_O_-Nucleophilic Amino-Alcohol Acyl-Transfer Catalysts: the Effect of Acidity of the Hydroxyl Group on the Activity of the Catalyst

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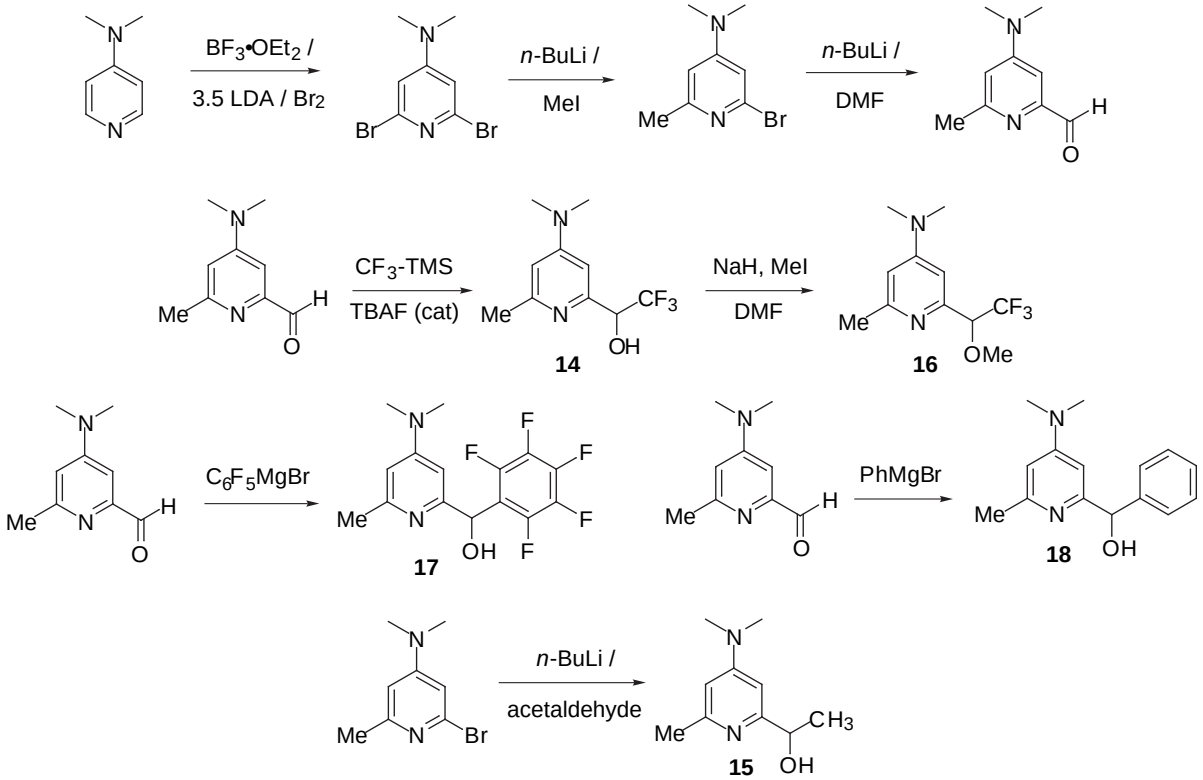
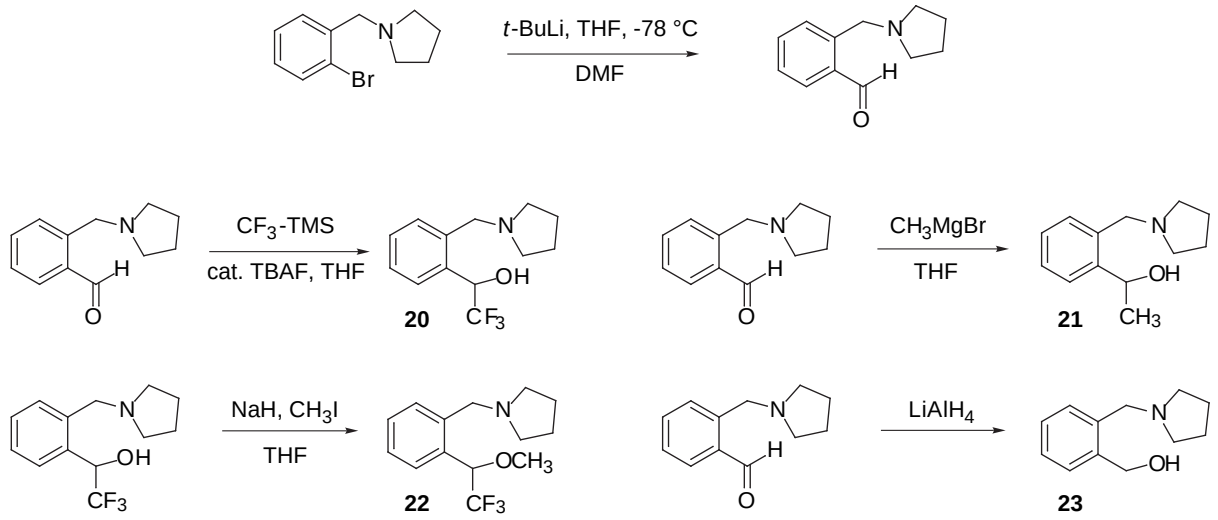
Compounds **14**, **16**, **17**, and **18** were prepared via 4-(dimethylamino)-6-methyl-pyridine-2-carbaldehyde, which was prepared from 4-DMAP, and compound **15** was prepared from 2-bromo-6-methyl-4-(dimethylamino)-pyridine as shown below.



Compounds **20 - 23** were prepared from 2-Pyrrolidin-1-ylmethyl-benzaldehyde[1] as shown below.



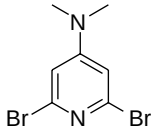
General experimental procedures:

All air or moisture sensitive reactions were performed in oven-dried glassware under a nitrogen atmosphere using solvents purified according to standard procedures.[2] ^{1}H NMR spectra were obtained at either 300 MHz or 500 MHz, ^{13}C NMR spectra were obtained at either 75 MHz or 125 MHz with ^{1}H decoupling (WALTZ), and ^{19}F spectra were obtained at either 376 MHz, or 470 MHz. All NMR data was obtained in chloroform-*d* as solvent. Chemical shifts are reported in ppm referenced to residual chloroform at 7.24 ppm for ^{1}H NMR and 77.0 ppm for ^{13}C NMR. ^{19}F NMR chemical shifts are reported relative to $CFCl_3$, set at 0.0 ppm. Infrared spectra were recorded as thin films on sodium chloride plates.

Kinetics of ethanolysis of *p*-Nitrophenyl Methoxyacetate:

Kinetic experiments for the methanolysis of *p*-nitrophenyl methoxyacetate were monitored by ^{1}H NMR at 500 MHz using a Varian Inova-500 spectrometer. Chloroform-*d* was freshly distilled from calcium hydride immediately prior to each experiment. Samples were prepared from stock solutions of the ester and the catalyst, neat methanol-d_4, and neat *p*-methylanisole (as a standard). The chloroform-*d* solutions were 0.1 M in ester, 1.0 M in methanol, and 0.01 M in catalyst at a total volume of 750 μL, plus 3 μL of standard. Reactants were combined directly into NMR tubes. Reactions were run at 20 $\pm$ 2 °C. An NMR spectrum was taken before the catalyst was added, and reaction progress was monitored by the disappearance of aromatic resonances of *p*-nitrophenyl methoxyacetate and the appearance of methylene protons of methyl-d_3 methoxyacetate. The state of the catalyst was monitored by the appearance and disappearance of the proton geminal to the hydroxy or acyloxy group in the unacylated and acylated catalyst. Percent compound was plotted as a function of time to analyze the pseudo-zero order reactions. The rates were calculated from the steady-state slopes corresponding to the growth of methyl-d_3 methoxyacetate. Reactions displayed clean conversion with no detectable formation of side products.

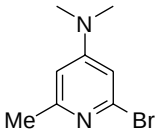
2,6-Dibromo-4-(dimethylamino)-pyridine



Boron trifluoride diethyl etherate (22.8 mL, 180 mmol, 1.1 equiv) was added via cannula to a solution of 4-dimethylaminopyridine (20.0 g, 164 mmol, 1.0 equiv) in tetrahydrofuran (700 mL)

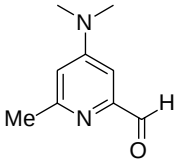
at 0 °C. The resulting suspension was allowed to stir at 0 °C for 30 minutes then cooled to -78 °C. In a separate flask, *n*-butyllithium (1.6 M in hexanes, 256 mL, 410 mmol, 2.5 equiv) was added via cannula to a 0 °C solution of diisopropyl amine (53.7 mL, 410 mmol, 2.5 equiv) in tetrahydrofuran (300 mL) and allowed to stir 30 minutes. The resulting lithium diisopropyl amide solution was then added via cannula to the –78 °C solution of the pyridine boron trifluoride complex. The mixture was stirred for 25 minutes after the addition was complete. Bromine (25 mL, 492 mmol, 3.0 equiv) was then added and the mixture was warmed to room temperature and allowed to stir overnight. Saturated sodium thiosulfate was added and the layers were separated. The aqueous phase was extracted with ethyl acetate (3x) and the combined organic layers were washed with brine and dried over $MgSO_4$. After removing the solvents under reduced pressure, the residue was purified by flash chromatography (2:1 hexanes/ethyl acetate) followed by recrystallization (hexanes/methylene chloride) to provide 10.5 g (23%) of 2,6-dibromo-4-(dimethylamino)-pyridine as a light pink crystalline solid: m.p. 148 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.58 (s, 2H), 2.97 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.64, 140.77, 108.92, 51.71, 39.46. IR 1586, 966, 811 cm^{-1}. TLC R_f = 0.48 (2:1 hexanes/ethyl acetate). Anal Calcd for $C_7H_8N_2Br_2$: C, 30.03; H, 2.88; N, 10.01. Found: C, 29.87; H, 2.80; N, 9.91.

2-Bromo-6-methyl-4-(dimethylamino)-pyridine



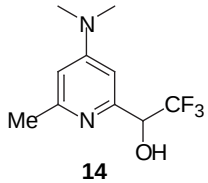
n-Butyllithium (1.6 M in hexanes, 8.4 mL, 13.4 mmol, 1.1 equiv) was added dropwise via cannula to a solution of 2,6-dibromo-4-(dimethylamino)-pyridine (3.42 g, 12.2 mmol, 1.0 equiv) in tetrahydrofuran (125 mL) at –78 °C. The mixture was warmed to –45 °C for 15 minutes, and then cooled again to –78 °C. Methyl iodide (1.17 mL, 18.3 mmol, 1.5 equiv) was added to the mixture via syringe and then warmed to –45 °C for 2 hours. After warming to room temperature, saturated ammonium chloride (100 mL) was added to the reaction mixture and the layers were separated. The aqueous layer was extracted twice with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and concentrated to a yellow oil. Flash chromatography (2:1 hexanes/ethyl acetate) provided 2.03 g (77%) of 2-bromo-6-methyl-4-(dimethylamino)-pyridine: m.p. 49 - 51 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.46 (d, *J* = 2.2 Hz, 1H), 6.26 (d, *J* = 2.2 Hz, 1H), 2.94 (s, 6H), 2.37 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.71, 156.12, 142.26, 106.75, 105.09, 39.25, 24.50. IR 1600, 1526, 1131 cm^{-1}. TLC R_f = 0.38 (2:1 hexanes/ethyl acetate). Anal Calcd for $C_8H_{11}N_2Br$: C, 44.67; H, 5.15; N, 13.02. Found: C, 44.87; H, 4.96; N, 12.98.

4-(Dimethylamino)-6-methyl-pyridine-2-carbaldehyde



n-Butyllithium (1.6 M in hexanes, 4.79 mL, 7.67 mmol, 1.1 equiv) was added via cannula to a solution of 2-bromo-6-methyl-4-(dimethylamino)-pyridine (1.5 g, 6.97 mmol, 1.0 equiv) in tetrahydrofuran (70 mL) at –78 °C. The mixture was allowed to stir for 45 minutes at –78 °C. Distilled *N*,*N*-dimethylformamide (810 µL, 10.5 mmol, 1.5 equiv) was added to the mixture via syringe and then warmed to room temperature. Saturated sodium carbonate (50 mL) was added and the mixture was extracted three times with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and concentrated. Flash chromatography (2:1 hexanes/ethyl acetate) provided 1.05 g (92%) of 4-(dimethylamino)-6-methyl-pyridine-2-carbaldehyde as a pale yellow solid: m.p. 76 – 77 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.91 (s, 1H), 7.00 (d, *J* = 2.2 Hz, 1H), 6.48 (d, *J* = 2.4 Hz, 1H), 3.00 (s, 6H), 2.49 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 194.77, 158.93, 155.14, 152.75, 109.05, 102.49, 51.70, 39.23, 24.49. TLC R_f = 0.13 (2:1 hexanes/ethyl acetate). Anal

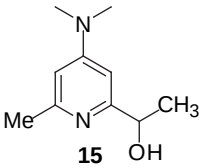
Calcd for $C_9H_{12}N_2O$: C, 65.83; H, 7.37; N, 17.06. Found: C, 65.71; H, 7.25; N, 16.96.



14

1-(4-Dimethylamino-6-methyl-pyridin-2-yl)-2,2,2-trifluoro-ethanol (14)

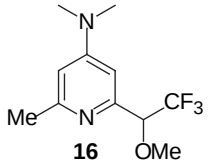
Tetrabutylammonium fluoride hydrate (1 M in tetrahydrofuran, 0.5 mL) was added via cannula to a 0 °C solution of 4-(dimethylamino)-6-methyl-pyridine-2-carbaldehyde (200 mg, 1.22 mmol, 1.0 equiv) and trimethyl(trifluoromethyl)silane (0.5 M in tetrahydrofuran, 2.92 mL, 1.46 mmol, 1.2 equiv) in tetrahydrofuran (3 mL). The solution was allowed to warm to room temperature and allowed to stir overnight. Hydrochloric acid (6 M, 400 µL, 2.44 mmol, 2.0 equiv) was added and the mixture was allowed to stir for 1 hour. Excess solid sodium carbonate was then added to neutralize the hydrochloric acid. The resulting mixture was diluted with ethyl acetate, filtered over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (ethyl acetate) provided 185 mg (65%) of **14** as a white solid: m.p. 124 – 125 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.36 (s, 2H), 6.10 (br, 1H), 4.82 (q, J_{H-F} = 6.9 Hz, 1H), 3.00 (s, 6H), 2.43 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.71, 155.46, 150.18, 124.38 (q, J_{C-F} = 283 Hz), 106.19, 102.12, 70.30 (q, J_{C-F} = 31.7 Hz), 39.26, 24.27. ^{19}F NMR (376 MHz, $CDCl_3$): δ -78.49 (d, J_{H-F} = 6.0 Hz). IR 3000 – 3150, 1610, 1161, 1119 cm^{-1}. TLC R_f = 0.29 (2:1 hexanes/ethyl acetate). Anal Calcd for $C_{10}H_{13}F_3N_2O$: C, 51.28; H, 5.59; N, 11.96. Found: C, 51.12; H, 5.48; N, 11.89.



15

1-(4-Dimethylamino-6-methyl-pyridin-2-yl)-ethanol (15)

n-Butyllithium (1.6 M in hexanes, 320 µL, 0.51 mmol, 1.1 equiv) was added via syringe to a solution of 2-bromo-6-methyl-4-(dimethylamino)-pyridine (100 mg, 0.465 mmol, 1.0 equiv) in tetrahydrofuran (5 mL) at –78 °C. The mixture was allowed to stir for 45 minutes at –78 °C. Distilled acetaldehyde (130 µL, 2.33 mmol, 5.0 equiv) was added to the mixture via syringe and then warmed to room temperature. Saturated sodium carbonate (5 mL) was added and the mixture was extracted three times with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and concentrated to a white solid. Flash chromatography using a gradient elution (ethyl acetate/methanol) provided 51 mg (61%) of **15**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.26 (d, J = 2.2 Hz, 1H), 6.24 (d, J = 2.4 Hz, 1H), 4.71 (q, J = 6.6 Hz, 1H), 2.98 (s, 6H), 2.42 (s, 3H), 1.45 (d, J = 6.4 Hz, 3H) . ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.46, 156.59, 155.61, 104.60, 99.34, 68.50, 39.29, 24.45, 24.42. IR 3100 – 3500, 1608, 1548, 1509, 1117, 1018 cm^{-1}. TLC R_f = 0.17 (methanol). Anal Calcd for $C_{10}H_{16}N_2O$: C, 66.64; H, 8.95; N, 15.54. Found: C, 67.02; H, 8.84; N, 15.30.

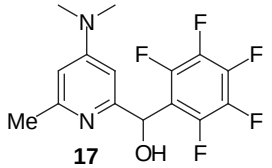


16

Dimethyl-[2-methyl-6-(2,2,2-trifluoro-1-methoxy-ethyl)-pyridin-4-yl]-amine (16)

A solution of 1-(4-dimethylamino-6-methyl-pyridin-2-yl)-2,2,2-trifluoro-ethanol (30.5 mg,

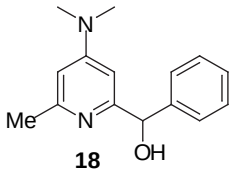
0.130 mmol, 1.0 equiv) in *N*,*N*-dimethylformamide (1 mL) was added via cannula to a suspension of sodium hydride (16 mg, 0.667 mmol, 5 equiv) in *N*,*N*-dimethylformamide (0.5 mL). The mixture turned orange after stirring 5 minutes. Methyl iodide was added via syringe to the alkoxide solution and then the reaction was allowed to stir overnight. The *N*,*N*-dimethylformamide was removed under reduced pressure. The remaining residue was dissolved in chloroform, washed with water, dried over $MgSO_4$ and concentrated. Purification by flash chromatography using a gradient elution (5:1 hexanes/ethyl acetate, 2:1 hexanes/ethyl acetate, then ethyl acetate) provided 13 mg (41%) of **16**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.58 (d, J = 2.0 Hz, 1H), 6.35 (d, J = 2.4 Hz, 1H), 4.56 (q, $J_{H\text{-}F}$ = 6.6 Hz, 1H), 3.45 (s, 3H), 2.99 (s, 6H), 2.43 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.88, 155.38, 152.43, 123.74 (q, $J_{C\text{-}F}$ = 282 Hz), 106.13, 102.24, 83.11 (q, $J_{C\text{-}F}$ = 30.0 Hz), 58.48, 39.22, 24.64. ^{19}F NMR (376 MHz, $CDCl_3$): δ -76.36 (d, $J_{H\text{-}F}$ = 9.0 Hz). IR 1615, 1548, 1511, 1271, 1163, 1133 cm^{-1}. TLC R_f = 0.47 (ethyl acetate). Anal Calcd for $C_{11}H_{15}F_3N_2O$: C, 53.22; H, 6.09; N, 11.28. Found: C, 53.05; H, 5.98; N, 10.88.



17

(4-Dimethylamino-6-methyl-pyridin-2-yl)-pentafluorophenyl-methanol (17)

Bromopentafluorobenzene (83.5 μL, 0.670 mmol, 1.1 equiv) was added via syringe to a flask containing magnesium turnings (22.0 mg, 0.914 mmol, 1.5 equiv) and diethyl ether (0.5 mL). The mixture was sonicated for 5 minutes at which point it appeared dark brown, and then diluted with diethyl ether (2 mL). The resulting Grignard reagent was then cannulated into a flask containing a solution of 4-(dimethylamino)-6-methyl-pyridine-2-carbaldehyde (100 mg, 0.609 mmol, 1.0 equiv) in diethyl ether. A bright yellow precipitate instantly formed. Water (5 mL) was added, which dissolved the precipitate and turned the solution light brown. The layers were separated and the aqueous phase was extracted three times with 5 mL portions of diethyl ether. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. NMR indicates a 6:1 ratio of desired product to starting material. Flash chromatography using a gradient elution (5:1 hexanes/ethyl acetate, then 2:1 hexanes/ethyl acetate) provided 95 mg (43%) of **17** as a solid: m.p. 115 – 116 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.30 (d, J = 2.2 Hz, 1H), 5.98 (d, 1.8 Hz, 1H), 5.95 (s, 1H), 2.92 (s, 6H), 2.45 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.57, 156.40, 155.65, 105.38, 99.47, 64.99, 39.25, 24.38. ^{19}F NMR (470 MHz, $CDCl_3$): δ -143.8 (dd, J = 22.1 Hz, 8.4 Hz), -155.9 (dd, J = 20.6 Hz, 20.6 Hz), -162.8 (ddd, J = 22.1 Hz, 20.6 Hz, 8.4 Hz). IR 3100 – 3500, 1609, 1505, 1120, 996 cm^{-1}. TLC R_f = 0.47 (ethyl acetate). Anal Calcd for $C_{15}H_{13}F_5N_2O$: C, 54.22; H, 3.94; N, 8.43. Found: C, 53.92; H, 3.85; N, 8.32.

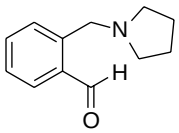


18

(4-Dimethylamino-6-methyl-pyridin-2-yl)-phenyl-methanol (18)

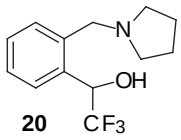
Bromobenzene (77.0 μL, 0.731 mmol, 1.5 equiv) was added via syringe to a flask containing magnesium turnings (24.0 mg, 0.974 mmol, 2.0 equiv) and diethyl ether (0.5 mL). The mixture was sonicated for 5 minutes at which point it appeared dark brown, and then diluted with diethyl ether (2 mL). The resulting Grignard reagent was then cannulated into a flask containing a solution of 4-(dimethylamino)-6-methyl-pyridine-2-carbaldehyde (80 mg, 0.487 mmol, 1.0 equiv) in diethyl ether. A bright yellow precipitate instantly formed. Water (5 mL) was added, which dissolved the precipitate and turned the solution light brown. The layers were separated and the

aqueous phase was extracted three times with 5 mL portions of diethyl ether. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography using a gradient elution (5:1 hexanes/ethyl acetate, then 2:1 hexanes/ethyl acetate) provided 68 mg (38%) of **18** as a solid: m.p. 141 – 142 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 (d, *J* = 7.5 Hz, 2H), 7.30 (dd, *J* = 7.5 Hz, 7.5 Hz, 2H), 7.23 (dd, *J* = 7.3 Hz, 7.3 Hz, 1H), 6.25 (d, *J* = 2.0 Hz, 1H), 6.06 (d, *J* = 2.0 Hz, 1H), 5.90 (br, 1H), 5.55 (s, 1H), 2.88 (s, 6H), 2.45 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.07, 156.28, 155.37, 144.20, 128.31, 127.37, 127.07, 104.81, 100.92, 74.52, 39.18, 24.51. IR 3200 – 3500, 1607, 1546, 1509, 1217, 1061 cm^{-1}. TLC R_f = 0.47 (ethyl acetate).



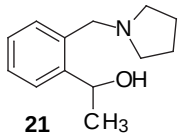
2-Pyrrolidin-1-ylmethyl-benzaldehyde.

t-Butyllithium (1.7 M in ether, 7.66 mL, 13.0 mmol, 2.3 equiv) was added via syringe to a -78 °C solution of 1-(2-bromo-benzyl)-pyrrolidine[1] (1.36 g, 5.66 mmol, 1.0 equiv) in tetrahydrofuran (50 mL). The mixture was allowed to stir 1 hour at -78 °C before *N*,*N*-dimethylformamide (1.0 mL, 13.0 mmol, 2.3 equiv) was added via syringe. The mixture was allowed to warm to room temperature and stir overnight. Ethyl acetate (50 mL) and saturated sodium bicarbonate (100 mL) were added to the reaction mixture. The layers were separated and the aqueous layer was extracted with 50 mL ethyl acetate. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to a brown oil. Flash chromatography using a gradient elution (ethyl acetate, then 30:10:2 hexanes/ethyl acetate/triethylamine) afforded 925 mg (86%) of 2-pyrrolidin-1-ylmethyl-benzaldehyde as an orange oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.40 (s, 1H), 7.80 (dd, *J* = 7.5 Hz, 1.0 Hz, 1H), 7.45 (ddd, *J* = 7.5 Hz, 7.5 Hz, 1.4 Hz, 1H), 7.34 (m, 2H), 3.90 (s, 2H), 2.45 (m, 4H), 1.69 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 193.18, 142.25, 134.63, 133.15, 129.77, 129.09, 127.36, 57.03, 53.70, 23.42. TLC R_f = 0.56 (30:10:2 hexanes /ethyl acetate/triethylamine). Anal Calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 75.77; H, 7.63; N, 7.33.



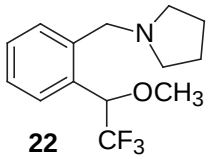
2,2,2-Trifluoro-1-(2-pyrrolidin-1-ylmethyl-phenyl)-ethanol (20) **20**

Tetrabutylammonium fluoride hydrate (catalytic) as a solution in tetrahydrofuran (0.5 mL) was added via cannula to a 0 °C solution of 2-pyrrolidin-1-ylmethyl-benzaldehyde (50 mg, 0.264 mmol, 1.0 equiv) and trimethyl(trifluoromethyl)silane (0.5 M in tetrahydrofuran, 0.634 mL, 0.317 mmol, 1.2 equiv) in tetrahydrofuran (0.5 mL). The solution was allowed to warm to room temperature and allowed to stir overnight. Hydrochloric acid (6 M, 88 μL, 0.528 mmol, 2.0 equiv) was added to the mixture and stirred for 1 hour. Excess solid sodium carbonate was then added to neutralize the hydrochloric acid. The resulting mixture was diluted with ethyl acetate, filtered over $MgSO_4$ and concentrated under reduced pressure to yield the hydrochloride salt as a white solid. The crude product was purified by flash chromatography (ethyl acetate, then 30:10:2 hexanes/ethyl acetate/triethylamine) to provide 53 mg (77%) of **20** as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.76 (s, 1H), 7.28 (m, 4H), 4.98 (q, $J_{H\text{-}F}$ = 8.1 Hz, 1H), 4.33 (d, *J* = 12.7 Hz, 1H), 3.25 (d, *J* = 12.5 Hz, 1H), 2.57 (m, 2H), 2.47 (m, 2H), 1.76 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 137.45, 135.03, 131.40, 129.03, 128.09, 125.68 (q, $J_{C\text{-}F}$ = 285 Hz), 75.96 (q, $J_{C\text{-}F}$ = 31.0 Hz), 59.74, 52.87, 23.24. ^{19}F NMR (376 MHz, $CDCl_3$): δ -76.60 (d, $J_{H\text{-}F}$ = 9.4 Hz). IR 3200 – 3400, 1260, 1162, 1128 cm^{-1}. TLC R_f = 0.49, streak (2:1 hexanes/ethyl acetate). Anal Calcd for $C_{13}H_{16}F_3NO$: C, 60.22; H, 6.22; N, 5.40. Found: C, 60.26; H, 6.15; N, 5.41.



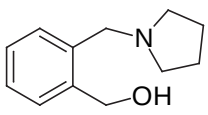
1-(2-Pyrrolidin-1-ylmethyl-phenyl)-ethanol (21) **21**

A solution of 2-pyrrolidin-1-ylmethyl-benzaldehyde (52 mg, 0.275 mmol, 1.0 equiv) in tetrahydrofuran (3 mL) was cooled to 0 °C. Methyl magnesium bromide (3.0 M in diethyl ether, 110 µL, 0.330 mmol, 1.2 equiv) was added to the solution via syringe and then the mixture was warmed to room temperature. After 5 minutes, an excess of water (5 mL) was added to quench the reaction. The reaction mixture was extracted with ethyl acetate. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (ethyl acetate) provided 29 mg (51%) of **21** as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.87 (s, 1H), 7.40 (d, *J* = 7.7 Hz, 1H), 7.29 (ddd, *J* = 7.5 Hz, 6.5 Hz, 2.4 Hz, 1H), 7.20 (m, 2H), 5.01 (q, *J* = 6.6 Hz, 1H), 4.21 (d, *J* = 12.3 Hz, 1H), 3.27 (d, *J* = 12.1 Hz, 1 H), 2.55 (m, 2H), 2.45 (m, 2 H), 1.67 (m, 4H), 1.58 (d, 6.6 Hz, 3H).). ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.27, 137.32, 130.59, 128.13, 127.11, 125.51, 66.18, 59.01, 53.22, 23.21, 20.26. TLC R_f = 0.29 (30:10:2 hexanes /ethyl acetate/triethylamine). Anal Calcd for $C_{13}H_{19}N_2O$: C, 76.06; H, 9.33; N, 6.82. Found: C, 76.42; H, 9.15; N, 6.87.



1-[2-(2,2,2-Trifluoro-1-methoxy-ethyl)-benzyl]-pyrrolidine (22) **22**

A solution 2,2,2-trifluoro-1-(2-pyrrolidin-1-ylmethyl-phenyl)-ethanol (101.8 mg, 0.393 mmol, 1.0 equiv) in tetrahydrofuran (2 mL) was added via cannula to a suspension of sodium hydride (50 mg, 1.96 mmol, 5.0 equiv) in tetrahydrofuran (2 mL) at room temperature. After 5 minutes, methyl iodide (125 µL, 1.96 mmol, 5.0 equiv) was added to the mixture via syringe. The reaction was allowed to stir 30 minutes. Brine was added dropwise to the mixture until the remaining sodium hydride was quenched (no visible activity observed) and then an additional 4 mL of brine was added. The mixture was then diluted with ethyl acetate and the layers were separated. The aqueous layer was extracted twice with ethyl acetate (5 mL) and the combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The crude oil was purified by flash chromatography (5:1 hexanes/ethyl acetate) to provide 49 mg (46%) of **22** as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.59 (d, *J* = 7.5 Hz, 1H), 7.33 (ddd, *J* = 7.3 Hz, 7.3 Hz, 1.6 Hz, 1H), 7.29 (ddd, *J* = 7.3 Hz, 7.3 Hz, 1.4 Hz, 1H), 7.23 (d, *J* = 7.3 Hz, 1H), 5.69 (q, $J_{H\text{-}F}$ = 87.0 Hz, 1H), 4.03 (d, *J* = 12.7, 1H), 3.34 (s, 3H), 3.22 (d, *J* = 12.9 Hz, 1 H), 2.48 (m, 2H), 2.37 (m, 2H), 1.72 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 139.18, 132.50, 130.04, 128.94, 128.00, 127.63, 124.40, (q, $J_{C\text{-}F}$ = 282 Hz), 75.38 (q, $J_{C\text{-}F}$ = 31.0 Hz), 58.68, 57.35, 53.83, 23.61. ^{19}F NMR (376 MHz, $CDCl_3$): δ -76.56 (d, $J_{H\text{-}F}$ = 9.0 Hz). IR 1268, 1168, 1134, 1087 cm^{-1}. TLC R_f = 0.67 (2:1 hexanes/ethyl acetate). Anal Calcd for $C_{14}H_{18}F_3NO$: C, 61.53; H, 6.64; N, 5.13. Found: C, 61.23; H, 6.51; N, 5.08.



(2-Pyrrolidin-1-ylmethyl-phenyl)-methanol (23) **23**

A solution of 2-pyrrolidin-1-ylmethyl-benzaldehyde (100 mg, 0.528 mmol, 1.0 equiv) in tetrahydrofuran (1 mL) was added via cannula to a suspension of lithium aluminum hydride (20.0

mg, 0.528 mmol, 1.0 equiv) in tetrahydrofuran (4 mL) at 0 °C. The mixture was warmed to room temperature and allowed to stir two hours. Sodium hydroxide (3.0 M) was added dropwise until a white precipitate formed. The mixture was diluted with ethyl acetate, filtered over $MgSO_4$, and concentrated to a white solid. The crude product was purified by flash chromatography (30:10:2 hexanes/ethyl acetate/triethylamine) to provide 85 mg (84%) of **23** as a pure white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 (m, 5H), 4.59 (s, 2H), 3.70 (s, 2H), 2.51 (m, 4H), 1.73 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 141.42, 137.98, 130.05, 129.75, 128.20, 127.69, 64.92, 59.25, 53.33, 23.21. IR 3300 – 3500, 3100 – 3300, 1022 cm^{-1}. TLC R_f = 0.32 (30:10:2 hexanes/ethyl acetate/triethylamine). Anal Calcd for $C_{12}H_{17}NO$: C, 75.36; H, 8.96; N, 7.32. Found: C, 75.52; H, 8.97; N, 7.37.

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[1] Prepared according to the procedure of Spector: Wilson, S.R.; Zucker, P.A.; Huang, R.; Spector, A. *J. Am. Chem. Soc* **1989**, *111*, 5936.

[2] Perrin, D.D. ; Armarego, W.L.F. Purification of Laboratory Chemicals Pergamon: Oxford, 1988.