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Note

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2,2,2-Trifluoroethoxy Aromatic Heterocycles: Hydrolytically Stable Alternatives to Heteroaryl Chlorides

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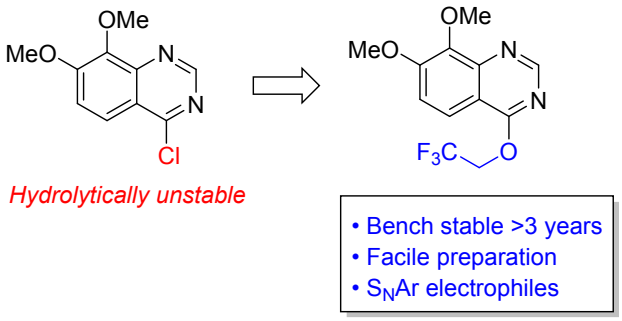
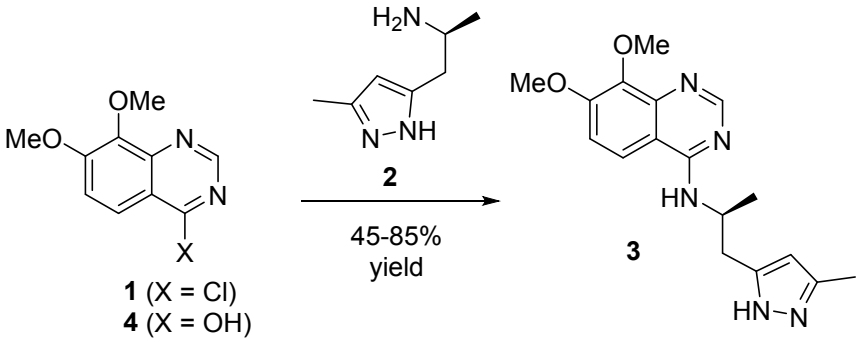
TOC/Abstract Graphic:



Abstract: Herein we describe the 2,2,2-trifluoroethoxy group as an alternative leaving group for hydrolytically unstable heteroaryl chlorides. This group provides improved shelf stability by years while maintaining reactivity toward nucleophiles in S_NAr reactions. A highlighted trifluoroethyl ether was shown to be tolerant to aqueous Suzuki conditions, permitting sequential Suzuki/S_NAr processes inaccessible to the heterocyclic chlorides. The strategic use of trifluoroethyl ethers enables storage of otherwise unstable heterocyclic chlorides and limits costly decomposition..

Nucleophilic aromatic substitution (S_NAr) is among the most prevalent chemical reactions in pharmaceutical research.[1] In the course of our work on quinazoline based PDE1 inhibitors,[2] S_NAr between the heterocyclic chloride (Het-Cl) **1** and the amine **2**, returned inconsistent yields (45–85%) of adduct **3** (Scheme 1). The variable yields were later attributed to the quality of the Het-Cl, with production lots from different sources found to contain varying amounts of the quinazoline hydrolysis product **4**. Further experimentation demonstrated that the Het-Cl **1** can undergo hydrolysis to the quinazolone **4** upon extended storage under ambient conditions or repeated manipulation in an acid-catalyzed process.[3] Thus, the HCl by-product of the hydrolysis catalyzes further decomposition of the substrate.

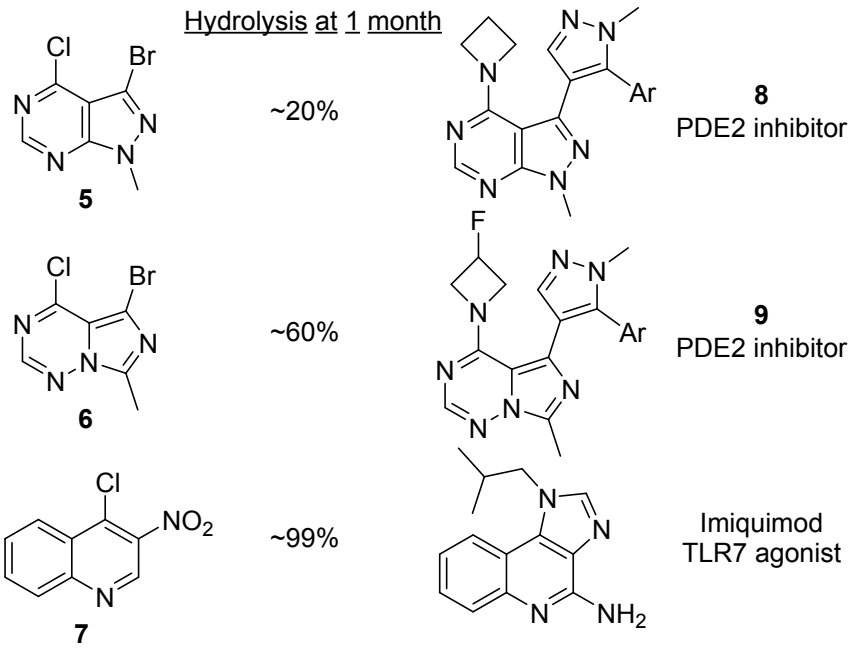
Scheme 1. Synthesis of Quinazoline 3



While limited amounts of Het-Cl hydrolysis during storage may prove of little consequence for many exploratory studies, the problem is exacerbated on larger reaction scale where cost must be minimized. In the manufacture of a pharmaceutical API, consistency in feedstock composition is a considerable concern that can be adversely affected by shipping and storage conditions. Even for medicinal chemistry discovery, which typically involves smaller quantities, the presence of labile Het-Cl functionality in advanced intermediates can complicate structure-activity relationship (SAR) exploration. In order to address this relatively common problem, we sought to identify a hydrolytically stable leaving group alternative to chloride that would be applicable to quinazolines as well as other reactive Het-Cl's.

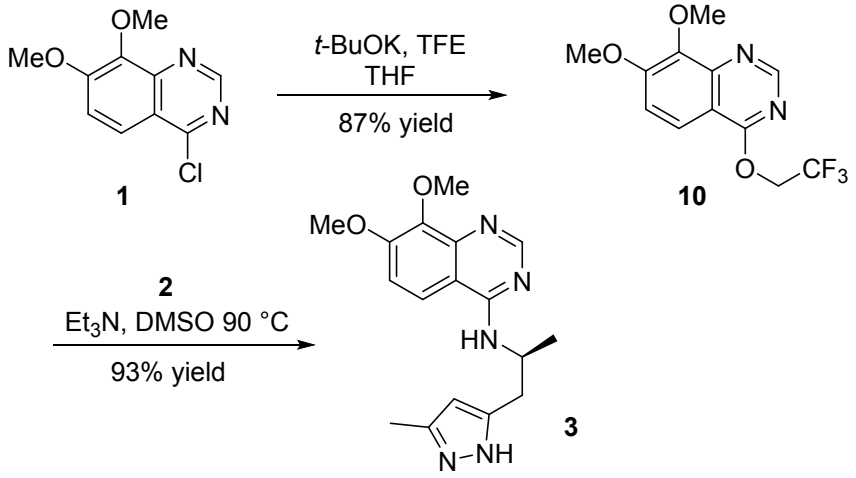
Thus, we have selected for discussion three other Het-Cl systems from our research programs that suffered significant hydrolysis during storage (chlorides **5**, **6**, and **7**, Scheme 2). In order to crudely quantify the extent of hydrolysis that occurred during typical storage, a freshly prepared sample of each chloride was placed in a capped vial under air and stored at room temperature. After one month, analysis by ^{1}H NMR indicated pyrazolopyrimidine **5**[4] and imidazotriazene **6**[5], cores found in PDE inhibitors **8**[6] and **9**[7], had hydrolyzed by ~20% and ~60%, respectively. A freshly prepared sample of reactive chloroquinoline **7**, an early intermediate in the synthesis of Imiquimod,[8] had fully degraded to the hydroxyquinoline over the same period of time.

Scheme 2. Decomposition of Heterocyclic Chlorides



In order to address this problem, we considered attributes of potential chloride replacements such as ease of installation, availability, and conjugate acid pK_a. Based on these factors we identified the 2,2,2-trifluoroethoxy group as a competent substitute (Scheme 3).[9] Preparation of ether **10** was accomplished by the reaction of the chloroquinazoline with *t*-BuOK and trifluoroethanol (TFE) in THF. Analysis of the ether showed complete shelf stability under ambient conditions with no measureable hydrolysis by ^{1}H NMR after two years. Conversely, a freshly prepared sample of chloride **1** had undergone 75% decomposition to the quinazolone **4** after one month. Upon application, displacement of the trifluoroethyl ether **10** with the amine **2** (Et_3N, DMSO, 90 °C) afforded adduct **3** in high yield. Trifluoroethanol is commercially available in bulk quantities and its physical properties (water miscible, bp 77–80 °C), facilitates its removal post reaction. Furthermore, the trifluoroethyl ether mitigates the risk of autocatalytic hydrolysis as trifluoroethanol is weakly acidic (pK_a 12.4 in H_2O)[10] in contrast to chloride (pK_a HCl = –5.9 in H_2O).[11] While this strategy requires an additional step for the conversion of the chloride into the ether, it assures the integrity of the material during storage and shipment. The latter points are of critical concern as one increases scale from research quantities to bulk lots for API manufacture. The ability to store S_NAr precursors at room temperature is also of value in a medicinal chemistry program for rapid SAR generation.

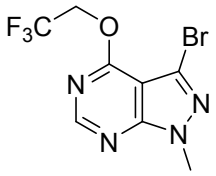
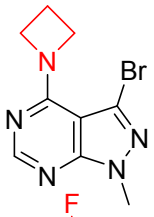
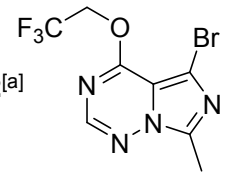
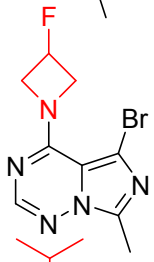
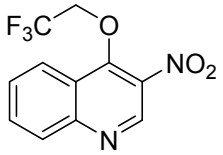
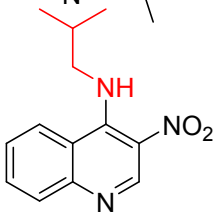
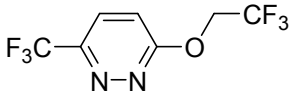
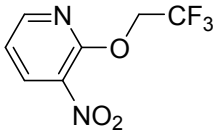
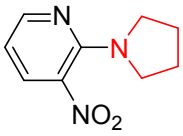
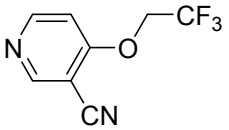
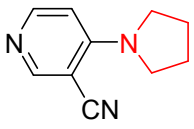
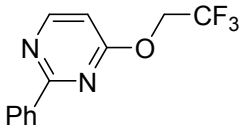
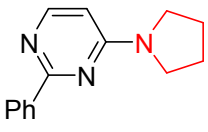
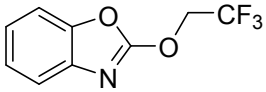
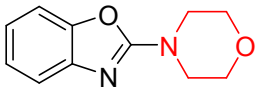
Scheme 3. Preparation and Reaction of Trifluoroethyl ether 10



Trifluoroethyl ethers **11**–**18** were easily prepared from the corresponding chlorides via displacement with trifluoroethoxide in either trifluoroethanol or THF as described in the Experimental Section (Table 1). To demonstrate the long term stability of select heterocycles, samples of trifluoroethyl ethers **11** and **12** were stored on the bench in screw capped vials under air. ^{1}H NMR analysis of the ethers after three years indicated no-detectible hydrolysis, thus demonstrating superior stability on storage compared to the corresponding chlorides (cf. **5** and **6**, Scheme 2).

Table 1. Substrate Table

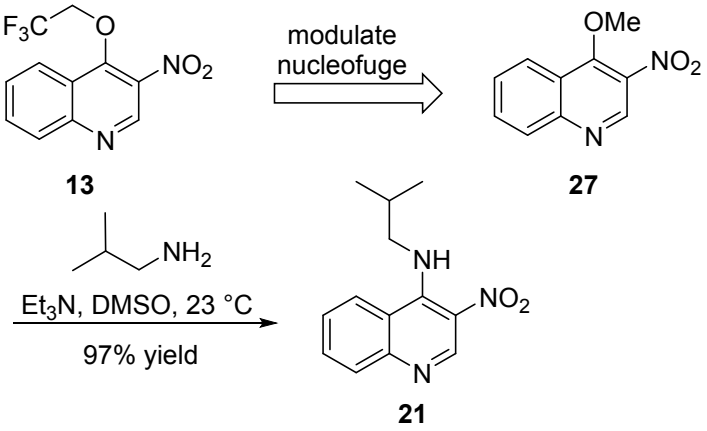
11-18 **19-26**

TFE ether	Product	temp (°C)	yield (%)
11 	**19** 	23	99
12[a] 	**20** 	23	95
13 	**21** 	23	96
14 	**22** 	120	84[b]
15 	**23** 	80	92
16 	**24** 	80	93
17 	**25** 	120	89
18 	**26** 	80	92

[a]DBU used as base. [b]55% conversion at 24 hours, yield is BRSM

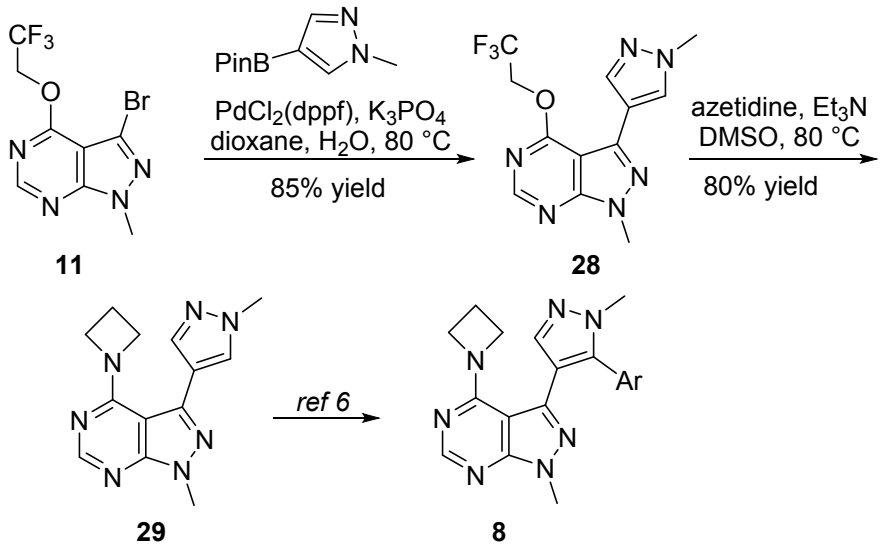
The reactivity of trifluoroethyl ethers **11**–**18** toward substitution was examined with various nitrogen nucleophiles as illustrated in Table 1. In general, each reacted smoothly (DMSO, Et_3N or DBU, rt to 120 °C) to afford the products in high yield (84–99%).[12] One particularly reactive system is represented by the nitroquinoline **13**. For this system, the chloride (**7**, Scheme 2) was found to be exceedingly unstable and even the corresponding trifluoroethyl ether suffered significant hydrolysis during storage.[13] In this case, the methyl ether **27** proved to be a more stable alternative capable of later displacement under mild conditions (Scheme 4).

Scheme 4. Tempering Reactivity of 13



To demonstrate the utility of the trifluoroethyl ether as a latent electrophile, we chose to explore a Suzuki coupling/S_NAr sequence. Bromide **11** was coupled with the pyrazole boronate under a standard set of Suzuki reaction conditions in the presence of water (Scheme 5). The coupling product **28** was obtained in high yield with no observable ether hydrolysis, whereas the corresponding chloride did not survive similar coupling conditions. Subsequent reaction with azetidine afforded the S_NAr product **29** without issue. This strategy was effectively exploited in the synthesis of the of pyrazolopyrimidine class of PDE2 inhibitors exemplified by **8**.

Scheme 5. Trifluoroethyl Ether Stability in Suzuki Coupling



In conclusion, we have presented a general strategy to address the instability of heteroaryl chlorides during storage by use of trifluoroethyl ether surrogates. Heteroaryl trifluoroethyl ethers exhibit improved hydrolytic stability as compared to the corresponding Het-Cl's under ambient conditions permitting storage without special requirements, yet maintain reactivity toward nitrogen nucleophiles in S_NAr reactions. The trifluoroethyl group is introduced under mild conditions and excess trifluoroethanol is easily removed from the reaction with an aqueous workup or evaporation. Use of the trifluoroethyl ether as a latent electrophile, exemplified in a sequential cross coupling-S_NAr protocol, permits the use of reactions not accessible to the corresponding Het-Cl's. This method should prove useful for mitigating the risk of heterocyclic feedstock hydrolysis for both medicinal and process scale efforts.

Experimental

General. All reagents and solvents were obtained from commercial sources and used without further purification. Reactions requiring heat were performed in aluminum heating blocks. Reaction progress was monitored by UPLC-MS (Waters Acquity, ESCI ±, APCI ±) or TLC (Analtech, Inc. silica gel GF 250 μm plates). ^{1}H NMR, ^{19}F NMR, and ^{13}C{^{1}H} NMR spectra were obtained on Bruker or Varian instruments (400, 376, and 100 MHz respectively). ^{1}H and ^{13}C chemical shifts are reported in ppm relative to chloroform (7.26 ppm and 77.00 ppm, respectively) or DMSO (2.50 ppm and 39.51 ppm, respectively). NMR multiplicities are reported as: s, singlet; d, doublet; t, triplet; quint, quintet; m, multiplet; br, broadened; ddd, doublet of doublet of doublets. IR (infrared) spectra were obtained on a Thermo Nicolet Avatar 360 FT-IR. High resolution mass spectra (HRMS) were obtained on an Agilent model 6220 MS (ESI-TOF). Melting points were recorded on a Sanford Research Systems OptiMelt and are uncorrected.

Synthesis of Trifluoroethyl Ethers, General Procedure A: To a solution of heteroaryl chloride (1 equiv) in 2,2,2-trifluoroethanol (0.2 M) at 0 °C was added potassium *tert*-butoxide (2 equiv). After 5 minutes the ice bath was removed and the reaction stirred at the indicated temperature. After complete conversion of the reaction (monitored by LCMS or TLC), all organics were evaporated. The crude residue was diluted with EtOAc or DCM, washed with water × 3, brine, dried over Na_2SO_4 or $MgSO_4$, filtered and concentrated. The product was purified as described.

General Procedure B: To a solution of heteroaryl chloride (1 equiv) and 2,2,2-trifluoroethanol (2 equiv) in THF (0.2 or 0.4 M) at 0 °C was added potassium *tert*-butoxide (1.2 equiv). After 5 minutes

the ice bath was removed and the reaction stirred at the indicated temperature. After complete conversion of the reaction (monitored by LCMS or TLC), all organics were evaporated. The crude residue was diluted with EtOAc or DCM, washed with water × 3, brine, dried over Na_2SO_4 or $MgSO_4$, filtered and concentrated. The product was purified as described.

7,8-Dimethoxy-4-(2,2,2-trifluoroethoxy)quinazoline ***(10)***. Following General Procedure B, 4-chloro-7,8-dimethoxyquinazoline (595 mg, 2.65 mmol), 2,2,2-trifluoroethanol (0.38 mL, 5.30 mmol), THF (6 mL), and *t*-BuOK (357 mg, 3.18 mmol) at room temperature for 1 hour resulted in the desired product as an off-white solid after recrystallization from hot heptane (650 mg, 2.26 mmol, 87% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (s, 1H), 7.98 (d, J = 9.0 Hz, 1H), 7.35 (d, J = 9.4 Hz, 1H), 4.98 (q, J_{HF} = 8.6 Hz, 2H), 4.11 (s, 3 H), 4.05 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ –73.57 (t, J_{HF} = 8.0 Hz); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 164.7, 155.8, 153.3, 146.1, 141.9, 125.3 (q, J_{CF} = 227.3 Hz), 119.8, 119.1, 115.9, 110.2. 62.2 (q, J = 35.2 Hz), 61.5, 56.7; IR (thin film) ν_{max} 1611, 1565, 1474 cm^{-1}; HRMS (ESI/QTOF) *m/z*: [M+H]$^+$ Calcd for $C_{12}H_{12}F_3N_2O_3$ 289.0795; Found 289.0802; Melting point 81.7–82.1 °C

3-Bromo-1-methyl-4-(2,2,2-trifluoroethoxy)-1H-pyrazolo[3,4-d]pyrimidine ***(11)***. Following General Procedure A, 3-bromo-4-chloro-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (7.03 g, 28.4 mmol), 2,2,2-trifluoroethanol (140 mL), and *t*-BuOK (6.37 g, 56.8 mmol) at room temperature for 18 hour resulted in the desired product as an off-white solid without further purification (8.22 g, 26.2 mmol, 93% yield)

Following General Procedure B, 3-bromo-4-chloro-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (500 mg, 2.02 mmol), 2,2,2-trifluoroethanol (0.291 mL, 4.04 mmol), THF (10 mL), and *t*-BuOK (378 mg, 2.53 mmol) at room temperature for 19 hours resulted in the desired product as an off-white solid after silica gel chromatography (0–10% EtOAc:heptane) (565 mg,1.82 mmol, 90% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H), 5.00 (q, J_{HF} = 8.2 Hz, 2H), 4.08 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ –73.60 (t, J_{HF} = 8.0 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 161.6, 155.6, 155.3, 123.0 (q, J_{CF} = 276 Hz), 117.9, 102.7, 62.5 (q, J_{CF} = 37 Hz), 34.5; IR (thin film) ν_{max} 1606, 1558, 1465 cm^{-1}; HRMS (ESI/QTOF) *m/z*: [M+H]$^+$ Calcd for $C_8H_7BrF_3N_4O$ 310.9750 and 312.9730; Found 310.9741 and 312.9717; Melting point 156.0–156.1 °C.

5-Bromo-7-methyl-4-(2,2,2-trifluoroethoxy)imidazo[5,1-f][1,2,4]triazine ***(12)***. Following General Procedure A, 5-bromo-4-chloro-7-methylimidazo[5,1-*f*][1,2,4]triazine (2.00 g, 8.08 mmol), 2,2,2-trifluoroethanol (40 mL), and *t*-BuOK (1.81 g, 16.2 mmol) at room temperature for 18 hour resulted in the desired product as an off-white solid without further purification (2.10 g, 6.75 mmol, 84% yield) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 4.95 (q, J_{HF} = 8.2 Hz, 2H), 2.70 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ –73.49 (t, J_{HF} = 8.0 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.8, 147.5, 142.1, 131.7 (q, J_{CF} = 277 Hz), 112.0, 109.4, 62.5 (q, J_{CF} = 37 Hz), 11.9; IR (thin film) ν_{max} 1606, 1520, 1474 cm^{-1}; HRMS (ESI/QTOF) *m/z*: [M+H]$^+$ Calcd for $C_8H_7BrF_3N_4O$ 310.9750 and 312.9730; Found 310.9743 and 312.9717; Melting point 107.1–107.6 °C.

3-Nitro-4-(2,2,2-trifluoroethoxy)quinolone ***(13)***. Following General Procedure A, 3-Nitro-4-chloroquinoline (742 mg, 3.56 mmol), 2,2,2-trifluoroethanol (17.8 mL), and *t*-BuOK (798 mg, 7.11 mmol) at room temperature for 20 hours resulted in the desired product as a beige amorphous solid without further purification (938 mg, 3.45 mmol, 97% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.40 (s, 1H), 8.30 (d, J = 7.8 Hz, 1H), 8.17 (d, J = 8.2 Hz, 1H), 8.04 (ddd, J = 1.4, 7.0, 8.4 Hz, 1H), 7.87 (t, J = 7.3 Hz, 1H), 5.14 (q, J_{HF} = 9.0 Hz, 2H); ^{19}F NMR (376 MHz, DMSO-d_6) δ –73.56 (t, J_{HF} = 8.0 Hz); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 155.8, 150.3, 146.4, 133.7, 133.3, 129.4, 128.8, 123.5, 123.2 (q, J_{CF} = 277 Hz), 122.0, 70.8 (q, J_{CF} = 35.2 Hz); IR (thin film) ν_{max} 1590, 1574, 1525, 1374, 1344, 1279, 1182 cm^{-1}; HRMS (ESI/QTOF) *m/z*: [M+H]$^+$ Calcd for $C_{11}H_8F_3N_2O_3$ 273.0482; Found 273.0475.

*3-(2,2,2-Trifluoroethoxy)-6-(trifluoromethyl)pyridazine (**14**)*. Following General Procedure A, 3-chloro-6-(trifluoromethyl)pyridazine (670 mg, 3.67 mmol, 75% pure), 2,2,2-trifluoroethanol (18.3 mL), and *t*-BuOK (823 mg, 7.33 mmol) at 60 °C for 6 hours resulted in the desired product as a light pink oil after silica gel chromatography (0–20% EtOAc:heptane) (500 mg, 2.03 mmol, 74% yield based on purity of chloride). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 8.0 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1H), 5.03 (q, J_{CF} = 8.0 Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ –66.48 (s), –73.80 (t, J_{HF} = 8.0 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 164.4, 149.0 (q, J_{CF} = 35 Hz), 127.3 (q, J_{CF} = 2 Hz), 122.9 (q, J_{CF} = 275 Hz), 121.2 (q, J_{CF} = 273 Hz), 118.0, 63.89 (q, J_{CF} = 37 Hz); IR (thin film) ν_{max} 1594, 1466, 1450 cm^{-1}; HRMS (ESI/QTOF) *m/z*: $[M+H]^+$ Calcd for $C_7H_4F_6N_2O$ 247.0301; Found 247.0300.

*3-Nitro-2-(2,2,2-trifluoroethoxy)pyridine (**15**)*. Following General Procedure A, 2-chloro-3-nitropyridine (2.00 g, 12.6 mmol), 2,2,2-trifluoroethanol (63 mL), and *t*-BuOK (2.83 g, 25.2 mmol) at 75 °C for 8 hours resulted in the desired product as a yellow waxy solid after silica gel chromatography (0–25% EtOAc:heptane) (2.51 g, 11.3 mmol, 90% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (dd, J = 4.7, 2.0 Hz, 1H), 8.34 (dd, J = 7.8, 2.0 Hz, 1H), 7.19 (dd, J = 8.0, 4.9 Hz, 1H), 4.93 (q, J_{CF} = 8.0 Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ –73.56 (t, J_{HF} = 8.0 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 154.1, 151.2, 135.6, 123.1 (q, J_{CF} = 275 Hz), 118.4, 118.1, 63.0 (q, J_{CF} = 37 Hz); IR (thin film) ν_{max} 1613, 1577, 1437 cm^{-1}; HRMS (ESI/QTOF) *m/z*: $[M+H]^+$ Calcd for $C_7H_6F_3N_2O_3$ 223.0320; Found 223.0324.

*4-(2,2,2-Trifluoroethoxy)nicotinonitrile (**16**)*. Following General Procedure A, 4-chloronicotinonitrile (1.00 g, 7.2 mmol), 2,2,2-trifluoroethanol (36 mL), and *t*-BuOK (722 mg, 14.4 mmol) at 70 °C for 17 hours resulted in the desired product as a colorless oil after silica gel chromatography (0–60% EtOAc:heptane) (1.36 g, 6.73 mmol, 93% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.64 (d, J = 8.0 Hz, 1H), 6.95 (d, J = 8.0 Hz, 1H), 4.56 (q, J_{CF} = 8.0 Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ –73.60 (t, J_{HF} = 7.5 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 163.9, 154.8, 154.3, 122.2 (q, J_{CF} = 277 Hz), 113.1, 107.2, 100.3, 65.4 (q, J_{CF} = 37 Hz); IR (thin film) ν_{max} 2235, 1731, 1590 cm^{-1}; HRMS (ESI/QTOF) *m/z*: $[M+H]^+$ Calcd for $C_8H_6F_3N_2O$ 203.0427; Found 203.0423.

*2-Phenyl-4-(2,2,2-trifluoroethoxy)pyrimidine (**17**)*. Following General Procedure A, 4-chloro-2-phenylpyrimidine (1.00 g, 5.25 mmol), 2,2,2-trifluoroethanol (26 mL), and *t*-BuOK (1.18 g, 10.5 mmol) at 75 °C for 17 hours resulted in the desired product as a white solid after silica gel chromatography (0–10% EtOAc:heptane) (1.25 g, 4.92 mmol, 94% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, J = 4.0 Hz, 1H), 8.41 (m, 2H), 7.50 (m, 3H), 6.77 (d, J = 4.0 Hz, 1H), 4.95 (q, J_{CF} = 8.0 Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ –73.51 (t, J_{HF} = 8.0 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 167.5, 164.3, 158.5, 136.8, 131.1, 128.6, 128.2, 123.3 (q, J_{CF} = 276 Hz), 106.2, 62.0 (q, J_{CF} = 37 Hz); IR (thin film) ν_{max} 1565, 1435, 1389 cm^{-1}; HRMS (ESI/QTOF) *m/z*: $[M+H]^+$ Calcd for $C_{12}H_{10}F_3N_2O$ 255.07397; Found 255.0733; Melting point 67.1–67.8 °C.

*2-(2,2,2-Trifluoroethoxy)-1,3-benzoxazole (**18**)*. Following General Procedure A, 2-chloro-1,3-benzoxazole (0.20 mL, 1.75 mmol), 2,2,2-trifluoroethanol (8.8 mL), and *t*-BuOK (393 mg, 3.5 mmol) at 70 °C for 18 hours resulted in the desired product as a colorless oil after silica gel chromatography (0–10% EtOAc:heptane) (320 mg, 1.47 mmol, 84% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (m, 1H), 7.38 (m, 1H), 7.29 (m,1H), 7.24 (m, 1H), 4.93 (q, J_{CF} = 7.8 Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ –74.20 (t, J_{HF} = 7.5 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 162.2, 148.9, 140.2, 124.1, 123.6, 122.2 (q, J_{CF} = 275 Hz), 118.4, 110.0, 66.9 (q, J_{CF} = 37 Hz); IR (thin film) ν_{max} 1628, 1579, 1458 cm^{-1}; HRMS (ESI/QTOF) *m/z*: $[M+H]^+$ Calcd for $C_9H_7F_3NO_2$ 218.0423; Found 218.0422.

*1-Methyl-3-(1-methyl-1H-pyrazol-4-yl)-4-(2,2,2-trifluoroethoxy)-1H-pyrazolo[3,4-d]pyrimidine (**28**)*. Trifluoroethyl ether **11** (200 mg, 0.64 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (174 mg, 0.84 mmol), potassium phosphate tribasic (410 mg, 1.93 mmol), and $PdCl_2$(dppf) DCM complex (27 mg, 0.03 mmol) were added to a degassed solution of dioxane (6.4 ml) and water (1.0

mL) followed by heating to 80 °C for 18 hours. After cooling to room temperature the reaction was diluted with water and extracted with EtOAc × 3. The combined organics were washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude material was purified by silica gel chromatography (0–70% EtOAc:heptane) to afford the adduct as a white solid (170 mg, 0.54 mmol, 85% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (s, 1H), 8.11 (s, 1H), 8.06 (s, 1H), 5.02 (q, J_{HF} = 8.6 Hz, 2H), 4.08 (s, 3H), 3.96 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ – 73.23 (t, 8 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 161.5, 155.7, 154.5, 138.3, 137.1, 130.1, 123.4 (q, J_{CF} = 277 Hz), 114.3, 99.3, 62.7 (q, J_{CF} = 37 Hz), 39.0, 34.1; IR (thin film) ν_{max} 1590, 1562, 1429 cm^{-1}; HRMS (ESI/QTOF) *m/z*: $[M+H]^+$ Calcd for $C_{12}H_{12}F_3N_6O$ 313.1019; Found 313.1023; Melting point 161.6–162.4 °C.

S_NAr, General Procedure C: A solution of trifluoroethyl ether (1 equiv) in DMSO (0.2 M) was added amine nucleophile (1.5 equiv) and Et_3N or DBU (1.5 equiv). The reaction was then heated for the indicated time. Upon completion (monitored by TLC or LCMS), the reaction was cooled to room temperature, diluted with water, and extracted into EtOAc × 3. The combined organics were washed with water × 3, brine, dried over Na_2SO_4 or $MgSO_4$, filtered and concentrated. The product was purified as described.

(S)-7,8-dimethoxy-N-(1-(3-methyl-1H-pyrazol-5-yl)propan-2-yl)quinazolin-4-amine ***(3)***.[2] Following General Procedure C, trifluoroethyl ether **10** (6.56 g, 22.7 mmol), 1-(3-methyl-1*H*-pyrazol-5-yl)propan-2-amine bis-hydrochloride (5.79 g, 27.3 mmol) triethylamine (9.21 g, 91 mmol) in DMSO (23 mL) at 90 °C for 24 hours, and was then diluted with water (65 mL) to dissolve the salts. After continued stirring with cooling to rt the product precipitated as a white solid. This was stirred for 3 hours at room temperature and another 1 h in an ice bath. The precipitate was collected via filtration, rinsed with a few mL of water, and dried overnight under a stream of air to afford the title compound as a white solid (6.96 g, 21.1 mmol, 93% yield).

4-(Azetidin-1-yl)-3-bromo-1-methyl-1H-pyrazolo[3,4-d]pyrimidine ***(19)***. Following General Procedure C, trifluoroethyl ether **11** (80 mg, 0.26 mmol), azetidine (0.026 mL, 0.38 mmol), triethylamine (0.054 mL, 0.38 mmol) in DMSO (1.9 mL) at 80 °C for 5 minutes afforded the desired product as a pale yellow solid without further purification (68 mg, 0.25 mmol, 99% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 1H), 4.56 (br s, 4H), 3.97 (s, 3H), 2.50 (quint, *J* = 7.7 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 156.1, 155.3, 154.6, 116.9, 100.9, 77.2, 34.1, 17.3; IR (thin film) ν_{max} 1574, 1554, 1467, 1440, 1315, 1292, 1256 cm^{-1}; HRMS (ESI/QTOF) *m/z*: $[M+H]^+$ Calcd for $C_9H_{11}BrN_5$ 268.0190 and 270.0170; Found 268.0193 and 270.0168; Melting point 178.2–178.6 °C

5-Bromo-4-(3-fluoroazetidin-1-yl)-7-methylimidazo[5,1-f][1,2,4]triazine ***(20)***. Following General Procedure C, trifluoroethyl ether **12** (366 mg, 1.18 mmol), 3-fluoroazetidine *p*-toluenesulfonate (433 mg, 1.75 mmol), triethylamine (0.490 mL, 3.50 mmol) in DMSO (4.0 mL) at 23 °C for 24 hours. The reaction was diluted with water (8 mL) and stirred for an additional 2 h. The precipitate was collected via filtration and rinsed with 4 mL water to afford the product as a white powder (320 mg, 1.12 mmol, 95% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 5.45 (app. doublet of heptets, 1 H, *J* = 3.1, 57.1 Hz), 4.86 (br, 2H), 4.68 (br, 2H), 2.63 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ –178.8 (m); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 154.2, 148.0, 141.5, 113.0, 106.7, 82.7 (d, J_{CF} = 200 Hz), 12.0; IR (thin film) ν_{max} 1449, 1403, 1105 cm^{-1}; HRMS (ESI/QTOF) *m/z*: $[M+H]^+$ Calcd for $C_9H_{10}BrFN_5$, 286.0098 and 288.0078; found, 286.0094 and 288.0069; melting point 181.0–181.3 °C

N-Isobutyl-3-nitroquinolin-4-amine[8] ***(21)***. Following General Procedure C, trifluoroethyl ether **13** (100 mg, 0.33 mmol), isobutylamine (48 mg, 0.65 mmol), triethylamine (0.136 mL, 0.65 mmol) in DMSO (1.7 mL) at 80 °C for 5 minutes afforded the desired product as a yellow solid after silica gel purification (0–50% EtOAc:heptane) (77 mg, 0.31 mmol, 96% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.15 (br s, 1H),

9.08 (s, 1H), 8.52 (d, *J* = 7.8 Hz, 1H), 7.92–7.82 (m, 2H), 7.60 (ddd, *J* = 1.4, 6.9, 8.5 Hz, 1H), 3.52 (t, *J* = 5.9 Hz, 2H), 2.01 (td, *J* = 6.7, 13.6 Hz, 1H), 0.94 (d, *J* = 6.6 Hz, 6H)

*4-(6-(Trifluoromethyl)pyridazin-3-yl)morpholine (**22**)*. Following General Procedure C, trifluoroethyl ether **14** (125 mg, 0.51 mmol), morpholine (0.066 mL, 0.76 mmol), triethylamine (0.10 mL, 0.76 mmol) in DMSO (2.5 mL) at 120 °C for 24 hours afforded the desired product as a white solid after silica gel chromatography (0–50% EtOAc:heptane) (60 mg, 0.26 mmol, 51% yield, 84% BRSM). 50 mg of trifluoroethyl ether **14** was recovered. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 9.8 Hz, 1H), 6.92 (d, *J* = 9.8 Hz, 1H), 3.83 (m, 4H), 3.72 (m, 4H); ^{19}F NMR (376 MHz, $CDCl_3$) δ –66.19 (s); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.3, 143.1 (q, J_{CF} = 35 Hz), 124.7 (q, J_{CF} = 2 Hz), 122.0 (q, J_{CF} = 275 Hz), 111.3, 66.3, 44.8; IR (thin film) ν_{max} 1867, 1599, 1451 cm^{-1}; HRMS (ESI/QTOF) *m/z*: $[M+H]^+$ Calcd for $C_9H_{11}F_3N_3O$ 234.0849; Found 234.0843; Melting point 150.5–153.0 °C

3-Nitro-2-(pyrrolidin-1-yl)pyridine[14] ***(23)***. Following General Procedure C, trifluoroethyl ether **15** (50 mg, 0.23 mmol), pyrrolidine (0.028 mL, 0.34 mmol), triethylamine (0.047 mL, 0.34 mmol) in DMSO (1.1 mL) at 80 °C for 20 hours afforded the desired product as an oil after silica gel chromatography (0–20% EtOAc:heptane) (40 mg, 0.21 mmol, 92% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (dd, *J* = 4.5, 1.8 Hz, 1H), 8.07 (dd, *J* = 8.0, 1.8 Hz, 1H), 6.64 (dd, *J* = 8.2, 4.7 Hz, 1H), 3.39 (m, 4H), 1.98 (m, 4H)

4-(Pyrrolidin-1-yl)nicotinonitrile[15] ***(24)***. Following General Procedure C, trifluoroethyl ether **16** (50 mg, 0.25 mmol), pyrrolidine (0.031 mL, 0.37 mmol), triethylamine (0.052 mL, 0.37 mmol) in DMSO (1.2 mL) at 80 °C for 18 hours afforded the desired product as a white solid after silica gel chromatography (0–100% EtOAc:heptane) (40 mg, 0.23 mmol, 93% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1H), 8.16 (d, *J* = 6.2 Hz, 1H), 6.39 (d, *J* = 6.2 Hz, 1H), 3.64 (m, 4H), 2.02 (m, 4H)

*2-Phenyl-4-(pyrrolidin-1-yl)pyrimidine (**25**)*. Following General Procedure C, trifluoroethyl ether **17** (75 mg, 0.30 mmol), pyrrolidine (0.037 mL, 0.44 mmol), triethylamine (0.062 mL, 0.44 mmol) in DMSO (1.5 mL) at 120 °C for 20 hours afforded the desired product as a white solid after silica gel chromatography (0–20% EtOAc:heptane) (59 mg, 0.26 mmol, 89% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (m, 2H), 8.25 (d, *J* = 5.9 Hz, 1H), 7.44 (m, 3H), 6.14 (d, J = 5.9 Hz, 1H), 3.52 (br m, 4H), 1.98 (br s, 4H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 163.4, 159.8, 154.9, 138.6, 129.9, 128.1, 127.9, 101.5, 46.1, 25.0; IR (thin film) ν_{max} 1569, 1542, 1447 cm^{-1}; HRMS (ESI/QTOF) *m/z*: $[M+H]^+$ Calcd for $C_{14}H_{16}N_3$ 226.1339; Found 226.1337; Melting point 95.4–97.3 °C.

2-Morpholino-1,3-benzoxazole[16] ***(26)***. Following General Procedure C, trifluoroethyl ether **18** (75 mg, 0.35 mmol), morpholine (0.045 mL, 0.52 mmol), triethylamine (0.072 mL, 0.52 mmol) in DMSO (1.7 mL) at 80 °C for 6 hours afforded the desired product as a white solid after silica gel chromatography (0–40% EtOAc:heptane) (65 mg, 0.32 mmol, 92% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (m, 1H), 7.28 (m, 1H), 7.19 (m,1H), 7.05 (m, 1H), 3.83 (m, 4H), 3.70 (m, 4H)

*4-Methoxy-2-nitroquinoline (**27**)*. To 4-chloro-3-nitroquinoline 7 (330 mg, 1.58 mmol) in methanol (4 mL) was added portionwise over 1 min. potassium *tert*-butoxide (213 mg, 1.90 mmol). After 10 min the mixture was partitioned between EtOAc (1 ×) and water. The combined organic phases were washed with brine, dried with MgSO4, and concentrated to afford an off white solid. This was recrystallized from EtOAc/heptane to afford of the title compound as an off white solid (260 mg, 1.27 mmol, 80% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.23 (s, 1 H), 8.33 (d, *J* = 8.6 Hz, 1H), 8.14 (d, *J* = 8.2 Hz, 1H), 7.89 (ddd, *J* = 1.6, 5.5, 7.9 Hz, 1 H), 7.69 (ddd, *J* = 1.2, 5.6, 8.2 Hz, 1H), 4.23 (s, 3 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 58.3, 150.3, 146.2, 133.6, 132.8, 129.7, 128.0, 123.8, 123.1, 63.2; IR (thin film) ν_{max} 1573, 1519, 1494 cm^{-1}; HRMS (ESI/QTOF) *m/z*: $[M+H]^+$ Calcd for $C_{10}H_9N_2O_3$ 205.0610; Found 205.0605; Melting point 101.2–102.1 °C

N-Isobutyl-3-nitroquinolin-4-amine[8] ***(21)*** via **27**. To 4-methoxy-3-nitroquinoline **27** (123 mg, 0.60 mmol) in DMSO (3 mL) was added dropwise isobutylamine (110 mg, 0.15 mmol). The yellow solution was stirred for 10 min and was then diluted with water (10 mL). The resultant yellow slurry was stirred for 1 h and the precipitate was collected via filtration, rinsed with water, and dried under a stream of air to of the title compound as a yellow powder (143 mg, 0.58 mmol, 97% yield).

4-(Azetidin-1-yl)-1-methyl-3-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[3,4-d]pyrimidine ***(29)***. Following General Procedure C, trifluoroethyl ether **28** (50 mg, 0.16 mmol), azetidine (0.016 mL, 0.24 mmol), DBU (0.036 mL, 0.24 mmol) in DMSO (0.80 mL) at 80 °C for 4 minutes afforded the desired product as an oil without further purification (35 mg, 0.13 mmol, 81% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.66 (s, 1H), 7.61 (s, 1H), 4.01 (s, 3H), 3.98 (m, 7 H), 2.27 (quint, J = 7.8 Hz, 2 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.0, 155.0, 154.3, 140.2, 136.0, 130.1, 115.3, 99.9, 52.9, 39.1, 33.8, 17.2; IR (thin film) ν_{max} 1573, 1558, 1470 cm^{-1}; HRMS (ESI/QTOF) *m/z*: $[M+H]^+$ Calcd for $C_{13}H_{16}N_7$ 270.1462; Found 270.1465

Supporting Information.

Copies of ^{1}H and ^{13}C NMR spectra are included in the supporting information. This material is available free of charge via the Internet at http://pubs.acs.org.

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