Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Site-Selective Benzylic C–H Hydroxylation in Electron-Deficient Azaheterocycles

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General Information

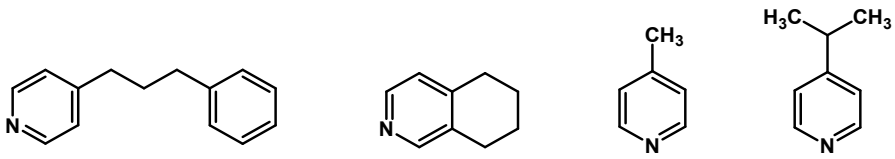
All reactions were performed with commercial reagents and solvents that were used as received, unless otherwise specified. Acetonitrile was purified by first sitting under an atmosphere of nitrogen over acidic alumina that had been heated overnight to >250 ºC for at least 2 hours. The alumina was removed by filtration through an oven-dried glass filter directly into a 1-liter Schlenk storage flask that contained 3Å molecular sieves that had been activated at > 250 ºC. The solvent was allowed to sit overnight before use, and it was maintained and transferred under a nitrogen atmosphere. 2,6-lutidine, 4-phenylpropylpyridine, and 4,7-diethylquinoline were distilled over barium oxide, and stored in a Schlenk storage flask (lutidine) or round-bottomed flasks (pyridine/quinoline) under nitrogen. Reagents and starting materials were purchased from Sigma Aldrich, Alfa Aesar, Combi-Blocks, TCI America; solvents were purchased from Fischer or Sigma-Aldrich. Concentration and removal of solvents was performed using an IKA rotary evaporator. Column chromatography was carried out using silica gel purchased from Silicycle®. For thin layer chromatography (TLC) analysis throughout this work, SiliCycle pre-coated TLC plates (250 μM) were used, using UV light as the visualizing agent and a 2,4-dinitrophenylhydrazine (DNP) stain as a developing solution.

Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker 400 Ultrashield (400 MHz), or a Bruker Ultrashield 600 plus (600 MHz), using chloroform-d ($CDCl_3$), dimethylsulfoxide-d6 (DMSO-d6), benzene-d6 (C_6D_6) or acetonitrile-d3 (CD_3CN) for optimized reaction conditions and $CDCl_3$ for obtaining both ^{1}H (7.26 ppm) and ^{13}C (77.03 ppm) NMR of the isolated products. Coupling constants (J values) are reported in Hertz (Hz) to the nearest 0.1 Hz. 1H NMR spectra are given in the following order: multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet), coupling constants, number of protons. The spectra were baseline corrected (Bernstein polynomials) and phase corrected. The integrations of the internal standard peak (3,5-dichloroanisole) and the product peak were compared to calculate the NMR yield as shown in the H-NMR. A relaxation delay of 10.0s was used to ensure accurate integration values.

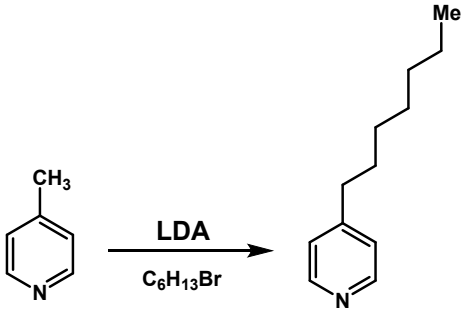
UV/Vis spectra were recorded with a Agilent Cary 60 spectrophotometer. High-resolution mass spectra (HRMS) were obtained via an Agilent 6520 QTOF LC/MS. Per-substrate reaction screening was done on an Agilent Infinity II system with an LC/MSD iQ single quadrupole MS detector and a diode array detector, using a 100 mm length InfinityLab Poroshell® 120 Phenyl-Hexyl column.

Synthesis of substrates

The following starting materials were purchased:



The remaining starting materials were prepared as follows.



4-Heptylpyridine [1,2] A flame dried flask 2-neck flask under N_2 was charged with 4-methylpyridine (957 mg, 10.27 mmol, 1.0 equiv.) and anhydrous THF (6 mL). The stirred solution was cooled to -78 °C, and freshly prepared lithium diisopropyl amide (LDA) (11.30 mmol, 1.1 equiv.) was added dropwise. The reaction was stirred at -78 °C for 30 min., followed by addition of $C_6H_{13}Br$ (1.72 mL, 12.32 mmol, 1.2 equiv.). The reaction mixture was stirred for an additional 30 min. at -78 °C and was then warmed to room temperature and stirred overnight. The reaction was quenched with aqueous NH_4Cl and extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography over silica gel (1:1 Hexane: EtOAc) afforded 0.649 g (3.66 mmol, 36%) of a light-yellow oil. The additional splitting leading to multiplets in the aromatic region of the H-NMR is possibly due to magnetic inequivalence of the aromatic protons. The ^{1}H NMR is consistent with the reported literature.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 – 8.45 (m, 2H, 5.8 Hz), 7.12 – 7.07 (m, 2H, 5.9 Hz), 2.62 – 2.55 (t, 2H, 7.6 Hz), 1.62 (p, *J* = 7.6 Hz, 2H), 1.34 – 1.24 (m, 8H), 0.90 – 0.85 (t, 3H, 6.8 Hz).

Ref: ($CDCl_3$) δ 0.88 (3H, t, J = 6.8 Hz), 1.28-1.32 (8H, m), 1.60-1.64 (2H, m), 2.60 (2H, t, J = 7.6 Hz), 7.10 (2H, d, J = 5.6 Hz), 8.48 (2H, d, J = 5.6 Hz)

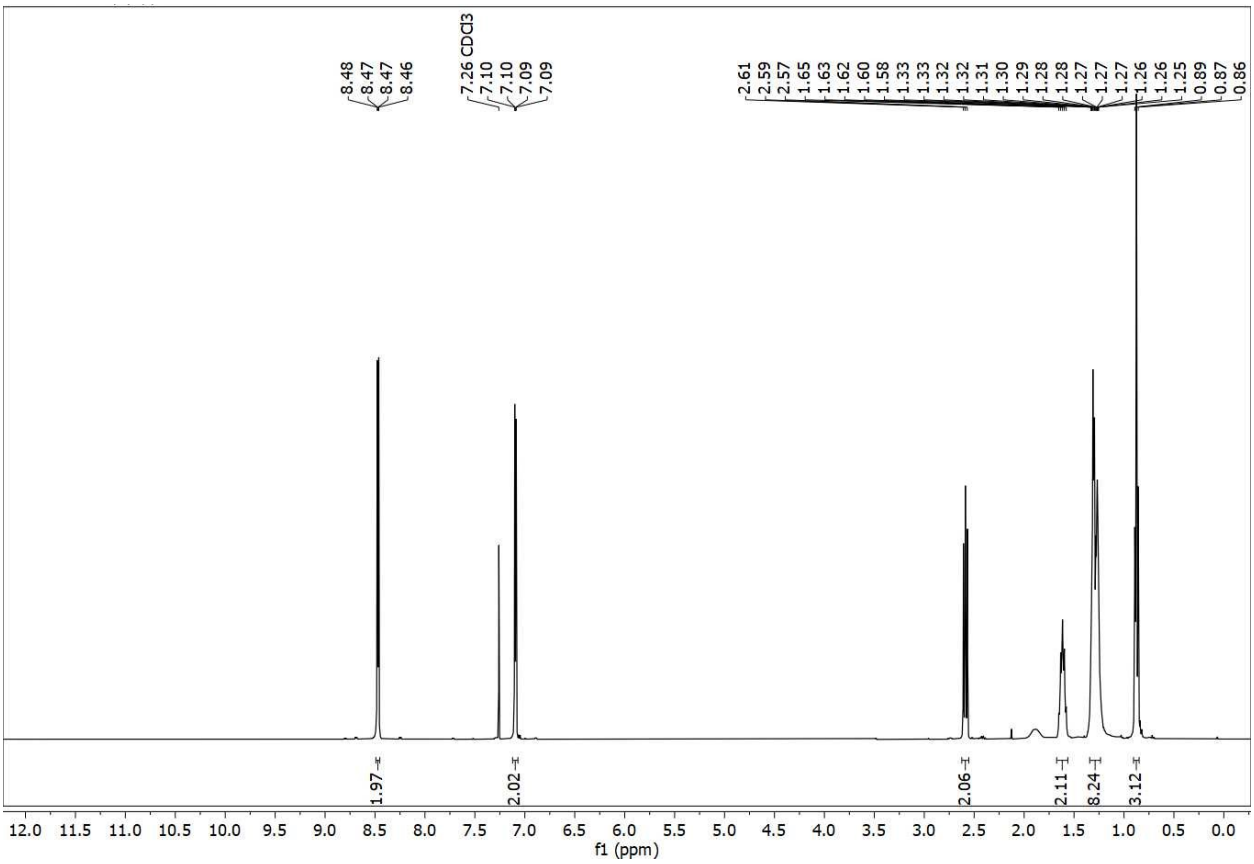
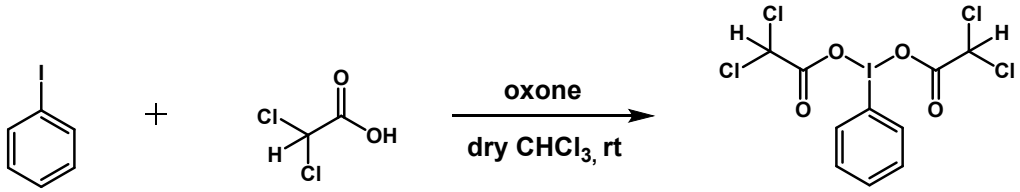


Figure S1: ^{1}H NMR of 4-Heptylpyridine



1,1-bis(dichloroacetoxy) iodobenzene [3] To a solution of iodobenzene (0.81 mL, 7.35 mmol, 1.0 equiv.) in a mixture of dichloroacetic acid (1.27 mL, 15.43 mmol, 2.1 equiv.) and dry chloroform (1.5 mL), oxone (6.78 g, 11.02 mmol, 1.5 equiv.) was added under stirring at room temperature. The reaction mixture was stirred at room temperature overnight. After completion of the reaction, the solvent was evaporated under vacuum and the residue was treated with chloroform (10 mL). The insoluble residue of inorganic salts was collected by filtration, washed with chloroform (5 mL) and discarded. Evaporation of combined chloroform extracts under reduced pressure afforded crude product, which was further purified by recrystallization from

$CHCl_2CO_2H$/hexane (1:10) to obtain 1.0 g of white solid (2.17 mmol, 29%). ^1H NMR was consistent with the literature values.[4]

^1H NMR (400 MHz, $CDCl_3$) δ 8.19 – 8.11 (m, 2H), 7.73 – 7.64 (m, 1H), 7.58 (ddt, *J* = 7.6, 6.9, 1.4 Hz, 2H), 5.89 (s, 2H).

Ref: ^1H NMR ($CDCl_3$): δ 8.14 (m, 2H), 7.66 (m, 1H) 7.57 (m, 3H), 5.88 (s, 2H)

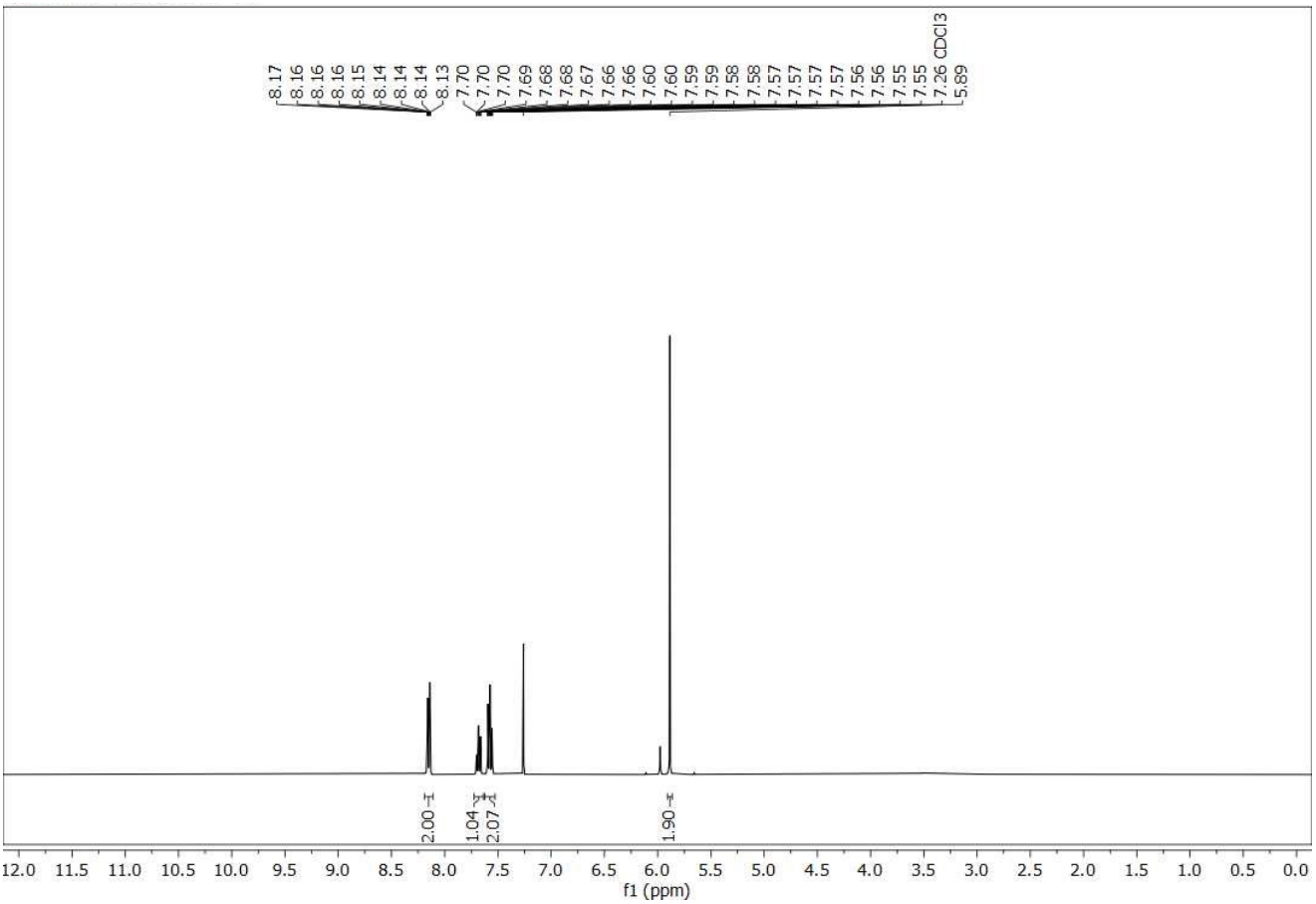
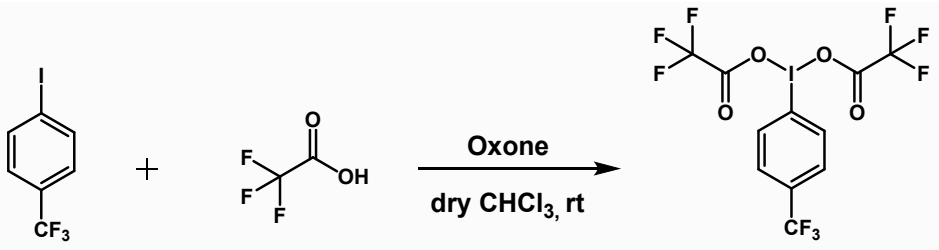


Figure S2: ^1H NMR of 1,1-bis(dichloroacetoxy) iodobenzene



1-[Bis(trifluoroacetoxy)iodo]-4-(trifluoromethyl) benzene[3] To a solution of 4-(trifluoromethyl) iodobenzene (0.5g, 1.83 mmol, 1.0 equiv.) in a mixture of trifluoroacetic acid (0.14 mL, 1.83 mmol, 1.0

equiv.) and dry chloroform (3.6 mL), oxone (1.69 g, 2.75 mmol, 1.5 equiv.) was added under stirring at room temperature. The reaction mixture was stirred at room temperature for 1.5 hr (the reaction was monitored by TLC using hexane/EtOAc 3:1 as eluent by disappearance of the iodoarene). After completion of the reaction, the solvent was evaporated under vacuum and the residue was treated with chloroform (10 mL). The insoluble residue of inorganic salts was collected by filtration, washed with chloroform (5 mL) and discarded. Evaporation of combined chloroform extracts under reduced pressure afforded crude product, which was further purified by recrystallization from CF_3CO_2H/hexane (1:10) to give 0.56 g of light-yellow solid (1.12 mmol, 61%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, *J* = 8.3 Hz, 2H), 7.88 (d, *J* = 8.3 Hz, 2H).

Ref: ^{1}H NMR ($CDCl_3$) δ 8.34 (d, J=7.9 Hz, 2H, ArH), 7.89 (d, J=7.9 Hz, 2H, ArH).

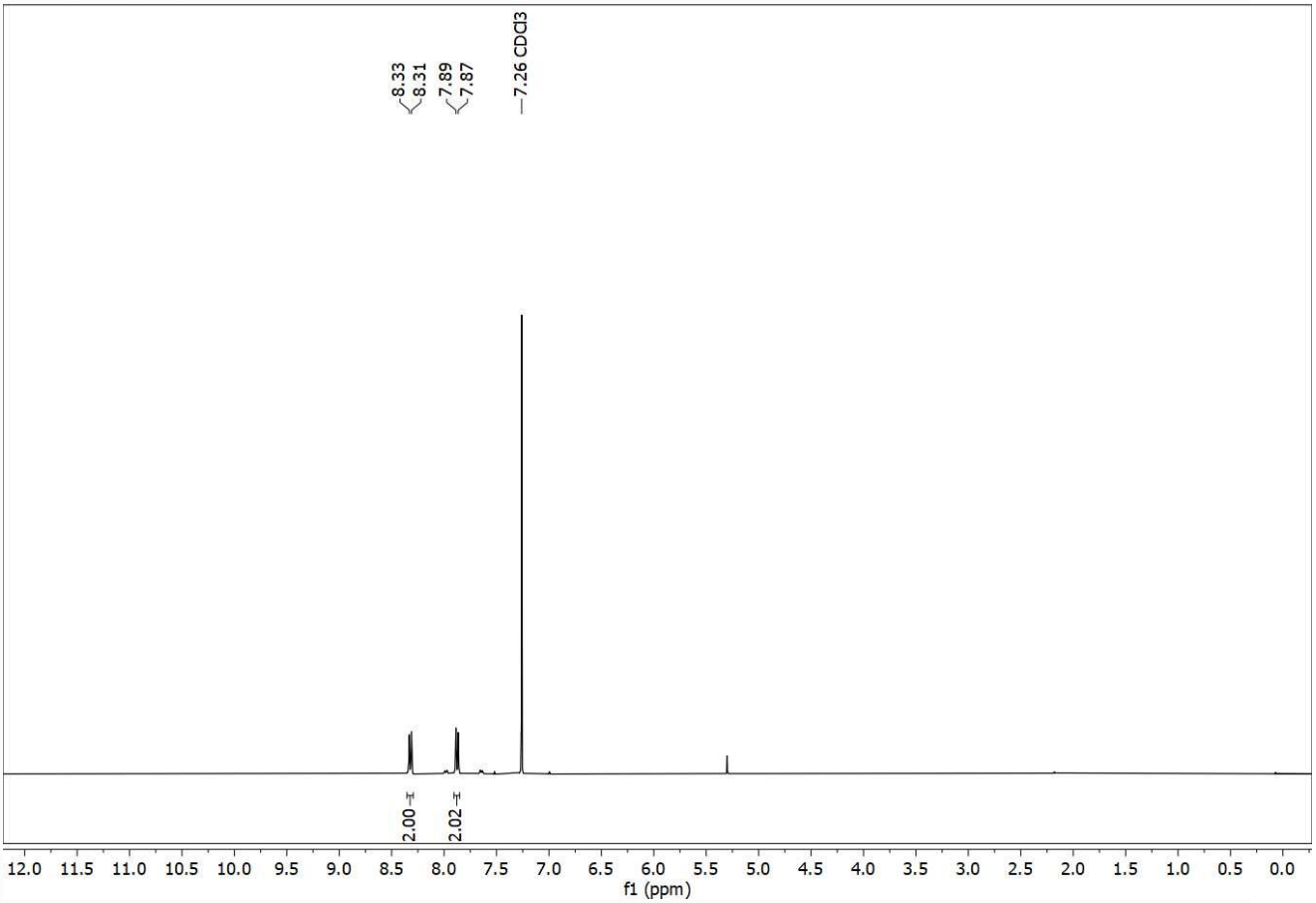
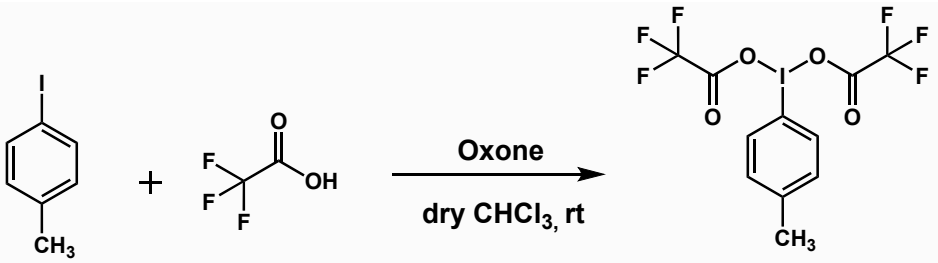


Figure S3: ^{1}H NMR of 1-[Bis(trifluoroacetoxy)iodo]-4-(trifluoromethyl) benzene



1-[Bis(trifluoroacetoxy)iodo]-4-methylbenzene [3,5] To a solution of 4-iodotoluene (0.5 g, 2.29 mmol, 1.0 equiv.) in a mixture of trifluoroacetic acid (0.17 mL, 2.29 mmol, 1.0 equiv.) and chloroform (3.6 mL), oxone (2.11g, 3.43 mmol, 1.5 equiv.) was added under stirring at room temperature. The reaction mixture was stirred at room temperature for 2.0 hrs (the reaction was monitored by TLC using hexane/EtOAc 3:1 as eluent by disappearance of the iodoarene). After completion of the reaction, the solvent was evaporated under vacuum and the residue was treated with chloroform (10 mL). The insoluble residue of inorganic salts was collected by filtration, washed with chloroform (5 mL) and discarded. Evaporation of combined chloroform extracts under reduced pressure afforded crude product, which was further purified by recrystallization from CF_3CO_2H/hexane (1:10) to give 0.12 g of white solid (0.27 mmol, 12%). ^{1}H NMR was consistent with previously reported spectra.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 – 8.06 (m, 2H, 8.4 Hz), 7.41 – 7.37 (m, 2H, 8.4 Hz), 2.50 (s, 3H).

Ref: ^{1}H NMR ($CDCl_3$:CF_3CO_2H 25:1) δ 8.10 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 2.51 (s, 3H).

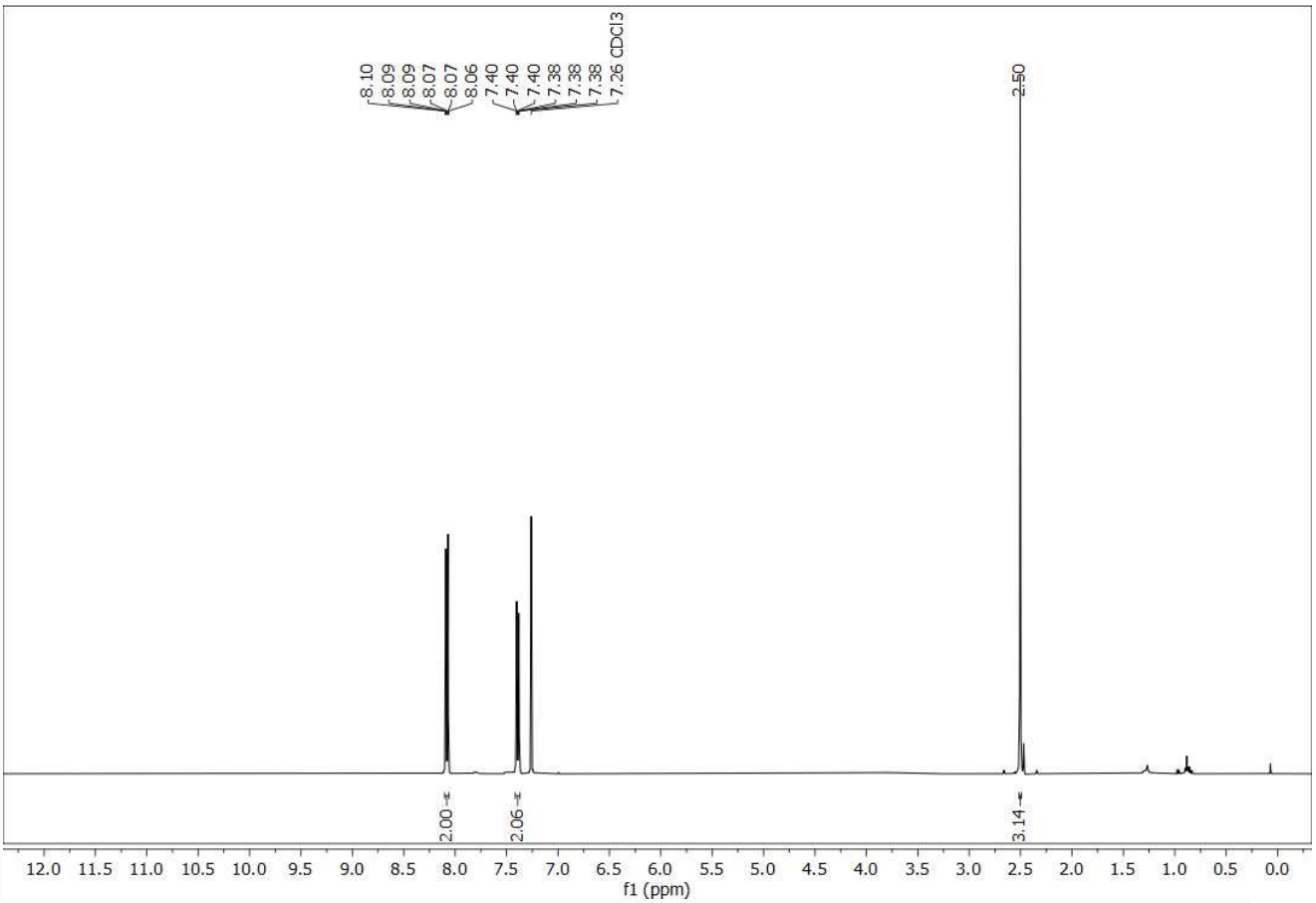
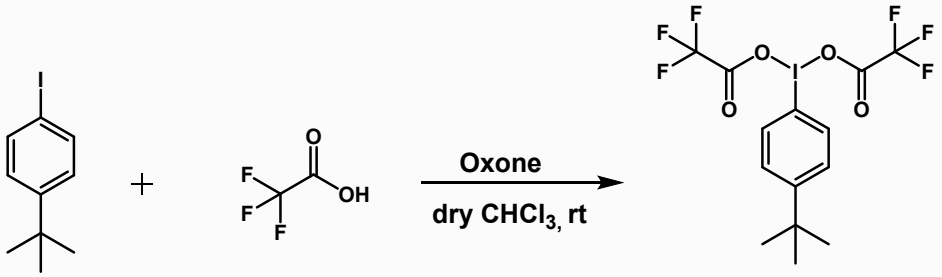


Figure S4: ^{1}H NMR of 1-[Bis(trifluoroacetoxy)iodo]-4-methylbenzene



1-[Bis(trifluoroacetoxy)iodo]-4-tert-butylbenzene [3,6] To a solution of 4-tert-butyliodobenzene (0.5g, 1.92 mmol, 1.0 equiv.) in a mixture of trifluoroacetic acid (0.14 mL, 1.92 mmol, 1.0 equiv.) and chloroform (3.6 mL), oxone (1.77 g, 2.88 mmol, 1.5 equiv.) was added under stirring at room temperature. The reaction mixture was stirred at room temperature overnight (the reaction was monitored by TLC using hexane/EtOAc 1:1 as eluent by disappearance of the iodoarene). After completion of the reaction, the solvent was evaporated under vacuum and the residue was treated with chloroform (10 mL). The insoluble residue of inorganic salts was collected by filtration, washed with chloroform (5 mL) and discarded. Evaporation of combined chloroform extracts under reduced pressure afforded crude product, which was

further purified by recrystallization from CF_3CO_2H/hexane (1:10) to give 0.44 g of yellow solid (0.90 mmol, 47%) with 30% of reactant (4-tert-butyliodobenzene). Therefore, the ratio between product and reactant being 7:3. The additional peaks in the H-NMR are due to residual reactant.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.5 Hz, 2H), 7.51 (d, *J* = 8.7 Hz, 2H), 1.37 (s, 9H).

Ref: ^{1}H NMR ($CDCl_3$) δ 7.85 (d, *J* = 8.6 Hz, 2H), 7.54 – 7.49 (m, 2H), 1.37 (s, 9H).

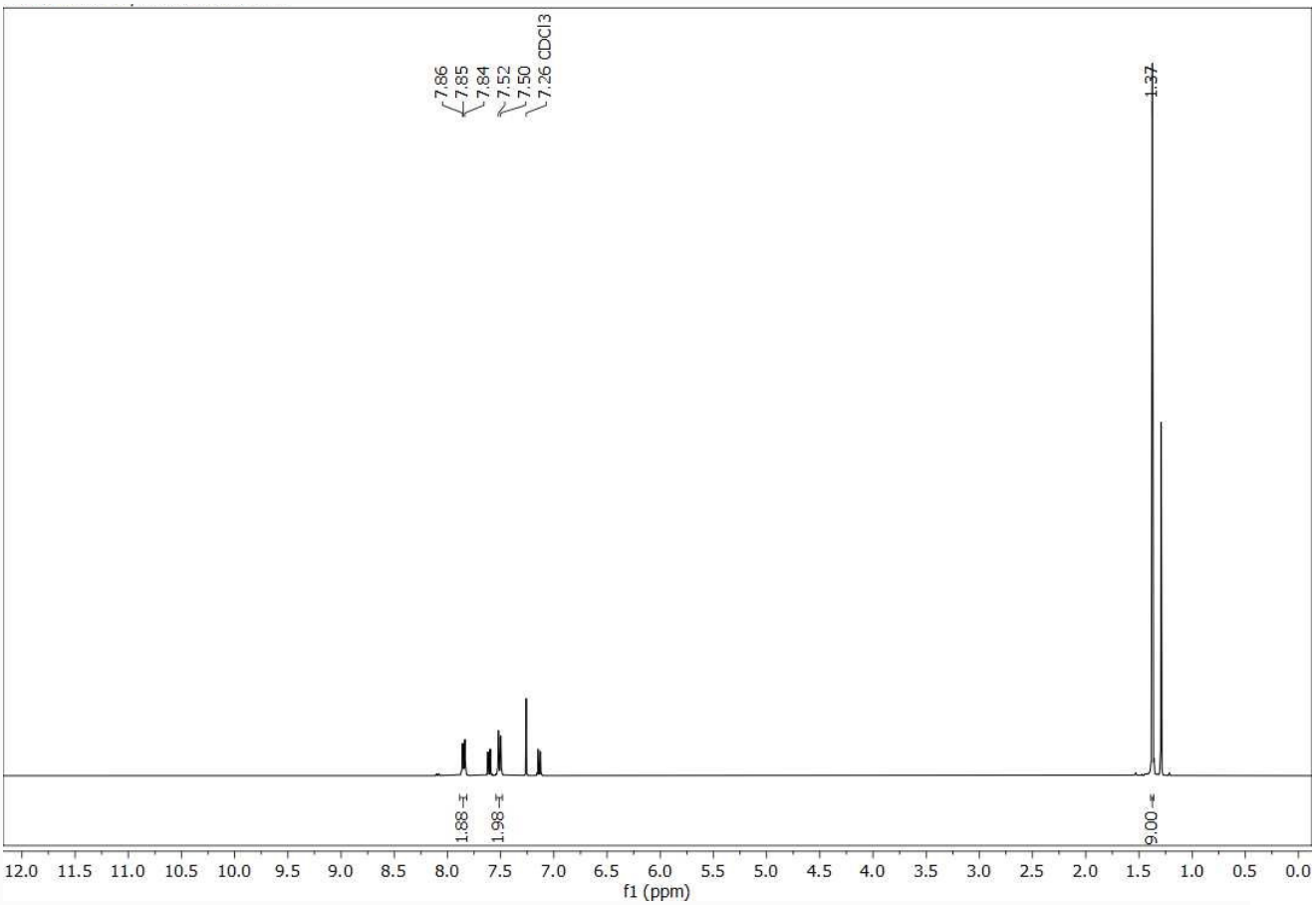
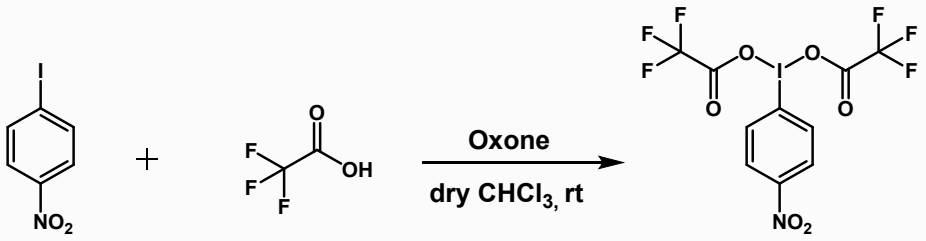


Figure S5: ^{1}H NMR of 1-[Bis(trifluoroacetoxy)iodo]-4-tert-butylbenzene



1-[Bis(trifluoroacetoxy)iodo]-4-nitrobenzene [3,6] To a solution of 4-nitrobenzene (1.8 g, 7.22 mmol, 1.0 equiv.) in a mixture of trifluoroacetic acid (21.66 mL, 7.22 mmol, 1.0 equiv.) and chloroform (7.22 mL), oxone (6.67 g, 10.84 mmol, 1.5 equiv.) was added under stirring at room temperature. The reaction mixture was stirred at room temperature until the reactant was consumed. After completion of the reaction, the solvent was evaporated under vacuum and the residue was treated with chloroform (10 mL). The insoluble residue of inorganic salts was collected by filtration, washed with chloroform (5 mL) and discarded. Evaporation of combined chloroform extracts under reduced pressure afforded crude product, which was further purified by recrystallization from CF_3CO_2H/hexane (1:10) to give 0.5 g of yellow solid (1.05 mmol, 14%). ^{1}H NMR consistent with those previously reported.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 – 8.37 (m, 4H).

Ref: ^{1}H NMR ($CDCl_3$/CF_3CO_2D, 22:1): δ 8.40-8.48 (m, 4H)

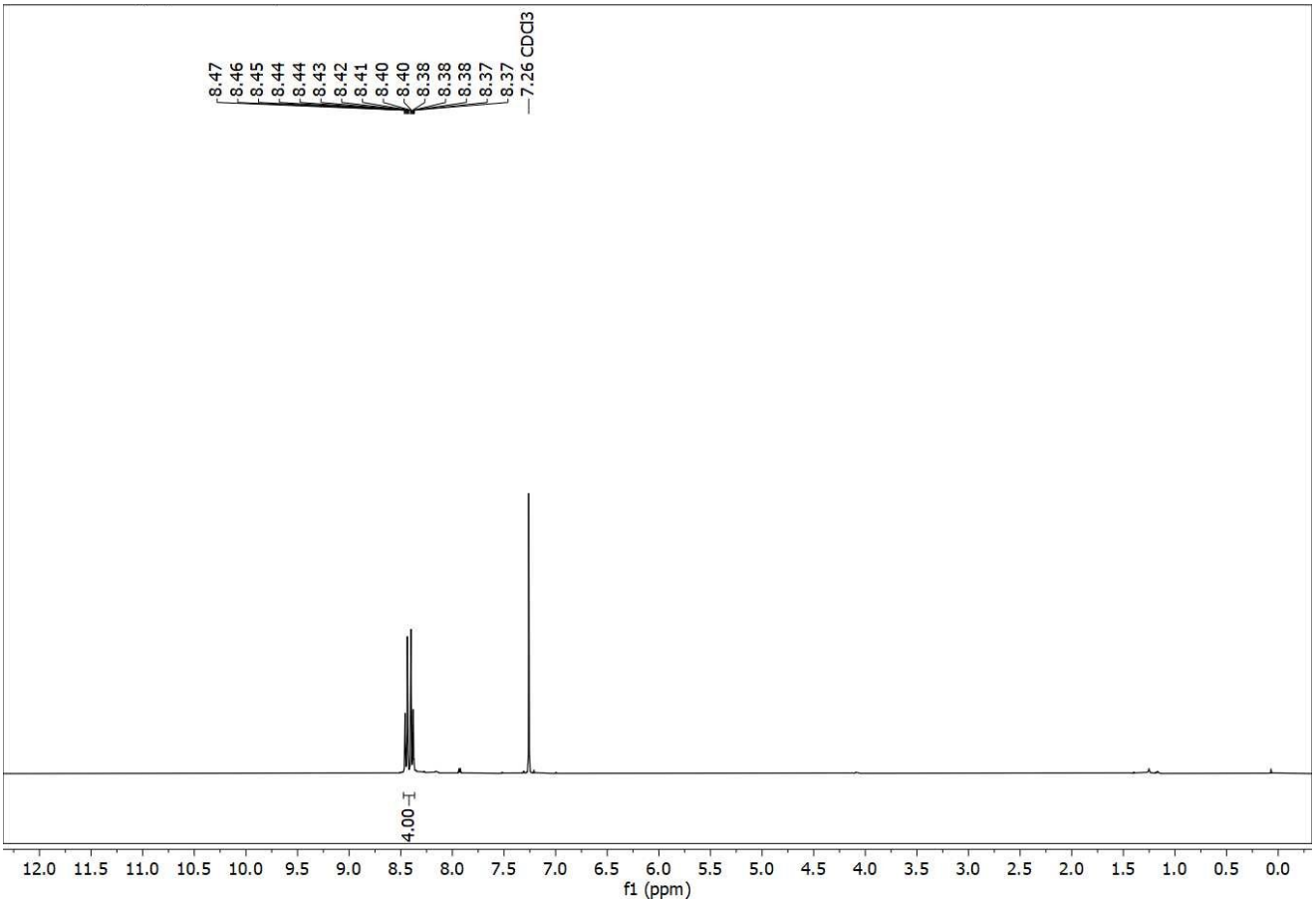
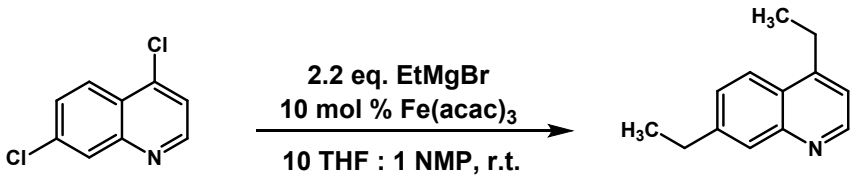


Figure S6: ^{1}H NMR of 1-[Bis(trifluoroacetoxy)iodo]-4-nitrobenzene



4,7-diethylquinoline [7] To a flame dried round-bottom flask equipped with a stir bar are added 4,7-dichloroquinoline (2.97 g, 15 mmol) and $Fe(acac)_3$ (0.531 mg, 1.5 mmol). The flask is evacuated and backfilled with nitrogen 3x, followed by the addition of THF (60 mL) and 6 mL of NMP (N-methyl-2-pyrrolidone). The reaction is stirred and cooled to 0 °C in an icebath, at which point 35 mmol of EtMgBr (3M in Et_2O) were added dropwise via syringe. Once the addition was complete the reaction was removed from the icebath and allowed to warm to room temperature and stirred at room temperature for 40 hrs. The reaction was then quenched with H_2O, poured into a separatory funnel, and extracted into EtOAc. The combined organic fractions were dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude mixture was purified by silica gel chromatography (30% EtOAc in Hexane) to give 200 mg (10.79 mmol, 72%) of a yellow oil. ^{1}H NMR consistent with those previously reported.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (d, *J* = 4.5 Hz, 1H), 7.95 (d, *J* = 8.6 Hz, 1H), 7.90 (s, 1H), 7.42 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.18 (d, *J* = 4.5 Hz, 1H), 3.09 (q, *J* = 7.9 Hz, 2H), 2.86 (q, *J* = 7.1 Hz, 2H), 1.40-1.33 (m, 6H).

Ref: ^{1}H NMR ($CDCl_3$) δ 8.77 (d, *J* = 4.5 Hz, 1H), 7.96 (d, *J* = 8.6 Hz, 1H), 7.91 (s, 1H), 7.42 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.18 (d, *J* = 4.4 Hz, 1H), 3.09 (q, *J* = 7.6 Hz, 2H), 2.86 (q, *J* = 7.6 Hz, 2H), 1.45 – 1.30 (m, 6H).

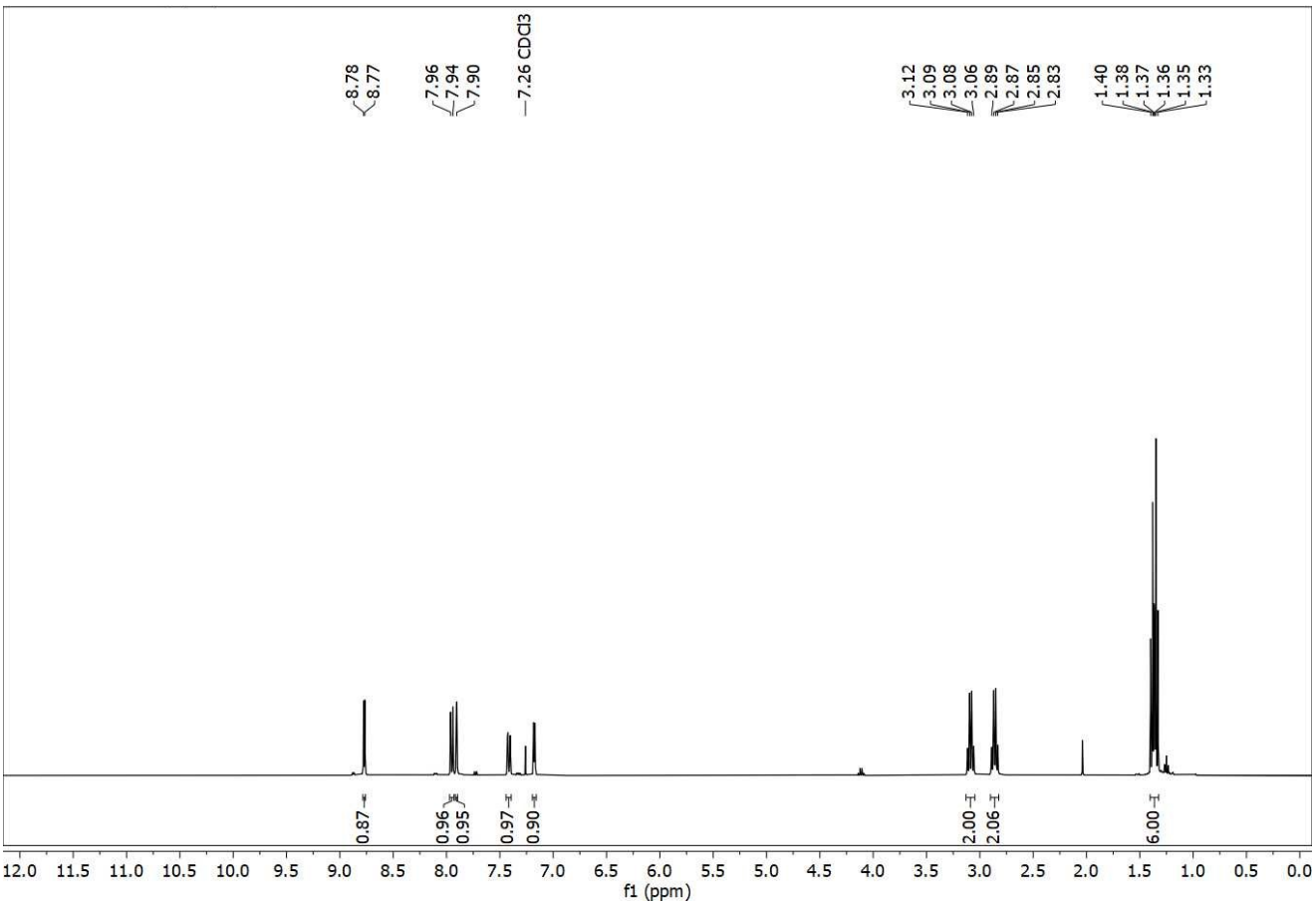
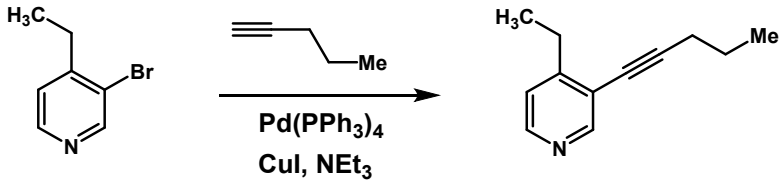


Figure S7: ^{1}H NMR of 4,7-diethylquinoline



4-ethyl-3-(1'-pentynyl)pyridine [8] An oven-dried 40-mL vial was charged with $Pd(PPh_3)_4$ (462 mg, 0.4 mmol) and CuI (76 mg, 0.4 mmol). The vial was evacuated and then refilled with nitrogen 3 times, then 3-bromo-4-ethylpyridine (744 mg, 4 mmol) dissolved in 11.2 mL NEt_3 (20 eq) was added, followed up 1-pentyne (790 µL, 8 mmol). The puncturable vial cap was replaced with a solid cap and the reaction was heated to 80 °C for 48 hours. The reaction was quenched with 1 mL of MeOH, concentrated *in vacuo*, filtered through celite using dichloromethane, washed with $NaHCO_3$ and brine, dried with $MgSO_4$ and concentrated *in vacuo*. Column chromatography over silica gel (10:1 DCM:EtOAc) afforded 249 mg (1.43 mmol, 36%) of a light yellow oil. ^{1}H NMR consistent with those previously reported.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1H), 8.38 (s, 1H), 7.10 (d, *J* = 5.0 Hz, 1H), 2.77 (q, *J* = 7.6 Hz, 2H), 2.44 (t, *J* = 7.0 Hz, 2H), 1.66 (h, *J* = 7.2 Hz, 2H), 1.24 (t, *J* = 7.6 Hz, 3H), 1.07 (t, *J* = 7.4 Hz, 3H).

Ref: ^{1}H NMR ($CDCl_3$) = 8.54 (s, 1H), 8.37 (d, *J* = 5.2 Hz, 1H), 7.10 (d, *J* = 5.2 Hz, 1H), 2.77 (q, *J* = 7.6 Hz, 2H), 2.45 (t, *J* = 6.9 Hz, 2H), 1.66 (h, *J* = 7.3 Hz, 2H), 1.24 (t, *J* = 7.6 Hz, 3H), 1.07 (t, *J* = 7.2 Hz, 3H).

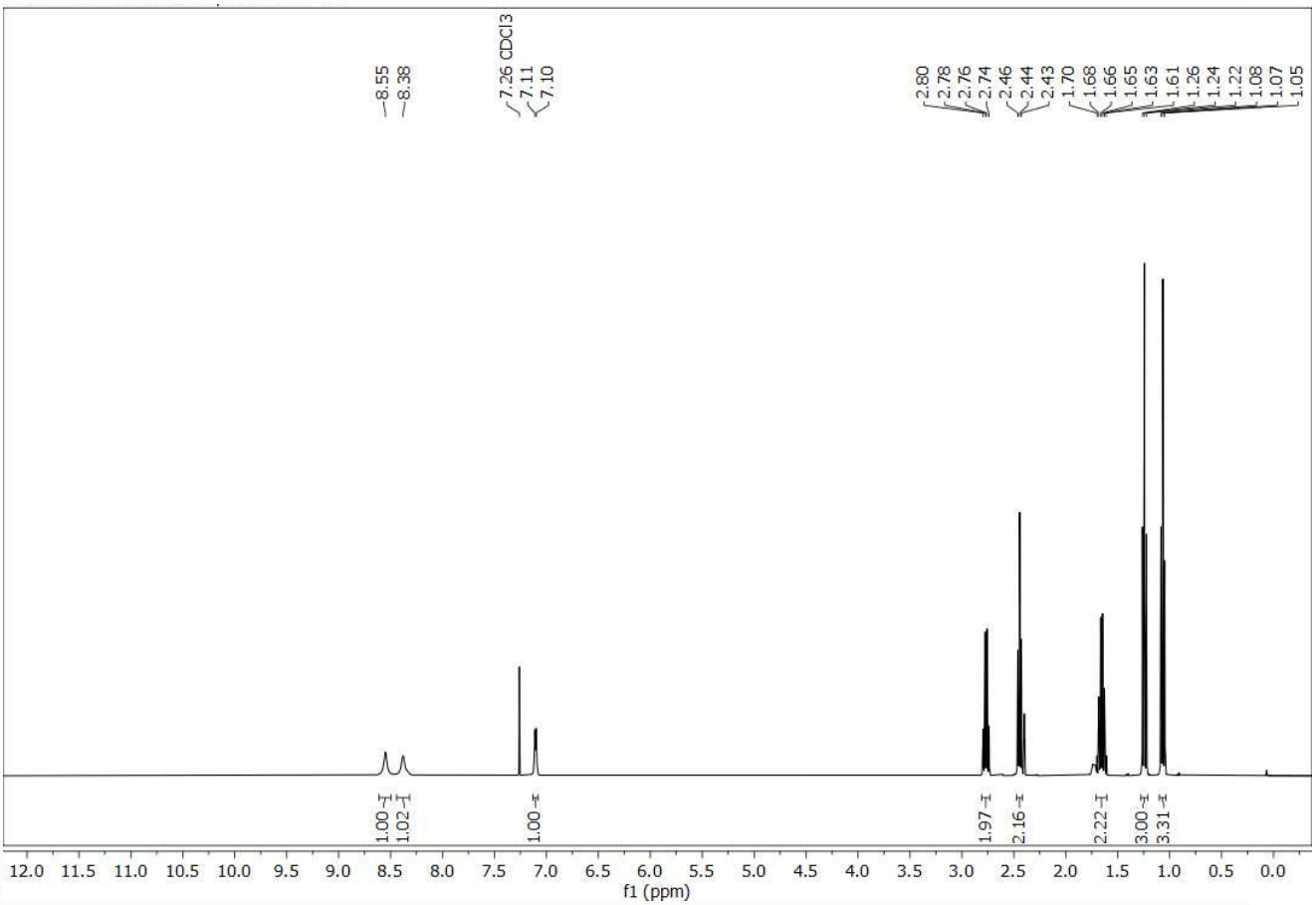
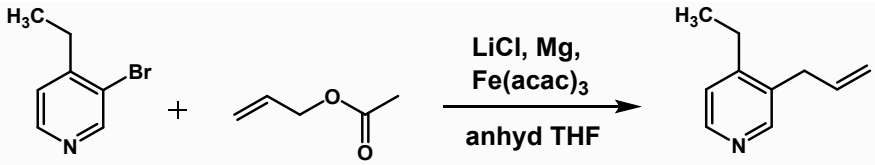


Figure S8: ^{1}H NMR of 4-ethyl-3-(1'-pentynyl)pyridine



3-allyl-4-ethylpyridine [9] A 25 mL round-bottomed flask was charged with Mg ribbons (107 mg, 1.43 mmol), dry LiCl (200 mg, 4.72 mmol), fitted with a rubber septum, and purged with nitrogen (1 min). Dry THF (6 mL) and 3-bromo-4-methylpyridine (0.5 mL, 3.78 mmol) were added via a syringe. The solution was stirred at r.t. for 2 h under nitrogen. Then it was cooled to 0°C and a solution of $Fe(acac)_3$ (0.15 mmol, 5 mol%) in dry THF (3 mL). Then allyl acetate (0.34 ml, 3.15 mmol) was added, and the solution was stirred for 45 min at 0°C. The reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3×10 mL). The combined organic phases were dried ($MgSO_4$), concentrated, and subjected to silica gel flash chromatography (2:1 Hexane: EtOAc) afforded 0.35 g (2.37 mmol, 63%) of pale-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, *J* = 5.0 Hz, 1H), 8.33 (s, 1H), 7.10 (d, *J* = 5.5 Hz, 1H), 5.94 (, 1H), 5.12 – 5.06 (m, 1H), 5.01 – 4.94 (m, 1H), 3.39 (d, *J* = 6.1 Hz, 2H), 2.63 (q, *J* = 7.6 Hz, 2H), 1.22 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.2, 150.4, 147.9, 136.0, 133.1, 123.0, 116.4, 34.2, 24.8, 13.8. HRMS m/z calculated for $C_{10}H_{13}N$, [M+H] = 148.1126, observed 148.1119.

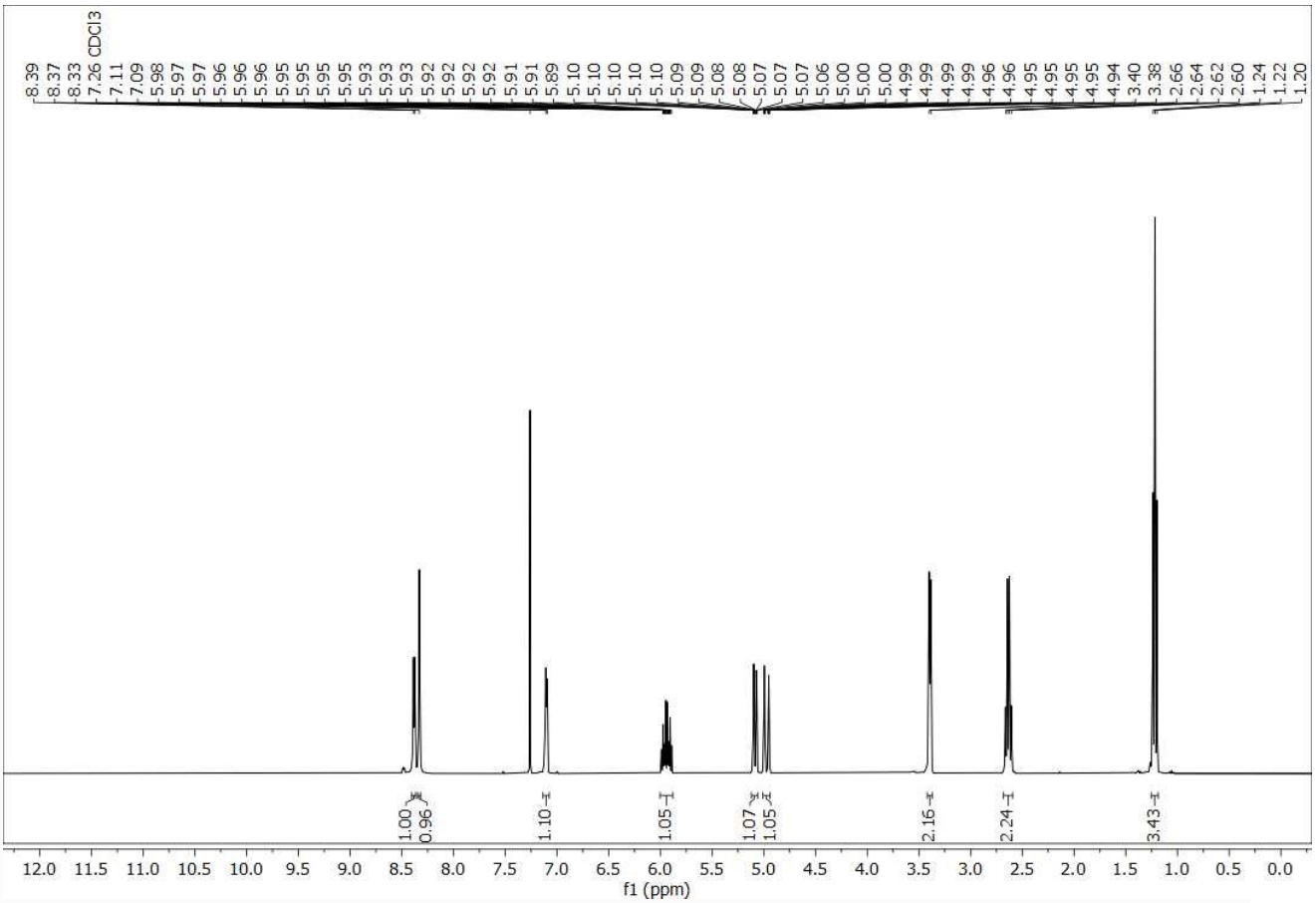


Figure S9: ^{1}H NMR of 3-allyl-4-ethylpyridine

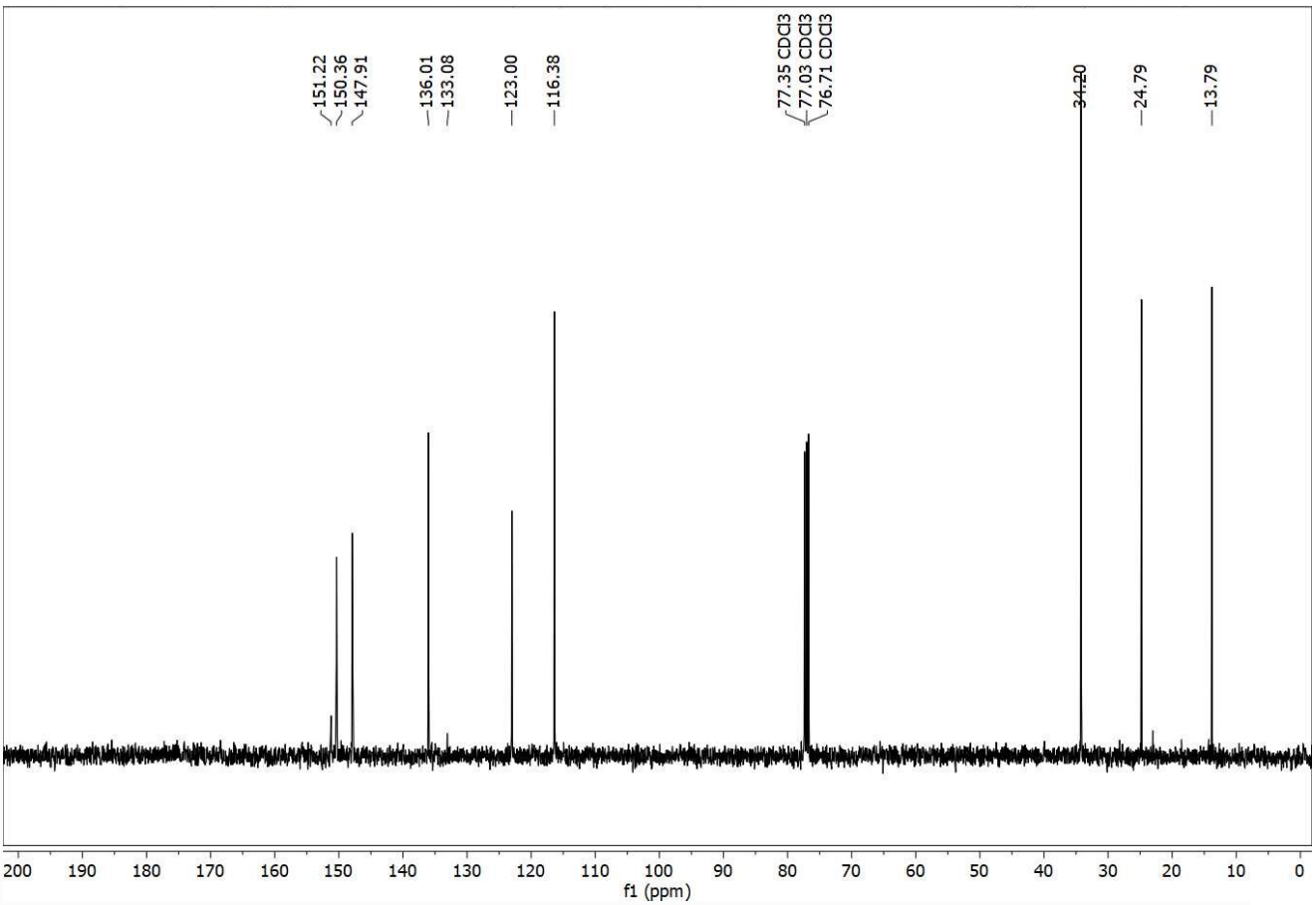
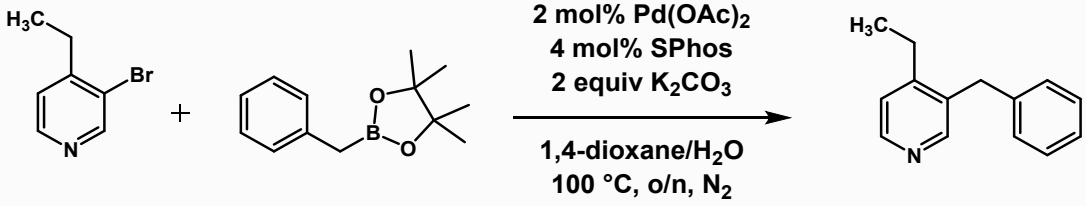


Figure S10: ^{13}C NMR of 3-allyl-4-ethylpyridine



4-Ethyl-3-(phenylmethyl)pyridine [10] To a 40 mL vial equipped with a stir bar was added 3-bromo-4-methylpyridine (1.0 g, 5.37 mmol, 1.2 equiv), 2-benzyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (974 mg, 4.47 mmol, 1.0 equiv), K_2CO_3 (123 mg, 8.94 mmol, 2 equiv), $Pd(OAc)_2$ (20.0 mg, 0.0894 mmol, 2 mol%) and SPhos (7.3 mg, 0.17 mmol, 4 mol%), followed by 1,4-dioxane (5.58 mL) and H_2O (2.23 mL). The vial was purged with nitrogen flow for 1 min and sealed, which was heated with stirring at 100 °C overnight. The reaction mixture was then cooled to room temperature, dried over Na_2SO_4, and filtered through a pad

of celite and concentrated. The residue was subjected to silica gel chromatography (2:1 hexane:EtOAc) to afford 0.26 g (1.31 mmol, 25% yield) of pale-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, *J* = 5.0 Hz, 1H), 8.38 (s, 1H), 7.31 – 7.25 (m, 2H), 7.23 – 7.17 (m, 1H), 7.15 – 7.09 (m, 3H), 4.02 (s, 2H), 2.57 (q, *J* = 7.5 Hz, 2H), 1.13 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 151.3, 150.9, 148.3, 139.6, 133.9, 128.5, 128.5, 126.3, 123.1, 36.2, 25.0, 13.5. HRMS m/z calculated for $C_{14}H_{15}N$, [M+H] = 198.1283, observed 198.1277.

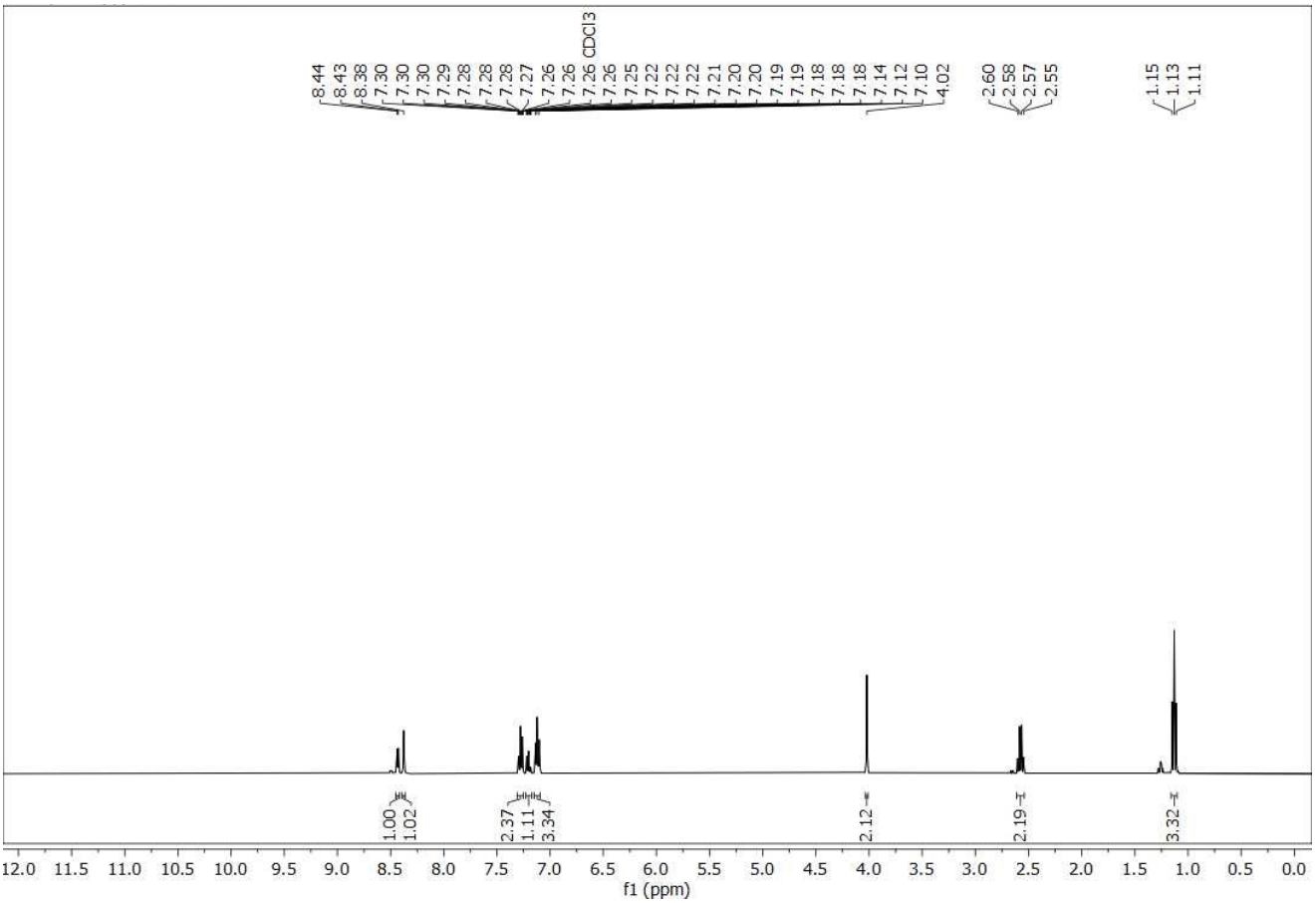


Figure S11: ^{1}H NMR of 4-Ethyl-3-(phenylmethyl)pyridine

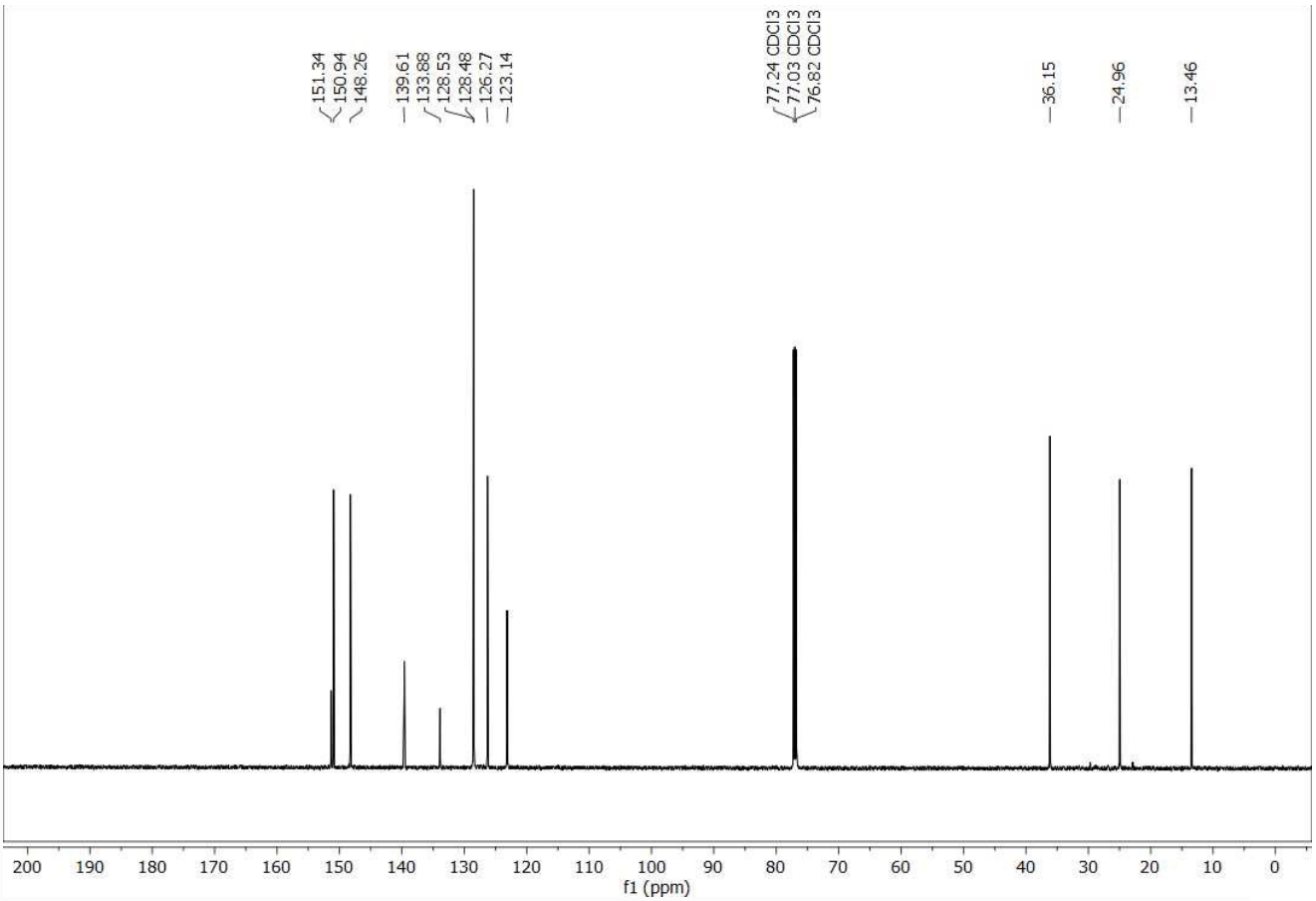
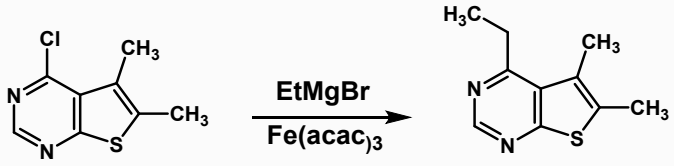


Figure S12: ^{13}C NMR of 4-Ethyl-3-(phenylmethyl)pyridine



4-Ethyl-2,3-dimethylbenzo[b]thiophene [8] A flame-dried 2-neck flask under N_2 was charged with 4-chloro-2,3-dimethylbenzo[b]thiophene (0.894 g, 4.49 mmol), $Fe(acac)_3$ (78.6 mg, 0.23 mmol), 12 mL anhydrous THF and 1 mL anhydrous NMP. To this stirred mixture at room temperature was added dropwise EtMgBr (3M in diethyl ether, 1.8 mL, 5.3 mmol). The reaction mixture was stirred for 1 hour, then quenched with H_2O. The resulting mixture was extracted with EtOAc, and the combined organic layers were washed once with aqueous NaCl, once with 1M aqueous sodium ascorbate, and four times with H_2O. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography over silica gel (2:1 hexane: EtOAc) afforded 400 mg (2.10 mmol, 47%) of a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (s, 1H), 3.21 (q, *J* = 7.5 Hz, 2H), 2.50 (d, *J* = 2.4 Hz, 6H), 1.38 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 165.2, 152.1, 133.9, 130.0, 124.7, 29.1, 14.5, 14.0, 13.6. HRMS calculated for $C_{10}H_{12}N_2S$, [M+H] is 193.0799, observed 193.0798.

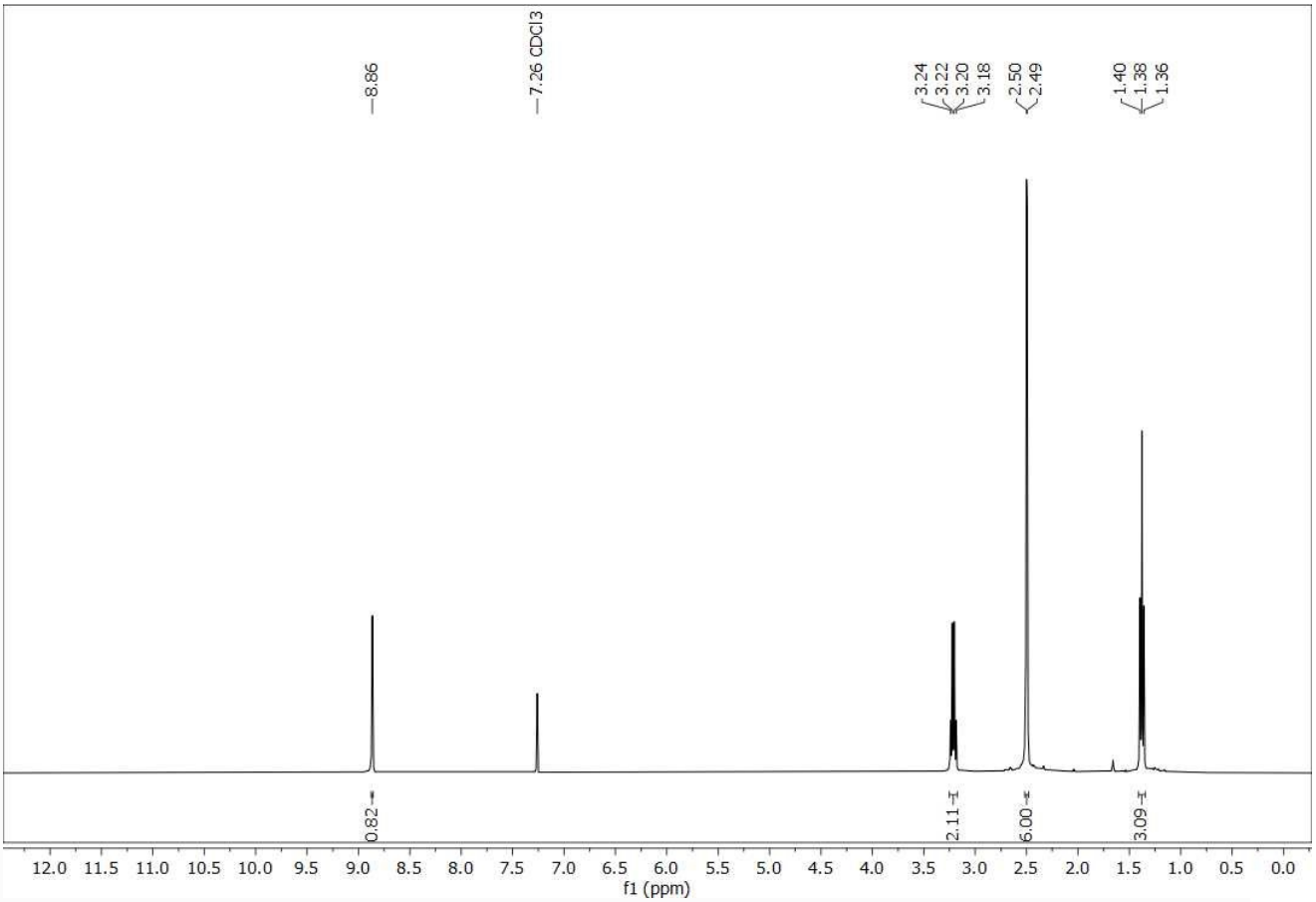


Figure S13: ^{1}H NMR of 4-Ethyl-2,3-dimethylbenzo[b]thiophene

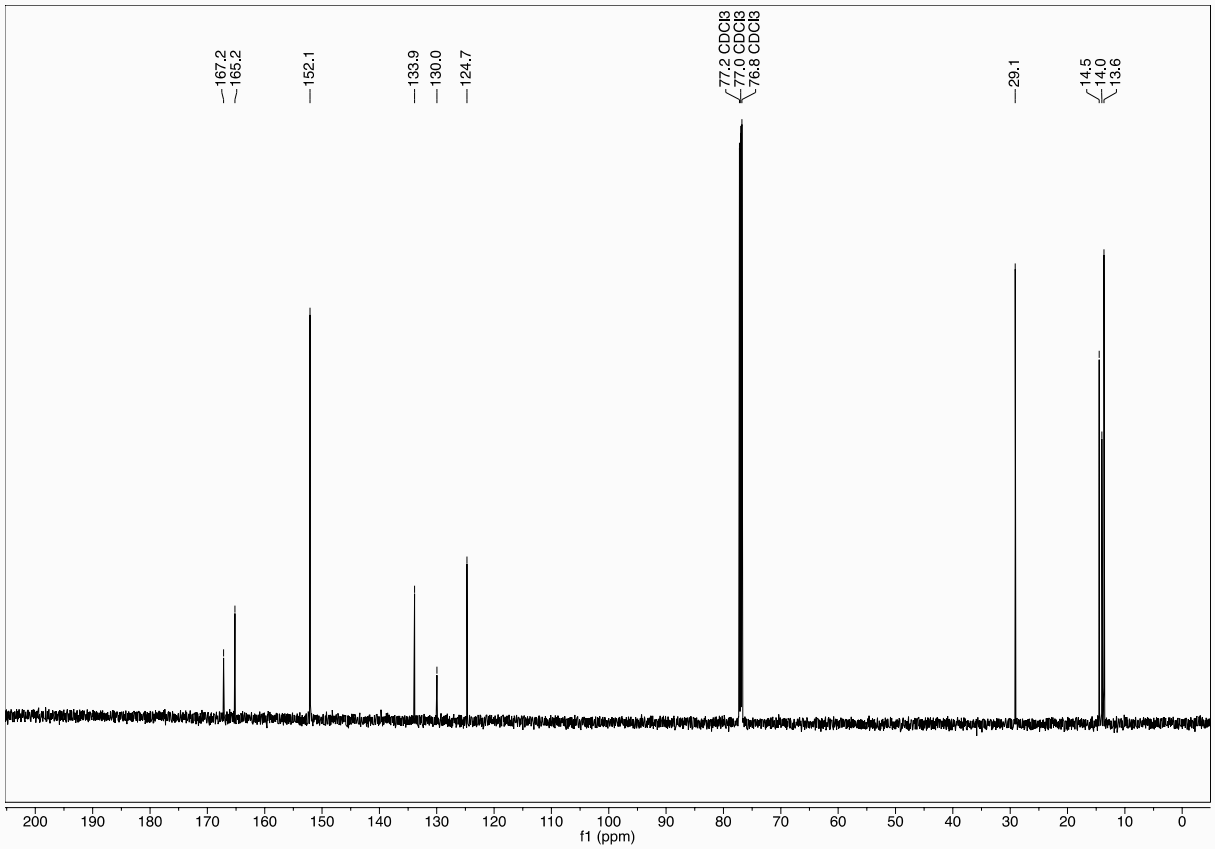
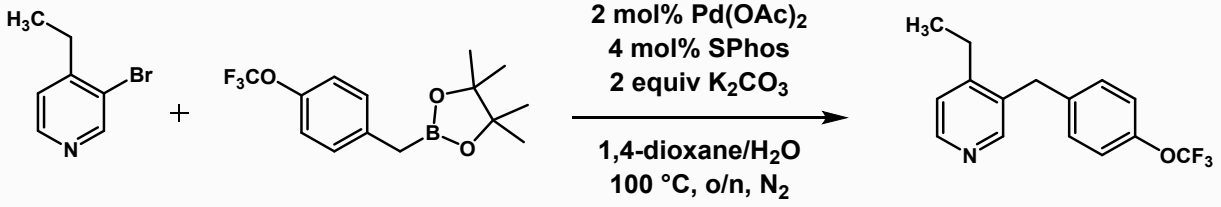


Figure S14: ^{13}C NMR of 4-Ethyl-2,3-dimethylbenzo[b]thiophene



4-ethyl-3-(4-(trifluoromethoxy)benzyl)pyridine [10] To a 40 mL vial equipped with a stir bar was added 3-bromo-4-methylpyridine (2.0 g, 10.74 mmol, 1.2 equiv), 4,4,5,5-tetramethyl-2-(4-(trifluoromethoxy)benzyl)-1,3,2-dioxaborolane (2.7 mg, 8.95 mmol, 1.0 equiv), K_2CO_3 (2.96 mg, 21.48 mmol, 2 equiv), $Pd(OAc)_2$ (40 mg, 0.179 mmol, 2 mol%) and SPhos (143.0 mg, 0.35 mmol, 4 mol%), followed by 1,4-dioxane (12.0 mL) and H_2O (5.0 mL). The vial was purged with nitrogen flow for 1 min and sealed, which was heated with stirring at 100 °C overnight. The reaction mixture was then cooled to room temperature, dried over Na_2SO_4, and filtered through a pad of celite and concentrated. The residue was subjected to silica gel chromatography (2:1 hexane: EtOAc) to afford 1.51 g (5.36 mmol, 65 % yield) of pale-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, *J* = 5.1 Hz, 1H), 8.35 (s, 1H), 7.14 (d, *J* = 5.1 Hz, 1H), 7.12 (s, 4H), 4.01 (s, 2H), 2.55 (q, *J* = 7.6 Hz, 2H), 1.13 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 151.3, 150.9, 148.5, 147.7, 138.4, 133.3, 129.7, 123.3, 121.1, 120.5 (q, *J* = 255 Hz), 35.4, 25.0, 13.4. ^{19}F NMR (376 MHz, $CDCl_3$) δ -58.00. HRMS calculated for $C_{15}H_{14}F_3NO$, [M+H] is 282.1106, observed 282.1106.

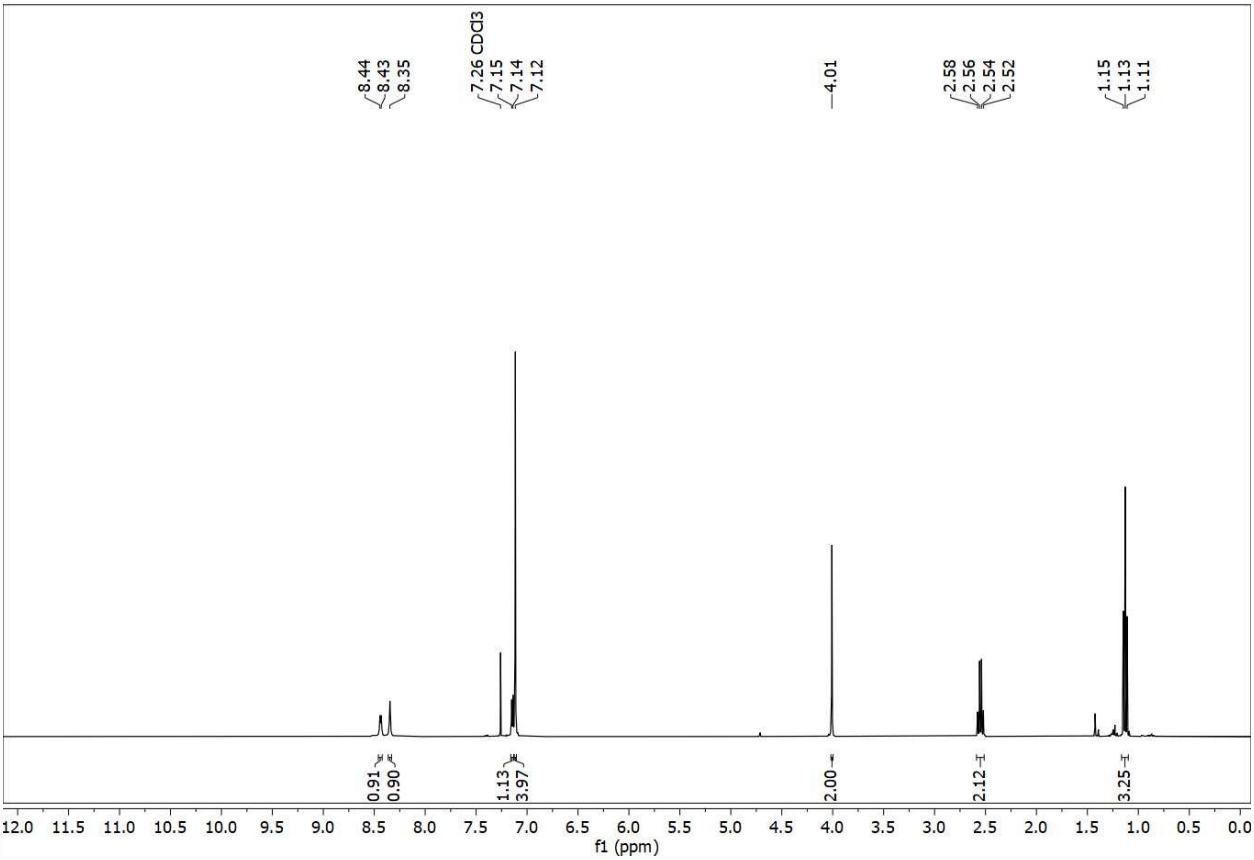


Figure S15: ^{1}H NMR of 4-ethyl-3-(4-(trifluoromethoxy)benzyl) pyridine

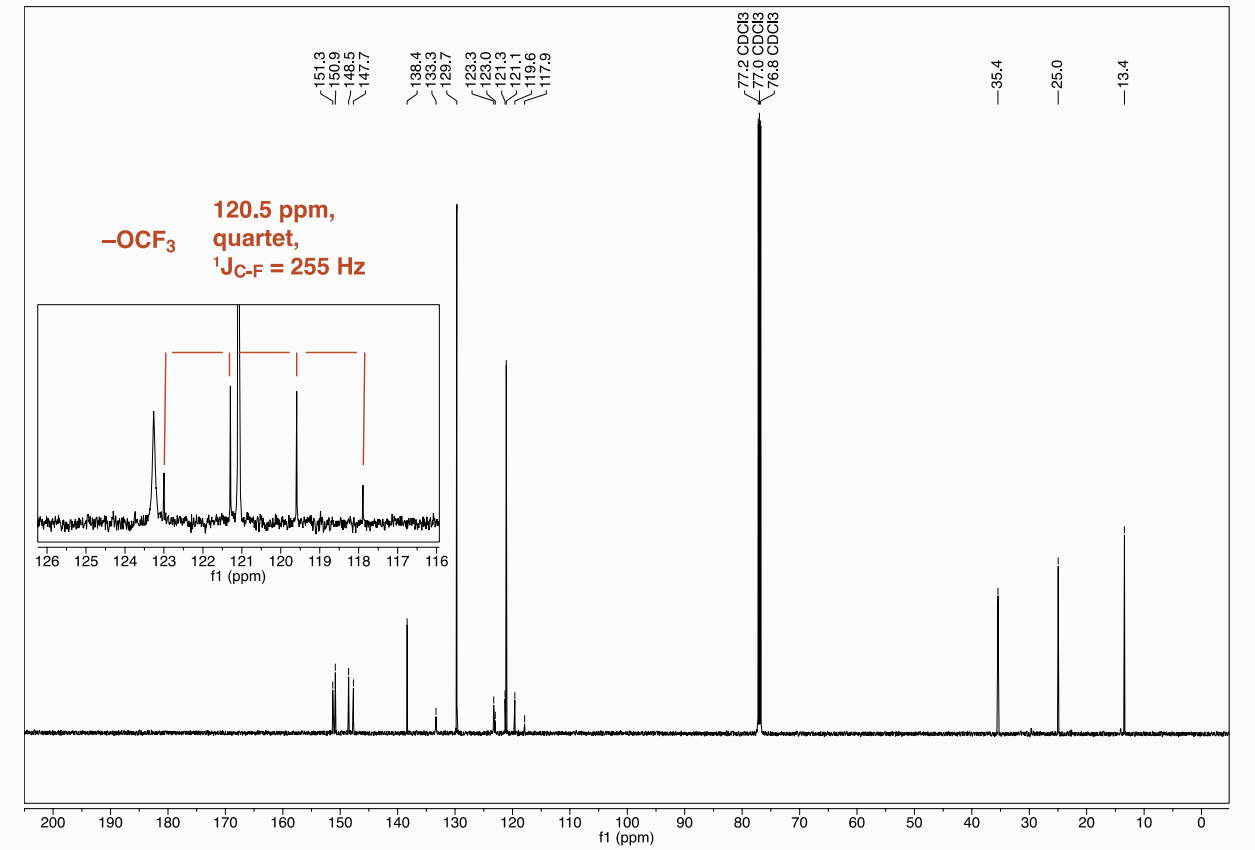


Figure S16: ^{13}C NMR of 4-ethyl-3-(4- (trifluoromethoxy)benzyl) pyridine

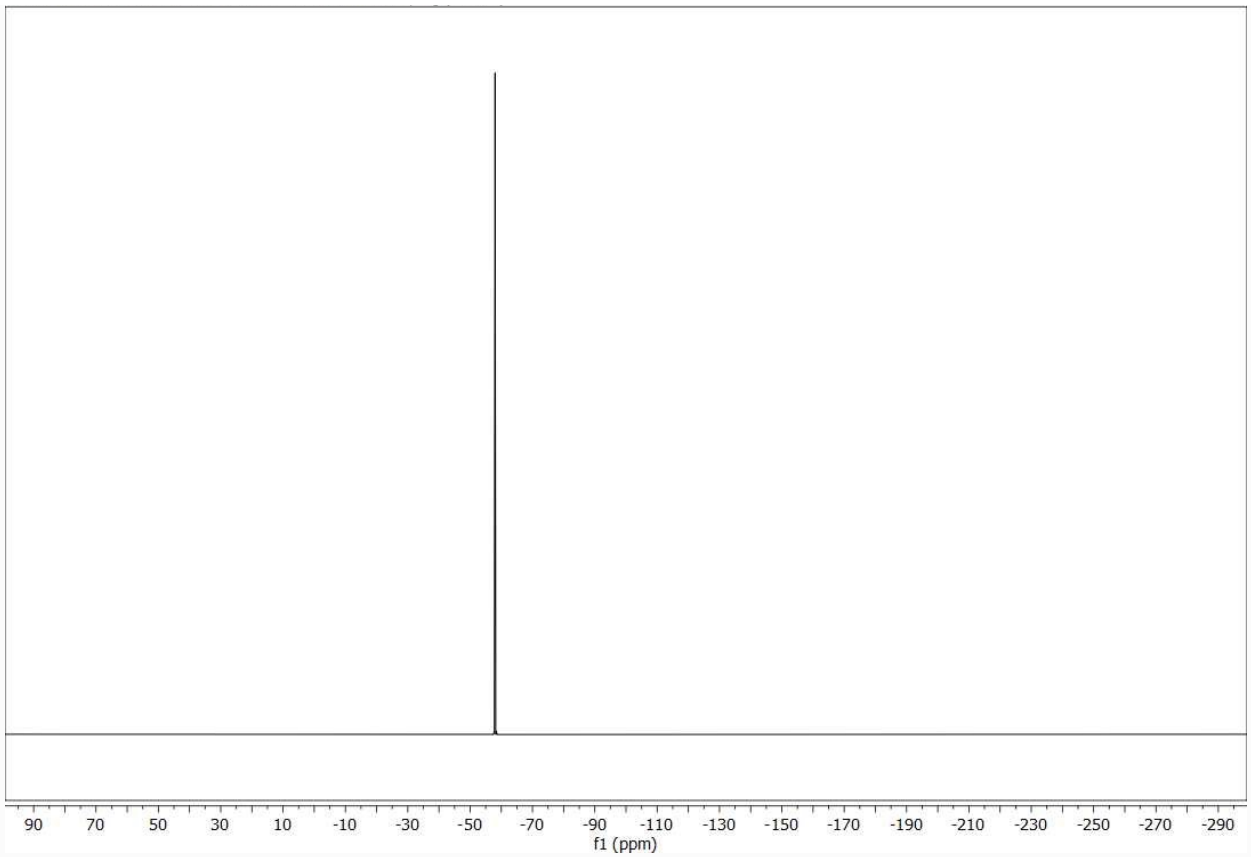
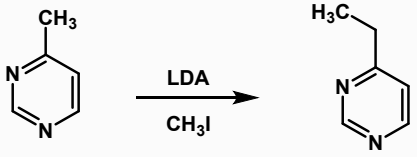


Figure S17: F NMR of 4-ethyl-3-(4-(trifluoromethoxy)benzyl) pyridine



4-Ethylpyrimidine [8] A flame dried flask 2-neck flask under N_2 was charged with 4-methylpyridine (1.03 g, 10.95 mmol) and 36 mL anhydrous THF. The stirred solution was cooled to -78 °C, and freshly prepared lithium diisopropyl amide (LDA) (11.82 mmol) was added dropwise. The reaction was stirred at -78 °C for 30 min., followed by addition of MeI (0.87 mL, 14.13 mmol). The reaction mixture was stirred for an additional 30 min. at -78 °C and was then warmed to room temperature and stirred for 3 hours. The reaction mixture was quenched with $NaHCO_3$ and extracted with dichloromethane. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography over silica gel (2:1 hexane: EtOAc) afforded 0.11 g (1.01 mmol, 9%) of a light-yellow oil. ^{1}H NMR consistent with the reported literature. [11]

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.11 (s, 1H), 8.60 (d, *J* = 5.2 Hz, 1H), 7.19 (d, *J* = 5.2 Hz, 1H), 2.80 (q, *J* = 7.5 Hz, 2H), 1.31 (t, *J* = 7.6 Hz, 3H).

Ref: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 (s, 1 H), 8.61 (d, J=5.1 Hz, 1 H), 7.20 (d, J=5.1 Hz, 1 H), 2.82 (q, J=7.7 Hz, 2 H), 1.33 (t, J=7.7 Hz, 3 H).

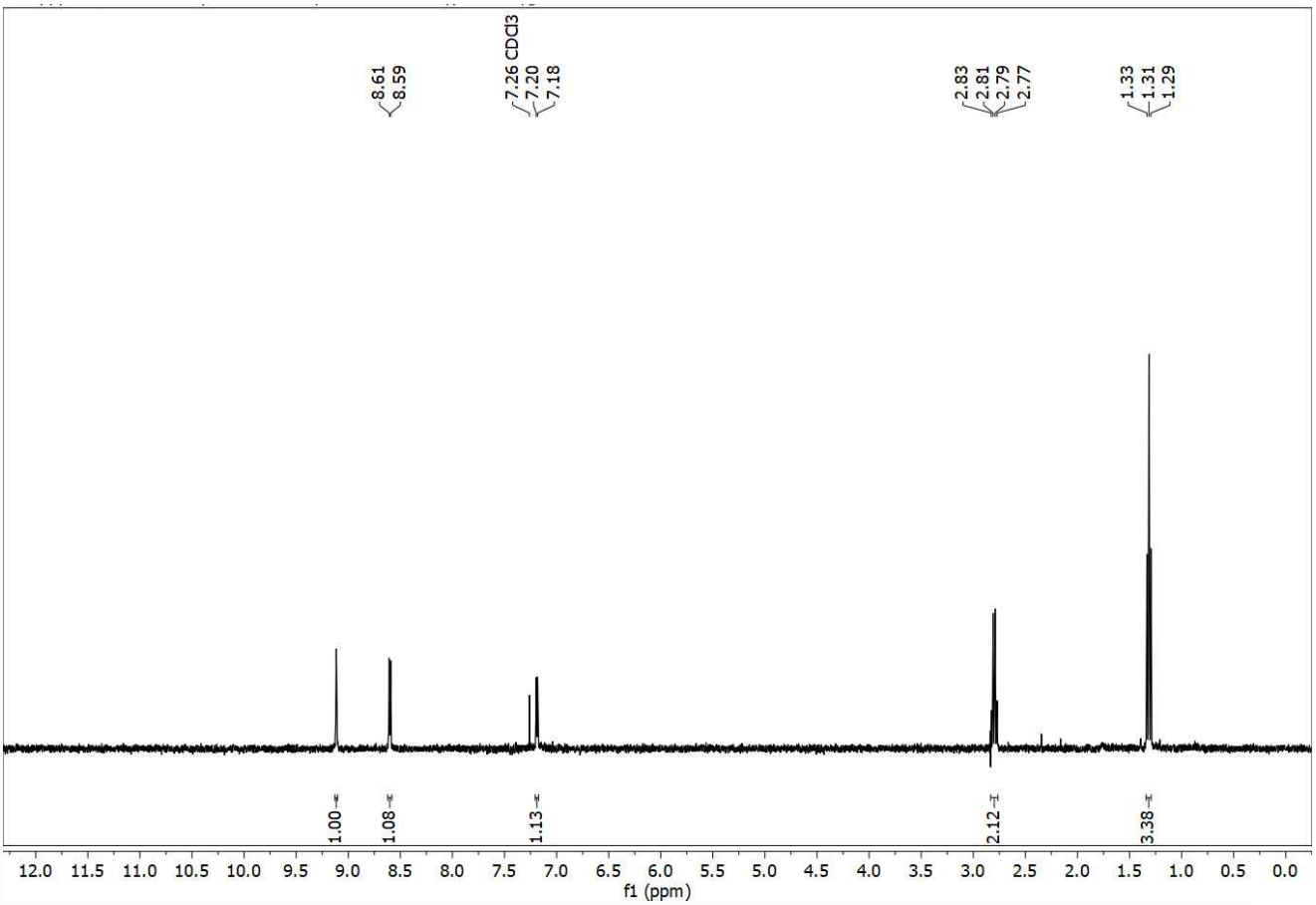
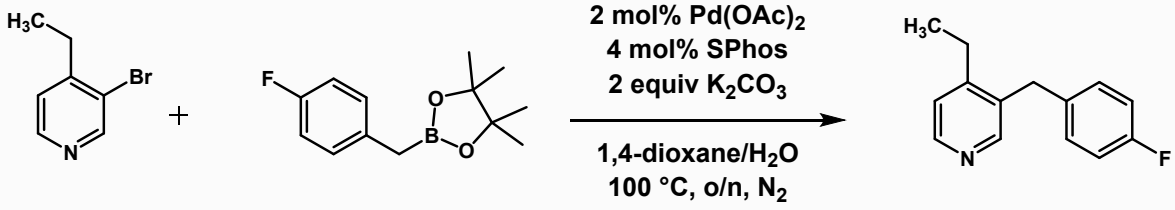


Figure S18: ^{1}H NMR of 4-Ethylpyrimidine



4-ethyl-3-(4-fluorobenzyl)pyridine [10] To a 40 mL vial equipped with a stir bar was added 3-bromo-4-methylpyridine (1.34 g, 10.16 mmol, 1.2 equiv), 2-(4-fluorobenzyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.0 mg, 8.47 mmol, 1.0 equiv), K_2CO_3 (2.34 mg, 16.94 mmol, 2.0 equiv), $Pd(OAc)_2$ (37.9 mg, 0.169 mmol, 2 mol%) and SPhos (138.0 mg, 0.33 mmol, 4 mol%), followed by 1,4-dioxane (12.0 mL)

and H_2O (5.0 mL). The vial was purged with nitrogen flow for 1 min and sealed, which was heated with stirring at 100 °C overnight. The reaction mixture was then cooled to room temperature, dried over Na_2SO_4, and filtered through a pad of celite and concentrated. The residue was subjected to silica gel chromatography (2:1 hexane: EtOAc) to afford 0.50 g (2.32 mmol, 24 % yield) of pale-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, J = 5.0 Hz, 1H), 8.34 (s, 1H), 7.13 (d, J = 5.6 Hz, 1H), 7.09 – 7.03 (m, 2H), 7.00 – 6.92 (m, 2H), 3.98 (s, 2H), 2.55 (q, J = 7.6 Hz, 2H), 1.12 (t, J = 7.6 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 161.4 (d, J = 245 Hz), 151.2, 150.9, 148.4, 135.3 (d, J = 3.0 Hz), 133.7, 129.8 (d, J = 7.6 Hz), 123.2, 115.3 (d, J = 21.1 Hz), 35.4, 24.9, 13.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ -116.86. HRMS calculated for $C_{14}H_{14}FN$, [M+H] is 216.1189, observed 216.1190.

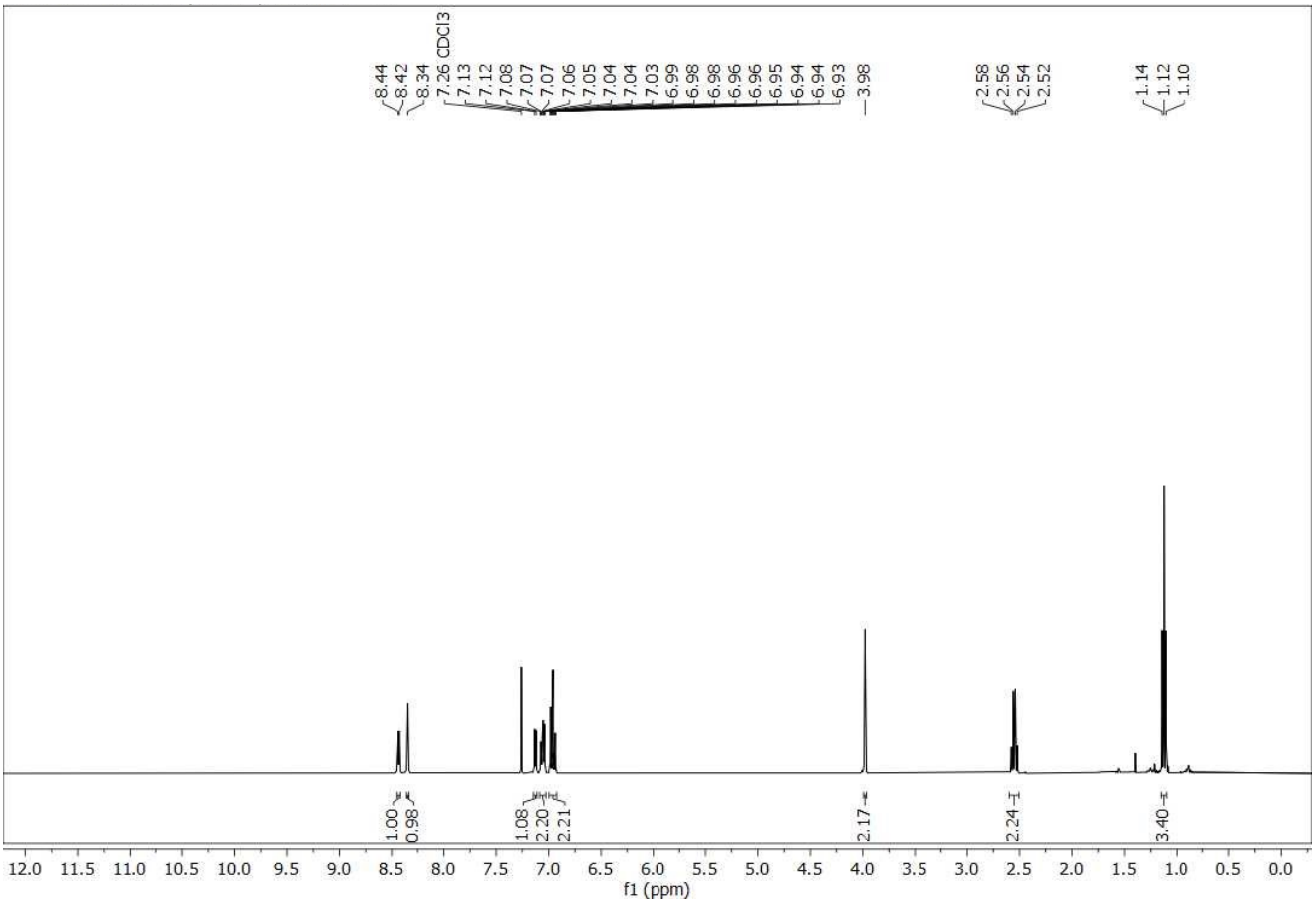


Figure S19: ^{1}H NMR of 4-ethyl-3-(4-fluorobenzyl)pyridine

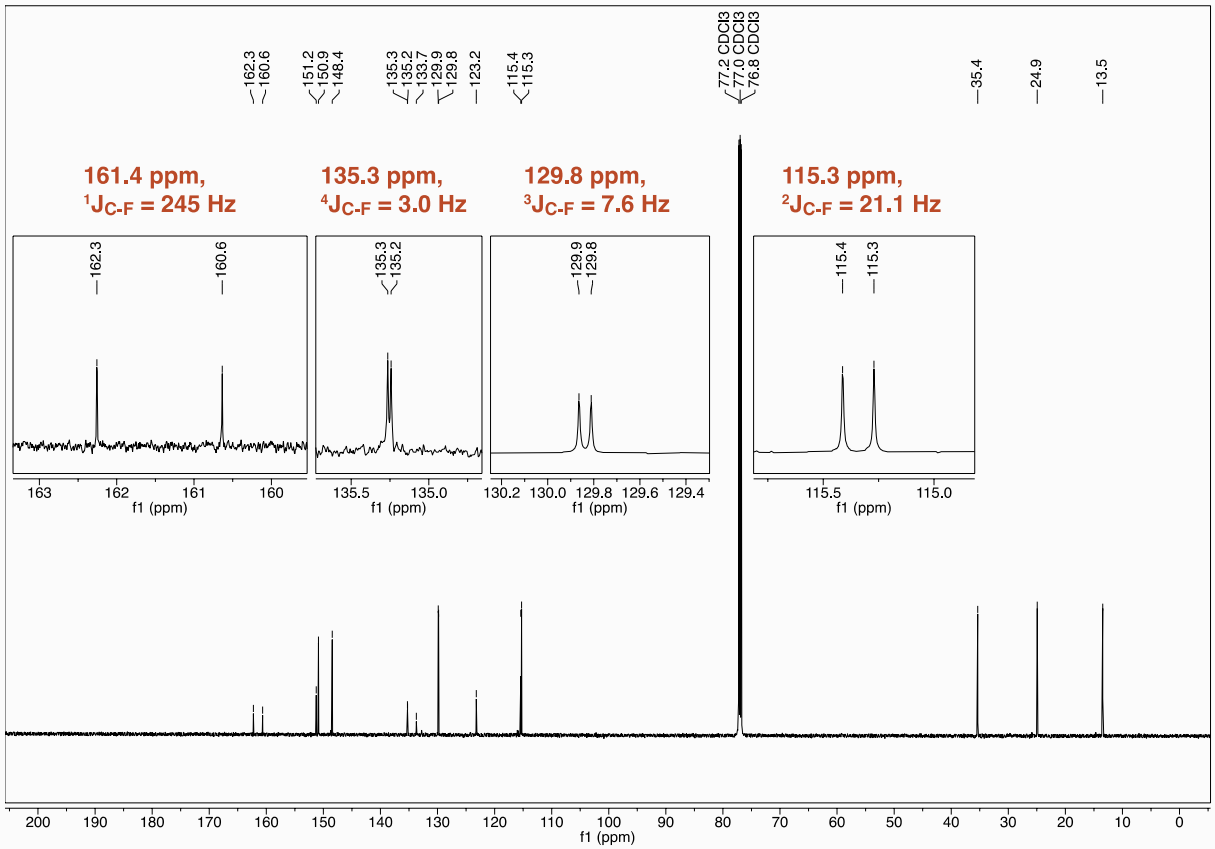


Figure S20: ^{13}C NMR of 4-ethyl-3-(4-fluorobenzyl)pyridine

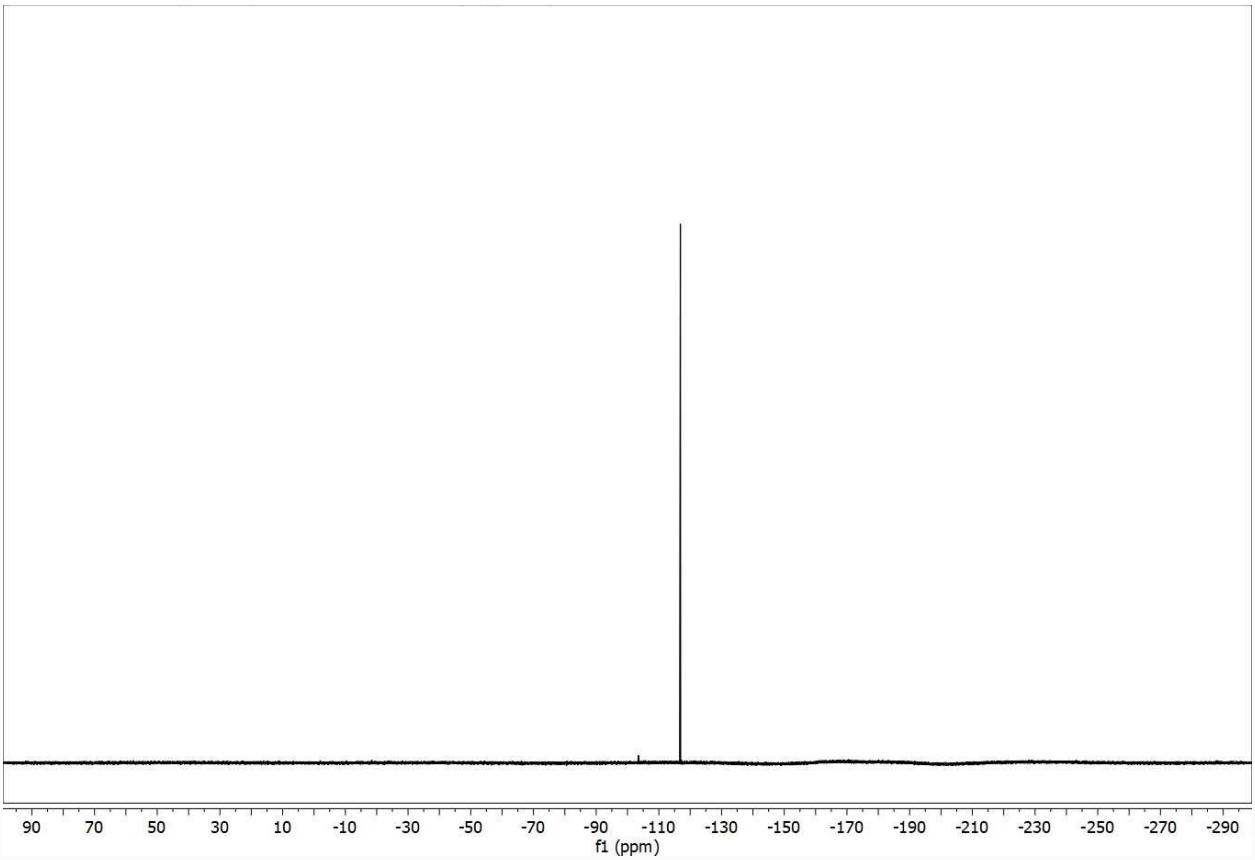
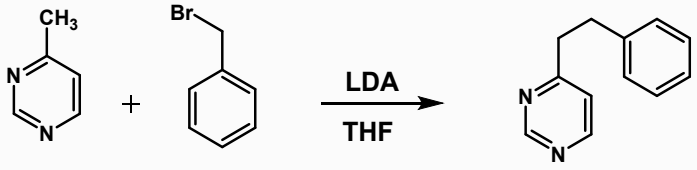


Figure S21: ^{19}F NMR of 4-ethyl-3-(4-fluorobenzyl)pyridine



4-phenethylpyrimidine [12,13]In an oven-dried round-bottom flask, diisopropylamine (3.60 mL, 25.5 mmol) were dissolved in anhydrous THF (27 mL), and the resulting solution cooled to -78°C under N_2 (1.6 M in hexanes) of an *n*-butyllithium solution (16 mL, 23.37 mmol) were added slowly, and the reaction was warmed to room temperature and stirred for 30 minutes at room temperature before being re-cooled to -78 °C. 4-methylpyridine (2.0 g, 21.25 mmol) was added and stirred a further 30 minutes at -78 °C, upon which (2.52 mL, 21.25 mmol) (bromomethyl)benzene were added. The reaction was again warmed to room temperature, quenched with 13 mL H_2O, and diluted with ethyl acetate. 1M HCl was added to pH 7–8, and the organic phase was thrice extracted with DCM. After drying over magnesium sulfate and removing volatiles with a rotary evaporator, the residue was subjected to silica gel chromatography (2:1 hexane: EtOAc) to yield 1.93g (10.47 mmol, 49%) yellow oil. ^{1}H NMR was consistent with those previously reported.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.14 (s, 1H), 8.54 (d, *J* = 5.2 Hz, 1H), 7.29 – 7.23 (m, 2H), 7.21 – 7.14 (m, 3H), 7.05 (dd, *J* = 5.2, 1.4 Hz, 1H), 3.06 (s, 4H).

Ref: ($CDCl_3$) δ 9.16 (s, 1H), 8.56 (d, *J* = 5.2 Hz, 1H), 7.29 (d, *J* = 6.8 Hz, 2H), 7.22-7.14 (m, 3H), 7.08 (d, *J* = 6.8 Hz, 1H), 3.07 (s, 4H).

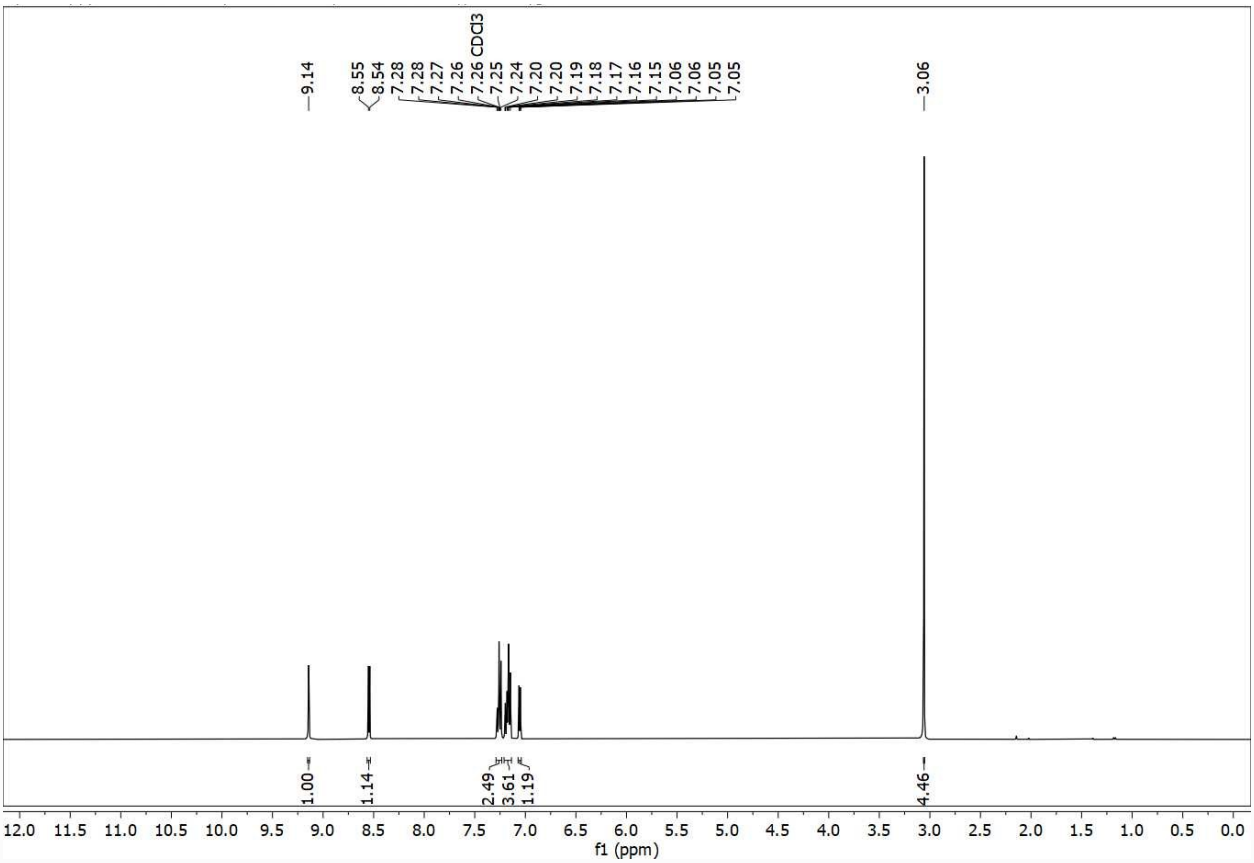
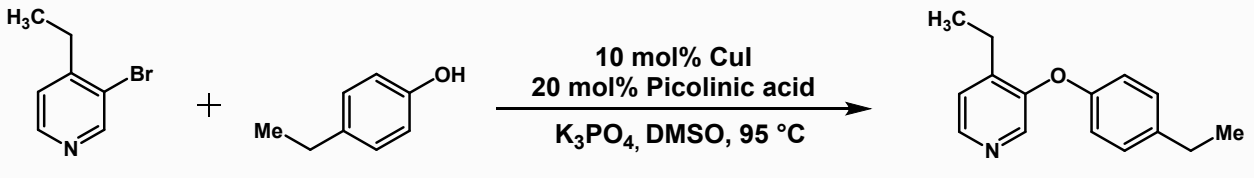


Figure S22: ^{1}H NMR of 4-phenethylpyrimidine



4-ethyl-3-(4-ethylphenoxy)pyridine [14]To an oven dried round bottomed flask equipped with stir-bar was added CuI (65 mg, 0.675 mmol), picolinic acid (170 mg, 1.35 mmol), K_3PO_4 (2.86 g, 13.5 mmol), and

4-ethylphenol (1 g, 8.1 mmol). The vial is sealed with a septum and then evacuated and backfilled with nitrogen 3x. DMSO (15 mL) was then added under counterflow of N_2, followed by 3-bromo-4-ethylpyridine (1.25 g, 6.75 mmol) weighed out in a syringe. The reaction was then heated to 95 °C for 72 hours. The reaction was then cooled to room temperature, at which point ethyl-acetate (~50 mL) and H_2O (~ 5 mL) were added to the reaction and stirred. The organic layer was then removed, and the aqueous layer was extracted with EtOAc two more times. The combined organics were dried with $MgSO_4$, filtered, and concentrated in-vacuo. Purified by silica gel chromatography (15 % ethyl acetate in hexanes) to give 0.35 g of yellow oil (1.53 mmol, 23%). Spectra was consistent with those previously reported.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 4.9 Hz, 1H), 8.17 (s, 1H), 7.21 (d, *J* = 5.5 Hz, 0H), 7.18 – 7.10 (m, 2H), 6.90 – 6.81 (m, 2H), 2.68 (q, *J* = 7.6 Hz, 2H), 2.63 (q, *J* = 7.6 Hz, 2H), 1.23 (t, *J* = 7.6 Hz, 6H).

Ref: ($CDCl_3$) δ 8.33 (d, J = 4.9 Hz, 1H), 8.19 (s, 1H), 7.24 (dt, J = 4.9, 0.7 Hz, 1H), 7.22 – 7.15 (m, 2H), 6.95 – 6.84 (m, 2H), 2.77 – 2.61 (m, 4H), 1.26 (t, J = 7.6 Hz, 6H).

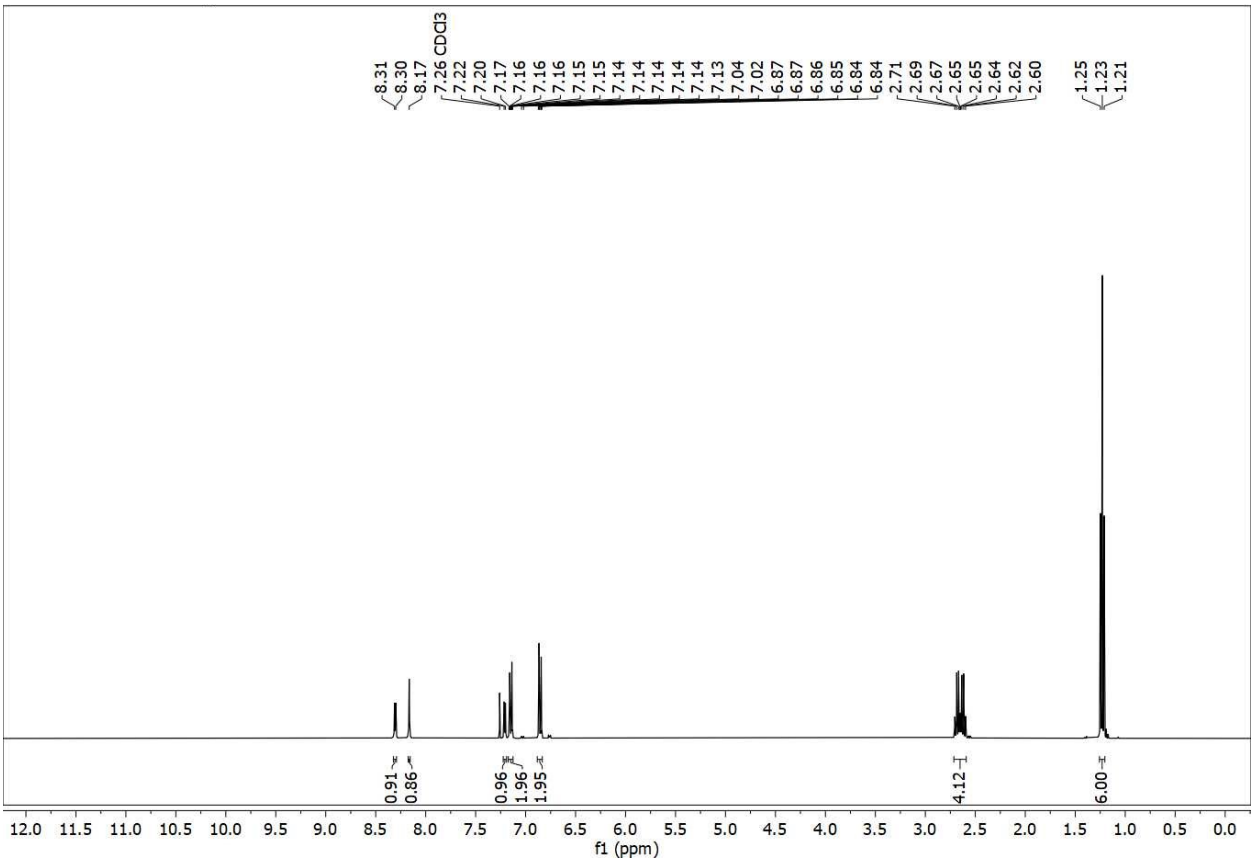
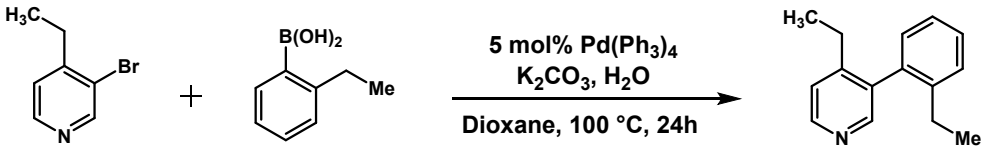


Figure S23: ^{1}H NMR of 4-ethyl-3-(4-ethylphenoxy)pyridine



4-ethyl-3-(2-ethylphenyl)pyridine[15] To a flask equipped with a stir bar was added 2-ethylbornic acid (450 mg, 3 mmol), K_2CO_3 (933 mg, 6.75 mmol), and Pd (PPh_3)$_4$ (145 mg, 0.125 mmol) were added. The flask was sealed with a septum and evacuated and backfilled with Nitrogen 3x. Dioxane (20 mL) followed by 3-bromo-4-ethylpyridine (465 mg, 2.5 mmol) and degassed H_2O (5 mL) were added via syringe with a contraflow of Nitrogen. Reaction was heated at 100 °C for 24 hours, at which point the reaction was cooled to room temperature and diluted with H_2O and poured into a separatory funnel. The organic layer was separated and the aqueous was extracted with EtOAc. The organics were combined and dried with $MgSO_4$, filtered, and concentrated in vacuo. Purified by silica gel chromatography (25% EtOAc in Hexanes) to give 350 mg yellow oil (1.65 mmol, 66 %). Spectra was consistent with those previously reported.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, *J* = 5.2 Hz, 1H), 8.34 (s, 1H), 7.39 – 7.31 (m, 2H), 7.28 – 7.22 (m, 2H), 7.09 (dt, *J* = 7.6, 1.1 Hz, 1H), 2.46 – 2.26 (m, 4H), 1.06 (dt, *J* = 13.8, 7.6 Hz, 6H).
Ref: ($CDCl_3$) δ 8.54 (d, J = 5.1 Hz, 1H), 8.36 (s, 1H), 7.46 – 7.32 (m, 2H), 7.32 – 7.21 (m, 2H), 7.11 (dt, J = 7.5, 1.0 Hz, 1H), 2.53 – 2.25 (m, 4H), 1.09 (dt, J = 12.8, 7.6 Hz, 6H).

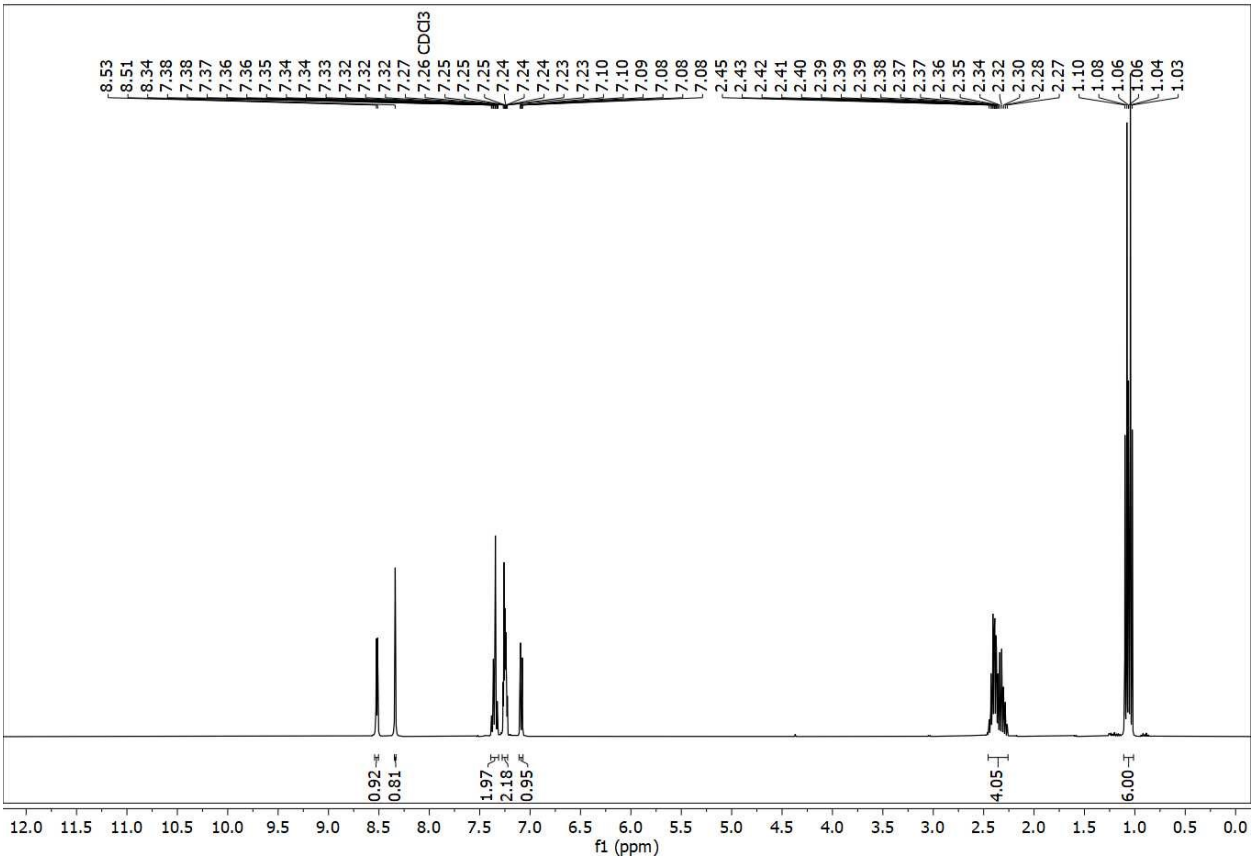
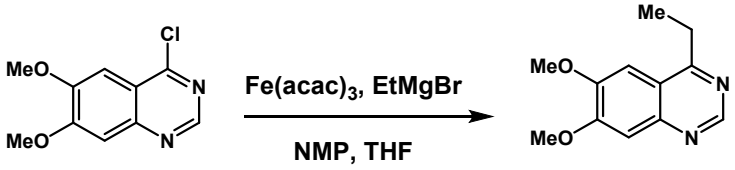


Figure S24: ^{1}H NMR of 4-ethyl-3-(2-ethylphenyl)pyridine



4-Ethyl-6,7-Dimethoxyquinazoline [8,16] A flame-dried 2-neck flask under N_2 was charged with 4-chloro-6,7-dimethoxyquinazoline (1g, 4.5 mmol), $Fe(acac)_3$ (78.6 mg, 0.23 mmol), 12 mL anhydrous THF and 1 mL anhydrous NMP. To this stirred mixture at room temperature was added dropwise EtMgBr (3M in diethyl ether, 1.8 mL, 5.3 mmol). The reaction mixture as stirred for 1 hour, then quenched with H_2O. The resulting mixture was extracted with EtOAc, and the combined organic layers were washed once with aqueous NaCl, once with 1M aqueous sodium ascorbate, and four times with H_2O. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography over silica gel (2:1 Hexane: EtOAc) afforded 728 mg (3.6 mmol, 80%) of a white solid. ^{1}H NMR consistent with literature.

Ref: ^{1}H NMR ($CDCl_3$) δ = 9.04 (s, 1H), 7.30 (s, 1H), 7.23 (s, 1H), 4.03 (d, J = 2.2 Hz, 6H), 3.20 (q, J = 7.6 Hz, 2H), 1.44 (t, J = 7.5 Hz, 3H)

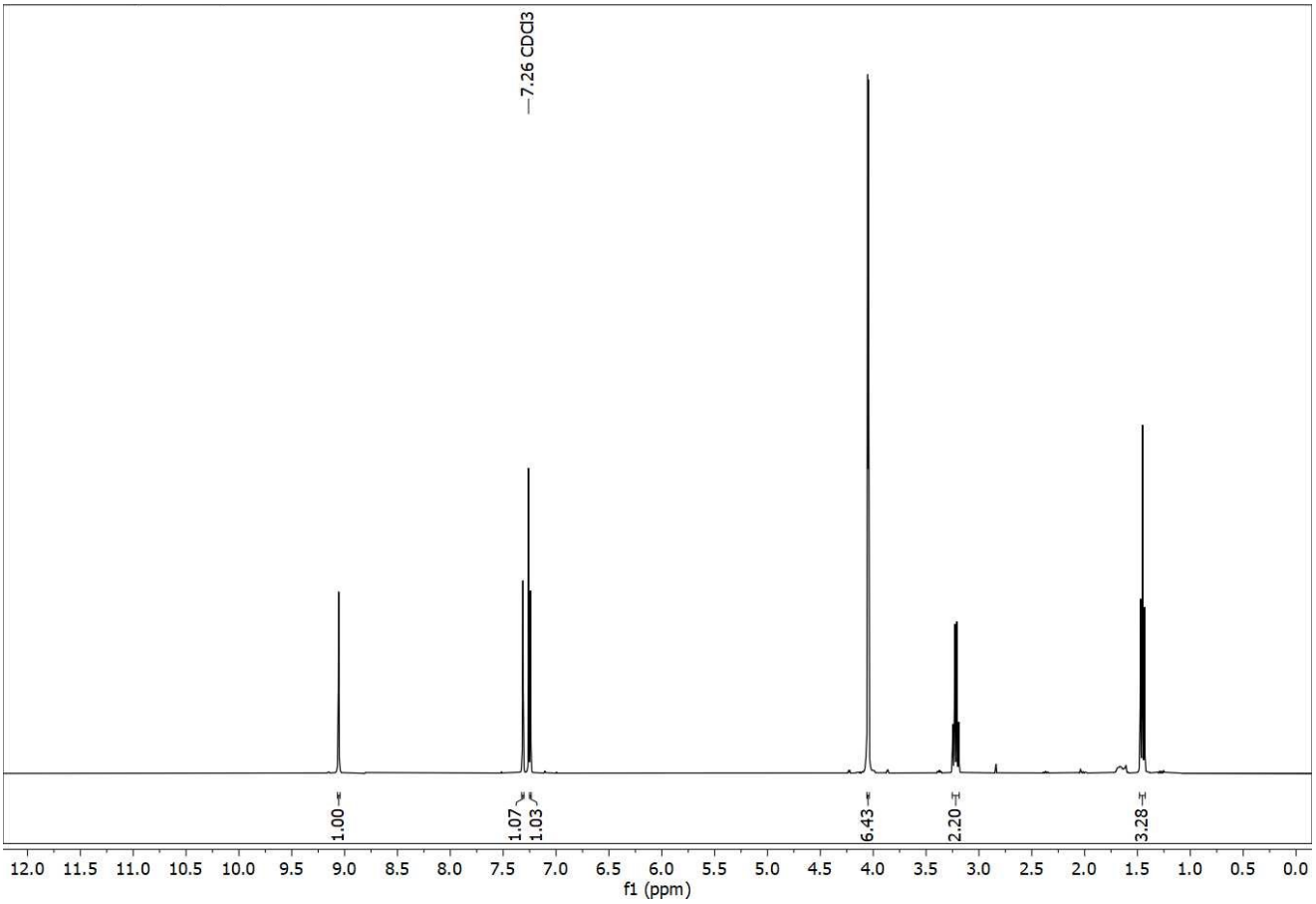
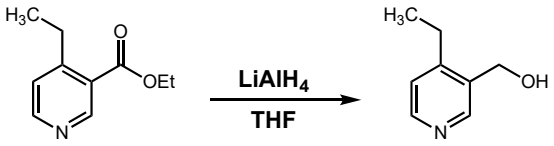


Figure S25: ^{1}H NMR of 4-ethyl-3-(2-ethylphenyl)pyridine



4-ethyl-3-(hydroxymethyl)pyridine Ethyl 4-ethylnicotinate (970 mg, 5.41 mmol) was charged in a 50 mL Schlenk flask, which was evacuated and backfilled with nitrogen. Anhydrous THF (14 mL) was added and the solution was cooled to 0 ºC using an ice-water bath. Lithium aluminum hydride (210 mg, 5.53 mmol) was weighed into an oven-dried 8 mL scintillation vial inside of a nitrogen-filled glovebox, and was then added to the reaction flask portion-wise against a flow of nitrogen. Upon completion of the addition, the ice bath was removed and the reaction was allowed to stir at room temperature for 3 hours.

Next, the reaction solution was cooled back down to 0 ºC and diluted with diethyl ether (ca. 20 mL). It was quenched by the addition of water (210 µL), aqueous 15% sodium hydroxide solution (210 µL), and additional water (630 µL). The reaction was allowed to warm to room temperature with stirring over 15

minutes, and was then dried using $MgSO_4$, and filtered through celite with the aid of additional diethyl ether. The product was purified by silica gel chromatography using a gradient of 5% to 10% methanol in ethyl acetate, concentrated by rotary evaporation, and additionally concentrated on high vacuum (<0.2 torr) for one hour to yield the desired product (401 mg, 2.92 mmol, 54%).

For other users looking to further optimize this protocol, there is one significant note of caution. TLC analysis after filtration suggested that there was still starting material present in the reaction, so we made further attempts using higher equivalencies of $LiAlH_4$, longer reaction times, or both. We were surprised to see starting material apparently persisting in the reaction, even under more forcing conditions. In one of these optimization reactions we decided to recover the unreacted starting material. To our surprise, this recovered material was *not* the starting material, but instead was 4-ethyl-3-methypyridine: these reducing conditions can completely deoxygenate the starting material. This by-product has an identical R_f to the starting material, so monitoring the reaction by TLC must be done with caution.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.49 – 8.39 (m, 2H), 7.14 (d, *J* = 5.0 Hz, 1H), 4.74 (d, *J* = 1.2 Hz, 2H), 2.75 (q, *J* = 7.6 Hz, 2H), 1.26 (t, *J* = 7.6, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) 151.7, 149.4, 149.2, 133.8, 123.2, 60.8, 24.5, 14.0. HRMS calculated for $C_8H_{11}NO$ [M+H]+ was 138.0913; found 138.0915.

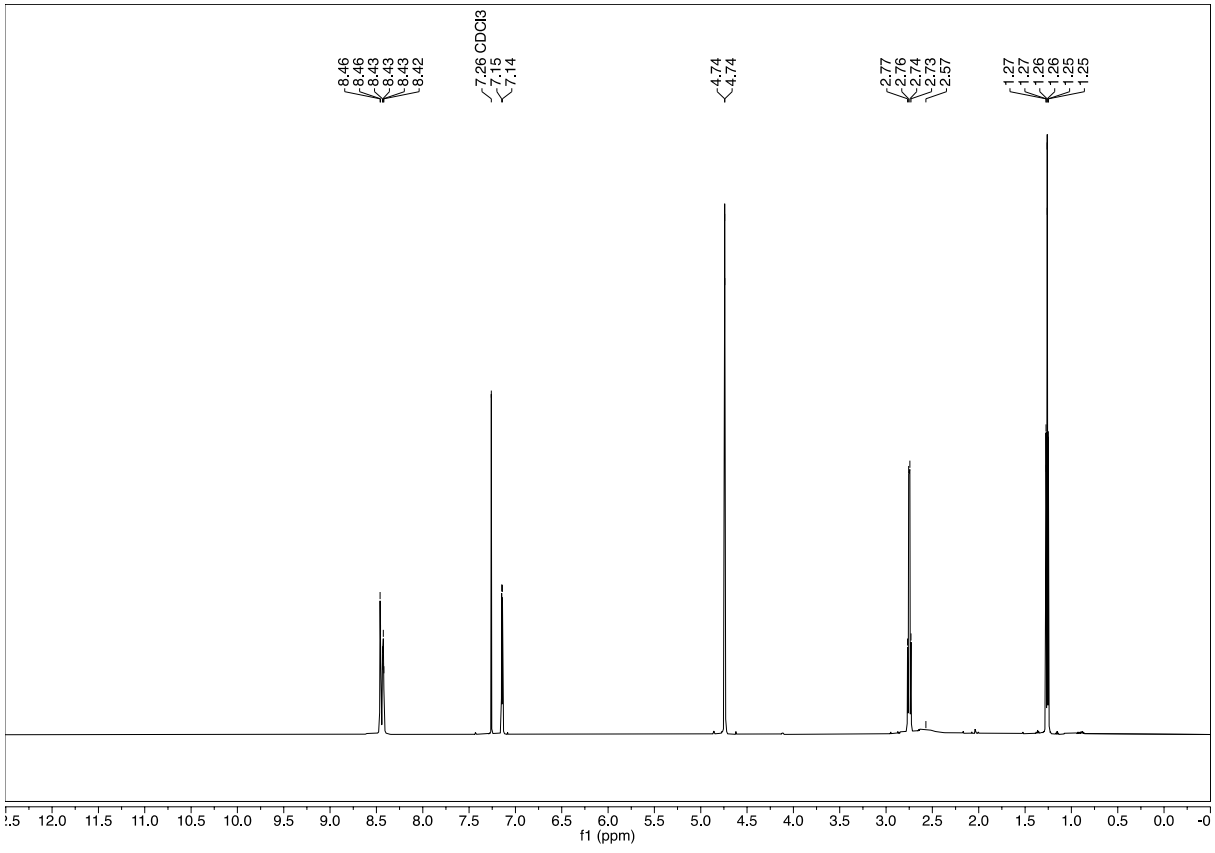


Figure S26: ^{1}H NMR of 4-ethyl-3-(hydroxymethyl)pyridine

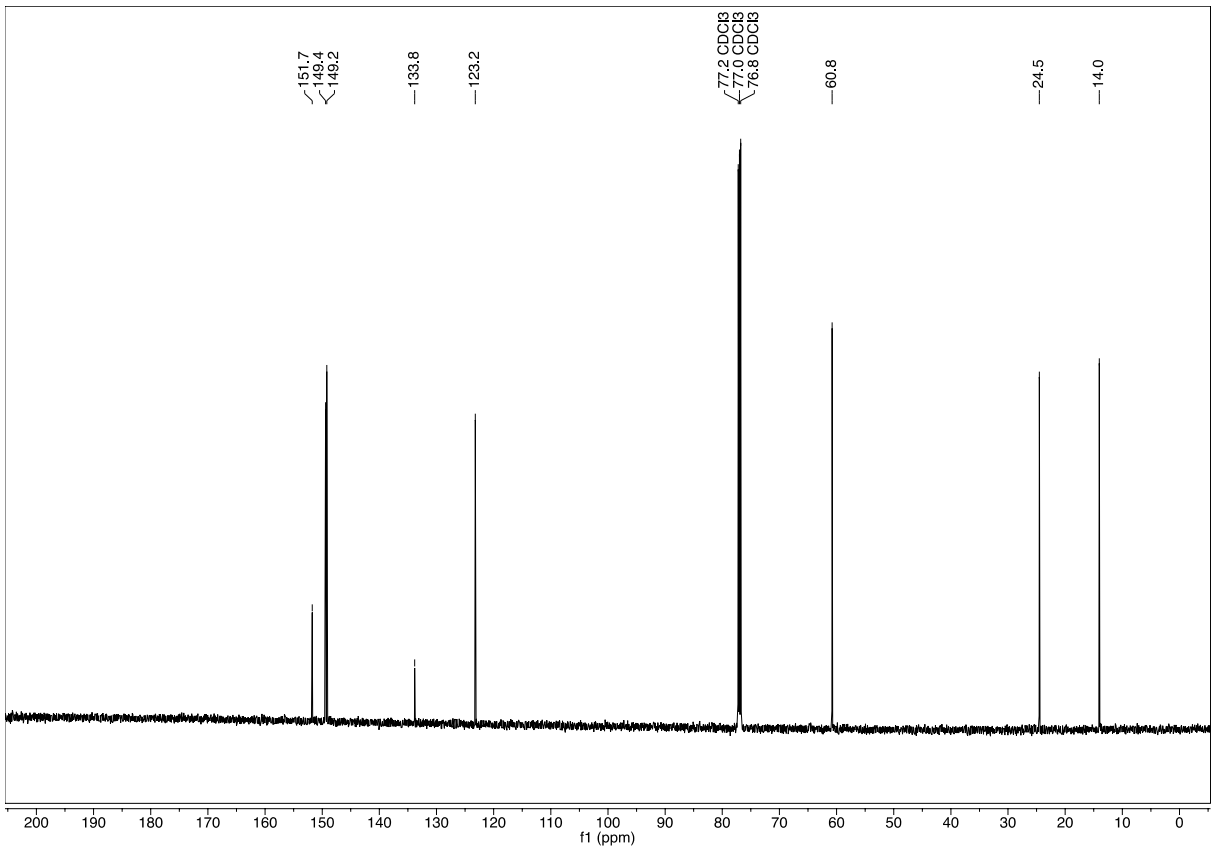
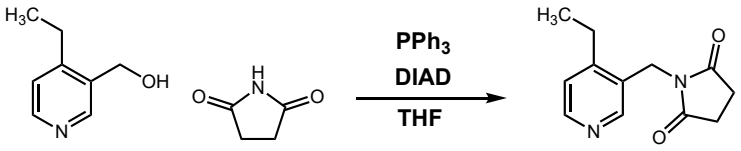


Figure S27: ^{13}C NMR of 4-ethyl-3-(hydroxymethyl)pyridine



4-ethyl-3-(succinimidylmethyl)pyridine Succinimide (220 mg, 2.22 mmol, 2.18 equiv.) and triphenylphosphine (315 mg, 1.20 mmol, 1.18 equiv.) were charged in a flame-dried 20 mL scintillation vial, which was fitted with a Teflon-lined septum cap and purged with flowing nitrogen. 4-ethyl-3-(hydroxymethyl)pyridine (140 mg, 1.02 mmol) was added to the vial via microliter syringe, followed by anhydrous THF (4 mL, 0.25 M concentration of substrate) and diisopropyl azodicarboxylate (240 µL, 1.22 mmol, 1.20 equiv.). The reaction was left to stir overnight. In the morning, the reaction mixture was directly concentrated onto silica gel, and the desired compound was obtained after column chromatography using a gradient elution from 4:1 hexanes:ethyl acetate to pure ethyl acetate, and concentration in vacuo (168 mg, 0.77 mmol, 75% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.47 (s, 1H), 8.42 (d, J = 5.1 Hz, 1H), 7.11 (d, J = 5.0 Hz, 1H), 4.72 (s, 2H), 2.82 (q, J = 7.6 Hz, 2H), 2.75 (s, 4H), 1.25 (t, J = 7.6 Hz, 4H). ^{13}C NMR (151

MHz, $CDCl_3$) δ 176.7, 151.2, 150.3, 150.3, 149.3, 129.1, 123.1, 37.1, 28.2, 24.8, 14.1. HRMS calculated for $C_{12}H_{14}N_2O_2$ $[M+H]^+$ 219.1128; found 219.1128.

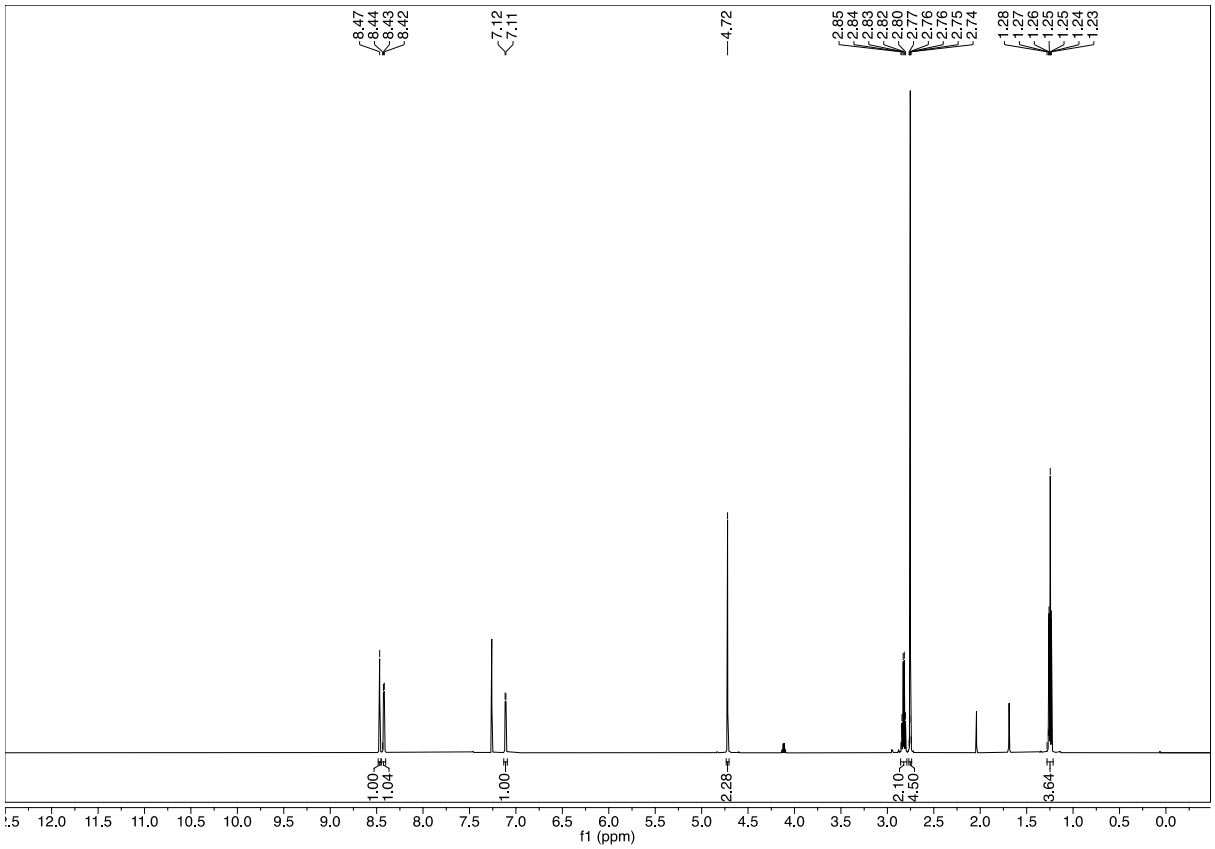


Figure S28: ^1H NMR 4-ethyl-3-(succinimidylmethyl)pyridine

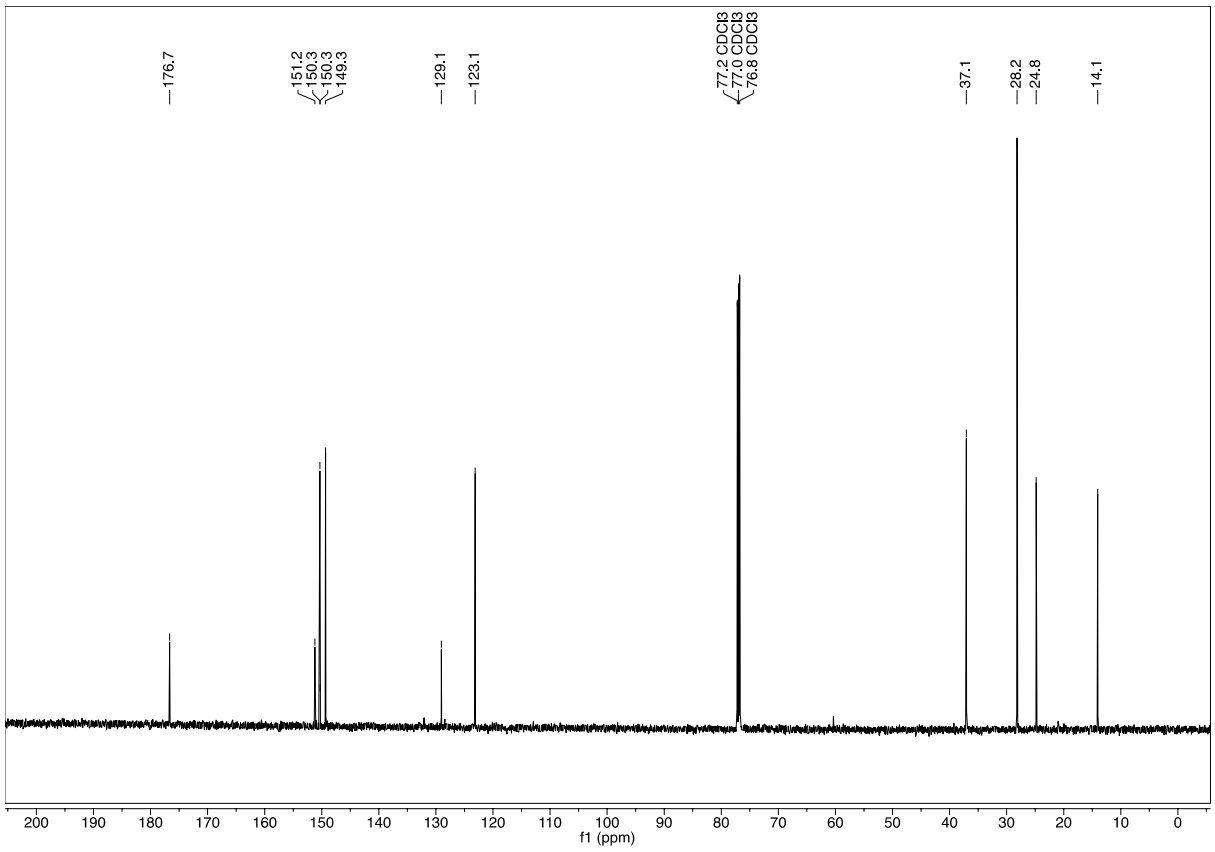
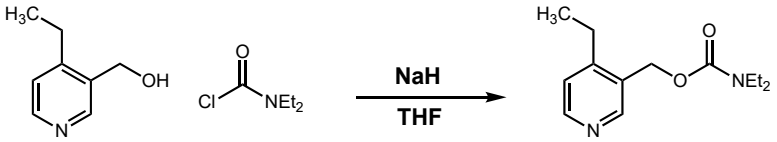


Figure S29: ^{13}C NMR 4-ethyl-3-(succinimidylmethyl)pyridine



4-ethyl-3-(hydroxymethyl)pyridyl *N*,*N*-diethylcarbamate Sodium hydride (60 wt% in mineral oil, 63 mg, 1.6 mmol, 1.05 equiv.) was weighed directly into an oven-dried 20 mL scintillation vial, which was then purged with flowing nitrogen. Anhydrous THF was added (7.5 mL, 0.2 M substrate concentration), followed by 4-ethyl-3-(hydroxymethyl)pyridine (206 mg, 1.50 mmol). Deprotonation was allowed to proceed for 15 minutes at room temperature. Next, *N*,*N*-diethylcarbamyl chloride (200 µL, 1.58 mmol, 1.05 equiv.) was added via microliter syringe, and the reaction was left to stir at room temperature with active monitoring performed by TLC. Upon complete consumption of the starting material, the reaction mixture was directly concentrated onto silica gel. The desired product (279 mg, 1.18 mmol, 79% yield) was isolated via silica gel chromatography using a gradient elution of 50% to 100% ethyl acetate (with the balance as hexanes), followed by concentration *in vacuo*. Rotational isomerism about the diethyl carbamate results in

broadening of the *N*-ethyl signals in the ^{1}H NMR, and inequivalent carbon atoms for the two ethyl group sidechains. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.54 (s, 1H), 8.48 (d, J = 5.1 Hz, 1H), 7.15 (d, J = 5.1, 1H), 5.17 (s, 2H), 3.40-3.20 (br, 4H), 2.71 (q, J = 7.6 Hz, 2H), 1.25 (t, J = 7.6 Hz, 3H), 1.18-1.05 (br, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 155.4, 151.6, 150.1, 150.1, 150.1, 149.7, 149.7, 130.2, 123.1, 123.0, 62.3, 41.9, 41.2, 24.7, 24.6, 14.1, 14.0, 13.4. HRMS calculated for $C_{13}H_{20}N_2O_2$ $[M+H]^+$ 237.1598; found 237.1602.

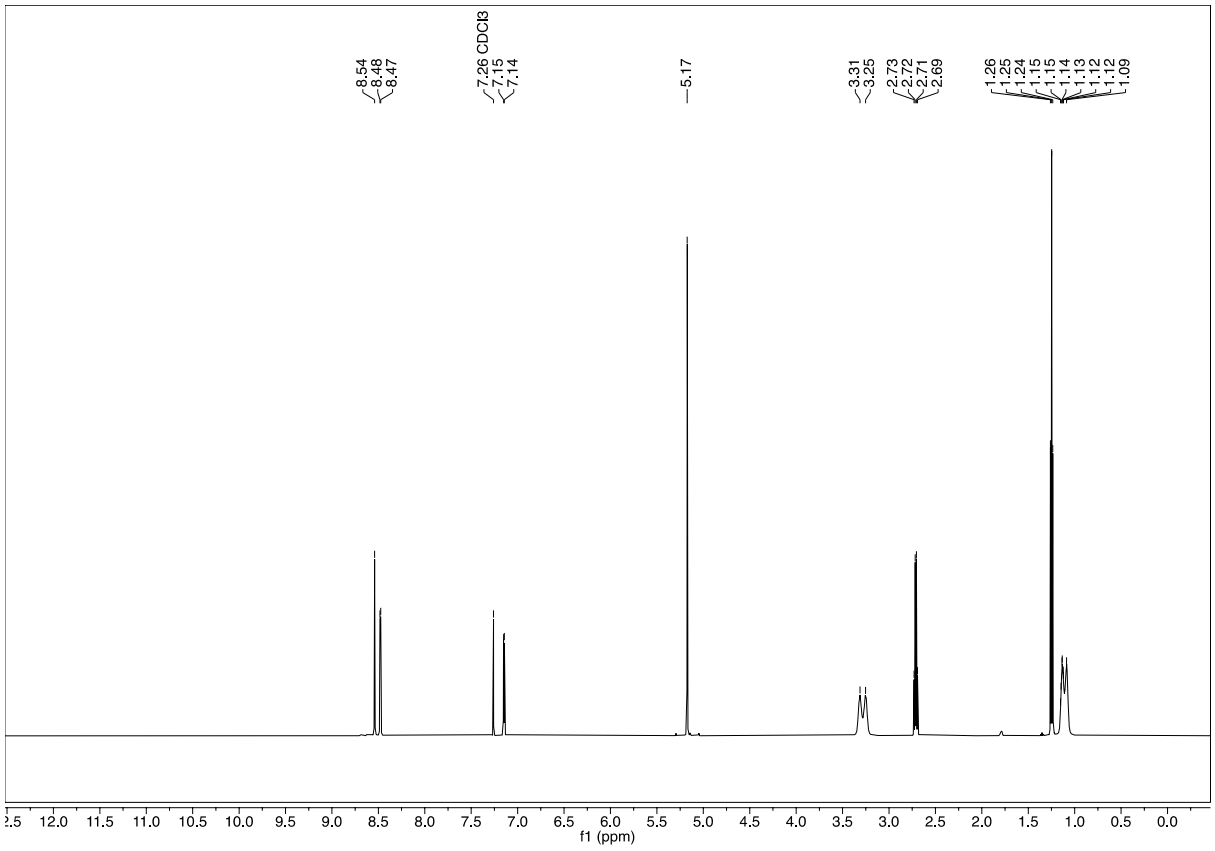


Figure S30: ^{1}H NMR of 4-ethyl-3-(hydroxymethyl)pyridyl *N*,*N*-diethylcarbamate

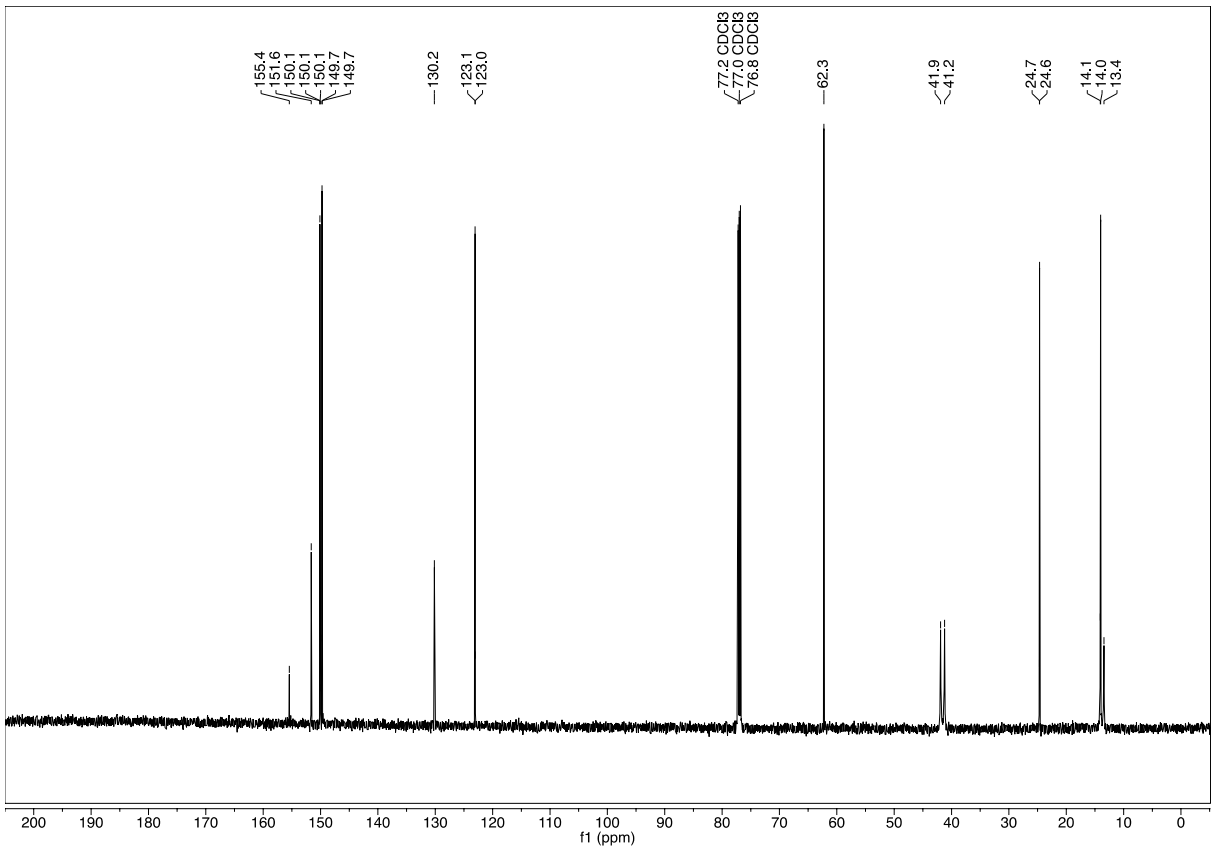
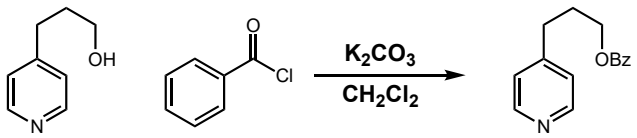


Figure S31: ^{13}C NMR of 4-ethyl-3-(hydroxymethyl)pyridyl *N*,*N*-diethylcarbamate



4-(3-benzoylpropyl)pyridine 4-pyridinepropanol (620 mg, 4.52 mmol) and potassium carbonate (803 mg, 5.81 mmol, 1.29 equiv.) were weighed directly into a 100 mL flame-dried round bottomed flask, which was then purged with flowing nitrogen. Anhydrous dichloromethane (24 mL, 0.19 M substrate concentration) was added at room temperature, followed by benzoyl chloride (640 µL, 5.51 mmol, 1.22 equiv.). The reaction was allowed to stir at room temperature overnight, and had transformed into a milky white solution. The organic mixture was thrice extracted with 1N HCl (aq.), and these aqueous extractions were washed once with ethyl acetate to remove any non-pyridine organic molecules. The acidic solution was neutralized by the portion-wise addition of solid sodium carbonate until pH > 8. The aqueous mixture that resulted was extracted thrice with ethyl acetate, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The desired product (868 mg, 3.60 mmol, 80% yield) was obtained after column chromatography on silica gel using 1:1 hexane:ethyl acetate eluent. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.54 – 8.48 (m, 2H), 8.04 – 7.98 (m, 2H), 7.57

(ddt, J = 7.7, 7.0, 1.3 Hz, 1H), 7.48 – 7.42 (m, 2H), 7.17 – 7.13 (m, 2H), 4.36 (t, J = 6.4 Hz, 2H), 2.79 (dd, J = 8.6, 6.8 Hz, 2H), 2.17 – 2.09 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) 166.5, 150.1, 149.9, 133.0, 130.1, 129.5, 128.4, 123.8, 63.9, 31.7, 29.2 HRMS calculated for $C_{15}H_{15}NO_2$ $[M+H]^+$ 242.1176; found 242.1180.

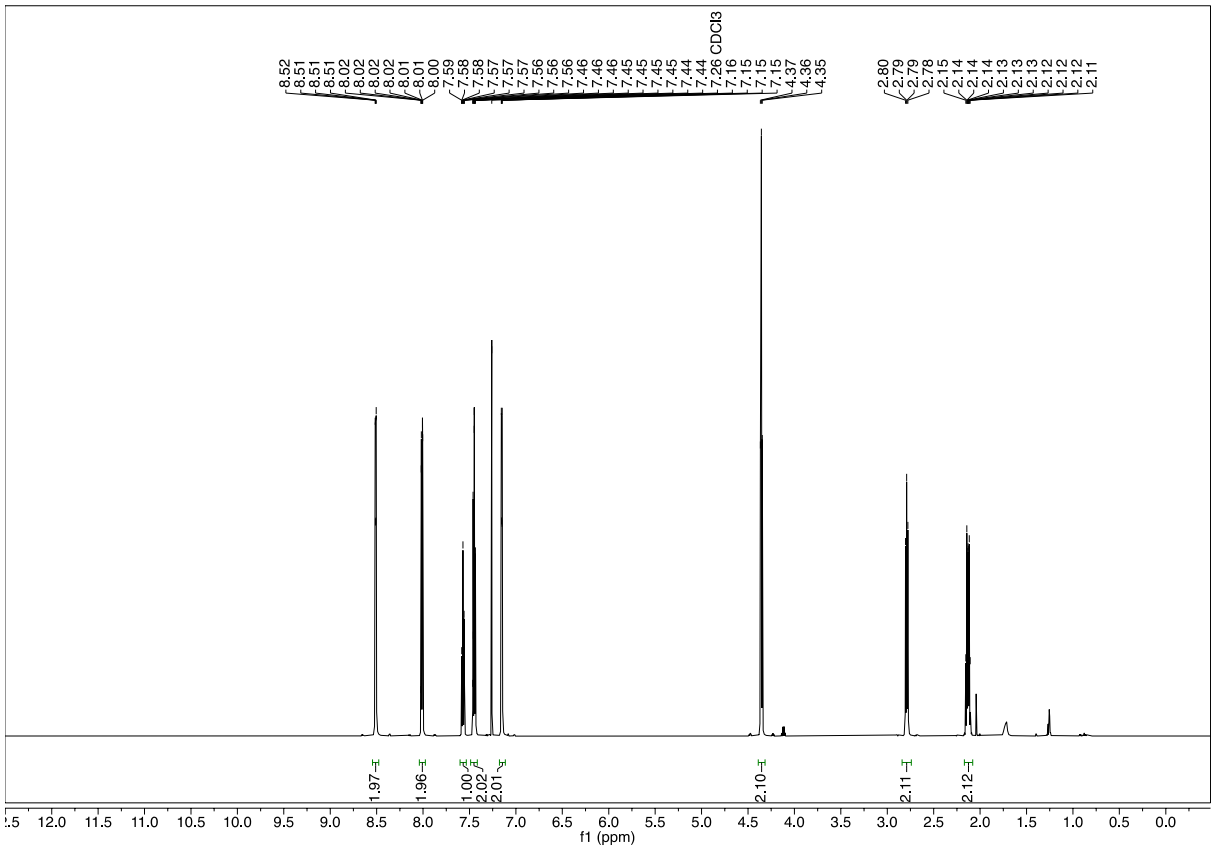


Figure S32: ^{1}H NMR of 4-(3-benzoylpropyl)pyridine

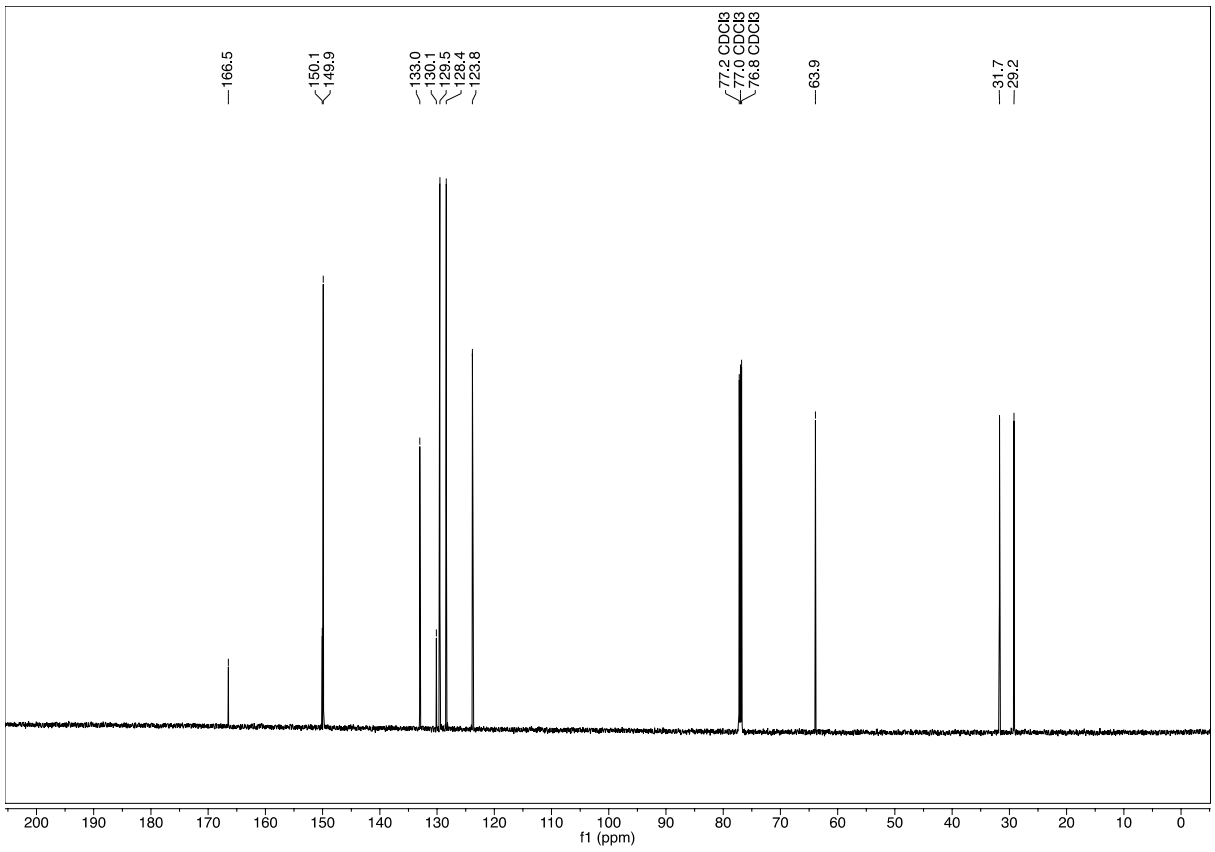
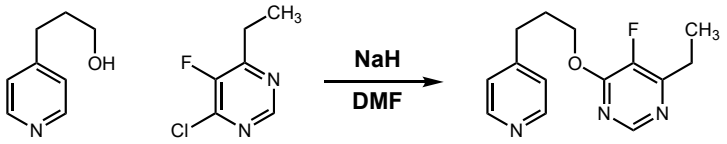


Figure S33: ^{13}C NMR of 4-(3-benzoylpropyl)pyridine



4-ethyl-5-fluoro-6-pyrimidinyl 4-pyridinepropyl ether 4-pyridinepropanol (412 mg, 3.00 mmol) was charged in an oven-dried 50 mL Schlenk flask, which was purged with flowing nitrogen. DMF (9 mL 0.33 M substrate concentration) was added, and the flask was cooled to 0 ºC using an ice-water bath. Sodium hydride (60 wt% suspension in mineral oil, 132 mg, 3.30 mmol, 1.1 equiv.) was added against flowing nitrogen, and the reactions was left to stir at 0 ºC for 20 minutes. Then, 6-chloro-4-ethyl-5-fluoropyrimidine (410 µL, 3.28 mmol, 1.09 equiv.) was added via syringe, and the reaction was left to slowly warm to room temperature overnight. In the morning, the reaction was quenched by the addition of water, which was extracted thrice with ethyl acetate. The combined organic layers were washed with water, then with brine, and finally dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The desired compound (283 mg, 1.08 mmol, 36% yield) was isolated by silica gel chromatography, using a gradient eluent from 6:1 to 2:1 hexanes:ethyl acetate. ^1H NMR (600 MHz, $CDCl_3$) δ 8.53 – 8.49 (m, 2H), 8.42 (s, 1H), 7.17 – 7.13 (m,

2H), 4.45 (t, J = 6.4 Hz, 2H), 2.86 – 2.78 (m, 4H), 2.22 – 2.13 (m, 2H), 1.29 (t, J = 7.6 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 157.8 (d, J = 10.6 Hz), 157.3 (d, J = 10.6 Hz), 152.1 (d, J = 10.6 Hz), 150.0, 149.9, 144.1 (d, J = 263 Hz), 123.8, 66.0, 31.4, 29.1, 23.9, 12.0. HRMS calculated for $C_{14}H_{16}FN_3O$ $[M+H]^+$ was 262.1350; found 262.1353.

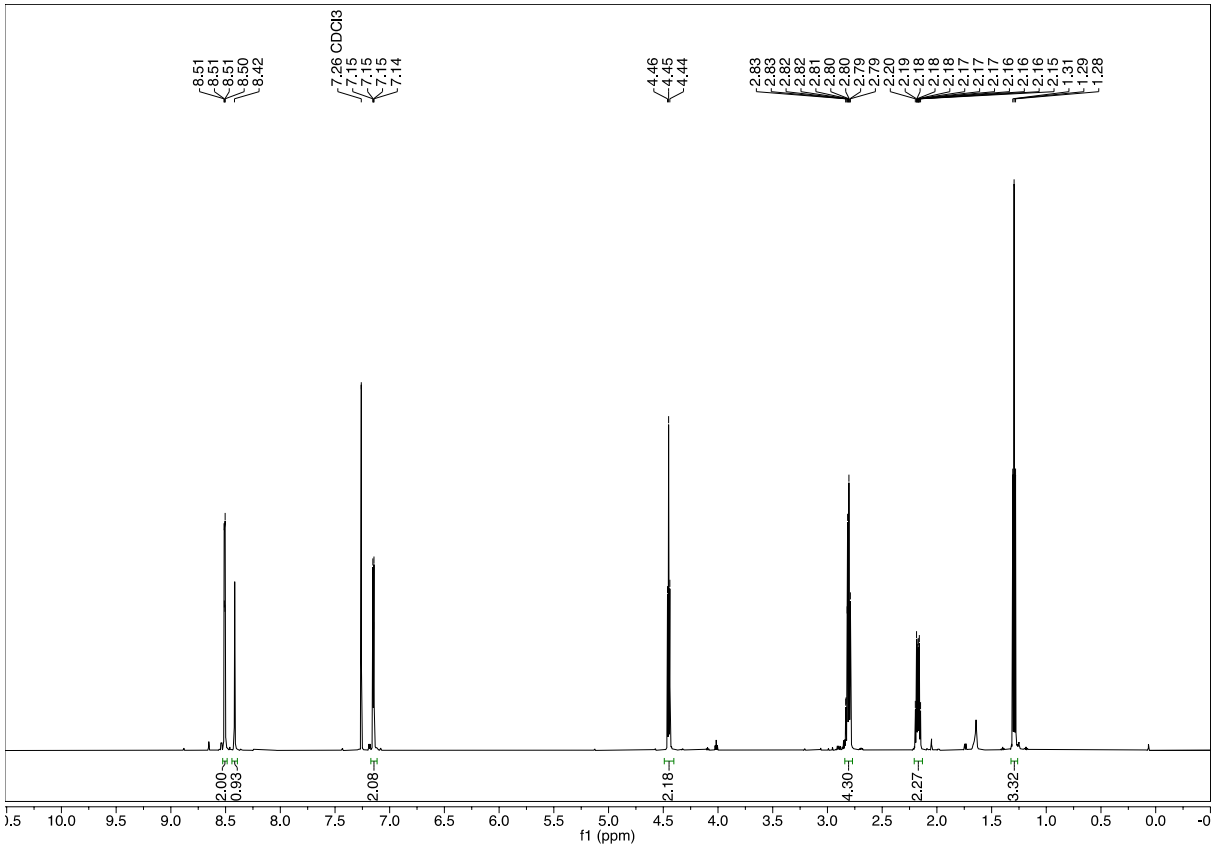


Figure S34: ^{1}H NMR of 4-ethyl-5-fluoro-6-pyrimidinyl 4-pyridinepropyl ether

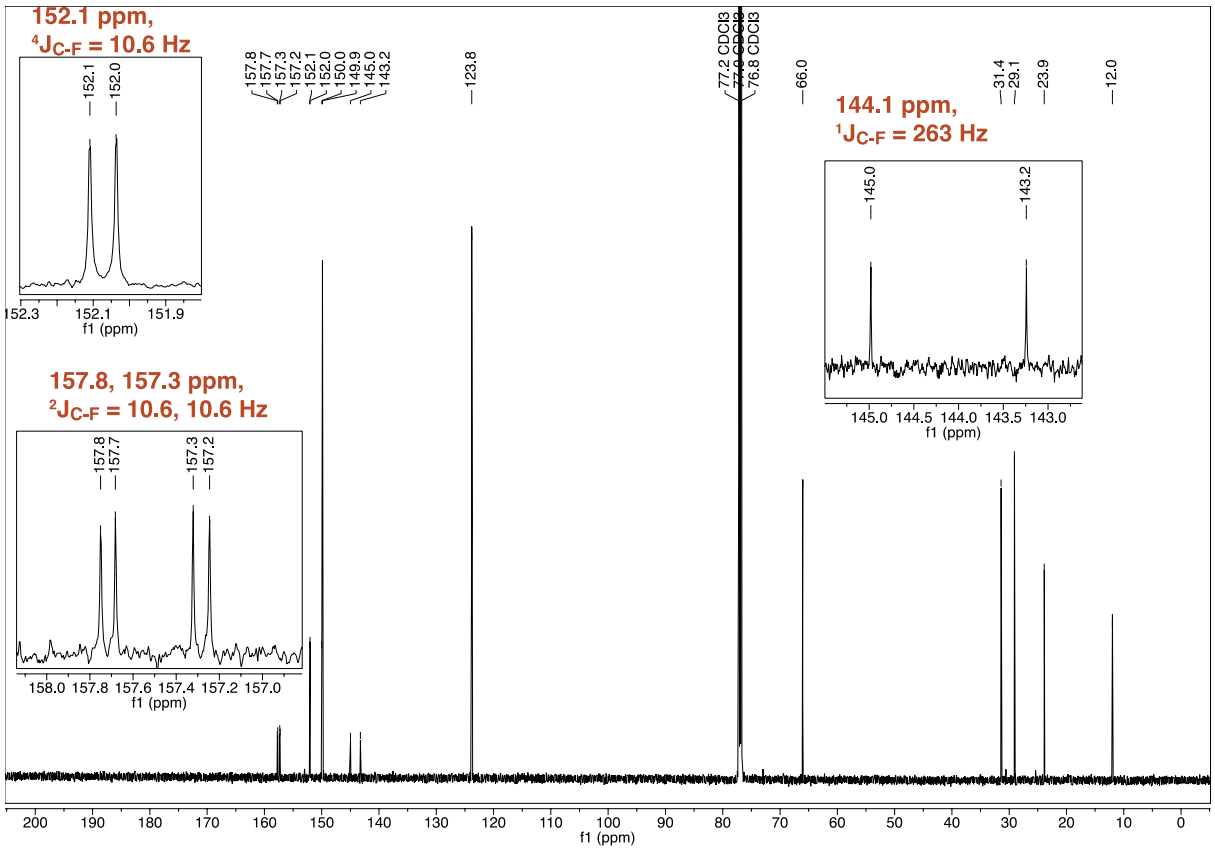
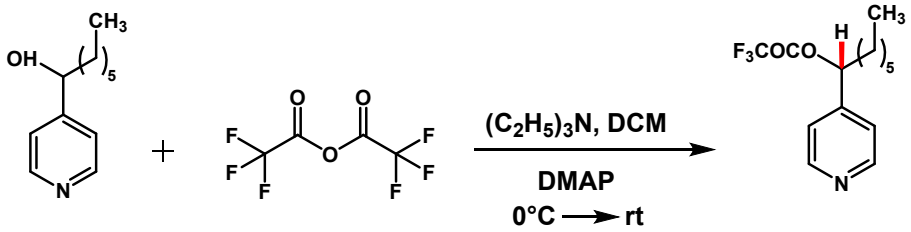


Figure S35: ^{13}C NMR of 4-ethyl-5-fluoro-6-pyrimidinyl 4-pyridinepropyl ether

Development of Reaction Conditions



1-(4-Pyridinyl)heptyl 2,2,2-trifluoroacetate [17] In an over-dried 8 mL vial with a stir bar, 1-(pyridin-4-yl) heptan-1-ol (0.15 g, 0.776 mmol) was dissolved in 1 mL DCM. Upon cooling to 0 °C, 4-Dimethylaminopyridine (94 mg, 0.776 mmol), triethylamine (157 mg, 0.726 mmol), trifluoroacetic anhydride (325 mg, 1.552 mmol) were added sequentially. The reaction mixture was gradually warmed to room temperature and was left over night. The reaction mixture was quenched with water and extracted using dichloromethane. The organic layer was washed with HCl, and brine solution followed by characterizing the crude reaction mixture using H-NMR as shown in figure 23 (below). The peak from δ =

5.91-5.85 ppm corresponds to the benzylic C-H and is used to determine the presence of the product while carrying optimization of the reaction conditions.

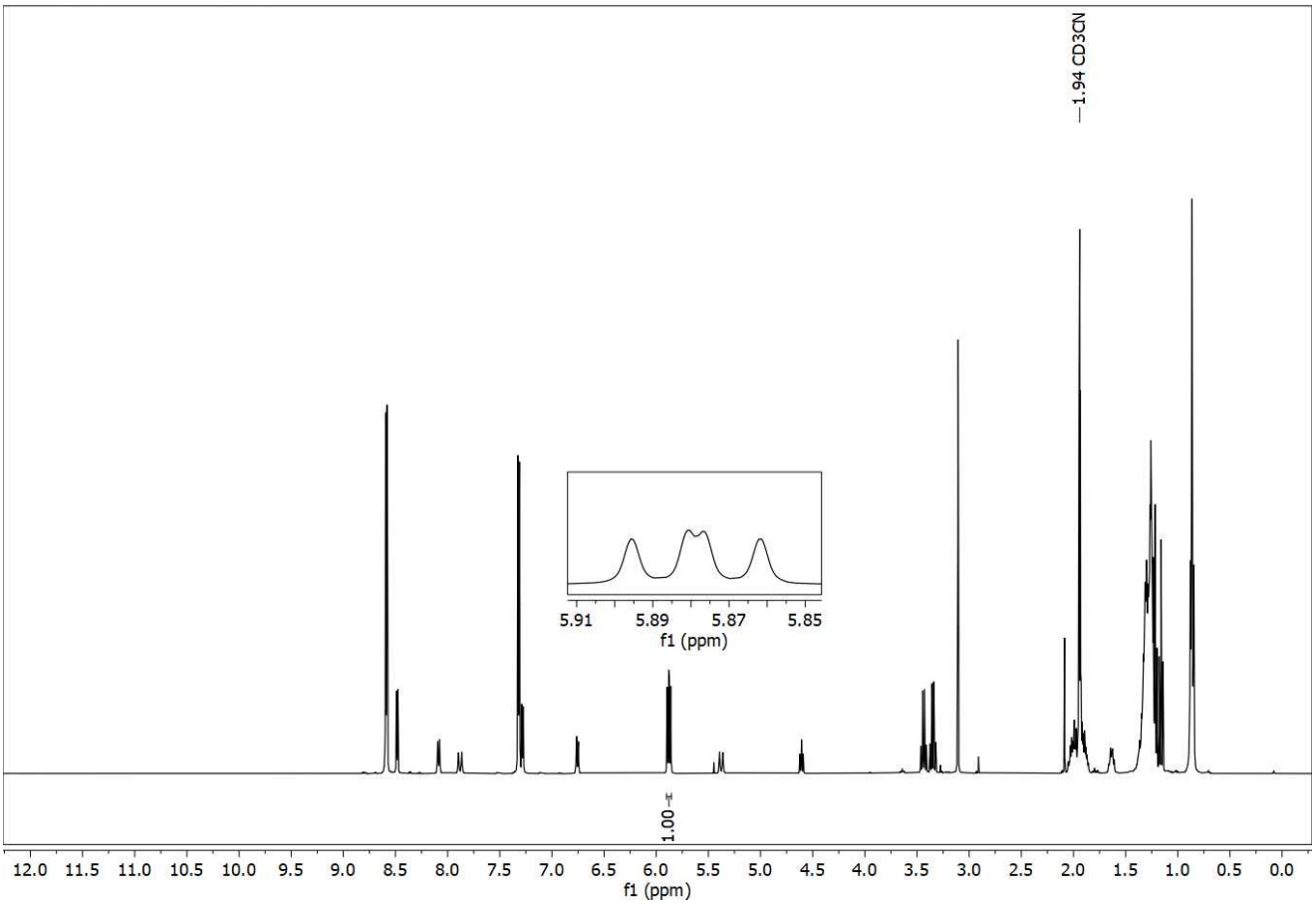
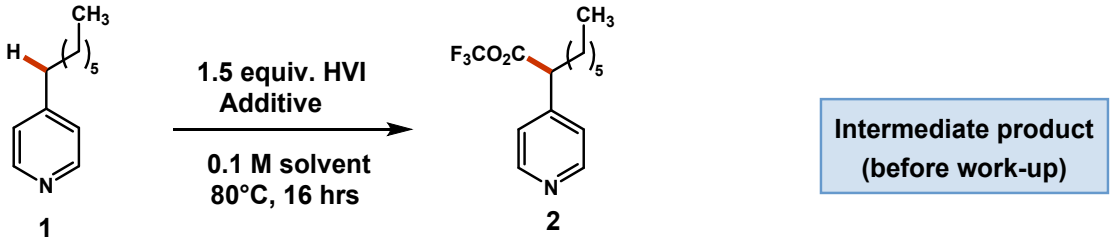
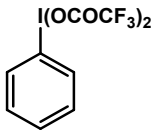


Figure S36: ^{1}H NMR of crude reaction mixture.

Evaluation of solvent, hypervalent iodine reagent (HVI) and additive for C-H Hydroxylation

Initial Exploration with hypervalent iodine reagent:





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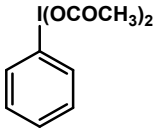

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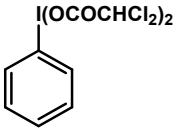


5

S.No.	Solvent	HVI	% NMR yield
1	$[D_3]$MeCN	3	43
2	$[D_6]C_6H_6$	3	44
3	$[D_6]$DMSO	3	0
4	$[D_3]$MeCN	4	0
5	$[D_6]C_6H_6$	4	0
6	$[D_6]$DMSO	4	0
7	$[D_3]$MeCN	5	0
8	$[D_6]C_6H_6$	5	14
9	$[D_6]$DMSO	5	0

Table 1: Reaction Conditions: PIFA (1.5 Equiv.), 0.1 M solvent, 80 °C, 16 hrs. Yield was determined by H-NMR analysis using 3,5-dichloroanisole (0.1 mmol) as the internal standard.

Into a series of oven-dried 8 mL vials equipped with Teflon-lined septa, hypervalent iodine reagents (0.15 mmol) were added followed by purging with nitrogen. Three separate stock solutions containing 4-heptyl pyridine (0.1 M, substrate) and 3,5-dichloroanisole (0.1 M, internal standard) were prepared using three solvents – d-MeCN, d-DMSO and d-C_6H_6 dried overnight under 3A° molecular sieves. 1.0 mL of this stock solution was transferred to each of the reaction vials, and the temperature was raised to 80 ºC. After 16 hours of reaction, the vials were taken off the heating plate and aliquots were removed from each vial and ^{1}H NMR spectra collected. It is believed that the pH difference between the screening reactions (acidic) and the DMAP/NEt_3 acylation conditions (basic) results in the benzylic C-H hydrogen chemical shifts moving downfield from δ = 5.91-5.85 ppm (Figure 23) to δ = 6.15-6.14 ppm.

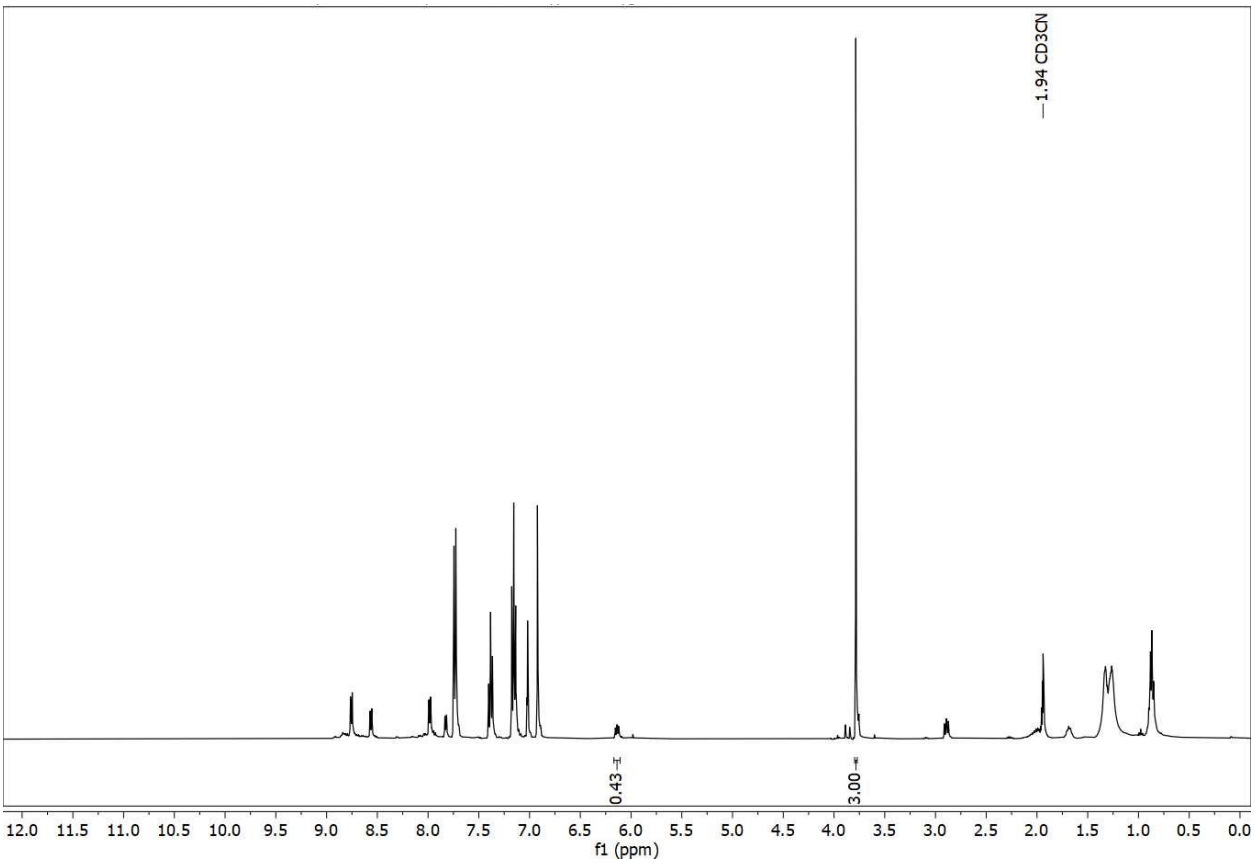
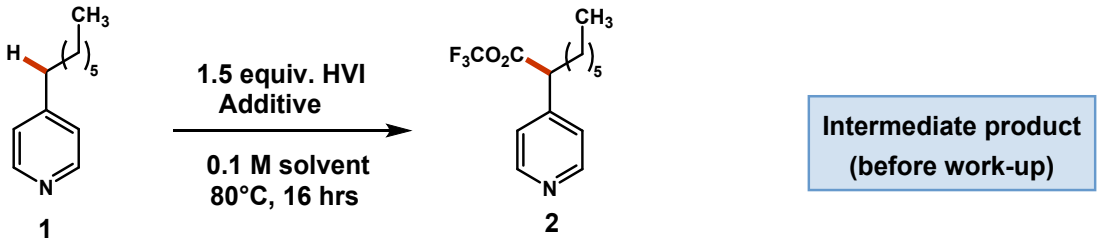


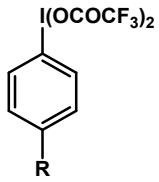
Figure S37: ^{1}H NMR of crude reaction mixture S.No. 1 (Table 1)

Understanding electron-withdrawing and donating effects on HVI:



HVI reagents

R = -CF_3 (6)
R = -$C(CH_3)_3$ (7)
R = -CF_3 (8)
R = -NO_2 (9)



From above-screening (Bis(trifluoroacetoxy)iodo) benzene in acetonitrile turned out to be the best HVI reagent. Therefore, into 4*8 mL oven-dried vials equipped with Teflon-lined septa, (0.15 mmol) incorporated with electron-withdrawing or donating groups in PIFA were added followed by purging with nitrogen. A stock solution containing 4-heptyl pyridine (0.1 M, substrate) and 3,5-dichloroanisole (0.1 M,

internal standard) were prepared using d-MeCN dried overnight under 3Å molecular sieves. 1.0 mL of this stock solution was transferred to each of the reaction vials, and the temperature was raised to 80 ºC. After 16 hours of reaction, the vials were taken off the heating plate and aliquots were removed from each vial and ^{1}H NMR was collected.

S.No.	Solvent	HVI	% NMR yield
1	[D_3]MeCN	6	17
2	[D_3]MeCN	7	17
3	[D_3]MeCN	8	24
4	[D_3]MeCN	9	21

Table 2: Reaction Conditions: PIFA (1.5 Equiv.), 0.1 M solvent, 80 °C, 16 hrs. Yield was determined by H-NMR analysis using 3,5-dichloroanisole (0.1 mmol) as the internal standard.

Initial Exploration with additive screening:

Into 8*8 mL oven-dried vials equipped with Teflon-lined septa, additives (0.1 mmol) were added followed by purging with nitrogen. A stock solution containing 4-heptyl pyridine (0.1 M, substrate) and 3,5-dichloroanisole (0.1 M, internal standard) were prepared using d-MeCN dried overnight under 3A° molecular sieves. 1.0 mL of this stock solution was transferred to each of the reaction vials, and the temperature was raised to 80 ºC. After 16 hours of reaction, the vials were taken off the heating plate and aliquots were removed from each vial and 1H NMR was collected.

S.No.	Additives	% NMR yield
1	2,6-Lutidine	44
2	CF_3COOH	35
3	KTFA	46
4	CF_3COONa	35
5	CH_3COONa	20
6	MgO	28
7	$N(Bu)_4PF_6$	18
8	H_2O	0

Table 3: Reaction Conditions: PIFA (1.5 Equiv.), 0.1 M solvent, additives (1.0 Equiv.), 80 °C, 16 hrs. Yield was determined by ^{1}H-NMR analysis using 3,5-dichloroanisole (0.1 mmol) as the internal standard.

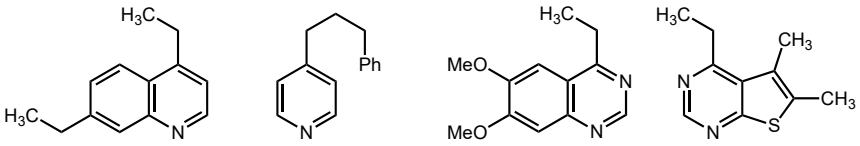
Final additive screening:

From above additive screening, Potassium trifluoroacetate (KTFA) and 2,6-Lutidine gave the best results. Therefore, into 8*8 mL oven-dried vials equipped with Teflon-lined septa were taken. In 4*8 mL vials different equivalents of KTFA were added and in remaining 4*8 mL vials different equivalents of 2,6-Lutidine were added followed by purging with nitrogen. A stock solution containing 4-heptyl pyridine (0.1 M, substrate) and 3,5-dichloroanisole (0.1 M, internal standard) were prepared using d-MeCN dried overnight under 3A° molecular sieves. 1.0 mL of this stock solution was transferred to each of the reaction vials, and the temperature was raised to 80 ºC. After 16 hours of reaction, the vials were taken off the heating plate and aliquots were removed from each vial and ^{1}H NMR was collected.

Entry	Additive	Equiv.	Temp	HVI equiv.	Conc.	Yield 2 (%)
1	2,6-Lutidine	1	73	0.9	0.1	44
2	2,6-Lutidine	2	80	1.5	0.25	70
3	2,6-Lutidine	2.5	80	2	0.35	42
4	2,6-Lutidine	3	63	2.5	0.5	25
5	KTFA	1	63	0.9	0.5	33
6	KTFA	2	80	1.5	0.35	44
7	KTFA	2.5	73	2	0.25	50
8	KTFA	3	80	2.5	0.1	39

Table 4: Variable reaction conditions. Yield was determined by H-NMR analysis using 3,5-dichloroanisole (0.1 mmol) as the internal standard.

Individual Heterocycle Optimization



Round 1: Latin Hypercube Search #1

To generate possible reaction conditions using Latin Hypercube Search, the following variable ranges were used: Concentration (0.1–1.0 M), oxidant equivalents (0.8–2.5 equiv.), 2,6-lutidine equivalents (.5–3.0 equiv.). Each full range was divided into 4 sub-sections of equal size, and a uniform random number generator was used to select a value between zero and 1 for each sub-section. That random number

represented the position along the sub-section range to use, with zero resulting in the minimum value from the sub-section, and one resulting in the maximum value, and any value in between scaling to the appropriate point between the minimum and maximum. For each substrate to be optimized, once these 4 values were selected for each variable, these settings were then randomly combined into specific experiments using python's random.shuffle() function. This resulted in the following specific experiments being selected for the first round of optimization:

Quinoline:	A [0.48 M, 1.41 equiv. oxidant, 1.38 equiv. lutidine]
	B [0.94 M, 2.42 equiv. oxidant, 1.58 equiv. lutidine]
	C [0.18 M, 1.23 equiv. oxidant, 0.83 equiv. lutidine]
	D [0.59 M, 1.91 equiv. oxidant, 2.71 equiv. lutidine]
Phenylpyridine:	A [0.71 M, 2.26 equiv. oxidant, 0.94 equiv. lutidine]
	B [0.86 M, 1.71 equiv. oxidant, 2.92 equiv. lutidine]
	C [0.41 M, 1.41 equiv. oxidant, 1.38 equiv. lutidine]
	D [0.23 M, 1.22 equiv. oxidant, 2.21 equiv. lutidine]
Quinazoline:	A [0.16 M, 1.29 equiv. oxidant, 0.89 equiv. lutidine]
	B [0.56 M, 1.89 equiv. oxidant, 2.55 equiv. lutidine]
	C [0.52 M, 1.16 equiv. oxidant, 2.21 equiv. lutidine]
	D [0.87 M, 2.16 equiv. oxidant, 1.54 equiv. lutidine]
Sulfur-Pyrim	A [0.36 M, 2.19 equiv. oxidant, 0.90 equiv. lutidine]
	B [0.21 M, 1.82 equiv. oxidant, 2.56 equiv. lutidine]
	C [0.82 M, 1.39 equiv. oxidant, 1.76 equiv. lutidine]
	D [0.75 M, 0.95 equiv. oxidant, 1.49 equiv. lutidine]

These experiments were set up using stock solutions according to the following procedure:

A lutidine/internal standard solution was created by weighing dimethyl terephthalate (50.4 mg, 0.26 mmol) directly into an oven-dried 8 mL scintillation vial, 2,6-lutidene (150 µL, 1.29 mmol), and anhydrous acetonitrile (2.6 mL). For the two liquid substrates (quinoline, phenylpyridine), substrate/lutidine/standard stock solutions were created by mixing 0.65 mmol of the reaction substrate (120 µL for 4,7-diethylquinoline, 125 µL for 3-phenylpropylpyridine) with 650 µL of the lutidine/standard solution.

For all substrates, the appropriate amount of iodine(III) oxidant, as per the list above (from 53 to 130 mg), was weighed directly into oven-dried 8 mL scintillation vials inside of a nitrogen-filled glovebox. For the two solid substrates (quinazoline, sulfur-pyrim), the substrates were portioned into the reaction vials inside the glovebox, at the same time the oxidant was transferred (4-ethyl-6,7-dimethoxyquinazoline: 27.3 mg; 4-

Ethyl-2,3-dimethylbenzo[b]thiophene: 24.0 mg). The vials threads were lined with Teflon tape, and were capped with Teflon-lined septa and appropriate screwcaps and remove from the glovebox.

Into the vials with solid substrates, 125 µL of the lutidine/standard stock solution were added. Into vials that only contained PIFA, 125 µL of the appropriate lutidine/standard/substrate stock solution (*i.e.* for either quinoline or phenylpyridine) was transferred. To reach the appropriate concentration and lutidine equivalencies, pure anhydrous acetonitrile and pure 2,6-lutidine were added as follows:

Quinoline: A [130 µL acetonitrile, 23 µL lutidene]
B [20 µL acetonitrile, 16 µL lutidene]
C [560 µL acetonitrile, 5 µL lutidene]
D [90 µL acetonitrile, 32 µL lutidene]

Phenylpyridine: A [50 µL acetonitrile, 6 µL lutidene]
B [20 µL acetonitrile, 35 µL lutidene]
C [180 µL acetonitrile, 13 µL lutidene]
D [420 µL acetonitrile, 25 µL lutidene]

Quinazoline: A [650 µL acetonitrile, 6 µL lutidene]
B [100 µL acetonitrile, 30 µL lutidene]
C [120 µL acetonitrile, 25 µL lutidene]
D [20 µL acetonitrile, 15 µL lutidene]

Sulfur-Pyrim A [220 µL acetonitrile, 6 µL lutidene]
B [480 µL acetonitrile, 30 µL lutidene]
C [30 µL acetonitrile, 18 µL lutidene]
D [40 µL acetonitrile, 14 µL lutidene]

Reactions ‘A’ and ‘C’ for all substrates were sealed with electrical tape and heated to 80 ºC. Reactions ‘B’ and ‘D’ for all substrates were sealed with electrical tape and heated to 50 ºC. At three time points—the first between 60-90 minutes, the second between 2-8 hours, the third between 16-24 hours—20µL samples were removed by syringe, and filtered through a small silica gel plug, eluting with pure ethanol, directly into a 2 mL LCMS vial. The MS component of the trace was used to identify the hydroxylated product, and then the diode array trace was used to quantify the desired product *relative* to the internal standard. For each of the four reaction conditions, for each substrate, the best product:standard ratio observed from those three time points was carried forward to the next step of the process. Those ratios were:

Quinoline: A [1.60 at 2 hours]
B [2.08 at 2 hours]
C [1.43 at 2 hours]

	D [2.30 at 2 hours]
Phenylpyridine:	A [1.06 at 1 hour]
	B [1.01 at 1 hour]
	C [1.42 at 2.5 hours]
	D [2.50 at 1 hour]
Quinazoline:	A [1.56 at 1 hour]
	B [3.27 at 1 hour]
	C [1.91 at 1 hour]
	D [2.12 at 1 hour]
Sulfur-Pyrim	A [1.56 at 2 hours]
	B [2.12 at 18 hours]
	C [1.67 at 2 hours]
	D [1.71 at 18 hours]

Round 2: Gaussian Process Regression

The open-source python 'GPyOpt' optimization package was used to suggest experiments for round #2. Temperature was ignored as a variable, as all of the experiments in this round were done at 65 ºC (*i.e.* midway between 50 and 80). GPyOpt.method.BayesianOptimization() was used to suggest new experiments, using Expected Improvement ("EI") as the acquisition_type, "local_penalization" as the evaluator_type, and Gaussian Process ("GP") as the model_type. The critical piece of code necessary to generate new experimental suggestions is shown directly below. In some cases, Gaussian Process Regression became focused on a single variable, suggesting essentially duplicate experiments that only changed by a very small value in that variable. In those cases, we found one could convince BayesianOptimization() to focus more broadly by entering one of the duplicate experiments into our list of completed experiments, but with an observed result of zero. In all cases, this encouraged the algorithm to explore new areas of experimental space. So, if the first batch of 4 experiments contained essentially all duplicate experiments, we would input one of those experiments as if we had previously peformed it with a result of zero, and now request *three* additional experiments. That is, we would not throw away all 4 of the suggested experiments, only the three redundant ones, and then we would request three replacements.

```python
def update_and_suggest_experiments(data,
                                   target_columns,
                                   variables,
                                   domain,
                                   batch_size):

    variable_names = [var['name'] for var in variables]
    # Filter completed experiments
    completed_experiments = data.dropna(subset=target_columns)

    # Extract the variables and outcomes for completed experiments
    X_completed = completed_experiments[variable_names].values
    Y_completed = completed_experiments[target_columns].values

    # Initialize the Bayesian Optimization
    optimizer = GPyOpt.methods.BayesianOptimization(f=None,
                                                    domain=domain,
                                                    X=X_completed,
                                                    Y=Y_completed,
                                                    acquisition_type='EI',
                                                    evaluator_type='local_penalization',
                                                    model_type='GP',
                                                    de_duplication=True,
                                                    batch_size=1)

    pending_x = []
    for _ in range(batch_size):
        # Suggest the next location considering current pending points
        next_point = optimizer.suggest_next_locations(pending_X=np.array(pending_x))

        # Add the suggested point to the list of pending experiments
        pending_x.append(next_point[0])  # Assuming next_point is a 2D array with a single row
    # Convert the accumulated pending experiments to a DataFrame
    suggestions_df = pd.DataFrame(pending_x, columns=variable_names)

    # Append the suggested experiments to the original DataFrame
    updated_data = pd.concat([data, suggestions_df], ignore_index=True)

    updated_data.to_csv('PhPy_updated_experiments.csv', index=False)

    return updated_data
```

This resulted in the following experiments being suggested for each substrate, which were set up and performed in an identical manner as for round #1, with every reaction being performed at 65 ºC.

Quinoline: A [0.99 M, 2.38 equiv. oxidant, 2.67 equiv. lutidine]
B [0.27 M, 2.23 equiv. oxidant, 0.85 equiv. lutidine]
C [0.87 M, 1.28 equiv. oxidant, 2.75 equiv. lutidine]
D [0.62 M, 2.26 equiv. oxidant, 2.65 equiv. lutidine]

Phenylpyridine: A [0.53 M, 1.39 equiv. oxidant, 0.94 equiv. lutidine]
B [0.77 M, 2.43 equiv. oxidant, 1.04 equiv. lutidine]
C [0.66 M, 1.02 equiv. oxidant, 0.77 equiv. lutidine]
D [0.50 M, 1.14 equiv. oxidant, 2.09 equiv. lutidine]

Quinazoline: A [0.84 M, 1.17 equiv. oxidant, 2.98 equiv. lutidine]
B [0.98 M, 2.10 equiv. oxidant, 1.40 equiv. lutidine]
C [0.42 M, 2.12 equiv. oxidant, 1.08 equiv. lutidine]
D [0.40 M, 1.16 equiv. oxidant, 1.41 equiv. lutidine]

Sulfur-Pyrim A [1.00 M, 0.80 equiv. oxidant, 2.83 equiv. lutidine]
B [0.25 M, 2.06 equiv. oxidant, 1.21 equiv. lutidine]
C [0.86 M, 1.47 equiv. oxidant, 2.36 equiv. lutidine]
D [0.39 M, 0.93 equiv. oxidant, 2.36 equiv. lutidine]

With stock solutions generated as in round #1, and the following pure liquids added:

Quinoline: A [110 µL acetonitrile, 6 µL lutidene]
B [40 µL acetonitrile, 8 µL lutidene]
C [60 µL acetonitrile, 4 µL lutidene]
D [130 µL acetonitrile, 23 µL lutidene]

Phenylpyridine: A [50 µL acetonitrile, 6 µL lutidene]
B [20 µL acetonitrile, 35 µL lutidene]
C [180 µL acetonitrile, 13 µL lutidene]
D [420 µL acetonitrile, 25 µL lutidene]

Quinazoline: A [20 µL acetonitrile, 36 µL lutidene]
B [0 µL acetonitrile, 13 µL lutidene]
C [170 µL acetonitrile, 8 µL lutidene]
D [190 µL acetonitrile, 13 µL lutidene]

Sulfur-Pyrim A [0 µL acetonitrile, 34 µL lutidene]
B [380 µL acetonitrile, 10 µL lutidene]
C [20 µL acetonitrile, 27 µL lutidene]
D [200 µL acetonitrile, 27 µL lutidene]

LCMS aliquots were taken as in Round #1, and again three time points were measured. The highest product:standard ratio was observed for these reactions as follows, and were carried on to the next round:

Quinoline: A [1.83 at 75 minutes]
B [1.08 at 7 hours]
C [2.03 at 75 minutes]
D [1.64 at 75 minutes]

Phenylpyridine: A [1.83 at 75 minutes]
B [1.05 at 7 hours]
C [2.03 at 75 minutes]
D [1.64 at 75 minutes]

Quinazoline: A [2.66 at 19 hours]
B [0.14 at 19 hours]
C [0.70 at 19 hours]
D [2.23 at 7 hours]

Sulfur-Pyrim A [1.44 at 7 hours]
B [2.58 at 19 hours]
C [2.17 at 7 hours]
D [1.49 at 7 hours]

Round #3: Latin Hypercube Search #2

For the final round of optimization, a Latin Hypercube Search was performed identically as it was in Round #1, with new ranges chosen as follows. The best result from Round #1 and Round #2 were used to define the minimum and maximum possible value for each variable, as well as the high and low temperature to be used, and then the specific experiments were chosen using a process identical to Round #1. This resulted in the following specific experiments, with 'A' and 'C' being performed at the 'high' temperature, and 'B' and 'D' being performed at the 'low' temperature:

Quinoline: A [0.62 M,1.36 equiv. oxidant, 2.73 equiv. lutidine]
(65/50 ºC) B [0.69 M, 1.52 equiv. oxidant, 2.71 equiv. lutidine]
C [0.76 M, 1.84 equiv. oxidant, 2.72 equiv. lutidine]
D [0.83 M, 1.68 equiv. oxidant, 2.74 equiv. lutidine]

Phenylpyridine: A [0.40 M, 1.19 equiv. oxidant, 2.10 equiv. lutidine]
(65/50 ºC) B [0.46 M, 1.17 equiv. oxidant, 2.16 equiv. lutidine]
C [0.26 M, 1.21 equiv. oxidant, 2.13 equiv. lutidine]
D [0.33 M, 1.15 equiv. oxidant, 2.19 equiv. lutidine]

Quinazoline: A [0.81 M, 1.80 equiv. oxidant, 2.82 equiv. lutidine]

(65/50 ºC) B [0.67 M, 1.62 equiv. oxidant, 2.71 equiv. lutidine]
C [0.74 M, 1.26 equiv. oxidant, 2.60 equiv. lutidine]
D [0.81 M, 1.44 equiv. oxidant, 2.93 equiv. lutidine]
Sulfur-Pyrim A [0.24 M, 1.90 equiv. oxidant, 1.72 equiv. lutidine]
(65/50 ºC) B [0.22 M, 2.03 equiv. oxidant, 1.38 equiv. lutidine]
C [0.21 M, 1.84 equiv. oxidant, 2.05 equiv. lutidine]
D [0.23 M, 1.96 equiv. oxidant, 2.39 equiv. lutidine]

LCMS aliquots were taken as in Round #1, and again three time points were measured. The highest product:standard ratio was observed for these reactions as follows, and these reactions were performed in deuterated solvent as described above to deliver per-substrate-optimized yields as shown in Figure 5.

Quinoline: A [2.10 at 1 hour]
B [3.09 at 3 hours] Scaled up and reported in Figure 5
C [1.79 at 3 hours]
D [2.44 at 3 hours]
Phenylpyridine: A [1.60 at 3 hours]
B [1.55 at 3 hours]
C [1.65 at 3 hours]
D [1.87 at 1 hour] Scaled up and reported in Figure 5
Quinazoline: A [1.97 at 1 hour]
B [2.84 at 21 hours]
C [3.01 at 3 hours] Scaled up and reported in Figure 5
D [2.64 at 3 hours]
Sulfur-Pyrim A [2.10 at 3 hours]
B [2.75 at 21 hours] Scaled up and reported in Figure 5
C [2.22 at 21 hours]
D [2.48 at 21 hours]

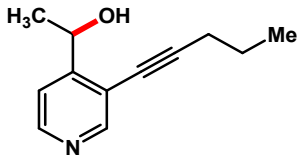
C-H Hydroxylation of Azaheterocycles

Unless otherwise noted, hydroxylated products were obtained via the procedure including an aqueous work-up listed directly below. For certain procedures, an anhydrous isolation procedure was implemented, as described subsequently below.

Isolated Yield Procedure via Aqueous Work-Up: An 8 mL vial with a puncturable cap and stir bar was oven-dried and cooled to room temperature under purging N_2. Inside a nitrogen filled glovebox, PIFA

(0.322 g, 0.75 mmol, 1.5 equiv.) was added to the vial. After the vial was removed from the glovebox, it was attached via small-diameter Tygon tubing to nitrogen atmosphere, followed by the addition of anhydrous MeCN (2 mL, 0.25 M), 2,6-Lutidine (115.8 μL, 1.0 mmol, 2.0 equiv.) and the substrate (0.5 mmol). The vial was sealed with electrical tape and the septa sealed with melted parafilm. The reaction mixture was heated to 80 ºC and stirred for 16 hrs. After cooling to room temperature, the reaction was quenched with EtOAc and saturated $NaHCO_3$ was added to obtain pH = 7-8. The extraction was carried using ethyl acetate (3* 15 mL) and the organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. All products were purified by column chromatography over silica gel (20:1 DCM: CH_3OH). During the purification of every single substrate by column chromatography, 2,4-dinitrophenylhydrazine stain (2,4-DNP) was used to identify any suspected carbonyl products (red/yellow color on TLC), which were then isolated and analyzed by H-NMR. NMR yields were gathered in a procedure analogous to that described in the preceeding section ('Development of Reaction Conditions').

Isolated Yield Procedure via Anhydrous Work-Up: An 8 mL vial with a puncturable cap and stir bar was oven-dried and cooled to room temperature under purging N_2. Inside a nitrogen filled glovebox, PIFA (0.322 g, 0.75 mmol, 1.5 equiv.) was added to the vial. After the vial was removed from the glovebox, it was attached via small-diameter Tygon tubing to nitrogen atmosphere, followed by the addition of anhydrous ACN (2 mL, 0.25 M), 2,6-Lutidine (115.8 μL, 1.0 mmol, 2.0 equiv.) and the substrate (0.5 mmol). The vial was sealed with electrical tape and the septa sealed with melted parafilm. The reaction mixture was heated to 80 ºC and stirred for 16 hrs. The reaction was cooled to room temperature, and at the same time, a flame-dried 100 mL round bottomed flask was charged with 1.0g of silica gel, and purged with flowing nitrogen. The reaction mixture was transferred by syringe onto this silica gel, with the reaction vial being washed with 2 mL of anhydrous dichloromethane, which was similarly transferred under nitrogen onto the silica gel. The reaction mixture was concentrated onto the silica gel *in vacuo*, and was then purified by silica gel chromatrography using hexanes/ethyl acetate eluent systems to deliver the presumed trifluoroacetate intermediates. These intermediates typically had slightly higher R_f values as compared to the corresponding starting materials in this system. Once these compounds were concentrated *in vacuo*, methanol (10 mL) was added to the round bottomed flask containing the trifluoroacetate, and was immediately removed *in vacuo*. This cycle of methanol addition/concentration was continued until no more trifluoroacetate remained as judged by TLC analysis. Once that had been achieved, the organic residue was dissolved in ethyl acetate and filtered through a small plug of sodium carbonate (contained in a Pasteur pipette) into a pre-tared 40 mL scintillation vial. The ethyl acetate was removed *in vacuo*, and residual ethyl acetate was further removed by exposure to high vacuum (<0.2 torr) to deliver the desired hydroxylated products.



4-ethyl-3-(1'-pentynyl) pyridin-4-ol - Hydroxylation was accomplished using general procedure and the product was purified by flash column chromatography (20:1 DCM: CH_3OH) to give pale yellow oil (42.5 mg, 0.224 mmol, 45%). ^{1}H-NMR yield obtained: 43%.

^{1}H NMR (400 MHz, CDCl3) δ 8.56 (s, 1H), 8.48 (d, J = 5.2 Hz, 1H), 7.46 (d, J = 5.1 Hz, 1H), 5.24 (q, J = 6.5 Hz, 1H), 2.58 (s, 1H), 2.47 (t, J = 7.0 Hz, 2H), 1.68 (h, J = 7.2 Hz, 2H), 1.52 (d, J = 6.5 Hz, 3H), 1.08 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.71, 152.60, 148.48, 118.99, 118.07, 98.73, 75.40, 67.64, 23.52, 22.06, 21.58, 13.55. HRMS calculated for $C_{12}H_{15}NO$, [M+H] is 190.1232, observed 190.1223.

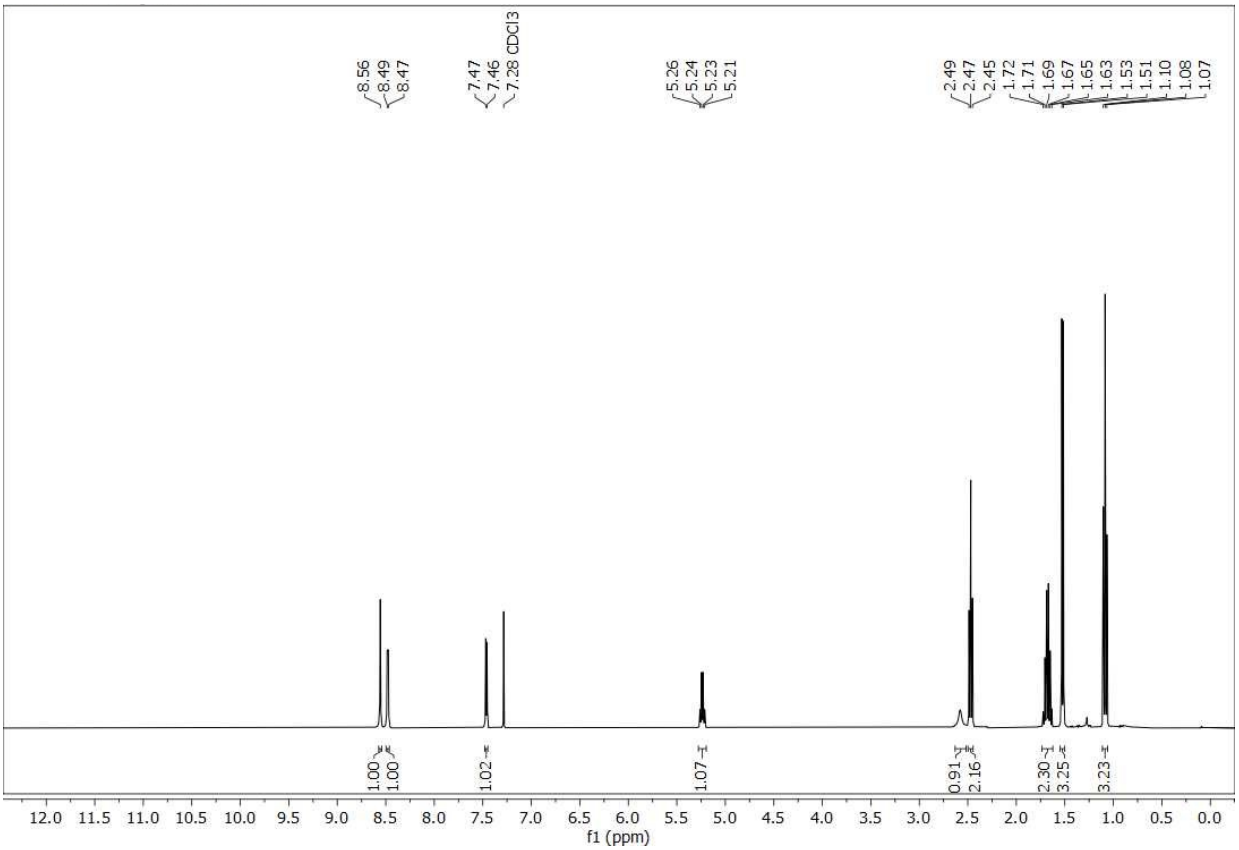


Figure S38: ^{1}H NMR of 4-ethyl-3-(1'-pentynyl) pyridin-4-ol

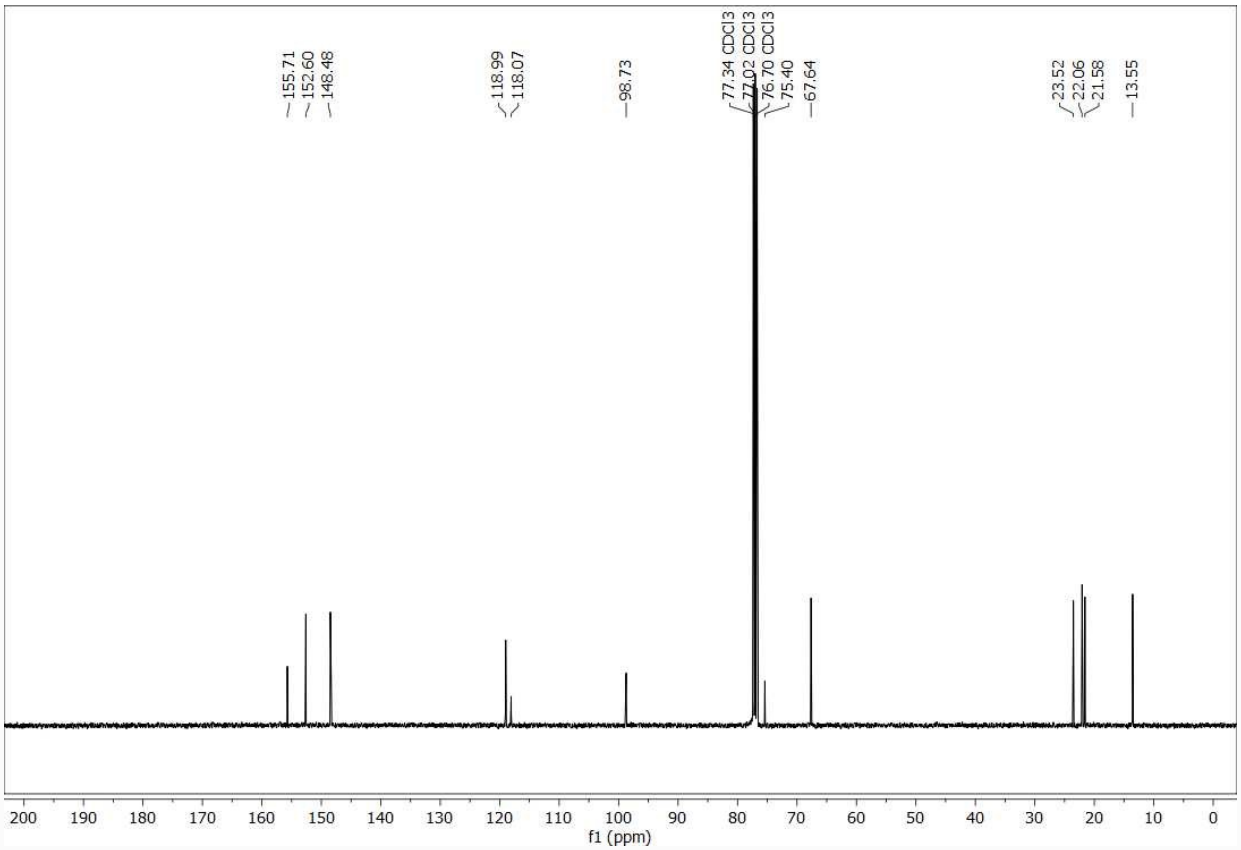
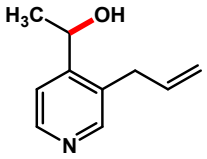


Figure S39: ^{13}C NMR of 4-ethyl-3-(1'-pentynyl) pyridin-4-ol



3-allyl-4-ethylpyridin-4-ol - Hydroxylation was accomplished using general procedure and the product was purified by flash column chromatography (20:1 DCM: CH_3OH) to give pale yellow oil (22 mg, 0.13 mmol, 27 %). H-NMR yield obtained: 54%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 – 8.22 (m, 2H), 7.50 (s, 1H), 6.01 – 5.88 (m, 1H), 5.15 – 5.08 (m, 2H), 4.97 (dq, *J* = 17.1, 1.7 Hz, 1H), 3.42 (d, *J* = 4.9 Hz, 2H), 1.45 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.9, 150.7, 150.2, 148.3, 136.2, 119.9, 116.7, 65.4, 33.8, 24.3. HRMS calculated for $C_{10}H_{13}NO$, [M+H] is 164.1075, observed 164.1083.

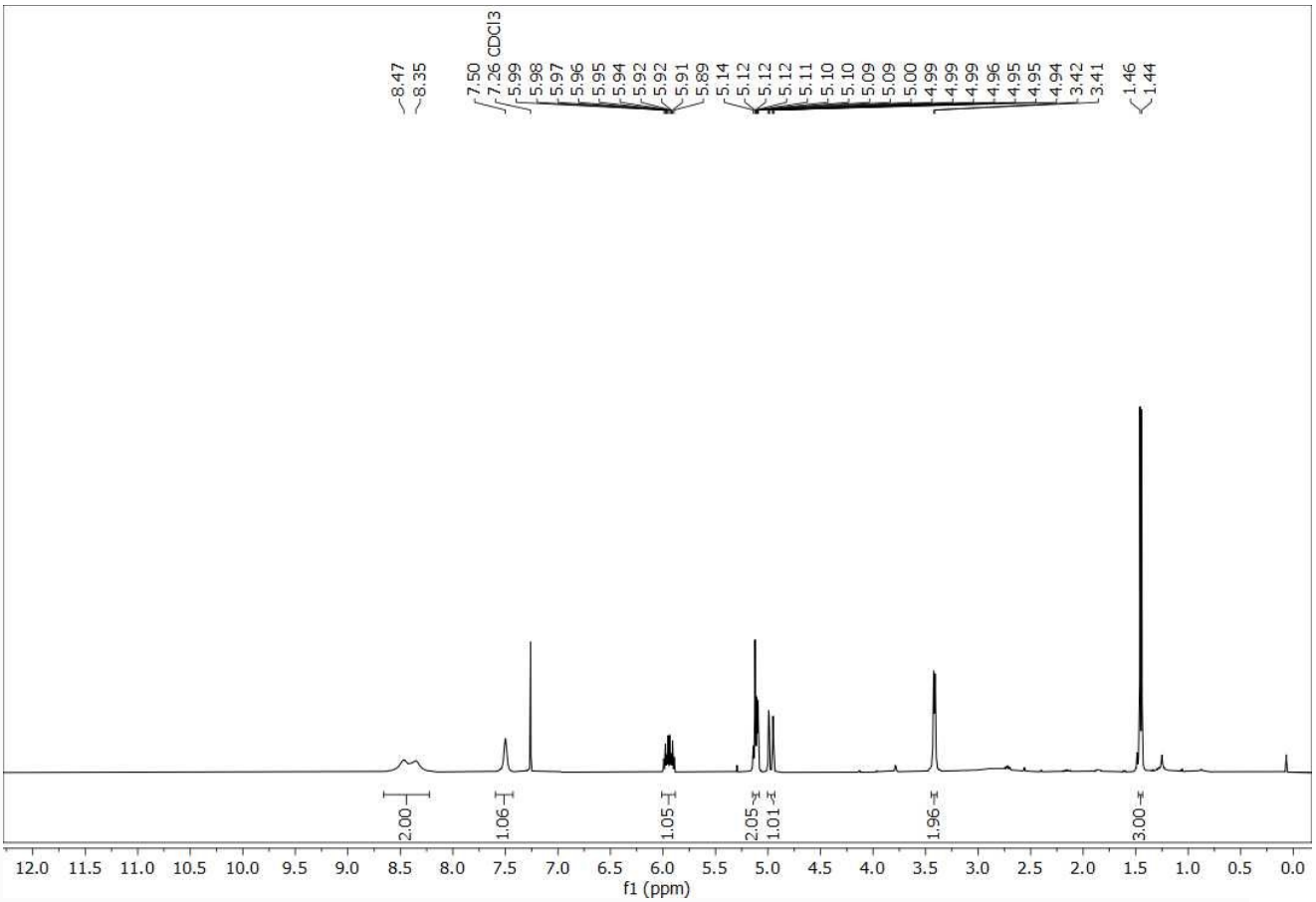


Figure S40: ^{1}H NMR of 3-allyl-4-ethylpyridin-4-ol

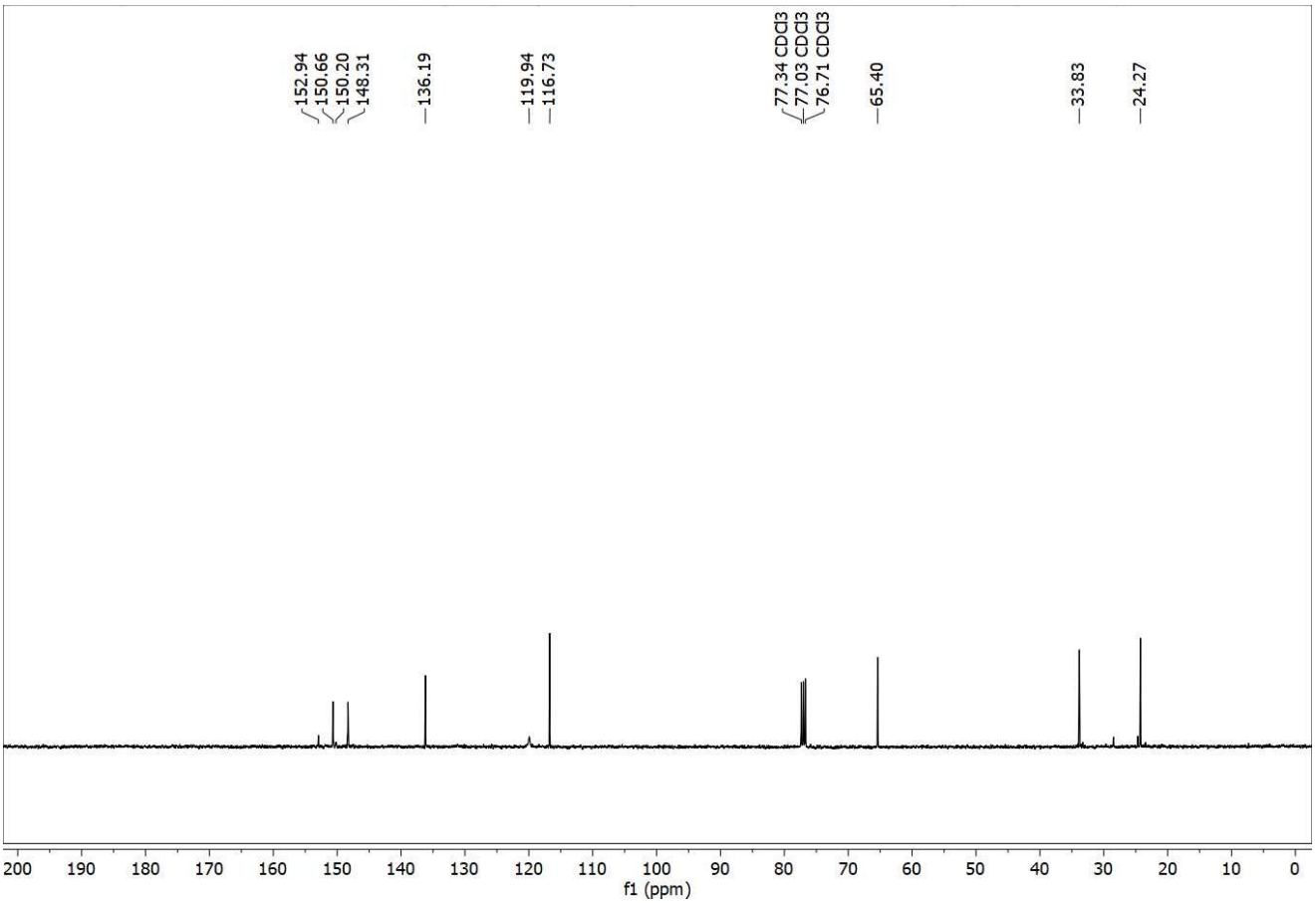
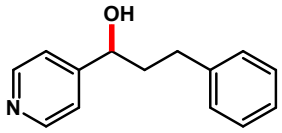


Figure S41: ^{13}C NMR of 3-allyl-4-ethylpyridin-4-ol



3-phenyl-1-(pyridin-4-yl)propan-1-ol - Hydroxylation was accomplished using general procedure and the product was purified by flash column chromatography (20:1 DCM: CH_3OH) to give brown oil (57.6 mg, 0.27 mmol, 54%). H-NMR yield obtained: 50%. ^{1}H NMR spectrum was consistent with those previously reported. [18]

^{1}H NMR (401 MHz, $CDCl_3$) δ 8.57 (s, 2H), 7.29 (m, 4H), 7.23 – 7.18 (m, 3H), 4.71 (dd, *J* = 7.7, 5.1 Hz, 1H), 2.73 (m, 2H), 2.10 – 2.01 (m, 2H).

Ref: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, J = 6.1 Hz, 2H), 7.29-7.25 (m, 4H), 7.20-7.16 (m, 3H), 4.70 (dd, J = 7.7, 5.0 Hz, 1H), 3.92 (brs, 1H), 2.79-2.70 (m, 2H), 2.07-1.98 (m, 2H).

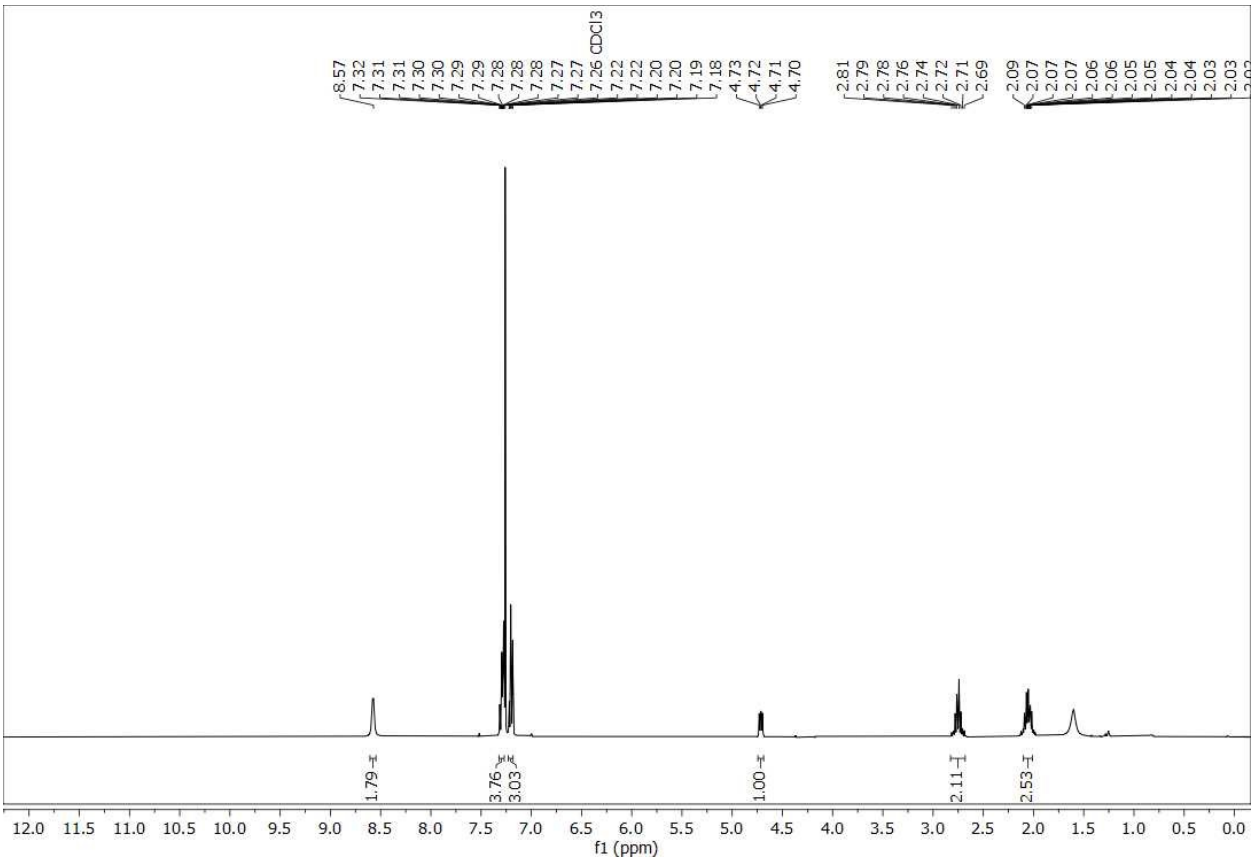
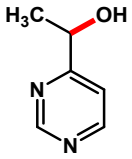


Figure S42: ^{1}H NMR of 3-phenyl-1-(pyridin-4-yl)propan-1-ol



4-Hydroxyethylpyrimidine - Hydroxylation was accomplished using general procedure and the product was purified by flash column chromatography (20:1 DCM: CH_3OH) to give yellow oil (22 mg, 0.17 mmol, 36%). H-NMR yield obtained: 50%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.16 (s, 1H), 8.70 (d, J = 5.2 Hz, 1H), 7.37 (d, J = 6.1 Hz, 1H), 4.87 (q, J = 6.7 Hz, 1H), 3.73 (s, 1H), 1.52 (d, J = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.7, 158.1, 157.2, 117.2, 68.7, 23.6. HRMS calculated for $C_6H_8N_2O$, [M+H] is 125.0715, observed 125.0712.

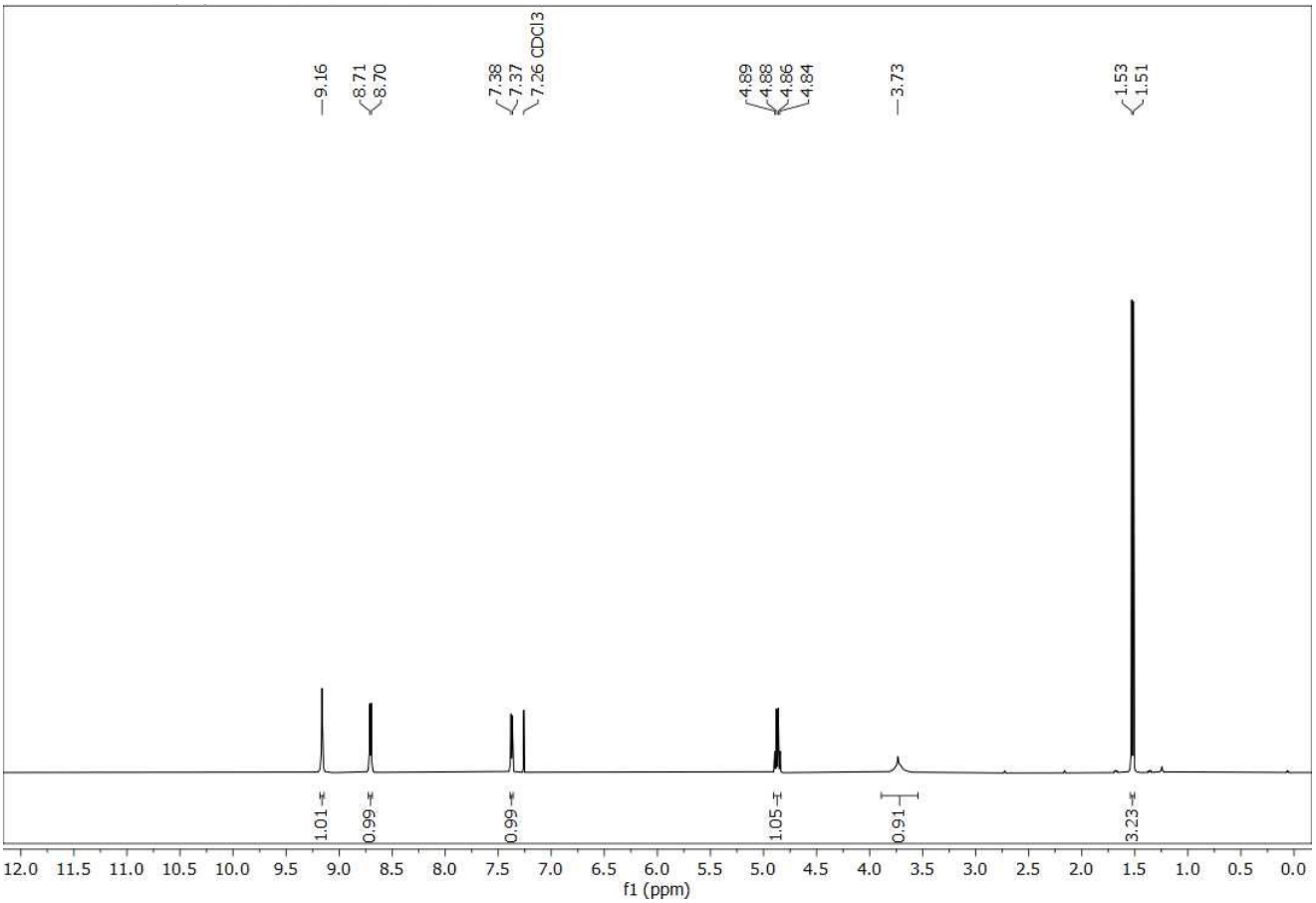


Figure S43: ^{1}H NMR of 4-Hydroxyethylpyrimidine

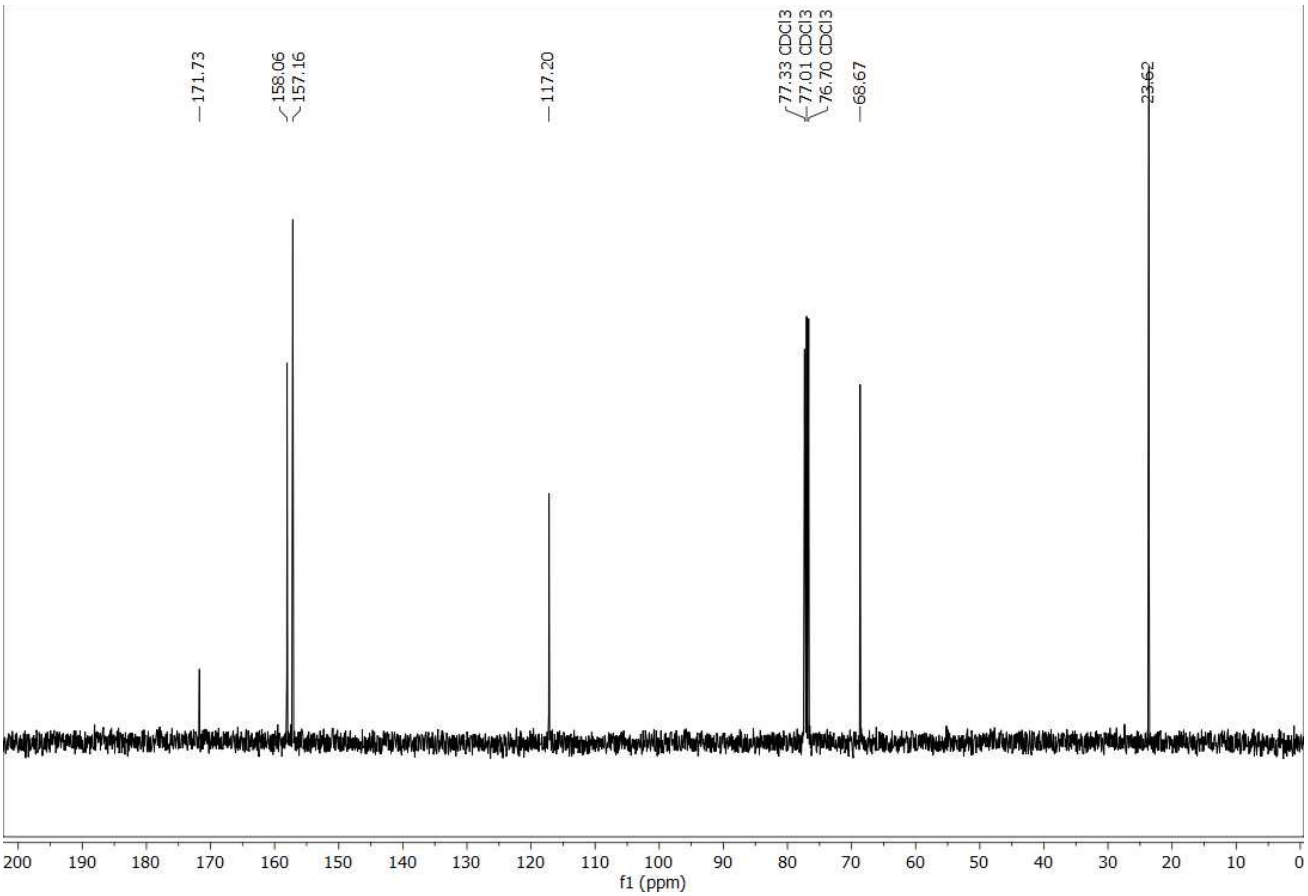
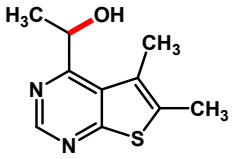


Figure S44: ^{13}C NMR of 4-Hydroxyethylpyrimidine



1-(5,6-dimethylthieno[2,3-d]pyrimidin-4-yl)ethanol - Hydroxylation was accomplished using the general procedure and the product was purified by flash column chromatography (20:1 DCM: CH_3OH) to give pale white solid containing approx. 33% reactant in it. (total amount of mixture - 56 mg). 1H-NMR yield obtained: 27%. It was extremely hard to separate the reactant and product due to almost similar Rf values. Even after running four columns, complete separation was not achieved.

As described in Figure 5, this substrate was subjected to an individual optimization protocol. By using these optimized conditions (0.22M, 50 ºC, 21 hour reaction time, 1.38 equiv. lutidine, 2.03 equiv. PIFA), as well as the anhydrous isolation protocol, 37.5 mg pure product was obtained. ^1H NMR (600 MHz, $CDCl_3$) δ 8.92 (s, 1H), 5.51 (q, J = 6.5 Hz, 1H), 4.74 – 4.71 (br s, –OH, 1H), 2.52 (s, 3H), 2.46 (s, 3H), 1.50 (d, J = 6.5 Hz, 3H). ^{13}C (151 MHz, $CDCl_3$) δ 167.6, 164.7, 151.1, 135.6, 127.6, 124.0, 65.9, 25.9, 14.1, 14.1. HRMS calculated for $C_{10}H_{12}N_2OS$, [M+H] is 209.0749, observed 209.0742.

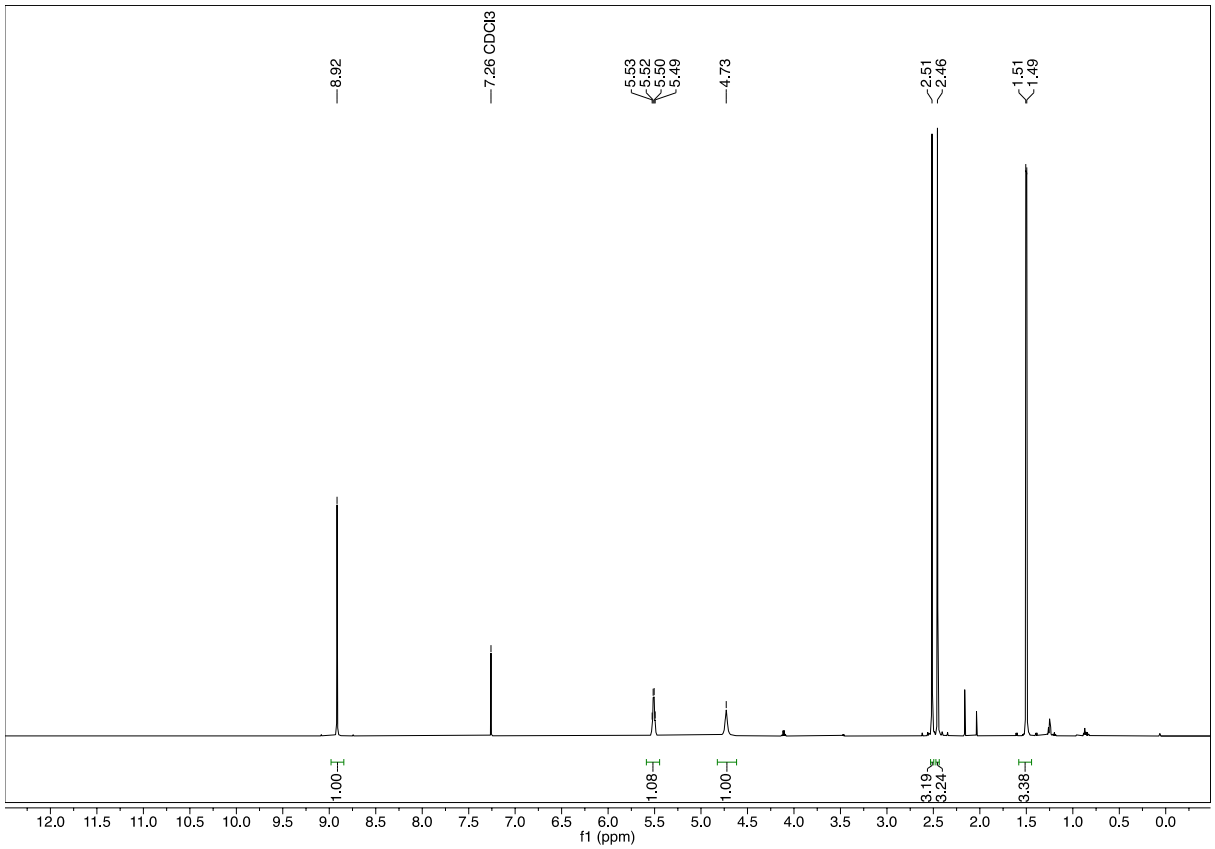


Figure S45: ^{1}H NMR of 1-(5,6-dimethylthieno[2,3-d]pyrimidin-4-yl)ethanol

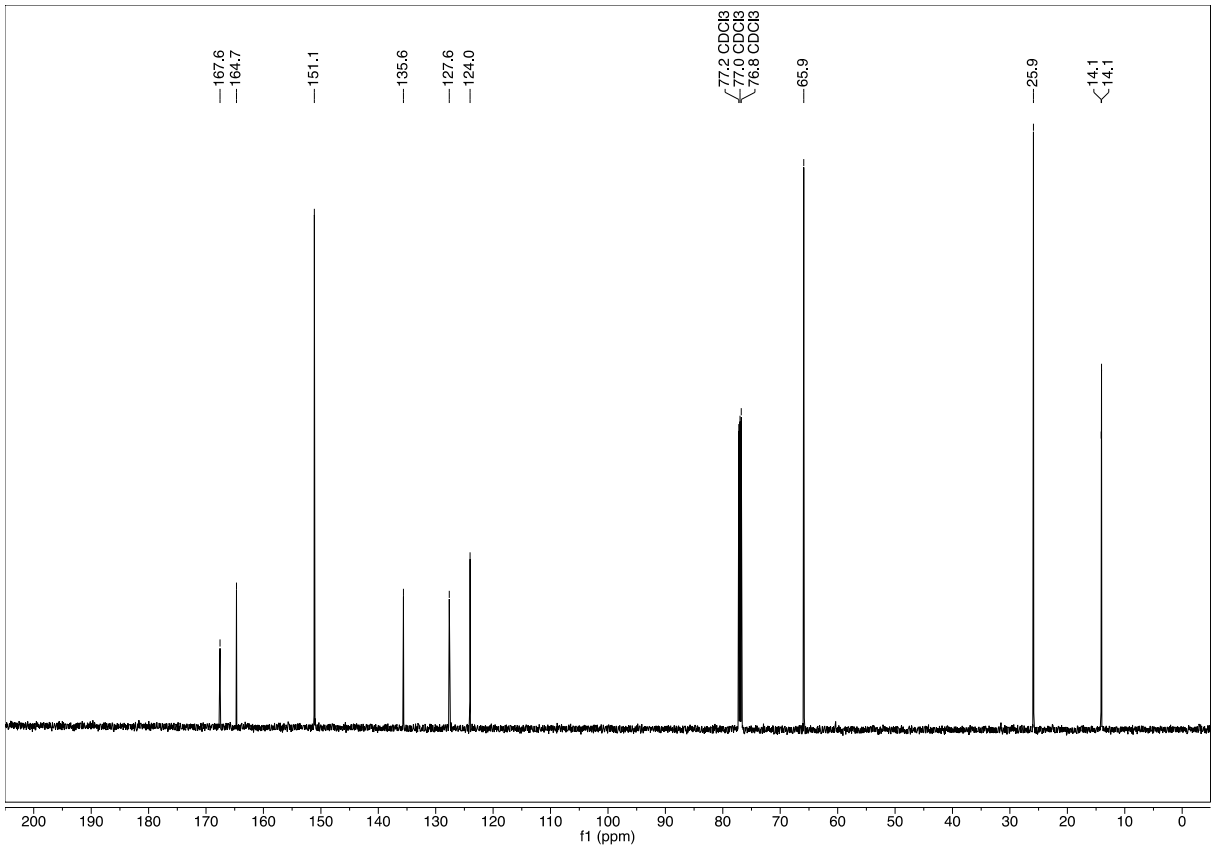
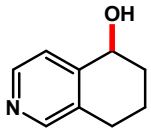


Figure S46: ^{13}C NMR of 1-(5,6-dimethylthieno[2,3-d]pyrimidin-4-yl)ethanol



5,6,7,8-tetrahydroisoquinolin-5-ol -Hydroxylation was accomplished using general procedure and the product was purified by flash column chromatography (20:1 DCM: CH_3OH) to give brown (viscous) oil (20.4 mg, 0.13 mmol, 28%). H-NMR yield obtained: 28%. ^{1}H NMR consistent with the reported literature.[19]

^{1}H NMR (401 MHz, $CDCl_3$) δ 8.36 (d, *J* = 5.1 Hz, 1H), 8.32 (s, 1H), 7.39 (d, *J* = 5.1 Hz, 1H), 4.73 (t, *J* = 6.1 Hz, 1H), 2.75 (m, 2H), 2.16 – 2.05 (m, 1H), 2.04 – 1.94 (m, 1H), 1.87 – 1.74 (m, 2H).

Ref: ^{1}H NMR ($CDCl_3$) δ 1.79 (m, 2 H), 1.90 - 2.16 (complex signal, 2 H), 2.76 (m, 2 H), 3.30 (broad s, 1 H, OH), 4.74 (m, 1 H), 7.38 (d, J = 5.1 Hz, 1 H), 8.33 (s, 1 H), 8.37 (d, J = 5.1 Hz, 1 H).

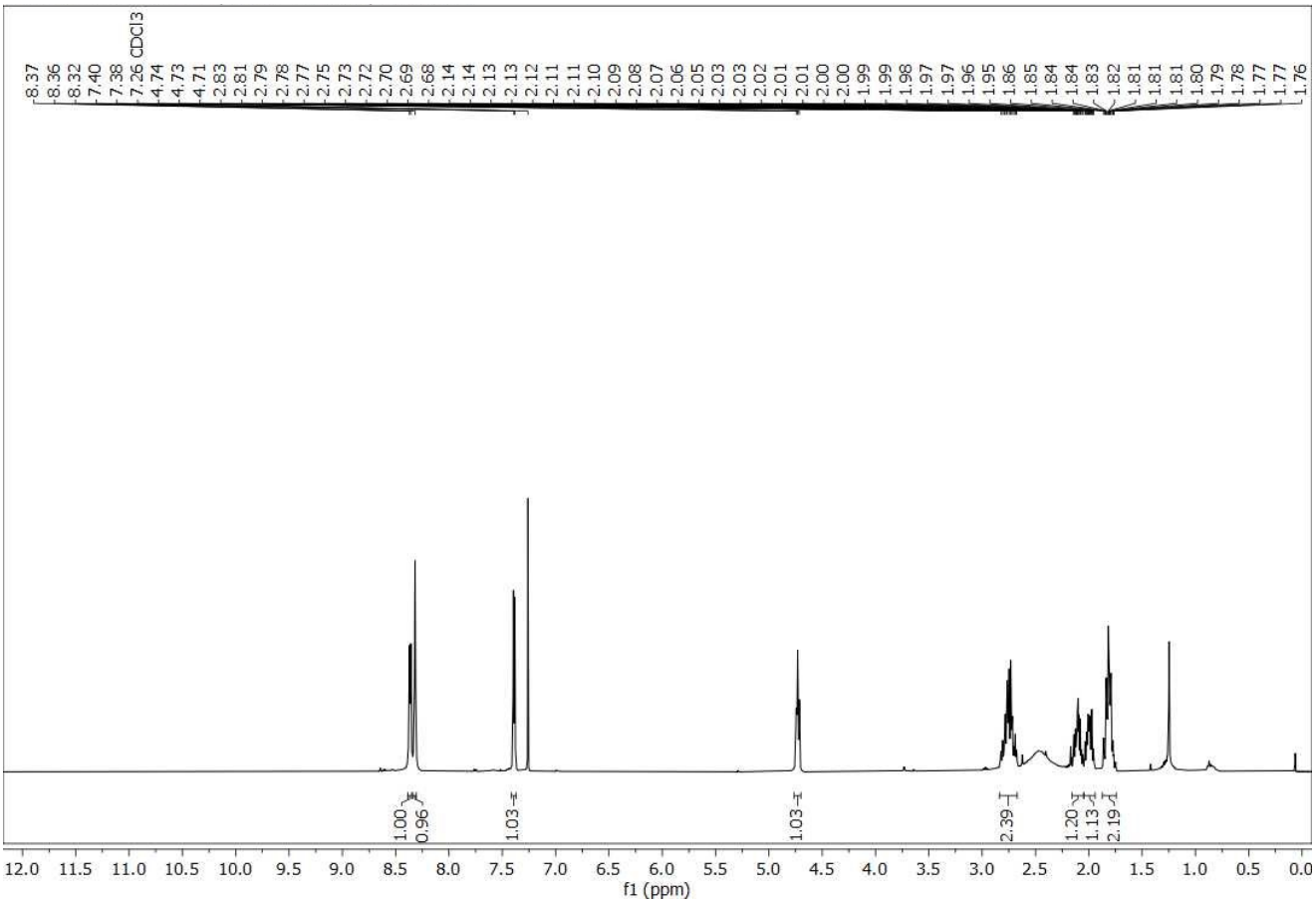
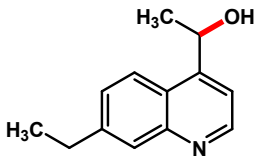


Figure S47: [1]H NMR of 5,6,7,8-tetrahydroisoquinolin-5-ol



1-(7-ethylquinolin-4-yl)ethanol - Hydroxylation was accomplished using general procedure and the product was purified by flash column chromatography (20:1 DCM: CH_3OH) to give dark yellow/brown oil (30.9 mg, 0.15 mmol, 30%). H-NMR yield obtained: 37%. 2,4-DNP stain changed colour with 1 TLC position. This spot was isolated and analyzed by [1]H NMR, and did not prove to be measurable amounts of ketone.

[1]H NMR (600 MHz, $CDCl_3$) δ 8.71 (d, *J* = 4.5 Hz, 1H), 7.91 (d, *J* = 8.6 Hz, 1H), 7.83 (dd, *J* = 1.9, 0.9 Hz, 1H), 7.50 (dd, *J* = 4.5, 0.8 Hz, 1H), 7.38 (dd, *J* = 8.7, 1.9 Hz, 1H), 5.62 (q, *J* = 6.5 Hz, 1H), 3.90-3.60 (br

s, –OH, 1H), 2.83 – 2.76 (m, 2H), 1.62 (d, J = 6.6 Hz, 3H), 1.30 (t, J = 7.6 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 151.5, 150.2, 148.3, 145.5, 127.7, 127.6, 123.6, 122.8, 116.0, 66.0, 28.8, 24.6, 15.1. HRMS calculated for $C_{13}H_{15}NO$ [M+H] 202.1232; observed 202.1224.

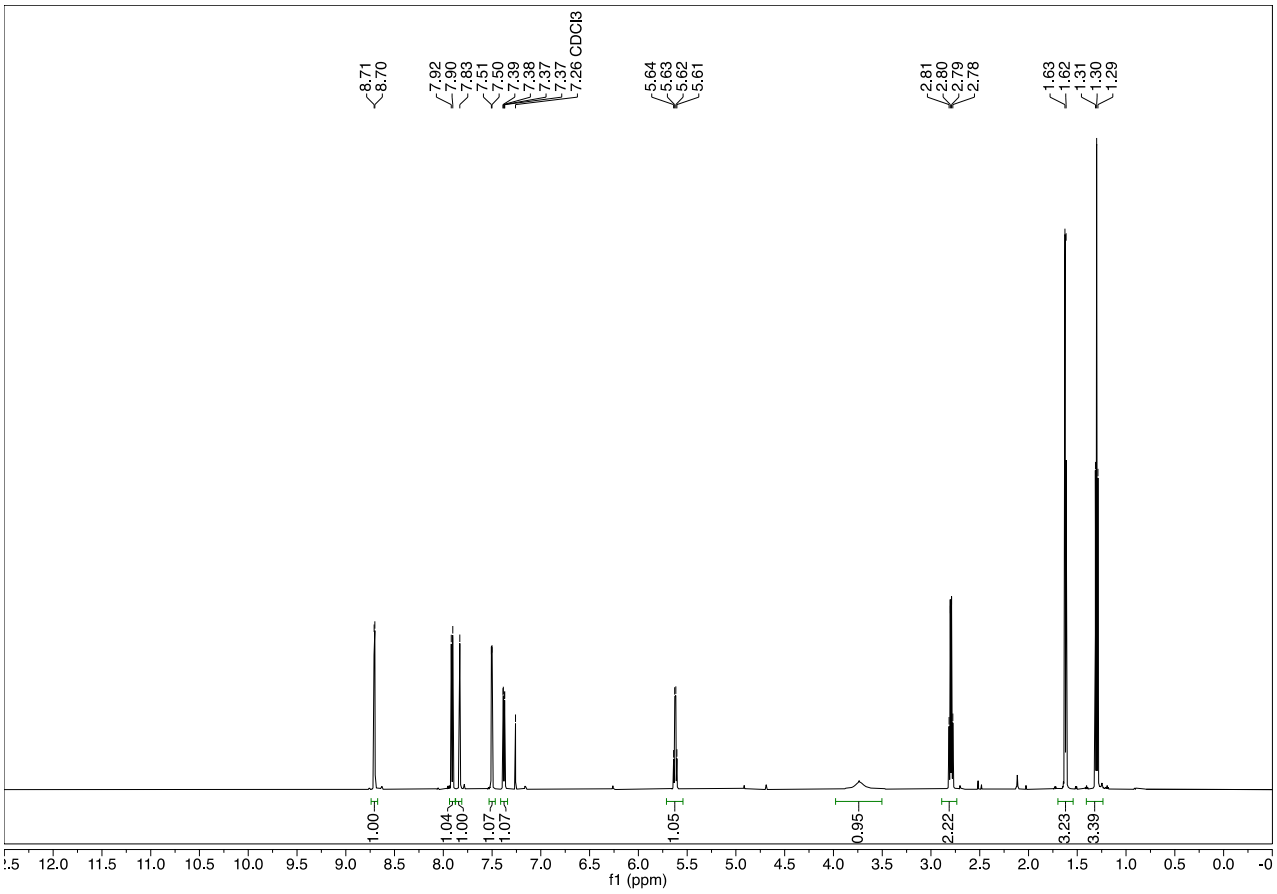


Figure S48: ^{1}H NMR of 1-(7-ethylquinolin-4-yl)ethanol

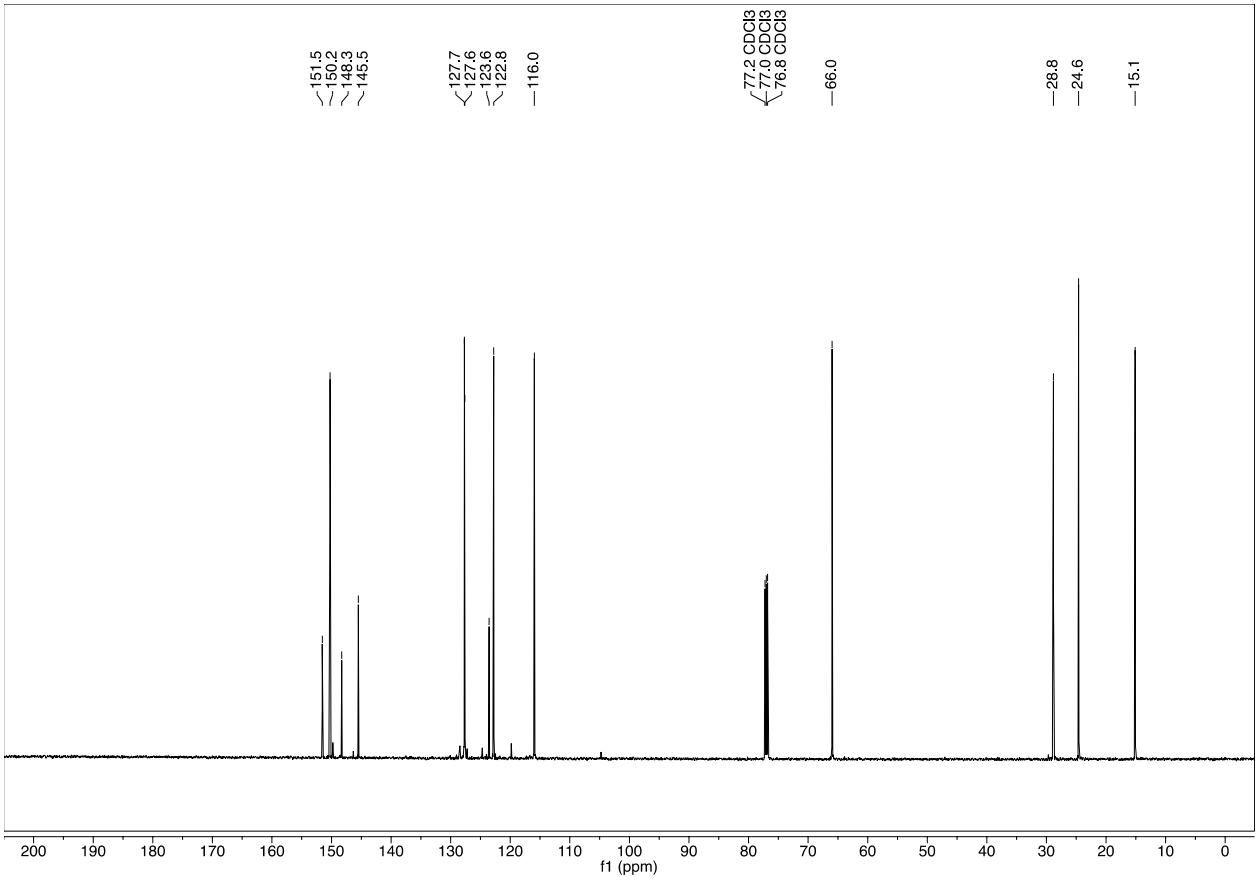
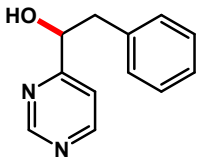


Figure S49: ^{13}C NMR of 1-(7-ethylquinolin-4-yl)ethanol



2-phenyl-1-(pyrimidin-4-yl)ethanol - Hydroxylation was accomplished using general procedure and the product was purified by flash column chromatography (20:1 DCM: CH_3OH) to give brown solid (66.2 mg, 0.32 mmol, 36%). H-NMR yield obtained: 35%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.18 (d, *J* = 1.5 Hz, 1H), 8.66 (d, *J* = 5.2 Hz, 1H), 7.35 – 7.23 (m, 4H), 7.22 – 7.14 (m, 2H), 4.96 (dd, *J* = 7.9, 5.0 Hz, 1H), 3.41 (s, 1H), 3.21 (dd, *J* = 13.7, 5.0 Hz, 1H), 3.02 (dd, *J* = 13.7, 7.9 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0, 158.1, 157.0, 136.8, 129.6, 128.6, 126.9, 118.0, 73.7, 44.3. HRMS calculated for $C_{12}H_{12}NO$, [M+H] is 201.1028, observed 201.1027.

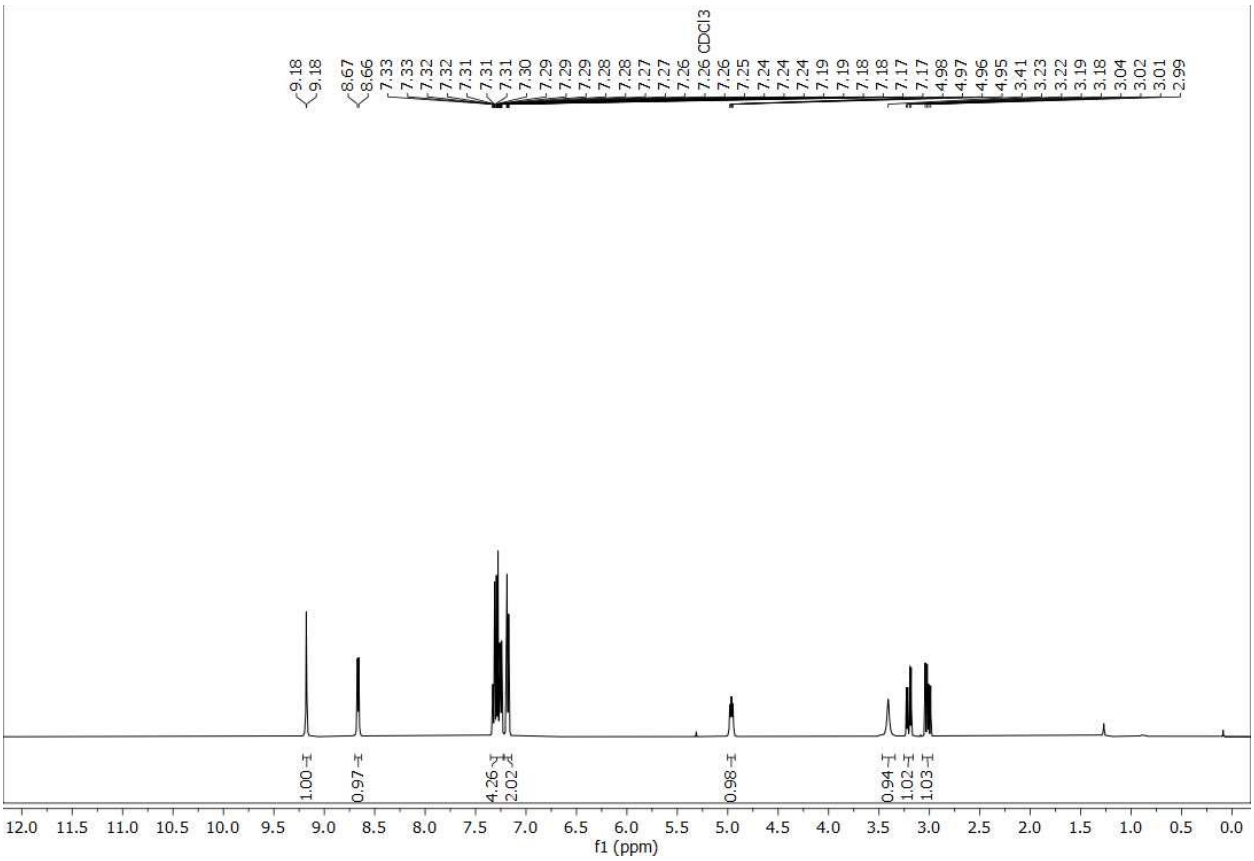


Figure S50: ^{1}H NMR of 2-phenyl-1-(pyrimidin-4-yl)ethanol

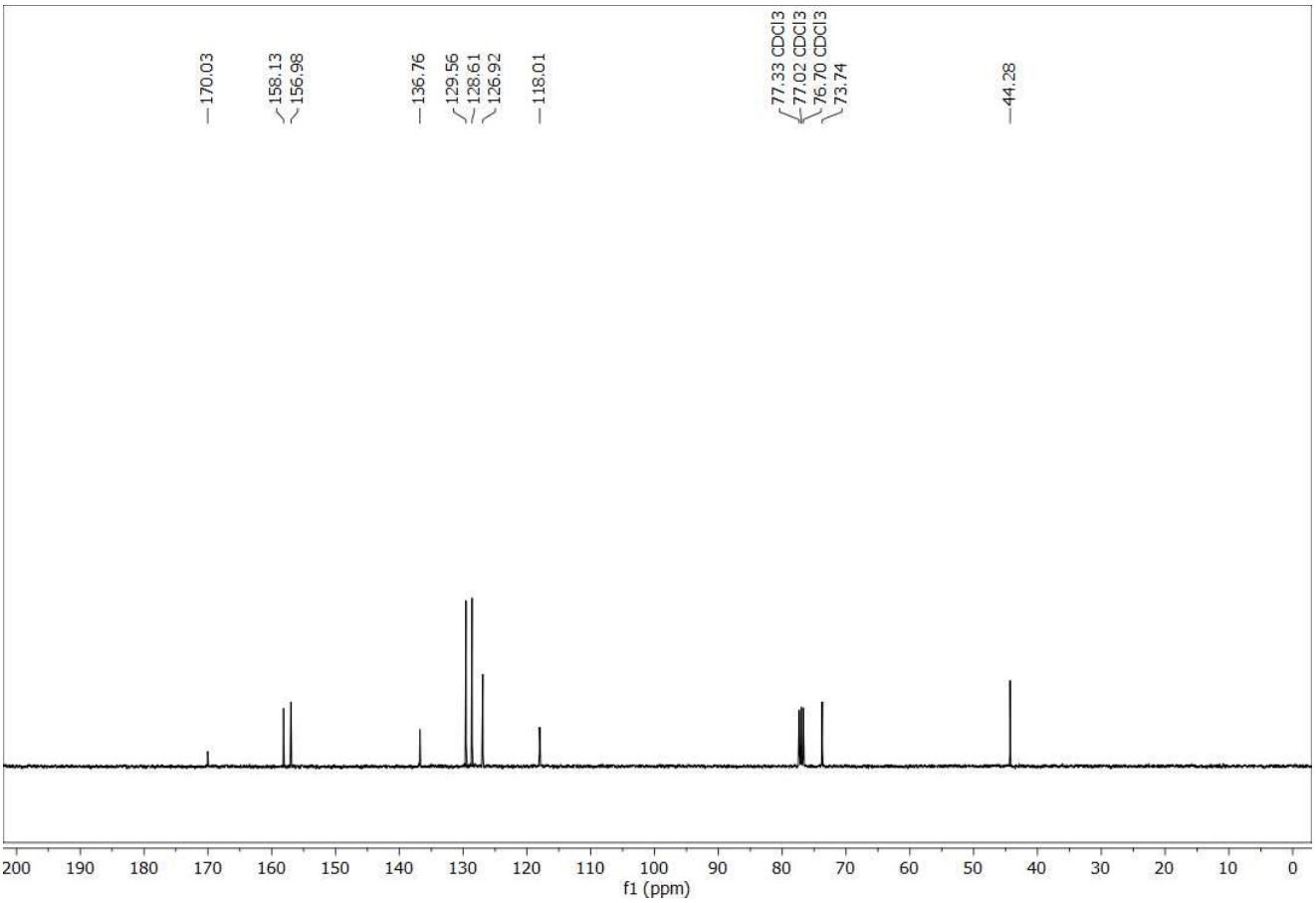
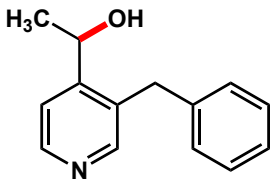


Figure S51: ^{13}C NMR of 2-phenyl-1-(pyrimidin-4-yl)ethanol



2-phenyl-1-(pyridin-4-yl)ethanol - Hydroxylation was accomplished using general procedure and the product was purified by flash column chromatography (20:1 DCM: CH_3OH) to give white solid (83.2 mg, 0.39 mmol, 78%). H-NMR yield obtained: 72%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 – 8.18 (m, 2H), 7.49 (d, J = 5.1 Hz, 1H), 7.31 – 7.16 (m, 3H), 7.07 (d, J = 7.3 Hz, 2H), 5.04 (q, J = 6.4 Hz, 1H), 4.01 (d, J = 2.7 Hz, 2H), 1.29 (dd, J = 6.4, 1.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.2, 151.1, 148.6, 139.5, 131.9, 128.7, 128.5, 126.6, 120.2, 65.4, 35.9, 24.0. HRMS calculated for $C_{14}H_{15}NO$, [M+H] is 214.1232, observed 214.1229.

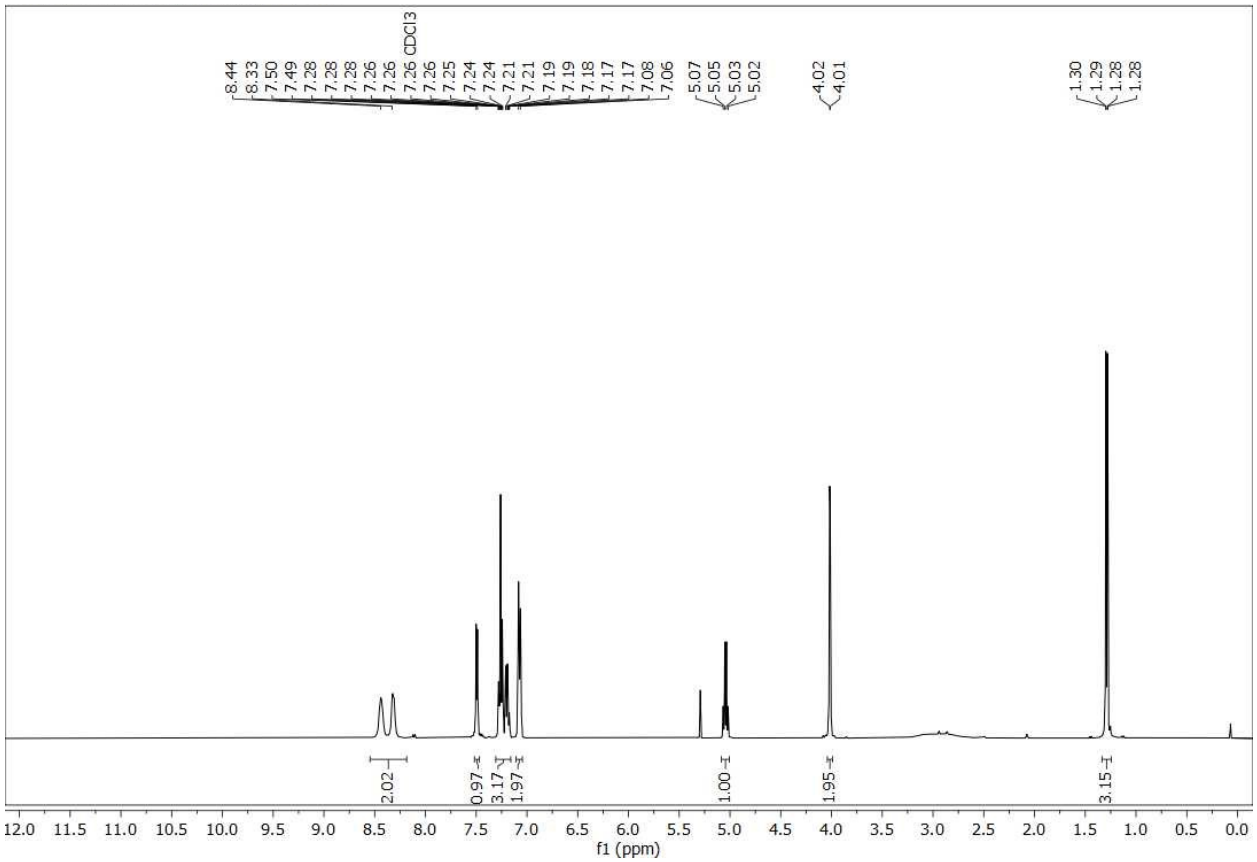


Figure S52: ^{1}H NMR of 2-phenyl-1-(pyridin-4-yl)ethanol

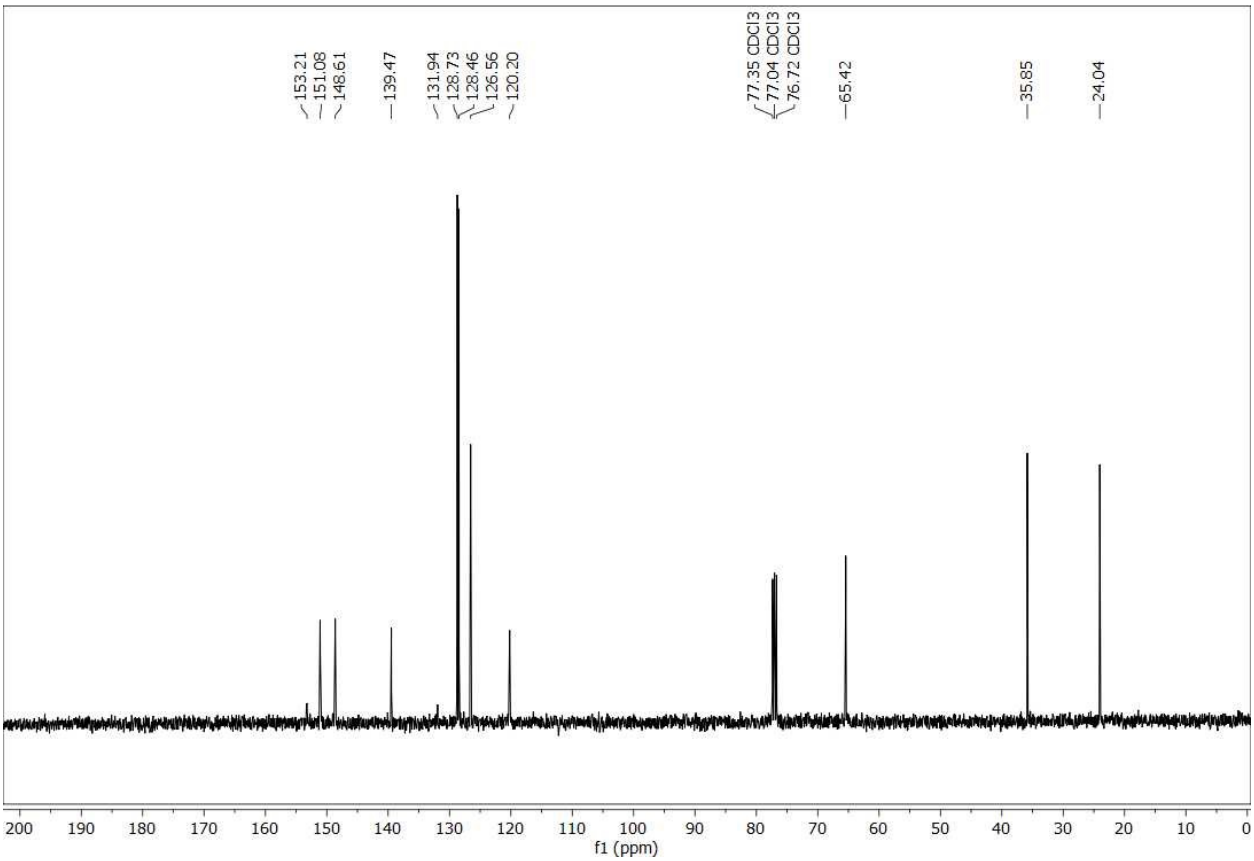
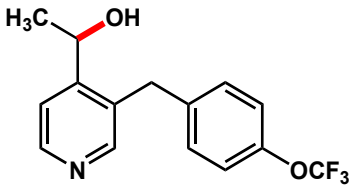


Figure S53: ^{13}C NMR of 2-phenyl-1-(pyridin-4-yl)ethanol



1-(3-(4-(trifluoromethoxy)benzyl)pyridin-4-yl)ethanol - Hydroxylation was accomplished using general procedure and the product was purified by flash column chromatography (20:1 DCM: CH_3OH) to give pale yellow oil (12.2 mg, 0.04 mmol, 25%). 1H-NMR yield obtained: 33%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (s, 1H), 8.35 (s, 1H), 7.51 (d, J = 5.0 Hz, 1H), 7.17 – 7.08 (m, 4H), 5.02 (q, J = 6.4 Hz, 1H), 4.04 (s, 2H), 1.32 (d, J = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.9, 151.2, 149.0, 147.9, 138.2, 129.7, 121.3, 120.5 (J = 227 Hz), 120.2, 65.6, 35.1, 24.1. For the expected –OCF_3 quartet, only the largest of the 1:3:3:1 peaks could be observed; they were observed in essentially unchanged chemical shift as compared to the starting material. One carbon peak was not observed, either due to signal:noise or accidental coincidence. ^{19}F NMR (376 MHz, $CDCl_3$) δ -57.96. HRMS calculated for $C_{15}H_{14}F_3NO_2$, [M+H] is 298.1055, observed 298.1059.

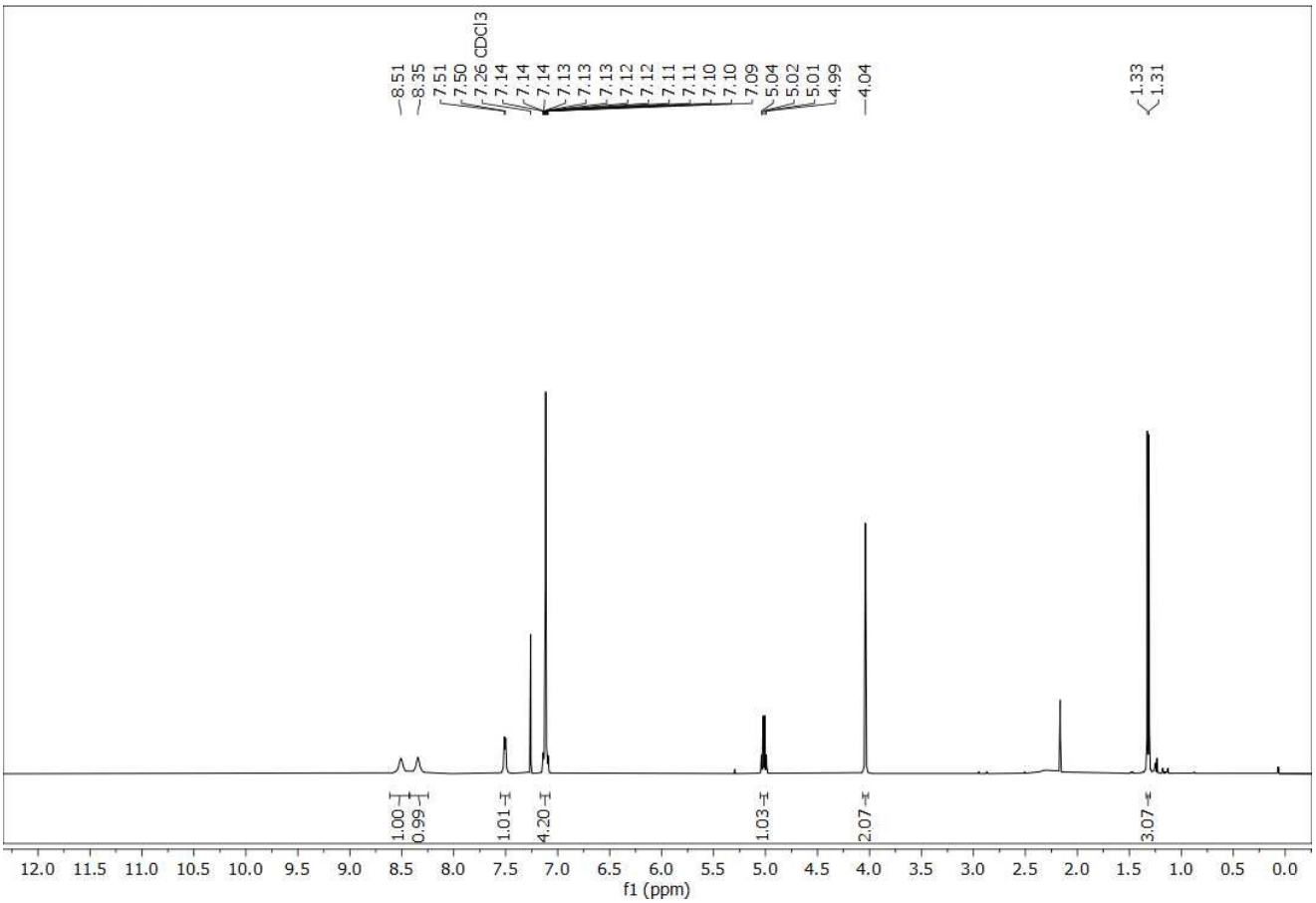


Figure S54: ^{1}H NMR of 1-(3-(4-(trifluoromethoxy)benzyl)pyridin-4-yl)ethanol

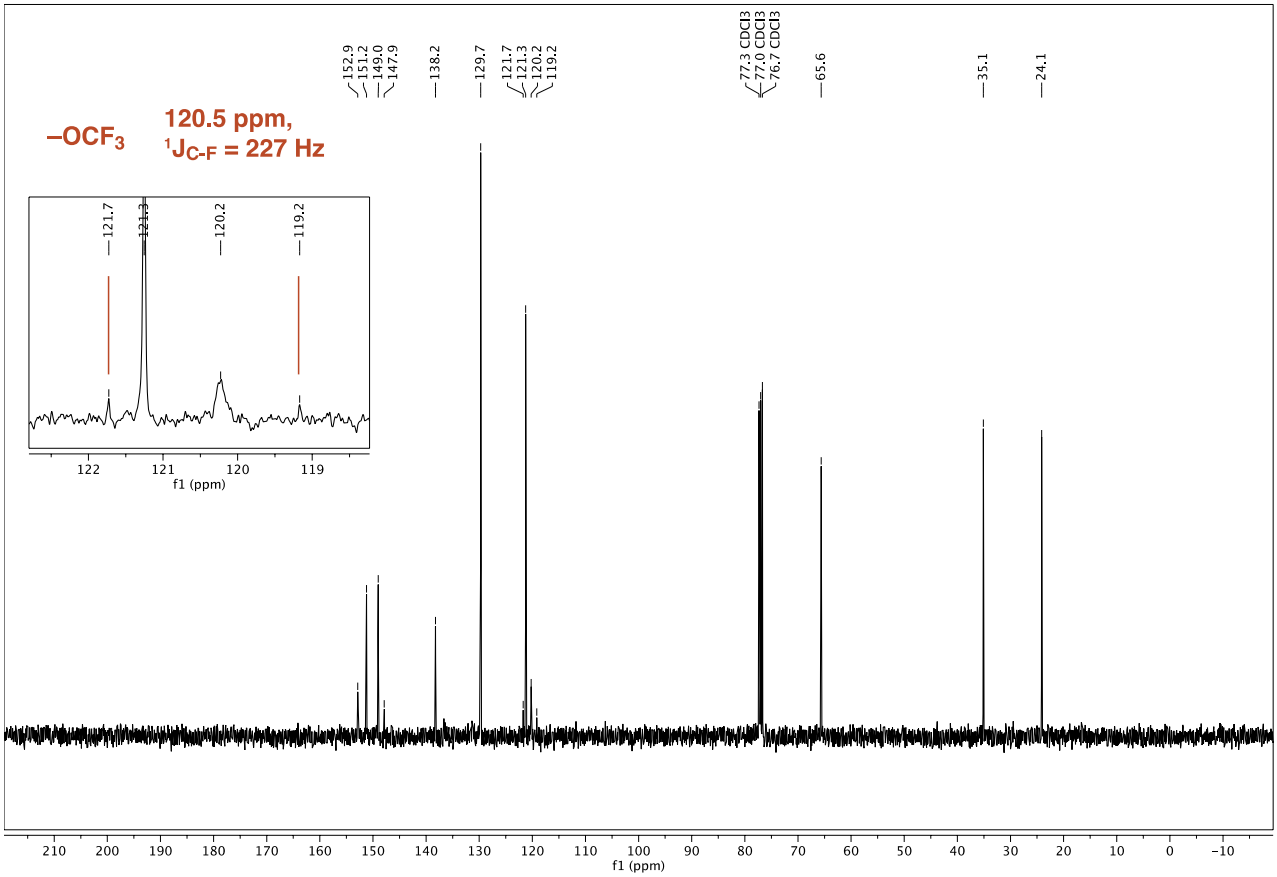


Figure S55: ^{13}C NMR of 1-(3-(4-(trifluoromethoxy)benzyl)pyridin-4-yl)ethanol

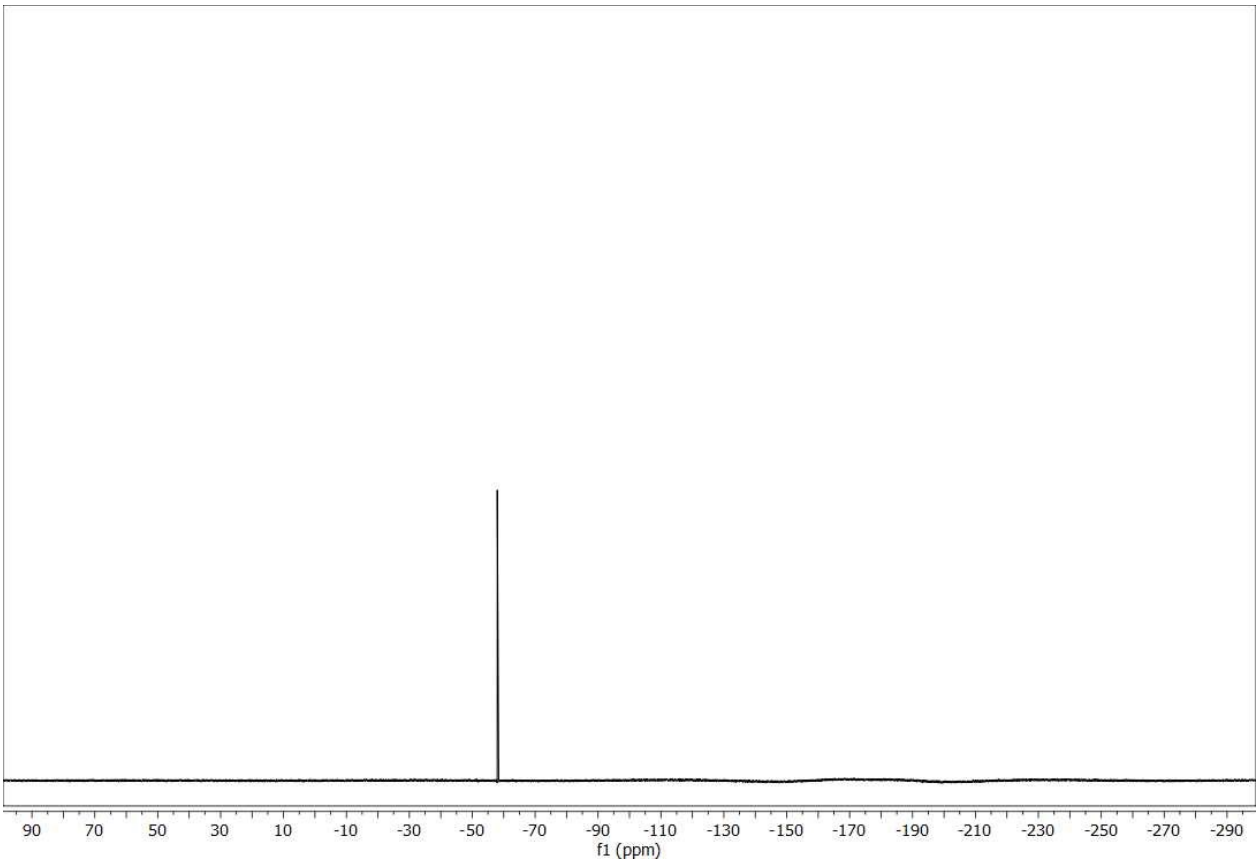
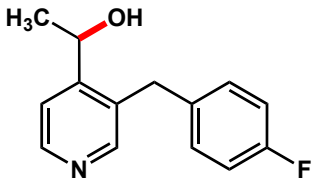


Figure S56: ^{19}F NMR of 1-(3-(4-(trifluoromethoxy)benzyl)pyridin-4-yl)ethanol



1-(3-(4-fluorobenzyl)pyridin-4-yl)ethanol - Hydroxylation was accomplished using general procedure and the product was purified by flash column chromatography (20:1 DCM: CH_3OH) to give brown oil (32 mg, 0.13 mmol, 28%). H-NMR yield obtained: 47% (for 0.125 mmol substrate).

^{1}H NMR (400 MHz, CDCl3) δ 8.43 (d, *J* = 5.0 Hz, 1H), 8.29 (s, 1H), 7.51 (d, *J* = 4.8 Hz, 1H), 7.03 (dd, *J* = 8.6, 5.4 Hz, 2H), 6.99 – 6.90 (m, 2H), 5.03 (q, *J* = 6.4 Hz, 1H), 3.98 (s, 2H), 1.30 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 161.6 (d, *J* = 245.1 Hz), 153.7, 150.6, 148.4, 135.0, 132.0, 129.9 (d, *J* = 8.1 Hz), 120.4, 115.6 (d, *J* = 21.2 Hz), 65.5, 35.0, 24.1. ^{19}F NMR (376 MHz, CDCl3) δ -116.33. HRMS calculated for $C_{14}H_{14}FNO$, [M+H] is 232.1138, observed 232.1138.

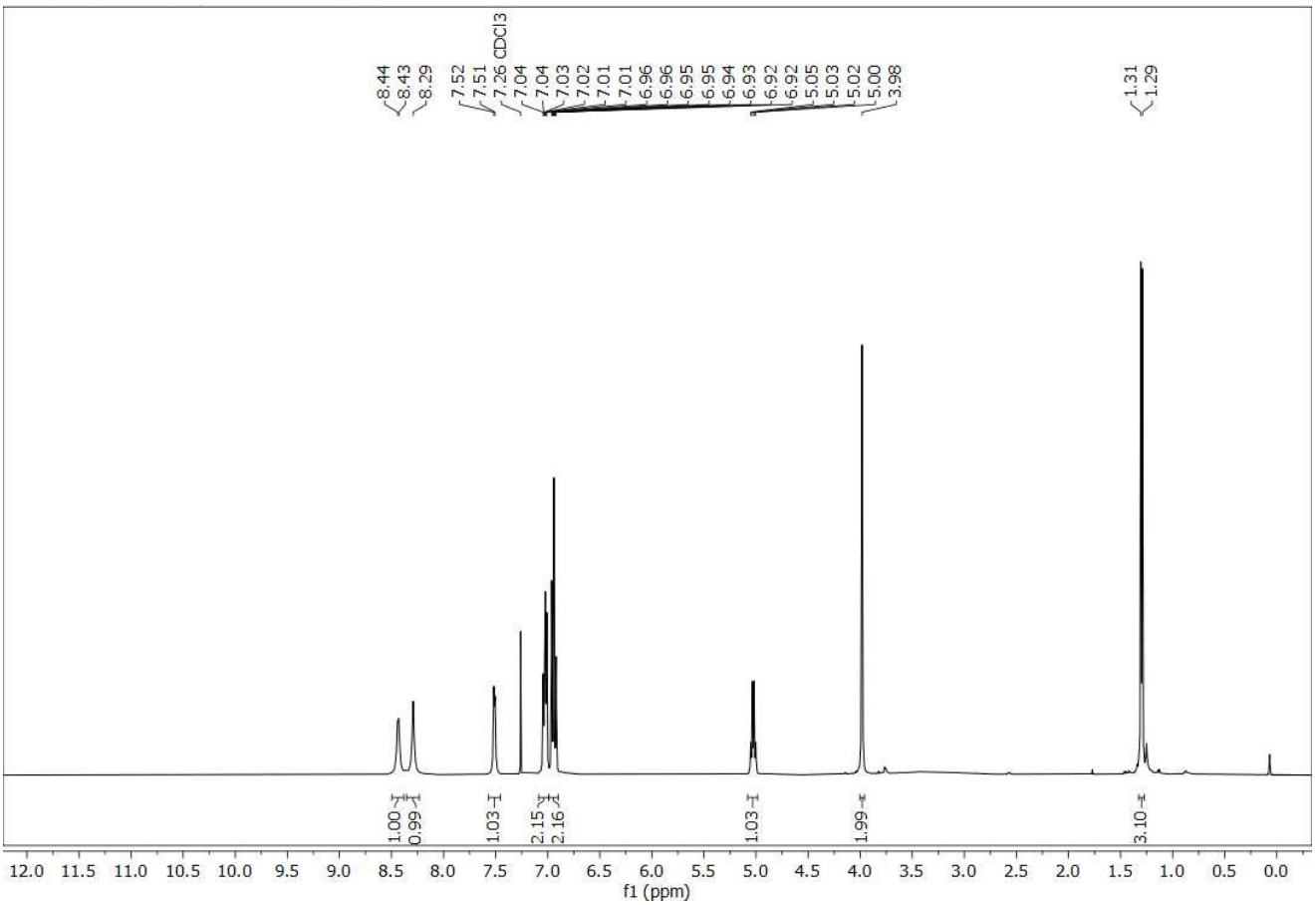


Figure S57: ^{1}H NMR of 1-(3-(4-fluorobenzyl)pyridin-4-yl)ethanol

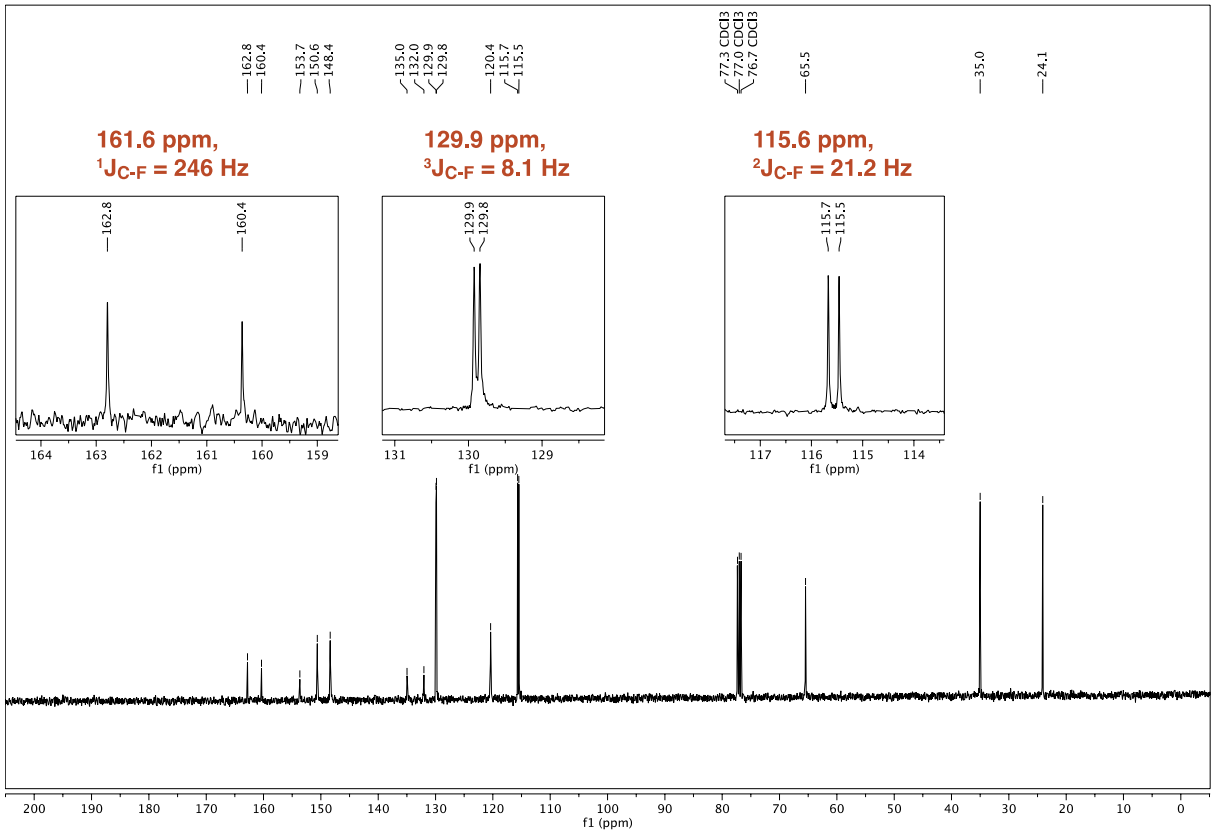


Figure S58: ^{13}C NMR of 1-(3-(4-fluorobenzyl)pyridin-4-yl)ethanol

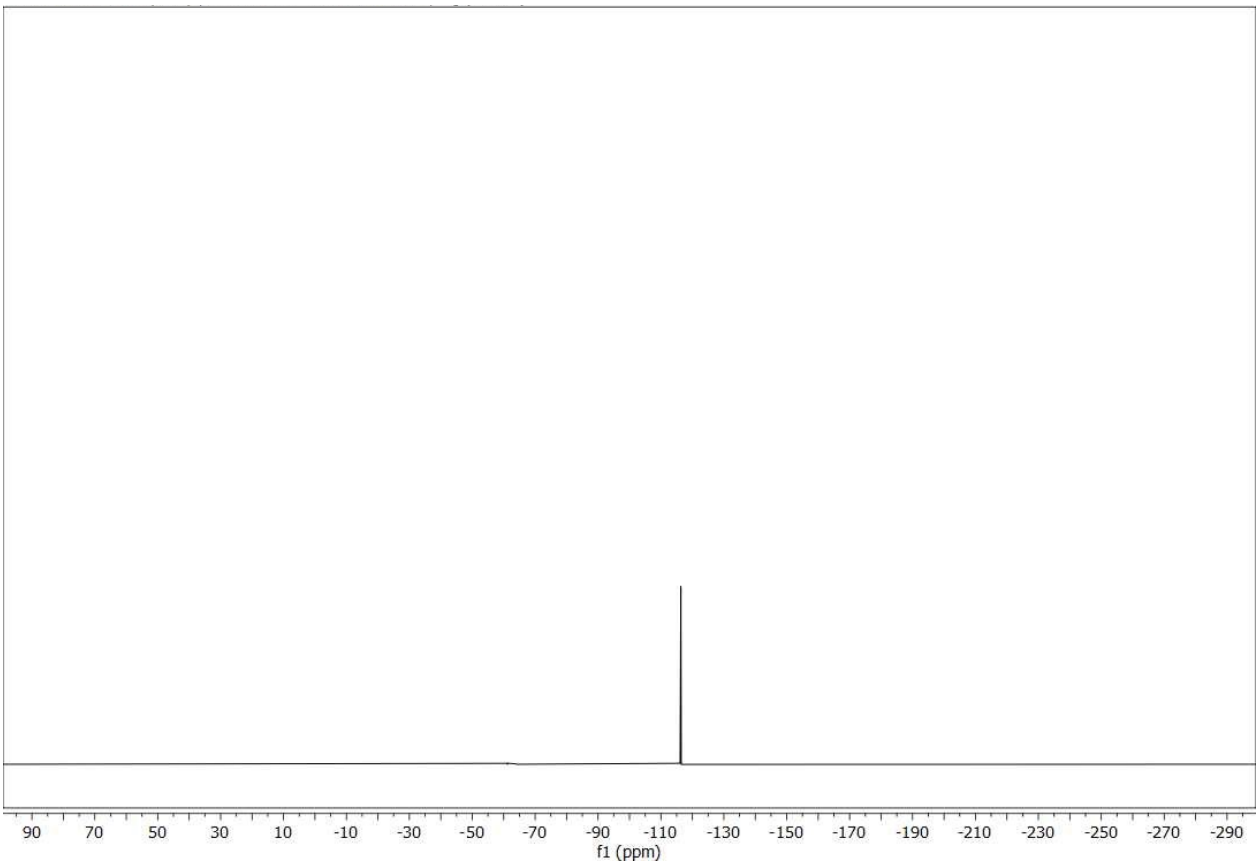
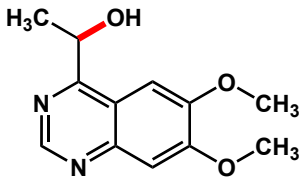


Figure S59: ^{19}F NMR of 1-(3-(4-fluorobenzyl)pyridin-4-yl)ethanol



(6,7-dimethoxyquinazolin-4-yl)ethanol - Hydroxylation was accomplished using general procedure and the product was purified by flash column chromatography (20:1 DCM: CH_3OH) to give yellow solid (52.3 mg, 0.22 mmol, 44%). H-NMR yield obtained: 46%.

^1H NMR (400 MHz, $CDCl_3$) δ 9.10 (s, 1H), 7.38 (s, 1H), 7.14 (s, 1H), 5.47 (q, J = 6.6 Hz, 1H), 4.06 (d, J = 10.0 Hz, 6H), 1.61 (d, J = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.0, 156.4, 151.8, 150.7, 148.2, 116.8, 107.3, 101.0, 77.2, 65.8, 56.5, 56.4, 24.6. HRMS calculated for $C_{12}H_{14}N_2O_3$, [M+H] is 235.1083, observed 235.1081.

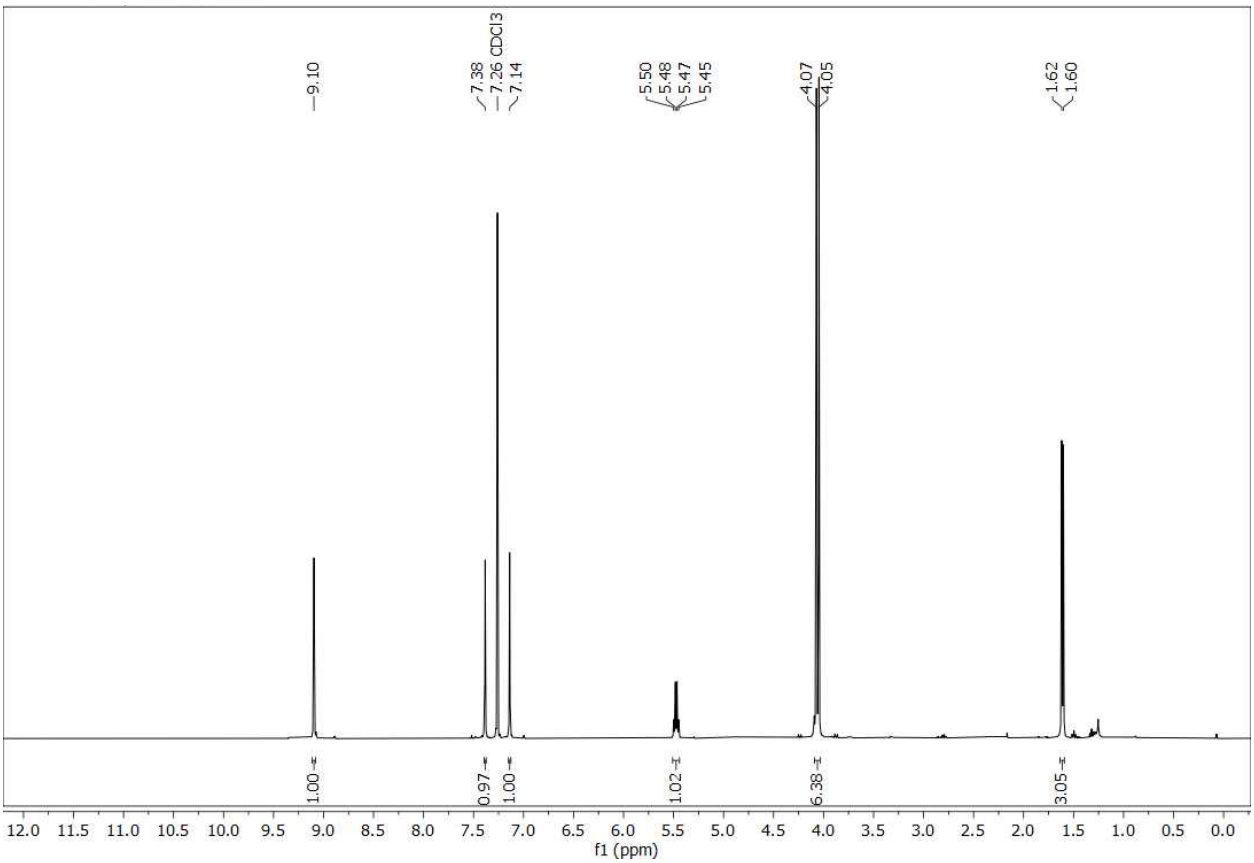


Figure S60: ^{1}H NMR of (6,7-dimethoxyquinazolin-4-yl)ethanol

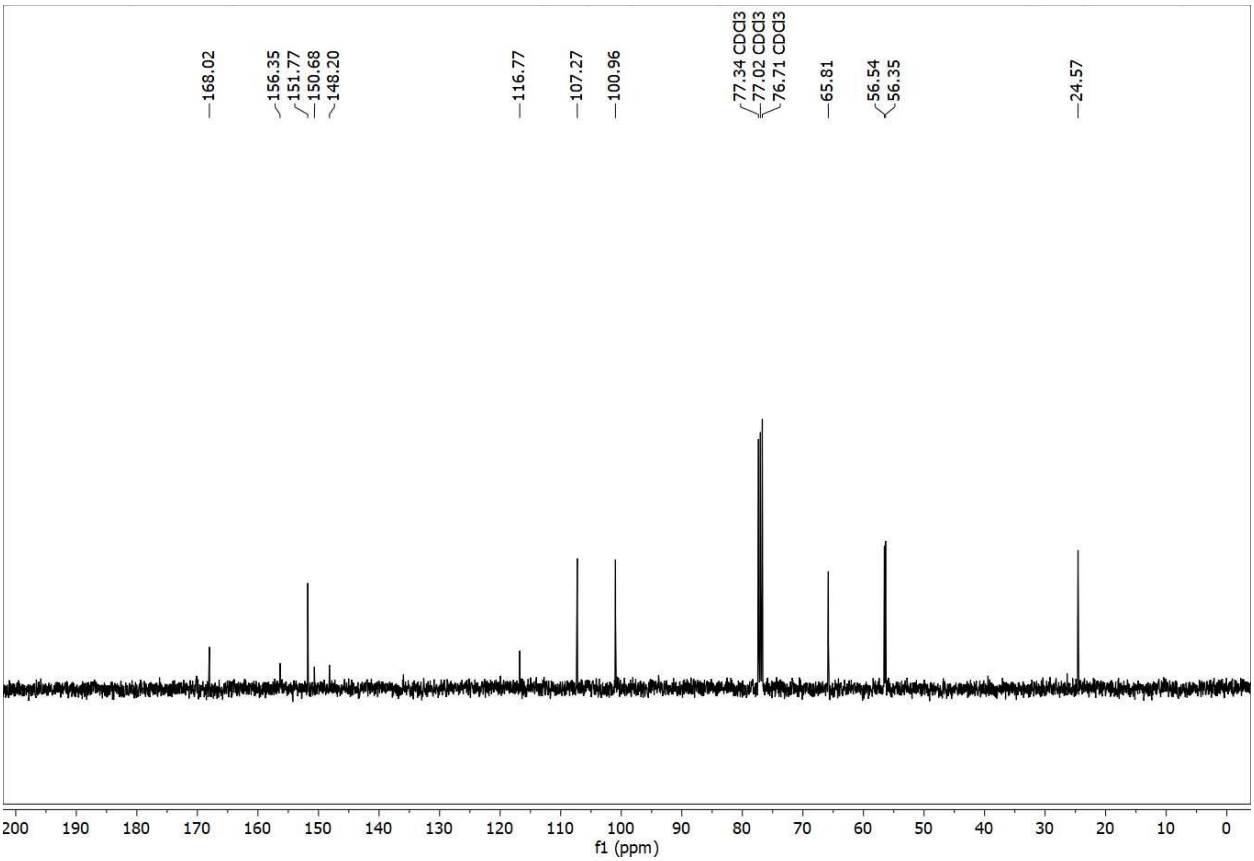
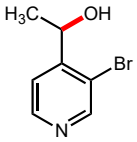


Figure S61: ^{13}C NMR of (6,7-dimethoxyquinazolin-4-yl)ethanol



(3-bromopyridin-4-yl)ethanol was obtained used the standard procedure as a light yellow oil using a gradient elution of 1% to 2% methanol in dichloromethane (43 mg, 0.21 mmol, 43% yield). ^{1}H NMR yield observed: 67%. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.53 (s, 1H), 7.55 (d, J = 5.0 Hz, 1H), 5.13 (q, J = 6.5 Hz, 1H), 3.57 (br s, –OH, 1H), 1.45 (d, J = 6.5 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 154.2, 151.4, 148.5, 121.6, 119.7, 68.1, 23.2 HRMS for C_7H_8BrNO $[M+H]^+$ was 201.9862; found 201.9860.

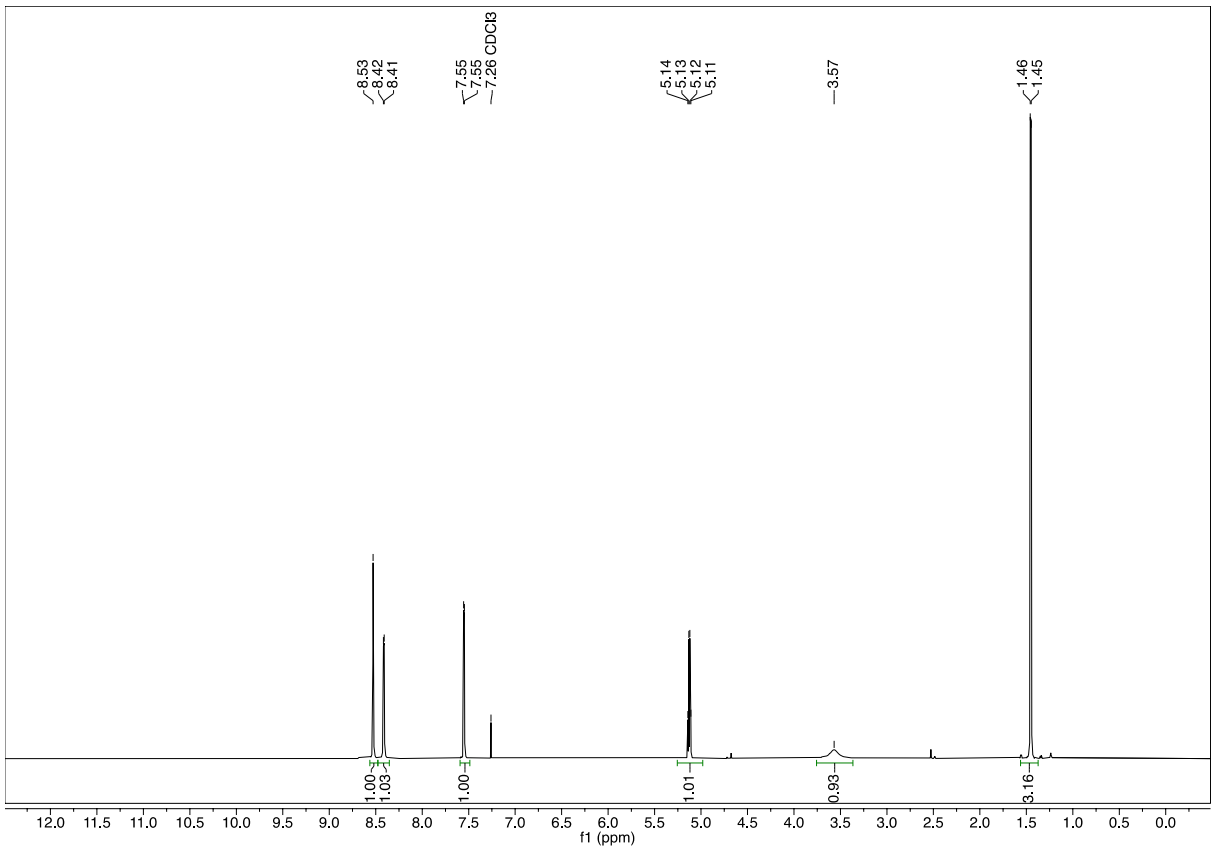


Figure S62: ^{1}H NMR of (3-bromopyridin-4-yl)ethanol

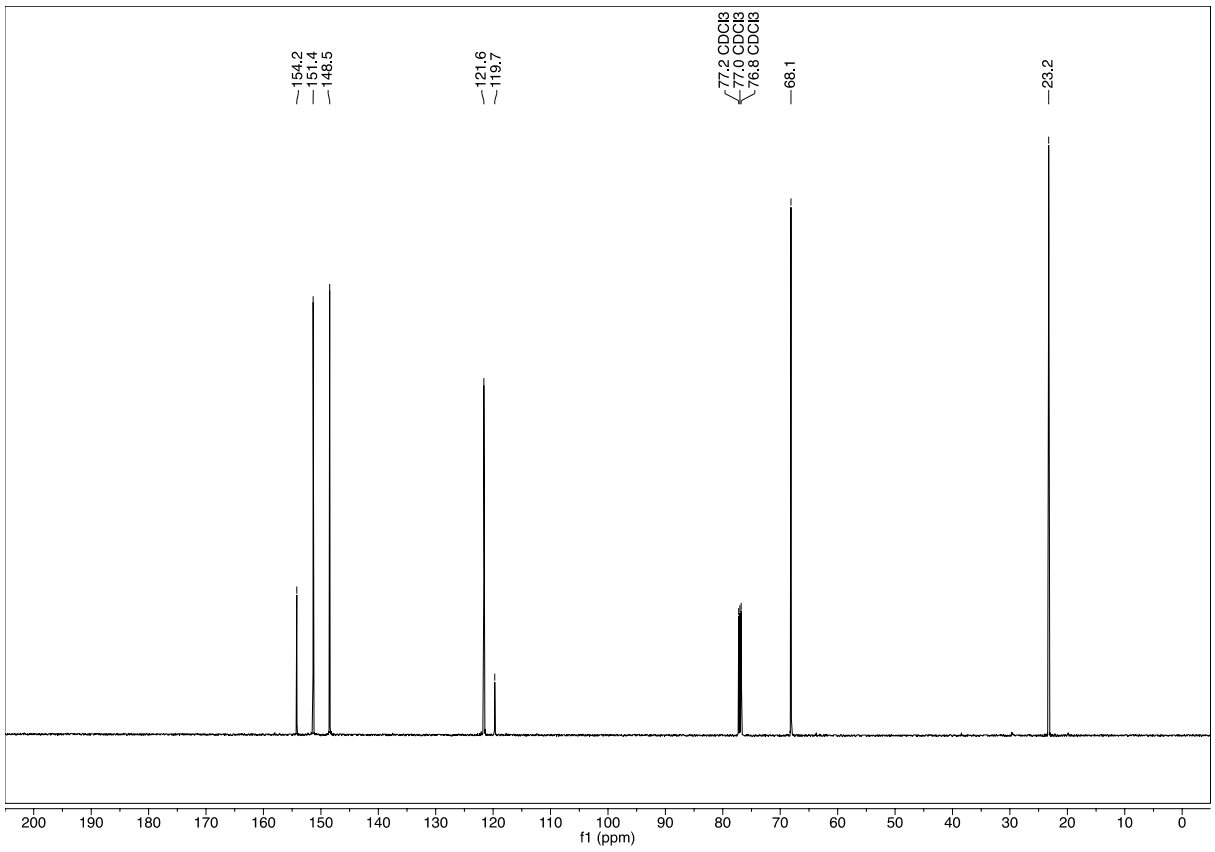
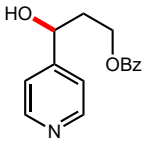


Figure S63: ^{13}C NMR of (3-bromopyridin-4-yl)ethanol



3-hydroxy-3-(4-pyridyl)propyl benzoate was obtained using the standard procedure as a clear oil using a gradient elution of 1% to 4% methanol in dichloromethane (67 mg, 0.26 mmol, 52% yield). ^{1}H NMR yield could not be observed due to overlapping peaks in the key region. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.56 (d, *J* = 6.1 Hz, 2H), 8.01 (d, *J* = 6.9 Hz, 2H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 2H), 7.32 (d, *J* = 6.0 Hz, 2H), 4.87 (dd, *J* = 9.1, 4.1 Hz, 2H), 4.68 (ddd, *J* = 11.4, 8.6, 4.7 Hz, 2H), 4.40 (dt, *J* = 11.1, 5.4 Hz, 2H), 2.96 (s, 1H), 2.21 (dddd, *J* = 14.3, 9.0, 5.5, 4.1 Hz, 1H), 2.12 (ddt, *J* = 14.3, 9.3, 5.0 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 166.9, 152.7, 150.0, 133.2, 129.8, 129.6, 128.5, 128.5, 120.6, 69.6, 61.5, 38.1. HRMS calculated for $C_{15}H_{15}NO_3$ $[M+H]^+$ 258.1125; found 258.1125.

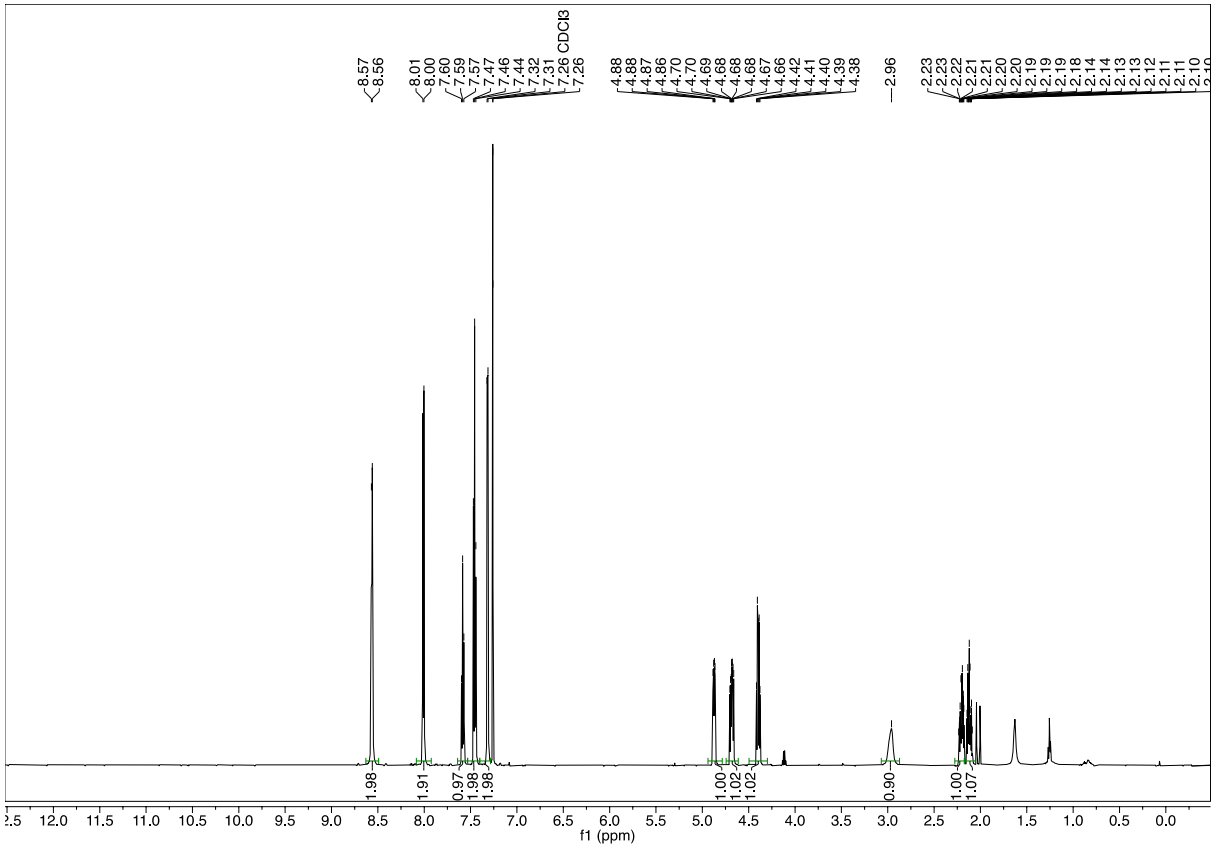


Figure S64: ^{1}H NMR of 3-hydroxy-3-(4-pyridyl)propyl benzoate

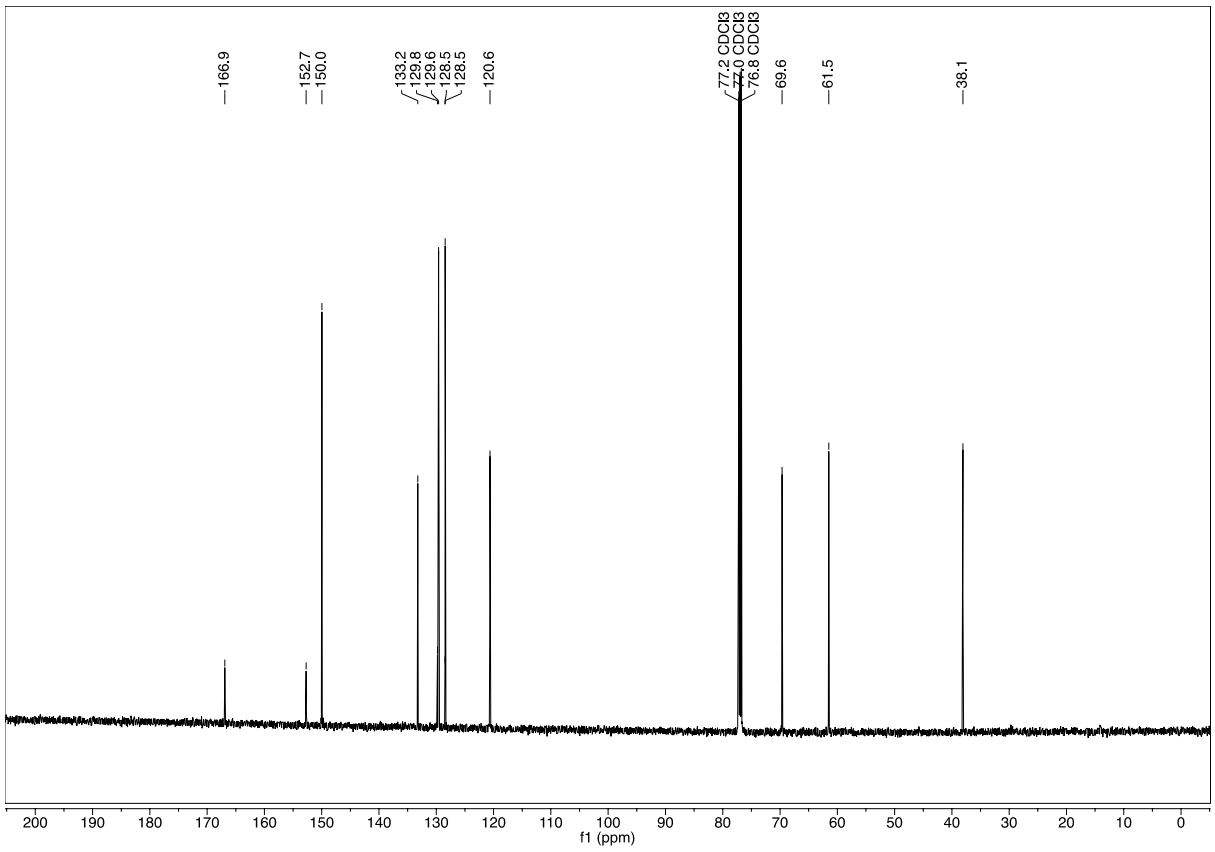
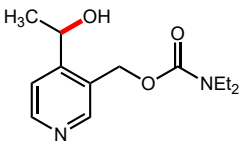


Figure S65: ^{13}C NMR of 3-hydroxy-3-(4-pyridyl)propyl benzoate



4-(1-hydroxyethyl)-3-(hydroxymethyl)pyridyl *N*,*N*-diethylcarbamate was obtained as a clear oil using the 'anhydrous' isolated yield procedure, with a gradient of 4:1 hexanes:ethyl acetate to 100% ethyl acetate (57 mg, 0.23 mmol, 45% yield). ^{1}H NMR yield observed: 52%. Rotational isomerism about the diethyl carbamate results in broadening of the *N*-ethyl signals in the ^{1}H NMR, and inequivalent carbon atoms for the two ethyl group sidechains.^{1}H NMR (600 MHz, $CDCl_3$) δ 8.52 (s, 1H), 8.50 (d, J = 5.2 Hz, 1H), 7.48 (d, J = 5.1 Hz, 1H), 5.24 (d, J = 12.9 Hz, 1H), 5.18 (qd, J = 6.4, 2.6 Hz, 1H), 5.12 (d, J = 12.9 Hz, 1H), 3.67-3.61 (br, –OH, 1H), 3.30-3.20 (br, 4H), 1.46 (d, J = 6.5 Hz, 3H), 1.13-1.04 (br, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 155.4, 153.1, 150.3, 149.9, 128.6, 120.0, 65.2, 61.6, 61.6, 41.9, 41.3, 24.1, 14.0, 13.3. HRMS for $C_{13}H_{20}N_2O_3$ $[M+H]^+$ was 253.1547; found 253.1542.

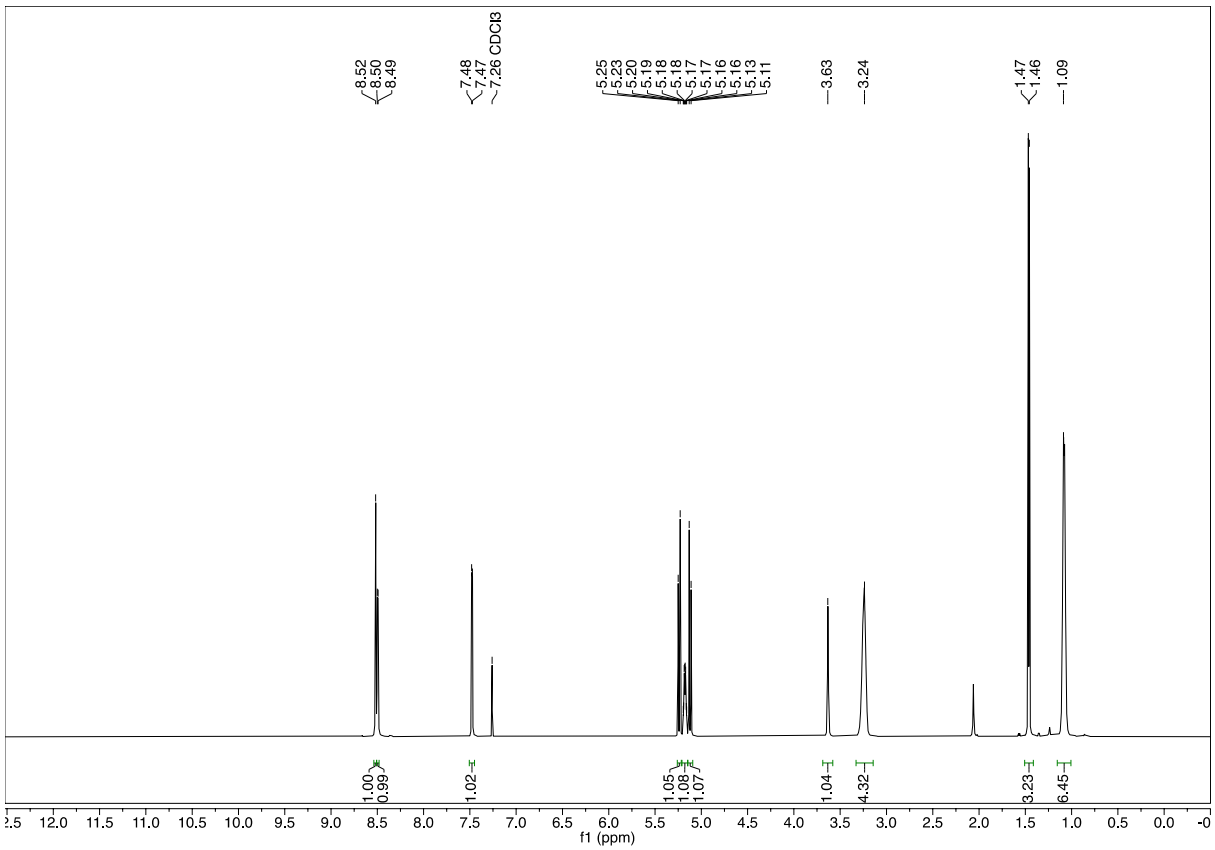


Figure S66: [1]H NMR of 4-(1-hydroxyethyl)-3-(hydroxymethyl)pyridyl *N*,*N*-diethylcarbamate

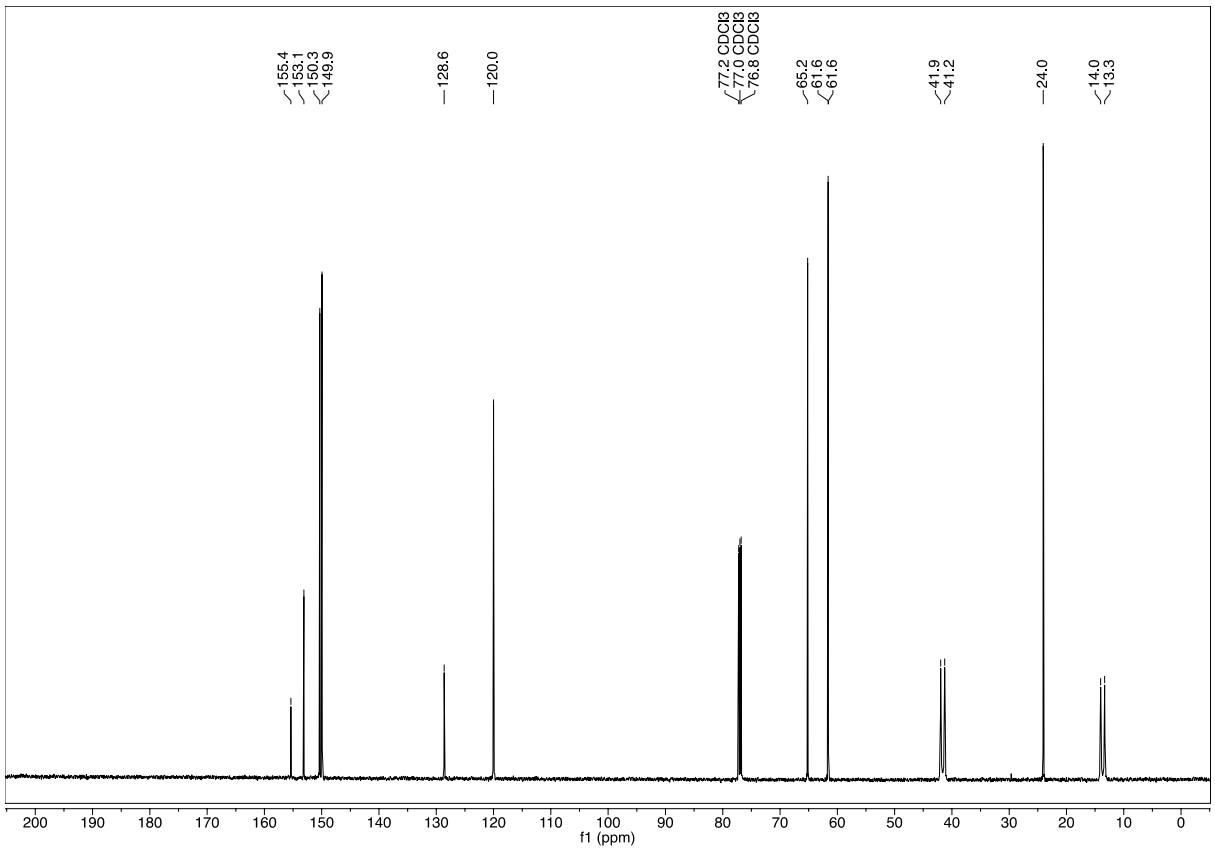
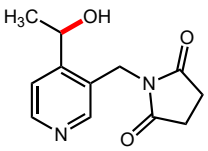


Figure S67: ^{13}C NMR of 4-(1-hydroxyethyl)-3-(hydroxymethyl)pyridyl *N*,*N*-diethylcarbamate



4-(1-hydroxyethyl)-3-(succinimidylmethyl)pyridine was obtained as a clear oil using the 'anhydrous' isolated yield procedure, with a gradient of 4:1 hexanes:ethyl acetate to 100% ethyl acetate (64 mg, 0.27 mmol, 55% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.48 (d, J = 5.2 Hz, 1H), 8.45 (s, 1H), 7.41 (d, J = 5.2 Hz, 1H), 5.37 (q, J = 6.5 Hz, 1H), 4.86 (d, J = 14.8 Hz, 1H), 4.70 (d, J = 14.8 Hz, 1H), 3.47-3.30 (br, –OH, 1H), 2.73 (s, 4H), 1.50 (d, J = 6.5 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 177.0, 152.4, 150.8, 149.7, 127.9, 120.2, 65.3, 36.4, 28.2, 23.6. HRMS for $C_{12}H_{24}N_2O_3$ $[M+H]^+$ was 235.1077; found 235.1075.

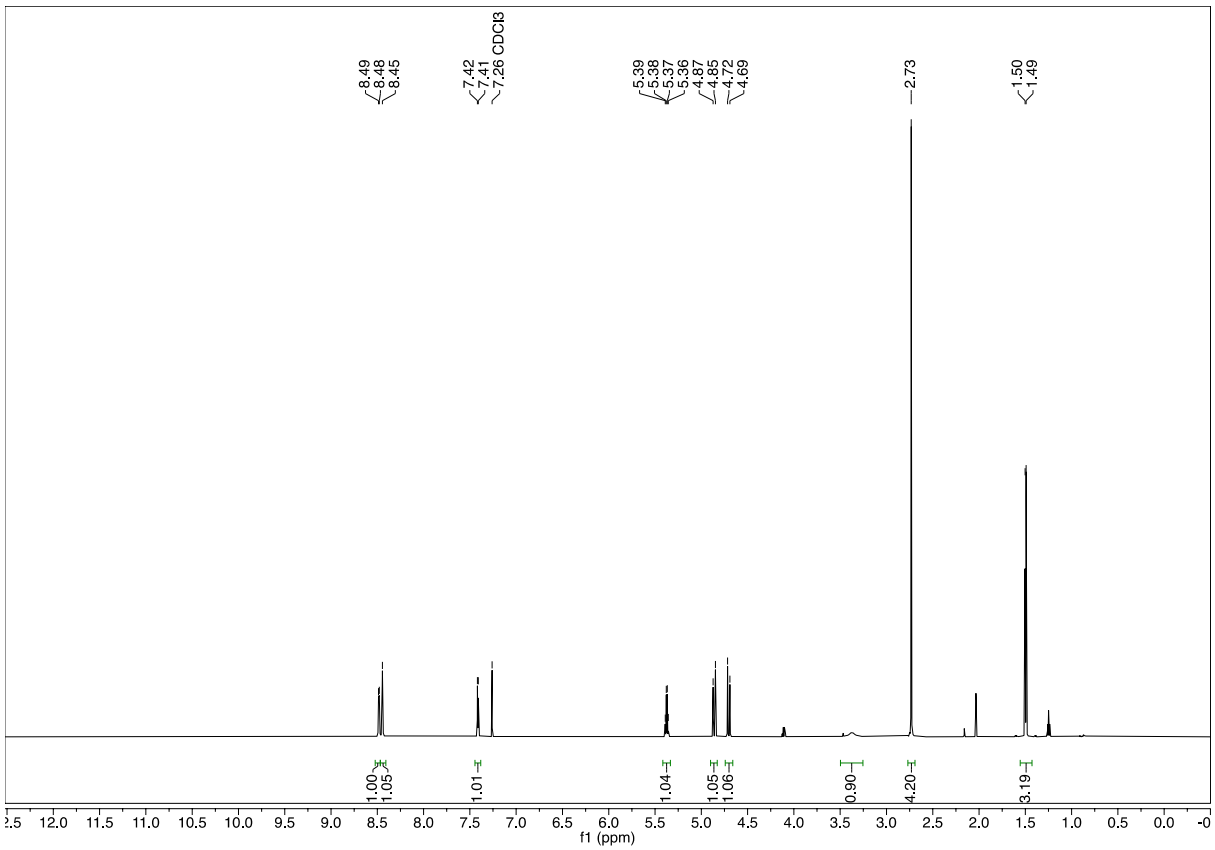


Figure S68: ^{1}H NMR of 4-(1-hydroxyethyl)-3-(succinimidylmethyl)pyridine

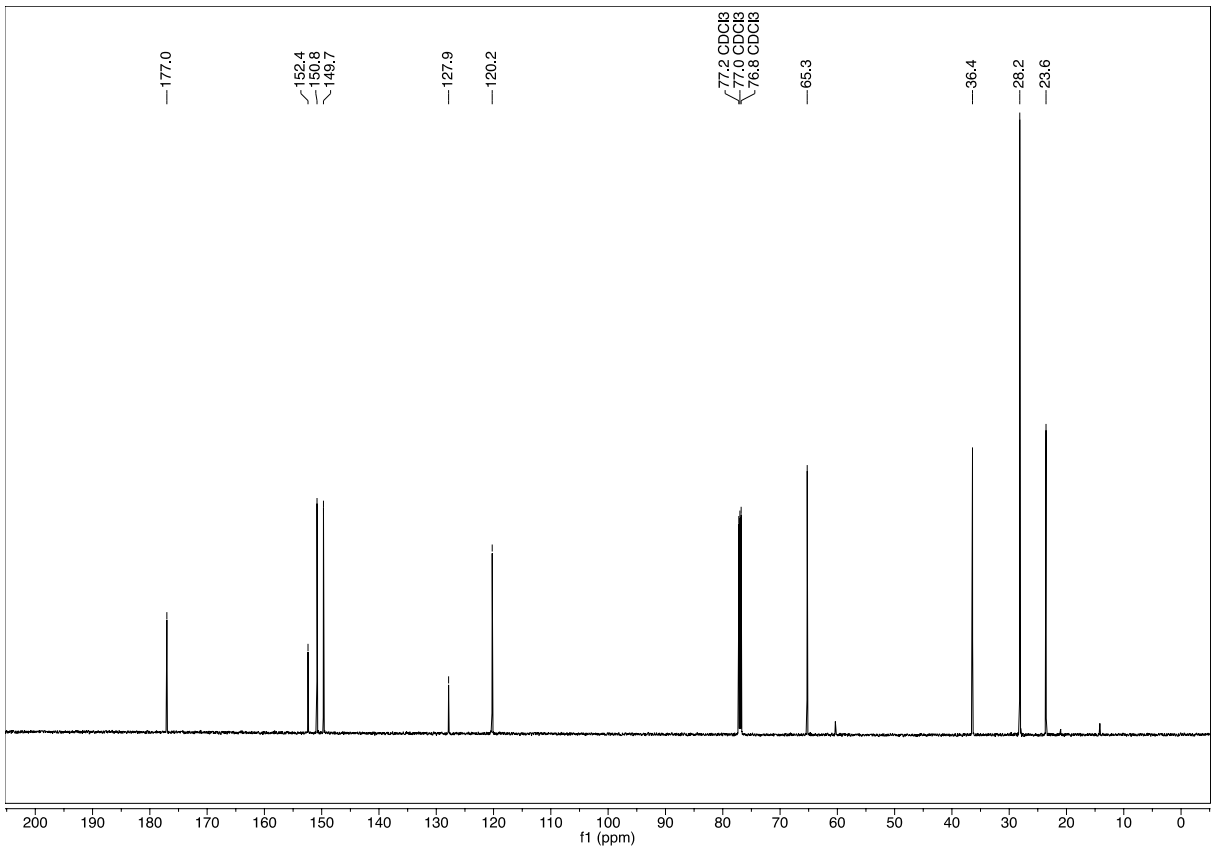


Figure S69: ^{13}C NMR of 4-(1-hydroxyethyl)-3-(succinimidylmethyl)pyridine

1-Methylfuro[3,4-*c*]pyridin-3(1*H*)-one was obtained—from ethyl 4-ethylnicotinate as the starting material—initially as a clear oil (39 mg, 0.26 mmol, 52% yield) using the 'anhydrous' isolation procedure with an eluent system of 4:1 hexanes:ethyl acetate. Upon standing overnight in a scintillation vial, the clear oil solidified into a colourless solid, with ^{1}H NMR analysis suggesting that this solid was the hydrate of the desired product. ^{1}H NMR yield observed was 57%. ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.18 (d, J = 1.2 Hz, 1H), 8.88 (d, J = 5.1 Hz, 1H), 7.44 (dt, J = 5.1, 1.0 Hz, 1H), 5.60 (q, J = 6.8 Hz, 1H), 1.67 (d, J = 6.8 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 168.4, 159.0, 153.5, 148.3, 122.2, 116.6, 77.3, 19.8. HRMS for $C_8H_7NO_2$ $[M+H]^+$ was 150.0550; found 150.0547.

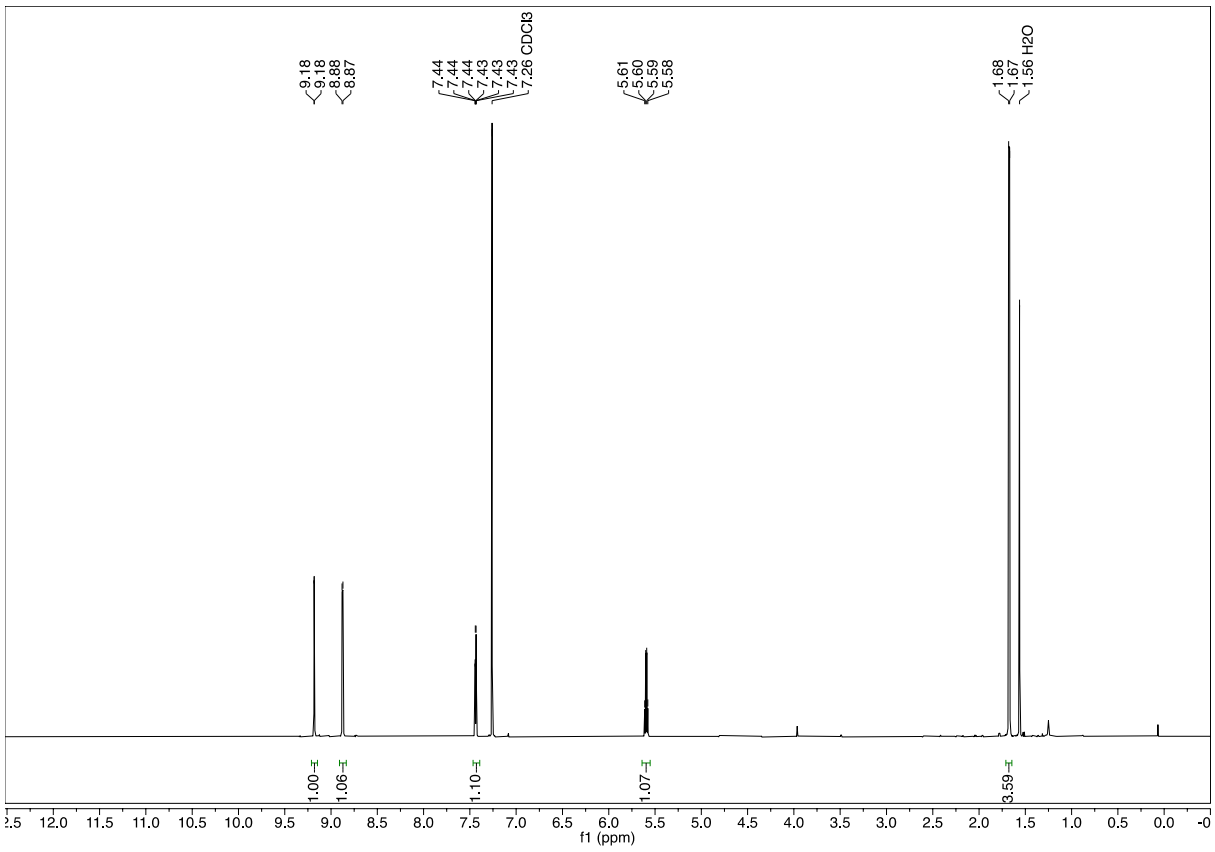


Figure S70: ^{1}H NMR of 1-Methylfuro[3,4-*c*]pyridin-3(1*H*)-one

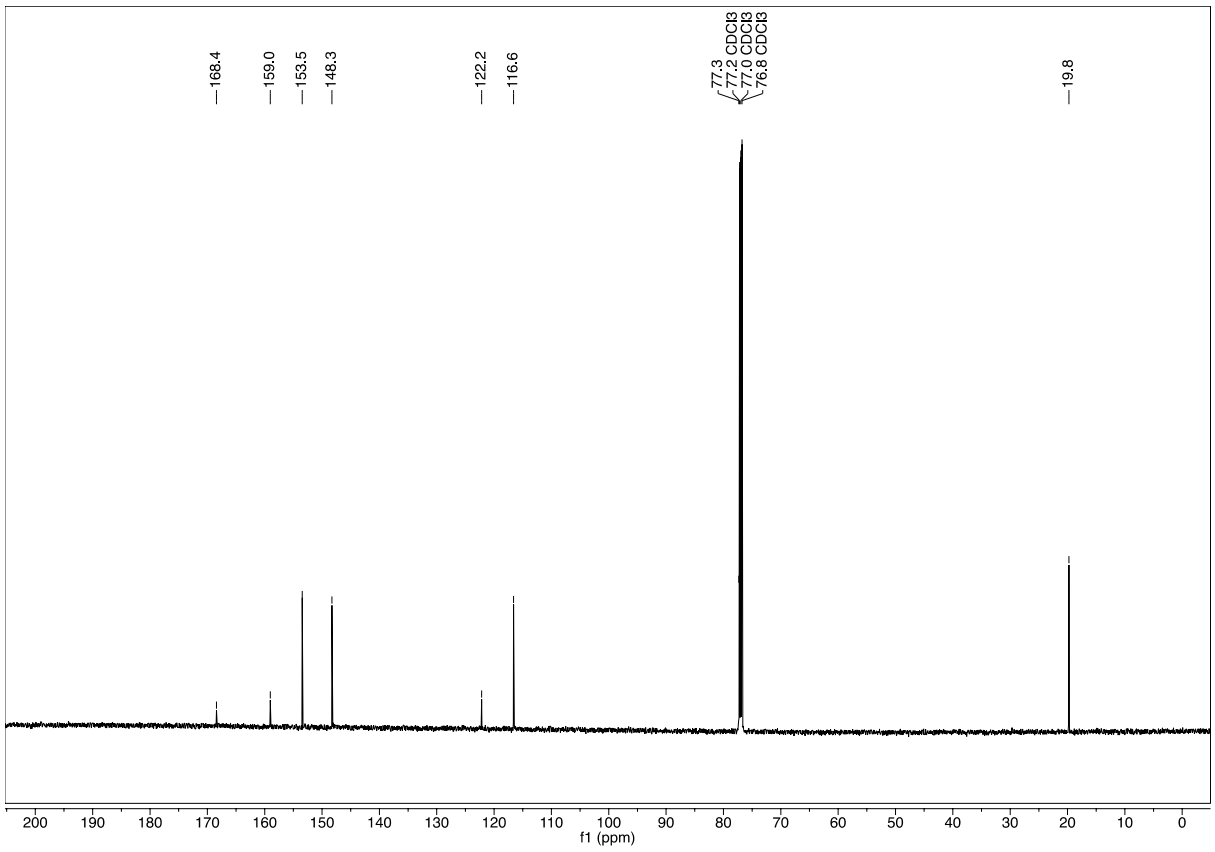
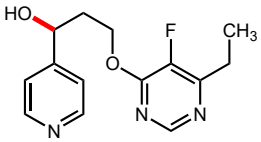


Figure S71: ^{13}C NMR of 1-Methylfuro[3,4-*c*]pyridin-3(1*H*)-one



4-ethyl-5-fluoro-6-pyrimidinyl 3-hydroxy-3-(4-pyridyl)propyl ether was obtained as a bright yellow oil using the 'anhydrous' isolated yield procedure, with a gradient of 4:1 hexanes:ethyl acetate to 100% ethyl acetate (40 mg, 0.14 mmol, 29% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.53 (s, 2H), 8.42 (s, 1H), 7.32 (d, *J* = 6.2 Hz, 2H), 4.87 (dd, *J* = 9.4, 3.7 Hz, 1H), 4.80 (ddd, *J* = 11.2, 8.9, 4.4 Hz, 1H), 4.51 (dt, *J* = 10.9, 5.2 Hz, 1H), 3.91 (s, 1H), 2.81 (qd, *J* = 7.6, 2.3 Hz, 2H), 2.26 (dddd, *J* = 14.4, 8.9, 5.3, 3.7 Hz, 1H), 2.11 (dddd, *J* = 14.5, 9.4, 5.1, 4.4 Hz, 1H), 1.29 (t, *J* = 7.6 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 157.8 (*J* = 10.6 Hz), 157.7 (*J* = 12.1 Hz), 153.0, 152.0 (*J* = 10.6 Hz), 149.8, 144.1 (*J* = 263 Hz), 120.7, 69.2, 64.1, 38.1, 23.9, 12.1, 11.9. HRMS calculated for $C_{14}H_{16}FN_3O_2$ was 278.1299; found 278.1298.

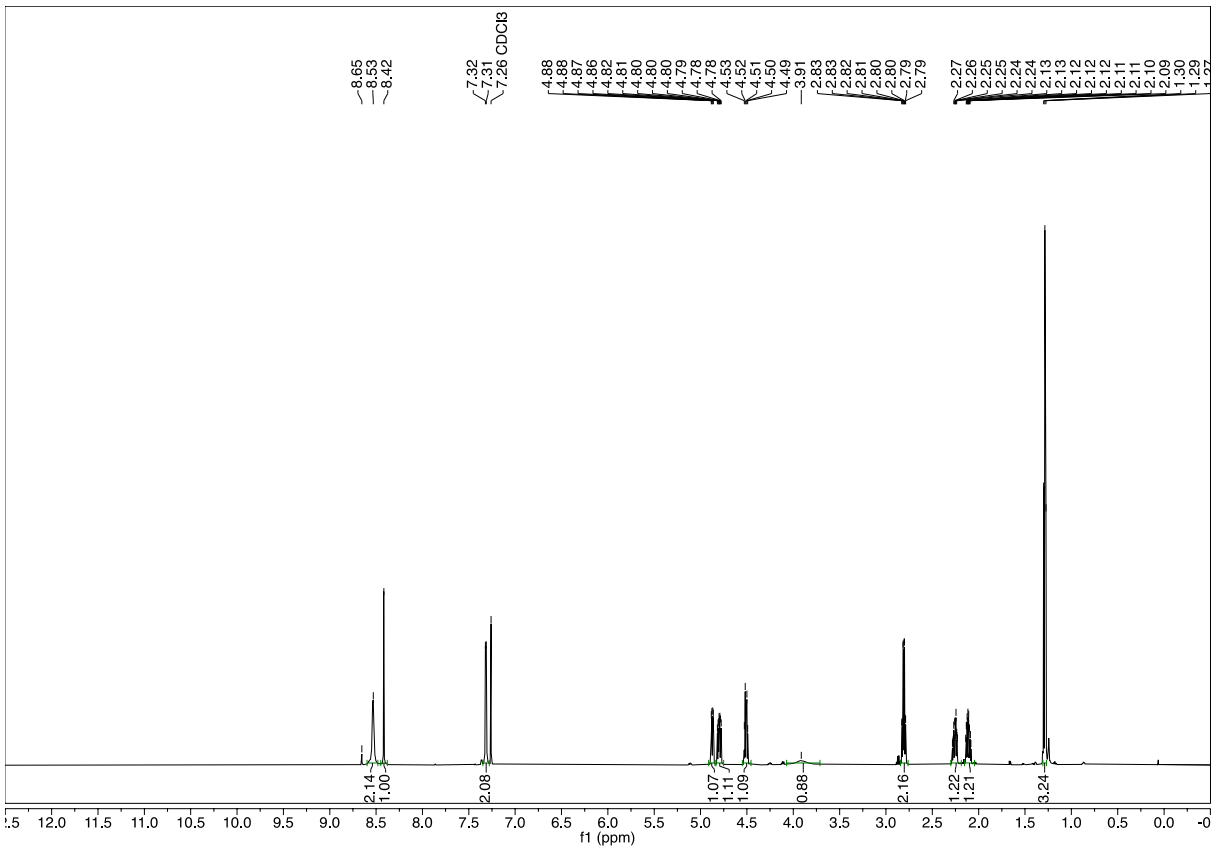


Figure S72: ^{1}H NMR of 4-ethyl-5-fluoro-6-pyrimidinyl 3-hydroxy-3-(4-pyridyl)propyl ether

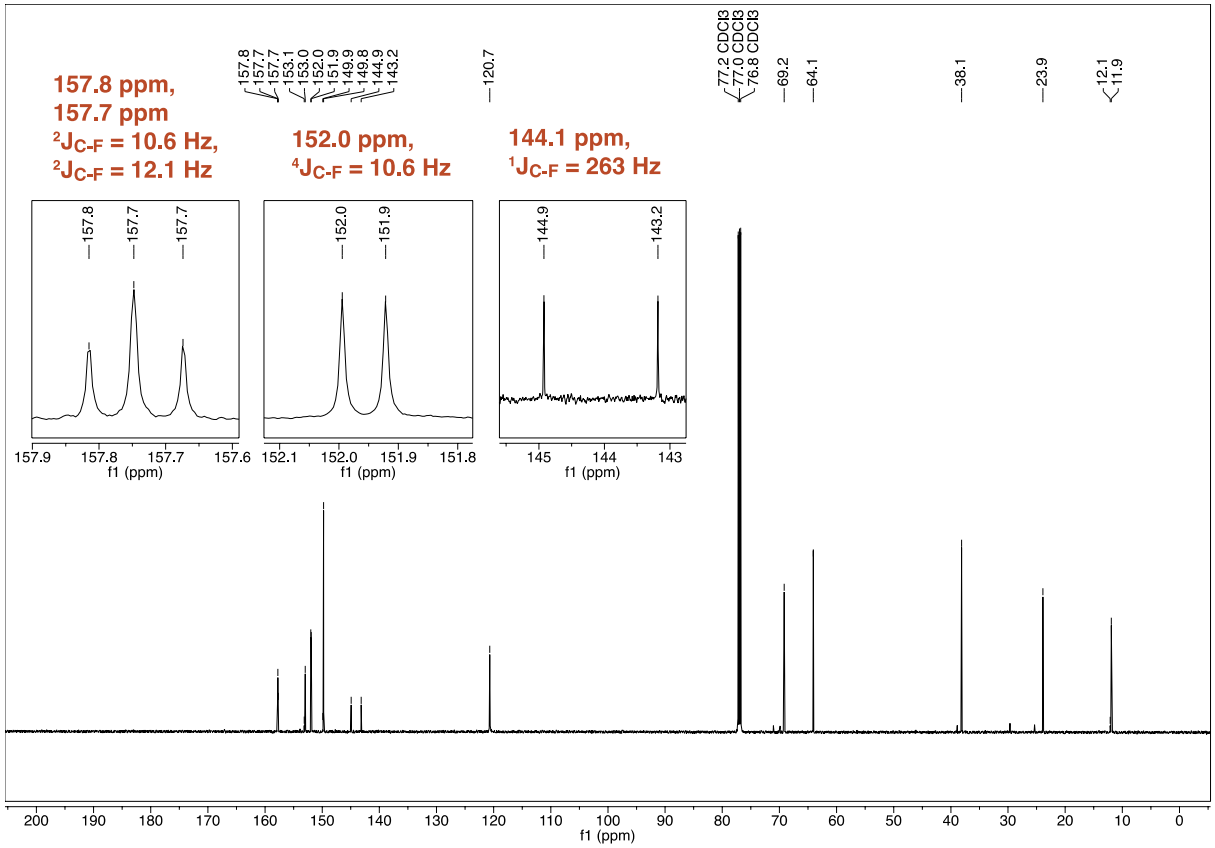
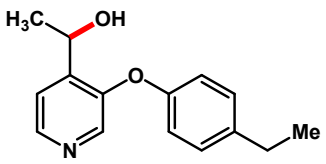


Figure S73: ^{1}H NMR of 4-ethyl-5-fluoro-6-pyrimidinyl 3-hydroxy-3-(4-pyridyl)propyl ether



(3-(4-ethylphenoxy)pyridin-4-yl)ethanol - H-NMR of the crude reaction mixture obtained did not provide the prominent peaks for the ethyl groups of the substrate showcasing the degradation of the reactant as observed in the Figure S74.

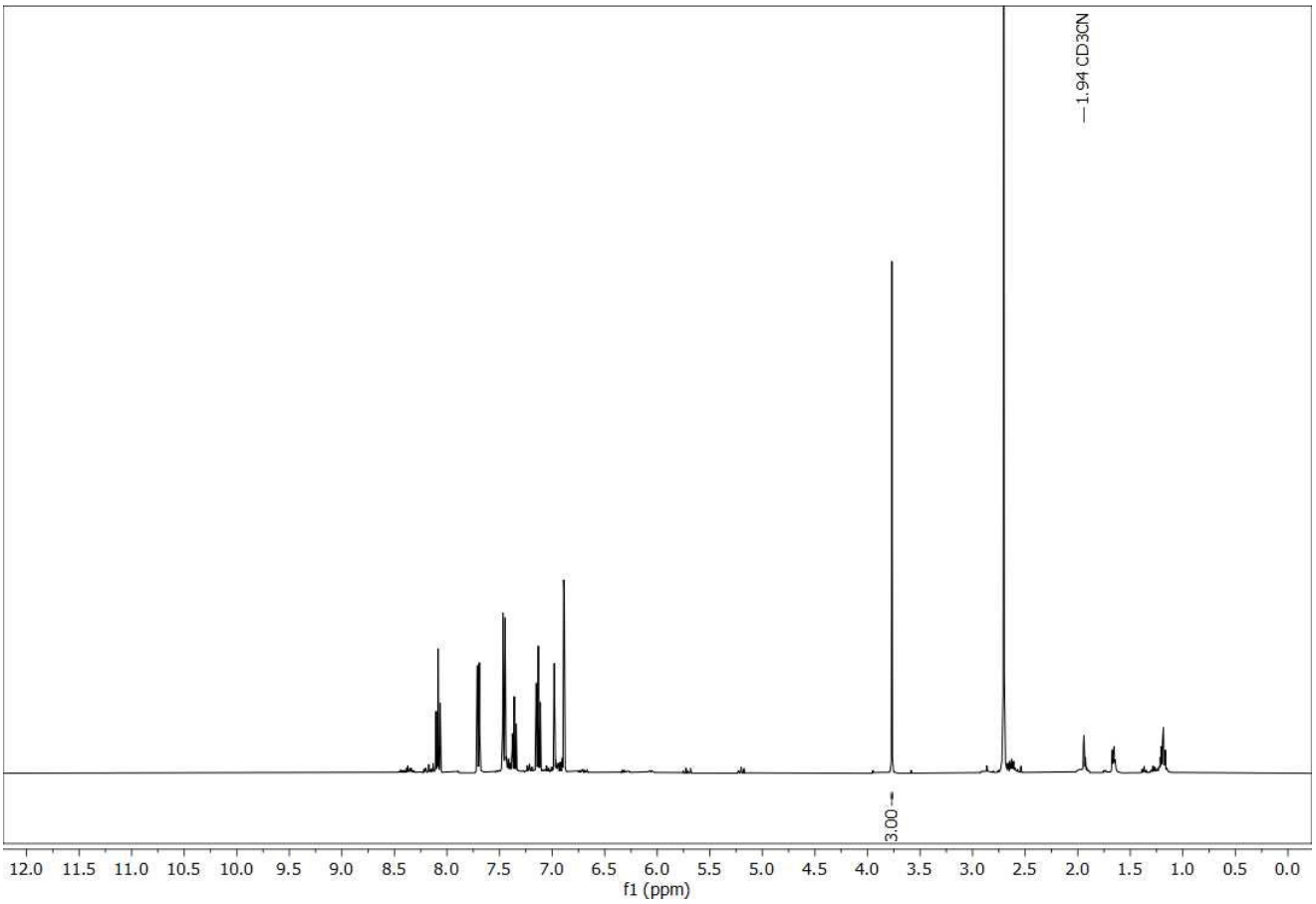
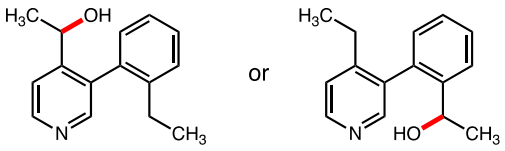


Figure S74: ^{1}H NMR of the crude reaction mixture of (3-(4-ethylphenoxy)pyridin-4-yl)ethanol



1H-NMR of the crude reaction mixture obtained with relaxation decay of 10 sec provided peaks for the benzylic -CH (quartet) around 5.78 and 5.65 ppm, doublet obtained from -CH_3 indicates that hydroxylation at both benzylic sites might be taking place.

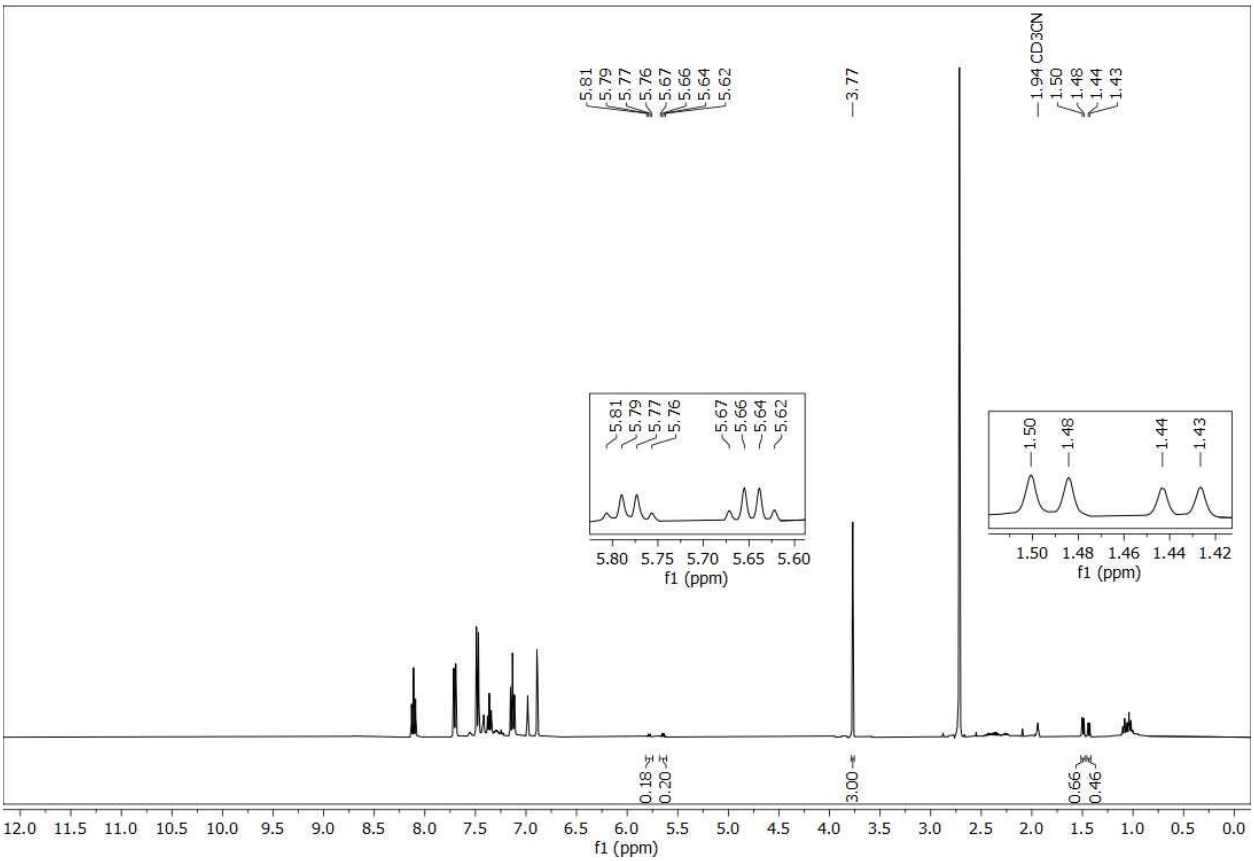
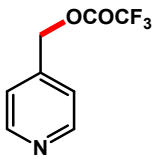


Figure S75: ^{1}H NMR of the crude reaction mixture of directly aryl-linked substrate.



1-(4-Pyridinyl) 2,2,2-trifluoroacetate - H-NMR of the crude reaction mixture in CD_3CN obtained with relaxation decay of 10 sec provided possible peak for the -CH_2 of 1-(4-Pyridinyl) 2,2,2-trifluoroacetate (5.46 ppm, NMR yield - 5%), and -CHO peak for 4-Pyridine carboxaldehyde (10.05 ppm, NMR yield - 9%). Absence of -CH_3 (2.33 ppm) peak from the reactant, 4-methylpyridine indicates that there is no unreacted reactant left.

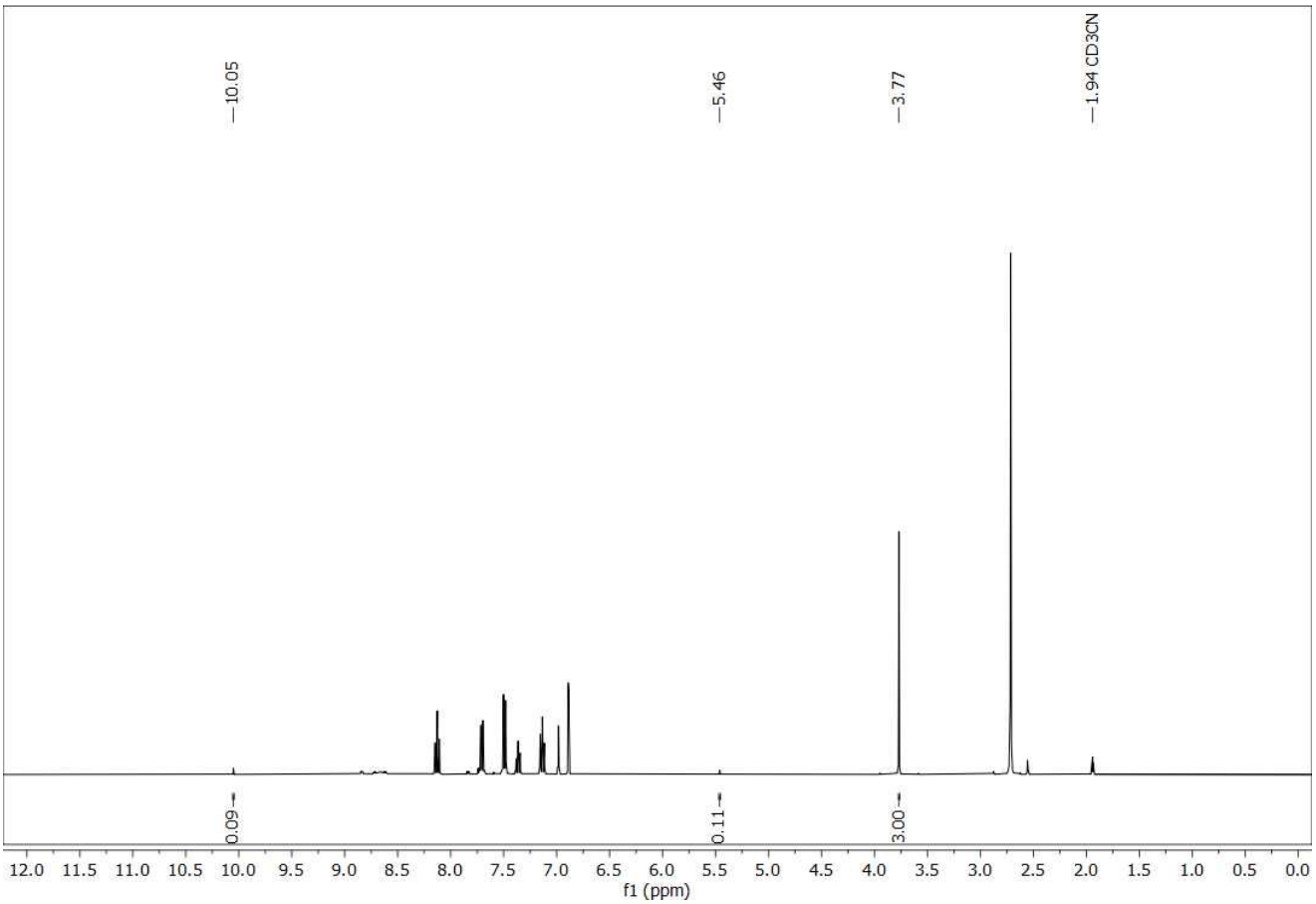
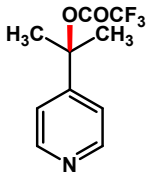


Figure S76: ^{1}H NMR of the crude reaction mixture



1-(4-Pyridinyl)isopropyl 2,2,2-trifluoroacetate - ^{1}H-NMR of the crude reaction mixture in CD_3CN obtained with relaxation decay of 10 sec provided possible peak for the -CH_3 of 1-(4-Pyridinyl) 2,2,2-trifluoroacetate (1.85 ppm, NMR yield - 11%) with approx. 5% amount of reactant left (-2*(CH_3) peak at 1.85 ppm).

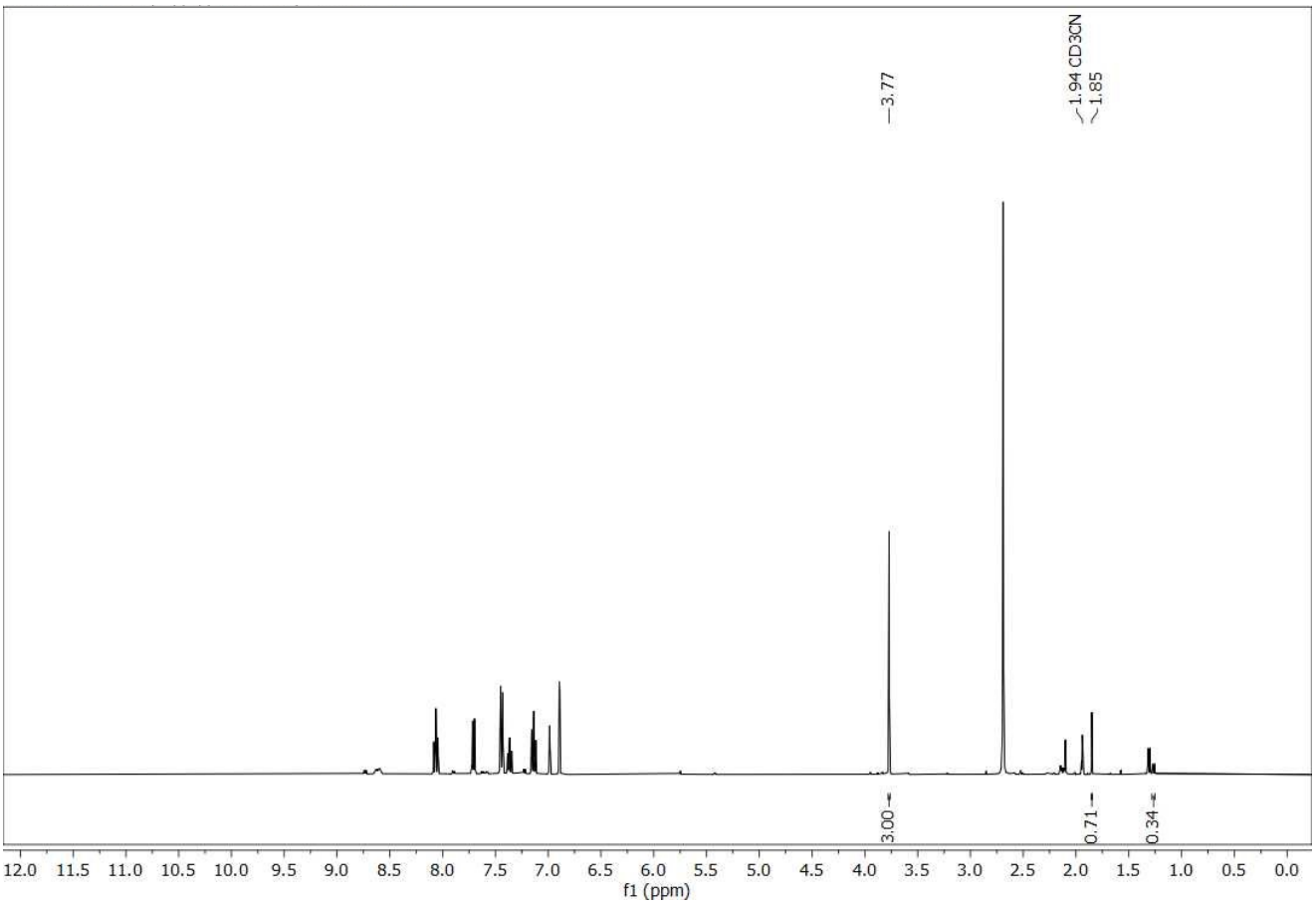
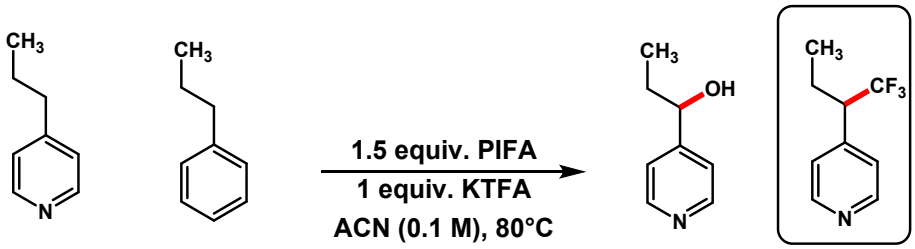


Figure S77: ^{1}H NMR of the crude reaction mixture

Reactions in support of a radical mechanism



4-(1,1,1-trifluorobutan-2-yl) pyridine – On carrying a competitive reaction between 4-propylpyridine and 4-propylbenzene, diagnostic peaks for compound 28 were obtained in the ^{19}F NMR of the crude reaction mixture. The presence of the compound indicates that the reaction might be proceeding via the formation of a radical. The peak obtained in the F-NMR for compound 28 is consistent with the literature. Ref: ($CDCl_3$) δ -69.92 (d, J = 9.2 Hz)[20]

^{19}F NMR (376 MHz) δ -69.87 (d, *J* = 9.4 Hz).

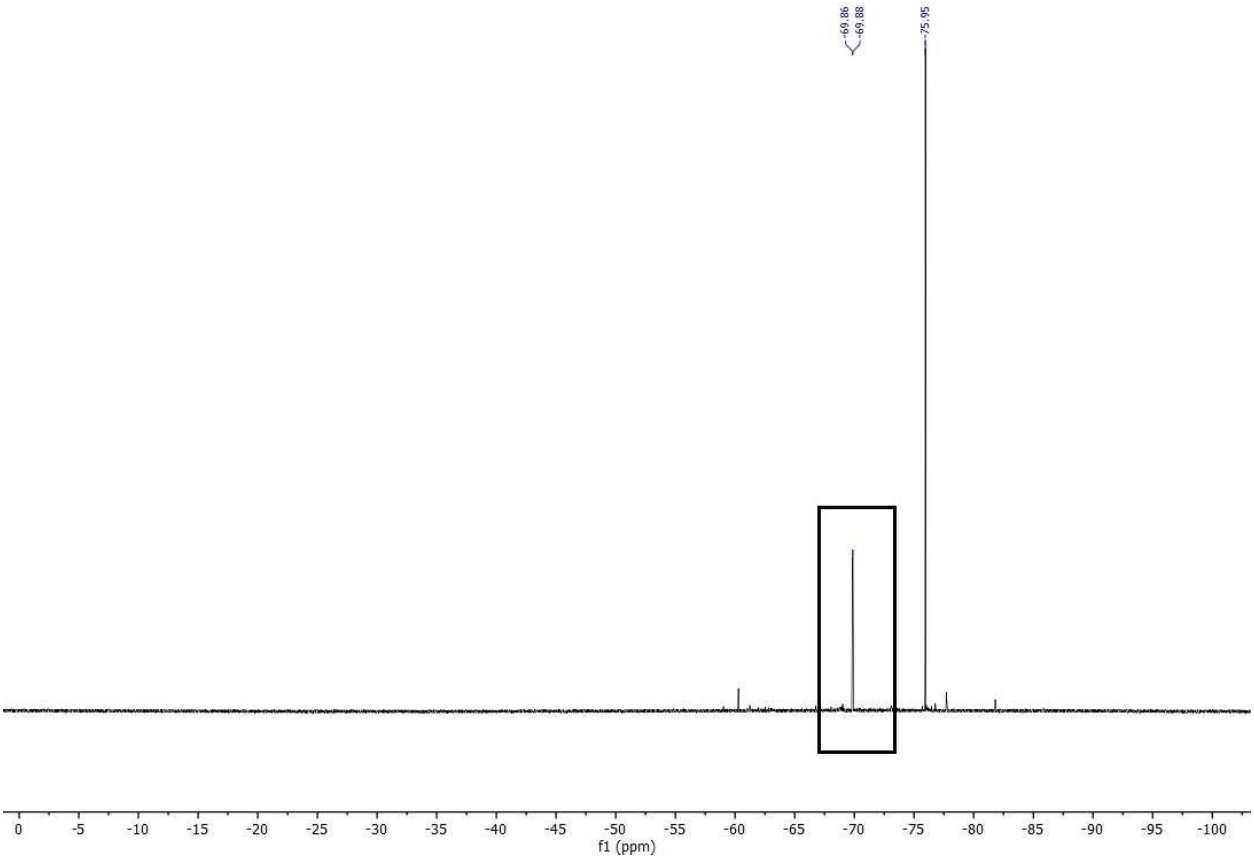
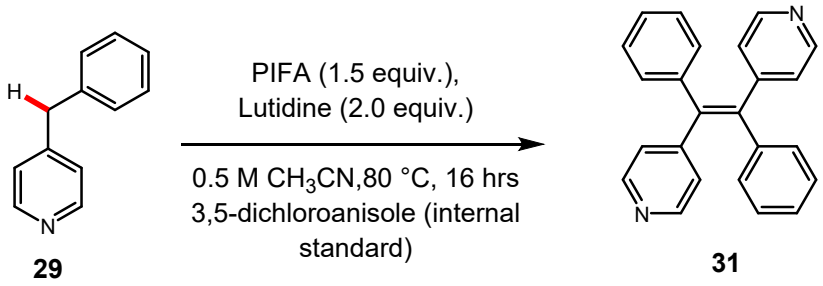


Figure S78. ^{19}F NMR of crude reaction mixture containing 4-(1,1,1-trifluorobutan-2-yl)pyridine

Dimer Characterization



29 **31**

***E*-1,2-diphenyl-1,2-di(pyridin-4-yl)ethene**[14] [bis(trifluoroacetoxy)iodo]benzene (42.30 mg, 0.5 mmol), PIFA (0.161g, 0.75 mmol), 2,6-Lutidine (57.9 uL, 1.0 mmol) added to an oven-dried 8 mL scintillation vial, followed by dry acetonitrile (2 mL) and the reaction was stirred for 18 hours at 80 °C. Subsequently,

the reaction was cooled to room temperature and concentrated on a rotary evaporator. To confirm the presence of the dimer, H-NMR of crude reaction mixture was compared with the H-NMR reported in the literature. Diagnostic peaks with chemical shift of 8.39 - 8.32, 7.21 – 7.14, 7.00 and 6.94 – 6.87 matched with the reported peaks. This molecule was previously isolated in 7% yield using KOTFA as an additive.[14]

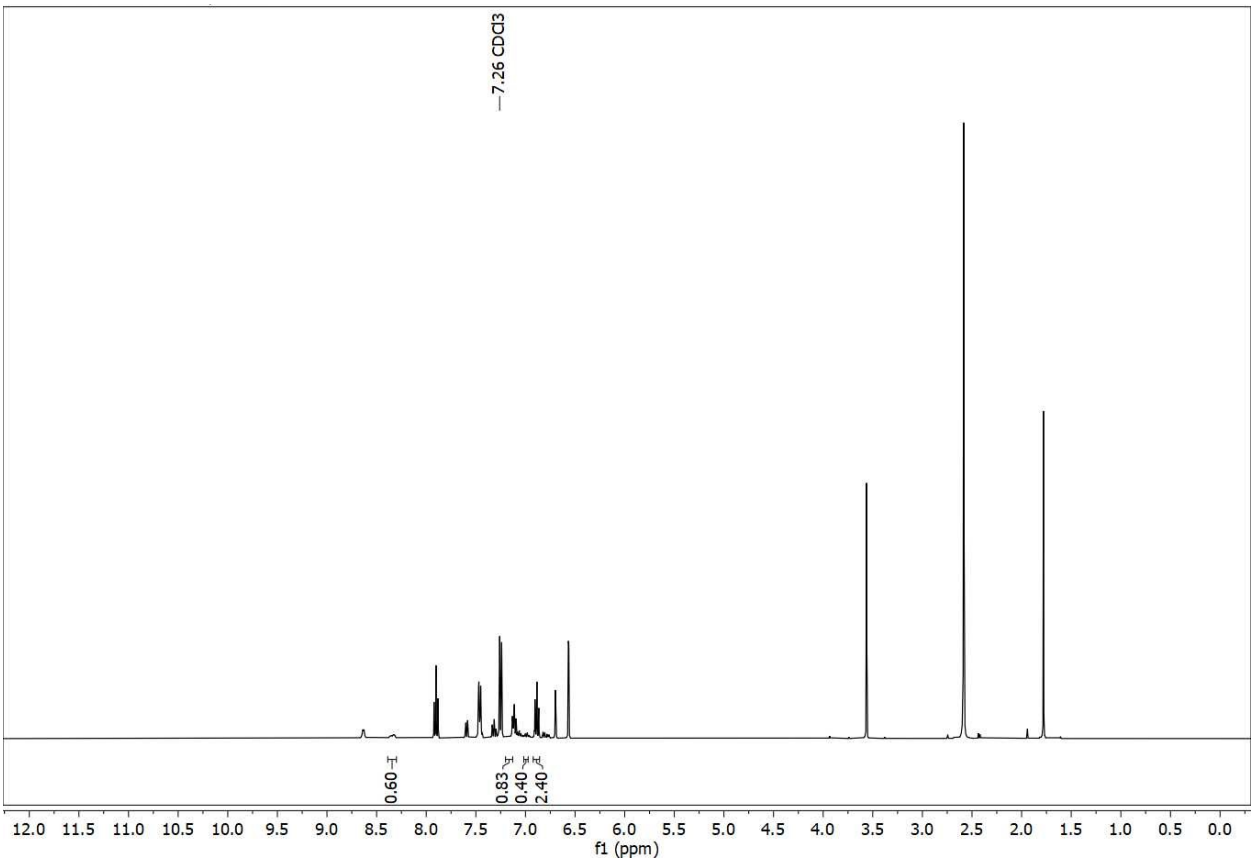
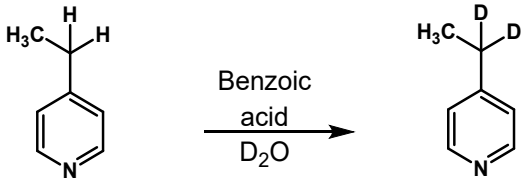


Figure S79. ^{1}H NMR spectrum of the crude reaction mixture for the formation of *E*-1,2-diphenyl-1,2-di(pyridin-4-yl)ethane

Kinetic Isotopic Effects



4-(ethyl-1,1-*d*2)pyridine [21] 4-Ethylpyridine (0.8 g, 7.55 mmol) was suspended along with benzoic acid (0.2 g, 1.63 mmol) in 10 mL D2O in a thick-walled glass pressure vessel. The suspension was capped and heated to 120 ºC in an oil bath for 24 hrs. After cooling to room temperature, the contents were transferred into a

separatory funnel with the aid of ethyl acetate, washed with 10% K_2CO_3, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude isotopically labelled substrate. H NMR analysis using ten second d1 delay time showed approximately 74% deuterium incorporation. The mixture was re-subjected to the labeling procedure (with benzoic acid and D_2O amounts appropriately adjusted) to deliver 4-ethylpyridine that was now >98% isotopically labelled at the desired position, as judged by the disappearance of the CH_2 quartet resonance found at 2.66 ppm. To get rid of ethyl acetate peaks the mixture was washed with acetonitrile to give the yellow oil (0.73 g) since acetonitrile is used as the solvent for C-H hydroxylation. The ratio of deuterated 4-ethylpyridine to ACN (peak at 2.00 ppm) in the H-NMR spectrum is 6.3: 1 and the mmoles for the kinetic study were adjusted accordingly when proteo-4-ethylpyridine was added.

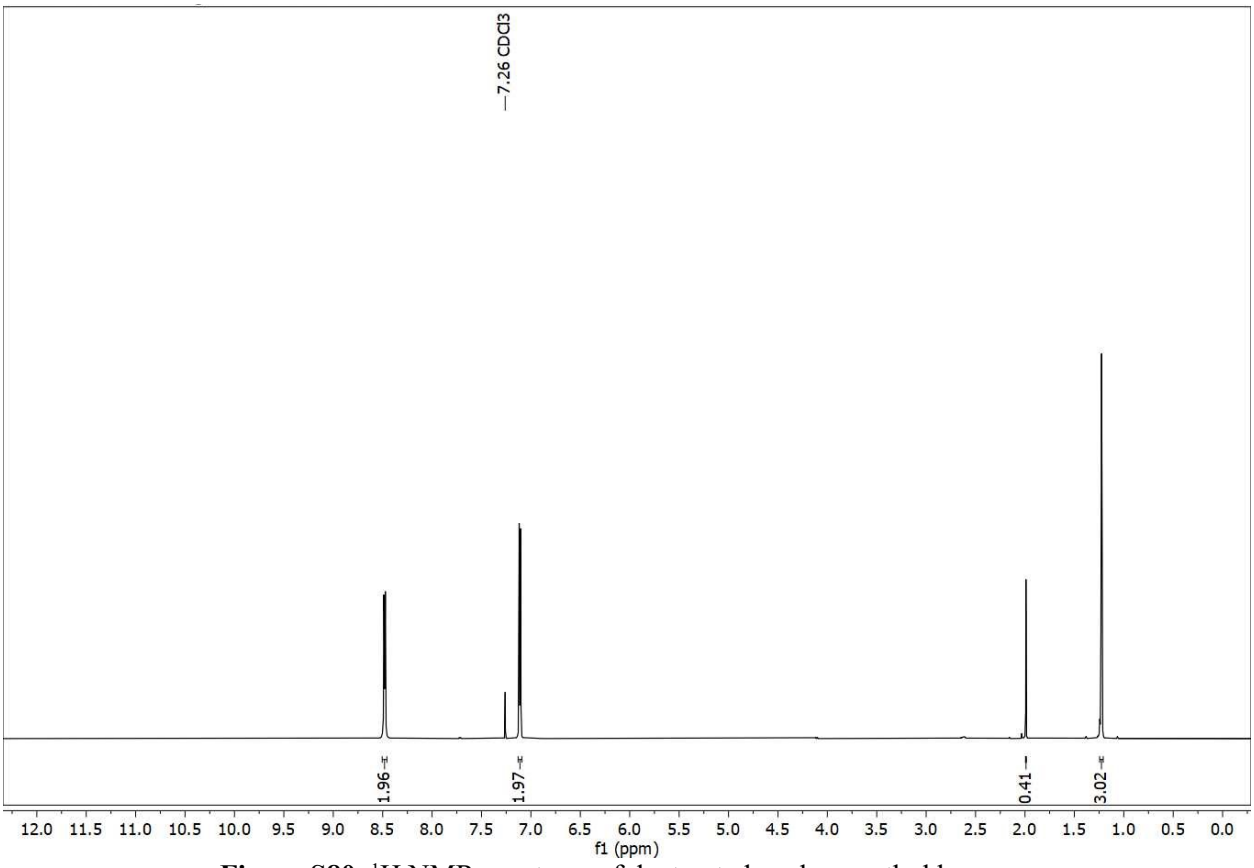
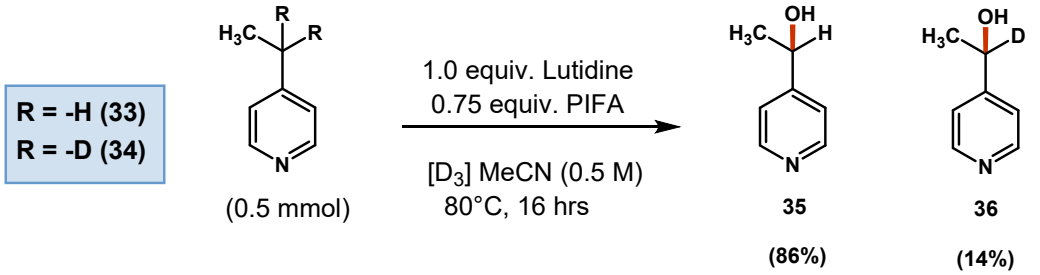


Figure S80. ^{1}H NMR spectrum of deuterated analogue ethyl benzene



KIE measurement: PIFA (0.322 g, 0.375 mmol, 0.75 equiv.) was transferred to an oven-dried 8 mL vial. 2 mL of anhydrous CD_3CN (dried under 3Å molecular sieves) was added followed by Lutidine (0.107 g, 0.5 mmol, 1.0 equiv.). 4-Ethylpyridine (53.6 mg, 0.5 mmol), and 4-(ethyl-1,1-*d2*) pyridine (54.6 mg, 0.5 mmol) were transferred using hamilton syringes. The reaction vial was sealed with a melted parafilm and was heated at 80 ºC for 16 hrs. After that period, the reaction was cooled to room temperature and the reaction mixture was transferred to a separatory funnel with the aid of ethyl acetate. The organic layer was washed with saturated $NaHCO_3$ solution. The combined organic layers were dried with MgSO4, filtered, and concentrated *in vacuo*. The starting material and products were recovered together using silica gel chromatography (4:1 hexanes:ethyl acetate eluent). Quantitative H NMR showed a KIE (k_H/k_D) of 6.1. The equivalents of PIFA and lutidine were reduced by half when compared to the optimized conditions to carry out the competition reaction between the two substrates so that the isotope labelled substrate would not begin to react after the complete consumption of the faster-reacting proteo-substrate.

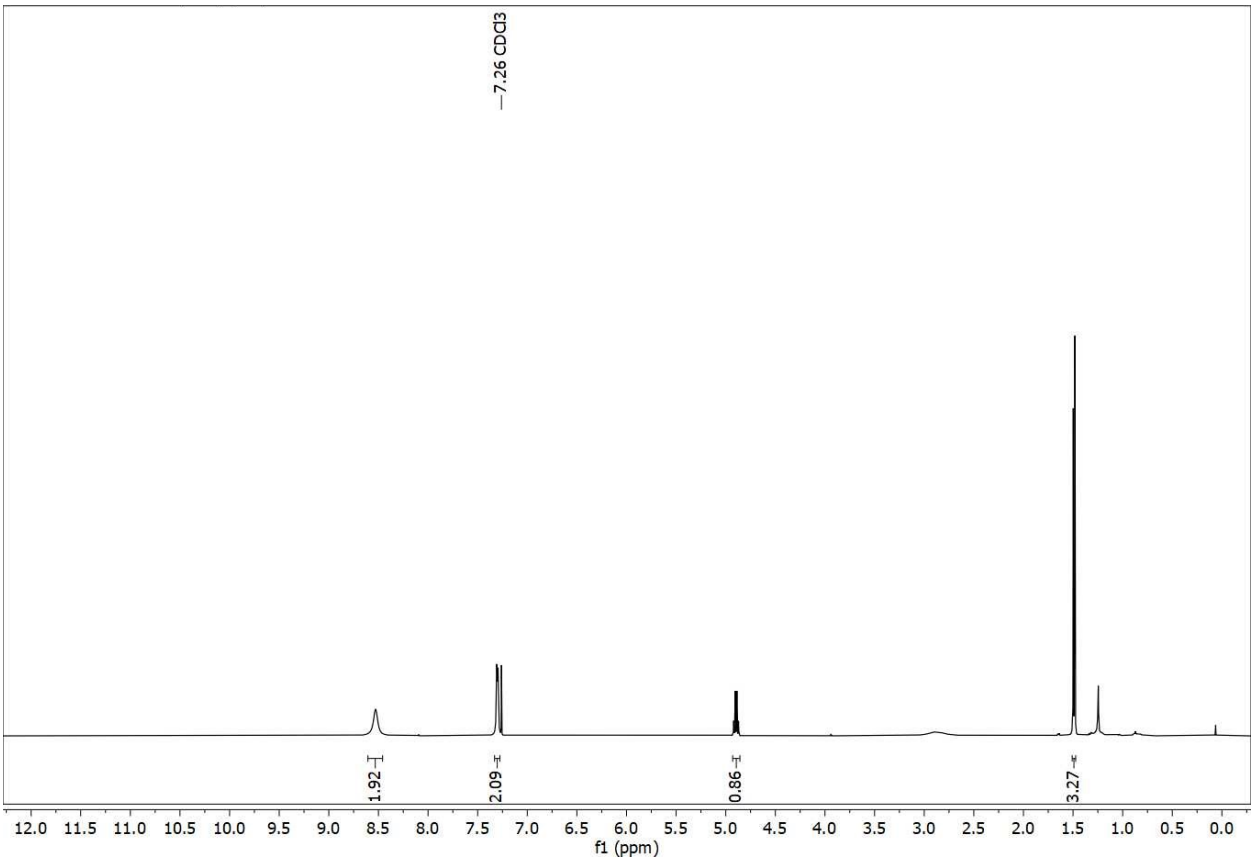
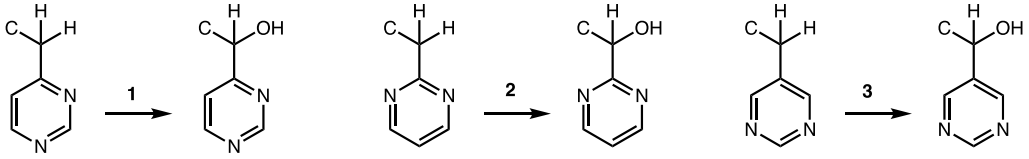


Figure S81. Measurement of KIE for intermolecular competition of 4-Ethylpyridine and its deuterated analogue

Details of SciFinder® Reaction Searches

Hydroxylation of pyrimidines

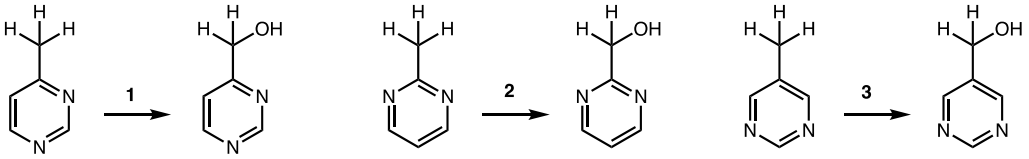


An ***unrestricted*** substructure search for (secondary C-H) pyrimidine hydroxylation (as shown directly above) on February 18, 2024 returns 2,429 results for **1**, 138 for **2**, and 40 for **3**.

For **1**, only 13 are single-step processes. Of these 13, 6 are in academic journal (*i.e.* 7 are from the patent literature). Of these, 3 deprotonate the benzylic position with LDA,[22] 1 deprotonates the benzylic position with butyllithium,[23] and 1 uses mCPBA to make an intermediate N-oxide, followed by Boekelheide rearrangement.[24] Upon further inspection, the 6th example proved to be erroneously coded into SciFinder® - a ketone starting material was reduced with $NaBH_4$.

For **2**, only 6 are single-step processes, 4 of which are from the academic publications. Of these, 1 is a telescoped reaction beginning with benzylic bromination,[25] 1 was only identified as a proposed structure from HRMS metabolite profiling, and 1 was erroneously coded (a missing -CH_2- group made the new -OH non-benzylic). The remaining example used KO^{t}Bu deprotonation followed by reactions with O_2.[26]

For **3**, only 3 are single-step processes, 1 of which is from an academic publication. That publication reported the direct production of the alcohol product in 8% yield by $KMnO_4$ oxidation.[27]



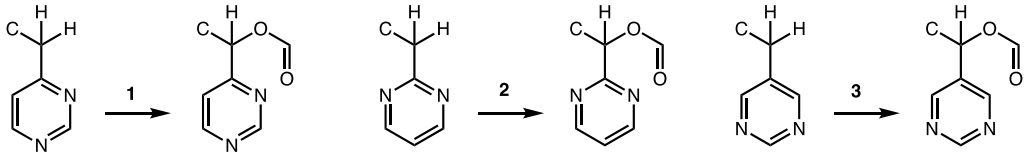
An ***unrestricted*** substructure search for (primary C-H) pyrimidine hydroxylation (as shown directly above) on February 18, 2024 returns 205 results for **1**, 34 for **2**, and 26 for **3**.

For **1**, 65 were single-step processes, 33 of which were from academic publications. This turned out to be quite erroneously high due to (i) N-oxide starting materials fitting our substructure search and (ii) potential symmetry. Of the 33 academic reports, with respect to (i), 6 of these 33 reports actually feature an N-oxide starting material, not the heterocycle itself. With respect to (ii), 23 of the 33 reports do not actually detail C-H functionalization: these reports had an unchanged methyl group in the 4/6-position of the pyrimidine, while in the second 4/6 position a simple functional group reaction (e.g. carbonyl reduction) is what delivered the C-OH group. Of the 4 remaining reports, 2 were telescoped 2-step reactions that used SeO_2 to create an aldehyde, followed by reduction.[28] 2 reports featured deprotonation by butyllithium and reaction with O_2.[29]

For **2**, 4 were one-step processes, with only 1 was from an academic publication. This was a mis-report due to the presence of two pyrimidines in the reaction, one featuring a methyl group and the second a hydroxymethyl group – no C-H functionalization took place.

For **3**, 10 were one-step processes, with 6 from academic publications. All 6 were oxidations of thymines, and were not viewed to be representative of the types of aromatic heterocycles that are the focus of this work.

Esterification of pyrimidines

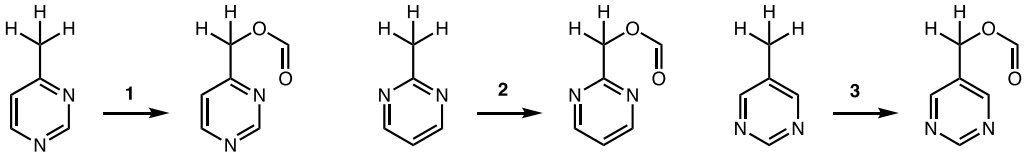


An ***unrestricted*** substructure search for (secondary C-H) pyrimidine esterification (as shown directly above) on February 18, 2024 returns 539 results for **1**, 1 for **2**, and 6 for **3**.

For **1**, 33 of these are single-step processes, with 3 of these from the academic literature. All 3 of these used N-oxides as the starting materials, not the heterocycle itself.

For **2**, the sole example used an N-oxide starting material.

For **3**, 2 of these are single step processes, with 1 of these from the academic literature. That result used a mixture of NHPI and ammonium iodate to directly produce and acetate ester at the benzylic position.[30]



An ***unrestricted*** substructure search for (primary C-H) pyrimidine esterification (as shown directly above) on February 18, 2024 returns 98 results for **1**, 17 for **2**, and 3 for **3**.

For **1**, 50 of these are single-step processes, with 46 of these from the academic literature. Similar to above, N-oxide starting materials and issues of symmetry compose most of these examples. 43 of the starting materials are N-oxides, and 1 of the examples is due to the 4/6 symmetry in a molecule with an unchanged methyl group. The remaining 2 examples are of the exact same reaction reported in two different publications (*i.e.* an identical substrate and identical reaction conditions), thus we have counted this as 1 example. Interestingly, as above, this reaction also involves the direct formation of an acetate ester in the presence of iodine and radical generating species (tert-butyl hydroperoxide).[31]

For **2**, 9 of these are single-step processes, with all 9 being from academic publications. All 9 featured N-oxide starting materials.

For **3**, none of the results were single-step processes.

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