The Synthesis of Substituted Pyridines from Imines and Alkynes via C-H Activation

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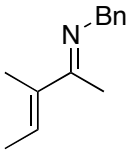
Supporting Information

General Experimental. All synthetic reactions were performed under inert atmosphere using syringe and cannula techniques. All catalytic reactions were assembled in a nitrogen-filled Vacuum Atmosphere inert atmosphere box. Oven-dried glassware was used in all cases. Unless otherwise noted, ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra were measured with a Bruker AVB-400 spectrometer in $CDCl_3$ or C_6D_6, as noted. NMR chemical shifts are reported in ppm relative to $CHCl_3$ (7.26 ppm for ^{1}H, and 77.23 ppm for ^{13}C) or C_6H_6 (7.15 ppm for ^{1}H, and 128.39 ppm for ^{13}C) as appropriate. All NOESY NMR spectra were recorded on a Bruker AV-500 spectrometer in $CDCl_3$. IR spectra were recorded on a Nicolet Avatar 360 FTIR spectrometer equipped with a single-bounce ZnSe attenuated total reflectance accessory, and only partial data are listed. Elemental analyses and mass spectrometry (HRMS) were carried out by the University of California at Berkeley Mass Spectrometry Facility.

Materials. Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification. Benzene was dried over alumina under a nitrogen atmosphere and degassed by purging with nitrogen for 5 minutes. Toluene was dried over alumina under a nitrogen atmosphere. Molecular sieves (3 Å) were heated at 300 °C under 0.5 mm Hg vacuum overnight to remove any traces of water and stored in an inert atmosphere box. Benzylamine was distilled within one week of use and stored under nitrogen over 3 Å molecular sieves. Acetylcyclohexene and 3-methyl-2-pentenone were distilled immediately prior to use. All commercially available alkynes were distilled, degassed using three freeze-pump-thaw cycles, and stored over 3 Å molecular sieves in an inert atmosphere box. $[RhCl(coe)_2]_2$ (also available through

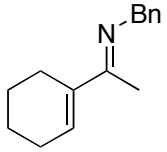
Strem Chemicals, Inc.)[1], as well as imines[2] **1**, **2**, and **6**, 1-trimethylsilyl-3-phenylpropyne,[3] and 1-phenylpropyne[4] were prepared as previously described.

General procedure for ketimine synthesis. In an inert atmosphere box, 3 Å molecular sieves and benzene were combined in an oven-dried 300 mL round bottom flask fitted with a septum and stir bar. The flask was removed from the inert atmosphere box and freshly distilled ketone and benzylamine were added via syringe under a nitrogen atmosphere. The resulting solution was stirred under a nitrogen atmosphere at ambient temperature for 16 h. The sieves were then removed via filtration over Celite, and the filtrate was concentrated *in vacuo*. Purification of the crude oil via Kugelrohr distillation at 0.05 mm Hg provided the ketimine in analytically pure form. The collection bulb was then immediately transferred to an inert atmosphere box, and the product was transferred to a vial and stored at -25 °C.



Ketimine 7. The general procedure was employed using 5.0 mL (45 mmol) of 3-methyl-2-pentenone, 4.8 mL (44 mmol) of benzylamine, 150 mL of benzene and 90 g of molecular sieves. Ketimine **7** was obtained after Kugelrohr distillation over a temperature range of 80 – 90 °C as a colorless oil (5.6 g, 30 mmol, 67%). IR (film): 3027, 2971, 2858, 1642, 1495, 1452, 1368, 730, 697 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 – 7.30 (m, 4H), 7.24 – 7.20 (m, 1H), 6.17 (q, J = 6.8 Hz, 1H), 4.63 (s, 2H), 2.03 (s, 3H), 1.94 (s, 3H), 1.81 (d, J = 6.8 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 168.14, 141.27, 139.59, 128.45, 127.91, 127.68, 126.50, 55.35, 14.73, 14.42, 13.00. LRMS (FAB+) Calcd

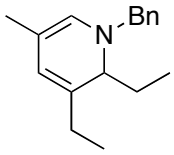
for $C_{13}H_{18}N$ $[MH]^+$ 188; Found 188. Anal. Calcd. for CHN: C, 83.37; H, 9.15; N, 7.48. Found: C, 82.98; H, 9.33; N, 7.55.



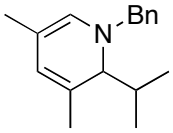
Ketimine 8. The general procedure was employed using 3.0 mL (23 mmol) of acetylcyclohexene, 2.6 mL (24 mmol) of benzylamine, 80 mL of benzene and 45 g of molecular sieves. Ketimine **8** was obtained after Kugelrohr distillation over a temperature range of 85 - 100 °C as a colorless oil (3.7 g, 17 mmol, 74%), which darkens to a bright yellow with no observable decrease in purity within 2 days of storage in an inert atmosphere box at -25 °C. IR (film): 3026, 2931, 2857, 1617, 1494, 1452, 1274, 1051, 731, 697 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.38 – 7.30 (m, 4H), 7.24 – 7.20 (m, 1H), 6.38 – 6.36 (m, 1H), 4.63 (s, 2H), 2.44 – 2.40 (m, 2H), 2.22 – 2.20 (m, 2H), 2.02 (s, 3H), 1.69 – 1.58 (m, 4H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 167.50, 141.28, 140.41, 130.93, 128.47, 127.70, 126.51, 55.24, 26.31, 25.23, 22.92, 22.43, 14.13. LRMS (FAB+) Calcd for $C_{15}H_{20}N$ $[MH]^+$ 214; Found 214. Anal. Calcd. for CHN: C, 84.46; H, 8.98; N, 6.57. Found: C, 84.47; H, 8.99; N, 6.44.

General procedure for dihydropyridine formation. The desired alkyne (3.0 mmol) was placed in a sealable glass vessel in an inert atmosphere box. To this was added $[RhCl(coe)_2]_2$ (0.015 mmol) dissolved in 2 mL of toluene, followed by diethyl-(4-*N,N*-dimethylamino)-phenyl)phosphine ((*p*-DMAPh)PEt_2) (0.03 mmol) dissolved in 2 mL of toluene, followed by the desired imine (0.6 mmol) dissolved in 2 mL of toluene. The tube was then sealed, removed from the inert atmosphere box, and heated in a 100 °C oil bath for the specified length of time. The tube was then allowed to cool to room

temperature, opened, and for pyridine syntheses, the resulting solution was carried on without evaporation. In cases where the dihydropyridine was isolated, the solvent was removed *in vacuo* and the resulting brown oil was purified on an activity III basic alumina column (2 cm x 20 cm) in the specified solvent system. The progress of the column was monitored by tlc on silica plates using 1:9 ethyl acetate:hexanes as the solvent system and using UV detection. Fractions containing product were combined and the solvent removed *in vacuo*. The resulting oil was stored in a -20 °C freezer.

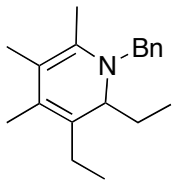


1-Benzyl-2,3-diethyl-5-methyl-1,2-dihydropyridine. The general procedure was employed on a larger scale using imine **1** (580 mg, 3.6 mmol), 3-hexyne (2.0 mL, 18 mmol), $[RhCl(coe)_2]_2$ (65 mg, 0.090 mmol), (*p*-DMAPh)PEt_2 (38 mg, 0.18 mmol), a reaction time of 2 h, and hexanes as the chromatography solvent. 1-Benzyl-2,3-diethyl-5-methyl-1,2-dihydropyridine (840 mg, 3.5 mmol, 97%) was obtained as a light yellow oil. The spectroscopic data agree with reported literature data.[2]



1-Benzyl-3,5-dimethyl-2-*iso*-propyl-1,2-dihydropyridine. The general procedure was employed on a larger scale using imine **1** (580 mg, 3.6 mmol), 4-methyl-2-pentyne (2.0 mL, 18 mmol), $[RhCl(coe)_2]_2$ (65 mg, 0.090 mmol), (*p*-DMAPh)PEt_2 (38 mg, 0.18 mmol), a reaction time of 2 h, and hexanes as the chromatography solvent. 1-Benzyl-3,5-dimethyl-2-*iso*-propyl-1,2-dihydropyridine (880 mg, 3.6 mmol, 100%) was obtained as a light yellow oil. IR (film): 2953, 2922, 1663, 1597, 1452, 1199, 972, 835,

729, 696 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ. 7.37 – 7.33 (m, 2H), 7.28 – 7.22 (m, 3H), 5.80 (s, 1H), 5.73 (s, 1H), 4.34 (d, *J* = 15.9 Hz, 1H), 4.25 (d, *J* = 15.9 Hz, 1H), 3.39 (d, *J* = 6.0 Hz, 1H), 1.97 – 1.87 (m, 1H), 1.76 (s, 3H), 1.73 (s, 3H), 1.01 – 0.98 (m, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 140.61, 129.52, 128.55, 126.96, 123.73, 120.58, 105.81, 67.10, 59.80, 32.88, 22.77, 19.37, 19.10, 17.69. HRMS (FAB+) Calcd for $C_{17}H_{23}N$ $[M]^+$ 241.1831; Found 241.1828.

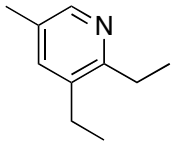


1-Benzyl-2,3-diethyl-4,5,6-trimethyl-1,2-dihydropyridine. The general procedure was employed on a larger scale using imine **7** (940 mg, 5.0 mmol), 3-hexyne (2.7 mL, 24 mmol), $[RhCl(coe)_2]_2$ (90 mg, 0.13 mmol), (*p*-DMAPh)PEt_2 (52 mg, 0.25 mmol), a reaction time of 2 h, and hexanes as the chromatography solvent. 1-Benzyl-2,3-diethyl-4,5,6-trimethyl-1,2-dihydropyridine (1.1 g, 3.9 mmol, 78%) was obtained as a light yellow oil. IR (film): 2959, 2928, 2868, 1649, 1580, 1453, 730, 697 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ. 7.29 – 7.17 (m, 5H), 4.20 (d, *J* = 15.7 Hz, 1H), 3.97 (d, *J* = 15.7 Hz, 1H), 3.07 – 3.04 (m, 1H), 2.21 – 2.12 (m, 1H), 1.86 (s, 3H), 1.80 – 1.72 (m, 7H), 1.44 – 1.32 (m, 1H), 1.21 – 1.11 (m, 1H), 0.84 (t, *J* = 7.5 Hz, 3H), 0.76 (t, *J* = 7.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 141.04, 132.67, 128.30, 128.06, 126.78, 125.92, 124.92, 111.86, 61.55, 54.21, 24.66, 24.65, 16.26, 14.30, 13.83, 13.23, 10.71. HRMS (FAB+) Calcd for $C_{19}H_{27}N$ $[M]^+$ 269.2144; Found 269.2138.

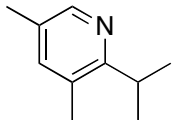
General procedures for pyridine synthesis. The toluene solution from the dihydropyridine formation (*vide supra*) was cooled to room temperature and used without further purification or evaporation.

Procedure A. 2,2,2-Trifluoroethanol (2 mL, 25% v/v) was added, the vessel was fitted with a drying tube and the solution was stirred in a 0 °C ice bath for 5 minutes before addition of 10% Pd/C (20 theoretical wt%). The solution was stirred at 0 °C while open to the air for the specified period of time. The drying tube was removed and the flask was fitted with a hydrogen balloon. The flask was evacuated and back-filled with H_2 five times, and then the solution was allowed to warm to room temperature. The solution was stirred at room temperature for 16 h under a hydrogen atmosphere. The hydrogen balloon was removed and the solution was filtered over Celite, rinsing thoroughly with diethyl ether. The filtrate was extracted three times with 30 mL of 1 N HCl. The aqueous extracts were combined and made alkaline (with 6 N NaOH; pH 14), and the resulting solution was back-extracted three times with 30 mL of diethyl ether. The organic extracts were combined, dried over $MgSO_4$, filtered, and evaporated *in vacuo* using a rotary evaporator with an ice bath to prevent evaporation of the desired product. The resulting oil was purified via column chromatography on silica gel (230 - 240 mesh) in the indicated solvent system. The progress of the column was monitored by tlc on silica plates using 1:1 diethyl ether:hexanes as the solvent system and using UV detection. Fractions containing product were combined and the solvent was removed *in vacuo* using a rotary evaporator with an ice bath to prevent evaporation of the desired product.

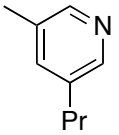
Procedure B. 2,2,2-Trifluoroethanol (2 mL, 25% v/v) and 10% Pd/C (20 theoretical wt%) were added. Reactions at room temperature were fitted with a drying tube, and those at 75 °C were transferred to a round bottom flask and fitted with a reflux condenser. The solution was stirred while open to air at the specified temperature for the specified time. At room temperature, the drying tube or reflux condenser was removed and the flask was fitted with a hydrogen balloon. The flask was evacuated and back-filled with H_2 five times and the solution was stirred at room temperature for 12 h under a hydrogen atmosphere. Work-up and purification were carried out according to Procedure A.



2,3-Diethyl-5-methylpyridine. The dihydropyridine was formed via the general procedure with imine **1** and 3-hexyne with a reaction time of 2 h. The resulting toluene solution was subjected to pyridine synthesis Procedure A with an oxidation time of 8 h at 0 °C. 2,3-Diethyl-5-methylpyridine was isolated after column chromatography (40:60 Et_2O:hexanes) as a colorless oil (72 mg, 0.48 mmol, 80%). IR (film): 2967, 2933, 2874, 1566, 1466, 1455, 1051, 886, 708 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.14 (s, 1H), 7.17 (s, 1H), 2.72 (q, *J* = 7.6 Hz, 2H), 2.54 (q, *J* = 7.6 Hz, 2H), 2.20 (s, 3H), 1.21 (t, *J* = 7.5 Hz, 3H), 1.14 (t, *J* = 7.6 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 158.17, 147.01, 136.69, 135.90, 130.36, 27.58, 25.04, 18.01, 14.89, 13.82. HRMS (EI+) Calcd for $C_{10}H_{15}N$ $[M]^+$ 149.1205; Found 149.1210.

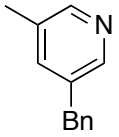


3,5-Dimethyl-2-*iso*-propylpyridine. The dihydropyridine was formed via the general procedure with imine **1** and 4-methyl-2-pentyne with a reaction time of 2 h. The resulting toluene solution was subjected to pyridine synthesis Procedure A with an oxidation time of 8 h at 0 °C. 3,5-Dimethyl-2-*iso*-propylpyridine was isolated after column chromatography (40:60 Et_2O:hexanes) as a colorless oil (62 mg, 0.41 mmol, 69%). IR (film): 2962, 2926, 2868, 1566, 1474, 1455, 1066, 881, 772, 716, 568 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.23 (s, 1H), 7.20 (s, 1H), 3.20 (septet, J = 6.8 Hz, 1H), 2.29 (s, 3H), 2.24 (s, 3H), 1.25 (d, J = 6.8 Hz, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 162.15, 147.27, 138.62, 130.10, 129.42, 31.07, 21.90, 18.77, 18.03. LRMS (ESI+) Calcd for $C_{10}H_{16}N$ $[MH]^+$ 150; Found 150.

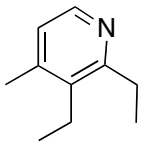


5-Methyl-3-*n*-propylpyridine. The dihydropyridine was formed via the general procedure with imine **1** and 1-(trimethylsilyl)pentyne with a reaction time of 10 h. The resulting toluene solution was subjected to pyridine synthesis Procedure B with an oxidation time of 16 h at 23 °C. 5-Methyl-3-*n*-propylpyridine was isolated after column chromatography (50:50 Et_2O:hexanes) as a pale yellow oil (47 mg, 0.34 mmol, 57%). IR (film): 2961, 2931, 2872, 1578, 1440, 1380, 1149, 713 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.26 (s, 1H), 8.24 (s, 1H), 7.29 (s, 1H), 2.54 (t, J = 7.4 Hz, 2H), 2.30 (s, 3H), 1.63 (sextet, J = 7.6 Hz, 2H), 0.94 (t, J = 7.3 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$):

δ 147.91, 147.38, 137.34, 136.70, 132.75, 35.10, 24.50, 18.54, 13.90. LRMS (ESI+) Calcd for $C_9H_{14}N$ $[MH]^+$ 136; Found 136.

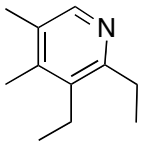


3-Benzyl-5-methylpyridine. The dihydropyridine was formed via the general procedure with imine **1** and 1-(trimethylsilyl)-3-phenylpropyne[3] with a reaction time of 10 h. The resulting toluene solution was subjected to pyridine synthesis Procedure B with an oxidation time of 16 h at 23 °C. 3-Benzyl-5-methylpyridine was isolated after column chromatography (50:50 Et_2O:hexanes) as a pale yellow oil (65 mg, 0.36 mmol, 60%). IR (film): 3026, 2919, 1596, 1495, 1453, 1440, 1030, 722, 699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.32 (s, 1H), 8.29 (s, 1H), 7.32 – 7.16 (m, 6H), 3.94 (s, 2H), 2.28 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 148.43, 147.55, 140.21, 137.10, 136.08, 133.09, 129.05, 128.85, 126.62, 39.11, 18.54. HRMS (EI+) Calcd for $C_{13}H_{13}N$ $[M]^+$ 183.1048; Found 183.1048.

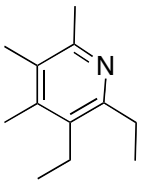


2,3-Diethyl-4-methylpyridine. The dihydropyridine was formed via the general procedure with imine **6** and 3-hexyne with a reaction time of 2 h. The resulting toluene solution was subjected to pyridine synthesis Procedure A with an oxidation time of 8 h at 0 °C. 2,3-Diethyl-4-methylpyridine was isolated after column chromatography (50:50 Et_2O:hexanes) as a colorless oil (48 mg, 0.32 mmol, 54%). IR (film): 2967, 2935, 2874, 1587, 1456, 1409, 823 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, J = 5.0 Hz, 1H),

6.85 (d, J = 5.0 Hz, 1H), 2.79 (q, J = 7.6 Hz, 2H), 2.63 (q, J = 7.6 Hz, 2H), 2.27 (s, 3H), 1.25 (t, J = 7.6 Hz, 3H), 1.10 (t, J = 7.6 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 160.95, 146.40, 145.21, 135.49, 123.51, 28.22, 21.66, 19.26, 14.23, 14.07. HRMS (EI+) Calcd for $C_{10}H_{15}N$ $[M]^+$ 149.1205; Found 149.1198.

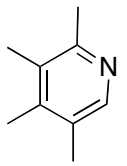


2,3-Diethyl-4,5-dimethylpyridine. The dihydropyridine was formed via the general procedure with imine **2** and 3-hexyne with a reaction time of 6 h. The resulting toluene solution was subjected to pyridine synthesis Procedure A with an oxidation time of 8 h at 0 °C. 2,3-Diethyl-4,5-dimethylpyridine was isolated after column chromatography (60:40 Et_2O:hexanes) as a pale yellow oil (59 mg, 0.36 mmol, 61%). IR (film): 2967, 2934, 2873, 1586, 1452, 1385, 1374, 1053 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.07 (s, 1H), 2.73 (q, J = 7.6 Hz, 2H), 2.61 (q, J = 7.6 Hz, 2H), 2.14 (s, 3H), 2.13 (s, 3H), 1.21 (t, J = 7.5 Hz, 3H), 1.06 (t, J = 7.5 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 158.59, 147.03, 143.67, 134.56, 129.63, 28.36, 21.75, 17.20, 14.85, 14.23. HRMS (EI+) Calcd for $C_{11}H_{17}N$ $[M]^+$ 163.1361; Found 163.1357.

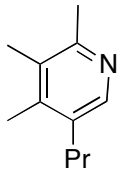


2,3-Diethyl-4,5,6-trimethylpyridine. The dihydropyridine was formed via the general procedure with imine **7** and 3-hexyne with a reaction time of 2 h. The resulting toluene solution was subjected to pyridine synthesis Procedure B with an oxidation time of 16 h at 75 °C. 2,3-Diethyl-4,5,6-trimethylpyridine was isolated after column

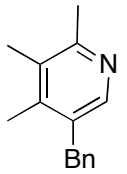
chromatography using a gradient of 20:80 to 40:60 Et_2O:hexanes as a pale yellow oil (87 mg, 0.49 mmol, 82%). IR (film): 2965, 2933, 2873, 1567, 1441, 1413, 1373, 1054, 675 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.76 (q, J = 7.6 Hz, 2H), 2.65 (q, J = 7.6 Hz, 2H), 2.47 (s, 3H), 2.21 (s, 3H), 2.16 (s, 3H), 1.25 (t, J = 7.6 Hz, 3H), 1.12 (t, J = 7.5 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 157.31, 153.02, 143.73, 132.46, 127.74, 28.82, 23.46, 22.10, 15.54, 15.46, 15.03, 14.34. HRMS (EI+) Calcd for $C_{12}H_{19}N$ $[M]^+$ 177.1518; Found 177.1519.



2,3,4,5-Tetramethylpyridine. The dihydropyridine was formed via the general procedure with imine **7** and 1-(trimethylsilyl)propyne with a reaction time of 2 h. The resulting toluene solution was subjected to pyridine synthesis Procedure A with an oxidation time of 12 h at 0 °C. 2,3,4,5-Tetramethylpyridine was isolated after column chromatography on activity III basic alumina eluting with 20:80 Et_2O:hexanes as a pale yellow oil (59 mg, 0.44 mmol, 73%). IR (film): 2990, 2922, 2867, 1590, 1446, 1394, 1212, 1082, 1007, 733, 639 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.07 (s, 1H), 2.48 (s, 3H), 2.21 (s, 3H), 2.20 (s, 3H), 2.18 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 154.28, 146.62, 144.04, 129.62, 129.49, 23.45, 17.32, 15.57, 15.28. HRMS (EI+) Calcd for $C_9H_{13}N$ $[M]^+$ 135.1048; Found 135.1049.

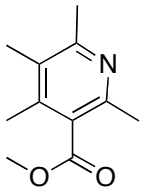


2,3,4-Trimethyl-5-*n*-propylpyridine. The dihydropyridine was formed via the general procedure with imine **7** and 1-(trimethylsilyl)pentyne with a reaction time of 6 h. The resulting toluene solution was subjected to pyridine synthesis Procedure B with an oxidation time of 16 h at 75 °C. 2,3,4-Trimethyl-5-*n*-propylpyridine was isolated after column chromatography using a gradient of 20:80 to 40:60 Et_2O:hexanes as a colorless oil (59 mg, 0.36 mmol, 60%). IR (film): 2959, 2933, 2871, 1587, 1466, 1400, 1206, 733 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.06 (s, 1H), 2.55 (t, J = 7.6 Hz, 2H), 2.48 (s, 3H), 2.20 (s, 3H), 1.54 (sextet, J = 7.7 Hz, 2H), 0.96 (t, J = 7.3 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 154.12, 146.68, 143.58, 133.76, 130.03, 33.41, 23.88, 23.45, 15.40, 15.29, 14.19. HRMS (EI+) Calcd for $C_{11}H_{17}N$ $[M]^+$ 163.1361; Found 163.1361.



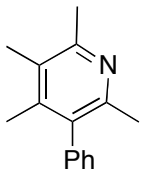
5-Benzyl-2,3,4-trimethylpyridine. The dihydropyridine was formed via the general procedure with imine **7** and 1-(trimethylsilyl)-3-phenylpropyne[3] with a reaction time of 8 h. The resulting toluene solution was subjected to pyridine synthesis Procedure B with an oxidation time of 16 h at 75 °C. 5-Benzyl-2,3,4-trimethylpyridine was isolated after column chromatography using a gradient of 20:80 to 40:60 Et_2O:hexanes as a pale yellow oil (72 mg, 0.34 mmol, 57%). IR (film): 3026, 2990, 2921, 1603, 1586, 1494, 1452, 1400, 1211, 1075, 729, 699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.15 (s, 1H), 7.27

– 7.24 (m, 2H), 7.18 (d, J = 7.5 Hz, 1H), 7.09 (d, J = 7.3 Hz, 2H), 3.97 (s, 2H), 2.52 (s, 3H), 2.19 (s, 3H), 2.10 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 155.15, 147.43, 144.48, 140.19, 131.98, 130.47, 128.65, 128.56, 126.28, 37.37, 23.59, 15.79, 15.38. HRMS (EI+) Calcd for $C_{15}H_{17}N$ $[M]^+$ 211.1361; Found 211.1359.



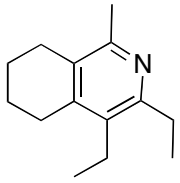
Methyl 2,4,5,6-tetramethylpyridine-3-carboxylate. The dihydropyridine was formed via the general procedure on a larger scale with imine **7** (380 mg, 2.0 mmol) and methyl 2-butynoate (1 mL, 10 mmol) with a reaction time of 24 h. For the synthesis of this specific pyridine, higher yields were obtained using purified DHP rather than crude material, and so the general procedure was not followed.[5] The DHP was purifed via column chromatography on activity III basic alumina eluting with a gradient of 0 – 2.5% ethyl acetate in hexanes. The DHP was obtained in moderate purity as a yellow solid (410 mg, 1.4 mmol, 70%). A portion of the chromatographed DHP (86 mg, 0.30 mmol) was measured out into a 25 mL round bottom flask equipped with a stir bar and reflux condenser. Toluene (2.4 mL) and 2,2,2-trifluoroethanol (TFE) (0.8 mL) were added, followed by Pd/C (17 mg, 20 wt %). The mixture was heated in a 120 °C oil bath open to the air for 2.5 days. An additional 1 mL of TFE was added to the solution every 8-12 h. The reaction mixture was cooled to room temperature, and then the reaction apparatus was fitted with a hydrogen-filled balloon. The flask was evacuated and then back-filled with H_2 five times. The reaction mixture was stirred under a hydrogen atmosphere at room temperature for 16 h. The hydrogen balloon was removed and the suspension was

filtered through Celite, rinsing thoroughly with dichloromethane. The solvents were removed *in vacuo* and the resulting oil was purified via column chromatography on silica gel, eluting with a gradient of 10:90 to 30:70 EtOAc:hexanes. Methyl 2,4,5,6-tetramethylpyridine-3-carboxylate (44 mg, 0.23 mmol, 76%) was obtained as a white solid (mp 52 – 55 °C, 53% yield over three steps). IR (film): 2296, 2956, 1724, 1638, 1568, 1436, 1377, 1267, 1193, 1162, 1051, 825, 785 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.92 (s, 3H), 2.51 (s, 3H), 2.46 (s, 3H), 2.21 (s, 3H), 2.19 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 170.04, 156.60, 150.59, 143.38, 128.14, 128.04, 52.52, 23.17, 22.34, 17.32, 14.84. HRMS (EI+) Calcd for $C_{11}H_{15}NO_2$ $[M]^+$ 193.1103; Found 193.1104.



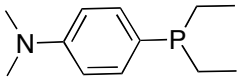
2,4,5,6-Tetramethyl-3-phenylpyridine. The dihydropyridine was formed via the general procedure with imine **7** and 1-phenylpropyne[4] with a reaction time of 2 h. The resulting toluene solution was subjected to pyridine synthesis Procedure B with an oxidation time of 12 h at 75 °C. The resulting oil was purified by column chromatography using 30:70 Et_2O:hexanes to elute 3,4,5,6-tetramethyl-2-phenylpyridine as a minor impurity (34 mg, 0.16 mmol, 27%) as a colorless oil. The solvent polarity was increased to 40:60 Et_2O:hexanes to elute the desired 2,4,5,6-tetramethyl-3-phenylpyridine (82 mg, 0.39 mmol, 65%). Spectroscopic data for the major isomer, 2,4,5,6-tetramethyl-3-phenylpyridine: IR (film): 2993, 2921, 1602, 1560, 1443, 1412, 970, 792, 763, 704 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 – 7.40 (m, 2H), 7.37 – 7.32 (m, 1H), 7.13 – 7.09 (m, 2H), 2.54 (s, 3H), 2.22 (s, 3H), 2.19 (s, 3H), 1.94 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz,

$CDCl_3$): δ 154.45, 152.17, 143.77, 140.23, 134.85, 129.50, 128.76, 127.40, 127.15, 23.75, 23.49, 17.48, 15.35. HRMS (EI+) Calcd for $C_{15}H_{17}N$ $[M]^+$ 211.1361; Found 211.1363. Spectroscopic data for the minor isomer, 3,4,5,6-tetramethyl-2-phenylpyridine: IR (film): 2994, 2919, 1563, 1496, 1211, 1075, 1020, 791, 701 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.46 – 7.39 (m, 4H), 7.36 – 7.32 (m, 1H), 2.55 (s, 3H), 2.27 (s, 6H), 2.20 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 155.49, 153.31, 144.96, 142.05, 129.42, 128.58, 128.25, 127.49, 126.93, 23.66, 17.12, 16.24, 15.62. HRMS (EI+) Calcd for $C_{15}H_{17}N$ $[M]^+$ 211.1361; Found 211.1348.



2,3-Diethyl-10-methyl-5,6,7,8-tetrahydroisoquinoline. The dihydropyridine was formed via the general procedure with imine **8** and 3-hexyne with a reaction time of 2 h. After cooling to room temperature, the reaction tube was opened, 2,2,2-trifluoroethanol (2 mL) and Pd/C (20 theoretical wt %) were added to the resulting toluene solution, and the vessel was re-sealed. The suspension was heated in a 120 °C oil bath for 16 h. The vessel was removed from the oil bath, cooled to room temperature and fitted with a hydrogen-filled balloon. The vessel was evacuated and then back-filled with H_2 five times, and then was stirred at room temperature under an atmosphere of hydrogen for 16 h. The resulting solution was filtered through Celite, rinsing thoroughly with dichloromethane. Solvents were removed *in vacuo* and 2,3-diethyl-10-methyl-5,6,7,8-tetrahydroisoquinoline was isolated after column chromatography using a gradient of 10:80 to 30:60 EtOAc:hexanes as a dark yellow oil (39 mg, 0.19 mmol, 32%). IR (film):

2965, 2933, 2871, 1567, 1451, 1425, 1374 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.76 (q, *J* = 7.6 Hz, 2H), 2.73 – 2.68 (m, 2H), 2.62 – 2.57 (m, 4H), 2.39 (s, 3H), 1.79 – 1.76 (m, 4H), 1.25 (t, *J* = 7.5 Hz, 3H), 1.11 (t, *J* = 7.5 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 156.86, 153.69, 143.99, 132.06, 128.29, 28.37, 26.74, 26.46, 22.78, 22.69, 22.36, 20.95, 15.06, 14.43. HRMS (EI+) Calcd for $C_{14}H_{21}N$ $[M]^+$ 203.1674; Found 203.1668.



4-(Diethylphosphino)-*N*,*N*-dimethylaniline. A 100 mL round bottom flask was fitted with a septum and cooled to room temperature under nitrogen. 4-Bromo-*N,N*-dimethylaniline (1.9 g, 9.5 mmol) was added to the flask and the flask was evacuated and back-filled with nitrogen three times. THF (20 mL) was added to the flask via syringe and the resulting solution was cooled to -78 °C. A 1.7 M solution of *tert*-butyllithium in hexanes (11.8 mL, 20 mmol) was added slowly via syringe. The resulting thick, yellow solution was stirred for 30 minutes at -78 °C. Chlorodiethylphosphine (1.0 g, 8.0 mmol) was added dropwise via syringe. The suspension became very thick, and stirring was impeded. The suspension was allowed to warm to 0 °C, at which point the solution became homogeneous. The resulting solution was stirred for 1.5 h at 0 °C. After warming it to room temperature, the solution was filtered through a silica plug, and washed with EtOAc (~300 mL). The solvent was removed from the filtrate *in vacuo* and the resulting thick yellow oil was purified via column chromatography on silica gel eluting with 50:50 dichloromethane:hexanes to remove *N,N*-dimethylaniline. The column was subsequently flushed with hexanes, and then a 5:95 EtOAc:hexanes solution was used to elute the desired phosphine product. Fractions containing product were evaporated to provide 4-(diethylphosphino)-*N,N*-dimethylaniline as a colorless oil (0.57

g, 2.7 mmol, 34%). IR (film): 2957, 2890, 2809, 1597, 1509, 1353, 1102, 946, 810, 766, 677 cm^{-1}. ^{1}H NMR (400 MHz, C_6D_6): δ 7.53 – 7.49 (m, 2H), 6.58 (d, *J* = 8.64, 2H), 2.50 (s, 6H), 1.66 – 1.54 (m, 4H), 1.09 – 1.01 (m, 6H). $^{13}C\{^{1}H\}$ NMR (100 MHz, C_6D_6): δ 151.69, 134.51 (d, *J* = 20.4 Hz), 124.30 (d, *J* = 12.4 Hz), 113.12 (d, *J* = 7.7 Hz), 40.30, 22.07 (d, *J* = 10.9 Hz), 10.77 (d, *J* = 14.9 Hz). $^{31}P\{^{1}H\}$ NMR (162 MHz, C_6D_6): δ -19.63 (d, *J* = 9.9 Hz). HRMS (EI+) Calcd for $C_{12}H_{20}NP$ $[M]^+$ 209.1333; Found 209.1336.

References:

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[5] Crude DHP can be carried on to the pyridine without initial isolation, however, the overall yield was decreased to 11% (compared to 53% overall yield using purified material).