

# Synthesis of 4-diphenylphosphanylmethyl- and 4-phenylthiomethyl-1,4-methano-11,11-dimethyl-1,2,3,4-tetrahydroacridine: new N–P and N–S camphor-derived chiral ligands for asymmetric catalysis

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**Abstract**—A new procedure has been developed for the preparation of camphor-annulated quinoline with different substituents on the 1-methyl group of the (+)-camphor backbone. Amongst them, two new N–P and N–S ligands, namely the 4-(diphenylphosphanylmethyl)- and 4-(phenylthiomethyl)-1,4-methano-11,11-dimethyl-1,2,3,4-tetrahydroacridine, have been employed in asymmetric palladium-catalyzed allylic substitution.

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## 1. Introduction

Optically active monoterpenes derived from naturally occurring compounds have been widely used as chiral building blocks for the synthesis of auxiliaries for asymmetric synthesis and ligands for asymmetric catalysis.<sup>1</sup> In the middle of the monoterpenes, a prominent position is occupied by optically active camphor, the framework of which has been incorporated into a variety of chiral ligands having homo- or heterodonor atoms.<sup>2</sup> In this context, many examples possess pyridine *N*-donors, such as 2,2'-bipyridines,<sup>3</sup> 1,10-phenanthrolines,<sup>4</sup> 2,2':6',2''-terpyridines,<sup>5</sup> pyridine-phosphines,<sup>6</sup> pyridine-thioethers<sup>7</sup> and pyridine-alcohols.<sup>8</sup>

These pyridine ligands can be divided into two types; those in which the camphor is annulated in the 2,3-positions to the  $\beta$ -face of the pyridine ring such as the 2,2'-bipyridine **1**<sup>3</sup> or 1,10-phenanthroline **2**<sup>4b</sup> (Fig. 1) and those in which the pyridine is contained as a pendant group on the C2, such as hydroxy-pyridine **3**,<sup>8d,e</sup> pyridine-phosphine **4**<sup>6b</sup> and pyridine-thioether **5**<sup>5b</sup> (Fig. 1). Only this last type of pyridine ligands bears a terpene skeleton containing another donor atom, located on C2 or C3.

Our interest in pyridine ligands,<sup>9</sup> prompted our investigations into camphor-based pyridine ligands containing an additional ligand on the 1-methyl group of the camphor backbone. Herein, we report the synthesis of 4-(diphenylphosphanylmethyl)- and 4-(phenylthiomethyl)-1,4-methano-11,11-dimethyl-1,2,3,4-tetrahydroacridine **7a** and **7b**, respectively, as representative examples of camphor-annulated pyridines of type **6** (Scheme 1). Moreover, in order to prove the ability of the new N–P and N–S ligands to form complexes with transition metals, they have been assessed in the asymmetric palladium-catalyzed allylic substitution.

## 2. Results and discussion

For the synthesis of ligands **7**, we envisaged that a convenient approach could involve the substitution of a proper substituent on the 4-methyl group of tetrahydroacridine **8** with a diphenylphosphino or phenylthio group. Compound **8** could, in turn, be obtained by Friedländer-modified condensation<sup>10</sup> between the camphor derivative **9** and 2-nitrobenzaldehyde **10** (Scheme 1).

Since the phosphorus derivative ligand **7a** was chosen as the target for our initial investigation, we examined the possibility of introducing the diphenylphosphino group via nucleophilic substitution of the trifluoromethanesulfonate (Scheme 2, **8**: X = OTf) with the diphenylphosphide

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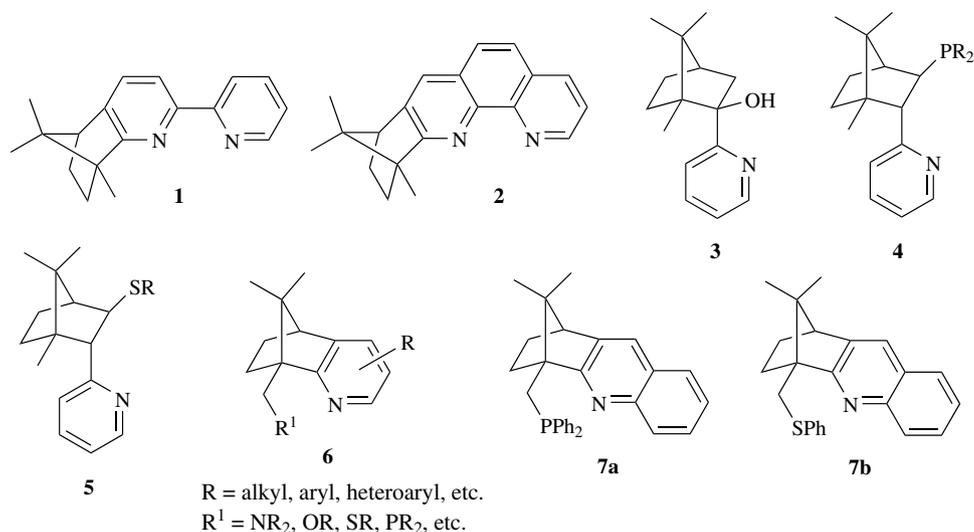
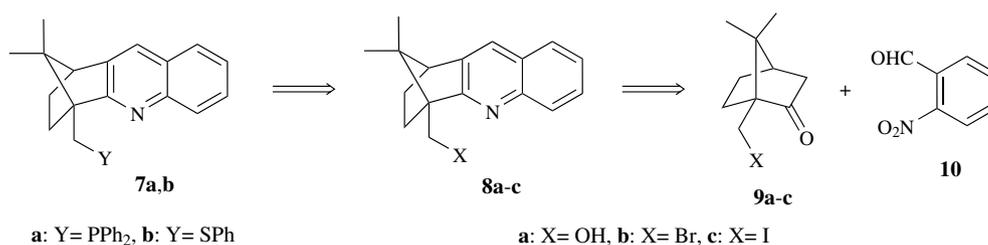


Figure 1.

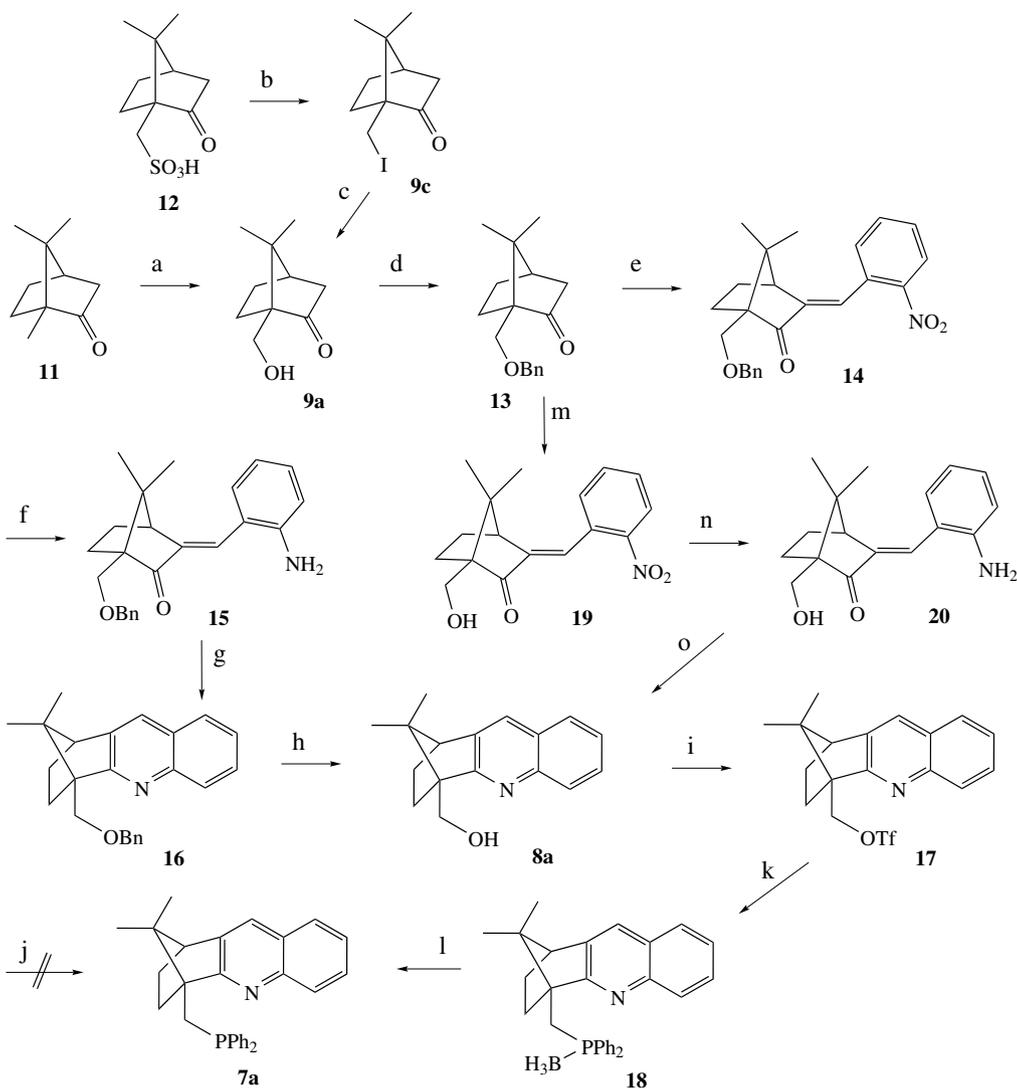


Scheme 1.

group. Accordingly, 10-hydroxycamphor **9a** was prepared in a three step sequence from (+)-camphor [(i) base-promoted Tf<sub>2</sub>O rearrangement, (ii) LiAlH<sub>4</sub> reduction of the obtained 2-methylenenorbor-1-yl triflate and finally (iii) *m*-CPBA-promoted rearrangement of reduced product 2-methylenebornan-1-ol].<sup>11</sup> Alternatively, **9a** can be obtained from 10-iodocamphor **9c** (displacement of the iodide by acetate ion followed by hydrolysis),<sup>12</sup> which can be readily obtained from 10-camphorsulfonic acid **12**.<sup>13</sup> The hydroxy group of **9a** was protected as a benzyl derivative (NaH, BnBr, THF, reflux, 2 h, 95%) and then the resultant camphor-derivative **13** was deprotonated by lithium diisopropylamide (LDA, -40 °C, 2 h). The lithium enolate was condensed with 2-nitrobenzaldehyde **10** to give the cross-aldo product **14** as a single geometric isomer (72% yield). The nitro group of **14** was then reduced by refluxing with powdered iron in acetic acid/ethanol/water (2:2:1)<sup>14</sup> to afford, in good yield (87%), the corresponding amine **15** that was finally converted into the camphor-fused quinoline **16** by heating at reflux in a degassed carbitol solution (catalytic H<sub>2</sub>SO<sub>4</sub>, 200 °C, 10 h, 89%). Unexpectedly, the removal of the benzyl protecting group from **15** proved problematic and after several failed attempts [(H<sub>2</sub>, Pd/C, EtOH, rt), (Me<sub>3</sub>SiI, CH<sub>2</sub>Cl<sub>2</sub>, rt or 60 °C, 48 h)<sup>15</sup> and (SnCl<sub>4</sub>, CH<sub>2</sub>Cl<sub>2</sub> or benzene, rt, 48 h)<sup>16</sup>] alcohol **8a** was obtained in 26% yield by treatment of **16** with boron trifluoride and sodium iodide (MeCN, rt, 24 h).<sup>17</sup>

We next examined the possibility of obtaining **8a** directly from alcohol **9a**, that would overcome the protection-deprotection steps. Thus, treatment of **9a** with two equivalents of LDA and then treatment with 2-nitrobenzaldehyde **10** gave condensation product **19**. The yield of the reaction was low (37%), but the two next steps, carried out in the usual way, were very successful (81% overall yield). Alcohol **8a** was converted into the corresponding triflate **17** [(Tf<sub>2</sub>O, Et<sub>3</sub>N, -45 °C to rt, 95%] which was then treated with lithium diphenylphosphide (LiPPh<sub>2</sub>, -60 °C to rt, 24 h). Unexpectedly, the reaction failed to give phosphine **7a**. Therefore, to overcome these problems, temporary protection of the phosphorus with BH<sub>3</sub> was examined.<sup>18</sup> Treatment of **17** with sodium diphenylphosphide-borane [Na(PPh<sub>2</sub>-BH<sub>3</sub>), THF, -30 °C to rt, 12 h] gave in good yield (77%) the phosphine-borane **18** which, by removal of BH<sub>3</sub> from the phosphorus with an excess of morpholine (70 °C, 2 h), afforded phosphine **7a** in 96% yield.

Although we have been able to obtain the desired N,P-ligand **7a**, a low yield of **8a** was restrictive. An alternative to the triflate leaving group is iodide; thus we devoted our attention to the possibility of obtaining **8c** (Scheme 1) from 10-iodocamphor **9c**, following the usual protocol (Scheme 3). Notwithstanding the rather harsh conditions required for the reduction and annulation steps (carbitol, 200 °C, 1 h), the iodomethyl-tetrahydroacridine **8c** was



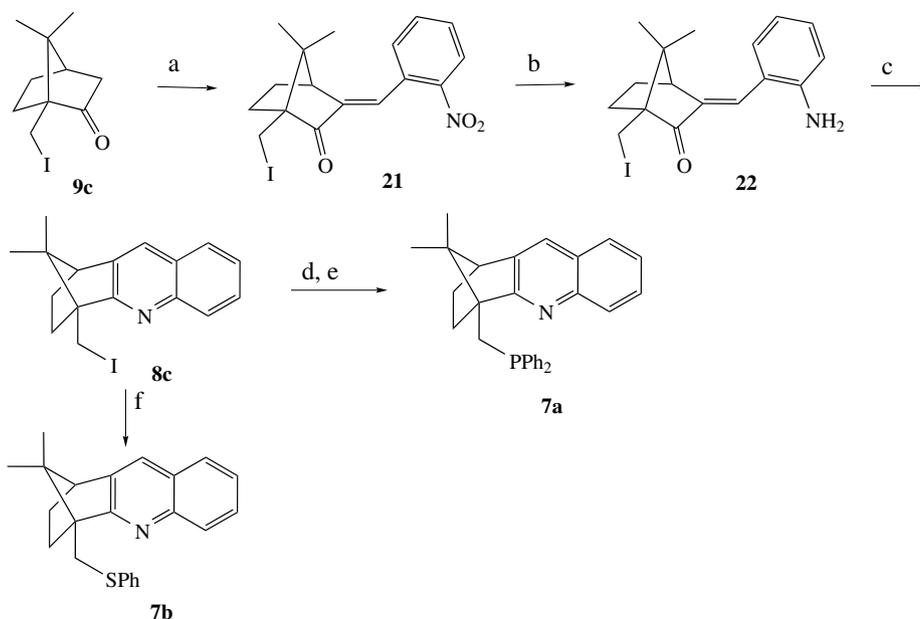
**Scheme 2.** Reagents and conditions: (a) (i)  $\text{Ti}_2\text{O}$ ,  $\text{CH}_2\text{Cl}_2$ , MTBMP, 95%, (ii)  $\text{LiAlH}_4$ ,  $\text{Et}_2\text{O}$ , then hydrolysis, 95%, (iii) *m*-CPBA,  $\text{CH}_2\text{Cl}_2$ , rt, 24 h, 78%; (b) (i)  $\text{I}_2$ ,  $\text{PPh}_3$ , toluene, reflux, 16 h, 92%, (ii)  $\text{KOH}$ ,  $\text{MeOH}$ , reflux, 6 h, 69%; (c)  $\text{KOAc}$ ,  $\text{AcOH}$ , 180 °C, 1.5 h, 88%; (d)  $\text{NaH}$ ,  $\text{BnBr}$ ,  $\text{THF}$ , reflux, 2 h, 95%; (e)  $\text{LDA}$ ,  $\text{THF}$ , -40 °C, 2 h, then 2-nitrobenzaldehyde, 72%; (f)  $\text{Fe}$ ,  $\text{AcOH}/\text{EtOH}/\text{H}_2\text{O}$  (2:2:1), catalytic  $\text{HCl}$ , reflux, 15 min, 87%; (g) carbitol, catalytic  $\text{H}_2\text{SO}_4$ , reflux, 10 h, 89%; (h)  $\text{BF}_3$ ,  $\text{NaI}$ ,  $\text{CH}_3\text{CN}$ , rt, 24 h, 26%; (i)  $\text{Ti}_2\text{O}$ ,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ , -45 °C to rt, 12 h, 95%; (j)  $\text{LiPPh}_2$ ,  $\text{THF}$ , -60 °C to rt, 24 h; (k)  $\text{LiPPh}_2(\text{BH}_3)$ ,  $\text{THF}$ , rt, 48 h, 76%; (l) morpholine, 70 °C, 2 h, 96%; (m)  $\text{LDA}$  (2.2 equiv),  $\text{THF}$ , -40 °C, 2 h, then 2-nitro benzaldehyde, 37%; (n)  $\text{Fe}$ ,  $\text{AcOH}/\text{EtOH}/\text{H}_2\text{O}$  (2:2:1), catalytic  $\text{HCl}$ , reflux, 15 min, 92%; (o) carbitol, catalytic  $\text{H}_2\text{SO}_4$ , reflux, 10 h, 88%.

obtained in a reasonable yield (58% from **9c**). Treatment of **8c** with sodium diphenylphosphide–borane [ $\text{Na}(\text{PPh}_2\text{BH}_3)$ ],  $\text{THF}$ , -30 °C to rt, 48 h] also proved satisfactory giving 76% yield of the phosphine–borane **18** that was finally deprotected to give **7a** in the usual way.

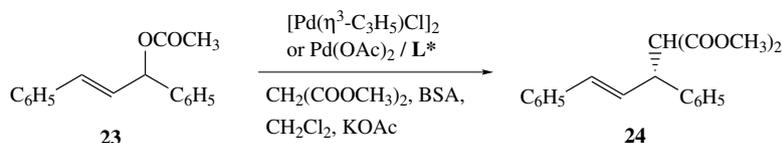
Iodo-compound **8c** was also converted in good yield (76%) to phenylthiomethyl-acridine **7b** by treatment with sodium benzenethiolate in *N,N*-dimethylformamide (70 °C, 5 h) (Scheme 3).

The catalytic activity of the new N–P<sup>19</sup> and N–S<sup>20</sup> ligands was tested in the palladium-catalyzed allylic substitution<sup>21</sup> and, in particular, the alkylation of 1,3-diphenylprop-2-enyl acetate **23** by using dimethyl malonate as the nucleophile in the presence of *N,O*-bis(trimethylsilyl)acetamide (BSA) and potassium acetate in methylene chloride

(Scheme 4). In the presence of 2.5% of bis( $\pi$ -allyl)palladium chloride), both ligands **7a** and **7b** ( $\text{Pd}/\text{ligand} = 1:4$ ) provided effective palladium catalysts to give the dimethyl (*R*)-1,3-diphenylprop-2-enyl malonate **24** in good yields (>90%) and reasonable reaction times (<20 h), although in modest enantiomeric excesses (44% and 22%, respectively). When the alkylation with ligand **7a** was performed using a  $\text{Pd}/\text{ligand}$  ratio of 1:2 and 1:1, similar reaction times, yields and selectivities (43% and 42% ee, respectively) were obtained. Allylic alkylation was also carried out using the borane protected ligand **18** and 10 mol % of palladium acetate ( $\text{Pd}/\text{ligand} = 1:1$ ), which was employed simultaneously to release the phosphorus from borane and as the  $\text{Pd}(0)$  source for the catalytic reaction.<sup>22</sup> The reaction afforded (*R*)-**24** in a longer time (60 h) and with lower yield (66%) and enantioselectivity (34% ee) with respect to the P-free ligand **7a**.



**Scheme 3.** Reagents and conditions: (a) LDA, THF,  $-40\text{ }^{\circ}\text{C}$ , 2 h, then 2-nitrobenzaldehyde, 72%; (b) Fe,  $\text{CH}_3\text{COOH}/\text{EtOH}/\text{H}_2\text{O}$  (2:2:1), catalytic HCl, reflux, 15 min, 87%; (c) carbitol, catalytic  $\text{H}_2\text{SO}_4$ , reflux, 1 h, 92%; (d)  $\text{LiPPh}_2(\text{BH}_3)$ , THF, rt, 48 h, 76%; (e) morpholine,  $70\text{ }^{\circ}\text{C}$ , 2 h, 96%; (f) NaSPh, DMF, reflux, 5 h, 76%.



**Scheme 4.**

### 3. Conclusion

In conclusion, we have developed a procedure for the preparation of camphor-annulated quinoline derivatives with different substituents on the 10-methyl group of the camphor backbone. Amongst them, the new bidentate N–P and N–S ligands **7a** and **7b**, respectively, have proven their catalytic activity in Pd-catalyzed allylic alkylation. Although the stereochemical result has been modest, it is premature to rule out the synthetic utility of these ligands at this time. Further experiments to investigate their reactivity and the conversion of the iodo-compound **8c** and/or hydroxy analogue **8a** in other camphor-based ligands are currently in progress.

### 4. Experimental

#### 4.1. General methods

Melting points were determined on a Büchi 510 capillary apparatus and are uncorrected. NMR spectra were obtained with a Varian VXR-300 spectrometer at 300 MHz for  $^1\text{H}$ , 75.4 MHz for  $^{13}\text{C}$  and 121.4 MHz for  $^{31}\text{P}$ . Chemical shifts are reported in ppm downfield from internal  $\text{Me}_4\text{Si}$  in  $\text{CDCl}_3$ . 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. Ethyl acetate and petroleum ether were distilled before use. THF was distilled from sodium–benzophenone ketyl and  $\text{CH}_2\text{Cl}_2$  from  $\text{P}_2\text{O}_5$ . Both solvents were degassed thoroughly with dry nitrogen directly before use. Alcohol **9a** was obtained from (+)-**11**<sup>11</sup> or **9c**.<sup>12</sup>

#### 4.2. (1*R*,4*R*)-1-Benzyloxymethyl-7,7-dimethylbicyclo-[2.2.1]heptan-2-one **13**

Alcohol **9a** (2.16 g, 12.9 mmol) was added dropwise to a mixture of NaH (0.324 g, 13.5 mol) in anhydrous THF (100 mL). After 3 h, benzyl bromide (2.3 g, 13.5 mmol) was added dropwise. The mixture was stirred at room temperature for 1 h and then heated at reflux for 2 h. The solvent was evaporated under vacuum and the residue taken up in  $\text{H}_2\text{O}$  and extracted with  $\text{Et}_2\text{O}$  ( $2 \times 50\text{ mL}$ ). The combined organic solution was dried over anhydrous  $\text{Na}_2\text{SO}_4$  and the solvent evaporated. Purification of the residue by distillation under vacuum gave **13**: 3.1 g (95%), bp  $150\text{ }^{\circ}\text{C}$  at 0.1 mm Hg;  $[\alpha]_{\text{D}}^{25} = +38.0$  ( $c$  1.77,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR:  $\delta$  2.34–2.22 (m, 5H), 4.53 (s, 2H), 3.64 (d, 1H,  $J = 10.5\text{ Hz}$ ), 3.59 (d, 1H,  $J = 10.5\text{ Hz}$ ), 2.39 (dddd, 1H,  $J = 18.3, 7.2, 4.2, 2.4\text{ Hz}$ ), 2.15–2.92 (m, 3H), 1.84 (d, 1H,  $J = 18.3\text{ Hz}$ ), 1.35 (d, 2H,  $J = 9.0\text{ Hz}$ ), 1.07 (s, 3H), 0.95 (s, 3H). Anal. Calcd for  $\text{C}_{17}\text{H}_{22}\text{O}_2$ : C, 79.03; H, 8.58. Found: C, 79.32; H, 8.61.

#### 4.3. (1*R*,4*S*)-3-(2-Nitrophenyl)methylene-1-benzyloxy-methyl-7,7-dimethyl[2.2.1]bicycloheptan-2-one **14**

A solution of **13** (1.55 g, 6 mmol) in THF (5 mL) was added dropwise over 15 min to a cooled (−40 °C) solution of LDA (6.6 mmol) in THF (90 mL) under an argon atmosphere. The solution was stirred for 2 h at −78 °C and then a solution of 2-nitrobenzaldehyde (0.91 g, 6 mmol) in THF (10 mL) was added dropwise over 10 min. The solution was stirred at −40 °C for 1 h and then allowed to warm to room temperature overnight. Water (5 mL) was added and the THF was evaporated under vacuum. The residue was poured into H<sub>2</sub>O (50 mL) and the resulting mixture extracted with ethyl acetate (3 × 50 mL). The combined organic solution was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and the solvent evaporated. Purification of the residue by flash chromatography (petroleum ether/EtOAc = 8:2) gave **14** (1.69 g, 72%): mp 107–109 °C; <sup>1</sup>H NMR: δ 8.08 (d, 1H, *J* = 8.1 Hz), 7.64 (t, 1H, *J* = 7.8 Hz), 7.57–7.22 (m, 7H), 7.34 (s, 1H), 4.58 (s, 2H), 3.77 (d, 1H, *J* = 10.5 Hz), 3.71 (d, 1H, *J* = 10.5 Hz), 2.69 (d, 1H, *J* = 3.9 Hz), 2.30–2.11 (m, 2H), 1.65–1.45 (m, 2H), 1.09 (s, 3H), 0.96 (s, 3H). Anal. Calcd for C<sub>24</sub>H<sub>25</sub>NO<sub>4</sub>: C, 73.64; H, 6.44; N, 3.58. Found: C, 73.85; H, 6.48; N, 3.56.

#### 4.4. (1*R*,4*S*)-3-(2-Aminophenyl)methylene-1-benzyloxy-methyl-7,7-dimethyl[2.2.1]bicycloheptan-2-one **15**

A mixture of **14** (0.78 g, 2 mmol), iron powder (0.826 g, 14.9 mmol), concentrated HCl (two drops) and EtOH/AcOH/H<sub>2</sub>O (2:2:1, 20 mL) was heated at reflux for 15 min and then stirred at room temperature for 20 min. The solution was filtered, diluted with H<sub>2</sub>O (200 mL), and extracted with ethyl acetate (3 × 100 mL). The combined organic phase was washed with a 5% aqueous NaOH solution (50 mL) and then with H<sub>2</sub>O (50 mL). The organic solution was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and the solvent evaporated. Purification of the residue by flash chromatography (petroleum ether/EtOAc = 8:2) gave **15** (0.63 g, 87%): mp 97–99 °C; <sup>1</sup>H NMR: δ 7.37–7.19 (m, 6H), 7.35 (s, 1H), 7.15 (t, 1H, *J* = 7.5 Hz), 6.77 (t, 1H, *J* = 7.5 Hz), 6.70 (d, 1H, *J* = 7.5 Hz), 4.57 (s, 2H), 3.87 (br s, 2H), 3.77 (d, 1H, *J* = 10.5 Hz), 3.70 (d, 1H, *J* = 10.5 Hz), 2.94 (d, 1H, *J* = 3.3 Hz), 2.28–2.13 (m, 2H), 1.53–1.42 (m, 2H), 1.10 (s, 3H), 0.93 (s, 3H). Anal. Calcd for C<sub>24</sub>H<sub>27</sub>NO<sub>2</sub>: C, 79.74; H, 7.53; N, 3.87. Found: C, 79.91; H, 7.55; N, 3.84.

#### 4.5. (1*S*,4*S*)-4-Benzyloxymethyl-1,4-methano-11,11-dimethyl-1,2,3,4-tetrahydroacridine **16**

A solution of **15** (0.72 g, 2 mmol) in degassed carbitol (9 mL) was heated at reflux under argon for 10 h. The cooled solution was then poured into H<sub>2</sub>O (250 mL) and the resulting mixture extracted with Et<sub>2</sub>O (3 × 100 mL). The combined organic solution was washed with H<sub>2</sub>O (5 × 100 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and the solvent evaporated to give an oil. Purification of this oil by flash chromatography (petroleum ether/EtOAc = 7:3) gave **16**: 0.61 mg (89%); oil; [α]<sub>D</sub><sup>25</sup> = +50.7 (*c* 3.22, CHCl<sub>3</sub>); <sup>1</sup>H NMR: δ 8.04 (d, 1H, *J* = 8.4 Hz), 7.67 (dd, 1H, *J* = 7.5, 1.2 Hz), 7.59 (s, 1H), 7.56 (dt, 1H, *J* = 7.5, 1.5 Hz), 7.46–

7.22 (m, 6H), 4.71 (s, 2H), 4.33 (d, 1H, *J* = 10.5 Hz), 4.10 (d, 1H, *J* = 10.5 Hz), 2.87 (d, 1H, *J* = 3.9 Hz), 2.53–2.42 (m, 1H), 2.59–2.30 (m, 1H), 1.32–1.20 (m, 2H), 1.21 (s, 3H), 0.65 (s, 3H). Anal. Calcd for C<sub>24</sub>H<sub>25</sub>NO: C, 83.93; H, 7.34; N, 4.08. Found: C, 83.73; H, 7.37; N, 4.06.

#### 4.6. (1*S*,4*S*)-4-Hydroxymethyl-1,4-methano-11,11-dimethyl-1,2,3,4-tetrahydroacridine **8a**

Freshly distilled boron trifluoride–ether (1.46 g, 10.3 mmol) was added dropwise to a solution of **16** (1.41 g, 4.1 mmol) and NaI (1.54 g, 10.3 mmol) in acetonitrile (20 mL). The mixture was stirred at room temperature for 24 h and then poured into ice-cold water (40 mL). This mixture was basified with 5% NaOH and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 30 mL). The combined organic extracts were washed with H<sub>2</sub>O (3 × 20 mL) followed by brine (2 × 20 mL). Evaporation of the solvent gave a residue which was purified by flash chromatography (petroleum ether/EtOAc = 7:3) to give **8a**: 0.27 g (26%); oil, [α]<sub>D</sub><sup>25</sup> = +21.3 (*c* 0.72, CHCl<sub>3</sub>); <sup>1</sup>H NMR: δ 7.97 (d, 1H, *J* = 8.1 Hz), 7.72 (s, 1H), 7.70 (d, 1H, *J* = 8.1 Hz), 7.57 (dt, 1H, *J* = 6.9, 0.9 Hz), 7.45 (dt, 1H, *J* = 6.9, 0.9 Hz), 4.76 (br s, 1H), 4.37 (d, 1H, *J* = 11.4 Hz), 4.01 (dd, 1H, *J* = 11.4, 6.3 Hz), 2.93 (d, 1H, *J* = 3.9 Hz), 2.26–2.13 (m, 1H), 2.07 (dt, 1H, *J* = 12.6, 3.6 Hz), 1.61 (ddd, 1H, *J* = 12.6, 9.0, 3.6 Hz), 1.17–1.11 (m, 1H), 1.06 (s, 3H), 0.66 (s, 3H). <sup>13</sup>C NMR: δ 171.5, 145.6, 139.6, 128.3, 127.7, 127.4, 127.4, 126.5, 125.3, 61.9, 57.4, 54.8, 51.7, 28.1, 25.8, 20.8, 19.0. Anal. Calcd for C<sub>17</sub>H<sub>19</sub>NO: C, 80.60; H, 7.56; N, 5.53. Found: C, 80.81; H, 7.53; N, 5.54.

#### 4.7. (1*R*,4*S*)-3-(2-Nitrophenyl)methylene-1-hydroxymethyl-7,7-dimethyl[2.2.1]bicycloheptan-2-one **19**

The procedure used for the preparation of **14**, but using 2.2 equiv of LDA with respect to **9a**, was followed. In this way compound **19** was obtained by flash chromatography (petroleum ether/EtOAc = 7:3 and then 1:1) in 37% yield: mp 134–136 °C; <sup>1</sup>H NMR: δ 8.10 (d, 1H, *J* = 7.8 Hz), 7.67 (t, 1H, *J* = 7.5 Hz), 7.55 (s, 1H), 7.53 (d, 1H, *J* = 7.8 Hz), 7.41 (t, 1H, *J* = 7.8 Hz), 4.01 (d, 1H, *J* = 12.0 Hz), 3.76 (d, 1H, *J* = 12.0 Hz), 2.73 (d, 1H, *J* = 3.9 Hz), 2.64 (br s, 1H), 2.24–2.09 (m, 1H), 1.96 (dt, 1H, *J* = 12.9, 3.6 Hz), 1.82–1.70 (m, 1H), 1.67–1.56 (m, 1H), 1.03 (s, 3H), 1.00 (s, 3H). Anal. Calcd for C<sub>17</sub>H<sub>19</sub>NO<sub>4</sub>: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.85; H, 6.35; N, 4.68.

#### 4.8. (1*R*,4*S*)-2-(Aminophenyl)methylene-1-hydroxymethyl-7,7-dimethyl[2.2.1]bicycloheptan-2-one **20**

Following the procedure used for the preparation of **15**, compound **20** was obtained by flash chromatography (petroleum ether/EtOAc = 7:3) in 92% yield: foam solid; <sup>1</sup>H NMR: δ 7.31 (s, 1H), 7.22 (d, 1H, *J* = 7.5 Hz), 7.15 (t, 1H, *J* = 7.5 Hz), 6.76 (t, 1H, *J* = 7.5 Hz), 7.71 (d, 1H, *J* = 7.5 Hz), 4.02 (br s, 2H), 3.98 (d, 1H, *J* = 12.0 Hz), 3.75 (d, 1H, *J* = 12.0 Hz), 2.98 (d, 1H, *J* = 4.2 Hz), 2.94 (br s, 1H), 2.25–2.15 (m, 1H), 1.94 (dt, 1H, *J* = 13.2, 3.3 Hz), 1.76–1.58 (m, 2H), 1.03 (s, 3H), 0.96 (s, 3H). Anal.

Calcd for  $C_{17}H_{21}NO_2$ : C, 75.25; H, 7.80; N, 5.16. Found: C, 75.25; H, 7.80; N, 5.16.

#### 4.9. (1*S*,4*S*)-4-Hydroxymethyl-1,4-methano-11,11-dimethyl-1,2,3,4-tetrahydroacridine **8a**

Following the procedure used for the preparation of **16**, the heating at reflux of the amine **20** for 1 h gave a crude product that by flash chromatography (petroleum ether/EtOAc = 7:3) afforded **8a** in 88% yield. Spectroscopic data of this compound were identical to all the data above.

#### 4.10. (1*S*,4*S*)-4-Trifluoromethanesulfonyloxymethyl-1,4-methano-11,11-dimethyl-1,2,3,4-tetrahydroacridine **17**

Triflic anhydride (0.31 mL, 1.88 mmol) was added dropwise to a cooled ( $-45\text{ }^\circ\text{C}$ ) solution of **8a** (1.25 mmol) and  $\text{Et}_3\text{N}$  (0.21 mL, 1.5 mmol) in anhydrous  $\text{CH}_2\text{Cl}_2$  (6 mL) under nitrogen. The resulting solution was allowed to warm to room temperature and stirred overnight. The mixture was treated with a saturated aqueous  $\text{Na}_2\text{CO}_3$  solution and extracted with  $\text{CH}_2\text{Cl}_2$ . The organic phase was washed with brine, dried over anhydrous  $\text{Na}_2\text{SO}_4$  and the solvent evaporated. The residue was purified by flash chromatography (petroleum ether/EtOAc = 8:2) to give **17**: 0.460 g (95%); yellow oil;  $^1\text{H}$  NMR:  $\delta$  8.01 (d, 1H,  $J = 8.4$  Hz), 7.73 (s, 1H), 7.72 (d, 1H,  $J = 8.4$  Hz), 7.58 (t, 1H,  $J = 6.9$  Hz), 7.45 (t, 1H,  $J = 6.9$  Hz), 5.40 (d, 1H,  $J = 12.0$  Hz), 5.15 (d, 1H,  $J = 12.0$  Hz), 2.96 (d, 1H,  $J = 3.6$  Hz), 2.40–2.18 (m, 2H), 1.35–1.17 (m, 2H), 1.19 (s, 3H), 0.69 (s, 3H). Anal. Calcd for  $C_{18}H_{18}F_3NO_3S$ : C, 56.10; H, 4.71; N, 3.63. Found: C, 56.32; H, 4.75; N, 3.66.

#### 4.11. Synthesis of the P-borane of (1*S*,4*S*)-4-diphenylphosphorylmethyl-1,4-methano-11,11-dimethyl-1,2,3,4-tetrahydroacridine **18**

A solution of diphenylphosphine borane (0.224 g, 1.22 mmol) in dry THF (3 mL) was added to a mixture of oil-free NaH (36.6 mg, 1.22 mmol) in dry THF (7 mL) at  $-30\text{ }^\circ\text{C}$  for 30 min. The mixture was then slowly warmed at room temperature and stirring continued for 1 h. The mixture was cooled again at  $-30\text{ }^\circ\text{C}$  and a solution of **17** (0.229 g, 0.61 mmol) in dry THF (3 mL) was added dropwise over 30 min. After addition, the cooling bath was turned off and when the temperature reached room temperature and the mixture was stirred for 12 h. The solvent was evaporated under reduced pressure and the residue taken up in  $\text{H}_2\text{O}$  (10 mL) and extracted with  $\text{CH}_2\text{Cl}_2$  ( $3 \times 20$  mL). The combined organic phase was dried on anhydrous  $\text{Na}_2\text{SO}_4$  and the solvent evaporated under vacuum. The residue was purified by chromatography on neutral alumina (petroleum ether/EtOAc = 98:2) to give **18**: 0.204 g (77%); mp  $146\text{--}148\text{ }^\circ\text{C}$ ;  $[\alpha]_D^{25} = -13.4$  ( $c$  0.65,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR:  $\delta$  8.35–8.26 (m, 2H), 8.02 (d, 1H,  $J = 8.4$  Hz), 7.84–7.56 (m, 5H), 7.50–7.36 (m, 7H), 3.93 (t, 1H,  $J = 16.8$  Hz), 2.91 (d, 1H,  $J = 3.9$  Hz), 2.60 (dt, 1H,  $J = 13.8, 3.5$  Hz), 2.30–2.10 (m, 2H), 1.40–0.70 (m, 3H, broad signals from  $\text{BH}_3$ ), 1.20 (s, 3H), 1.09 (dt, 1H,  $J = 12.9, 3.5$  Hz), 0.89–0.80 (m, 1H), 0.56 (s, 3H).  $^{13}\text{C}$  NMR:  $\delta$  170.0, 146.3, 139.4, 133.5–128.5 (m, PPh<sub>2</sub>), 128.4, 127.9, 127.7, 127.4, 126.2, 125.4, 57.6, 55.2, 50.3,

28.0, 26.6, 22.6, 22.2, 20.1.  $^{31}\text{P}$  NMR:  $\delta$  15.8–13.5 (br s). Anal. Calcd for  $C_{29}H_{31}BNP$ : C, 80.01; H, 7.18; N, 3.22; Found: C, 80.12; H, 7.19; N, 3.20.

#### 4.12. (1*S*,4*S*)-4-Diphenylphosphorylmethyl-1,4-methano-11,11-dimethyl-1,2,3,4-tetrahydroacridine **7a**

A solution of the P-borane **18** (130.5 mg, 0.3 mmol) in morpholine (2 mL) was heated under argon at  $70\text{ }^\circ\text{C}$  for 2 h. After the reaction mixture was cooled, the excess morpholine was eliminated under vacuum and the residue purified by flash chromatography (petroleum ether/EtOAc = 95:5) to give **7a**: 0.120 g, (96%); mp  $47\text{--}52\text{ }^\circ\text{C}$  (sticky solid);  $[\alpha]_D^{25} = +29.4$  ( $c$  0.48,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR:  $\delta$  8.00 (d, 1H,  $J = 8.4$  Hz), 7.76–7.52 (m, 8H), 7.45–7.26 (m, 6H), 3.15 (d, 1H,  $J = 15.0, 3.6$  Hz), 2.90 (d, 1H,  $J = 2.4$  Hz), 2.45 (dd, 1H,  $J = 15.0, 2.7$  Hz), 2.21–2.02 (m, 2H), 1.46–1.38 (m, 1H), 1.32–1.21 (m, 1H), 1.12 (s, 3H), 0.59 (s, 3H).  $^{13}\text{C}$  NMR:  $\delta$  171.2, 146.6, 139.6, 133.4–132.6 (m), 129.1, 128.4–127.3 (m), 125.8, 125.2, 56.7, 56.3, 56.1, 51.2, 29.7, 26.6, 20.1, 20.0.  $^{31}\text{P}$  NMR:  $\delta$   $-21.6$ . Anal. Calcd for  $C_{29}H_{28}NP$ : C, 82.63; H, 6.70; N, 3.32. Found: C, 82.81; H, 6.74; N, 3.31.

#### 4.13. (1*R*,4*S*)-3-(2-Nitrophenyl)methylene-1-iodomethyl-7,7-dimethyl[2.2.1]bicycloheptan-2-one **21**

Following the procedure used for the preparation of **14**, compound **21** was obtained after chromatographic purification on neutral aluminum oxide (petroleum ether/ethyl acetate = 9:1): 62%; mp  $84\text{--}86\text{ }^\circ\text{C}$ ;  $^1\text{H}$  NMR:  $\delta$  8.08 (d, 1H,  $J = 8.1$  Hz), 7.65 (t, 1H,  $J = 7.8$  Hz), 7.55 (s, 1H), 7.39 (t, 1H,  $J = 7.8$  Hz), 7.37 (d, 1H,  $J = 8.1$  Hz), 3.44 (d, 1H,  $J = 10.5$  Hz), 3.21 (d, 1H,  $J = 10.5$  Hz), 2.78 (d, 1H,  $J = 3.9$ ), 2.22–2.09 (m, 2H), 1.80–1.70 (m, 1H), 1.70–1.55 (m, 1H), 1.09 (s, 3H), 0.92 (s, 3H). Anal. Calcd for  $C_{17}H_{18}INO_3$ : C, 49.65; H, 4.41; N, 3.41. Found: C, 49.83; H, 4.43; N, 3.44.

#### 4.14. (1*R*,4*S*)-3-(2-Aminophenyl)methylene-1-iodomethyl-7,7-dimethyl[2.2.1]bicycloheptan-2-one **22**

Following the procedure used for the preparation of **15**, compound **22** was obtained in 73% yield after chromatographic purification on neutral aluminum oxide (petroleum ether/ethyl acetate = 9:1): oil;  $^1\text{H}$  NMR:  $\delta$  7.31 (s, 1H), 7.23–7.08 (m, 2H), 6.80–6.66 (m, 2H), 4.00 (br s, 2H), 3.41 (d, 1H,  $J = 10.5$  Hz), 3.05 (d, 1H,  $J = 10.5$  Hz), 3.01 (d, 1H,  $J = 3.9$  Hz), 2.25–2.15 (m, 2H), 1.75–1.55 (m, 2H), 1.08 (s, 3H), 0.87 (s, 3H). Anal. Calcd for  $C_{17}H_{20}INO$ : C, 53.56; H, 5.29; N, 3.67. Found: C, 53.75; H, 5.31; N, 3.69.

#### 4.15. (1*S*,4*S*)-4-Iodomethyl-1,4-methano-11,11-dimethyl-1,2,3,4-tetrahydroacridine **8c**

Following the procedure used for the preparation of **16**, the heating under reflux of the amine **22** for 1 h gave a crude product that by chromatographic purification on neutral alumina (petroleum ether/ethyl acetate = 95:5) afforded **8c** in 92% yield: mp  $100\text{--}102\text{ }^\circ\text{C}$ ,  $[\alpha]_D^{25} = -49.3$  ( $c$  0.13,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR:  $\delta$  8.06 (d, 1H,  $J = 8.4$  Hz), 7.76–6.69

(m, 1H), 7.72 (s, 1H), 7.60 (dt, 1H,  $J = 6.9, 1.5$  Hz), 7.45 (dt, 1H,  $J = 6.9, 1.2$  Hz), 4.02 (d, 1H,  $J = 10.5$  Hz), 3.61 (d, 1H,  $J = 10.5$  Hz), 3.01 (d, 1H,  $J = 3.9$  Hz), 2.38–2.18 (m, 2H), 1.52–1.42 (m, 1H), 1.35–1.24 (m, 1H), 1.22 (s, 3H), 0.63 (s, 3H).  $^{13}\text{C}$  NMR:  $\delta$  168.9, 146.4, 138.9, 129.1, 127.8, 127.7, 127.4, 126.2, 125.5, 65.8, 56.7, 55.4, 52.3, 32.4, 26.3, 20.3, 20.4. Anal. Calcd for  $\text{C}_{17}\text{H}_{18}\text{IN}$ : C, 56.21; H, 4.99; N, 3.86. Found: C, 56.42; H, 4.97; N, 3.89.

#### 4.16. (1*S*,4*S*)-4-Phenylthiomethyl-1,4-methano-11,11-dimethyl-1,2,3,4-tetrahydroacridine **7b**

Benzenethiol (0.165 g, 1.5 mmol) was added dropwise to a mixture of oil-free NaH (36.0 mg, 1.5 mmol) in dry DMF (3 mL) at 0 °C. After 30 min at room temperature, a solution of **8c** (0.181 g, 0.5 mmol) in dry DMF (2 mL) was added dropwise and the resulting mixture heated under nitrogen at 70 °C for 5 h. After cooling the solution was taken up in  $\text{H}_2\text{O}$  (50 mL) and extracted with  $\text{Et}_2\text{O}$ . The organic phase was dried on anhydrous  $\text{Na}_2\text{SO}_4$  and the solvent evaporated under vacuum. The residue was purified by flash chromatography (petroleum ether/ $\text{EtOAc} = 95:5$ ) to give **7b**: 0.131 g (76%); oil;  $[\alpha]_{\text{D}}^{25} = -7.2$  ( $c$  0.67,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR:  $\delta$  8.07 (d, 1H,  $J = 8.1$  Hz), 7.74–7.69 (m, 2H), 7.59 (dt, 1H,  $J = 8.1, 1.5$  Hz), 7.54–7.40 (m, 3H), 7.31 (t, 2H,  $J = 7.5$  Hz), 7.17 (t, 1H,  $J = 7.5$  Hz), 3.99 (d, 1H,  $J = 13.3$  Hz), 3.41 (d, 1H,  $J = 13.3$  Hz), 2.94 (d, 1H,  $J = 4.2$  Hz), 2.47–2.35 (m, 1H), 2.30–2.19 (m, 1H), 1.49–1.41 (m, 1H), 1.34–1.21 (m, 1H), 1.21 (s, 3H), 0.66 (s, 3H).  $^{13}\text{C}$  NMR:  $\delta$  170.4, 146.5, 139.3, 138.7, 128.9, 127.8, 127.7, 127.4, 126.2, 125.4, 57.1, 56.4, 51.6, 32.2, 28.46, 26.3, 20.5. Anal. Calcd for  $\text{C}_{23}\text{H}_{23}\text{NS}$ : C, 79.96; H, 6.71; N, 4.05. Found: C, 79.84; H, 6.73; N, 4.07.

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

A solution of the catalyst was prepared as follows: (a) with ligand **7b** by stirring under argon the ligand (0.08 mmol, 10 mol %) and  $[\text{Pd}(\eta^3\text{-C}_3\text{H}_5\text{Cl})_2]$  (8 mg, 2.5 mol %) in dry  $\text{CH}_2\text{Cl}_2$  (2 mL) at room temperature for 1 h; (b) with ligand **7a** by stirring under argon the ligand (0.02 or 0.04 or 0.08 mmol, 2.5 or 5 or 10 mol %, respectively) and  $[\text{Pd}(\eta^3\text{-C}_3\text{H}_5\text{Cl})_2]$  (8 mg, 2.5 mol %) in dry  $\text{CH}_2\text{Cl}_2$  (2 mL) at room temperature for 1 h; (c) with ligand **18** by stirring the ligand (0.08 mmol, 10 mol %) and  $\text{Pd}(\text{OAc})_2$  (4.5 mg, 2.5 mol %) in dry  $\text{CH}_2\text{Cl}_2$  (2 mL) at room temperature for 1 h. This solution was treated successively with a solution of *rac*-(*E*)-1,3-diphenyl-2-propenyl acetate (0.8 mmol) in  $\text{CH}_2\text{Cl}_2$  (1 mL), dimethyl malonate (2.4 mmol), *N,O*-bis(trimethylsilyl)acetamide (2.4 mmol) and a few crystals of anhydrous potassium acetate. The reaction mixture was stirred until conversion was complete as shown by TLC analysis (petroleum ether/diethyl 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 over  $\text{Na}_2\text{SO}_4$  and evaporated under reduced pressure. The residue was purified by flash chromatography (light petroleum/diethyl ether = 3:1) to afford dimethyl 1,3-diphenylprop-2-enylmalonate. The enantiomeric excess was determined from the  $^1\text{H}$  NMR spectrum in the presence of enantiomerically pure shift

reagent  $\text{Eu}(\text{hfc})_3$ ; 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.<sup>21</sup>

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