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Synthesis of 3-(Hetero)aryl Tetrahydropyrazolo[3,4-c]pyridines by Suzuki−Miyaura Cross-Coupling Methodology

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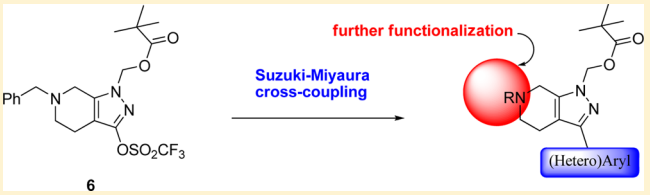
Supporting Information

ABSTRACT: A new synthetic route to 3-(heteroaryl) tetrahydropyrazolo[3,4-*c*]pyridines has been developed that uses the Suzuki−Miyaura cross-coupling of a triflate **6** with (hetero)aryl boronic acids or esters. Using $Pd(OAc)_2$ and XPhos or an XPhos precatalyst, a diverse range of substituents at the C3 position of the tetrahydropyrazolo[3,4-*c*]pyridine skeleton were prepared. The use of pivaloyloxymethyl and benzyl protection also offers the potential to differentially functionalize the pyrazole and tetrahydropyridine nitrogens.



Tetrahydropyrazolopyridine rings are widely used in medicinal chemistry; in particular, compounds featuring tetrahydropyrazolo[4,3-*c*]pyridines are reported to exhibit a range of different biological properties depending on the substitution pattern, for example, as a cannabinoid receptor modulator[1a] or as a potential treatment for diabetes.[1b] A bioisostere, tetrahydropyrazolo[3,4-*c*]pyridine is less prevalent; one example is reported to inhibit the activity of Heat Shock Protein 90[2] (Figure 1).

Although 3-substituted tetrahydropyrazolo[4,3-*c*]pyridines such as **1** can be readily prepared in a one-pot procedure from *tert*-butyl 4-oxopiperidine-1-carboxylate and an acid chloride (Scheme 1),[3] the synthesis of tetrahydropyrazolo-[3,4-*c*]pyridine derivatives of the type **2** are less efficiently described. Their reported synthesis starts by forming the lithium enolate of *tert*-butyl 3-oxopiperidine-1-carboxylate; however, as this produces a mixture of enolates, subsequent reaction with an acid chloride results in an inseparable mixture of diketones **3** and **4**. Consequently, reaction of this mixture with hydrazine gives not only the desired 3-substituted tetrahydropyrazolo[3,4-*c*]pyridine **2** but also a regioisomer tetrahydropyrazolo[4,3-*b*]pyridine **5**, often as an inseparable mixture (Scheme 1).[1a]

As part of a drug discovery program, we were interested in 3-(heteroaryl) tetrahydropyrazolo[3,4-*c*]pyridines but required an approach that would allow for their synthesis as a single regioisomer, ready variation of the C3 position and be amenable to selective derivatization of the heterocyclic nitrogens. We reasoned that synthesis of the triflate **6** would open up cross-coupling chemistry and thus allow for the incorporation of a wide variety of substituents at the C3 position. Suitable protection of the nitrogens with benzyl and pivaloyloxymethyl (POM) would further provide scope for selective functionalization of the heterocyclic nitrogens (Scheme 2).

Tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridin-3-ol ring **7** is readily made in 83% yield by reaction of ethyl 1-benzyl-3-oxopiperidine-4-carboxylate with hydrazine hydrate.[4] Initial attempts at making the triflate **8** from *N*-phenyltrifluoromethanesulfonimide with DBU in DCM failed, but switching the solvent to pyridine provided **8** in 54% yield.[5] Finally, **6** was made in 63% yield when sodium hydride was added to a mixture of chloromethyl pivalate and **8**. The structure of **6** was confirmed by NOE experiments, which showed an enhancement of the piperidine C7 proton signals when the methylene on the POM was irradiated. This confirmed that alkylation had occurred adjacent to the piperidine ring (as drawn in **6**, Scheme 2).

With a route that allowed us access to multigram quantities of versatile intermediate **6** in hand, we were able to study how it performed during a Suzuki−Miyaura cross-coupling (SMC) reaction. A brief catalyst screen using $Pd(PPh_3)_4$, $Pd(dppf)Cl_2$, $Pd(dtbpf)Cl_2$, $Pd(Amphos)Cl_2$, and $Pd(OAc)_2$ with XPhos identified that the most efficient conditions for the reaction of **6** (1 equiv) with a boronic acid or ester (1.2−1.5 equiv) were $Pd(OAc)_2$ (5 mol %), XPhos (10 mol %), and K_2CO_3, (3 equiv) in DME/water (3:1), at 80 °C. This afforded a range of coupled products in 17−86% yields (Table 1, entries **9**−**17**).[6] Notably, boronic acids containing electron-donating groups all coupled in good yields (entries **9**−**11**). The synthesis of **11** represents a significantly more efficient synthesis of this aryl substitution pattern seen in **2** (Scheme 1), an intermediate in the synthesis of a Heat Shock Protein (HSP 90) inhibitor (Figure 1).[2] Those boronic acids containing electron-withdrawing substituents at the *para* position were also well tolerated (entries **12** and **13**). However, boronic acids with an *ortho* electron-withdrawing group were less successful. For

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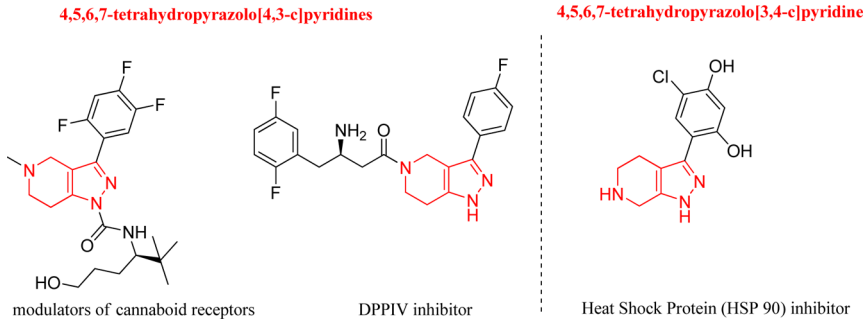
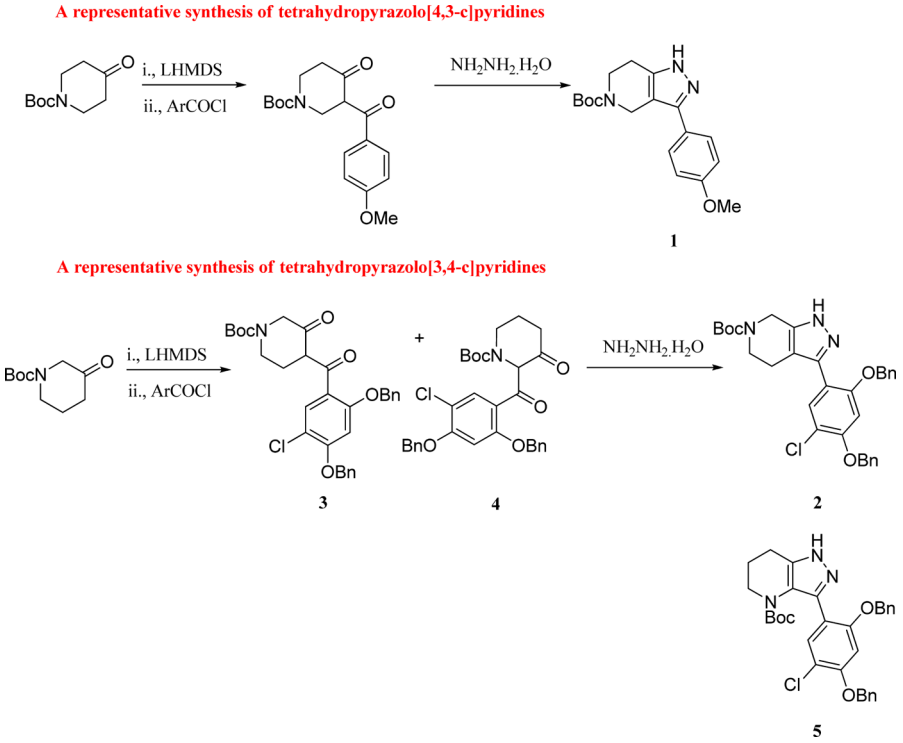
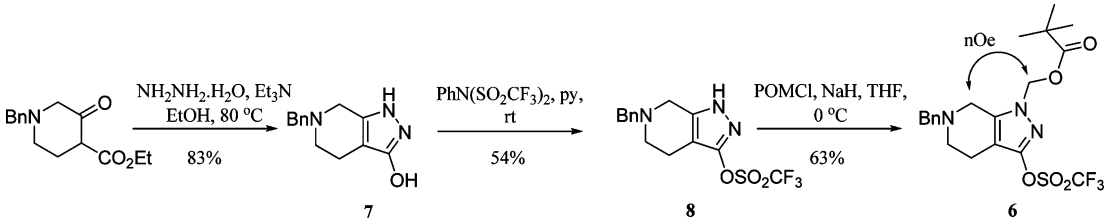


Figure 1. Selected examples of bioactive compounds featuring the tetrahydropyrazolopyridine core.

Scheme 1. General Route to Tetrahydropyrazolo[4,3-*c*] and [3,4-*c*] Pyridines



Scheme 2. Synthesis of Intermediate 6



example, the *ortho*-trifluoromethyl analogue **14** was obtained in 17% yield, but more typically, they failed, e.g., *ortho*-fluorophenylboronic acids. Similarly, the reaction of 3-pyridylboronic acid also failed to produce any desired product, although heterocyclic boronic acids or esters of quinoline, indole, and pyrazole all coupled in good yields (entries **15**–**17**).

In an effort to improve the range of substrates that would undergo an SMC reaction with **6**, we looked at using the XPhos precatalyst **18** reported by Buchwald et al. as a suitable reagent for coupling reactions of unstable boronic acids.[7] We were pleased to find that using **18** dramatically improved the SMC reaction of **6** to such an extent that boronic acids or esters that failed to couple when using $Pd(OAc)_2$ and XPhos were now isolated in excellent yields (Table 1, entries **19**–**24**). For example, when **6** was reacted with 2,4,5-trifluorophenylboronic acid, **18** (2 mol %), K_3PO_4, (2 equiv), THF, water (3:1) at rt for 30 min, **19** was isolated in 92% yield; similarly, other challenging fluorinated arylboronic acids coupled in high yields (entries **20** and **21**). In some cases, higher catalyst loading was required to achieve an efficient conversion. For example, only 16% of **22** was isolated when **6** was reacted with 3-pyridylboronic acid and 4 mol % of **18** at 40 °C, but this

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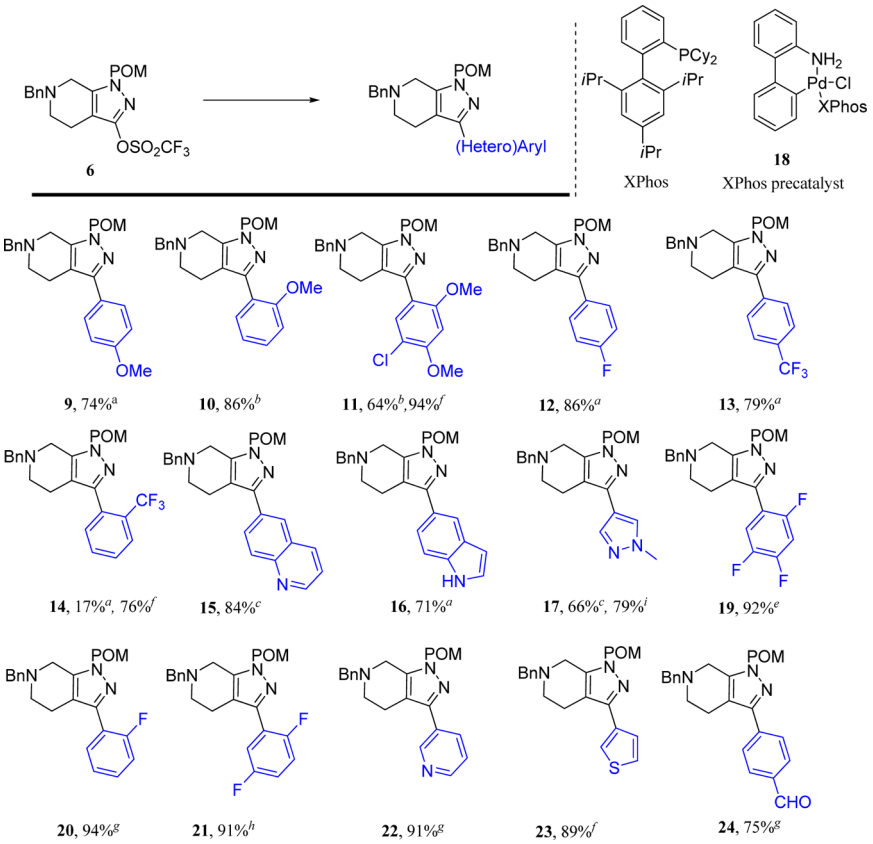
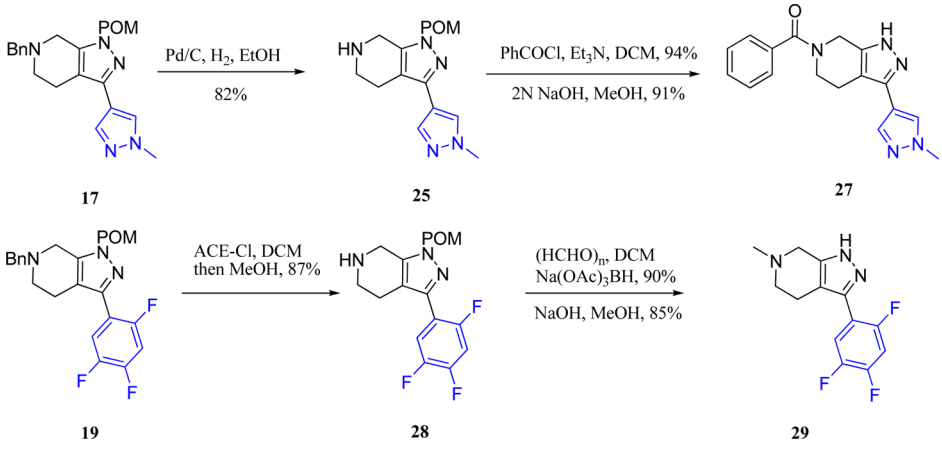
Table 1. Suzuki–Miyaura Cross-Coupling Reaction of 6



	reagents and conditions					
	ArOTf **6**	boronic acid/ester	precatalyst	base	solvent	temp
a	1 equiv	1.2 equiv $ArB(OH)_2$	5 mol % $Pd(OAc)_2$, 10 mol % XPhos	3 equiv K_2CO_3	DME:water 3:1	80 °C
b	1 equiv	1.5 equiv $ArB(OH)_2$	5 mol % $Pd(OAc)_2$, 10 mol % XPhos	3 equiv K_2CO_3	DME:water 3:1	80 °C
c	1 equiv	1.2 equiv ArBPin	5 mol % $Pd(OAc)_2$, 10 mol % XPhos	3 equiv K_2CO_3	DME:water 3:1	80 °C
d	1 equiv	1.5 equiv ArBPin	5 mol % $Pd(OAc)_2$, 10 mol % XPhos	3 equiv K_2CO_3	DME:water 3:1	80 °C
e	1 equiv	1.5 equiv $ArB(OH)_2$	2 mol % **18**	2 equiv K_3PO_4	THF:water 3:1	rt
f	1 equiv	1.5 equiv $ArB(OH)_2$	8 mol % **18**	2 equiv K_3PO_4	THF:water 3:1	rt
g	1 equiv	1.5 equiv $ArB(OH)_2$	8 mol % **18**	2 equiv K_3PO_4	THF:water 3:1	40 °C
h	1 equiv	1.5 equiv $ArB(OH)_2$	4 mol % **18**	2 equiv K_3PO_4	THF:water 3:1	40 °C
i	1 equiv	1.5 equiv ArBPin	4 mol % **18**	2 equiv K_3PO_4	THF:water 3:1	40 °C

Scheme 3. Examples of Derivatization of the Pyrazolo Tetrahydropyridine Skeleton



increased to 91% when 8 mol % of **18** was used. Similarly, when 8 mol % of **18** was used at rt, 2-(trifluoromethyl)phenylboronic acid couples in an improved 76% yield (entry **14**). Indeed, reactions that proceeded in moderate yields with $Pd(OAc)_2$ and

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XPhos were also isolated in improved yields, (entries **11** and **17**).

Removal of the *N*-benzyl protecting group either by hydrogenation over palladium on charcoal (Scheme 3, **17** to **25**) or by using chloroethyl chloroformate (ACE-Cl)[8] (Scheme 3, **19** to **28**) allows for selective functionalization of the piperidine. For example, the reaction of **25** with benzoyl chloride forms the amide **26**, which is deprotected with 2 N NaOH to afford **27** in 94% yield, and *N*-methylation of **28** by reductive amination with formaldehyde, followed by removal of the POM group, forms **29** in good overall yield, (Scheme 3).

In summary, we have described an improved approach toward 3-(hetero)aryl substituted tetrahydropyrazolo[3,4-*c*]-pyridines. The SMC reaction of the triflate **6** with a variety of substituted boronic acids or esters afforded ready access to a range of 3-(hetero)aryl products as single regioisomers. Removal of the *N*-benzyl protecting group allows further substitution of the core, and removal of the POM protecting group gives the potential to increase diversity. The chemistry described herein should extend the utility of this hitherto under-reported heterocycle.

EXPERIMENTAL SECTION

6-Benzyl-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridin-3-ol (7).[4] Hydrazine hydrate (4.8 mL, 99.7 mmol) was added to a stirred solution of ethyl 1-benzyl-3-oxopiperidine-4-carboxylate hydrochloride (27 g, 90.7 mmol) and Et_3N (12.6 mL, 90.7 mmol) in EtOH (300 mL), and the mixture was stirred at 80 °C for 90 min. The reaction mixture was allowed to cool, and the precipitate was collected by filtration, washed with EtOH (20 mL), and dried under vacuum to give **7** as a white powder, mp 244 °C (dec) (17.3 g, 83%). ^{1}H NMR (400 MHz, DMSO) δ 2.32 (t, J = 5.7 Hz, 2H), 2.63 (t, J = 5.7 Hz, 2H), 3.31 (s, 2H), 3.65 (s, 2H), 7.22−7.3 (m, 1H), 7.34 (d, J = 4.4 Hz, 4H); ^{13}C NMR (101 MHz, DMSO) δ 19.4, 48.7, 50.5, 60.9, 96.4, 126.9, 128.1, 128.7, 138.5, 139.0, 157.4; IR (DCM) ν 2792, 1599, 1264, 1118, 741 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{13}H_{16}N_3O$ $[M + H]^+$ m/z 230.1293, found 230.1291.

6-Benzyl-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridin-3-yl Trifluoromethanesulfonate (8). *N*-Phenyl-bis(trifluoromethanesulfonimide) (26.9 g, 75.4 mmol) was added to a stirred solution of **7** (17.3 g, 75.4 mmol) in pyridine (100 mL), and the mixture was stirred at rt for 24 h and then evaporated to dryness. The residue was partitioned between ether (150 mL) and 2 M K_2CO_3 (100 mL). The aqueous mixture was separated and extracted with ether (150 mL). The ether extracts were combined, dried over $MgSO_4$, and concentrated, and the residue was purified by silica gel chromatography (0−60% EtOAc in heptane) to give **8** as a colorless oil, which solidified on standing, mp 112.4−114.5 °C (14.6 g, 54%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.61 (t, J = 5.8 Hz, 2H), 2.80 (t, J = 5.8 Hz, 2H), 3.52 (s, 2H), 3.72 (s, 2H), 7.26−7.41 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 19.0, 48.4, 49.9, 61.6, 104.2, 118.7 (q, J = 320 Hz), 127.6, 128.5, 129.0, 137.6, 140.3, 150.4; IR (DCM) ν 3187, 2808, 1426, 1332, 1215, 1137, 1051, 878 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{14}H_{15}F_3N_3O_3S$ $[M + H]^+$ m/z 362.0781, found 362.0786.

(6-Benzyl-3-(((trifluoromethyl)sulfonyl)oxy)-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridin-1-yl)methyl Pivalate (6). Sodium hydride (1.94 g, 48.6 mmol, 60% mineral dispersion) was added portionwise to a stirred solution of **8** (14.6 g, 40.5 mmol) and chloromethyl pivalate (7.0 mL, 48.6 mmol) in THF (200 mL) at 0 °C, under nitrogen. The solution was stirred at 0 °C for 20 min and then quenched with saturated NH_4Cl (125 mL) and extracted with heptane (2 × 200 mL). The organic extracts were combined, dried over $MgSO_4$, and concentrated, and the residue was purified by silica gel chromatography (10−40% EtOAc in heptane) to give **6** as a pale yellow gum (12.1 g, 63%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (s, 9H), 2.58 (t, J = 5.8 Hz, 2H), 2.77 (t, J = 5.8 Hz, 2H), 3.61 (s, 2H), 3.74 (s, 2H), 5.74 (s, 2H), 7.26−7.44 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 19.2, 26.8, 38.8, 48.3, 49.4, 61.4, 70.2, 106.3, 118.7 (q, J = 322 Hz), 127.5, 128.5, 128.9, 137.6, 141.2, 150.5, 177.3; IR (DCM) ν 2976, 2808, 1743, 1448, 1217, 1138, 1034, 822 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{20}H_{25}F_3N_3O_5S$ $[M + H]^+$ m/z 476.1468, found 476.1462.

General Procedure for Suzuki Coupling of 6 with $Pd(OAc)_2$ and XPhos (Method A). $Pd(OAc)_2$ (5 mol %) was added to a degassed mixture of the appropriate boronic acid or ester (1.2 equiv unless stated otherwise), **6** (1 mmol), XPhos (10 mol %), and K_2CO_3 (3 equiv) in DME (7 mL) and water (2.3 mL) at rt under nitrogen, and the resulting mixture was stirred at 80 °C for the time indicated. After being allowed to cool to rt, the reaction mixture was diluted with EtOAc (50 mL) and washed with water (20 mL) and brine (20 mL). The organic layer was dried over $MgSO_4$ and concentrated, and the resulting residue was purified by silica gel chromatography.

General Procedure for Suzuki Coupling; Using XPhos Precatalyst 18 (Method B). XPhos precatalyst **18** (2−8 mol %), **6** (261 mg, 0.55 mmol), and the appropriate boronic acid or ester (1.5 equiv unless stated otherwise) were added to THF (10 mL) and water (3.3 mL), and the mixture was degassed for 10 min. To this was added K_3PO_4 (233 mg, 1.10 mmol), and the reaction was stirred at rt to 40 °C for the time indicated. The reaction mixture was diluted with water (50 mL) and extracted with ether (2 × 50 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure, and the resulting residue was purified by silica gel chromatography (0−60% EtOAc in heptane) unless otherwise specified.

(6-Benzyl-3-(4-methoxyphenyl)-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridin-1-yl)methyl Pivalate (9). Using Method A; the reaction mixture was stirred at 80 °C for 2 h. Isolated **9** as a white solid, mp 115−116 °C (323 mg, 74%). ^{1}H NMR (400 MHz, DMSO) δ 1.08 (s, 9H), 2.73 (s, 4H), 3.61 (s, 2H), 3.74 (s, 2H), 3.79 (s, 3H), 5.91 (s, 2H), 6.97−7.01 (m, 2H), 7.25−7.3 (m, 1H), 7.32−7.39 (m, 4H), 7.62−7.67 (m, 2H); ^{13}C NMR (101 MHz, DMSO) 22.0, 26.6, 38.2, 47.9, 49.9, 55.1, 60.6, 70.8, 112.2, 114.0, 125.9, 127.0, 127.4, 128.2, 128.6, 138.2, 139.2, 147.5, 158.8, 176.4; IR (DCM) ν 2972, 2934, 1737, 1613, 1530, 1454, 1249, 1127, 1030, 962 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{26}H_{32}N_3O_3$ $[M + H]^+$ m/z 434.2438, found 434.2438.

(6-Benzyl-3-(2-methoxyphenyl)-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridin-1-yl)methyl Pivalate (10). Using Method A; from 1.5 equiv of 2-methoxyphenylboronic acid (228 mg, 1.50 mmol), and the reaction was heated to 80 °C for 20 min. Isolated **10** as a yellow gum (435 mg, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1H NMR (400 MHz, $CDCl_3$) δ 1.16 (s, 9H), 2.58 (t, J = 5.7 Hz, 2H), 2.73 (t, J = 5.7 Hz, 2H), 3.66 (s, 2H), 3.77 (s, 2H), 3.83 (s, 3H), 5.90 (s, 2H), 6.95 (d, J = 8.3 Hz, 1H), 6.99 (td, J = 7.5, 1.0 Hz, 1H), 7.26−7.37 (m, 4H), 7.37−7.42 (m, 2H), 7.48 (dd, J = 7.5, 1.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 22.1, 27.0, 38.9, 48.8, 50.5, 55.4, 62.0, 70.9, 111.0, 115.8, 120.8, 122.5, 127.3, 128.4, 129.1, 129.5, 131.1, 138.2, 148.3, 157.2, 177.6; IR ν 2969, 2933, 1733, 1467, 1128 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{26}H_{32}N_3O_3$ $[M + H]^+$ m/z 434.2438, found 434.2440.

(6-Benzyl-3-(5-chloro-2,4-dimethoxyphenyl)-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridin-1-yl)methyl Pivalate (11). Using Method A; (5-chloro-2,4-dimethoxyphenyl)boronic acid[9](329 mg, 1.52 mmol, 1.5 equiv), and the reaction mixture was heated to 80 °C for 2 h. Isolated **11** as a white solid (322 mg, 64%).

Using Method B; XPhos precatalyst **18** (35 mg, 8 mol %). The reaction was stirred at rt for 2 h and isolated **11** as a cream solid, mp147−149 °C (259 mg, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (s, 9H), 2.54 (t, J = 5.7 Hz, 2H), 2.72 (t, J = 5.7 Hz, 2H), 3.65 (s, 2H), 3.76 (s, 2H), 3.83 (s, 3H), 3.94 (s, 3H), 5.88 (s, 2H), 6.55 (s, 1H), 7.26−7.31 (m, 1H), 7.31−7.37 (m, 2H), 7.37−7.42 (m, 2H), 7.49 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) 22.1, 27.0, 38.9, 48.8, 50.4, 55.9, 56.3, 62.0, 70.8, 96.9, 114.0, 115.6, 115.9, 127.3, 128.4, 129.0, 131.8, 138.1, 138.3, 146.9, 155.8, 156.8, 177.6; IR 2968, 2933, 2874, 2847, 1736, 1607, 1437, 1327, 1278, 1209, 1128, 1030, 962 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{27}H_{33}ClN_3O_4$ $[M + H]^+$ m/z 498.2154, found 498.2158.

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(6-Benzyl-3-(4-fluorophenyl)-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridin-1-yl)methyl Pivalate (12). Using Method A; the reaction was heated to 80 °C for 1 h. Isolated **12** as a white solid, mp 109.8 °C (435 mg, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (s, 9H), 2.73 (s, 4H), 3.63 (s, 2H), 3.74 (s, 2H), 5.93 (s, 2H), 7.2−7.31 (m, 3H), 7.31−7.42 (m, 4H), 7.71−7.8 (m, 2H); ^{13}C NMR (101 MHz, DMSO) δ 21.9, 26.5, 38.2, 47.8, 49.8, 60.6, 70.8, 112.5, 115.5 (d, J = 21.5 Hz), 127.0, 128.1 (d, J = 8.1 Hz), 128.2, 128.6, 129.8 (d, J = 3 Hz), 138.2, 139.5, 146.8, 161.6 (d, J = 244 Hz), 176.4; IR (DCM) ν 2973, 2931, 2802, 1735, 1527, 1488, 1112 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{25}H_{29}FN_3O_2$ $[M + H]^+$ m/z 422.2238, found 422.2236.

(6-Benzyl-3-(4-(trifluoromethyl)phenyl)-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridin-1-yl)methyl Pivalate (13). Using Method A; the reaction was heated to 80 °C for 30 min. Isolated **13** as a white solid, mp 96.7 °C (372 mg, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (s, 9H), 2.75−2.91 (m, 4H), 3.66 (s, 2H), 3.78 (s, 2H), 5.90 (s, 2H), 7.27−7.44 (m, 5H), 7.65 (d, J = 8.2 Hz, 2H), 7.85 (d, J = 8.2 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) 22.7, 26.9, 38.9, 48.7, 50.3, 61.8, 70.8, 113.9, 125.5 (q, J = 3.7), 127.1 (q, J = 252 Hz), 125.6, 126.8, 127.5, 128.5, 129.5 (q, J = 33 Hz), 137.1, 137.9, 139.6, 147.9, 177.5; IR (DCM) ν 3062, 3022, 2975, 2933, 2806, 2761, 1735, 1819, 1324, 1124 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{26}H_{29}F_3N_3O_2$ $[M + H]^+$ m/z 472.2206, found 472.2209.

(6-Benzyl-3-(2-(trifluoromethyl)phenyl)-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridin-1-yl)methyl Pivalate (14). Using Method A; the reaction was heated to 80 °C for 6 h. Isolated **14** as a colorless gum (83 mg, 17%).

Using Method B; XPhos precatalyst **18** (35 mg, 8 mol %). The reaction was stirred at rt for 3 h and isolated **14** as a colorless gum, (198 mg, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (s, 9H), 2.44 (t, J = 5.4 Hz, 2H), 2.75 (t, J = 5.3 Hz, 2H), 3.71 (s, 2H), 3.78 (s, 2H), 7.26−7.43 (m, 7H), 7.47 (t, J = 7.6 Hz, 1H), 7.55 (t, J = 7.1 Hz, 1H), 7.74 (d, J = 7.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 20.5, 26.9, 38.8, 48.5, 50.0, 61.6, 70.3, 115.1, 123.9 (q, J = 274 Hz), 126.3 (q, J = 5.1 Hz) 127.4, 128.3, 128.4, 129.1, 129.8 (q, J = 30.3 Hz), 131.2, 132.0, 132.4, 137.9, 138.0, 148.4, 177.5; IR (DCM) ν 2960, 2931, 2872, 1738, 1441, 1315, 1165, 1130, 1036, 966 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{26}H_{29}F_3N_3O_2$ $[M + H]^+$ m/z 472.2206, found 472.2210.

(6-Benzyl-3-(quinolin-6-yl)-4,5,6,7-tetrahydro-1*H*-pyrazolo-[3,4-*c*]pyridin-1-yl)methyl Pivalate (15). Using Method A; the reaction was heated to 80 °C for 30 min. Isolated **15** as a white solid, mp 131.7 °C (236 mg, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (s, 9H), 2.85 (t, J = 5.6 Hz, 2H), 2.94 (t, J = 5.4 Hz, 2H), 3.69 (s, 2H), 3.80 (s, 2H), 5.94 (s, 2H), 7.28−7.46 (m, 6H), 8.1−8.23 (m, 4H), 8.89 (dd, J = 4.2, 1.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 22.8, 27.0, 38.9, 48.8, 50.4, 61.8, 70.8, 113.9, 121.4, 125.1, 127.4, 128.4, 128.5, 128.6, 129.0, 129.7, 131.9, 136.2, 138.0, 139.6, 148.0, 148.5, 150.4, 177.5; IR (DCM) ν 2973, 2931, 1735, 1276, 1126, 1108 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{28}H_{31}N_4O_2$ $[M + H]^+$ m/z 455.2441, found 455.2441.

(6-Benzyl-3-(1*H*-indol-5-yl)-4,5,6,7-tetrahydro-1*H*-pyrazolo-[3,4-*c*]pyridin-1-yl)methyl Pivalate (16). Using Method A; the reaction was heated to 80 °C for 30 min. Isolated **16** as a white solid, mp 82.4 °C (313 mg, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (s, 9H), 2.80 (t, J = 5.3 Hz, 2H), 2.87 (t, J = 5.3 Hz, 2H), 3.66 (s, 2H), 3.78 (s, 2H), 5.91 (s, 2H), 6.55 (ddd, J = 3.0, 2.0, 0.9 Hz, 1H), 7.14−7.2 (m, 1H), 7.25−7.44 (m, 6H), 7.63 (dd, J = 8.5, 1.6 Hz, 1H), 7.92−7.99 (m, 1H), 8.29 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 22.7, 27.0, 38.9, 48.8, 50.5, 61.8, 70.9, 103.1, 111.2, 113.2, 119.2, 121.5, 124.6, 125.5, 127.3, 128.1, 128.5, 129.0, 135.6, 138.1, 139.0, 150.7, 177.7; IR (DCM) ν 3409, 3239, 2973, 2931, 1735, 1444, 1276, 1126, 1110, 1029, 966 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{27}H_{31}N_4O_2$ $[M + H]^+$ m/z 443.2442, found 443.2441.

(6-Benzyl-3-(1-methyl-1*H*-pyrazol-4-yl)-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridin-1-yl)methyl Pivalate (17). Using Method A; the reaction was heated to 80 °C for 2 h. Isolated **17** (267 mg, 66%) as a white solid.

Using Method B; from **6** (520 mg, 1.09 mmol), XPhos precatalyst **18** (68.8 mg, 0.09 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (341 mg, 1.64 mmol), and K_3PO_4 (464 mg, 2.19 mmol) in THF (10 mL)/water (3.33 mL), and the reaction was stirred for 30 min at 40 °C. Isolated **17** as a white solid, mp 112.3 °C (354 mg, 79%). ^{1}H NMR (400 MHz, DMSO) δ 1.07 (s, 9H), 2.62 (t, J = 5.1 Hz, 2H), 2.73 (t, J = 5.5 Hz, 2H), 3.58 (s, 2H), 3.72 (s, 2H), 3.87 (s, 3H), 5.87 (s, 2H), 7.22−7.31 (m, 1H), 7.3−7.41 (m, 4H), 7.69 (s, 1H), 7.98 (s, 1H); ^{13}C NMR (101 MHz, DMSO) δ 21.0, 26.6, 38.2, 38.5, 47.8, 49.7, 60.5, 70.7, 112.1, 114.7, 127.0, 128.1, 128.2, 128.6, 136.1, 138.3, 138.7, 142.3, 176.5; IR (DCM) ν 2973, 2933, 1735, 1602, 1276, 1128 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{23}H_{30}N_5O_2$ $[M + H]^+$ m/z 408.2394, found 408.2394.

(6-Benzyl-3-(2,4,5-trifluorophenyl)-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridin-1-yl)methyl Pivalate (19). Using Method B; XPhos precatalyst **18** (9.6 mg, 2 mol %). The reaction was stirred at rt for 30 min and isolated **19** as a yellow gum (258 mg, 92%).^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (s, 9H), 2.63 (t, J = 5.1 Hz, 2H), 2.76 (t, J = 5.7 Hz, 2H), 3.65 (s, 2H), 3.77 (s, 2H), 5.89 (s, 2H), 6.97 (td, J = 6.6, 9.8 Hz, 1H), 7.25−7.42 (m, 5H), 7.47 (ddd, J = 6.6, 8.9, 10.7 Hz, 1H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 21.7 (d, J = 7.3 Hz), 26.9, 38.8, 48.6, 50.3, 61.8, 70.6, 105.9 (dd, J = 20.9, 28.4 Hz), 115.3, 117.7 (d, J = 17.2 Hz), 118.2 (dd, J = 5.9, 20 Hz), 127.4, 128.5, 128.9, 137.9, 139.2, 143.9, 146.9 (ddd, J = 3.2, 12.3, 236 Hz), 149.9 (dt, J = 1.8, 13.3, 252.3 Hz), 155.0 (dd, J = 7.7, 256 Hz), 177.4; IR ν 2973, 2929, 2873, 1739, 1531, 1470, 1139; HRMS (ESI-TOF) calcd for $C_{25}H_{27}F_3N_3O_2$ $[M + H]^+$ m/z 458.2050, found 458.2050.

(6-Benzyl-3-(2-fluorophenyl)-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridin-1-yl)methyl Pivalate (20). Using Method B; XPhos precatalyst **18** (35 mg, 8 mol %). The reaction was stirred at 40 °C for 2 h and isolated **20** as an orange gum (214 mg, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (s, 9H), 2.66 (t, J = 5.3 Hz, 2H), 2.76 (t, J = 5.7 Hz, 2H), 3.66 (s, 2H), 3.77 (s, 2H), 5.91 (s, 2H), 7.07−7.2 (m, 2H), 7.27−7.44 (m, 6H), 7.61 (td, J = 7.5, 1.8 Hz, 1H); ^{13}C NMR (176 MHz, $CDCl_3$) 21.7 (d, J = 6.9), 26.9, 38.8, 48.7, 50.3, 61.8, 70.7, 115.4, 115.9 (d, J = 22.1 Hz), 121.2 (d, J = 14.6 Hz), 124.1 (d, J = 3.1 Hz), 127.3, 128.4, 129.0, 129.7 (d, J = 8.1 Hz), 130.8 (d, J = 3.6 Hz), 138.0, 138.7, 145.7, 160.1 (d, J = 249), 177; IR (DCM) ν 2972, 2931, 2802, 1738, 1460, 1277, 1128, 1030, 966 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{25}H_{29}FN_3O_2$ $[M + H]^+$ m/z 422.2238, found 422.2241.

(6-Benzyl-3-(2,5-difluorophenyl)-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridin-1-yl)methyl Pivalate (21). Using Method B; XPhos precatalyst **18** (17 mg, 4 mol %). The reaction was stirred at 40 °C for 30 min and isolated **21** as a yellow gum (217 mg, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (s, 9H), 2.66 (t, J = 5.2 Hz, 2H), 2.76 (t, J = 5.7 Hz, 2H), 3.66 (s, 2H), 3.77 (s, 2H), 5.90 (s, 2H), 6.94−7.11 (m, 2H), 7.27−7.42 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) 21.8 (d, J = 7.5), 27.0, 38.9, 48.7, 50.3, 61.9, 70.7, 115.4, 116.0 (dd, J = 24.2, 8.6 Hz), 116.9 (dd, J = 25.4, 8.8 Hz), 116.9 (dd, J = 24.8, 4.3 Hz), 122.6 (dd, J = 17.6, 8.3 Hz), 127.4, 128.5, 129.0, 138.0, 139.1, 144.8, 156.1 (dd, J = 248, 2.0 Hz), 156.1 (dd, J = 244.4, 2.0 Hz), 177.5; IR (DCM) ν 2972, 2931, 2804, 1738, 1468, 1127, 972 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{25}H_{28}F_2N_3O_2$ 440.2144 $[M + H]^+$ m/z, found 440.2147.

(6-Benzyl-3-(pyridin-3-yl)-4,5,6,7-tetrahydro-1*H*-pyrazolo-[3,4-*c*]pyridin-1-yl)methyl Pivalate (22). Using Method B; XPhos precatalyst **18** (35 mg, 8 mol %). The reaction was stirred at 40 °C for 3 h and purified by silica gel chromatography (40−100% EtOAc in heptane, followed by 10% MeOH) to give **22** as a pale brown gum (219 mg, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (s, 9H), 2.82 (s, 4H), 3.65 (s, 2H), 3.78 (s, 2H), 5.90 (s, 2H), 7.26−7.43 (m, 6H), 8.06 (dt, J = 1.9, 7.9 Hz, 1H), 8.55 (dd, J = 1.7, 4.8 Hz, 1H), 8.91−9.04 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 22.2, 27.0, 38.9, 48.7, 50.4, 61.8, 70.7, 113.8, 123.5, 127.5, 128.5, 129.0, 129.6, 133.9, 137.9, 139.6, 146.5, 147.9, 148.8, 177.5; IR (DCM) ν 3061, 2972, 2931, 1736, 1277, 1128, 1032, 966 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{24}H_{29}N_4O_2$ 405.2285 $[M + H]^+$ m/z, found 405.2285.

(6-Benzyl-3-(thiophen-3-yl)-4,5,6,7-tetrahydro-1*H*-pyrazolo-[3,4-*c*]pyridin-1-yl)methyl Pivalate (23). Using Method B; XPhos precatalyst **18** (35 mg, 8 mol %). The reaction was stirred at rt for 20 min and isolated **23** as a white solid, mp 134.1−135.7 °C (200 mg, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (s, 9H), 2.71−2.88 (m, 4H), 3.63 (s, 2H), 3.77 (s, 2H), 5.88 (s, 2H), 7.27−7.42 (m, 6H),

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7.47−7.55 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) 22.2, 26.9, 38.9, 48.7, 50.2, 61.7, 70.8, 113.3, 121.4, 125.6, 126.4, 127.4, 128.5, 129.0, 134.7, 138.2, 139.0, 177.5; IR (DCM) ν 2972, 2802, 1736, 1462, 1277, 1126, 1034, 964 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{23}H_{28}N_3O_2S$ 410.1897 $[M + H]^+$ m/z, found 410.1898.

(6-Benzyl-3-(4-formylphenyl)-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridin-1-yl)methyl Pivalate (24). Using Method B; XPhos precatalyst **18** (35 mg, 8 mol %). The reaction was stirred at 40 °C for 8 h and isolated **24** as an orange gum (177 mg, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (s, 9H), 2.79−2.89 (m, 4H), 3.66 (s, 2H), 3.78 (s, 2H), 5.91 (s, 2H), 7.28−7.44 (m, 5H), 7.84−7.98 (m, 4H), 10.02 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 22.8, 27.0, 38.9, 48.7, 50.3, 61.8, 70.8, 114.3, 127.0, 127.5, 128.5, 129.0, 130.1, 135.4, 137.9, 139.6, 139.7, 147.9, 177.5, 191.9; IR (DCM) ν 2970, 2931, 2870, 1738, 1700, 1608, 1277, 1211, 1127, 1034, 966 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{26}H_{30}N_3O_3$ 432.2282 $[M + H]^+$ m/z, found 432.2286.

(3-(1-Methyl-1*H*-pyrazol-4-yl)-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridin-1-yl)methyl Pivalate (25). A mixture of 10% palladium on charcoal (13.32 mg) and **17** (340 mg, 0.83 mmol) in EtOH (10 mL) was stirred under an atmosphere of hydrogen at rt for 17 h. The reaction mixture was filtered through Celite, the filtrate was evaporated, and the residue was purified by silica gel chromatography (0−5% MeOH in DCM) to give **25** as a white solid, mp 105 °C (216 mg, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (s, 9H), 2.64 (t, J = 5.7 Hz, 2H), 3.08 (t, J = 5.7 Hz, 2H), 3.93 (s, 3H), 3.99 (s, 2H), 5.89 (s, 2H), 7.69 (s, 1H), 7.79 (d, J = 0.57 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 23.0, 27.0, 38.9, 39.0, 41.8, 43.4, 70.5, 113.0, 115.6, 127.6, 137.3, 139.4, 143.7, 177.7; IR (DCM) ν 3415, 3319, 2973, 2933, 1731, 1600, 1276, 1130 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{16}H_{24}N_5O_2$ 318.1930 $[M + H]^+$ m/z, found 318.1928.

(6-Benzoyl-3-(1-methyl-1*H*-pyrazol-4-yl)-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridin-1-yl)methyl Pivalate (26). A solution of benzoyl chloride (0.072 mL, 0.62 mmol) in DCM (2 mL) was added to a solution of **25** (187 mg, 0.59 mmol) and Et_3N (0.090 mL, 0.65 mmol) in DCM (5 mL) at 0 °C under nitrogen. The resulting solution was allowed to warm to rt over 1 h, concentrated, and purified by silica gel chromatography (10−50% EtOAc in heptane) to give **26** as a colorless gum (233 mg, 94%). ^{1}H NMR (500 MHz, DMSO at 373 K) δ 1.11 (9H, s), 2.69 (2H, t), 3.69 (2H, t), 3.86 (3H, s), 4.77 (2H, s), 5.93 (2H, s), 7.41−7.51 (5H, m), 7.66 (1H, d), 7.89 (1H, s); ^{13}C NMR (126 MHz, DMSO) δ 20.9, 26.0, 37.7, 37.8, 70.2, 111.9, 114.0, 126.1, 127.5, 127.8, 129.0, 135.6, 135.7, 136.4, 142.2, 169.6, 175.9, two carbons obscurred by DMSO); IR (DCM) ν 2975, 2935, 2871, 1735, 1635, 1600, 1430, 1294, 1122 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{23}H_{28}N_5O_3$ 422.2187 $[M + H]^+$ m/z, found 422.2187.

(3-(1-Methyl-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-pyrazolo[3,4-*c*]pyridin-6(7*H*)-yl)(phenyl)methanone (27). 2 N NaOH (2.2 mL, 4.01 mmol) was added to a solution of **26** (128 mg, 0.30 mmol) in MeOH (5 mL), and the solution was stirred at rt for 2 h. The reaction mixture was concentrated, diluted with EtOAc (20 mL), and washed with water (5 mL) and saturated NH_4Cl (15 mL). The organic layer was evaporated, and the residue was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5 μ silica, 50 mm diameter, 100 mm length, 5−95% H_2O/1% NH_3 to MeCN) to give **27** as a pale yellow gum (85 mg, 91%). ^{1}H NMR (500 MHz, DMSO at 373 K) δ 2.70 (t, J = 5.8 Hz, 2H), 3.72 (t, J = 5.3 Hz, 2H), 3.87 (s, 3H), 4.62 (s, 2H), 7.39−7.5 (m, 5H), 7.69 (s, 1H), 7.88 (s, 1H), 12.36 (s, 1H); ^{13}C NMR (126 MHz, DMSO at 373 K) δ 20.8, 37.9, 42.1, 43.0, 108.3, 112.1, 126.1, 126.9, 127.8, 128.9, 133.9, 135.4, 135.9, 142.9, 169.4; IR (DCM) ν 3211, 2929, 1625, 1436 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{17}H_{18}N_5O$ 308.1511 $[M + H]^+$ m/z, found 308.1510.

(3-(2,4,5-Trifluorophenyl)-4,5,6,7-tetrahydro-1*H*-pyrazolo-[3,4-*c*]pyridin-1-yl)methyl Pivalate (28). ACE-Cl (0.052 mL, 0.48 mmol) was added to a stirred solution of **19** (253 mg, 0.55 mmol) in DCM (10 mL), and the solution was stirred at rt for 1 h. MeOH (10 mL) was added, and the solution was stirred at rt for 17 h. The reaction mixture was evaporated, and the residue was purified by silica gel chromatography (0−10% MeOH in DCM) to give **28** as a pale yellow solid, mp 93.7−95.7 °C (176 mg, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (s, 9H), 2.55 (t, J = 4.8, Hz, 2H), 3.03 (t, J = 5.7 Hz, 2H), 4.04 (s, 2H), 5.93 (s, 2H), 6.99 (td, J = 6.5, 9.8 Hz, 1H), 7.46 (ddd, J = 6.7, 8.9, 10.7 Hz, 1H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 18.8 (d, J = 9.86 Hz), 26.9, 38.8, 39.7, 41.7, 70.1, 106.0 (dd, J = 20.9, 28.4 Hz), 113.1, 116.5 (dt, J = 5.6, 16.9 Hz), 118.4 (dd, J = 5.0, 20.1 Hz), 132.7, 144.5, 147.0 (ddd, J = 3.1, 12.8, 246 Hz), 150.4 (dt, J = 13.5, 254 Hz), 154.9 (dd, J = 8.4, 248. Hz), 177.9; IR (DCM) ν 2974, 2935, 1738, 1531, 1468, 1279, 1182, 1134, 1034, 966, 843 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{18}H_{21}F_3N_3O_2$ 368.1581 $[M + H]^+$ m/z, found 368.1581.

6-Methyl-3-(2,4,5-trifluorophenyl)-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine (29). Formaldehyde (37 wt % solution in water) (0.262 mL, 3.22 mmol) was added to a stirred solution of **28** (296 mg, 0.81 mmol) in DCM (10 mL) and MeOH (1 mL) at rt. After 15 min, sodium triacetoxyborohydride (426 mg, 2.01 mmol) was added, and the mixture was stirred at rt for 1 h, diluted with DCM (50 mL), and washed with saturated $NaHCO_3$ (50 mL). The aqueous layer was reextracted with DCM (2 × 75 mL), and the organic extracts were combined, dried over $MgSO_4$, filtered, and evaporated to afford a pale orange gum (276 mg, 90%). This was dissolved in MeOH (5 mL), and 2 N NaOH (2.2 mL, 4.01 mmol) was added. The resulting solution was stirred at rt for 2 h. The reaction mixture was concentrated, diluted with EtOAc (20 mL), and washed with water (5 mL), and saturated NH_4Cl (15 mL). The organic layer was evaporated, and the residue was purified by ion exchange chromatography, using an SCX column (1 M NH_3/MeOH) to give **29** as a orange gum (183 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.52 (s, 3H), 2.67−2.76 (m, 2H), 2.79 (t, J = 5.6, 5.6 Hz, 2H), 3.60 (s, 2H), 7.04 (td, J = 10.2, 10.1, 6.6 Hz, 1H), 7.38 (ddd, J = 10.7, 8.6, 6.8 Hz, 1H), 10.27 (s, 1H); ^{13}C NMR (176 MHz, DMSO) δ 21.2 (d, J = 7.0 Hz), 45.2, 52.5, 106.5 dd, J = 28.2, 22.8 Hz), 111.7, 117.3 (d, J = 15.8 Hz), 146.1 (dd, J = 242, 8.8 Hz), 148.6 (dd, J = 248, 14.1 Hz), 154.0 (d, J = 256 Hz), IR (DCM) ν 2943, 2926, 2852, 2795, 1527, 1472, 1190, 1084, 881, 820 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{13}H_{13}F_3N_3$ 268.1056 $[M + H]^+$ m/z, found 268.1057.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra for all synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(9) 5-Chloro-2,4-dimethoxyphenyl)boronic acid was prepared as follows: butyllithium (3.60 mL, 5.76 mmol) was added to a solution of 1-bromo-5-chloro-2,4-dimethoxybenzene[10] (1.38 g, 5.49 mmol) in THF (30 mL) at −70 °C, under nitrogen; after 5 min, trimethyl borate (0.612 mL, 5.49 mmol) was added dropwise and the resulting solution was stirred at −70 °C for a further 30 min. The reaction mixture was quenched with 2 M HCl (10 mL) and extracted into EtOAc (75 mL), and the organic layer was washed with water (50 mL) and saturated brine (50 mL), dried over $MgSO_4$, filtered, and evaporated to afford a solid that was triturated with ether, filtered, and dried under vacuum to give (5-chloro-2,4-dimethoxyphenyl)boronic acid as a white solid, mp 134−136 °C (656 mg, 55%). ^{1}H NMR (400 MHz, DMSO) 3.88 (s, 3H), 3.92 (s, 3H), 6.74 (s, 1H), 7.53 (s, 1H), 7.57 (s, 2H); ^{13}C NMR (101 MHz, DMSO) 55.9, 56.1, 96.9, 112.3, 135.9, 157.1, 164.1, C-B not seen; GCMS (EI) *m/z* [M − HBO_2] calcd for $C_8H_9ClO_2$ 172.0291; found 172.0297.

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