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Enantiomerically pure pyridine and 2,2′-bipyridine thioethers: new N–S chiral ligands for asymmetric catalysis. Palladium-catalyzed allylic alkylation

Giorgio Chelucci,[a,*] Nicola Culeddu,[b] Antonio Saba [a] and Raffaela Valenti [a]

[a] *Dipartimento di Chimica, Università di Sassari, via Vienna 2, I-07100 Sassari, Italy*

[b] *Istituto A.T.C.A.P.A., C.N.R., via Vienna 2, I-07100 Sassari, Italy*

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Abstract

Diastereomeric pure pyridine and 2,2′-bipyridine thioethers, derived from (+)-camphor, were prepared and assessed in the enantioselective palladium-catalyzed allylic substitution of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate. Enantioselectivities of up to 76% were obtained. © 1999 Elsevier Science Ltd. All rights reserved.

1. Introduction

In contrast to the great number of chiral pyridine derivatives used as ligands for metal complexes in asymmetric catalysis, only a few examples of sulfur-containing pyridine ligands have so far been reported.[1] Recently, we and Kellog's group introduced the use of chiral thioalkylpyridines as ligands for palladium-catalyzed allylic substitutions. Thus, while we prepared and assessed the diastereomerically pure 8-phenylthio tetrahydroquinoline **1**[1a] and the 2-(1-*p*-tolylsulfinylalkyl)pyridines **2**,[1b] obtaining enantioselectivities up to 83%, Kellog achieved a higher enantiomeric excess (98%, under optimized conditions) using the pyridine thioether **3**[1d] (Scheme 1). This interesting result prompted us to undertake a study on the synthesis and application in asymmetric catalysis of new pyridine and 2,2′-bipyridine thioethers, derived from (+)-camphor, with the general structures **4** and **5**. The palladium-catalyzed allylic substitutions has been used to explore the catalytic potential of these ligands.[2]

* Corresponding author. E-mail: chelucci@ssmain.uniss.it

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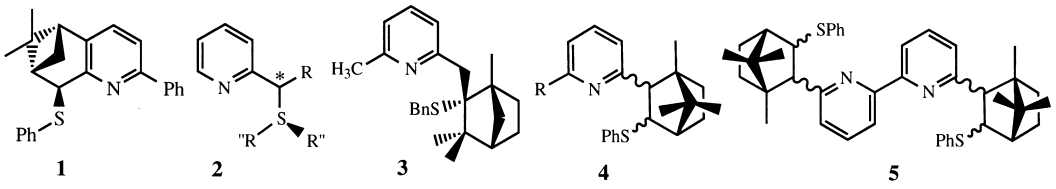
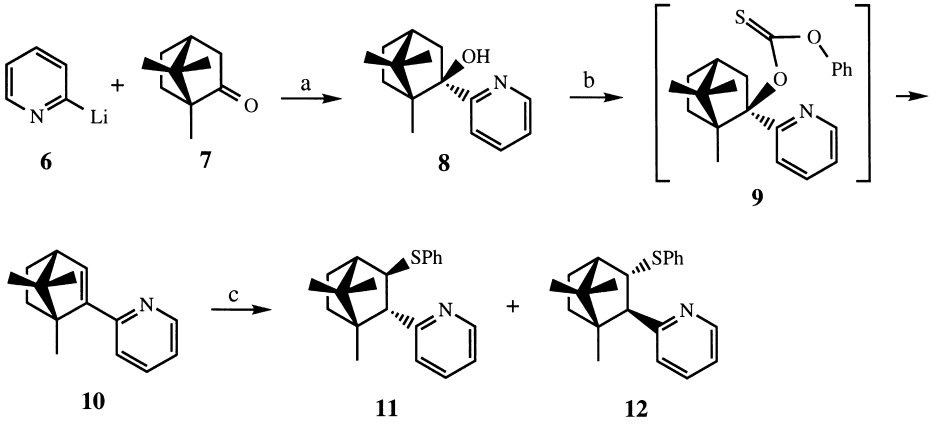


Scheme 1.

2. Results and discussion

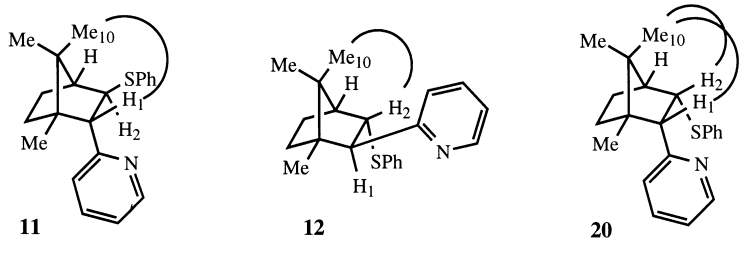
2.1. Synthesis of the ligands

We started our investigations with the synthesis of the simpler pyridine thioether of type **4** (R=H). Thus, the known pyridyl alcohol **8**,[3] prepared by addition of 2-pyridyl lithium to (+)-camphor, was dehydrated by treatment with sodium hydride (1 equiv.) in benzene followed by *p*-tolylchlorothionoformate (Scheme 2).[4] The alkene **10** was directly obtained without the detection of the expected thiocarbonate ester intermediate **9**. When the alkene was treated with thiophenol in boiling acetic acid the desired Michael addition occurred to give a mixture of diastereomeric thioethers **11** and **12** in about a 1:4 ratio which were then obtained in pure form through chromatography on silica gel.



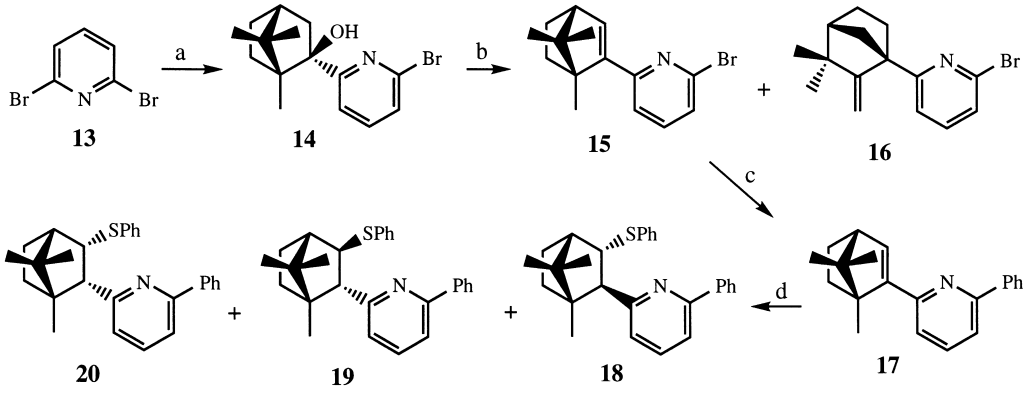
Scheme 2. a: Literature; b: NaH, benzene, 50°C, 30 min then *p*-tolylchlorothionoformate, 12 h rt and 1 h at reflux; c: PhSH, AcOH, reflux, 24 h

The assignment of the stereochemistry of **11** and **12** was determined on the basis of both the coupling constants and their ^{1}H–^{1}H NOESY maps which, in the case of **11**, correlates the proton H_1 with the Me_{10}, suggesting that the two H_1 and H_2 protons have a *trans* orientation on the ring. The same correlation exists in the compound **12** between the H_2 proton and the Me_{10} (Scheme 3).



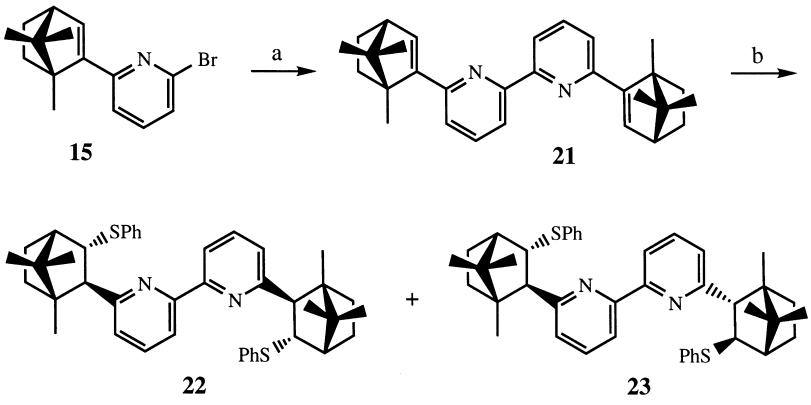
Scheme 3.

Moreover, since we and others have shown that in C_1-symmetric heterobidentate ligands containing the pyridine ring such as thioethers of type **3**[1d] and oxazolinylpyridines[5] the presence of a substituent on the 6-position of the pyridine had the effect of increasing the enantioselectivity of the reaction, we devoted our attention to the preparation of compounds of type **4** (R=Ph) in which the pyridine bears a phenyl group on the 6 position. In this case, monolithiation of the commercially available 2,6-dibromopyridine **13** with *n*-butyllithium in ether followed by trapping with (+)-camphor gave the tertiary alcohol **14** (Scheme 4). Initial attempts to dehydrate **14** to the corresponding alkene **15** in the usual way failed and then other methods which can avoid the formation of ionic intermediates, because skeletal rearrangements of fragmentations may occur,[6] were evaluated. However, the formation of *S*-methylxanthate failed and, unexpectedly, dehydration using the Burgess[7] reagent afforded exclusively the olefin **16**. In contrast, treatment of **14** with the thionyl chloride in pyridine[8] gave a 1:4 mixture of the olefins **15** and **16** which were separated by chromatography. No appreciable change in the ratio of products was obtained when the reaction temperature was varied from 25 to −25°C. Then, the bromopyridine **15** was cross-coupled with phenylboronic acid in the presence of a catalytic amount of $Pd(PPh_3)_4$[9] to give the pyridine **17** in satisfactory yield (95%). Finally, the reaction of **17** with thiophenol in boiling acetic acid afforded a mixture of thioethers **18**, **19** and **20** in about a 4:2:1 ratio. It is interesting to note that in this case it has been obtained, with the expected *trans* isomers **18** and **19**, the *cis* isomer **20** which has been separated from the others through chromatography on silica gel. The mixture of *trans* isomers was difficult to purify, so we were able to obtain in the pure form only the more abundant isomer **18**. The configurational assignment of the stereochemistry of **18** and **19** was determined comparing their ^{1}H NMR with those of correletated compounds **11** and **12**. That of **20** was assigned on the basis of its ^{1}H–^{1}H NOESY map which shows a correlation of both H_1 and H_2 protons with the Me_{10}, suggesting that the two protons have a *cis* orientation on the ring (Scheme 3).



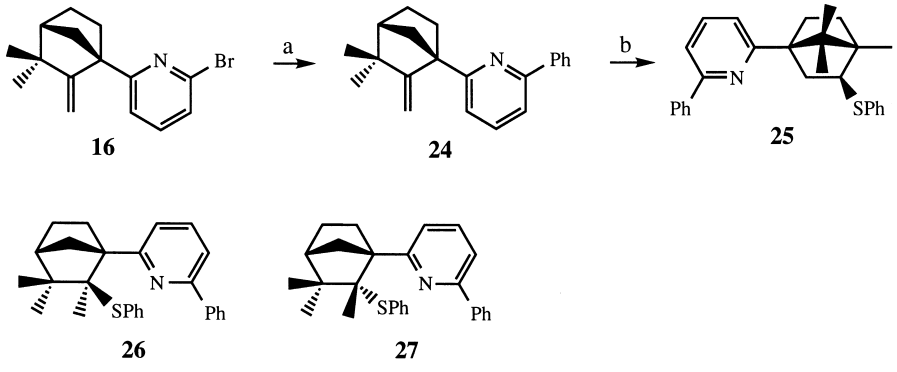
Scheme 4. a: *n*-BuLi, −78°C, 2 h then **7**; b: $SOCl_2$, pyridine, 0°C then 1 h at rt; c: $PhB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, toluene/MeOH, reflux; d: PhSH, AcOH, reflux, 72 h

Then, we devoted our attention to the synthesis of the dipyridine of type **5**. For this purpose the bromopyridine **15** was homocoupled in the presence of nickel(0)[10] to give the bipyridine **21** (Scheme 5). The debrominated derivative of **15** was the major by-product of the coupling reaction. Its formation could be substantially reduced by using carefully degassed DMF solutions. Addition of thiophenol to the double bonds of the bipyridine **21** occurred and a mixture of C_2-symmetric bipyridine **22** and C_1-symmetric bipyridine **23** in about a 9:2 ratio was obtained. From this mixture only the more abundant and useful ligand **22** was recovered in 66% yield. The stereochemistry of these bipyridines was assigned on the basis of the comparison of their ^{1}H NMR spectra with those of the related compounds **11** and **12**.



Scheme 5. a: $NiCl_2$ $6H_2O$, Zn, PPh_3, DMF; b: PhSH, AcOH, reflux, 3 h

With the compounds of type **16** in hand we evaluated the possibility to obtain a new class of pyridine thioethers by the addition of thiophenol to the double bond of **24**, obtained by cross-coupling of **16** with phenylboronic acid in the presence of Pd(0) (Scheme 6). However, several attempts to obtain the addition of thiophenol using acetic acid and perchloric acid as an acid catalyst failed. However, a new compound was obtained when a solution of **24** and thiophenol was heated under reflux in the presence of 50% sulfuric acid. The examination of its ^{1}H, COSY and NOESY NMR spectra excluded the expected structure **26** or **27** (Scheme 6) but it supports the isomeric structure **25**. Its formation is strengthened by earlier observations that 1-*p*-anisylcamphene, 1-*p*-anisylbornene and 2-*p*-anisyl-2-borneol undergo rearrangement by treatment with acetic acid and sulfuric acid to produce almost exclusively 4-*p*-anisyl-2-*exo*-bornyl acetate.[11]

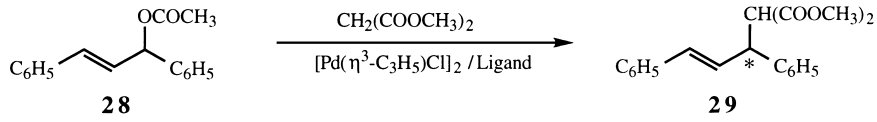


Scheme 6. a: $PhB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, toluene/MeOH, reflux; b: PhSH, 50% H_2SO_4, reflux

2.2. Palladium-catalyzed allylic alkylation

With the new ligands in hand, their ability to provide asymmetric induction in the palladium-catalyzed alkylation of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate was examined. Allylic substitutions were carried out at room temperature employing Trost's procedure which used $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ as procatalyst and a mixture of dimethyl malonate, *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and potassium acetate in a methylene chloride solution.[12] The results obtained under control of the new ligands are summarized in Table 1. All pyridine thioethers were not able to provide a reactive palladium catalyst. The ligands **11** and **12** required about 5 days to completely convert the starting

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



28 **29**

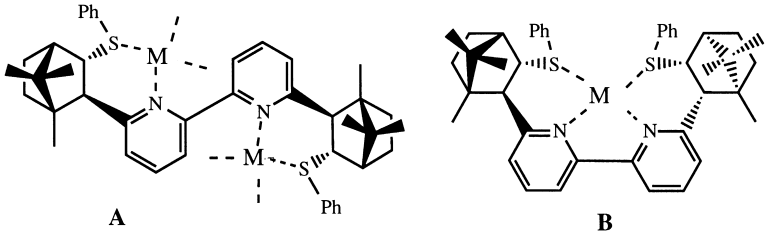
Entry	Ligand	React. time, d	Conv.[b]	Yield[c]	% Ee[d]	Conf.[e]
1	**11**	4,4	100	84	30	S
2	**12**	4,2	100	85	26	R
3	**18**	7	39	n.d.	76	R
4	**20**	7	28	n.d.	3	S
6	**22**	7	48	76	48	R

[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), N,O-bis(trimethylsilyl)acetamide (BSA) (1.2 mmol) and KOAc (3.5 % mol) in CH_2Cl_2 (2 ml) at room temperature. [b]Determined by ^{1}H-NMR of the crude reaction mixture. [c]Isolated yields. [d]Determined by ^{1}H-NMR using Eu(hfc)$_3$ as chiral shift reagent. [e]The assignement is based on the sign of the optical rotation: Leutenegger, U.; Umbricht, G.; Fahrni, C.; Matt, P.V.; Pfaltz, A. *Tetrahedron*, **1992**, *48*, 2143.

material **28** to dimethyl 1,3-diphenylprop-2-enylmalonate **29** which showed a low enantiomeric excess (30 and 26%, respectively). It should be noted that both diastereomers **11** and **12** gave a similar level of stereodifferentiation but opposite configuration of **29**, indicating that they behave as pseudoenantiomers.

A dramatic effect on both stereoselectivity and catalytic activity was observed by the presence in the 6-position of the pyridine ring of a phenyl group. Thus, the ligand **18** gave a 77% enantiomeric excess but it provided a less effective palladium catalyst with respect to the related ligand **12**; in fact the reaction required 7 days to achieve a 39% conversion. The *trans* isomer **20** was very ineffective regarding both catalytic activity and stereoselectivity.

Finally, the bipyridine **22**, showing a comparable reactivity with respect to the related ligand **18**, afforded poorer enantioselectivity (48%). It should be noted that for ligand **22** it is possible to single out, on the basis of a molecular modelling study, two limit conformations, both maintaining a C_2-symmetry: in the former case it could behave as bis-bidentate ligands (**A**, Scheme 7), whereas in the latter it could coordinate to a metal atom in a tetradentate fashion (**B**, Scheme 7).



Scheme 7.

In conclusion we have developed new diastereomerically pure pyridine and 2,2′-bipyridine thioethers, and demonstrated their catalytic activity and stereodifferentianting ability in the palladium-catalyzed enantioselective alkylation of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate. A deeper investi-

gation aimed at the determination of the catalytic species involved in the examined catalytic process and to the application of this kind of ligand in other enantioselective reactions is now in progress.

3. Experimental

3.1. General methods

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.

3.2. Starting material

(1*R*,2*R*,4*R*)-2-*exo*-Hydroxy-2-*endo*-(pyridin-2-yl)-1,7,7-trimethylbicyclo[2.2.1]heptane **8** was prepared according to a reported procedure.[3] 2-Bromopyridine, 2,6-dibromopyridine, (+)-camphor (98% pure, $[\alpha]^{25}_D$ +44.1 (*c* 10, C_2H_5OH) and *p*-tolylchlorothionoformate were purchased from Aldrich A.G.

3.3. (1R,4R)-2-(Pyridin-2-yl)-1,7,7-trimethylbicyclo[2.2.1]-2-heptene **10**

A solution of **8** (2.17 g, 9.4 mmol) in benzene (10 ml) was added dropwise to a mixture of NaH (0.23 g, 9.6 mmol) in benzene (30 ml). After 2 h at room temperature the mixture was heated at 50°C for 0.5 h. After cooling to room temperature, *p*-tolylchlorothionoformate (1.93 g, 10.3 mmol) was added. The mixture was stirred for 12 h at room temperature and was then heated under reflux for 1 h. The reaction mixture was taken up in 10% NaOH and the separated organic phase was dried over anhydrous Na_2SO_4 and the solvent evaporated off. The residue was purified by flash chromatography on a silica gel column (eluent: petroleum ether:methylene chloride=2:8) to give unreacted **8** (1.2 g) and **10**: 0.51 g (58%, based on the converted starting material); oil; $[\alpha]^{25}_D$ −131.2 (*c* 1.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 8.57 (m, 1H), 7.57 (dt, 1H, J=7.5, 1.8 Hz), 7.29 (dt, 1H, J=7.5, 1.2 Hz), 7.07 (ddd, 1H, J=7.5, 4.8, 1.2 Hz), 6.35 (d, 1H, J=3.3 Hz), 2.44 (t, 1H, J=3.6 Hz), 2.01–1.91 (m, 1H), 1.75–1.67 (m, 1H), 1.46–1.37 (m, 1H), 1.26 (s, 3H), 1.14–1.06 (m, 1H), 0.90 (s, 3H), 0.84 (s, 3H). Anal. calcd for $C_{15}H_{19}N$: C, 84.46; H, 8.98; N, 6.56. Found: C, 84.25; H, 8.77; N, 6.38.

3.4. (1R,2S,3R,4S)-3-exo-Phenylthio-2-endo-(2-pyridinyl)-1,7,7-trimethylbicyclo[2.2.1]heptane **11** and (1R,2R,3S,4S)-3-endo-phenylthio-2-exo-(2-pyridinyl)-1,7,7-trimethylbicyclo[2.2.1]heptane **12**

Acetic acid (10 drops) was added to a solution of **10** (0.5 g, 2.4 mmol) and thiophenol (5 ml), and the resulting mixture was heated under reflux for 24 h. The reaction mixture was taken up in ethyl ether and the resulting solution was washed with 10% NaOH. The separated organic phase was dried over anhydrous Na_2SO_4, the solvent was evaporated off and the residue was purified by flash chromatography on silica gel (eluent: petroleum ether:methylene chloride=2:8) to give **11** and **12**.

Compound **11**: 0.078 g (10%); R_f 0.66; oil; $[\alpha]^{25}_D$ −46.33 (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 8.52 (d, 1H, J=3.9 Hz), 7.54 (dt, 1H, J=7.8, 1.5 Hz), 7.39 (dd, 2H, J=7.2, 1.5 Hz), 7.22–7.05 (m, 5H), 4.96 (d, 1H, J=6.6 Hz), 2.73 (d, 1H, J=7.8 Hz), 2.21 (t, 1H, J=9.6 Hz), 2.01 (t, 1H, J=3.6 Hz), 1.75–1.66 (m, 2H),

1.44 (m, 1H), 1.10 (s, 3H), 0.89 (s, 3H), 0.67 (s, 3H). Anal. calcd for $C_{21}H_{25}NS$: C, 77.97; H, 7.79; N, 4.33. Found: C, 77.85; H, 7.66; N, 4.45.

Compound **12**: 0.289 g (38%); R_f 0.57; oil; $[\alpha]^{25}_D$ +61.46 (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 8.57 (dd, 1H, J=5.1, 0.9 Hz), 7.54 (dt, 1H, J=7.5, 1.8 Hz), 7.23–7.04 (m, 7H), 4.21 (d, 1H, J=6.8 Hz), 3.35 (dd, 1H, J=6.8, 2.1 Hz), 2.03 (d, 1H, J=4.2 Hz), 1.90 (m, 1H), 1.58 (m, 2H), 1.30 (s, 3H), 1.10 (m, 1H), 0.93 (s, 3H), 0.82 (s, 3H). Anal. calcd for $C_{21}H_{25}NS$: C, 77.97; H, 7.79; N, 4.33. Found: C, 77.87; H, 7.76; N, 4.22.

*3.5. (1*R,*2*R,*4*R*)-2*-exo-*Hydroxy-2*-endo-*(6-bromopyridin-2-yl)-1,7,7-trimethylbicyclo[2.2.1]heptane* **14**

A solution of 2,6-dibromopyridine (4.74 g, 20 mmol) in anhydrous diethyl ether was cooled at −78°C and the resulting suspension was treated with a 1.6 M solution of *n*-butyllithium in *n*-hexane (13.7 ml, 22 mmol) over a period of 10 min. The precipitate dissolved and a clear yellow solution resulted. After stirring at this temperature for 2 h a solution of (+)-camphor (3.0 g, 20 mmol) in diethyl ether (10 ml) was added dropwise. The solution was stirred for 30 min at −78°C and was then allowed to warm slowly to room temperature. Water was added, the organic phase was separated and the aqueous phase extracted with ethyl ether. The combined organic phase was dried over anhydrous Na_2SO_4, the solvent was evaporated off and the residue was purified by flash chromatography on silica gel (eluent: petroleum ether:ethyl acetate=7:3) to give pure **14**: 2.05 g (33%); mp 113°C; $[\alpha]^{25}_D$ −65.3 (*c* 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 7.52 (t, 1H, J=7.6 Hz), 7.40 (d, 1H, J=7.6 Hz), 7.36 (d, 1H, J=7.6 Hz), 4.35 (s, 1H), 2.27 (m, 1H), 2.14 (d, 1H, J=13.9 Hz), 1.90 (t, 1H, J=4.4 Hz), 1.79 (m, 1H), 1.30 (m, 2H), 1.24 (s, 3H), 0.90 (s, 3H), 0.85 (s, 3H), 0.75 (m, 1H). Anal. calcd for $C_{15}H_{20}BrNO$: C, 56.77; H, 6.13; N, 4.73. Found: C, 56.87; H, 6.26; N, 4.52.

*3.6. (1*R,*4*R*)-2-(6-Bromopyridin-2-yl)-1,7,7-trimethylbicyclo[2.2.1]-2-heptene* **15** *and (1*R,*4*R*)-2-methylidene-1-(6-bromopyridin-2-yl)-3,3-dimethylbicyclo[2.2.1]heptane* **16**

Thionyl chloride (0.48 ml, 6.6 mmol) was added dropwise to a cooled (0°C) solution of **14** (2.0 g, 6.45 mmol) in pyridine (10 ml). The mixture was kept at 0°C for 30 min and then stirred at room temperature for 1 h. A 10% solution of sodium carbonate was added and the resulting mixture was extracted with ethyl ether. The separated organic phase was dried over anhydrous Na_2SO_4, the solvent was evaporated off and the residue was purified by chromatography on silica gel (eluent: petroleum ether:methylene chloride=8:2) to give pure **15** and **16**.

Compound **15**: 0.34 g (19%); oil; $[\alpha]^{25}_D$ −146.3 (*c* 2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 7.40 (t, 1H, J=7.8 Hz), 7.25 (d, 1H, J=7.8 Hz), 7.22 (d, 1H, J=7.8 Hz), 6.44 (d, 1H, J=3.3 Hz), 2.43 (t, 1H, J=3.3 Hz), 1.95 (m, 1H), 1.67 (m, 1H), 1.35 (m, 1H), 1.27 (s, 3H), 1.06 (m, 1H), 0.85 (s, 3H), 0.83 (s, 3H). Anal. calcd for $C_{15}H_{18}BrN$: C, 61.50; H, 6.21; N, 4.79. Found: C, 61.65; H, 6.26; N, 4.62.

Compound **16**: 1.33 g (75%); oil; $[\alpha]^{25}_D$ +73.7 (*c* 1.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 7.47 (t, 1H, J=7.6 Hz), 7.30 (d, 1H, J=7.6 Hz), 7.19 (d, 1H, J=7.6 Hz), 4.60 (s, 1H), 4.24 (s, 1H), 2.29 (dd, 1H, J=9.8, 2.0 Hz), 2.08–1.99 (m, 2H), 1.84 (m, 2H), 1.68–1.58 (m, 2H), 1.14 (s, 3H), 1.13 (s, 3H). Anal. calcd for $C_{15}H_{18}BrN$: C, 61.50; H, 6.21; N, 4.79. Found: C, 61.55; H, 6.36; N, 4.82.

*3.7. (1*R,*4*R*)-2-(6-Phenylpyridin-2-yl)-1,7,7-trimethylbicyclo[2.2.1]-2-heptene* **17**

A solution of **15** (1.4 g, 4.8 mmol) and tetrakis(triphenylphosphane)palladium(0) (0.16 g, 0.14 mmol) in toluene (9.6 ml) was treated with a solution of Na_2CO_3 (1.01 g, 9.5 mmol) in H_2O (4.8 ml) followed

by a solution of phenylboronic acid (0.7 g, 5.7 mmol) in methanol (2.4 ml). The mixture was stirred at 80–85°C for 14 h. After cooling at room temperature, a solution of concentrated aqueous NH_3 (2.4 ml) in saturated aqueous Na_2CO_3 (24 ml) was added, and the mixture was extracted with CH_2Cl_2 (3×40 ml). The combined organic layers were washed with brine (50 ml) and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave a residue with was purified by flash chromatography (eluent: petroleum ether:methylene chloride=8:2) to give pure **17**: 1.30 g (95%); oil; $[\alpha]^{25}_D$ −153.2 (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 8.06 (d, 2H, J=7.8 Hz), 7.61 (t, 1H, J=7.8 Hz), 7.52 (d, 1H, J=7.8 Hz), 7.50–7.34 (m, 3H), 7.27 (d, 1H, J=7.6 Hz), 6.38 (d, 1H, J=3.7 Hz), 2.44 (t, 1H, J=3.4 Hz), 2.01–1.91 (m, 1H,), 1.76–1.68 (m, 1H), 1.55–1.47 (m, 1H), 1.39 (s, 3H), 1.17–1.06 (m, 1H), 0.91 (s, 3H), 0.85 (s, 3H). Anal. calcd for $C_{21}H_{23}N$: C, 87.50; H, 8.01; N, 4.84. Found: C, 87.55; H, 8.16; N, 4.89.

*3.8. (1*R,*2*S,*3*R,*4*S)-*3*-exo-*Phenylthio-2*-endo-*(6-phenylpyridin-2-yl)-1,7,7-trimethylbicyclo[2.2.1]heptane* ***18****, (1*R,*2*R,*3*S,*4*S)-*3*-endo-*phenylthio-2*-exo-*(6-phenylpyridin-2-yl)-1,7,7-trimethylbicyclo[2.2.1]-heptane* ***19*** *and (1*R,*2*R,*3*R,*4*S)-*3*-exo-*phenylthio-2*-exo-*(6-phenylpyridin-2-yl)-1,7,7-trimethylbicyclo-[2.2.1]heptane* ***20***

Acetic acid (20 drops) was added to a solution of **17** (1.25 g, 4.3 mmol) and thiophenol (12.5 ml), and the resulting mixture was heated under reflux for 72 h. The reaction mixture was taken up in ethyl ether and the resulting solution was washed with 10% NaOH. The separated organic phase was dried over anhydrous Na_2SO_4, the solvent was evaporated off and the residue was purified by chromatography on silica gel (eluent: petroleum ether:ethyl acetate=20:1) to give **18**, **19** and **20**.

Compound **18**: 0.67 g (39%); mp 84–85°C; $[\alpha]^{25}_D$ −108.4 (*c* 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 8.07 (dd, 2H, J=8.7, 1.8 Hz), 7.62–7.49 (m, 2H), 7.49–7.39 (m, 3H), 7.19 (m, 2H), 7.07 (m, 2H), 6.99 (m, 2H), 4.49 (d, 1H, J=6.3 Hz), 3.41 (dd, 1H, J=6.6, 2.1 Hz), 2.07 (d, 1H, J=4.5 Hz), 1.91 (m, 1H), 1.66 (m, 2H), 1.31 (s, 3H), 1.12 (m, 1H), 0.96 (s, 3H), 0.87 (s, 3H). Anal. calcd for $C_{27}H_{29}NS$: C, 81.16; H, 7.32; N, 3.51. Found: C, 81.31; H, 7.26; N, 3.57.

Compound **19**: 0.38 g (90% pure by ^{1}H NMR); ^{1}H NMR ($CDCl_3$) (selected data) δ: 8.00 (dd 1H, J=8.1, 1.8 Hz), 5.17 (m, 1H), 2.80 (d, 1H, J=8.0 Hz), 1.16 (s, 3H), 0.90 (s, 3H), 0.74 (s, 3H).

Compound **20**: 0.19 g (11%); oil; $[\alpha]^{25}_D$ −141.3 (*c* 1.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 8.25 (dd, 2H, J=3.3, 1.5 Hz), 7.61 (d, 1H, J=3.9 Hz), 7.49 (m, 3H), 7.39 (m, 3H), 7.26–7.23 (m, 2H), 7.18–7.13 (m, 1H), 7.10–7.04 (m, 1H), 4.18 (dt, 1H, J=11.4, 3.3 Hz), 3.63 (dd, 1H, J=11.4, 1.8 Hz), 2.52 (m, 1H), 2.03–1.92 (m, 2H), 1.74–1.67 (m, 1H), 1.18 (m, 1H), 1.15 (s, 3H), 1.03 (s, 3H), 0.77 (s, 3H). Anal. calcd for $C_{27}H_{29}NS$: C, 81.16; H, 7.32; N, 3.51. Found: C, 81.21; H, 7.46; N, 3.67.

*3.9. 6,6′-Bis{(1*R,*4*R)-*1,7,7-trimethylbicyclo[2.2.1]-2-hepten-2-yl}-2,2′-bipyridine* ***21***

Zinc powder (0.44 g, 7 mmol) was added at 60°C to a stirred mixture of nickel(II) chloride hexahydrate (1.59 g, 7.0 mmol) and triphenylphosphine (6.4 g, 24 mmol) in DMF (50 ml). After 1 h, a solution of **15** (1.78 g, 6.0 mmol) in DMF (30 ml) was added. The mixture was stirred at 80°C for 21 h, and then taken up with ether and washed with dilute ammonia solution (120 ml), H_2O (100 ml), and finally with 5% HCl (100 ml). The organic phase was dried over anhydrous Na_2SO_4, the solvent was evaporated off and the residue chromatographed on silica gel (eluent: petroleum ether:methylene chloride=8:2) to give pure **21**: 1.06 g (82%); mp 126–128°C; $[\alpha]^{25}_D$ −185.7 (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 8.26 (dd, 1H, J=7.6, 0.7 Hz), 7.68 (t, 1H, J=7.7 Hz), 7.34 (dd, 1H, J=7.7, 0.9 Hz), 6.37 (d, 1H, J=3.3 Hz), 2.45 (t, 1H, J=3.5 Hz), 1.98 (m, 1H), 1.74 (m, 1H), 1.52 (m, 1H), 1.39 (s, 3H), 1.13 (m, 1H), 0.91 (s, 3H), 0.86 (s, 3H). Anal. calcd for $C_{30}H_{36}N_2$: C, 84.86; H, 8.55; N, 6.60. Found: C, 84.65; H, 8.57; N, 6.73.

3.10. 6,6′-Bis{(1R,2S,3R,4S)-3-exo-phenylthio-1,7,7-trimethylbicyclo[2.2.1]heptan-2-endo-yl}-2,2′-bipyridine **22** and 6-{(1R,2S,3R,4S)-3-exo-phenylthio-1,7,7-trimethylbicyclo[2.2.1]heptan-2-endo-yl}-6′-{(1R,2R,3S,4S)-3-endo-phenylthio-1,7,7-trimethylbicyclo[2.2.1]heptan-2-exo-yl}-2,2′-bipyridine **23**

Acetic acid (20 drops) was added to a solution of **21** (1.06 g, 2.5 mmol) and thiophenol (10 ml), and the resulting mixture was heated under reflux for 3 h. The reaction mixture was taken up in ethyl ether and the resulting solution was washed with 10% NaOH. The separated organic phase was dried over anhydrous Na_2SO_4, the solvent was evaporated off and the residue was purified by flash chromatography (eluent: petroleum ether:methylene chloride=2:8) to give **22** and **23**.

Compound **22**: 1.06 g (66%); mp 157–158°C; $[\alpha]^{25}_D$ −124.4 (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 8.31 (d, 1H, J=7.8 Hz), 7.66 (t, 1H, J=7.8 Hz), 7.21 (d, 2H, J=7.2 Hz), 7.01–6.96 (m, 4H), 4.48 (d, 1H, J=6.4 Hz), 3.43 (dd, 1H, J=6.4, 1.7 Hz), 2.1 (d, 1H, J=4.4 Hz), 1.94 (m, 1H), 1.67 (m, 2H), 1.33 (s, 3H), 1.13 (m, 1H), 0.96 (s, 3H), 0.87 (s, 3H). Anal. calcd for $C_{42}H_{48}N_2S_2$: C, 78.21; H, 7.50; N, 4.34. Found: C, 78.35; H, 7.66; N, 4.41.

Compound **23**: ^{1}H NMR ($CDCl_3$) (selected data) δ: 8.24 (d, 1H, J=7.8 Hz), 8.17 (d, 1H, J=7.8 Hz), 5.15 (d, 1H, J=7.8 Hz), 4.47 (d, 1H, J=6.9 Hz), 3.43 (dd, 1H, J=6.9, 2.1 Hz), 2.80 (d, 1H, J=7.8 Hz).

3.11. (1R)-2-Methylidene-1-(6-phenylpyridin-2-yl)-3,3-dimethylbicyclo[2.2.1]heptane **24**

A solution of **16** (0.75 g, 2.56 mmol) and tetrakis(triphenylphosphine)palladium (0.09 g, 0.075 mmol) in toluene (5.2 ml) was treated with a solution of Na_2CO_3 (0.54 g, 5.1 mmol) in H_2O (2.6 ml) followed by a solution of phenylboronic acid (0.38 g, 3.1 mmol) in methanol (1.3 ml). The mixture was stirred at 80–85°C for 14 h. After cooling at room temperature, a solution of concentrated aqueous NH_3 (1.3 ml) in saturated aqueous Na_2CO_3 (12.7 ml) was added, and the mixture was extracted with CH_2Cl_2 (3×20 ml). The combined organic layers were washed with brine (25 ml) and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave a residue which was purified by flash chromatography (eluent: petroleum ether:methylene chloride=2:8) to give pure **24**: 0.66 g (89%); oil; $[\alpha]^{25}_D$ +60.3 (*c* 1.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 8.07 (d, 2H, J=7.8 Hz), 7.61–7.50 (m, 2H), 7.43–7.32 (m, 3H), 7.12 (d, 1H, J=7.5 Hz), 4.60 (s, 1H), 4.31 (s, 1H), 2.40 (dd, 1H, J=9.8, 1.7 Hz), 2.21–2.14 (m, 1H), 2.01 (d, 1H, J=3.4 Hz), 1.88 (m, 2H), 1.65 (m, 2H), 1.16 (s, 6H). Anal. calcd for $C_{21}H_{23}N$: C, 87.15; H, 8.01; N, 4.84. Found: C, 87.35; H, 8.06; N, 4.71.

3.12. (1S,3S,4S)-3-exo-Phenylthio-1-(6-phenylpyridin-2-yl)-4,7,7-trimethylbicyclo[2.2.1]heptane **25**

A mixture of **24** (0.56 g, 1.9 mmol), thiophenol (4 ml) and 50% sulfuric acid (0.5 ml) was heated under reflux for 96 h. The mixture was taken up in ethyl ether and washed with 10% NaOH. The separated organic phase was dried over anhydrous Na_2SO_4, the solvent was evaporated off and the residue was purified by chromatography on neutral aluminium oxide (eluent: petroleum ether:ethyl ether=95:5) to give pure **25**: 0.26 g (34%); oil; $[\alpha]^{25}_D$ +1.87 (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 8.07 (d, 2H, J=7.3 Hz), 7.60–7.51 (m, 2H), 7.44–7.31 (m, 5H), 7.24 (t, 2H, J=8.1 Hz), 7.15 (t, 2H, J=8.8 Hz), 3.41 (dd, 1H, J=5.9, 3.2 Hz), 2.93–2.85 (m, 1H), 2.62 (m, 1H), 2.37 (dd, 1H, J=9.3, 4.2 Hz), 1.87 (dt, 1H, J=12.2, 4.6 Hz), 1.63–1.52 (m, 1H), 1.48–1.36 (m, 1H), 1.20 (s, 3H), 1.0 (s, 3H), 0.84 (s, 3H). Anal. calcd for $C_{27}H_{29}NS$: C, 81.16; H, 7.32; N, 3.51. Found: C, 81.25; H, 7.46; N, 3.61.

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

A solution of ligand (0.04 mmol, 10 mol%) and [{Pd(η^3-C_3H_5)Cl}$_2$] (4 mg, 2.5 mol%) in dry CH_2Cl_2 (2 ml) was stirred at room temperature for 15 min. This solution was treated successively with a solution of *rac*-(*E*)-1,3-diphenyl-2-propenyl acetate (0.4 mmol) in CH_2Cl_2 (1 ml), dimethyl malonate (1.2 mmol), *N*,*O*-bis(trimethylsilyl)acetamide (1.2 mmol) and anhydrous potassium acetate (3.5 mol%). The reaction mixture was stirred for the appropriate time (see Table 1) until conversion was complete as shown by TLC analysis (light petroleum:ether=3:1). The reaction mixture was diluted with ether (25 ml), 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-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.

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