Palladium-catalysed Asymmetric Allylic Substitution: a Ligand Design Incorporating Steric and Electronic Effects

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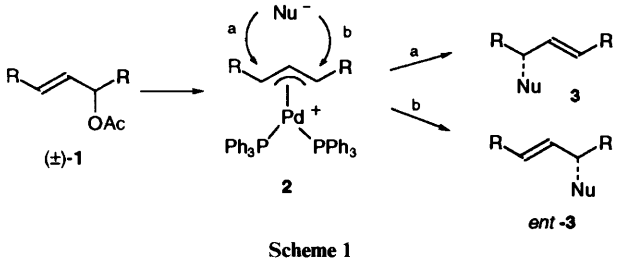
Enantiomerically pure ligands containing a 4,5-dihydrooxazole moiety tethered to an auxiliary sulfur or phosphorus donor have been prepared. These ligands have been exploited for palladium-catalysed asymmetric allylic substitution, providing enantioselectivities of 40–96% ee. The origin of the enantioselectivity in the catalytic reaction is discussed in terms of the steric and electronic influences provided by the ligand.

Palladium-catalysed allylic substitutions have been used extensively to provide chemo-, regio-, diastereo- and enantioselectivity in synthetic processes.[1]

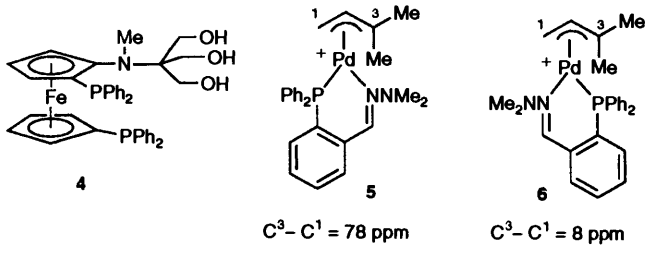
Whilst enantioselective palladium-catalysed allylic substitutions can be designed in a variety of ways, we chose to focus on reactions which proceed through a *meso* η^3-allyl intermediate. By suitable choice of starting allyl acetate, the η^3-allyl moiety will be symmetrical. Asymmetric induction will be achieved if the incoming nucleophile can be directed selectively to one terminus of the allyl group. Thus, the reaction of the racemic allyl acetate **1** with a palladium catalyst in the presence of triphenylphosphine will afford a *meso* palladium intermediate **2**. Nucleophilic addition to this intermediate will provide the substitution product **3** or *ent*-**3**, depending upon which of the allyl termini is attacked (see Scheme 1).



Scheme 1

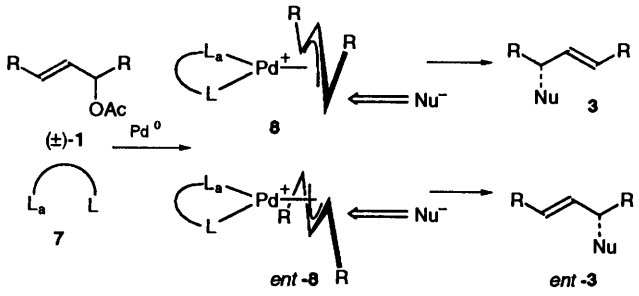
Any enantiomerically pure ligand coordinated to the palladium will be situated a long way from the incoming nucleophile, and it would appear that an asymmetric variant of this process will therefore prove to be problematic. However, palladium-catalysed asymmetric allylic substitution has been achieved by a number of research groups, often with good levels of enantioselectivity.[2,3] Hayashi and co-workers have designed ligands **4**, which they suggest are capable of chelating to the palladium, and also to the incoming nucleophile, thereby providing the required stereocontrol.[4] This strategy has been successful, providing up to 96% enantiomeric excess (ee) in certain palladium-catalysed allylic substitutions.[5]

However, the results of Åkermark, Vitagliano and co-workers suggested to us that perhaps electronic effects in a ligand could be exploited to control the approach of an incoming nucleophile.[6] These workers have demonstrated that the reactivity of the palladium–allyl complex is dependent upon the nature of the ligands coordinated to it. Strongly π-accepting ligands such as phosphines and phosphites generate highly reactive palladium complexes, whereas nitrogen ligands afford less reactive species. Furthermore, comparison of the ^{13}C NMR spectra of the isolated palladium–allyl complexes **5** and **6** demonstrate that the phosphine is able to withdraw electron density from the position *trans* to itself. The C_3 carbon of the allyl unit has a tendency to appear downfield of the C_1 carbon, due to the ability of the adjacent methyl groups to support the positive charge. For complex **5**, the π-accepting phosphine ligand is *trans* to C_3, and is able to withdraw electron density from this position, and so the signal due to C_3 moves still further downfield. For complex **6**, the phosphine withdraws electron density from C_1 and so the shift difference between C_1 and C_3 is substantially reduced.



Our intention was to exploit these effects and to produce a ligand **7** which contained two different donor atoms, only one of which could behave as a π-acceptor. We therefore assumed that a nucleophile would preferentially add to the allyl terminus *trans* to the better π-acceptor, since this will possess greater positive charge character. During the catalytic cycle of the palladium-catalysed allylic substitution process, the η^3-allyl intermediate will no longer be symmetrical, but will exist in two enantiomeric forms **8** and *ent*-**8**. It is expected that the nucleophilic substitution product **3** will be formed if the reaction proceeds through **8**. However, the product is expected to be *ent*-**3** if the reaction proceeds through *ent*-**8** (see Scheme 2).

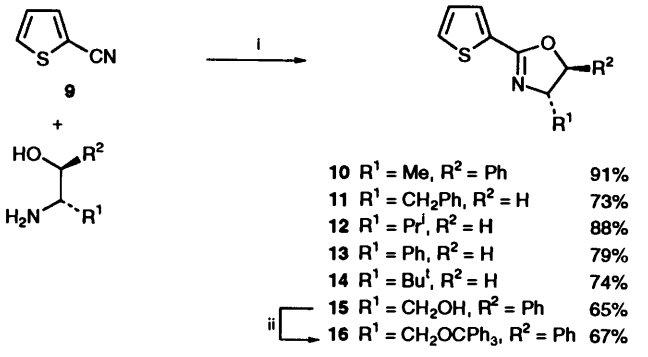
Design considerations for a ligand which can provide asymmetric induction will include the incorporation of two different donor atoms, an asymmetric environment which can control the orientation of the allyl moiety and synthetic accessibility. We have prepared ligands in which a 4,5-dihydrooxazole group is tethered to either a sulfur or phosphorus donor. We chose the 4,5-dihydrooxazole group because of its excellent pedigree as a ligand for asymmetric synthesis.[7] Furthermore, Pfaltz and co-workers had reported the use of C_2-symmetric bis(4,5-dihydrooxazoles) as ligands for palladium-catalysed allylic substitution.[2] Since the initiation of this project, the research groups of Pfaltz,[8] Helmchen[9] and Nicholas[10] have reported 4,5-dihydrooxazole based ligands for use with palladium catalysts.



Scheme 2

Results and Discussion

The ligands **10–15** were prepared by adaptation of a literature procedure[11] from thiophene-2-carbonitrile **9** and the corresponding amino alcohol by treatment with catalytic amounts of zinc chloride in chlorobenzene at reflux for 48 h (see Scheme 3). Ligand **16** was prepared from **15** by tritylation with trityl chloride.



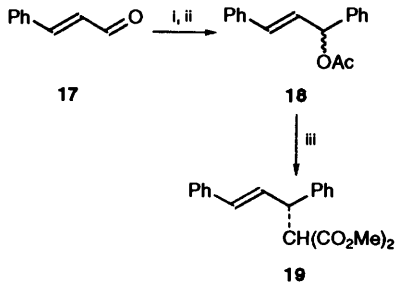
Scheme 3 *Reagents and conditions:* i, cat. $ZnCl_2$, PhCl, reflux; ii, Ph_3CCl, Et_3N

With a family of compounds available, we examined the performance of these ligands in palladium-catalysed allylic substitution.[12] Racemic 1,3-diphenylprop-2-enyl acetate **18** was prepared by the reaction of cinnamaldehyde **17** with phenylmagnesium bromide, and acetylation of the so-formed alcohol with acetic anhydride in pyridine in 80% overall yield. The reaction of **18** in tetrahydrofuran (THF) at reflux with dimethyl sodiomalonate in the presence of catalytic amounts of allylpalladium chloride dimer and catalytic amounts of the ligands **10–16** afforded the substitution product **19**, with the (*S*)-(−)-enantiomer predominating, as determined by comparison of the sign of rotation with previously reported values[2] (see Scheme 4). The yield and enantioselectivity of the process varied depending upon which ligand was employed in the reaction, as indicated in Table 1. Ligands **10**, **11** and **15**, which contained a small substituent in the 4-position of the 4,5-dihydrooxazole ring, afforded only low enantioselectivity. However, ligands **13**, **14** and **16** which contained a large substituent in the 4-position of the 4,5-dihydrooxazole ring were not able to provide a good yield when they were employed as ligands. The most promising ligand was the valinol-derived* thienyl-4,5-dihydrooxazole **12**. We therefore examined the use of this ligand in a variety of solvents and concentrations and also varied the ratio of ligand to palladium. These results are also summarised in Table 1. THF appears to be the most appropriate solvent. The dramatic lowering in enantioselectivity observed in changing to the more coordinating solvent dimethylformamide (DMF) suggests that the ligand may be being displaced by the solvent. Furthermore, we noted that increasing the ratio of ligand to palladium and also increasing the concentration of the palladium and ligand (without altering the ratio) affords an increase in enantioselectivity. These facts strongly suggest a low affinity between the ligand and the palladium, although association constants have not been determined.

* Valinol = 2-amino-3-methylbutan-1-ol.

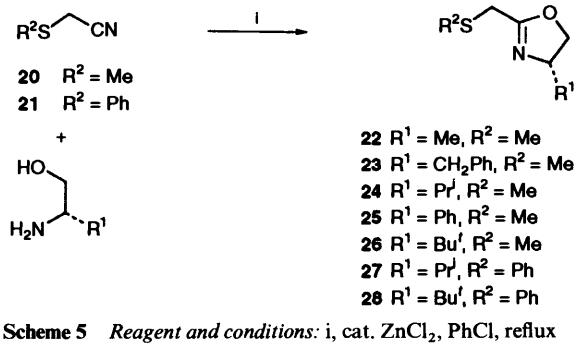
Table 1 Enantioselectivities obtained using 2-(2-thienyl)-4,5-dihydro-1,3-oxazoles **10–16**

Ligand	Solvent	Pd:L	Yield (%)	ee of **19** (%)
10	THF	1:2	56	6
11	THF	1:2	68	24
12	THF	1:2	63	68
12	DMF	1:2	91	12
12	CH_2Cl_2	1:2	35	30
12	THF	1:1	23	34
12	THF	1:4	85	76
12	THF	1:10	89	81
12	THF	1:2	39	40
12	THF	1:2	85	80
13	THF	1:2	Trace	—
14	THF	1:2	Trace	—
15	THF	1:2	65	5
16	THF	1:2	Trace	—



Scheme 4 *Reagents and conditions:* i, PhMgBr, Et_2O, 83%; ii, Ac_2O, C_5H_5N, 96%; iii, $NaCH(CO_2Me)_2$, $[\{Pd(\eta^3\text{-}C_3H_5)Cl\}_2]$ (5 mol%), ligand **10–16** (10 mol%), THF

In view of the binding problems with the thienyl ligands, and their inability to promote a fast reaction, we turned our attention to an alternative environment for the sulfur atom.[13] Sulfides have been used widely as ligands for transition metals, and sulfides can also behave as π-acceptors. (Methylsulfanyl)-acetonitrile **20** was converted into the 2-substituted 4,5-dihydrooxazoles **22–26** upon treatment with the corresponding amino alcohol in the presence of a catalytic amount of zinc chloride in chlorobenzene at reflux (see Scheme 5). Similarly,



Scheme 5 *Reagent and conditions:* i, cat. $ZnCl_2$, PhCl, reflux

(phenylsulfanyl)acetonitrile **21** was converted into 4,5-dihydrooxazoles **27** and **28** under identical conditions. The sulfanylmethyl-4,5-dihydrooxazoles **22–28** were employed as ligands

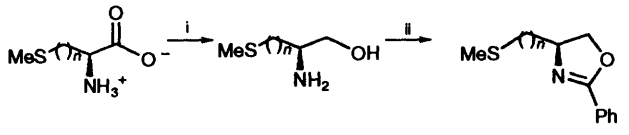
Table 2 Enantioselectivities obtained using sulfanylmethyl-4,5-dihydro-1,3-oxazoles **22–28**

Ligand	Solvent	Pd:L	Yield (%)	ee of **19** (%)
22	THF	1:2	68	51
23	THF	1:2	56	40
24	THF	1:2	74	70
25	THF	1:2	67	60
26	THF	1:2	71	66
26	THF	1:4	69	75
26	THF	1:10	71	75
27	CH_2Cl_2	1:2	52	76
28	THF	1:2	0	—
28	CH_2Cl_2	1:2	0	—

in the palladium-catalysed asymmetric allylic substitution, and the results are detailed in Table 2.

In contrast to the thienyl-4,5-dihydrooxazoles, all of the sulfanylmethyl-4,5-dihydrooxazoles, except **28**, are effective as ligands for the palladium-catalysed allylic substitution. Moderate enantioselectivities are obtained even when the 4-substituent is small. There is much less dependence upon the ratio of ligand to palladium for these ligands, suggesting that they are able to complex to palladium more strongly. It is also of importance from a practical stand-point that, since these ligands provide a more reactive catalytic species, the reactions may now be conducted at ambient temperature.

The auxiliary donor atom may be tethered to the 4,5-dihydrooxazole unit at other positions and by various linkers. Ligands **10–15** and **22–28** have the auxiliary donor atom tethered to the 2-position of the 4,5-dihydrooxazole. Alternatively, the auxiliary donor atom may be tethered to the 4-position, and still provide a bidentate ligand. Two such ligands have been prepared. Reduction of *S*-methyl-L-cysteine **29** and methionine **30** with lithium aluminium hydride afforded the corresponding amino alcohols **31** and **32**. Treatment of the amino alcohols with methyl benzimidate hydrochloride **33** in dichloromethane at reflux[14] yielded the 4,5-dihydrooxazoles **34** and **35**, respectively (see Scheme 6).

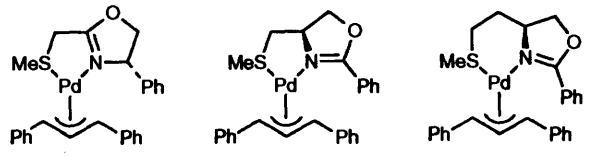


29 *n* = 1 **31** *n* = 1 40% **34** *n* = 1 54%
30 *n* = 2 **32** *n* = 2 78% **35** *n* = 2 80%

Scheme 6 *Reagents and conditions:* i, $LiAlH_4$, THF, reflux 16 h; ii, PhC(=NH)OMe·HCl **33**, CH_2Cl_2, reflux, 18 h

In the palladium-catalysed allylic substitution, these ligands were found to be effective. When ligand **34** was employed, the reaction afforded the substitution product **19** in 86% yield and with 56% ee, whereas ligand **35** afforded the product **19** with 79% yield and 88% ee. All of the ligands reported in this paper have been prepared from the same configuration of amino alcohol. However, the ligands **34** and **35** afford the opposite enantiomer in the substitution product **19** in comparison with the ligands where the auxiliary donor atom is tethered to the 2-position of the 4,5-dihydrooxazole. We believe that this may be attributed to the structural reorganisation which has been created in the ligand construction. Comparison of the isomeric ligands **34** and **25** reveals that in terms of the asymmetric environment provided by these ligands when they are chelated to the palladium, these structures are quasi-enantiomeric. This is illustrated by comparison of the palladium complexes **36** and **37**.

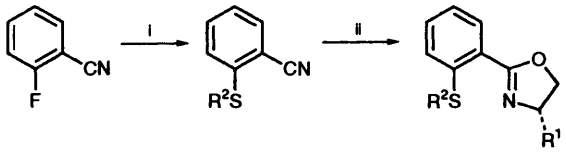
The greater enantioselectivity provided by ligand **35** in comparison with ligand **34** may be rationalised by the longer



36 **37** **38**

tether length between the donor atoms. As the tether length increases, the size of the chelate increases which, in turn, places the asymmetric environment of the ligand closer to the allyl moiety complexed to the palladium. Inspection of complexes **37** and **38** reveals the closer proximity between the ligands attached to the palladium in the case of complex **38** in which the ligand has a longer tether length.

In order to further explore the benefits of employing a longer tether length, we have investigated ligands in which an aromatic linker is used to tether the ligating atoms. Sulfur ligands **42–46** have been prepared by the reaction of *o*-methylsulfanylbenzonitrile **40** with amino alcohols in the presence of a catalytic amount of zinc chloride in chlorobenzene at reflux (see Scheme 7). *o*-Phenylsulfanylbenzonitrile **41** was readily



39

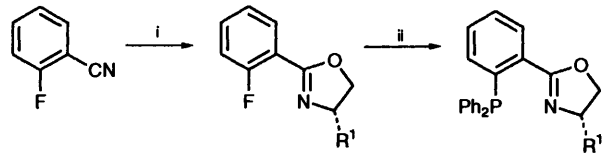
40 R^2 = Me
41 R^2 = Ph 93%

42 R^1 = Me, R^2 = Me 60%
43 R^1 = CH_2Ph, R^2 = Me 42%
44 R^1 = Pr^i, R^2 = Me 56%
45 R^1 = Ph, R^2 = Me 58%
46 R^1 = Bu^t, R^2 = Me 53%
47 R^1 = Pr^i, R^2 = Ph 73%
48 R^1 = Bu^t, R^2 = Ph 62%

Scheme 7 *Reagents and conditions:* i, PhSNa, THF, reflux; ii, amino alcohol, cat. $ZnCl_2$, PhCl, reflux

prepared by treatment of *o*-fluorobenzonitrile **39** with sodium benzenethiolate in THF at reflux for 48 h. Conversion of **41** into the 4,5-dihydrooxazoles **47** and **48** was similarly achieved upon treatment with the corresponding amino alcohols under the standard conditions.

The phosphine ligands **54–58** were prepared by treatment of the fluoro 4,5-dihydrooxazoles **49–53** with potassium diphenylphosphide in THF at reflux (see Scheme 8). The fluoro



39

49 R^1 = Me 47%
50 R^1 = CH_2Ph 48%
51 R^1 = Pr^i 46%
52 R^1 = Ph 49%
53 R^1 = Bu^t 56%

54 R^1 = Me 80%
55 R^1 = CH_2Ph 76%
56 R^1 = Pr^i 76%
57 R^1 = Ph 84%
58 R^1 = Bu^t 92%

Scheme 8 *Reagents and conditions:* i, amino alcohol, cat. $ZnCl_2$, PhCl, reflux; ii, $KPPh_2$, THF

compounds **49–53** had been prepared from *o*-fluorobenzonitrile **39** under the standard conditions. The application of ligands **42–48** and **54–58** in the palladium-catalysed allylic substitution of the allyl acetate **18** afforded the substitution product **19** with very high levels of enantioselectivity in some cases, as outlined in Table 3.

Table 3 Enantioselectivities obtained using aryl 4,5-dihydro-1,3-oxazoles **42–58**

Ligand	Solvent	Pd:L	Yield (%)	ee of **19** (%)
42	THF	1:2	91	40
43	THF	1:2	90	52
44	THF	1:2	98	58
45	THF	1:2	84	66
46	THF	1:2	86	80
47	THF	1:2	91	78
47	CH_2Cl_2	1:2	96	90
48	CH_2Cl_2	1:2	92	96
54	THF	1:2	88	90
55	THF	1:2	96	92
56	THF	1:2	92	94
57	THF	1:2	96	92
58	THF	1:2	99	90

Table 4 Enantioselectivities obtained using **59** as the nucleophile

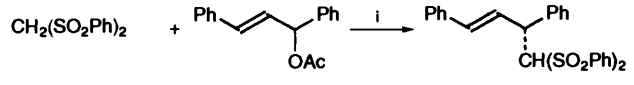
Ligand	Solvent	Pd:L	Yield (%)	ee (%)[a]
56	THF[b]	1:2	87	88
56	CH_2Cl_2[b]	1:2	76	39
56	DMF[c]	1:2	78	93

[a] Determined by S. Jackson (Glaxo) using a Chiralcel OJ column. [b] $NaCH(SO_2Ph)_2$ was insoluble in these solvents, therefore, bis(trimethylsilyl)acetamide was employed as base. [c] $NaCH(SO_2Ph)_2$ was used as the nucleophile.

The methylsulfanyl ligands **42–46** afford reasonable levels of enantioselectivity for the palladium-catalysed allylic substitution process.[15] However, by using the diaryl sulfides **47** and **48**, a dramatic improvement in enantioselectivity is observed. For those reactions examined, using the protocol involving bis(trimethylsilyl)acetamide (BSA),[16] improvements were noted in the yield and enantioselectivity over the protocol using dimethyl sodiomalonate as the incoming nucleophile.

The phosphine ligands **54–58** provided consistently high enantioselectivity for the palladium-catalysed allylic substitution process. There is only a small variation in the enantioselectivity observed when the size of the 4,5-dihydrooxazole R-group is varied significantly. The phosphine 4,5-dihydrooxazoles also give a very short reaction time in comparison with any of the other ligands examined, and also in comparison with triphenylphosphine as the supporting ligand.

We have also investigated the use of bis(sulfone) **59** as a nucleophile for the palladium-catalysed allylic substitution. Thus, treatment of **18** in the presence of the bis(sulfone) **59** and bis(trimethylsilyl)acetamide with catalytic amounts of the ligand **56**, potassium acetate and allylpalladium chloride dimer affords the substitution product **60** (see Scheme 9). None of the



59 **18** **60**

Scheme 9 *Reagent:* i, $[\{Pd(\eta^3\text{-}C_3H_5)Cl\}_2]$ (5 mol%), ligand (4 mol%)

sulfur ligands afforded a catalyst which was able to produce the desired substitution product **60**. The results and enantioselectivities obtained are detailed in Table 4.

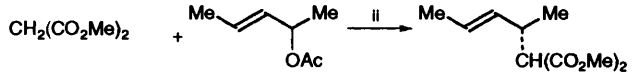
The use of pent-3-en-2-yl acetate **62** as a substrate affords the substitution product **63** upon treatment with dimethyl malonate **61** under the palladium-catalysed conditions, as summarised in Table 5 (see also Scheme 10). The yields and enantioselectivities are lower for substrate **62** in comparison with the results obtained for the diphenyl substrate **18**.

We assume that the palladium-catalysed reaction may

Table 5 Enantioselectivities obtained with the substrate **62**

Ligand	Solvent	Pd:L	Yield (%)[a]	ee (%)
12	THF[b]	1:2	100	10
12	CH_2Cl_2[c]	1:2	0	—
24	THF	1:2	100	51
24	CH_2Cl_2	1:2	0	—
35	CH_2Cl_2	1:2	93	36
44	CH_2Cl_2	1:2	46	34
56	CH_2Cl_2	1:2	52	62

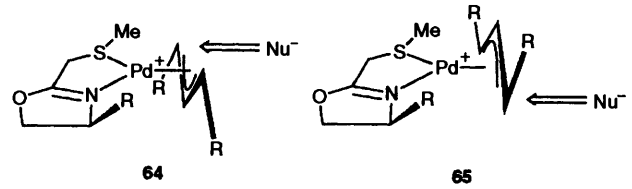
[a] Due to the volatility of the starting material and product, the yields are based on GC results (SGE BP1 capillary column). [b] $NaCH(CO_2Me)_2$ was used as the nucleophile in THF at reflux. [c] Bis(trimethylsilyl)-acetamide was used as the base.



61 **62** **63**

Scheme 10 *Reagents:* i, $[\{Pd(\eta^3\text{-}C_3H_5)Cl\}_2]$ (5 mol%), ligand (10 mol%)

proceed *via* one of two diastereoisomeric palladium–allyl complexes **64** and **65**. In order to rationalise the observed enantiomeric outcome, the reaction may occur selectively through complex **64** and the nucleophile approaches *cis* to the better π-acceptor. Alternatively, the reaction proceeds selectively through complex **65** and the nucleophile approaches



64 **65**

trans to the better π-acceptor. In the light of the preceding discussion, it seems more probable that the nucleophile will approach *trans* to the better π-acceptor. However, inspection of the two diastereoisomers suggests that complex **65** will be disfavoured due to the steric interaction between the 4-substituent of the 4,5-dihydrooxazole and the allyl moiety. Either the transition state is more distorted than represented here, or the two diastereoisomeric allyl complexes are in rapid equilibrium, and the reaction proceeds through the less favoured, but possibly more reactive, intermediate **65**.[17] For ligands **10–16**, it is possible that the thienyl group functions as a π-donor, and hence it might be expected that the reaction will proceed *via* attack *cis* to the sulfur, but such an argument is not possible for the sulfide ligands. Very recent crystallographic and NMR spectroscopic studies from the Helmchen group indicate that a complex similar to **65** is, in fact, the major species at equilibration and is also the more reactive of the two diastereoisomers.[18] However, it must be stressed that at this stage we have no evidence for the bidentate behaviour of sulfur-containing 4,5-dihydrooxazole ligands, and any analogies with the phosphorus analogues are only offered tentatively.

The stereochemical outcome of the reaction may be dependent upon the rate of equilibration between the assumed diastereoisomeric intermediates. Since acetate is known to equilibrate palladium allyl species,[19] we decided to examine the effect of adding acetate to the reaction. We chose to use the ligand **44** for this study, since the levels of enantioselectivity are moderate and, therefore, either enhancement or reduction of the enantioselectivity would be readily observed. In fact, a reduction of enantioselectivity was observed. In the presence of 1 equiv. of potassium acetate, the ee of the substitution product

19 dropped to 48% ee (whereas in the absence of added acetate 58% ee was achieved). The addition of 10 equiv. of potassium acetate or sodium acetate lowered the selectivity to 30 and 34% ee, respectively. Acetate ion is liberated during the course of the reaction, and it might be expected that the enantioselectivity of the reaction would decrease as the reaction progresses, and the acetate concentration increases. However, by removing aliquots as the reaction progressed, we observed essentially no variation in enantiomeric excess as a function of conversion.

In summary, we have shown that sulfur- and phosphorus-containing 4,5-dihydrooxazoles are effective ligands for palladium-catalysed allylic substitution. The ligands have been designed to rely upon an electronic disparity between the two donor atoms in the putative chelate structure and have been shown to provide good levels of enantioselectivity in the substitution products.

Experimental

Commercially available solvents and reagents were used throughout without further purification, except for those detailed below which were purified as described. Light petroleum refers to the fraction boiling in the range 40–60 °C, and was distilled through a 36-cm Vigreux column before use. Ether refers to diethyl ether and was dried by storage over sodium wire for several days. THF was distilled from sodium benzophenone ketyl under nitrogen, prior to use. Dichloromethane (DCM) was distilled from phosphorus pentoxide. DMF was dried by stirring it over calcium hydride for 15 h, after which it was decanted and distilled under reduced pressure before storage over 4 Å molecular sieves under nitrogen.

Analytical thin layer chromatography was carried out using aluminium backed plates coated with Merck Kieselgel 60 GF_{254}. Plates were visualised under UV light (at 254 and/or 360 nm) or by staining with phosphomolybdic acid reagent, followed by heating. Flash chromatography was carried out using Merck Kieselgel 60 H silica or Sorbsil C 60 silica gel. Pressure was applied at the column head with hand bellows. Samples were applied pre-adsorbed on silica or as a saturated solution in an appropriate solvent. IR spectra were recorded in the range 4000–600 cm^{-1} using a Nicolet FT-205 spectrometer, with internal calibration. Spectra were recorded as solutions in chloroform. Elemental analyses were carried out on a Perkin-Elmer 2400 Elemental Analyser. ^1H and ^{13}C NMR spectra were recorded using Bruker AC-250 and Bruker WH-400 (SERC NMR Spectroscopy Centre, Warwick) instruments. High and low resolution mass spectra were recorded on a Kratos MS80 instrument or on a VG Analytical ZAB-E instrument (SERC mass spectroscopy service Swansea). Optical rotations were measured using an Optical Activity AA 100 polarimeter and are given in 10^{-1} deg cm^2 g^{-1}. Melting points were measured on an Electrothermal digital melting point apparatus and are uncorrected.

The preparation of ligands **10–14**, **22–26**, **42–46** and **49–58** has been detailed elsewhere.[20] Preparation of **18** was based on a literature method.[21]

(4S,5S)-4,5-*Dihydro*-4-*hydroxymethyl*-5-*phenyl*-2-(2-*thienyl*)-1,3-*oxazole* **15**.—In a 50-cm^3 Schlenk flask, zinc chloride (68 mg, 0.5 mmol) was melted under high vacuum and cooled under nitrogen. After cooling to room temperature, chlorobenzene (30 cm^3) was added to it followed by thiophene-2-carbonitrile (1.1 g, 10 mmol) and (1*S*,2*S*)-(+)-2-amino-1-phenylpropane-1,3-diol (2.5 g, 15 mmol). The mixture was heated under reflux for 48 h. The solvent was removed under reduced pressure to give an oily residue, which was dissolved in dichloromethane (30 cm^3). The solution was extracted three times with water (20 cm^3) and the aqueous phase with dichloromethane (30 cm^3). The combined organic phases were dried (Na_2SO_4) and evaporated under reduced pressure to give a crude solid which was dissolved in ether and the solution cooled to −78 °C to give the *title compound* (65%) as a colourless crystalline solid, m.p. 160–162 °C (Found: C, 65.0; H, 5.0; N, 5.4. $C_{14}H_{13}NO_2S$ requires C, 64.9; H, 5.1; N, 5.4%); $[\alpha]_D^{25}$ +50.0 (*c* 1.02 in $CHCl_3$); ν_{max}/cm^{-1} 1670 (C=N); δ_H(400 MHz; $CDCl_3$) 3.75 (1 H, dd, *J* 3.2 and 11.9, C*H*H′–OH), 4.02 (1 H, br s, OH), 4.11 (1 H, dd, *J* 3.2 and 11.9, CH*H*′–OH), 4.21 (1 H, dt, *J* 3.2 and 8.1, CH–N), 5.60 (1 H, d, *J* 8.1, CH–O), 7.01 (1 H, m, thiophene HC=), 7.30–7.40 (5 H, m, arom. CH) and 7.42–7.57 (1 H, m, thiophene HC=); δ_C(100 MHz; $CDCl_3$) 62.9 (CH_2–OH), 76.7 (CH–N), 83.0 (CH–O), 125.8–130.9 (arom. C–H), 129.4–139.2 (arom. =C) and 160.4 (C=N); *m*/*z* (EI) 260 (MH^+, 100%), 230 (27) and 111 (9).

(4S,5S)-4,5-*Dihydro*-5-*phenyl*-2-(2-*thienyl*)-4-*triphenylmethoxymethyl*-1,3-*oxazole* **16**.—To a stirred mixture of (4*S*,5*S*)-4,5-dihydro-4-hydroxymethyl-5-phenyl-2-(2-thienyl)-1,3-oxazole **15** (0.50 g, 1.9 mmol), triethylamine (0.59 g, 5.7 mmol) and 4-dimethylaminopyridine (DMAP) (1–2 crystals) in dichloromethane (20 cm^3) at room temperature was added trityl chloride (0.58 g, 2.0 mmol). The mixture was stirred overnight (12 h), when TLC (light petroleum–ether 3:1) indicated that the starting material had been consumed. The mixture was extracted with dichloromethane (30 cm^3) and the organic extract washed with water (30 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by flash chromatography (light petroleum–ether 3:1) to afford the *title compound* (67%) as a colourless crystalline solid, m.p. 126–127 °C (Found: C, 79.5; H, 5.7; N, 2.8. $C_{33}H_{27}NO_2S$ requires C, 79.1; H, 5.4; N, 2.8%); $[\alpha]_D^{25}$ +35.7 (*c* 0.98 in $CHCl_3$); ν_{max}/cm^{-1} 1643 (C=N); δ_H(250 MHz; $CDCl_3$) 3.29 (1 H, dd, *J* 7.3 and 9.2, C*H*H′–OTr),* 3.55 (1 H, dd, *J* 3.9 and 9.2, CH*H*′–OTr), 4.37 (1 H, m, CH–N), 5.46 (1 H, d, *J* 6.3, CH–O) and 7.09–7.67 (23 H, m, arom. CH); δ_C(63 MHz; $CDCl_3$) 65.7 (*C*H_2–OTr), 75.2 (CH–N), 84.9 (CH–O), 86.8 (*C*Ph_3), 125.9–130.6 (arom. CH), 140.8 and 143.8 (arom. =C) and 159.9 (C=N); *m*/*z* (EI) 501 (M^+, 5%), 320 (10), 244 (32), 228 (100), 165 (56) and 111 (25).

General Procedure for Preparation of 4-*Substituted* (4S)-4,5-*Dihydro*-2-*phenylsulfanylmethyl*-1,3-*oxazoles*.—In a 50-cm^3 Schlenk flask, zinc chloride (68 mg, 0.5 mmol) was melted under high vacuum and cooled under nitrogen to room temperature. Chlorobenzene (30 cm^3) was then added to it followed by (phenylsulfanyl)acetonitrile (10 mmol) and the amino alcohol (15 mmol). The mixture was heated under reflux for 48 h after which it was evaporated under reduced pressure to give an oily residue, which was dissolved in dichloromethane (30 cm^3). The solution was extracted with water (3 × 20 cm^3) and the aqueous phase with dichloromethane (30 cm^3). The combined organic phases were dried (Na_2SO_4) and then evaporated under reduced pressure to give a residue which was purified by flash chromatography (light petroleum–ether, 3:1) to afford the product.

(4S)-4,5-*Dihydro*-4-*isopropyl*-2-*phenylsulfanylmethyl*-1,3-*oxazole* **27**. (Found: M^+, 235.1026. $C_{13}H_{17}NOS$ requires *M*, 235.1038), $[\alpha]_D^{25}$ −14.3 (*c* 0.7 in $CHCl_3$); ν_{max}/cm^{-1} 1662 (C=N); δ_H(250 MHz; $CDCl_3$) 0.78 (3 H, d, *J* 6.8, CH_3), 0.86 (3 H, d, *J* 6.8, CH_3), 1.66 [1 H, m, $(CH_3)_2CH$], 3.70 (1 H, d, *J* 9.1, SC*H*H), 3.74 (1 H, d, *J* 9.1, SCH*H*), 3.87 (1 H, m, CHN), 3.93 (1 H, t, *J* 8.1, C*H*HO), 4.23 (1 H, dd, *J* 8.1 and 9.2, C*H*HO) and 7.20–7.46 (5 H, m, arom. CH); δ_C(63 MHz; $CDCl_3$) 17.8 (CH_3), 18.5 (CH_3), 30.8 (SCH_2), 32.3 (CH), 70.6 (CH_2), 72.1 (CH), 126.7, 127.9, 128.8, 129.2, 129.4 and 129.9 (arom. C) and 164.1 (C=N).

* Tr = trityl.

(4S)-4,5-*Dihydro*-4-tert-*butyl*-2-*phenylsulfanylmethyl*-1,3-*oxazole* **28**. (Found: M^+, 249.1195. $C_{14}H_{19}NOS$ requires *M*, 249.1187) $[\alpha]_D^{25}$ −17.7 (*c* 0.58 in $CHCl_3$); ν_{max}/cm^{-1} 1665 (C=N); δ_H(250 MHz; $CDCl_3$) 0.89 [9 H, s, $(CH_3)_3$], 3.72 (1 H, d, *J* 13.8, SC*H*H), 3.76 (1 H, d, *J* 13.8, SCH*H*), 3.81 (1 H, t, *J* 8.8, C*H*HO or CHN), 4.04 (1 H, t, *J* 8.1, C*H*HO or CHN), 4.07 (1 H, t, *J* 9.3, C*H*HO or CHN) and 7.23–7.48 (5 H, m, arom. CH); δ_C(63 MHz; $CDCl_3$) 25.7 (CH_3), 30.8 (CH_2), 35.5 [*C*$(CH_3)_3$], 69.2 (CH_2), 76.0 (CH), 126.7, 127.1, 127.3, 128.9, 129.8 and 129.9 (arom. C) and 164.2 (C=N).

(R)-2-*Amino*-3-(*methylsulfanyl*)*propan*-1-*ol* **31**.—*S*-Methyl-L-cysteine **29** (1.96 g, 14.5 mmol) was added slowly to $LiAlH_4$ (1.8 g, 48 mmol) in THF (30 cm^3) and the resultant mixture was refluxed gently overnight under nitrogen. The reaction was quenched by the careful addition to the mixture of water (2 cm^3), 15% aqueous NaOH (2 cm^3) and water (6 cm^3) with stirring until the grey salts had decomposed to form a white precipitate. The solids were filtered off and washed with ether. The organic fractions were dried ($MgSO_4$) and evaporated to dryness to yield a yellow oil which was distilled (Kugelrohr, air bath 120 °C at 7 mmHg) to afford a colourless oil (686 mg, 40%).[22] δ_H(250 MHz; $CDCl_3$) 2.11 (3 H, s, SCH_3), 2.26 (3 H, br s, OH and NH_2), 2.42 (1 H, m, C*H*$_2$SCH$_3$), 2.62 (1 H, m, C*H*$_2$SCH$_3$), 3.02 (1 H, m, *H*CNH$_2$), 3.42 (1 H, m, C*H*$_2$OH) and 3.64 (1 H, m, *H*$_2$COH); ν_{max}/cm^{-1} (neat) 3350–3150 (OH and NH_2), 1600 (NH), 1400 (OH) and 1050 (C–O).

(S)-2-*Amino*-4-(*methylsulfanyl*)*butan*-1-*ol* **32**.—L-Methionine **30** (2.98 g, 20 mmol) was added slowly to $LiAlH_4$ (2.4 g, 64 mmol) in THF (30 cm^3) and the resultant mixture was refluxed gently overnight, under nitrogen. The reaction was quenched by the careful addition to the mixture of water (2.5 cm^3), 15% aqueous NaOH (2.5 cm^3) and water (7.5 cm^3) with stirring until the grey salts had decomposed to form a white precipitate. The solids were filtered off and washed with ether. The organic fractions were dried ($MgSO_4$) and evaporated to dryness to yield a yellow oil which was distilled (Kugelrohr, air bath 120 °C at 7 mmHg) to afford a colourless oil (2.25 g, 78%);[22] δ_H(250 MHz; $CDCl_3$) 1.58 (1 H, m, SCH_2), 1.62–1.82 (4 H, m, OH, NH_2 and SCH_2), 2.12 (3 H, s, SCH_3), 2.60 (2 H, m, C*H*$_2$CHN), 3.00 (1 H, m, *H*CNH$_2$), 3.25 (1 H, m, C*H*$_2$OH) and 3.61 (1 H, m, C*H*$_2$OH); ν_{max}/cm^{-1} (neat) 3350–3150 (OH and NH_2), 1600 (NH), 1400 (OH) and 1050 (C–O).

(4R)-4,5-*Dihydro*-4-(*methylsulfanyl*)*methyl*-2-*phenyl*-1,3-*oxazole* **34**.—(*R*)-2-Amino-3-(methylsulfanyl)propan-1-ol **31** (700 mg, 6.3 mmol) in dry CH_2Cl_2 (5 cm^3) was added to a mixture of DMAP (3 mg) and methyl benzimidate hydrochloride (1.19 g, 6.92 mmol) and stirred at room temperature for 48 h before being refluxed for 7 h. The reaction mixture was washed with water and the aqueous layer extracted with DCM (3 × 50 cm^3). The combined extracts were dried ($MgSO_4$) and evaporated to dryness to yield a yellow oil. This was purified by flash chromatography with ether as the eluent to afford the *title compound* (430 mg, 48%) as a pale yellow oil. (Found: M^+, 207.0729. $C_{11}H_{13}NOS$ requires *M*, 207.0718; $[\alpha]_D^{25}$ −11.11 (*c* 1.35 in $CHCl_3$); ν_{max}/cm^{-1} (neat) 1650 (C=N), 1275 (SMe) and 1050 (C–O); *m*/*z* 207 (M^+); δ_H(250 MHz; $CDCl_3$) 2.19 (3 H, s, SCH_3), 2.63–2.97 (2 H, m, CH_2S), 4.30 (2 H, m, CH_2O), 4.55 (1 H, m, CHN) and 7.37–7.96 (5 H, m, arom. CH); δ_C(63 MHz; $CDCl_3$) 16.1 (SCH_3), 39.3 (*C*H_2SMe), 66.4 (CHN), 72.0 (CH_2O), 127.5–131.5 (arom. CH) and 165 (C=N).

(4S)-4,5-*Dihydro*-4-[2-(*methylsulfanyl*)*ethyl*]-2-*phenyl*-1,3-*oxazole* **35**.—(*S*)-2-Amino-4-(methylsulfanyl)butan-1-ol **32** (410 mg, 3 mmol) in dry CH_2Cl_2 (5 cm^3) was added to a mixture of DMAP (3 mg) and methyl benzimidate hydrochloride (0.58 g, 3.38 mmol) and stirred at room temperature for 24 h before being refluxed for 14 h. The reaction mixture was washed with water and the aqueous layer extracted with DCM (3 × 50 cm^3). The combined extracts were dried ($MgSO_4$) and evaporated to dryness to yield a yellow oil. The crude product was purified by flash chromatography with light petroleum–ether (1:1) as the eluent to afford the title compound (525 mg, 70%)[14] as a colourless oil; ν_{max}/cm^{-1} (neat) 1650 (C=N), 1275 (SMe) and 1050 (C–O); *m*/*z* 221 (M^+); δ_H(250 MHz; $CDCl_3$) 1.98 (2 H, m, C*H*$_2$CHN), 2.14 (3 H, s, SCH_3), 2.67 (2 H, m, CH_2S), 4.06 (1 H, m, CHN), 4.49 (2 H, m, CH_2O) and 7.37–7.47 (5 H, m, arom. CH); δ_C(63 MHz; $CDCl_3$) 15.4 (SCH_3), 30.7 (CH_2SMe), 35.4 (*C*H_2CHN), 65.7 (CHN), 72.3 (CH_2O), 128.2–131.2 (arom. C) and 163 (C=N).

2-(*Phenylsulfanyl*)*benzonitrile* **41**.—To a stirred mixture of sodium hydride (9 mmol) in THF (5 cm^3) was added a solution of benzenethiol (9 mmol) in THF (2 cm^3). To the resulting white precipitate was added a solution of 2-fluorobenzonitrile (8 mmol) in THF (2 cm^3). The mixture was stirred under reflux for 48 h during which time the solution became clear. The reaction mixture was poured into dichloromethane (20 cm^3) and washed with 15% aqueous NaOH (20 cm^3) then water (20 cm^3). The aqueous layers were extracted with dichloromethane (2 × 50 cm^3) and the combined extracts were dried (Na_2SO_4) and then concentrated under reduced pressure. The crude product was purified by flash chromatography (light petroleum–ether 3:1) to afford the title compound (93%) as a colourless crystalline solid, m.p. 35–37 °C (lit.,[23] 39–40 °C); ν_{max}/cm^{-1} 2220 (CN); *m*/*z* (EI) 211 (M^+, 100%), 109 (60) and 51 (42).

General Procedure for Preparation of 4-*Substituted* (4S)-4,5-*Dihydro*-2-[2-(*phenylsulfanyl*)*phenyl*]-1,3-*oxazoles*.—In a 50-cm^3 Schlenk flask, zinc chloride (68 mg, 0.5 mmol) was melted under high vacuum and cooled under nitrogen to room temperature. Chlorobenzene (30 cm^3) was then added to it followed by 2-(phenylsulfanyl)benzonitrile **41** (10 mmol) and the amino alcohol (15 mmol). The mixture was heated under reflux for 48 h. The solvent was removed under reduced pressure to give an oily residue, which was dissolved in dichloromethane (30 cm^3). The solution was extracted with water (3 × 20 cm^3) and the aqueous phase with dichloromethane (30 cm^3). The combined organic extracts were dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by flash chromatography (light petroleum–ether 3:1) to afford the product.

(4S)-4,5-*Dihydro*-4-*isopropyl*-2-[2-(*phenylsulfanyl*)*phenyl*]-1,3-*oxazole* **47**. A colourless oil (73%) (Found: M^+, 297.1187. $C_{18}H_{19}NOS$ requires *M*, 297.1187); $[\alpha]_D^{25}$ −42.5 (*c* 0.4 in $CHCl_3$); ν_{max}/cm^{-1} 1650 (C=N); δ_H(250 MHz; $CDCl_3$) 0.99 (3 H, d, *J* 6.7, C*H*$_3$–CH), 1.10 (3 H, d, *J* 6.7, C*H*$_3$–CH), 1.85 [1 H, m, C*H*$(CH_3)_2$], 4.17 (2 H, m, C*H*–N, C*H*H′–O), 4.43 (1 H, dd, *J* 8.7 and 7.1, CH*H*′–O) and 6.87–7.64 (9 H, m, arom. CH); δ_C(63 MHz; $CDCl_3$) 18.4 (*C*H_3–CH), 18.9 (*C*H_3–CH), 33.0 [*C*H$(CH_3)_2$], 69.8 (CH_2–O), 73.4 (CH–N), 124.4, 126.4, 127.6, 128.6, 128.8, 129.9, 132.9, 133.6 and 134.9 (arom. C–H), 125.0, 141.0 and 142.9 (arom. =C) and 162.2 (C=N); *m*/*z* (EI) 297 (M^+, 92%), 254 (100), 220 (53), 197 (100) and 137 (29).

(4S)-4-tert-*Butyl*-4,5-*Dihydro*-2-[2-(*phenylsulfanyl*)*phenyl*]-1,3-*oxazole* **48**. A colourless oil (62%) (Found: M^+, 311.1344. $C_{19}H_{21}NOS$ requires *M*, 311.1344); $[\alpha]_D^{25}$ −37.5 (*c* 0.24 in $CHCl_3$); ν_{max}/cm^{-1} 1644 (C=N); δ_H(250 MHz; $CDCl_3$) 1.03 [9 H, s, C$(CH_3)_3$], 4.27 (3 H, m, C*H*–N, C*H*$_2$–O) and 6.83–7.81 (9 H, m, arom. CH); δ_C(63 MHz; $CDCl_3$) 25.9 (CH_3 × 3), 34.0 [*C*$(CH_3)_3$], 68.2 (CH_2–O), 77.4 (CH–N), 124.3, 126.4, 127.5, 128.6, 129.5, 129.7, 129.8, 130.5 and 135.1 (arom. C–H), 125.0, 130.0 and 141.0 (arom. =C) and 162.4 (C=N); *m*/*z* (EI) 311 (M^+, 41%), 254 (100), 197 (32), 151 (26) and 109 (19).

General Procedure for Palladium-catalysed Allylic Alkylation with Dimethyl Sodiomalonate as Nucleophile.—To [{Pd(η^3-C_3H_5)Cl}$_2$] (4 mg, 2.5 mol%) was added a solution of the ligand (10 mol%) in dry THF (1 cm^3) and *rac*-(*E*)-1,3-diphenylprop-2-enyl acetate **18** (0.4 mmol). The solution was stirred for 15 min at room temperature after which the resulting yellow solution was treated with dimethyl sodiomalonate (0.4 mmol) in dry THF (2 cm^3). The reaction mixture was stirred at room temperature for 12–96 h, until conversion was complete as shown by TLC analysis [light petroleum–ether 3:1 R_f (starting material) = 0.42, R_f (product) = 0.30]. The reaction mixture was diluted with ether (25 cm^3), transferred to a separatory funnel and washed twice with ice-cold saturated aqueous ammonium chloride. The organic phase was dried ($MgSO_4$) and then concentrated under reduced pressure. The residue was purified by flash chromatography (light petroleum–ether, 3:1) to afford **19**.

General Procedure for Palladium-catalysed Allylic Alkylation using BSA Procedure.—To [{Pd(η_3-C_3H_5)Cl}$_2$] (4 mg, 2.5 mol%) was added a solution of the ligand (10 mol%) in dry DCM (1 cm^3). The solution was stirred for 15 min at room temperature after which the resulting yellow solution was treated successively with a solution of *rac*-(*E*)-1,3-diphenylprop-2-enyl acetate **18** (0.4 mmol) in DCM (1 cm^3), dimethyl malonate (1.2 mmol), *N*,*O*-bis(trimethylsilyl)acetamide (1.2 mmol), and anhydrous potassium acetate (3 mol%). The reaction mixture was stirred at room temperature for 12–96 h, until conversion was complete according to TLC analysis. The reaction mixture was diluted with ether (25 cm^3), transferred to a separatory funnel and washed twice with ice-cold saturated aqueous ammonium chloride. The organic phase was dried ($MgSO_4$) and then concentrated under reduced pressure. The residue was purified by flash chromatography (light petroleum–ether 3:1) to afford **19**.

Dimethyl 1,3-diphenylprop-2-enylmalonate **19**. ν_{max}/cm^{-1} 1765s, 1740s, 1605w, 1500m, 1460m, 1440s, 1325m and 1265s; δ_H(250 MHz; $CDCl_3$) 3.53 (3 H, s, CO_2CH_3), 3.70 (3 H, s, CO_2CH_3), 3.95 (1 H, d, *J* 11, C*H*E$_2$),* 4.27 (1 H, dd, *J* 11 and 8, PhC*H*CE$_2$), 6.32 (1 H, dd, *J* 15 and 8, *H*C=CHPh), 6.48 (1 H, d, *J* 15, HC=C*H*Ph) and 7.15–7.44 (10 H, m, arom. CH); δ_C(63 MHz; $CDCl_3$) 49.1 (CH), 52.4 and 52.6 (CH_3), 57.6 (CH), 126.3, 127.1, 127.5, 127.8, 128.4, 128.7, 129.1 and 131.8 (HC= alkene and arom.), 136.8 and 140.1 (arom. C) and 167.7 and 168.1 (C=O).

General Procedure for Palladium-catalysed Allylic Alkylation with Bis(phenylsulfonyl)methane as Nucleophile.—*rac*-(*E*)-1,3-Diphenylprop-2-enyl acetate **18** (700 mg, 2.8 mmol), bis(phenylsulfonyl)methane (828 mg, 2.8 mmol), [{Pd(η^3-C_3H_5)Cl}$_2$] (2 mol% in Pd), ligand (4 mol%) and *N*,*O*-bis(trimethylsilyl)acetamide (5.6 mmol, 1.13 g) were mixed together in THF (10 cm^3) and a catalytic amount of potassium acetate (10 mg) was added to the mixture. After the reaction mixture had been heated at reflux for 24–48 h it was allowed to cool to room temperature. The contents of the flask were diluted with dichloromethane and then washed with saturated aqueous ammonium chloride (50 cm^3), saturated brine (2 × 50 cm^3) and water (50 cm^3). The combined extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure. Column chromatography (dichloromethane) of the residue afforded a colourless solid (1.23 g, 2.5 mmol, 89%), m.p. 163–164 °C (Found: M$^+$, 488.1159. $C_{28}H_{24}S_2O_4$ requires *M*, 488.1159); ν_{max}/cm^{-1} 1331.5 and 1150.2; δ_H(250 MHz; $CDCl_3$) 4.71 (1 H, dd, *J* 2.5 and 9.2, CH=CH–C*H*), 5.10 [1 H, d, *J* 2.5, C*H*(SO$_2$Ph)$_2$], 6.25 (1 H, d, *J* 15.7, C*H*=CH–CH), 6.85 (1 H, dd, *J* 9.2 and 15.7, CH=C*H*–CH), 7.23–7.66 (18 H, m, arom. CH) and 8.04 (m, 2 H, arom. CH); δ_C(63 MHz; $CDCl_3$) 47.5, 89.0, 124.1, 126.5, 127.2, 127.7, 128.1, 128.3, 128.6, 128.8, 128.9, 130.1, 133.9, 134.5, 134.8, 136.5, 137.8, 140.5 and 140.6.

Alternative procedure. rac-(*E*)-1,3-Diphenylprop-2-enyl acetate **18** (700 mg, 2.8 mmol), [{Pd(η^3-C_3H_5)PdCl}$_2$] (2 mol% in Pd) and ligand (4 mol%) were mixed in DMF (2 cm^3) and stirred for 15 min. A solution of the sodium salt of bis(phenylsulfonyl)methane (2.9 mmol in DMF; 0.36 mol dm^{-3}) was added to the mixture which was then treated as above.

Procedure for Palladium-catalysed Allylic Alkylation of (E)-*Pent-3-en-2-yl Acetate* **62**.—The reaction was performed under an inert atmosphere. To the reaction flask was added [{Pd(η^3-C_3H_5)Cl}$_2$] (4 mg, 0.01 mmol) and ligand (10 mol%) in dichloromethane (2 cm^3) and the mixture was stirred for 10 min. The acetate **62** (51 mg, 0.4 mmol) in dichloromethane (2 cm^3) was then added to the mixture and stirring was continued for a further 20 min before addition of dimethyl malonate (160 mg, 1.2 mmol) and *N*,*O*-bis(trimethylsilyl)acetamide (245 mg, 1.2 mmol) in dichloromethane (1 cm^3) and a catalytic amount of sodium acetate (3 mol%). Stirring was continued until all the starting material had been consumed as shown by TLC (silica/light petroleum–ether 3:1). The reaction mixture was diluted with ether (10 cm^3) and washed with saturated aqueous ammonium chloride (10 cm^3). The separated organic layer was dried ($MgSO_4$) and concentrated to provide a yellow oil which was purified by column chromatography to yield **63** as a colourless oil; δ_H(250 MHz; $CDCl_3$) 1.28 (3 H, d, *J* 6.2, CH_3), 1.68 (3 H, d, *J* 6.8, CH_3), 2.03 (3 H, s, OCH_3), 5.27–5.32 (1 H, m, CH), 5.43–5.53 (1 H, m, CH) and 5.65–5.76 (1 H, m, CH).

Determination of Enantiomeric Excess.—The enantiomeric excess was determined by ^{1}H NMR spectroscopy [250 MHz, $CDCl_3$, 0.8 equiv. of Eu(hfbc)$_3$]. For one of the two CO_2Me-singlets (the one at lower field) a splitting was observed.[24]

* E = CO_2Me.

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