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Chiral P,Olefin Ligands with Rotamers for Palladium-Catalyzed Asymmetric Allylic Substitution Reactions

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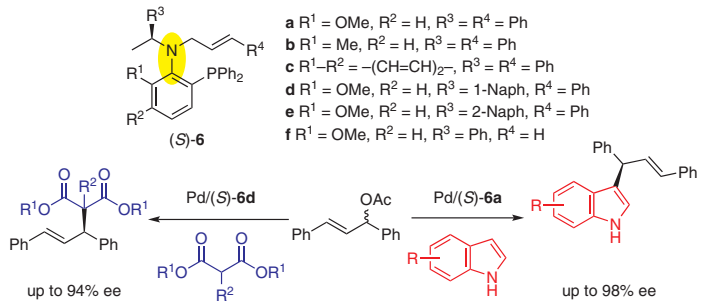

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Abstract We synthesized a series of phosphine–olefin-type chiral aminophosphines, and we confirmed that these each exists as two rotamers at the C(aryl)–N(amine) bond. We also investigated the ability of these aminophosphines to act as chiral ligands for Pd-catalyzed asymmetric allylic substitution reactions, such as the alkylation of allylic acetates with malonates or indoles, and we found they gave high enantioselectivities (up to 98% ee).

Key words phosphines, ligands, rotamers, asymmetric catalysis, palladium catalysis, allylic acetates

Chiral ligands are important molecules that effect asymmetric inductions in various transition-metal-catalyzed reactions such as Pd-catalyzed asymmetric allylic substitution reactions.[1] Phosphine–olefin-type chiral ligands have been developed and successfully used for transition-metal-catalyzed asymmetric reactions.[2,3] We recently reported the synthesis of phosphine–olefin-type chiral ligands (a*R*)-**1** and (a*R*)-**2** with C(aryl)–N(amine) bond axial chirality (Figure 1).[4,5] In these ligands, one substituent of the nitrogen atom at the axially chiral C(aryl)–N(amine) bond was a bulky alkyl group, such as a 1- or 2-adamantyl group. We also synthesized the aminophosphine **3**, which has a less-hindered substituent, in this case a cyclohexyl group; this compound did not display axial chirality of the C(aryl)–N(amine) bond.[5] We also reported that analogues of aminophosphine (a*R*)-**1c** without an internal olefin group, such as the aminophosphine (a*R*)-**4**, were ineffective as chiral ligands in a Pd-catalyzed asymmetric allylic substitution reaction.[4a]

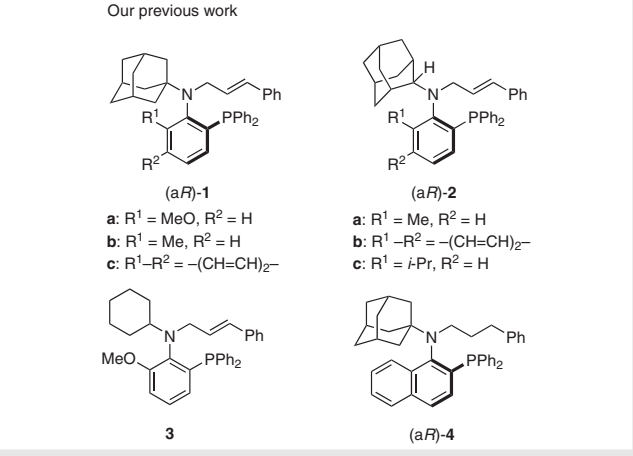

Figure 1 Axially chiral-type P,olefin ligands **1** and **2**, achiral-type P,olefin ligand **3**, and axially chiral-type P,N ligand **4**

Miyano's group reported the synthesis of such P,N ligands as the aminophosphine (*S*)-**5**, obtained from *N*-methyl-[(1*S*)-1-phenylethyl]amine (Figure 2). They also reported that a ^{1}H NMR analysis of (*S*)-**5** showed the existence of two conformational isomers, both of which were inseparable atropisomers as rotamers at the C(aryl)–N(amine) bond. However, (*S*)-**5** was not an effective chiral ligand for Pd-catalyzed asymmetric allylic substitution.[6]

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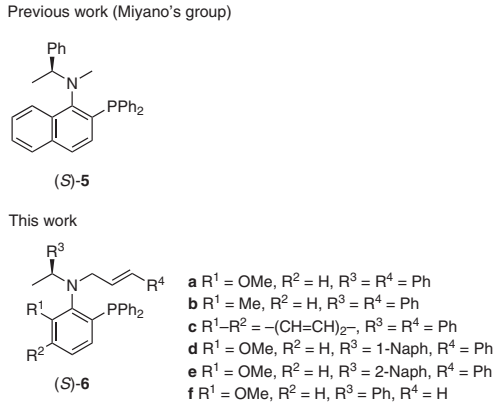
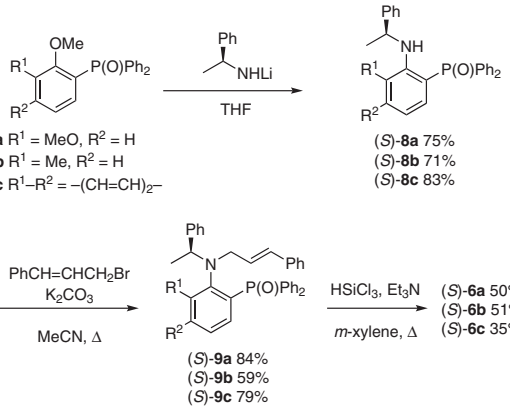


Figure 2 Chiral P,N ligand **5** and chiral P,olefin ligands **6**

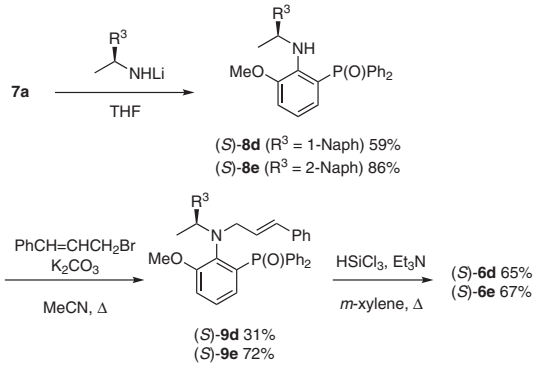
For our investigations into phosphine–olefin-type chiral ligands with axial chirality, we were interested in phosphine–olefin-type ligands that exist as two rotamers. Here, we report the synthesis of phosphine–olefin-type chiral aminophosphines (*S*)-**6** from [(1*S*)-1-phenylethyl]amine or its derivatives. We also report the application of these products as chiral ligands for Pd-catalyzed asymmetric allylic substitution reactions with high enantioselectivities (up to 98% ee).

Chiral aminophosphines (*S*)-**6a–c** were prepared in three steps from the corresponding phosphine oxides **7**[7,8] through an S_NAr reaction with the nucleophilic lithium amide from [(1*S*)-1-phenylethyl]amine followed by N-alkylation with cinnamyl bromide and reduction of the resulting phosphine oxides **9a–c** with trichlorosilane–triethylamine (Scheme 1).



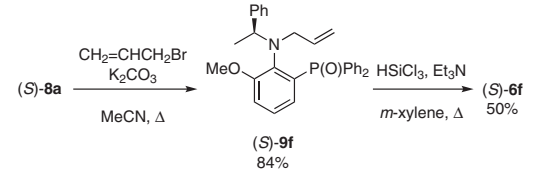
Scheme 1 Preparation of aminophosphines (*S*)-**6a–c**

We similarly prepared the chiral aminophosphines (*S*)-**6d** and (*S*)-**6e** from phosphine oxide **7a** by using [(1*S*)-1-(1-naphthyl)ethyl]amine or [(1*S*)-1-(2-naphthyl)ethyl]amine, respectively, instead of [(1*S*)-1-phenylethyl]amine (Scheme 2).[9]



Scheme 2 Preparation of aminophosphines (*S*)-**6d** and (*S*)-**6e**

Chiral aminophosphine (*S*)-**6f** was prepared from phosphine oxide (*S*)-**8a** through N-alkylation with allyl bromide and reduction of the resulting phosphine oxide (*S*)-**9f** (Scheme 3). We confirmed that aminophosphines (*S*)-**6a–f** each exist as two rotamers (ratio: 60:1 to 2:1) by ^{31}P and/or ^{1}H NMR analysis in $CDCl_3$.



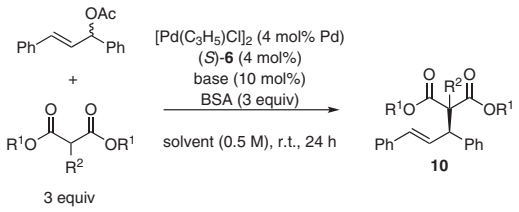
Scheme 3 Preparation of aminophosphines (*S*)-**6f**

We investigated the ability of aminophosphines (*S*)-**6** to act as chiral ligands for such Pd-catalyzed asymmetric allylic substitution reactions as the alkylation of allylic acetates with malonates.[10] The reaction of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate was performed as a model reaction (Table 1). The reaction with 2 mol% of $[Pd(C_3H_5)Cl]_2$ and 4 mol% of (*S*)-**6a** as a catalyst (Pd/ligand = 1:1) and 10 mol% of NaOAc as a base in toluene containing 3.0 equivalents of *N*,*O*-bis(trimethylsilyl)acetamide (BSA) at room temperature for 24 hours gave the corresponding product (*S*)-**10a** in 85% yield and 84% ee (Table 1, entry 1). We also tested (*S*)-**6b–f** as chiral ligands in this reaction, and we found that (*S*)-**6d** was the most effective ligand with a high enantioselectivity (93% ee; entry 4). We then examined the effect of changing the base in the reaction with (*S*)-**6d** in toluene (entries 4, 7, and 8). When LiOAc or KOAc was used as the base, the enantioselectivity decreased to 76 and 91% ee, respectively. We next investigated the effects of various solvents (entries 4 and 9–12). When THF was used as the solvent, the enantioselectivity of the product decreased dramatically to 58% ee (entry 9), but when the reaction was carried out in dichloromethane or acetonitrile, the enantioselectivity of the product decreased slightly (entries 10 and 11). When the reaction was carried out in (trifluoromethyl)benzene, the enantioselectivity increased to 94% ee

(entry 12). By using the optimized conditions (entry 12), we then examined the scope of the allylic alkylation of various malonates with allylic esters in the presence of (*S*)-**6d** and NaOAc in (trifluoromethyl)benzene at room temperature for 24 hours.[11] The reaction of 1,3-diphenylprop-2-enyl acetate with diethyl malonate instead of dimethyl malonate gave the corresponding product (*S*)-**10b** in 81% ee (entry 13). On using di-*tert*-butyl malonate, the enantioselectivity of the product decreased dramatically to 59% ee (entry 14). On the other hand, the reactions of dibenzyl malonate and diethyl methylmalonate gave the corresponding products (*S*)-**10d** and (*R*)-**10e** with 79 and 76% ee, respectively (entries 15 and 16). When the reaction was carried out with 1,3-di(4-chlorophenyl)prop-2-enyl acetate instead of 1,3-diphenylprop-2-enyl acetate, the corresponding product (*S*)-**10f** was obtained at a similar level of enantioselectivity (93% ee; entry 17). On the other hand, with 1,3-diphenylprop-2-enyl pivalate instead of the acetate, the enantioselectivity of product **10a** decreased to 81% ee (entry 18).

Next, we investigated the ability of aminophosphines (*S*)-**6** to act as chiral ligands for the Pd-catalyzed asymmetric allylic substitution reaction of indoles.[12] The reaction of 1,3-diphenylprop-2-enyl acetate with indole was performed in the presence of 3 mol% of $[Pd(C_3H_5)Cl]_2$ and 6 mol% of ligand (Pd/ligand = 1:1) as a model reaction (Table 2). The reaction with (*S*)-**6a** as a ligand and two equivalents of K_2CO_3 as a base in acetonitrile at 40 °C for 18 hours gave the corresponding product (*R*)-**11a** in 66% yield with good enantioselectivity (95% ee) (Table 2, entry 1). We tested the other aminophosphines (*S*)-**6b–f** in this reaction and found that aminophosphine (*S*)-**6a** was the most effective ligand

Table 1 Palladium-Catalyzed Asymmetric Allylic Substitution Reactions in the Presence of (*S*)-**6**[a]

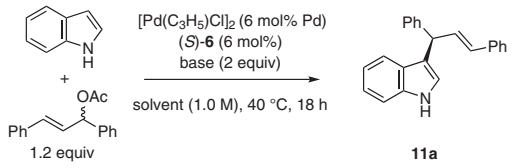


Entry	Ligand	R^1	R^2	Solvent	Base	Product	Yield[b] (%)	ee[c] (%)
1	(*S*)-**6a**	Me	H	PhMe	NaOAc	**10a**	85	84
2	(*S*)-**6b**	Me	H	PhMe	NaOAc	**10a**	73	51
3	(*S*)-**6c**	Me	H	PhMe	NaOAc	**10a**	62	28
4	(*S*)-**6d**	Me	H	PhMe	NaOAc	**10a**	87	93
5	(*S*)-**6e**	Me	H	PhMe	NaOAc	**10a**	76	88
6	(*S*)-**6f**	Me	H	PhMe	NaOAc	**10a**	90	83
7	(*S*)-**6d**	Me	H	PhMe	LiOAc	**10a**	92	76
8	(*S*)-**6d**	Me	H	PhMe	KOAc	**10a**	85	91
9	(*S*)-**6d**	Me	H	THF	NaOAc	**10a**	80	58
10	(*S*)-**6d**	Me	H	CH_2Cl_2	NaOAc	**10a**	76	84
11	(*S*)-**6d**	Me	H	MeCN	NaOAc	**10a**	90	88
12	(*S*)-**6d**	Me	H	$PhCF_3$	NaOAc	**10a**	86	94
13	(*S*)-**6d**	Et	H	$PhCF_3$	NaOAc	**10b**	63	81
14	(*S*)-**6d**	*t*-Bu	H	$PhCF_3$	NaOAc	**10c**	61	59
15	(*S*)-**6d**	Bn	H	$PhCF_3$	NaOAc	**10d**	78	79
16	(*S*)-**6d**	Et	Me	$PhCF_3$	NaOAc	**10e**	52	76
17[d]	(*S*)-**6d**	Me	H	$PhCF_3$	NaOAc	**10f**	83	93
18[e]	(*S*)-**6d**	Me	H	$PhCF_3$	NaOAc	**10a**	84	81

[a] The reactions were carried out on 0.2 mmol scale of the allyl ester in various solvents (0.4 mL) at r.t. with 3.0 equiv of malonate and BSA in the presence of base (10 mol%), (*S*)-**6** (4 mol%) and $[Pd(C_3H_5)Cl]_2$ (2 mol%; 4 mol% Pd).
[b] Isolated yield.
[c] Determined by HPLC analysis on a chiral column.
[d] This reaction was carried out using 1,3-di(4-chlorophenyl)prop-2-enyl acetate instead of 1,3-diphenylprop-2-enyl acetate.
[e] This reaction was carried out using 1,3-diphenyl-2-propenyl pivalate instead of 1,3-diphenyl-2-propenyl acetate.

(entry 1). We next investigated the effects of various solvents with K_2CO_3 (entries 1 and 7–10). The use of THF, dichloromethane, or (trifluoromethyl)benzene as a solvent instead of acetonitrile gave (*R*)-**11a** with a similar level of enantioselectivity (entries 7–9). When the reaction was carried out in toluene, the enantioselectivity of (*R*)-**11a** rose to 97% ee (entry 10). We also changed the base for the reaction in toluene (entries 10–13). On using Na_2CO_3 and Cs_2CO_3 as a base, the enantioselectivity of (*R*)-**11a** decreased (entries 11 and 12). When the reaction was carried out with KOAc instead of K_2CO_3, the product (*R*)-**11a** was obtained at a similar level of enantioselectivity (97% ee) and in a good yield (74%) (entry 17).

Table 2 Optimization of the Palladium-Catalyzed Asymmetric Allylic Substitution Reaction of Indole in the Presence of (*S*)-**6**[a]

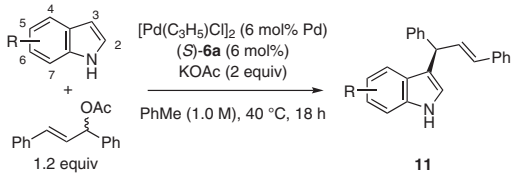


Entry	Ligand	Base	Solvent	Yield[b] (%)	ee[c] (%)
1	(*S*)-**6a**	K_2CO_3	MeCN	66	95
2	(*S*)-**6b**	K_2CO_3	MeCN	72	84
3	(*S*)-**6c**	K_2CO_3	MeCN	73	85
4	(*S*)-**6d**	K_2CO_3	MeCN	76	87
5	(*S*)-**6e**	K_2CO_3	MeCN	79	89
6	(*S*)-**6f**	K_2CO_3	MeCN	52	73
7	(*S*)-**6a**	K_2CO_3	THF	81	94
8	(*S*)-**6a**	K_2CO_3	CH_2Cl_2	76	95
9	(*S*)-**6a**	K_2CO_3	$PhCF_3$	62	95
10	(*S*)-**6a**	K_2CO_3	PhMe	60	97
11	(*S*)-**6a**	Na_2CO_3	PhMe	78	93
12	(*S*)-**6a**	Cs_2CO_3	PhMe	66	93
13	(*S*)-**6a**	KOAc	PhMe	74	97

[a] The reactions were carried out on a 0.2 mmol scale of indole in various solvent (0.4 mL) at 40 °C with 1.2 equivalents of 1,3-diphenylprop-2-enyl acetate and 2 equivalents of base in the presence of (*S*)-**6** (6 mol%) and $[Pd(C_3H_5)Cl]_2$ (3 mol%; 6 mol% Pd).
[b] Isolated yield.
[c] Determined by HPLC analysis on a chiral column.

Using the optimized conditions (Table 2, entry 17), we examined the scope of the allylic alkylation of various indoles with 1,3-diphenylprop-2-enyl acetate in the presence of (*S*)-**6a** in toluene with KOAc at 40 °C (Table 3).[13] The reactions of the 6-substituted indoles gave the corresponding products (*R*)-**11b–h** in good to high enantioselectivities (77–97% ee; Table 3, entries 2–8). The reactions with bromoindoles and 2-phenylindole also proceeded with high enantioselectivities (entries 9–12). When the reaction was carried out with 1,3-diphenylprop-2-enyl pivalate instead of the acetate, product (*R*)-**11a** was obtained at a similar level of enantioselectivity (98% ee; entry 13).

Table 3 Palladium-Catalyzed Asymmetric Allylic Alkylation of Indoles in the Presence of (*S*)-**6a**[a]

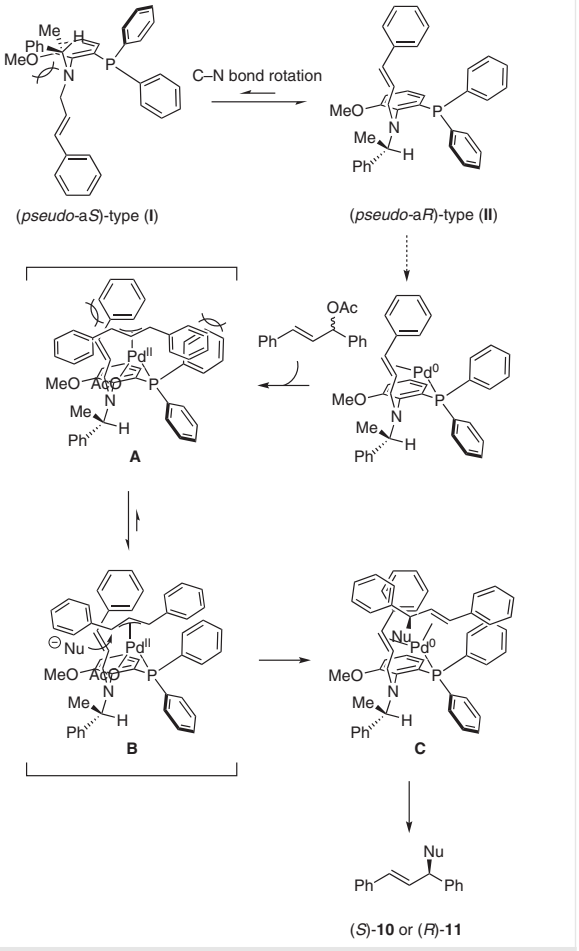


Entry	R	Product	Yield[b] (%)	ee[c] (%)
1	H	**11a**	74	97
2	6-Me	**11b**	54	91
3	6-MeO	**11c**	71	82
4	6-BnO	**11d**	56	77
5	6-O_2N	**11e**	68	95
6	6-F	**11f**	73	97
7	6-Cl	**11g**	74	97
8	6-Br	**11h**	67	95
9	5-Br	**11i**	58	97
10	4-Br	**11j**	64	94
11	7-Br	**11k**	46	94
12	2-Ph	**11l**	85	96
13[d]	H	**11m**	64	98

[a] The reactions were carried out on 0.2 mmol scale of indole derivative in PhMe (0.4 mL) at 40 °C with 1.2 equivalents of the allyl ester and 2 equivalents of KOAc in the presence of (*S*)-**6a** (6 mol%) and $[Pd(C_3H_5)Cl]_2$ (3 mol%; 6 mol% Pd).
[b] Isolated yield.
[c] Determined by HPLC analysis on a chiral column.
[d] This reaction was carried out using 1,3-diphenylprop-2-enyl pivalate instead of 1,3-diphenylprop-2-enyl acetate.

According to the observed stereochemical outcome as well as our previous relevant reports,[4,5] we propose a possible pathway for product formation (Scheme 4). We recently reported that the chiral ligands (a*R*)-**1** with C(aryl)–N(amine) bond axial chirality gave (*S*)-products **10** in a Pd-catalyzed asymmetric allylic substitution reactions with malonates.[4a] We also reported that the chiral ligands (a*R*)-**1** and (a*R*)-**2** gave (*R*)-products **11** in allylic substitution reactions with indoles.[4b,5] In the case of (*S*)-**6a**, these reactions gave (*S*)-products **10** and (*R*)-products **11**, respectively. A single-crystal X-ray analysis of (*S*)-**9a**,[14] a derivative of (*S*)-**6a** oxidized at the phosphorus atom, showed that torsion at the C(aryl)–N(amine) bond provides a stable (*pseudo*-a*R*)-type rotamer (see Supplementary Information, Figure S1). As shown in Scheme 4, the *pseudo*-axial chirality of (*S*)-**6a** at the C(aryl)–N(amine) bond also seems to provide a (*pseudo*-a*R*)-type rotamer **II** that is more stable than the corresponding (*pseudo*-a*S*)-type rotamer **I**. Such Pd(II) com-

plexes as M-type **A** and W-type **B** intermediates are formed from (*pseudo*-a*R*)-type (*S*)-**6a**. Intermediate **B** is favored over intermediate **A** due to the steric effect. A nucleophile preferentially attacks the carbon at the position *trans* to the phosphorus of the ligand from the outside.[3p,15] Finally, (*S*)-products **10** or (*R*)-products **11** are obtained from Pd(0) complex **C**.



Scheme 4 Possible stereochemical pathway

In conclusion, we found two rotamers at the C(aryl)–N(amine) bond exist for the phosphine–olefin-type chiral aminophosphines (*S*)-**6** (ratio: 60:1 to 2:1). A Pd-catalyzed asymmetric allylic alkylation of 1,3-diphenylprop-2-enyl acetate with malonates using the aminophosphine (*S*)-**6d** as a chiral ligand gave the desired products (*S*)-**10** with good enantioselectivities (up to 94% ee). We also found that a Pd-catalyzed asymmetric allylic alkylation of 1,3-diphenylprop-2-enyl acetate with indoles in the presence of the chiral ligand (*S*)-**6a** gave the desired products (*R*)-**11** with high enantioselectivities (up to 98% ee).

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690901.

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(9) **[2-(Diphenylphosphoryl)-6-methoxyphenyl][(1*S*)-1-phenylethyl]amine [(*S*)-8a]**

A 1.6 M solution of BuLi in hexane (9.4 mL, 15.0 mmol) was slowly added to a solution of [(1*S*)-1-phenylethyl]amine (1.82 g, 15.0 mmol) in THF (35 mL) at –80 °C. Phosphine oxide **7a** (1.69 g, 5.0 mmol) was added at r.t., and the mixture was stirred for 21 h at r.t. The mixture was then diluted with Et_2O, and the reaction was quenched with sat. aq NH_4Cl. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by chromatography [silica gel, hexane–EtOAc (2:1)] to give a beige solid; yield: 1.60 g (75%, 3.74 mmol); mp 124–126 °C; $[\alpha]_D^{20}$ +99.1 (*c* 0.50, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.68–7.53 (m, 6 H), 7.50–7.41 (m, 4 H), 7.36 (br s, 1 H), 7.15–7.12 (m, 2 H), 7.06–7.03 (m, 3 H), 6.79 (d, *J* = 7.1 Hz, 1 H), 6.56 (dt, *J* = 3.6 and 7.8 Hz, 1 H), 6.42 (ddd, *J* = 1.4, 7.7, 14.0 Hz, 1 H), 5.10 (t, *J* = 6.1 Hz, 1 H), 3.69 (s, 3 H), 1.33 (d, *J* = 6.8 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.7 (d, J_{CP} = 11.6 Hz), 146.4, 144.1 (d, J_{CP} = 5.5 Hz), 133.0 (d, J_{CP} = 103.9 Hz), 132.6 (d, J_{CP} = 104.5 Hz), 132.2 (d, J_{CP} = 10.1 Hz) (2 C), 132.0 (d, J_{CP} = 9.9 Hz) (2 C), 131.8 (d, J_{CP} = 2.5 Hz), 131.7 (d, J_{CP} = 2.5 Hz), 128.4 (d, J_{CP} = 12.2 Hz) (4 C), 127.9 (2 C), 126.2 (2 C), 126.0, 125.6 (d, J_{CP} = 11.0 Hz), 117.5 (d, J_{CP} = 15.5), 115.6 (d, J_{CP} = 2.5 Hz), 115.5 (d, J_{CP} = 104.2 Hz), 55.5, 55.4, 24.6. ^{31}P NMR (121 MHz, $CDCl_3$): δ = 37.5. EI-MS: *m*/*z* (%): 427 (M^+, 30), 412 (100). HRMS (ESI-Orbitrap): *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{27}NO_2P$: 428.1774; found: 428.1766.

[2-(Diphenylphosphoryl)-6-methoxyphenyl][(1*S*)-1-phenylethyl][(2*E*)-3-phenylprop-2-en-1-yl]amine [(*S*)-9a]

To the solution of the phosphine oxide (*S*)-**8a** (2.14 g, 5.0 mmol) in MeCN (50 mL) at r.t. were added K_2CO_3 (3.46 g, 25 mmol) and cinnamyl bromide (1.18 g, 6.0 mmol) in MeCN (20 mL), and the mixture was stirred at 60 °C for 22 h. The mixture was then filtered and concentrated under reduced pressure. The residue was purified by chromatography [silica gel, hexane–EtOAc (5:1)] to give a white solid; yield: 2.29 g (84%, 4.22 mmol); mp 169–171 °C; $[\alpha]_D^{20}$ +53.1 (*c* 0.36, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.84–7.73 (m, 4 H), 7.47–7.38 (m, 8 H), 7.24–7.01 (m, 10 H), 6.66 (ddd, *J* = 1.2, 7.7, 13.9 Hz, 1 H), 5.83 (d, *J* = 15.9 Hz, 1 H), 5.33 (ddd, *J* = 7.0, 7.0, 15.9 Hz, 1 H), 4.67 (q, *J* = 6.0 Hz, 1 H), 3.73 (dd, *J* = 7.5, 7.6 Hz, 1 H), 3.67 (s, 3 H), 3.26 (dd, *J* = 6.5, 15.1 Hz, 1 H), 1.11 (d, *J* = 6.7 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.1 (d, J_{CP} = 11.5 Hz), 145.3, 143.8 (d, J_{CP} = 4.4 Hz), 137.8, 134.7 (d, J_{CP} = 106.6 Hz), 134.0 (d, J_{CP} = 105.3 Hz), 133.0 (d, J_{CP} = 103.8 Hz), 132.1 (d, J_{CP} = 9.0 Hz) (2 C), 131.1(931) (d, J_{CP} = 2.6 Hz), 131.1(925) (d, J_{CP} = 9.4 Hz) (2 C), 131.0 (d, J_{CP} = 2.8 Hz), 129.5, 128.9, 128.5 (2 C), 128.2 (d, J_{CP} = 12.2 Hz) (2 C), 128.1 (d, J_{CP} = 11.7 Hz) (2 C), 128.0 (2 C), 127.6 (2 C), 126.7 (d, J_{CP} = 12.4 Hz), 126.4, 126.3, 126.2 (d, J_{CP} = 3.3 Hz), 126.0 (2 C), 115.6 (d, J_{CP} = 2.3 Hz), 62.3, 56.9, 55.1, 22.4. ^{31}P NMR (121 MHz, $CDCl_3$): δ = 27.5. EI-MS: *m*/*z* (%) = 543 (M^+, 0.15), 438 (100). HRMS (ESI-Orbitrap): *m*/*z* [M + H]$^+$ calcd for $C_{36}H_{35}NO_2P$: 544.2400; found: 544.2388.

X-ray diffraction analysis: Colorless plate crystals (0.20 × 0.10 × 0.020 mm^3) from hexane–$CHCl_3$; monoclinic space group *P*21, *a* = 12.4152(3) Å, *b* = 8.9538(2) Å, *c* = 13.5274(3) Å, β = 103.4670(10)°, *V* = 1462.40(6) Å^3, *Z* = 2, ρ = 1.235 g/cm^3, μ (Cu Kα) = 1.54178 mm^{-1}. The structure was solved by the direct method of full-matrix least–squares, where the final *R* and R_w were 0.0327, 0.0875, respectively, for 4982 reflections.

[2-(Diphenylphosphino)-6-methoxyphenyl][(1*S*)-1-phenylethyl][(2*E*)-3-phenylprop-2-en-1-yl]amine [(*S*)-6a]

To a mixture of phosphine oxide (*S*)-**9a** (1.09 g, 2.0 mmol) and Et_3N (3.1 mL, 22 mmol) in *m*-xylene (10 mL) was added $HSiCl_3$ (2.0 mL, 20 mmol) at 0 °C under Ar. The mixture was stirred at 120 °C for 24 h then cooled to r.t. and diluted with Et_2O. The reaction was quenched with 2 M aq NaOH, and the organic layer was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by chromatography [silica gel, hexane–EtOAc (50:1)]. to give a white solid; yield 0.530 g (50%. 1.0 mmol); mp 55–56 °C; $[\alpha]_D^{20}$ +59.6 (*c* 0.51, $CHCl_3$); rotamer ratio = 20:1.

^{1}H NMR (300 MHz, $CDCl_3$): δ (major rotamer) = 7.66 (d, *J* = 8.0 Hz, 2 H), 7.37–7.04 (m, 19 H), 6.86 (dd, *J* = 1.0, 8.1 Hz, 1 H), 6.53 (ddd, *J* = 1.3, 2.8, 7.6 Hz, 1 H), 6.04–5.94 (m, 1 H), 5.85 (d, *J* = 15.9 Hz, 1 H), 4.59 (q, *J* = 6.5 Hz, 1 H), 3.83 (s, 3 H), 3.58–3.42 (m, 2 H), 0.89 (d, *J* = 6.7 Hz, 3 H); δ (minor rotamer) = 7.66 (d, *J* = 7.4 Hz, 2 H), 7.37–7.04 (m, 19 H), 6.64 (dd, *J* = 1.0, 8.1 Hz, 1 H), 6.42–6.39 (m, 1 H), 6.09 (d, *J* = 16.1 Hz, 1 H), 5.76–5.68 (m, 1 H), 4.81 (q, *J* = 6.5 Hz, 1 H), 3.75 (s, 3 H), 3.58–3.42 (m, 2 H), 1.50 (d, *J* = 6.9 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.3 (d, J_{CP} = 3.9 Hz), 147.1, 141.9 (d, J_{CP} = 4.2 Hz), 141.1 (d, J_{CP} = 22.0 Hz), 138.7 (d, J_{CP} = 14.4 Hz), 138.5 (d, J_{CP} = 15.1 Hz), 137.6, 134.2 (d, J_{CP} = 20.5 Hz) (2 C), 134.0 (d, J_{CP} = 20.5 Hz) (2 C), 130.1, 129.0, 128.2(8) (d, J_{CP} = 2.0 Hz) (2 C), 128.2(6), 128.2(2) (d, J_{CP} = 1.0 Hz) (2 C), 128.1(4) (2 C), 128.0(9) (d, J_{CP} = 1.0 Hz) (2 C), 128.0(3), 128.0(1) (2 C), 126.9, 126.6, 126.4 (2 C), 126.1 (2 C), 111.9, 61.6, 56.3, 55.1, 23.5. ^{31}P NMR (121 MHz, $CDCl_3$): δ (major rotamer) = −16.0; δ (minor rotamer) = −14.1. EI-MS: *m*/*z* (%) = 527 (M^+, 8.2), 422 (100). HRMS (ESI-Orbitrap): *m*/*z* [M + H]$^+$ calcd for $C_{36}H_{35}NOP$: 528.2451; found: 528.2441.

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(11) **Palladium-Catalyzed Allylic Alkylation of Malonates; General Procedure**

BSA (0.15 mL, 0.60 mmol) and the appropriate allylic ester (0.20 mmol) were added to a mixture of $[Pd(C_3H_5)Cl]_2$ (1.48 mg, 4 μmol), (*S*)-**6d** (4.64 mg, 8 μmol), and NaOAc (1.64 mg, 20 μmol)

in $PhCF_3$ (0.4 mL) at r.t. under Ar, and the mixture was stirred for 10 min. A dialkyl malonate (0.60 mmol) was added, and stirring was continued for 24 h at r.t. The mixture was then diluted with Et_2O and water. The organic layer was washed with brine then dried ($MgSO_4$), filtered, and concentrated in a rotary evaporator. The residue was purified by column chromatography [silica gel, hexane–EtOAc (10:1)].

Dimethyl [(1*S*,2*E*)-1,3-Diphenylprop-2-en-1-yl]malonate [(*S*)-10a][16]

Colorless oil; yield: 55.7 mg (86%, 0.172 mmol, 94% ee); $[\alpha]_D^{20}$ –21.6 (*c* 0.51, $CHCl_3$). HPLC [Daicel CHIRALPAK AD-H, 0.46 × 25 cm, λ = 254 nm, hexane–*i*-PrOH (90:10), 0.5 mL/min]: t_R = 26.3 min (minor), 33.3 min (major). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.18 (m, 10 H), 6.48 (d, *J* = 15.8 Hz, 1 H), 6.33 (dd, *J* = 8.4, 15.7 Hz, 1 H), 4.27 (dd, *J* = 8.1, 8.6 Hz, 1 H), 3.95 (d, *J* = 10.8 Hz, 1 H), 3.70 (s, 3 H), 3.52 (s, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.2, 167.8, 140.2, 136.8, 131.9, 129.1, 128.7, 128.5, 127.9, 127.6, 127.2, 126.4, 57.7, 52.7, 52.5, 49.2. EI-MS: *m*/*z* (%) = 324 (M^+, 13).

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(13) **Palladium-Catalyzed Allylic Alkylation of Indoles; General Procedure**

PhMe (0.2 mL) was added to a mixture of indole or a substituted indole (0.2 mmol), the appropriate 1,3-diarylprop-2-enyl acetate (60.6 mg, 0.24 mmol), (*S*)-**6a** (6.3 mg, 12 μmol), $[Pd(C_3H_5)Cl]_2$ (2.2 mg, 6 μmol), and KOAc (39.3 mg, 0.4 mol) at r.t. under Ar, and the mixture was stirred for 18 h at 40 °C. The reaction was quenched with H_2O, and the mixture was diluted with Et_2O. The organic layer was washed with H_2O and brine then dried ($MgSO_4$), filtered, and concentrated in a rotary evaporator. The residue was purified by column chromatography [silica gel, hexane–EtOAc–Et_3N (20:2:1)].

3-[(1*R*,2*E*)-1,3-Diphenylprop-2-en-1-yl]-1*H*-indole [(*R*)-11a][4]

Yellow solid; yield: 48.0 mg (74%, 0.146 mmol, 97% ee); mp 118–120 °C; $[\alpha]_D^{20}$ –35.3 (*c* 0.19, $CHCl_3$). HPLC [Daicel CHIRALPAKIB, 0.46 × 25 cm, λ = 254 nm, hexane–EtOH (99:1), 0.7 mL/min]: t_R = 56.3 min (major), 63.9 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (br s, 1 H), 7.43–7.15 (m, 13 H), 7.04–7.00 (m, 1 H), 6.90 (d, *J* = 2.4 Hz, 1 H), 6.73 (dd, *J* = 7.4, 15.8 Hz, 1 H), 6.43 (d, *J* = 15.9 Hz, 1 H), 5.12 (d, *J* = 7.3 Hz, 1 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 143.3, 137.5, 136.6, 132.5, 130.5, 128.5 (2 C), 128.4, 127.1, 126.8, 126.4, 126.3, 122.6, 122.1, 119.9, 119.4, 118.7, 111.1, 46.2. EI-MS: *m*/*z* (%) 309 (M^+, 100).

(14) CCDC 1938333 contains the supplementary crystallographic data for compound (*S*)-**9a**. The data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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