Chiral Nonracemic Pyridine Thiols and Thioethers Applied in Palladium-Catalyzed Allylic Substitution. An Example of Near-Perfect Enantioselection

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Received April 6, 1998

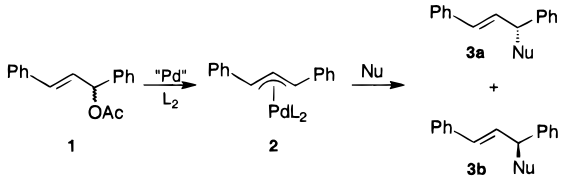
Pyridine thiols and dithiols have been synthesized by base-induced addition of 2,6-lutidine to thiofenchone. These thiols were converted to their thioether derivatives by alkylation. Application of these compounds in palladium-catalyzed allylic substitution on 1,3-diphenylprop-2-enyl acetate gave nearly absolute enantiomeric excess (98%) and high chemical yield (96%). Isolation of a palladium allylic intermediate gave insight in the origin of chiral recognition for these systems.

One of the more successful approaches to catalytic asymmetric carbon−carbon bond formation is by means of transition-metal catalysis.[1] In particular, palladium-catalyzed allylic substitution is a well-studied reaction used to obtain chemo-, regio-, diastereo-, and enantioselectivity.[2] Because the reaction is well understood, palladium-catalyzed substitution on racemic 1,3-diphenylprop-2-enyl acetate **1** with malonate esters (Nu in Scheme 1) is an excellent model for testing design principles of asymmetric ligands.

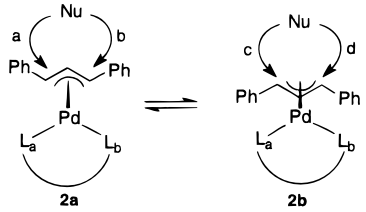
C_2-Symmetrical bidentate ligands (L_2) based on phosphines or phosphites have been used most frequently.[3] In the absence of such symmetry elements, one is faced with the additional challenge of control over two intermediates, **2a** and **2b**, and the possible directions of attack, **a**−**d** as illustrated in Scheme 2.

Although nonsymmetrical bidentate ligands allow more permutations, the character of the ligands themselves can provide the means of control. Different ligating atoms have different effects on the reactivity of palladium π-allyl complexes.[4] For example, phosphites and phosphines are strongly π-accepting and therefore highly activating, whereas nitrogen ligands activate less well. Attack of the nucleophile is expected to take place trans to the best π-acceptor, since the better π-acceptor is able to withdraw electron density from the position trans to itself and induce greater electron deficiency at this terminus.

Scheme 1. Palladium-Catalyzed Allylic Substitution of 1,3-Diphenylprop-2-enyl Acetate



Scheme 2. Palladium Allyl Intermediates



Design and development of ligands, both C_2-symmetric and not, has focused mainly on chiral nonracemic phosphorus-containing ligands and has led to, for example, BINAPO by Trost,[5] the ferrocenyl phosphites employed by Hayashi[6] and Togni,[7] QUINAP by Brown,[8] and more recently, the monophosphines by Zhang.[9] Well-defined structural elements in the rigid complexes ensure high chiral recognition.

A practical difficulty with such ligands is, in many cases, high sensitivity to oxidation by oxygen. Less oxidation sensitive amines and sulfides are also capable of stabilizing the low-valent state of palladium, and recently, some interest has shifted in the direction of non-phosphorus-containing ligands. Some examples of non-phosphorus-containing ligands, which are both catalytically active and give good chiral recognition, are sparteine[10] and stilbenediamine derivatives,[11] semicor-

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(1) For a review, see: (a) Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1978**, *10*, 175. (b) Bosnich, B.; Fryzuk, M. D. *Top. Stereochem.* **1981**, *12*, 119. (c) Frost, C. G.; Williams, J. M. J. *Tetrahedron: Asymmetry* **1992**, *3*, 1089. (d) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395.

(2) Ojima, I., Ed. *Catalytic Asymmetric Synthesis*; VCH: New York, 1993.

(3) (a) Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581. (b) Rosini, C.; Franzini, L.; Rafaelli, A.; Salvadori, P. *Synthesis* **1992**, 503. (c) Andres, J. M.; Martinez, M. A.; Pedrosa, R.; Perez-Encabo, A. *Tetrahedron: Asymmetry* **1994**, *5*, 57.

(4) (a) Åkermark, B.; Hansson, S.; Krakenberger, B.; Vitagliano, A.; Zetterberg, K. *Organometallics* **1984**, *3*, 679. (b) Åkermark, B.; Hansson, S.; Vitagliano, A. *J. Am. Chem. Soc.* **1990**, *112*, 4587. (c) Åkermark, B.; Krakenberger, B.; Hansson, S.; Vitagliano, A. *Organometallics* **1987**, *6*, 620.

(5) Trost, B. M.; Murphy, D. J. *Organometallics* **1985**, *4*, 1143.

(6) Hayashi, T.; Yamamoto, A.; Hagihara, T.; Ito, Y. *Tetrahedron Lett.* **1986**, *27*, 191.

(7) Togni, A.; Breutel, C.; Schnyder, A.; Spindler, F.; Landert, H.; Tijani, A. *J. Am. Chem. Soc.* **1994**, *116*, 4062.

(8) Brown, J. M.; Hulmes, D. I.; Guiry, P. J. *Tetrahedron* **1994**, *50*, 4493.

(9) Chen, Z.; Jiang, Q.; Zhu, G.; Xiao, D.; Cao, P.; Guo, C.; Zhang, X. *J. Org. Chem.* **1997**, *62*, 4521.

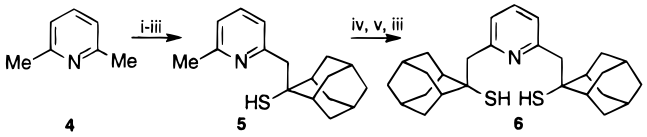
(10) Togni, A. *Tetrahedron: Asymmetry* **1991**, *2*, 683.

S0022-3263(98)00629-X CCC: $15.00
Published on Web 07/17/1998

rins and bisoxazolines,[12] ephedra-based amino sulfides,[13] sulfur-containing oxazoline ligands,[14] (hydroxyalkyl)-pyridinooxazolines,[15] C_2-symmetrical bis(aziridines),[16] and more recently, bis(oxazolinylpyridinyl)dioxolanes.[17]

Sulfides form a good perspective for development of new ligands, since sulfur is a soft complexation site and palladium is a soft metal ion, factors which will generally lead to a strong complex. Furthermore, back-donation of π-electron density from the metal to the empty relatively low-energy d orbitals of the sulfur can contribute to the strength of the Pd(II)−S bond.[18] In contrast to *trivalent* phosphines and phosphites, *divalent* sulfide cannot be intrinsically chiral. On complexation to a metal, chirality can be induced at sulfur. However, the difficulty in controlling this aspect is likely the reason that few sulfur-containing ligands have been reported or used. We, however, recently reported a new method for the easy preparation of C_2-symmetrical chiral and non-chiral "pyridine dithiols" (condensation products of 2,6-lutidine with 2 equiv of thioketone).[19] "Single armed" derivatives are intermediates in this reaction and are also of interest. We anticipated that on use of structurally rigid thioketones a variety of thiol- or sulfide-containing ligands could be obtained in which the coordination geometry is defined at the outset. The palladium-catalyzed allylic substitution has been used to explore the catalytic potential of these ligands.

Scheme 3[a]

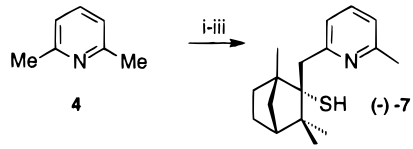


[a] Reagents and conditions : (i) Bu^{n}Li (1.1 equiv), THF, −80 °C; (ii) −80 → −40 °C; (iii) R_2C=S; (iv) Bu^{n}Li (2.1 equiv), THF, −80 °C; (v) −80 → −50 °C.

Ligand Synthesis

The approach to the preparation of pyridine diols, reported by Berg and Holm[20] and ourselves,[21] can be extended to the preparation of certain pyridinethiols and dithiols by using thioketones (Scheme 3). This method is more straightforward and efficient (overall yield up to 70%) than the multistep synthesis that has been reported previously.[22]

Scheme 4[a]

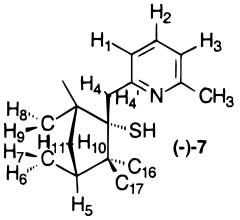


[a] Reagents and conditions: (i) Bu^{n}Li (1.1 equiv), THF, −60 °C; (ii) −60 → −40 °C; (iii) *S*-thiofenchone.

Using thioadamantanone, achiral pyridine thiol **5** and dithiol **6** were synthesized.[19] No products from carbanion addition to the sulfur atom of the thioketone were isolated. Attempts to prepare the bis-condensed product **6** in a one-step one-pot or in a two-step one-pot reaction gave rise to lower yields.[23] Chiral nonracemic pyridinethiols and dithiols were prepared using optically pure (*S*)-thiofenchone, prepared from (*S*)-(+)-fenchone (ee = 98%) or (*R*)-thiofenchone (from (*R*)-(−)-fenchone ee = 96%)).[24] In this approach, the monocondensation product **7** (see further for stereochemical assignment) could be isolated in 89% yield as either enantiomer (Scheme 4). We were surprised to isolate a single diastereomer; reaction of 2,6-lutidine with fenchone itself leads to roughly equal amounts of exo and endo attack.

Attempts to synthesize the condensation product of 2,6-lutidine **4** with optically pure thiocamphor failed due to preferred formation of the thioenolate; this competing reaction in the case that relatively acidic α-protons are present appears to be a limitation of the direct approach of Scheme 4.

By means of HETCOR, COSY, and NOESY experiments on (−)-**7**, addition was established to have taken place from the exo side of thiofenchone. This is more



clearly determined from spectra of the (−)-**7**·HCl complex of the monothiol adduct, prepared by passing HCl gas through a solution of (−)-**7** in dichloromethane. This complex has a locked conformation on the NMR chemical shift scale, and an AB system is observed for the benzylic protons H_4 and H_4' (see structure (−)-**7** for the numbering scheme, which is based on simplicity of illustration), whereas for the free ligand a singlet was found. The pyridine protons H_1 , H_2, and H_3 of the HCl complex are shifted 0.50, 0.67, and 1.74 ppm downfield, respectively. This is consistent with protonation of the pyridine nitrogen. Furthermore, most protons of the thiofenchone

(11) Gamez, P.; Dunjic, B.; Fache, F.; Lemaire, M. *J. Chem. Soc., Chem. Commun.* **1994**, 1417.

(12) (a) Müller, D.; Umbright, G.; Weber, B.; Pfaltz, A. *Helv. Chim. Acta.* **1991**, *74*, 232. (b) Leutenegger, U.; Umbright, G.; Fahrni, C.; Matt, v. P.; Pfaltz, A. *Tetrahedron* **1992**, *48*, 2143. (c) Pfaltz, A. *Acta Chim. Scand.* **1996**, *50*, 189.

(13) Koning, B.; Hulst, R.; Kellogg, R. M. *Recl. Trav. Chim. Pays-Bas* **1996**, *115*, 49.

(14) Allen, J. V.; Coote, S. J.; Dawson, G.; Frost, C. G.; Martin, C. J.; Williams, J. M. J. *J. Chem. Soc., Chem. Commun.* **1994**, 2065.

(15) Nordström, K.; Macedo, E.; Moberg, C. *J. Org. Chem.* **1997**, *62*, 1604.

(16) Tanner, D.; Andersson, P. G.; Hardem, A.; Somfai, P. *Tetrahedron Lett.* **1994**, *35*, 4631.

(17) Chelucci, G. *Tetrahedron: Asymmetry* **1997**, *8*, 2667.

(18) Wilkinson, G. In *Comprehensive Coordination Chemistry*; Pergamon Press: New York, 1987; Vol. 5.

(19) Koning, B.; Hulst, R.; Bouter, A.; Buter, J.; Meetsma, A.; Kellogg, R. M. *Chem. Commun.* **1997**, 1065.

(20) Berg, J. M.; Holm, R. H. *J. Am. Chem. Soc.* **1985**, *107*, 917.

(21) Edema, J. J. H.; Libbers, R.; Ridder, A. M.; Kellogg, R. M.; van Bolhuis, F.; Kooijman, H.; Spek, A. L. *J. Chem. Soc., Chem. Commun.* **1993**, 625.

(22) (a) Holm, R. H.; Berg, J. M. *Acc. Chem. Res.* **1986**, *19*, 363. (b) Kaptein, B.; Barf, G.; Kellogg, R. M.; Van Bolhuis, F. *J. Org. Chem.* **1990**, *55*, 1890.

(23) The one-step one-pot approach involves double deprotonation with 2.2 equiv of *n*-BuLi followed by 2 equiv of thioketone. In the two-step one-pot approach, the monocondensation product is not isolated, and a second equivalent of *n*-BuLi and thioketone are added after the monoadduct has been formed.

(24) Determined on a 20% permethylated β-cyclodextrin column; length 30 m.

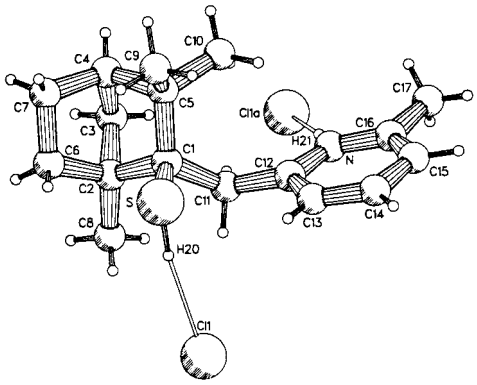


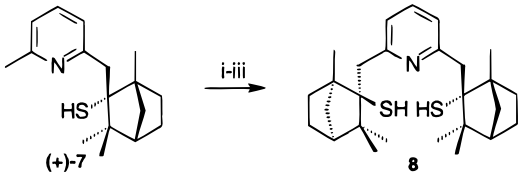
Figure 1. X-ray structure of (−)-**7**·HCl.

moiety are shifted downfield relative to the uncomplexed ligand, and assignment of the specific protons is simplified. From HETCOR spectra, the signal at δ 1.68 could be assigned to H_5 since it clearly belongs to a CH group (see the Supporting Information).

Furthermore, HETCOR gives three sets of signals for the three CH_2 groups of the fenchone moiety (δ 1.37 and 2.28; δ 1.20 and 2.40; δ 1.43 and 1.64). On the basis of the coupling constants of the signals at δ 1.37 and 2.28 in the ^{1}H NMR, the fact that they exhibited COSY interactions only with each other (see the Supporting Information), and the NOE correlation with H_5, we assigned these signals to the bridge protons. The signal at δ 2.28 has NOE interactions with the signal at δ 1.37, the benzylic protons, and two of the methyl groups, and therefore, we assigned this signal to H_{10}. The signal at δ 1.37 has interactions with signals at δ 2.28, 1.20, and 1.43, the latter two being from the exo-protons H_9 and H_7, leaving the signals at δ 1.64 and 2.40 for the endo protons H_6 and H_8. The signal at δ 1.64 has an NOE interaction with the C_{16} methyl group, and therefore, it could be assigned as H_6, and subsequently, the signal at δ 2.40 could be assigned as H_8. The exo protons could now be assigned as H_7 and H_9 for the signals at δ 1.43 and 1.20, respectively. From the correlation of the bridge proton H_{10} with the benzylic protons, it is clear that addition has taken place from the exo side of the thioketone. It cannot be taken for granted that addition of a nucleophile will occur exclusively from the exo side. Although, for example, dissolving metal reductions of fenchone produce almost exclusively endo alcohol (addition of hydride equivalent from the exo side),[25] we[26] observed that addition of 2,6-lutidine (as the monolithio derivative) occurs roughly equally from the exo and endo sides. On the other hand, 1,3-dipolar addition of diazo compounds to thiofenchone gives a single adduct thought to be exo addition product.[27]

By good fortune, we obtained satisfactory crystals and were able to confirm this structural assignment of the (−)-**7**·HCl complex by crystallographic means (Figure 1). The packing diagram (not shown) reveals a polymeric chain with alternating HCl molecules and the ligand moiety. The proton of hydrogen chloride is coordinated to the pyridine nitrogen of one molecule, and the chlorine is coordinated to the thiol hydrogen of a second molecule. This unit is continuously repeated. The crystal structure of hydrochloric acid in solid argon also consists of polymeric strands.[28] However, previous crystal structures of complexes with pyridinediols and dithiols (two arms instead of one) show encapsulation of monomeric hydrochloric acid into the cavity of these molecules.[19,21]

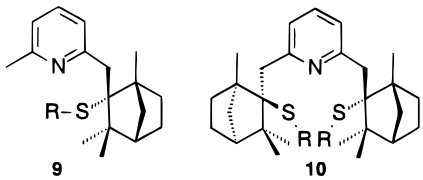
Scheme 5[a]



[a] Reagents and conditions: (i) Bu^{n}Li (2.1 equiv), THF, −70 °C; (ii) −70 → −40 °C; (iii) R_2C=S.

The monoadduct (+)-**7** was further functionalized following the general approach of Scheme 3. Addition of *n*-BuLi (2.2 equiv) to a solution of the monoadduct (+)-**7** in THF, followed by the addition of 1.1 equiv of thiofenchone, led to the dithioladduct **8** in 79% yield (Scheme 5).

The mono- and the dithioladduct were alkylated to afford the corresponding thioethers (+)-**9** and dithioethers **10**. For the preparation of the methyl thioethers, K_2CO_3 was used as base and methyl iodide as the methylating reagent; the mono- and dithioether adduct were obtained in 76% and 94% yields for (+)-**9a** (R = CH_3) and **10a** (R = CH_3), respectively. For the preparation of the homochiral series, ethyl, isopropyl, *n*-propyl, and benzyl thioethers (+)-**9b**−**d**, (−)-**9e**, and **10b**−**e** sodium hydride were used to deprotonate the thiol. These thioethers were isolated in 50−89% yield.



Palladium-Catalyzed Allylic Substitution

In initial experiments, thiols (+)-**7** and **8** were used as ligands in the palladium-catalyzed alkylation of 1,3-diphenylprop-2-enyl acetate **1**. These experiments were carried out in dry dichloromethane at room temperature in the presence of $[(\eta^3C_3H_5)PdCl]_2$ and the ligand. The nucleophile was generated either from dimethyl malonate in the presence of bis(trimethylsilyl)acetamide (BSA) and a catalytic amount of potassium acetate or from dimethyl malonate and sodium hydride. With sodium hydride as base, very low conversions and low to moderate selectivities were found after 36 h (Table 1). Using BSA as base resulted in an increase in yield for (+)-**7**; however, no product was found when **8** was used. The low reactivity with these ligands is probably due to deprotonation of the thiol group by the bases. In order to bypass problems arising from the reactivity of the thiol groups, the thioethers (+)-**9a**−**d**, (−)-**9e**, and **10** were examined. The first experiments were carried out with thioethers (+)-**9a** and (+)-**9b** using NaH as base to deprotonate the malonate. These experiments afforded the product **3** in 35 and 70% isolated yield and 46 and 81% ee for (+)-**9a**

(25) Rautenstrauch, V. *J. Chem. Soc., Chem. Commun.* **1986**, 1558.
(26) Koning, B.; Kellogg, R. M. To be published.
(27) Barton, D. H. R.; Guziec, F. S.; Shahak, I. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1794.

(28) Wells, A. I. In *Structural Inorganic Chemistry*, 5th ed.; Clarendon Press: Oxford, 1990.

Table 1. Test Results with Thiols (+)-7 and 8 and Thioethers (+)-9a−d, (−)-9e, and 10

ligand	R_2	T (°C)	base	equiv of base/NuH	yield (%)	ee[a] (%)	confgn[a]
(+)-**7**	H	rt	NaH	1.5/1.5	2	80	*S*
8	H	rt	NaH	1.5/1.5	4	23	*R*
(+)-**7**	H	rt	BSA/KOAc	1.2/1.5	10	81	*S*
8	H	rt	BSA/KOAc	1.2/1.5			
(+)-**9a**	Me	rt	NaH	1.5/1.5	35	46	*R*
(+)-**9b**	Et	rt	NaH	1.5/1.5	70	81	*R*
(+)-**9a**	Me	rt	BSA/KOAc	1.2/1.5	80	53	*R*
(+)-**9b**	Et	rt	BSA/KOAc	1.2/1.5	84	91	*R*
(+)-**9c**	*i*-Pr	rt	BSA/KOAc	1.2/1.5	93	82	*R*
(+)-**9d**	*n*-Pr	rt	BSA/KOAc	1.2/1.5	90	81	*R*
(−)-**9e**	benzyl	rt	BSA/KOAc	1.2/1.5	96	92	*R*
10a	Me	rt	BSA/KOAc	1.2/1.5	83	78	*R*
10b	Et	rt	BSA/KOAc	1.2/1.5	80	84	*R*
10c	*n*-Pr	rt	BSA/KOAc	1.2/1.5	89	85	*R*
10d	*i*-Pr	rt	BSA/KOAc	1.2/1.5	80	85	*R*
10e	benzyl	rt	BSA/KOAc	1.2/1.5	90	85	*R*

[a] The enantiomeric excess was determined by ^{1}H NMR using Eu(hfc)$_3$ as chiral shift reagent, and the absolute configurations were established by comparing the optical rotation with literature values for material of established absolute configuration.[12,29]

and (+)-**9b**, respectively, after a reaction time of 18 h. Using BSA as base, higher selectivities and conversions were found for these ligands at shorter reaction times (10 h). The next step was application of BSA as base in combination with the other thioethers (+)-**9c**−**d**, (−)-**9e**, and **10a**−**e**. The reactions proceeded smoothly and were complete within 10 h. The product **3** was obtained in high yield and in moderate to high enantiomeric excess as summarized in Table 1.

The benzyl thioethers (−)-**9e** and **10e** were found to perform best under these conditions, and these ligands were selected for optimization of the allylic substitution (Table 2). Replacement of dichloromethane by acetonitrile led to an increase of the enantioselectivity when (−)-**9e** was used. The enantioselectivity using (−)-**9e** was further optimized by using 3 equiv of base and nucleophile together with lower reaction temperature. For (−)-**9e**, this is theoretically the highest enantioselectivity that could be obtained since the starting material (*R*)-(−)-fenchone can only be purchased in 96% enantiomeric purity. We therefore synthesized ligand (+)-**9e** under the same conditions used for (−)-**9e** starting from the more expensive (*S*)-(+)-fenchone, which can be purchased in 98% enantiomeric purity. Application of (+)-**9e** in the allylic substitution reaction afforded the product **3** in 96% isolated yield and 98% ee. No notable increase in the selectivity was found when **10e** was applied under the optimized conditions.

In order to get more insight in the reaction mechanism and the mechanism of introduction of chirality into the product, the allylic intermediate **11** was synthesized. This complex was prepared from (+)-**9c** and [(η^3C$_3$H$_5$)PdCl]$_2$ using AgPF$_6$ to replace the chloride. The ^{1}H NMR spectrum showed a mixture of the two diastereomeric complexes **11a** and **11b** in which the allylic moiety is coordinated either exo or endo to the palladium relative to the thioether. The ratio between the two diastereomeric complexes was determined to be 3:4 at 20.0 °C (see the Supporting Information). Temperature-dependent studies of this complex showed an increase in the preference for **11b** as the temperature decreased. Elucidation of the ^{1}H NMR spectrum was accomplished by COSY and NOESY experiments. From the integrals of the specific signals and from the COSY experiments, we could assign the signals at δ 2.94, 3.58, 4.33, 4.88, and 5.88 as belonging to the minor diastereomer and the signals at δ 3.39, 3.65, 4.33, 4.68, and 5.70 to the major diastereomer. The signals in the ^{1}H NMR spectrum at δ 5.70 and 5.88 correspond to the protons H_2 of the diastereomeric complexes as was deduced from their integrals, couplings, and chemical shifts. Assuming that the coupling constant between H_2 protons and the protons cis to H_2 is smaller than the coupling between the trans protons, we assigned the signals at δ 4.33, 4.68, and 4.88 to the protons cis relative to H_2. The signals at δ 2.94, 3.39, 3.58, and 3.65 were assigned as the protons trans to the H_2 protons. Remarkable in the spectrum is that there is no geminal coupling between the protons of the terminal CH_2 group of the allylic moiety, as is also found for the geminal protons in the [(η^3C$_3$H$_5$)PdCl]$_2$ complex.[30] Since the protons H_3 of the allylic moiety trans to the sulfur atom are slightly less electron rich due to the electron-withdrawing character of the sulfur, they will adsorb at lower field than the H_1 protons trans to nitrogen, and therefore, they could be assigned as the signals at δ 4.68 and 4.88. Therefore, the signal at 4.33 corresponds to the H_1 protons of both diastereomers. Likewise, the signals at δ 3.58 and 3.65 correspond to the protons $H_{3'}$ trans to the sulfur atom and the signals at δ 2.94 and 3.49 correspond to the protons $H_{1'}$.

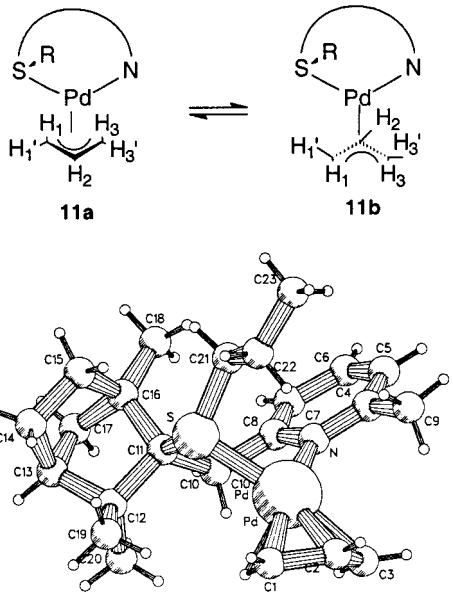


Figure 2. X-ray structure of **11a** without the counterion PF_6^-.

More information about the complex was obtained from the X-ray diffraction (Figure 2). Only the minor isomer corresponding to structure **11a** crystallized from the mixture. At first it was assumed that the structure of the major diastereomer had been determined. NOESY experiments, however, gave convincing data to suppose

(29) von Matt, P.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 566.

(30) Elschenbroick, Ch.; Salzer, A. In *Organometallics*, 2nd ed.; VCH: Weinheim, 1992; p 285.

(31) Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre. Deposition numbers are 101825, 101829, and 101830. Copies of the data can be obtained free of charge on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: int code +(1223)336-033, E-mail: teched@chemcrys.cam.ac.uk).

Table 2. Optimization with Thioethers (−)-9e, (+)-9e, and 10e

ligand	R_2	T (°C)	solvent	base	equiv of base/NuH	yield %)	ee[a]	confgn[a]
(−)-**9e**	benzyl	rt	CH_3CN	BSA/KOAc	1.2/1.5	94	93	*R*
(−)-**9e**	benzyl	0	CH_3CN	BSA/KOAc	1.2/1.5	96	95	*R*
(−)-**9e**	benzyl	0	CH_3CN	BSA/KOAc	3/3	95	96	*R*
(+)-**9e**	benzyl	0	CH_3CN	BSA/KOAc	3/3	96	98	*S*
10e	benzyl	0	CH_3CN	BSA/KOAc	3/3	75	86	*R*

[a] The enantiomeric excess was determined by ^1H NMR using $Eu(hfc)_3$ as chiral shift reagent, and the absolute configurations were established by comparing the optical rotation with literature values for material of established absolute configuration.[12,29]

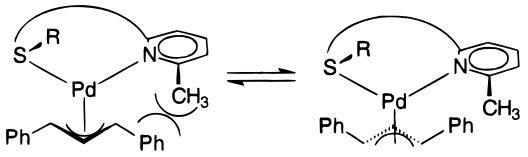
otherwise. In the NOESY spectrum, we observed an interaction between H_3 of the allyl group (δ 4.88) and the 6-methyl group of the pyridine ring (δ 2.64) and an interaction between $H_{1'}$ (δ 2.94) and one of the methyl groups from the fenchone moiety (δ 1.41). From these interactions, we concluded that this is the structure that is found in the X-ray diffraction since herein the H_3 proton is adjacent to the methyl group and the $H_{1'}$ positioned closely to the fenchone methyl group. The minor diastereomer thus corresponds to structure **11a**. For the major diastereomer, we find an NOE interaction for $H_{3'}$ (δ 3.65) with the pyridine methyl group (δ 2.80) and an NOE interaction between H_1 (δ 4.33) and one of the methyl groups from the fenchone moiety (δ 1.30), indicating that this corresponds to structure **11b**.

In the crystal structure, the palladium is coordinated to the sulfur, the nitrogen atom, and C_1, C_2, and C_3 of the allylic moiety embedded in a square-planar coordination for palladium. The bond length of Pd−C_3 (trans to sulfur) is somewhat longer than the Pd−C_1 bond length, giving C_3 some more π character. Therefore, C_1 and C_3 are expected to exhibit distinctly different reactivities toward nucleophiles.

Causes of Induction and Comparison with C_2 Ligands

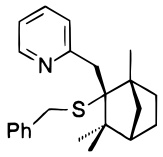
The yields of the allylic substitution are good, the reaction times are acceptable, and the ee's of the optimized reactions are virtually absolute. The thioethers (+)-**9a**−**d** and (−)-**9e** constantly provide substitution product **3** of R absolute configuration. The bulk of the substituent on sulfur has a moderate correlation with improved enantiomeric excesses. The structure of the complex **11a** (Figure 2) confirms our expectation that sulfide is rigidly coordinated in a six-membered ring and that the fenchyl methyl groups force a single absolute configuration, in this case S, on the coordinated sulfur. The isolated methyl group at the 6-position of the pyridine ring plays a key role in determining the orientation of the π-allyl complex; one end of the allyl group is forced against the steric bulk of the fenchyl methyls, whereas the 6-methyl group exerts controlling influence on the other end of the allyl group. We believe that for the 1,3-diphenylallyl group used here these interactions enforce structure **12b** rather than **12a** in which the phenyl groups are oriented toward the steric bulk on both sides. Attack of the malonate nucleophile should logically occur away from the greatest steric bulk, in other words on the side of the pyridine ring bearing only the 6-methyl group. This is electronically also expected as the soft nucleophile attacks trans to the softer sulfide, which is the better π acceptor. This leads to the observed *R* configuration of **3**.

The role of the methyl group at the 6-position of the pyridine ring is readily demonstrated to be profound.



12a **12b**

Compound **14** lacking the 6-methyl group was prepared. Allylic substitution proceeded readily, and **3** was obtained in good yield but only in 47% ee and *as the S enantiomer*. Clearly, control over the manner of complexation has been lost by elimination of this small but essential methyl group.



14

When the C_2-symmetrical dithioethers **10** are applied, the chemical yields and the enantioselectivities are still high. The substituents R on the sulfur do not have a great impact on the stereoselectivity of the reaction, whereas for the ligands (+)-**9a**−**d** and (−)-**9e** there is a reasonable correlation between the size of the substituent R and the ee of **3** (Table 1).

To obtain more insight into this allylic substitution, we attempted to isolate the Pd-allylic intermediate of **10e** and $[(\eta^3C_3H_5)PdCl]_2$. However, a structure was isolated that was characterized by COSY and ^1H NMR as being fully symmetrical (see the Supporting Information) but devoid of allyl group. The ligand is unambiguously coordinated as can be seen in the downfield shift of the pyridine protons and the increase in coupling between the two diastereotopic benzylic protons of the thioether. The observation that the system still exhibits a C_2 symmetry is proof for the complexation of the palladium to both sulfur atoms; otherwise, an asymmetrical system would have been obtained. Recrystallization of this complex from dichloromethane by isothermal distillation of hexane into the solution afforded the Pd−Cl complex **15** as BF_4^- salt as was established by X-ray diffraction (Figure 3). The palladium−allyl complex involved in reaction seems to be too labile and degrades to **15**. This instability has thwarted all subsequent attempts to obtain the desired palladium−allyl complex. The palladium chloride complex **15** exhibits square-planar coordination of the palladium to the sulfur and nitrogen atoms.

Speculations for the explanation of the stereochemical outcome for the dithioethers at this stage, without knowing the active catalytic species, are inappropriate.

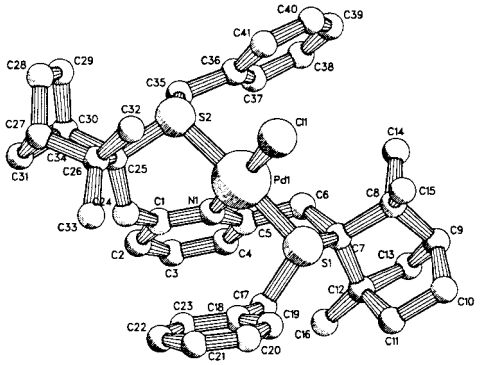


Figure 3. X-ray structure of **15** without the counterion BF_4^-.

Conclusions

In these easily accessible systems, we have found a new class of ligands for the palladium-catalyzed allylic substitution reaction. The optimized results with the monothioethers can scarcely be improved in terms of yield and ee. The possibility of introducing other groups at the 6 position of the pyridine ring (as *tert*-butyl) give these systems high potential for other catalytic applications. Such possibilities are currently being explored.

Experimental Section

General Remarks. All reactions were carried out under an argon atmosphere. The following solvents were distilled prior to use: THF was distilled from Na wire, acetonitrile and dichloromethane were distilled over CaH_2, and diethyl ether, ethyl acetate, and hexane were distilled over P_2O_5. Column chromatography was performed on alumina (Merck 90, II/III, 0.063−0.200 mm) or silica gel (Aldrich 60, 230−400 mesh). Elemental microanalyses were carried out in the analytical department of this laboratory. (*R*)- and (*S*)-thiofenchone were prepared following literature procedures starting from (*R*)-(−)-fenchone and (*S*)-(+)-fenchone, respectively.[32] All other starting materials were purchased from Aldrich, Acros, or Fluka.

2-Methyl-6-[[(1*S*,2*S*)-1,3,3-trimethyl-2-sulfanylbicyclo-[2.2.1]hept-2-yl]methyl]pyridine ((−)-7). To a solution of 2,6-lutidine (**4**) (0.35 g, 3.3 mmol) in 50 mL of THF at −60 °C was added *n*-butyllithium (1.6 M in hexane, 2.1 mL, 3.4 mmol). The mixture was stirred for 1 h at −40 °C and cooled to −60 °C again. A solution of (*S*)-thiofenchone (0.56 g, 3.3 mmol) in 5 mL of THF was added, and the mixture was stirred at −60 °C for 1 h. The cooling bath was removed, and the mixture was allowed to stir at ambient temperature overnight. The mixture was poured into 15 mL of 5 N HCl and stirred for 1 h before being neutralized with 2 N NaOH. The mixture was extracted three times with dichloromethane. The combined organic layers were washed with brine and dried over $MgSO_4$. The product was purified by means of Kugelrohr distillation (135 °C, 2.0 mmHg), yielding a colorless solid (0.81 g, 2.9 mmol, 89%): mp 113−114 °C; $[\alpha]^{23}_D$ −87.5 (*c* 3.6, methanol); ^{1}H NMR δ 0.79 (s, 3H), 1.15 (m, 2H), 1.19 (s, 3H), 1.26 (s, 3H), 1.40 (m, 1H), 1.64 (m, 1H), 1.76 (m, 1H), 1.93 (m, 1H), 2.19 (m, 1H), 2.52 (s, 3H), 3.30 (s, 2H), 4.67 (br, SH), 6.92 (d, J = 7.63 Hz, 1H), 7.06 (d, J = 7.93 Hz, 1H), 7.42 (dd, J = 7.63, 7.93 Hz, 1H); ^{13}C NMR δ 18.19 (q), 24.38 (t), 27.31 (q), 28.79 (q), 33.62 (t), 40.27 (t), 45.54 (s), 47.89 (t), 50.85 (d), 54.37 (s), 62.34 (s), 119.80 (d), 121.47 (d), 136.03 (d), 156.20 (s), 161.15 (s); HRMS calcd 275.171, found 275.171. Anal. Calcd for $C_{17}H_{25}NS$: C, 74.13; H, 9.15; N, 5.08. Found: C, 74.10; H, 9.11; N, 5.10.

2-Methyl-6-[[(1*R*,2*R*)-1,3,3-trimethyl-2-sulfanylbicyclo-[2.2.1]hept-2-yl]methyl]pyridine ((+)-7). This compound was prepared using the same procedure as for (−)-**7** starting from 2,6-lutidine and (*S*)-thiofenchone, affording (+)-**7** in comparable yields: mp 114−115 °C; $[\alpha]^{23}_D$ = +85.8 (*c* 3.6, methanol).

2-Methyl-6-[[(1*S*,2*S*)-1,3,3-trimethyl-2-sulfanylbicyclo-[2.2.1]hept-2-yl]methyl]pyridine. HCl ((−)-7·HCl). A solution of the monoadduct (−)-**7** (0.25 g, 0.91 mmol) in dichloromethane (10 mL) was passed through a stream of HCl for 2 min. The mixture was stirred for 2 h, and the solvent was carefully evaporated at reduced pressure to yield the crude HCl complex, which was recrystallized from hexane/dichloromethane (0.27 g, 0.87 mmol, 95%): mp 181−182 °C; $[\alpha]^{23}_D$ = −62.1 (*c* 2.9, chloroform); H NMR δ 0.89 (s, 3H), 1.08 (s, 3H), 1.16 (s, 3H), 1.20 (m, 1H), 1.37 (d, J = 10.99 Hz, 1H), 1.43 (m, 1H), 1.52 (s, SH), 1.64 (m, 1H), 1.69 (m, 1H), 2.28 (d, J = 10.99 Hz, 1H), 2.40 (m, 1H), 2.98 (s, 3H), 3.26 (d, J = 17.2 Hz, 1H), 4.43 (d, J = 17.2 Hz, 1H), 7.42 (d, J = 7.69 Hz, 1H), 8.09 (dd, J = 8.05, 7.69 Hz, 1H), 8.80 (d, J = 8.05 Hz, 1H); C-NMR δ 17.65 (q), 24.44 (t), 26.07 (q), 29.39 (q), 33.68 (t), 40.20 (t), 44.44 (t), 45.31 (s), 50.68 (d), 56.15 (s), 63.29 (s), 124.39 (d), 124.83 (d), 143.09 (d), 153.48 (s), 157.91 (s); HRMS calcd 311.147, found 275.171 (− HCl). Anal. Calcd for $C_{17}H_{26}$-NSCl: C, 65.46; H, 8.40; N, 4.49; Cl, 11.37. Found: C, 65.16; H, 8.22; N, 4.42; Cl, 11.38.

2,6-Bis[[(1*R*,2*R*)-1,3,3-trimethyl-2-sulfanylbicyclo-[2.2.1]hept-2-yl]methyl]pyridine (8). To a solution of (+)-**7** (0.29 g, 1.05 mmol) in 50 mL of THF at −70 °C was added *n*-butyllithium (1.6 M in hexane, 1.4 mL, 2.2 mmol). The mixture was stirred for 90 min at −40 °C and cooled to −70 °C again. A solution of (*R*)-thiofenchone (0.20 g, 1.19 mmol) in 5 mL of THF was added, and the mixture was stirred at −70 °C for 1 h. The cooling bath was removed, and the mixture was allowed to stir at ambient temperature overnight. The mixture was poured into 15 mL of 5 N HCl solution and stirred for 1 h before it was neutralized with a 2 N NaOH solution. The mixture was extracted three times with dichloromethane. The combined organic layers were washed with brine and dried over $MgSO_4$. The product was purified by means of column chromatography (silica gel, hexane/dichloromethane (2:1)) yielding **8** as a colorless solid (0.37 g, 0.83 mmol, 79%): mp 139−140 °C; $[\alpha]^{23}_D$ −80 (*c* 4.0, $CHCl_3$); ^{1}H NMR δ 0.83 (s, 6H), 1.15 (m, 2H), 1.16 (s, 6H) 1.20 (s, 6H), 1.23 (d, J = 10.5 Hz, 2H), 1.41 (m, 2H), 1.65 (d, J = 4.4 Hz, 2H), 1.73 (m, 2H), 1.97 (d, J = 10.5 Hz, 2H), 2.26 (d, J = 16.6 Hz, 2H), 2.28 (m, 2H), 3.35 (d, J = 16.6 Hz, 2H), 3.36 (s, 2SH), 7.46 (m, 3H); ^{13}C NMR δ 18.15 (q), 24.65 (t), 27.39 (q), 29.34 (q), 33.79 (t), 40.30 (t), 45.44 (s), 49.18 (t), 51.02 (d), 55.08 (s), 62.74 (s), 121.57 (d), 135.54 (d), 169.24 (s); HRMS calcd 443.268, found 443.268. Anal. Calcd for $C_{27}H_{41}NS_2$: C, 73.08; H, 9.31; N, 3.16. Found: C, 73.08; H, 9.31; N, 3.15.

General Procedure A for the Synthesis of Thioethers (+)-9a and 10a. To 1.0 mmol of thiol or dithiol adduct, dissolved in 50 mL of acetone, were added K_2CO_3 (1.5 equiv) and iodomethane (2.0 equiv). The mixture was stirred at reflux conditions overnight. After being cooled to rt, the mixture was filtered and the solvent evaporated. The product was purified by means of column chromatography (silica gel, hexane/diethyl ether 6:1).

General Procedure B for the Synthesis of Thioethers 9 and 10. To 1.0 mmol of thiol or dithiol adduct, dissolved in 50 mL of THF, was added sodium hydride (1.5 equiv) and stirring continued for 10 min. To this solution was added the alkyl halide (1.5 equiv) and stirring continued overnight at rt. Water (10 mL) was added, and the mixture was extracted twice with dichloromethane. The combined organic layers were washed with brine and dried over $MgSO_4$. The product was purified by means of column chromatography (silica gel, hexane/diethyl ether 6:1).

2-Methyl-6-[[(1*R*,2*R*)-1,3,3-trimethyl-2-(methylsulfanyl)-bicyclo[2.2.1]hept-2-yl]methyl]pyridine ((+)-9a). This compound was prepared according to general procedure A starting from (+)-**7** (0.50 g, 1.82 mmol), K_2CO_3 (0.37 g, 2.7 mmol), and iodomethane (0.51 g, 3.6 mmol) to yield a colorless solid that was recrystallized from hexane (0.40 g, 1.38 mmol, 76%): mp 65−67 °C; $[\alpha]^{23}_D$ +21 (*c* 1.2, $CHCl_3$); ^{1}H NMR δ 0.87 (s, 3H),

(32) Scheeren, J. W.; Ooms, P. H. J.; Nivard, R. J. F. *Synthesis* **1973**, 149.

1.15 (s, 3H), 1.18 (s, 3H), 1.2 (m, 2H), 1.37−1.55 (m, 2H), 1.7 (m, 1H), 1.98 (s, 3H), 2.04 (m, 1H), 2.53 (s, 3H), 2.6 (m, 1H), 3.34 (dd, J = 17.57, 22.96 Hz, 2H), 6.94 (d, J = 7.57 Hz, 1H), 7.48 (dd, J = 7.57, 8.05 Hz, 1H), 8.20 (d, J = 8.05 Hz, 1H); ^{13}C NMR δ 13.58 (q), 20.07 (q), 24.23 (q), 24.49 (q), 24.68 (t), 29.44 (q), 34.61 (t), 41.39 (t), 41.99 (t), 46.78 (s), 51.11 (d), 56.15 (s), 60.78 (s), 120.20 (d), 120.52 (d), 135.99 (d), 156.73 (s), 160.82 (s); HRMS calcd 289.185, found 289.186. Anal. Calcd for $C_{18}H_{27}NS$: C, 74.69; H, 9.40; S, 11.08. Found: C, 74.93; H, 9.44; S, 11.05.

2-Methyl-6-[[(1*R*,2*R*)-1,3,3-trimethyl-2-(ethylsulfanyl)-bicyclo[2.2.1]hept-2-yl]methyl]pyridine ((+)-9b). For this compound, general procedure B was used, starting from (+)-**7** (0.50 g, 1.82 mmol), sodium hydride (0.09 g, 3.6 mmol) and ethyl bromide (0.29 g, 2.7 mmol). (+)-**9b** was obtained as a colorless solid after Kugelrohr distillation (0.5 mmHg, 150 °C) (0.43 g, 1.42 mmol, 78%): mp 65−66 °C; $[\alpha]^{23}_D$ +10 (*c* 7.8, $CHCl_3$); HRMS calcd 303.203, found 303.202. Anal. Calcd for $C_{19}H_{29}NS$: C, 75.19; H, 9.63; N, 4.61. Found: C, 75.12; H, 9.64; N, 4.57.

2-Methyl-6-[[(1*R*,2*R*)-1,3,3-trimethyl-2-(isopropylsulfanyl)bicyclo[2.2.1]hept-2-yl]methyl]pyridine ((+)-9c). This material was synthesized according to the general procedure B starting from (+)-**7** (0.50 g, 1.82 mmol), sodium hydride (0.09 g, 3.6 mmol), and isopropyl bromide (0.33 g, 2.7 mmol). The product was obtained after Kugelrohr distillation (0.5 mmHg, 160 °C) as a colorless solid (0.50 g, 1.58 mmol, 87%): mp 47-48 °C; $[\alpha]^{23}_D$ +40 (*c* 3.7, $CHCl_3$); HRMS calcd 317.218, found 317.218. Anal. Calcd for $C_{20}H_{31}NS$: C, 75.65; H, 9.84; N, 4.41. Found: C, 75.60; H, 9.85; N, 4.35.

2-Methyl-6-[[(1*R*,2*R*)-1,3,3-trimethyl-2-(*n*-propylsulfanyl)bicyclo[2.2.1]hept-2-yl]methyl]pyridine ((+)-9d). Preparation of this compound was accomplished according to general procedure B starting from (+)-**7** (1.00 g, 3.63 mmol), sodium hydride (0.17 g, 7.08 mmol), and *n*-propyl iodide (0.92 g, 5.41 mmol) to afford (+)-**9d** after Kugelrohr distillation (0.5 mmHg, 170 °C) as a colorless solid (0.78 g, 2.46 mmol, 68%): mp 42−43 °C; $[\alpha]^{23}_D$ +13.8 (*c* 4.0, $CHCl_3$); HRMS calcd 317.218, found 317.220. Anal. Calcd for $C_{20}H_{31}NS$: C, 75.65; H, 9.84; S, 10.10. Found: C, 76.02; H, 9.84; S, 10.06.

2-Methyl-6-[[(1*R*,2*R*)-1,3,3-trimethyl-2-(benzylsulfanyl)-bicyclo[2.2.1]hept-2-yl]methyl]pyridine ((−)-9e). This compound was prepared according to procedure B starting from (+)-**7** (0.39 g, 1.42 mmol), sodium hydride (0.05 g, 2.1 mmol), and benzyl bromide (0.29, 1.7 mmol) to yield a colorless solid (0.42 g, 1.25 mmol, 81%): mp 57−58 °C; $[\alpha]^{23}_D$ −28 (*c* 2.2, $CHCl_3$); HRMS calcd 365.217, found 365.218. Anal. Calcd for $C_{24}H_{31}NS$: C, 78.85; H, 8.55; N, 3.83. Found: C, 78.83; H, 8.73; N, 3.71.

2-Methyl-6-[[(1*S*,2*S*)-1,3,3-trimethyl-2-(benzylsulfanyl)-bicyclo[2.2.1]hept-2-yl]methyl]pyridine ((+)-9e). This compound was prepared as described above but starting from (−)-**7**: mp 57−58 °C; $[\alpha]^{23}_D$ +30 (*c* 2.0, $CHCl_3$).

2,6-Bis[[(1*R*,2*R*)-1,3,3-trimethyl-2-(methylsulfanyl)-bicyclo[2.2.1]hept-2-yl]methyl]pyridine (10a). This material was prepared according to general procedure A starting from **8** (1.0 g, 2.26 mmol), K_2CO_3 (0.48 g, 3.4 mmol), and methyl iodide (0.62 g, 4.5 mmol) to yield **10a** as a colorless solid that was recrystallized from hexane (1.0 g, 2.12 mmol, 94%): mp 164−165 °C; $[\alpha]^{23}_D$ +33 (*c* 1.2, $CHCl_3$); ^{1}H NMR δ 0.87 (s, 6H), 1.14 (s, 6H), 1.18 (s, 6H), 1.20 (m, 4H), 1.42 (m, 2H), 1.53 (d, J = 4.39 Hz, 2H), 1.72 (m, 2H), 1.96 (s, 6H), 1.98 (m, 2H), 2.61 (m, 2H), 3.21 (d, J = 17.58 Hz, 2H), 3.43 (d, J = 17.58 Hz, 2H), 7.50 (t, J = 7.86, 1H), 8.13 (d, J = 7.86 Hz, 2H); ^{13}C NMR δ 13.57 (q), 20.16 (q), 24.20 (q), 24.75 (t), 29.43 (q), 34.66 (t), 41.34 (t), 41.99 (t), 46.71 (s), 51.10 (d), 56.05 (s), 60.91 (s), 120.77 (d), 135.38 (d), 159.87 (s); HRMS calcd 471.298, found 471.299. Anal. Calcd for $C_{29}H_{45}NS_2$: C, 73.83; H, 9.61; N, 2.97. Found: C, 73.67; H, 9.61; N, 2.95.

2,6-Bis[[(1*R*,2*R*)-1,3,3-trimethyl-2-(ethylsulfanyl)bicyclo-[2.2.1]hept-2-yl]methyl]pyridine (10b). For this compound, general procedure B was used, starting from **8** (0.45 g, 1.02 mmol), sodium hydride (0.06 g, 2.50 mmol), and ethyl bromide (0.27 g, 2.48 mmol). Compound **10b** was obtained as a colorless solid that was recrystallized from methanol at −20 °C (0.45 g, 0.91 mmol, 89%): mp 38−39 °C; $[\alpha]^{23}_D$ +15 (*c* 4.0, $CHCl_3$); HRMS calcd 499.333, found 499.333. Anal. Calcd for $C_{31}H_{49}NS_2$: C, 74.49; H, 9.88; N, 2.80. Found: C, 72.96; H, 10.05; N, 2.73.

2,6-Bis[[(1*R*,2*R*)-1,3,3-trimethyl-2-(isopropylsulfanyl)-bicyclo[2.2.1]hept-2-yl]methyl]pyridine (10c). This compound was prepared according to the general procedure B starting from **8** (1.00 g, 2.26 mmol), sodium hydride (0.14 g, 5.83 mmol), and isopropyl bromide (0.69 g, 5.61 mmol). The dithioether was recrystallized from ethanol at −20 °C to yield **10c** as a colorless solid (0.60 g, 1.14 mmol, 50%): mp 82−84 °C; $[\alpha]^{23}_D$ +41 (*c* 2.0, $CHCl_3$); HRMS calcd 527.362, found 527.364. Anal. Calcd for $C_{33}H_{53}NS_2$: C, 75.08; H, 10.12; N, 2.65. Found: C, 74.97; H, 10.22; N, 2.69.

2,6-Bis[[(1*R*,2*R*)-1,3,3-trimethyl-2-(*n*-propylsulfanyl)-bicyclo[2.2.1]hept-2-yl]methyl]pyridine (10d). From **8** (0.48 g, 1.08 mmol), sodium hydride (0.07 g, 2.92 mmol), and *n*-propyl iodide (0.46 g, 2.71 mmol), **10d** was obtained as a solid that was recrystallized from ethanol at −20 °C (0.36 g, 0.68 mmol, 63%): mp 90−91 °C; $[\alpha]^{23}_D$ +24.1 (*c* 4.1, $CHCl_3$); HRMS calcd 527.362, found 527.361. Anal. Calcd for $C_{33}H_{53}NS_2$: C, 75.08; H, 10.12; N, 2.65. Found: C, 75.02; H, 10.16; N, 2.70.

2,6-Bis[[(1*R*,2*R*)-1,3,3-trimethyl-2-(benzylsulfanyl)-bicyclo[2.2.1]hept-2-yl]methyl]pyridine (10e). From **8** (0.50 g, 1.13 mmol), sodium hydride (0.11 g, 4.58 mmol), and benzyl bromide (0.58 g, 3.39 mmol), **10e** was obtained as a colorless solid that was recrystallized from dichloromethane/ethanol (0.56 g, 0.90 mmol, 80%): mp 135−136 °C; $[\alpha]^{23}_D$ −100 (*c* 2.6, $CHCl_3$); HRMS calcd 623.362, no proper HRMS could be obtained; CI(NH_3) gave a molecular ion at *m*/*e* 624. Anal. Calcd for $C_{41}H_{53}NS_2$: C, 78.92; H, 8.56; S, 10.28. Found: C, 78.75; H, 8.63; S, 10.25.

Palladium−Allyl Complex of (+)-9c (11). A solution of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (0.10 g, 0.27 mmol) and (+)-**9c** (0.20 g, 0.63 mmol) in dichloromethane (10 mL) was stirred for 1 h and treated with $AgPF_6$ (0.16 g, 0.63 mmol) in 10 mL of THF. Stirring continued for 10 min, and the mixture was filtered over Celite. The solution was washed with brine and dried over $MgSO_4$. After evaporation of the solvent, the solid was recrystallized from hexane/dichloromethane by slow evaporation of the solvent, yielding **11** as colorless crystals (0.24 g, 0.52 mmol, 94%); **11** isomerized upon dissolution: ^{1}H NMR of **11a** δ 0.83 (t, J = 7.32 Hz, 3H), 1.17 (s, 3H), 1.26 (m, 1H), 1.27 (s, 3H), 1.38 (m, 2H), 1.46 (m, 1H), 1.57 (s, 3H), 1.64 (m, 2H), 1.81 (m, 1H), 1.92 (m, 1H), 2.08 (m, 1H), 2.17 (m, 1H), 2.35 (m, 1H), 2.64 (s, 3H), 2.94 (d, J = 12.21 Hz, 1H), 3.58 (d, J = 13.67 Hz, 1H), 3.64 (d, J = 12.20 Hz, 1H), 3.76 (d, J = 12.20 Hz, 1H), 4.33 (d, J = 6.35 Hz, 1H), 4.88 (d, J = 5.38 Hz, 1H), 5.89 (m, 1H), 7.38 (d, J = 7.81 Hz, 1H), 7.65 (d, J = 7.81 Hz, 1H), 7.84 (dd, J = 7.81, 7.81 Hz, 1H). ^{1}H NMR of **11b**: δ 0.90 (t, J = 7.32 Hz, 3H), 1.18 (s, 3H), 1.26 (m, 1H), 1.30 (s, 3H), 1.38 (m, 2H), 1.41 (s, 3H), 1.46 (m, 1H), 1.62 (m, 2H), 1.64 (m, 2H), 1.75 (m, 1H), 1.92 (m, 1H), 2.08 (m, 2H), 2.17 (m, 1H), 2.80 (s, 3H), 3.39 (d, J = 13.18 Hz, 1H), 3.40 (d, J = 14.16 Hz, 1H), 3.47 (d, J = 14.16 Hz, 1H), 4.33 (d, J = 6.35 Hz, 1H), 4.67 (d, J = 6.84 Hz, 1H), 5.70 (m, 1H), 7.41 (d, J = 7.32 Hz, 1H), 7.59 (d, J = 7.82 Hz, 1H), 7.84 (dd, J = 7.32, 7.82 Hz, 1H).

2-[[(1*R*,2*R*)-1,3,3-Trimethyl-2-sulfanylbicyclo[2.2.1]hept-2-yl]methyl]pyridine (13). To a solution of 2-methylpyridine (3.20 g, 34.4 mmol) in 150 mL of THF at −70 °C was added *n*-butyllithium (1.6 M in hexane, 21 mL, 33.6 mmol). The mixture was stirred for 30 min at −40 °C and cooled to −70 °C again. A solution of (*R*)-thiofenchone (4.70 g, 27.9 mmol) in 15 mL of THF was added and the mixture allowed to reach ambient temperature in 3 h. To the mixture was added 15 mL of 5 N HCl. Stirring was continued for 15 min and the solution subsequently neutralized with 2 N NaOH. The mixture was extracted three times with dichloromethane, and the combined organic layers were washed with brine and dried over $MgSO_4$. The product was purified by means of column chromatography (silica gel, hexane/diethyl ether 9:1) and recrystallization from hexane to yield **13** as colorless needles (7.11 g, 27.2 mmol, 81%): mp 96−97 °C; $[\alpha]^{23}_D$ +109 (*c* 2.8,

CH_2Cl_2); ^{1}H NMR δ 0.80 (s, 3H), 1.15 (m, 2H), 1.19 (s, 3H), 1.24 (s, 3H), 1.4 (m, 1H), 1.65 (m, 1H), 1.76 (m, 1H), 1.95 (d, J = 10.25 Hz, 1H), 2.20 (m, 1H), 3.34 (s, 2H), 4.30 (s, SH), 7.08 (dd, J = 5.12, 6.95 Hz, 1H), 7.31 (d, J = 8.06 Hz, 1H), 7.54 (dd, J = 8.06, 6.95 Hz, 1H), 8.49 (d, J = 5.12 Hz, 1H); ^{13}C NMR 18.31 (q), 24.56 (t), 27.28 (q), 28.97 (q), 33.77 (t), 40.42 (t), 45.63 (s), 48.23 (t), 50.95 (d), 54.58 (s), 120.62 (d), 124.73 (d), 135.74 (d), 147.57 (d), 161.92 (s); HRMS calcd 261.156, found 261.155. Anal. Calcd for $C_{16}H_{23}NS$: C, 73.51; H, 8.87; N, 5.36. Found: C, 73.73; H, 8.88; N, 5.41.

2-[[(1*R*,2*R*)-1,3,3-Trimethyl-2-(benzylsulfanyl)bicyclo-[2.2.1]hept-2-yl]methyl]pyridine (14). This compound was prepared from **13** (0.75g, 2.87 mmol), sodium hydride (0.10g, 4.3 mmol), and benzyl bromide (0.51, 2.98 mmol) according to general procedure B. The product was recrystallized from hexane at −20 °C to afford **14** as a colorless solid (0.60g, 1.72 mmol, 60%): mp 104−105 °C; $[\alpha]^{23}_D$ −43 (*c* 3.5, $CHCl_3$); ^{1}H NMR δ 0.91 (s, 3H), 1.16 (s, 3H), 1.23 (m, 2H), 1.28 (s, 3H), 1.48 (m, 1H), 1.58 (d, J = 4.39 Hz, 1H), 1.77 (m, 1H), 2.02 (d, J = 9.52 Hz, 1H), 2.75 (m, 1H), 3.42 (d, J = 17.57 Hz, 1H), 3.53 (d, J = 10.25 Hz, 1H), 3.6 (d, J = 17.57 Hz, 1H), 3.82 (d, J = 10.25 Hz, 1H), 7.2 (m, 5H), 7.64 (dd, J = 7.69, 8.06 Hz, 1H), 8.47 (d, J = 8.06 Hz, 1H), 8.53 (d, J = 4.03 Hz); ^{13}C NMR δ 20.24 (q), 24.07 (q), 24.80 (t), 29.36 (q), 34.75 (t), 34.88 (t), 42.07 (s), 42.39 (t), 47.18 (s), 51.02 (d), 56.09 (s), 120.86 (d), 123.95 (d), 126.85 (d), 128.34 (d), 128.94 (d), 135.72 (d), 137.58 (s), 148.47 (d), 161.39 (s); HRMS calcd 351.202, no proper HRMS could be obtained; CI(NH_3) gave a molecular ion at *m*/*e* 352. Anal. Calcd for $C_{23}H_{29}NS$: C, 78.58; H, 8.31; N, 3.98. Found: C, 78.29; H, 8.33; N, 3.98.

Palladium Chloride Complex of 10e. A solution of [Pd(η^3-C_3H_5)Cl]$_2$ (37 mg, 0.10 mmol) and **10e** (0.10 g, 0.16 mmol) in dichloromethane (10 mL) was stirred for 1 h and treated with $AgBF_4$ (39 mg, 0.20 mmol) in 10 mL of THF. Stirring continued for 30 min, and the mixture was filtered over Celite. The solution was washed with brine and dried over $MgSO_4$. After evaporation of the solvent, the complex was obtained as a yellow solid that was recrystallized from dichloromethane by isothermal distillation of hexane into the solution. Compound **15** was obtained as yellow crystals suitable for X-ray crystallization (0.12 g, 0.14 mmol, 88%): ^{1}H NMR δ 0.68 (s, 6H), 1.28 (s, 6H), 1.38 (d, J = 10.42 Hz, 2H), 1.44 (s, 6H), 1.46 (m, 2H), 1.62 (m, 2H), 1.74 (d, J = 3.74 Hz, 2H), 1.95 (m, 4H), 2.19 (d, J = 11.2 Hz, 2H), 2.46 (d, J = 13.2 Hz, 2H), 3.32 (d, J = 14.6 Hz, 2H), 3.71 (d, J = 13.2 Hz, 2H), 3.74 (d, J = 14.6 Hz, 2H), 7.16 (d, J = 7.47 Hz, 4H), 7.33 (t, J = 7.62 Hz, 2H), 7.42 (dd, J = 7.62, 7.47 Hz, 4H), 8.12 (d, J = 7.77 Hz, 2H), 8.34 (t, J = 7.77 Hz, 1H).

Acknowledgment. B.K. is partially supported by the Netherlands Scientific Organization (N.W.O.) administered by the Office for Chemical Research (S.O.N.).

Supporting Information Available: Crystal data collection, data reduction, and structure solution and refinement for (−)-**7**·HCl, **11b**, and **15**,[31] product characterization of (+)-**9b**−**d**, (−)-**9e**, and **10b**−**e**, COSY and HETCOR spectra of (−)-**7**·HCl, and ^{1}H NMR spectra of **11** and **15** (12 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO9806299