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Journal of Molecular Catalysis A: Chemical 191 (2003) 1–8

JOURNAL OF MOLECULAR CATALYSIS A: CHEMICAL

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# Chiral 2-(2-phenylthiophenyl)-5,6,7,8-tetrahydroquinolines: new N–S ligands for asymmetric catalysis Palladium-catalyzed allylic alkylation and copper-catalyzed cyclopropanation reactions

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Received 18 December 2001; accepted 14 March 2002

**Abstract**

Diastereomeric pure 2-(2-phenylthiophenyl)-5,6,7,8-tetrahydroquinolines were prepared and assessed in the enantioselective palladium-catalyzed allylic substitution of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate and in the copper-catalyzed cyclopropanation of styrene with ethyldiazoacetate. Enantioselectivity up to 63% was obtained.


*Keywords:* Chiral tetrahydroquinolines; Palladium complex; Copper complex; Allylic substitution; Cyclopropanation; Enantioselectivity

## 1. Introduction

Enantioselective reactions using metal complexes with hetero-donor ligands in which at least one donor atom is a pyridine nitrogen are an actively pursued research area [1]. In this contest only a few examples of sulfur-containing pyridine ligands have been so far reported. Representative examples **1**–**5** [2–6] of this class of S–N ligands are depicted in Scheme 1.

Continuing our interest in the synthesis and application in asymmetric catalysis of heterotopic nitrogen ligands based on the pyridine framework [6–11], we have designed a new class of pyridine-thioethers. In this paper we report the synthesis of the chiral 2-(2-phenylthiophenyl)-5,6,7,8-tetrahydroquinolines **6**–**9** (Scheme 2) derived from naturally occurring compounds and the results obtained with this kind of ligands in two reactions frequently investigated as a probe for the effectiveness of new ligands, namely the enantioselective palladium-catalyzed allylic substitution of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate and the copper-catalyzed cyclopropanation of styrene with ethyldiazoacetate.

## 2. Results and discussion

### 2.1. Synthesis of the ligands

For the synthesis of this class of ligands we considered the Kröhnke methodology that demands the

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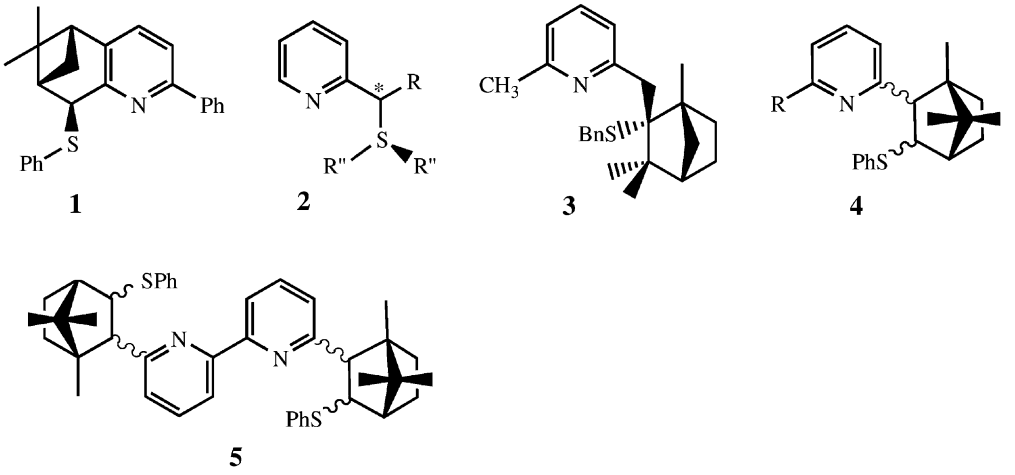
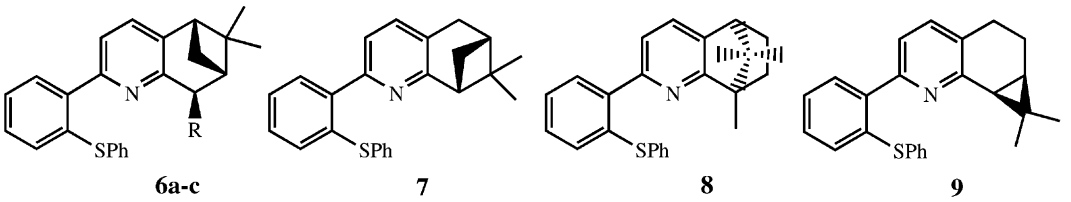
1381-1169/02/$ – see front matter 
PII: S1381-1169(02)00173-5



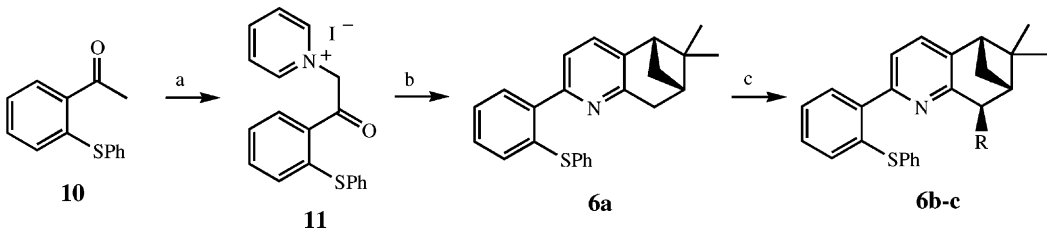

Scheme 1.




**6a**: R= H, **6b**: R= *i*-Pr,
**6c**: R=*n*-Bu

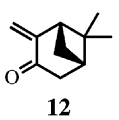
Scheme 2.

reaction of an α,β-unsaturated ketone with a pyridinium salt [12]. Thus, the pyridinium iodide **11**, prepared by reaction of 2-thiophenylacetophenone (**10**) with iodine in pyridine, underwent annelation with (−)-pinocarvone (**12**) in the presence of ammonium acetate to give the tetrahydroquinoline **6a** (Scheme 3). With **6a** in hand, two of its derivatives were prepared by introducing a proper substituent on




**R= b** : *i*-Pr, **c**: *n*-Bu

a: $I_2$, Pyridine; b: **12**, AcOH, $AcONH_4$, 120°C, 4h; c: LDA, THF, 2h at -40 °C , then *i*-PrI or *n*-BuBr, THF, -78 °C, then slowly r.t..




Scheme 3.

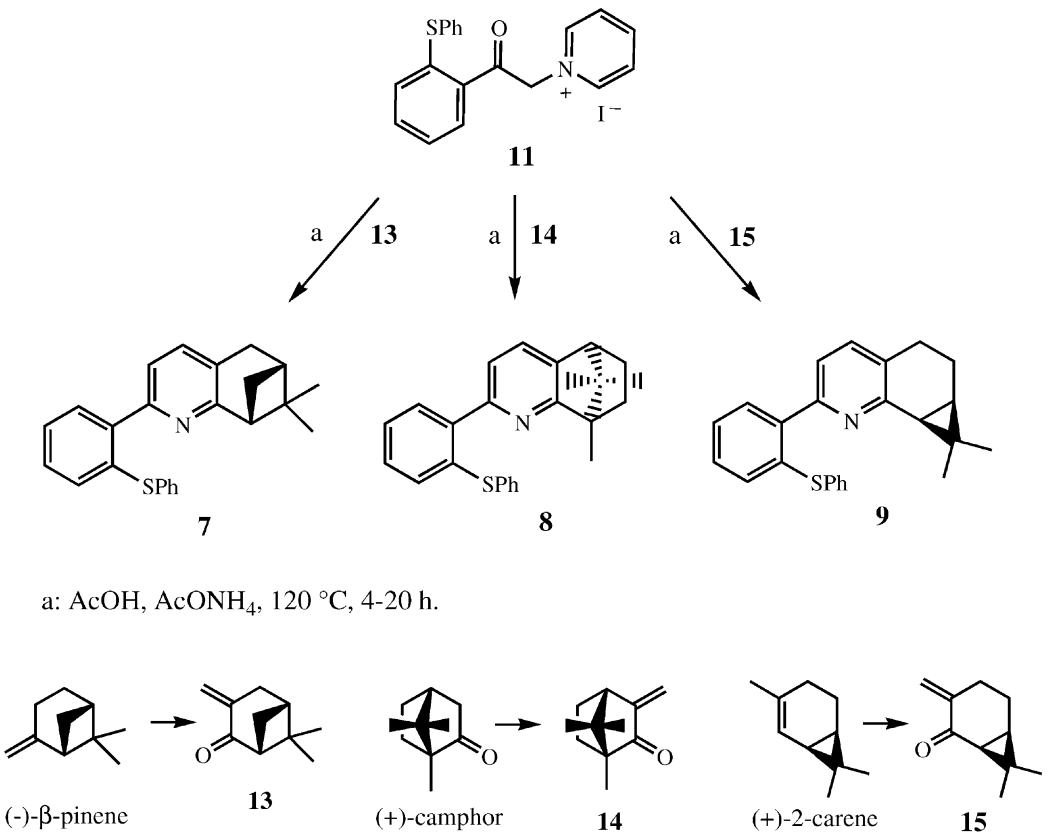
the C8 of the tetrahydroquinoline ring. In order to do it, the red solution of lithiated **6a**, obtained by treatment with lithium diisopropylamide (LDA) at −40 °C for 2 h was quenched with isopropyl iodide or butyl bromide to give the corresponding compounds **6b** and **6c**.

Having obtained the desired pyridine-thioether **6**, the Kröhnke condensation was extended to other α,β-methylene ketones. Thus, compounds **13**, **14** and **15** obtained from (−)-β-pinene, (+)-camphor and (+)-2-carene yielded the quinolines **7**, **8** and **9** (46, 24, 24% yields, respectively) (Scheme 4).

### 2.2. Palladium-catalyzed allylic alkylation

Enantioselective reactions based on palladium-catalyzed allylic substitutions are currently an actively pursued research area [13,14]. In contrast to the great variety of nitrogen-containing ligands, with C1 as well as C2 symmetry, which have proven to induce impressive levels of enantioselectivity in the catalyzed asymmetric C–C bond forming reactions with allylic compounds [1], rare examples of application in this reaction of sulfur-containing pyridine ligands have been reported [2–6]. In order to further define the scope and limitations of this kind of ligands we examined these new pyridine-thioethers in the enantioselective palladium-catalyzed allylic substitution of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate, which serve as model substrate and reagent to compare the outcome of different ligands.

Allylic substitution of *rac*-1,3-diphenylprop-2-enyl acetate was initially performed in $CH_2Cl_2$ at room temperature in the presence of (π-allyl)palladium-ligand complex generated in situ from 2.5 mol% of




Scheme 4.

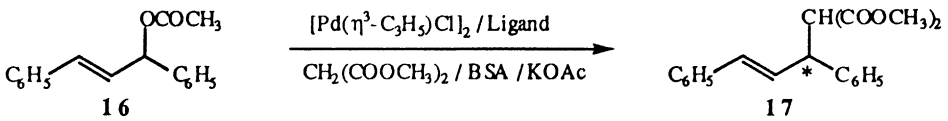
$[Pd(\eta^3\text{–}C_3H_5)Cl]_2$ and 10 mol% of the appropriate ligand. The nucleophile was generated employing Trost's procedure which entails the use of dimethyl malonate in the presence of *N*,*O*-bis(trimethylsilyl) acetamide (BSA) and a catalytic amount of potassium acetate [15]. The reactions were run for 7 days to ensure a reasonable reaction time useful to compare the outcomes of all ligands. The results are shown in Table 1.

Under these conditions pyridine-thioethers provided insufficiently reactive palladium catalysts affording only a partial conversion of the starting material (10–75%). All ligands gave the dimethyl 1,3-diphenylprop-2-enyl malonate (**17**) in moderate yield and in low to moderate enantiomeric excess (20–63%).

Surprisingly, both ligands **6a** and **6c** gave the reaction product **17** with the opposite sense of chirality indicating that in the case of **6c** the steric course of the reaction is basically dictated by the stereocenter originating from the introduction of the alkyl substituent on the basic structure **6a** and that this stereocenter has a mismatching stereotopic relationship with those preexisting on the bridge (though involvement of the stereocenter on the sulfur atom, created after complexation with palladium, would not be excluded).

Though the protocol using the malonate anion generated by Trost's procedure is generally the best way to carry out allylic substitution reactions, the use of sodium dimethyl malonate, generated using sodium hydride in THF, may in some cases offer best results.

Table 1
Allylic alkylation of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate




**16** **17**

| Ligand | Method[a] | Conversion[b] | Yield (%)[c] | ee (%)[d] | Configuration[e] |
|---|---|---|---|---|---|
| **6a** | A | 42 | 54 | 20 | *S* |
| **6b** | A | 10 | – | – | – |
| **6c** | A | 49 | 61 | 32 | *R* |
| **7** | A | 75 | 77 | 29 | *S* |
| **8** | A | 33 | 65 | 20 | *S* |
| **9** | A | 29 | 72 | 63 | *R* |
| **6a** | B | 0 | – | – | – |
| **6a** | B[f] | 53[g] | 39 | 2 | *S* |
| **6a** | C | 0 | – | – | – |
| **6a** | C[f] | 49[g] | 45 | 5 | *S* |
| **6a** | D | 46 | 63 | 22 | *S* |

[a] Method A: Reaction of the ligand (10 mol%) and $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2.5 mol%) with 1,3-diphenylprop-2-enyl acetate (0.4 mmol), $CH_2(COOMe)_2$ (1.2 mmol), BSA (1.2 mmol) and KOAc (3.5 mol%) in $CH_2Cl_2$ (2 ml) at room temperature for 7 days. Method B: Reaction of the ligand (10 mol%) and $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2.5 mol%) with 1,3-diphenylprop-2-enyl acetate (0.8 mmol), $NaCH(COOMe)_2$ (1.2 mmol), in THF (2 ml) at room temperature for 7 days. Method C: Reaction of the ligand (10 mol%) and $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2.5 mol%) with 1,3-diphenylprop-2-enyl acetate (0.8 mmol), $NaCH(COOMe)_2$ (1.2 mmol), 15-crown-5 (1.2 mmol) in $CH_3CN$ (10 ml) at room temperature for 7 days. Method D: Reaction of the ligand (10 mol%) and $[\{Pd(\eta^3\text{-}C_3H_5)Cl\}_2]$ (2.5 mol%) in $CH_2Cl_2$ (1 ml) for 30 min, followed by a solution of 1,3-diphenylprop-2-enyl acetate (0.8 mmol) in $CH_2Cl_2$ (0.5 ml). Then, a solution of dimethyl malonate (2.4 mmol), BSA (2.4 mmol) and tetrabutylammonium fluoride trihydrate (2.4 mmol) in $CH_2Cl_2$ (3.5 ml) was added over 1 h. The reaction was then carried out at room temperature for 7 days.

[b] Determined by $^1$H-NMR of the crude reaction mixture.

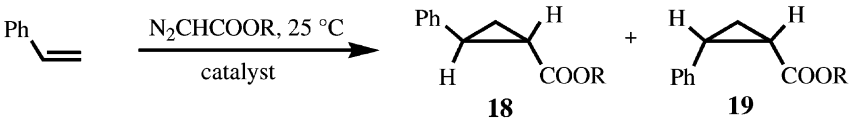
[c] Isolated yields based on converted starting material.

[d] Determined by $^1$H-NMR spectroscopy using $Eu(hfc)_3$ as chiral shift reagent.

[e] Assignment based on the sign of the optical rotation [22].

[f] Reaction carried out at reflux temperature.

[g] Conversion after 2 days.




Scheme 5.

To test the effectiveness of this procedure ligand **6a** was employed. Also under these conditions the reaction failed at room temperature, but partial conversion (53%) occurred after 2 days at reflux temperature. However, the reaction was non-enantioselective (2%).

It has been reasoned that one of the critical factors in controlling the selective addition of nucleophiles to π-allyl palladium intermediates is the nature of the ion pair of the attacking nucleophile [14,16,17]. Thus, the complexation of the cation with crown ether [18] or the use of tetraalkylammonium as a bulky counterion [19] can have a dramatic effect on the course of the process.

Therefore, in an effort to increase both conversion and enantioselectivity of the reaction, ligand **6a** was again chosen to test other two methods for the generation of the malonate anion. When the reaction was carried out in acetonitrile with sodium dimethyl malonate, generated using sodium hydride, in the presence of 15-crown-5 [19], no reaction was observed after 7 days at room temperature. Performing the reaction at reflux temperature partial conversion (49% after 2 days) of the starting material **16** was achieved, but **17** did not show enantiomeric excess (5%).

In contrast, the method employing tetrabutylammonium malonate, generated from dimethyl malonate and BSA/tetrabutylammonium fluoride [19] in $CH_2Cl_2$, was able to give **17** also at room temperature though in low conversion (46% after 7 days). However, no advance of the enantioselecivity (22% ee) was observed.

### 2.3. Copper-catalyzed asymmetric cyclopropanation

Among various methods used to carry out cyclopropanation reactions [20,21], the cyclopropanation of styrene with ethyl diazoacetate catalyzed by copper(II)-complexes was chosen as the model for the evaluation of the efficiency of pyridine-thioethers **6**–**9** (Scheme 5). The cyclopropanation reaction was carried out at room temperature by slow addition (2 h) of ethyl diazoacetate to a solution of styrene in methylene chloride containing the copper(I)-ligand. This adduct was previously prepared in situ from copper(II)-triflate and the ligands and activated by stirring with a few equivalents of ethyl diazoacetate.

The copper(II)-pyridine-thioethers complexes exhibited an acceptable efficiency and afforded the *trans*-cyclopropane **18** and *cis*-cyclopropane **19** with good yields (74–85%). These diastereomeric cyclopropanes were, however, obtained with low *trans*–*cis* diastereoselectivity (the **18**:**19** ratio was about 65:35) and they did not show significant enantioexcesses (2–5%).

In conclusion, we have prepared a new class of chelating ligands of type N–S and demonstrated their catalytic activity in enantioselective palladium-catalyzed allylic substitutions and cyclopropanation reactions.

## 3. Experimental

### 3.1. General methods

Boiling points are uncorrected. Melting points were determined on a Buchi 510 capillary apparatus and are uncorrected. The $^1$H-NMR (300 MHz) spectra were obtained with a Varian VXR-300 spectrometer. Optical rotations were measured with a Perkin-Elmer 241 polarimeter in a 1 dm tube. Elemental analyses were performed on a Perkin-Elmer 240 B analyzer. 2-Thiophenylacetophenone (**10**) was purchased from Aldrich. (−)-Pinocarvone (**12**) was obtained by oxidation of (1*R*)-(+)-α-pinene (90% ee by GLC, Aldrich) [23]. (1*R*,5*R*)-6,6-Dimethyl-3-methylenebicyclo[3.1.-

1]heptan-2-one (**13**) [24], (1*S*,6*R*)-7,7-dimethyl-3-methylenebicyclo[2.2.1]heptan-2-one (**15**) [24], (1*R*,4*S*)-3-methylene[1.7.7]trimethylbicyclo[4.1.0]heptan-2-one (**14**) [24] were prepared from (1*S*)-(−)-β-pinene ($[\alpha]_D^{25}$ −22.0 (neat) (99%, Aldrich)), (1*R*)-(+)-camphor ($[\alpha]_D^{25}$ +44.1 (*c* 10, $C_2H_5OH$), (98%, Aldrich)) and (1*R*)-(+)-2-carene ($[\alpha]_D^{20}$ +90.0 (*c* 6, $C_2H_5OH$), (97%, Aldrich)), respectively, following published methods.

### 3.2. 1-[2-(2-Phenylthiophenyl)-2-oxoethyl] pyridinium iodide (**11**)

To a mixture of sublimated iodine (17.8 g, 0.07 mol) and dry pyridine (25 ml) was added a solution of 2-thiophenylacetophenone (**10**) (16.0 g, 0.07 mol) in dry pyridine (10 ml). The mixture was heated at 100 °C for 1 h and then most of the pyridine was evaporated under reduced pressure. The residue was taken up in $CH_2Cl_2$ and the solid was filtered off. Recrystallization from 95% ethanol afforded **11** as yellow crystals: 21.7 g (72%); m.p. 190–192 °C. Anal. Calcd. for $C_{19}H_{16}NOS$: C, 74.49; H, 5.27; N, 4.57. Found: C, 74.65; H, 5.33; N, 4.44.

### 3.3. (5S,7S)-(+)-5,6,7,8-Tetrahydro-6,6-dimethyl-2-(2-phenylthiophenyl)-5,7-methanoquinoline (**6a**)

A mixture of 1-[2-(2-phenylthiophenyl)-2-oxoethyl] pyridinium iodide (**11**) (10.8 g, 25 mmol), ammonium acetate (15 g) and glacial acetic acid (34 ml) was heated at 100 °C for 10 min. Then a solution of (−)-pinocarvone (**12**) (26 mmol) in glacial acetic acid (5 ml) was added dropwise and the resulting solution was heated at 120 °C for 4 h. After cooling the mixture was taken up in $H_2O$ (1 l) and extracted with ethyl ether (3 × 200 ml). The combined organic phases were dried over anhydrous $Na_2SO_4$, the solvent was evaporated and the residue was purified by flash chromatography (petroleum ether:ethyl acetate = 7:3) to give **6a** as a yellow solid: 3.93 g (44%); m.p. 104–105 °C; $[\alpha]_D^{25}$ +70.0 (*c* 0.65, $CHCl_3$); $^1$H-NMR ($CDCl_3$) $\delta$: 7.54 (d, 1H, 7.5 Hz), 7.34–7.19 (m, 10H), 3.16 (d, 2H, $J$ = 3.0 Hz), 2.78 (t, 1H, $J$ = 5.7 Hz), 2.40–2.64 (m, 1H), 2.42–2.34 (m, 1H), 1.41 (s, 3H), 1.33 (d, 1H, $J$ = 9.6 Hz), 0.65 (s, 3H). Anal. Calcd. for $C_{24}H_{23}NS$: C, 80.63; H, 6.48; N, 3.92; S, 8.97. Found: C, 80.74; H, 6.55; N, 3.72; S, 8.88.

### 3.4. (6R,8R)-()-5,6,7,8-Tetrahydro-7,7-dimethyl-2-(2-phenylthiophenyl)-6,8-methanoquinoline (**7**)

Compound **7** was prepared following the procedure described for the preparation of **6a** using **13** instead of **12**. The crude reaction product was purified by flash chromatography (petroleum ether:ethyl acetate = 7:3) to give **7** as a white solid: 3.03 g (34%); m.p. 119–121 °C; $[\alpha]_D^{25}$ +53.1 (*c* 1.0, $CHCl_3$); $^1$H-NMR ($CDCl_3$) $\delta$: 7.55 (d, 1H, $J$ = 8.1 Hz), 7.44 (d, 1H, $J$ = 7.8 Hz), 7.39–7.17 (m, 9H), 3.07 (t, 1H, $J$ = 5.4 Hz), 2.96 (s, 2H), 2.76–2.69 (m, 1H), 2.37–2.30 (m, 1H), 1.42 (s, 3H), 1.35 (d, 1H, $J$ = 9.9 Hz), 0.68 (s, 3H). Anal. Calcd. for $C_{24}H_{23}NS$: C, 80.63; H, 6.48; N, 3.92; S, 8.97. Found: C, 80.55; H, 6.58; N, 3.84; S, 8.76.

### 3.5. (5S,8R)-(−)-5,6,7,8-Tetrahydro-8,9,9-trimethyl-2-(2-phenylthiophenyl)-5,8-methanoquinoline (**8**)

Compound **8** was prepared following the procedure described for the preparation of **6a** using **14** instead of **12** and carrying out the reaction for 20 h at 120 °C. The crude reaction product was purified by flash chromatography (petroleum ether:ethyl acetate = 7:3) to give **8** as a white solid: 2.12 g (22%); m.p. 106–108 °C; $[\alpha]_D^{25}$ −45.4 (*c* 1.3, $CHCl_3$); $^1$H-NMR ($CDCl_3$) $\delta$: 7.56 (d, 1H, $J$ = 7.5 Hz), 7.42–7.14 (m, 10H), 2.86 (d, 1H, $J$ = 2.0 Hz), 2.19–2.07 (m, 1H), 1.95–1.80 (m, 1H), 1.36 (s, 3H), 1.36–1.12 (m, 2H), 1.00 (s, 3H), 0.58 (s, 3H). Anal. Calcd. for $C_{25}H_{25}NS$: C, 80.83; H, 6.79; N, 3.77; S, 8.61. Found: C, 80.75; H, 6.88; N, 3.94; S, 8.55.

### 3.6. (7R,8S,8R)-(−)-5,6,7,8-Tetrahydro-9,9-dimethyl-2-(2-phenylthiophenyl)-7,8-methanoquinoline (**9**)

Compound **9** was prepared following the procedure described for the preparation of **6a** using **15** instead of **12**. The crude reaction product was purified by flash chromatography (petroleum ether:ethyl acetate = 7:3) to give **9** as a yellow oil: 3.12 g (35%); $[\alpha]_D^{25}$ −64.3 (*c* 0.24, $CHCl_3$); $^1$H-NMR ($CDCl_3$) $\delta$: 7.55 (d, 1H, $J$ = 6.9 Hz), 7.40–7.16 (m, 10H), 2.80 (m, 1H), 2.54 (m, 1H), 2.06 (m, 2H), 1.80 (m, 1H), 1.32 (m, 1H),

1.25 (s, 3H), 0.84 (s, 3H). Anal. Calcd. for $C_{24}H_{23}NS$: C, 80.63; H, 6.48; N, 3.92; S, 8.97. Found: C, 80.55; H, 6.53; N, 3.81; S, 8.79.

### *3.7. (5S,7S,8R)-(+)-5,6,7,8-Tetrahydro-6,6-dimethyl-8-(1-methylethyl)-2-(2-phenylthiophenyl)-5,7-methanoquinoline (**6b**)*

A solution of the pyridine (**6a**) (2 mmol) in anhydrous THF (2 ml) was added at −40 °C to a solution of LDA (2 mmol) in anhydrous THF (10 ml). The resulting solution was stirred at −40 °C for 2 h and then a solution of the isopropyl iodide (2 mmol) in THF (2 ml) was added dropwise at −40 °C. After 0.5 h at −40 °C, the solution was allowed to reach slowly room temperature and then treated with $H_2O$. The organic phase was separated and the aqueous phase extracted twice with $CH_2Cl_2$. The combined organic phases were dried over anhydrous $Na_2SO_4$, the solvent was evaporated and the residue was purified by flash chromatography (petroleum ether:ethyl acetate = 9:1) to give **6b** as a pale yellow oil: 0.192 g (24%); $[\alpha]_D^{25}$ +146.0 (*c* 0.7, $CHCl_3$); $^1$H-NMR ($CDCl_3$) $\delta$: 7.56 (d, 1H, $J$ = 7.8 Hz), 7.41–7.15 (m, 10H), 3.18–2.98 (m, 2H), 2.74 (t, 1H, $J$ = 5.7 Hz), 2.62–2.54 (m, 1H), 2.38 (t, 1H, $J$ = 4.5 Hz), 1.44 (d, 1H, $J$ = 10.8 Hz), 1.42 (s, 3H), 1.13 (d, 3H, $J$ = 6.9), 0.82 (d, 3H, $J$ = 6.9 Hz), 0.65 (s, 3H). Anal. Calcd. for $C_{27}H_{29}NS$: C, 81.16; H, 7.32; N, 3.51; S, 8.01. Found: C, 80.94; H, 7.31; N, 3.62; S, 7.88.

### *3.8. (5S,7S,8R)-(+)-5,6,7,8-Tetrahydro-6,6-dimethyl-8-butyl-2-(2-phenylthiophenyl)-5,7-methanoquinoline (**6c**)*

Compound **6c** was prepared following the procedure described for the preparation of **6b** using butyl bromide. The crude reaction product was purified by flash chromatography (petroleum ether:ethyl acetate = 9:1) to give **6c** as a pale yellow oil: 0.62 g (75%); $[\alpha]_D^{25}$ +137.5 (*c* 0.4, $CHCl_3$); $^1$H-NMR ($CDCl_3$) $\delta$: 7.56 (d, 1H, $J$ = 7.2 Hz), 7.37 (dd, 2H, $J$ = 8.1, 1.8 Hz), 7.30–7.16 (m, 8H), 3.03 (m, 1H), 2.76 (t, 1H, $J$ = 5.7 Hz), 2.52 (m, 1H), 2.44 (m, 1H), 2.34 (m, 1H), 1.55–1.30 (m, 5H), 1.43 (s, 3H), 1.36 (d, 1H, $J$ = 9.9 Hz), 0.93 (t, 3H, $J$ = 6.9 Hz), 0.63 (s, 3H). Anal. Calcd. for $C_{28}H_{31}NS$: C, 81.31; H, 7.56; N, 3.39; S, 7.74. Found: C, 81.44; H, 7.77; N, 3.22; S, 7.66.

### *3.9. Allylic alkylation of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate: general procedure*

*Method A.* A solution of ligand (0.04 mmol, 10 mol%) and $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (4 mg, 2.5 mol%) in dry $CH_2Cl_2$ (2 ml) was stirred at room temperature for 1 h. This solution was treated successively with a solution of *rac*-(*E*)-1,3-diphenyl-2-propenyl acetate (**16**) (0.4 mmol) in $CH_2Cl_2$ (1 ml), dimethyl malonate (1.2 mmol), BSA (1.2 mmol) and anhydrous potassium acetate (3.5 mol%). The reaction mixture was monitored by TLC analysis [light petroleum: ethyl ether = 3:1]. The reaction mixture was diluted with ether (25 ml) and washed with ice-cold saturated aqueous ammonium chloride. The organic phase was dried ($Na_2SO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography [light petroleum:ether = 3:1] to afford dimethyl 1,3-diphenylprop-2-enyl malonate (**17**). The enantiomeric excess was determined from the $^1$H-NMR spectrum in the presence of enantiomerically pure shift reagent Eu(hfc)$_3$; splitting of the signals for one of the two methoxy groups was observed. If the right-hand peak of these two is larger, then this is typical of the (*S*)-enantiomer in excess, which was confirmed by comparing the specific rotation obtained with literature values [22].

*Method B. rac*-16 (0.8 mmol) was added by a syringe to a solution of sodium dimethylmalonate (1.2 mmol) in dry THF (6 ml). To this solution was added a solution prepared by stirring the ligand (0.08 mmol, 10 mol%) and $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (8 mg, 2.5 mol%) in dry THF (2 ml) at room temperature for 1 h. The reaction mixture was monitored by TLC and then worked up as described in the BSA procedure.

*Method C. rac*-**16** (0.8 mmol) was added by a syringe to a solution of sodium dimethylmalonate (1.2 mmol) and 15-crown-5 (1.2 mmol) in dry acetonitrile (1.2 ml). To this solution was added a solution prepared by stirring the ligand (0.08 mmol, 10 mol%) and $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (8 mg, 2.5 mol%) in dry acetonitrile (2.5 ml) at room temperature for 1 h. The reaction mixture was monitored by TLC and then worked up as described in the BSA procedure.

*Method D.* A solution of ligand (0.08 mmol, 10 mol%) and $[\{Pd(\eta^3\text{-}C_3H_5)Cl\}_2]$ (8 mg, 2.5 mol%) in dry $CH_2Cl_2$ (1 ml) was stirred at room temperature for 30 min and then a solution of *rac*-**16** (0.8 mmol) in

$CH_2Cl_2$ (0.5 ml). After 5 min, a solution of dimethyl malonate (2.4 mmol), BSA (2.4 mmol) and tetrabutylammomium fluoride trihydrate (2.4 mmol) in $CH_2Cl_2$ (3.5 ml) was added over 1 h and stirring continued at room temperature. The reaction mixture was monitored by TLC analysis [light petroleum:ether = 3:1] and then worked up as described in the BSA procedure.

### *3.10. Asymmetric cyclopropanation of styrene using Cu(II)-complexes: typical procedure*

The ligand (35 mmol) in $CH_2Cl_2$ (1.5 ml) was added to a suspension of $Cu(OTf)_2$ (11.4 mg, 31 mmol) in $CH_2Cl_2$ (1.5 ml). After 2 h, styrene (0.715 ml, 6.25 mmol) and ethyl diazoacetate (0.315 mmol) were added. After 30 min, ethyl diazoacetate (2.5 mmol) in $CH_2Cl_2$ (2.5 ml) was added dropwise over a period of 2 h and then the mixture was stirred for 16 h. The solvent was evaporated under vacuum and the residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 15/1) to afford a mixture of ethyl *trans*- and *cis*-2-phenyl-cyclopropane-1-carboxylates as colorless oil. The *trans*/*cis* ratio and the ee were determined by GC analysis on a diethyl-*t*-butylsilyl-β-cyclodextrin capillary column 25 m × 0.25 mm operated at 60 °C for 5 min, then programmed at 3 °C/min to 160 °C [retention times: 33.2 (1*S*,2*S*) and 33.5 (1*R*,2*R*) min for *trans* **18**; retention times: 31.4 (1*R*,2*S*) and 31.8 (1*S*,2*R*) min for *cis* **19**].

## Acknowledgements

Financial support by M.U.R.S.T. is gratefully acknowledged.

## References

[1] F. Fache, E. Schulz, M.L. Tommasino, M. Lemaire, Chem. Rev. 100 (2000) 2159.
[2] G. Chelucci, M.A. Cabras, Tetrahedron: Asymmetry 7 (1996) 965.
[3] G. Chelucci, D. Berta, A. Saba, Tetrahedron 53 (1997) 3843.
[4] G. Chelucci, D. Berta, D. Fabbri, G.A. Pinna, A. Saba, F. Ulgheri, Tetrahedron: Asymmetry 9 (1998) 1933.
[5] B. Koning, A. Meetsma, R.M. Kellogg, J. Org. Chem. 63 (1998) 5533.
[6] G. Chelucci, N. Culeddu, A. Saba, R. Valenti, Tetrahedron: Asymmetry 10 (1999) 3537.
[7] G. Chelucci, A. Saba, F. Soccolini, Tetrahedron 57 (2001) 9989.
[8] G. Chelucci, S. Craba, A. Saba, F. Soccolini, G. Sotgiu, J. Mol. Catal. A 164 (2000) 179.
[9] G. Chelucci, S. Gladiali, M.G. Sanna, H. Brunner, Tetrahedron: Asymmetry 11 (2000) 3419.
[10] G. Chelucci, A. Saba, G. Sanna, F. Soccolini, Tetrahedron: Asymmetry 11 (2000) 3427.
[11] G. Chelucci, G.A. Pinna, A. Saba, G. Sanna, J. Mol. Catal. A 159 (2000) 423.
[12] F. Kröhnke, Synthesis (1976) 1.
[13] G. Helmchen, J. Organomet. Chem. 576 (1999) 203.
[14] B.M. Trost, D.L. Van Vranken, Chem. Rev. 96 (1996) 395.
[15] B.M. Trost, D.J. Murphy, Organometallics 4 (1985) 1143.
[16] B.M. Trost, R.C. Bunt, J. Am. Chem. Soc. 116 (1994) 4089.
[17] P. Sennhenn, B. Gabrer, G. Helmchen, Tetrahedron Lett. 35 (1994) 8595.
[18] M.J. Brown, D.I. Hulmes, P.J. Guiry, Tetrahedron 50 (1994) 4493.
[19] S.R. Gilbertson, C.-W.T. Chang, J. Org. Chem. 63 (1998) 8424.
[20] M.P. Doyle, M.N. Protonova, Tetrahedron 54 (1998) 7919.
[21] V.K. Singh, A.D. Gupta, G. Sekar, Synthesis (1997) 137.
[22] U. Leutenegger, G. Umbricht, C. Fahrni, P.V. Matt, A. Pfaltz, Tetrahedron 48 (1992) 2143.
[23] E.D. Mihelich, D.J. Eickhoff, J. Org. Chem. 48 (1983) 4135.
[24] M. Gianini, A. von Zelewsky, Synthesis (1996) 702.