Ruthenium-Catalyzed Anti-Markovnikov Hydroamination of Vinylarenes

Supporting Information

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General comments. All reactions were performed under a nitrogen atmosphere using standard Schlenk and drybox techniques. Vinylarenes, amines, ligands, ruthenium catalyst precursors except Ru(2, 3-dimethyl-1, 3-butadiene)(acac)₂, 1, 4-dioxane anhydrous, triflic acid, and trifluoroacetic acid were purchased from commercial sources and were used without further purification. Ru(2, 3-dimethyl-1, 3-butadiene)(acac)₂ was synthesized by literature procedures.¹ NMR spectra were recorded on Bruker DPX 400 and 500 MHz instruments. Elemental analyses were performed by Robertson Microlit Laboratories, Madison, NJ.

General Procedure for the Ruthenium-Catalyzed Hydroamination of Vinylarenes (Table 2). In a drybox, Ru(cod)(2-methylallyl)₂ (16.0 mg, 50 μ mol) and 1,5-bis(diphenylphosphino)pentane (30.8 mg, 70 μ mol) were suspended in 0.20 mL of dioxane in a screw-capped vial. Vinylarenes (2.00 mmol) and amines (1.00 mmol) were placed into a second small vial and dissolved in 0.30 mL of 1,4-dioxane. The vials were sealed with a cap containing a PTFE septum and removed from the drybox. Triflic acid (8.8 μ l, 0.10 mmol) was added to the catalyst suspension. The solution of vinylarenes and amines was then added to the catalyst suspension. The reaction mixture was stirred at 100 °C for 24 h. After heating, the reaction mixture was directly adsorbed onto silica gel and purified by flash column chromatography.

***N*-(2-Phenethyl)morpholine (Table 2, Entry 1).**² The general procedure was followed with styrene (229 μ l, 2.00 mmol) and morpholine (87.2 mg, 1.00 mmol). The reaction mixture was purified by flash column chromatography (20% EtOAc in hexane) to give 183 mg (96%) of the hydroamination product: ¹H NMR (400 MHz, CDCl₃, TMS) δ 2.44 (t, *J* = 4.6 Hz, 4H), 2.55-2.62 (m, 2H), 2.77-2.83 (m, 2H), 3.74 (t, *J* = 4.6 Hz, 4H), 7.17-7.23 (m, 3H), 7.25-7.31 (m, 2H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ 33.3, 53.6, 60.8, 66.9, 126.0, 128.3, 128.6, 140.0.

***N*-(2-Phenethyl)piperidine (Table 2, Entry 2).**² The general procedure was followed with styrene (229 μ l, 2.00 mmol) and piperidine (85.0 mg, 1.00 mmol). The reaction mixture was purified by flash column chromatography (20% EtOAc in hexane) to give 173 mg (91%) of the hydroamination product: ¹H NMR (400 MHz, CDCl₃, TMS) δ 1.40-1.49 (m, 2H), 1.57-1.66 (m, 4H), 2.34-2.56 (m, 4H), 2.51-2.55 (m, 2H), 2.77-2.83 (m, 2H), 7.14-7.22 (m, 3H), 7.24-7.31 (m, 2H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ 24.4, 25.9, 33.5, 54.5, 61.4, 125.9, 128.3, 128.7, 140.6.

1-Phenyl-4-(2-phenylethyl)piperazine (Table 2, Entry 3).³ The general procedure was followed with styrene (458 μ l, 4.00 mmol) and 4-phenylpiperazine (162 mg, 1.00 mmol). The

reaction mixture was purified by flash column chromatography (20% EtOAc in hexane) to give 171 mg (64%) of the hydroamination product: ^1H NMR (400 MHz, CDCl_3 , TMS) δ 2.61-2.68 (m, 2H), 2.69 (t, J = 5.0 Hz, 4H), 2.81-2.88 (m, 2H), 3.23 (t, J = 5.0 Hz, 4H), 6.86 (t, J = 7.3 Hz, 1H), 6.94 (d, J = 8.1 Hz, 2H), 7.17-7.33 (m, 7H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 33.6, 49.1, 53.2, 60.5, 116.0, 119.6, 126.0, 128.4, 128.7, 129.1, 140.2, 151.2.

1-(2-Phenylethyl)-4-*tert*-butyl piperazinecarboxylate (Table 2, Entry 4).³ The general procedure was followed with styrene (229 μl , 2.00 mmol) and *tert*-Butyl 1-piperazinecarboxylate (187 mg, 1.00 mmol). The reaction mixture was purified by flash column chromatography (20% EtOAc in hexane) to give 263 mg (90%) of the hydroamination product: ^1H NMR (400 MHz, CDCl_3 , TMS) δ 1.45 (s, 9H), 2.46 (t, J = 4.5 Hz, 4H), 2.56-2.64 (m, 2H), 2.77-2.84 (m, 2H), 3.46 (t, J = 5.0 Hz, 4H), 7.17-7.23 (m, 3H), 7.25-7.32 (m, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 28.4, 33.4, 43.4 (broad), 52.9, 60.4, 79.5, 126.0, 128.3, 128.6, 140.0, 154.7.

***N*-(2-Phenethyl)-4-piperidone ethylene ketal (Table 2, Entry 5).**⁴ The general procedure was followed with styrene (229 μl , 2.00 mmol) and 4-piperidone ethylene ketal (143 mg, 1.00 mmol). The reaction mixture was purified by flash column chromatography (50% EtOAc in hexane) to give 203 mg (82%) of the hydroamination product: ^1H NMR (500 MHz, CDCl_3 , TMS) δ 1.79 (t, J = 5.7 Hz, 4H), 2.57-2.64 (m, 4H), 2.61-2.67 (m, 2H), 2.78-2.84 (m, 2H), 3.96 (s, 4H), 7.17-7.23 (m, 3H), 7.25-7.31 (m, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 34.2, 35.1, 51.6, 60.4, 64.5, 107.5, 126.2, 128.6, 128.9, 140.8.

***N*-(2-Phenethyl)tetrahydroisoquinoline (Table 2, Entry 6).**⁵ The general procedure was followed with styrene (458 μl , 4.00 mmol) and 1, 2, 3, 4-tetrahydro-isoquinoline (136 mg, 1.02 mmol). The reaction mixture was purified by flash column chromatography (20% EtOAc in hexane) to give 157 mg (65%) of the hydroamination product: ^1H NMR (500 MHz, CDCl_3 , TMS) δ 2.75-2.81 (m, 2H), 2.81 (t, J = 5.8 Hz, 2H), 2.89-2.96 (m, 4H), 3.72 (s, 2H), 7.01-7.06 (m, 1H), 7.08-7.16 (m, 3H), 7.18-7.23 (m, 1H), 7.23-7.27 (m, 2H), 7.27-7.32 (m, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 29.3, 34.2, 51.2, 56.3, 60.5, 125.8, 126.3, 126.3, 126.8, 128.6, 128.9, 129.0, 134.5, 134.9, 140.6.

***N*-(2-Phenethyl)hexylmethylaniline (Table 2, Entry 7).**⁶ The general procedure was followed with styrene (458 μl , 4.00 mmol) and *N*-methylhexylaniline (115 mg, 1.00 mmol). The reaction mixture was stirred at 80 $^\circ\text{C}$ for 48 h. After the heating, the reaction mixture was purified by flash column chromatography (20% EtOAc in hexane) to give 138 mg (63%) of the

hydroamination product: ^1H NMR (500 MHz, CDCl_3 , TMS) δ 0.88 (t, $J = 7.0$ Hz, 3H), 1.24-1.35 (m, 6H), 1.42-1.52 (m, 2H), 2.30 (s, 3H), 2.39 (t, $J = 7.7$ Hz, 2H), 2.57-2.63 (m, 2H), 2.74-2.80 (m, 2H), 7.16-7.22 (m, 3H), 7.25-7.30 (m, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 14.3, 22.9, 27.5, 27.6, 32.1, 34.1, 42.5, 58.0, 59.9, 126.1, 128.6, 128.9, 140.9.

***N*-(2-Phenethyl)benzylmethylamine (Table 2, Entry 8).**⁷ The general procedure was followed with styrene (458 μl , 4.00 mmol) and *N*-methyl benzylamine (121 mg, 1.00 mmol). The reaction mixture was stirred at 80 °C for 48 h. After the heating, the reaction mixture was purified by flash column chromatography (10% EtOAc in hexane) to give 113 mg (50%) of the hydroamination product: ^1H NMR (500 MHz, CDCl_3 , TMS) δ 2.28 (t, $J = 2.4$ Hz, 3H), 2.62-2.67 (m, 2H), 2.79-2.86 (m, 2H), 3.56 (s, 2H), 7.16-7.21 (m, 3H), 7.21-7.33 (m, 7H); $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 34.2, 42.4, 59.4, 62.4, 126.1, 127.1, 128.4, 128.5, 129.0, 129.2, 139.3, 140.8.

***N*-[2-(2, 5-Dimethylphenyl)ethyl]morpholine (Table 2, Entry 9).** The general procedure was followed with 2, 5-dimethylstyrene (293 μl , 2.00 mmol) and morpholine (86.9 mg, 1.00 mmol). The reaction mixture was purified by flash column chromatography (20% EtOAc in hexane) to give 177 mg (81%) of the hydroamination product. ^1H NMR (500 MHz, CDCl_3 , TMS) δ 2.30 (s, 3H), 2.30 (s, 3H), 2.51-2.57 (m, 2H), 2.53-2.60 (m, 4H), 2.75-2.81 (m, 2H), 3.77 (t, $J = 4.7$ Hz, 4H), 6.94 (d, $J = 7.7$ Hz, 1H), 6.97 (s, 1H), 7.04 (d, $J = 7.7$ Hz, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 19.1, 21.1, 30.7, 54.0, 60.0, 67.2, 127.2, 130.3, 130.4, 133.0, 135.7, 138.2; Anal. Calcd for $\text{C}_{14}\text{H}_{21}\text{NO}$: C, 76.67; H, 9.65; N, 6.39. Found: C, 76.95; H, 9.90; N, 6.21.

***N*-[2-(4-Methylphenyl)ethyl]morpholine (Table 2, Entry 10).**² The general procedure was followed with 4-methylstyrene (264 μl , 2.00 mmol) and morpholine (88.5 mg, 1.02 mmol). The reaction mixture was purified by flash column chromatography (20% EtOAc in hexane) to give 150 mg (72%) of the hydroamination product. ^1H NMR (400 MHz, CDCl_3 , TMS) δ 2.31 (s, 3H), 2.52 (t, $J = 4.5$ Hz, 4H), 2.57 (m, 2H), 2.76 (m, 2H), 3.74 (t, $J = 4.5$ Hz, 4H), 7.09 (s, 4H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 20.9, 32.7, 53.6, 60.9, 66.8, 128.4, 129.0, 135.4, 136.9.

***N*-[2-(3-Methoxyphenyl)ethyl]morpholine (Table 2, Entry 11).** The general procedure was followed with 3-methoxystyrene (278 μl , 2.00 mmol), morpholine (86.5 mg, 0.99 mmol) and 0.25 mL of 1, 4-dioxane. The reaction mixture was stirred at 110 °C for 48 h. After the heating, the reaction mixture was purified by flash column chromatography (20% EtOAc in

hexane) to give 200 mg (91%) of the hydroamination product. ^1H NMR (500 MHz, CDCl_3 , TMS) δ 2.47-2.56 (m, 4H), 2.57-2.63 (m, 2H), 2.76-2.81 (m, 2H), 3.74 (t, $J = 4.5$ Hz, 4H), 3.80 (s, 3H), 6.73-6.78 (m, 1H), 6.76 (s, 1H), 6.80 (d, $J = 7.6$ Hz, 1H), 7.17-7.23 (m, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 33.6, 53.9, 55.4, 60.9, 67.2, 111.5, 114.8, 121.3, 129.6, 142.0, 159.9; Anal. Calcd for $\text{C}_{13}\text{H}_{19}\text{NO}_2$: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.46; H, 8.94; N, 6.28.

***N*-[2-(3-Trifluoromethylphenyl)ethyl]morpholine (Table 2, Entry 12).**² The general procedure was followed with 3-trifluoromethylstyrene (297 μl , 2.00 mmol), morpholine (87.2 mg, 1.00 mmol) and 0.25 mL of 1,4-dioxane. The reaction mixture was stirred at 110 °C for 24 h. After the heating, the reaction mixture was purified by flash column chromatography (20% EtOAc in hexane) to give 185 mg (71%) of the hydroamination product. ^1H NMR (400 MHz, CDCl_3 , TMS) δ 2.45-2.55 (m, 4H), 2.58-2.65 (m, 2H), 2.84-2.92 (m, 2H), 3.76 (t, $J = 4.6$ Hz, 4H), 7.39-7.44 (m, 2H), 7.46-7.52 (m, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 33.0, 53.6, 60.3, 66.9, 123.0 (q, $J = 3.8$ Hz), 124.2 (q, $J = 272.2$ Hz), 125.4 (q, $J = 3.8$ Hz), 128.8, 130.7 (q, $J = 32.2$ Hz), 132.1, 141.0.

***N*-[2-(4-Trifluoromethylphenyl)ethyl]morpholine (Table 2, Entry 13).** The general procedure was followed with 4-trifluoromethylstyrene (296 μl , 2.00 mmol) and morpholine (87.4 mg, 1.00 mmol). The reaction mixture was purified by flash column chromatography (40% EtOAc in hexane) to give 131 mg (51%) of the hydroamination product. ^1H NMR (500 MHz, CDCl_3 , TMS) δ 2.52 (t, $J = 4.1$ Hz, 4H), 2.58-2.63 (m, 2H), 2.83-2.89 (m, 2H), 3.73 (t, $J = 4.7$ Hz, 4H), 7.32 (d, $J = 7.9$ Hz, 2H), 7.54 (d, $J = 7.9$ Hz, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 33.4, 53.9, 60.5, 67.2, 124.5 (q, $J = 271.7$ Hz), 125.5 (q, $J = 3.6$ Hz), 128.7 (q, $J = 33.1$ Hz), 129.2, 144.6; Anal. Calcd for $\text{C}_{13}\text{H}_{16}\text{F}_3\text{NO}$: C, 60.22; H, 6.22; N, 5.40. Found: C, 60.05; H, 6.25; N, 5.34.

***N*-1-(2-Phenylpropyl)morpholine (Table 2, Entry 14).**⁸ The general procedure was followed with α -methylstyrene (195 μl , 1.50 mmol) and morpholine (88.2 mg, 1.01 mmol). The reaction mixture was stirred at 80 °C for 72 h. After the heating, the reaction mixture was purified by flash column chromatography (20% EtOAc in hexane) to give 83 mg (40%) of the hydroamination product. ^1H NMR (500 MHz, CDCl_3 , TMS) δ 1.28 (d, $J = 7.0$ Hz, 3H), 2.34-2.41 (m, 2H), 2.42-2.51 (m, 4H), 2.94 (ddd, $J = 13.9, 8.4, 6.9$ Hz, 1H), 3.63-3.72 (m, 4H), 7.17-7.23 (m, 3H), 7.27-7.32 (m, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 20.1, 37.3, 54.2, 66.8, 67.3, 126.3, 127.4, 128.5, 146.2.

Reactions of 2, 5-Dimethyl Styrene with Morpholine in the Presence of *N*-(1-Phenethyl)morpholine (eq 2). In a drybox, morpholine (17.4 μ l, 0.20 mmol), 2, 5-dimethyl styrene (58.5 μ l, 0.40 mmol) and *N*-(1-phenethyl)morpholine (38.2 mg, 0.20 mmol) were added to a screw-capped vial containing a suspension of Ru(cod)(2-methylallyl)₂ (3.2 mg, 10 μ mol) and 1, 5-bis(diphenylphosphino)pentane (6.2 mg, 14 μ mol) in 0.10 mL of 1, 4-dioxane. The vial was sealed with a cap containing a PTFE septum and removed from the drybox. Triflic acid (1.8 μ l, 20 μ mol) was added by syringe to the suspension. The reaction mixture was stirred at 100 °C. After 24 h, the molar ratios of *N*-(2-phenethyl)morpholine, *N*-[2-(2, 5-dimethylphenyl)ethyl]-morpholine and *N*-(1-phenethyl)morpholine were determined to be 0:76:99 by GC analysis after addition of dodecane as internal standard.

Reactions of 2, 5-Dimethyl Styrene with Morpholine in the Presence of *N*-(2-Phenylethyl)-4-*tert*-butyl piperazinecarboxylate (eq 3). In a drybox, morpholine (17.4 μ l, 0.20 mmol), 2, 5-dimethyl styrene (58.5 μ l, 0.40 mmol) and 1-(2-phenethyl)-4-*tert*-butyl piperazinecarboxylate (58.1 mg, 0.20 mmol) were added to a screw-capped vial containing a suspension of Ru(cod)(2-methylallyl)₂ (3.2 mg, 10 μ mol) and 1, 5-bis(diphenylphosphino)pentane (6.2 mg, 14 μ mol) in 0.10 mL of 1, 4-dioxane. The vial was sealed with a cap containing a PTFE septum and removed from the drybox. Triflic acid (1.8 μ l, 20 μ mol) was added by syringe to the suspension. The reaction mixture was stirred at 100 °C. After 24 h, the yields of *N*-[2-(2, 5-dimethylphenyl)ethyl]-morpholine and *N*-(2-phenethyl)morpholine were determined as 78% and 0% by GC analysis after addition of dodecane as internal standard. The remaining amount of 1-(2-phenethyl)-4-*tert*-butyl piperazinecarboxylate was determined to be 93% of the original quantity by ¹H-NMR spectroscopy with dodecane as the internal standard.

Reactions of Styrene with Piperidine in the Presence of (*E*)-*N*-(2-Phenylethenyl)morpholine (eq 4). In a drybox, piperidine (19.8 μ l, 0.20 mmol), styrene (45.8 μ l, 0.40 mmol) and (*E*)-*N*-(2-phenylethenyl)morpholine (3.8 mg, 20 μ mol) were added to a screw-capped vial containing a suspension of Ru(cod)(2-methylallyl)₂ (6.4 mg, 20 μ mol) and 1, 5-bis(diphenylphosphino)pentane (12.4 mg, 28 μ mol) in 0.10 mL of 1, 4-dioxane. The vial was sealed with a cap containing a PTFE septum and removed from the drybox. Triflic acid (1.8 μ l, 20 μ mol) was added by syringe to the suspension. The reaction mixture was stirred at 100 °C. After 24 h, the molar ratios of *N*-(2-phenethyl)piperidine, (*E*)-*N*-(2-phenylethenyl)piperidine, *N*-(2-phenethyl)morpholine and (*E*)-*N*-(2-phenylethenyl)morpholine were determined to be

94:0:5:5 by GC analysis after addition of dodecane as internal standard.

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