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Preparation of new chiral pyridine–phosphine ligands and their Pd-catalyzed asymmetric allylic alkylations

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Abstract—Enantiomerically pure 2-(diphenylphosphino)methyl-*N*-[1-(2-pyridinyl)ethyl]pyrrolidines **1** and **2** have been prepared by the stereospecific substitution of enantiomerically pure 1-(2-pyridinyl)ethyl methanesulfonate **6** with enantiomerically pure 2-(diphenylphosphino)methylpyrrolidine. Asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate **11** with dimethyl malonate sodium salt using the (*S*,*S*)-ligand **1** affords the (*R*)-product **12** with up to 86% e.e. in good yield.

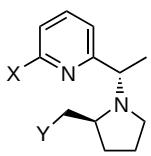
1. Introduction

Chiral ligands are widely used for asymmetric reaction in organic synthesis.[1] To date, a large number of chiral ligands have been prepared, and their usefulness for asymmetric reactions has been investigated.[2] Nevertheless, the search for new chiral ligands and catalysts is continually increasing, since there is high demand for new and efficient chiral ligands for application in transition metal-catalyzed asymmetric synthesis.[3] A considerable number of *P*,*N*-ligands having phosphine and nitrogen functional moieties have been reported in the past few years[4–6] and, in connection with this, phosphine ligands bearing a pyridine ring are of particular interest to us.[6] We have developed a synthetic method for chiral pyridine derivatives, and both enantiomeric isomers for various pyridine derivatives are now available.[7–9] We have extended our chiral pyridine synthesis to phosphine-containing 1-(2-pyridinyl)ethylamine derivatives. Herein, we describe the synthesis of new chiral pyridine–phosphine ligands **1** and **2** (Fig. 1) and their applications in asymmetric catalysis.

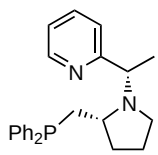
2. Results and discussion

2.1. Preparation of *P*,*N*-ligands 1–3

We have reported the substitution reaction of chiral 1-(2-pyridinyl)ethyl methanesulfonate with nucleophiles,[7] which takes place stereospecifically with complete inversion of the configuration, allowing the synthesis of new homochiral pyridines bearing a variety of functionalities, including amino, alkylamino, cyclicamino, azido, alkylsulfenyl, aryloxy, acyloxy and acylthio groups at the stereogenic carbon.[7,8] An example for the coupling of chiral pyridine with pyrrolidine is shown in Scheme 1. The enantiomerically pure (*R*)-1-(2-pyridinyl)ethanol prepared by lipase-catalyzed kinetic acetylation with vinyl acetate[9] was mesylated and reacted with pyrrolidine in DMSO at 60°C.

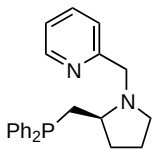


1



1a'

a : X = H, Y=PPh_2
b : X = Ph, Y=PPh_2
c : X = 3,5-dimethylphenyl, Y=PPh_2
d : X = 2,6-dimethylphenyl, Y=PPh_2
e : X = H, Y=OCH_3



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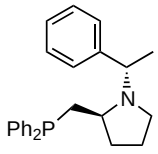

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Figure 1.

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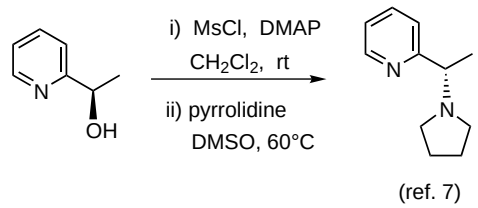
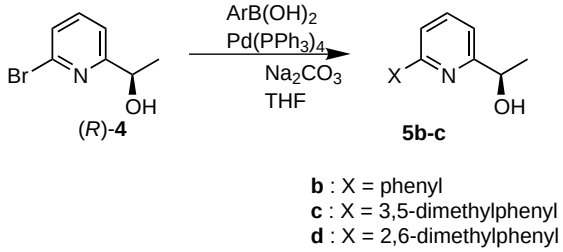
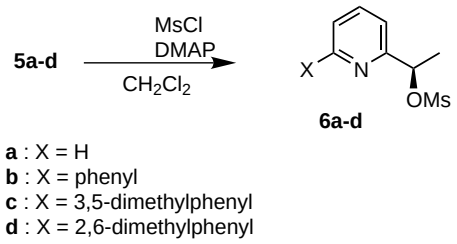


Scheme 1.

For the synthesis of ligands **1**–**3** using the above reaction, chiral pyridine and (diphenylphosphino)-methylpyrrolidine fragments are required. According to this synthetic analysis, mesylates **6a**–**d**, which can be derived from 1-(2-pyridinyl)ethanol **5a**–**d**, will be used as the chiral pyridine fragment. Therefore, we first planned to prepare enantiomerically pure **5b**–**d**. Suzuki cross-coupling reaction of (*R*)-1-[2-(6-bromopyridinyl)]ethanol (*R*)-4[9a] with phenylboronic acid using $Pd(PPh_3)_4$ as a catalyst in the presence of aq. Na_2CO_3 gave (*R*)-1-[2-(6-phenylpyridinyl)]ethanol **5b** in 77% yield. Similarly, **5c** and **5d** were produced from 3,5-dimethylphenylboronic acid and 2,6-dimethylphenylboronic acid in 69 and 97% yields, respectively. Mesylation of **5a**–**d** with methanesulfonyl chloride in the presence of DMAP in CH_2Cl_2 gave the corresponding mesylate **6a**[7] in 97%, **6b** in 98%, **6c** in 69% and **6d** in 97% yields, respectively (Schemes 2 and 3).

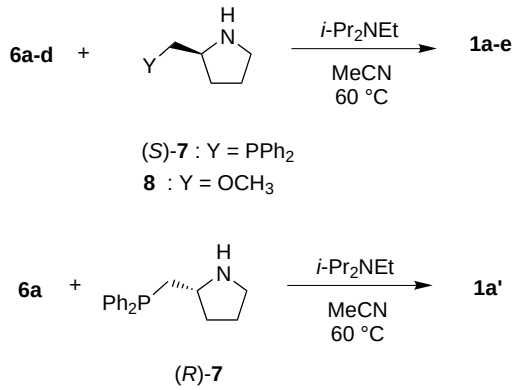


Scheme 2.



Scheme 3.

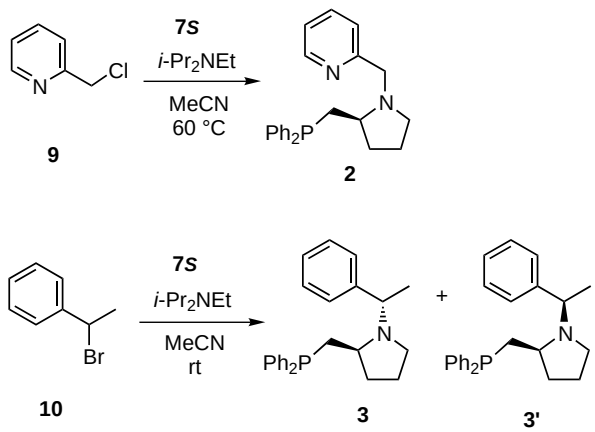
Initially, we conducted the coupling reaction of **6a** with (*S*)-2-(diphenylphosphino)methylpyrrolidine (*S*)-**7**[10] in DMSO. Although the reaction was completed smoothly over 6 h to give **1a** (2*S*,1′*S*-isomer), isolation of **1a** from DMSO was troublesome. Cationic resin was required for the purification. However, when acetonitrile was employed for the reaction in the presence of *N*,*N*-diisopropylethylamine at 60°C, the reaction took 17 h to obtain the desired **1a** in satisfactory yield. Since the diastereoisomeric (2*S*,1′*R*)-isomer could not be detected in the NMR spectrum of the crude products, it was concluded that no isomerization occurred under the reaction conditions (Scheme 4).



Scheme 4.

In the same manner, the reaction of **6b**–**d** with (*S*)-**7** gave **1b**–**d** proceeded in 91, 78 and 86% yields, respectively. No diastereoisomeric products were observed in these reactions. Methoxymethyl derivative **1e** was obtained by the coupling of **6a** and (*S*)-prolinol methyl ether **8**[11] in 96% yield under the same reaction conditions. Since no isomerization occurred during the substitution, all the ligands were assumed to be enantiomerically pure.

The diastereomer **1a**′ was independently prepared in 70% yield by the coupling of **6a** with (*R*)-**7**, *N*-(2-pyridinylmethyl)pyrrolidine **2** was also obtained in 68% yield. Phenethyl ligands **3** and **3**′, in which the pyridine ring in **1a** and its diastereoisomer was replaced with a phenyl ring, were also synthesized (Scheme 5). Racemic α-phenethylchloride was treated with (*S*)-**7** in acetonitrile to give **3** in 37% yield and **3**′ in 34% yield after



Scheme 5.

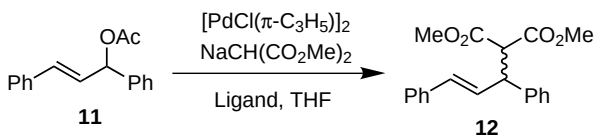
separation by HPLC. The relative stereochemistries of **3** and **3′** are comparable to those for **1** possessing (*S*,*S*)-configuration and **1a′** possessing (*S*,*R*)-configuration. Since the stereogenic center on the pyrrolidine ring derived from (*S*)-**7** intrinsically possesses (*S*)-configuration, the absolute stereochemistries of **3** and **3′** were assigned as (*S*,*S*) and (*R*,*S*). In the proton NMR spectra, both methyl and methine protons of pyridinylethyl and phenethyl groups in the more polar isomers **1a** and **3** appear at lower field than those in the less polar isomers **1a′** and **3′**. Thus, the methyl and methine protons are observed at 1.33 and 3.98 ppm in **1a** and 1.39 and 3.78 ppm in **3**, respectively, whilst the corresponding protons for **1a′** and **3′** resonate at higher field (1.27 and 3.91 ppm for **1a′** and 1.22 and 3.68 ppm for **3′**).

2.2. Asymmetric allylic alkylation

Pd-catalyzed asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate and a dialkyl malonate sodium salt is an established and popular method for testing the asymmetric induction ability of a chiral ligand.[12] Ligands **1**–**3** were applied in the Pd-catalyzed asymmetric allylic alkylation, the results of which are shown in Table 1. All of the ligands showed excellent reactivity at 0°C. In comparison with the results for **1a** and **1a′** (entries 1 and 2), the stereogenic center of the pyridinylethyl group influenced the enantioselectivity. (*S*,*S*)-Ligand **1a** gave the (*R*)-isomer in 58% e.e., while (*R*,*S*)-ligand **1a′** gave the (*S*)-isomer with 26% e.e.[13] It is interesting that ligand **2** lacking a methyl group also produces the (*R*)-isomer with similar e.e. (51%, entry 10) to that for **1a**. This result indicated that the absolute configuration of the product was controlled by the chirality of the pyrrolidine moiety. The introduction of an aryl group at C(6) of the pyridine ring increased the selectivity up to 75–77% (entries 3–5). However, the presence of methyl substituents on the aryl ring did not influence the selectivity. The diphenylphosphine moiety was found to be essential; ligand **1e**, in which the diphenylphosphinomethyl group was replaced with a methoxymethyl group, gave the highest chemical yield but poor selectivity (entry 6). Since this type of ligand showed excellent chemical reactivity, the reaction was carried out at low temperature. In fact, the reaction was able to be conducted at −40°C for ligands **1b**, **1c** and **1d**, giving (*R*)-products in good yields and increasing the selectivity up to 84–86% e.e. (entries 7–9). Unexpectedly, phenethyl ligands **3**, and **3′** also showed good selectivity. This result indicated that the pyridine ring nitrogen is unnecessary for high selectivity (entries 11 and 12). Since a simple *N*-benzyl substituted 2-(diphenylphosphino)methylpyrrolidine also worked well in this asymmetric reaction,[14] we concluded that an *N*-substituent on the 1-(2-pyridinyl)ethyl group and a 1-arylethyl group on the pyrrolidine ring are important for the asymmetric induction (Scheme 6).

2.3. Mechanistic considerations

The ligands **1a** and **1a′** possess three possible electron-donor atoms for coordination with palladium. Initially, we expected that the nitrogen atom of the pyridine ring and the phosphorus atom of the phosphine unit would be employed as electron-donors for the bidentate ligand during the formation of the Pd complex (A in Fig. 2), where the chiral pyrrolidine moiety might not only play a role as a tether for connecting the pyridinyl and phosphinyl units but also control the conformation of the complex in cooperation with another stereogenic center present in the pyridinylethyl unit. In fact, the complex was well arranged to have a favorable conformation for high asymmetric induction at least in the molecular model. However, the fact that the nitrogen of the pyridine ring is not essential for increasing the enantioselectivity indicates that the pyrrolidine group is more important, and also suggests that the Pd complex



Scheme 6.

Table 1. Pd-catalyzed asymmetric allylic alkylation

Entry	Ligand	Temp. (°C)	Time (h)	Yield[a] (%)	E.e.[b] (%)	Configuration[c]
1	**1a**	0	3	81	58	*R*
2	**1a′**	0	3	85	26	*S*
3	**1b**	0	3	68	76	*R*
4	**1c**	0	3	72	77	*R*
5	**1d**	0	3	79	75	*R*
6	**1e**	0–rt	18	94	6	*S*
7	**1b**	−40	40	79	84	*R*
8	**1c**	−40	40	72	84	*R*
9	**1d**	−40	40	74	86	*R*
10	**2**	0	3	93	51	*R*
11	**3**	0	3	75	73	*R*
12	**3′**	0	3	58	60	*R*

[a] Isolated yields.
[b] Determined by HPLC using a chiral column.
[c] Determined by optical rotation.

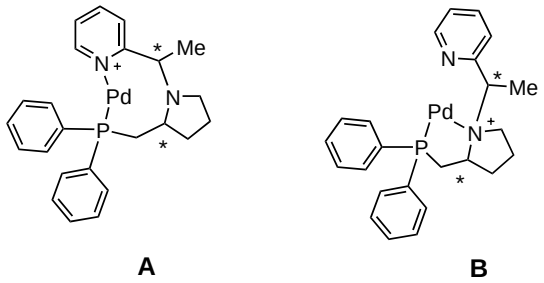


Figure 2.

shown as B in Fig. 2 is formed with bonding via the nitrogen atom of the pyrrolidine and not the pyridine ring nitrogen.

Based on the experimental results, we considered the reaction mechanism of the Pd-catalyzed allylic alkylation. Plausible transition-state structures of the *P*,*N*-ligand–Pd–π-allyl complexes are shown in Fig. 3 (**1a** and **1a**′ are used for the ligand). Each intermediate is able to adopt two preferred conformations, showing as 'M-orientation' in M-form and 'W-orientation' in W-form of the π-allyl groups. Since the W-form is assumed to have greater steric interference between the phenyl group and C(5) methylene group on the pyrrolidine ring, the M-form would be preferred. In addition, nucleophiles usually have favored attacking on the terminal π-allylic carbon located *trans* to the phosphorous donor, because it is a better π-acceptor carbon in the case of the *P*,*N*-ligand.[15] Therefore, when **1a** was used, an (*R*)-product would be expected to be formed through the M-form intermediate **I** by nucleophilic attack of malonate at the position indicated by the arrow. In fact, the (*R*)-isomer was produced selectively. When a hydrogen of the (*S*)-stereogenic center in the pyridinylethyl unit is placed on the front side of **I**, both the pyridinyl and methyl groups can take positions with no severe steric congestion. On the other hand, when the corresponding hydrogen of the (*R*)-stereogenic center derived from **1a**′ occupies the same front side, steric interactions between the methyl groups and the methylene hydrogens at C(2) of the pyrrolidine ring are inevitable. The electron donating property of a nitrogen atom on the pyridine ring may weakly influence the Pd center or π-allyl acceptor but surely destabilizes the intermediate. This undesirable effect at the pyridine ring leads to decreased enantioselectivity. The aryl group with or without methyl substituents, located at the 6-position on the pyridine ring, might interfere with the nitrogen atom of the pyridine ring close to the Pd center or π-allyl acceptor.

3. Conclusion

Several homochiral *P*,*N*-ligands **1** having chiral (2-pyridinyl)ethyl and 2-(diphenylphosphino)methylpyrrolidinyl moieties have been newly synthesized in enantiomerically pure form in good yields. Pd-catalyzed asymmetric allylic alkylation using ligands **1** proceeded even at low temperature (where the level of asymmetric induction increases) to give the allylated products with up to 86% e.e.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were recorded on a JEOL LA-300 apparatus at 300 and 75.5 MHz, respectively. Mass spectra were obtained on a JEOL-SX 102A instrument. IR spectra were recorded on a JASCO FT/IR-410 spectrometer. Optical rotations were mea-

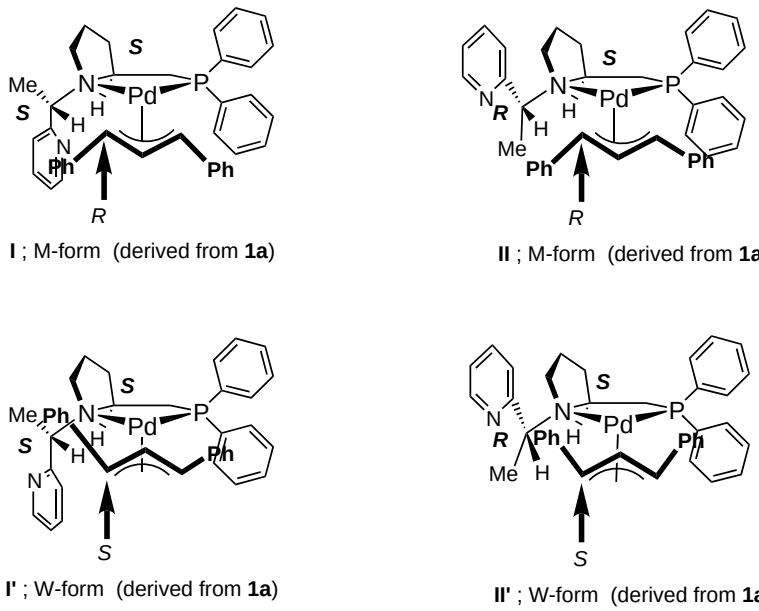


Figure 3.

sured on a JASCO DIP-360 instrument. Thin-layer chromatography (TLC) was performed by using Merck $60F_{254}$ precoated with silica gel on glass plate. Silica gel (Merck $60F_{254}$ 230–400 mesh) was used for flash chromatography.

4.2. General method for the substitution reaction of mesylate 6 with pyrrolidines

A carefully degassed mixture of mesylate **6a**–**d** (0.5 mmol), pyrrolidine **7** or **8** (0.5–1.0 mmol, depending on the economic value of the mesylate and pyrrolidine) and *N*,*N*-diisopropylethylamine (2 mmol) in acetonitrile (2 ml) was heated at 60°C under an argon atmosphere. After the reaction completed, the heating bath was removed and the solvent was evaporated under reduced pressure. Chloroform was added and the mixture was washed with water and brine. The organic layer was dried over $MgSO_4$ and condensed. The residual oil was purified by flash column chromatography on silica gel to give **1a**–**e** and **1′a**. Yields, physical and spectroscopic data together with reaction time and solvents used for column chromatography follow.

4.2.1. (2*S*)-2-(Diphenylphosphino)methyl-*N*-[(1*S*)-1-(2-pyridinyl)ethyl]pyrrolidine 1a. Reaction time 17 h; solvent for chromatography, 50% EtOAc in hexane. Yield 67%; oil; $R_f=0.45$ (2% Et_3N in EtOAc); $[\alpha]_D^{24}=-175$ (*c* 2.1, $CHCl_3$); IR (neat): ν_{max} 3053, 2968, 2871, 1433 cm^{-1}; ^1H NMR (300 MHz): δ 1.39 (d, $J=6.6$ Hz, 3H), 1.55–1.66 (m, 1H), 1.70–1.95 (m, 4H), 2.58–2.76 (m, 3H), 2.90–3.00 (br, 1H), 4.00 (q, $J=6.6$ Hz, 1H), 6.96 (d, $J=7.7$ Hz, 1H), 7.09 (ddd, $J=7.3$, 4.8 and 1.1 Hz, 1H), 7.23–7.40 (m, 10H), 7.48 (td, $J=7.7$ and 1.8 Hz, 1H), 8.50 (ddd, 4.8, 1.8 and 1.1 Hz, 1H); ^{13}C NMR (75 MHz): δ 20.3 (CH_3), 22.5 (C-4), 31.2 (d, $J=8.6$ Hz, C-3), 32.6 (br d, C-6), 48.5 (C-5), 57.5 (d, $J=18.5$ Hz, C-2), 60.3 (*C*H), 121.9, 122.6, 128.3 (4C), 128.4, 128.7, 132.4 (d, $J=17.3$ Hz, 2C), 133.3, (d, $J=19.8$ Hz, 2C), 136.0, 138.1 (d, $J=16.1$ Hz), 139.4, 148.9, 163.2; MS (EI) *m*/*z* 374 (M^+); HRMS (EI) *m*/*z* calcd for $C_{24}H_{27}N_2P$ 374.1912, found 374.1918 (M^+).

4.2.2. (2*S*)-2-(Diphenylphosphino)methyl-*N*-[(1*S*)-1-[2-(6-phenylpyridinyl)]ethyl]pyrrolidine 1b. Reaction time 24 h; solvent for chromatography, 30% EtOAc in hexane. Yield 91%; oil; $R_f=0.26$ (40% EtOAc in hexane); $[\alpha]_D^{24}=-178$ (*c* 2.0, $CHCl_3$); IR (neat) ν_{max}: 3057, 3012, 2970, 2873, 1444 cm^{-1}; ^1H NMR (300 MHz): δ 1.46 (d, $J=7.0$ Hz, 3H), 1.52–1.66 (m, 1H), 1.66–1.88 (m, 3H), 2.04 (td, $J=12.5$ and 2.6 Hz, 1H), 2.72 (dq, $J=11.0$ and 3.3 Hz, 2H), 2.80–2.90 (m, 1H), 2.95–3.05 (m, 1H), 4.13 (q, $J=7.0$ Hz, 1H), 6.87 (dd, $J=7.6$ and 1.8 Hz, 1H), 7.10–7.25 (m, 3H), 7.27–7.35 (m, 5H), 7.36–7.50 (m, 5H), 7.51–7.60 (m, 2H), 8.00 (dd, 8.1 and 1.5 Hz, 2H); ^{13}C NMR (75 MHz): δ 20.3 (CH_3), 22.4 (C-4), 31.3 (d, $J=8.7$ Hz, C-3), 32.7 (d, $J=13.7$ Hz, C-6), 47.7 (C-5), 57.4 (d, $J=18.7$ Hz, C-2), 59.6 (*C*H), 118.2, 120.8, 126.8, 128.3 (d, $J=6.2$ Hz, 4C), 128.5, 128.6 (4C), 128.7, 132.5 (d, $J=18.7$ Hz, 2C), 133.1 (d, $J=19.9$ Hz, 2C), 136.5, 138.5 (d, $J=13.7$ Hz), 139.5, 139.6 (d, $J=12.5$ Hz), 155.9, 161.8; MS (EI) *m*/*z* 450 (M^+); HRMS (EI) *m*/*z* calcd for $C_{30}H_{31}N_2P$ 450.2225, found 450.2231 (M^+).

4.2.3. (2*S*)-*N*-[(1*S*)-1-[2-[6-(3,5-Dimethylphenyl)pyridinyl]]ethyl]-2-(diphenylphosphino)methylpyrrolidine 1c. Reaction time 30 h; solvent for chromatography, 30% EtOAc in hexane. Yield 78%; oil; $R_f=0.15$ (30% EtOAc in hexane); $[\alpha]_D^{24}=-153$ (*c* 0.9, $CHCl_3$); IR (neat) ν_{max}: 3055, 3014, 2958, 2927, 1446 cm^{-1}; ^1H NMR (300 MHz): δ 1.45 (d, $J=7.0$ Hz, 3H), 1.53–1.89 (m, 5H), 2.36 (s, 6H), 2.68–2.88 (m, 3H), 2.93–3.00 (m, 1H), 4.12 (q, $J=7.0$ Hz, 1H), 6.90 (quint, $J=4.4$ Hz, 1H), 7.02 (s, 1H), 7.11–7.32 (m, 8H), 7.42 (td, $J=7.3$ and 2.2 Hz, 2H), 7.52 (d, $J=1.1$ Hz, 1H), 7.53 (s, 1H), 7.60 (s, 2H); ^{13}C NMR (75 MHz): δ 20.6 (CH_3), 21.4 (2C, Ar-CH_3), 22.5 (C-4), 31.3 (d, $J=10.0$ Hz, C-3), 32.6 (d, $J=13.7$ Hz, C-6), 47.9 (C-5), 57.4 (d, $J=17.4$ Hz, C-2), 60.0 (*C*H), 118.5, 120.6, 124.8 (2C), 128.3 (d, $J=6.2$ Hz, 4C), 128.3, 128.5, 130.4 (2C), 132.6 (d, $J=18.7$ Hz, 2C), 133.1 (d, $J=18.7$ Hz, 2C), 136.4, 138.1, 138.4 (d, $J=13.7$ Hz), 139.6, 139.7 (d, $J=11.2$ Hz), 156.4, 162.0; MS (EI) *m*/*z* 478 (M^+); HRMS (EI) *m*/*z* calcd for $C_{32}H_{35}N_2P$ 478.2538, found 478.2540 (M^+).

4.2.4. (2*S*)-*N*-[(1*S*)-1-[2-[6-(2,6-Dimethylphenyl)pyridinyl]]ethyl]-2-(diphenylphosphino)methylpyrrolidine 1d. Reaction time 20 h; solvent for chromatography, 30% EtOAc in hexane. Yield 86%; oil; $R_f=0.15$ (30% EtOAc in hexane); $[\alpha]_D^{24}=-156$ (*c* 1.9, $CHCl_3$); IR (neat) ν_{max}: 3055, 3014, 2958, 2927, 1454 cm^{-1}; ^1H NMR (300 MHz): δ 1.38 (d, $J=7.0$ Hz, 3H), 1.51–1.93 (m, 4H), 1.97 (s, 6H), 2.00–2.19 (m, 1H), 2.54 (dt, $J=13.2$ and 3.7 Hz, 1H), 2.74–2.84 (m, 1H), 2.85–2.97 (m, 2H), 4.01 (q, $J=7.0$ Hz, 1H), 6.96 (d, $J=7.7$ Hz, 1H), 7.02 (d, $J=7.7$ Hz, 1H), 7.06 (d, $J=7.3$ Hz, 2H), 7.13–7.38 (m, 9H), 7.39–7.44 (m, 2H), 7.57 (t, $J=7.7$ Hz, 1H); ^{13}C NMR (75 MHz): δ 20.2 (2C, Ar-CH_3), 21.1 (CH_3), 22.8 (C-4), 31.4 (d, $J=10.0$ Hz, C-3), 33.5 (d, $J=13.7$ Hz, C-6), 49.0 (C-5), 57.7 (d, $J=18.7$ Hz, C-2), 61.0 (*C*H), 120.1, 122.4, 127.4 (2C), 127.6, 128.2 (4C), 128.3, 128.5, 132.5 (d, $J=17.4$ Hz, 2C), 133.1 (d, $J=18.7$ Hz, 2C), 135.7, 136.2 (2C), 138.6 (d, $J=13.7$ Hz), 139.4 (d, $J=12.5$ Hz), 140.8, 158.9, 162.6; MS (EI) *m*/*z* 478 (M^+); HRMS (EI) *m*/*z* calcd for $C_{32}H_{35}N_2P$ 478.2538, found 478.2531 (M^+).

4.2.5. (2*S*)-2-Methoxymethyl-*N*-[(1*S*)-1-(2-pyridinyl)-ethyl]pyrrolidine 1e. Reaction time 10 h; solvent for chromatography, 80% EtOAc in hexane. Yield 96%; oil; $R_f=0.17$ (2% Et_3N in EtOAc); $[\alpha]_D^{25}=-85$ (*c* 1.3, $CHCl_3$); IR (neat) ν_{max}: 2970, 2873, 1589, 1471 cm^{-1}; ^1H NMR (300 MHz): δ 1.48 (d, $J=6.8$ Hz, 3H), 1.55–1.85 (m, 4H), 2.45–2.55 (m, 1H), 2.82–2.90 (m, 1H), 2.97–3.03 (m, 1H), 3.23 (dd, $J=9.4$ and 7.9 Hz, 1H), 3.34 (s, 3H), 3.39 (dd, $J=9.4$ and 4.2 Hz, 1H), 3.98 (q, $J=6.8$ Hz, 1H), 7.13 (ddd, $J=7.5$, 4.8 and, 1.1 Hz, 1H), 7.32 (d, $J=7.7$ Hz, 1H), 7.63 (td, $J=7.7$ and 1.8 Hz, 1H), 8.55 (dt, $J=4.8$ and 1.8 Hz, 1H); ^{13}C NMR (75 MHz): δ 20.8 (CH_3), 23.4 (C-4), 28.8 (C-3), 51.2 (C-5), 59.0 (-O*C*H$_3$), 59.0 (C-6), 63.2 (*C*H), 76.8 (C-2), 121.8, 122.4, 136.0, 148.9, 163.3; MS (FAB) *m*/*z* 221 (M^++H); HRMS (FAB) *m*/*z* calcd for $C_{13}H_{21}N_2O$ 221.1654, found 221.1662 (M^++H).

4.2.6. (2*R*)-2-(Diphenylphosphino)methyl-*N*-[(1*S*)-1-(2-pyridinyl)ethyl]pyrrolidine 1a′. Reaction time 8 h; solvent for chromatography, 60% EtOAc in hexane. Yield 70%; oil; R_f=0.47 (2% Et_3N in EtOAc); $[\alpha]_D^{26}$=+66 (*c* 1.3, $CHCl_3$); IR (neat) ν_{max}: 3051, 2966, 2871, 1433 cm^{-1}; ^1H NMR (300 MHz): δ 1.27 (d, *J*=6.6 Hz, 3H), 1.60–1.83 (m, 3H), 1.85–2.00 (m, 2H), 2.24 (dt, *J*=9.2 and 4.0 Hz, 1H), 2.53 (q, *J*=7.7 Hz, 1H) 2.75–3.00 (br, 2H), 3.91 (q, *J*=6.6 Hz, 1H), 7.09 (ddd, *J*=7.3, 5.1 and 1.1 Hz, 1H), 7.24–7.40 (m, 11H), 7.56 (td, *J*=7.7 and 1.8 Hz, 1H), 8.50 (ddd, 4.8, 1.8 and 1.1 Hz, 1H); ^{13}C NMR (75 MHz): δ 16.5 (CH_3), 22.9 (C-4), 31.2 (d, *J*=8.7 Hz, C-3), 33.5 (d, *J*=13.7 Hz, C-6), 49.2 (C-5), 58.9 (d, *J*=15.9 Hz, C-2), 61.6 (*C*H), 121.8, 122.3, 128.3 (4C), 128.4, 128.6, 132.4 (d, *J*=18.6 Hz, 2C), 133.1 (d, *J*=18.5 Hz, 2C), 136.2, 138.4 (d, *J*=13.6 Hz), 139.3 (d, *J*=12.4 Hz), 148.8, 164.2; MS (EI) *m*/*z* 374 (M^+); HRMS (EI) *m*/*z* calcd for $C_{24}H_{27}N_2P$ 374.1912, found 374.1915 (M^+).

4.3. Preparation of 6-aryl substituted 1-(2-pyridinyl)-ethanol 5b–d

To a mixture of 1-[2-(6-bromopyridinyl)]ethanol **4*R*** (0.5 mmol), arylboronic acid (2.0 mmol) in THF (20 ml), were added $Pd(PPh_3)_4$ (0.025 mmol) and Na_2CO_3 (2.5 ml, 2.0 M aq. solution). The mixture was degassed and heated under reflux for 8 h for phenylboronic acid, 24 h for 3,5-dimethylphenylboronic acid and 50 h for 2,6-dimethylphenylboronic acid. After cooling, the solvent was evaporated. EtOAc was added and washed with aq. $NaHCO_3$, water, brine and dried over $MgSO_4$. Solvent was removed and the residue was purified by flash column chromatography on silica gel. Yields, physical and spectroscopic data together with reaction time and solvents used for column chromatography follow.

4.3.1. (*R*)-1-[2-(6-Phenylpyridinyl)]ethanol 5b. Reaction time 8 h; solvent for chromatography, 10% Et_2O in benzene. Yield 84%. Physical and spectroscopic data was reported.[9a]

4.3.2. (*R*)-1-[2-[6-(3,5-Dimethylphenyl)pyridinyl]]ethanol 5c. Reaction time 24 h; solvent for chromatography 15% EtOAc in hexane. Yield 69%; oil; R_f=0.27 (20% EtOAc in hexane); $[\alpha]_D^{24}$=−21 (*c* 2.2, $CHCl_3$); IR (neat) ν_{max}: 3400, 2974, 2920 cm^{-1}; ^1H NMR (300 MHz): δ 1.55 (d, *J*=6.2 Hz, 3H), 2.40 (s, 6H), 4.85 (br, 1H), 4.94 (br q, *J*=6.2 Hz, 1H), 7.07 (br s, 1H), 7.17 (d, *J*=7.3 Hz, 1H), 7.61 (d, *J*=7.3 Hz, 1H), 7.62 (s, 2H), 7.73 (t, *J*=7.7 Hz, 1H); ^{13}C NMR (75 MHz): δ 21.4 (CH_3), 24.4 (2C, Ar-CH_3), 68.5 (*C*H), 118.0, 119.0, 124.8 (2C), 130.8 (2C), 137.5, 138.3, 138.7, 155.9, 162.3; MS (EI) *m*/*z* 227 (M^+); HRMS (EI) *m*/*z* calcd for $C_{15}H_{17}NO$ 227.1310, found 227.1307 (M^+).

4.3.3. (*R*)-1-[2-[6-(2,6-Dimethylphenyl)pyridinyl]]ethanol 5d. Reaction time 50 h; solvent for chromatography 20% EtOAc in hexane. Yield 97%; oil; R_f=0.10 (10% Et_2O in benzene); $[\alpha]_D^{24}$=−5 (*c* 0.9, $CHCl_3$); IR (neat) ν_{max}: 3388, 2972, 2924 cm^{-1}; ^1H NMR (300 MHz): δ 1.53 (d, *J*=6.3 Hz, 3H), 2.05 (s, 6H), 4.36 (d, *J*=4.6 Hz, 1H), 4.94 (qd, *J*=6.3 and 4.6 Hz, 1H), 7.11–7.15 (m, 3H), 7.20 (d, *J*=6.6 Hz, 1H), 7.23 (d, *J*=6.6 Hz, 1H), 7.76 (t, *J*=7.8 Hz, 1H); ^{13}C NMR (75 MHz): δ 20.2 (2C, Ar-CH_3), 24.5 (CH_3), 68.8 (*C*H), 117.6, 123.0, 127.6 (2C), 128.0, 135.8, 137.0 (2C), 140.2, 158.2, 162.9; MS (EI) *m*/*z* 227 (M^+); HRMS (EI) *m*/*z* calcd for $C_{15}H_{17}NO$ 227.1310, found 227.1305 (M^+).

4.4. Mesylation of 5

To a solution of 1-(2-pyridinyl)ethanol **5** (0.50 mmol), Et_3N (4.0 mmol) and DMAP (0.15 mmol) in CH_2Cl_2 (5 ml) was added MsCl (1.5 mmol) at 0°C. The mixture was stirred for 30 min at the same temperature. Then, water and EtOAc were added. The organic layer was separated and washed with water and brine and dried over $MgSO_4$. After the solvent was removed, the residue was purified by flash column chromatography on silica gel to give **6b–d**. Yields, physical and spectroscopic data together with solvents used for column chromatography follow.

4.4.1. (*R*)-1-[2-(6-Phenylpyridinyl)]ethyl methanesulfonate 6b. Solvent for chromatography 15% EtOAc in hexane. Yield 98%; oil; R_f=0.49 (20% EtOAc in hexane); $[\alpha]_D^{24}$=+62 (*c* 1.8, $CHCl_3$); IR (neat) ν_{max}: 2987, 2937, 1972, 1733 cm^{-1}; ^1H NMR (300 MHz): δ 1.84 (d, *J*=6.6 Hz, 3H), 2.95 (s, 3H), 5.87 (q, *J*=6.6 Hz, 1H), 7.40–7.51 (m, 4H), 7.72 (d, *J*=7.7 Hz, 1H), 7.81 (t, *J*=7.7 Hz, 1H) 8.01–8.05 (m, 2H); ^{13}C NMR (75 MHz): δ 21.7 (CH_3), 38.8 (SO_2-CH_3), 81.1 (*C*H), 118.9, 120.0, 126.9 (2C), 128.8 (2C), 129.3, 137.9, 138.6, 156.9, 158.0; MS (EI) *m*/*z* 277 (M^+); HRMS (EI) *m*/*z* calcd for $C_{14}H_{15}NO_3S$ 277.0772, found 277.0773 (M^+).

4.4.2. (*R*)-1-[2-[6-(3,5-Dimethylphenyl)pyridinyl]]ethyl methanesulfonate 6c. Solvent for chromatography 5% Et_2O in benzene. Yield 91%; oil; R_f=0.49 (10% Et_2O in benzene); $[\alpha]_D^{24}$=+25 (*c* 1.9, $CHCl_3$); IR (neat) ν_{max}: 2985, 2937, 1734 cm^{-1}; ^1H NMR (300 MHz): δ 1.83 (d, *J*=6.6 Hz, 3H), 2.40 (s, 6H), 2.94 (s, 3H), 5.86 (q, *J*=6.6 Hz, 1H), 7.07 (s, 1H), 7.39 (dd, *J*=7.3 and 1.1 Hz, 1H), 7.61 (s, 2H), 7.68 (dd, *J*=7.3 and 1.1 Hz, 1H), 7.79 (t, *J*=7.7 Hz, 1H); ^{13}C NMR (75 MHz): δ 21.4 (CH_3), 21.8 (2C, Ar-CH_3), 38.7 (SO_2-CH_3), 81.3 (*C*H), 118.7, 120.2, 124.8 (2C), 130.9 (2C), 137.7, 138.3, 138.7, 157.3, 158.0; MS (EI) *m*/*z* 305 (M^+); HRMS (EI) *m*/*z* calcd for $C_{16}H_{19}NO_3S$ 305.1085, found 305.1081 (M^+).

4.4.3. (*R*)-1-[2-[6-(2,6-Dimethylphenyl)pyridinyl]]ethyl methanesulfonate 6d. Solvent for chromatography 10% Et_2O in benzene. Yield 92%; oil; R_f=0.44 (10% Et_2O in benzene); $[\alpha]_D^{25}$=+53 (*c* 1.1, $CHCl_3$); IR (neat) ν_{max}: 3026, 2983, 1587 cm^{-1}; ^1H NMR (300 MHz): δ 1.78 (d, *J*=6.6 Hz, 3H), 2.03 (s, 6H), 2.96 (s, 3H), 5.84 (q, *J*=6.6 Hz, 1H), 7.11 (d, *J*=7.3 Hz, 2H), 7.12–7.23 (m, 2H), 7.45 (d, *J*=7.6 Hz, 1H), 7.83 (t, *J*=7.7 Hz, 1H); ^{13}C NMR (75 MHz): δ 20.2 (2C, Ar-CH_3), 22.0 (CH_3), 38.6 (SO_2-CH_3), 80.8 (*C*H), 118.4, 124.3, 127.7 (2C), 128.1, 135.6, 137.4 (2C), 139.9, 158.4, 159.6; MS (EI) *m*/*z* 305 (M^+); HRMS (EI) *m*/*z* calcd for $C_{16}H_{19}NO_3S$ 305.1085, found 305.1088 (M^+).

4.5. (*S*)-2-(Diphenylphosphino)methyl-*N*-(2-pyridinyl)-methylpyrrolidine 2

A solution of 2-pyridinylmethyl chloride hydrochloride **9** (61 mg, 0.37 mmol) and (*S*)-**7** (50 mg, 0.18 mmol) in a mixture of $^{i}Pr_2NEt$ and acetonitrile (1:2, 1.2 ml) was degassed and heated at 60°C for 6 h under an Ar atmosphere. After cooling, the mixture was concentrated, and $CHCl_3$ was added. The resulting solution was washed with water and brine, dried over Na_2SO_4. The solvent was removed and the residue was purified by flash column chromatography on silica gel eluted with EtOAc to give **2** (44 mg, 68%). Oil; $R_f=0.51$ (5% Et_3N in EtOAc); $[\alpha]_D^{24}=-115$ (*c* 1.65, $CHCl_3$); IR (neat) ν_{max}: 3055, 2962, 2873, 1435 cm^{-1}; ^1H NMR (300 MHz): δ 1.60–1.85 (m, 3H), 1.95–2.26 (m, 3H), 2.50–2.65 (m, 2H), 2.97 (br t, $J=7.7$ Hz, 1H), 3.37 (d, $J=13.6$ Hz, 1H), 4.14 (d, $J=13.6$ Hz, 1H), 7.11 (dd, $J=7.3$ and 5.1 Hz, 1H), 7.25–7.35 (m, 7H), 7.36–7.50 (m, 4H), 7.57 (td, $J=7.7$ and 1.8 Hz, 1H), 8.51 (ddm, $J=4.0$ and 0.7 Hz, 1H); ^{13}C NMR (75 MHz): δ 22.2 (C-4), 31.6 (d, $J=7.5$ Hz, C-3), 33.7 (d, $J=13.7$ Hz, C-6), 54.0 (C-5), 59.9 (CH_2), 62.0 (d, $J=18.7$ Hz, C-2), 121.7, 123.0, 128.3 (d, $J=7.5$ Hz, 4C), 128.4, 128.7, 132.5 (d, $J=18.7$ Hz, 2C), 133.0 (d, $J=19.9$ Hz, 2C), 136.2, 138.4 (d, $J=13.7$ Hz), 139.3 (d, $J=12.5$ Hz), 149.0, 159.5; MS (EI) *m*/*z* 360 (M^+); HRMS (EI) *m*/*z* calcd for $C_{23}H_{25}N_2P$ 360.1755, found 360.1759 (M^+).

4.6. (2*S*)-2-(Diphenylphosphino)methyl-*N*-[(1*S*)-1-phenylethyl]pyrrolidine 3 and its diastereoisomer 3′

A solution of 1-(phenyl)ethyl bromide **10** (100 mg, 0.37 mmol) and (*S*)-**7** (137 mg, 0.74 mmol) in a mixture of $^{i}Pr_2NEt$ and acetonitrile (1:3, 1.2 ml) was degassed and stirred for 6 h at room temperature. After the same work up as described for **2**, a mixture of **3** and **3′** (116 mg) was obtained in 84% yield. The mixture was separated by HPLC. Polar diastereomer **3**; (51 mg, 37%); oil; $R_f=0.23$ (30% EtOAc in hexane); $[\alpha]_D^{25}=-173$ (*c* 0.9, $CHCl_3$); IR (neat) ν_{max}: 3055, 2966, 2873, 1585 cm^{-1}; ^1H NMR (300 MHz): δ 1.33 (d, $J=6.8$ Hz, 3H), 1.53–1.63 (m, 1H), 1.70–1.90 (m, 3H), 1.94–2.05 (m, 1H), 2.36–2.46 (m, 1H), 2.54 (ddd, $J=13.0$, 4.8 and 2.9 Hz, 1H), 2.60–2.70 (m, 1H), 2.80–2.90 (m, 1H), 3.78 (q, $J=6.8$ Hz, 1H), 7.00 (dd, $J=6.6$ and 2.4 Hz, 2H), 7.17–7.21 (m, 3H), 7.23–7.38 (m, 8H), 7.39–7.44 (m, 2H); ^{13}C NMR (75 MHz): δ 21.6 (CH_3), 22.5 (C-4), 31.2 (d, $J=8.7$ Hz, C-3), 33.5 (d, $J=13.7$ Hz, C-6), 48.4 (C-5), 57.0 (d, $J=19.8$ Hz, C-2), 58.8 (*C*H), 126.8, 128.1 (d, $J=8.7$ Hz, 2C), 128.2 (d, $J=10.0$ Hz, 2C), 128.3, 128.4 (2C), 128.5, 128.7 (2C), 132.4 (d, $J=17.4$ Hz, 2C), 133.4 (d, $J=19.9$ Hz, 2C), 138.4 (d, $J=14.9$ Hz), 139.5 (d, $J=13.1$ Hz), 141.6; MS (EI) *m*/*z* 373 (M^+); HRMS (EI) *m*/*z* calcd for $C_{25}H_{28}NP$ 373.1959, found 373.1958 (M^+). Less polar diastereomer **3′**; (47 mg, 34%); oil; $R_f=0.23$ (30% EtOAc in hexane); $[\alpha]_D^{25}=-81$ (*c* 0.8, $CHCl_3$); IR (neat) ν_{max}: 3055, 2966, 2873, 1585 cm^{-1}; ^1H NMR (300 MHz): δ 1.22 (d, $J=6.6$ Hz, 3H), 1.60–1.95 (m, 5H), 2.23 (ddd, $J=13.2$, 4.8 and 3.3 Hz, 1H), 2.45 (q, $J=7.7$ Hz, 1H), 2.78–2.90 (m, 2H), 3.68 (q, $J=6.6$ Hz, 1H), 7.20–7.40 (m, 15H); ^{13}C NMR (75 MHz): δ 18.4 (CH_3), 23.0 (C-4), 31.2 (d, $J=8.7$ Hz, C-3), 33.9 (d, $J=13.7$ Hz, C-6), 50.0 (C-5), 58.9 (d, $J=18.7$ Hz, C-2), 60.6 (*C*H), 126.7, 127.7 (2C), 128.2 (4C), 128.3 (2C), 128.4, 128.5, 132.4 (d, $J=18.7$ Hz, 2C), 133.1 (d, $J=18.7$ Hz, 2C), 138.3 (d, $J=13.7$ Hz), 139.4 (d, $J=12.5$ Hz), 145.3; MS (EI) *m*/*z* 373 (M^+); HRMS (EI) *m*/*z* calcd for $C_{25}H_{28}NP$ 373.1959, found 373.1954 (M^+).

4.7. Palladium-catalyzed allylic alkylation

A mixture of ligand **1**, **2**, or **3** (0.06 mmol) and $[PdCl(\pi\text{-}C_3H_5)]_2$ (10.0 mg, 0.02 mmol) was stirred in THF (1 ml) for 15 min at room temperature. Then, 1,3-diphenyl-2-propenyl acetate **11** (134 mg, 0.54 mmol) in THF (1 ml) was added to the mixture, and stirred for 30 min. The mixture was added to a solution of dimethyl malonate sodium salt (0.25 M in THF, 1.08 mmol) in THF (4 ml). After the starting material was consumed by tlc analysis, benzene and 10% aq. HCl were added, and the mixture was heated under reflux for 1 h. The aqueous layer was re-extracted with Et_2O. All the organic extracts were combined, washed with saturated aq. $NaHCO_3$, water and brine and dried over Na_2SO_4. After the solvent was removed, the residue was purified by flash column chromatography on silica gel eluted with 10% EtOAc in hexane to give **12** as an oil. The absolute configuration of **12** was determined by comparison of its chiroptical value with that of the reported data.[13] The e.e. value was determined by HPLC analysis attached with an optically active column (Daicel OJ).

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