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New chiral phosphine–amide ligands in palladium-catalysed asymmetric allylic alkylations

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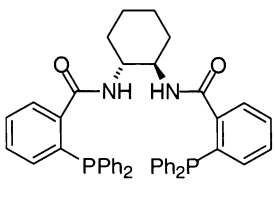
Abstract—Palladium-catalysed asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate **8a** with a dimethyl malonate–BSA–LiOAc system has been successfully carried out in the presence of new chiral phosphine–amide, such as **5**, in good yields and high enantiomeric excesses of up to 85%. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Palladium-catalysed asymmetric allylic alkylation is a useful process for asymmetric C–C bond-forming reactions. To achieve high enantioselectivity in the catalytic reaction, a variety of chiral ligands have been studied.[1] Recently, *P*,*N*-bidentate ligands were found to be efficient chiral sources for this reaction.[2] We previously reported phosphine–hydrazone bidentate ligands, such as 2-diphenylphosphinobenzaldehyde SAMP hydrazone (DPPBA–SAMP),[3] and phosphine–amine bidentate ligands, such as (*S*)-1-[2′-(diphenylphosphino)-1′-naphthalenyl]-2-(methoxymethyl)pyrrolidine, as efficient chiral sources.[4]

Trost's ligand, **1**, usually forms *P*,*P*-chelate complexes with Pd.[5] However, when the ratio of Pd:**1** was raised (i.e. ≥ 1), *P*,*O*-coordination between phosphine and amide carbonyl was generated.[6] More recently, Kim reported that *P*,*N*-bidentate ligand **2** generated *P*,*O*-chelation complexes on the basis of X-ray crystal structure analysis.[7]

Trost reported palladium-catalysed asymmetric allylic alkylation using ligands **3**, which, unlike **1**, cannot serve as bidentate diphosphine ligands.[5] On the other hand, Clayden has reported palladium-catalysed asymmetric allylic alkylation using phosphine–amide ligand **4**, which has the chirality of a stereogenic axis and a



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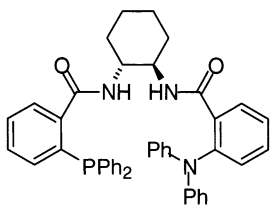

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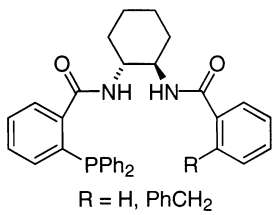

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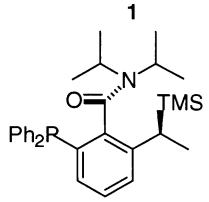

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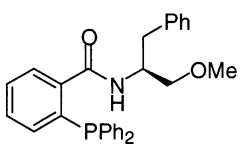

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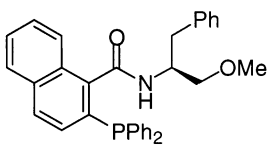

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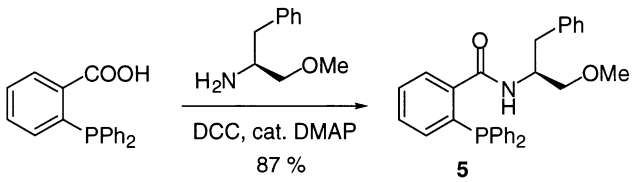
silicon-bearing stereogenic centre.[8] Herein, we report the palladium-catalysed asymmetric allylic alkylation using new chiral phosphine–amide type ligands of the type **5** and **6**.

2. Results and discussion

2.1. Synthesis of the phosphine–amide ligands

Ligand **5** was easily prepared from the reaction of 2-diphenylphosphinobenzoic acid with (*S*)-2-amino-1-methoxy-3-phenylpropane[9] in a good 87% yield (Scheme 1).



Scheme 1.

Ligand **6** was prepared by the amidation of methyl 2-hydroxy-1-naphthoate with (*S*)-2-amino-1-methoxy-3-phenylpropane hydrochloride (AMPP·HCl) in the presence of trimethylaluminium followed by the triflation of **7**, and the nickel-catalysed phosphinylation of **8** (Scheme 2).

2.2. Palladium-catalysed asymmetric allylic alkylation

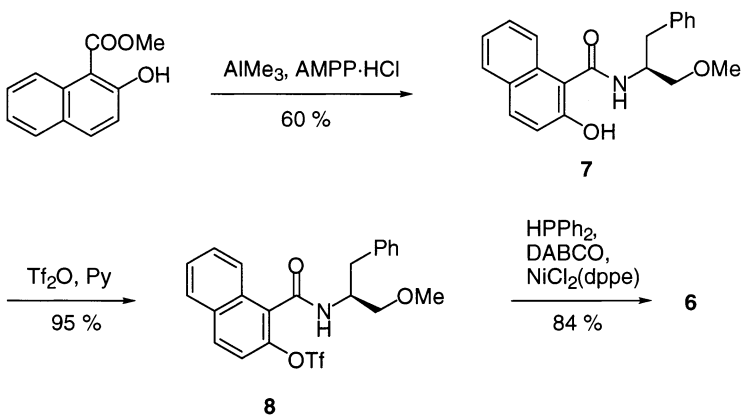
We then examined the chiral phosphine–amide ligands **5** and **6** in the palladium-catalysed asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate **9a** with dimethyl malonate **10a** (Scheme 3). This reaction was carried out in the presence of 2 mol% of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, 4 mol% of chiral ligand, and a mixture of *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and 2 mol% of LiOAc at room temperature. We investigated the effect of solvents on this reaction (Table 1). When the reaction was carried out in ether, enantioselectivity was higher than for the other solvents (Table 1, entry 1 versus entries 2–7). Using ligand **6**, we obtained product **11a** in good yield (98%), but the enantiomeric excess was a moderate 74% (entry 8).

The use of NaOAc or KOAc instead of LiOAc, decreased the enantioselectivity of **11a** (entries 2 and 3, Table 2). Using NaH as a base instead of BSA–LiOAc also decreased both enantioselectivity and yield (entry 6). While reactivity depended slightly on reaction temperature, the enantioselectivity was not temperature dependent (entries 1 and 7–9). We obtained the highest enantioselectivity at 4°C, with an e.e. of 85% (entry 7).

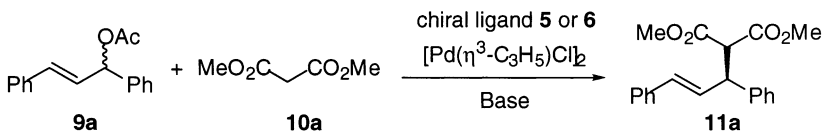
Table 1. Asymmetric allylic alkylation using chiral phosphine–amide ligands **5** and **6**[a]

Entry	Ligand	Solvent	Yield (%)[b]	E.e. (%)[c]
1	**5**	MeCN	95	75
2	**5**	DMF	88	69
3	**5**	THF	98	79
4	**5**	CH_2Cl_2	95	76
5	**5**	Ether	95	84
6	**5**	PhMe	95	78
7	**5**	Hexane	91	72
8	**6**	Ether	98	74

[a] The reaction was carried out at rt for 24 h.
[b] Isolated yields.
[c] Determined by HPLC analysis using a chiral column (Chiralcel OD).



Scheme 2.



Scheme 3.

Table 2. Asymmetric allylic alkylation using chiral phosphine–amide ligand **5**[a]

Entry	Temp. (°C)	Base	Yield (%)[b]	E.e. (%)[c]
1	Rt	BSA–LiOAc	95	84
2	Rt	BSA –NaOAc	94	76
3	Rt	BSA–KOAc	95	78
4	Rt	BSA $-Cs_2CO_3$	98	74
5	Rt	BSA–Li_2CO_3	91	74
6	Rt	NaH	34	42
7	4	BSA–LiOAc	94	85
8	−20	BSA–LiOAc	93	83
9[d]	−35	BSA–LiOAc	98	84

[a] The reaction was carried out for 24 h.
[b] Isolated yields.
[c] Determined by HPLC analysis using a chiral column (Chiralcel OD).
[d] The reaction was carried out for 7 days.

When 1,3-diphenyl-2-propenyl pivalate **9b** was used instead of 1,3-diphenyl-2-propenyl acetate **9a**, the reaction with a dimethyl malonate **10a** gave product **11a** in good yield with 84% e.e. (entry 2, Table 3). On the other hand, with diethyl methylmalonate **10b**, the reaction gave the corresponding product **11b** in low enantioselectivity (entries 3 and 4).

The ^{1}H NMR of the **5**·(π-allyl)Pd complex (δ_P 25.6) showed a small downfield shift ($\Delta\delta = 0.45$ ppm) of the amidic proton relative to free **5**, which indicates that the Pd complex of ligand **5** was generated with a similar *P,O*-chelation mode between phosphine and amide carbonyl, as observed in the case of ligand **2**.[7]

3. Conclusion

We have prepared new chiral phosphine–amide ligands of the type **5** and using these ligands the palladium-catalysed asymmetric allylic alkylation proceeded with good enantiomeric excesses of up to 85%.

4. Experimental

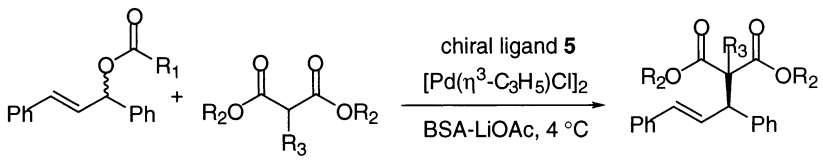
4.1. General methods

Melting points were measured on a Yanagimoto or a Shibata micromelting point apparatus. NMR spectra were recorded on a JEOL A-400 or a Bruker DPX-300 system with TMS as an internal standard. IR spectra were recorded on a Hitachi 260-10 or a JASCO FT/IR-230 spectrometer. Mass spectra were recorded on a JEOL JMS-HX110, a JEOL JMS-700, a Shimadzu GCMS-QP2000A or a Hitachi M-80B mass spectrometer. Optical rotations were measured on a JASCO DIP-370 or an HORIBA SEPA-200 polarimeter.

4.2. Preparation of (*S*)-*N*-(1-benzyl-2-methoxyethyl)-2-(diphenylphosphino)benzamide 5

To a mixture of DCC (3.0 mmol, 0.63 g), DMAP (0.13 mmol, 0.016 g) in CH_2Cl_2 (15 mL) was added (*S*)-(+)-2-amino-1-methoxy-3-phenylpropane (2.5 mmol, 0.42 g) and 2-(diphenylphosphino)benzoic acid (2.5 mmol, 0.77 g) at room temperature under an argon atmosphere. After 24 h, the reaction mixture was filtered, evaporated under reduced pressure, and purified by recrystallisation from a CH_2Cl_2–hexane mixture: 87% (1.4 mmol, 0.63 g); mp 110–112°C. $[\alpha]_D^{20}$ −14.5 (*c* 0.80, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.73–2.85 (m, 2H), 3.13–3.19 (m, 2H), 3.24 (s, 3H), 4.28–4.85 (m, 1H), 6.24 (d, $J = 8.3$ Hz, 1H), 6.93–7.51 (m, 19H). ^{31}P NMR ($CDCl_3$): δ −9.92. ^{13}C NMR ($CDCl_3$): δ 36.94, 50.65, 58.82, 71.54, 126.31–141.71 (m, Ar-C), 168.42. IR (KBr): 3350, 3060, 2940, 2860, 2360, 1640, 1580, 1510, 1480, 1460, 1440, 1395, 1340, 1100, 740, 700 cm^{-1}. FABMS (*m*/*z*): 454 (M+1). HRMS (FAB) calcd for $C_{29}H_{29}NO_2P$ (M+H): 454.1936; found: 454.1936.

Table 3. Asymmetric allylic alkylation using chiral phosphine–amide ligand **5**[a]



9a R_1 = Me **b** R = $C(Me)_3$ **10a** R_2 = Me, R_3 = H **b** R_2 = Et, R_3 = Me **11a** R_2 = Me, R_3 = H **b** R_2 = Et, R_3 = Me

Entry	9	10	11	Yield (%)[b]	E.e. (%)[c]
1	**a**	**a**	**a**	95	85
2	**b**	**a**	**a**	81	84
3	**a**	**b**	**b**	92	48
4	**b**	**b**	**b**	95	53

[a] The reaction was carried out for 24 h.
[b] Isolated yields.
[c] Determined by HPLC analysis using a chiral column (Chiralcel OD).

4.3. Preparation of (*S*)-*N*-(1-benzyl-2-methoxyethyl)-2-hydroxynaphthalenecarboxamide 7

To a mixture of (*S*)-(+)-2-amino-1-methoxy-3-phenylpropane hydrochloride (2.0 mmol, 0.403 g) in benzene (5 mL) was added a trimethylaluminium in hexane (2.06 mmol, 2.1 mL, 0.98 M) at room temperature under an argon atmosphere. The mixture was stirred under reflux for 3 h and a benzene (3 mL) solution of methyl 2-hydroxy-1-naphthoate (1.0 mmol, 0.202 g) was added to the mixture. After 4 h, the reaction mixture was cooled to room temperature. The mixture was diluted with ethyl acetate and water. The organic phase was washed with brine and dried over Na_2SO_4. The filtrate was concentrated under reduced pressure to give the residue, which was then purified by silica gel column chromatography. Compound **7** was afforded in 60% (0.60 mmol, 0.200 g) yield; mp 122.2–123.0°C. $[\alpha]_D^{25}$ −54.4 (*c* 0.16, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.00–3.12 (m, 2H), 3.40 (s, 3H), 3.48 (dd, J=3.5 and 9.5 Hz, 1H), 3.83 (dd, J=3.9 and 9.5 Hz, 1H), 4.62–4.67 (m, 1H), 6.64 (d, J=8.3 Hz, 1H), 7.15 (d, J=8.9 Hz, 1H), 7.23–7.40 (m, 6H), 7.41–7.46 (m, 1H), 7.75–7.81 (m, 2H), 7.87 (d, J=8.5 Hz, 1H), 11.31 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 37.40, 51.12, 59.10, 72.26, 109.82, 119.30, 122.54, 123.34, 126.77, 128.04, 128.69, 129.32, 129.37, 130.66, 133.78, 137.72, 159.29, 169.45. IR (KBr): 3261, 3178, 3068, 2950, 1637, 1540, 1513, 1436, 1344, 1292, 1263, 1207, 1105, 1072, 958, 829, 732, 698 cm^{-1}. FABMS (*m*/*z*): 335 (M+1). HRMS (FAB) calcd for $C_{21}H_{22}NO_3$ (M+H): 336.1600; found: 336.1583.

4.4. Preparation of (*S*)-*N*-(1-benzyl-2-methoxyethyl)-2-(trifluoromethanesulfonyloxy)naphthalenecarboxamide 8

To a mixture of amide **7** (0.5 mmol, 0.167 g), pyridine (1.2 mmol, 0.1 mL) and benzene (1 mL) was added trifluoromethanesulfonic anhydride (0.83 mmol, 0.14 mL) at 0°C, and the mixture was stirred at room temperature for 6 h. After removal of the solvent, the residue was diluted with ethyl acetate and then washed with 5% aq. HCl, satd $NaHCO_3$, and brine. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give **8** in 95% (0.476 mmol, 0.222 g) yield; mp 127.0–127.7°C. $[\alpha]_D^{25}$ −23.7 (*c* 0.35, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.99–3.14 (m, 2H), 3.38 (s, 3H), 3.45–3.50 (m, 1H), 3.55 (dd, J=3.8 and 9.4 Hz, 1H), 4.68–4.78 (m, 1H), 6.43 (d, J=8.7 Hz, 1H), 7.25–7.40 (m, 6H), 7.47–7.55 (m, 3H), 7.84–7.88 (m, 1H), 7.93 (d, J=9.1 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 37.55, 51.10, 58.94, 72.14, 118.58 (q, J=4.2 Hz), 118.86, 125.70, 126.62, 127.50, 128.06, 128.25, 128.44, 128.65, 129.53, 130.68, 131.63, 132.32, 137.89, 142.64, 163.36. IR (KBr): 3309, 3062, 2925, 1648, 1544, 1423, 1220, 1139, 954, 835, 813, 732, 617 cm^{-1}. FABMS (*m*/*z*): 468 (M+1). HRMS (FAB) calcd for $C_{22}H_{21}F_3NO_5S$ (M+H): 468.1093; found: 468.1107.

4.5. Preparation of (*S*)-*N*-(1-benzyl-2-methoxyethyl)-2-(diphenylphosphino)naphthalenecarboxamide 6

To a solution of $NiCl_2$dppe (0.015 mmol, 0.008 g) in DMF (0.3 mL) was added diphenylphosphine (0.4 mmol, 0.07 mL) at room temperature, and then the resulting solution was heated at 100°C. After heating at 100°C for 30 min, a solution of amide **8** (0.3 mmol, 0.140 g) and DABCO (0.34 mmol, 0.040 g) in DMF (0.7 mL) was added at once, the resulting solution was kept at 100°C for 24 h, and then the solution was cooled to room temperature. The solution was diluted with ethyl acetate and then washed with water and brine. The organic phase was dried over Na_2SO_4, concentrated under reduced pressure and the residue was purified by silica gel column chromatography to give **6** in 84% (0.25 mmol, 0.126 g) yield; mp 57.0–58.0°C. $[\alpha]_D^{25}$ −18.7 (*c* 0.17, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.76–2.92 (m, 1H), 2.99–3.10 (m, 1H), 3.15 (s, 3H), 3.31–3.33 (m, 2H), 4.66–4.78 (m, 1H), 6.07 (d, J=8.8 Hz, 1H), 7.10–7.17 (m, 1H), 7.19–7.38 (m, 15H), 7.38–7.44 (m, 1H), 7.45–7.54 (m, 1H), 7.55–7.67 (m, 1H), 7.68–7.74 (m, 1H), 7.75–7.82 (m, 1H). ^{31}P NMR ($CDCl_3$): δ −12.75. ^{13}C NMR ($CDCl_3$): δ 37.32, 50.68, 58.77, 72.06, 125.75–142.85 (m, Ar-C), 168.40 (d, J=5.0 Hz). IR (KBr): 3409, 3293, 3054, 2923, 1656, 1496, 1251, 1182, 1120, 1026, 908, 817, 744, 698, 514 cm^{-1}. FABMS (*m*/*z*): 504 (M+1). HRMS (FAB) calcd for $C_{33}H_{31}NO_2P$ (M+H): 504.2092; found: 504.2072.

4.6. General procedure for asymmetric allylic alkylations

To a mixture of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (0.01 mmol, 0.004 g), chiral amide (0.02 mmol), and lithium acetate (0.01 mmol, 0.001 g) in ether (1 mL) was added BSA (1.5 mmol, 0.37 mL), racemic 1,3-diphenyl-2-propenyl acetate **9a** (0.5 mmol, 0.126 g), and dimethyl malonate **10a** (1.5 mmol, 0.17 mL) at room temperature under an argon atmosphere. After stirring for 24 h, the reaction mixture was diluted with ether and water. The organic layer was washed with brine and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give the residue, which was purified by column chromatography to give **11a** (Table 1, entry 5) in 95% yield; 84% e.e.; $[\alpha]_D^{20}$=+16.0 (*c* 1.0, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.51 (s, 3H), 3.70 (s, 3H), 3.95 (d, J=11.0 Hz, 1H), 4.27 (dd, J=8.5 and 11.0 Hz, 1H), 6.44 (dd, J=8.5 and 15.8 Hz, 1H), 6.71 (d, J=15.8 Hz, 1H), 7.19–7.33 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 49.20, 52.45, 52.63, 57.66, 126.40, 127.18, 127.58, 127.86, 128.48, 128.73, 129.12, 131.85, 136.83, 140.18, 167.79, 168.21; EIMS (*m*/*z*): 324 (M^+, 30). **11b** (Table 3, entry 4): 95% yield; 53% e.e.; $[\alpha]_D^{20}$=+10.6 (*c* 1.0, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.13–1.28 (m, 6H), 1.47 (s, 3H), 4.04–4.18 (m, 2H), 4.14–4.20 (m, 2H), 4.29 (d, 8.9 Hz, 1H), 6.44 (d, 15.8 Hz, 1H), 6.71 (dd, 8.9 and 15.8 Hz, 1H), 7.18–7.34 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.94, 14.03, 18.81, 46.19, 53.72, 58.89, 61.34, 126.33, 127.10, 127.31, 128.20, 128.43, 128.86, 129.61, 132.58, 170.92, 171.19; EIMS (*m*/*z*): 366 (M^+, 3).

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