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Regioselective C2-arylation of imidazo[4,5-*b*]pyridines†

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Jonathan Macdonald, Victoria Oldfield, Vassilios Bavetsias and Julian Blagg*

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We show that *N*3-MEM-protected imidazo[4,5-*b*]pyridines undergo efficient C2-functionalisation *via* direct C–H arylation. Twenty-two substituted imidazo[4,5-*b*]pyridines are prepared and iterative, selective elaboration of functionalised imidazo[4,5-*b*]pyridines gives 2,7- and 2,6-disubstituted derivatives in good yields from common intermediates. Mechanistic observations are consistent with a concerted-metallation-deprotonation mechanism facilitated by coordination of copper(I)iodide to the imidazo-[4,5-*b*]pyridine.

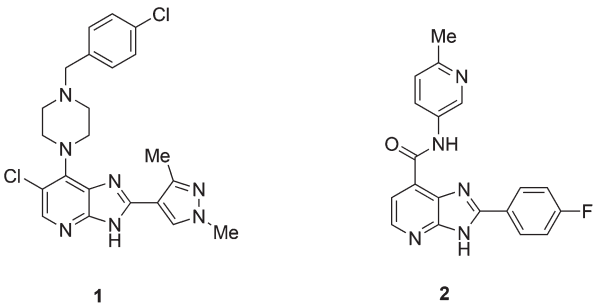
Introduction

Direct arylation is a highly active area of research that is increasingly applied as an alternative to the cross-coupling of an organometallic species with an aryl halide.[1] The use of an unfunctionalised aromatic or heteroaromatic system as one reaction partner is a major advantage and many useful methodologies have been reported for the direct arylation of heterocycles using palladium,[2] palladium and copper,[3] rhodium,[4] and gold[5] catalytic systems.

We became interested in direct C2-functionalisation of the imidazo[4,5-*b*]pyridine heterocycle, a versatile purine isostere and important ring system which has seen a recent growth in medicinal chemistry application of potential therapeutic benefit; for example in protein kinase inhibitors for the treatment of cancer,[6] inflammatory disease[7] and diabetes.[8] Recently disclosed compounds of potential therapeutic interest containing this scaffold include **1**, a potent dual FLT3/Aurora kinase inhibitor targeted for the treatment of acute myeloid leukemia[6a] and **2**, a potent inhibitor of GSK3β highlighted as a potential drug candidate for the treatment of type 2 diabetes (Fig. 1).[8] Common to the imidazo[4,5-*b*]pyridine kinase pharmacophore is the requirement for both the *N*3-hydrogen bond donor and the *N*4-hydrogen bond acceptor which are essential for binding to the hinge region of kinases as exemplified by protein crystal structures of exemplar compounds bound to Aurora A[6a] and GSK3β[8] respectively.

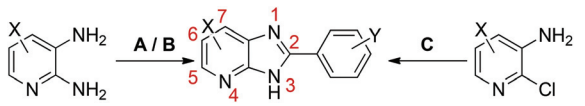
Substitution at C2 of the imidazo[4,5-*b*]pyridine scaffold extends into the kinase solvent channel and is also frequently required for potent biochemical activity. Current synthetic approaches to the imidazo[4,5-*b*]pyridine scaffold often incorporate the C2 substituent early in the sequence through ring closure of an appropriate 2,3-disubstituted pyridine derivative, which may itself require a multistep synthesis (Scheme 1, Routes A and B).[9] Recently published alternatives involve elaboration of a 2-chloro-3-aminopyridine (Scheme 1, Route C),[10] and Suzuki coupling of 3-substituted-2-iodo-3*H*-imidazo-[4,5-*b*]pyridine.[11]

Given the importance of C2-substituted imidazo[4,5-*b*]pyridines in medicinal chemistry, we were keen to explore the divergent synthesis of C2-aryl- and heteroaryl-substituted imidazo[4,5-*b*]pyridines *via* a C–H activation protocol. Intermolecular C–H activation has been reported on benzimidazole and purine templates using copper and palladium catalysis;[12]



1 2

Fig. 1 Example imidazo[4,5-*b*]pyridines of potential therapeutic interest.



Scheme 1 Precedented approaches to C2-substituted imidazo[4,5-*b*]-pyridines. Reaction partner: (A) aryl aldehyde;[9a,b] (B) aryl carboxylic acid;[9c] (C) primary aryl carboxamide.[10]

Cancer Research UK Cancer Therapeutics Unit, Division of Cancer Therapeutics, The Institute of Cancer Research, Haddow Laboratories, Sutton, Surrey SM2 5NG, UK. E-mail: julian.blagg@icr.ac.uk

†Electronic supplementary information (ESI) available: Synthetic schemes to key intermediates, supplementary tables, data from kinetic isotope experiments and copies of spectroscopic data for new compounds is available free of charge. See DOI: 10.1039/c3ob27477b

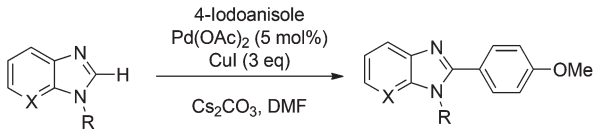
and there are recent reports of intramolecular C–H insertion using *N*-substituted imidazo[4,5-*b*]pyridines.[13] We sought an intermolecular C–H arylation protocol to directly functionalise imidazo[4,5-*b*]pyridines at C2, thereby circumventing the need to incorporate this substituent early in a synthetic sequence. During the preparation of this manuscript, the Langer group published the synthesis of 7-trifluoromethylimidazo[4,5-*b*]pyridines from 5-aminoimidazoles and 1,1,1-trifluoropentane-2,4-diones followed by subsequent C2-arylation of the resultant 7-trifluoromethylimidazo[4,5-*b*]pyridines using both Pd/Cu and Ni catalysis.[14] Here we describe the application of C–H arylation at the C2 position of the imidazo[4,5-*b*]pyridine scaffold to facilitate iterative and selective elaboration to 2,7- and 2,6-disubstituted derivatives in good yield.

Results and discussion

Our initial goal was the direct C2-functionalisation of imidazo[4,5-*b*]pyridines in the presence of the unprotected imidazole NH. C–H Activation on unprotected imidazole and benzimidazole scaffolds has been reported;[12d] however, application of these conditions to directly arylate the unprotected imidazo[4,5-*b*]pyridine scaffold at C2 with 4-iodoanisole proved unsuccessful with only recovered starting material isolated (Table 1, entry 1).

Reaction of the corresponding unprotected benzimidazole, *N*-methyl benzimidazole or *N*3-methyl imidazo[4,5-*b*]pyridine (see Scheme S1† for preparation) with 4-iodoanisole proceeded smoothly in moderate yield in the presence or absence of microwave irradiation to give the corresponding C2-arylated product (Table 1, entries 2–5). We reasoned that the difference in reactivity between an unprotected imidazo[4,5-*b*]pyridine and benzimidazole substrate (Table 1, entries 1 and 2) may be associated with the 3,4-orientation of nitrogen atoms in the imidazo[4,5-*b*]pyridine acting as a bidentate coordinating ligand for the metal catalyst.

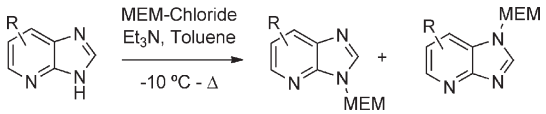
Table 1 C2–H Arylation of benzimidazole, imidazo[4,5-*b*]pyridine and *N*-substituted derivatives



Conditions **A**: μW, 200 °C 1 h
Conditions **B**: Sealed tube, 140 °C 16-24 h

Entry	X	R	Product	Isolated yield (%)	Conditions
1	N	H	**9**	0	A
2	CH	H	**10**	62	A
3	CH	Me	**11**	66	A
4	N	Me	**12**	50	A
5	N	Me	**12**	44	B
6	N	MEM	**13a**	54	A
7	N	MEM	**13a**	78	B
8	N	*N*1-MEM	—	0	B
9	N	SEM	**14**	66	B
10	N	Boc	—	0	B

Heterocycle (1 eq.), 4-iodoanisole (2 eq.), $Pd(OAc)_2$ (5 mol%), CuI (3 eq.), Cs_2CO_3 (2.5 eq.), DMF.



3 R = H
4 R = 6-Br
5 R = 7-Cl

6a (H) 55-69 % **6b** 10-18 %
7a (6-Br) 62-77 % **7b** <10-21 %
8a (7-Cl) 85-92 % **8b** <5 %

Scheme 2 Preparation of MEM-protected imidazo[4,5-*b*]pyridines.

Protection of the parent imidazo[4,5-*b*]pyridine ring system **3** with a MEM group gave **6a**, with its regioisomer **6b** as a minor product separable by column chromatography and distinguishable by 2D NMR (see ESI†).[15] *N*3-Protection of 6-Br- and 7-Cl-imidazo[4,5-*b*]pyridines (**4** and **5**) was also achieved, with high regioselectivity observed in the case of the 7-chloro substituent (**5**) which presumably hinders competing substitution at *N*1 (Scheme 2).

The *N*3-MEM isomer (**6a**) reacted smoothly and regioselectively under conditions previously reported on a protected purine scaffold by Čerňa *et al.*[16] [4-iodoanisole (2 eq.), $Pd(OAc)_2$ (5 mol%), CuI (3 eq.) and Cs_2CO_3 (2.5 eq.) in DMF, Table 1, entries 6 and 7] to give the desired C2-arylated product (**13a**). However, the corresponding *N*1-protected isomer (**6b**) failed to react (Table 1, entry 8), consistent with the hypothesis that 3,4-orientation of the two nitrogen atoms in the imidazo[4,5-*b*]pyridine scaffold inhibits reaction. *N*3-Protection with SEM (see Scheme S2† for preparation) is also compatible with C2-selective arylation (Table 1, entry 9), whilst the use of Boc as an *N*3-protecting group (see Scheme S2† for preparation) led to unproductive deprotection under the reaction conditions (Table 1, entry 10).

To optimise the regioselective C2-arylation of *N*3-MEM-protected imidazo[4,5-*b*]pyridine (**6a**), we screened a variety of reaction conditions, including those reported in the literature for C–H arylation on alternative heterocyclic systems. We found that conditions reported by Bellina which lack a carbonate base are ineffective on the imidazo[4,5-*b*]pyridine scaffold (Table 2, entry 2);[17] in addition, no conversion is observed in the absence of CuI (Table 2, entry 3) which is required in excess for optimal conversion (Table 2, entry 4). Only limited conversion is obtained in the absence of palladium (Table 2, entry 5) and use of MgO as a C–H arylation promoter gave no conversion in our hands (Table 2, entry 6).[18]

Multiple alternative direct arylation conditions have been reported in the literature, however all gave inferior results; for example, use of K_2CO_3 as base,[19] the addition of piperidine to hinder substrate chelation of palladium,[12a] and a Pd(II)/Cu(II) co-catalytic system[20] (Table 3, entries 1–3). Similarly application of the copper-free conditions of Larrosa[21] and Fagnou[2c] gave limited conversion (Table 3, entries 4 and 5); however, with the addition of CuI, complete reaction was observed

under Fagnou conditions (Table 3, entries 6 and 7). We observed that aryl bromides gave complete conversion under optimised reaction conditions, whilst aryl chlorides gave partial conversion (Table 3, entries 8 and 9); however an aryl boronic acid coupling partner was unreactive under a variety of conditions. In summary, optimal direct arylation conditions require the presence of $Pd(OAc)_2$, CuI and a carbonate base (Table 2, entry 1); the addition of PivOH or $PCy_3{\cdot}HBF_4$ is tolerated but not essential for reaction.

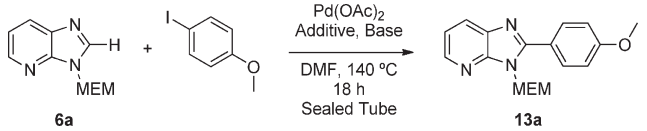
We employed the optimal reaction conditions (Table 2, entry 1) with a variety of aryl and heteroaryl coupling partners to assess the scope and efficiency of regioselective C2-arylation (Table 4, conditions B). We observed that electron-poor aryl halides generally resulted in lower isolated yields and, in these cases, we found that addition of $PCy_3{\cdot}HBF_4$,[22] reduced temperature (120 °C) and use of aryl bromide substrates gave higher isolated yields although reaction times were extended (Table 4, conditions C). No competing C–H arylation at the C5 position was observed, except for product **13e**, where trace amounts of a putative C2,5-bis-arylated side product were detected using conditions B.

The MEM protected products **13a–l** were deprotected using aq. HCl to afford the desired 2-substituted imidazo[4,5-*b*]pyridines, **9** and **15b–l** (38–98%; see ESI, Table S1†).

We were keen to apply these optimised direct arylation conditions to the synthesis of more heavily substituted imidazo [4,5-*b*]pyridine scaffolds by selective, iterative functionalisation of multiple vectors. Regioselective substitution of the 6-position of **7a** or the 7-position of **8a** by Pd-mediated cross-coupling (see ESI Schemes S4–S7†) followed by direct C2-arylation gave the desired disubstituted compounds (Table 5, **16a** to **16j**). 6-Bromo-imidazo[4,5-*b*]pyridine **7a** underwent 2,6-bis-arylation under C–H arylation conditions; however, we observed that the 7-chloro-imidazo[4,5-*b*]pyridine **8a** underwent regioselective C2-arylation with a notable increase in rate of reaction upon the addition of PivOH (30 mol%) (Table 5, entries 7–10). This regioselective transformation affords the opportunity for subsequent C7-functionalisation of the imidazo[4,5-*b*]pyridine scaffold.

Several mechanistic rationales have been proposed for C–H arylation reactions on heteroaromatic scaffolds, two of which are most relevant to the reaction conditions described here (Scheme 3). Bellina and Rossi first proposed a classical cross-coupling mechanism involving transmetallation of an organo-copper intermediate that is in equilibrium with a substrate/Cu(I) complex (Scheme 3, mechanism A).[23] This mechanism would be expected to proceed with catalytic CuI; however, our work, as well as that preceding it, has demonstrated a need for greater than stoichiometric amounts of Cu(I). A possible explanation is that a large molar excess of CuI could bias the equilibrium towards the substrate/Cu(I) complex. This mechanism is consistent with the work of Fairlamb, who proposed pre-coordination of CuI to purine nucleosides followed by deprotonation/cupration of the C8–H bond to form an organo-copper species that subsequently undergoes transmetallation into a

Table 2 Optimisation of conditions using *N*3-MEM imidazo[4,5-*b*]pyridine (**6a**) and 4-iodoanisole[a]

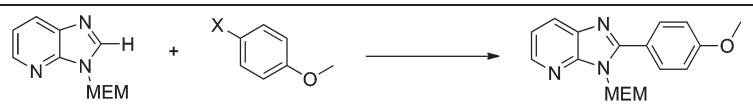


6a **13a**

Entry	Palladium	Additive (eq.)	Base	% Conv.[b]/(% yield)[c]
1	$Pd(OAc)_2$	CuI (3.0)	Cs_2CO_3	100 (78)
2	$Pd(OAc)_2$	CuI (3.0)	—	0
3	$Pd(OAc)_2$	—	Cs_2CO_3	0
4	$Pd(OAc)_2$	CuI (1.0)	Cs_2CO_3	50
5	—	CuI (3.0)	Cs_2CO_3	12
6	$Pd(OAc)_2$	MgO (3.0)	Cs_2CO_3	0

[a] Conditions: heterocycle (1 eq.), 4-iodoanisole (2 eq.), $Pd(OAc)_2$ (5 mol %), CuI (3 eq.), Cs_2CO_3 (2.5 eq.), DMF. [b] Conversion reported as ratio of starting material to product measured by LCMS. [c] Isolated Yield.

Table 3 Alternative conditions applied to *N*3-MEM-protected imidazo[4,5-*b*]pyridine **6a**

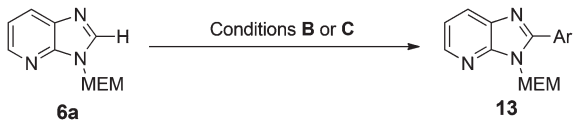


6a **13a**

Entry	X	Pd	Cu (eq.)	Additive(s)	Base	Solvent	*T* (°C)	% Conv.[a] (% yield)[b]
1	I	$Pd(OAc)_2$	CuI (3.0)	—	K_2CO_3	DMF	140	100 (60)
2	I	$Pd(OAc)_2$	CuI (2.0)	Piperidine	Cs_2CO_3	DMF	150	81 (38)
3	I	$Pd(OAc)_2$	$Cu(OAc)_2$	PPh_3	K_2CO_3	Toluene	110	0
4	I	$Pd(OAc)_2$	—	$o NO_2C_6H_4CO_2H$	Ag_2O	DMF	25	0
5	Br	$Pd(OAc)_2$	—	PivOH, $PCy_3{\cdot}HBF_4$	K_2CO_3	DMA	140	28 (19)
6	Br	$Pd(OAc)_2$	CuI (3.0)	PivOH, $PCy_3{\cdot}HBF_4$	K_2CO_3	DMF	140	100
7	Br	$Pd(OAc)_2$	CuI (3.0)	PivOH	K_2CO_3	DMF	140	100
8	Br	$Pd(OAc)_2$	CuI (3.0)	—	Cs_2CO_3	DMF	140	100 (75)
9	Cl	$Pd(OAc)_2$	CuI (3.0)	—	Cs_2CO_3	DMF	140	67

Reaction times 16–40 h.[a] % Conversion by LCMS ratio of product to starting material. [b] Isolated yield.

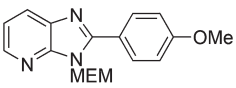
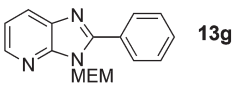
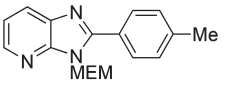
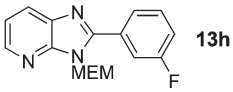
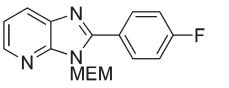
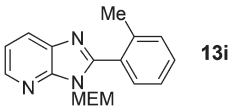
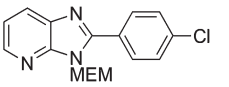
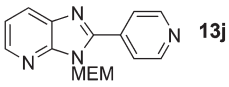
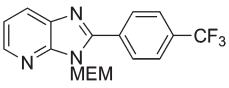
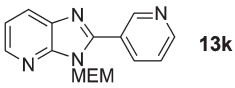
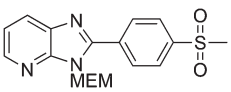
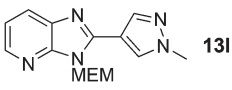
Table 4 Synthesis of C2-substituted *N*3-MEM imidazo[4,5-*b*]pyridines



6a 13

Conditions **B**: ArI (2.0 eq.), $Pd(OAc)_2$ (5 mol%), CuI (3 eq.), Cs_2CO_3 (2.5 eq.) DMF, 140 °C, 16–24 h.

Conditions **C**: ArBr (2.0 eq.), $Pd(OAc)_2$ (5 mol%), $PCy_3{\cdot}HBF_4$ (10 mol%) CuI (3 eq.), Cs_2CO_3 (2.5 eq.) DMF, 120 °C, 24–40 h.

Entry	Product	Isolated yield	Entry	Product	Isolated yield
1	 **13a**	B: 78%	7	 **13g**	B: 67%
2	 **13b**	B: 75%	8	 **13h**	B: 60%
3	 **13c**	B: 84%	9	 **13i**	B: 75%
4	 **13d**	B: 40% C: 60%	10	 **13j**	B: 47% C: 67%
5	 **13e**	B: 35% C: 77%	11	 **13k**	B: 70%
6	 **13f**	B: 46%	12	 **13l**	B: 35% C: 64%

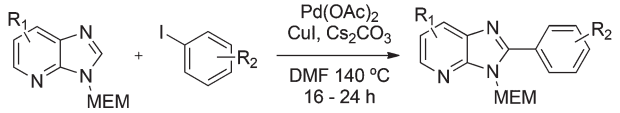
classical Pd catalytic cycle.[12a,24] Fagnou proposed an alternative Concerted-Metallation-Deprotonation (CMD) mechanism involving base-assisted C–H bond cleavage[25] (Scheme 3, Mechanism B) and consistent with mechanistic studies by Macgregor.[26] Recently, Gorelsky has investigated $Pd(OAc)_2$ and CuI mediated direct arylation on azoles, and proposed that Cu does not insert into the C–H bond, but lowers the pK_a of the neighbouring C2–H by coordination of an azole heteroatom, thereby facilitating a CMD-type mechanism.[27]

A control experiment using C2-arylation conditions in the absence of CuI and $Pd(OAc)_2$ but in the presence of acetone-d_6 showed 87% incorporation of deuterium at C2 (Scheme S8†), suggesting that C2 can be deprotonated under the reaction conditions in the absence of a coordinated metal. We measured the rate of two independent parallel C–H arylation reactions using C2–H and C2–D imidazo[4,5-*b*]pyridine, where the steady state approximation was maintained by using a large excess of 4-iodoanisole.[28] We observed a kinetic isotope effect (k_H/k_D = 2.6) consistent with C2–H bond cleavage occurring in the rate-determining step (ESI, Charts S1 and S2†). We therefore postulate that CuI is necessary to increase the acidity of the C2 proton, facilitating a CMD-type insertion mechanism and consistent with the proposal of Gorelsky (Scheme 3, Mechanism B).[27] As pivalic acid is not essential for smooth reaction, carbonate base and/or acetate anion from $Pd(OAc)_2$ may also serve to enhance the rate of the CMD step by acting as a proton shuttle, as previously proposed.[25d]

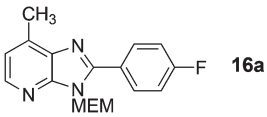
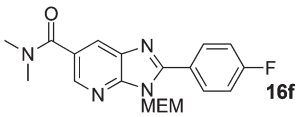
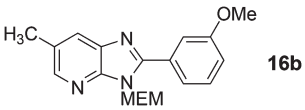
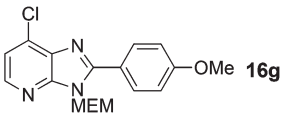
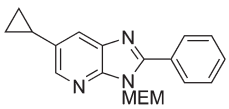
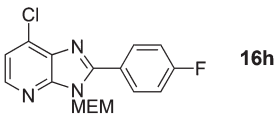
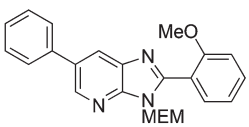
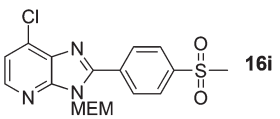
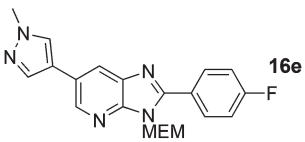
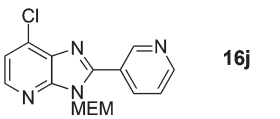
Conclusion

In summary, we have shown that the *N*3-MEM-protected imidazo[4,5-*b*]pyridine template can be regioselectively functionalised at C2 *via* direct C–H arylation using palladium, copper and basic carbonate conditions. The addition of a phosphine ligand increases the conversion and isolated yields in the case of electron deficient coupling partners. 22 C2-substituted imidazo[4,5-*b*]pyridines have been prepared. Application of these C–H arylation conditions to the iterative and regioselective elaboration of functionalised imidazo[4,5-*b*]pyridines gives 2,7- and 2,6-disubstituted derivatives from common intermediates in an approach amenable to the divergent synthesis of analogues and which is applicable to rapid medicinal chemistry exploration of this emerging purine isostere and ATP competitive kinase pharmacophore. There are two postulated mechanisms for this type of C–H arylation; our observations are consistent with C–H arylation of *N*3-MEM-protected imidazo[4,5-*b*]pyridines proceeding predominantly *via* a CMD mechanism whereby coordination of copper(I)

Table 5 Direct arylation of 6- and 7-substituted imidazo[4,5-*b*]pyridines



16

Entry	Product	Isolated yield	Entry	Product	Isolated yield
1	 **16a**	93%	6[a]	 **16f**	72%
2	 **16b**	69%	7[b]	 **16g**	85%
3	 **16c**	63%	8[b]	 **16h**	85%
4	 **16d**	44%	9[b,c]	 **16i**	69%
5	 **16e**	60%	10[b]	 **16j**	69%

[a] Includes $PCy_3{\cdot}HBF_4$ (10 mol%). [b] Includes pivalic acid (30 mol%). [c] Aryl bromide was used.

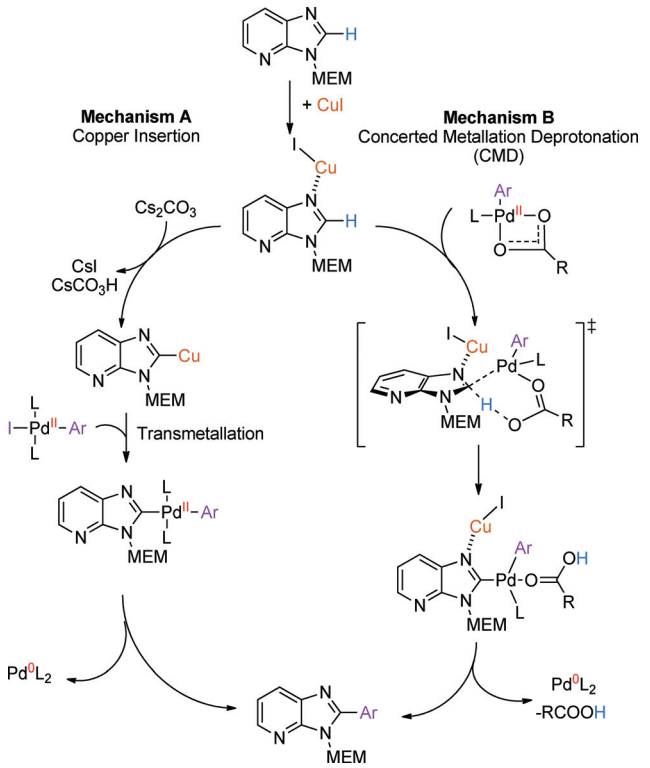
iodide to the imidazo[4,5-*b*]pyridine scaffold enhances the acidity of the C2-proton.

Experimental section

All anhydrous solvents and reagents were obtained from commercial suppliers and used without any further purification unless otherwise noted. A Biotage Initiator 60 instrument was used for all microwave-assisted reactions, using sealed reaction vessels with the temperature measured by an external IR sensor. Analytical TLC was performed on pre-coated aluminum sheets of silica (60 F254 nm) and visualised by short-wave UV light at λ_{254}. Flash column chromatography was carried out on silica gel (0.040–0.065 mm) and Flash Si-II silica gel cartridges. Purification by ion exchange was carried out using SCX-II and NH_2 cartridges. Semi-automated purification was carried out on a Biotage SP1 purification system, using SNAP cartridges, or SINGLE StEP flash column cartridges. Solvent systems are reported by column volume (CV) with the solvent flow rate as stated. Melting points were determined on an EZ-Melt automated melting point apparatus. IR spectra were recorded on a Bruker Alpha P FT-IR spectrometer. Absorption maxima (ν_{max}) are quoted in wavenumbers (cm^{-1}). ^1H NMR spectra were recorded at 500 MHz using an internal deuterium lock. Chemical shifts were measured in parts per million (ppm) using the following internal references for residual protons in the solvent: $CDCl_3$ (δ_H 7.26), CD_3OD (δ_H 3.32) and DMSO-d_6 (δ_H 2.50). Data is presented as follows: chemical shift, multiplicity, coupling constant (*J*) in Hz, and integration. The following abbreviations are used for the splitting patterns: s for singlet, d for doublet, t for triplet, m for multiplet and br for broad. ^{13}C NMR spectra were recorded at 126 MHz using an internal deuterium lock. The following internal references were used: $CDCl_3$ (δ_C 77.0), CD_3OD (δ_C 49.0) and DMSO-d_6 (δ_C 39.5). LCMS analyses were performed using ESI/APCI, with a Purospher STAR RP-18, 30 × 4 mm column and a flow rate of 1.5 mL min^{-1}. UV detection was at 254 nm. High Resolution MS analyses were performed using ESI/APCI. The references masses are: Caffeine $[M + H]^+$ = 195.087652, Reserpine $[M + H]^+$ = 609.280657, hexakis(1*H*,1*H*,3*H*-tetrafluoropentoxy)-phosphazene $[M + H]^+$ = 922.009798.

General procedure to MEM-protection of imidazo[4,5-*b*]-pyridines

To a stirred suspension of the appropriate imidazo[4,5-*b*]pyridine derivative in toluene was added Et_3N (1.5 eq.) and the mixture stirred at −10 °C for 30 min before the dropwise addition of



Scheme 3 Postulated mechanisms of C–H arylation.

MEM-Chloride (2 eq.) in toluene over 1 hour. Upon complete addition the mixture was heated to reflux for 4 h. On cooling the solution was concentrated *in vacuo*. The crude oil was purified by flash column chromatography, conditions given.

3-((2-Methoxyethoxy)methyl)-3*H*-imidazo[4,5-*b*]pyridine, 6a. Imidazo[4,5-*b*]pyridine, **3** (2.38 g, 20 mmol) was reacted following general procedure A. The crude oil was purified by flash column chromatography (cyclohexane to CH_2Cl_2 then gradient to 5% MeOH in CH_2Cl_2) to yield the product as a pale yellow oil (2.3 g, 11.1 mmol, 55%). ^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 8.41 (dd, J = 4.8, 1.4 Hz, 1H), 8.21 (s, 1H), 8.07 (dd, J = 8.0, 1.4 Hz, 1H), 7.27–7.24 (m, 1H), 5.75 (s, 2H), 3.71–3.69 (m, 2H), 3.50–3.48 (m, 2H), 3.32 (s, 3H); ^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 147.2, 144.7, 144.2, 135.2, 128.1, 118.7, 72.8, 71.5, 68.8, 59.0; LCMS t_R = 1.61 min, m/z = 208 $(M + H)^+$; purity (AUC) ≥ 95%; HRMS $(M + H)^+$ *calculated* for $C_{10}H_{14}N_3O_2$ = 208.1081, *found* = 208.1085.

Product **6b** was also isolated under these reaction conditions; regioisomers were assigned by 2D NMR (see ESI†).

1-((2-Methoxyethoxy)methyl)-1*H*-imidazo[4,5-*b*]pyridine, 6b. Yellow oil (410 mg, 10%); ^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 8.64 (dd, J = 4.8, 1.6 Hz, 1H), 8.24 (s, 1H), 7.93 (dd, J = 8.1, 1.6 Hz, 1H), 7.33–7.29 (m, 1H), 5.68 (s, 2H), 3.63–3.57 (m, 2H), 3.55–3.51 (m, 2H), 3.38 (s, 3H); ^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 156.7, 145.1, 144.6, 125.8, 118.2, 118.2, 75.1, 71.3, 67.4, 58.6; LCMS t_R = 1.21 min, m/z = 208 $(M + H)^+$; purity (AUC) ≥ 95%; HRMS $(M + H)^+$ *calculated* for $C_{10}H_{14}N_3O_2$ = 208.1081, *found* = 208.1090.

6-Bromo-3-((2-methoxyethoxy)methyl)-3*H*-imidazo[4,5-*b*]pyridine, 7a. To 6-bromoimidazo[4,5-*b*]pyridine, **4** (1.98 g, 10.0 mmol) and Et_3N (2.08 mL, 15 mmol) in toluene (200 mL) was added drop wise MEM-Chloride (2.28 mL, 20 mmol) in toluene (100 mL) over 1 hour, following general procedure A. The crude oil was purified by flash column chromatography (0–60% EtOAc in cyclohexane) to afford named product as a yellow oil (1870 mg, 6.5 mmol, 65%). ^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 8.48 (d, J = 1.9 Hz, 1H), 8.25 (bs, 2H), 5.74 (s, 2H), 3.72–3.59 (m, 2H), 3.53–3.49 (m, 2H), 3.34 (s, 3H); ^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 145.7, 145.4, 136.2, 130.5, 114.5, 73.1, 71.5, 69.0, 59.1, one C does not appear; LCMS t_R = 2.22 min, m/z = 286, 288 $(M + H)^+$ bromine isotopic splitting pattern; purity (AUC) ≥ 95%; HRMS $(M + H)^+$ *calculated* for $C_{10}H_{13}BrN_3O_2$ = 286.0186, *found* = 286.0178.

Product **7b** was also isolated under these reaction conditions; regioisomers were assigned by 2D NMR.

6-Bromo-1-((2-methoxyethoxy)methyl)-1*H*-imidazo[4,5-*b*]pyridine, 7b. Yellow oil (59 mg, 0.21 mmol, 21%). ^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 8.64 (d, J = 2.0 Hz, 1H), 8.21 (s, 1H) 8.07 (d, J = 2.0 Hz, 1H), 5.64 (s, 2H), 3.60–3.58 (m, 2H), 3.54–3.52 (m, 2H), 3.36 (s, 3H); ^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 155.2, 146.6, 145.8, 126.8, 121.7, 114.8, 75.7, 71.8, 68.1, 59.1; LCMS t_R = 2.20 min, m/z = 286, 288 $(M + H)^+$ bromine splitting pattern; purity (AUC) ≥ 95%; HRMS $(M + H)^+$ *calculated* for $C_{10}H_{13}BrN_3O_2$ = 286.0186, *found* = 286.0181.

7-Chloro-3-((2-methoxyethoxy)methyl)-3*H*-imidazo[4,5-*b*]pyridine, 8a. To 7-chloroimidazo[4,5-*b*]pyridine, **5** (767 mg, 5 mmol) and Et_3N (1.04 mL, 7.5 mmol) in toluene (100 mL) was added drop wise MEM-Chloride (1.14 mL, 10 mmol) in toluene (50 mL) over 1 hour, following general procedure A. The resulting oil was taken in EtOAc and washed with H_2O, the aqueous layer was re-extracted with CH_2Cl_2, organics combined, dried ($MgSO_4$), and concentrated *in vacuo*. The crude material was purified by flash column chromatography (Cyclohexane to CH_2Cl_2 then gradient to 5% MeOH in CH_2Cl_2) to yield the product as a yellow foam (1118 mg, 4.6 mmol, 92%). ^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 8.33 (d, J = 5.2 Hz, 1H), 8.28 (s, 1H), 7.33 (d, J = 5.2 Hz, 1H), 5.77 (s, 2H), 3.73–3.71 (m, 2H), 3.54–3.50 (m, 2H,), 3.36 (s, 3H); ^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 147.7, 145.1, 144.5, 135.1, 133.0, 119.4, 73.4, 71.5, 69.1, 59.1; LCMS t_R = 2.05 min, m/z = 242 $(M + H)^+$; purity (AUC) ≥ 95%. HRMS $(M + H)^+$ *calculated* for $C_{10}H_{13}ClN_3O_2$ = 242.0691, *found* = 242.0693.

Product **8b** was also isolated under these reaction conditions; regioisomers were assigned by 2D NMR.

7-Chloro-1-((2-methoxyethoxy)methyl)-1*H*-imidazo[4,5-*b*]pyridine, 8b. Yellow gum (48 mg, 0.2 mmol, 4%). ^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 8.45 (d, J = 5.1 Hz, 1H), 8.27 (s, 1H), 7.27 (m, 1H), 5.87 (s, 2H), 3.67–3.60 (m, 2H), 3.56–3.50 (m, 2H), 3.33 (s, 3H); ^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 158.1, 147.1, 145.6, 127.1, 123.1, 120.0, 76.1, 71.8, 67.8, 59.1; LCMS t_R = 1.97 min, m/z = 242 $(M + H)^+$; purity (AUC) ≥ 95%. HRMS $(M + H)^+$ *calculated* for $C_{10}H_{13}ClN_3O_2$ = 242.0691, *found* = 208.0690.

General conditions A: microwave-assisted C–H arylation conditions

The appropriate substrate (1.0 mmol), CuI (570 mg, 3.0 mmol), 4-iodoanisole (470 mg, 2.0 mmol), Cs_2CO_3

(812 mg, 2.5 mmol) and $Pd(OAc)_2$ (11.2 mg, 5.0 mol%) were placed into a dried microwave vial and evacuated/filled with argon. DMF (5.0 mL) was added and the reaction mixture heated in a microwave reactor at 200 °C for 30 min. The reaction mixture was cooled to RT, diluted with EtOAc (10 mL) and stirred for 0.5 h in saturated NH_4Cl solution (30 mL). After extraction with EtOAc, the organics were washed with water, brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography, conditions given.

General conditions B: C–H arylation conditions

$Pd(OAc)_2$ (5.6 mg, 0.025 mmol), CuI (285 mg, 1.5 mmol), Cs_2CO_3 (406 mg, 1.25 mmol) and aryl iodide (if solid, 1.0 mmol) were combined under air in a sealable reaction tube. The tube was flushed with argon and 3-((2-methoxyethoxy)methyl)-3*H*-imidazo[4,5-*b*]pyridine, **6a** (104 mg, 0.5 mmol) was added, followed by anhydrous DMF (5 mL) and the appropriate aryl iodide (1.0 mmol). The tube was sealed and heated to 140 °C for 40–72 h. Upon complete conversion by LC-MS, the reaction was concentrated *in vacuo*. The crude mixture was purified by column chromatography, conditions given.

General conditions C: optimised C–H arylation conditions for electron poor aryl halides

$Pd(OAc)_2$ (2.8 mg, 0.0125 mmol), CuI (143 mg, 0.75 mmol), $PCy_3{\cdot}HBF_4$ (9 mg, 0.025 mmol), Cs_2CO_3 (203 mg, 0.625 mmol) and the appropriate aryl bromide (0.5 mmol) were combined under air in a sealable reaction tube. The tube was flushed with argon and 3-((2-methoxyethoxy)methyl)-3*H*-imidazo[4,5-*b*]-pyridine, **6a** (52 mg, 0.25 mmol) was added, followed by anhydrous DMF (2.5 mL) and aryl halide (if liquid, 0.5 mmol). The tube was sealed and heated to 120 °C for 40–72 h. Upon complete conversion by LC-MS, the reaction was concentrated *in vacuo*. The crude mixture was purified by column chromatography, conditions given.

2-(4-Methoxyphenyl)-1*H*-benzimidazole, 10. Prepared using general procedure A from benzimidazole. Purification by flash column chromatography (0–5% MeOH in CH_2Cl_2) yielded product as a yellow solid (139 mg, 62%); m.p. 202–205 °C; literature m.p. 215–217 °C;[12d] ^{1}H NMR: (500 MHz, DMSO-d_6) δ_H 12.99 (bs, 1H), 8.15 (bs, 2H), 7.58 (bs, 2H), 7.18 (bs, 2H), 7.11 (bs, 2H), 3.84 (s, 3H); ^{13}C NMR: (126 MHz, DMSO-d_6) δ_C 160.4, 128.1, 122.9, 122.3, 121.3, 118.6, 114.4, 110.9, 55.3; LCMS t_R = 1.64 min, *m*/*z* 225 $(M + H)^+$; purity (AUC) ≥ 95%; HRMS $(M + H)^+$ *calculated* for $C_{14}H_{13}N_2O$ = 225.1022, *found* = 225.1018.

2-(4-Methoxyphenyl)-1-methyl-1*H*-benzimidazole, 11. Prepared using general procedure A from *N*-methylbenzimidazole. Purification by flash column chromatography (0–5% MeOH in CH_2Cl_2) yielded product as a white solid (157 mg, 66%). R_f = 0.63 (MeOH : CH_2Cl_2 5 : 95); ^{1}H NMR: (500 MHz, DMSO-d_6) δ_H 7.80 (d, *J* = 8.6 Hz, 2H), 7.65 (d, *J* = 7.5 Hz, 1H), 7.57 (d, *J* = 7.5 Hz, 1H), 7.27 (t, *J* = 7.5 Hz, 1H), 7.22 (t, *J* = 7.5 Hz, 1H), 7.12 (d, *J* = 8.6 Hz, 2H), 3.859 (s, 3H), 3.855 (s, 3H); ^{13}C NMR: (126 MHz, DMSO-d_6) δ_C 160.3, 153.0, 142.5, 136.6, 130.7, 122.4, 122.0, 121.7, 118.7, 114.1, 110.3, 55.3, 31.6; LCMS t_R = 1.41 min, *m*/*z* 239 $(M + H)^+$; purity (AUC) ≥ 95%; HRMS $(M + H)^+$ *calculated* for $C_{15}H_{15}N_2O$ = 239.1179, *found* = 239.1174.

2-(4-Methoxyphenyl)-3-methyl-3*H*-imidazo[4,5-*b*]pyridine, 12. Prepared using general procedure B with *N*3-methylimidazo-[4,5-*b*]pyridine (**S2**) in place of 3-((2-methoxyethoxy)methyl)-3*H*-imidazo[4,5-*b*]pyridine (**6a**), and 4-iodoanisole. Purification by flash column chromatography (10–100% EtOAc in cyclohexane) yielded product as a cream solid (53 mg, 44%). ^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 8.40 (dd, *J* = 4.8, 1.4 Hz, 1H), 8.06 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.84–7.79 (m, 2H), 7.26 (dd, *J* = 8.0, 4.8 Hz, 1H), 7.11–7.05 (m, 2H), 4.00 (s, 3H), 3.91 (s, 3H); ^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 161.2, 154.8, 149.1, 143.4, 135.2, 130.7, 126.8, 122.3, 118.4, 114.3, 55.4, 30.5; LCMS t_R = 2.27 min, *m*/*z* = 240 $(M + H)^+$; purity (AUC) ≥ 95%; HRMS $(M + H)^+$ *calculated* for $C_{14}H_{14}N_3O$ = 240.1131, *found* = 240.1139.

3-((2-Methoxyethoxy)methyl)-2-(4-methoxyphenyl)-3*H*-imidazo-[4,5-*b*]pyridine, 13a. Prepared using general procedure B and 4-iodoanisole. Purification by flash column chromatography (20–80% EtOAc in CH_2Cl_2) yielded the product as a brown solid (122 mg, 78%); m.p. 105–108 °C; ^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 8.37 (dd, *J* = 4.8, 1.4 Hz, 1H), 8.14–8.09 (m, 2H), 8.06 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.30–7.25 (m, 1H), 7.10–7.04 (m, 2H), 5.76 (s, 2H), 4.00–3.93 (m, 2H), 3.90 (s, 3H) 3.64–3.59 (m, 2H), 3.40 (s, 3H); ^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 161.55, 155.4, 149.3, 143.7, 135.0, 131.2, 126.9, 121.9, 119.0, 72.0, 71.5, 69.7, 59.0, 53.4; LCMS t_R = 2.63 min, *m*/*z* = 314 $(M + H)^+$; purity (AUC) ≥ 95%; HRMS $(M + H)^+$ *calculated* for $C_{17}H_{20}N_3O_3$ = 314.1499, *found* = 314.1484.

2-(4-Methoxyphenyl)-3-((2-(trimethylsilyl)ethoxy)methyl)-3*H*-imidazo[4,5-*b*]pyridine, 14. Prepared using general procedure B with *N*3-SEM-imidazo[4,5-*b*]pyridine (**S4**) in place of 3-((2-methoxyethoxy)methyl)-3*H*-imidazo[4,5-*b*]pyridine (**6a**), and 4-iodoanisole. Purification by flash column chromatography (0–50% EtOAc in cyclohexane) affords product as an orange oil (117 mg, 66%); ^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 8.40 (dd, *J* = 4.8, 1.4 Hz, 1H), 8.17–8.10 (m, 2H), 8.09 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.29 (dd, *J* = 8.0, 4.8 Hz, 1H), 7.13–7.05 (m, 2H), 5.71 (s, 2H), 3.93 (s, 3H), 3.92–3.87 (m, 2H), 1.08–1.01 (m, 2H), 0.01 (s, 9H); ^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 161.2, 155.3, 148.5, 143.8, 131.3, 126.7, 121.6, 119.1, 114.3, 71.3, 67.3, 55.4, 18.1, −1.2; LCMS t_R = 3.52 min, *m*/*z* = 356 $(M + H)^+$; purity (AUC) ≥ 95%; HRMS $(M + H)^+$ *calculated* for $C_{19}H_{26}N_3O_2Si$ = 356.1789, *found* = 356.1790.

3-((2-Methoxyethoxy)methyl)-2-(4-tolyl)-3*H*-imidazo[4,5-*b*]-pyridine, 13b. Prepared by general procedure B using 4-iodotoluene. Purification by column chromatography (0–30% EtOAc in cyclohexane) afforded the product as a pale orange oil (112 mg, 75%). R_f = 0.51 (cyclohexane : EtOAc 1 : 4); ^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 8.37 (dd, *J* = 4.8, 1.4 Hz, 1H), 8.05 (dd, *J* = 8.0, 1.4 Hz, 1H), 8.02 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.25 (dd, *J* = 8.0, 4.8 Hz, 1H), 5.75 (s, 2H), 3.92–3.96 (m, 2H), 3.57–3.60 (m, 2H), 3.37 (s, 3H), 2.43 (s, 3H); ^{13}C NMR:

(126 MHz, $CDCl_3$) δ_C 155.6, 149.3, 143.9, 140.8, 134.9, 129.6, 129.6, 127.0, 126.6, 119.0, 72.0, 71.5, 68.9, 59.0, 21.5; LCMS t_R = 2.35 min, m/z = 298 $(M + H)^+$; purity (AUC) ≥ 95%; HRMS $(M + H)^+$ *calculated* for $C_{17}H_{20}N_3O_2$ = 298.1550, *found* = 298.1558.

2-(4-Fluorophenyl)-3-((2-methoxyethoxy)methyl)-3*H*-imidazo[4,5-*b*]pyridine, 13c. Prepared by general procedure B using 1-fluoro-4-iodobenzene. Purification by flash column chromatography (20–70% EtOAc in cyclohexane) yielded product as a brown solid (127 mg, 84%); m.p. 64–66 °C; ^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 8.42 (dd, J = 4.8, 1.4 Hz, 1H), 8.22–8.15 (m, 2H), 8.10 (dd, J = 8.0, 1.4 Hz, 1H), 7.31 (dd, J = 8.0, 4.8 Hz, 1H), 7.30–7.22 (m, 2H), 5.77 (s, 2H), 4.02–3.95 (m, 2H), 3.64–3.60 (m, 2H) 3.39 (s, 3H); ^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 163.8 (d, J = 251.7 Hz), 154.0, 148.7, 143.7, 134.3, 131.3 (d, J = 8.6 Hz), 126.8, 125.2 (d, J = 3.3 Hz), 118.7, 115.6 (d, J = 21.8 Hz), 71.4, 71.0, 68.5, 58.2; ^{19}F NMR: (500 MHz, $CDCl_3$) δ_F −109.4; LCMS t_R = 2.65 min, m/z = 302 $(M + H)^+$; purity (AUC) ≥ 95%; HRMS $(M + H)^+$ *calculated* for $C_{16}H_{17}FN_3O_2$ = 302.1299, *found* = 302.1298.

2-(4-Chlorophenyl)-3-((2-methoxyethoxy)methyl)-3*H*-imidazo[4,5-*b*]pyridine, 13d. Prepared by general procedure C using 1-chloro-4-iodobenzene. Purification by flash column chromatography (0–60% EtOAc in cyclohexane) yielded the product as a yellow solid (48 mg, 60%); m.p. 63–66 °C; ^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 8.42 (dd, J = 4.8, 1.4 Hz, 1H), 8.15–8.08 (m, 3H), 7.56–7.53 (m, 2H), 7.31 (dd, J = 8.0, 4.8 Hz, 1H), 5.76 (s, 2H), 4.02–3.92 (m, 2H), 3.64–3.58 (m, 2H), 3.40 (s, 3H); ^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 154.2, 149.1, 144.5, 137.1, 134.6, 131.0, 129.3, 127.8, 127.4, 119.3, 71.9, 71.5, 69.0, 59.0; LCMS t_R = 2.91 min, m/z = 318 $(M + H)^+$; purity (AUC) = 93%; HRMS $(M + H)^+$ *calculated* for $C_{16}H_{17}ClN_3O_2$ = 318.1004, *found* = 318.1006.

3-((2-Methoxyethoxy)methyl)-2-(4-(trifluoromethyl)phenyl)-3*H*-imidazo[4,5-*b*]pyridine, 13e. Prepared by general procedure C using 1-bromo-4-(trifluoromethyl)benzene. Purification by flash column chromatography (20–60% EtOAc in CH_2Cl_2) yielded the product as a deep brown solid (68 mg, 77%); m.p. 88–96 °C; ^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 8.47 (dd, J = 4.8, 1.4 Hz, 1H), 8.32 (d, J = 8.2 Hz, 2H), 8.15 (dd, J = 8.0, 1.4 Hz, 1H), 7.84 (d, J = 8.2 Hz, 2H), 7.41 (dd, J = 8.0, 4.8 Hz, 1H), 5.80 (s, 2H), 4.01–3.95 (m, 2H), 3.65–3.58 (m, 2H) 3.41 (s, 3H); ^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 153.2, 148.6, 144.3, 133.3 (d, J = 228 Hz), 131.8 (d, J = 33 Hz) 129.6, 127.2, 125.3 (d, J = 4 Hz), 123.4 (d, J = 272 Hz), 119.0, 71.5, 71.0, 68.6, 58.5, one C does not appear; ^{19}F NMR: (500 MHz, $CDCl_3$) δ_F −62.9; LCMS t_R = 2.93 min, m/z = 352; purity (AUC) ≥ 95%; HRMS $(M + H)^+$ *calculated* for $C_{17}H_{17}F_3N_3O_2$ = 352.1267, *found* = 352.1253.

3-((2-Methoxyethoxy)methyl)-2-(4-(methylsulfonyl)phenyl)-3*H*-imidazo[4,5-*b*]pyridine, 13f. Prepared by general procedure B using 1-iodo-4-(methylsulfonyl)benzene. Purification by flash column chromatography (20–60% EtOAc in CH_2Cl_2) yielded product as a deep brown solid (83 mg, 46%); m.p. 148–152 °C; ^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 8.45 (dd, J = 4.8, 1.3 Hz, 1H), 8.39 (d, J = 8.5 Hz, 2H), 8.13–8.11 (m, 3H), 7.33 (dd, J = 8.0, 4.8 Hz, 1H), 5.78 (s, 2H), 4.00–3.94 (m, 2H), 3.63–3.57 (m, 2H) 3.38 (s, 3H), 3.12 (s, 3H); ^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 153.1, 149.0, 145.1, 142.0, 134.7, 130.6, 127.9, 119.6, 71.9, 71.4, 69.1, 59.0, 44.5; LCMS t_R = 2.28 min, m/z = 362 $(M + H)^+$; purity (AUC) = 90%; HRMS $(M + H)^+$ *calculated* for $C_{17}H_{20}N_3O_4S$ = 362.1175, *found* = 362.1190.

3-((2-Methoxyethoxy)methyl)-2-phenyl-3*H*-imidazo[4,5-*b*]pyridine, 13g. Prepared by general procedure B using 4-iodobenzene. Purification by flash column chromatography (20% EtOAc in CH_2Cl_2) yielded named product as a brown oil (95 mg, 67%); ^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 8.41 (dd, J = 4.8, 1.4 Hz, 1H), 8.16–8.12 (m, 2H), 8.10 (dd, J = 8.0, 1.4 Hz, 1H), 7.59–7.54 (m, 3H), 7.30 (dd, J = 8.0, 4.8 Hz, 1H), 5.78 (s, 2H), 4.00–3.94 (m, 2H), 3.64–3.58 (m, 2H) 3.40 (s, 3H); ^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 155.4, 149.2, 144.2, 134.9, 130.5, 129.7, 129.5, 128.9, 127.3, 119.1, 72.0, 71.6, 69.0, 59.0; LCMS t_R = 2.57, m/z = 284 $(M + H)^+$; purity (AUC) = 88%; HRMS $(M + H)^+$ *calculated* for $C_{16}H_{18}N_3O_2$ = 284.1394, *found* = 284.1378.

2-(3-Fluorophenyl)-3-((2-methoxyethoxy)methyl)-3*H*-imidazo[4,5-*b*]pyridine, 13h. Prepared by general procedure B using 1-fluoro-3-iodobenzene. Purification by flash column chromatography (0–50% EtOAc in cyclohexane) yielded product as an orange oil (90 mg, 60%); ^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 8.47 (dd, J = 4.8, 1.4 Hz, 1H), 8.16 (dd, J = 8.0, 1.4 Hz, 1H), 7.99 (d, J = 7.8 Hz, 1H), 7.94 (m, 1H), 7.57 (td, J = 8.0, 5.8 Hz, 1H), 7.36 (dd, J = 8.0, 4.8 Hz, 1H), 7.29 (m, 1H), 5.82 (s, 2H), 4.03–3.95 (m, 2H), 3.66–3.60 (m, 2H), 3.41 (s, 3H); ^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 163.8 (d, J = 252 Hz) 154.0, 148.7, 134.3, 131.3 (d, J = 9 Hz), 126.8, 125.2 (d, J = 4 Hz), 118.7, 115.6 (d, J = 22 Hz) 71.4, 71.0, 68.5, 58.5; ^{19}F NMR: (500 MHz, $CDCl_3$) δ_F −111.3; LCMS t_R = 2.70 min, m/z = 302 $(M + H)^+$; purity (AUC) = 94%. HRMS $(M + H)^+$ = *calculated* for $C_{16}H_{17}FN_3O_2$ = 302.1299, *found* = 302.1305.

3-((2-Methoxyethoxy)methyl)-2-(*o*-tolyl)-3*H*-imidazo[4,5-*b*]pyridine, 13i. Prepared by general procedure B using 1-iodo-2-methylbenzene. Purification by flash column chromatography (0–60% EtOAc in CH_2Cl_2) yielded product as a brown oil (111 mg, 75%); ^{1}H NMR: (500 MHz, DMSO-d_6) δ_H 8.43 (d, J = 4.7 Hz, 1H), 8.16 (d, J = 7.6 Hz, 1H), 7.56 (d, J = 7.6 Hz, 1H) 7.49 (t, J = 7.1 Hz, 1H) 7.43 (d, J = 7.1 Hz, 1H) 7.40–7.34 (m, 2H), 5.47 (s, 2H), 3.58–3.53 (m, 2H), 3.36–3.30 (m, 2H) 3.12 (s, 3H), 2.25 (s, 3H); ^{13}C NMR: (126 MHz, DMSO-d_6) δ_C 144.4, 138.4, 134.8, 131.0, 130.6, 130.5, 129.7, 127.6, 126.1, 119.4, 72.1, 71.3, 68.7, 58.4, 20.0, two quaternary C's do not appear; LCMS t_R = 2.55, m/z = 298 $(M + H)^+$; purity (AUC) ≥ 95%; HRMS $(M + H)^+$ = *calculated* for $C_{17}H_{20}N_3O_2$ = 298.1550, *found* = 298.1545.

3-((2-Methoxyethoxy)methyl)-2-(pyridin-4-yl)-3*H*-imidazo[4,5-*b*]pyridine, 13j. Prepared by general procedure C using 4-bromopyridine. Purification by flash column chromatography (0–6% MeOH in CH_2Cl_2) yielded the product as a yellow oil (48 mg, 67%); ^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 9.05 (bs, 2H), 8.47 (dd, J = 4.8, 1.4 Hz, 1H), 8.29–8.08 (m, 3H), 7.34 (dd, J = 8.0, 4.8 Hz, 1H), 5.82 (s, 2H), 4.00–3.93 (m, 2H), 3.64–3.58 (m, 2H) 3.39 (s, 3H), ^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 152.1, 148.6, 144.7, 136.3, 134.2, 127.5, 119.1, 73.4, 71.0, 68.6, 58.5, 2 quaternary C's do not appear; LCMS t_R = 2.04 min, m/z

= 285 $(M + H)^+$; purity (AUC) ≥ 95%; HRMS $(M + H)^+$ *calculated* for $C_{15}H_{17}N_4O_2$ = 285.1346, *found* = 285.1348.

3-((2-Methoxyethoxy)methyl)-2-(pyridin-3-yl)-3*H*-imidazo[4,5-*b*]pyridine, 13k. Prepared by general procedure B using 3-iodopyridine. Purification by flash column chromatography (0–6% MeOH in CH_2Cl_2) yielded product as a yellow oil (99 mg, 70%); ^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 9.40 (bs, 1H), 8.83 (bs, 1H), 8.51 (d, J = 8.0 Hz, 1H), 8.46 (dd, J = 4.8, 1.3 Hz, 1H), 8.14 (dd, J = 8.0, 1.3 Hz, 1H), 7.57–7.46 (m, 1H), 7.34 (dd, J = 8.0, 4.8 Hz, 1H), 5.80 (s, 2H), 4.01–3.94 (m, 2H), 3.65–3.58 (m, 2H), 3.40 (s, 3H); ^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 152.0, 150.7, 149.9, 148.5, 144.2, 136.4, 134.4, 127.2, 123.1, 118.9, 71.4, 71.0, 68.6, 58.5, one quaternary C does not appear; LCMS t_R = 2.12 min, m/z = 285 $(M + H)^+$; purity (AUC) ≥ 95%; HRMS $(M + H)^+$ *calculated* for $C_{15}H_{17}N_4O_2$ = 285.1346, *found* = 285.1343.

3-((2-Methoxyethoxy)methyl)-2-(1-methyl-1*H*-pyrazol-4-yl)-3*H*-imidazo[4,5-*b*]pyridine, 13l. Prepared by general procedure C using 4-bromo-1-methyl-1*H*-pyrazole. Purification by flash column chromatography (0–5% MeOH in CH_2Cl_2) yielded product as a yellow oil (46 mg, 64%); ^{1}H NMR: (500 MHz, CD_3OD) δ_H 8.44 (bs, 1H), 8.38 (d, J = 4.8 Hz, 1H), 8.25 (bs, 1H), 8.14–8.01 (m, 1H), 7.41–7.33 (m, 1H), 5.84 (s, 2H), 4.05 (s, 3H) 3.87–3.80 (m, 2H), 3.60–3.52 (m, 2H), 3.31 (s, 3H); ^{13}C NMR: (126 MHz, CD_3OD) δ_C 143.5, 139.3, 134.3, 132.2, 125.9, 119.0, 111.4, 71.5, 71.1, 68.2, 57.6, 38.0, 2 quaternary C's do not appear; LCMS t_R = 2.12 min, m/z = 288 $(M + H)^+$; purity (AUC) ≥ 95%; HRMS $(M + H)^+$ *calculated* for $C_{14}H_{18}N_5O_2$ = 288.1455, *found* = 288.1451.

2-(4-Fluorophenyl)-3-((2-methoxyethoxy)methyl)-7-methyl-3*H*-imidazo[4,5-*b*]pyridine, 16a. Intermediate **S10** (34 mg, 0.154 mmol), $Pd(OAc)_2$ (1.7 mg, 0.0077 mmol), CuI (88 mg, 0.462 mmol) and Cs_2CO_3 (125 mg, 0.385 mmol) were combined in a sealed tube and flushed with argon, before the addition of anhydrous DMF (0.8 mL) and 4-fluoroiodobenzene (35 μL, 0.308 mmol). The tube was sealed and heated to 140 °C for 14 h. The crude mixture was concentrated and purified on a Biotage SP1 (12 g SINGLE StEP column, 15 mL min^{-1}, gradient 0–50% EtOAc in cyclohexane over 12 CV) to afford product as a cream solid (45 mg 93%). ^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 8.28 (d, J = 4.8 Hz, 1H), 8.18–8.14 (m, 2H), 7.27–7.23 (m, 2H), 7.12 (dd, J = 4.8, 1.0 Hz, 1H), 5.73 (s, 2H), 3.97–3.95 (m, 2H), 3.61–3.59 (m, 2H), 3.40 (s, 3H), 2.75 (s, 3H); ^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 164.2 (d, J = 251 Hz), 153.4, 148.4, 144.1, 139.2, 134.2, 132.0 (d, J = 8 Hz), 125.6, 120.3, 116.1 (d, J = 22 Hz), 72.0, 71.5, 68.9, 59.0, 16.4; ^{19}F NMR: (500 MHz, $CDCl_3$) δ_F −109.7; LCMS t_R = 2.80 min, m/z = 316 $(M + H)^+$; purity (AUC) ≥ 95%; HRMS $(M + H)^+$ *calculated* for $C_{17}H_{19}FN_3O_2$ = 316.1461, *found* = 316.1459, $(M + Na)^+$ *calculated* for $C_{17}H_{18}FN_3O_2Na$ = 338.1281, *found* = 338.1279.

3-((2-Methoxyethoxy)methyl)-2-(3-methoxyphenyl)-6-methyl-3*H*-imidazo[4,5-*b*]pyridine, 16b. Intermediate **S8** (165 mg, 0.74 mmol), $Pd(OAc)_2$ (8.3 mg, 0.037 mmol), CuI (422 mg, 2.2 mmol) and Cs_2CO_3 (601 mg, 1.85 mmol) were combined in a vial under an N_2 atmosphere, DMF (3 mL) and 3-iodoanisole (176 μL, 1.48 mmol) were added and the mixture heated to 140 °C for 16 h. The mixture was concentrated *in vacuo* and purified by column chromatography (0–100% EtOAc in cyclohexane) to afford product as a yellow oil (166 mg, 69%); ^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 8.23 (d, J = 1.8 Hz, 1H), 7.87 (d, J = 1.8 Hz, 1H), 7.71–7.65 (m, 2H), 7.43 (t, J = 8.0 Hz, 1H), 7.09–7.05 (m, 1H), 5.73 (s, 2H), 3.96–3.91 (m, 2H), 3.89 (s, 3H), 3.60–3.54 (m, 2H), 3.35 (s, 3H), 2.48 (s, 3H); ^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 159.9, 155.3, 147.6, 144.9, 134.8, 130.8, 129.9, 128.6, 127.3, 121.9, 117.2, 114.2, 72.0, 71.6, 68.8, 58.9, 55.4, 18.6, LCMS t_R = 2.92 min, m/z = 328 $(M + H)^+$; purity (AUC) ≥ 95%; HRMS: $(M + H)^+$ *calculated* for $C_{18}H_{22}N_3O_3$ = 328.1656, *found* = 328.1663.

6-Cyclopropyl-3-((2-methoxyethoxy)methyl)-2-phenyl-3*H*-imidazo[4,5-*b*]pyridine, 16c. Intermediate **S9** (186 mg, 0.75 mmol), $Pd(OAc)_2$ (8.4 mg, 0.0375 mmol), CuI (428 mg, 2.25 mmol) and Cs_2CO_3 (618 mg, 1.9 mmol) were combined in a vial under an N_2 atmosphere, DMF (5 mL) and iodobenzene (168 μL, 1.50 mmol) were added and the mixture heated to 140 °C for 18 h. The crude mixture was concentrated *in vacuo* and purification by column chromatography (20%–80% EtOAc in cyclohexane) afforded product as an orange oil (152 mg, 63%). ^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 8.26 (d, J = 2.1 Hz, 1H), 8.13–8.07 (m, 2H), 7.70 (d, J = 2.1 Hz, 1H), 7.56–7.48 (m, 3H), 5.72 (s, 2H), 3.98–3.87 (m, 2H), 3.62–3.53 (m, 2H), 3.37 (s, 3H), 2.06 (tt, J = 8.5, 5.1 Hz, 1H), 1.07–1.00 (m, 2H), 0.79–0.72 (m, 2H); ^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 154.9, 147.2, 143.2, 134.5, 134.3, 129.9, 129.1, 128.3, 123.1, 71.5, 71.0, 68.3, 58.4, 12.7, 8.3, one quaternary C does not appear; LCMS t_R = 2.49 min, m/z = 324 $(M + H)^+$; purity (AUC) ≥ 95%; HRMS *calculated* for $C_{19}H_{22}N_3O_2$ = 324.1707, *found* = 324.1709.

3-((2-Methoxyethoxy)methyl)-2-(2-methoxyphenyl)-6-phenyl-3*H*-imidazo[4,5-*b*]pyridine, 16d. Intermediate **S5** (210 mg, 0.74 mmol), $Pd(OAc)_2$ (8.3 mg, 0.037 mmol), CuI (422 mg, 2.2 mmol) and Cs_2CO_3 (601 mg, 1.85 mmol) were combined in a vial under an N_2 atmosphere, DMF (3 mL) and 2-iodoanisole (192 μL, 1.18 mmol) were added and the mixture heated to 140 °C for 16 h. The crude mixture was concentrated *in vacuo* and purification by column chromatography (10–100% EtOAc in cyclohexane) afforded product as a yellow oil (132 mg, 46%). ^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 8.68 (d, J = 2.1 Hz, 1H), 8.27 (d, J = 2.1 Hz, 1H), 7.70–7.62 (m, 3H), 7.58–7.50 (m, 3H), 7.46–7.40 (m, 1H), 7.14 (td, J = 7.5, 1.0 Hz, 1H), 7.06 (dd, J = 8.4, 1.0 Hz, 1H), 5.72 (s, 2H), 3.86 (s, 3H), 3.65–3.57 (m, 2H), 3.45–3.36 (m, 2H), 3.28 (s, 3H); ^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 147.4, 143.0, 138.6, 134.9, 132.4, 131.6, 131.6, 128.6, 127.1, 127.0, 125.3, 120.5, 110.7, 72.3, 70.9, 68.3, 58.4, 55.2, 3 quaternary C's not observed; LCMS t_R = 2.53 min, m/z = 390 $(M + H)^+$; purity (AUC) ≥ 95%; HRMS $(M + H)^+$ *calculated* for $C_{23}H_{24}N_3O_3$ = 390.1812, *found* = 390.1823.

2-(4-Fluorophenyl)-3-((2-methoxyethoxy)methyl)-6-(1-methyl-1*H*-pyrazol-4-yl)-3*H*-imidazo[4,5-*b*]pyridine, 16e. Intermediate **S6** (60 mg, 0.209 mmol), $Pd(OAc)_2$ (2.3 mg, 0.104 mmol), CuI (119 mg, 0.627 mmol), Cs_2CO_3 (170 mg, 0.522 mmol) were combined in a sealed tube flushed with argon gas, DMF (1 mL) and 4-fluoroiodobenzene (48 μL, 0.418 mmol) was added. The tube was heated to 140 °C for 14 h. The crude material was concentrated and purification on Biotage SP1

(12 g SINGLE StEP column, 15 mL min^{-1}, 3 CV CH_2Cl_2, then gradient over 12CV of 0–100% (5% MeOH in CH_2Cl_2)) afforded a yellow oil of product (48 mg, 60%). ^{1}H NMR: (500 MHz, CD_3OD) δ_H 8.61 (s, 1H), 8.14 (s, 1H), 8.10 (dd, J = 8.4, 5.2 Hz, 2H), 8.07 (s, 1H), 7.91 (s, 1H), 7.34 (t, J = 8.4 Hz, 2H), 5.69 (s, 2H), 3.95 (s, 3H), 3.93–3.86 (m, 2H), 3.61–3.54 (m, 2H), 3.32 (s, 3H); ^{13}C NMR: (126 MHz, CD_3OD) δ_C 164.4 (d, J = 251.1 Hz), 142.1, 136.2, 131.8 (d, J = 8.7 Hz), 128.2, 125.3, 122.6, 120.1, 115.7 (d, J = 22.2 Hz), 72.0, 71.3, 68.6, 57.7, 37.7; ^{19}F NMR: (500 MHz, CD_3OD) δ_F −110.9; LCMS t_R = 2.81 min, m/z = 382 $(M + H)^+$; purity (AUC) ≥ 95%; HRMS $(M + H)^+$ *calculated* for $C_{20}H_{21}FN_5O_2$ = 382.1674, *found* = 382.1672; $(M + Na)^+$ *calculated* for $C_{20}H_{20}FN_5O_2Na$ = 404.1493, *found* = 404.1486.

2-(4-Fluorophenyl)-3-((2-methoxyethoxy)methyl)-*N*,*N*-dimethyl-3*H*-imidazo[4,5-*b*]pyridine-6-carboxamide, 16f. Intermediate **S7** (35 mg, 0.126 mmol), $Pd(OAc)_2$ (1.4 mg, 0.006 mmol), CuI (72 mg, 0.378 mmol), $PCy_3{\cdot}HBF_4$ (4.6 mg, 0.013 mmol), and Cs_2CO_3 (102 mg, 0.315 mmol) were combined in a sealed tube flushed with argon. DMF (1.3 mL) and 4-fluoroiodobenzene (29 μL, 0.252 mmol) were added and the mixture heated to 140 °C for 16 h. The mixture was concentrated and purification by flash column chromatography (20–80% EtOAc in cyclohexane) afforded the product as a brown oil (34 mg, 72%). ^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 8.54 (d, J = 1.8 Hz, 1H), 8.21–8.14 (m, 2H), 8.14 (d, J = 1.8 Hz, 1H), 7.30–7.23 (m, 2H), 5.77 (s, 2H), 3.99–3.93 (m, 2H), 3.64–3.58 (m, 2H), 3.40 (s, 3H), 3.19 (bs, 3H) 3.10 (bs, 3H); ^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 169.6, 143.6, 131.9 (d, J = 9 Hz), 126.2, 116.2 (d, J = 21 Hz), 72.1, 71.4, 69.1, 59.1, 40.0 and 35.8, all aromatic CH's accounted for, 6 of 7 quaternary C's do not appear; ^{19}F NMR: (500 MHz, $CDCl_3$) δ_F −108.6; LCMS t_R = 2.54 min, m/z = 373 $(M + H)^+$; purity (AUC) = 93%; HRMS $(M + H)^+$ *calculated* for $C_{19}H_{22}FN_4O_3$ = 373.1670, *found* = 373.1667.

7-Chloro-3-((2-methoxyethoxy)methyl)-2-(4-methoxyphenyl)-3*H*-imidazo[4,5-*b*]pyridine, 16g. Prepared according to general procedure B from intermediate **8a** (as 1.0 M solution in DMF) and 4-iodoanisole, with added PivOH (15 mg, 0.15 mmol). Purification by flash column chromatography (0–50% EtOAc in CH_2Cl_2) yielded product as a cream solid (74 mg, 85%); ^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 8.26 (d, J = 5.3 Hz, 1H), 8.16–8.11 (m, 2H), 7.31 (d, J = 5.3 Hz, 1H), 7.09–7.05 (m, 2H), 5.74 (s, 2H), 3.98–3.92 (m, 2H), 3.91 (s, 3H) 3.64–3.58 (m, 2H), 3.40 (s, 3H); ^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 161.8, 156.1, 150.0, 143.8, 133.6, 133.0, 131.6, 121.3, 119.4, 114.4, 72.4, 71.5, 69.0, 59.1, 53.4, one quaternary C does not appear; LCMS t_R = 2.90 min, m/z = 348 $(M + H)^+$; purity (AUC) ≥ 95%; HRMS $(M + H)^+$ *calculated* for $C_{17}H_{18}ClN_3O_3$ = 348.1109, *found* = 348.1112.

7-Chloro-2-(4-fluorophenyl)-3-((2-methoxyethoxy)methyl)-3*H*-imidazo[4,5-*b*]pyridine, 16h. Prepared according to general procedure B from intermediate **8a** (as 1.0 M solution in DMF) and 4-fluoroiodobenzene, with added PivOH (15 mg, 0.15 mmol). Crude product purified by flash column chromatography (0–50% EtOAc in cyclohexane) to afford product as a white solid (142 mg, 85%). ^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 8.29 (d, J = 5.2 Hz, 1H), 8.22–8.14 (m, 2H), 7.33 (d, J = 5.2 Hz, 1H), 7.28–7.20 (m, 2H), 5.74 (s, 2H), 3.98–3.92 (m, 2H), 3.64–3.57 (m, 2H), 3.39 (s, 3H); ^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 164.44 (d, J = 252.1 Hz), 155.1, 149.8, 144.3, 134.1, 132.8, 132.1 (d, J = 8.5 Hz), 125.1 (d, J = 3.5 Hz), 119.6, 116.1 (d, J = 21.8 Hz), 72.4, 71.4, 69.1, 59.1; ^{19}F NMR: (500 MHz, $CDCl_3$) δ_F −108.73; LCMS t_R = 2.91 min, m/z = 336 $(M + H)^+$; purity (AUC) ≥ 95%; HRMS $(M + H)^+$ *calculated* for $C_{16}H_{16}FClN_3O_2$ = 336.0910, *found* = 336.0911.

7-Chloro-3-((2-methoxyethoxy)methyl)-2-(4-(methylsulfonyl)-phenyl)-3*H*-imidazo[4,5-*b*]pyridine, 16i. Prepared according to general procedure B from intermediate **8a** (as 1.0 M solution in DMF) and 4-bromophenylmethyl sulfone, with added PivOH (15 mg, 0.15 mmol). Purification by flash column chromatography (0–50% EtOAc in CH_2Cl_2) yielded product as a yellow solid (275 mg, 69%); ^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 8.44–8.39 (m, 2H), 8.35 (d, J = 5.2 Hz, 1H), 8.17–8.10 (m, 2H) 7.38 (d, J = 5.2 Hz, 1H), 5.77 (s, 2H), 3.99–3.94 (m, 2H), 3.63–3.58 (m, 2H) 3.39 (s, 3H), 3.13 (s, 3H); ^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 153.7, 149.7, 145.2, 142.3, 134.9, 134.1, 132.8, 130.9, 127.9, 120.0, 72.4, 71.4, 69.3, 59.1, 44.5; LCMS t_R = 2.55 min, m/z = 396 $(M + H)^+$; purity (AUC) ≥ 95%; HRMS $(M + H)^+$ *calculated* for $C_{17}H_{19}ClN_3O_4S$ = 396.0785, *found* = 396.0772.

7-Chloro-3-((2-methoxyethoxy)methyl)-2-(pyridin-3-yl)-3*H*-imidazo[4,5-*b*]pyridine, 16j. Prepared according to general procedure B from intermediate **8a** (as 1.0 M solution in DMF) and 3-iodopyridine, with added PivOH (15 mg, 0.15 mmol). Purified by flash column chromatography (0–5% MeOH in CH_2Cl_2) affording product as a cream solid (110 mg, 69%). ^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 9.38 (dd, J = 2.4, 0.8 Hz, 1H), 8.82 (dd, J = 4.8, 1.8 Hz, 1H), 8.50 (dt, J = 7.9, 1.8 Hz, 1H), 8.34 (d, J = 5.2 Hz, 1H), 7.51 (ddd, J = 7.9, 4.8, 0.8 Hz, 1H), 7.37 (d, J = 5.2 Hz, 1H), 5.77 (s, 2H), 3.99–3.90 (m, 2H), 3.64–3.56 (m, 2H), 3.39 (s, 3H); ^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 153.2, 151.6, 150.6, 149.7, 144.9, 137.1, 134.6, 132.9, 125.4, 123.5, 119.8, 72.3, 71.4, 69.3, 59.08; LCMS t_R = 2.45 min, m/z = 319 $(M + H)^+$; purity (AUC) ≥ 95%; HRMS $(M + H)^+$ *calculated* for $C_{15}H_{16}ClN_4O_2$ = 319.0956, *found* = 319.0956.

Synthesis of deprotected products 9 and 15b–l
General procedure D

The MEM-protected intermediate was taken in a 1 : 1 mixture of THF and 12 M HCl and stirred at rt for 16 h. The reaction mixture was neutralised with sat. aq. $NaHCO_3$ and stirred for 1 h. Where product precipitated, this was collected by filtration and triturated with Et_2O. Where product did not precipitate, the solution was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude mixture was purified by column chromatography where required; conditions are given. Note: For all deprotected C2-aryl imidazo[4,5-*b*]-pyridine products, carbon 7 does not appear in ^{13}C NMR spectra, it can be visualised by taking the sample in DMSO-d_6 and adding 1 drop of HCl.

2-(4-Methoxyphenyl)-3*H*-imidazo[4,5-*b*]pyridine, 9. Prepared by general procedure D, product precipitated on neutralization and collected by filtration. Product was obtained as an off-

white solid (312 mg, 98%). Lit m.p.[9a] 228–230 °C, observed m.p. 227–229 °C; ^{1}H NMR: (500 MHz, CD_3OD) δ_H 8.34 (d, J = 4.2, Hz, 1H), 8.16–8.11 (m, 2H), 7.98 (d, J = 7.9, Hz, 1H), 7.30 (dd, J = 8.0, 4.9 Hz, 1H), 7.17–7.07 (m, 2H), 3.91 (s, 3H); ^{13}C NMR: (126 MHz, CD_3OD) δ_C 162.2, 143.3, 128.5, 121.3, 118.1, 114.2, 54.6, C7 and four quaternary C's do not appear; LCMS t_R = 1.88 min, m/z = 226 $(M + H)^+$; purity (AUC) ≥ 95%; HRMS $(M + H)^+$ *calculated* for $C_{13}H_{12}N_3O$ = 226.0975, *found* = 226.0975.

2-(4-Tolyl)-3*H*-imidazo[4,5-*b*]pyridine, 15b. Prepared by general procedure D, product precipitated on neutralization and collected by filtration. Product was obtained as a white solid (86 mg, 86%). Lit. m.p. 261–262 °C;[29] observed m.p. 252–255 °C; ^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 13.76 (s, 1H), 8.45 (dd, J = 1.1, 4.9 Hz, 1H), 8.19 (m, 3H), 7.45 (d, J = 7.9 Hz, 2H), 7.34 (dd, J = 4.9, 8.0 Hz, 1H), 2.51 (3H, s); ^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 154.0, 149.5, 142.6, 141.3, 137.2, 129.9, 127.0, 127.2, 127.6, 118.4, 21.6, C7 does not appear; LCMS t_R = 1.81 min, m/z = 210 $(M + H)^+$; purity (AUC) ≥ 95%; HRMS $(M + H)^+$ *calculated* for $C_{13}H_{12}N_3$ = 210.1026, *found* = 210.1025.

2-(4-Fluorophenyl)-3*H*-imidazo[4,5-*b*]pyridine, 15c. Prepared by general procedure D, product precipitated on neutralization and collected by filtration. Product was obtained as a cream solid (53 mg, 97%). Lit. m.p. 289–290 °C;[30] observed m.p. 285–287 °C; ^{1}H NMR: (500 MHz, CD_3OD) δ_H 8.38 (dd, J = 4.9, 1.4 Hz, 1H), 8.25–8.17 (m, 2H), 8.03 (dd, J = 8.0, 1.4 Hz, 1H), 7.37–7.30 (m, 3H); ^{13}C NMR: (126 MHz, CD_3OD) δ_C 164.5 (d, J = 250.7), 143.8, 129.2 (d, J = 8.9 Hz), 125.6, 118.4, 115.8 (d, J = 22.4 Hz), four C's do not appear; ^{19}F NMR: (500 MHz, CD_3OD) δ_F −111.1; LCMS t_R = 1.97 min, m/z = 214 $(M + H)^+$; purity (AUC) ≥ 95%; HRMS $(M + H)^+$ *calculated* for $C_{12}H_9FN_3$ = 214.0775, *found* = 214.0784; CHN Microanalysis *calculated* for $C_{12}H_8FN_3$ = C, 67.60; H, 3.78; N, 19.71%, *observed* = C, 67.54; H, 3.78; N, 19.67%.

2-(4-Chlorophenyl)-3*H*-imidazo[4,5-*b*]pyridine, 15d. Prepared by general procedure D, product precipitated on neutralization and collected by filtration. Product was obtained as a cream solid (15 mg, 50%). Lit. m.p. 300 °C;[9a] Observed 301–304 °C; ^{1}H NMR: (500 MHz, CD_3OD) δ_H 8.38 (dd, J = 4.8, 1.5 Hz, 1H), 8.19–8.14 (m, 2H), 8.03 (dd, J = 8.0, 1.5 Hz, 1H), 7.63–7.58 (m, 2H), 7.32 (dd, J = 8.0, 4.8 Hz, 1H); ^{13}C NMR: (126 MHz, CD_3OD) δ_C 143.8, 129.0, 128.3, 118.3, 100.0, five C's do not appear; LCMS t_R = 2.51 min, m/z = 230 $(M + H)^+$; purity (AUC) ≥ 95%; HRMS $(M + H)^+$ *calculated* for $C_{12}H_9ClN_3$ = 230.0480, *found* = 230.0482.

2-(4-(Trifluoromethyl)phenyl)-3*H*-imidazo[4,5-*b*]pyridine, 15e. Prepared by general procedure D, crude material was purified by flash column chromatography (0–50% EtOAc in CH_2Cl_2), to yield product as a white solid (14 mg, 53%); m.p. 289–293 °C; ^{1}H NMR: (500 MHz, CD_3OD) δ_H 8.43 (dd, J = 4.8, 1.4 Hz, 1H), 8.36 (d, J = 8.1 Hz, 2H), 8.08 (dd, J = 8.0, 1.4 Hz, 1H), 7.90 (d, J = 8.2 Hz, 2H), 7.37 (dd, J = 8.0, 4.8 Hz, 1H); ^{13}C NMR: (126 MHz, CD_3OD) δ_C 144.4, 127.4, 125.8, 125.7, 118.8, C7 and five quaternary C's do not appear; ^{19}F NMR: (500 MHz, CD_3OD) δ_F −64.4; LCMS t_R = 2.79 min, m/z = 264; purity (AUC) ≥ 95%; HRMS $(M + H)^+$ *calculated* for $C_{13}H_9N_3F_3$ = 264.0743, *found* = 264.0752; CHN Microanalysis *calculated* for $C_{13}H_8F_3N_3$ = C, 59.32; H, 3.06; N, 15.96%, *observed* = C, 59.29; H, 3.13; N, 16.03%.

2-(4-(Methylsulfonyl)phenyl)-3*H*-imidazo[4,5-*b*]pyridine, 15f. Prepared by general procedure D, product precipitated on neutralization and collected by filtration. Product was obtained as a light orange solid (27 mg, 67%). Lit. m.p.[31] 286 °C, observed 268–270 °C; IR ν_{max}/cm^{-1} 1283s and 1266s (S═O); ^{1}H NMR: (500 MHz, CD_3OD) δ_H 8.47–8.42 (m, 2H), 8.39 (dd, J = 4.8, 1.5 Hz, 1H), 8.17–8.12 (m, 2H), 8.07 (dd, J = 8.0, 1.5 Hz, 1H), 7.32 (dd, J = 8.0, 4.8 Hz, 1H), 3.21 (s, 3H); ^{13}C NMR: (126 MHz, CD_3OD) δ_C 143.9, 127.8, 127.6, 118.2, 42.8, C7 and five quaternary C's do not appear; LCMS t_R = 1.83 min, m/z = 274 $(M + H)^+$; purity (AUC) ≥ 95%; HRMS $(M + H)^+$ *calculated* for $C_{13}H_{12}N_3O_2S$ = 274.0645, *found* = 274.0641.

2-Phenyl-3*H*-imidazo[4,5-*b*]pyridine, 15g. Prepared by general procedure D. Purified by flash column chromatography (20% EtOAc in CH_2Cl_2) to yield product as an off-white solid (136 mg, 81%). Lit. m.p. 288–290 °C;[9a] observed m.p. 283–285 °C; ^{1}H NMR: (500 MHz, CD_3OD) δ_H 8.39 (dd, J = 4.8, 1.0 Hz, 1H), 8.21–8.14 (m, 2H), 8.03 (dd, J = 8.0, 1.0 Hz, 1H), 7.64–7.55 (m, 3H), 7.33 (dd, J = 8.0, 4.9 Hz, 1H); ^{13}C NMR: (126 MHz, CD_3OD) δ_C 143.8, 130.8, 128.9, 126.8, 118.4, C7 and four quaternary C's do not appear; LCMS t_R = 1.81, m/z = 196 $(M + H)^+$; purity (AUC) ≥ 95%; HRMS $(M + H)^+$ *calculated* for $C_{12}H_{10}N_3$ = 196.0869, *found* = 196.0864.

2-(3-Fluorophenyl)-3*H*-imidazo[4,5-*b*]pyridine, 15h. Prepared by general procedure D, product precipitated on neutralization and collected by filtration. Product was obtained as a white solid (54 mg, 90%). Lit. m.p. >300 °C,[9a] observed 271–274 °C; ^{1}H NMR: (500 MHz, CD_3OD) δ_H 8.40 (dd, J = 4.8, 1.4 Hz, 1H), 8.05 (dd, J = 8.0, 1.4 Hz, 1H), 8.01 (ddd, J = 0.9, 1.7, 7.8 Hz, 1H), 7.93 (ddd, J = 1.7, 2.4, 9.9 Hz, 1H), 7.61 (td, 5.3, 8.0 Hz, 1H) 7.38–7.29 (m, 2H); ^{13}C NMR: (126 MHz, CD_3OD) δ_C 164.5 (d, J = 250.7 Hz), 143.8, 129.2 (d, J = 8.9 Hz), 125.6, 118.4, 115.8 (d, J = 22.4 Hz), C7 and four quaternary C's do not appear; ^{19}F NMR: (500 MHz, CD_3OD) δ_F −113.9; LCMS t_R = 2.16 min, m/z = 214.0 $(M + H)^+$; purity (AUC) ≥ 95%; HRMS $(M + H)^+$ *calculated* for $C_{12}H_9FN_3$ = 214.0775, *found* = 214.0779.

2-(*o*-Tolyl)-3*H*-imidazo[4,5-*b*]pyridine, 15i. Prepared by general procedure D, product precipitated on neutralization and collected by filtration. Product was obtained as a cream solid (56 mg, 76%). Observed m.p. 205–207 °C; ^{1}H NMR: (500 MHz, CD_3OD) δ_H 8.40 (d, J = 4.3, 1H), 8.06 (d, J = 7.8, Hz, 1H), 7.68 (d, J = 7.7 Hz, 1H), 7.51–7.32 (m, 4H) 1.02 (s, 3H); ^{13}C NMR: (126 MHz, CD_3OD) δ_C 143.5 (C_5), 137.5, 136.8, 130.9, 130.1 129.5, 125.8, 118.2, 19.2, C7 and three quaternary C's do not appear; LCMS t_R = 1.85 min, m/z = 210 $(M + H)^+$; purity (AUC) ≥ 95%; HRMS $(M + H)^+$ *calculated* for $C_{13}H_{12}N_3$ = 210.1026, *found* = 210.1024.

2-(Pyridin-4-yl)-3*H*-imidazo[4,5-*b*]pyridine, 15j. Prepared by general procedure D. Purification by flash column chromatography (0–8% MeOH in CH_2Cl_2) yielded product as a white solid (18 mg, 46%); Lit. m.p. 297 °C,[32] observed m.p. 295–296 °C; ^{1}H NMR: (500 MHz, CD_3OD) δ_H 7.77 (dd, J = 4.6, 1.6 Hz, 2H), 8.46 (d, J = 4.8 Hz, 1H), 8.16 (dd, J = 4.6,

1.7 Hz, 2H), 8.11 (d, J = 7.8 Hz, 1H), 7.39 (dd, J = 8.1, 4.8 Hz, 1H); ^{13}C NMR: (126 MHz, CD_3OD) δ_C 151.3, 146.4, 138.9, 122.5, 120.6, C7 and three quaternary C's do not appear; LCMS t_R = 1.28 min, m/z = 197 $(M + H)^+$; purity (AUC) ≥ 95%; HRMS $(M + H)^+$ *calculated* for $C_{11}H_9N_4$ = 197.0822, *found* = 197.0819.

2-(Pyridin-3-yl)-3*H*-imidazo[4,5-*b*]pyridine, 15k. Prepared by general procedure D. Purification by flash column chromatography (0–8% MeOH in CH_2Cl_2) yielded product as a white solid (20 mg, 38%); Lit m.p. 284 °C,[30] observed m.p. 283–285 °C; ^{1}H NMR: (500 MHz, DMSO-d_6) δ_H 13.66 (bs, 1H), 9.34 (d, J = 1.8 Hz, 1H), 8.72 (dd, J = 4.9, 1.5 Hz, 1H), 8.61–8.53 (m, 1H), 8.46–8.38 (m, 1H), 8.08 (d, J = 8.1 Hz, 1H), 7.66 (dd, J = 8.0, 4.9 Hz, 1H), 7.36 (dd, J = 8.1, 4.9 Hz, 1H); ^{13}C NMR: (126 MHz, CD_3OD) δ_C 156.9, 152.1, 148.8, 145.8, 136.4, 127.5, 125.7, 120.2, C7 and two quaternary C's do not appear; LCMS (Method B) t_R = 1.42 min, m/z = 197 $(M + H)^+$; purity (AUC) ≥ 95%; HRMS $(M + H)^+$ *calculated* for $C_{11}H_9N_4$ = 197.0822, *found* = 197.0819; CHN Microanalysis *calculated* for $C_{11}H_8N_4$ = C, 67.34; H, 4.11; N, 28.55%, *observed* = C, 67.29; H, 4.13; N, 28.49%.

2-(1-Methyl-1*H*-pyrazol-4-yl)-3*H*-imidazo[4,5-*b*]pyridine, 15l. Prepared by general procedure D. Purification by flash column chromatography (0–10% MeOH in CH_2Cl_2) yielded product as an off-white solid (19 mg, 48%); Observed m.p. 274–278 °C; ^{1}H NMR: (500 MHz, CD_3OD) δ_H 8.32 (bs, 1H), 8.29 (s, 1H), 8.13 (s, 1H), 7.95 (dd, J = 8.0, 1.2 Hz, 1H), 7.29 (dd, J = 8.0, 4.9 Hz, 1H), 4.01 (s, 3H); ^{13}C NMR: (126 MHz, CD_3OD) δ_C 151.6, 149.1, 142.8, 137.9, 130.9, 122.4, 118.1, 112.5, two quaternary C's do not appear; LCMS t_R = 1.14 min, m/z = 200 $(M + H)^+$; purity (AUC) ≥ 95%; HRMS $(M + H)^+$ *calculated* for $C_{10}H_{10}N_5$ = 200.0931, *found* = 200.0929; CHN Microanalysis *calculated* for $C_{10}H_9N_5$ = C, 60.29; H, 4.55; N, 35.16%, *observed* = C, 60.23; H, 4.59; N, 35.02%.

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