Supporting Information

C-H Bonds as Ubiquitous Functionality: A General Approach to Complex Arylated Pyrazoles via Sequential Regioselective C-arylation and N-alkylation Enabled by SEM-group Transposition

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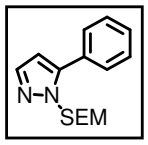
I. General Information

All manipulations of air and/or water sensitive compounds were performed using standard Schlenk techniques under an atmosphere of argon passed through Drierite. Arylation reactions were carried out in capped glass vials (VWR, 8 mL) equipped with a magnetic stir bar and Teflon-lined cap and heated in a 34-well reaction block (Chemglass). All solvents were passed through a column of alumina under an argon atmosphere and used without further purification, with the exception of 1,4-dioxane, which was used as received (Aldrich, anhydrous). All chemicals were purchased from Sigma-Aldrich, Acros, or Strem (palladium complexes and phosphines) and used as received unless otherwise noted. Phosphines were stored under Ar in a glovebox between uses. Flash chromatography was carried out on SILICYCLE silica gel (230-400 mesh). Nuclear Magnetic Resonance spectra were recorded at 300 K on Bruker Advance DPX 300 or 400 Fourier transform NMR spectrometers in $CDCl_3$ and proton spectra referenced to TMS or the solvent residual peak (δ 7.26) and the solvent residual peak (δ 77.0) in ^{13}C NMR. Some spectra were recorded in DMSO-d_6 and were referenced to the solvent residual peak (δ 2.50) in proton spectra. Mass spectra were recorded on a JEOL LCmate (Ionization mode: APCI+). HPLC was performed on a Waters Millennium32 Analytical system with a 996 photodiode array detector using an Xterra RP_{18} 5μm column (4.6 x 150mm) with a Waters 600 Controller; fractions were detected at 254 nm with a Waters 2487 Dual λ Absorbance Detector and data was analyzed using OpenLynx software. All HPLC methods were conducted using 80% acetonitrile / water (with 0.1% trifluoroacetic acid) for 35 minutes, unless otherwise noted.

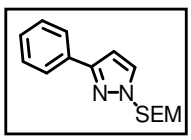
II. Synthesis of Starting Materials

1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole (**1**) was synthesized from the commercially available pyrazole (Aldrich) according to literature procedure.[1]

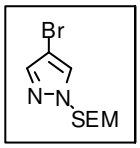
3-Phenyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole (5) and 5-Phenyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole (2): 3-Phenylpyrazole was used as purchased from Acros Organics. The compound (2.88 g, 20 mmol) was dissolved in 30 mL THF and cooled to 0 ºC under an argon atmosphere. NaH (0.72 g, 30 mmol, 1.5 eq.) was added slowly at 0 ºC and the resulting mixture was allowed to stir for 30 minutes, or until hydrogen evolution was complete. SEMCl (3.7 mL, 3.5 g, 21 mmol, 1.05 eq.) was added slowly and the reaction allowed to warm to room temperature and stirred for an additional 12 hours. The reaction was quenched with 5 mL deionized water, extracted with ether, washed with brine, dried with $MgSO_4$ and the solvent removed. After workup, the resulting crude mixture was separated via column chromatography with 10% diethyl ether in hexanes, to produce 1.92 g (35%) of **5**, and 3.12 g (57%) of **2**.



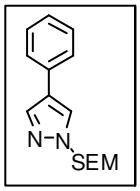
5-Phenyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole (2): ^{1}H NMR (400 MHz, $CDCl_3$): 7.62 (m, 2H), 7.56 (d, J = 1.8 Hz, 1H), 7.37 – 7.48 (m, 3H), 6.40 (d, J = 1.8 Hz, 1H), 5.43 (s, 2H), 3.74 (t, J = 8.2 Hz, 2H), 0.95 (t, J = 8.2 Hz, 2H), -0.01 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.4, 139.3, 130.3, 128.9, 128.8, 128.5, 106.7, 77.9, 66.7, 17.9, -1.45. MS (LR-APCI): calculated for $C_{15}H_{22}N_2OSi$: 274.2, measured 275.5 $(M+H)^+$.



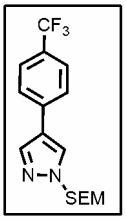
3-Phenyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole (5): ^{1}H NMR (400 MHz, $CDCl_3$): 7.83 (m, 2H), 7.59 (d, J = 2.4 Hz, 1H), 7.41 (m, 2H), 7.31 (m, 1H) , 6.64 (d, J = 2.4 Hz, 1H), 5.47 (s, 2H), 3.64 (t, J = 8.2 Hz, 2H), 0.94 (t, J = 8.2 Hz, 2H), -0.01 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.0, 133.3, 130.8, 128.6, 127.7, 125.8, 104.1, 80.2, 66.7, 17.7, -1.45. MS (LR-APCI): calculated for $C_{15}H_{22}N_2OSi$: 274.2, measured 275.6 $(M+H)^+$.



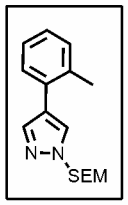
4-Bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole: 4-Bromopyrazole was used as purchased or synthesized according to the literature.[2] 4-Bromopyrazole (5.50 g, 37.4 mmol) was dissolved in 50 mL THF and cooled to 0 ºC under an argon atmosphere. NaH (1.35 g, 56.3 mmol, 1.5 eq.) was added slowly at 0 ºC and the resulting mixture was allowed to stir for 30 minutes, or until hydrogen evolution was complete. SEMCl (6.93 mL, 6.55 g, 39.3 mmol, 1.05 eq.) was added slowly and the reaction allowed to warm to room temperature and stirred for an additional 12 hours. The reaction was quenched with 10 mL deionized water, extracted with ether, washed with brine, dried with $MgSO_4$ and the solvent removed. After workup, the resulting crude mixture was distilled under high vacuum to produce a colorless, clear liquid (9.30 g, 90%). Characterization of this compound was identical to that found in the literature.[1]



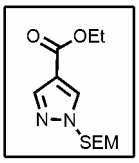
4-Phenyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole (3): 4-Bromo-1-((2-trimethylsilyl)ethoxy)methyl-1*H*-pyrazole (3.39 g, 12.2 mmol), phenylboronic acid (2.00 g, 16.5 mmol, 1.35 eq.), palladium (II) acetate (0.137 g, 0.61 mmol, 5 mol %), tricyclohexylphosphine (0.340 g, 1.2 mmol, 10 mol %), and cesium carbonate (7.76 g, 23.8 mmol, 2 eq.) were weighed in air and added to a round-bottom flask, evacuated and backfilled with Ar three times. Dioxane (70 mL) was added via syringe and the reaction mixture refluxed at an oil bath temperature of 105 ºC for 6-12 hours. Deionized water (10 mL) and ethyl acetate (100 mL) were added to the reaction mixture and separated, the aqueous fraction extracted with ethyl acetate, the organic fractions combined, dried over $MgSO_4$, and the solvent removed. The crude, brown, viscous material was purified via column chromatography with a 100% hexanes to 10% EtOAc:hexanes gradient, after which it was necessary to distill the remaining starting material out of the column purified product under vacuum to produce 2.72 g (81% isolated, 90% by ^{1}H NMR of the crude product) of viscous, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (s, 1H), 7.82 (s, 1H), 7.50 (d, J = 7.8 Hz, 2H), 7.38 (t, J = 7.8 Hz, 2H), 7.26 (m, 1H) , 5.46 (s, 2H), 3.60 (t, J = 8.2 Hz, 2H), 0.93 (t, J = 8.2 Hz, 2H), -0.02 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.5, 132.4, 129.0, 126.7, 126.2, 125.7, 124.3, 80.5, 66.9, 17.9, -1.4. MS (LR-APCI): calculated for $C_{15}H_{22}N_2OSi$: 274.2, measured 275.3 $(M+H)^+$.



4-(4-(Trifluoromethyl)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole: 4-Bromo-1-SEM-1H-pyrazole (1.4 g, 5 mmol), 4-(trifluoromethyl) phenylboronic acid (1.3 g, 6.8 mmol, 1.35 eq.), $Pd(PPh_3)_4$ (0.29 g, 0.25 mmol, 5 mol%), cesium carbonate (2.8 g, 8.5 mmol, 1.7 eq.) and dioxane (10 mL) were added to a 20 mL vial under an argon atmosphere, and the reaction mixture was heated at 105ºC for 12 hours. Deionized water (10 mL) and ethyl acetate (100 mL) were added to the reaction mixture, the product extracted with ethyl acetate, the organic fractions dried with $MgSO_4$, and the solvent removed. The crude, brown, viscous material was purified via column chromatography with 10% EtOAc in hexanes to produce 1.25 g (73%) of colorless liquid. Alternatively, 5 mol% $Pd(OAc)_2$ and 10% PCy_3 may be used as the catalyst system to afford a 78% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (s, 1H), 7.86 (s, 1H), 7.60 (AB q, J = 8.8 Hz, 4H), 5.47 (s, 2H), 3.62 (t, J = 8.2 Hz, 2H), 0.94 (t, J = 8.2 Hz, 2H), -0.02 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.5, 135.9, 128.8, 126.7, 125.9, 125.85, 125.6, 123.0, 80.5, 67.0, 17.8, -1.46. MS (LR-APCI): calculated for $C_{16}H_{21}F_3N_2OSi$: 342.1, measured 343.3 $(M+H)^+$.



4-*o*-Tolyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole: 4-Bromo-1-SEM-1*H*-pyrazole (0.7 g, 2.5 mmol), 2-methylphenylboronic acid (0.46 g, 3.4 mmol, 1.35 eq.), $Pd(PPh_3)_4$ (0.145 g, 0.125 mmol, 5 mol%), cesium carbonate (1.4 g, 4.25 mmol, 1.7 eq.) and 1,4-dioxane (10 mL) were added to a 20 mL vial under an argon atmosphere, and the reaction mixture was heated at 105ºC for 12 hours. Deionized water (10 mL) and ethyl acetate (100 mL) were added to the reaction mixture, the product extracted with ethyl acetate, dried over $MgSO_4$, and the solvent removed. The crude, viscous material was purified via column chromatography with 5% EtOAc in hexanes to product 0.4 g (55%) of colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (s, 1H), 7.66 (s, 1H), 7.33 – 7.35 (m, 1H), 7.20 – 7.27 (m, 3H), 5.47 (s, 2H), 3.62 (t, J = 8.2 Hz, 2H), 2.40 (s, 3H), 0.93 (t, J = 8.2 Hz, 2H), -0.02 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.6, 135.3, 131.9, 130.6, 129.1, 128.1, 126.9, 126.0, 123.2, 80.3, 66.7, 21.2, 17.8, -1.49. MS (LR-APCI): calculated for $C_{16}H_{24}N_2OSi$: 288.2, measured 289.4 $(M+H)^+$.

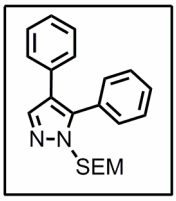


4-Ethoxycarbonyl-1-((2-(trimethylsilyl)ethoxy)methyl-1*H*-pyrazole:

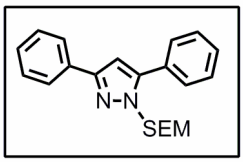
4-Ethoxycarbonyl-1H-pyrazole (1 g, 7.1 mmol) was dissolved in 20 mL THF. NaH (0.25 g, 10.4 mmol, 1.5 eq.) was added to the solution, and the resulting mixture was allowed to stir for 30 min. at room temperature. SEMCl (1.4 mL, 1.3 g, 7.8 mmol, 1.1 eq.) was added slowly and the reaction stirred for an additional 12 hours. The reaction was quenched with 10 mL dionized water, extracted with ether, dried with $MgSO_4$ and the solvent removed. After workup, the resulting crude mixture was purified via column chromatography with 10% EtOAc in hexanes to produce a colorless, clear liquid (1.6 g, 83%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.05 (s, 1H), 7.93 (s, 1H), 5.43 (s, 2H), 4.30 (q, J = 7.2 Hz, 2H), 3.57 (t, J = 8.2 Hz, 2H), 1.35 (t, J = 7.2 Hz, 3H), 0.91 (t, J = 8.2 Hz, 2H), -0.01 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.9, 141.2, 132.8, 116.3, 80.6, 67.2, 60.3, 17.7, 14.3, -1.50. (LR-APCI): calculated for $C_{12}H_{22}N_2O_3Si$: 270.1, measured 271.4 $(M+H)^+$.

III. Procedure for pyrazole arylation

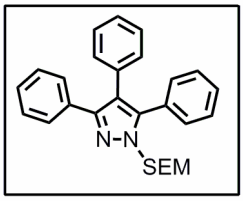
These reactions were performed from 0.25 to 3 mmol scales. To a vial equipped with a stir bar, the susbstrate (1 equiv.), $Pd(OAc)_2$ (5 mol%), $P(^nBu)Ad_2$ (7.5 mol%), K_2CO_3 (3 equiv.) and pivalic acid (25 mol%) were added. Reagents were weighed in air, and all were stored on the benchtop with the exception of the phosphine, which was stored under Ar in a glovebox between uses, and $Pd(OAc)_2$, which was either stored in the glovebox or in a desiccator. The vial was sealed with a Teflon-capped septum and evacuated and backfilled with Ar three times. DMA (2.5M) and the aryl bromide (1.5 equiv.) were added via syringe. (If solid, the aryl bromide was added with the solids.) The septum was quickly replaced with a Teflon-lined cap under an Ar stream and the reaction mixture heated to 140 ºC for 12 hours. After cooling to room temperature, the dark brown mixture was diluted with 10 mL water and 100 mL ethyl acetate, the layers separated, and the aqueous fraction back-extracted with EtOAc (30 mL x 3). The organic fractions were combined and dried with $MgSO_4$, the solvent removed, and the material purified via flash chromatography using the eluents specified.



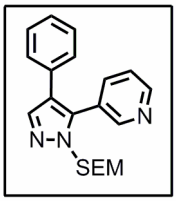
4,5-Diphenyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole (4):
Procedure described above. Produced a yellow, dense oil in 80% yield, 5% compound **7**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (s, 1H), 7.42 (m, 5H), 7.19 – 7.23 (m, 5H), 5.34 (s, 2H), 3.69 (t, *J* = 8.2 Hz, 2H), 0.93 (t, *J* = 8.2 Hz, 2H), -0.01 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.5, 138.7, 132.4, 130.5, 129.9, 128.8, 128.7, 128.4, 127.7, 126.3, 121.8, 77.9, 67.1, 18.0, -1.1. MS (LR-APCI): calculated for $C_{21}H_{26}N_2OSi$: 350.2, measured 351.5 $(M+H)^+$.



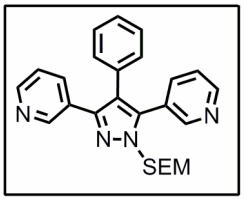
3,5-Diphenyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole (6):
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (m, 2H), 7.68 (m, 2H), 7.40 – 7.50 (m, 5H), 7.34 (m, 1H), 6.72 (s, 1H), 5.48 (s, 2H), 3.82 (t, *J* = 8.2 Hz, 2H), 0.98 (t, *J* = 8.2 Hz, 2H), 0.01 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.1, 145.9, 133.3, 130.3, 128.9, 128.7, 128.6, 128.6, 127.8, 125.8, 104.1, 77.8, 66.7, 17.9, -1.41. MS (LR-APCI): calculated for $C_{21}H_{26}N_2OSi$: 350.2, measured 351.4 $(M+H)^+$.



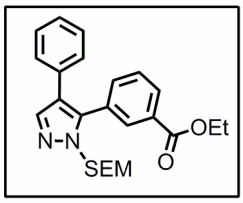
3,4,5-Triphenyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole (7): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (m, 2H), 7.36 (m, 5H), 7.28 (m, 3H), 7.19 (m, 3H), 7.07 (m, 2H), 5.43 (s, 2H), 3.77 (t, J = 8.2 Hz, 2H), 0.96 (t, J = 8.2 Hz, 2H), 0.0 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.4, 142.7, 133.3, 133.2, 130.5, 130.4, 129.6, 128.5 (br.), 128.3 (br.), 128.1, 127.5, 126.5, 120.1, 77.9, 66.8, 17.9, -1.40. MS (LR-APCI): calculated for $C_{27}H_{30}N_2OSi$: 426.3, measured 427.1 $(M+H)^+$.



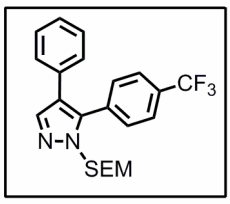
4-Phenyl-5-(3-pyridyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole (8): Pale yellow, dense oil; 65% yield (15% 4-phenyl-3,5-di-(3-pyridyl)-1-(SEM)-1*H*-pyrazole, **8b**), isolated via flash chromatography with a gradient from 100% hexanes, to 1:3 EtOAc:hexanes, to 2:3 EtOAc:hexanes as the eluent. ^{1}H NMR (400 MHz, $CDCl_3$): 8.66 (d, J = 2.0 Hz, 1H), 8.65 (bs, 1H), 7.81 (dt, J_1 = 7.6 Hz, J_2 = 2.0 Hz, 1H), 7.78 (s, 1H), 7.37 (ddd, J_1 = 13.2 Hz, J_2 = 5.0 Hz, J_3 = 1.0 Hz, 1H), 7.15-7.28 (overlapped m, 5H), 5.34 (s, 2H), 3.71 (t, J = 8.4 Hz, 2H), 0.94 (t, J = 8.4 Hz, 2H), 0.0 (s, 9H). Aromatic protons on the pyridine ring assigned with COSY 2-D NMR. ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.0, 149.9, 138.9, 137.8, 136.9, 132.2, 128.7, 127.8, 126.7, 126.1, 123.4, 123.1, 78.1, 66.9, 17.9, -1.5. MS (LR-APCI): calculated for $C_{20}H_{25}N_3OSi$: 351.2, measured 352.5 $(M+H)^+$.



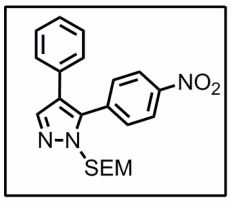
4-Phenyl-3,5-di-(3-pyridyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole (8b): White solid, 15% yield under arylation and isolation conditions. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.74 (m, 1H), 8.59 (m, 2H), 8.50 (dd, J_1 = 4.8 Hz, J_2 = 1.6 Hz, 1H), 7.73 (dm, J = 8.0 Hz, 2H), 7.28 (ddd, J_1 = 8.0 Hz, J_2 = 6.4 Hz, J_3 = 0.8 Hz, 1H), 7.17 – 7.20 (m, 3H), 7.18 (ddd, J_1 = 8.0 Hz, J_2 = 6.4 Hz, J_3 = 0.8 Hz, 1H), 7.05 (m, 2H), 5.42 (s, 2H), 3.79 (t, J = 8.4 Hz, 2H), 0.97 (t, J = 8.4 Hz, 2H), -0.01 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.8, 149.7, 149.2, 148.7, 146.5, 139.5, 137.6, 135.2, 131.9, 130.3, 128.9, 128.7, 127.4, 125.5, 123.2, 123.0, 121.6, 78.2, 67.1, 17.9, -1.4. MS (LR-APCI): calculated for $C_{25}H_{28}N_4OSi$: 428.2, measured 429.2 $(M+H)^+$.



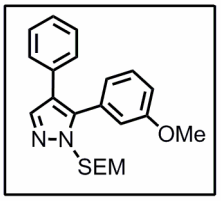
5-(3-Ethoxycarbonylphenyl)-4-phenyl-1-((2-(trimethylsilyl)ethoxy) methyl)-*1H*-pyrazole (9): Yellow, viscous oil; 82% yield, isolated with flash chromatography with a gradient of 0% to 10% EtOAc in hexanes. ^{1}H NMR (300 MHz, CDCl3): δ 8.16 (t, J = 1.5 Hz, 1H), 8.10 (dt, J_1 = 7.8 Hz, J_2 = 1.5 Hz, 1H), 7.79 (s, 1H), 7.57 (dt, J_1 = 7.8 Hz, J_2 = 1.5 Hz, 1H), 7.48 (td, J_1 = 7.5 Hz, J_2 = 0.3 Hz, 1H), 7.15 – 7.23 (m, 5 H), 5.33 (s, 2H), 4.36 (q, J = 7.0 Hz, 2H), 3.67 (t, J = 8.2 Hz, 2H), 1.36 (t, J = 7.0 Hz, 3H), 0.94 (t, J = 8.2 Hz, 2H), -0.01 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.0, 139.4, 138.7, 134.8, 132.5, 131.5, 131.1, 130.2, 130.0, 128.5, 127.7, 126.5, 122.3, 78.0, 66.7, 61.2, 17.9, 14.2, -1.5. MS (LR-APCI): calculated for $C_{24}H_{30}N_2O_3Si$: 422.2, measured 423.6 $(M+H)^+$.



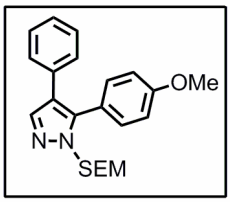
4-Phenyl-5-(4-(trifluoromethyl)phenyl)-1-((2-(trimethylsilyl)ethoxy) methyl)-1*H*-pyrazole (10): Pale yellow, viscous oil; 74 % yield, isolated via flash chromatography with a gradient from 100% hexanes to 10% EtOAc in hexanes as the eluent. ^{1}H NMR (400 MHz, CDCl3): δ 7.77 (s, 1H), 7.66 (d, J = 8.2 Hz, 2H), 7.58 (d, J = 8.2 Hz, 2H), 7.16 – 7.26 (m, 5H), 5.34 (s, 2H), 3.74 (t, J = 8.2 Hz, 2H), 0.95 (t, J = 8.2 Hz, 2H), 0.00 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.9, 133.5, 132.3, 130.8, 128.6, 127.9, 126.7, 125.7, 125.6, 122.7, 78.1, 67.0, 18.0, -1.4. MS (LR-APCI): calculated for $C_{22}H_{25}F_3N_2OSi$: 418.2, measured 419.7 $(M+H)^+$.



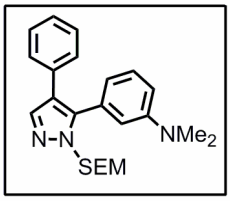
5-(4-Nitrophenyl)-4-phenyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole (11): Dense, yellow oil; 58% yield. Flash chromatography on silica with 10% EtOAc in hexanes as the eluent provided material of 60-90% purity. For characterization, this material was further purified by preparative RP-HPLC using the conditions previously described, retention time 13.12 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (d, J = 9.0 Hz, 2H), 7.76 (s, 1H), 7.66 (d, J = 9.0 Hz, 2H), 7.23 – 7.27 (m, 3H), 7.14 – 7.17 (m, 2H), 5.36 (s, 2H), 3.77 (t, J = 8.3 Hz, 2H), 0.97 (t, J = 8.3 Hz, 2H), 0.01 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.8, 139.0, 138.0, 136.3, 132.0, 131.4, 128.7, 128.0, 127.0, 123.9, 123.4, 78.2, 67.2, 18.0, -1.4. MS (LR-APCI): calculated for $C_{21}H_{25}N_3O_3Si$: 395.2, measured 396.4 $(M+H)^+$.



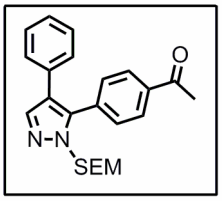
5-(3-Methoxyphenyl)-4-phenyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole (12): Yellow, viscous oil; 76% yield. Isolated via flash chromatography with 5% EtOAc in hexanes as the eluent. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (s, 1H), 7.33 (m, 2H), 7.29 (m, 1H), 7.22 – 7.26 (m, 3H), 6.98 – 7.05 (m, 3H), 5.39 (s, 2H), 3.78 (s, 3H), 3.72 (t, *J* = 8.3 Hz, 2H), 0.98 (t, *J* = 8.3 Hz, 2H), 0.03 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.6, 140.2, 138.6, 132.7, 130.9, 129.7, 128.4, 127.6, 126.3, 122.7, 121.7, 115.6, 114.7, 77.8, 66.7, 55.1, 17.9, -1.5. MS (LR-APCI): calculated for $C_{22}H_{28}N_2O_2Si$: 380.2, measured 381.2 $(M+H)^+$.



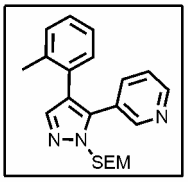
5-(4-Methoxyphenyl)-4-phenyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole (13): 35% yield. Flash chromatography on silica with 5% EtOAc in hexanes as the eluent provided material of ~80% purity. For characterization, this material was further purified by RP-HPLC using conditions previously described. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (s, 1H), 7.35 (d, *J* = 8.8 Hz, 2H), 7.22 – 7.34 (m, 5H), 6.94 (d, *J* = 8.8 Hz, 2H), 5.32 (s, 2H), 3.85 (s, 3H), 3.70 (t, *J* = 8.2 Hz, 2H), 0.94 (t, *J* = 8.2 Hz, 2H), 0.00 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.9, 140.3, 138.6, 133.0, 131.7, 128.4, 127.6, 126.2, 121.9, 121.5, 114.2, 77.8, 66.7, 55.3, 18.0, -1.4. MS (LR-APCI): calculated for $C_{22}H_{28}N_2O_2Si$: 380.2, measured 381.2 $(M+H)^+$.



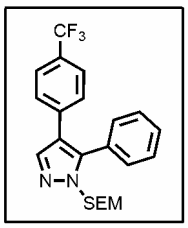
5-(3-Dimethylaminophenyl)-4-phenyl-1-((2-(trimethylsilyl)ethoxy) methyl) -1*H*-pyrazole (14): Light yellow, viscous oil; 74% yield, isolated via flash chromatography with a gradient from 50:50 hexanes:CH_2Cl_2 to 100% CH_2Cl_2 to 1% MeOH in CH_2Cl_2 as the eluent. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (s, 1H), 7.16 – 7.28 (m, 6H), 6.73 – 6.78 (m, 3H), 5.36 (s, 2H), 3.69 (t, *J* = 8.4 Hz, 2H), 2.90 (s, 6H), 0.93 (t, *J* = 8.4 Hz, 2H), 0.00 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.4, 141.4, 138.6, 133.0, 130.3, 129.3, 128.3, 127.6, 126.1, 121.3, 118.3, 114.4, 112.6, 77.8, 66.7, 40.4, 18.0, -1.5. MS (LR-APCI): calculated for $C_{23}H_{31}N_3OSi$: 393.2, measured 394.4 $(M+H)^+$.



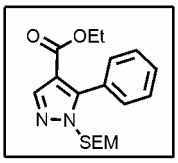
4-Phenyl-5-(4-phenyl ethanone)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole (**15**): 58% yield; isolated via flash chromatography with 10% EtOAc in hexanes as the eluent. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, *J* = 8.4 Hz, 2H), 7.77 (s, 1H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.16 – 7.26 (m, 5H), 5.34 (s, 2H), 3.73 (t, *J* = 8.4 Hz, 2H), 2.63 (s, 3H), 0.95 (t, *J* = 8.4 Hz, 2H), -0.00 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.5, 139.2, 138.9, 137.0, 134.5, 132.4, 130.7, 128.6, 127.8, 126.6, 122.6, 78.1, 67.0, 26.6, 17.9, -1.43.



5-(3-pyridyl)-4-(o-tolyl)-1--((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole (16): 79% colorless oil; isolated by flash chromatography with 4% EtOAc in hexanes as the eluent. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.54 (d, J = Hz, 2H), 7.71 (dt, J_1 = 8.0 Hz, J_2 = 1.8 Hz, 1H), 7.26 (s, 1H), 7.24 (dd, J_1 = 7.8 Hz, J_2 = 5.0 Hz, 1H), 7.14 – 7.15 (m, 2H), 7.04 – 7.10 (m, 2H), 5.40 (s, 2H), 3.76 (t, J = 8.2 Hz, 2H), 2.03 (s, 3H), 0.95 (t, J = 8.2 Hz, 2H), -0.01 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.2, 149.3, 139.9, 137.8, 136.8, 136.5, 131.6, 130.8, 130.2, 127.5, 126.0, 125.7, 123.2, 122.4, 78.2, 66.9, 20.2, 17.8, -1.51. MS (LR-APCI): calculated for $C_{22}H_{28}N_2OSi$: 365.2, measured 366.0 $(M+H)^+$.

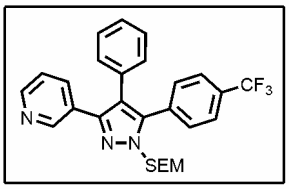


5-Phenyl-4-(4-(trifluoromethyl)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole (17): 69 % yield. Isolated by flash chromatography using 5% EtOAc:hexanes as the eluent. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (s, 1H), 7.38 – 7.46 (m, 7H), 7.27 (d, *J* = 8.1 Hz, 2H), 5.33 (s, 2H), 3.69 (t, *J* = 8.4 Hz, 2H), 0.93 (t, *J* = 8.4 Hz, 2H), -0.01 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.1, 138.6, 136.6, 130.4, 128.3, 129.2, 128.9, 127.6, 125.4, 125.36, 120.5, 77.9, 66.9, 17.9, -1.44. MS (LR-APCI): calculated for $C_{22}H_{25}F_3N_2OSi$: 418.2, measured 419.5 $(M+H)^+$.

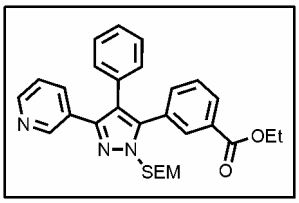


4-Ethoxycarbonyl-5-phenyl-1-((2-(trimethylsilyl)ethoxy)methyl-1*H*-pyrazole (18): 75% yield of colorless oil; isolated by flash chromatography with 10% EtOAc in hexanes as the eluent. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (s, 1H), 7.44 – 7.52 (m, 5H), 5.27 (s, 2H), 4.17 (q, *J* = 7.2 Hz, 2H), 3.65 (t, *J* = 8.2 Hz, 2H), 1.18 (t, *J* = 7.2 Hz, 3H), 0.89 (t, *J* = 8.2 Hz, 2H), -0.02 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.9, 147.0, 141.7, 130.4, 129.5, 128.3, 128.0, 113.5, 77.9, 67.2, 60.0, 17.9, 14.1, -1.46. MS (LR-APCI): calculated for $C_{18}H_{26}N_2O_3Si$: 346.2, measured 347.4 $(M+H)^+$.

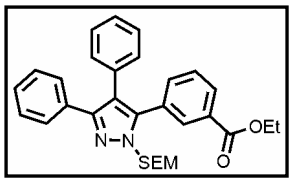
Triarylated Pyrazoles



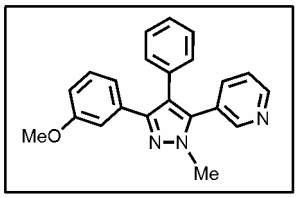
5-(4-(Trifluoromethyl)phenyl)-4-phenyl-3-(3-pyridyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole (23): White solid, 77% yield**,** isolated via flash chromatography with a gradient of 10% to 25% EtOAc in hexanes. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.75 (m, 1H), 8.50 (m, 1H), 7.73 (dt, J_1 = 8.0 Hz, J_2 = 1.8 Hz, 1H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.23 (m, 3H), 7.19 (dd, J_1 = 7.6 Hz, J_2 = 5.2 Hz, 1H), 7.05 (m, 2H), 5.42 (s, 2H), 3.82 (t, *J* = 8.4 Hz, 2H), 0.98 (t, *J* = 8.4 Hz, 2H), -0.01 (s, 9H). ^{13}C NMR: δ 149.2, 148.7, 146.5, 141.4, 135.2, 132.9, 132.0, 130.6, 130.6 (q, J= 32.5 Hz), 130.3, 129.0, 128.7, 127.3, 125.4, 123.0, 121.1, 78.2, 67.2, 17.9, -1.5. MS (LR-APCI): calculated for $C_{27}H_{28}F_3N_3OSi$: 495.2, measured 496.2 $(M+H)^+$.



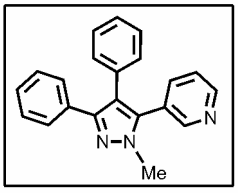
5-(3-Ethoxycarbonylphenyl)-3-(3-pyridyl)-4-phenyl-1-((2-(trimethylsilyl)ethoxy) methyl)-1*H*-pyrazole (25): 88% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.75 (m, 1H), 8.50 (m, 1H), 8.11 (s, 1H), 8.03 (d, *J* = 8.0 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.41 (t, *J* = 8.0 Hz, 1H), 7.19 (m, 4H), 7.05 (m, 2H), 5.42 (s, 2H), 4.34 (q, *J* = 7.2 Hz, 2H), 3.76 (t, *J* = 8.2 Hz, 2H), 1.35 (t, *J* = 7.2 Hz, 3H), 0.98 (t, *J* = 8.2 Hz, 2H), -0.01 (s, 9H).
^{13}C NMR: δ 165.9, 149.3, 148.6, 146.4, 142.0, 135.3, 134.6, 132.2, 131.4, 130.9, 130.4, 129.8, 129.6, 129.1, 128.5, 127.1, 123.0, 121.0, 78.2, 77.0, 61.1, 17.9, 14.2, -1.45. MS (LR-APCI): calculated for $C_{29}H_{33}N_3O_3Si$: 498.2, measured 499.4 $(M+H)^+$.



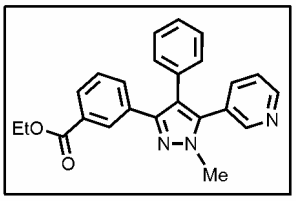
5-(3-Ethoxycarbonylphenyl)-3,4-di-phenyl-1-((2-trimethylsilyl) ethoxy) methyl)-1*H*-pyrazole (26): Yellow-white solid; 64% yield, isolated via flash chromatography with 20% EtOAc in hexanes as the eluent. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (t, J = 1.6 Hz, 1H), 8.01 (dt, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 1H), 7.37 – 7.49 (m, 5H), 7.26 (m, 2H), 7.18 (m, 3H), 7.05 (m, 2H), 5.41 (s, 2H), 4.33 (q, J = 7.2 Hz, 2H), 3.74 (t, J = 8.4 Hz, 2H), 1.36 (t, J = 7.2 Hz, 3H), 0.96 (t, J = 8.4 Hz, 2H), -0.01 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.0, 149.4, 141.7, 134.7, 133.2, 132.9, 131.5, 130.8, 130.5, 130.0, 129.6, 128.5, 128.3, 128.2, 128.1, 127.6, 126.7, 120.6, 78.1, 66.8, 61.1, 17.9, 14.3, -1.4. MS (LR-APCI): calculated for $C_{30}H_{34}N_2O_3Si$: 497.2, measured 498.4 $(M+H)^+$.



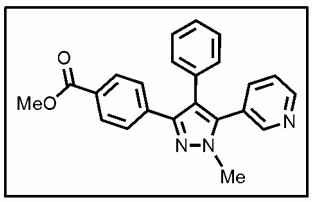
3-(3-Methoxyphenyl)-1-methyl-4-phenyl-1*H*-pyrazole (27): White solid; 75% yield, isolated via flash chromatography with a gradient of 0% to 1% MeOH:CH_2Cl_2, and further purified by recrystallization from methanol. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.59 (dd, J_1 = 3.3 Hz, J_2 = 1.5 Hz, 1H), 8.56 (d, J = 1.5, 1H), 7.52 (dt, J_1 = 7.8 Hz, J_2 = 1.8 Hz, 1H), 7.27 (m, 1H), 7.17 (m, 1H), 7.03 (m, 3H), 6.99 (s, 1H), 6.79 (d, J = 8.1 Hz, 1H), 3.90 (s, 3H), 3.64 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.4, 150.6, 149.6, 148.5, 138.8, 137.4, 134.3, 132.8, 130.5, 129.2, 128.4, 126.9, 126.3, 123.3, 120.4, 120.3, 114.1, 112.7, 55.0, 37.5. MS (LR-APCI): calculated for $C_{22}H_{19}N_3O$: 341.2, measured 342.2 $(M+H)^+$.



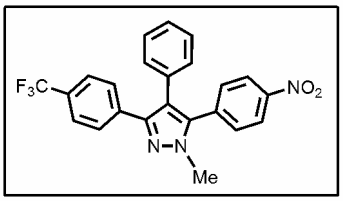
1-Methyl-3,4-di-phenyl-5-(3-pyridyl)-1*H*-pyrazole (28): 67% yield, isolated via flash chromatography with a gradient from 5% to 20% EtOAc in hexanes as the eluent. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.58 (d, J = 9.3 Hz, 2H), 7.53 (dt, J = 7.8 Hz, 1H), 7.45 – 7.48 (m, 2H), 7.26 – 7.29 (m, 4H), 7.18 – 7.20 (m, 3H), 7.03 – 7.06 (m, 2H), 3.91 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.6, 149.6, 148.7, 138.8, 137.4, 133.0, 132.7, 130.4, 128.4, 128.2, 128.0, 127.5, 126.8, 126.4, 123.3, 120.2, 37.5. MS (LR-APCI): calculated for $C_{21}H_{17}N_3$: 310.2, measured 311.7 $(M+H)^+$.



3-(3-Ethoxycarbonylphenyl)-1-methyl-4-phenyl-5-(3-pyridyl)-1*H*-pyrazole (29): 53 % yield, isolated via flash chromatography with a gradient from 10% to 80% EtOAc in hexanes as the eluent. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.60 (d, *J* = 8.0 Hz, 1H), 8.18 (s, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.59 (d, *J* = Hz, 1H), 4.29 (q, *J* = 7.0 Hz, 2H), 3.90 (s, 3H), 1.30 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.4, 150.6, 149.7, 147.8, 139.0, 137.4, 133.4, 132.4, 132.2, 130.7, 130.4, 129.0, 128.6, 128.5, 128.2, 127.0, 123.4, 120.5, 60.8, 37.6, 14.2. MS (LR-APCI): calculated for $C_{24}H_{21}N_3O_2$: 383.2, measured 384.3 $(M+H)^+$.



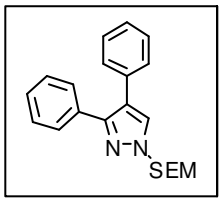
1-Methyl-3-(4-methoxycarbonylphenyl)-4-phenyl-5-(3-pyridyl)-1*H*-pyrazole (30): 54% yield, isolated via flash chromatography with a gradient from 100% hexanes to 30% EtOAc:hexanes to remove impurities, then a gradient from 50% to 100% EtOAc:hexanes to elute the compound. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.62 (d, *J* = 3.6 Hz, 1H), 8.56 (s, 1H), 8.56 (d, *J* = 6.8 Hz, 2H), 7.53 (m, 3H), 7.31 (dd, J_1 = 8.0 Hz, J_2 = 5.2 Hz, 1H), 7.21 (m, 3H), 7.02 (m 2H), 3.93 (s, 3H), 3.89 (t, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.0, 150.6, 149.8, 147.6, 139.2, 137.6, 137.5, 132.4, 130.3, 129.6, 129.0, 128.6, 127.8, 127.1, 126.1, 123.4, 120.8, 52.0, 37.7. MS (LR-APCI): calculated for $C_{23}H_{19}N_3O_2$: 369.2, measured 370.3 $(M+H)^+$.



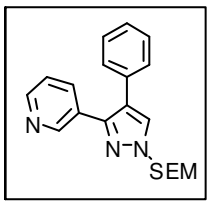
1-Methyl-5-(4-nitrophenyl)-4-phenyl-3-(4-(trifluoromethyl)phenyl)-1*H*-pyrazole (31): Pale yellow-white solid; 43% yield, isolated via flash chromatography with 10% EtOAc in hexanes as the eluent. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (d, *J* = 7.0 Hz, 2H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 7.0 Hz, 2H), 7.24 – 7.26 (m, 3H), 7.01 – 7.04 (m, 2H), 3.94 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.7, 147.3, 140.2, 136.4, 136.2, 132.1, 131.0, 130.3, 128.7, 128.0, 127.4, 125.2, 125.18, 123.8, 120.7, 115.6, 37.8. MS (LR-APCI): calculated for $C_{23}H_{16}F_3N_3O_2$: 423.1, measured 423.7 $(M+H)^+$.

IV. Procedure for SEM-switch

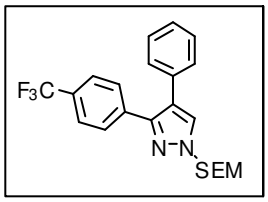
The substrate (**17**, 69.3 mg, 0.20 mmol) was weighed into an oven-dried vial and placed under argon, capped with a Teflon septum cap, and dissolved by stirring in 0.15 mL acetonitrile (approximately 100 μL per 50 mg) injected through the septum. SEMCl (3.5 μL, 10 mol%) was added via syringe and the mixture stirred under Ar for 5 minutes before sealing the vial with a Teflon coated cap and heating to 95 ºC for 24 hours. After 24 hours, the solvent was removed *in vacuo* and the crude material analyzed by ^{1}H NMR, which showed a 90% conversion between the starting material and the SEM-switched material. Flash chromatography of this mixture with 20% EtOAc:hexanes, with 2-3 times the amount of silica normally used for flash chromatography,[3] produced a pale yellow, viscous oil (58.2 mg, 84%).



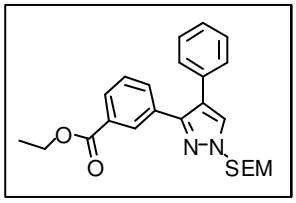
3,4-Diphenyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole (19): 85% conversion by ^{1}H NMR**.** Inseparable by flash chromatography and HPLC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (s, 1H), 7.49 – 7.52 (m, 2H), 7.42 (s, 1H), 7.29 – 7.35 (m, 7H), 5.49 (s, 2H), 3.70 (t, J = 8.2 Hz, 2H), 0.96 (t, J = 8.2 Hz, 2H), -0.00 (s, 9H).



4-Phenyl-3-(3-pyridyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole (20): Synthesis and isolation described above, 84% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.76 (d, J = 1.6 Hz, 1H), 8.53 (dd, J_1 = 4.8 Hz, J_2 = 1.6 Hz, 1H), 7.79 (dt, J_1 = 8.0 Hz, J_2 = 2 Hz, 1H), 7.69 (s, 1H), 7.21 – 7.35 (m, 6H), 5.50 (s, 2H), 3.71 (t, J = 8.2 Hz, 2H), 0.97 (t, J = 8.2 Hz, 2H), 0.01 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.3, 148.7, 146.3, 135.4, 132.4, 129.7, 129.3, 128.7, 128.6, 127.1, 123.1, 122.5, 80.5, 67.1, 17.8, -1.43. MS (LR-APCI): calculated for $C_{20}H_{25}N_3OSi$: 351.2, measured 352.8 $(M+H)^+$.



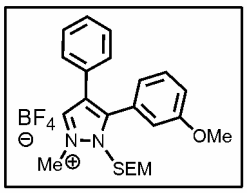
4-phenyl-3-(4-(trifluoromethyl)phenyl)-1-((2-(trimethylsilyl) ethoxy)methyl)-1*H*-pyrazole (21): 91% conversion by ^{1}H NMR, isolated 80%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (s, 1H), 7.63 (d, *J* = 8.2 Hz, 2H), 7.55 (d, *J* = 8.2 Hz, 2H), 7.26 - 7.34 (m, 5H), 5.50 (s, 2H), 3.71 (t, *J* = 8.2 Hz, 2H), 0.97 (t, *J* = 8.2 Hz, 2H), 0.01 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.8, 136.9, 132.6, 129.8, 128.7, 128.6, 128.4, 127.1, 125.2, 125.16, 122.4, 80.5, 67.1, 17.8, -1.4. MS (LR-APCI): calculated for $C_{22}H_{25}F_3N_2OSi$: 418.2, measured 419.3 $(M+H)^+$.



3-(3-Ethoxycarbonylphenyl)-4-phenyl-1-((2-(trimethylsilyl)ethoxy) methyl)-1*H*-pyrazole (22): 90% conversion by ^{1}H NMR. Inseparable by several attempts using flash chromatography and HPLC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (s, 1H), 7.96 (d, *J* = 8.0 Hz, 1H), 7.66 (s, 1H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.27 – 7.35 (m, 5H), 5.48 (s, 2H), 4.31 (q, *J* = 7.2 Hz, 2H), 3.69 (t, *J* = 8.2 Hz, 2H), 1.32 (t, *J* = 7.2 Hz, 3H), 0.96 (t, *J* = 8.2 Hz, 2H), -0.01 (s, 9H).

V. General procedure for formation of pyrazolium salts[4]

The pyrazole (0.2 to 2 mmol) was weighed into an oven-dried flask or vial, a stir bar added, and then evacuated and flushed with Ar three times before dissolving in dry CH_2Cl_2 (0.25M), added via syringe. To this solution, trimethyloxonium tetrafluoroborate (1.2 equivalents) was rapidly added under an Ar stream after weighing in air, and the reaction mixture stirred for at least 1 hour. The solvent was removed and the crude material dried via high vacuum before verifying the presence of the product with ^{1}H NMR. Several of the salts are fluorescent under UV and are relatively unstable if not used within a day; store under vacuum or Ar at -2 to -8 ºC if unable to proceed with the deprotection immediately.

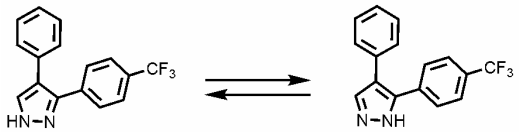


3-(3-Methoxyphenyl)-1-methyl-4-phenyl-2-((2-(trimethylsilyl)ethoxy) methyl)-1*H*-pyrazolium tetrafluoroborate (32): crude ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.57 (s, 1H), 7.46 (t, J = 8.0 Hz, 1H), 7.26 – 7.29 (m, 3H), 7.17 (dd, J_1 = 8.4 Hz, J_2 = 1.8 Hz, 1H), 7.01 - 7.03 (m, 3H), 5.71 (s, 2H), 4.37 (s, 3H), 3.85 (s, 3H), 3.37 (t, J = 8.2 Hz, 2H), 0.82 (t, J = 8.2 Hz, 2H), -0.02 (s, 9H).

VI. Deprotection of SEM group from SEM-protected pyrazoles and pyrazolium salts[5]

The pyrazole, **23**, (30.7 mg, 0.062 mmol) was dissolved in 95% ethanol (4 mL) and 3 N HCl (1 mL) was added. The reaction mixture was refluxed for 3 hours. To quench, 10% aqueous (by weight) NaOH solution was added until the mixture was neutralized as measured with pH paper, 5 mL deionized water and 50 mL ethyl acetate added, and the layers were separated. (Alternatively, a basic work-up with saturated aqueous sodium bicarbonate added until pH is neutral is also sufficient.) After back-extraction from the aqueous layer with EtOAc (15 mL x 3), the organic fractions were combined, dried with Na_2SO_4, and the solvent removed. The crude material was purified via flash chromatography on silica gel with a gradient from 100% hexanes to 50:50 EtOAc:hexanes to produce a pale white solid (17.0 mg, 75%).

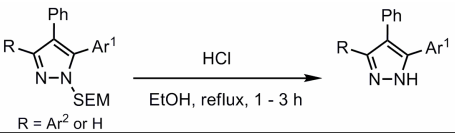
Scheme S1. Free (NH)-pyrazole tautomerism



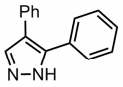
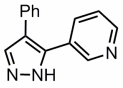
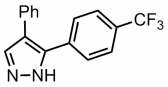
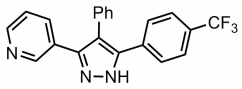
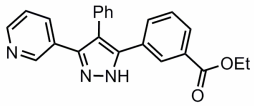
Determination of the Tautomer Ratio for Selected Free (NH)-Pyrazoles in DMSO-*d*$_6$

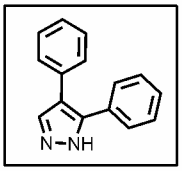
Free (NH)-pyrazoles exist in solution as mixtures of tautomers (Scheme S1). In DMSO-*d*$_6$ the two NH signals are resolved in ^{1}H NMR (δ 13-14.5), enabling determination of the tautomer ratio. The assignment of these peaks to individual tautomers has not been carried out here. However, according to literature,[6] the major tautomer for the diarylpyrazoles is 3,4-diaryl-1*H*-pyrazole (e.g., **S3a**).

Table S1. Deprotected diaryl- and triaryl-pyrazoles

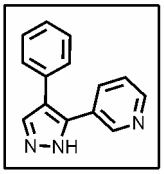


R = Ar^2 or H

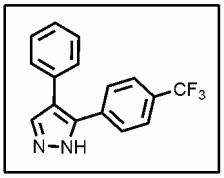
Entry	Product		Isolated Yield
1		**S1**	90%
2		**S2**	99%
3		**S3**	72%
4		**24**	75%
5		**S4**	75%



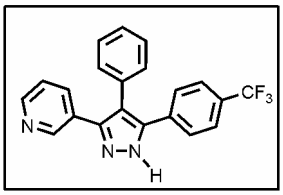
4,5-Diphenyl-1*H*-pyrazole (S1): ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.52 (bs, 1H), 7.63 (s, 1H), 7.46 – 7.48 (m, 2H), 7.24 – 7.34 (m, 8H). ^{1}H NMR (400 MHz, DMSO-d_6 at 298 K): δ 13.19 (bs, ~40% Pz N-H tautomer), 13.05 (bs, ~60% Pz N-H tautomer), 7.40 (bm, 3H), 7.22 – 7.33 (m, 7H). ^{13}C NMR (75MHz, $CDCl_3$): δ 135.1, 133.1, 131.3, 128.6, 128.5, 128.4, 128.2, 128.0, 127.9, 126.6. MS (LR-APCI): calculated for $C_{15}H_{12}N_2$: 220.1, measured 221.0 $(M+H)^+$.



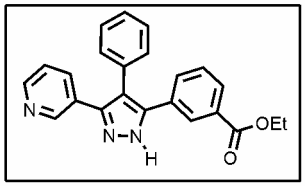
4-Phenyl-5-(3-pyridyl)-1*H*-pyrazole (S2): ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.93 (bs, 1H), 8.80 (bs, 1H), 8.56 (bs, 1H), 7.71 (d, J = 8.1 Hz, 1H), 7.68 (s, 1H), 7.21 – 7.34 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.9, 148.8, 143.0, 135.6, 132.5, 132.3, 128.7, 128.5, 127.0, 123.3, 120.9. MS (LR-APCI): calculated for $C_{14}H_{11}N_3$: 221.1, measured 222.1 $(M+H)^+$.



4-Phenyl-5-(4--(trifluoromethyl)phenyl)-1*H*-pyrazole (S3): ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.2 (s, 1H), 7.65 (s, 1H), 7.56 (d, *J* = 8.7 Hz, 2H), 7.52 (d, *J* = 8.7 Hz, 2H), 7.24 – 7.35 (m, 5H). ^{1}H NMR (400 MHz, DMSO-d_6 at 298 K): δ 13.43 (bs, 29% Pz N-H tautomer), 13.26 (71% Pz N-H tautomer), 8.01 (s, 1H), 7.69 (d, *J* = 8.0 Hz, 2H), 7.63 (d, *J* = 8.0 Hz, 2H), 7.33 – 7.37 (m, 2H), 7.26 – 7.29 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.6, 132.5, 130.1, 129.8, 128.7, 128.6, 128.3, 127.1, 125.5, 125.46, 122.7, 120.9. MS (LR-APCI): calculated for $C_{16}H_{11}F_3N_2$: 288.1, measured 288.8 $(M+H)^+$.

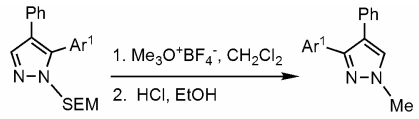


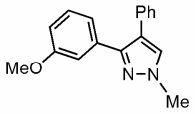
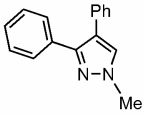
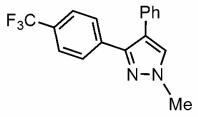
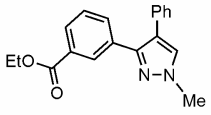
4-Phenyl-5-(4-(trifluoromethyl)phenyl)-3-(3-pyridyl)-1*H*-pyrazole (24): 75% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.70 (bs, 1H), 8.52 (bs, 1H), 7.61 (d, *J* = 8.4 Hz, 1H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.45 (d, *J* = 8.4, 2H), 7.31 (d, *J* = 3.0 Hz, 4H), 7.11 – 7.21 (m, 5H). ^{1}H NMR (500 MHz, DMSO-d_6): δ 13.82 (bs, ~56% Pz N-H tautomer), 13.80 (~44% Pz N-H tautomer), 8.45 – 8.52 (m, 2H), 7.64 – 7.45 (m, 3H), 7.52 – 7.59 (m, 2H), 7.33 – 7.47 (m, 4H), 7.21 – 7.25 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.0, 148.6, 135.1, 134.4, 132.1, 130.5, 129.0, 128.8, 128.6, 127.9, 127.8, 125.8, 125.6, 125.5, 123.4, 119.0. MS (LR-APCI): calculated for $C_{21}H_{14}F_3N_3$: 365.1, measured 366.4 $(M+H)^+$.

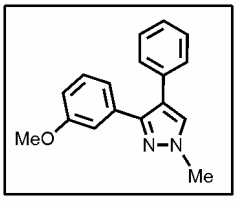


5-(3-Ethoxycarbonylphenyl)-4-phenyl-5-(3-pyridyl)-1*H*-pyrazole (S4): ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.72 (s, 1H), 8.51 (d, *J* = 3.3 Hz, 1H), 8.12 (s, 1H), 7.95 (d, *J* = 7.5 Hz, 1H), 7.65 (d, *J* = 7.8 Hz, 1H), 7.45 (d, *J* = 7.8 Hz, 1H), 7.30 – 7.32 (m, 4H), 7.16 – 7.20 (m, 3H), 4.31 (q, *J* = 7.2 Hz, 2H), 1.32 (t, *J* = 7.2 Hz, 3H). No Pz N-H visible in $CDCl_3$. ^{1}H NMR (400 MHz, DMSO-d_6 at 298 K): δ 14.25 (bs, ~61% N-H Pz tautomer), 14.03 (bs, ~39% N-H Pz tautomer), 8.93 – 8.95 (d, *J* = 2.0 Hz, 1H), 8.86 – 8.89 (d, *J* = 4.0 Hz, 1H), 8.40 – 8.70 (bs, 1H), 8.21 – 8.28 (d, *J* = 7.6 Hz, 1H), 8.13 (d, *J* = 8.0 Hz, 1H), 8.05 (d, *J* = 8.0 Hz, 1H), 7.23 – 7.82 (m, 4H), 7.58 – 7.65 (m, 3H), 4.65 (q, *J* = 7.2 Hz, 2H), 1.67 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.1, 148.9, 148.7, 135.1, 132.3, 131.9, 131.2, 130.7, 130.5, 129.3, 128.9, 128.8, 128.5, 127.6, 61.2, 14.3. MS (LR-APCI): calculated for $C_{23}H_{19}N_3O_2$: 369.2, measured 370.4 $(M+H)^+$.

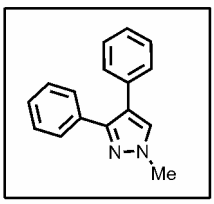
Table S2. Regioselectively N-methylated 3,4-aryl pyrazoles



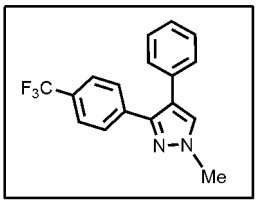
Entry	Product		Isolated Yield (2 steps)
1		**33**	70%
2		S5	82%
3		S6	66%
4		S7	77%



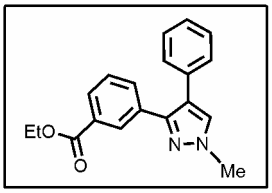
3-(3-Methoxyphenyl)-1-methyl-4-phenyl-1*H*-pyrazole (33): Synthesized using the procedure described above, only at room temperature in 1 hour. 75% yield over 2 steps, isolated with a gradient from 100% CH_2Cl_2 to 1% MeOH:CH_2Cl_2. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44 (s, 1H), 7.16 – 7.29 (m, 6H), 7.04 – 7.08 (m, 2H), 6.80 – 6.84 (ddd, J_1 = 8.1 Hz, J_2 = 2.7 Hz, J_3 = 0.9 Hz, 1H), 3.96 (s, 3H), 3.68 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.4, 148.6, 134.8, 133.3, 130.2, 129.2, 128.7, 128.4, 126.5, 120.9, 120.7, 113.9, 113.0, 55.1, 39.0. MS (LR-APCI): calculated for $C_{17}H_{16}N_2O$: 264.1, measured 265.3 $(M+H)^+$.



1-Methyl-3,4-diphenyl-1*H*-pyrazole (S5): Same procedure as **33**; 82% yield over two steps. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48 - 7.50 (m, 2H), 7.47 (s, 1H), 7.26 – 7.30 (m, 8H), 3.98 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 133.5, 133.3, 130.9, 130.2, 128.5, 128.4, 128.2, 127.5, 126.5, 39.0. MS (LR-APCI): calculated for $C_{16}H_{14}N_2$: 234.1, measured 234.8 (M+1).



1-Methyl-4-phenyl-3-(4-(trifluoromethyl)phenyl)-1*H*-pyrazole (S6): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, *J* = 8.0 Hz, 2H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.48 (s, 1H), 7.24 – 7.33 (m, 5H), 4.00 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.2, 137.1, 132.8, 130.6, 128.7, 128.6, 128.2, 126.9, 125.2, 125.16, 122.5, 121.4, 39.1. MS (LR-APCI): calculated for $C_{17}H_{13}F_3N_2$: 302.1, measured 302.9 $(M+H)^+$.



1-Methyl-3-(3-ethoxycarbonylphenyl)-4-phenyl-1*H*-pyrazole (S7): ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (s, 1H), 7.95 (dt, J_1 = 7.8 Hz, J_2 = 1.3 Hz, 1H), 7.62 (dt, J_1 = 7.8 Hz, J_2 = 1.3 Hz, 1H), 7.46 (s, 1H), 7.33 (t, *J* = 7.8 Hz, 1H), 7.24 – 7.30 (m, 5H), 4.31 (q, *J* = 7.2 Hz, 2H), 3.98 (s, 3H), 1.32 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.7, 147.8, 133.8, 133.0, 132.5, 130.7, 130.3, 129.2, 128.6, 128.5, 128.2, 126.7, 121.1, 60.8, 39.1, 14.3, -0.018. MS (LR-APCI): calculated for $C_{17}H_{13}F_3N_2$: 306.1, measured 307.3 $(M+H)^+$.

VII. References

1. Fugina, N; Holzer, W.; Wasicky, M. *Heterocycles* **1992**, *34*, 303 – 313.
2. Zhao, Z.-G.; Wang, Z.-X. *Synth. Comm.* **2007**, *37*, 137 – 147.
3. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43* (14), 2923 – 2925.
4. Nakagawa, Y.; Aki, O.; Sirakawa, K. *Chem. Pharm. Bull.* **1972**, *20*, 2209 – 2214.
5. Luo, G.; Chen, L.; Dubowchik, G. *J. Org. Chem.* **2006**, *71*, 5392 – 5395.
6. (a) Trofimenko, S.; Yap, G. P. A.; Jove, F. A.; Claramunt, R. M.; García, M. A.; Santa Maria, M. D.; Alkorta, I.; Elguero, J. *Tetrahedron* **2007**, *63*, 8104 – 8111. (b) Vors, J.-P.; Gerbaud, V.; Gabas, N.; Canselier, J. P.; Jagerovic, N.; Jimeno, M. L.; Elguero, J. *Tetrahedron* **2003**, *59*, 555 – 560. (c) Aguilar – Parrilla, F.; Cativiela, C.; Diaz de Villegas, M. D.; Elguero, J.; Foces-Foces, C.; Laureiro, J. I. G.; Cano, F. H.; Limbach, H.-H.; Smith, J. A. S.; Toiron, C. *J. Chem. Soc. Perkin Trans. 2*, **1992**, 1737-1742. (d) Habraken, C. L.; Moore, J. A. *J. Org. Chem*. **1965**, *30*, 1892 – 1896.

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