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Chiral *S,S*-donor ligands in palladium-catalysed allylic alkylation

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Abstract—Chiral dithioether ligands have been tested in the model Pd-catalysed allylic alkylation reaction of (±)-3-acetoxy-1,3-diphenyl-1-propene with dimethyl malonate, giving high enantioselectivity (up to 81% e.e.) for the first time in this type of system. Pd(II)-allylic intermediates, $[Pd(\eta^3\text{-}1,3\text{-}Ph_2\text{-}C_3H_3)(dithioether)]PF_6$ were prepared and characterised both in solution by NMR spectroscopy and solid state. The X-ray structure for $[Pd(\eta^3\text{-}1,3\text{-}Ph_2\text{-}C_3H_3)(L)]PF_6$ (L = (*R,R*)-7,8-*O*-isopropylidene-1,5-dithiacyclononane) was determined.

1. Introduction

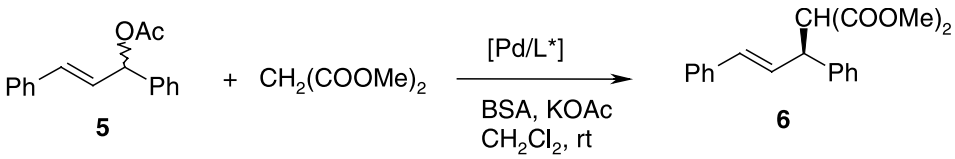
Asymmetric allylic substitution processes catalysed by transition metal complexes have received enormous attention in the last two decades.[1,2] The use of hard–soft heterodonor ligands is a highly efficient strategy to control the enantioselectivity through the different electronic effects of the donor atoms.[3–12]

A different approach is based on the chiral discrimination induced by the C_2 or C_1 backbone symmetry of homo–donor ligands. Thus, excellent enantioselectivity has been obtained with chiral oxazoline derivatives,[13,14] the Trost *P,P*-ligands[15,16] or ferrocenyl diphosphines.[17] Nevertheless, chiral homo–donor ligands such as diphosphine[18–21] and dithioether[22] derivatives have only given modest asymmetric induction. This low enantioselectivity can be attributed to the fact that the donor sites are not different enough to discriminate between both terminal allylic carbons in the intermediate species. In particular, dithioether *S,S*-donor ligands have shown good activity and enantioselectivity in several catalytic organic processes.[23–26] In the case of thioethers, it must be noted that a new stereogenic centre is created upon coordination of the sulphur atom to the metal. Although the configurational inversion of sulphur may lead to the existence of different diastereomeric species, a beneficial effect on enantioselectivity has been observed in some cases.[12]

Herein, we prove that the enantioselectivity provided by dithioether catalytic systems can be increased to high values with the appropriate combination of chiral backbone rigidity and the substituent at sulphur atom.

2. Results and discussion

Palladium systems containing **1**–**4** ligands[23,24,27] (Fig. 1) were tested in the alkylation of (±)-3-acetoxy-1,3-diphenyl-1-propene **5** using dimethyl malonate as the nucleophile (Eq. (1)) under basic Trost conditions.[21]



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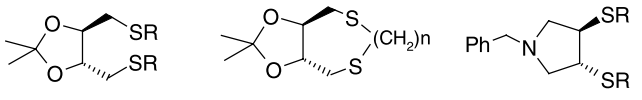


1a: R = Ph
1b: R = *i*Pr

2: n = 2
3: n = 3

4a: R = Ph
4b: R = *i*Pr

Figure 1.

The results obtained are shown in Table 1. The selected ligands contain a rigid five-member heterocycle backbone (*O*-isopropylidene for **1**–**3**, or pyrrolidine for **4**) and upon coordination to the metal, give chelates of different size.

Table 1. Results of asymmetric allylic alkylation of (±)-3-acetoxy-1,3-diphenyl-1-propene with dimethyl malonate[a]

Entry	L	Time (days)	Conversion[b] (%)	E.e.[c] (%)
1	**1b**	7	74	27 (*R*)
2	**2**	1	100	13 (*S*)
3	**3**	1	100	42 (*S*)
4	**4a**	7	100	81 (*S*)
5	**4b**	2.5	100	30 (*S*)

[a] Results determined from duplicate experiments.
[b] Conversion determined by ^{1}H NMR based on substrate.
[c] E.e. determined by HPLC on a Chiralcel-OD column. Absolute configuration, in parentheses, determined by optical rotation: Leutenegger, U.; Umbricht, G.; Fahrni, C.; Matt, P. V.; Pfaltz, A. *Tetrahedron* **1992**, *48*, 2143.

The tested systems showed, in general, low activities in agreement with other related published homo–donor ligands.[13–18]

Under in situ conditions, the Pd/**1a** system was not active after seven days of reaction. This fact can be explained because the starting material $[Pd(C_3H_5)Cl]_2$ did not react with **1a**, probably due to the low donor ability of the sulfur atom bonded to the phenyl group.[28] The Pd/**1b** system showed low activity and selectivity (entry 1, Table 1) which can be related to the highly flexible seven-membered metallocycle and/or diastereomeric species generated by *S* inversion. In an attempt to fix the absolute sulphur configuration, the bicyclic dithioethers **2** and **3** (entries 2 and 3, Table 1) were tested and, indeed, an improvement in the enantioselectivity was observed in the case of the system with ligand **3**. Moreover, in both cases an unexpected increase in catalytic activity was also achieved.

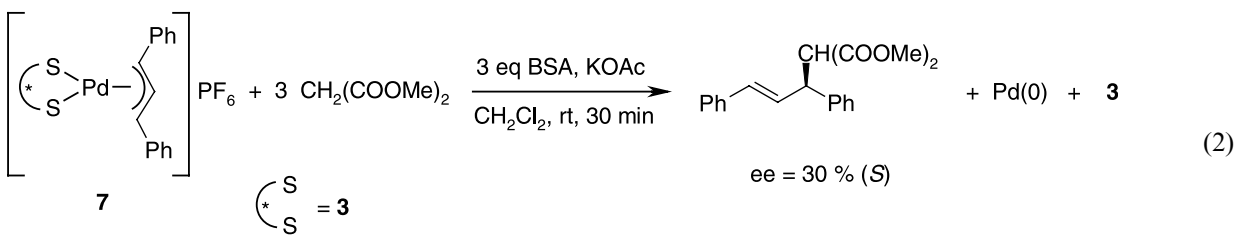
To decrease the flexibility of the metallic rings, ligands **4a** and **4b** with a pyrrolidine backbone were employed. With ligand **4a** containing a phenyl thioether moiety, the enantioselectivity increased notably to 81% (entry 4, Table 1). The Pd/**4b** system was found to induce lower selectivity, but had better activity (entry 5, Table 1).

In order to understand these results, we synthesised and examined the 1,3-diphenylallyl palladium complexes **7** and **8** of general formula $[Pd(\eta^3\text{-}1,3\text{-}Ph_2\text{-}C_3H_3)L]PF_6$ containing the ligands (L) **3** and **4a**, respectively.[29]

The X-ray crystal structure of (R_S,R_C,R_C,S_S)-**7** was determined (Fig. 2) and selected bond distances and angles are listed in Table 2. The investigation showed the existence of two non-equivalent molecules (**7A** and **7B**), which differ mainly in the relative position of the phenyl allylic rings being in **7A** nearly coplanar, and in **7B** twisted, (see torsion angles, Table 2). Palladium has typical square-planar environment, being bonded to the sulphur atoms and the diphenyl allyl group. Palladium coordination to the dithioether ligand leads to a boat conformation six-membered ring with the propylene moiety and a twisted chair conformation seven-membered ring with the isopropylidene fragment. Both molecules show an *exo* conformation (central allylic carbon and the isopropylidene ring pointing towards the same direction). In **7A** the terminal allylic carbon-palladium distances are different (2.163(8) and 2.197(8) Å) while in **7B** no important difference is observed. Considering that both species are quite similar, an average for the *exo* structure is expected in solution.

The ^{1}H NMR spectrum for **7** at 233 K (Fig. 3) shows the existence of two species, which must be attributed to the *exo*- and *endo*-(R_S,R_C,R_C,S_S)-**7** diastereomers. At higher temperatures (studied temperature range: 233–320 K), signals are broad and no differentiation between isomers is possible. In order to assign the major species to the *exo* or *endo* isomer, the stoichiometric alkylation between **7** and dimethyl malonate under similar catalytic conditions, was carried out (Eq. (2)). The substitution product **6** was obtained in a ratio 65(*S*)/35(*R*), comparable to the catalytic data (71(*S*)/29(*R*)). This good matching between diastereomeric and enantiomeric excesses led us to assign the *exo* isomer as the major species, assuming that the nucleophilic attack rate on the allyl moiety is similar for both diastereomers.[20,30,31]

In the case of **8**, at 223 K, the ^{1}H NMR spectrum (Fig. 4) showed the presence of four species in a ratio



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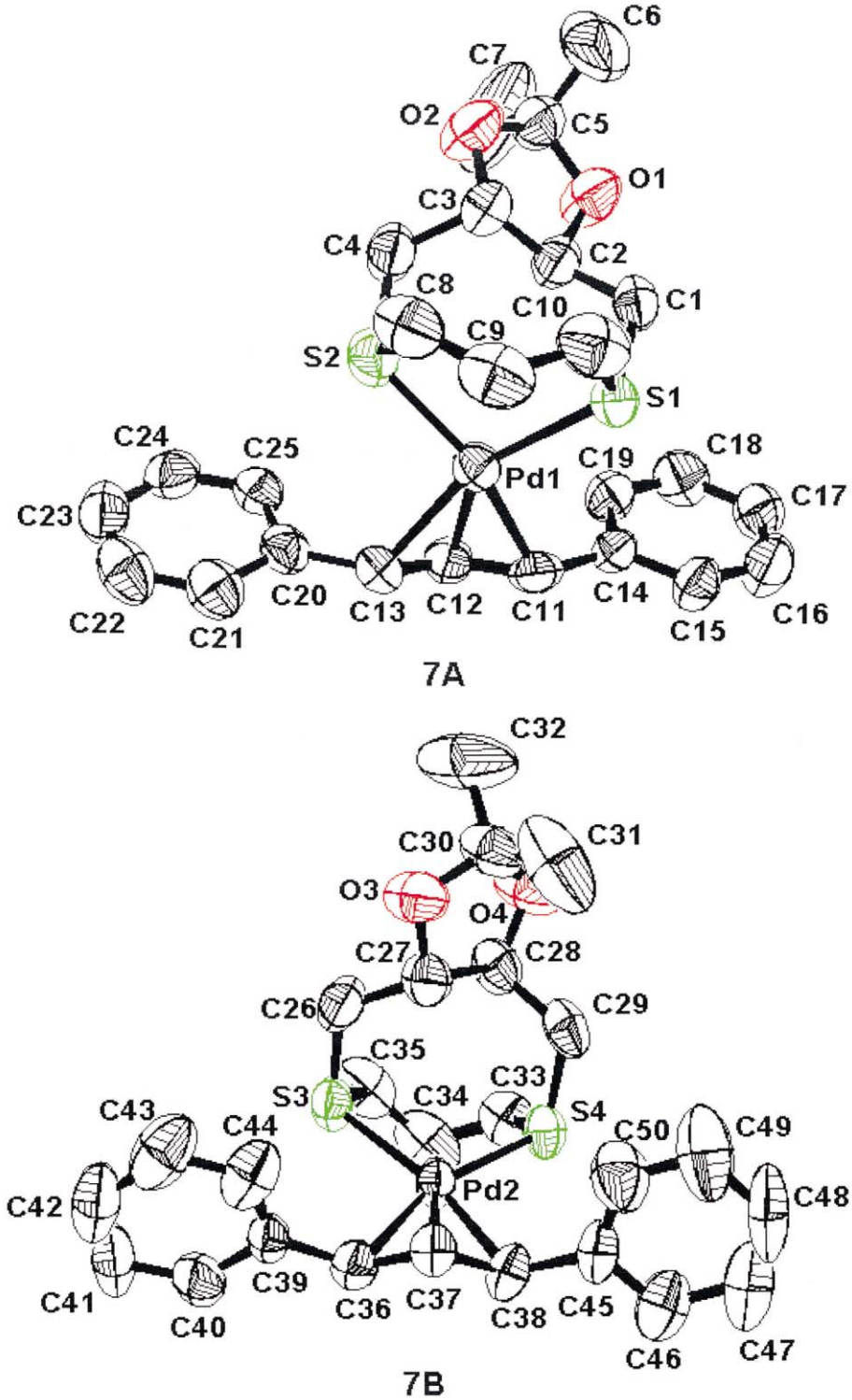

Figure 2. ORTEP drawing of the molecular structures of $[Pd(\eta^3\text{-}1,3\text{-}Ph_2\text{-}C_3H_3)\mathbf{3}]PF_6$ showing the isomers **7A** and **7B**. The PF_6^- anions and hydrogen atoms have been omitted for clarity.

50/22/17/11, which can be attributed to different isomers of **8**.[32] However, the formation of different intermediates did not prevent high e.e.s from being obtained

3. Conclusion

In conclusion, palladium complexes with the homo–donor chiral dithioether ligands presented here are active in the model allylic alkylation reaction affording high enantioselectivity when a rigid backbone containing *S*-phenyl substituents is used. The structural studies, in solution and solid-state, and the stoichiometric allylic alkylation allow a better understanding of the catalytic behaviour observed.

Table 2. Bond lengths (Å), angles (°) and torsion angles (°) for **7A** and **7B**

7A		**7B**	
Pd(1)–C(11)	2.163(8)	Pd(2)–C(36)	2.185(10)
Pd(1)–C(12)	2.153(8)	Pd(2)–C(37)	2.162(8)
Pd(1)–C(13)	2.197(8)	Pd(2)–C(38)	2.178(9)
Pd(1)–S(1)	2.357(2)	Pd(2)–S(3)	2.357(2)
Pd(1)–S(2)	2.370(2)	Pd(2)–S(4)	2.363(2)
S(1)–Pd(1)–S(2)	96.20(8)	S(3)–Pd(2)–S(4)	96.97(9)
Pd(1)–C(11)–C(14)–C(15)	108.0(8)	Pd(2)–C(36)–C(39)–C(40)	110.5(8)
Pd(1)–C(11)–C(14)–C(19)	−69.1(10)	Pd(2)–C(36)–C(39)–C(44)	−69.0(11)
Pd(1)–C(13)–C(20)–C(21)	−113.6(8)	Pd(2)–C(38)–C(45)–C(46)	−122.1(10)
Pd(1)–C(13)–C(20)–C(25)	65.0(10)	Pd(2)–C(38)–C(45)–C(50)	51.4(13)

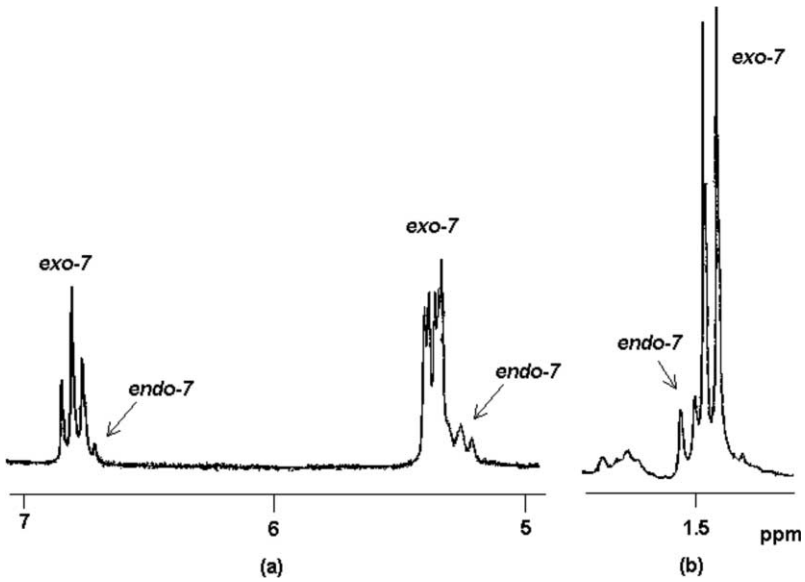

Figure 3. (a) Allylic and (b) methyl protons in the ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **7** at 233 K showing the observed signals for the two diastereomers.

Further work is in progress in the synthesis of other dithioether ligands in order to increase the enantioselectivity of this reaction.

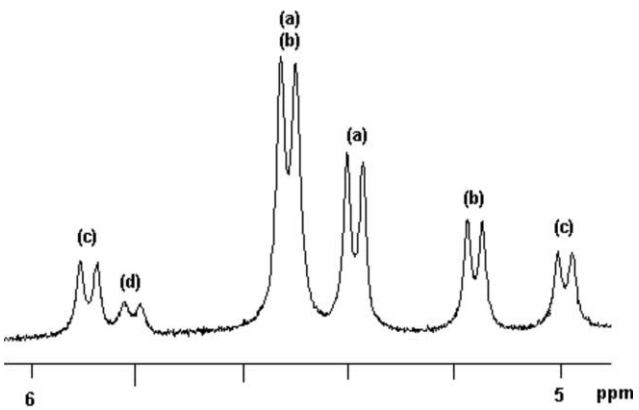

Figure 4. Allylic region of the ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **8** at 223 K showing the peaks corresponding to four diastereomers (a–d).

4. Experimental

4.1. General procedures

All syntheses of the palladium complexes were carried out using standard Schlenk techniques under a nitrogen atmosphere. Solvents were distilled and deoxygenated before use. All other reagents were used as supplied. The complexes $[Pd(C_3H_5)Cl]_2$[33] and $[Pd(1,3\text{-}Ph_2\text{-}C_3H_3)Cl]_2$[29] were prepared as previously reported. HPLC analysis was performed on a Waters Series 600 chromatograph (chiralcel-OD chiral column) with a UV detector. The ^{1}H NMR spectra were registered on Varian Gemini 300 and 400 MHz instruments and were referenced in the usual way.

4.2. Synthesis of complexes 7 and 8

The corresponding ligand **3** (0.124 g, 0.53 mmol) or **4a** (0.200 g 0.53 mmol) and the complex $[Pd(1,3\text{-}Ph_2\text{-}$

$C_3H_3)Cl]_2$ (0.177 g, 0.26 mmol) were dissolved in a mixture of absolute ethanol, chloroform, dichloromethane and methanol (1:1:1:1, 40 cm^3) at rt under nitrogen. Then, NH_4PF_6 (0.26 g, 1.60 mmol) was added. The mixture was stirred for 36 h and filtered. The solvent was removed under reduced pressure. Dichloromethane (15 cm^3) was added and the organic phase was washed several times with water, until the pH of the organic phase was neutral. The organic phase was dried over anhydrous Na_2SO_4, filtered and the filtrate evaporated under reduced pressure. After addition of diethyl ether (10 cm^3), an orange solid was obtained. The product was separated by filtration and dried under reduced pressure. Data for **7**: yield: 0.288 g (80%). Anal. calcd for **7**: C, 44.19; H, 4.57; S, 9.42. Found: C, 44.87; H, 4.92; S, 9.98%. MS (FAB positive): m/z 534 ($[M-PF_6]^+$); δ_H (**7**) ($CDCl_3$): 1.21 (s, CH_3, 3H), 1.25 (s, CH_3, 3H), 1.6 (m, CH_2, 1H), 2.2 (b, CH_2, 2H), 2.4 (m, CH_2, 2H), 2.6 (b, CH_2, 2H), 2.9 (m, CH_2, 1H), 3.1 (b, CH_2, 1H), 3.3 (b, CH_2, 1H), 4.2 (m, CH, 1H), 4.3 (m, CH, 1H), 5.5 (d, CH_{anti}, 2H), 6.8 (t, $CH_{central}$, 1H); δ_C (**7**): 26.0 (CH_3), 26.3 (CH_3), 29.3 (CH_2), 30.0 (CH_2), 33.0 (CH_2), 38.0 (CH_2), 38.1 (CH_2), 76.6 (CH), 83.0 (CH), 87.0 (CH_{anti}), 88.0 (CH_{anti}), 108 ($CH_{central}$), 109 (C), 127.1–135.5 (Ph).

Data for **8**: yield 0.363 g (83%). Anal. calcd for **8**·1.5$C_4H_{10}O$: C, 56.28; H, 5.14; N, 1.56; S, 7.15. Found for **8**·1.5$C_4H_{10}O$: C, 56.83; H, 5.17; N, 1.60; S, 7.26%. m/z 677 ($[M-PF_6]^+$).

4.3. Crystallography

Monocrystals of **7** were obtained by slow diffusion of hexane over a chloroform solution of the complex. The crystal data was collected using a Bruker SMART CCD-based diffractometer operating at rt. Intensities were collected with graphite monochromatized Mo Kα radiation ($\lambda=0.71069$ Å), using $\omega/2\theta$ scan-technique. Cell parameters were retrieved using SMART software[34] and refined using SAINT[35] on all observed reflections. Data reduction was performed using the SAINT software. Absorption corrections used SADABS.[36] The structure was solved by the direct method using the SHELXS-97 program[37] and refined by the least-squares method on F^2 using SHELXL-97,[38] which is incorporated in SHELXTL-PC V 5.1.[39] All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included in calculated positions and refined as a riding model.

4.4. Crystal data for 7†

$C_{25}H_{31}F_6O_2PPdS_2$, $M=678.99$, triclinic, $a=10.6789(5)$, $b=10.9958(5)$, $c=13.6171(6)$ Å, $\alpha=87.1820(10)$, $\beta=78.6150(10)$, $\gamma=67.7980(10)°$, $U=1450.71(11)$ Å^3, $T=298$ (2) K, space group $P\bar{1}$, $Z=2$, μ(Mo Kα)=0.898 mm^{-1}, 10302 reflections measured, 8451 unique ($R_{int}=0.0138$) which were used in all calculations. The final R indices are $R_1=0.0520$ for 6898 data with $F_o>4\sigma(F_o)$, $wR_2=0.139$ (all data).

† Crystallographic data (excluding structure factors) for the structure **7** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 158615.

4.5. Palladium-catalysed allylic alkylation

A solution of $[Pd(C_3H_5)Cl]_2$ (3.66 mg, 0.01 mmol, 1 mol%) and the ligand **1**, **2**, **3**, or **4** (2.5 mol%) in CH_2Cl_2 (2 cm^3) was stirred for 0.5 h, and treated with a solution of (±)-1,3-diphenyl-2-propenyl acetate (252 mg, 1 mmol) in CH_2Cl_2 (2 cm^3), followed by dimethyl malonate (396 mg, 3 mmol), BSA (610 mg, 3 mmol), and a catalytic amount of KOAc. The mixture was stirred at rt until the substrate had been totally consumed (unless stated otherwise), monitored by TLC (eluent: hexane/ethyl acetate, 4/1). Then, the solution was diluted with diethyl ether, filtered over Celite, and washed successively with an aqueous solution of ammonium chloride (10%) and water (2×10 cm^3). The organic phase was dried over anhydrous Na_2SO_4, filtered off, and solvent removed under reduced pressure. The product was purified by column chromatography (SiO_2; ethyl acetate), followed by heating at 130°C under vacuum. The e.e.s were determined by HPLC on a Chiralcel OD column, using hexane/*iso*-PrOH, 99/1, as eluent, in a flow of 0.3 cm^3/min and pressure 10 bar. At these conditions, the retention times are 34.0 min for (*R*)-**6** and 36 min for (*S*)-**6**.

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References

1. Trost, B. M.; van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395–422.
2. Pfaltz, A.; Lautens, M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer: Heidelberg, 1999; Vol. 2, Chapter 24, pp. 833–884.
3. Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336–345 and references cited therein.
4. Gómez, M.; Jansat, S.; Muller, G.; Panyella, D.; van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Goubitz, K.; Fraanje, J. *Organometallics* **1999**, *18*, 4970–4981.
5. Frost, C. G.; Williams, J. M. J. *Tetrahedron Lett.* **1993**, *34*, 2015–2018.
6. Williams, J. M. J. *Synlett* **1996**, 705–710 and references cited therein.

7. Chesney, A.; Bryce, M. R.; Chubb, R. W. J.; Batsanov, A. S.; Howard, J. A. K. *Tetrahedron: Asymmetry* **1997**, *8*, 2337–2346.
8. Adams, H.; Anderson, J. C.; Cubbon, R.; James, D. S.; Mathias, J. P. *J. Org. Chem.* **1999**, *64*, 8256–8262.
9. Imai, Y.; Zhang, W.; Kida, T.; Nakatsuji, Y.; Ikeda, I. *Synlett* **1999**, 1319–1321.
10. Barbaro, P.; Currao, A.; Herrmann, J.; Nesper, R.; Pregosin, P. S.; Salzmann, R. *Organometallics* **1996**, *15*, 1879–1888.
11. Hiroi, K.; Suzuki, Y.; Kaneko, Y.; Kato, F.; Abe, I.; Kawagishi, R. *Polyhedron* **2000**, *19*, 525–528.
12. Evans, D. A.; Campos, K. R.; Tedrow, J. S.; Michael, F. E.; Gagné, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 7905–7920.
13. Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1–45.
14. Pfaltz, A. *Acc. Chem. Res.* **1993**, *26*, 339–345.
15. Trost, B. M. *Acc. Chem. Res.* **1996**, *29*, 355–364 and references cited therein.
16. Lee, S.-G.; Lim, C. W.; Song, C. E.; Kim, K. M.; Jun, C. H. *J. Org. Chem.* **1999**, *64*, 4445–4451.
17. Zhang, W.; Shimanuki, T.; Kida, T.; Nakatsuji, Y.; Ikeda, I. *J. Org. Chem.* **1999**, *64*, 6247–6251.
18. Togni, A.; Breutel, C.; Schnyder, A.; Spindler, F.; Landert, H.; Tijani, A. *J. Am. Chem. Soc.* **1994**, *116*, 4062–4066.
19. Trost, B. M.; Strege, P. E. *J. Am. Chem. Soc.* **1977**, *99*, 1649–1651.
20. Auburn, P. R.; Mackenzie, P. B.; Bosnich, B. *J. Am. Chem. Soc.* **1985**, *107*, 2033–2046.
21. Trost, B. M.; Murphy, D. J. *Organometallics* **1985**, *4*, 1143–1145.
22. Enders, D.; Peters, R.; Lochtman, R.; Raabe, G.; Runsink, J.; Bats, J. W. *Eur. J. Org. Chem.* **2000**, 3399–3426.
23. Diéguez, M.; Orejón, A.; Masdeu-Bultó, A. M.; Echarri, R.; Castillón, S.; Claver, C.; Ruiz, A. *J. Chem. Soc., Dalton Trans.* **1997**, 4611–4618.
24. Diéguez, M.; Ruiz, A.; Claver, C.; Pereira, M. M.; d'A. Rocha Gonsalves, A. M. *J. Chem. Soc., Dalton Trans.* **1998**, 3517–3522.
25. Pàmies, O.; Diéguez, M.; Net, G.; Ruiz, A.; Claver, C. *J. Chem. Soc., Dalton Trans.* **1999**, 3439–3444.
26. Bayón, J. C.; Claver, C.; Masdeu-Bultó, A. M. *Coord. Chem. Rev.* **1999**, *193*, 73–145.
27. Flores-Santos, L.; Diéguez, M.; Claver, C.; Masdeu-Bultó, A. M.; Martin, E., to be published elsewhere.
28. Analogous behaviour was observed using $[PdCl_2(PhCN)_2]$ with **1a**: Diéguez, M.; Ruiz, A.; Masdeu-Bultó, A. M.; Claver, C. *J. Chem. Soc., Dalton Trans.* **2000**, 4154–4159.
29. Synthesis based on the method described in: von Matt, P.; Lloyd-Jones, G. C.; Minidis, A. B. E.; Pfaltz, A.; Macko, L.; Neuburger, M.; Zehnder, M.; Rüegger, H.; Pregosin, P. S. *Helv. Chim. Acta* **1995**, *78*, 265–284.
30. Mackenzie, P. B.; Whelan, J.; Bosnich, B. *J. Am. Chem. Soc.* **1985**, *107*, 2046–2054.
31. Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83–134.
32. The isomers come from the different possibilities: *exo*/*endo*, depending on the relative position of the allyl group and backbone ligand; *syn*/*anti*, depending on the sulphur absolute configuration; and/or, *syn*/*anti*, depending on the relative position of allylic phenyl group.
33. Tatsuno, Y.; Yoshida, T.; Otsuka, S. *Inorg. Synth.* **1990**, *28*, 342–345.
34. V. 4.210, Bruker Analytical X-ray Systems, Madison, WI, 1995.
35. V. 4.050, Bruker Analytical X-ray Systems, Madison, WI, 1995.
36. Program for absorption corrections using Bruker CCD based on the method of Robert Blessing: Blessing, R. H. *Acta Crystallogr.* **1995**, *A51*, 33.
37. Sheldrick, G. M. *SHELXS*-97, *A Computer Program for Crystal Structure Determination*; University of Göttingen: Germany, 1997.
38. Sheldrick, G. M. *SHELXL*-97, *A Computer Program for Crystal Structure Refinement*; University of Göttingen: Germany, 1997.
39. PC version, Bruker Analytical X-ray Systems, Madison, WI, 1995.