Supporting Information for:

One-Pot Synthesis of Metallated Pyridines from Two Acetylenes, a Nitrile, and a Titanium(II) Alkoxide

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Experimental Section

General. ^{1}H and ^{13}C NMR spectra were taken on a Varian Gemini-300 spectrometer at 300 and 75 MHz, respectively. $CDCl_3$ was used as the solvent. Chemical shifts are reported in parts per million shift (δ value) from Me_4Si (δ 0 ppm for ^{1}H) or based on the middle peak of the solvent ($CDCl_3$) (δ 77.00 ppm for ^{13}C NMR) as an internal standard. Signal patterns are indicated as br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Coupling constants (*J*) are given in hertz. Infrared (IR) spectra were recorded on a JASCO A-100 spectrometer and are reported in wave numbers (cm^{-1}). Ti(O-*i*-Pr)$_4$ was distilled and stocked under argon atmosphere. Isopropylmagnesium chloride was prepared in Et_2O as a 1.3-1.7 M solution from isopropyl chloride and magnesium turnings by the usual procedure, titrated, and stocked under an argon atmosphere. All reactions were carried out under argon. Dry solvents (THF, ethyl ether, CH_2Cl_2) were purchased from Kanto Chemicals Co. (Japan). Chemicals were purified or dried in a standard manner, if necessary.

***N*,*N*-Diethyl-2-nonynamide** (**1**). This is a known compound [Hamada, T.; Suzuki, D.; Urabe, H.; Sato, F. *J. Am. Chem. Soc*. **1999**, *121*, 7342-7344].

***N*,*N*-Diethyl-3-hexyl-5-phenyl-2-picolinamide** (**7**). To a stirred solution of *N*,*N*-diethyl-2-nonynamide (48 mg, 0.228 mmol) and Ti(O-*i*-Pr)$_4$ (0.084 mL, 0.285 mmol) in 2 mL of Et_2O was added *i*-PrMgCl (1.53 M in Et_2O, 0.418 mL, 0.637 mmol) at -78 ℃ under argon to give a yellow homogeneous solution. The solution was warmed to -50 ℃ over 30 min, during which

period its color turned red. After stirring at -50 ℃ for an additional 5 h, ethynylbenzene (0.020 mL, 0.182 mmol) was introduced to the reaction mixture at -50 ℃ and the solution was stirred for another 3 h. Then, pulverized *p*-toluenesulfonylnitrile (49 mg, 0.273 mmol) was added and the reaction mixture was stirred for 3 h at -50 ℃. The reaction was terminated by the addition of water (0.05 mL) and quickly warmed up to room temperature. The resulting heterogeneous mixture was dried over anhydrous sodium sulfate and filtered through a short pad of Celite. The filtrate was concentrated *in vacuo* to give a crude oil. Careful analysis of the crude product by ^{1}H NMR spectroscopy did not show the presence of any isomeric products. The crude product was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (43 mg, 70%) as a colorless oil, which was fully characterized by ^{1}H and ^{13}C NMR, IR, and elemental analyses.

^{1}H NMR δ 0.88 (t, *J* = 7.2 Hz, 3H), 1.14 (t, *J* = 7.2 Hz, 3H), 1.21-1.43 (m, 6H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.66 (quintet, *J* = 7.8 Hz, 2H), 2.68 (t, *J* = 7.8 Hz, 2H), 3.18 (q, *J* = 7.2 Hz, 2H), 3.61 (q, *J* = 7.2 Hz, 2H), 7.37-7.52 (m, 3H), 7.55-7.61 (m, 2H), 7.75 (d, *J* = 2.1 Hz, 1H), 8.64 (d, *J* = 2.1 Hz, 1H). Irradiation of the proton at δ 8.64 ppm (Py-H) showed 14% nOe enhancement to the peak at δ 7.55-7.61 ppm (Ph-H). Irradiation of the proton at δ 2.68 ppm (PyCH_2) showed 7% nOe enhancement to the peak at δ 7.75 ppm (Py-H). Thus, the regiochemistry has been confirmed.

^{13}C NMR δ 12.69, 13.84, 13.92, 22.43, 29.20, 30.43, 31.49, 31.62, 38.98, 42.81, 127.25, 128.27, 129.15, 135.16, 135.78, 136.57, 137.65, 144.99, 153.23, 168.60.

IR (neat) 3020, 2960, 2860, 1636 (C=O), 1559, 1458, 1379, 1294, 1214, 1100, 869, 790, 730 cm^{-1}.

Anal. Calcd for $C_{22}H_{30}N_2O$: C, 78.06; H, 8.93. Found: C, 78.30; H, 9.16.

***N*,*N*-Diethyl-6-deuterio-3-hexyl-5-phenyl-2-picolinamide** (**7**-*d*).

^{1}H NMR δ 0.88 (t, *J* = 7.2 Hz, 3H), 1.14 (t, *J* = 7.2 Hz, 3H), 1.21-1.43 (m, 6H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.66 (quintet, *J* = 7.8 Hz, 2H), 2.68 (t, *J* = 7.8 Hz, 2H), 3.18 (q, *J* = 7.2 Hz, 2H), 3.61 (q, *J* = 7.2 Hz, 2H), 7.37-7.52 (m, 3H), 7.55-7.61 (m, 2H), 7.75 (s, 1H). The peak at δ 8.64 ppm (Py-H) of *N*,*N*-diethyl-3-hexyl-5-phenyl-2-picolinamide (**7**) disappeared to show 97% deuterium incorporation.

***N*,*N*-Diethyl-3-hexyl-6-iodo-5-phenyl-2-picolinamide** (**8**). To a stirred solution of *N*,*N*-diethyl-2-nonynamide (30 mg, 0.143 mmol) and Ti(O-*i*-Pr)$_4$ (0.053 mL, 0.179 mmol) in 2 mL of Et_2O was added *i*-PrMgCl (1.36 M in Et_2O, 0.295 mL, 0.401 mmol) at -78 ℃ under argon to give a yellow homogeneous solution. The solution was warmed to -50 ℃ over 30 min, during

which period its color turned red. After stirring at -50 ℃ for an additional 5 h, ethynylbenzene (0.013 mL, 0.115 mmol) was introduced to the reaction mixture at -50 ℃ and the solution was stirred for another 3 h. Then, pulverized *p*-toluenesulfonylnitrile (31 mg, 0.172 mmol) was added. After stirring for 3 h at -50 ℃, I_2 (109 mg, 0.429 mmol) in 1 mL of THF was added and the solution was rapidly warmed up to room temperature. After being stirred for 1 h at that temperature, the reaction was terminated by the addition of water (0.05 mL). The resulting heterogeneous mixture was dried over anhydrous sodium sulfate and filtered through a short pad of Celite. The filtrate was concentrated *in vacuo* to give a crude oil. Careful analysis of the crude product by ^{1}H NMR spectroscopy did not show the presence of any isomeric products. The crude product was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (37 mg, 70%) as a colorless oil, which was fully characterized by ^{1}H and ^{13}C NMR, IR, and elemental analyses.

^{1}H NMR δ 0.86 (t, *J* = 6.9 Hz, 3H), 1.20-1.40 (m, 6H), 1.22 (t, *J* = 7.2 Hz, 3H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.59 (quintet, *J* = 7.8 Hz, 2H), 2.60 (t, *J* = 7.8 Hz, 2H), 3.20 (q, J = 7.2 Hz, 2H), 3.58 (q, J = 7.2 Hz, 2H), 7.33-3.39 (m, 2H), 7.38 (s, 1H), 7.42-7.47 (m, 3H). Irradiation of the proton at δ 2.60 ppm ($PyCH_2$) showed 11% nOe enhancement to the peak at δ 7.38 ppm (Py-H), supporting the assigned structure.

^{13}C NMR δ 12.61, 13.54, 13.87, 22.37, 29.08, 30.20, 30.86, 31.39, 39.21, 43.01, 117.51, 128.32, 128.46, 129.33, 135.00, 138.53, 141.26, 144.01, 154.01, 166.95.

IR (neat) 3100, 3060, 3030, 2960, 2927, 2850, 1636 (C=O), 1577, 1458, 1405, 1363, 1219, 1155, 1101, 1029, 915, 861, 757, 699 cm^{-1}.

Anal. Calcd for $C_{22}H_{29}IN_2O$: C, 56.90; H, 6.29. Found: C, 56.77; H, 6.60.

***N*,*N*-Diethyl-6-allyl-3-hexyl-5-phenyl-2-picolinamide** (**9**). To a stirred solution of *N*,*N*-diethyl-2-nonynamide (48 mg, 0.228 mmol) and $Ti(O\text{-}i\text{-}Pr)_4$ (0.084 mL, 0.285 mmol) in 2 mL of Et_2O was added *i*-PrMgCl (1.54 M in Et_2O, 0.410 mL, 0.637 mmol) at -78 ℃ under argon to give a yellow homogeneous solution. The solution was warmed to -50 ℃ over 30 min, during which period its color turned red. After stirring at -50 ℃ for an additional 5 h, ethynylbenzene (0.020 mL, 0.182 mmol) was introduced to the reaction mixture at -50 ℃ and the solution was stirred for another 3 h. Then, pulverized *p*-toluenesulfonylnitrile (49 mg, 0.273 mmol) was added and the reaction mixture was stirred for 3 h at -50 ℃. $Li_2Cu(CN)Cl_2$ (0.50 M in THF, 0.569 mL, 0.285 mmol) was added and the mixture was stirred for 1 h at -50 ℃. Then, allyl bromide (0.030 mL, 0.341 mmol) was added and the reaction mixture was gradually warmed to 0 ℃ over 30 min. After being stirred for 1 h at 0 ℃, the reaction was terminated by the addition of water (0.05 mL) and quickly warmed up to room temperature. The resulting heterogeneous mixture was dried over

anhydrous sodium sulfate and filtered through a short pad of Celite. The filtrate was concentrated *in vacuo* to give a crude oil. Careful analysis of the crude product by ^{1}H NMR spectroscopy did not show the presence of any isomeric products. The crude product was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (35 mg, 52%) as a colorless oil, which was fully characterized by ^{1}H and ^{13}C NMR, IR, and elemental analyses.

^{1}H NMR δ 0.86 (t, *J* = 6.9 Hz, 3H), 1.17 (t, *J* = 7.2 Hz, 3H), 1.20-1.40 (m, 6H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.60 (quintet, *J* = 7.8 Hz, 2H), 2.62 (t, *J* = 7.8 Hz, 2H), 3.17 (q, *J* = 7.2 Hz, 2H), 3.49 (d, *J* = 6.3 Hz, 2H), 3.60 (q, *J* = 7.2 Hz, 2H), 4.85 (d/d, *J* = 1.5, 17.1 Hz, 1H), 4.97 (d/d, *J* = 1.5, 10.2 Hz, 1H), 5.99 (d/d/t, *J* = 10.2, 17.1, 6.3 Hz, 1H), 7.25-7.35 (m, 2H), 7.36-7.50 (m, 3H), 7.40 (s, 1H).

^{13}C NMR δ 12.65, 13.79, 13.90, 22.40, 29.19, 30.39, 31.08, 31.46, 38.92, 39.45, 42.78, 115.78, 127.64, 128.36, 129.14, 132.48, 136.66, 137.00, 138.99, 139.52, 152.94, 153.91, 168.77.

IR (neat) 3080, 3060, 3030, 2960, 2931, 2860, 1634 (C=O), 1549, 1418, 1379, 1318, 1218, 1151, 1093, 996, 913, 860, 770, 702 cm^{-1}.

Anal. Calcd for $C_{25}H_{34}N_2O$: C, 79.32; H, 9.05. Found: C, 79.23; H, 9.24.

***N*,*N*-Diethyl-6-(2,2-bis(ethoxycarbonyl)-1-methylethyl)-3-hexyl-5-phenyl-2-picolinamide (10).** To a stirred solution of *N*,*N*-diethyl-2-nonynamide (48 mg, 0.228 mmol) and Ti(O-*i*-Pr)$_4$ (0.084 mL, 0.285 mmol) in 2 mL of Et_2O was added *i*-PrMgCl (1.54 M in Et_2O, 0.410 mL, 0.637 mmol) at -78 ℃ under argon to give a yellow homogeneous solution. The solution was warmed to -50 ℃ over 30 min, during which period its color turned red. After stirring at -50 ℃ for an additional 5 h, ethynylbenzene (0.020 mL, 0.1821 mmol) was introduced to the reaction mixture at -50 ℃ and the solution was stirred for another 3 h. Then, pulverized *p*-toluenesulfonylnitrile (49 mg, 0.273 mmol) was added and the reaction mixture was stirred for 3 h at -50 ℃. $Li_2Cu(CN)Cl_2$ (0.50 M in THF, 0.569 mL, 0.285 mmol) was added and the mixture was stirred for 1 h at -50 ℃. Then, diethyl ethylidenemalonate (0.062 mL, 0.341 mmol) was added and the reaction mixture was gradually warmed to 0 ℃ over 30 min. After being stirred for 1 h at 0 ℃, the reaction was terminated by the addition of water (0.05 mL) and quickly warmed up to room temperature. The resulting heterogeneous mixture was dried over anhydrous sodium sulfate and filtered through a short pad of Celite. The filtrate was concentrated *in vacuo* to give a crude oil. Careful analysis of the crude product by ^{1}H NMR spectroscopy did not show the presence of any isomeric products. The crude product was chromatographed on silica gel (hexane-ethyl acetate) to

afford the title compound (55 mg, 58%) as a colorless oil, which was fully characterized by ^{1}H and ^{13}C NMR, IR, and elemental analyses.

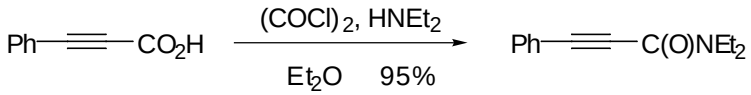
^{1}H NMR δ 0.85 (t, *J* = 7.2 Hz, 3H), 1.04 (d, *J* = 7.5 Hz, 3H), 1.09 (t, *J* = 7.2 Hz, 3H), 1.12 (t, *J* = 7.2 Hz, 3H), 1.20-1.40 (m, 6H), 1.22 (t, *J* = 7.2 Hz, 3H), 1.25 (t, *J* = 7.2 Hz, 3H), 1.40-1.75 (m, 2H), 2.58 (t, *J* = 7.8 Hz, 2H), 3.11 (q, *J* = 7.2 Hz, 1H), 3.12 (q *J* = 7.2 Hz, 1H), 3.53 (d/q, *J* = 14.4, 7.2 Hz, 1H), 3.67 (d/q, *J* = 14.4, 7.2 Hz, 1H), 3.76-4.26 (m, 5H), 4.31 (d, *J* = 11.5 Hz, 1H), 7.37-7.47 (m, 5H), 7.44 (s, 1H).

^{13}C NMR δ 12.66, 13.78, 13.90, 13.95, 13.97, 19.36, 22.41, 29.23, 30.42, 31.13, 31.48, 36.29, 38.75, 42.51, 56.43, 60.90, 61.18, 127.64, 128.52, 129.26, 132.62, 136.56, 139.28, 139.34, 152.40, 157.14, 168.64, 168.79, 169.63.

IR (neat) 3080, 3060, 2980, 2932, 2890, 2860, 1733 (C=O), 1640 (C=O), 1419, 1368, 1221, 1160, 1090, 1030, 860, 760, 703 cm^{-1}.

Anal. Calcd for $C_{31}H_{44}N_2O_5$: C, 70.96; H, 8.45. Found: C, 70.90; H, 8.34.

***N*,*N*-Diethyl-3-phenyl-2-propynamide (15).** This was prepared as follows.



^{1}H NMR δ 1.16 (t, *J* = 7.2 Hz, 3H), 1.26 (t, *J* = 7.2 Hz, 3H), 3.46 (q, *J* = 7.2 Hz, 2H), 3.65 (q, *J* = 7.2 Hz, 2H), 7.30-7.41 (m, 3H), 7.49-7.55 (m, 2H).

^{13}C NMR δ 12.68, 14.22, 39.18, 43.48, 81.86, 88.94, 120.75, 128.51, 129.89, 132.33, 154.04.

IR (neat) 3060, 2977, 2930, 2078, 2220, 1626, 1490, 1427, 1381, 1288, 1219, 1138, 1072, 923, 759, 734, 691 cm^{-1}.

Anal. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51. Found: C, 77.40; H, 7.88.

***N*,*N*-Diethyl-3,5-dihexyl-2-picolinamide (19).** To a stirred solution of *N*,*N*-diethyl-2-nonynamide (30 mg, 0.143 mmol) and Ti(O-*i*-Pr)$_4$ (0.053 mL, 0.179 mmol) in 2 mL of Et$_2$O was added *i*-PrMgCl (1.36 M in Et$_2$O, 0.295 mL, 0.401 mmol) at -78 ℃ under argon to give a yellow homogeneous solution. The solution was warmed to -50 ℃ over 30 min, during which period its color turned red. After stirring at -50 ℃ for an additional 5 h, 1-octyne (0.017 mL, 0.115 mmol) was introduced to the reaction mixture at -50 ℃ and the solution was stirred for another 3 h. Then, pulverized *p*-toluenesulfonylnitrile (31 mg, 0.172 mmol) was added and the reaction mixture was

stirred for 3 h at -50 ℃. The reaction was terminated by the addition of water (0.05 mL) and quickly warmed up to room temperature. The resulting heterogeneous mixture was dried over anhydrous sodium sulfate and filtered through a short pad of Celite. The filtrate was concentrated *in vacuo* to give a crude oil. Careful analysis of the crude product by ^{1}H NMR spectroscopy did not show the presence of any isomeric products. The crude product was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (25 mg, 63%) as a colorless oil, which was fully characterized by ^{1}H and ^{13}C NMR, IR, and elemental analyses.

^{1}H NMR δ 0.78-0.95 (m, 6H), 1.08 (t, *J* = 7.2 Hz, 3H), 1.14-1.42 (m, 12H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.58 (symmetric m, 4H), 2.57 (t, *J* = 7.8 Hz, 4H), 3.11 (q, *J* = 7.2 Hz, 2H), 3.57 (q, *J* = 7.2 Hz, 2H), 7.35 (d, *J* = 2.1 Hz, 1H), 8.22 (d, *J* = 2.1 Hz, 1H). Irradiation of the proton at δ 2.57 ppm ($PyCH_2$) showed 18% nOe enhancement to the peak at δ 7.35 ppm (Py-H) and 9% nOe enhancement to the peak at δ 8.22 ppm (Py-H). Thus, the regiochemistry has been confirmed.

^{13}C NMR δ 12.66, 13.78, 13.90 (2 peaks), 22.43 (2 peaks), 28.73, 29.16, 30.39, 30.93, 31.46, 31.49 (2 peaks), 32.74, 38.93, 42.76, 134.66, 137.21, 138.02, 146.52, 151.92, 168.89.

IR (neat) 2960, 2928, 2860, 1636 (C=O), 1559, 1458, 1379, 1294, 1214, 1100, 869, 790, 730 cm^{-1}.

Anal. Calcd for $C_{22}H_{38}N_2O$: C, 76.25; H, 11.05. Found: C, 76.05; H, 11.01.

***N*,*N*-Diethyl-6-deuterio-3,5-dihexyl-2-picolinamide (19-*d*).**

^{1}H NMR δ 0.78-0.95 (m, 6H), 1.08 (t, *J* = 7.2 Hz, 3H), 1.14-1.42 (m, 12H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.58 (symmetric m, 4H), 2.57 (t, *J* = 7.8 Hz, 4H), 3.11 (q, *J* = 7.2 Hz, 2H), 3.57 (q, *J* = 7.2 Hz, 2H), 7.35 (s, 1H). The peak at δ 8.22 ppm (Py-H) of *N*,*N*-diethyl-3,5-dihexyl-2-picolinamide (**19**) disappeared to show 96% deuterium incorporation.

One mmol-Scale Preparation of *N*,*N*-Diethyl-3,5-dihexyl-2-picolinamide (19). To a stirred solution of *N*,*N*-diethyl-2-nonynamide (251 mg, 1.20 mmol) and Ti(O-*i*-Pr)$_4$ (0.443 mL, 1.50 mmol) in 10 mL of Et_2O was added *i*-PrMgCl (1.40 M in Et_2O, 2.14 mL, 3.00 mmol) at -78 ℃ under argon to give a yellow homogeneous solution. The solution was warmed to -50 ℃ over 30 min, during which period its color turned red. After stirring at -50 ℃ for an additional 5 h, 1-octyne (0.142 mL, 0.96 mmol) was introduced to the reaction mixture at -50 ℃ and the solution was stirred for another 3 h. Then, pulverized *p*-toluenesulfonylnitrile (261 mg, 1.44 mmol) was added and the reaction mixture was stirred for 3 h at -50 ℃. The reaction was terminated by the addition of water (0.5 mL) and quickly warmed up to room temperature. The resulting heterogeneous

mixture was dried over anhydrous sodium sulfate and filtered through a short pad of Celite. The filtrate was concentrated *in vacuo* to give a crude oil, which was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (205 mg, 62%) as a colorless oil. Its physical properties were identical with those reported above.

***N,N*-Diethyl-5-(2-benzyloxyethyl)-3-hexyl-2-picolinamide** (**20**). To a stirred solution of *N,N*-diethyl-2-nonynamide (42 mg, 0.199 mmol) and Ti(O-*i*-Pr)$_4$ (0.073 mL, 0.249 mmol) in 2 mL of Et$_2$O was added *i*-PrMgCl (1.28 M in Et$_2$O, 0.435 mL, 0.557 mmol) at -78 ℃ under argon to give a yellow homogeneous solution. The solution was warmed to -50 ℃ over 30 min, during which period its color turned red. After stirring at -50 ℃ for an additional 5 h, 4-(benzyloxy)-1-butyne (26 mg, 0.159 mmol) in 1 mL of Et$_2$O was introduced to the reaction mixture at -50 ℃ and the solution was stirred for another 3 h. Then, pulverized *p*-toluenesulfonylnitrile (43 mg, 0.239 mmol) was added and the reaction mixture was stirred for 3 h at -50 ℃. The reaction was terminated by the addition of water (0.05 mL) and quickly warmed up to room temperature. The resulting heterogeneous mixture was dried over anhydrous sodium sulfate and filtered through a short pad of Celite. The filtrate was concentrated *in vacuo* to give a crude oil. Careful analysis of the crude product by ^{1}H NMR spectroscopy did not show the presence of any isomeric products. The crude product was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (43 mg, 68%) as a colorless oil, which was fully characterized by ^{1}H and ^{13}C NMR, IR, and elemental analyses.

^{1}H NMR δ 0.87 (t, *J* = 7.5 Hz, 3H), 1.09 (t, *J* = 7.2 Hz, 3H), 1.22-1.40 (m, 6H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.58 (quintet, *J* = 7.8 Hz, 2H), 2.57 (t, *J* = 7.8 Hz, 2H), 2.90 (t, *J* = 6.6 Hz, 2H), 3.11 (q, *J* = 7.2 Hz, 2H), 3.57 (q, *J* = 7.2 Hz, 2H), 3.69 (t, *J* = 6.6 Hz, 2H), 4.51 (s, 2H), 7.25-7.35 (m, 5H), 7.44 (d, *J* = 2.1 Hz, 1H), 8.28 (d, *J* = 2.1 Hz, 1H). Irradiation of the proton at δ 8.28 ppm (Py-H) showed 2% nOe enhancement to the peak at δ 2.90 ppm (PyCH$_2$). Irradiation of the proton at δ 2.90 ppm (PyCH$_2$) showed 3% nOe enhancement to the peak at δ 7.44 ppm (Py-H) and 8% nOe enhancement to the peak at δ 8.28 ppm (Py-H). Thus, the regiochemistry has been confirmed.

^{13}C NMR δ 12.65, 13.78, 13.91, 22.42, 29.19, 30.38, 31.43, 31.47, 33.20, 38.93, 42.74, 70.25, 73.05, 127.67, 127.72, 128.46, 134.67, 134.69, 137.90, 138.16, 146.86, 152.44, 168.77.

IR (neat) 3090, 3060, 3030, 2960, 2928, 2860, 1634 (C=O), 1456, 1362, 1294, 1213, 1101, 736, 698 cm^{-1}.

Anal. Calcd for $C_{25}H_{36}N_2O_2$: C, 75.72; H, 9.15. Found: C, 75.82; H, 9.09.

***N*,*N*-Diethyl-5-(2-benzyloxyethyl)-6-deuterio-3-hexyl-2-picolinamide (20-*d*).**

^{1}H NMR δ 0.87 (t, *J* = 7.5 Hz, 3H), 1.09 (t, *J* = 7.2 Hz, 3H), 1.22-1.40 (m, 6H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.58 (quintet, *J* = 7.8 Hz, 2H), 2.57 (t, *J* = 7.8 Hz, 2H), 2.90 (t, *J* = 6.6 Hz, 2H), 3.11 (q, *J* = 7.2 Hz, 2H), 3.57 (q, *J* = 7.2 Hz, 2H), 3.69 (t, *J* = 6.6 Hz, 2H), 4.51 (s, 2H), 7.25-7.35 (m, 5H), 7.44 (s, 1H). The peak at δ 8.28 ppm (Py-H) of *N*,*N*-diethyl-5-(2-benzyloxyethyl)-3-hexyl-2-picolinamide (**20**) disappeared to show 98% deuterium incorporation.

***N*,*N*-Diethyl-3-hexyl-5-(trimethylsilyl)-2-picolinamide (21).** To a stirred solution of *N*,*N*-diethyl-2-nonynamide (30 mg, 0.143 mmol) and Ti(O-*i*-Pr)$_4$ (0.053 mL, 0.179 mmol) in 2 mL of Et$_2$O was added *i*-PrMgCl (1.36 M in Et$_2$O, 0.295 mL, 0.401 mmol) at -78 ℃ under argon to give a yellow homogeneous solution. The solution was warmed to -50 ℃ over 30 min, during which period its color turned red. After stirring at -50 ℃ for an additional 5 h, (trimethylsilyl)acetylene (0.016 mL, 0.115 mmol) was introduced to the reaction mixture at -50 ℃ and the solution was stirred for another 3 h. Then, pulverized *p*-toluenesulfonylnitrile (31 mg, 0.172 mmol) was added and the reaction mixture was stirred for 3 h at -50 ℃. The reaction was terminated by the addition of water (0.05 mL) and quickly warmed up to room temperature. The resulting heterogeneous mixture was dried over anhydrous sodium sulfate and filtered through a short pad of Celite. The filtrate was concentrated *in vacuo* to give a crude oil. Careful analysis of the crude product by ^{1}H NMR spectroscopy did not show the presence of any isomeric products. The crude product was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (20 mg, 55%) as a colorless oil, which was fully characterized by ^{1}H and ^{13}C NMR, IR, and elemental analyses.

^{1}H NMR δ 0.29 (s, 9H), 0.87 (t, *J* = 7.5 Hz, 3H), 1.11 (t, *J* = 7.2 Hz, 3H), 1.15-1.40 (m, 6H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.59 (quintet, *J* = 7.8 Hz, 2H), 2.59 (t, *J* = 7.8 Hz, 2H), 3.13 (q, *J* = 7.2 Hz, 2H), 3.58 (q, *J* = 7.2 Hz, 2H), 7.62 (d, *J* = 1.5 Hz, 1H), 8.46 (d, *J* = 1.5 Hz, 1H). Irradiation of the proton at δ 0.29 ppm (SiMe$_3$) showed 5% nOe enhancement to the peak at δ 7.62 ppm (Py-H) and 5% nOe enhancement to the peak at δ 8.46 ppm (Py-H). Irradiation of the proton at δ 2.59 ppm (PyCH$_2$) showed 8% nOe enhancement to the peak at δ 7.62 ppm (Py-H). Thus, the regiochemistry has been confirmed.

^{13}C NMR δ -1.49, 12.65, 13.81, 13.92, 22.46, 29.23, 30.56, 31.48, 31.65, 38.83, 42.72, 134.00, 135.08, 142.49, 150.58, 154.62, 168.70.

IR (neat) 2960, 2930, 2860, 1636 (C=O), 1577, 1425, 1363, 1251, 1219, 1136, 1099, 926, 840, 752, 695, 658 cm^{-1}.

Anal. Calcd for $C_{19}H_{34}N_2OSi$: C, 68.21; H, 10.24. Found: C, 67.83; H, 10.01.

***N*,*N*-Diethyl-6-deuterio-3-hexyl-5-(trimethylsilyl)-2-picolinamide (21-*d*)**

^{1}H NMR δ 0.29 (s, 9H), 0.87 (t, *J* = 7.5 Hz, 3H), 1.11 (t, *J* = 7.2 Hz, 3H), 1.15-1.40 (m, 6H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.59 (quintet, *J* = 7.8 Hz, 2H), 2.59 (t, *J* = 7.8 Hz, 2H), 3.13 (q, *J* = 7.2 Hz, 2H), 3.58 (q, *J* = 7.2 Hz, 2H), 7.62 (s, 1H). The peak at δ 8.46 ppm (Py-H) of *N*,*N*-diethyl-3-hexyl-5-(trimethylsilyl)-2-picolinamide (**21**) disappeared to show 97% deuterium incorporation.

***N*,*N*-Diethyl-3,5-diphenyl-2-picolinamide (22).** To a stirred solution of *N*,*N*-diethyl-3-phenyl-2-propynamide (23 mg, 0.114 mmol) and Ti(O-*i*-Pr)$_4$ (0.042 mL, 0.143 mmol) in 2 mL of Et_2O was added *i*-PrMgCl (1.28 M in Et_2O, 0.250 mL, 0.320 mmol) at -78 ℃ under argon to give a yellow homogeneous solution. The solution was warmed to -50 ℃ over 30 min, during which period its color turned red. After stirring at -50 ℃ for an additional 5 h, ethynylbenzene (0.010 mL, 0.091 mmol) was introduced to the reaction mixture at -50 ℃ and the solution was stirred for another 3 h. Then, pulverized *p*-toluenesulfonylnitrile (25 mg, 0.137 mmol) was added and the reaction mixture was stirred for 3 h at -50 ℃. The reaction was terminated by the addition of water (0.05 mL) and quickly warmed up to room temperature. The resulting heterogeneous mixture was dried over anhydrous sodium sulfate and filtered through a short pad of Celite. The filtrate was concentrated *in vacuo* to give a crude oil. Careful analysis of the crude product by ^{1}H NMR spectroscopy did not show the presence of any isomeric products. The crude product was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (20 mg, 67%) as a colorless oil, which was fully characterized by ^{1}H and ^{13}C NMR, IR, and elemental analyses.

^{1}H NMR δ 0.87 (t, *J* = 7.2 Hz, 3H), 1.01 (t, *J* = 7.2 Hz, 3H), 2.95 (q, *J* = 7.2 Hz, 3H), 3.44 (q, *J* = 7.2 Hz, 3H), 7.38-7.60 (m, 8H), 7.60-7.68 (m, 2H), 7.93 (d, *J* = 2.1 Hz, 1H), 8.84 (d, *J* = 2.1 Hz, 1H). Irradiation of the proton at δ 8.84 ppm (Py-H) showed 5% nOe enhancement to the peak at δ 7.62 ppm (Ph-H). Thus, the regiochemistry has been confirmed.

^{13}C NMR δ 11.99, 13.35, 38.61, 42.43, 127.27, 128.42, 128.52, 128.68, 128.93, 129.25, 134.37, 135.76, 136.76, 137.20, 146.74 (2 peaks), 152.43, 168.39.

IR (neat) 3060, 3030, 2976, 2930, 1635 (C=O), 1559, 1419, 1294, 1218, 1109, 1010, 906, 887, 835, 800, 756, 698, 664 cm^{-1}.

Anal. Calcd for $C_{22}H_{22}N_2O$: C, 79.97; H, 6.71; N, 8.48. Found: C, 80.20; H, 7.02; N, 8.53.

***N*,*N*-Diethyl-6-deuterio-3,5-diphenyl-2-picolinamide (22-*d*).**

^{1}H NMR δ 0.87 (t, *J* = 7.2 Hz, 3H), 1.01 (t, *J* = 7.2 Hz, 3H), 2.95 (q, *J* = 7.2 Hz, 3H), 3.44 (q, *J* = 7.2 Hz, 3H), 7.38-7.60 (m, 8H), 7.60-7.68 (m, 2H), 7.93 (s, 1H). The peak at δ 8.84 ppm (Py-H) of *N*,*N*-diethyl-3,5-diphenyl-2-picolinamide (**22**) disappeared to show 96% deuterium incorporation.

***t*-Butyl 3,5-Dihexyl-2-picolinoate (24a).** To a stirred solution of *t*-butyl 2-nonynoate (100 mg, 0.475 mmol) and Ti(O-*i*-Pr)$_4$ (0.175 mL, 0.594 mmol) in 7 mL of Et$_2$O was added *i*-PrMgCl (1.53 M in Et$_2$O, 0.418 mL, 0.637 mmol) at -78 ℃ under argon to give a yellow homogeneous solution. The solution was warmed to -50 ℃ over 30 min, during which period its color turned red. After stirring at -50 ℃ for an additional 5 h, 1-octyne (0.056 mL, 0.380 mmol) was introduced to the reaction mixture at -50 ℃ and the solution was stirred for another 3 h. Then, pulverized *p*-toluenesulfonylnitrile (103 mg, 0.571 mmol) was added and the reaction mixture was subsequently allowed to warm to -10 ℃. After being stirred for 3 h at that temperature, the reaction was terminated by the addition of water (0.10 mL) and quickly warmed up to room temperature. The resulting heterogeneous mixture was dried over anhydrous sodium sulfate and filtered through a short pad of Celite. The filtrate was concentrated *in vacuo* to give a crude oil. Careful analysis of the crude product by ^{1}H NMR spectroscopy did not show the presence of any isomeric products. The crude product was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (66 mg, 50%) and *t*-butyl 3,5-dihexyl-6-(*p*-toluenesulfonyl)-2-picolinoate (**24b**) (32 mg, 16 %) as colorless oils, which were fully characterized by ^{1}H and ^{13}C NMR, IR, and elemental analyses.

^{1}H NMR δ 0.85 (t, *J* = 7.8 Hz, 6H), 1.15-1.42 (m, 12H), 1.47-1.67 (m, 4H), 1.60 (s, 9H), 2.58 (t, *J* = 7.8 Hz, 2H), 2.77 (t, *J* = 7.8 Hz, 2H), 7.32 (d, *J* = 2.1 Hz, 1H), 8.30 (d, *J* = 2.1 Hz, 1H). Irradiation of the proton at δ 2.77 ppm (PyCH$_2$) showed 10% nOe enhancement to the peak at δ 7.32 ppm (Py-H). Irradiation of the proton at δ 2.58 ppm (PyCH$_2$) showed 6% nOe enhancement to the peak at δ 7.32 ppm (Py-H) and 9% nOe enhancement to the peak at δ 8.30 ppm (Py-H). Thus, the regiochemistry has been confirmed.

^{13}C NMR δ 13.86 (2 peaks), 22.39, 22.41, 27.99, 28.62, 29.16, 30.76, 31.24, 31.43, 31.54, 32.62 (2 peaks), 82.07, 137.21, 138.28, 139.79, 147.09, 147.68, 166.45.

IR (neat) 2960, 2930, 2858, 1717 (C=O), 1457, 1392, 1368, 1314, 1256, 1154, 1109, 849, 730 cm^{-1}.

Anal. Calcd for $C_{22}H_{37}NO_2$: C, 76.03; H, 10.73. Found: C, 76.35; H, 10.21.

***t*-Butyl 3,5-Dihexyl-6-(*p*-toluenesulfonyl)-2-picolinoate (24b).**

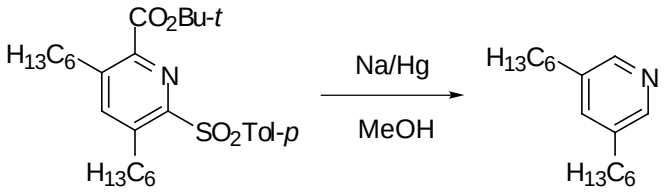
^{1}H NMR δ 0.75–0.92 (m, 6H), 1.10-1.78 (m, 16H), 1.45 (s, 9H), 2.43 (s, 3H), 2.81 (t, *J* = 7.8 Hz, 2H), 3.17 (t, *J* = 7.8 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 7.49 (s, 1H), 7.92 (d, *J* = 8.1 Hz, 2H).

^{13}C NMR δ 13.89, 13.93, 21.48, 22.39, 22.48, 27.74, 29.05, 29.16, 30.86, 31.01, 31.06, 31.45, 31.49, 32.08, 81.98, 129.08, 129.96, 136.16, 139.45, 141.45, 142.52, 144.20, 145.62, 153.90, 164.62.

IR (neat) 3070, 3020, 2960, 2928, 2858, 1721 (C=O), 1597, 1461, 1368, 1316 (S=O), 1149 (S=O), 1125, 1085, 850, 812, 710, 673 cm^{-1}.

Anal. Calcd for $C_{29}H_{43}NO_4S$: C, 69.42; H, 8.64. Found: C, 69.52; H, 8.46.

The regiochemistry of the title compound was determined by the derivatization to symmetrical 3,5-dihexylpyridine via the reduction with sodium amalgam in methanol [Nájera, C.; Yus, M. *Tetrahedron* **1999**, *55*, 10547-10658].



3,5-Dihexylpyridine. ^{1}H NMR δ 0.88 (t, *J* = 7.5 Hz, 6H), 1.14-1.40 (m, 8H), 1.45-1.68 (m, 8H), 2.57 (t, *J* = 7.5 Hz, 4H), 7.29 (symmetric m, 1H), 8.25 (d, *J* = 2.0 Hz, 2H).

Sulfonylpyridine **24b** is most likely formed via the aerial oxidation of dihydropyridines produced by the hydrolysis of the intermediate titanium complexes such as **11**, **12**, **14**, etc. in Scheme 3 in the text. In the proposed intermediates, hapto^2-pyridine-Ti(O-*i*-Pr)$_2$ complexes **12**, **14**, etc., the conjugation of the pyridine nucleus to a strong electron-withdrawing group decreases the electron density of the nitrogen, which retards the elimination of the sulfonyl group from the intermediates. As esters are generally a better electron-withdrawing group than amides (in resonance and inductive effects), the slow and incomplete elimination of the sulfonyl group in this ester version could be explained.

2-(2-Benzyloxyethyl)-4,5-dibutylpyridine (27). To a stirred solution of 5-decyne (0.020 mL, 0.111 mmol) and Ti(O-*i*-Pr)$_4$ (0.041 mL, 0.139 mmol) in 1.5 mL of Et$_2$O was added *i*-PrMgCl (1.36 M in Et$_2$O, 0.229 mL, 0.312 mmol) at -78 ℃ under argon to give a yellow homogeneous solution. The solution was warmed to -50 ℃ over 30 min, during which period its color turned black. After stirring at -50 ℃ for an additional 3 h, 4-(benzyloxy)-1-butyne (14 mg,

0.089 mmol) was introduced to the reaction mixture at -50 ℃ and the solution was stirred for another 2 h. Then, pulverized *p*-toluenesulfonylnitrile (30 mg, 0.167 mmol) was added and the reaction mixture was subsequently allowed to warm to -10 ℃. After being stirred for 3 h at that temperature, the reaction was terminated by the addition of water (0.05 mL) and quickly warmed up to room temperature. The resulting heterogeneous mixture was dried over anhydrous sodium sulfate and filtered through a short pad of Celite. The filtrate was concentrated *in vacuo* to give a crude oil. Careful analysis of the crude product by ^{1}H NMR spectroscopy did not show the presence of any isomeric products. The crude product was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (16 mg, 55%) as a colorless oil, which was fully characterized by ^{1}H and ^{13}C NMR, IR, and elemental analyses.

^{1}H NMR δ 0.95 (t, *J* = 7.5 Hz, 6H), 1.39 (sextet, *J* = 7.5 Hz, 4H), 1.54 (symmetric m, 4H), 2.56 (t, *J* = 7.5 Hz, 2H), 2.58 (t, *J* = 7.5 Hz, 2H), 3.04 (t, *J* = 6.9 Hz, 2H), 3.84 (t, *J* = 6.9 Hz, 2H), 4.53 (s, 2H), 6.98 (s, 1H), 7.15-7.30 (m, 5H), 8.24 (s, 1H). Irradiation of the proton at δ 2.56 ppm ($PyCH_2$) and δ 2.58 ppm ($PyCH_2$) showed 8% nOe enhancement to the peak at δ 6.98 ppm (Py-H) and 10% nOe enhancement to the peak at δ 8.24 ppm (Py-H). Irradiation of the proton at δ 3.04 ppm ($PyCH_2$) showed 8% nOe enhancement to the peak at δ 6.98 ppm (Py-H). Alternatively, the coupling constant less than 2.0 Hz supports the para relationship between the two pyridine protons. Thus, the regiochemistry has been confirmed.

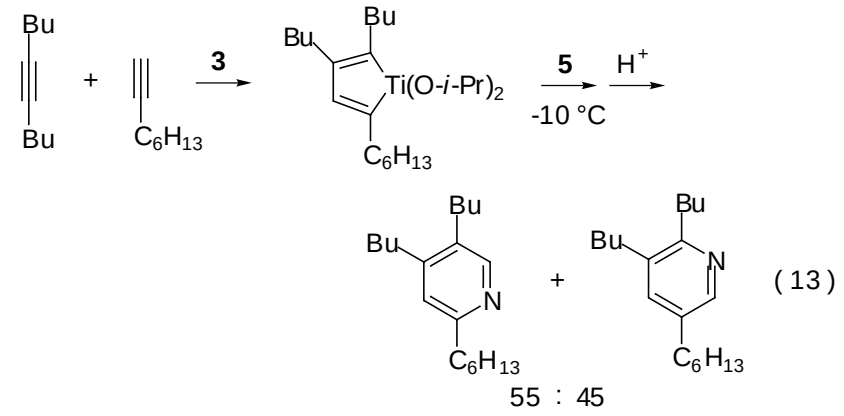
^{13}C NMR δ 13.79, 13.81, 22.55, 22.64, 29.31, 31.52, 32.33, 33.12, 38.13, 69.86, 72.92, 123.68, 127.54 (2 peaks), 127.68, 128.37, 133.71, 138.60, 149.82, 156.33.

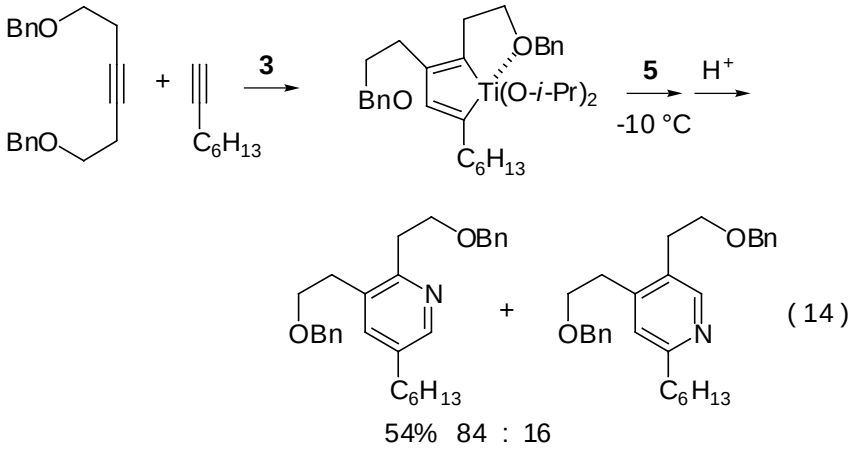
IR (neat) 3090, 3070, 3030, 3000, 2956, 2930, 2860, 1653, 1603, 1559, 1507, 1457, 1103, 1030, 735, 698 cm^{-1}.

Anal. Calcd for $C_{22}H_{31}NO$: C, 81.18; H, 9.60. Found: C, 81.31; H, 9.80.

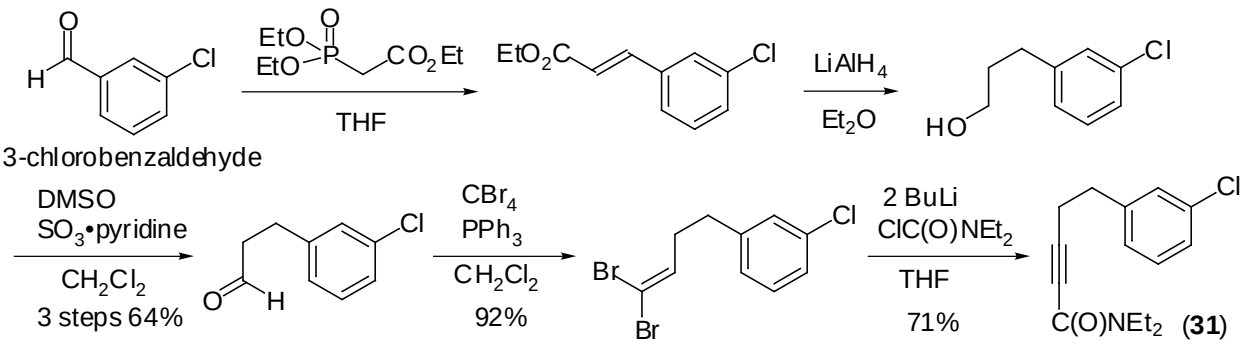
The following control experiments (eqs 13 and 14) clearly show that the benzyloxy group works as an efficient regiocontrolling element in the present pyridine synthesis. First, eq 13 below shows that simple 5-decyne and 1-octyne (without benzyl ether moiety in the side chains) and the sufonylnitrile produced an almost equimolar mixture of the two expected regioisomeric trialkylpyridines. However, even in such a case, the intermediate titanacyclopentadiene proved to exhibit a slight preference for the formation of a 2,4,5-trialkylpyridine over a 2,3,5-trialkylpyridine (55:45). Second, as shown in eq 14 below, when the 5-decyne was replaced by the oxygenated counterpart, 1,6-dibezyloxy-3-hexyne, the intermediate titanacycle led to the formation (84:16) of the 2,3,5-trialkylpyridine rather than the 2,4,5-trialkylpyridine, showing that the benzyl ether moiety has a decisive and reverse regiochemical preference to overcome the intrinsic preference of the

aforementioned titanacycle having no benzyl ether moiety. On the other hand, when another acetylene, 1-octyne, was changed to oxygenated acetylene such as 4-benzyloxy-1-butyne as shown in eq 5 of the text, the intrinsic regiochemical preference of the titanacycle and the directing effect of the benzyloxy group now match each other to enhance the regioselectivity of the nitrile incorporation to the highest degree to give the 2,4,5-trialkylpyridine **27** virtually as a single isomer.





***N,N*-Diethyl-5-(3-chlorophenyl)-2-pentynamide (31).** This was prepared as follows.



^{1}H NMR δ 1.08 (t, *J* = 7.2 Hz, 3H), 1.10 (t, *J* = 7.2 Hz, 3H), 2.66 (t, *J* = 7.2 Hz, 2H), 2.85 (t, *J* = 7.2 Hz, 2H), 3.37 (q, *J* = 7.2 Hz, 2H), 3.41 (q, *J* = 7.2 Hz, 2H), 7.06-7.13 (m, 1H), 7.17-7.25 (m, 3H).

^{13}C NMR δ 12.61, 14.05, 20.54, 33.42, 38.92, 43.21, 75.24, 90.01, 126.67, 126.79, 128.59, 129.84, 134.30, 141.92, 153.91.

IR (neat) 3066, 2976, 2933, 2870, 2221, 1623 (C=O), 1474, 1429, 1380, 1314, 1279, 1222, 1173, 1079, 998, 945, 862, 782, 737, 685 cm^{-1}.

Anal. Calcd for $C_{15}H_{18}ClNO$: C, 68.30; H, 6.88. Found: C, 68.51; H, 6.74.

***N*,*N*-Diethyl-3-[2-(3-chlorophenyl)ethyl]-5-phenyl-2-picolinamide** (**33**). To a stirred solution of *N*,*N*-diethyl-5-(3-chlorophenyl)-2-pentynamide (**31**) (573 mg, 2.17 mmol) and Ti(O-*i*-Pr)$_4$ (0.962 mL, 3.26 mmol) in 25 mL of Et_2O was added *i*-PrMgCl (1.35 M in Et_2O, 4.83 mL, 6.52 mmol) at -78 ℃ under argon to give a yellow homogeneous solution. The solution was warmed to -50 ℃ over 30 min, during which period its color turned red. After stirring at -50 ℃ for an additional 5 h, ethynylbenzene (0.286 mL, 2.61 mmol) was introduced to the reaction mixture at -50 ℃ and the solution was stirred for another 3 h. Pulverized *p*-toluenesulfonylnitrile (472 mg, 2.61 mmol) was added, and the reaction mixture was warmed to room temperature and stirred for 5 h. The reaction was terminated by the addition of water (1 mL). The resulting heterogeneous mixture was dried over anhydrous sodium sulfate and filtered through a short pad of Celite. The filtrate was concentrated *in vacuo* to give a crude oil. Careful analysis of the crude product by ^{1}H NMR spectroscopy did not show the presence of any isomeric products. The crude product was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (522 mg, 61%) as a colorless oil, which was fully characterized by ^{1}H and ^{13}C NMR, IR, and elemental analyses.

^{1}H NMR δ 1.13 (t, *J* = 7.2 Hz, 3H), 1.31 (t, *J* = 7.2 Hz, 3H), 2.97 (s, 4H), 3.11 (q, *J* = 7.2 Hz, 2H), 3.62 (q, *J* = 7.2 Hz, 2H), 7.00-7.27 (m, 5H), 7.32-7.58 (m, 4H), 7.64 (d, *J* = 2.1 Hz, 1H), 8.66 (d, *J* = 2.1 Hz, 1H). The coupling constant between the two pyridine protons suggests that these are in the meta relationship.

^{13}C NMR δ 12.75, 13.85, 33.68, 36.42, 39.19, 42.79, 126.38, 126.87, 127.14, 128.33, 128.71, 129.10, 129.77, 133.58, 134.24, 136.04, 136.52, 137.27, 143.21, 145.29, 153.12.

IR (neat) 3058, 3025, 2968, 2932, 2870, 1652 (C=O), 1456, 1380, 1294, 1135, 1096, 999, 944, 782, 759, 697 cm^{-1}.

Anal. Calcd for $C_{24}H_{25}ClN_2O$: C, 73.36; H, 6.41. Found: C, 73.30; H, 6.61.

3-[2-(3-Chlorophenyl)ethyl]-5-phenyl-2-pyridinecarboxaldehyde (**34**). To $Cp_2Zr(H)Cl$ (202 mg, 0.783 mmol) was added *N*,*N*-diethyl-3-[2-(3-chlorophenyl)ethyl]-5-phenyl-2-picolinamide (**33**) (135 mg, 0.344 mmol) in THF (10 mL) at room temperature under argon. After stirring at room temperature for 30 min, the reaction mixture was concentrated *in vacuo* and chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (104 mg, 94%) as a colorless oil, which was fully characterized by ^{1}H and ^{13}C NMR, IR, and elemental analyses.

^{1}H NMR δ 2.91 (t, *J* = 7.2 Hz, 2H), 3.39 (t, *J* = 7.2 Hz, 2H), 7.07-7.29 (m, 4H), 7.42-7.62 (m, 5H), 7.65 (d, *J* = 2.1 Hz, 1H), 8.91 (d, *J* = 2.1 Hz, 1H), 10.25 (s, 1H).

^{13}C NMR δ 34.00, 36.57, 126.46, 126.98, 127.48, 128.87, 129.19, 129.37, 129.78, 134.27, 136.45, 137.71, 138.99, 139.53, 143.21, 146.58, 148.55, 195.14.

IR (neat) 3060, 3033, 2925, 2854, 2715, 1700 (C=O), 1597, 1559, 1476, 1275, 1203, 1079, 904, 763, 721, 694 cm^{-1}.

Anal. Calcd for $C_{20}H_{16}ClNO$: C, 74.65; H, 5.01. Found: C, 74.39; H, 5.23.

3-[2-(3-Chlorophenyl)ethyl]-2-[hydroxy(1-methylpiperidin-4-yl)methyl]-5-phenylpyridine (**35**). To a stirred solution of 3-[2-(3-chlorophenyl)ethyl]-5-phenyl-2-pyridinecarboxaldehyde (**34**) (213 mg, 0.662 mmol) in 6 mL of THF was added (1-methylpiperidin-4-yl)magnesium chloride (0.06 M in THF, 22 mL, 1.32 mmol) at room temperature under argon. After stirring at room temperature for 10 min, the reaction was terminated by the addition of an aqueous solution of NH_4Cl (20 mL). The organic products were extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate, and concentrated *in vacuo* to give a crude oil. The crude product was chromatographed on silica gel (CH_2Cl_2-methanol) to afford the title compound (200 mg, 72%) as a colorless oil, which was fully characterized by ^{1}H and ^{13}C NMR, IR, and elemental analyses.

^{1}H NMR δ 1.50-1.95 (m, 7H), 2.25 (s, 3H), 2.80-3.10 (m, 7H), 4.73 (d, *J* = 4.2 Hz, 1H), 7.00-7.10 (m, 1H), 7.15-7.28 (m, 3H), 7.35-7.55 (m, 5H), 7.58 (d, *J* = 2.1 Hz, 1H), 8.66 (d, *J* = 2.1 Hz, 1H).

^{13}C NMR δ 26.51, 28.53, 32.67, 36.46, 42.40, 45.93, 55.53, 55.57, 72.85, 126.67, 126.73, 127.10, 128.19, 128.67, 129.14, 129.95, 133.05, 134.42, 135.49, 135.91, 137.43, 142.75, 144.94, 157.42.

IR (neat) 3400, 3066, 3025, 2936, 2854, 2789, 2731, 2682, 1457, 1385, 1279, 1156, 1123, 1083, 1042, 911, 772, 740, 707 cm^{-1}.

Anal. Calcd for $C_{26}H_{29}ClN_2O$: C, 74.18; H, 6.94. Found: C, 74.20; H, 7.03.

3-[2-(3-Chlorophenyl)ethyl]-5-phenylpyridine-2-yl 1-methylpiperidin-4-yl ketone (**36**). To a stirred solution of oxalyl chloride (0.041 mL, 0.470 mmol) in 2 mL of CH_2Cl_2 was added dimethyl sulfoxide (0.070 mL, 0.252 mmol) at -50 ℃ under argon. After 10 min, 3-[2-(3-chlorophenyl)ethyl]-2-[hydroxy(1-methylpiperidin-4-yl)methyl]-5-phenylpyridine (**35**) (152 mg, 0.361mmol) in 1 mL of CH_2Cl_2 was added dropwise over 10 min at -50 ℃. After 15 min, NEt_3 (0.281 mL, 0.202 mmol) was added at -50 ℃ and the reaction mixture was stirred for 2 h at that temperature. The reaction was terminated by the addition of an aqueous solution of NH_4Cl (5 mL). The organic products were extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate, and concentrated *in vacuo* to give a crude oil. The crude product was chromatographed on silica gel (CH_2Cl_2-methanol) to afford the title compound (137 mg, 91%) as a colorless oil, which was fully characterized by ^{1}H and ^{13}C NMR, IR, and elemental analyses.

^{1}H NMR δ 1.68-2.22 (m, 6H), 2.34 (s, 3H), 2.86-3.02 (m, 4H), 3.20 (t, *J* = 7.2 Hz, 2H), 3.82 (t/t, *J* = 4.2, 11.1 Hz, 1H), 7.00-7.33 (m, 4H), 7.38-7.62 (m, 5H), 7.59 (d, *J* = 2.1 Hz, 1H), 8.74 (d, *J* = 2.1 Hz, 1H).

^{13}C NMR δ 27.84, 34.92, 37.14, 43.49, 46.22, 55.16, 126.35, 127.03, 127.30, 128.87, 129.27, 129.75, 134.22, 136.87, 137.75, 137.83, 138.56, 143.47, 145.12, 150.50, 205.83.

IR (neat) 3058, 3025, 2932, 2854, 2782, 2731, 2682, 1684 (C=O), 1597, 1448, 1378, 1288, 1208, 1079, 973, 904, 763, 696 cm^{-1}.

Anal. Calcd for $C_{26}H_{27}ClN_2O$: C, 74.54; H, 6.50. Found: C, 74.70; H, 6.72.

8-Chloro-6,11-dihydro-11-(1-methylpiperidin-4-ylidene)-3-phenyl-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine (**30**). To a stirred solution of 3-[2-(3-chlorophenyl)ethyl]-5-phenylpyridine-2-yl 1-methylpiperidin-4-yl ketone (**36**) (40 mg, 0.095 mmol) in 0.25 mL of trifluoromethanesulfonic acid was stirred at 65 ℃ for 8 h. The reaction was quenched using ice water and was made alkaline with potassium hydroxide to a final pH of 10. The organic products were extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo* to give a crude oil. The crude product was chromatographed on silica gel (CH_2Cl_2-methanol) to afford the title compound (35 mg, 91%) as a colorless oil, which was fully characterized by ^{1}H and ^{13}C NMR, IR, and elemental analyses.

^{1}H NMR δ 2.22-2.58 (m, 6H), 2.39 (s, 3H), 2.60-3.00 (m, 4H), 3.32-3.52 (m, 2H), 7.14 (s, 1H), 7.08-7.21 (m, 3H), 7.32-7.58 (m, 5H), 7.61 (d, *J* = 2.1 Hz, 1H), 8.62 (d, *J* = 2.1 Hz, 1H).

^{13}C NMR δ 30.05, 30.31, 31.63, 31.77, 45.52, 45.53, 56.67, 126.10, 126.85, 127.89, 128.78, 128.90, 130.25, 132.85, 133.13, 133.49, 135.15, 135.94, 136.51, 137.33, 137.68, 139.54, 144.84, 155.31.

IR (neat) 3058, 3025, 2937, 2854, 2785, 2731, 2690, 1457, 1374, 1281, 1173, 1131, 991, 904, 815, 762, 736, 697 cm^{-1}.

Anal. Calcd for $C_{26}H_{25}ClN_2$: C, 77.89; H, 6.28. Found: C, 77.62; H, 6.68.

2-(Chloromethyl)-3,4-diphenylpyridine (**47**).

^{1}H NMR δ 4.54 (s, 2H), 7.03-7.07 (m, 2H), 7.15-7.20 (m, 6H) 7.27-7.29 (m, 2H), 7.32 (d, J = 4.8 Hz, 1H), 8.69 (d, J = 4.8 Hz, 1H). Irradiation of the proton at δ 4.54 ppm (PyC$\underline{H}_2$Cl) showed 4% nOe enhancement to the peak at δ 7.16 ppm (Ph-H). Thus, the regiochemistry has been confirmed.

^{13}C NMR δ 45.50, 124.51, 127.71 (2 carbons), 128.02 (2 carbons), 128.23 (2 carbons), 129.26 (2 carbons), 130.27 (2 peaks), 135.90, 136.46, 138.70, 149.00, 150.23, 154.78.

IR (neat) 3085, 3056, 3030, 2921, 2360, 2345, 1578, 1496, 1457, 1444, 1400, 1331, 1261, 1161, 1093, 1073, 1028, 1007, 850, 809, 761, 700, 661 cm^{-1}.

Anal. Calcd for $C_{18}H_{14}NCl$: C, 77.28; H, 5.04. Found: C, 76.97; H, 5.06.

2-(Chloromethyl)-6-deuterio-3,4-diphenylpyridine (**47**-*d*).

^{1}H NMR δ 4.54 (s, 2H), 7.03-7.07 (m, 2H), 7.15-7.20 (m, 6H) 7.27-7.29 (m, 2H), 7.32 (s, 1H). The peak at δ 8.69 ppm (α-Py-H) of 2-(chloromethyl)-3,4-diphenylpyridine disappeared to show nearly complete deuterium incorporation.

2-(Chloromethyl)-3,4-bis(4-methoxyphenyl)pyridine (**48**).

^{1}H NMR δ 3.76 (s, 3H), 3.81 (s, 3H), 4.53 (s, 2H), 6.73 (d, J = 9 Hz, 2H), 6.84 (d, J = 8.7 Hz, 2H), 6.98 (d, J = 9 Hz, 2H), 7.08 (d, J = 8.7 Hz, 2H), 7.28 (d, J = 4.8 Hz, 1H), 8.63 (d, J = 4.8 Hz, 1H).

^{13}C NMR δ 45.68, 55.12, 55.15, 113.55 (2 carbons), 113.77 (2 carbons), 124.48, 128.83, 130.61 (2 carbons), 131.12, 131.42 (2 carbons), 135.54, 148.77, 150.01, 155.11, 159.08, 159.21.

IR (neat) 3040, 3000, 1610, 1517, 1458, 1293, 1250, 1179, 1034, 830 cm^{-1}.

Anal. Calcd for $C_{20}H_{18}ClNO_2$: C, 70.69; H, 5.34. Found: C, 71.06; H, 5.78.

2-(Chloromethyl)-4-phenyl-3-(trimethylsilyl)pyridine (**49**).

^{1}H NMR δ 0.07 (s, 9H), 4.85 (s, 2H), 7.06 (d, J = 4.8 Hz, 1H), 7.22-7.26 (m, 2H), 7.39-7.42 (m, 3H), 8.58 (d, J = 4.8 Hz, 1H).

^{13}C NMR δ 2.11, 48.17, 124.38, 128.25 (3 carbons), 128.87 (2 carbons), 132.49, 142.74, 149.09, 158.82, 161.67.

IR (neat) 3081, 3058, 3026, 2954, 2926, 2898, 2854, 1564, 1529, 1495, 1444, 1428, 1368, 1253, 1148, 1122, 1079, 1043, 845, 762, 702, 659 cm^{-1}.

Anal. Calcd for $C_{15}H_{18}ClNSi$: C, 65.31; H, 6.58. Found: C, 65.47; H, 6.41.

2-(Chloromethyl)-4-(4-methoxyphenyl)-3-(trimethylsilyl)pyridine (**50**).

^{1}H NMR δ 0.10 (s, 9H), 3.86 (s, 3H), 4.84 (s, 2H), 6.79 (d, J = 8.7 Hz, 2H), 7.49 (d, J = 5.1 Hz, 1H), 7.16 (d, J = 8.7 Hz, 2H), 8.55 (d, J = 5.1 Hz, 1H).

^{13}C NMR δ 2.23, 48.21, 55.30, 113.64 (2 carbons), 124.56, 129.82, 130.06 (2 carbons), 135.32, 149.03, 158.62, 159.88, 161.71.

IR (neat) 3060, 3030, 2854, 1609, 1566, 1539, 1514, 1367, 1247, 1164, 1025, 832, 758, 667, cm^{-1}.

Anal. Calcd for $C_{16}H_{20}ClNOSi$: C, 62.83; H, 6.59. Found: C, 63.15; H, 6.60.

2-(Methoxymethyl)-4-(1-methyl-2-pyrrolyl)-3-(trimethylsilyl)pyridine (**51**).

^{1}H NMR δ 0.03 (s, 9H), 3.42 (s, 3H), 3.45 (s, 3H), 4.69 (br s, 2H), 6.03 (d/d, J = 3.6, 1.8 Hz, 1H), 6.16 (d/d, J = 3.6, 2.7 Hz, 1H), 6.69 (d/d, J = 2.7, 1.8 Hz, 1H), 7.04 (d, J = 4.8 Hz, 1H), 8.51 (d, J = 4.8 Hz, 1H).

^{13}C NMR δ 1.06, 34.23, 58.15, 77.21, 108.01, 111.29, 122.51, 124.93, 133.30, 134.96, 147.87, 149.17, 163.58.

IR (neat) 3102, 3030, 2927, 2896, 2820, 1574, 1540, 1527, 1480, 1448, 1419, 1411, 1362, 1312, 1245, 1198, 1101, 1047, 967, 923, 896, 843, 782 680 cm^{-1}.

Anal. Calcd for $C_{15}H_{22}N_2OSi$: C, 65.65; H, 8.08. Found: C, 65.78; H, 8.36.

2-(Methoxymethyl)-4-phenyl-3-(trimethylsilyl)pyridine (**52**). To a stirred solution of 1-phenyl-2-(trimethylsilyl)ethyne (20 mg, 0.115 mmol) and Ti(O-*i*-Pr)$_4$ (0.042 mL, 0.143 mmol) in 1.0 mL of Et_2O was added *i*-PrMgCl (1.11 M in Et_2O, 0.258 mL, 0.287 mmol) at -78 °C under argon to give a yellow homogeneous solution. The solution was warmed to -50 °C over 30 min, during which period its color turned black. After stirring at –50 °C for 2 h, *N*-benzyl-*N*-ethynyl-*p*-toluenesulfonamide (**42**) (26.2 mg, 0.092 mmol) in Et_2O (1.0 mL) was introduced to the reaction mixture at -50 °C and the solution was stirred for another 4 h. α-Methoxyacetonitrile (0.013 mL,

0.172 mmol) was added and the reaction mixture was gradually warmed to 0 °C. After being stirred overnight at the same temperature, the reaction was terminated by the addition of H_2O (0.1 mL) and the homogeneous mixture was filtered through a short pad of Celite with the aid of ether. The organic phase was concentrated to give a crude oil, which was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound as a yellow oil (15.1 mg, 56%).

^{1}H NMR δ 0.00 (s, 9H), 3.45 (s, 3H), 4.70 (s, 2H), 7.06 (d, J = 4.8 Hz, 1H), 7.27-7.43 (m, 5H), 8.50 (d, J = 4.8 Hz, 1H). Irradiation of the proton at δ 0.00 ppm (Si<u>Me</u>$_3$) showed 3% nOe enhancement to the peak at δ 4.70 ppm (PyC<u>H</u>$_2$O). Thus, the regiochemistry has been confirmed.

^{13}C NMR δ 1.85 (Si<u>Me</u>$_3$), 58.16 (CH$_2$O<u>Me</u>), 77.20 (Py<u>C</u>H$_2$O), 123.93, 127.26, 128.12, 128.21 (2 carbons), 128.98 (2 carbons), 132.12, 143.27, 148.12, 163.38.

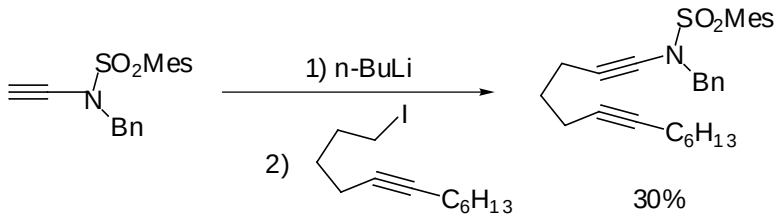
IR (neat) 3080, 3058, 3026, 2981, 2950, 2927, 2896, 2820, 1563, 1530, 1455, 1446, 1432, 1363, 1246, 1197, 1183, 1100, 1046, 969, 842, 764, 702, 682 cm^{-1}.

Anal. Calcd for $C_{16}H_{21}NOSi$: C, 70.80; H, 7.80. Found: C, 70.69; H, 7.88.

6-Deuterio-2-(methoxymethyl)-4-phenyl-3-(trimethylsilyl)pyridine (**52**-*d*).

^{1}H NMR δ 0.00 (s, 9H), 3.45 (s, 3H), 4.70 (s, 2H), 7.06 (s, 1H), 7.27-7.43 (m, 5H). The peak at δ 8.50 ppm (α-Py-H) of 2-(methoxymethyl)-4-phenyl-3-(trimethylsilyl)pyridine disappeared to show nearly complete deuterium incorporation.

***N*-Benzyl-*N*-(1,6-tridecadiyn-1-yl)mesitylenesulfonamide** (**54**). This was prepared as follows. The yield was not optimized.



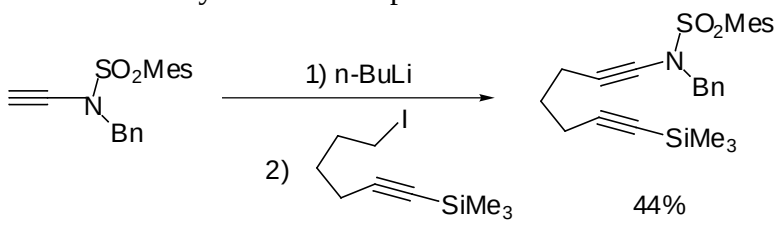
^{1}H NMR δ 0.89 (t, J = 6.9 Hz, 3H), 1.25-1.49 (m, 10H), 1.93 (t/t, J = 2.4, 6.9 Hz, 2H), 2.12 (t/t, J = 2.4, 6.9 Hz, 2H), 2.20 (t, J = 9.9 Hz, 2H), 2.32 (s, 3H), 2.65 (s, 6H), 4.56 (s, 2H), 6.98 (s, 2H), 7.29-7.34 (m, 5H).

^{13}C NMR δ 13.92, 17.45 (2 peaks), 18.60, 20.90, 22.44, 22.93 (2 carbons), 28.20, 28.43, 28.97, 31.26, 53.83, 71.26, 73.14, 79.03, 80.68, 128.14 (2 carbons), 128.50 (2 carbons), 128.84 (2 carbons), 132.00 (2 carbons), 135.23, 140.89 (2 peaks), 143.44.

IR (neat), 3065, 3032, 2931, 2858, 1604, 1456, 1344, 1165, 1055, 1028, 912, 853, 733, 700, 661 cm^{-1}.

Anal. Calcd for $C_{29}H_{37}NO_2S$: C, 75.12; H, 8.04. Found: C, 75.43; H, 7.95.

***N*-Benzyl-*N*-[7-(trimethylsilyl)-1,6-heptadiyn-1-yl]mesitylenesulfonamide** (**55**). This was prepared as follows. The yield was not optimized.



^{1}H NMR δ 0.15 (s, 9H), 1.47 (quintet, J = 6.9 Hz, 2H), 1.98 (t, J = 6.9 Hz, 2H), 2.23 (t, J = 6.9 Hz, 2H), 2.33 (s, 3H), 2.65 (s, 6H), 4.57 (s, 2H), 6.98 (s, 2H), 7.30-7.34 (m, 5H).

^{13}C NMR δ 0.01, 17.46, 18.48, 20.95, 22.96 (2 carbons), 27.72, 53.83, 71.07, 73.33, 84.78, 106.51, 128.21 (2 carbons), 128.55 (2 carbons), 128.87 (2 carbons), 132.05 (2 carbons), 135.20, 140.92 (2 peaks), 143.51.

IR (neat), 3298, 3065, 3032, 2957, 2866, 2173, 1604, 1560, 1457, 1405, 1345, 1249, 1187, 1165, 1055, 1027, 843, 760, 701 cm^{-1}.

Anal. Calcd for $C_{26}H_{33}NO_2SSi$: C, 69.13; H, 7.36. Found: C, 69.10; H, 7.16.

4,5-(1,3-Propylene)-3-hexyl-2-(methoxymethyl)pyridine (**56**).

^{1}H NMR δ 0.89 (t, J = 6.9 Hz, 3H), 1.18-1.53 (m, 8H), 2.09 (quintet, J = 7.5 Hz, 2H), 2.65 (t, J = 7.5 Hz, 2H), 2.88 (t, J = 7.5 Hz, 2H), 2.93 (t, J = 7.5 Hz, 2H), 3.41 (s, 3H, OMe), 4.58 (s, 2H), 8.29 (s, 1H). Irradiation of the proton at δ 2.65 ppm (PyC$\underline{H}_2$CH$_2$) showed 3% nOe enhancement to the peak at δ 4.58 ppm (PyC$\underline{H}_2$O). Thus, the regiochemistry has been confirmed.

^{13}C NMR δ 8.91, 17.47, 19.75, 24.17, 24.57, 24.89, 25.40, 26.08, 26.50, 53.34, 69.01, 128.66, 134.76, 137.34, 147.30, 148.53.

IR (neat) 3060, 2955, 2926, 2856, 2819, 2480, 2389, 1572, 1456, 1409, 1376, 1309, 1259, 1240, 1192, 1176, 1156, 1099, 959, 907, 803, 844, 725 cm^{-1}.

Anal. Calcd for $C_{16}H_{25}NO$: C, 77.68; H, 10.19. Found: C, 77.48; H, 9.75.

4,5-(1,3-Propylene)-2-(methoxymethyl)-4-(trimethylsilyl)pyridine (**57**). To a stirred solution of *N*-benzyl-*N*-[7-(trimethylsilyl-1,6-heptadiyn-1-yl)]mesitylenesulfonamide (46.4 mg, 0.10 mmol) and Ti(O-*i*-Pr)$_4$ (0.037 mL, 0.125 mmol) in 1 mL of Et$_2$O was added *i*-PrMgCl (1.49 M in Et$_2$O, 0.181 mL, 0.270 mmol) at -78 °C under argon to give a yellow homogeneous solution. The solution was warmed to -50 °C over 30 min. After stirring at -50 °C for an additional 5 h, α-methoxyacetonitrile (0.011 mL, 0.150 mmol) was introduced to the reaction mixture at -50 °C. After the solution was stirred for another 3 h at 0 °C, the reaction was terminated by the addition of

H_2O (0.1 mL) and the heterogeneous mixture was filtered through a short pad of Celite with the aid of ether. The filtrate was concentrated to an oil, which was chromatographed on silica gel to afford the title compound as a colorless oil (21 mg, 89%).

^{1}H NMR δ 0.37 (s, 9H), 2.04 (quintet, J = 7.5 Hz, 2H), 2.86 (t, J = 7.5 Hz, 2H), 2.97 (t, J = 7.5 Hz, 2H), 3.36 (s, 3H), 4.58 (s, 2H), 8.40 (s, 1H). Irradiation of the proton at δ 0.37 ppm (Si<u>Me</u>$_3$) showed 3% nOe enhancement to the peak at δ 4.58 ppm (PyC<u>H</u>$_2$OMe). Thus, the regiochemistry has been confirmed.

^{13}C NMR δ 1.49, 25.06, 29.53, 35.23, 57.92, 77.21, 129.81, 138.50, 144.85, 159.35, 160.94.

IR (neat) 3020, 2953, 2926, 2872, 2854, 2819, 1575, 1548, 1410, 1366, 1247, 1091, 883, 844, 767, 695 cm^{-1}.

Anal. Calcd for $C_{13}H_{21}NOSi$: C, 66.33; H, 8.99. Found: C, 66.33; H, 8.99.

2-(Methoxymethyl)-3,4-diphenylpyridine (**60**).

^{1}H NMR δ 3.36 (s, 3H), 4.36 (s, 2H), 7.03-7.25 (m, 10H), 7.30 (d, J = 5.1 Hz, 1H), 8.68 (d, J = 5.1 Hz, 1H).

^{13}C NMR δ 58.71, 73.84, 123.97, 127.36, 127.52, 127.96 (4 carbons), 129.35 (2 carbons), 130.41 (2 carbons) 135.67, 136.89, 139.09, 148.53, 149.61, 155.40.

2-(Benzylamino)-6-(methoxymethyl)-4,5-diphenylpyridine (**62**). To a stirred solution of diphenylacetylene (21 mg, 0.120 mmol) and Ti(O-*i*-Pr)$_4$ (0.044 mL, 0.150 mmol) in 1.0 mL of Et_2O was added *i*-PrMgCl (1.49 M in Et_2O, 0.217 mL, 0.323 mmol) at –78 ˚C under argon to give a yellow homogeneous solution. The solution was warmed to –50 ˚C over 30 min, during which period its color turned black. After stirring at –50 ˚C for 3 h, *N*-benzyl-*N*-ethynyl-2-mesitylenesulfonamide (**65**) (30 mg, 0.096 mmol) in 1.0 mL of Et_2O was introduced to the reaction mixture at –50 ˚C and the solution was stirred for another 4 h. Then, α-methoxyacetonitrile (0.013 mL, 0.180 mmol) was added and the reaction mixture was gradually warmed to room temperature over 2 h. After being stirred for 3 h at the same temperature, the reaction was terminated by the addition of H_2O (0.1 mL) and the heterogeneous mixture was filtered through a short pad of Celite with the aid of ether. The organic phase was concentrated to give a crude oil, ^{1}H NMR analysis of which showed the presence of the title compound and 2-(methoxymethyl)-3,4-diphenylpyridine (84:16). The crude product was chromatographed on silica gel (hexane-ethyl acetate) to afford the pure title compound (23 mg, 62%) as a white solid.

^{1}H NMR δ 3.34 (s, 3H), 4.22 (s, 2H), 4.53 (d, J = 5.7 Hz, 2H), 5.21 (br t, J = 5.7 Hz, 1H), 6.39 (s, 1H), 6.99 (m, 2H), 7.06 (m, 2H), 7.11-7.20 (m, 6H), 7.28-7.42 (m, 5H). Irradiation of

proton at δ 4.22 ppm (PyC$\underline{H}_2$O) showed 4% nOe enhancement to the peak at δ 7.06 ppm (*p*-MePh-$\underline{H}$). Thus, the regiochemistry has been confirmed.

^{13}C NMR δ 46.68, 58.64, 73.76, 105.99, 125.98, 126.59, 127.17, 127.34, 127.53 (2 carbons), 127.68 (2 carbons), 127.73 (2 carbons), 128.70 (2 carbons), 129.22 (2 carbons), 131.14 (2 carbons), 137.77, 139.06, 140.17, 151.63, 153.58, 157.72.

IR (nujol) 3298, 3080, 3059, 3033, 2953, 2923, 2853, 1607, 1596, 1505, 1489, 1456, 1443, 1408, 1377, 1351, 1323, 1313, 1267, 1238, 1208, 1190, 1177, 1100, 1085, 1031, 959, 914, 878, 771, 763, 753, 703, 667 cm^{-1}.

Anal. Calcd for $C_{26}H_{24}N_2O$: C, 82.07; H, 6.36. Found: C, 81.68; H, 6.54.

M.p. 136 ˚C.

2-(Benzylamino)-6-[methoxy(phenyl)methyl]-4,5-diphenylpyridine (**66**). To a stirred solution of diphenylacetylene (30 mg, 0.163 mmol) and Ti(O-*i*-Pr)$_4$ (0.062 mL, 0.210 mmol) in 1.0 mL of Et_2O was added *i*-PrMgCl (1.62 M in Et_2O, 0.281 mL, 0.454 mmol) at –78 ˚C under argon to give a yellow homogeneous solution. The solution was warmed to –50 ˚C over 30 min, during which period its color turned black. After stirring at –50 ˚C for 3 h, *N*-benzyl-*N*-ethynyl-2-mesitylenesulfonamide (**65**) (42 mg, 0.135 mmol) in 1.0 mL of Et_2O was introduced to the reaction mixture at –50 ˚C and the solution was stirred for 5 h. Then, 2-methoxy-2-phenylacetonitrile (0.036 mL, 0.245 mmol) was added and the reaction mixture was subsequently allowed to warm to room temperature. After being stirred for 5 h at the same temperature, the reaction was terminated by the addition of H_2O (0.1 mL) and the heterogeneous mixture was filtered through Celite with the aid of ether. The organic phase was concentrated to give a crude oil, ^{1}H NMR analysis of which showed the presence of the title compound and 2-[methoxy(phenyl)methyl]-3,4-diphenylpyridine (53:47). The crude product was chromatographed on silica gel (hexane-ethyl acetate) to afford the pure title compound (31 mg, 50%) as a white solid.

^{1}H NMR δ 3.27 (s, 3H), 4.49 (d/d, J = 13.8, 3.9 Hz, 1H), 4.59 (d/d, J = 13.8, 3.9 Hz, 1H), 5.13 (br m, 1H), 5.22 (s, 1H), 6.33 (s, 1H), 6.84 (d, J = 6.9 Hz, 1H), 6.97-7.00 (m, 2H), 7.11-7.39 (m, 17H).

^{13}C NMR δ 46.58, 56.85, 81.81, 105.95, 126.56, 126.87, 127.05, 127.20, 127.46 (2 carbons), 127.55 (2 carbons), 127.73 (2 carbons), 127.80, 127.91 (2 carbons), 128.44 (2 carbons), 128.95 (2 carbons), 130.98 (2 carbons), 131.79 (2 carbons), 137.73, 139.13, 139.97, 140.42, 151.06, 155.38, 157.52.

IR (nujol) 3413, 3085, 3059, 3023, 2925, 2854, 1594, 1575, 1548, 1456, 1408, 1377, 1365, 1303, 1248, 1212, 1156, 1090, 1028, 1004, 970, 916, 844, 782, 758, 728, 700 cm^{-1}.

M.p. 109 ˚C.

The regiochemistry was deduced by analogy based on the structure of 2-(benzylamino)-6-(methoxymethyl)-4,5-diphenylpyridine (**62**) and 2-(benzylamino)-6-(methoxymethyl)-4,5-bis(*p*-methoxyphenyl)pyridine (**69**).

This compound has so many aromatic rings that we were not able to obtain a correct elemental analysis even though the combustion was carried out in the presence of an oxidant such as tungsten oxide.

2-(Benzylamino)-6-(methoxymethyl)-4,5-di(*p*-tolyl)pyridine (**67**). To a stirred solution of di(*p*-tolyl)acetylene (25 mg, 0.120 mmol) and Ti(O-*i*-Pr)$_4$ (0.044 mL, 0.150 mmol) in 1.0 mL of Et_2O was added *i*-PrMgCl (1.46 M in Et_2O, 0.221 mL, 0.323 mmol) at –78 ˚C under argon to give a yellow homogeneous solution. The solution was warmed to –50 ˚C over 30 min, during which period its color turned black. After stirring at –50 ˚C for 3 h, *N*-benzyl-*N*-ethynyl-2-mesitylenesulfonamide (**65**) (30 mg, 0.096 mmol) in 1.0 mL of Et_2O was introduced to the reaction mixture at –50 ˚C and the solution was stirred for 4 h. Then, α-methoxyacetonitrile (0.013 mL, 0.180 mmol) was added and the reaction mixture was gradually warmed to –5 ˚C over 5 h. After being stirred overnight at the same temperature, the reaction was terminated by the addition of H_2O (0.1 mL) and the heterogeneous mixture was filtered through a short pad of Celite with the aid of ether. The organic phase was concentrated to give a crude oil, ^{1}H NMR analysis of which showed the presence of the title compound and 2-(methoxymethyl)-3,4-di(*p*-tolyl)pyridine (87:13). The crude product was chromatographed on silica gel (hexane-ethyl acetate) to afford the pure title compound (22 mg, 53%) as a colorless oil.

^{1}H NMR δ 2.25 (s, 3H), 2.30 (s, 3H), 3.34 (s, 3H), 4.21 (s, 2H), 4.52 (d, J = 5.4 Hz, 2H), 5.16 (br t, J = 5.4 Hz, 1H), 6.36 (s, 1H), 6.88-7.02 (m, 7H), 7.25-7.41 (m, 4H).

^{13}C NMR δ 20.97, 21.05, 46.70, 58.58, 73.75, 106.03, 125.92, 127.29, 127.52 (2 carbons), 128.45 (2 carbons), 128.48 (2 carbons), 128.67 (2 carbons), 129.12 (2 carbons), 130.94 (2 carbons), 134.79, 136.04, 136.85, 137.36, 139.16, 151.57, 153.68, 157.64.

IR (neat) 3284, 3080, 3059, 3028, 2952, 2923, 2854, 1594, 1568, 1505, 1483, 1460, 1446, 1377, 1357, 1297, 1235, 1218, 1195, 1108, 1092, 1025, 952, 861, 827, 819, 728, 704 cm^{-1}.

Anal. Calcd for $C_{28}H_{28}N_2O$: C, 82.32; H, 6.91. Found: C, 82.36, H, 6.98.

The regiochemistry was deduced by analogy based on the structure of 2-(benzylamino)-6-(methoxymethyl)-4,5-diphenylpyridine (**62**) and 2-(benzylamino)-6-(methoxymethyl)-4,5-bis(*p*-methoxyphenyl)pyridine (**69**).

2-(Benzylamino)-6-(methoxymethyl)-4,5-di(*m*-tolyl)pyridine (**68**). To a stirred solution of di(*m*-tolyl)acetylene (25 mg, 0.120 mmol) and Ti(O-*i*-Pr)$_4$ (0.044 mL, 0.150 mmol) in 1.0 mL of Et_2O was added *i*-PrMgCl (1.46 M in Et_2O, 0.221 mL, 0.323 mmol) at –78 ˚C under argon to give a yellow homogeneous solution. The solution was warmed to –50 ˚C over 30 min, during which period its color turned black. After stirring at –50 ˚C for 3 h, *N*-benzyl-*N*-ethynyl-2-mesitylenesulfonamide (**65**) (30 mg, 0.096 mmol) in 1.0 mL of Et_2O was introduced to the reaction mixture at –50 ˚C and the solution was stirred for 5 h. Then, α-methoxyacetonitrile (0.013 mL, 0.180 mmol) was added and the reaction mixture was gradually warmed to room tempperature over 3 h. After being stirred overnight at the same temperature, the reaction was terminated by the addition of H_2O (0.1 mL) and the heterogeneous mixture was filtered through a short pad of Celite with the aid of ether. The organic phase was concentrated to give a crude oil, ^{1}H NMR analysis of which showed the presence of the title compound and 2-(methoxymethyl)-3,4-di(*m*-tolyl)pyridine (83:17). The crude product was chromatographed on silica gel (hexane-ethyl acetate) to afford the pure title compound (22 mg, 57%) as a colorless oil.

^{1}H NMR δ 2.19 (s, 3H), 2.24 (s, 3H), 3.35 (s, 3H), 4.22 (s, 2H), 4.53 (d, J = 5.7 Hz, 2H), 5.18 (br t, J = 5.7 Hz, 1H), 6.38 (s, 1H), 6.75-7.09 (m, 8H), 7.25-7.42 (m, 5H).

^{13}C NMR δ 21.13, 21.20, 46.72, 58.56, 73.75, 105.93, 126.13, 126.33, 127.23, 127.31, 127.45, 127.48, 127.56 (2 carbons), 127.83, 128.21, 128.68 (2 carbons), 129.99, 131.86, 137.05, 137.24, 137.69, 139.15, 140.13, 151.68, 153.50, 157.66.

IR (neat) 3280, 3090, 3060, 3030, 2923, 2855, 2813, 1600, 1584, 1552, 1505, 1464, 1417, 1380, 1351, 1337, 1326, 1271, 1240, 1215, 1189, 1092, 1031, 956, 908, 871, 797, 754, 698, 668 cm^{-1}.

Anal. Calcd for $C_{28}H_{28}N_2O$: C, 82.32; H, 6.91. Found: C, 82.18; H, 7.15.

The regiochemistry was deduced by analogy based on the structure of 2-(benzylamino)-6-(methoxymethyl)-4,5-diphenylpyridine (**62**) and 2-(benzylamino)-6-(methoxymethyl)-4,5-bis(*p*-methoxyphenyl)pyridine (**69**).

2-(Benzylamino)-6-(methoxymethyl)-4,5-bis(*p*-methoxyphenyl)pyridine (**69**). To a stirred solution of bis(*p*-methoxyphenyl)acetylene (29 mg, 0.120 mmol) and Ti(O-*i*-Pr)$_4$ (0.044 mL, 0.150 mmol) in 1.0 mL of Et_2O was added *i*-PrMgCl (1.46 M in Et_2O, 0.221 mL, 0.323 mmol) at –78 ˚C under argon to give a yellow homogeneous solution. The solution was warmed to –50 ˚C over 30 min, during which period its color turned red. After stirring at –50 ˚C for 3 h, *N*-benzyl-*N*-ethynyl-2-mesitylenesulfonamide (**65**) (30 mg, 0.096 mmol) in 1.0 mL of Et_2O was introduced to the reaction mixture at –50 ˚C and the solution was stirred for 4 h. Then, α-methoxyacetonitrile (0.013 mL, 0.180 mmol) was added and the reaction mixture was subsequently

allowed to warm to room temperature. After being stirred for 4 h at the same temperature, the reaction was terminated by the addition of H_2O (0.1 mL) and the heterogeneous mixture was filtered through a short pad of Celite with the aid of ether. The organic phase was concentrated to give a crude oil, ^{1}H NMR analysis of which showed the presence of the title compound and 2-(methoxymethyl)-3,4-bis(*p*-methoxyphenyl)pyridine (76:24). The crude product was chromatographed on silica gel (hexane-ethyl acetate) to afford the pure title compound (27 mg, 67%) as a colorless oil.

^{1}H NMR δ 3.35 (s, 3H), 3.73 (s, 3H), 3.78 (s, 3H), 4.21 (s, 2H), 4.52 (d, J = 5.7 Hz, 2H), 5.15 (br t, J = 5.7 Hz, 1H), 6.35 (s, 1H), 6.67 (d, J = 9.0 Hz, 2H), 6.75 (d, J = 9.0 Hz, 2H), 6.92 (d, J = 9.0 Hz, 2H), 6.97 (d, J = 9.0 Hz, 2H), 7.24-7.41 (m, 5H). Irradiation of proton at δ 4.21 ppm (PyC$\underline{H}_2$O) showed 7% nOe enhancement to the peak at δ 6.97 ppm (*p*-MeOPh-H). Thus, the regiochemistry has been confirmed.

^{13}C NMR δ 46.69, 55.07 (2 carbons), 58.65, 73.74, 105.93, 113.20 (2 carbons), 113.23 (2 carbons), 125.60, 127.30, 127.50 (2 carbons), 128.69 (2 carbons), 130.11, 130.46 (2 carbons), 132.14 (2 carbons), 132.60, 139.13, 151.41, 153.70, 157.64, 158.31, 158.81.

IR (neat) 3265, 3084, 3065, 3029, 3000, 2924, 2969, 2955, 2835, 1599, 1574, 1548, 1513, 1495, 1463, 1451, 1385, 1355, 1293, 1242, 1177, 1153, 1095, 1034, 954, 906, 827, 799, 734, 699 cm^{-1}.

Anal. Calcd for $C_{28}H_{28}N_2O_3$: C, 76.34; H, 6.41. Found: C, 76.16; H, 6.36.

2-(Benzylamino)-4,5-bis(*p*-methoxyphenyl)-6-[methoxy(phenyl)methyl]pyridine (**70**). To a stirred solution of bis(*p*-methoxyphenyl)acetylene (34 mg, 0.163 mmol) and Ti(O-*i*-Pr)$_4$ (0.062 mL, 0.210 mmol) in 1.0 mL of Et_2O was added *i*-PrMgCl (1.62 M in Et_2O, 0.281 mL, 0.454 mmol) at –78 ˚C under argon to give a yellow homogeneous solution. The solution was warmed to –50 ˚C over 30 min, during which period its color turned red. After stirring at –50 ˚C for 2 h, *N*-benzyl-*N*-ethynyl-2-mesitylenesulfonamide (**65**) (42 mg, 0.135 mmol) in 1.0 mL of Et_2O was introduced to the reaction mixture at –50 ˚C and the solution was stirred for 5 h. Then, 2-methoxy-2-phenylacetonitrile (0.036 mL, 0.245 mmol) was added and the reaction mixture was subsequently allowed to warm to room temperature. After being stirred for 5 h at the same temperature, the reaction was terminated by the addition of H_2O (0.1 mL) and the heterogeneous mixture was filtered through a short pad of Celite with the aid of ether. The organic phase was concentrated to give a crude oil, ^{1}H NMR analysis of which showed the presence of the title compound and 2-[methoxy(phenyl)methyl]-3,4-bis(*p*-methoxyphenyl)pyridine (60:40). The crude product was chromatographed on silica gel (hexane-ethyl acetate) to afford the pure title compound (32 mg, 53%) as a colorless oil.

^{1}H NMR δ 3.26 (s, 3H), 3.72 (s, 3H), 3.81 (s, 3H), 4.47 (d/d, J = 14.7, 5.7 Hz, 1H), 4.57 (d/d, J = 14.7, 5.7 Hz, 1H), 5.08 (br t, J = 5.7 Hz, 1H), 5.21 (s, 1H), 6.29 (s, 1H), 6.66 (d, J = 8.7 Hz, 2H), 6.74 (s, 2H), 6.83 (d, J = 8.7 Hz, 1H), 6.91 (d, J = 8.7 Hz, 2H), 7.10 (d, J = 8.7 Hz, 1H), 7.21-7.37 (m, 10H).

^{13}C NMR δ 46.52, 55.03, 55.09, 56.75, 81.84, 105.96, 113.14 (3 carbons), 113.47, 125.38, 127.20, 127.33, 127.74 (2 carbons), 127.89 (2 carbons), 128.15 (2 carbons), 128.61 (2 carbons), 130.32, 130.38 (2 carbons), 132.17, 132.73, 132.98, 139.49, 140.81, 151.07, 156.03, 157.78, 158.40, 158.67.

IR (neat) 3418, 3085, 3061, 3029, 3000, 2958, 2931, 2835, 1598, 1575, 1548, 1515, 1495, 1463, 1455, 1354, 1290, 1245, 1178, 1156, 1091, 1032, 970, 911, 832, 802, 738, 720, 700 cm^{-1}.

Anal. Calcd for $C_{34}H_{32}N_2O_3$: N, 5.42. Found: N, 4.93.

The regiochemistry was deduced by analogy based on the structure of 2-(benzylamino)-6-(methoxymethyl)-4,5-diphenylpyridine (**62**) and 2-(benzylamino)-6-(methoxymethyl)-4,5-bis(*p*-methoxyphenyl)pyridine (**69**).

2-(Benzylamino)-6-(methoxymethyl)-4,5-bis(*p*-chlorophenyl)pyridine (**71**). To a stirred solution of bis(*p*-chlorophenyl)acetylene (40 mg, 0.163 mmol) and Ti(O-*i*-Pr)$_4$ (0.062 mL, 0.210 mmol) in 1.0 mL of Et_2O and 0.5 mL of toluene (to dissolve the acetylene) was added *i*-PrMgCl (1.62 M in Et_2O, 0.281 mL, 0.454 mmol) at -78 °C under argon to give a yellow homogeneous solution. The solution was warmed to -50 °C, during which period its color turned black. After stirring at -50 °C for 5 h, *N*-benzyl-*N*-ethynylmesitylenesulfonamide (**65**) (42.3 mg, 0.135 mmol) in Et_2O (1 mL) was introduced to the reaction mixture at -50 °C and the solution was stirred for another 5 h. Then, α-methoxyacetonitrile (0.018 mL, 0.245 mmol) was added. The reaction was warmed to 0 °C and stirred overnight at the same temperature. Then, the reaction was terminated by the addition of H_2O (0.1 mL) and the heterogeneous mixture was filtered through a short pad of Celite with the aid of ether. The organic phase was concentrated to give a crude oil, which was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (43.5 mg, 72 %) as a white solid.

^{1}H NMR δ 3.34 (s, 3H), 4.17 (s, 2H), 4.53 (d, J = 5.7 Hz, 2H), 5.23 (br t, J = 5.7 Hz, 1H), 6.32 (s, 1H), 6.90 (d, J = 8.4 Hz, 2H), 6.99 (d, J = 8.1 Hz, 2H), 7.13 (d, J = 8.1 Hz, 2H), 7.19 (d, J = 8.4 Hz, 2H), 7.26-7.40 (m, 5H).

^{13}C NMR δ 46.54, 58.68, 73.87, 105.98, 124.50, 127.42 127.50 (2 carbons), 128.11 (2 carbons), 128.21 (2 carbons), 128.74 (2 carbons), 130.46 (2 carbons), 132.36 (2 carbons), 132.86, 133.56, 136.00, 138.27, 138.85, 150.31, 153.82, 157.80.

IR (nujol) 3257, 3060, 3020, 2952, 2924, 2854, 1601, 1570, 1559, 1491, 1458, 1376, 1364, 1376, 1260, 1093, 1015, 955, 826, 798, 752, 728, 698, cm^{-1}.

Anal. Calcd for $C_{26}H_{22}Cl_2N_2O$: C, 69.49; H, 4.93. Found: C, 69.40; H, 5.02.

M.p. 118 ˚C.

Demethylation of the Methyl Ether.

6-(Benzylamino)-3,4-di(*p*-tolyl)pyridine-2-methanol (**72**). This was carried out according to: Grieco, P.; Nishizawa, M.; Oguri, T,; Burke, S.; Marinovic, N. *J. Am. Chem. Soc.* **1977**, *99*, 5773-5780.

To a solution of 2-(benzylamino)-6-(methoxymethyl)-4,5-di(*p*-tolyl)pyridine (**67**) (17.7 mg, 0.043 mmol) in methylene chloride (1.1 mL) cooled to -78 °C was added boron tribromide (40 μL, 0.43 mmol). After stirring at -78 °C for 30 min, the reaction was warmed to -12 °C. The solution was stirred for 1.5 h and was quenched at -12 °C by the addition of Et_2O (0.13 mL). After the reaction mixture was warmed to room temperature and was stirred for 30 min, 1*N* NaOH (1 mL) was added. The organic layer was separated, dried (Na_2SO_4), and concentrated to give a crude oil, which was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (13.3 mg, 84 %) as a solid.

^{1}H NMR δ 1.26 (br s, 1H), 2.26 (s, 3H), 2.30 (s, 3H), 4.37 (d, J = 0.6 Hz, 2H), 4.60 (d, J = 5.7 Hz, 2H), 5.01 (br t, J = 5.7 Hz, 1H), 6.37 (s, 1H), 6.85-7.04 (m, 8H), 7.29 (m, 5H).

^{13}C NMR δ 21.01, 21.08, 46.40, 61.95, 105.81, 122.92, 127.42, 127.55 (2 carbons), 128.60 (2 carbons), 128.80 (2 carbons), 128.93 (2 carbons), 129.12 (2 carbons), 130.47 (2 carbons), 133.43, 136.45, 136.70, 137.13, 139.28, 151.37, 154.79, 156.42.

IR (nujol) 3323, 3030, 2923, 2853, 1607, 1521, 1457, 1376, 1092, 819, 754, 698 cm^{-1}.

Anal. Calcd for $C_{27}H_{26}N_2O$: C, 82.20; H, 6.64. Found: C, 82.14; H, 6.72.

M.p. 165 ˚C.

3,5-Dihexyl-6-(methoxymethyl)-2-pyridinecarbaldehyde (**79**). To a stirred solution of *N*,*N*-diethyl-2-nonynamide (40 mg, 0.191 mmol) and Ti(O-*i*-Pr)$_4$ (0.071 mL, 0.239 mmol) in 2 mL of Et_2O was added *i*-PrMgCl (1.44 M in Et_2O, 0.345 mL, 0.497 mmol) at -78 ℃ under argon to give a yellow homogeneous solution. The solution was warmed to -50 ℃ over 30 min, during which period its color turned red. After stirring at -50 ℃ for an additional 5 h, 1-octyne (0.023 mL, 0.153 mmol) was added to the reaction mixture at -50 ℃ and the solution was stirred for another 3 h. Then α-methoxyacetonitrile (0.010 mL, 0.134 mmol) was added and the reaction mixture was subsequently warmed to -30 ℃. After being stirred for 5 h at that temperature, the

reaction was terminated by the addition of H_2O (0.2 mL) and the reaction mixture was filtered through Celite. The organic phase was concentrated *in vacuo* to give a crude oil. Careful analysis of the crude product by ^1H NMR spectroscopy did not show the presence of any isomeric products. The crude product was chromatographed on silica gel (hexane-ether) to afford the title compound (36 mg, 84%) as a colorless oil which was fully characterized by ^1H and ^{13}C NMR, IR, and elemental analyses.

^1H NMR δ 0.87 (t, J = 6.9 Hz, 3H), 0.89 (t, J = 6.9 Hz, 3H), 1.24-1.42 (m, 12H), 1.50-1.65 (m, 4H), 2.73 (t, J = 7.8 Hz, 2H), 3.01 (t, J = 7.8 Hz, 2H), 3.45 (s, 3H), 4.64 (s, 2H), 7.41 (s, 1H), 10.15 (s, 1H). Irradiation of proton at δ 4.64 ppm (PyC$\underline{H}_2$O) showed 2% nOe enhancement to the peak at δ 2.73 ppm (PyC$\underline{H}_2$). Thus, the regiochemistry has been confirmed.

^{13}C NMR δ 13.92 (2 peaks), 22.43, 22.47, 29.14 (2 peaks), 30.40, 30.76, 31.21, 31.43, 31.50, 31.52, 58.66, 73.87, 140.28 (2 peaks), 141.65, 147.04, 153.28, 195.35.

IR (neat) 2956, 2927, 2857, 2819, 1711 (C=O), 1550, 1465, 1412, 1377, 1356, 1308, 1251, 1215, 1192, 1104, 960, 917, 779, 725 cm^{-1}.

Anal. Calcd for $C_{20}H_{33}NO_2$: C, 75.19; H, 10.41. Found: C, 74.86; 10.30.

2-(Deuterioformyl)-3,5-dihexyl-6-(methoxymethyl)pyridine (**79**-*d*).

^1H NMR δ 0.87 (t, J = 6.9 Hz, 3H), 0.89 (t, J = 6.9 Hz, 3H), 1.24-1.42 (m, 12H), 1.50-1.65 (m, 4H), 2.73 (t, J = 7.8 Hz, 2H), 3.01 (t, J = 7.8 Hz, 2H), 3.45 (s, 3H), 4.64 (s, 2H), 7.41 (s, 1H). The peak at δ 10.15 ppm (CHO) of 3,5-dihexyl-6-(methoxymethyl)-2-pyridinecarbaldehyde (**79**) disappeared to show 83% deuterium incorporation.

One mmol-Scale Preparation of 3,5-Dihexyl-6-(methoxymethyl)-2-pyridinecarbaldehyde (**79**). To a stirred solution of *N*,*N*-diethyl-2-nonynamide (251 mg, 1.20 mmol) and Ti(O-*i*-Pr)$_4$ (0.443 mL, 1.50 mmol) in 20 mL of Et_2O was added *i*-PrMgCl (1.40 M in Et_2O, 2.14 mL, 3.00 mmol) at -78 ℃ under argon to give a yellow homogeneous solution. The solution was warmed to -50 ℃ over 30 min, during which period its color turned red. After stirring at -50 ℃ for an additional 5 h, 1-octyne (0.142 mL, 0.96 mmol) was added to the reaction mixture at -50 ℃ and the solution was stirred for another 3 h. Then α-methoxyacetonitrile (0.063 mL, 0.84 mmol) was added and the reaction mixture was subsequently warmed to -30 ℃. After being stirred for 5 h at that temperature, the reaction was terminated by the addition of H_2O (1.5 mL) and the reaction mixture was filtered through Celite. The organic phase was concentrated *in vacuo* to give a crude oil, which was chromatographed on silica gel (hexane-ether) to afford the title compound (194 mg, 72%) as a colorless oil. Its physical properties were identical with those reported above.

When the same reaction was terminated by the addition of deuterium oxide, **79**-*d* with 99% deuterium incorporation at the aldehyde hydrogen was obtained.

3-Hexyl-6-(methoxymethyl)-5-(trimethylsilyl)-2-pyridinecarbaldehyde (**80**). To a stirred solution of *N*,*N*-diethyl-2-nonynamide (40 mg, 0.191 mmol) and Ti(O-*i*-Pr)$_4$ (0.071 mL, 0.239 mmol) in 2 mL of Et$_2$O was added *i*-PrMgCl (1.44 M in Et$_2$O, 0.345 mL, 0.497 mmol) at -78 ℃ under argon to give a yellow homogeneous solution. The solution was warmed to -50 ℃ over 30 min, during which period its color turned red. After stirring at -50 ℃ for an additional 5 h, (trimethylsilyl)acetylene (0.021 mL, 0.153 mmol) was added to the reaction mixture at -50 ℃ and the solution was stirred for another 3 h. Then α-methoxyacetonitrile (0.010 mL, 0.134 mmol) was added and the reaction mixture was subsequently warmed to -30 ℃. After being stirred for 5 h at that temperature, the reaction was terminated by the addition of H$_2$O (0.2 mL) and the reaction mixture was filtered through Celite. The organic phase was concentrated *in vacuo* to give a crude oil. Careful analysis of the crude product by ^{1}H NMR spectroscopy did not show the presence of any isomeric products. The crude product was chromatographed on silica gel (hexane-ether) to afford the title compound (27 mg, 65%) as a colorless oil which was fully characterized by ^{1}H and ^{13}C NMR, IR, and elemental analyses.

^{1}H NMR δ 0.36 (s, 9H), 0.88 (t, J = 6.9 Hz, 3H), 1.25-1.43 (m, 6H), 1.55 (m, 2H), 3.01 (t, J = 7.8 Hz, 2H), 3.45 (s, 3H), 4.65 (s, 2H), 7.74 (s, 1H), 10.17 (s, 1H).

^{13}C NMR δ 0.44, 13.94, 22.49, 29.16, 30.93, 31.35, 31.51, 58.37, 76.19, 138.27, 139.22, 146.86, 148.69, 159.76, 195.82.

IR (neat) 2955, 2928, 2857, 2819, 1712 (C=O), 1485, 1424, 1367, 1336, 1294, 1250, 1196, 1111, 1015, 917, 842, 770, 690 cm^{-1}.

Anal. Calcd for $C_{17}H_{29}NO_2Si$: C, 66.40; H, 9.51. Found: C, 66.60; H, 9.87.

3-Hexyl-6-(methoxymethyl)-5-phenyl-2-pyridinecarbaldehyde (**81**). To a stirred solution of *N*,*N*-diethyl-2-nonynamide (40 mg, 0.191 mmol) and Ti(O-*i*-Pr)$_4$ (0.071 mL, 0.239 mmol) in 2 mL of Et$_2$O was added *i*-PrMgCl (1.44 M in Et$_2$O, 0.345 mL, 0.497 mmol) at -78 ℃ under argon to give a yellow homogeneous solution. The solution was warmed to -50 ℃ over 30 min, during which period its color turned red. After stirring at -50 ℃ for an additional 5 h, ethynylbenzene (0.017 mL, 0.153 mmol) was added to the reaction mixture at -50 ℃ and the solution was stirred for another 3 h. Then α-methoxyacetonitrile (0.010 mL, 0.134 mmol) was added and the reaction mixture was subsequently warmed to -30 ℃. After being stirred for 5 h at that temperature, the reaction was terminated by the addition of H$_2$O (0.2 mL) and the reaction mixture

was filtered through Celite. The organic phase was concentrated *in vacuo* to give a crude oil. Careful analysis of the crude product by ^{1}H NMR spectroscopy did not show the presence of any isomeric products. The crude product was chromatographed on silica gel (hexane-ether) to afford the title compound (21 mg, 51%) as a colorless oil which was fully characterized by ^{1}H and ^{13}C NMR, IR, and elemental analyses.

^{1}H NMR δ 0.88 (t, J = 6.9 Hz, 3H), 1.25-1.43 (m, 6H), 1.61 (m, 2H), 3.09 (t, J = 7.8 Hz, 2H), 3.44 (s, 3H), 4.49 (s, 2H), 7.44-7.50 (m, 5H), 7.57 (s, 1H), 10.26 (s, 1H).

^{13}C NMR δ 13.93, 22.45, 29.16, 30.73, 31.24, 31.51, 58.71, 73.25, 128.49, 128.61, 129.09, 137.91, 140.02, 141.04 141.09, 148.35, 152.26, 195.38.

IR (neat), 3061, 2955, 2927, 2857, 2821, 1709 (C=O), 1642, 1544, 1496, 1456, 1376, 1303, 1191, 1146, 1099, 1001, 957, 769, 702 cm^{-1}.

Anal. Calcd for $C_{20}H_{25}NO_2$: C, 77.14; H, 8.09. Found: C, 76.81; H, 8.44.

3,5-Dihexyl-6-(benzyloxymethyl)-2-pyridinecarbaldehyde (**82**). To a stirred solution of *N*,*N*-diethyl-2-nonynamide (40 mg, 0.191 mmol) and Ti(O-*i*-Pr)$_4$ (0.071 mL, 0.239 mmol) in 2 mL of Et_2O was added *i*-PrMgCl (1.44 M in Et_2O, 0.345 mL, 0.497 mmol) at -78 ℃ under argon to give a yellow homogeneous solution. The solution was warmed to -50 ℃ over 30 min, during which period its color turned red. After stirring at -50 ℃ for an additional 5 h, 1-octyne (0.023 mL, 0.153 mmol) was added to the reaction mixture at -50 ℃ and the solution was stirred for another 3 h. Then α-(benzyloxy)acetonitrile (0.010 mL, 0.134 mmol) was added and the reaction mixture was subsequently warmed to -30 ℃. After being stirred for 5 h at that temperature, the reaction was terminated by the addition of H_2O (0.2 mL) and the reaction mixture was filtered through Celite. The organic phase was concentrated *in vacuo* to give a crude oil. Careful analysis of the crude product by ^{1}H NMR spectroscopy did not show the presence of any isomeric products. The crude product was chromatographed on silica gel (hexane-ether) to afford the title compound (48 mg, 90%) as a colorless oil which was fully characterized by ^{1}H and ^{13}C NMR, IR, and elemental analyses.

^{1}H NMR δ 0.88 (t, J = 6.9 Hz, 6H), 1.23-1.40 (m, 12H), 1.50-1.61 (m, 4H), 2.71 (t, J = 7.5 Hz, 2H), 3.01 (t, J = 7.5 Hz, 2H), 4.63 (s, 2H), 4.74 (s, 2H), 7.29-7.39 (m, 5H), 7.41 (s, 1H), 10.15 (s, 1H). Irradiation of proton at δ 4.74 ppm ($PyCH_2O$) showed 3% nOe enhancement to the peak at δ 2.71 ppm ($PyCH_2$). Thus, the regiochemistry has been confirmed.

^{13}C NMR δ 13.89, 13.90, 22.42, 22.45, 25.14, 29.12, 19.16, 30.46, 30.73, 31.21, 31.47, 31.50, 71.67, 72.98, 127.84, 128.17, 128.43, 137.93, 140.26, 140.36, 141.99, 146.97, 153.34, 195.30.

IR (neat) 3088, 3064, 3031, 2955, 2927, 2857, 1710 (C=O), 1496, 1457, 1412, 1359, 1307, 1251, 1213, 1175, 1091, 1028, 913, 842, 734, 698 cm^{-1}.

Anal Calcd for $C_{26}H_{37}NO_2$: C, 78.94; H, 9.43. Found: C, 78.67; H, 9.21.

3,5-Dihexyl-6-(1-methoxynonyl)-2-pyridinecarbaldehyde (**83**). To a stirred solution of *N*,*N*-diethyl-2-nonynamide (40 mg, 0.191 mmol) and Ti(O-*i*-Pr)$_4$ (0.071 mL, 0.239 mmol) in 2 mL of Et_2O was added *i*-PrMgCl (1.44 M in Et_2O, 0.345 mL, 0.497 mmol) at -78 ℃ under argon to give a yellow homogeneous solution. The solution was warmed to -50 ℃ over 30 min, during which period its color turned red. After stirring at -50 ℃ for an additional 5 h, 1-octyne (0.023 mL, 0.153 mmol) was added to the reaction mixture at -50 ℃ and the solution was stirred for another 3 h. Then 2-methoxydecanenitrile (0.025 mg, 0.134 mmol) was added and the reaction mixture was subsequently warmed to -30 ℃. After being stirred for 5 h at that temperature, the reaction was terminated by the addition of H_2O (0.2 mL) and the reaction mixture was filtered through Celite. The organic phase was concentrated *in vacuo* to give a crude oil. Careful analysis of the crude product by ^1H NMR spectroscopy did not show the presence of any isomeric products. The crude product was chromatographed on silica gel (hexane-ether) to afford the title compound (41 mg, 71%) as a colorless oil which was fully characterized by ^1H and ^{13}C NMR, IR, and elemental analyses.

^1H NMR δ 0.86 (t, J = 6.9 Hz, 3H), 0.88 (t, J = 6.9 Hz, 3H), 0.90 (t, J = 6.9 Hz, 3H), 1.24-1.42 (m, 24H), 1.54-1.62 (m, 4H), 1.80 (m, 1H), 1.98 (m, 1H), 2.74 (t, J = 8.1 Hz, 1H), 2.75 (t, J = 8.7 Hz, 1H), 3.00 (t, J = 7.5 Hz, 2H), 3.26 (s, 3H), 4.54 (d/d, J = 6.0, 7.8 Hz, 1H), 7.37 (s, 1H), 10.15 (s, 1H).

^{13}C NMR δ 14.14, 14.17, 14.19, 22.64, 22.67, 22.73, 26.08, 29.31, 29.38 (2 peaks), 29.53, 29.65, 30.83, 31.04, 31.33, 31.37, 31.69 (2 peaks), 31.91, 34.89, 56.78, 81.23, 138.89, 140.12, 140.27, 147.24, 156.10, 195.58.

IR (neat) 2955, 2926, 2856, 2820, 1711 (C=O), 1466, 1378, 1251, 1214, 1102, 918, 779, 724, 669 cm^{-1}.

Anal. Calcd for $C_{28}H_{49}NO_2$: C, 77.90; H, 11.44. Found: C, 77.73; H, 11.59.

A 70:30 Diastereomeric Mixture of 2-[2-Chloro-2-cyano-1-(diethylamino)ethyl]-6-(chloromethyl)-3,5-dihexylpyridine (**87**). To a stirred solution of *N*,*N*-diethyl-2-nonynamide (40 mg, 0.191 mmol) and Ti(O-*i*-Pr)$_4$ (0.071 mL, 0.239 mmol) in 2 mL of Et_2O was added *i*-PrMgCl (1.44 M in Et_2O, 0.345 mL, 0.497 mmol) at -78 ℃ under argon to give a yellow homogeneous solution. The solution was warmed to -50 ℃ over 30 min, during

which period its color turned red. After stirring at -50 °C for an additional 5 h, 1-octyne (0.023 mL, 0.153 mmol) was added to the reaction mixture at -50 °C and the solution was stirred for another 3 h. Then α-chloroacetonitrile (0.024 mL, 0.382 mmol) was added and the reaction mixture was subsequently warmed to -30 °C. After being stirred for 5 h at that temperature, the reaction was terminated by the addition of H_2O (0.2 mL) and the reaction mixture was filtered through Celite. The organic phase was concentrated *in vacuo* to give a crude oil. Careful analysis of the crude product by ^1H NMR spectroscopy did not show the presence of any other isomeric products. The crude product was chromatographed on silica gel (hexane-ether) to afford a 70:30 diastereomeric mixture of the title compound (36 mg, 52%) as a colorless oil which was characterized by ^1H NMR, IR, and elemental analyses.

^1H NMR (major isomer) δ 0.90 (t, J = 6.9 Hz, 6H), 0.93 (t, J = 6.9 Hz, 3H), 0.96 (t, J = 6.9 Hz, 3H), 1.25-1.43 (m, 12H), 1.55-1.68 (m, 4H), 2.63 (m, 2H), 2.68 (t, J = 7.8 Hz, 2H), 2.87 (m, 2H), 2.89 (m, 2H), 4.56 (d, J = 10.2 Hz, 1H), 4.63 (d, J = 10.5 Hz, 1H), 4.69 (d, J = 10.5 Hz, 1H), 5.61 (d, J = 10.2 Hz, 1H), 7.33 (s, 1H).

^1H NMR (minor isomer, only characteristic peaks are shown) δ 4.53 (d, J = 9.3 Hz, 1H), 5.47 (d, J = 9.3 Hz, 1H).

IR (neat) 2958, 2928, 2858, 2249, 1559, 1455, 1379, 1252, 1214, 1163, 1111, 1067, 923, 780, 749, 712 cm^{-1} for a 70:30 mixture of diastereomeric isomers.

Anal. Calcd for $C_{25}H_{41}Cl_2N_3$: C, 66.06; H, 9.09. Found: C, 65.93; H, 9.00 for a 70:30 mixture of diastereomeric isomers.

A 10:1 Diastereomeric Mixture of 2-[1-Chloro-2-cyano-2-(diethylamino)ethyl]-6-(chloromethyl)-3,5-dihexylpyridine (**88**). A 70:30 diastereomeric mixture of 2-[2-chloro-2-cyano-1-(diethylamino)ethyl]-6-(chloromethyl)-3,5-dihexylpyridine (**87**) was allowed to stand overnight in $CDCl_3$ to yield a 10:1 diastereomeric mixture of 2-[1-chloro-2-cyano-2-(diethylamino)ethyl]-6-(chloromethyl)-3,5-dihexylpyridine. Careful analysis of the crude product by ^1H NMR spectroscopy did not show the presence of any other isomeric products. The crude product was chromatographed on silica gel (hexane-ether) to afford a 10:1 diastereomeric mixture of the title compound (35 mg, 50%) as a colorless oil, which was characterized by ^1H NMR, IR, and elemental analyses.

^1H NMR (major isomer) δ 0.90 (t, J = 6.9 Hz, 6H), 0.93 (t, J = 7.2 Hz, 6H), 1.25-1.43 (m, 12H), 1.52-1.69 (m, 4H), 2.53 (m, 2H), 2.62 (t, J = 7.8 Hz, 2H), 2.64 (m, 2H), 2.73 (m, 2H), 4.64 (d, J = 10.8 Hz, 1H), 4.70 (d, J = 10.8 Hz, 1H), 5.14 (s, 2H), 7.32 (s, 1H). Irradiation of the proton at δ 5.14 ppm (PyC$\underline{H}_2$Cl) showed 1% nOe enhancement to the peak at δ 2.53 ppm (N(C$\underline{H}_2$CH$_3$)$_2$).

Irradiation of the proton at δ 5.14 ppm (PyC$\underline{H}_2$Cl) showed 4% nOe enhancement to the peak at δ 2.62 ppm (PyC$\underline{H}_2$). Irradiation of the proton at δ 5.14 ppm (PyC$\underline{H}_2$Cl) showed 6% nOe enhancement to the peak at δ 2.64 ppm (N(C$\underline{H}_2$CH$_3$)$_2$). Thus, the regiochemistry has been confirmed.

^{1}H NMR (minor isomer, only characteristic peaks are shown) δ 4.81 (d, J = 10.5 Hz, 1H), 5.19 (d, J = 10.5 Hz, 1H).

IR (neat) 2958, 2929, 2857, 2225, 1617, 1577, 1560, 1452, 1379, 1254, 1203, 1162, 1115, 1071, 923, 903, 787, 702 cm^{-1} for a 10:1 mixture of diastereomeric isomers.

Anal. Calcd for $C_{25}H_{41}Cl_2N_3$: C, 66.06; H, 9.09. Found: C, 65.82; H, 9.01 for a 10:1 mixture of diastereomeric isomers**.**

(*E*)- and (*Z*)-6-Allyl-2-(2-cyano-1,3-butadienyl)-3,5-dihexylpyridine (**89**). To a stirred solution of *N*,*N*-diethyl-2-nonynamide (40 mg, 0.191 mmol) and Ti(O-*i*-Pr)$_4$ (0.071 mL, 0.239 mmol) in 2 mL of Et$_2$O was added *i*-PrMgCl (1.44 M in Et$_2$O, 0.345 mL, 0.497 mmol) at -78 ℃ under argon to give a yellow homogeneous solution. The solution was warmed to -50 ℃ over 30 min, during which period its color turned red. After stirring at -50 ℃ for an additional 5 h, 1-octyne (0.023 mL, 0.153 mmol) was added to the reaction mixture at -50 ℃ and the solution was stirred for another 3 h. Then α-vinylacetonitrile (**84**) (0.031 mL, 0.382 mmol) was added and the reaction mixture was subsequently warmed to -30 ℃. After being stirred for 5 h at that temperature, the reaction was terminated by the addition of H$_2$O (0.2 mL) and the reaction mixture was filtered through Celite. The organic phase was concentrated *in vacuo* to give a crude oil. The crude product was chromatographed on silica gel (hexane-ether) to afford (*E*)-6-allyl-2-(2-cyano-1,3-butadienyl)-3,5-dihexylpyridine (24 mg, 43%) and (*Z*)-6-allyl-2-(2-cyano-1,3-butadienyl)-3,5-dihexylpyridine (20 mg, 37%) as colorless oils, which were fully characterized by ^{1}H and ^{13}C NMR, IR, and elemental analyses.

^{1}H NMR (*E* isomer) δ 0.89 (t, J = 6.9 Hz, 3H), 0.90 (t, J = 6.9 Hz, 3H), 1.26-1.40 (m, 12H), 1.49-1.59 (m, 4H), 2.59 (t, J = 6.0 Hz, 2H), 2.63 (t, J = 6.0 Hz, 2H), 3.59 (d, J = 6.6 Hz, 2H), 5.08 (d, J = 16.8 Hz, 1H), 5.12 (d, J = 10.5 Hz, 1H), 5.54 (d, J = 10.5 Hz, 1H), 5.88 (d, J = 17.4 Hz, 1H), 6.09 (d/d/t, J = 10.5, 16.8, 6.6 Hz, 1H), 7.21 (s, 1H), 7.24 (s, 1H), 8.01 (d/d, J = 10.5, 17.4 Hz, 1H). Irradiation of proton at δ 3.59 ppm (PyC$\underline{H}_2$CH) showed 5% nOe enhancement to the peak at δ 2.63 ppm (PyCH$_2$). Thus, the regiochemistry has been confirmed.

^{1}H NMR (*Z* isomer) δ 0.89 (t, J = 6.9 Hz, 3H), 0.90 (t, J = 6.9 Hz, 3H), 1.27-1.40 (m, 12 H), 1.49-1.59 (m, 4H), 2.62 (t, J = 8.1 Hz, 4H), 3.66 (d, J = 6.6 Hz, 2H), 5.11 (d, J = 10.2 Hz, 1H), 5,13 (d, J = 16.8 Hz, 1H), 5.49 (d, J = 10.2 Hz, 1H), 5.93 (d, J = 17.1 Hz, 1H), 6.43 (d/d/t, J =

10.2, 16.8, 6.6 Hz, 1H), 6.54 (d/d, J = 10.2, 17.1 Hz, 1H), 7.20 (s, 1H), 7.23 (s, 1H). Irradiation of proton at δ 6.54 ppm (C(CN)C<u>H</u>=CH_2) showed 4% nOe enhancement to the peak at δ 7.20 ppm (PyC<u>H</u>=C). Thus, the stereochemistry has been confirmed.

^{13}C NMR (*E* isomer) δ 13.93, 13.99, 22.46, 22.47, 28.94, 29.13, 30.13, 31.12, 31.47, 31.55, 31.87, 32.12, 38.23, 116.15, 116.72, 118.53, 121.87, 130.66, 136.01, 136.62, 136.77, 136.82, 138.50, 148.19, 155.67.

^{13}C NMR (*Z* isomer) δ 13.91, 13.93, 22.45, 22.48, 28.90, 29.14, 30.14, 31.18, 31.47, 31.55, 31.68, 31.92, 39.23, 114.54, 115.91, 116.06, 119.62, 134.28, 135.47, 136.31, 137.49, 138.33, 138.94, 146.36, 155.96.

IR (*E* isomer, neat) 3081, 2955, 2928, 2857, 2221, 1637, 1617, 1534, 1466, 1458, 1437, 1412, 1378, 1251, 1196, 1115, 993, 917, 842, 725 cm^{-1}.

IR (*Z* isomer, neat) 3076, 2955, 2928, 2856, 2218, 1638, 1604, 1540, 1466, 1457, 1437, 1405, 1378, 1298, 1258, 1217, 1115, 1082, 976, 913, 726 cm^{-1}.

Anal. (*E* isomer) Calcd for $C_{25}H_{36}N_2$: C, 82.36; H, 9.95. Found: C, 82.56; H, 9.81.

6-(Bromomethyl)-3,5-dihexyl-2-picolinamide (**92**). To a stirred solution of *N*,*N*-diethyl-2-nonynamide (40 mg, 0.191 mmol) and Ti(O-*i*-Pr)$_4$ (0.071 mL, 0.239 mmol) in 2 mL of Et_2O was added *i*-PrMgCl (1.36 M in Et_2O, 0.365 mL, 0.497 mmol) at -78 ℃ under argon to give a yellow homogeneous solution. The solution was warmed to -50 ℃ over 30 min, during which period its color turned red. After stirring at -50 ℃ for an additional 5 h, 1-octyne (0.023 mL, 0.153 mmol) was added to the reaction mixture at -50 ℃ and the solution was stirred for another 3 h. Then α-bromoacetonitrile (0.020 mL, 0.287 mmol) was added and the reaction mixture was subsequently allowed to warm to room temperature. After being stirred for 5 h at that temperature, the reaction was terminated by the addition of H_2O (0.2 mL) and the reaction mixture was filtered through Celite. The organic phase was concentrated *in vacuo* to give a crude oil. Careful analysis of the crude product by ^{1}H NMR spectroscopy did not show the presence of any isomeric products. The crude product was chromatographed on silica gel (hexane-ether) to afford the title compound (37 mg, 55%) as a colorless oil which was fully characterized by ^{1}H and ^{13}C NMR, IR, and elemental analyses.

^{1}H NMR δ 0.86 (t, J = 6.9 Hz, 3H), 0.89 (t, J = 6.9 Hz, 3H), 1.14 (t, J = 6.9 Hz, 3H), 1.19 (t, J = 6.9 Hz, 3H), 1.23-1.42 (m, 12H), 1.52-1.68 (m, 4H), 2.58 (t, J = 7.8 Hz, 2H), 2.68 (t, J = 7.8 Hz, 2H), 3.08 (q, J = 7.2 Hz, 2H), 3.56 (q, J = 7.2 Hz, 2H), 4.57 (s, 2H), 7.35 (s, 1H). Irradiation of proton at δ 4.57 ppm (PyC<u>H$_2$</u>Br) showed 4% nOe enhancement to the peak at δ 2.68 ppm (PyC<u>H$_2$</u>). Thus, the regiochemistry has been confirmed.

^{13}C NMR δ 12.61, 13.72, 13.88 (2 peaks), 22.40, 22.43, 29.08, 29.13, 30.27, 30.33, 31.26, 31.44, 31.49, 31.59, 31.74, 39.03, 42.86, 135.29, 136.92, 138.85, 151.14, 151.81, 168.39.
IR (neat) 2956, 2929, 2857, 1634 (C=O), 1482, 1458, 1420, 1379, 1363, 1316, 1278, 1240, 1220, 1135, 1116, 1099, 920, 861, 787, 732, 669 cm^{-1}.
Anal. Calcd for $C_{23}H_{39}BrN_2O$: C, 62.86; H, 8.94. Found: C, 62.75; H, 9.26.

(S)-3,5-Dihexyl-6-[1-(benzyloxy)ethyl]-2-pyridinecarboxaldehyde (**95**). To a stirred solution of *N*,*N*-diethyl-2-nonanamide (35.5 mg, 0.168 mmol) and Ti(O-*i*-Pr)$_4$ (0.062 mL, 0.210 mmol) in 1.5 mL of Et_2O was added *i*-PrMgCl (1.575 M in Et_2O, 0.278 mL, 0.437 mmol) at -78 ℃ under argon to give a yellow homogeneous solution. The solution was warmed to -50 ℃ over 30 min, during which period its color turned red. After stirring at -50 ℃ for 5 h, 1-octyne (0.020 mL, 0.134 mmol) was introduced to the reaction mixture at -50 ℃ and the solution was stirred for 3 h. Then, (*S*)-2-(benzyloxy)propanenitrile (19 mg, 0.118 mmol) in 1 mL of Et_2O was added and the reaction mixture was subsequently warmed to -30 ℃. After stirring for 5 h at that temperature, the reaction was terminated by the addition of water (0.06 mL) and quickly warmed up to room temperature. The resulting heterogeneous mixture was dried over anhydrous sodium sulfate and filtered through a short pad of Celite with the aid of ether. The combined filtrates were concentrated *in vacuo* to give a crude oil, careful analysis of which by ^{1}H NMR spectroscopy did not show the presence of any isomeric products. The crude product was chromatographed on silica gel (hexane-diethyl ether) to afford the title compound (33 mg, 68%) as a colorless oil.
^{1}H NMR δ 0.85-0.91 (m, 6H), 1.24-1.59 (m, 16H), 1.62 (d, *J* = 6.6 Hz, 3H), 2.67 (m, 2H), 3.01 (t, *J* = 7.8 Hz, 2H), 4.44 (d, *J* = 12.0 Hz, 1H), 4.51 (d, *J* = 12.0 Hz, 1H), 4.93 (q, *J* = 6.6 Hz, 1H), 7.31-7.32 (m, 5H), 7.37 (s, 1H), 10.18 (s, 1H). Irradiation of the proton at δ 4.93 ppm (C<u>H</u>Me) showed 5% nOe enhancement to the peak at δ 1.62 ppm (CH<u>Me</u>), 5% nOe enhancement to the peak at δ 2.67 ppm (PyC<u>H$_2$</u>), 3% nOe enhancement to the peak at δ 4.44 ppm (C<u>H$_2$</u>Ph), and 3% nOe enhancement to the peak at δ 4.51 ppm (C<u>H$_2$</u>Ph). Thus, the regiochemistry has been confirmed.
^{13}C NMR δ 13.91, 13.95, 20.03, 22.44, 22.49, 29.23 (2 peaks), 30.72, 30.84, 31.09, 31.21, 31.46, 31.55, 70.54, 74.64, 127.66, 127.90, 128.40, 138.41, 139.38, 140.38, 140.44, 147.37, 156.78, 195.92.
IR (neat) 3064, 3030, 2927, 2856, 1710, 1457, 1375, 1103, 734, 697 cm^{-1}.
Anal. Calcd for $C_{27}H_{39}NO_2$: C, 79.17; H, 9.60. Found: C, 79.12; H, 9.28.
$[\alpha]_D^{28}$ -53.5 (*c* 2.00, $CHCl_3$) for a sample of >99% ee.

(*S*)-3,5-Dihexyl-6-[1-(benzyloxy)ethyl]-2-pyridinemethanol (for Determination of the Enantiopurity of 95). To a stirred solution of (*S*)-3,5-dihexyl-6-[1-(benzyloxy)ethyl]-2-pyridinecarboxaldehyde (**95**) (20 mg, 0.049 mmol) in 5% H_2O / EtOH (1.0 mL) was added $NaBH_4$ (3 mg, 0.08 mmol) at room temperature under argon. After stirring at room temperature for 1 h, the reaction mixture was concentrated and extracted with Et_2O (1 mL). The organic phase was washed with water (1 mL × 2), dried (Na_2SO_4) and concentrated to a crude oil, which was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (19 mg, 94%) as a colorless oil.

^{1}H NMR δ 0.86-0.92 (m, 6H), 1.24-1.63 (m, 16H), 1.58 (d, *J* = 6.3 Hz, 3H), 2.46 (t, 2H), 2.60-2.67 (m, 2H), 4.36 (d, *J* = 11.7 Hz, 1H), 4.44 (d, *J* = 11.7 Hz, 1H), 4.71 (s, 2H), 4.90 (q, *J* = 6.3 Hz, 1H), 5.18 (s, 1H), 7.25-7.34 (m, 5H), 7.30 (s, 1H).

^{13}C NMR δ 13.91 (2 peaks), 20.30, 22.44, 22.46, 29.08, 29.20, 29.49, 29.67, 30.67, 31.27, 31.52 (2 peaks), 60.79, 70.30, 74.31, 127.56, 127.86, 128.38, 132.89 , 134.73, 138.52, 138.58, 152.44, 153.70.

IR (neat) 3384, 3063, 3029, 2928, 2857, 1454, 1416, 1099, 1060, 734, 697 cm^{-1}.

Anal. Calcd for $C_{27}H_{39}NO_2$: C, 78.78; H, 10.04. Found: C, 78.95; H, 9.95.

$[\alpha]_D^{28}$ -38.4 (*c* 1.00, $CHCl_3$) for a sample of >99% ee.

The ee value of this sample was determined to be more than 99% based on the Mosher ester method.

Characteristic peaks of the (*R*)-MTPA ester from (*S*)-MTPACl and (*S*)-3,5-dihexyl-6-[1-(benzyloxy)ethyl]-2-pyridinemethanol: ^{1}H NMR δ 4.32 (d, *J* = 12.0 Hz, 1H, C$\underline{H}_2$Ph), 4.41 (d, *J* = 12.0 Hz, 1H, C$\underline{H}_2$Ph).

Characteristic peaks of the (*S*)-MTPA ester from (*R*)-MTPACl and (*S*)-3,5-dihexyl-6-[1-(benzyloxy)ethyl]-2-pyridinemethanol: ^{1}H NMR δ 4.33 (d, *J* = 12.0 Hz, 1H, C$\underline{H}_2$Ph), 4.43 (d, *J* = 12.0 Hz, 1H, C$\underline{H}_2$Ph).

Thus, the enantiopurity of **95** was determined to be at least 99% ee.

(*S*)-3-Hexyl-6-[1-(benzyloxy)ethyl]-5-(trimethylsilyl)-2-pyridinecarboxaldehyde (96). To a stirred solution of *N*,*N*-diethyl-2-nonanamide (35.5 mg, 0.168 mmol) and Ti(O-*i*-Pr)4 (0.062 mL, 0.210 mmol) in 1.5 mL of Et2O was added *i*-PrMgCl (1.575 M in Et2O, 0.278 mL, 0.437 mmol) at -78 ℃ under argon to give a yellow homogeneous solution. The solution was warmed to -50 ℃ over 30 min, during which period its color turned red. After stirring at -50 ℃ for 5 h, (trimethylsilyl)acetylene (0.018 ml, 0.134 mmol) was introduced to the reaction mixture at -50 ℃ and the solution was stirred for 3 h. Then (*S*)-2-(benzyloxy)propanenitrile (19 mg, 0.118 mmol) in 1 mL of Et_2O was added and the reaction mixture

was subsequently warmed to -30 ℃. After stirring for 5 h at that temperature, the reaction was terminated by the addition of water (0.06 mL) and quickly warmed up to room temperature. The resulting heterogeneous mixture was dried over anhydrous sodium sulfate and filtered through a short pad of Celite with the aid of ether. The combined filtrates were concentrated to a crude oil, careful analysis of which by ^{1}H NMR spectroscopy did not show the presence of any isomeric products. The crude product was chromatographed on silica gel (hexane-diethyl ether) to afford the title compound (27 mg, 57%) as a colorless oil.

^{1}H NMR δ 0.31 (s, 9H), 0.90 (t, *J* = 6.6 Hz, 3H), 1.31-1.56 (m, 8H), 1.59 (d, *J* = 6.3 Hz, 3H), 3.01 (t, *J* = 7.8 Hz, 2H), 4.48 (s, 2H), 4.92 (q, *J* = 6.3 Hz, 1H), 7.25-7.33 (m, 5H), 7.69 (s, 1H), 10.23 (s, 1H). Irradiation of the proton at δ 4.92 ppm (C<u>H</u>Me) showed 1% nOe enhancement to the peak at δ 0.31 ppm ($SiMe_3$), 1% nOe enhancement to the peak at δ 1.59 ppm (CH<u>Me</u>), and 2% nOe enhancement to the peak at δ 4.48 ppm (C<u>H$_2$</u>Ph). Thus, the regiochemistry has been confirmed.

^{13}C NMR δ 0.06, 13.94, 21.32, 22.50, 29.25, 30.84, 31.43, 31.52, 70.21, 76.66, 127.61, 127.86, 128.40, 137.46, 137.65, 138.46, 146.33, 149.71, 163.91, 196.56.

IR (neat) 3063, 3030, 2960, 2928, 2857, 1711 (C=O), 1457, 1364, 1253, 1102, 841, 734, 697 cm^{-1}.

Anal. Calcd for $C_{24}H_{35}NO_2Si$: C, 72.49; H, 8.87. Found: C, 72.84; H, 8.50.

$[\alpha]_D^{29}$ -42.0 (*c* 0.60, $CHCl_3$) for a sample of >99% ee.

(*S*)-3-Hexyl-6-[1-(benzyloxy)ethyl]-5-(trimethylsilyl)-2-pyridinemethanol (for Determination of the Enantiopurity of 96). To a stirred solution of (*S*)-3-hexyl-6-[1-(benzyloxy)ethyl]-5-(trimethylsilyl)-2-pyridinecarboxaldehyde (**96**) (20 mg, 0.050 mmol) in 5% H_2O / EtOH (1.0 mL) was added $NaBH_4$ (3 mg, 0.08 mmol) at room temperature under argon. After stirring at room temperature for 1 h, the reaction mixture was concentrated and extracted with Et_2O (1 mL). The organic phase was washed with water (1 mL × 2), dried (Na_2SO_4) and concentrated to a crude oil, which was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (18 mg, 92%) as a colorless oil.

^{1}H NMR δ 0.33 (s, 9H), 0.90 (t, *J* = 6.6 Hz, 3H), 1.32-1.52 (m, 8H), 1.55 (d, *J* = 6.3 Hz, 3H), 2.48 (t, *J* = 7.8 Hz, 2H), 4.35 (d, *J* = 11.4 Hz, 1H), 4.40 (d, *J* = 11.4 Hz, 1H), 4.74 (s, 2H), 4.89 (q, *J* = 6.3 Hz, 1H), 5.32 (s, 1H), 7.24-7.44 (m, 5H), 7.55 (s, 1H).

^{13}C NMR δ 0.28, 13.92, 21.72, 22.46, 29.14, 29.57, 29.95, 31.49, 60.90, 70.14, 76.76, 127.53, 127.78, 128.40, 130.60, 132.14, 138.65, 146.37, 156.05, 161.60.

IR (neat) 3367, 3057, 3033, 2960, 2929, 2854, 1437, 1417, 1251, 1100, 1067, 839, 733, 697 cm^{-1}.

$[\alpha]_D^{29}$ -44.6 (*c* 1.0, $CHCl_3$) for a sample of >99% ee.

The ee value of this sample was determined to be more than 99% based on the Mosher ester method.

A characteristic peak of the (*R*)-MTPA ester from (*S*)-MTPACl and (*S*)-3-hexyl-6-[1-(benzyloxy)ethyl]-5-(trimethylsilyl)-2-pyridinemethanol: ^{1}H NMR (C_6D_6) δ 3.65 (s, 3H, OMe).

A characteristic peak of the (*S*)-MTPA ester from (*R*)-MTPACl and (*S*)-3-hexyl-6-[1-(benzyloxy)ethyl]-5-(trimethylsilyl)-2-pyridinemethanol: ^{1}H NMR (C_6D_6) δ 3.57 (s, 3H, OMe).

Thus, the enantiopurity of **96** was determined to be at least 99% ee.

(*S*)-3-Hexyl-6-[1-(benzyloxy)ethyl]-5-phenyl-2-pyridinecarboxaldehyde (**97**).
^{1}H NMR δ 0.89 (t, *J* = 7.2 Hz, 3H), 1.26-1.65 (m, 8H), 1.57 (d, *J* = 6.3 Hz, 3H), 3.08 (t, J = 7.8 Hz, 2H), 4.33 (s, 2H), 4.84 (q, *J* = 6.3 Hz, 1H), 7.15-7.43 (m, 10H), 7.48 (s, 1H), 10.30 (s, 1H).
^{13}C NMR δ 13.92, 19.94, 22.45, 29.23, 30.65, 31.20, 31.50, 70.45, 72.87, 127.53, 127.98, 128.19, 128.26, 128.54, 129.06, 138.06, 138.31, 139.08, 140.14, 140.75, 148.89, 156.12, 195.99.
IR (neat) 3061, 3030, 2960, 2927, 2856, 1709 (C=O), 1455, 1365, 1096, 745, 700 cm^{-1}.
Anal. Calcd for $C_{27}H_{31}NO_2$: C, 80.76; H, 7.78. Found: C, 80.44; H, 7.71.
$[\alpha]_D^{29}$ -22.7 (*c* 0.64, $CHCl_3$) for a sample of >99% ee.

(*S*)-3-Hexyl-6-[1-(benzyloxy)ethyl]-5-phenyl-2-pyridinemethanol (for Determination of the Enantiopurity of 97). This was prepared by the reduction of (*S*)-3-hexyl-6-[1-(benzyloxy)ethyl]-5-phenyl-2-pyridinecarboxaldehyde (**97**) with $NaBH_4$ in 96% yield, according to the procedure from (S)-3,5-dihexyl-6-[1-(benzyloxy)ethyl]-2-pyridinecarboxaldehyde (**95**) to (*S*)-3,5-dihexyl-6-[1-(benzyloxy)ethyl]-2-pyridinemethanol.
^{1}H NMR δ 0.89 (t, *J* = 6.9 Hz, 3H), 1.26-1.63 (m, 8H), 1.55 (d, *J* = 6.3 Hz, 3H), 2.53 (t, J = 7.8 Hz, 2H), 4.22 (d, *J* = 11.4 Hz, 1H), 4.27 (d, *J* = 11.4 Hz, 1H), 4.79 (q, *J* = 6.3 Hz, 1H), 4.80 (s, 2H), 5.22 (s, 1H), 7.14-7.44 (m, 10H), 7.37 (s, 1H).
^{13}C NMR δ 13.90, 20.33, 22.41, 29.11, 29.37, 29.66, 31.48, 61.09, 70.27, 72.97, 127.46, 127.67, 127.90, 128.27, 128.44, 129.39, 132.89, 135.80, 138.43, 138.49, 138.84, 153.33, 154.77.
IR (neat) 3384, 3060, 3029, 1453, 1416, 1365, 1096, 1062, 735, 700 cm^{-1}.
$[\alpha]_D^{29}$ 0.50 (*c* 0.80, $CHCl_3$) for a sample of >99% ee.

The ee value of this sample was determined to be more than 99% based on the Mosher ester method.

A characteristic peak of the (*R*)-MTPA ester from (*S*)-MTPACl and (*S*)-3-hexyl-6-[1-(benzyloxy)ethyl]-5-phenyl-2-pyridinemethanol: ^{1}H NMR δ 4.30 (d, *J* = 12.0 Hz, 1H, C<u>H</u>$_2$Ph).

A characteristic peak of the (*S*)-MTPA ester from (*R*)-MTPACl and (*S*)-3-hexyl-6-[1-(benzyloxy)ethyl]-5-phenyl-2-pyridinemethanol: ^{1}H NMR δ 4.28 (d, *J* = 12.0 Hz, 1H, C<u>H</u>$_2$Ph).

Thus, the enantiopurity of **97** was determined to be at least 99% ee.

(*S*)-3,5-Dihexyl-6-[phenyl(benzyloxy)methyl]-2-pyridinecarboxaldehyde (**98**).
^{1}H NMR δ 0.83-0.93 (m, 6H), 1.14-1.65 (m, 16H), 2.59 (m, 2H), 3.02 (t, *J* = 7.8 Hz, 2H), 4.55 (d, *J* = 12.0 Hz, 1H), 4.67 (d, *J* = 12.0 Hz, 1H), 5.87 (s, 1H), 7.25-7.50 (m, 11H), 10.19 (s, 1H).
^{13}C NMR δ 13.89, 13.93, 22.37, 22.47, 29.18, 29.21, 30.41, 30.65, 30.99, 31.19, 31.39, 31.52, 71.13, 81.86, 127.16, 127.55, 127.75, 128.02, 128.24, 128.43, 138.15, 139.69, 140.31, 140.98, 141.32, 146.93, 155.81, 195.75.
IR (neat) 3066, 3030, 2926, 2856, 1710 (C=O), 1457, 1095, 1068, 1028, 735, 698 cm^{-1}.
Anal. Calcd for $C_{32}H_{41}NO_2$: C, 81.48; H, 8.76. Found: C, 81.45; H, 8.71.
$[\alpha]_D^{29}$ -26.0 (*c* 0.4, $CHCl_3$) for a sample of >99% ee.

(*S*)-3,5-Dihexyl-6-[phenyl(benzyloxy)methyl]-2-pyridinemethanol (for Determination of the Enantiopurity of 98). This was prepared by the reduction of (*S*)-3,5-dihexyl-6-[phenyl(benzyloxy)methyl]-2-pyridinecarboxaldehyde (**98**) with $NaBH_4$ in 95% yield, according to the procedure from (S)-3,5-dihexyl-6-[1-(benzyloxy)ethyl]-2-pyridinecarboxaldehyde (**95**) to (*S*)-3,5-dihexyl-6-[1-(benzyloxy)ethyl]-2-pyridinemethanol.
^{1}H NMR δ 0.84-0.91 (m, 6H), 1.17-1.59 (m, 16H), 2.44 (t, *J* = 7.8 Hz, 2H), 2.57 (m, 2H), 4.52 (d, *J* = 12.0 Hz, 1H), 4.60 (d, *J* = 12.0 Hz, 1H), 4.67 (s, 2 H), 5.00 (s, 1H), 5.80 (s, 1H), 7.28-7.48 (m, 11H).
^{13}C NMR δ 13.92, 13.94, 22.44 (2 peaks), 29.09, 29.23, 29.43, 29.65, 30.62, 30.92, 31.51 (2 peaks), 60.76, 71.04, 81.22, 127.29, 127.51, 127.73, 128.13, 128.23, 128.43, 133.10, 135.54, 138.19, 138.87, 140.54, 151.96, 152.58.
IR (neat) 3372, 3066, 3025, 2929, 2858, 1453, 1420, 1251, 1100, 1067, 1028, 839, 733, 697 cm^{-1}.
$[\alpha]_D^{29}$ -1.2 (*c* 1.0, $CHCl_3$) for a sample of >99% ee.

The ee value of this sample was determined to be more than 99% based on the Mosher ester method.

A characteristic peak of the (*R*)-MTPA ester from (*S*)-MTPACl and (*S*)-3,5-dihexyl-6-[phenyl(benzyloxy)methyl]-2-pyridinemethanol: ^{1}H NMR δ 5.43 (d, *J* = 12.0 Hz, 1H, C<u>H</u>$_2$OMTPA).

A characteristic peak of the (*S*)-MTPA ester from (*R*)-MTPACl and (*S*)-3,5-dihexyl-6-[phenyl(benzyloxy)methyl]-2-pyridinemethanol: ^{1}H NMR δ 5.46 (d, *J* = 12.0 Hz, 1H, C<u>H</u>$_2$OMTPA).

Thus, the enantiopurity of **98** was determined to be at least 99% ee.

(*S*)-3-Hexyl-6-[phenyl(benzyloxy)methyl]-5-phenyl-2-pyridinecarboxaldehyde (99).

^{1}H NMR δ 0.89 (t, *J* = 6.9 Hz, 3H), 1.28-1.67 (m, 8H), 3.05 (m, 2H), 4.38 (d, *J* = 12.0 Hz, 1H), 4.59 (d, *J* = 12.0 Hz, 1H), 5.87 (s, 1H), 7.16-7.44 (m, 15H), 7.46 (s, 1H), 10.25 (s, 1H).

^{13}C NMR δ 13.91, 22.43, 29.20, 30.56, 31.16, 31.46, 70.61, 78.60, 127.74, 127.83, 128.17 (2 peaks), 128.33 (2 peaks), 128.38, 128.44, 129.41, 137.93 (2 peaks), 139.05, 139.87, 140.36, 140.92, 148.84, 154.76, 195.83.

IR (neat) 3061, 3029, 2927, 2856, 1707 (C=O), 1495, 1453, 1065, 754, 698 cm^{-1}.

Anal. Calcd for $C_{32}H_{33}NO_2$: C, 82.90; H, 7.17. Found: C, 82.80; H, 7.25.

$[\alpha]_D^{25}$ -0.20 (*c* 1.5, $CHCl_3$) for a sample of >99% ee.

(*S*)-3-Hexyl-6-[phenyl(benzyloxy)methyl]-5-phenyl-2-pyridinemethanol. (**for Determination of the Enantiopurity of 99**). This was prepared by the reduction of (*S*)-3-hexyl-6-[phenyl(benzyloxy)methyl]-5-phenyl-2-pyridinecarboxaldehyde (**99**) with $NaBH_4$ in 96% yield, according to the procedure from (S)-3,5-dihexyl-6-[1-(benzyloxy)ethyl]-2-pyridinecarboxaldehyde (**95**) to (*S*)-3,5-dihexyl-6-[1-(benzyloxy)ethyl]-2-pyridinemethanol.

^{1}H NMR δ 0.90 (t, *J* = 6.9 Hz, 3H), 1.28-1.63 (m, 8H), 2.50 (t, *J* = 7.8 Hz, 2H), 4.34 (d, *J* = 11.4 Hz, 1H), 4.51 (d, *J* = 11.4 Hz, 1H), 4.75 (s, 2H), 5.03 (s, 1H), 5.69 (s, 1H), 7.25-7.44 (m, 16H).

^{13}C NMR δ 13.87, 22.37, 29.04, 29.25, 29.56, 31.43, 61.00, 70.68, 79.19, 127.63, 127.68, 127.70, 127.80, 128.16, 128.19, 128.33, 128.38, 129.40, 132.86 , 136.13, 138.03, 138.64, 138.75, 140.19, 151.76, 154.54.

IR (neat) 3381, 3061, 3029, 2927, 2857, 1495, 1453, 1415, 1063, 1028, 734, 699 cm^{-1}.

$[\alpha]_D^{29}$ -0.75 (*c* 0.40, $CHCl_3$) for a sample of >99% ee.

The ee value of this sample was determined to be more than 99% based on the Mosher ester method.

Characteristic peaks of the (*R*)-MTPA ester from (*S*)-MTPACl and (*S*)-3-hexyl-6-[phenyl(benzyloxy)methyl]-5-phenyl-2-pyridinemethanol: ^{1}H NMR δ 3.47 (s, 3H, OMe), 4.44 (d, *J* = 12.0 Hz, 1H, C<u>H</u>$_2$Ph).

Characteristic peaks of the (*S*)-MTPA ester from (*R*)-MTPACl and (*S*)-3-hexyl-6-[phenyl(benzyloxy)methyl]-5-phenyl-2-pyridinemethanol: ^{1}H NMR δ 3.50 (s, 3H, OMe), 4.46 (d, *J* = 12.0 Hz, 1H, C$\underline{H}_2$Ph).

Thus, the enantiopurity of **99** was determined to be at least 99% ee.

Complete References for 15c and 15d.

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