**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**

# 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.

## 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.[1] 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.[2] In this context, many examples possess pyridine *N*-donors, such as 2,2′- bipyridines,[3] 1,10-phenthrolines,[4] 2,2′:6′,2″-terpyridines,[5] pyridine–phosphines,[6] pyridine–thioethers[7] and pyridine–alcohols.[8] These pyridine ligands can be divided into two types; those in which the camphor is annulated in the 2,3-positions to the b-face of the pyridine ring such as the 2,2′-bipyridine 1[3] or 1,10-phenanthroline 2[4b] (Fig. 1) and those in which the pyridine is contained as a pendant group on the C2, such as hydroxy-pyridine 3,[8d,e] pyridine–phosphine 4[6b] and pyridine–thioether 5[5b] (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,[9] 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-(diphenyl- phosphanylmethyl)- and 4-(phenylthiomethyl)-1,4-meth- ano-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[10] 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 group.

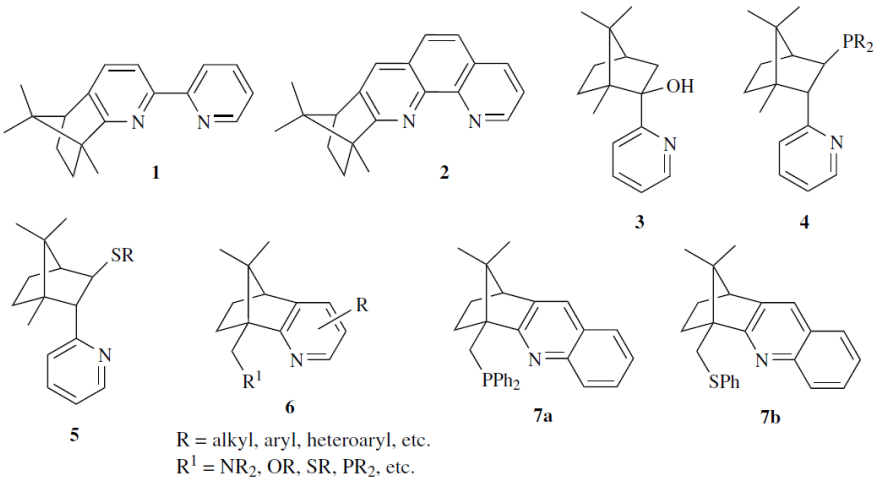
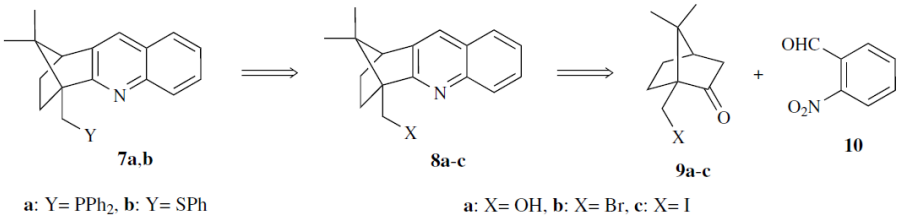


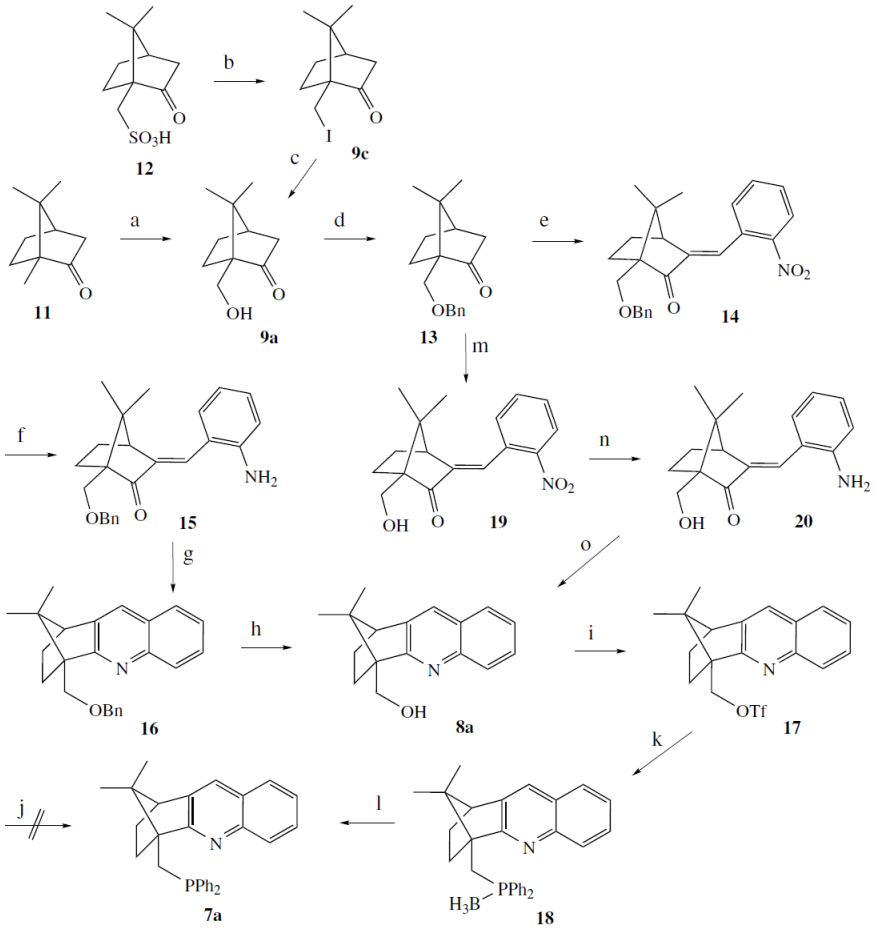

**Figure 1.**




**Scheme 1.**

Accordingly, 10-hydroxycamphor 9a was prepared in a three step sequence from (+)-camphor [(i) base-promoted $Tf_2O$ rearrangement, (ii) $LiAlH_4$ reduction of the obtained 2-methylenenorbor-1-yl triflate and finally (iii) *m*-CPBA-promoted rearrangement of reduced product 2-methylenebornan-1-ol.[11] Alternatively, 9a can be obtained from 10-iodocamphor 9c (displacement of the iodide by acetate ion followed by hydrolysis),[12] which can be readily obtained from 10-camphorsulfonic acid 12.[13] 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-aldol 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)[14] 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 (cata- lytic $H_2SO_4$, 200 °C, 10 h, 89%). Unexpectedly, the removal of the benzyl protecting group from 15 proved problematic and after several failed attempts [($H_2$, Pd/C, EtOH, rt), ($Me_3SiI$, $CH_2Cl_2$, rt or 60 °C, 48 h)[15] and ($SnCl_4$, $CH_2Cl_2$ or benzene, rt, 48 h)[16]] alcohol 8a was obtained in 26% yield by treatment of 16 with boron trifluoride and sodium iodide (MeCN, rt, 24 h).[17]

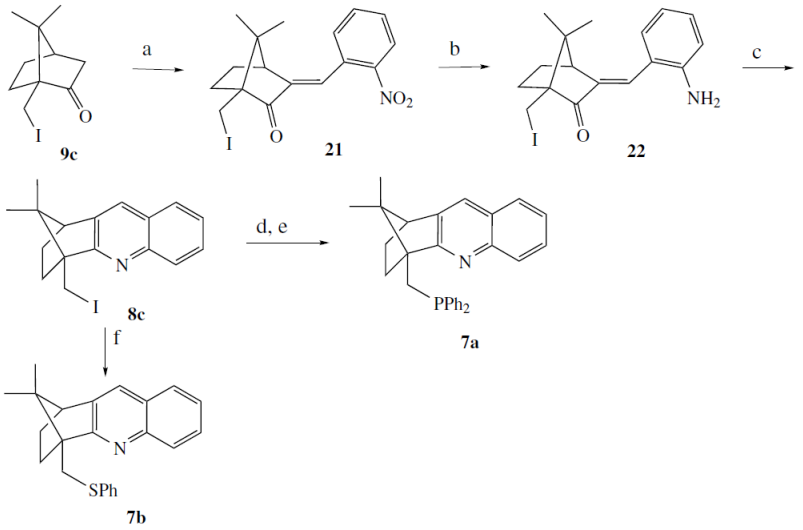
We next examined the possibility of obtaining 8a directly from alcohol 9a, that would overcome the protection– deprotection steps. Thus, treatment of 9a with two equivalents of LDA and then treatment with 2-nitrobenzaldehyde 10 gave condensation product 19. The yield of the reaction was low (37%), but 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 [($Tf_2O$, $Et_3N$, 45 °C to rt, 95%] which was then treated with lithium diphenylphosphide ($LiPPh_2$, 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 $BH_3$ was examined.[18] Treatment of 17 with sodium diphenylphosphide–borane [Na($PPh_2$–$BH_3$), THF, 30 °C to rt, 12 h)] gave in good yield (77%) the phosphine–borane 18 which, by removal of $BH_3$ from the phosphorus with an excess of morpholine (70 °C, 2 h), afforded phosphine 7a in 96% yield.




**Scheme 2.** Reagents and conditions: (a) (i) $Tf_2O$, $CH_2Cl_2$, MTBMP, 95%, (ii) $LiAlH_4$, $Et_2O$, then hydrolysis, 95%, (iii) *m*-CPBA, $CH_2Cl_2$, rt, 24 h, 78%; (b) (i) $I_2$, $PPh_3$, toluene, reflux, 16 h, 92%, (ii) KOH, MeOH, reflux, 6 h, 69%; (c) KOAc, AcOH, 180 °C, 1.5 h, 88%; (d) NaH, BnBr, THF, reflux, 2 h, 95%; (e) LDA, THF, −40 °C, 2 h, then 2-nitrobenzaldehyde, 72%; (f) Fe, AcOH/EtOH/$H_2O$ (2:2:1), catalytic HCl, reflux, 15 min, 87%; (g) carbitol, catalytic $H_2SO_4$, reflux, 10 h, 89%; (h) $BF_3$, NaI, $CH_3CN$, rt, 24 h, 26%; (i) $Tf_2O$, $Et_3N$, $CH_2Cl_2$, −45 °C to rt, 12 h, 95%; (j) $LiPPh_2$, THF, −60 °C to rt, 24 h; (k) $LiPPh_2(BH_3)$, THF, rt, 48 h, 76%; (l) morpholine, 70 °C, 2 h, 96%; (m) LDA (2.2 equiv), THF, −40 °C, 2 h, then 2-nitro benzaldehyde, 37%; (n) Fe, AcOH/EtOH/$H_2O$ (2:2:1), catalytic HCl, reflux, 15 min, 92%; (o) carbitol, catalytic $H_2SO_4$, reflux, 10 h, 88%.

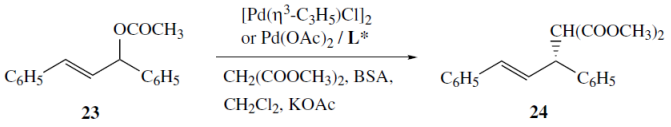
Although we have been able to obtain the desired N,P-ligand 7a, a low yield of 8a was restrictive. An alternative to the triflate leaving group is iodide; thus we devoted our attention to the possibility of obtaining 8c (Scheme 1) from 10-iodocamphor 9c, following the usual protocol (Scheme 3). Notwithstanding the rather harsh conditions required for the reduction and annulation steps (carbitol, 200 °C, 1 h), the iodomethyltetrahydroacridine 8c was obtained in a reasonable yield (58% from 9c). Treatment of 8c with sodium diphenylphosphide–borane [$Na(PPh_2–BH_3)$, 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).




**Scheme 3.** Reagents and conditions: (a) LDA, THF, −40 °C, 2 h, then 2-nitrobenzaldehyde, 72%; (b) Fe, $CH_3COOH/EtOH/H_2O$ (2:2:1), catalytic HCl, reflux, 15 min, 87%; (c) carbitol, catalytic $H_2SO_4$, reflux, 1 h, 92%; (d) $LiPPh_2(BH_3)$, THF, rt, 48 h, 76%; (e) morpholine, 70 °C, 2 h, 96%; (f) NaSPh, DMF, reflux, 5 h, 76%.

The catalytic activity of the new N–P[19] and N–S[20] ligands was tested in the palladium-catalyzed allylic substitution[21] 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(p-allylpalladium chloride), both ligands 7a and 7b (Pd/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 Pd/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 (Pd/ligand = 1:1), which was employed simultaneously to release the phosphorus from borane and as the Pd(0) source for the catalytic reaction.[22] 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 4.**

## 3. Conclusion

In conclusion, we have developed a procedure for the prep- aration 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 $^1H$, 75.4 MHz for $^{13}C$ and 121.4 MHz for $^{31}P$. Chemical shifts are reported in ppm downfield from internal $Me_4Si$ in $CDCl_3$. 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 $CH_2Cl_2$

from $P_2O_5$. Both solvents were degassed thoroughly with dry nitrogen directly before use. Alcohol 9a was obtained from (+)-11[11] or 9c.[12]

### 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 mmol) and 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 $H_2O$ and extracted with $Et_2O$ (2x50 mL). The combined organic solution was dried over anhydrous $Na_2SO_4$ and the solvent evaporated. Purification of the residue by distillation under vacuum gave 13 (3.1 g, 95%), bp 150 °C at 0.1 mm Hg; $[\alpha]^{25}_D$ +38:0 (*c* 1.77, $CHCl_3$); $^1$H NMR: $\delta$ 2.34–2.22 (m, 5H), 4.53 (s, 2H), 3.64 (d, 1H, *J* = 10.5 Hz), 3.59 (d, 1H, *J* = 10.5 Hz), 2.39 (dddd, 1H, *J* = 18.3, 7.2, 4.2, 2.4 Hz), 2.15–2.92 (m, 3H), 1.84 (d, 1H, *J* = 18.3 Hz), 1.35 (d, 2H, *J* = 9.0 Hz), 1.07 (s, 3H), 0.95 (s, 3H). Anal. Calcd for $C_{17}H_{22}O_2$: 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 $H_2O$ (50 mL) and the resulting mixture extracted with ethyl acetate (3x 50 mL). The combined organic solution was dried over anhydrous $Na_2SO_4$ 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; $^1$H NMR: $\delta$ 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 $C_{24}H_{25}NO_4$: 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 power (0.826 g, 14.9 mmol), concentrated HCl (two drops) and EtOH/ AcOH/$H_2O$ (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 $H_2O$ (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 $H_2O$ (50 mL). The organic solution was dried over anhydrous $Na_2SO_4$ 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; $^1$H NMR: $\delta$ 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 $C_{24}H_{27}NO_2$: C, 79.74; H, 7.53; N, 3.87. Found: C, 79.98; 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 $H_2O$ (250 mL) and the resulting mixture extracted with $Et_2O$ (3 x 100 mL). The combined organic solution was washed with $H_2O$ (5 · 100 mL), dried over anhydrous Na SO , and the sol 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 $C_{24}H_{25}NO$: 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 $CH_2Cl_2$ (3x30 mL). The combined organic extracts were washed with $H_2O$ (3 · 20 mL) followed by brine (2 x 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, $a_D$ 21:3 (*c* 0.72, $CHCl_3$); H NMR: $\delta$ 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). $^{13}$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 $C_{17}H_{19}NO$: 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; $^1$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 $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.88; 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; $_1$H NMR: δ 7.31 (s, 1H), 7.22 (d, 1H, J = 7.5 Hz), 7.15 (t, 1H, J = 7.5 Hz), (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 drop- wise to a cooled (-45 °C) solution of 8a (1.25 mmol) and $Et_3N$ (0.21 mL, 1.5 mmol) in anhydrous $CH_2Cl_2$ (6 mL) under nitrogen. The resulting solution was allowed to warm to room temperature and stirred overnight. The mix- ture was treated with a saturated aqueous $Na_2CO_3$ solution and extracted with $CH_2Cl_2$. The organic phase was washed with brine, dried over anhydrous $Na_2SO_4$ 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; $^1$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-diphenylphos- phanylmethyl-1,4-methano-11,11-dimethyl-1,2,3,4-tetra- hydroacridine 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 °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 °C and a solution of 17 (0.229 g, 0.61 mmol) in dry THF (3 mL) was added drop- wise 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 $H_2O$ (10 mL) and extracted with $CH_2Cl_2$ (3x 20 mL). The combined organic phase was dried on anhydrous $Na_2SO_4$ 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 146–148 °C; $[a]^{25}{}_{D}$ —13:4 (*c* 0.65 $CHCl_3$); $^1$H NMR: δ *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 $BH_3$), 1.20 (s, 3H), 1.09 (dt, 1H, *J* = 12.9, 3.5 Hz), 0.89–0.80 (m, 1H), 0.56 (s, 3H). $^{13}$C NMR: δ 170.0, 146.3, 139.4, 133.5–128.5 (m, $PPh_2$), 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. $^{31}$P NMR: δ 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-Diphenylphosphanylmethyl-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 °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 47–52 °C (sticky solid); *a* $^{25}$ 29:4 (*c* 0.48, $CHCl_3$); $^1$H NMR: δ 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). $^{13}$C NMR: δ 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. $^{31}$P NMR: δ 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 purifi- cation on neutral aluminum oxide (petroleum ether/ethyl acetate = 9:1): 62%; mp 84–86 °C; $^1$H NMR: δ 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 chromato- graphic purification on neutral aluminum oxide (petroleum ether/ethyl acetate = 9:1): oil; $^1$H NMR: δ 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 100–102 °C, ½*a*]$^{25}$ ¼ —49:3 (*c* 0.13, 128.4, 127.9,

127.7, 127.4, 126.2, 125.4, 57.6, 55.2, 50.3, $CHCl_3$); $^1$H NMR: δ8.06 (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). $^{13}$C NMR: δ 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 $C_{17}H_{18}IN$: 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 solu- tion 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 $H_2O$ (50 mL) and extracted with $Et_2O$. The organic phase was dried on anhydrous $Na_2SO_4$ and the sol- vent evaporated under vacuum. The residue was purified by flash chromatography (petroleum ether/EtOAc = 95:5) to give 7b: 0.131 g (76%); oil; [*a*] ¼ —7:2 (*c* 0.67, $CHCl_3$); $^1$H NMR: δ8.07 (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). $^{13}$C NMR: δ170.4, 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 $C_{23}H_{23}NS$: 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 $[Pd(g^3\text{-}C_3H_5)Cl]_2$ (8 mg, 2.5 mol %) in dry $CH_2Cl_2$ (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 $[Pd(g^3\text{-}C_3H_5)Cl]_2$ (8 mg, 2.5 mol %) in dry $CH_2Cl_2$ (2 mL) at room temperature for 1 h; (c) with ligand 18 by stirring the ligand (0.08 mmol, 10 mol %) and $Pd(OAc)_2$ (4.5 mg, 2.5 mol %) in dry $CH_2Cl_2$ (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 $CH_2Cl_2$ (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 $Na_2SO_4$ 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 $^1$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.[21]

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