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t-BuOK-Mediated Hydrophosphination of Functionalized Alkenes: A Novel Synthesis of Chiral P,N- and P,P-Ligands

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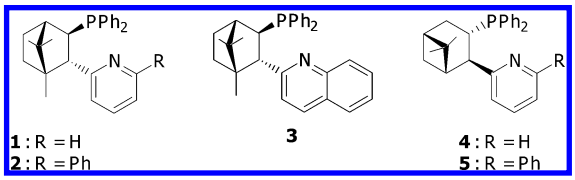
A novel synthesis of effective chiral P,N- and P,P-ligands has been developed by using a *t*-BuOK-mediated hydrophosphination of chiral alkenylpyridines and alkenylphosphine oxides. Ir complexes of chiral P,N-ligands **1** and **3** gave high enantioselectivities for the hydrogenation of (*Z*)-α-(acetamido)cinnamate **25** and (*E*)-1,2-diphenylpropene leading to the hydrogenated products with up to 97% ee.

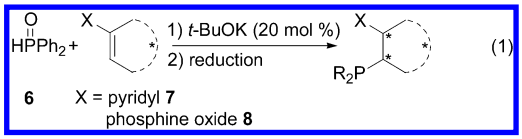
Introduction

Tertiary phosphines are an important class of compounds. They are widely employed both as ligands for transition metal complexes and in various catalytic processes.[1] Thus, there is a considerable interest in developing new methodologies allowing the stereoselective formation of carbon−phosphorus bonds. Taking atom economy principles into consideration,[2] a route involving the addition of phosphines (HPR_2) to alkenes would be desirable. This reaction has been reported in the literature and was carried out in the presence of a radical initiators,[3] strong basic conditions,[4] or transition metal catalysis.[5] The use of phosphine−borane complexes is also possible and enables selective hydrophosphinations.[6] Recently, we reported that *t*-BuOK-mediated addition reactions of nucleophiles (carbonyl derivatives and phosphanes) led to a variety of functionalized alkenes.[7] We have applied this method for the preparation of modular pyridine-type P,N-ligands **1**−**5** (Scheme 1). These modular P,N-ligands were proved to be efficient ligands for Ir-catalyzed enantioselective hydrogenation reactions[8] and Pd-catalyzed allylic substitution reactions.[9]

SCHEME 1



Herein, we wish to report the full details for the synthesis of novel chiral P,N-ligands **1**−**5** and the extension to the synthesis of chiral P,P-ligands using *t*-BuOK-mediated hydrophosphination of alkenylpyridine **7** and alkenylphosphine oxide **8** (eq 1).



Results and Discussion

On the basis of our preliminary preparation of *rac-trans*-aminophosphine oxide **9** and *rac-trans*-aminophosphine **10** (Scheme 2),[7c] we turned our attention to the preparation of novel chiral P,N-ligands of type **1**−**5**, starting from readily available chiral building blocks such as (+)-camphor (**10**) and (+)-nopinone (**13**).

The preparation of the corresponding alkenyl triflates has been performed according to the literature.[10] Treatment of the lithium enolate anions of commercially available (+)-camphor (**11**) and (+)-nopinone (**13**) with *N*-phenyltrifluoromethanesulfonamide (Tf_2NPh) in THF

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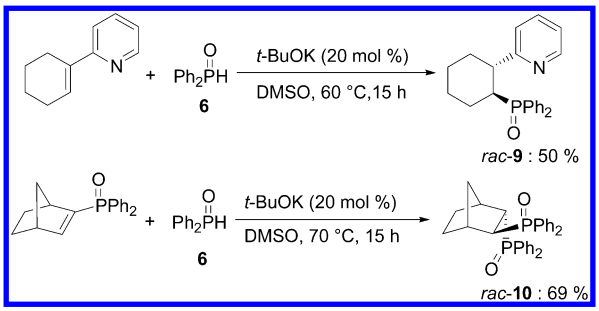
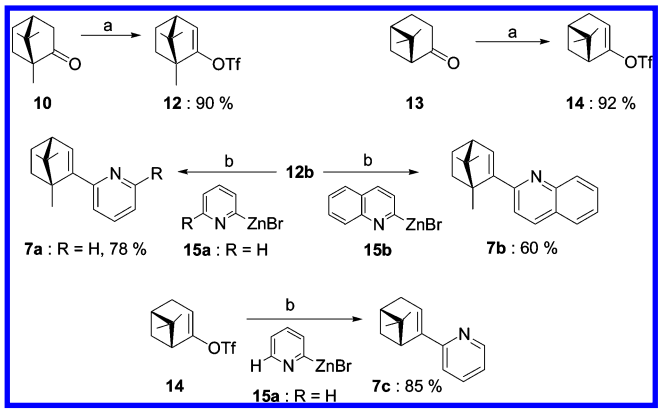
SCHEME 2



SCHEME 3[a]



[a] Reagent and conditions: (a) LDA, THF, Tf_2NPh, −78 to 0 °C, 16 h; (b) $Pd(dba)_2$ (2 mol %), dppf (2 mol %), THF, LiCl, 70 °C, 16 h.

at 0 °C led to the desired alkenyl triflates in 90−92% yield (Scheme 3). The chiral alkenyl triflates **12**−**14** smoothly underwent Negishi cross-coupling reactions[11] with 2-pyridylzinc bromide **15a** prepared from commercially available 2-bromopyridine by direct Br−Li exchange, affording the desired 2-alkenylpyridines **7a** and **7c** in 78−85% yield (Scheme 3). 2-Alkenylquinoline **7b** was obtained in satisfactory yield (60%) through a Pd-catalyzed cross-coupling of 2-quinolylzinc bromide **15b** with alkenyl triflate **12** in the presence of LiCl as shown in Scheme 3.

We have then examined the preparation of substituted bromopyridines **7d**,**e**. A method developed by Cai[12] allows the formation of monometalated species. Subsequent transmetalation with anhydrous zinc bromide, followed by Negishi cross-coupling reactions, led to the expected coupling products **16a**,**b** in 34−70% yield. Afterward, the bromopyridines **16a**,**b** underwent a Suzuki cross-coupling reactions with phenylboronic acid in the presence of a catalytic amount of $Pd(PPh_3)_4$ giving 2-alkenyl-6-phenylpyridines **7d**,**e**, respectively, in high yields (Scheme 4).[13]

Initially, treatment of alkenylpyridine **7a** with Ph_2PH using *t*-BuOK in DMSO led to a mixture of P,N-ligand **1** and aminophosphine oxide **17a**. Attempts to purify the mixture by recrystallization or column chromatography either using silica gel or alumina oxide were unsuccessful. We considered the performance of the hydrophosphination with $Ph_2P(O)H$ (**6**), followed by reduction of **17a** to aminophosphine **1**. Thus, the addition of phosphine oxide **6** to alkenylpyridine **7a** in the presence of substoichiometric amounts of *t*-BuOK (20 mol %) in DMSO furnished aminophosphine oxide **17a** in 87% yield as a single diastereomer (Scheme 5). Under these standard conditions, a new class of modular chiral aminophosphine oxides **17a**−**e** was prepared in good yields (72−87% yield). The products were characterized by NOESY NMR experiments and by X-ray crystal structure analysis.[8] Having the novel aminophosphine oxides **17a**−**e** in hand, the reduction of **17a**−**e** was achieved with $HSiCl_3$ and Et_3N in toluene upon heating to 120 °C, yielding chiral aminophosphines **1**−**5** in 61−92% yield (Scheme 5).[14]

After these successful results for the synthesis of chiral P,N-ligands, we extended our methodology for the synthesis of chiral 1,2-diphosphines. Helmchen et al. previously reported the addition of diphenylphosphine to Michael acceptors.[15] Thus, we applied our methodology for the synthesis of chiral 1,2-diphosphines by the addition of phosphine oxide **6** to the alkenylphosphine oxide **8a** in the presence of *t*-BuOK (20 mol %) in DMSO. Unfortunately, we observed solely starting material **8a** even after heating to 90 °C for 16 h (Scheme 6).

Assuming that the steric hindrance of the substituents on the phosphine oxide was accountable for this failure, we changed the substituents on the phosphine oxide from phenyl to 2-furyl group. First, Pd-catalyzed cross-coupling[16] of di-2-furylphosphine oxide **18** with alkenyl triflate **12** led to alkenylphosphine oxide **8b** in 58% yield. Treatment of alkenylphosphine oxide **8b** with phosphine oxide **6** in the presence of *t*-BuOK (20 mol %) provided chiral diphosphine oxide **20** in 70% yield. The reduction of phosphine oxides **19** was performed under the same conditions ($HSiCl_3/Et_3N$ in toluene) furnishing the chiral diphosphine ligand **20** in 68% yield (Scheme 7).

We have tested the novel chiral P,N-ligands **1**−**5** and chiral P,P-ligand **20** in asymmetric catalysis. Pfaltz et al. have reported that iridium phosphinooxazoline complexes are highly effective catalysts for enantioselective hydrogenation reactions of olefins including unfunctionalized alkenes.[17] Following Pfaltz's procedure,[18] Ir complexes **1**−**4** were readily prepared by heating a solution of $[Ir(cod)Cl]_2$ and the respective P,N-ligands **1**−**4** in CH_2Cl_2 (1 h). After treatment with sodium tetrakis[3,5-bis-

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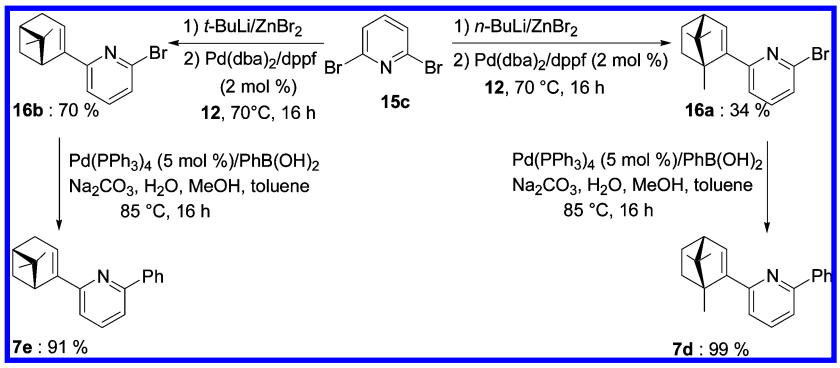
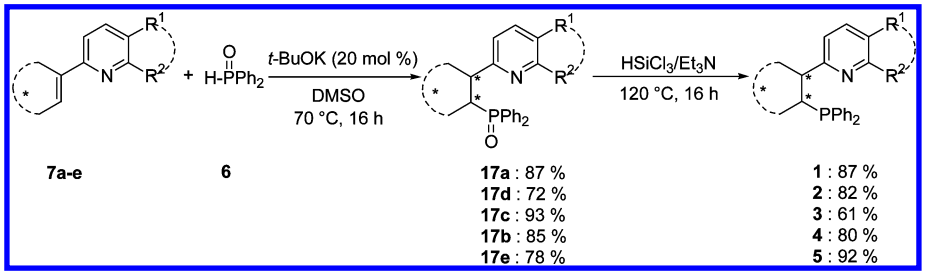
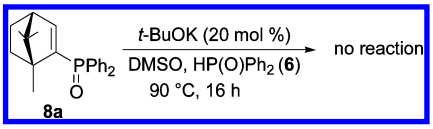
SCHEME 4



SCHEME 5



SCHEME 6



(trifluoromethyl)phenyl]borate (NaBARF) in a biphasic $CH_2Cl_2-H_2O$ system, the resulting orange BARF salts (Ir−**1**−**4**) were purified by column chromatography on silica gel (50% CH_2Cl_2 in pentane). These complexes were stable toward oxygen and moisture (Scheme 8).

Among the Ir complexes of **1**−**4**, Ir−**3** exhibited high enantioselectivities in hydrogenation reactions of (*E*)-1,2-diphenylpropene and 2-(4-methoxyphenyl)-1-phenyl-1-propene leading to the hydrogenated products **21** and **22** in 95% ee (Scheme 9). Additionally, trisubstituted functionalized alkenes such as ethyl 3-phenylbutenoate (**23**), 2-methyl-3-phenylallyl alcohol (**24**), and 2-methyl-3-phenylallyl acetate (**25**) were also hydrogenated in the presence of Ir−**3** (1 mol %; 50 bar of H_2, rt, 12 h). The hydrogenated products were obtained with moderate to good enantioselectivities (58−80% ee; see Scheme 9).

The hydrogenation of unsaturated enamides such as **26** to amino acid derivatives such as **27** is of special interest. This enantioselective hydrogenation was extensively studied using Rh catalysts.[19] To the best of our knowledge, no enantioselective Ir-catalyzed hydrogenation reactions of these substrates were reported. We describe for the first time that the hydrogenation of **26** in the presence of Ir−**1** provided phenylalanine derivative **27** in high enantioselectivity (97% ee) with full conversion. Remarkably, this reaction was carried out under 1 bar of H_2 at 50 °C, 16 h (Scheme 10).

The asymmetric hydroboration of styrene with catecholborane using chiral BINAP gave high enantioselectivity as shown by Hayashi.[20] We have used the chiral ligand **20** in the Rh-catalyzed asymmetric hydroboration of styrene and have found a complete regioselectivity of hydroboration leading to the branched alcohol **28** after oxidation (30% H_2O_2, 2 M NaOH) in 72% yield and moderate enantioselectivity (61% ee, Scheme 11).

Conclusion

In summary, novel chiral P,N-ligands **1**−**5** have been prepared in high yield through *t*-BuOK-mediated addition of phosphine oxides **6** to alkenylpyridines **7a**−**e**. They are effective ligands in Ir-catalyzed asymmetric hydrogenation reactions of (*E*)-1,2-diphenylpropene leading to the hydrogenated product in 95% ee. Remarkably, we also reported for the first time that novel chiral P,N-ligands could be used for asymmetric Ir-catalyzed hydrogenation reactions of dehydroamino acid derivatives such as (*Z*)-α-(acetamido)cinnamate **26** leading to phenylalanine derivative **27** in high enantioselectivity (97% ee). We have described the preparation of chiral diphosphine ligand **20** through addition of $Ph_2P(O)H$ (**6**) to alkenylphosphine oxide **8b** in the presence of substoichiometric amounts of *t*-BuOK (20 mol %) in DMSO. Application in asymmetric catalysis such as Rh-catalyzed hydroboration of styrene using chiral ligand **20** gave only moderate enantioselectivity of **28** (61% ee). Further applications in new asymmetric catalysis as well as the synthesis of chiral modular chiral P,P-ligands are currently underway in our laboratories.

Experimental Section

General Procedure for Negishi Cross-Coupling Reactions. A solution of *n*-BuLi (13.4 mL, 1.5 M in hexane, 20 mmol) was added dropwise at −78 °C to a solution of

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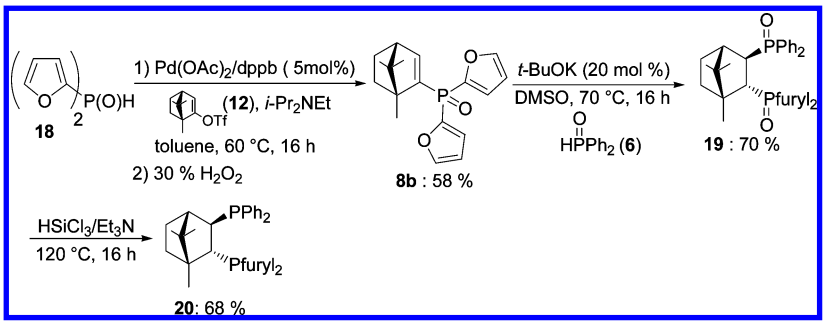
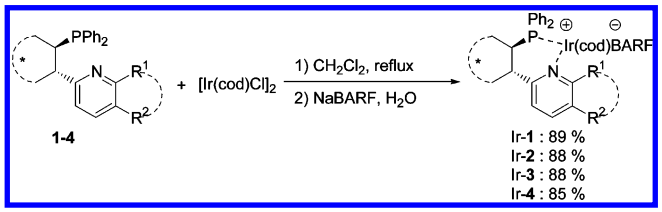
SCHEME 7



SCHEME 8



2-bromopyridine (20 mmol) in THF (20 mL). The reaction mixture was stirred at −78 °C for 30 min, and then a solution of $ZnBr_2$ (12.4 mL, 1.7 M in THF, 21 mmol) was added dropwise. After 15 min at −78 °C, the reaction mixture was allowed to warm to room temperature for 30 min, and then a solution of the alkenyl triflate (10 mmol), $Pd(dba)_2$ (115 mg, 0.2 mmol, 2 mol %), and dppf (111 mg, 0.2 mmol, 2 mol %) in THF (15 mL) was added dropwise. The reaction mixture was heated to reflux (70 °C) for 15 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (40 mL), and the aqueous phase was extracted with Et_2O (3 × 60 mL). The organic phase was washed with brine and dried ($MgSO_4$) and concentrated in vacuo. Purification by flash chromatography yielded the desired product.

2-[(1*R*,4*R*)-1,7,7-Trimethylbicyclo[2.2.1]hept-2-en-2-yl]-pyridine (7a): 78% yield as a pale yellow liquid. Purification by flash chromatography using 20% Et_2O in pentane: $[\alpha]^{27}_D$ −176.4 (*c* 1.825, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.47 (ddd, J = 4.8, 1.8, 0.9 Hz, 1H), 7.48 (dt, J = 7.5, 1.8 Hz, 1H), 7.20 (m, 1H), 6.97 (ddd, J = 7.5, 4.8, 1.2 Hz, 1H), 6.26 (d, J = 3.3 Hz, 1H), 2.35 (t, J = 3.6 Hz, 1H), 1.92−1.82 (m, 1H), 1.68−1.56 (m, 1H), 1.40−1.28 (m, 1H), 1.17 (s, 3H), 1.08−0.96 (m, 1H), 0.81 (s, 3H), 0.75 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.8, 149.8, 149.4, 136.1, 135.9, 121.5, 121.3, 57.3, 55.3, 52.2, 32.1, 26.0, 20.1, 14.5, 12.8; IR (KBr, cm^{-1}) 2953, 2872, 1583, 1560, 1464, 1430, 1385, 775.

2-Bromo-6-[(1*R*,5*S*)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl]pyridine (16a): 34% yield as a pale yellow liquid. Purification by flash chromatography using 2% Et_2O in pentane: ^1H NMR (300 MHz, $CDCl_3$) δ 7.32 (t, J = 7.7 Hz, 1H), 7.20−7.12 (m, 2H), 6.37 (d, J = 3.3 Hz, 1H), 2.34 (t, J = 3.6 Hz, 1H), 1.94−1.82 (m, 1H), 1.64−1.55 (m, 1H), 1.36−1.28 (m, 1H), 1.20 (s, 3H), 1.08−0.98 (m, 1H), 0.78 (s, 3H), 0.75 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.6, 148.3, 141.6, 138.3, 137.7, 125.2, 119.7, 57.3, 55.2, 52.2, 31.9, 26.0, 20.0, 19.9, 12.7; IR (KBr, cm^{-1}) 1575, 1543, 1432, 1387, 1158, 1117, 985, 787.

2-[(1*R*,4*R*)-1,7,7-Trimethylbicyclo[2.2.1]hept-2-en-2-yl]-quinoline (7b): 60% yield as a white solid. Purification by flash chromatography using 5% Et_2O in pentane: mp 96−98 °C; $[\alpha]^{23}_D$ −181.3 (*c* 0.45, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.98−7.86 (m, 2H), 7.62−7.50 (m, 2H), 7.40−7.28 (m, 2H), 6.44 (d, J = 3.6 Hz, 1H), 2.39 (t, J = 3.6 Hz, 1H), 1.95−1.84 (m, 1H), 1.70−1.61 (m, 1H), 1.48−1.37 (m, 1H), 1.35 (s, 3H), 1.07−0.98 (m, 1H), 0.83 (s, 3H), 0.77 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.5, 150.1, 148.3, 137.8, 135.6, 130.0, 129.4, 127.6, 127.0, 125.9, 120.2, 57.1, 55.7, 52.5, 32.1, 26.2, 20.2, 19.9, 13.1; IR (KBr, cm^{-1}) 1600, 1500, 1424, 1232, 1107, 820, 765; MS (EI, 70 eV) 263 (M^+, 70), 248 (100), 220 (62); HRMS calcd for $C_{19}H_{21}N$ (M^+) 263.1674, found 263.1658.

2-[(1*R*,5*S*)-6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl]-pyridine (7c): 89% yield as a pale yellow liquid. Purification by flash chromatography using 5% Et_2O in pentane: $[\alpha]^{23}_D$ −27.0 (*c* 0.725, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.46 (ddd, J = 4.8, 1.8, 0.9 Hz, 1H), 7.48 (dt, J = 7.5, 1.8 Hz, 1H), 7.32−7.25 (m, 1H), 6.97 (ddd, J = 7.5, 4.8, 0.9 Hz, 1H), 6.30−6.26 (m, 1H), 3.03−2.97 (m, 1H), 2.48−2.32 (m, 4H), 1.30 (s, 3H), 1.21 (d, J = 8.7 Hz, 1H), 0.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.2, 149.4, 147.8, 136.4, 124.5, 121.6, 119.3, 43.2, 41.1, 38.2, 32.4, 31.9, 26.6, 21.3; IR (KBr, cm^{-1}) 1624, 1585, 1562, 1432, 1465, 1365, 770; MS (EI, 70 eV) 198 (M^+, 47), 184 (100), 156 (14); HRMS calcd for $C_{14}H_{17}N$ (M^+) 199.1361, found 199.1388.

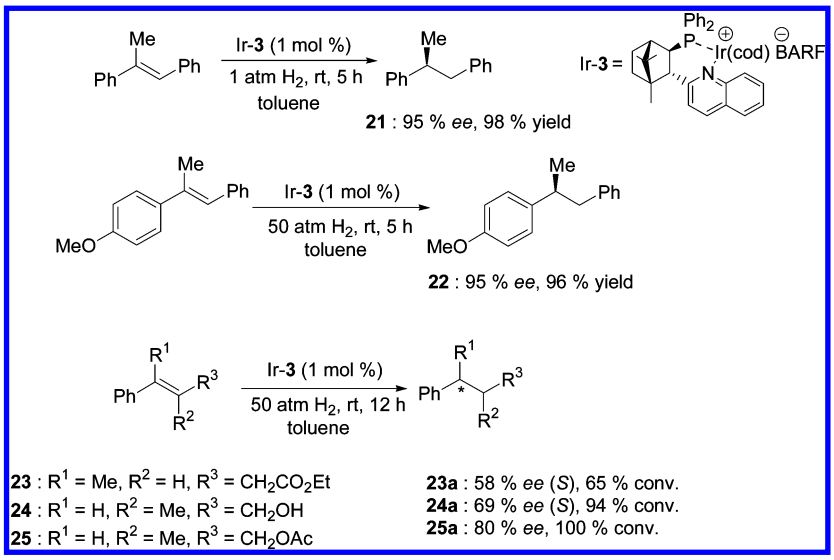
2-Bromo-6-[(1*R*,5*S*)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl]pyridine (16b): 70% yield as a pale yellow liquid. Purification by flash chromatography using 2% Et_2O in pentane: ^1H NMR (300 MHz, $CDCl_3$) δ 7.35 (t, J = 7.8 Hz, 1H), 7.24−7.14 (m, 2H), 6.48−6.42 (m, 1H), 2.93 (dd, J = 5.7, 1.5 Hz, 1H), 2.48−2.36 (m, 3H), 2.14−2.08 (m, 1H), 1.31 (s, 3H), 1.18 (d, J = 9.0 Hz, 1H), 0.77 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 146.3, 142.1, 138.8, 126.5, 125.7, 117.6, 42.9, 40.9, 38.3, 32.5, 31.9, 26.6, 21.4; IR (KBr, cm^{-1}) 1621, 1574, 1545, 1434, 1160, 1122, 782; MS (EI, 70 eV) 278 ($[M + H]^+$, 70), 236 (100), 154 (46); HRMS calcd for $C_{14}H_{16}BrN$ (M^+) 277.0466, found 277.0476.

General Procedure for Suzuki Cross-Coupling Reactions. A solution of bromopyridine (0.50 mmol) and $Pd(PPh_3)_4$ (23 mg, 0.02 mmol, 4 mol %) in toluene (2 mL) was treated with a solution of Na_2CO_3 (106 mg, 1 mmol) in H_2O (1 mL), followed by a solution of $PhB(OH)_2$ (64 mg, 0.53 mmol) in MeOH (1 mL). The mixture was stirred at 85 °C for 16 h. After the mixture cooled to 25 °C, a solution of concentrated aqueous NH_3 (0.25 mL) in saturated Na_2CO_3 (2.5 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine and dried ($MgSO_4$). Removal of the solvent in vacuo gave a residue that was purified by flash column chromatography, yielding the desired product.

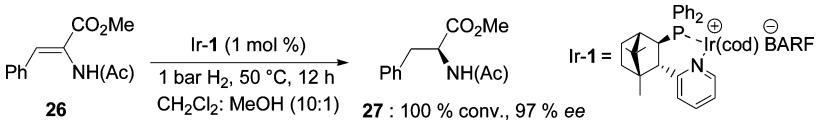
2-Phenyl-6-[(1*R*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]hept-2-en-2-yl]pyridine (7d): 99% yield as a pale yellow liquid. Purification by flash chromatography using 2% Et_2O in pentane; $[\alpha]^{21}_D$ −166.5 (*c* 0.585, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.10−7.96 (m, 2H), 7.54 (t, J = 7.7 Hz, 1H), 7.48−7.28 (m, 4H), 7.20 (dd, J = 7.5, 1.2 Hz, 1H), 6.31 (d, J = 3.3 Hz, 1H), 2.37 (t, J = 3.6 Hz, 1H), 1.94−1.82 (m, 1H), 1.68−1.60 (m, 1H), 1.48−1.42 (m, 1H), 1.31 (s, 3H), 1.08−0.98 (m, 1H), 0.83 (s, 3H), 0.78 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.3, 154.7, 148.6, 138.8, 135.5, 127.6, 127.5, 125.8, 118.3, 116.1, 55.7, 54.1, 50.9, 30.7, 24.8, 18.7, 18.5, 11.7.

2-[(1*R*,5*S*)-6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl]-6-phenylpyridine (7e): 91% yield as a pale yellow liquid. Purification by flash chromatography using 2% Et_2O in pentane; $[\alpha]^{25}_D$ −13.2 (*c* 0.56, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.02−7.96 (m, 2H), 7.58 (t, J = 7.8 Hz, 1H), 7.48−7.24 (m, 5H), 6.50−6.46 (m, 1H), 3.17 (dd, J = 5.7, 1.5 Hz, 1H), 2.40 (m, 3H), 2.52−2.49 (m, 1H), 1.34 (s, 3H), 1.24 (d, J = 8.7 Hz,

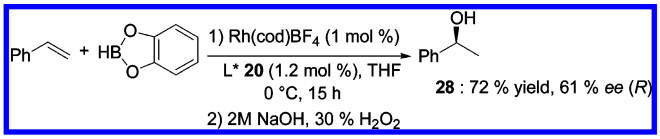
SCHEME 9



SCHEME 10



SCHEME 11



1H), 0.82 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.5, 156.4, 147.9, 140.2, 137.1, 129.0, 128.9, 127.3, 124.4, 118.1, 117.3, 43.0, 41.1, 38.3, 32.5, 31.9, 26.8, 21.4; IR (KBr, cm^{-1}) 1587, 1565, 1456, 1365, 760; MS (EI, 70 eV) 275 (M^+, 100), 260 (78), 232 (85); HRMS calcd for $C_{20}H_{21}N$ (M^+) 275.1674, found 275.1679.

General Procedure for the Preparation of Chiral 1,2-Aminophosphine Oxides 17a−e and Chiral 1,2-Diphosphine Oxide 19. To a stirred solution of *t*-BuOK (22 mg, 0.2 mmol, 20 mol %) in DMSO (1 mL) were successively added $Ph_2P(O)H$ (**6**) (202 mg, 1 mmol) and 2-alkenylpyridine (1 mmol) in DMSO (2 mL) under argon. The reaction mixture was stirred at 70 °C for 15 h. After the mixture cooled to room temperature, water (5 mL) and CH_2Cl_2 were added (20 mL). The organic phase was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Purification by flash chromatography yielded the desired product.

2-[(1*S*,2*R*,3*S*,5*R*)-3-(Diphenylphosphoryl)-6,6-dimethylbicyclo[3.1.1]hept-2-yl]pyridine (17a): 87% yield as a white solid. Purification by flash chromatography using 10% Et_2O in CH_2Cl_2: mp 132−139 °C; $[\alpha]^{23}_D$ +78.9 (*c* 0.56, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40−8.30 (m, 1H), 7.96−7.86 (m, 2H), 7.52−7.36 (m, 5H), 7.32−7.24 (m, 1H), 7.10−6.88 (m, 4H), 6.67−6.60 (m, 1H), 3.71 (dd, J = 8.4, 6.3 Hz, 1H), 3.50 (ddd, J = 20.7, 8.7, 2.1 Hz, 1H), 2.20 (d, J = 9.2, 3.8 Hz, 1H), 1.96−1.80 (m, 2H), 1.72−1.60 (m, 1H), 1.41 (s, 3H), 1.20−1.08 (m, 1H), 0.92 (s, 3H), 0.75 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.7, 148.5, 135.4, 134.6 (d, J = 94.0 Hz), 133.4 (d, J = 94.0 Hz), 131.6−131.3 (m), 130.7 (d, J = 2.7 Hz), 128.9 (d, J = 11 Hz), 127.7 (d, J = 11 Hz), 125.6, 121.4, 53.3 (d, J = 2.9 Hz), 52.2 (d, J = 5.1 Hz), 51.0, 48.1, 45.2 (d, J = 70.4 Hz), 32.3 (d, J = 13.7 Hz), 28.2, 21.2, 20.2, 14.5; ^{31}P NMR (81 MHz, $CDCl_3$) δ 32.8; IR (KBr, cm^{-1}) 1589, 1478, 1433, 1390, 1206, 1147, 740; MS (EI, 70 eV) 415 (M^+, 6), 332 (30), 214 (100); HRMS calcd for $C_{27}H_{30}NOP$ (M^+) 415.2065, found 415.2061. Anal. Calcd for $C_{27}H_{30}NOP$: C, 78.05; H, 7.28; N, 3.37. Found: C, 77.82; H, 7.17; N, 3.27.

2-[(1*S*,2*R*,3*S*,4*S*)-3-(Diphenylphosphoryl)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]-6-phenylpyridine (17d): 72% yield as a white solid. Purification by flash chromatography using 10% Et_2O in CH_2Cl_2: mp 69−72 °C; $[\alpha]^{22}_D$ −68.9 (*c* 0.505, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09−7.96 (m, 2H), 7.84−7.74 (m, 2H), 7.48−7.24 (m, 10H), 6.96−6.88 (m, 1H), 6.80−6.72 (m, 2H), 6.61 (m, 1H), 3.95 (m, 1H), 3.53 (ddd, J = 10.5, 4.2, 0.9 Hz, 1H), 2.22 (dd, J = 4.8, 2.1 Hz, 1H), 2.00−1.88 (m, 2H), 1.74−1.70 (m, 1H), 1.40 (s, 3H), 1.22−1−13 (m, 1H), 0.93 (s, 3H), 0.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 155.2, 140.0, 136.4, 135.5, 134.8, (d, J = 96.0 Hz), 133.2 (d, J = 96.0 Hz), 131.6−131.4 (m), 130.7 (d, J = 2.3 Hz), 129.1, 128.8 (d, J = 11.0 Hz), 127.6 (d, J = 11.0 Hz), 126.9, 124.0, 117.8, 53.6 (d, J = 2.9 Hz), 52.1 (d, J = 5.2 Hz), 51.1, 48.1, 45.4 (d, J = 70 Hz), 32.6 (d, J = 13.7 Hz), 28.4, 21.1, 20.2, 14.6; ^{31}P NMR (81 MHz, $CDCl_3$) δ 32.6; IR (KBr, cm^{-1}) 1570, 1438, 1195, 1115; MS (EI, 70 eV) 477 (M^+, 7), 276 (100); HRMS calcd for $C_{33}H_{34}NOP$ (M^+) 491.2378, found 491.2380.

(1*S*,2*R*,3*R*,5*R*)-6,6-Dimethyl-2-(2-naphthyl)bicyclo[3.1.1]hept-3-yl(diphenyl)phosphine Oxide (17c): 93% yield as a white solid. Purification by flash chromatography using 5% Et_2O in CH_2Cl_2: mp 70−78 °C; $[\alpha]^{28}_D$ +83.4 (*c* 0.525, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00−7.80 (m, 3H), 7.70−7.55 (m, 3H), 7.44−6.55 (m, 6H), 6.78−6.58 (m, 4H), 4.01 (t, J = 7.5 Hz, 1H), 3.58 (dd, J = 20, 2.1 Hz, 1H), 2.17 (dd, J = 9.3, 3.8 Hz, 1H), 1.93−1.60 (m, 3H), 1.35 (s, 3H), 1.18−0.95 (m, 1H), 0.85 (s, 3H), 0.75 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.1, 147.5, 135.1, 134.9 (d, J = 96.0 Hz), 133.1 (d, J = 96.0 Hz), 131.6−131.4 (m), 130.4 (d, J = 2.7 Hz), 129.6−128.8 (m), 127.6−127.4 (m), 127.2, 125.9, 123.9, 54.2 (d, J = 2.4 Hz), 52.7 (d, J = 4.6 Hz), 51.3, 48.0, 45.0 (d, J = 70.0 Hz), 32.4 (d, J = 14.0 Hz), 28.3, 21.2, 20.2, 14.9; ^{31}P NMR (81 MHz, $CDCl_3$) δ 32.9; IR (KBr, cm^{-1}) 1600, 1503, 1437, 1194, 1114, 837; MS (EI, 70 eV) 465 (M^+, 3), 382 (7), 264 (100); HRMS calcd for $C_{31}H_{32}NOP$ (M^+) 465.2222, found 465.2245. Anal. Calcd for $C_{31}H_{32}NOP$: C, 79.97; H, 6.93; N, 3.01. Found: C, 79.64; H, 6.94; N, 3.05.

2-[(1*S*,2*R*,3*S*,5*R*)-3-(Diphenylphosphoryl)-6,6-dimethylbicyclo[3.1.1]hept-2-yl]pyridine (17b): 85% yield as a white solid. Purification by flash chromatography using 5% Et_2O in CH_2Cl_2: mp 57−63 °C; $[\alpha]^{26}_D$ −24.0 (*c* 0.56, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29−8.25 (m 1H), 8.00−7.90 (m, 2H), 7.60−7.52 (m, 2H), 7.44−7.40 (m, 3H), 7.22−7.16 (m, 1H), 7.02−6.88 (m, 3H), 6.84−6.76 (m, 1H), 6.70 (d, J = 7.8 Hz, 1H), 4.80−4.67 (m, 1H), 3.72 (ddd, J = 22.0, 6.6, 2.7 Hz, 1H), 2.40−2.12 (m, 4H), 1.93−1.85 (m, 1H), 1.72 (d, J = 9.9 Hz, 1H), 1.01 (s, 3H), 0.72 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.6 (d, J = 2.7 Hz), 147.2, 135.9, 133.8 (d, J = 82.0 Hz), 132.5 (d, J = 82.0 Hz), 131.8−131.6 (m), 131.0 (d, J = 2.7 Hz), 128.9 (d, J = 11.2 Hz), 127.6 (d, J = 11.2 Hz), 123.9, 121.0, 48.3 (d, J = 5.6 Hz), 46.6, 40.7 (d, J = 3.8 Hz), 39.1, 30.9, 27.9, 26.5 (d, J = 2.1 Hz), 25.2 (d, J = 71.0 Hz), 22.7; ^{31}P NMR (81 MHz, $CDCl_3$) δ 38.4; IR (KBr, cm^{-1}) 1589, 1473, 1437, 1191, 1117; MS (EI, 70 eV) 401 (M^+, 13), 283 (18), 200 (100); HRMS calcd for $C_{26}H_{28}NOP$ (M^+) 401.1906, found 401.1906.

2-[(1*S*,2*R*,3*S*,5*R*)-3-(Diphenylphosphoryl)-6,6-dimethylbicyclo[3.1.1]hept-2-yl]-6-phenylpyridine (17e): 78% yield as a white solid. Purification by flash chromatography using 5% Et_2O in CH_2Cl_2: mp 67−73 °C; $[\alpha]^{29}_D$ +59.2 (*c* 0.76, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04−7.86 (m, 4H), 7.52−7.20 (m, 10 H), 6.94−6.56 (m, 4H), 5.00−4.88 (m, 1H), 3.78 (ddd, J = 22.0, 6.6, 2.7 Hz, 1H), 2.44−2.12 (m, 4H), 1.94−1.88 (m, 1H), 1.68 (d, J = 9.6 Hz, 1H), 1.03 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.6 (d, J = 2.3 Hz), 154.4, 140.2, 136.9, 133.8 (d, J = 95.0 Hz), 132.5 (d, J = 95.0 Hz), 131.8−131.5 (m), 130.9 (d, J = 2.7 Hz), 129.1 (d, J = 3.2 Hz), 128.9, 127.5 (d, J = 11.3 Hz), 126.9, 122.4, 117.4, 48.3 (d, J = 5.8 Hz), 46.9, 40.9 (d, J = 4.1 Hz), 39.3, 31.4, 28.0, 26.6 (d, J = 2.0 Hz), 25.4 (d, J = 71.0 Hz), 24.9, 23.0; ^{31}P NMR (81 MHz, $CDCl_3$) δ 37.9; IR (KBr, cm^{-1}) 1590, 1571, 1445, 1191, 1117; MS (EI, 70 eV) 477 (M^+, 7), 276 (100); HRMS calcd for $C_{32}H_{32}NOP$ (M^+) 477.2222, found 477.2213.

[(1*R*,2*S*,3*R*,4*S*)-3-(Diphenylphosphoryl)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl][di(2-furyl)]phosphine Oxide (19): 70% yield as a white solid. Purification by flash chromatography using 50% Et_2O in CH_2Cl_2: mp 271−273 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66−7.52 (m, 5H), 7.38−7.20 (m, 7H), 6.89 (ddd, J = 3.3, 1.8, 0.6 Hz, 1H), 6.45 (ddd, J = 3.3, 1.8, 0.6 Hz, 1H), 6.37−6.34 (m, 1H), 5.92−5.89 (m, 1H), 3.50−3.32 (m, 2H), 2.48−2.38 (m, 1H), 1.80−1.52 (m, 3H), 1.40−1.14 (m, 1H), 1.04 (s, 3H), 0.60 (s, 3H), 0.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.7 (d, J = 99.3 Hz), 148.0−147.9 (m), 145.9 (d, J = 99.3 Hz), 135.3 (d, J = 24.7 Hz), 134.0 (d, J = 24.7 Hz), 131.5−131.1 (m), 128.7−128.4 (m), 122.6−122.0 (m), 111.5 (d, J = 8.5 Hz), 111.3 (d, J = 8.5 Hz), 52.0, 51.2 (d, J = 12.0 Hz), 49.9 (d, J = 5.0 Hz), 47.6 (d, J = 44.0 Hz), 46.5 (d, J = 4.5 Hz), 41.5 (d, J = 65.1 Hz), 31.4 (d, J = 14.1 Hz), 31.2 (d, J = 6.2 Hz), 19.8, 19.7; ^{31}P NMR (81 MHz, $CDCl_3$) δ 26.3 (d, J = 7.7 Hz), 9.8 (d, J = 7.7 Hz); IR (KBr, cm^{-1}) 1460, 1438, 1200, 1133, 1012, 913, 771, 751, 714; EI (70 eV) 518 (M^+, 15), 337 (61.2), 317 (100), 201 (29.9); HRMS calcd for $C_{30}H_{32}O_4P_2$ (M^+) 518.1776, found 518.1760. Anal. Calcd for $C_{30}H_{32}O_4P_2$: C, 69.49; H, 6.22. Found: C, 69.06; H, 6.45.

General Procedure for the Reduction of Phosphine Oxides 17a−e and 19 to Aminophosphines 1−5 and Diphosphine 20. A tube was charged with the phosphine oxide (0.5 mmol), toluene (15 mL), trichlorosilane (0.5 mL, 10 equiv, 5 mmol), and triethylamine (1.4 mL, 20 equiv, 10 mmol) under argon, sealed, and heated for 16 h at 120 °C. After cooling to 25 °C, the reaction mixture was transferred to a 100 mL flask filled with argon. Toluene and excess trichlorosilane were evaporated in vacuo. The residue was dissolved in toluene (15 mL) and carefully quenched with degassed 10% aqueous $NaHCO_3$ (3 mL). The separated organic phase was filtered and transferred by cannulation in a second flask flushed with argon. Toluene was evaporated in vacuo, and the residue was washed with Et_2O (30 mL). After filtration, remaining solvents were evaporated in vacuo, yielding the desired product.

2-[(1*S*,2*S*,3*R*,4*S*)-3-(Diphenylphosphino)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]pyridine (1): 87% yield as a viscous liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38−8.34 (m, 1H), 7.48−7.40 (m, 2H), 7.27−6.97 (m, 7H), 6.80−6.64 (m, 3H), 6.46−6.40 (m, 1H), 3.33−3.24 (m, 1H), 3.06−2.95 (m, 1H), 1.95−1.60 (m, 4H), 1.44 (s, 3H), 1.20−1.12 (m, 1H), 0.94 (s, 3H), 0.72 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.6, 147.0, 139.0 (d, J = 15.0 Hz), 136.3 (d, J = 15.0 Hz), 133.6, 133.6−133.1 (m), 131.4 (d, J = 17.3 Hz), 127.3−126.7 (m), 126.1 (d, J = 7.6 Hz), 123.6, 119.3, 55.6 (d, J = 9.9 Hz), 50.4 (d, J = 3.85 Hz), 50.0, 48.1 (d, J = 12.5 Hz), 42.6 (d, J = 13.7 Hz), 29.9 (d, J = 7.3 Hz), 27.3, 20.0, 19.8 (d, J = 20.0 Hz), 13.4; ^{31}P NMR (81 MHz, $CDCl_3$) δ −2.1; IR (KBr, cm^{-1}) 1589, 1478, 1433, 1112, 740; MS (EI, 70 eV) 399 (M^+, 27), 316 (39), 214 (100), 183 (59); HRMS calcd for $C_{27}H_{30}NP$ (M^+) 399.2116, found 399.2116.

2-[(1*S*,2*R*,3*S*,4*S*)-3-(Diphenylphosphino)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]-6-phenylpyridine (2): 82% yield as a viscous liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00−7.92 (m, 2H), 7.48−6.96 (m, 12H), 6.80−6.60 (m, 3H), 6.32 (m, 1H), 3.62 (t, J = 8.1 Hz, 1H), 3.02−2.92 (m, 1H), 1.96−1.68 (m, 4H), 1.38 (s, 3H), 1.12−1.00 (m, 1H), 0.88 (s, 3H), 0.68 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 153.7, 139.2 (d, J = 15.0 Hz), 138.9, 136.2 (d, J = 15.0 Hz), 134.5, 133.3 (d, J = 18.8 Hz), 131.4 (d, J = 18.8 Hz), 127.6−127.2 (m), 126.8, 126.1 (d, J = 8.0 Hz) 125.6, 122.3, 115.7, 55.7 (d, J = 10.0 Hz), 50.4 (d, J = 4.1 Hz), 50.3, 48.1 (d, J = 12.8 Hz), 42.4 (d, J = 13.4 Hz), 30.1 (d, J = 7.0 Hz), 27.4, 19.9, 19.7, 13.5; ^{31}P NMR (81 MHz, $CDCl_3$) δ −2.1; MS (EI, 70 eV) 475 (M^+, 26), 392 (18), 290 (100), 182 (32); HRMS calcd for $C_{33}H_{34}NP$ (M^+) 475.2429, found 475.2447.

2-[(1*S*,2*R*,3*S*,4*S*)-3-(Diphenylphosphino)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]quinoline (3): 61% yield as a viscous liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (m, 1H), 7.60−7.20 (m, 9H), 7.06−6.98 (m, 2H), 6.60−6.40 (m, 4H), 3.65 (t, J = 8.1 Hz, 1H), 3.16 (m, 1H), 1.92−1.72 (m, 4H), 1.40 (s, 3H), 1.08−1.00 (m, 1H), 0.88 (s, 3H), 0.72 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.1, 146.3, 139.2 (d, J = 15.0 Hz), 136.1 (d, J = 15.0 Hz), 133.5−133.1 (m), 131.4 (d, J = 17.2 Hz), 128.3, 127.4−126.8 (m), 126.0−125.8 (m), 125.4, 124.2, 122.2, 56.4 (d, J = 10.1 Hz), 50.9 (d, J = 3.8 Hz), 50.5, 48.1 (d, J = 12.8 Hz), 42.3 (d, J = 13.7 Hz), 30.0 (d, J = 7.4 Hz), 27.4, 20.0, 19.7, 13.7; ^{31}P NMR (81 MHz, $CDCl_3$) δ −1.5; IR (KBr, cm^{-1}) 1618, 1600, 1435, 834; MS (EI, 70 eV) 449 (M^+, 28), 366 (17), 264 (100), 156 (33); HRMS calcd for $C_{31}H_{32}NP$ (M^+) 449.2272, found 449.2301.

2-[(1*S*,2*R*,3*S*,5*R*)-3-(Diphenylphosphino)-6,6-dimethylbicyclo[3.1.1]hept-2-yl]pyridine (4): 80% yield as a viscous liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24−8.20 (m, 1H), 7.66−7.58 (m, 2H), 7.32−7.12 (m, 6H), 6.88−6.68 (m, 5H), 4.34−4.22 (m, 1H), 3.35 (ddd, J = 18.3, 6.0, 2.4, 1H), 2.44−2.20 (m, 3H), 1.92−1.74 (m, 2H), 1.41 (d, J = 8.7 Hz, 1H), 1.02 (s, 3H), 0.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.4 (d, J = 2.6 Hz), 146.2, 136.8 (d, J = 15.5 Hz), 136.2 (d, J = 15.5 Hz), 134.1−132.6 (m), 132.7 (d, J = 18.7 Hz), 127.6−127.1 (m), 126.2 (d, J = 7.0 Hz), 122.0, 119.1, 50.7 (d, J = 2.6 Hz), 47.8 (d, J = 4.9 Hz), 40.6 (d, J = 2.3 Hz), 38.1 (d, J = 1.6 Hz), 30.4 (d, J = 17.8 Hz), 30.0, 26.5, 21.7, 21.4 (d, J = 8.1 Hz); ^{31}P NMR (81 MHz, $CDCl_3$) δ 10.5; IR (KBr, cm^{-1}) 1588, 1565, 1472, 1431, 1386; MS (EI, 70 eV) 385 (M^+, 6), 308 (48), 200 (100); HRMS calcd for $C_{26}H_{28}NP$ (M^+) 385.1959, found 385.1992.

2-[(1*S*,2*R*,3*S*,5*R*)-3-(Diphenylphosphino)-6,6-dimethylbicyclo[3.1.1]hept-2-yl]-6-phenylpyridine (5): yield 92% as a viscous liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00−7.94 (m, 2H), 7.68−7.60 (m, 2H), 7.42−7.20 (m, 10H), 6.82−6.66 (m, 3H), 6.61 (m, 1H), 4.64−4.54 (m, 1H), 3.44−3.32 (m, 1H), 2.44−2.28 (m, 3H), 1.96−1.80 (m, 2H), 1.44−1.36 (m, 1H), 1.04 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.9 (d, J = 2.3 Hz), 153.0, 138.9, 136.9 (d, J = 15.5 Hz), 136.1 (d, J = 15.5 Hz), 135.0, 133.2 (d, J = 18.8 Hz), 132.7 (d, J = 18.8 Hz), 127.6−127.2 (m), 126.1 (d, J = 7.4 Hz), 125.6, 120.5, 115.5, 50.7 (d, J = 19.0 Hz), 47.7 (d, J = 5.2 Hz), 40.7 (d, J = 2.5

Hz), 38.4, 30.6 (d, J = 18.5 Hz), 30.3, 26.6, 21.9, 21.4 (d, J = 8.3 Hz); ^{31}P NMR (81 MHz, $CDCl_3$) 10.1; MS (EI, 70 eV) 461 (M^+, 2), 384 (5), 276 (100); HRMS calcd for $C_{32}H_{32}NP$ (M^+) 461.2272, found 461.2241.

[(1*R*,2*S*,3*R*,4*S*)-3-(Diphenylphosphino)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl][di(2-furyl)]phosphine (20): 68% yield as a foam; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60−7.48 (m, 1H), 7.32−7.04 (m, 11H), 6.60−6.54 (m, 1H), 6.28−6.20 (m, 2H), 5.80−5.72 (m, 1H), 3.40−3.28 (m, 1H), 2.48−2.36 (m, 1H), 2.24−2.12 (m, 1H), 1.84−1.70 (m, 1H), 1.40−1.20 (m, 2H), 0.89 (s, 3H), 0.84−0.72 (m, 1H), 0.58 (s, 3H), 0.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.8 (d, J = 18.5 Hz), 148.2 (d, J = 12.3 Hz), 145.3, 138.5−138.1 (m), 134.3 (d, J = 21.0 Hz), 131.6 (d, J = 21.0 Hz), 127.5−126.6 (m), 120.8 (d, J = 24.5 Hz), 119.6 (d, J = 25.7 Hz), 109.7−109.5 (m), 50.2−50.0 (m), 49.3−48.1 (m), 43.9−43.3 (m), 30.6 (d, J = 2.6 Hz), 29.3 (d, J = 23.9 Hz), 18.7, 12.8; ^{31}P NMR (81 MHz, $CDCl_3$) δ 8.00 (d, J = 2.3 Hz) and −57.5; EI (70 eV) 486 (M^+, 100), 350 (39), 252 (49), 165 (41); HRMS calcd for $C_{30}H_{32}O_2P_2$ (M^+) 486.1878, found 486.1870.

General Procedure for Ir-Catalyzed Enantioselective Hydrogenation Reactions of α-Acetamidocinnamate Ester 27. Ir complex catalyst **1** (4.7 mg, 3 μmol, 1 mol %), methyl (*Z*)-α-(acetamido)cinnamate **26** (66 mg, 0.3 mmol), CH_2Cl_2 (3 mL), and MeOH (0.3 mL) were placed in an autoclave. The autoclave was sealed and pressurized to 1 bar of H_2, and the mixture was stirred at 50 °C for 2 h. CH_2Cl_2 and MeOH were removed, and the crude product was passed through a short silica gel column with Et_2O as the eluent. After evaporation of the solvent, (*S*)-**27** was obtained in quantitative yield (97% ee): GC (140 °C, column) t_r/min = 10.5 (*R*), 11.5 (*S*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24−7.14 (m, 3H), 7.02−7.00 (m, 2H), 6.04 (d, J = 7.2 Hz, 1H), 4.84−4.76 (m, 1H), 3.64 (s, 3H), 3.12−2.96 (m, 2H), 1.89 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 169.0, 135.3, 128.6, 127.9, 126.4, 52.5, 51.6, 37.1, 22.4.

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Supporting Information Available: Experimental procedures for all compounds not described in the text, ^{1}H and ^{13}C NMR spectra of compounds **1**−**5**, **17a**−**e**, **19**, and **20**, and X-ray data for **17a**, **17e**, and **19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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