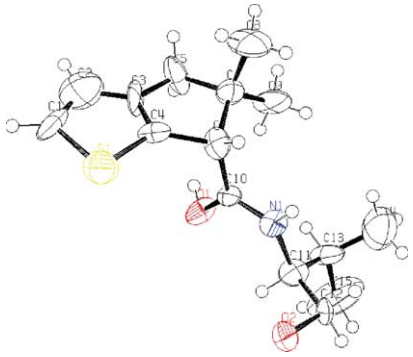


Figure 2. ORTEP drawing.

90% by ^{1}H and ^{13}C NMR spectra thus suggesting that enantiomeric excess of enriched (+)-**4** and (−)-**4** was 90%. After column chromatography (see Experimental), amides (+)-**5**, (−)-**5**, (+)-**6** and (−)-**6** were obtained as single diastereoisomers with de >98%.

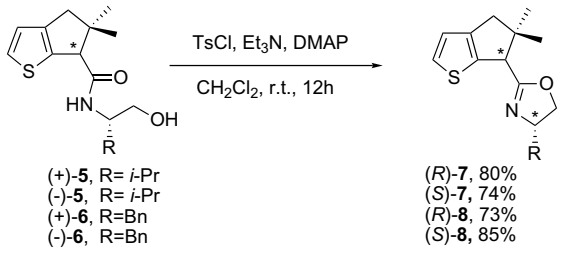
The absolute configuration of the carbon atom at the 6-position in (+)-**5** was determined (Fig. 2) to be (*R*) by a single-crystal X-ray structural analysis.[9] Consequently, an (*R*)-configuration at the 6-position of (+)-**4** was established. The absolute configuration of (−)-**4** would thus follow to be (*S*). In an analogous way, the absolute configuration at C-6 in (+)-**6** and (−)-**6** could be deduced to be (*R*) and (*S*), respectively (Fig. 2).

The synthetic plan revealed that the oxazoline core could be synthesized via a ring-forming procedure developed by Evans[10] by treating the hydroxyamides with *p*-toluensulfonyl chloride and TEA in the presence of catalytic quantities of DMAP (Scheme 3).

CPTOx's (*i*-Pr), (*R*)-**7** and (*S*)-**7** were thus obtained according to this procedure from (+)-**5** and (−)-**5** and CPTOx's (Bn). (*R*)-**8** and (*S*)-**8** were similarly synthesized starting from (+)-**6** and (−)-**6**. After purification, the average yields of isolated products for the whole process starting from carboxylic acids (+)-**4** and (−)-**4**, were around 50%.

2.1. Pd-catalyzed allylic substitution

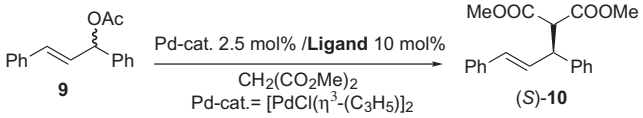
Palladium-catalyzed allylic alkylation with soft carbon nucleophiles is a useful tool for C–C bond formation.[11] In the reaction of 1,3-diphenylacetate with dimethyl malonate, chiral ligands may lead to enantioselectivity. The new ligands **7** and **8** shown in Scheme 3 were tested in this catalytic system to see if they were able to bind to a suitable palladium precursor and interact with the allylic substrate. Allylic substitutions on acetate **9** were carried out using $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, and a mixture of dimethylmalonate *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and potassium acetate in methylene chloride at 40 °C. The ligand and palladium procatalyst were premixed in CH_2Cl_2 at room temperature for 1 h prior to the reaction. After a suitable reaction time, isolated product **10** was essayed for enantiomeric excess by employing HPLC analysis on a Daicel Chiralcel OD-column with absolute configuration determined by comparison with literature values.[12]



Scheme 3.

Table 1 summarizes the yields and the enantioselectivities reached. Ligands **7** and **8** gave effective palladium catalysis affording the dimethyl 1,3-diphenylprop-2-enylmalonate **10** in very high yields, with the only difference in reaction rates being detected in favour of the (*S*)-configured ligands. When the influence of the ratio of ligand versus palladium on the enantiomeric excess was tested, no sizeable variation in activity was observed between a 1:1 ratio (see entry 5) and a 2:1. This indicated that these ligands could act as bidentate species towards the metal centre and that the active catalytic species formed is more rapidly obtained and stabilized in the presence of an excess amount of ligand. The assumption that the catalytic species is an ML_1-type complex formed between 1 mol of CPTOx per Pd atom and therefore that these N,S-ligands are quite strongly bound to the metal centre, is further supported by the ESI spectrum of the Pd-ligands complex (see Experimental). Good levels of enantioselectivity were observed throughout and substituents on the oxazoline ring did not appear to be influential to ensure different enantiodiscrimination. However a surprising result deals with the fact that irrespective of the configuration of the ligands [(*R*) or (*S*)] all the complexes induce an excess of the enantiomer with an (*S*)-configuration as shown in Table 1. To rationalize the direction of the enantioselectivity, we assumed according to the accepted notion, that

Table 1. Allylic alkylation of *rac*-**9** with CPTOx's ligands



Entry	Ligand	Solvent	Time (h)	Yield of **10** (%)	Ee (%)
1	(*R*)-**7**	CH_2Cl_2	136	95	66 (*S*)
2	(*S*)-**7**		70	91	70 (*S*)
3	(*R*)-**8**		96	92	62 (*S*)
4	(*S*)-**8**		30	93	73 (*S*)
5[a]	(*S*)-**8**		60	94	74 (*S*)
6	(*S*)-**8**	Toluene	48	96	51 (*S*)
7	(*R*)-**7**/(*S*)-**7** 1/1	CH_2Cl_2	112	96	69 (*S*)
8	(*R*)-**8**/(*S*)-**8** 1/3		96	94	73 (*S*)

[a] Reaction of the ligand (5 mol%) and Pd-cat (2.5 mol%).

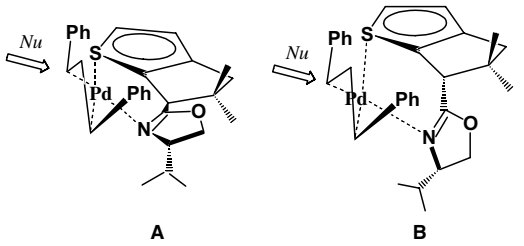


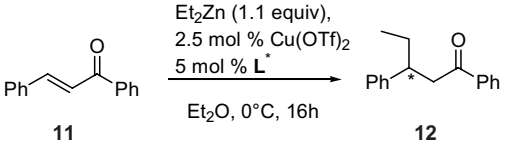
Figure 3.

nucleophilic attack of the π-allyl complex occurs, *trans* to the better π-acceptor end of the chelate ligand from the most stable Pd-allyl intermediate. In ligands **7** and **8** the thiophene moiety would behave as a π-donor since it is a π-excessive aromatic and also in agreement with literature data[6a,13] that the oxazoline N atom is the better π-acceptor. The plausible key π-allyl palladium intermediates A and B involved in the reaction of 1,3-diphenylpropenyl acetate in the presence of ligands (*S*)-**7** and (*R*)-**7** are depicted in Figure 3.

We infer that for the 1,3-diphenylallyl group used here W configured (π-allyl)palladium complex intermediates A and B (*exo*) are enforced rather than those M configured (*endo*) in which the phenyl groups would be oriented towards the steric bulk. Attack of the malonate nucleophile should logically occur away from the greatest steric bulk (Fig. 3) on the side of the thiophene ring. This is also expected electronically[14] as the soft nucleophile attacks *trans* to the oxazoline nitrogen, which is the better π-acceptor and would thus lead in both cases to the observed (*S*)-configuration of **10**.

Finally as shown in Table 1 (entries 7 and 8), mixtures of diastereoisomers can be successfully applied in the asymmetric allylic alkylation. Thus in the experiment reported in entry 7, an enantiomeric excess of 69% in favour of the (*S*)-configured product, which is comparable to the 66% (entry 1) and 70% (entry 2) obtained in the sole presence of (*R*)-**7** or (*S*)-**7**, respectively, was achieved with a catalyst that had 0% de. Similarly using unequal mixtures of diastereomeric 9-CPTOx's (entry 8) led to almost the same results obtained with the pure diastereomers. There are quite a few cases in the literature in which mixtures of diastereoisomers have been employed.[15] We feel that in our case these unexpected results cannot be explained by drastically different reaction rates of the two diastereoisomers[16] and therefore by the predominance of one catalyst on the stereochemical outcome, or by the occurrence of nonlinear effects.[17] Rather we assume that the previously mentioned capacity of the CPTOx's ligands in the (*R*)- or (*S*)-configuration to stabilize only the *exo*-palladium complexes A and B, combined with the electronic bias exerted by the two chelating centres, which dictates the nucleophilic attack along the same trajectory, might account for these results. It is important to realize that such a phenomenon could be of preparative importance in those cases where no complete stereoselectivity in a ligand functionalization process is feasible since the resulting diastereomeric mixture as such could be highly useful in enantioselective catalysis. In the present context it could allow, for instance, the synthesis of CTPOx ligands starting directly from *rac*-**4**. Finally very preliminary results obtained in the 1,4-conjugated addition of diethylzinc to chalcone **11** (Table 2) suggest that this peculiar behaviour of CTPOx ligands is only restricted to the allylic alkylation.

Table 2. Asymmetric conjugate addition of *trans*-chalcone **11** with CPTOx's ligands



Ligand	Yield of **12** (%)	Ee (%)	Configuration
(*R*)-**8**	35	44	*R*
(*S*)-**8**	33	7	*S*

Using CTPOx (*S*)-**8**, (though the addition product is obtained in both cases in moderate yields) a marked decrease in enantioselectivity was observed together with an inversion of configuration of the addition product **12** on going from the (*R*)- to the (*S*)-configured ligand. Evidently the configuration at C-6 plays in this case an important role in determining the reaction stereoselectivity as the consequence of a different reaction mechanism.

3. Conclusions

We have prepared four new bidentate S–N ligands with multiple stereogenic elements and with (*S*)-oxazoline and (6*R*)- or (6*S*)-cyclopenta[*b*]thiophene moieties as homochiral cores. The ligands, available in five simple synthetic steps in good yields and fairly large amounts, were stable and reusable. They were tested in Pd-catalyzed asymmetric allylic alkylation, reaching in all cases almost quantitative yields of the alkylation product and up to 74% ee. With these ligands the observation that the prevailing (*S*)-configuration obtained in the substitution product is not connected with the configuration at C-6, indicates that the catalysts provide a unique chiral environment, which orientates the allyl fragment into a predisposed conformation around the Pd-allyl axis and dictates the reaction at one end of the allyl fragment. This intriguing issue turns out to be of high interest allowing, in several cases, the use of diastereomeric mixtures of new ligands in asymmetric catalysis.

4. Experimental

Melting points (uncorrected) were determined with a Büchi melting point apparatus. ^{1}H NMR and ^{13}C NMR spectra were recorded using $CDCl_3$ solutions at 300, 400

and 600 MHz for 1H and 75.46, 100.6 and 150.92 MHz for ^{13}C. Chemical shifts (δ) are reported in ppm relative to $CHCl_3$ ($\delta = 7.26$ for ^1H and $\delta = 77.0$ for ^{13}C or 7.24 and 128.0 ppm for C_6D_6). J values are given in Hz. ^1H NMR and ^{13}C NMR spectral assignments were made by DEPT, gCOSY and gHSQC 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. $[\alpha]_D^{20}$ values were determined with a Perkin–Elmer Polarimeter 341. 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. Toluene was distilled from sodium. Et_2O was distilled from phosphorus pentoxide. 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 with 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 needed. Lithium aluminium hydride (1 M THF) was purchased by Aldrich. Ee measured on a Daicel Chiralcel OD column at $\lambda = 254$ nm; absolute configuration was determined by comparison with known data.

4.1. 5,5-Dimethyl-4,5-dihydro-6*H*-cyclopenta[*b*]thiophen-6-one 1

Powdered KOH (13.5 g, 240.6 mmol) was mixed with toluene (70 mL) and 18-crown-6 (18.5 mg, 0.07 mmol). The starting ketone (5.6 g, 36.8 mmol) was added and the obtained mixture heated to 70 °C. Iodomethane (32 g, 225.4 mmol) was then added and after 12 h of refluxing, the mixture was cooled and quenched by the addition of water (50 mL). The two layers were separated, and the aqueous layer was extracted twice with ether (2×50 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. Purification by distillation under vacuum (bp 114–116 °C/1.8 mmHg) afforded 5.58 g (91%) of **1** as a colourless oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.91 (d, $J = 4.8$ Hz, 1H), 7.01 (d, $J = 4.8$ Hz, 1H), 2.87 (s, 2H), 1.28 (s, 6H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 201.9 (s), 164.9 (s), 140.5 (d), 138.6 (s), 123.9 (d), 51.6 (s), 40.3 (t), 25.4 (q); IR ν_{max} (thin film, NaCl plate) 1704.8 cm^{-1}; GC–MS m/z (relative intensity) 166 (65); TLC: $R_f = 0.56$ (light petroleum/EtOAc 85/15).

4.2. 5,5-Dimethyl-5,6-dihydro-4*H*-cyclopenta[*b*]thiophen-6-yl acetate 2

$NaBH_4$ (1.6 g, 42.3 mmol) was added portionwise to a stirred ice cooled solution of ketone **1** (5.58 g, 33.6 mmol) in dry methanol (150 mL). Stirring was continued for 12 h at room temperature. The mixture was then cooled in a ice bath, and water (60 mL) then added. The methanol was removed and the aqueous phase extracted with ether (3×50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated. Chromatography on silica gel of the crude (Et_2O/light petroleum 1/2) yielded 5.2 g (92%) of alcohol as a white solid, mp 69–70 °C. ^1H NMR ($CDCl_3$, 75.3 MHz) δ 7.31 (d, $J = 4.8$ Hz, 1H), 6.79 (d, $J = 4.8$ Hz, 1H), 4.64 (s, 1H), 2.70 (d, $J = 15.3$ Hz, 1H), 2.48 (d, $J = 15.3$ Hz, 1H), 1.65 (m, 1H, OH), 1.22 (s, 3H), 1.19 (s, 3H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 146.7 (s), 142.9 (s), 130.0 (d), 122.6 (d), 80.2 (d), 49.5 (s), 41.6 (t), 28.5 (q), 23.2 (q); IR ν_{max} (thin film, NaCl plate) 3599.6, 3465.5 cm^{-1}; GC–MS m/z (relative intensity) 168 (8), 150 (43); TLC: $R_f = 0.47$ (light petroleum/EtOAc 85/15). Acetyl chloride (3.7 g, 3.4 mL, 47.6 mmol) was slowly added to a stirred ice cooled solution of alcohol (4.0 g, 23.8 mmol), DMAP (586 mg, 4.8 mmol) and pyridine (9.4 g, 9.6 mL, 119 mmol) in anhydrous diethyl ether (120 mL) under N_2. After 12 h at room temperature, to the mixture cooled in an ice bath, water (30 mL) and ether (50 mL) were added. The organic phase was separated and washed with a copper sulfate saturated solution (3×30 mL) and brine (30 mL). After drying over Na_2SO_4, and ether removal, rapid chromatography on silica gel of the crude (Et_2O/light petroleum 1/9) afforded 4.5 g (21.4 mmol, 90%) of **2** as a colourless oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.33 (d, $J = 4.8$ Hz, 1H), 6.78 (d, $J = 4.8$ Hz, 1H), 5.54 (s, 1H), 2.77 (d, $J = 15.3$ Hz, 1H), 2.50 (d, $J = 15.3$ Hz, 1H), 2.06 (s, 3H), 1.23 (s, 3H), 1.22 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.3 MHz) δ 171.0 (s), 148.6 (s), 138.9 (s), 131.3 (d), 122.2 (d), 81.2 (d), 48.5 (s), 42.1 (t), 28.8 (q), 23.5 (q), 21.0 (q); IR ν_{max} (thin film, NaCl plate) 1733.4 cm^{-1}; ESIMS m/z 233 (M+Na); TLC: $R_f = 0.85$ (light petroleum/EtOAc 85/15).

4.3. 5,5-Dimethyl-5,6-dihydro-4*H*-cyclopenta[*b*]thiophene-6-carbonitrile 3

To a stirred solution of acetate **2** (4.5 g, 21.4 mmol) and TMSCN (2.5 g, 3.2 mL, 25.7 mmol) in dry CH_2Cl_2 (150 mL), cooled to 0 °C under N_2, BF_3–Et_2O (3.6 g, 3.2 mL, 25.7 mmol) was slowly added. After stirring at room temperature for 2 h, to the mixture cooled in an ice bath, water (50 mL) was added. The organic phase was separated off, and the aqueous phase extracted with CH_2Cl_2 (2×30 mL). The combined organic layers were washed with 10% solution of Na_2CO_3 (2×30 mL), and dried over Na_2SO_4. Evaporation of the solvent gave 3.8 g (100%) of the crude product as a dark oil. This was purified by means of a bulb to bulb distillation (120–130 °C/1 mmHg) yielding 3.4 g (19.3 mmol, 90%) of **3** as a light-yellow oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.28 (dd, $J = 1.2$, 5.1 Hz, 1H), 6.79 (d, $J = 5.1$ Hz, 1H), 3.83 (s, 1H), 2.74 (dd, $J = 1.2$, 15.3 Hz, 1H), 2.63 (dd, $J = 1.2$, 15.3 Hz, 1H), 1.43 (s, 3H), 1.35 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.3 MHz) δ 146.6 (s), 134.5 (s), 129.9 (d), 122.6 (d), 118.3 (s), 50.4 (s), 43.7 (d), 42.6 (t), 28.9

(q), 26.6 (q); IR ν_{max} (thin film, NaCl plate) 2240.0 cm^{-1}; ESIMS m/z 200 (M+Na); TLC: $R_f = 0.58$ (light petroleum/EtOAc 85/15).

4.4. 5,5-Dimethyl-5,6-dihydro-4*H*-cyclopenta[*b*]thiophene-6-carboxylic acid 4

To a stirred solution of nitrile **3** (3.4 g, 19.2 mmol) in ethylene glycol (150 mL), NaOH was added (24 g, 0.6 mol) in one portion. The resulting mixture was heated to 140–150 °C for 3 h, then the solution cooled to 0 °C and water (100 mL) and Et_2O (100 mL) added followed by HCl 3 M (pH ≈ 1). The two layers were separated and the aqueous layer extracted twice with ether (2 × 30 mL). The combined organic layers were extracted three times with sodium carbonate solution 10% (3 × 35 mL). The aqueous phases were combined and the carboxylic acid liberated from its salt by cautious addition of HCl 3 M (pH ≈ 1). The aqueous layer was extracted three times with ether (3 × 40 mL). The organic phases were dried over Na_2SO_4, filtered and concentrated under vacuum. The yellow solid was purified by chromatography (silica gel, Et_2O/light petroleum 1/1) to give 3.46 g (17.7 mmol, 92%) of **4** as a colourless solid, mp 107–108 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.97 (br m, 1H), 7.27 (dd, $J = 1.2$, 5.1 Hz, 1H), 6.80 (d, $J = 5.1$ Hz, 1H), 3.78 (s, 1H), 2.71 (dd, $J = 1.2$, 15.3 Hz, 1H), 2.64 (dd, $J = 1.2$, 15.3 Hz, 1H), 1.42 (s, 3H), 1.22 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.3 MHz) δ 179.1 (s), 145.8 (s), 137.4 (s), 129.1 (d), 122.2 (d), 57.7 (d), 50.6 (s), 43.6 (t), 29.5 (q), 24.9 (q); IR ν_{max} (thin film, NaCl plate) 3526.6, 3253.4, 1705.8 cm^{-1}; ESIMS m/z 195 (M−H); TLC: $R_f = 0.23$ (light petroleum/EtOAc 85/15).

4.5. Resolution of the (*R*)-(+)-4 and (*S*)-(−)-4 enantiomers of 5,5-dimethyl-5,6-dihydro-4*H*-cyclopenta[*b*]thiophene-6-carboxylic acid 4

(±)-Carboxylic acid (±)-**4** (3.36 g, 17.1 mmol) was dissolved in acetone (100 mL) and (*S*)-(−)-α-phenethylamine [(*S*)-PEA] (2.1 g, 2.2 mL, 17.1 mmol) was added. After 1.5 h, the obtained salt [(+)-**4**-(*S*)-PEA] was filtered and dried under vacuum. The salt was recrystallized twice from acetone to give (*S*)-(−)-α-phenethylammonium-(+)-carboxylate as a white solid (1.9 g, 6.0 mmol, 35%), $[\alpha]_D^{20}$ +22.2 (*c* 0.75, $CHCl_3$). The salt was suspended in Et_2O (50 mL) and treated first with HCl (1 M, 3 × 15 mL) and then with water (15 mL). The free acid dissolved in Et_2O was dried over Na_2SO_4 and concentrated under reduced pressure to give (+)-**4** (1.07 g, 5.47 mmol, 32%) $[\alpha]_D^{20}$ +46 (*c* 0.5, $CHCl_3$). From the mother liquor it was possible to recover 2 g (10.2 mmol) of the racemic (enriched) carboxylic acid (±)-**4**, which was resolved following exactly the same procedure, but using (*R*)-(+)-α-phenethylamine (1.23 g, 1.29 mL, 10.2 mmol) [(*R*)-PEA]. After two crystallizations from acetone, 1.94 g (6.12 mmol, 60% yield) of (−)-**4**-(*R*)-PEA were recovered, $[\alpha]_D^{20}$ −23.3 (*c* 0.75, $CHCl_3$). After the acidic work-up, (−)-**4** $[\alpha]_D^{20}$ −46.6 (*c* 0.5, $CHCl_3$), was isolated in 34% yield (1.14 g, 5.81 mmol), from the starting *rac*-**4**.

4.6. (6*R*)-(+)-*N*-[(1*S*)-1-(Hydroxymethyl)-2-methylpropyl]-5,5-dimethyl-5,6-dihydro-4*H*-cyclopenta[*b*]thiophene-6-carboxamide (+)-5

N,*N*-dicyclohexylcarbodiimide (DCC) (200 mg, 0.97 mmol) was added to a stirred cooled solution (0 °C) of (+)-carboxylic acid (+)-**4** (180 mg, 0.92 mmol) in CH_2Cl_2 (7 mL). After 20 min, (2*S*)-(−)-2-amino-2-isopropyl-ethan-1-ol (100 mg, 0.97 mmol) was added in one portion. The reaction mixture was stirred at room temperature for 2 h, and the urea then filtered. The organic layer was diluted with Et_2O (30 mL) and washed successively with sodium carbonate solution 10% (10 mL), HCl (1 M, 10 mL) and then brine (10 mL). After filtration and evaporation of the solvents, the crude product was purified by flash chromatography (MeOH/$CHCl_3$ 0.5/99.5), affording 181 mg (70%) of (+)-**5** as a white solid: mp 106–108 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.31 (d, $J = 5.1$ Hz, 1H), 6.85 (d, $J = 5.1$ Hz, 1H), 5.66 (br m, 1H), 3.76 (m, 1H), 3.67 (dd, $J = 3.0$, 10.8 Hz, 1H), 3.59 (s, 1H), 3.56 (dd, $J = 6.6$, 10.8 Hz, 1H), 2.70 (d, $J = 14.7$ Hz, 1H), 2.59 (d, $J = 14.7$ Hz, 1H), 1.81 (m, 2H, OH), 1.37 (s, 3H), 1.23 (s, 3H), 0.91 (d, $J = 6.9$ Hz, 3H), 0.82 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.6 (s), 147.1 (s), 138.4 (s), 129.8 (d), 122.9 (d), 64.0 (t), 60.0 (d), 56.9 (d), 50.2 (s), 43.1 (t), 30.8 (q), 28.7 (d), 25.2 (q), 19.6 (q), 18.1 (q); IR ν_{max} (thin film, NaCl plate) 3378.7, 1650.9, 1509.6 cm^{-1}; ESIMS m/z 280 (M−H), 304 (M+Na); $[\alpha]_D^{20}$ +55.7 (*c* 0.5, $CHCl_3$); TLC: $R_f = 0.75$ ($CHCl_3$/MeOH 9/1), 0.48 ($CHCl_3$/MeOH 95/5).

For a single-crystal X-ray analysis, the amide (+)-**5** was recrystallized from hexane/Et_2O giving the product as white crystals. The absolute configuration of the asymmetric carbon atom at the 6-position of diastereoisomer (+)-**5** was established as (*R*). Consequently, an (*R*)-configuration at the 6-position of (+)-**4** was also established.

4.7. (6*S*)-(−)-*N*-[(1*S*)-1-(Hydroxymethyl)-2-methylpropyl]-5,5-dimethyl-5,6-dihydro-4*H*-cyclopenta[*b*]thiophene-6-carboxamide (−)-5

Following the same procedure as for (+)-**5**, but starting from (−)-**4**, (−)-**5** was obtained in 65% yield as a colourless oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.28 (dd, $J = 0.9$, 4.8 Hz, 1H), 6.82 (d, $J = 4.8$ Hz, 1H), 5.79 (br m, 1H), 3.62 (m, 1H), 3.60 (m, 1H), 3.54 (s, 1H), 3.40 (m, 1H), 2.67 (dd, $J = 0.9$, 15.3 Hz, 1H), 2.56 (d, $J = 15.3$ Hz, 1H), 2.28 (m, 1H, OH), 1.85 (m, 1H), 1.33 (s, 3H), 1.19 (s, 3H), 0.87 (d, $J = 6.9$ Hz, 3H), 0.81 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.3 MHz) δ 172.7 (s), 147.1 (s), 138.4 (s), 129.8 (d), 122.9 (d), 63.9 (t), 60.1 (d), 57.5 (d), 50.2 (s), 43.2 (t), 30.8 (q), 28.5 (d), 25.3 (q), 19.5 (q), 18.4 (q); $[\alpha]_D^{20}$ −86.7 (*c* 0.5, $CHCl_3$).

4.8. (6*R*)-(+)-*N*-[(1*S*)-1-Benzyl-2-hydroxyethyl]-5,5-dimethyl-5,6-dihydro-4*H*-cyclopenta[*b*]thiophene-6-carboxamide (+)-6

Following the same procedure as for (+)-**5**, (+)-**6** was obtained in 73% yield as a white solid: mp 95–96 °C. ^1H

NMR ($CDCl_3$, 400 MHz) δ 7.25 (m, 4H), 7.09 (dd, $J = 1.6$, 8.0 Hz, 2H), 6.80 (d, $J = 4.4$ Hz, 1H), 5.76 (d, $J = 7.2$ Hz, 1H), 4.20 (m, 1H), 3.61 (dd, $J = 4.0$, 11.2 Hz, 1H), 3.53 (dd, $J = 5.2$, 11.2 Hz, 1H), 3.46 (s, 1H), 3.18 (m, 1H, OH), 2.85 (dd, $J = 6.8$, 14.0 Hz, 1H), 2.72 (dd, $J = 8.0$, 14.0 Hz, 1H), 2.61 (dd, $J = 1.2$, 15.0 Hz, 1H), 2.52 (d, $J = 15.0$ Hz, 1H), 1.28 (s, 3H), 1.14 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.4 (s), 147.0 (s), 138.3 (s), 137.0 (s), 129.8 (d), 129.1 (d), 128.6 (d), 126.6 (d), 122.8 (d), 64.6 (t), 59.9 (d), 52.8 (d), 50.3 (s), 43.0 (t), 36.8 (t), 30.8 (q), 25.1 (q); IR ν_{max} (thin film, NaCl plate) 3408.3, 1664.6, 1501.1 cm^{-1}; ESIMS m/z 328 (M−H); $[\alpha]_D^{20}$ +38.9 (c 0.5, $CHCl_3$); TLC: $R_f = 0.77$ ($CHCl_3$/MeOH 9/1), 0.51 ($CHCl_3$/MeOH 95/5).

4.9. (6*S*)-(−)-*N*-[(1*S*)-1-Benzyl-2-hydroxyethyl]-5,5-dimethyl-5,6-dihydro-4*H*-cyclopenta[*b*]thiophene-6-carboxamide (−)-6

Following the procedure used for (+)-**5**, (−)-**6** was obtained in 85% yield as a colourless oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.30 (d, $J = 4.8$ Hz, 1H), 7.25 (m, 3H), 7.06 (dd, $J = 1.8$, 8.1 Hz, 2H), 6.81 (d, $J = 4.8$ Hz, 1H), 5.57 (br m, 1H), 4.09 (m, 1H), 3.70 (dd, $J = 3.3$, 11.4 Hz, 1H), 3.59 (dd, $J = 5.4$, 11.4 Hz, 1H), 3.46 (s, 1H), 2.88 (dd, $J = 6.3$, 13.8 Hz, 1H), 2.74 (m, 1H, OH), 2.60 (dd, $J = 9.3$, 13.8 Hz, 1H), 2.39 (d, $J = 15.0$ Hz, 1H), 2.19 (d, $J = 15.0$ Hz, 1H), 1.25 (s, 3H), 0.88 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.3 MHz) δ 172.4 (s), 147.1 (s), 138.0 (s), 137.4 (s), 129.8 (d), 128.9 (d), 128.5 (d), 126.5 (d), 122.7 (d), 64.3 (t), 59.8 (d), 53.1 (d), 50.1 (s), 42.6 (t), 36.7 (t), 30.8 (q), 24.8 (q); $[\alpha]_D^{20}$ −61.7 (c 0.5, $CHCl_3$).

4.10. (6*R*)-(−)-2-(5,5-Dimethyl-5,6-dihydro-4*H*-cyclopenta[*b*]thiophen-6-yl)-(4*S*)-4-isopropyl-4,5-dihydro-1,3-oxazole (*R*)-7

To a solution of (+)-**5** (160 mg, 0.57 mmol) in CH_2Cl_2 (4 mL) were added successively at room temperature *p*-TsCl (163 mg, 0.85 mmol), DMAP (3.5 mg, 5 mol%) and dry triethylamine (173 mg, 0.240 mL, 1.7 mmol). After 12 h, sodium carbonate solution 10% (5 mL) was added and the solution stirred for 30 min and then extracted once with CH_2Cl_2 (2 mL). The organic layer was dried over Na_2SO_4, filtered and the filtrate purified by chromatography (silica gel, AcOEt/light petroleum 1/9) without any reduction in volume of the crude. After purification, compound (*R*)-**7** was obtained in 80% (120 mg) yield as a pale yellow oil.

^1H NMR (C_6D_6, 300 MHz) δ 6.96 (dd, $J = 1.2$, 4.8 Hz, 1H), 6.62 (d, $J = 4.8$ Hz, 1H), 3.80 (dd, $J = 7.8$, 9.6 Hz, 1H), 3.79 (s, 1H), 3.69 (m, 1H), 3.53 (dd, $J = 7.5$, 7.8 Hz, 1H), 2.56 (d, $J = 14.4$ Hz, 1H), 2.41 (dd, $J = 1.2$, 14.4 Hz, 1H), 1.53 (m, 1H), 1.27 (s, 3H), 1.15 (s, 3H), 0.88 (d, $J = 6.9$ Hz, 3H), 0.74 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (C_6D_6, 75.3 MHz) δ 165.8 (s), 145.0 (s), 140.2 (s), 129.0 (d), 122.2 (d), 72.4 (d), 70.0 (t), 52.6 (d), 49.9 (s), 44.0 (t), 33.1 (d), 29.6 (q), 25.0 (q), 19.0 (q), 18.7 (q); IR ν_{max} (thin film, NaCl plate) 1656.1 (O–C=N) cm^{-1}; ESIMS m/z 264 (M+H), 286 (M+Na); $[\alpha]_D^{20}$ −68.0 (c 0.5, $CHCl_3$); TLC: $R_f = 0.53$ (light petroleum/EtOAc 85/15).

4.11. (6*S*)-(−)-2-(5,5-Dimethyl-5,6-dihydro-4*H*-cyclopenta[*b*]thiophen-6-yl)-(4*S*)-4-isopropyl-4,5-dihydro-1,3-oxazole (*S*)-7

Following the procedure used for (*R*)-**7**, (*S*)-**7** was obtained in 74% yield as a pale yellow oil. ^1H NMR (C_6D_6, 300 MHz) δ 6.97 (dd, $J = 0.9$, 5.1 Hz, 1H), 6.62 (d, $J = 5.1$ Hz, 1H), 3.84 (m, 2H), 3.60 (m, 2H), 2.53 (dd, $J = 0.9$, 14.4 Hz, 1H), 2.40 (dd, $J = 1.5$, 14.4 Hz, 1H), 1.52 (m, 1H), 1.25 (s, 3H), 1.15 (s, 3H), 0.96 (d, $J = 6.9$ Hz, 3H), 0.77 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (C_6D_6, 75.3 MHz) δ 165.7 (s), 145.0 (s), 140.3 (s), 128.9 (d), 122.2 (d), 72.5 (d), 70.3 (t), 52.5 (d), 50.0 (s), 43.9 (t), 33.5 (d), 29.5 (q), 25.0 (q), 18.9 (q×2); $[\alpha]_D^{20}$ −71.6 (c 0.5, $CHCl_3$).

4.12. (6*R*)-(−)-(4*S*)-4-Benzyl-2-(5,5-dimethyl-5,6-dihydro-4*H*-cyclopenta[*b*]thiophen-6-yl)-4,5-dihydro-1,3-oxazole (*R*)-8

Following the procedure used for (*R*)-**7**, (*R*)-**8** was obtained in 73% yield as a pale yellow oil. ^1H NMR (C_6D_6, 300 MHz) δ 7.12–6.96 (m, 6H), 6.63 (d, $J = 4.8$ Hz, 1H), 4.18 (m, 1H), 3.75 (s, 1H), 3.69 (dd, $J = 8.4$, 9.3 Hz, 1H), 3.60 (dd, $J = 7.8$, 8.4 Hz, 1H), 2.96 (dd, $J = 5.4$, 13.5 Hz, 1H), 2.54 (dd, $J = 0.6$, 14.7 Hz, 1H), 2.45 (dd, $J = 8.1$, 13.5 Hz, 1H), 2.40 (dd, $J = 1.5$, 14.7 Hz, 1H), 1.25 (s, 3H), 1.11 (s, 3H); ^{13}C NMR (C_6D_6, 75.3 MHz) δ 166.4 (s), 145.0 (s), 140.0 (s), 138.6 (s), 129.7 (d), 129.1 (d), 128.6 (d), 126.6 (d), 122.2 (d), 71.5 (t), 67.7 (d), 52.4 (d), 50.0 (s), 43.9 (t), 42.1 (t), 29.5 (q), 24.9 (q); IR ν_{max} (thin film, NaCl plate) 1656.6 (O–C=N) cm^{-1}; ESIMS m/z 312 (M+H), 334 (M+Na); $[\alpha]_D^{20}$ −0.5 (c 0.5, $CHCl_3$); TLC: $R_f = 0.40$ (light petroleum/EtOAc 85/15).

4.13. (6*S*)-(−)-(4*S*)-4-Benzyl-2-(5,5-dimethyl-5,6-dihydro-4*H*-cyclopenta[*b*]thiophen-6-yl)-4,5-dihydro-1,3-oxazole (*S*)-8

Following the procedure used for (*R*)-**7**, compound (*S*)-**8** was obtained in 85% yield as a pale yellow oil. ^1H NMR (C_6D_6, 300 MHz) δ 7.18–7.02 (m, 5H), 6.99 (dd, $J = 1.2$, 4.8 Hz, 1H), 6.63 (d, $J = 4.8$ Hz, 1H), 4.14 (m, 1H), 3.73 (s, 1H), 3.70 (dd, $J = 8.4$, 9.3 Hz, 1H), 3.62 (dd, $J = 7.8$, 8.4 Hz, 1H), 2.85 (dd, $J = 6.0$, 13.8 Hz, 1H), 2.55 (dd, $J = 0.9$, 14.4 Hz, 1H), 2.53 (dd, $J = 7.5$, 13.8 Hz, 1H), 2.40 (dd, $J = 1.2$, 14.4 Hz, 1H), 1.24 (s, 3H), 1.11 (s, 3H); ^{13}C NMR (C_6D_6, 75.3 MHz) δ 166.3 (s), 145.1 (s), 140.1 (s), 138.5 (s), 129.9 (d), 129.0 (d), 128.6 (d), 126.6 (d), 122.2 (d), 71.5 (t), 67.5 (d), 52.4 (d), 50.1 (s), 43.9 (t), 42.0 (t), 29.5 (q), 24.9 (q); $[\alpha]_D^{20}$ −41.3 (c 0.5, $CHCl_3$).

4.14. General procedure for palladium-catalyzed allylic alkylation

In a 10 mL flame-dried Schlenk tube $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (4.6 mg, 0.0125 mmol, 2.5 mol%) and the chiral ligand (0.05 mmol, 10 mol%) were dissolved under argon in dry and degassed CH_2Cl_2 (1 mL) and the resulting solution

stirred at room temperature. After 1 h, were added successively solutions of 1,3-diphenylprop-3-en-1-yl acetate (126 mg, 0.5 mmol) and dimethyl malonate (198 mg, 1.5 mmol) respectively in 1 and 0.5 mL of dry and degassed CH_2Cl_2, followed by *N*,*O*-(trimethylsilyl)acetamide (BSA, 304 mg, 1.5 mmol, 0.366 mL) and a catalytic amount of potassium acetate (1 mol%). The resulting mixture was stirred at 40 °C for 30–136 h and the solvent concentrated in vacuo to afford a dark crude product. The excess of dimethyl malonate was removed by means of a bulb to bulb distillation (65–75 °C/2 mmHg) and the dark crude mixture was purified by flash chromatography (AcOEt/light petroleum 1/9), affording 91–96% of product as a colourless oil that solidified on standing. The enantiomeric excesses were determined by HPLC analysis on a Daicel Chiralcel OD column at $\lambda = 254$ nm; flow rate 0.3 mL/min; eluent: hexane/*i*-PrOH 95/5, $t_R = 68$ min, $t_S = 72$ min.

4.15. (*R*)-8/Pd-allyl complex

To a solution of ligand (*R*)-**8** (34 mg, 0.11 mmol) dissolved in MeOH (1.5 mL), $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (20 mg, 0.055 mmol) was added. After stirring the resulting solution at room temperature for 30 min, $LiClO_4$ (60 mg, 0.55 mmol) in 1 mL MeOH was added. Stirring was continued at room temperature for 1 h, followed by aqueous work-up and extraction with CH_2Cl_2. Filtration through a Celite pad and solvent evaporation afforded the Pd complex as a yellow powder. ESIMS *m*/*z* 458 (M), 312.

4.16. General procedure for copper catalyzed conjugate addition of Et_2Zn to chalcone

In a 10 mL flame-dried flask, a solution of $Cu(OTf)_2$ (9 mg, 0.025 mmol, 2.5 mol%) and the chiral ligand (0.05 mmol, 5 mol%) in dry toluene (5 mL) was stirred at room temperature under argon. After 1 h, chalcone (208 mg, 1 mmol) was added. The solution was then cooled to −20 °C and $ZnEt_2$ (1.1 mmol, 1.1 mL of a 1 M solution of diethylzinc in hexane) was added dropwise. The mixture was stirred at 0 °C for 5 or 16 h. The reaction was quenched with HCl (1 M, 5 mL) and the aqueous layer extracted twice with ether (2 × 5 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, filtered and evaporated. Purification by chromatography on silica gel (AcOEt/light petroleum 2/98), yielded 35% of product as a colourless oil that solidified on standing. The enantiomeric excesses were determined by HPLC analysis on a Daicel Chiralcel OD column at $\lambda = 254$ nm; flow rate 1 mL/min; eluent: hexane/*i*-PrOH 95/5, $t_S = 12.4$ min, $t_R = 14.1$ min.

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