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Note

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Modular Synthesis of Di- and Tri-substituted Imidazoles from Ketones and Aldehydes: A Route to Kinase Inhibitors

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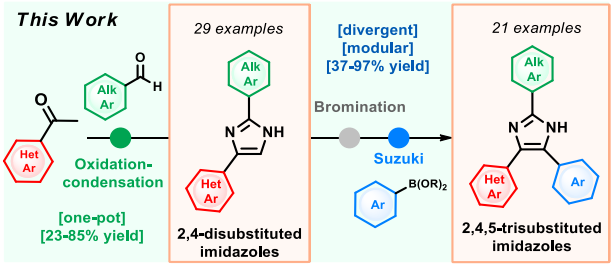


Abstract

An one-pot and modular approach to the synthesis of 2,4(5)-disubstituted imidazoles was developed based on ketone oxidation, employing catalytic HBr and DMSO, followed by imidazole condensation with aldehydes. This methodology afforded twenty-nine disubstituted *NH*-imidazoles (23%-85% yield). A three step synthesis of twenty kinase inhibitors was achieved by employing this oxidation-condensation protocol, followed by bromination and Suzuki coupling in the imidazole ring to yield trisubstituted *NH*-imidazoles (23%-69%, three steps). This approach was also employed in the synthesis of known inhibitor GSK3037619A.

Accessibility and availability of small organic molecules remains one of the major challenges in the drug discovery process[1]. Efficient and rapid approaches to access these molecules are highly desirable in order to provide medicinal chemists and chemical biologists the right tools in their scientific endeavors[2]. In this context, synthetic organic chemistry plays a pivotal role in creating pathways to access these molecules in a short, economic and efficient way from commercially and widely available building blocks. Moreover, the synthetic approach must offer versatility by allowing modular changes in

a divergent fashion in order to generate several different molecules from a single precursor.

Substituted imidazoles are one class of such small organic molecules with broad interest, ranging from applications in materials and polymer science[3,4] to their use as ionic liquids[5], and as therapeutic agents[6] and bioactive molecules such as the marine alkaloids Nortopsentins A-C[7] (Figure 1). Methods to access these scaffolds have been intensely explored and can be roughly divided into two approaches. The first approach involves the formation of the imidazole ring from suitable precursors[8] while the second involves the functionalization of a preformed imidazole ring[9]. Combinations of both approaches can also be employed to efficiently assemble substituted imidazoles[10–14].

In our search for selective and potent inhibitors of the kinase STK10[15], which is a serine-threonine kinase important due to its role in lymphocyte migration[16–19], we were challenged with the task of providing an efficient, modular and divergent synthetic route for rapid evaluation of the structure-activity relationship (SAR) of trisubstituted pyridyl-imidazole **1** (Figure 1), focusing on changes in the naphthyl moiety since previous synthetic approach introduced the naphthalene in the first step of a six-step route[20].

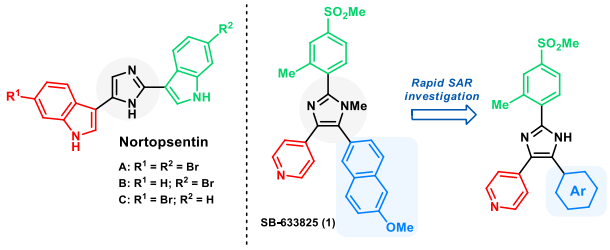


Figure 1. Bioactive Nortopsentins A-C and pyridyl-imidazole kinase inhibitor SB-633825 **(1)**

Previous work from Laufer[12] and Springer[21] already provided access to trisubstituted pyridyl imidazoles in a divergent and modular fashion, although with the use of protecting groups thus increasing the step count by two (Figure 2). The use of oxalyl boronates by Yudin offers a regioselective, protecting group-free and modular approach to imidazoles. However, the key intermediate is accessed in five steps and the cross-coupled product is obtained in moderate yields[11] (Figure 2).

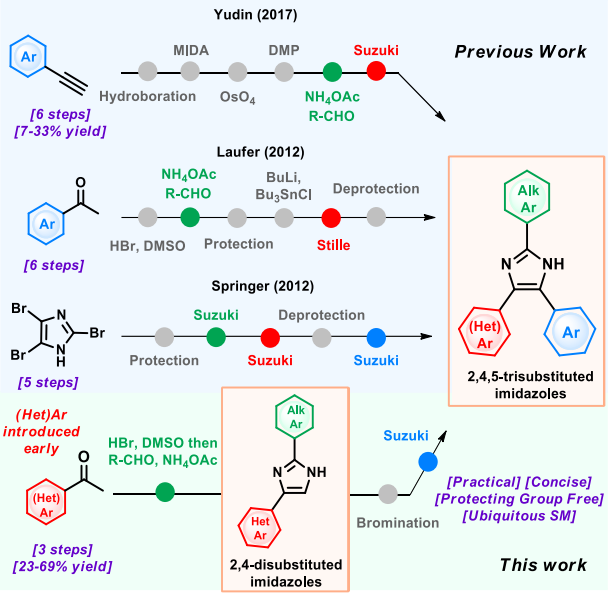
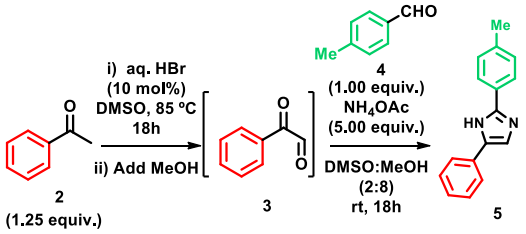


Figure 2. Modular Access to 2,4,5-trisubstituted imidazoles

We sought to address both challenges by implementing an efficient step- and redox-economical approach to disubstituted 2,4(5)-*NH* imidazoles, followed by Suzuki reaction to introduce the aromatic substituent in a protecting group-free fashion. Herein, we report an improved one-pot approach to disubstituted 2,4(5)-*NH* imidazoles consisting of a sequential Kornblum oxidation[22], followed by Radziszewski[23] imidazole condensation which allowed the synthesis of twenty-nine 2,4(5)-disubstituted imidazoles in yields ranging from 23% to 85%. Moreover, representative imidazoles **32** and **36** were further functionalized to rapidly access a small kinase inhibitor library of twenty trisubstituted 2,4,5-*NH* imidazoles in yields ranging from 23% to 69% for three steps.

Initially, we investigated the possibility of obtaining the 2,4(5)-*NH* imidazole **5** employing the sequential oxidation-condensation protocol with acetophenone **2** and *p*-tolualdehyde **4** as representative carbonyl substrates. After extensive optimization, it was found that formation of glyoxal (**3**) from acetophenone (**2**) could be achieved employing a catalytic amount (10 mol%) of aqueous HBr in DMSO at 85 ºC and after addition of the glyoxal **3** in a MeOH:DMSO (6:4) solution to a mixture of *p*-tolualdehyde **4** and NH_4OAc in MeOH, the desired imidazole was isolated in 69% yield (Table 1, Entry 1).

Table 1. Optimization of the reaction conditions for the synthesis of the disubstituted imidazole **5**



Entry	Changes from the conditions described above	Yield[b]
1	none	69 (69)
2	2 (1.00 equiv.), HBr aq. (200 mol%), 60 °C, 24h	48
3	2 (1.00 equiv.), HBr aq. (50 mol%), 60 °C, 72h	57
4	2 (1.00 equiv.), HBr aq. (50 mol%), 85 °C, 12h	55
5	2 (1.00 equiv.), HBr aq. (10 mol%), 85 °C, 18h	61
6	no HBr aq.	0
7	DMSO:MeOH (7:3)[c]	45
8	DMSO:EtOH (2:8)[c]	49
9	DMSO:MeOH:DMF (2:3:5)[c]	45
10	DMSO:MeOH:PhMe (2:3:5)[c]	47
11	with isolation of 3 (stepwise procedure)	(52)

[a]Oxidation step performed using acetophenone **2** (**Table 1**), aqueous HBr (48% w/w, 8.9 M) (**Table 1**) and DMSO (0.50 M). Condensation step performed by slow addition (30 min) of glyoxal **3** solution in DMSO:MeOH (4:6, v/v, 0.19 M relative to acetophenone **2**) to a mixture of tolualdehyde **4** (0.3 mmol) and NH_4OAc (1.5 mmol) in MeOH (1.5 mL, 0.2 M). Final solvent composition: DMSO:MeOH (8:2). [b]Yield after work-up as determined by ^1H NMR analysis of the crude reaction mixture with 1,3,5-trimethoxybenzene as the internal standard. Isolated yield given in parentheses.[c]Final solvent composition

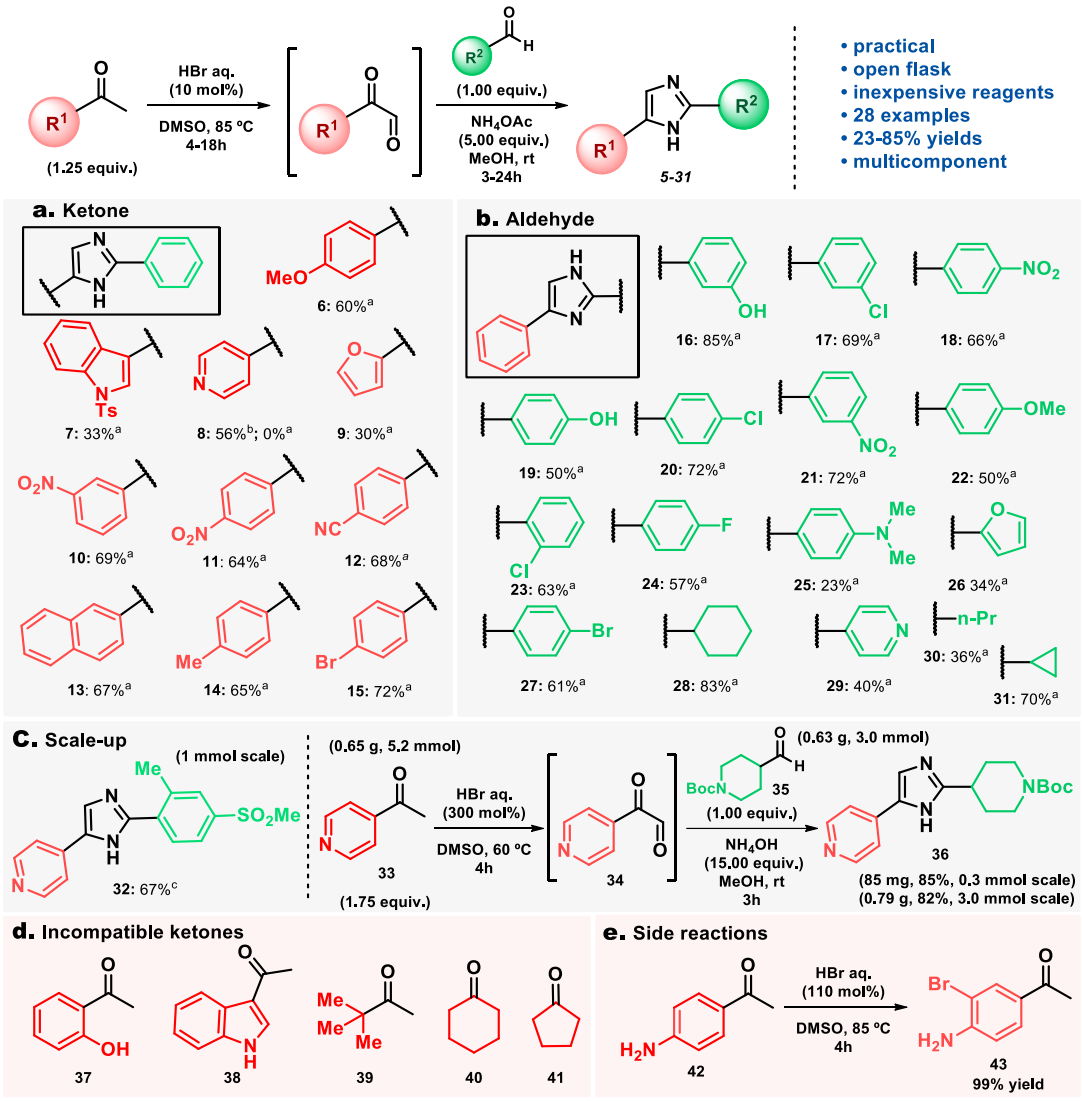
Decreasing HBr loading (entries 2-3 and 4-5) resulted in longer reaction times (oxidation step) with a some improvement in the yield. Importantly, increasing reaction temperature did not have an impact on the yield (entries 4-5) but the oxidation reaction proceeded faster. When the reaction was carried out in the absence of HBr (entry 6), neither glyoxal **3** nor imidazole **5** were observed. When the amount of acetophenone was increased (entry 1), a better yield was observed and 1.25 equiv. was selected as the optimum amount. Changing from MeOH to EtOH (oxidation step, entry 8) or adding polar aprotic solvents (DMF and DMSO, entries 7 and 9) and apolar solvents (PhMe, entry 10) in the condensation step did not provide better yields. (See Supp. Info. Table S1 for all conditions employed).

The substrate scope (Scheme 1) was then explored using different methyl ketones and aldehydes. The transformation proved to tolerate well the electronic properties of the substituted acetophenones employed. Notably, substituted acetophenones bearing electron-donating (**6**, **14**), electron-withdrawing (**10**, **11**, **12**, **15**), electron-neutral (**13**) and pyridine (**8**) were good substrates for this transformation and products were isolated in yields ranging from 56-72% (Scheme 1a). However, the 3-indole and 2-furyl derivatives

7 and **9**, respectively, performed poorly under standard conditions while 2-hydroxyacetophenone (**37)** did not show reactivity even when higher amounts of HBr (300 mol%) were employed. For 3-acetylindole (**38**), it was necessary to increase the HBr loading to 300 mol% at 85 ºC to accomplish consumption of the starting material but the imidazole product was not obtained under these conditions. Saturated ketones (**40** and **41**) were consumed under standard oxidation conditions without formation of the imidazole product (Scheme 1d). Interestingly, when 4-aminoacetophenone (**42**) was reacted with 110 mol% of HBr, the brominated side product **43** was obtained (Scheme 1e).

Considering the aldehyde scope, benzaldehydes bearing electron-withdrawing groups (**17**, **18**, **20**, **21**, **23**, **24**, **27**), such as halides and nitro groups, performed better than those bearing electron donating groups (**19**, **22**) with the exception of the phenolic derivative **16** which was isolated in 85% yield. This behavior might be due to the electron distribution in the aromatic ring of the substituted benzaldehyde which is more reactive when electron withdrawing groups are present. Interestingly, saturated cyclic aldehydes such as cyclopropyl (**31**) and cyclohexyl (**28**) carboxyaldehydes were good substrates for this transformation (70% and 83% yield, respectively), although *n*-butyraldehyde derivative **30** was isolated in only 36%. Overall, the imidazoles **16-31** from the aldehyde scope were isolated in yields ranging from 23-85% from the corresponding aldehydes (Scheme 1b). The disubstituted imidazole **32** was obtained in 67% yield after optimization of the reaction conditions for this specific substrate (See Supp. Info. Table S2). It was also possible to employ the commercially available Boc-protected aldehyde **35** under a slightly modified conditions using NH_4OH as a basic ammonia source to neutralize the HBr in order to avoid unwanted deprotection. The disubstituted imidazole **36** was isolated in 85% yield in 0.3 mmol scale and the reaction proved to be scalable in a 3.0 mmol scale, affording **36** in 82% yield. (Scheme 1c). This one-pot approach for di-substituted imidazoles has the following advantages when compared to stepwise procedure: 1) avoids glyoxal isolation which can be troublesome[23]; 2) starts from ubiquitous and/or easily accessible starting materials; 3) employs aqueous HBr as the catalyst and DMSO as oxidant, and 4) is amenable to scale-up. On the other hand, the 4(5)-position of the imidazole ring is restricted to aryl substitutents and is not compatible with acid sensitive substrates, such as indoles. (Scheme 1d).

Scheme 1. Scope of the oxidation-condensation approach to 2,4(5)-disubstituted imidazoles



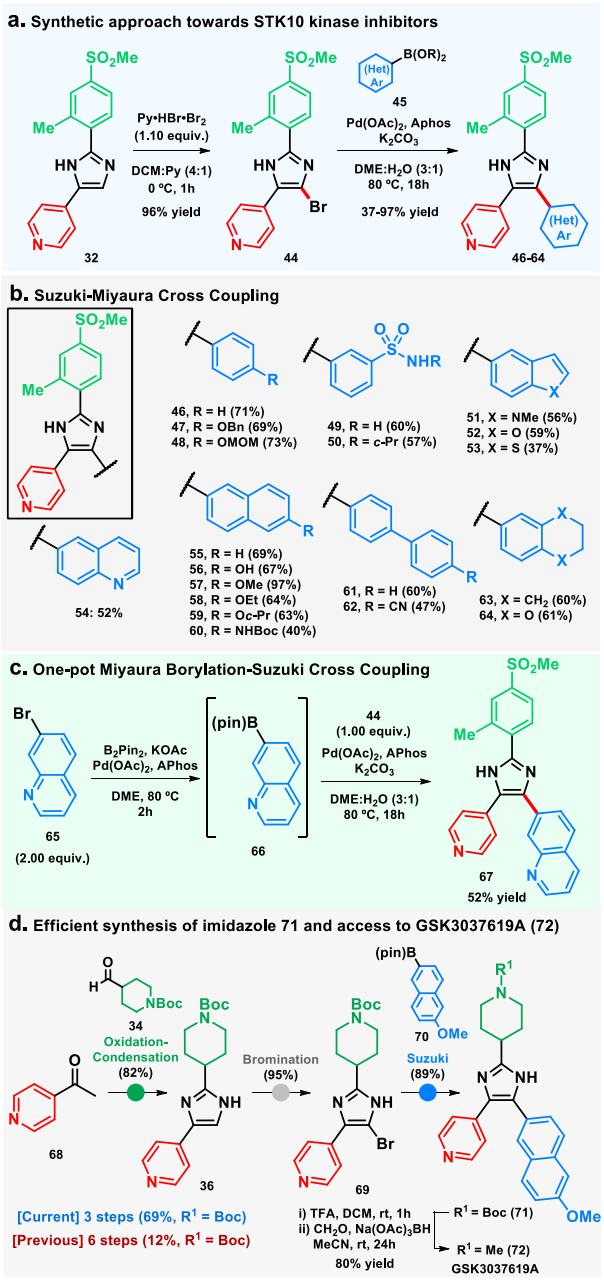
Reaction scale: 0.30 mmol. Reactions performed employing the ketone (1.25 equiv.), aldehyde (1.00 equiv.), NH_4OAc (5.00 equiv.), DMSO (0.75 mL), MeOH (2.75 mL). Yields described corresponds to isolated yields after column cromatography. [a]Ketone (1.25 equiv.), 48% HBr aq. (10 mol%), DMSO, 85 °C, 18h then aldehyde (1.00 equiv.), NH_4OAc (5.00 equiv.), MeOH, rt, 24h. [b]Ketone (1.25 equiv.), 48% HBr aq. (300 mol%), DMSO, 85 °C, 8h then aldehyde (1.00 equiv.), NH_4OAc (5.00 equiv.), MeOH, rt, 24h. [c]Ketone (1.75 equiv.), 48% HBr aq. (300 mol%), DMSO, 85 °C, 18h then aldehyde (1.00 equiv.), NH_4OAc (10.00 equiv.), MeOH, rt, 24h.

To show further applicability of the method, disubstituted imidazole **32** was functionalized at C-5 position of the imidazole ring to afford a small library of pyridyl-imidazoles inhibitors for testing against STK10 and SLK kinases[15]. This was accomplished by bromination of the 2,4-disubstituted imidazole[24] **32**, followed by Suzuki-Miyaura cross coupling[25] with boronic acids or esters (Scheme 2a). In this case, nineteen 2,4,5-trisubstituted imidazoles **46-64** were obtained in yields ranging from 37-97% from the common intermediate **44** (Scheme 2b). Interestingly, it was possible to perform a one-pot Miyaura borylation and Suzuki cross-coupling starting from bromide **65** to access trisubstituted imidazole **67** in 52% yield (Scheme 2c). Moreover, the

trisubstituted imidazole **71**, which was synthetized by Yudin in six steps (12% overall yield)[11], could be accessed in three steps (69% overall yield) from 4-acetylpyridine (**68**) employing the same strategy as for imidazoles **46-64** (Scheme 2d). From this advanced intermediate **71**, the known inhibitor GSK3037619A (**72**) could be synthesized in a one-pot procedure in 70% yield (Scheme 2d).

Compounds **57** (R = OMe) and **59** (R = O*c*-Pr) were subjected to binding displacement assays[11] against STK10 and SLK kinases and displayed K_i values of 146 nM and 700 nM, respectively, against STK10, and 180 nM and 230 nM, respectively, for SLK. The weaker binding of the cyclopropyl derivative to STK10 might be explained by a more significant space restriction in the hydrophobic pocket of STK10 to bulkier substituents at the 6-position compared to SLK.

Scheme 2. Synthesis of 2,4,5-trisubstituted imidazole STK10 kinase inhibitors



In conclusion, we developed an improved one-pot procedure for the synthesis of 2,4(5)-disubstituted *NH*-imidazoles employing widely available starting materials such as methyl ketones and aldehydes and demonstrated the utility of the methodology by using it as a key step in a short, modular and divergent synthetic route to 2,4,5-trisubstituted pyridyl-imidazole inhibitors of the STK10 kinase and for the synthesis of the GSK3037619A in 4 steps (48% overall yield). This approach enabled rapid exploration of the SAR at the C-5 position of the imidazole ring and permits regioselective variation at the C-2 and C-4 positions for future exploration.

1. Experimental Section

General Information

Unless stated otherwise, synthesis of 2,4-disubstituted imidazoles was performed using undistilled solvent, without any precaution to exclude air and moisture, in 5 mL vials and was stirred with Teflon-coated magnetic bars (1 cm x 0.5 cm). Suzuki couplings for preparation of 2,4,5-trisubstituted imidazoles were performed under nitrogen atmosphere in 100 mm x 13 mm (9 mL) culture tubes and were stirred with Teflon-coated magnetic bars (1 cm x 0.5 cm). Dry dimethoxyethane (DME, 99.5%) and dry dimethylformamide (DMF, 99.5%) were purchased from Sigma-Aldrich and stored under 3Å molecular sieves and nitrogen-purged before use. Dichloromethane (DCM) and triethylamine (Et_3N) were pretreated with calcium hydride and distilled before use. Pyridine was distilled from calcium hydride and stored over 4Å molecular sieves. Tetrahydrofuran was dried over 4Å molecular sieves and distilled from sodium metal and benzophenone before use. All other solvents and commercial reagents were used as supplied without further purification unless stated otherwise. All reactions involving heating were carried out using aluminum blocks and a contact thermometer. Reactions were monitored by thin layer chromatography (silica gel 60 F254 in aluminum foil, Merck) and visualization was achieved under UV light (254 nm) followed by staining in potassium permanganate ($KMnO_4$), Dragendorff stain (Dragendorff), dinitrophenylhydrazine stain (DNFH), *p*-Anisaldehyde stain (*p*-ASD*)* or Curcumin stain and heating. Silica gel 60 F254 (200-400 Mesh, Merck) was used for purifications by standard flash column chromatography. NMR spectra were recorded on a Bruker Avance DPX 250MHz (250 MHz ^{1}H, 63 MHz ^{13}C), Bruker Avance III 400 (400 MHz ^{1}H, 101 MHz ^{13}C), Bruker Avance III 500 (500 MHz ^{1}H, 126 MHz ^{13}C) or Bruker Avance III 600 (600 MHz ^{1}H, 151 MHz ^{13}C). The chemical shifts are expressed in parts per million (ppm) relative to the residual solvent signal as an internal reference ([1] $CDCl_3$: ^{1}H RMN = 7.26, ^{13}C RMN = 77.16; [2] DMSO-d_6: ^{1}H RMN = 2.50, ^{13}C RMN = 39.52; [3] Acetone-d_6: ^{1}H RMN = 2.05, ^{13}C RMN = 206.26; [4] Methanol-d_4: ^{1}H RMN = 3.31, ^{13}C RMN = 49.00.). Multiplicities are reported with the following symbols: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and multiples thereof. High resolution mass spectra (ESI) were acquired on a Xevo Q-Tof Mass Spectrometer (Waters, Manchester, UK) equipped with a nanoESI type ionization source. IR spectra were recorded using a Thermo Scientific Nicolet IS5 spectrometer, using Thermo Scientific ID3 ATR. Melting points were

recorded on a MP50 Metler-Toledo melting point apparatus and are uncorrected. STK10 and SLK binding displacement assays were performed as previously described[11].

Optimization of the reaction conditions. *5-phenyl-2-(p-tolyl)-1H-imidazole (**5**)*. A 6 mL vial was charged with acetophenone **2** (46.0 mg, 0.375 mmol, 1.25 equiv.), DMSO (0.75 mL, 0.5 M), concentrated aqueous HBr (48% w/w, 8.9 M) (4.24 μL, 0.03 mmol, 10 mol%), deionized water (71 μL) and a magnetic stirrer bar under air. The reaction mixture was stirred in a pre-heated aluminum block at 85 ºC and was followed by TLC analysis (30% EtOAc/Hex, *p*-ASD). After consumption of starting material, the reaction mixture was cooled to room temperature and diluted with MeOH (1.25 mL, 0.19 M, final concentration relative to acetophenone 2**,** 2:8 mixture of DMSO:MeOH). This stock DMSO:MeOH solution was added dropwise over 30 minutes via syringe to a 6 mL vial containing *p*-tolualdehyde **4** (37.0 mg, 0.30 mmol, 1.00 equiv.), NH_4OAc (116 mg, 1.50 mmol, 5.00 equiv.) and MeOH (1.5 mL, 0.2 M in relation to **4**). The reaction mixture was stirred at room temperature for 18h and then poured directly into a separatory funnel containing a mixture of satd. $NaHCO_3$ and satd. $Na_2S_2O_3$ (1:1, 1x 20 mL) and EtOAc (10 mL). The phases were separated and the aqueous phase was extracted with EtOAc (5x 5 mL). The organic phases were combined, washed with satd. NaCl solution (1x 5 mL), dried over Na_2SO_4, filtered and concentrated in the rotaevaporator. The residue was diluted with EtOAc (5 mL) and a 1 mL aliquot was taken and concentrated in vacuo. To this, 1,3,5-trimethoxybenzene (10.2 mg, 0.06 mmol) and acetone-d_6 (0.6 mL) was added and the sample was analyzed by ^{1}H NMR. The crude mixtures were combined and purification of the residue by silica gel chromatography, eluting with EtOAc in hexanes (19 cm x 20 mm, gradient elution, 0% → 30%, 5% increases, 50 mL runs, 5-10 mL fractions) yielded **5** as a white solid (69% yield, 48.0 mg, 0.21 mmol). **R_f =** 0.30 (30% EtOAc/Hex, UV, Dragendorff stain); **^{1}H NMR (500 MHz, DMSO-*d*6) δ** 12.55 (s, 1H), 7.89 (d, *J* = 7.9 Hz, 2H), 7.86 (d, *J* = 7.6 Hz, 2H), 7.72 (s, 1H), 7.36 (t, *J* = 7.5 Hz, 2H), 7.28 (d, *J* = 7.9 Hz, 2H), 7.20 (t, *J* = 7.2 Hz, 1H), 2.34 (s, 3H).;**^{13}C{^{1}H} NMR (126 MHz, DMSO-*d*6) δ** 146.0, 140.9, 137.5, 134.8, 129.3, 128.4, 126.1, 125.2, 124.9, 124.4, 114.0, 20.9. Spectroscopic data are in accordance with the literature[26]

Ketone Scope: General Procedure A. A 6 mL vial was charged with the corresponding acetophenone (0.375 mmol, 1.25 equiv.), DMSO (0.75 mL, 0.5 M), concentrated aqueous HBr (48% w/w, 8.9 M) (4.24 μL, 0.03 mmol, 10 mol%), deionized water (71 μL) and a magnetic stirrer bar under air. The reaction mixture was stirred in a

pre-heated aluminum block at 85 ºC and was followed by TLC analysis (EtOAc/Hex, *p*-ASD). After consumption of starting material, the reaction mixture was cooled to room temperature and diluted with MeOH (1.25 mL, 0.19 M, final concentration relative to the corresponding acetophenone**,** 4:6 mixture of DMSO:MeOH). This stock DMSO:MeOH solution was added dropwise over 30 minutes via syringe to a 6 mL vial containing benzaldehyde (32.0 mg, 0.30 mmol, 1.00 equiv.), NH_4OAc (116 mg, 1.50 mmol, 5.00 equiv.) and MeOH (1.5 mL, 0.2 M in relation to benzaldehyde). The reaction mixture was stirred at room temperature for 18h and then poured directly into a separatory funnel containing a mixture of satd. $NaHCO_3$ and satd. $Na_2S_2O_3$ (1:1, 1x 20 mL) and EtOAc (10 mL). The phases were separated, and the aqueous phase was extracted with EtOAc (5x 5 mL). The organic phases were combined, washed with satd. NaCl solution (1x 5 mL), dried over Na_2SO_4, filtered and concentrated in the rotaevaporator. The residue was purified by silica gel column chromatography.

Aldehyde Scope: General Procedure B. A 6 mL vial was charged with acetophenone (46.0 mg, 0.375 mmol, 1.25 equiv.), DMSO (0.75 mL, 0.5 M), concentrated aqueous HBr (48% w/w, 8.9 M) (4.24 μL, 0.0375 mmol, 10 mol%), deionized water (71 μL) and a magnetic stirrer bar under air. The reaction mixture was stirred in a pre-heated aluminum block at 85 ºC and was followed by TLC analysis (EtOAc/Hex, *p*-ASD). After consumption of starting material, the reaction mixture was cooled to room temperature and diluted with MeOH (1.25 mL, 0.19 M, final concentration relative to the corresponding acetophenone**,** 4:6 mixture of DMSO:MeOH). This stock DMSO:MeOH solution was added dropwise over 30 minutes via syringe to a 6 mL vial containing the corresponding aldehyde (0.30 mmol, 1.00 equiv.), NH_4OAc (116 mg, 1.50 mmol, 5.00 equiv.) and MeOH (1.5 mL, 0.2 M in relation to the aldehyde). The reaction mixture was stirred at room temperature for 18h and then poured directly into a separatory funnel containing a mixture of satd. $NaHCO_3$ and satd. $Na_2S_2O_3$ (1:1, 1x 20 mL) and EtOAc (10 mL). The phases were separated, and the aqueous phase was extracted with EtOAc (5x 5 mL). The organic phases were combined, washed with satd. NaCl solution (1x 5 mL), dried over Na_2SO_4, filtered and concentrated in the rotaevaporator. The residue was purified by silica gel column chromatography.

*4-(4-Methoxyphenyl)-2-phenyl-1H-imidazole (**6**)*. The title compound was prepared according to general procedure A, using 4'-methoxyacetophenone (58.0 mg, 0.375 mmol, 1.25 equiv.), benzaldehyde (32.0 mg, 0.30 mmol, 1.00 equiv.). Purification

by silica gel chromatography, eluting with EtOAc in hexanes (19 cm x 20 mm, gradient elution, 0% → 30%, 5% increases, 50 mL runs, 5-10 mL fractions) yielded **6** as a pale yellow solid (59% yield, 44.0 mg, 0.18 mmol). **R_f =** 0.12 (30% EtOAc/Hex, Dragendorff stain); **^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ** 12.55 (br. s, 1H), 7.99 (d, *J* = 7.4 Hz, 2H), 7.78 (d, *J* = 8.7 Hz, 2H), 7.63, (d, *J* = 1.4 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 2H), 7.35 (t, *J* = 7.3 Hz, 1H), 6.95 (d, *J* = 8.7 Hz, 2H), 3.77 (s, 3H); **^{13}C{^{1}H} NMR (126 MHz, DMSO-*d*$_6$) δ** 158.3, 157.9, 146.3, 145.5, 141.0, 130.7, 128.7, 128.6, 128.0, 127.5, 125.9, 125.6, 125.5, 125.0, 124.8, 114.3, 113.9, 113.0, 55.2, 55.0; **ν_{max} (cm^{-1}, thin film, ATR):** 2925 (br), 1602 (s), 1517 (w), 1480 (w), 1443 (w), 1312 (s), 1213 (w), 1147 (s), 1109 (m), 1075 (w), 1075 (w), 999 (w), 958 (m), 877 (w), 768 (s), 762 (s), 744 (s), 733 (s), 700 (m); **HRMS (ESI+/TOF) m/z:** $[M+H]^+$ Calcd for $C_{16}H_{15}N_2O$ 251.1184; Found 251.1173; **mp:** 175.0 – 177.8 °C (EtOAc) (lit. 170 – 174 °C). Spectroscopic data are in accordance with the literature[27].

*3-(2-Phenyl-1H-imidazol-5-yl)-1-tosyl-1H-indole (**7**).* The title compound was prepared according to general procedure A, using 1-(1-tosyl-1H-indol-3-yl)ethanone (**S2**) (58.0 mg, 0.375 mmol, 1.25 equiv.), benzaldehyde (32.0 mg, 0.30 mmol, 1.00 equiv.). Purification by silica gel chromatography, eluting with EtOAc in hexanes (17 cm x 20 mm, gradient elution, 0% → 60%, 5% increases, 45 mL runs, 15 mL fractions) yielded **7** as a white solid (35% yield, 44.0 mg, 0.11 mmol). **R_f =** 0.17 (30% EtOAc/Hex, UV, Dragendorff stain). **^{1}H NMR (600 MHz, DMSO-*d*$_6$/D$_2$O/TFA) δ** 8.54 (s, 1H), 8.30 (s, 1H), 8.10 – 8.07 (m, 2H), 8.01 (d, *J* = 8.3 Hz, 1H), 7.99 (d, *J* = 8.0 Hz, 1H), 7.91 (d, *J* = 8.5 Hz, 2H), 7.71 – 7.68 (m, 3H), 7.49 (t, *J* = 7.8 Hz, 1H), 7.44 – 7.39 (m, 3H), 2.30 (s, 3H). **^{13}C{^{1}H} NMR (151 MHz, DMSO-*d*$_6$/D$_2$O/TFA) δ** 146.6, 144.5, 134.5, 133.8, 132.8, 130.8, 129.9, 127.5, 127.2, 127.0, 126.4, 126.3, 125.6, 124.8, 123.1, 121.0, 117.3, 113.8, 109.8, 21.3. **ν_{max} (cm^{-1}, thin film, ATR):** 2847 (br), 1594 (w), 1460 (w), 1445 (m), 1396 (w), 1376 (m), 1304 (w), 1279 (w), 1176 (s), 1133 (m), 1113 (m), 1092 (m), 1050 (w), 1024 (w), 985 (m), 966 (w), 903 (w), 817 (w), 746 (s), 709 (s), 688 (s), 660 (s). **HRMS (ESI+/TOF) m/z:** $[M+H]^+$ Calcd for $C_{24}H_{20}N_3O_2S$ 414.1276; Found 414.1264. **mp:** 249.0 °C (dec.).

*4-(2-Phenyl-1H-imidazol-5-yl)pyridine (**8**).* The title compound was prepared according to general procedure A, using 4-acetylpyridine (**68**) (47.0 mg, 0.375 mmol, 1.25 equiv.), benzaldehyde (32.0 mg, 0.30 mmol, 1.00 equiv.). Purification by silica gel chromatography, eluting with MeOH in DCM (19 cm x 20 mm, gradient elution, 0% →

6%, 0.5% increases, 30 mL runs, 7 mL fractions) yielded **8** as a yellow solid (56% yield, 37.0 mg, 0.17 mmol). **R_f =** 0.18 (EtOAc, Dragendorff stain); **^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ** 12.90 (br s, 1H), 8.53 (d, *J* = 5.0 Hz, 2H), 8.10 – 7.98 (m, 3H), 7.80 (d, *J* = 6.0 Hz, 2H), 7.49 (t, *J* = 7.4 Hz, 2H), 7.39 (t, *J* = 7.4 Hz, 2H); **^{13}C{^{1}H} NMR (125 MHz, DMSO-*d*$_6$) δ** 150.3, 147.2, 142.1, 139.1, 130.7, 129.3, 129.0, 125.6, 119.3, 117.9; **ν_{max} (cm^{-1}, thin film, ATR):** 2923, 1601, 1571, 1493, 1458, 1424, 1159, 1093, 999, 950, 821, 838, 780, 774, 712, 705, 694, 685, 677; **HRMS (ESI+/TOF) m/z:** $[M+H]^+$ Calcd for $C_{14}H_{12}N_3$ 222.1031; Found 222.1037; **mp:** 209.5 – 210.6 °C (lit. 212 – 214 °C). Spectroscopic data are in accordance with the literature[10].

*4-(Furan-2-yl)-2-phenyl-1H-imidazole (**9**).* The title compound was prepared according to general procedure A, using 4-acetylfuran (41.0 mg, 0.375 mmol, 1.25 equiv.), benzaldehyde (32.0 mg, 0.30 mmol, 1.00 equiv.). Purification by silica gel chromatography, eluting with EtOAc in hexanes (18 cm x 15 mm, gradient elution, 0% → 35%, 5% increases, 30 mL runs, 7 mL fractions) yielded a yellow oil which was triturated with 5% DCM/hexanes to yield **9** as a white solid (30% yield, 19.0 mg, 0.09 mmol). **R_f =** 0.33 (30% EtOAc/Hex, Dragendorff stain); **^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ** 12.71 (br s, 1H), 7.97 (d, *J* = 7.3, 2H), 7.62 (s, 1H), 7.52 (s, 1H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.37 (t, *J* = 7.4 Hz, 1H) 6.59 (s, 1H), 6.53 (s, 1H); **^{13}C{1H} NMR (126 MHz, DMSO-*d*$_6$) δ** 150.3, 146.0, 141.1, 133.9, 130.3, 128.7, 128.3, 125.0, 113.9, 111.4, 103.7; **ν_{max} (cm^{-1}, thin film, ATR):** 3130 (w), 2739 (w, br), 1560 (w), 1494 (w), 1460 (w), 1407 (w), 1297 (w), 1212 (w), 1160 (m), 1143 (m), 1092 (w), 1068 (w), 1011 (m), 969 (m), 889 (m), 786 (s), 741 (s), 719 (s), 695 (s), 681 (s); **HRMS (ESI+/TOF) m/z:** $[M+H]^+$ Calcd for $C_{13}H_{11}N_2O$ 211.0871; Found 211.0878.; **mp:** 145.4 – 148.7 °C (EtOAc) (lit. 154 – 156 °C (EtOH)).

*5-(3-Nitrophenyl)-2-phenyl-1H-imidazole (**10**).* The title compound was prepared according to general procedure A, using 3'-nitroacetophenone (63.0 mg, 0.375 mmol, 1.25 equiv.), benzaldehyde (32.0 mg, 0.30 mmol, 1.00 equiv.). Purification by silica gel chromatography, eluting with EtOAc in hexanes (18 cm x 15 mm, gradient elution, 0% → 35%, 5% increases, 30 mL runs, 7 mL fractions) yielded **10** as a bright yellow solid (69% yield, 55.0 mg, 0.21 mmol). **R_f =** 0.17 (30% EtOAc/Hex, Dragendorff stain); **^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ** 12.87 (br s, 1H), 8.68 (s, 1H), 8.30 (d, *J* = 7.7 Hz, 1H), 8.10 – 8.00 (m, 4H) 7.67 (t, *J* = 8.0 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 2H) 7.40 (t, *J* = 7.2 Hz, 1H); **^{13}C{^{1}H} NMR (126 MHz, DMSO-*d*$_6$) δ** 148.4, 146.5, 138.9, 136.5, 130.5, 130.2,

130.0, 128.8, 128.4, 125.1, 120.7, 118.4, 116.3; **ν_{max} (cm^{-1}, thin film, ATR):** 3383 (m), 1561 (w), 1541 (w), 1516 (s), 1290 (w), 1118 (m), 1103 (w), 893 (m), 872 (w), 821 (m), 782 (s), 745 (s), 737 (s), 718 (s), 695 (s), 687 (s); **HRMS (ESI+/TOF) m/z:** $[M+H]^+$ Calcd for $C_{15}H_{12}N_3O_2$ 266.0930 ; Found 266.0933. **mp**: 183.7 – 185.3 °C (EtOAc) (lit. 181.1 – 183.9 °C). Spectroscopic data are in accordance with the literature[28]

*5-(4-Nitrophenyl)-2-phenyl-1H-imidazole (**11**).* The title compound was prepared according to general procedure A, using 4'-nitroacetophenone (63.0 mg, 0.375 mmol, 1.25 equiv.), benzaldehyde (32.0 mg, 0.30 mmol, 1.00 equiv.). Purification by silica gel chromatography, eluting with EtOAc in hexanes (18 cm x 15 mm, gradient elution, 0% → 35%, 5% increases, 30 mL runs, 7 mL fractions) yielded **11** as a bright yellow solid (64% yield, 51.0 mg, 0.19 mmol). **R_f =** 0.20 (30% EtOAc/Hex, Dragendorff stain); **^{1}H NMR (500 MHz, DMSO-d_6) δ** 12.97 (br s, 1H), 8.25 (d, *J* = 8.8 Hz, 2H), 8.14 – 8.10 (m, 3H), 8.30 (d, *J* = 7.8 Hz, 2H), 7.49 (t, *J* = 7.6 Hz, 2H), 7.40 (t, *J* = 7.4 Hz, 2H); **^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ** 147.0, 145.3, 141.4, 139.1, 130.1, 128.8, 125.1, 124.8, 124.1, 118.0; **ν_{max} (cm^{-1}, ATR):** 3352, 2359, 2344, 1598, 1506, 1489, 1458, 1333, 1178, 1131, 1109, 945, 858, 791, 780, 753, 717, 696; **HRMS (ESI+/TOF) m/z:** $[M+H]^+$ Calcd for $C_{15}H_{12}N_3O_2$ 266.0930; Found 266.0929; **mp:** 187.2 – 188.7 °C (EtOAc) (lit. 190 – 191 °C)– turned brown upon heating. Spectroscopic data are in accordance with the literature[29].

*4-(2-Phenyl-1H-imidazol-5-yl)benzonitrile (**12**).* The title compound was prepared according to general procedure A, using 4-acetylbenzonitrile (55.0 mg, 0.375 mmol, 1.25 equiv.), benzaldehyde (32.0 mg, 0.30 mmol, 1.00 equiv.). Purification by silica gel chromatography, eluting with EtOAc in hexanes (18 cm x 15 mm, gradient elution, 0% → 60%, 5% increases, 12x 30 mL runs, then 10% increases, 2x 30 mL runs, 10 mL fractions) yielded **12** as a yellow solid (68% yield, 50.0 mg, 0.20 mmol). **R_f =** 0.18 (30% EtOAc/Hex, Dragendorff stain); **^{1}H NMR (500 MHz, DMSO-d_6) δ** 12.88 (br. s, 1H), 8.10 – 7.97 (m, *5*H), 7.82 (d, *J* = 8.2 Hz, 2H), 7.49 (t, *J* = 7.7 Hz, 2H), 7.39 (t, *J* = 7.5 Hz, 1H); **^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ** 146.6, 139.4, 139.2, 132.5, 130.2, 128.8, 125.0, 124.8, 119.3, 117.1, 108.0; **ν_{max} (cm^{-1}, thin film, ATR):** 3294 (m) , 2923 (w) , 2851 (w), 2539 (w), 2226 (m), 1604 (m), 1539 (w), 1491 (w), 1458 (w), 1416 (w), 1133 (m), 945 (w), 849 (m), 728 (s), 699 (s); **HRMS (ESI+/TOF) m/z:** $[M+H]^+$ Calcd for $C_{16}H_{12}N_3$ 246.1031; Found 246.1032. **mp** 209.0 – 211.8 °C (EtOAc)

*5-(Naphthalen-2-yl)-2-phenyl-1H-imidazole (**13**).* The title compound was

prepared according to general procedure A, using 2'-acetonaphtone (64.0 mg, 0.375 mmol, 1.25 equiv.), benzaldehyde (32.0 mg, 0.30 mmol, 1.00 equiv.). Purification by silica gel chromatography, eluting with MeOH in DCM (18 cm x 15 mm, gradient elution, 0% → 5%, 0.5% increases, 30 mL runs, 7 mL fractions) yielded **13** as a pale yellow solid (67% yield, 54.0 mg, 0.20 mmol). **R_f =** 0.33 (30% EtOAc/Hex, Dragendorff stain); **^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ** 12.73 (br. s, 1H), 8.38 (s, 1H), 8.10 – 8.00 (m, 3H), 7.97 – 7.85 (m, 4H), 7.54 – 7.48 (m, 3H), 7.45 (t, *J* = 7.5 Hz, 1H), 7.38 (t, *J* = 7.4 Hz, 1H); **^{13}C{^{1}H} NMR (126 MHz, DMSO-*d*$_6$) δ** 146.1, 141.0, 133.4, 132.2, 131.9, 130.5, 128.7, 128.2, 127.9, 129.7, 127.6, 126.3, 125.2, 125.0, 123.7, 121.8, 115.0; **ν_{max} (cm^{-1}, thin film, ATR):** 2850, 1630, 1602, 1572, 1500, 1484, 1464, 1454, 1401, 1263, 1138, 1126, 1070, 891, 859, 820, 792, 784, 748, 693; **HRMS (ESI+/TOF) m/z:** $[M+H]^+$ Calcd for $C_{19}H_{15}N_2$ 271.1235; Found 271.1231. **mp** 223.9 – 225.0 °C (MeOH/DCM).

*5-(4-Methylphenyl)-2-phenyl-1H-imidazole (**14**).* The title compound was prepared according to general procedure A, using 4'-methylacetophenone (53.0 mg, 0.375 mmol, 1.25 equiv.), benzaldehyde (32.0 mg, 0.30 mmol, 1.00 equiv.). Purification by silica gel chromatography, eluting with EtOAc in hexanes (18 cm x 15 mm, gradient elution, 0% → 25%, 5% increases, 30 mL runs, 7 mL fractions) yielded **14** as a pale yellow solid (65% yield, 46.0 mg, 0.20 mmol). **R_f =** 0.37 (30% EtOAc/Hex, Dragendorff stain); **^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ** 12.60 (br s, 1H), 8.00 (d, *J* = 7.1 Hz, 2H), 7.80 – 7.64 (m, 3H), 7.46 (t, *J* = 7.8 Hz, 2H), 7.35 (t, *J* = 7.3 Hz, 1H), 7.18 (d, *J* = 7.0 Hz, 2H), 2.31 (s, 3H); **^{13}C{^{1}H} NMR (126 MHz, DMSO-*d*$_6$) δ** 145.6, 141.2, 135.2, 131.9, 130.7, 129.4, 129.0, 128.7, 128.0, 124.9, 124.4, 113.7, 20.8; **ν_{max} (cm^{-1}, thin film, ATR):** 2985, 1606, 1576, 1498, 1458, 1399, 1137, 1084, 962, 823, 803, 786, 721, 710, 695; **HRMS (ESI+/TOF) m/z:** $[M+H]^+$ Calcd for $C_{16}H_{15}N_2$ 235.1235; Found 235.1222; **mp:** 172.8 – 174.0 °C (EtOAc) (lit 179 °C [benzene]) – turned violet upon heating. Spectroscopic data are in accordance with the literature[30,31]

*5-(4-Bromophenyl)-2-phenyl-1H-imidazole (**15**).* The title compound was prepared according to general procedure A, using 4'-bromoacetophenone (75.0 mg, 0.375 mmol, 1.25 equiv.), benzaldehyde (32.0 mg, 0.30 mmol, 1.00 equiv.). Purification by silica gel chromatography, eluting with EtOAc in hexanes (18 cm x 15 mm, gradient elution, 0% → 25%, 5% increases, 30 mL runs, 7 mL fractions) yielded **15** as a pale yellow solid (72% yield, 65.0 mg, 0.22 mmol). **R_f =** 0.21 (30% EtOAc/Hex, Dragendorff stain); **^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ** 12.72 (br s, 1H), 7.99 (d, *J* = 7.5 Hz, 2H), 7.86 – 7.80 (m,

3H), 7.55 (d, *J* = 8.3 Hz, 2 H), 7.47 (t, *J* = 7.6 Hz, 2H), 7.37 (t, *J* = 7.4 Hz, 1H); **^{13}C{^{1}H} NMR (125 MHz, DMSO-*d*$_6$) δ** 146.1, 139.9, 134.0, 131.4, 130.4, 128.8, 128.3, 126.4, 125.0, 118.9, 115.0; **ν_{max} (cm^{-1}, thin film, ATR):** 2925 (br), 2360 (w), 1602 (s), 1517 (w), 1480 (w), 1443 (w), 1312 (s), 1213 (w), 1147 (s), 1109 (m), 1075 (w), 1075 (w), 999 (w), 958 (m), 877 (w), 768 (s), 762 (s), 744 (s), 733 (s), 700 (m); **HRMS (ESI+/TOF) m/z:** $[M+H]^+$ Calcd for $C_{15}H_{12}N_2Br$ 299.0184, 301.0164; Found 299.0180, 301.0167; **mp:** 169.2 – 172.5 (EtOAc) (lit. 169 - 171 °C) – turned brown upon heating. Spectroscopic data are in accordance with the literature[28,30].

*3-(5-Phenyl-1H-imidazol-2-yl)phenol (**16**).* The title compound was prepared according to general procedure B, using acetophenone (46.0 mg, 0.375 mmol, 1.25 equiv.), 3-hydroxybenzaldehyde (37.0 mg, 0.30 mmol, 1.00 equiv.). Purification by silica gel chromatography, eluting with EtOAc in hexanes (19 cm x 20 mm, gradient elution, 0% → 30%, 5% increases, 50 mL runs, 5-10 mL fractions) yielded **16** as a white yellow solid (85% yield, 60.0 mg, 0.25 mmol). **R$_f$ =** 0.30 (30% EtOAc/Hex, UV, Dragendorff stain); **^{1}H NMR (400 MHz, MeOD-*d*$_4$) δ** 7.76 (dd, *J* = 1.1, 8.3 Hz, 2H), 7.44 (s, 1H), 7,41 – 7.36 (m, 4H), 7.30 – 7.23 (m, 2H), 6.83 (ddd, *J* = 1.1, 2.4, 8.0 Hz, 1H); **^{13}C{^{1}H} NMR (126 MHz, MeOD-*d*$_4$) δ** 159.1, 149.0, 132.7, 131.0, 129.7, 128.0, 126.1, 117.9, 116.9, 113.7 (**Note:** Due to slow relaxation, some ^{13}C{^{1}H} NMR signals were difficult to identify[28]. Concerning this compound, three signals are missing); **HRMS (ESI+/TOF) m/z:** $[M+H]^+$ Calcd for $C_{15}H_{13}N_2O$ 237.1028; Found 237.1011.

*2-(3-Chlorophenyl)-5-phenyl-1H-imidazole (**17**).* The title compound was prepared according to general procedure B, using acetophenone (46.0 mg, 0.375 mmol, 1.25 equiv.) and 3-chlorobenzaldehyde (42.0 mg, 0.30 mmol, 1.00 equiv.). Purification by silica gel chromatography, eluting with EtOAc in hexanes (19 cm x 20 mm, gradient elution, 0% → 30%, 5% increases, 50 mL runs, 5-10 mL fractions) yielded **17** as a pale yellow solid (69% yield, 53.0 mg, 0.21 mmol). **R$_f$ =** 0.40 (30% EtOAc/Hex, UV, Dragendorff stain); **^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ** 12.80 (s, 1H), 8.06 (s, 1H), 7.97 (d, *J* = 7.5 Hz, 1H), 7. 91 – 7.76 (m, 3H), 7.50 (t, *J* = 7.9 Hz, 1H), 7.42 (ddd, *J* = 8.0, 2.1, 0.9 Hz, 1H), 7.38 (t, *J* = 7.3 Hz, 2H), 7.22 (t, *J* = 6.9 Hz, 1H); **^{13}C{^{1}H} NMR (126 MHz, DMSO-*d*$_6$) δ** 144.4, 141.4, 133.6, 132.5, 130.7, 128.9, 128.5, 127.8, 127.0, 126.4, 124.4, 123.4, 114.9; **HRMS (ESI+/TOF) m/z:** $[M+H]^+$ Calcd for $C_{15}H_{12}ClN_2$ 255.0689, 257.0663; Found 255.0693, 257.0670. Spectroscopic data are in accordance with the literature[23].

*2-(4-Nitrophenyl)-5-phenyl-1H-imidazole (**18**).* The title compound was prepared according to general procedure B, using acetophenone (46.0 mg, 0.375 mmol, 1.25 equiv.) and 4-nitrobenzaldehyde (46.0 mg, 0.30 mmol, 1.00 equiv.). Purification by silica gel chromatography, eluting with EtOAc in hexanes (19 cm x 20 mm, gradient elution, 0% → 30%, 5% increases, 50 mL runs, 5-10 mL fractions) yielded **18** as an orange solid (67% yield, 53.0 mg, 0.21 mmol). **R_f =** 0.20 (30% EtOAc/Hex, Dragendorff stain); **^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ** 13.13 (s, 1H), 8.34 (d, *J* = 8.9 Hz, 2H), 8.23 (d, *J* = 8.8 Hz, 2H), 7.93 (s, 1H), 7.89 (d, *J* = 7.6 Hz, 2H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.24 (t, *J* = 7.3 Hz, 1H); **^{13}C{^{1}H} NMR (63 MHz, DMSO-*d*$_6$) δ** 146.5, 143.8, 142.4, 136.3, 134.1, 128.5, 126.7, 125.5, 124.5, 124.3, 116.3; **HRMS (ESI+/TOF) m/z:** $[M+H]^+$ Calcd for $C_{15}H_{12}N_3O_2$ 266.0930; Found 266.0933. Spectroscopic data are in accordance with the literature[32].

*4-(4-Phenyl-1H-imidazol-2-yl)phenol (**19**).* The title compound was prepared according to general procedure B, using acetophenone (46.0 mg, 0.375 mmol, 1.25 equiv.) and 4-hydroxybenzaldehyde (37.0 mg, 0.30 mmol, 1.00 equiv.). Purification by silica gel chromatography, eluting with EtOAc in hexanes (19 cm x 20 mm, gradient elution, 0% → 30%, 5% increases, 50 mL runs, 5-10 mL fractions) yielded **19** as a yellow solid (51% yield, 36.0 mg, 0.15 mmol). **R_f =** 0.30 (30% EtOAc/Hex, Dragendorff stain); **^{1}H NMR (250 MHz, DMSO-*d*$_6$) δ** 12.34 (s, 1H), 9.68 (s, 1H), 7.90 – 7.71 (m, 4H), 7.65 (s, 1H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.18 (t, *J* = 7.2 Hz, 1H), 6.84 (d, *J* = 8.5 Hz, 2H). **^{13}C{^{1}H} NMR (63 MHz, DMSO-*d*$_6$) δ** 157.6, 146.4, 140.5, 134.9, 128.4, 126.5, 126.0, 124.3, 122.0, 115.4, 113.3 **ν_{max} (cm^{-1}, thin film, ATR):** 3221, 2926, 1773,1701, 1609, 1541, 1496, 1460, 1367, 1275, 1175, 1099, 1029, 948, 908, 837, 761, 738, 694, 661, 635. **HRMS (ESI+/TOF) m/z:** $[M+H]^+$ Calcd for $C_{15}H_{13}N_2O$ 237,1028; Found 237,1013. **mp**: 227 ºC (dec.).

*2-(3-Chlorophenyl)-5-phenyl-1H-imidazole (**20**).* The title compound was prepared according to general procedure B, using acetophenone (46.0 mg, 0.375 mmol, 1.25 equiv.) and 4-chlorobenzaldehyde (42.0 mg, 0.30 mmol, 1.00 equiv.). Purification by silica gel chromatography, eluting with EtOAc in hexanes (19 cm x 20 mm, gradient elution, 0% → 30%, 5% increases, 50 mL runs, 5-10 mL fractions) yielded **20** as a pale yellow solid (72% yield, 55.0 mg, 0.22 mmol). **R_f =** 0.40 (30% EtOAc/Hex, UV, Dragendorff stain); **^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ** 12.74 (s, 1H), 8.01 (d, *J* = 8.5 Hz, 2H), 7.86 (d, *J* = 7.4 Hz, 2H), 7.79 (d, *J* = 1.8 Hz, 1H), 7.54 (d, *J* = 8.5 Hz, 2H), 7.37 (t, *J*

= 7.7 Hz, 2H), 7.21 (t, *J* = 7.3 Hz, 1H); **^{13}C{^{1}H} NMR (126 MHz, DMSO-*d*$_6$) δ** 144.8, 141.3, 134.5, 132.6, 129.4, 128.8, 128.4, 126.5, 126.3, 124.4, 114.7; **HRMS (ESI+/TOF) m/z:** $[M+H]^+$ Calcd for $C_{15}H_{12}ClN_2$ 255.0689, 257.0663; Found 255.0694, 257.0677. Spectroscopic data are in accordance with the literature[32].

*2-(3-Nitrophenyl)-5-phenyl-1H-imidazole (**21**).* The title compound was prepared according to general procedure B, using acetophenone (46.0 mg, 0.375 mmol, 1.25 equiv.) and 3-nitrobenzaldehyde (46.0 mg, 0.30 mmol, 1.00 equiv.). Purification by silica gel chromatography, eluting with EtOAc in hexanes (19 cm x 20 mm, gradient elution, 0% → 30%, 5% increases, 50 mL runs, 5-10 mL fractions) yielded **21** as a yellow solid (67% yield, 53.0 mg, 0.21 mmol). **R$_f$ =** 0.20 (30% EtOAc/Hex, Dragendorff stain); **^{1}H NMR (250 MHz, DMSO-*d*$_6$) δ** 13.06 (s, 1H), 8.84 (s, 1H), 8.43 (d, *J* = 7.8 Hz, 1H), 8.20 (dd, *J* = 8.1, 2.1 Hz, 1H), 7.93 – 7.91 (m, 4H), 7.39 (t, *J* = 7.5 Hz, 2H), 7.24 (t, *J* = 7.0 Hz, 1H); **^{13}C{^{1}H} NMR (63 MHz, DMSO-*d*$_6$) δ** 148.4, 143.8, 141.7, 134.2, 132.1, 130.9, 130.5, 128.5, 126.5, 124.5, 122.5, 119.2, 115.4; **HRMS (ESI+/TOF) m/z:** $[M+H]^+$ Calcd for $C_{15}H_{12}N_3O_2$ 266.0930; Found 266.0950.

*2-(4-Methoxyphenyl)-5-phenyl-1H-imidazole (**22**).* The title compound was prepared according to general procedure B, using acetophenone (46.0 mg, 0.375 mmol, 1.25 equiv.) and *p*-anisaldehyde (41.0 mg, 0.30 mmol, 1.00 equiv.). Purification by silica gel chromatography, eluting with EtOAc in hexanes (19 cm x 20 mm, gradient elution, 0% → 40%, 5% increases, 50 mL runs, 5-10 mL fractions) yielded **22** as a white solid (50% yield, 38.0 mg, 0.15 mmol); **R$_f$ =** 0.30 (30% EtOAc/Hex, UV, Dragendorff stain); **^{1}H NMR (400 MHz, DMSO-*d*$_6$/D$_2$O/TFA) δ** 7.99 (s, 1H), 7.95 (d, *J* = 8.8 Hz, 2H), 7.80 (d, *J* = 7.6 Hz, 2H), 7.50 (t, *J* = 7.5 Hz, 2H), 7.43 (t, *J* = 7.2 Hz, 1H), 7.16 (d, *J* = 8.8 Hz, 2H), 3.82 (s, 3H); **^{13}C{^{1}H} NMR (101 MHz, DMSO-*d*$_6$/D$_2$O/TFA) δ** 163.0, 145.3, 133.9, 130.1, 130.0, 129.8, 127.2, 126.4, 116.3, 115.7, 115.6, 56.3; **HRMS (ESI+/TOF) m/z:** $[M+H]^+$ Calcd for $C_{16}H_{15}N_2O$ 251.1184; Found 251.1186.

*2-(2-Chlorophenyl)-5-phenyl-1H-imidazole (**23**).* The title compound was prepared according to general procedure B, using acetophenone (46.0 mg, 0.375 mmol, 1.25 equiv.) and 2-chlorobenzaldehyde (42.0 mg, 0.30 mmol, 1.00 equiv.). Purification by silica gel chromatography, eluting with EtOAc in hexanes (19 cm x 20 mm, gradient elution, 0% → 30%, 5% increases, 50 mL runs, 5-10 mL fractions) yielded **23** as a white solid (63% yield, 48.0 mg, 0.19 mmol). **R$_f$ =** 0.50 (30% EtOAc/Hex, UV, Dragendorff stain); **^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ** 12.43 (s, 1H), 7.78 (d, *J* = 2.0 Hz, 1H), 7.88 –

7.84 (m, 3H), 7.58 (dd, *J* = 1.9, 7.2 Hz, 1H), 7.48 – 7.43 (m, 2H), 7.37 (t, *J* = 7.6 Hz, 2H), 7.21 (t, *J* = 7.3 Hz, 1H); **^{13}C{^{1}H} NMR (126 MHz, DMSO-*d*$_6$) δ** 143.3, 140.8, 134.5, 131.2, 130.8, 130.2, 130.0, 129.9, 128.4, 127.3, 126.3, 124.4, 114.5; **ν_{max} (cm^{-1}, thin film, ATR):** 3059, 1708, 1607, 1567, 1482, 1453, 1111, 1086, 1049, 946, 694. **HRMS (ESI+/TOF) m/z:** $[M+H]^+$ Calcd for $C_{15}H_{12}ClN_2$ 255.0689, 257.0663; Found 255.0690, 257.0670; **mp:** 161.0 – 162.0 °C (EtOAc).

*2-(4-Fluorophenyl)-5-phenyl-1H-imidazole (**24**).* The title compound was prepared according to general procedure B, using acetophenone (46.0 mg, 0.375 mmol, 1.25 equiv.) and 4-fluorobenzaldehyde (38.0 mg, 0.30 mmol, 1.00 equiv.). Purification by silica gel chromatography, eluting with EtOAc in hexanes (19 cm x 20 mm, gradient elution, 0% → 30%, 5% increases, 50 mL runs, 5-10 mL fractions) yielded **24** as a pale yellow solid (57% yield, 41.0 mg, 0.17 mmol). **R$_f$ =** 0.30 (30% EtOAc/Hex, UV, Dragendorff stain); **^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ** 12.65 (s, 1H), 8.04 (dd, *J* = 8.6, 5.5 Hz, 2H), 7.86 (d, *J* = 7.4 Hz, 2H), 7.76 (s, 1H), 7.37 (t, *J* = 7.6 Hz, 2H), 7.32 (t, *J* = 8.8 Hz, 2H), 7.21 (t, *J* = 7.3 Hz, 1H); **^{13}C{^{1}H} NMR (126 MHz, DMSO-*d*$_6$) δ** 162.0 (d, $^{1}J_{CF}$ = 245.1 Hz), 145.1, 141.1, 134.6, 128.5, 127.30 (d, $^{4}J_{CF}$ = 2.5 Hz, 1C), 127.04 (d, $^{3}J_{CF}$ = 8.4 Hz), 126.2, 124.4, 115.74 (d, $^{2}J_{CF}$ = 22.1 Hz), 114.3; **HRMS (ESI+/TOF) m/z:** $[M+H]^+$ Calcd for $C_{15}H_{12}FN_2$ 239.0984; Found 239.0985. Spectroscopic data are in accordance with the literature[33].

*N,N-Dimethyl-4-(5-phenyl-1H-imidazol-2-yl)aniline (**25**).* The title compound was prepared according to general procedure B, using acetophenone (46.0 mg, 0.375 mmol, 1.25 equiv.) and 4-(dimethylamino)benzaldehyde (46.0 mg, 0.30 mmol, 1.00 equiv.). - Purification by silica gel chromatography, eluting with EtOAc in hexanes (19 cm x 20 mm, gradient elution, 30% → 50%, 5% increases, 50 mL runs, 5-10 mL fractions) yielded **25** as a yellow solid (23% yield, 18.0 mg, 0.07 mmol). **R$_f$ =** 0.40 (30% EtOAc/Hex, UV, Dragendorff stain); **^{1}H NMR (400 MHz, DMSO-*d*$_6$/D$_2$O/TFA) δ** 7.88 (s, 1H), 7.83 (d, *J* = 9.1 Hz, 2H), 7.77 (d, *J* = 7.1 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 2H), 7.42 (t, *J* = 7.4 Hz, 1H), 6.85 (d, *J* = 9.2 Hz, 2H), 2.98 (s, 6H); **^{13}C{^{1}H} NMR (101 MHz, DMSO-*d*$_6$/D$_2$O/TFA) δ** 153.1, 146.4, 133.3, 130.0, 129.0, 127.5, 126.3, 115.7, 112.7, 109.5, 40.4; **ν_{max} (cm^{-1}, thin film, ATR):** 2919, 2850, 1615, 1545, 1500, 1443, 1396, 1363, 1227, 1202, 1170, 945, 820, 760, 738, 695; **HRMS (ESI+/TOF) m/z:** $[M+H]^+$ Calcd for $C_{17}H_{18}N_3$ 264,1501; Found 264,1502; **mp:** 142.0 – 145.0 °C (EtOAc).

*2-(Furan-2-yl)-5-phenyl-1H-imidazole (**26**).* The title compound was prepared

according to general procedure B, using acetophenone (46.0 mg, 0.375 mmol, 1.25 equiv.) and furfural (29.0 mg, 0.30 mmol, 1.00 equiv.). Purification by silica gel chromatography, eluting with EtOAc in hexanes (19 cm x 20 mm, gradient elution, 0% → 20%, 5% increases, 50 mL runs, 5-10 mL fractions) yielded **26** as a white solid (34% yield, 22.0 mg, 0.11 mmol). **R_f =** 0.10 (30% EtOAc/Hex, UV, Dragendorff stain); **^{1}H NMR (400 MHz, DMSO-*d*$_6$/D$_2$O/TFA) δ** 8.00 (s, 1H), 7.99 (s, 1H), 7.78 (d, *J* = 7.5 Hz, 2H), 7.50 (t, *J* = 7.5 Hz, 2H), 7.46 – 7.41 (m, 2H), 6.80 (dd, *J* = 3.3, 1.5 Hz, 1H); **^{13}C{^{1}H} NMR (101 MHz, DMSO-*d*$_6$/D$_2$O/TFA) δ** 147.8, 138.8, 136.7, 134.0, 130.3, 130.1, 127.1, 126.3, 116.4, 115.5, 113.9; **HRMS (ESI+/TOF) m/z:** $[M+H]^+$ Calcd for $C_{13}H_{11}N_2O$ 211.0871; Found 211.0871. Spectroscopic data are in accordance with the literature[34]

*2-(4-Bromophenyl)-5-phenyl-1H-imidazole (**27**).* The title compound was prepared according to general procedure B, using acetophenone (46.0 mg, 0.375 mmol, 1.25 equiv.) and 4-bromobenzaldehyde (56.0 mg, 0.30 mmol, 1.00 equiv.). Purification by silica gel chromatography, eluting with EtOAc in hexanes (19 cm x 20 mm, gradient elution, 0% → 30%, 5% increases, 50 mL runs, 5-10 mL fractions) yielded **27** as a white solid (61% yield, 55.0 mg, 0.18 mmol). **R_f =** 0.20 (30% EtOAc/Hex, UV, Dragendorff stain); **^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ** 12.75 (s, 1H), 7.94 (d, *J* = 8.5 Hz, 2H), 7.86 (d, *J* = 7.2 Hz, 2H), 7.79 (s, 1H), 7.67 (d, *J* = 8.5 Hz, 2H), 7.37 (t, *J* = 7.7 Hz, 2H), 7.21 (t, *J* = 7.3 Hz, 1H); **^{13}C{^{1}H} NMR (126 MHz, DMSO-*d*$_6$) δ** 144.8, 141.3, 134.5, 131.7, 129.8, 128.5, 126.9, 126.3, 124.4, 121.2, 114.7; **ν_{max} (cm^{-1}, thin film, ATR):** 3069, 1703, 1603, 1486, 1466, 1452, 1431, 1364, 1298, 1269, 1228, 1143, 1085, 1971, 1010, 949, 911, 830, 729, 694; **HRMS (ESI+/TOF) m/z:** $[M+H]^+$ Calcd for $C_{15}H_{12}BrN_2$ 299.0184, 301.0164; Found 299.0186, 301.0171; **mp**: 196.0 – 198.0 °C (EtOAc).

*2-Cyclohexyl-5-phenyl-1H-imidazole (**28**).* The title compound was prepared according to general procedure B, using acetophenone (46.0 mg, 0.375 mmol, 1.25 equiv.) and cyclohexanecarboxaldehyde (34.0 mg, 0.30 mmol, 1.00 equiv.). Purification by silica gel chromatography, eluting with EtOAc in hexanes (19 cm x 20 mm, gradient elution, 0% → 40%, 5% increases, 50 mL runs, 5-10 mL fractions) yielded **28** as a white solid (83% yield, 56.0 mg, 0.25 mmol). **R_f =** 0.20 (30% EtOAc/Hex, UV, Dragendorff stain); **^{1}H NMR (500 MHz, CDCl$_3$) δ** 8.35 (br s, 1H), 7.66 (d, *J* = 7.3 Hz, 2H), 7.32 (t, *J* = 7.7 Hz, 2H), 7.22 – 7.17 (m, 2H), 2.74 (tt, *J* = 12.0, 3.5 Hz, 1H), 1.98 (d, *J* = 11.7 Hz, 2H), 1.75 (d, *J* = 13.2 Hz, 2H), 1.66 (d, *J* = 12.6 Hz, 1H), 1.50 (dq, *J* = 12.4, 3.1 Hz, 2H),

1.32 – 1.12 (m, 3H); **$^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ** 153.9, 137.1, 133.1, 128.7, 126.7, 124.9, 115.7, 38.1, 32.2, 26.2, 25.9; **HRMS (ESI+/TOF) m/z:** $[M+H]^+$ Calcd for $C_{15}H_{19}N_2$ 227.1548; Found 227.1558. Spectroscopic data are in accordance with the literature[33–35].

*4-(5-Phenyl-1H-imidazol-2-yl)pyridine (**29**).* The title compound was prepared according to general procedure B, using acetophenone (46.0 mg, 0.375 mmol, 1.25 equiv.) and 4-pyridinecarboxaldehyde (33.0 mg, 0.30 mmol, 1.00 equiv.). Purification by silica gel chromatography, eluting with EtOAc in hexanes (19 cm x 20 mm, gradient elution, 50% → 100%, 5% increases, 50 mL runs, 5-10 mL fractions) yielded **29** as a pale yellow solid (83% yield, 56.0 mg, 0.25 mmol). **R_f =** 0.01 (30% EtOAc/Hex, UV, Dragendorff stain); **^{1}H NMR (400 MHz, DMSO-*d*$_6$/D_2O/TFA) δ** 8.81 (d, *J* = 6.6 Hz, 2H), 8.40 (d, *J* = 6.6 Hz, 2H), 8.04 (s, 1H), 7.85 (d, *J* = 7.6 Hz, 2H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.34 (t, *J* = 7.3 Hz, 1H); **$^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-*d*$_6$/D_2O/TFA) δ** 143.5, 143.2, 142.0, 141.6, 131.4, 129.8, 129.1, 125.9, 122.2, 122.0; **HRMS (ESI+/TOF) m/z:** $[M+H]^+$ Calcd for $C_{14}H_{12}N_3$ 222.1031; Found 222.1030. Spectroscopic data are in accordance with the literature[23].

*5-Phenyl-2-propyl-1H-imidazole (**30**).* The title compound was prepared according to general procedure B, using acetophenone (46.0 mg, 0.375 mmol, 1.25 equiv.) and butyraldehyde (23.0 mg, 0.30 mmol, 1.00 equiv.). Purification by silica gel chromatography, eluting with EtOAc in hexanes (19 cm x 20 mm, gradient elution, 30% → 70%, 5% increases, 50 mL runs, 5-10 mL fractions) yielded **30** as a white solid (36% yield, 20.0 mg, 0.11 mmol). **R_f =** 0.10 (30% EtOAc/Hex, UV, Dragendorff stain); **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.84 (s, 1H), 7.67 (d, *J* = 7.4 Hz, 2,H), 7.33 (t, *J* = 7.7 Hz, 2H), 7.23 – 7.17 (m, 2H), 2.68 (t, *J* = 7.6 Hz, 2H), 1.70 (sx, *J* = 7.5 Hz, 2H), 0.89 (t, *J* = 7.4 Hz, 3H); **$^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ** 149.7, 137.6, 133.1, 128.8, 126.8, 124.8, 115.5, 30.6, 22.2, 13.9; **HRMS (ESI+/TOF) m/z:** $[M+H]^+$ Calcd for $C_{12}H_{15}N_2$ 187.1235; Found 187.1243. Spectroscopic data are in accordance with the literature[36,37].

*2-Cyclopropyl-5-phenyl-1H-imidazole (**31**).* The title compound was prepared according to general procedure B, using acetophenone (46.0 mg, 0.375 mmol, 1.25 equiv.) and cyclopropanecarboxaldehyde (23.0 mg, 0.30 mmol, 1.00 equiv.). Purification by silica gel chromatography, eluting with EtOAc in hexanes (19 cm x 20 mm, gradient elution, 0% → 40%, 5% increases, 50 mL runs, 5-10 mL fractions) yielded **31** as a white solid (70% yield, 39.0 mg, 0.21 mmol). **R_f =** 0.10 (30% EtOAc/Hex, UV, Dragendorff

stain); **^{1}H NMR (400 MHz, DMSO-*d*$_6$/D$_2$O/TFA) δ** 7.76 (s, 1H), 7.67 (d, *J* = 7.4 Hz, 2H), 7.46 (t, *J* = 7.5 Hz, 2H), 7.39 (t, *J* = 7.3 Hz, 1H), 2.30 – 2.20 (m, 1H), 1.28 – 1.20 (m, 2H), 1.18 – 1.11 (m, 2H); **^{13}C{^{1}H} NMR (101 MHz, DMSO-*d*$_6$/D$_2$O/TFA) δ** 150.9, 132.5, 130.0, 129.9, 127.3, 125.9, 114.7, 9.7, 7.5; **ν_{max} (cm^{-1}, thin film, ATR):** 3034, 2910, 1606, 1566, 1545, 1524, 1483, 1451, 1425, 1313, 1166, 1135, 1090, 1027, 1005, 881, 756, 727, 693; **HRMS (ESI+/TOF) m/z:** $[M+H]^+$ Calcd for $C_{12}H_{13}N_2$ 185.1079; Found 185.1080; **mp:** 160.0 – 162.0 °C (EtOAc).

*4-(2-(2-Methyl-4-(methylsulfonyl)phenyl)-1H-imidazol-5-yl)pyridine (**32**).* A 10 mL round-bottom flask was charged with 4-acetylpyridine (**68**) (219 mg, 1.70 mmol, 1.70 equiv.), magnetic stirrer bar and DMSO (3.5 mL, 0.5 M) under air and concentrated HBr aqueous (48% w/w, 8.9 M) (595 mL, 5.25 mmol, 3.0 equiv.) was added dropwise. The reaction mixture was stirred in pre-heated oil bath at 60 ºC for 8h. After consumption of the starting material, indicated by TLC analysis (EtOAc, *p*-ASD*)*, the reaction mixture was left to reach room temperature and MeOH (5.7 mL, 0.19 M) was added. This reaction mixture was added dropwise over 30 minutes via syringe to a solution of 2-methyl-4-(methylsulfonyl)benzaldehyde (**S5**) (198 mg, 1.00 mmol, 1.00 equiv.) and NH_4OAc (771 mg, 10.0 mmol, 10.0 equiv.) in MeOH (5 mL, 0.2 M in relation to **S5)** at room temperature. The reaction mixture was stirred at room temperature for 18h and the solvent was removed in the rotaevaporator, the residue was diluted with 10% MeOH/DCM (10 mL) and poured into separatory funnel containing satd. $NaHCO_3$ (1x 40 mL) and 10% MeOH/DCM (1x 15 mL). The phases were separated, and the aqueous phase was extracted with 10% MeOH/DCM (7x 10 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated in the rotaevaporator. Purification by silica gel chromatography, eluting with MeOH in DCM (gradient elution 5% → 9%) yielded **31** as a pale yellow solid (67% yield, 210 mg, 0.67 mmol). **R_f =** 0.17 (EtOAc, Dragendorff stain); **^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ** 12.92 (br. s, 1H), 8.54 (d, *J* = 5.9 Hz, 2H), 8.14 (s, 1H), 7.94 – 7.90 (m, 2H), 7.85 (d, *J* = 8.8 Hz, 1H), 7.81 (d, *J* = 5.9 Hz, 2H), 3.26 (s, 3H), 2.75 (s, 3H); **^{13}C{^{1}H} NMR (126 MHz, DMSO-*d*$_6$) δ** 149.9, 145.4, 141.5, 140.0, 138.8, 137.6, 134.1, 129.6, 128.9, 124.4, 118.8, 117.7, 43.5, 21.4; **ν_{max} (cm^{-1}, ATR):** 2673, 1607, 1302, 1150, 1106, 1077, 1004, 965, 950, 828, 763, 739, 709, 690; **HRMS (ESI+/TOF) m/z:** $[M+H]^+$ Calcd for $C_{16}H_{16}N_3O_2S$ 314.0963; Found 314.0938.; **mp** 225.4 – 227.3 °C (MeOH/DCM).

*tert-Butyl 4-(5-(pyridin-4-yl)-1H-imidazol-2-yl)piperidine-1-carboxylate (**36**).* A

50 mL round-bottom flask was charged with 4-acetylpyridine (**68**) (645 mg, 5.16 mmol, 1.75 equiv.), magnetic stirrer bar and DMSO (10.8 mL, 0.5 M) under air and concentrated HBr aqueous (48% w/w, 8.9 M) (1.75 mL, 15.5 mmol, 3.0 equiv.) was added dropwise. The reaction mixture was stirred in pre-heated oil bath at 60 ºC for 4h. After consumption of the starting material, indicated by TLC analysis (EtOAc, *p*-ASD*)*, the reaction mixture was left to reach room temperature and MeOH (18.3 mL, 0.18 M relative to 4-acetylpyridine) was added. This reaction mixture was added dropwise over 30 minutes via syringe to a solution of 1-(tert-Butoxycarbonyl)-4-piperidinecarboxaldehyde (**35**) (629 mg, 2.95 mmol, 1.00 equiv.) and NH_4OH (6.4 mL, 44.3 mmol, 15.0 equiv.) in MeOH (14.8 mL, 0.2 M in relation to **35)** at room temperature. The reaction mixture was stirred at room temperature for 4h and poured into separatory funnel containing satd. $NaHCO_3$ (1x 40 mL) and EtOAc (1x 40 mL). The phases were separated, and the aqueous phase was extracted with EtOAc (3x 40 mL), dried over Na_2SO_4, filtered and concentrated in the rotaevaporator. Purification by silica gel chromatography, eluting with EtOH:EtOAc:NH_4OH:Hexane (11:34:5:50) (18 cm x 40 mm, isocratic elution, (11:34:5:50) EtOH:EtOAc:NH_4OH:Hex, 1 L run, 20 mL fractions) yielded **36** as a white solid (82% yield, 793 mg, 2.40 mmol). $\mathbf{R_f}$ = 0.40 **(**EtOH:EtOAc:NH_4OH:Hexane (11:34:5:50), UV, Dragendorff stain). **^{1}H NMR (500 MHz, DMSO-*d*6) δ** 12.10 (br. s, 1H), 8.46 (d, *J* = 6.0 Hz, 2H), 7.77 (br. s, 1H), 7.66 (d, *J* = 6.0 Hz, 2H), 3.99 (d, *J* = 12.4 Hz, 2H), 2.96 – 2.78 (m, 3H), 1.90 (dd, *J* = 13.0, 2.3 Hz, 2H), 1.59 (dq, *J* = 12.3, 3.9 Hz, 2H), 1.41 (s, 9H). **^{13}C{^{1}H} NMR (126 MHz, DMSO-*d*6) δ** 153.9, 152.1, 149.7, 118.5, 78.6, 43.2, 35.2, 30.4, 28.1. **Note:** Due to slow relaxation, some $^{13}C\{^1H\}$ NMR signals were not identified in the spectra[28]. Specifically, the $^{13}C\{^1H\}$ NMR data for compound **36** lacks three of the twelve expected signals. **ν_{max} (cm^{-1}, thin film, ATR):** 2867 (br), 1690 (s), 1603 (s), 1553 (w), 1429 (m), 1363 (w), 1285 (w), 1248 (w), 1230 (w), 1212 (w), 1173 (s), 1151 (m), 1126 (m), 1038 (w), 1004 (m), 942 (w), 876 (w), 766 (s), 720 (w), 686 (m). **HRMS (ESI+/TOF) m/z:** $[M+H]^+$ Calcd for $C_{18}H_{25}N_4O_2$ 329.1978; Found 329.1964 **. mp:** 215.0 °C (dec.)

1-(4-Amino-3-bromophenyl)ethenone (43). A 6 mL vial was charged with the 4'-aminoacetophenone (51.0 mg, 0.375 mmol, 1.00 equiv.), DMSO (0.75 mL, 0.5 M), concentrated aqueous HBr (48% w/w, 8.9 M) (47 µL, 0.41 mmol, 110 mol%), deionized water (47 µL) and a magnetic stirrer bar under air. The reaction mixture was stirred in a pre-heated aluminum block at 85 ºC and was followed by TLC analysis (30% EtOAc/Hex,

p-ASD). The reaction mixture was poured directly into a separatory funnel containing a mixture of satd. $NaHCO_3$ and satd. $Na_2S_2O_3$ (1:1, 1x 20 mL) and EtOAc (10 mL). The phases were separated, and the aqueous phase was extracted with EtOAc (5x 5 mL). The organic phases were combined, washed with satd. NaCl solution (1x 5 mL), dried over Na_2SO_4, filtered and concentrated in the rotaevaporator. Purification by silica gel chromatography, eluting with EtOAc in hexanes (18 cm x 15 mm, gradient elution, 0% → 35%, 5% increases, 30 mL runs, 10 mL fractions) yielded **33** as a pale yellow solid (99% yield, 64.0 mg, 0.30 mmol). **R_f =** 0.53 (30% EtOAc/Hex, *p*-ASD); **^{1}H NMR (500 MHz, $CDCl_3$) δ** 8.05 (d, *J* = 1.8 Hz, 1H), 7.73 (dd, *J* = 8.4, 1.8 Hz, 1H), 6.74 (d, *J* = 8.4 Hz, 1H), 4.60 (br s, 2H), 2.49 (s, 3H); **^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ** 195.5, 148.5, 133.9, 129.5, 128.9, 114.3, 108.3, 26.2. Spectroscopic data are in accordance with the literature[38].

*4-(4-Bromo-2-(2-methyl-4-(methylsulfonyl)phenyl)-1H-imidazol-5-yl)pyridine (**44**).* Following a modified literature procedure[24], a 25 mL round-bottom flask was charged with **32** (595 mg, 1.90 mmol, 1.00 equiv.), dry DCM (8.4 mL), dry pyridine (2.1 mL) and a magnetic stirrer bar under inert atmosphere. The RBF was covered with aluminum foil and the reaction mixture was cooled to 0 ºC in an ice/water bath and stirred for 15 minutes. Solid Py•HBr•Br_2 (pyridinium hydrobromide perbromide, 743 mg, 2.09 mmol, 1.10 equiv.) was added in portions, by briefly removing the Suba seal, and the reaction mixture was stirred at 0 ºC for 1 hour. After consumption of the starting material, indicated by TLC analysis (100% EtOAc, Dragendorff), the solvent was removed in the rotaevaporator. The residue was partitioned between 1M aq. $NaHSO_3$ (1x 75 mL) and 10% MeOH/DCM (1x 60 mL). The phases were separated and the aqueous layer was extracted with 10% MeOH/DCM (3x 60 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated in the rotaevaporator. The residue was triturated with hexanes, filtered and washed with hexanes until all pyridine was removed, indicated by TLC analysis, and dried in vacuo to afford **44** as a yellow solid (96% yield, 716 mg, 1.83 mmol). **R_f =** 0.47 (EtOAc, UV, Dragendorff stain); **^{1}H NMR (500 MHz, DMSO-d_6) δ** 13.32 (s, 1H), 8.70 (s, 2H), 8.00 – 7.79 (m, 5H), 3.28 (s, 3H), 2.65 (s, 3H); **^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ** 150.5, 146.7, 141.3, 138.6, 136.1, 133.7, 130.4, 129.9, 126.6, 124.8, 120.8, 116.0, 43.9, 21.3; **ν_{max} (cm^{-1}, thin film, ATR):** 2765 (br), 1606 (s), 1573 (w), 1533 (w), 1491 (w), 1448 (w), 1422 (w), 1301 (s), 1222 (w), 1205 (w), 1150 (s), 1105 (m), 1077 (m), 1004 (m), 986 (w), 964 (m), 950 (m), 892 (w), 875 (w), 828 (s),

762 (s), 739 (m), 708 (w), 699 (w); **HRMS (ESI+/TOF) m/z:** $[M+H]^+$ Calcd for $C_{16}H_{15}BrN_3O_2S$ 392.0068, 394.0049; Found 392.0053, 394.0034; **mp:** 225.0 °C (dec.) – turned brown at 210.0 °C.

Suzuki-Miyaura Cross-Coupling: General Procedure C. A culture tube (13 mm x 100 mm, 9 mL) was charged with the corresponding bromo-imidazol (0.10 mmol, 1.00 equiv.), corresponding boronic ester or boronic acid (0.125 mmol, 1.25 equiv.) and a magnetic stirrer bar under inert atmosphere. Then, degassed DME (0.5 mL) was added followed by addition of a premixed solution of $Pd(OAc)_2$ (10 mol%) and Aphos (24 mol%) in degassed DME (0.25 mL). The reaction mixture was stirred for 5 minutes at room temperature and then 1.2 M aqueous K_2CO_3 (0.25 mL, 3.00 equiv.) degassed solution was added and the mixture was stirred for additional 5 minutes. After this time, the reaction mixture was stirred in a pre-heated aluminum block at 80 ºC for 18h. After consumption of the starting material, indicated by TLC analysis (7% EtOH/$CHCl_3$, Dragendorff), the reaction mixture was allowed to reach room temperature and it was diluted with 10% MeOH/DCM (~7 mL), filtered through a pad (20 mm diameter) composed of Celite (top, 1 cm) and silica gel (bottom, 3 cm). The pad was washed with 10% MeOH/DCM (25-50 mL) and the filtrate was concentrated under in the reduced pressure. The crude product was adsorbed over basic alumina and purification was performed by silica gel column chromatography.

*4-(2-(2-Methyl-4-(methylsulfonyl)phenyl)-4-phenyl-1H-imidazol-5-yl)pyridine (**46**).* The title compound was prepared according to general procedure C, using **44** (39.0 mg, 0.10 mmol, 1.00 equiv.), phenylboronic acid (15.0 mg, 0.125 mmol, 1.25 equiv.), $Pd(OAc)_2$ (2.3 mg, 10 mol%) and Aphos (6.7 mg, 24 mol%). Purification by silica gel chromatography, eluting with EtOH in $CHCl_3$ (21 cm x 10 mm, gradient elution, 0% → 4%, 0.5% increases, 20 mL runs, 3-4 mL fractions) followed by repurification in silica gel using EtOAc (4 cm x 30 mm, isocratic elution, 100% EtOAc, 150 mL run, 10 mL fractions) yielded **46** as a white solid (71% yield, 28.0 mg, 0.07 mmol). **^{1}H NMR (500 MHz, DMSO-*d*$_6$/D$_2$O/TFA) δ** 8.66 (d, *J* = 7.0 Hz, 2H), 8.05 (d, *J* = 7.0 Hz, 2H), 7.99 (d, *J* = 8.2 Hz 1H), 7.93 (d, *J* = 1.1 Hz, 2H), 7.87 (dd, *J* = 8.2, 1.5 Hz, 1H) 7.66 – 7.61 (m, 2H), 7.60 – 7.55 (m, 2H), 3.24 (s, 3H), 2.75 (s, 3H); **^{13}C{^{1}H} NMR (126 MHz, DMSO-*d*$_6$/D$_2$O/TFA) δ** 150.9, 146.8, 141.5, 141.1, 138.9, 137.3, 133.5, 131.5, 130.3, 130.2, 129.9, 129.8, 129.5, 129.5, 124.8, 122.4, 43.8, 21.5; **ν_{max} (cm^{-1}, thin film, ATR):** 3084 (br), 2928 (w), 1601 (s), 1501 (w), 1486 (w), 1444 (w), 1327 (m), 1303 (s), 1214 (w),

1147 (s), 1108 (m), 1074 (m), 999 (w), 962 (m), 951 (m), 879 (w), 832 (s), 777 (m), 762 (s), 742 (s), 702 (s); **HRMS (ESI+/TOF) m/z:** $[M+H]^+$ Calcd for $C_{22}H_{20}N_3O_2S$ 390.1276; Found 390.1273. **mp:** 265.0 °C (dec.).

*4-(4-(4-(Benzyloxy)phenyl)-2-(2-methyl-4-(methylsulfonyl)phenyl)-1H-imidazol-5-yl)pyridine (**47**).* The title compound was prepared according to general procedure C, using **44** (39.0 mg, 0.10 mmol, 1.00 equiv.), 4-benzyloxyphenylboronic acid (29.0 mg, 0.125 mmol, 1.25 equiv.), $Pd(OAc)_2$ (2.3 mg, 10 mol%) and Aphos (6.7 mg, 24 mol%). Purification by silica gel chromatography, eluting with EtOH in $CHCl_3$ (21 cm x 10 mm, gradient elution, 0% → 6%, 0.5% increases, 20 mL runs, 3-4 mL fractions) followed by repurification in silica gel using MeOH in DCM eluent (21 cm x 10 mm, gradient elution, 0% → 6%, 0.5% increases, 20 mL runs, 7 mL fractions) yielded **47** as a pale yellow solid (69% yield, 34.0 mg, 0.07 mmol). **^{1}H NMR (500 MHz, DMSO-*d*$_6$/D$_2$O/TFA) δ** 8.57 (d, *J* = 7.0 Hz, 2H), 8.04 (d, *J* = 7.0 Hz, 1H), 7.93 – 7.88 (m, 2H), 7.84 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.52 (d, *J* = 8.7 Hz, 2H), 7.44 (d, *J* = 7.5 Hz, 2H), 7.38 (t, *J* = 7.4 Hz, 2H), 7.32 (t, *J* = 7.2 Hz, 1H), 7.16 (d, *J* = 8.8 Hz, 2H), 5.14 (s, 2H), 3.20 (s, 3H), 2.67 (s, 3H); **^{13}C{^{1}H} NMR (126 MHz, DMSO-*d*$_6$/D$_2$O/TFA) δ** 160.3, 151.0, 146.9, 141.7, 141.5, 139.5, 137.6, 137.3, 133.6, 131.4, 131.0, 130.8, 130.2, 129.4, 129.0, 128.6, 125.3, 122.9, 121.6, 116.5, 70.3, 44.1, 21.5; **ν_{max} (cm^{-1}, thin film, ATR):** 3041 (w), 2921 (w), 1732 (w), 1605 (s), 1513 (m), 1488 (w), 1469 (w), 1445 (w), 1303 (m), 1289 (m), 1243 (m), 1151 (s), 1143 (s), 1072 (w), 974 (m), 831 (s), 808 (w), 767 (s), 742 (m); **HRMS (ESI+/TOF) m/z:** $[M+H]^+$ Calcd for $C_{29}H_{26}N_3O_3S$ 496.1695 466.1589; Found 496.1688; **mp:** 245.0 – 248.5 °C (MeOH/DCM) – turned brown upon heating

*4-(4-(4-(Methoxymethoxy)phenyl)-2-(2-methyl-4-(methylsulfonyl)phenyl)-1H-imidazol-5-yl)pyridine (**48**).* The title compound was prepared according to general procedure C, using **44** (39.0 mg, 0.10 mmol, 1.00 equiv..), 4-(methoxymethoxy)phenyl boronic acid (23.0 mg, 0.125 mmol, 1.25 equiv.), $Pd(OAc)_2$ (2.3 mg, 10 mol%) and Aphos (6.7 mg, 24 mol%). Purification by silica gel chromatography, eluting with EtOH in $CHCl_3$ (21 cm x 10 mm, gradient elution, 0% → 6%, 0.5% increases, 20.0 mL runs, 3-4 mL fractions) followed by repurification in silica gel using MeOH in DCM eluent (21 cm x 10 mm, gradient elution, 0% → 6%, 0.5% increases, 20 mL runs, 7 mL fractions) yielded **48** as a white solid (73% yield, 33.0 mg, 0.07 mmol). **^{1}H NMR (500 MHz, DMSO-*d*$_6$/D$_2$O) δ** 8.38 (d, *J* = 4.7 Hz, 2H), 7.89 – 7.83 (m, 2H), 7.80 (d, *J* = 8.53, 1H), 7.50 (d, *J* =4.7 Hz, 2H), 7.42 (d, *J* = 8.53, 2H) 7.10 (d, *J* = 8.15 Hz, 2H), 5.20 (s, 2H),

3.37 (s, 3H), 3.19 (s, 3H), 2.66 (s, 3H); **^{13}C{^{1}H} NMR (126 MHz, DMSO-*d*$_6$/D$_2$O) δ** 157.8, 150.0, 145.7, 143.2, 140.6, 139.0, 134.9, 134.4, 131.9, 130.9, 130.5, 130.1, 125.1, 123.8, 121.8, 117.4, 94.5, 56.6, 44.2, 21.6 (**Note**: extra signals in the 13C{^{1}H} NMR spectra are due to the presence of tautomers); **ν_{max} (cm^{-1}, thin film, ATR):** 2925 (w), 1600 (s), 1513 (m), 1491 (w), 1444 (w), 1309 (m), 1238 (m), 1214 (w), 1200 (w), 1143 (s), 1108 (m), 1000 (m), 970 (s), 955 (m), 918 (w), 834 (s), 761 (s), 741 (s); **HRMS (ESI+/TOF) m/z:** $[M+H]^+$ Calcd for $C_{24}H_{24}N_3O_4S$ 450.1487; Found 450.1467; **mp:** 225.0 – 226.4 °C (MeOH/DCM)**.**

*3-(2-(2-Methyl-4-(methylsulfonyl)phenyl)-5-(pyridin-4-yl)-1H-imidazol-4-yl)benzenesulfonamide (**49**).* The title compound was prepared according to general procedure C, using **44** (39.0 mg, 0.10 mmol, 1.00 equiv..), (3-aminosulfonylphenyl)boronic acid (26.0 mg, 0.125 mmol, 1.25 equiv.), $Pd(OAc)_2$ (2.3 mg, 10 mol%) and Aphos (6.7 mg, 24 mol%). Purification by preparative TLC, eluting with EtOH in $CHCl_3$ (20 cm x 20 cm plate, 10% EtOH/$CHCl_3$, two runs) yielded **49** as a white solid (62% yield, 29.0 mg, 0.06 mmol). **^{1}H NMR (500 MHz, DMSO-*d*$_6$/D$_2$O/TFA) δ** 8.66 (d, *J* = 6.2 Hz, 2H), 8.06 – 8.01 (m, 3H), 7.99 - 7.90 (m, 3H), 7.89 – 7.84 (m, 2H), 7.75 (t, *J* = 7.7, 1H) 3.23 (s, 3H), 2.73 (s, 3H); **^{13}C{^{1}H} NMR (126 MHz, DMSO-*d*$_6$/D$_2$O/TFA) δ** 150.5, 147.5, 145.2, 141.8, 141.3, 139.1, 136.0, 133.6, 133.0, 131.8, 130.8, 130.6, 130.4, 130.0, 127.1, 126.5, 125.0, 123.0, 43.9, 21.5; **ν_{max} (cm^{-1}, thin film, ATR):** 3296 (br), 2931 (w), 1606 (m), 1479 (w), 1410 (w), 1342 (m), 1303 (m), 1205 (w), 1161 (s), 1156 (s), 1118 (w), 1079 (w), 1108 (w), 976 (w), 859 (w), 833 (m), 806 (w), 764 (m), 746 (m), 690 (s); **HRMS (ESI+/TOF) m/z:** $[M+H]^+$ Calcd for $C_{22}H_{21}N_4O_4S_2$ 469.1004; Found 469.0997; **mp:** 234.0 – 236.2 °C (EtOH/$CHCl_3$).

*N-Cyclopropyl-3-(2-(2-methyl-4-(methylsulfonyl)phenyl)-5-(pyridin-4-yl)-1H-imidazol-4-yl)benzenesulfonamide (**50**).* The title compound was prepared according to general procedure C, using **44** (39.0 mg, 0.10 mmol, 1.00 equiv..), 3-(cyclopropylsulfamoyl)phenylboronic acid (31.0 mg, 0.125 mmol, 1.25 equiv.), $Pd(OAc)_2$ (2.3 mg, 10 mol%) and Aphos (6.7 mg, 24 mol%). Purification by silica gel chromatography, eluting with EtOH in $CHCl_3$ (21 cm x 10 mm, gradient elution, 3% → 8%, 0.5% increases, 20 mL runs, 3-4 mL fractions) yielded **50** as a white solid (57% yield, 29.0 mg, 0.06 mmol). **^{1}H NMR (500 MHz, DMSO-*d*$_6$/D$_2$O/TFA) δ** 8.63 (d, *J* = 6.8 Hz, 2H), 8.02 (d, *J* = 6.8 Hz, 2H), 7.97-7.84 (m, 6H), 7.79 (t, *J* = 7.7 1H), 3.21 (s, 3H), 2.70 (s, 3H). 2.15 - 2.09 (m, 1H), 0.51 - 0.45 (m, 2H), 0.41 - 0.36 (m, 2H); **^{13}C{^{1}H} NMR (126**

MHz, DMSO-*d*$_6$/D$_2$O/TFA) δ 150.6, 147.7, 141.9, 141.7, 141.5, 139.4, 136.1, 133.8, 133.7, 131.9, 131.3, 130.9, 130.8, 130.1, 128.6, 127.7, 125.2, 123.4, 44.1, 24.7, 21.5, 5.9; **ν_{max} (cm^{-1}, thin film, ATR):** 3077 (br), 2925 (w), 2835 (w), 1608 (m), 1539 (w), 1475 (w), 1413 (w), 1334 (m), 1318 (m), 1222 (w), 1161 (s), 1119 (w), 1103 (w), 1030 (w), 1008 (w), 961 (m), 890 (w), 836 (m), 765 (w), 695 (m); **HRMS (ESI+/TOF) m/z:** $[M+H]^+$ Calcd for $C_{25}H_{25}N_4O_4S_2$ 509.1317; Found 509.1317; **mp**: 212.7 – 215.7 °C (EtOH/$CHCl_3$).

*1-Methyl-5-(2-(2-methyl-4-(methylsulfonyl)phenyl)-5-(pyridin-4-yl)-1H-imidazol-4-yl)-1H-indole (**51**).* The title compound was prepared according to general procedure C, using **44** (39.0 mg, 0.10 mmol, 1.00 equiv..), *N*-methylindole-5-boronic acid (22.0 mg, 0.125 mmol, 1.25 equiv.), $Pd(OAc)_2$ (2.3 mg, 10 mol%) and Aphos (6.7 mg, 24 mol%). Purification by silica gel chromatography, eluting with EtOH in $CHCl_3$ (21 cm x 10 mm, gradient elution, 0% → 6%, 0.5% increases, 20 mL runs, 3-4 mL fractions) followed by repurification in silica gel using MeOH in DCM eluent (21 cm x 10 mm, gradient elution, 0% → 6%, 0.5% increases, 20 mL runs, 7 mL fractions) yielded **41** as a white solid (56% yield, 25.0 mg, 0.06 mmol). **R$_f$** = 0.45 (7% EtOH/$CHCl_3$, Dragendorff stain); **^{1}H NMR (400 MHz, DMSO-*d*$_6$/D$_2$O/TFA) δ** 8.56 (d, *J* = 7.0 Hz, 2H), 8.04 (d, *J* = 7.0 Hz, 2H), 7.97 (d, *J* = 8.2 Hz, 1H), 7.92 (d, *J* = 1.4 Hz, 1H), 7.86 (dd, *J* = 1.6, 8.2 Hz, 1H), 7.83 (d, *J* = 1.2 Hz, 1H), 7.60 (d, *J* = 8.5 Hz, 1H), 7.41 (d, *J* = 3.0 Hz, 1H), 7.34 (dd, *J* = 8.5, 1.5 Hz, 1H), 6.54 (d, *J* = 3.0 Hz, 1H), 3.82 (s, 3H), 3.22 (s, 1H), 2.73 (s, 3H). (**Note:** signal at δ 8.09 ppm corresponds to residual $CHCl_3$ in the sample). **^{13}C{^{1}H} NMR (126 MHz, DMSO-*d*$_6$/D$_2$O/TFA) δ** 151.1, 146.5, 141.5, 141.3, 139.5, 139.2, 137.5, 133.5, 131.8, 130.8, 130.6, 130.1, 129.0, 125.1, 122.5, 122.4, 122.0, 119.6, 111.4, 44.0, 33.2, 21.5 (**Note:** signal at δ 79.5 ppm corresponds to residual $CHCl_3$ in the sample and one carbon signal missing in the spectra); **ν_{max} (cm^{-1}, thin film, ATR):** 2914 (w), 2683 (br), 1603 (s), 1507 (w), 1485 (w), 1441 (w), 1430 (w), 1378 (w), 1309 (s), 1286 (w), 1243 (w), 1210 (w), 1154 (s), 1112 (m), 1090 (m), 1071 (w), 1003 (w), 964 (m), 951 (m), 893 (w), 832 (s), 815 (w), 763 (m), 741 (m), 730 (m), 701 (w); **HRMS (ESI+/TOF) m/z:** $[M+H]^+$ Calcd for $C_{25}H_{23}N_4O_2S$ 443.1542; Found 443.1529; **mp:** 294.0 °C (dec.).

*4-(4-(Benzofuran-5-yl)-2-(2-methyl-4-(methylsulfonyl)phenyl)-1H-imidazol-5-yl)pyridine (**52**).* The title compound was prepared according to general procedure C, using **44** (39.0 mg, 0.10 mmol, 1.00 equiv.), benzofuran-5-boronic acid (21.0 mg, 0.125 mmol, 1.25 equiv.), $Pd(OAc)_2$ (2.3 mg, 10 mol%) and Aphos (6.7 mg, 24 mol%).

Purification by silica gel chromatography, eluting with EtOH in $CHCl_3$ (21 cm x 10 mm, gradient elution, 0% → 6%, 0.5% increases, 20 mL runs, 3-4 mL fractions) followed by repurification in silica gel using MeOH in DCM eluent (21 cm x 10 mm, gradient elution, 0% → 6%, 0.5% increases, 20 mL runs, 7 mL fractions) yielded **52** as a white solid (59% yield, 26.0 mg, 0.06 mmol). **R_f =** 0.45 (7% EtOH/$CHCl_3$, Dragendorff stain); **^{1}H NMR (500 MHz, DMSO-*d*$_6$/D$_2$O/TFA) δ** 8.57 (d, *J* = 6.9 Hz, 1H),), 8.04 – 8.00 (m, 3H), 7.95 (d, *J* = 8.2 Hz, 1H), 7.92 (d, *J* = 8.5 Hz, 1H), 7.86 (dd, *J* = 8.5, 1.4 Hz, 1H), 7.76 (d, *J* = 8.5 Hz, 1H), 7.52 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.03 (d, *J* = 1.4 Hz, 1H), 3.21 (s, 3H), 2.72 (s, 3H) (**Note:** signal at δ 8.09 ppm corresponds to residual $CHCl_3$ in the sample); **^{13}C{^{1}H} NMR (126 MHz, DMSO-*d*$_6$/D$_2$O/TFA) δ** 155.6, 151.0, 147.9, 146.9, 141.6, 141.4, 139.4, 138.0, 133.7, 131.4, 130.7, 130.1, 128.9, 126.2, 125.2, 124.3, 123.1, 122.8, 113.1, 107.8, 44.1, 21.6 (**Note:** signal at δ 79.5 ppm corresponds to residual $CHCl_3$ in the sample); **ν_{max} (cm^{-1}, thin film, ATR):** 2925 (w), 1601 (s), 1457 (w), 1444 (w), 1307 (m), 1210 (w), 1196 (w), 1150 (s), 1107 (m), 1086 (w), 1070 (w), 956 (m), 869 (w), 833 (m), 763 (s), 743 (s); **HRMS (ESI+/TOF) m/z:** $[M+H]^+$ Calcd for $C_{24}H_{20}N_3O_3S$ 430.1225; Found 430.1207; **mp:** 232.0 – 233.4 °C (MeOH/DCM).

*4-(4-(Benzo[b]thiophen-5-yl)-2-(2-methyl-4-(methylsulfonyl)phenyl)-1H-imidazol-5-yl)pyridine (**53**).* The title compound was prepared according to general procedure C, using **44** (39.0 mg, 0.10 mmol, 1.00 equiv.), 2-(benzo[b]thiophen-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane[39] (**S6**) (33.0 mg, 0.125 mmol, 1.25 equiv.), $Pd(OAc)_2$ (2.3 mg, 10 mol%) and Aphos (6.7 mg, 24 mol%). Purification by silica gel chromatography, eluting with EtOH in $CHCl_3$ (21 cm x 10 mm, gradient elution, 0% → 6%, 0.5% increases, 20 mL runs, 3-4 mL fractions) followed by repurification in silica gel using MeOH in DCM eluent (21 cm x 10 mm, gradient elution, 0% → 6%, 0.5% increases, 20 mL runs, 7 mL fractions) yielded **53** as a yellow solid (34% yield, 15.0 mg, 0.03 mmol). **R_f =** 0.45 (7% EtOH/$CHCl_3$, Dragendorff stain); **^{1}H NMR (500 MHz, DMSO-*d*$_6$/D$_2$O/TFA) δ** 8.56 (d, *J* = 6.9 Hz, 2H), 8.16 – 8.12 (m, 2H), 8.04 (d, *J* = 6.9 Hz, 2H), 7.95 (d, *J* = 8.2 Hz, 1H), 7.85 (dd, *J* =8.1, 1.6 Hz, 1H) 7.81 (d, *J* = 5.4 Hz, 1H), 7.54 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.52 (d, *J* = 5.4 Hz, 1H), 3.21 (s, 3H), 2.71 (s, 3H); **^{13}C{^{1}H} NMR (126 MHz, DMSO-*d*$_6$/D$_2$O/TFA) δ** 151.1, 147.2, 141.7, 141.4, 141.3, 140.8, 139.5, 137.9, 133.8, 131.5, 130.8, 130.2, 129.9, 125.6, 125.5, 125.3, 125.1, 125.0, 124.5, 123.0, 44.1, 21.6; **ν_{max} (cm^{-1}, thin film, ATR):** 2919 (w), 2853 (w), 1602 (s), 1488 (w), 1434 (m), 1427 (w), 1304 (s), 1213 (w), 1201 (w), 1142 (s), 1103 (m), 1072 (w), 1049

(w), 992 (w), 975 (m), 955 (m), 835 (m), 816 (m), 766 (s); **HRMS (ESI+/TOF) m/z:** $[M+H]^+$ Calcd for $C_{24}H_{20}N_3O_2S_2$ 446.0991; Found 446.0985; **mp:** 274.0 °C (dec.).

*4-(2-(2-Methyl-4-(methylsulfonyl)phenyl)-4-(naphthalen-2-yl)-1H-imidazol-5-yl)pyridine (**54**).* The title compound was prepared according to general procedure C, using **44** (39.0 mg, 0.10 mmol, 1.00 equiv.), 2-naphthaleneboronic acid (22.0 mg, 0.125 mmol, 1.25 equiv.), $Pd(OAc)_2$ (2.3 mg, 10 mol%) and Aphos (6.7 mg, 24 mol%). Purification by silica gel chromatography, eluting with EtOH in $CHCl_3$ (21 cm x 10 mm, gradient elution, 0% → 6%, 0.5% increases, 20 mL runs, 3-4 mL fractions) followed by repurification in silica gel using MeOH in DCM eluent (21 cm x 10 mm, gradient elution, 0% → 6%, 0.5% increases, 20 mL runs, 7 mL fractions) yielded **54** as a white solid (69% yield, 31.0 mg, 0.07 mmol). **R_f =** 0.42 (7% EtOH/$CHCl_3$, Dragendorff stain); **^{1}H NMR (500 MHz, DMSO-*d*$_6$/D$_2$O/TFA) δ** 8.59 (d, *J* = 6.9 Hz, 2H), 8.21 (s, 1H), 8.09 – 8.04 (m, 3H), 8.02 – 7.95 (m, 3H), 7.92 (s, 1H), 7.87 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.66 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.64 – 7.57 (m, 2H), 3.22 (s, 3H), 2.74 (s, 3H) (**Note:** signal at δ 8.09 ppm corresponds to residual $CHCl_3$ in the sample); **^{13}C{^{1}H} NMR (126 MHz, DMSO-*d*$_6$/D$_2$O/TFA) δ** 151.1, 147.3, 141.7, 141.3, 139.3, 137.5, 133.8, 133.8, 133.5, 131.8, 130.7, 130.1, 129.8, 129.2, 129.0, 128.5, 128.2, 127.9, 126.9, 126.8, 125.1, 123.0, 44.1, 21.6 (**Note:** signal at δ 79.5 ppm corresponds to residual $CHCl_3$ in the sample); **HRMS (ESI+/TOF) m/z:** $[M+H]^+$ Calcd for $C_{26}H_{22}N_3O_2S$ 440.1433; Found 440.1418.

*6-(2-(2-Methyl-4-(methylsulfonyl)phenyl)-5-(pyridin-4-yl)-1H-imidazol-4-yl)quinoline (**55**).* The title compound was prepared according to general procedure C, using **44** (39.0 mg, 0.10 mmol, 1.00 equiv..), quinoline-6-boronic acid (22.0 mg, 0.125 mmol, 1.25 equiv.), $Pd(OAc)_2$ (2.3 mg, 10 mol%) and Aphos (6.7 mg, 24 mol%). Purification by silica gel chromatography, eluting with EtOH in $CHCl_3$ (21 cm x 10 mm, gradient elution, 0% → 8%, 0.5% increases, 20 mL runs, 3-4 mL fractions) followed by repurification in silica gel using MeOH in DCM eluent (21 cm x 10 mm, gradient elution, 0% → 8%, 0.5% increases, 20 mL runs, 7 mL fractions) yielded **55** as a white solid (52% yield, 23.0 mg, 0.05 mmol). **R_f =** 0.42 (7% EtOH/$CHCl_3$, Dragendorff stain); **^{1}H NMR (500 MHz, DMSO-*d*$_6$/D$_2$O/TFA) δ** 9.22 (d, *J* = 5.1 Hz, 1H), 9.12 (d, *J* = 8.3 Hz, 1H), 8.62 – 8.56 (m, 3H), 8.33 (d, *J* = 8.8 Hz, 1H), 8.27 (dd, *J* = 8.9, 1.4 Hz, 1H), 8.11 – 8.05 (m, 3H), 7.96 (d, *J* = 8.2 Hz, 1H), 7.92 (s, 1H), 7.87 (d, *J* = 8.1 Hz, 1H), 3.21 (s, 3H), 2.72 (s, 3H); **^{13}C{^{1}H} NMR (126 MHz, DMSO-*d*$_6$/D$_2$O/TFA) δ** 150.4, 148.3, 147.2, 146.9, 142.0, 141.6, 139.6, 139.1, 135.8, 135.3, 133.9, 132.4, 131.3, 130.9, 130.3, 130.0, 129.6,

125.3, 123.8, 123.6, 123.4, 44.2, 21.6; **ν_{max} (cm^{-1}, thin film, ATR):** 1729 (w), 1598 (m), 1510 (w), 1490 (w), 1304 (m), 1141 (s), 1103 (w), 1073 (w), 954 (m), 883 (w), 836 (m), 765 (m), 743 (w); **HRMS (ESI+/TOF) m/z:** $[M+H]^+$ Calcd for $C_{24}H_{24}N_3O_4S$ 450.1487; Found 450.1467; **mp:** 225.0 – 227.0 °C (dec.) - turned brown at 160.0 °C.

*6-(2-(2-Methyl-4-(methylsulfonyl)phenyl)-5-(pyridin-4-yl)-1H-imidazol-4-yl)naphthalen-2-ol (**56**).* The title compound was prepared according to general procedure C, using **44** (39.0 mg, 0.10 mmol, 1.00 equiv..), 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-ol (**S7**) (34.0 mg, 0.125 mmol, 1.25 equiv.), $Pd(OAc)_2$ (2.3 mg, 10 mol%) and Aphos (6.7 mg, 24 mol%). Purification by silica gel chromatography, eluting with EtOH in $CHCl_3$ (21 cm x 10 mm, gradient elution, 4% → 9%, 0.5% increases, 20 mL runs, 3-4 mL fractions) followed by repurification in silica gel using MeOH in DCM eluent (21 cm x 10 mm, gradient elution, 4% → 9%, 0.5% increases, 20 mL runs, 7 mL fractions) yielded **56** as a pale yellow solid (67% yield, 30.0 mg, 0.07 mmol). **R_f =** 0.28 (7% EtOH/$CHCl_3$, Dragendorff stain); **^{1}H NMR (500 MHz, DMSO-*d*$_6$/D$_2$O/TFA) δ** 8.58 (d, *J* = 6.7 Hz, 2H), 8.10 – 8.04 (m, 3H), 7.97 (d, *J* = 8.1 Hz, 1H), 7.92 (s, 1H), 7.88 – 7.81 (m, 3H) 7.54 (dd, *J* = 8.5, 1.2 Hz, 1H), 7.22 (d, *J* = 1.9 Hz, 1H), 7.16 (dd, *J* = 8.8, 2.2 Hz, 1H), 3.21 (s, 3H), 2.72 (s, 3H); **^{13}C{^{1}H} NMR (126 MHz, DMSO-*d*$_6$/D$_2$O/TFA) δ** 157.0, 151.1, 147.1, 141.6, 141.4, 139.4, 138.0, 135.7, 133.7, 131.4, 131.0, 130.7, 130.2, 129.2, 128.3, 128.0, 127.1, 125.2, 123.5, 122.8, 120.3, 109.5, 44.1, 21.6; **ν_{max} (cm^{-1}, thin film, ATR):** 3221 (br), 2927 (w), 2851 (w), 1626 (w), 1608 (s), 1572 (w), 1436 (w), 1396 (w), 1305 (s), 1250 (w), 1211 (m), 1163 (w), 1144 (s), 1124 (w), 1114 (m), 1038 (m), 1013 (w), 1001 (w), 947 (m), 915 (w), 878 (s, 837 (m), 829 (m), 820 (w), 767 (s); **HRMS (ESI+/TOF) m/z:** $[M+H]^+$ Calcd for $C_{26}H_{22}N_3O_3S$ 456.1382; Found 456.1358; **mp:** 250.0 °C (dec.).

*4-(4-(6-Methoxynaphthalen-2-yl)-2-(2-methyl-4-(methylsulfonyl)phenyl)-1H-imidazol-5-yl)pyridine (**57**).* The title compound was prepared according to general procedure C, using **44** (79.0 mg, 0.20 mmol, 1.00 equiv.), 6-methoxy-2-naphthaleneboronic acid (53.0 mg, 0.25 mmol, 1.25 equiv.), $Pd(OAc)_2$ (4.6 mg, 10 mol%), Aphos (13.4 mg, 24 mol%), K_2CO_3 (83 mg, 0.06 mmol, 3.00 equiv.), degassed DME (1.5 mL) and distilled H_2O (0.5 mL). Purification by silica gel chromatography, eluting with EtOH in DCM (21 cm x 20 mm, gradient elution, 0% → 8%, 0.5% increases, 20 mL runs, 3-4 mL fractions) yielded **57** as a white solid (97% yield, 91.0 mg, 0.19 mmol). **R_f =** 0.37 (7% EtOH/$CHCl_3$, Dragendorff stain); **^{1}H NMR (DMSO-*d*$_6$/D$_2$O/TFA)**

δ 8.58 (d, *J* = 7.0 Hz, 2H), 8.12 (s, 1H), 8.05 (d, *J* = 7.0 Hz, 2H), 7.98 (d, *J* = 1.7 Hz, 1H), 7.96 (d, *J* = 2.2 Hz, 1H), 7.92 (s, 1H), 7.89 (d, *J* = 9.0 Hz, 1H), 7.86 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.60 (dd, *J* = 8.5, 1.5, 1H), 7.40 (d, *J* = 2.3 Hz, 1H), 7.23 (dd, *J* = 9.0, 2.5 Hz, 1H), 3.88 (s, 3H), 3.22 (s, 3H), 2.73 (s, 3H); **^{13}C{^{1}H} NMR (126 MHz, DMSO-*d*$_6$/D$_2$O/TFA)** δ 159.1, 151.1, 147.1, 141.6, 141.3, 139.3, 137.8, 135.4, 133.7, 131.6, 130.7, 130.6, 130.1, 129.0, 129.0, 128.7, 127.2, 125.1, 124.4, 122.8, 120.3, 106.8, 56.1, 44.1, 21.6; **ν_{max} (cm^{-1}, thin film, ATR):** 3125 (br), 1629 (w), 1600 (s), 1498 (w), 1302 (s), 1263 (m), 1205 (m), 1147 (s), 1110 (m), 1070 (w), 953 (m), 859 (m), 835 (m), 767 (m), 740 (w); **HRMS (ESI+/TOF) m/z:** $[M+H]^+$ Calcd for $C_{27}H_{24}N_3O_3S$ 470.1538; Found 470.1551; **mp:** 256.0 °C (dec.) – turned brown at 254.0 °C.

*4-(4-(6-Ethoxynaphthalen-2-yl)-2-(2-methyl-4-(methylsulfonyl)phenyl)-1H-imidazol-5-yl)pyridine (**58**).* The title compound was prepared according to general procedure C, using **44** (39.0 mg, 0.10 mmol, 1.00 equiv.), 2-(6-ethoxynaphthalen-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**S9**) (37.0 mg, 0.125 mmol, 1.25 equiv.), $Pd(OAc)_2$ (2.3 mg, 10 mol%) and Aphos (6.7 mg, 24 mol%). Purification by silica gel chromatography, eluting with EtOH in $CHCl_3$ (21 cm x 10 mm, gradient elution, 0% → 6%, 0.5% increases, 20 mL runs, 3-4 mL fractions) followed by repurification in silica gel using MeOH in DCM eluent (16 cm x 10 mm, gradient elution, 0% → 6%, 0.5% increases, 20 mL runs, 7 mL fractions) yielded **58** as a white solid (64% yield, 31.0 mg, 0.06 mmol). **R_f** = 0.43 (7% EtOH/$CHCl_3$, Dragendorff stain); **^{1}H NMR (500 MHz, DMSO-*d*$_6$/D$_2$O/TFA) δ** 8.58 (d, *J* = 6.8 Hz, 2H), 8.11 (s, 1H), 8.06 (d, *J* = 6.8 Hz, 2H), 7.97 (d, *J* = 8.3 Hz, 1H), 7.95 (d, *J* = 8.6 Hz, 1H) 7.92 (s, 1H), 7.90 – 7.84 (m, 2H), 7.59 (dd, *J* = 8.5, 1.4 Hz, 1H), 7.38 (d, *J* = 1.9 z, 1H), 7.21 (dd, *J* = 8.9, 2.3 Hz, 1H), 3.22 (s, 3H), 2.73 (s, 3H), 1.38 (t, *J* = 7.0 Hz, 3H). (**Note:** (CH_2) of the ethoxy group is not observed due to superposition of HOD signal) **^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ** 13.10 (s, 1H), 8.45 (d, *J* = 4.8 Hz, 2H), 8.09 (s, 1H), 8.04 (d, *J* = 8.1 Hz, 1H), 7.95 – 7.85 (m, 4H) 7.61 – 7.50 (m, 3H), 7.40 (d, *J* = 2.2 Hz, 1H), 7.23 (dd, *J* = 8.9, 2.5 Hz, 1H), 4.19 (q, *J* = 7.0 Hz, 2H), 3.28 (s, 3H), 2.82 (s, 3H), 1.43 (t, *J* = 7.0 Hz, 3H); **^{13}C{^{1}H} NMR (126 MHz, DMSO-*d*$_6$/D$_2$O/TFA) δ** 158.3, 151.1, 147.1, 141.6, 141.3, 139.3, 137.8, 135.4, 133.7, 131.6, 130.68, 130.65, 130.1, 129.0, 128.9, 128.6, 127.2, 125.1, 124.3, 122.8, 120.6, 107.4, 64.2, 44.1, 21.6, 15.1; **^{13}C{^{1}H} NMR (126 MHz, DMSO-*d*$_6$/D$_2$O) δ** 157.3, 149.7, 145.1, 142.2, 140.0, 137.9, 134.3, 134.2, 134.0, 131.6, 129.7, 129.6, 129.3, 128.3, 127.9, 127.4, 127.1, 125.1, 124.4, 120.8, 119.7, 106.7, 63.3, 43.5, 21.5, 14.7**; ν_{max} (cm^{-1},**

thin film, ATR): 3033 (br), 2928 (w), 1631 (w), 1600 (s), 1497 (w), 1442 (w), 1400 (w), 1319 (m), 1300 (m), 1261 (m), 1207 (w), 1144 (s), 1094 (m), 1041 (m), 994 (m), 834 (m), 768 (s), 742 (s), 700 (w); **HRMS (ESI+/TOF) m/z:** $[M+H]^+$ Calcd for $C_{28}H_{26}N_3O_3S$ 484.1695; Found 484.1697; **mp:** 250.0 °C (dec.).

*4-(4-(6-Cyclopropoxynaphthalen-2-yl)-2-(2-methyl-4-(methylsulfonyl)phenyl)-1H-imidazol-5-yl)pyridine (**59**).* The title compound was prepared according to general procedure C, using **44** (39.0 mg, 0.10 mmol, 1.00 equiv.), 2-(6-cyclopropoxynaphthalen-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane[40] (**S11**) (37.0 mg, 0.125 mmol, 1.25 equiv.), $Pd(OAc)_2$ (2.3 mg, 10 mol%) and Aphos (6.7 mg, 24 mol%). Purification by silica gel chromatography, eluting with EtOH in $CHCl_3$ (21 cm x 10 mm, gradient elution, 0% → 6%, 0.5% increases, 20 mL runs, 3-4 mL fractions) followed by repurification in silica gel using MeOH in DCM eluent (21 cm x 10 mm, gradient elution, 0% → 6%, 0.5% increases, 20 mL runs, 7 mL fractions) yielded **59** as a white solid (63% yield, 31.0 mg, 0.06 mmol); **R_f =** 0.33 (7% EtOH/$CHCl_3$, Dragendorff stain); **^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ** 13.10 (s, 1H), 8.65 – 8.39 (m, 2H), 8.15 – 7.76 (m, 6H), 7.68 – 7.48 (m, 4H) 7.87 – 7.81 (m, 3H) 7.29 – 7.13 (m, 1H), 4.00 (s, 1H), 3.28 (s, 3H), 2.82 (s, 3H), 0.92 – 0.85 (m, 2H), 0.79 – 0.71 (m, 2H).; **^{1}H NMR (600 MHz, DMSO-*d*$_6$/D$_2$O/TFA) δ** 8.67 (d, *J* = 7.0 Hz, 2H), 8.19 (s, 1H), 8.07 (d, *J* = 7.0 Hz, 2H), 8.04 (d, *J* = 8.2 Hz, 1H), 8.02 (d, *J* = 8.6 Hz, 1H), 7.96 (s, 1H), 7.93 (d, *J* = 9.0 Hz, 1H), 7.90 (dd, *J* = 1.5, 8.2 Hz, 1H), 7.68 – 7.65 (m, 2H), 7.27 (dd, *J* = 2.4, 8.9 Hz, 1H), 3.27 (s, 3H), 2.80 (s, 3H), 0.92 – 0.87 (m, 2H), 0.75 – 0.72 (m, 2H) (**Note:** The (CH) of the cyclopropoxy group is not observed due to superposition of HOD signal); **^{13}C{^{1}H} NMR (126 MHz, DMSO-*d*$_6$) δ** 157.4, 149.7, 145.1, 142.1, 140.0, 137.9, 134.4, 134.0, 129.7, 129.5, 129.2, 128.6, 127.8, 127.4, 127.1, 125.3, 124.3, 120.7, 119.3, 108.0, 51.0, 43.5, 21.5, 6.0 (**Note**: Two carbon signals in the ^{13}C{^{1}H} NMR are missing) **^{13}C{^{1}H} NMR (151 MHz, DMSO-*d*$_6$/D$_2$O/TFA) δ** 158.0, 150.9, 146.7, 141.4, 140.9, 138.6, 137.4, 134.8, 133.4, 131.6, 130.2, 129.9, 129.8, 128.8, 128.7, 128.2, 127.0, 124.7, 124.4, 122.1, 119.8, 108.3, 51.4, 43.6, 21.5, 6.2; **ν_{max} (cm^{-1}, thin film, ATR):** 3038 (w), 2927 (w), 1629 (w), 1603 (s), 1573 (w), 1494 (w), 1445 (w), 1354 (w), 1304 (m), 1260 (m), 1216 (m), 1149 (s), 1120 (w), 1107 (m), 1074 (w), 996 (w), 986 (s), 966 (w), 953 (m), 872 (w), 836 (s), 804 (w), 764 (s), 742 (m); **HRMS (ESI+/TOF) m/z:** $[M+H]^+$ Calcd for $C_{29}H_{26}N_3O_3S$ 496.1695; Found 496.1715; **mp:** 268.0 °C (dec.).

tert-Butyl (6-(2-(2-methyl-4-(methylsulfonyl)phenyl)-5-(pyridin-4-yl)-1H-

*imidazol-4-yl)naphthalen-2-yl)carbamate (**60**).* The title compound was prepared according to general procedure C, using **44** (39.0 mg, 0.10 mmol, 1.00 equiv..), tert-butyl (6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-yl)carbamate[41] (**S13**) (46.0 mg, 0.125 mmol, 1.25 equiv.), $Pd(OAc)_2$ (2.3 mg, 10 mol%) and Aphos (6.7 mg, 24 mol%). Purification by silica gel chromatography, eluting with EtOH in $CHCl_3$ (21 cm x 10 mm, gradient elution, 0% → 6%, 0.5% increases, 20 mL runs, 3-4 mL fractions) followed by repurification in silica gel using MeOH in DCM eluent (21 cm x 10 mm, gradient elution, 0% → 6%, 0.5% increases, 20 mL runs, 7 mL fractions) yielded **60** as a yellow solid (40% yield, 22.0 mg, 0.04 mmol). **R_f =** 0.47 (7% EtOH/$CHCl_3$, Dragendorff stain) ; **^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ** 13.09 (s, 1H), 9.67 (s, 1H), 8.45 (d, J = 3.6 Hz, 2H), 8.17 (s, 1H) 8.10 – 8.00 (m, 2H), 7.95 – 7.82 (m, 4H), 7.63 – 746 (m, 4H), 3.27 (s, 3H), 2.81 (s, 3H), 1.52 (s, 9H) (**Note:** Minor peaks in the ^{1}H NMR are due to the presence of a tautomers in the sample); **^{13}C{^{1}H} NMR (126 MHz, DMSO-*d*$_6$) δ** 152.9, 150.0, 149.7, 145.2, 142.2, 140.1, 138.1, 137.9, 134.4, 133.9, 133.4, 131.5, 129.6, 129.5, 129.3, 129.0, 128.7, 127.7 (2x), 127.0, 125.7, 124.4, 122.0, 120.8, 120.3, 113.4, 79.5, 43.5, 28.2, 21.5 (**Note:** Extra peaks in the ^{13}C{^{1}H} NMR are due to the presence of tautomers in the sample); **ν_{max} (cm^{-1}, thin film, ATR):** 2925 (w), 2848 (w), 1724 (m), 1712 (m), 1603 (s), 1494 (w), 1367 (w), 1305 (m), 1238 (m), 1150 (s), 1108 (w), 1052 (w), 1025 (w), 958 (m), 884 (m), 835 (m), 764 (m); **HRMS (ESI+/TOF) m/z:** $[M+H]^+$ Calcd for $C_{31}H_{31}N_4O_4S$ 555.2066; Found 555.2047; **mp:** 180.0 °C (dec.).

*4-(5-([1,1'-Biphenyl]-4-yl)-2-(2-methyl-4-(methylsulfonyl)phenyl)-1H-imidazol-4-yl)pyridine (**61**).* The title compound was prepared according to general procedure C, using **44** (39.0 mg, 0.10 mmol, 1.00 equiv.), 4-biphenylboronic acid (25.0 mg, 0.125 mmol, 1.25 equiv.), $Pd(OAc)_2$ (2.3 mg, 10 mol%) and Aphos (6.7 mg, 24 mol%). Purification by silica gel chromatography, eluting with EtOH in $CHCl_3$ (21 cm x 10 mm, gradient elution, 0% → 4%, 0.5% increases, 20 mL runs, 3-4 mL fractions) followed by repurification in silica gel using MeOH in DCM eluent (21 cm x 10 mm, gradient elution, 0% → 4.5%, 0.5% increases, 20 mL runs, 7 mL fractions) yielded **61** as a pale yellow solid (60% yield, 28.0 mg, 0.06 mmol). **R_f =** 0.42 (7% EtOH/$CHCl_3$, Dragendorff stain); **^{1}H NMR (500 MHz, DMSO-*d*$_6$/D$_2$O/TFA) δ** 8.60 (d, *J* =6.9 Hz, 2H), 8.09 (d, *J* = 6.9 Hz, 2H), 7.94 (d, *J* = 8.2 Hz, 1H), 7.91 (s, 1H) 7.87 – 7.81 (m, 3H) 7.74 – 7.68 (m, 4H), 7.49 (t, *J* = 7.7 Hz, 2H), 7.39 (t, *J* = 7.3 Hz, 1H); **^{13}C{^{1}H} NMR (126 MHz, DMSO-*d*$_6$/D$_2$O/TFA) δ** 150.9, 147.3, 142.3, 141.8, 141.5, 139.8, 139.6, 137.3, 133.6, 131.5,

130.9, 130.4, 130.2, 130.0, 129.0, 128.4, 128.3, 127.5, 125.3,123.3, 44.2, 21.6; **ν_{max} (cm^{-1}, thin film, ATR):** 2925 (br), 2360 (w), 1602 (s), 1517 (w), 1480 (w), 1443 (w), 1312 (s), 1213 (w), 1147 (s), 1109 (m), 1075 (w), 1075 (w), 999 (w), 958 (m), 877 (w), 768 (s), 762 (s), 744 (s), 733 (s), 700 (m); **HRMS (ESI+/TOF) m/z:** $[M+H]^+$ Calcd for $C_{28}H_{24}N_3O_2S$ 466.1589 ; Found 466.1571; **mp**: 241.0 °C (dec.).

*4'-(2-(2-Methyl-4-(methylsulfonyl)phenyl)-5-(pyridin-4-yl)-1H-imidazol-4-yl)-[1,1'-biphenyl]-4-carbonitrile (**62**)*. The title compound was prepared according to general procedure C, using **44** (39.0 mg, 0.10 mmol, 1.00 equiv..), 4'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,1'-biphenyl]-4-carbonitrile (39.0 mg, 0.125 mmol, 1.25 equiv.), $Pd(OAc)_2$ (2.3 mg, 10 mol%) and Aphos (6.7 mg, 24 mol%). Purification by silica gel chromatography, eluting with EtOH in $CHCl_3$ (21 cm x 10 mm, gradient elution, 0% → 4%, 0.5% increases, 20 mL runs, 3-4 mL fractions) followed by repurification in silica gel using MeOH in DCM eluent (21 cm x 10 mm, gradient elution, 0% → 5%, 0.5% increases, 20 mL runs, 7 mL fractions) yielded **62** as a white solid (47% yield, 23.0 mg, 0.05 mmol); **R_f** = 0.35 (7% EtOH/$CHCl_3$, Dragendorff stain); **^{1}H NMR (500 MHz, DMSO-*d*$_6$/D$_2$O/TFA) δ** 8.61 (d, *J* = 6.8 Hz, 1H), 8.10 (d, *J* = 6.8 Hz, 1H), 7.97 – 7.88 (m, 8H), 7.86 (d, *J* = 8.1 Hz, 1H), 7.75 (d, *J* = 8.3 Hz, 1H), 3.21 (s, 1H), 2.71 (s, 1H); **^{13}C{^{1}H} NMR (126 MHz, DMSO-*d*$_6$/D$_2$O/TFA) δ** 151.0, 147.5, 144.4, 141.8, 141.4, 140.1, 139.4, 136.9, 133.7, 133.7, 131.8, 130.8, 130.5, 130.2, 129.9, 128.7, 128.4, 125.2, 123.2, 119.7, 111.2, 44.1, 21.6; **ν_{max} (cm^{-1}, thin film, ATR):** 3083 (br), 2846 (br), 2359 (w), 2225 (w), 1604 (m), 1499 (w), 1410 (w), 1310 (m), 1301 (m), 1150 (s), 1111 (m), 1077 (w), 1004 (w), 972 (w), 959 (w), 880 (w), 825 (s), 765 (m), 765 (m), 745 (m), 715 (w), 693 (m); **HRMS (ESI+/TOF) m/z:** $[M+H]^+$ Calcd for $C_{29}H_{23}N_4O_2S$ 491.1542 ; Found 491.1530; **mp**: 255.0 °C (dec.).

*4-(2-(2-Methyl-4-(methylsulfonyl)phenyl)-4-(5,6,7,8-tetrahydronaphthalen-2-yl)-1H-imidazol-5-yl)pyridine (**63**)*. The title compound was prepared according to general procedure C, using **44** (39.0 mg, 0.10 mmol, 1.00 equiv..), 4,4,5,5-tetramethyl-2-(5,6,7,8-tetrahydronaphthalen-2-yl)-1,3,2-dioxaborolane (**S15**) (33.0 mg, 0.125 mmol, 1.25 equiv.), $Pd(OAc)_2$ (2.3 mg, 10 mol%) and Aphos (6.7 mg, 24 mol%). Purification by silica gel chromatography, eluting with EtOH in $CHCl_3$ (21 cm x 10 mm, gradient elution, 0% → 5.5%, 0.5% increases, 20 mL runs, 3-4 mL fractions) followed by repurification in silica gel using MeOH in DCM eluent (21 cm x 10 mm, gradient elution, 0% → 5.5%, 0.5% increases, 20 mL runs, 7 mL fractions) yielded **63** as a white solid (61% yield, 27.0

mg, 0.06 mmol). **R_f =** 0.33 (7% EtOH/$CHCl_3$, UV, Dragendorff stain); **^{1}H NMR (500 MHz, DMSO-*d*$_6$/D$_2$O/TFA) δ** 8.61 (d, *J* = 6.6 Hz, 2H), 8.08 (d, *J* = 6.8 Hz, 2H), 7.94 (d, *J* = 8.3 Hz, 1H), 7.91 (s, 1H), 7.85 (d, *J* = 8.3 Hz, 1H), 7.32 (s, 1H), 7.29 (d, *J* = 7.9 Hz, 1H), 7.22 (d, *J* = 7.9 Hz, 1H), 3.22 (s, 3H), 2.80 – 2.73 (m, 4H), 2.71 (s, 3H), 1.78 – 1.72 (m, 4H); **^{13}C{^{1}H} NMR (126 MHz, DMSO-*d*$_6$/D$_2$O/TFA) δ** 151.2, 146.8, 141.5, 141.2, 139.6, 139.1, 138.6, 137.8, 133.6, 131.2, 130.6, 130.5, 130.0, 129.9, 126.6, 126.4, 125.0, 122.6, 44.0, 29.3, 29.2, 23.0, 21.5 (**Note**: The signal at δ 23.0 ppm in the ^{13}C{^{1}H} NMR corresponds to two carbons from the tetrahydronaphthalene moiety); **ν_{max} (cm^{-1}, thin film, ATR):** 2935 (w), 2856 (w), 1599 (s), 1429 (w), 1309 (s), 1212 (w), 1147 (s), 1106 (m), 1076 (w), 998 (w), 963 (w), 952 (w), 871 (w), 827 (m), 808 (w), 765 (s), 738 (m); **HRMS (ESI+/TOF) m/z:** $[M+H]^+$ Calcd for $C_{26}H_{26}N_3O_2S$ 444.1746; Found 444.1761; **mp:** 252.0 °C (dec.).

*4-(4-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)-2-(2-methyl-4-(methylsulfonyl)phenyl)-1H-imidazol-5-yl)pyridine (**64**)*. The title compound was prepared according to general procedure C, using **44** (39.0 mg, 0.10 mmol, 1.00 equiv.), 1,4-benzodioxane-6-boronic acid (25.0 mg, 0.125 mmol, 1.25 equiv.), $Pd(OAc)_2$ (2.3 mg, 10 mol%) and Aphos (6.7 mg, 24 mol%). Purification by silica gel chromatography, eluting with EtOH in $CHCl_3$ (21 cm x 10 mm, gradient elution, 0% → 5%, 0.5% increases, 20 mL runs, 3-4 mL fractions) followed by repurification in silica gel using MeOH in DCM eluent (15 cm x 10 mm, gradient elution, 0% → 6%, 0.5% increases, 20 mL runs, 7 mL fractions) yielded **64** as a pale yellow solid (60% yield, 27.0 mg, 0.06 mmol). **R_f =** 0.37 (7% EtOH/$CHCl_3$, Dragendorff stain); **^{1}H NMR (500 MHz, DMSO-*d*$_6$/D$_2$O/TFA) δ** 8.59 (d, *J* =7.0 Hz, 2H), 8.06 (d, *J* = 7.0 Hz, 2H), 7.91 (d, *J* = 8.2 Hz, 1H), 7.89 (d, J = 1.4, 1H) 7.84 (dd, J = 8.2, 1.8 Hz, 1H), 7.10 (d, J = 2.1, 1H), 7.05 (dd *J* = 8.3, 2.1 Hz, 1H), 7.00 (d, *J* = 8.3 Hz, 1H), 4.30 – 4.25 (m, 4H), 3.20 (s, 3H), 2.67 (s, 3H); **^{13}C{^{1}H} NMR (126 MHz, DMSO-*d*$_6$/D$_2$O/TFA) δ** 150.9, 146.8, 145.6, 144.6, 141.7, 141.5, 139.5, 137.2, 133.5, 130.9, 130.8, 130.2, 125.2, 123.0, 123.0, 122.1, 118.9, 118.4, 65.1, 64.9, 44.1, 21.5; **ν_{max} (cm^{-1}, thin film, ATR):** 2668 (br), 2360 (w), 1603 (s), 1541 (w), 1512 (w), 1489 (w), 1461 (w), 1442 (w), 1311 (s), 1287 (s), 1253 (m), 1154 (s), 1112 (w), 1097 (w), 1063 (s), 1049 (w), 1006 (w), 977 (w), 965 (w), 951 (m), 931 (w), 893 (w), 875 (w), 865 (m), 841 (w), 830 (s), 764 (m), 741 (m.), **HRMS (ESI+/TOF) m/z:** $[M+H]^+$ Calcd for $C_{24}H_{22}N_3O_4S$ 448.1331; Found 448.1315; **mp:** 299.0 °C (dec.).

One-pot Miyaura Borylation-Suzuki Coupling. *7-(2-(2-Methyl-4-*

(methylsulfonyl)phenyl)-5-(pyridin-4-yl)-1H-imidazol-4-yl)quinoline (**67**)**:** A culture tube (13 mm x 100 mm, 9 mL) was charged with 7-bromoquinoline (***65***) (42.0 mg, 0.20 mmol, 2.00 equiv.), $B_2(pin)_2$ (80.0 mg, 0.30 mmol, 3.00 equiv.) and KOAc (59.0 mg, 0.60 mmol, 6.00 equiv.) and a magnetic stirrer bar under nitrogen. Degassed DME (0.15 mL) was added followed by a premixed solution of $Pd(OAc)_2$ (2.4 mg, 0.011 mmol, 5 mol% relative to **65**) and Aphos (7.1 mg, 0.025 mmol, 12% relative to **65**) in DME (0.35 mL). The reaction mixture was stirred in a pre-heated aluminum block at 80 ºC for 2h. After consumption of the starting material, indicated by TLC analysis (30% EtOAc/Hex, $KMnO_4$), the reaction mixture was cooled to room temperature, the culture tube was opened under a nitrogen flow and **44** (39.0 mg, 0.10 mmol, 1.00 equiv.) was added followed by addition of a premixed solution of $Pd(OAc)_2$ (1.2 mg, 0.005 mmol, 5 mol% relative to **44**) and Aphos (3.6 mg, 0.01 mmol, 12 mol% relative to **44**) in DME (0.15 mL). Then, DME (0.10 mL) and 1.2 M K_2CO_3 aqueous solution (0.25 mL, 0.30 mml, 3.00 equiv.) were added and the reaction mixture was purged with nitrogen for 5 minutes. The reaction mixture was stirred in a pre-heated aluminum block at 80 ºC for 18h. After consumption of the **44**, indicated by TLC analysis (7% EtOH/$CHCl_3$, Dragendorff), the reaction mixture was allowed to reach room temperature and it was diluted with 10% MeOH/DCM (~7 mL), filtered through a pad (20 mm diameter) composed of Celite (top, 1 cm) and silica gel (bottom, 3 cm). The pad was washed with 10% MeOH/DCM (25-50 mL) and the filtrate was concentrated under in the reduced pressure. The crude product was adsorbed over basic alumina and purified by silica column chromatography, eluting with EtOH in $CHCl_3$ (21 cm x 10 mm, gradient elution, 0% → 7%, 0.5% increases, 20 mL runs, 3-4 mL fractions) followed by repurification in silica gel using MeOH in DCM eluent (21 cm x 10 mm, gradient elution, 0% → 8%, 0.5% increases, 20 mL runs, 7 mL fractions) to yield **67** as a white solid (50% yield, 22.0 mg, 0.05 mmol). $\mathbf{R_f}$ **=** 0.45 (7% EtOH/$CHCl_3$, Dragendorff stain); **^{1}H NMR (500 MHz, DMSO-*d*$_6$/D$_2$O/TFA) δ** 9.22 (d, *J* = 5.2 Hz, 1H), 9.12 (d, *J* = 8.4 Hz, 1H), 8.66 (d, *J* = 6.8 Hz, 2H), 8.44 (s, 1H), 8.41 (d, *J* = 8.6 Hz, 1H), 8.13 (d, *J* = 6.8 Hz, 2H), 8.09 (d, *J* = 8.5 Hz, 1H), 8.07 – 8.03 (m, 1H), 7.99 (d, *J* = 8.1 Hz, 1H), 7.94 (s, 1H), 7.89 (d, *J* = 8.1 Hz, 1H), 3.23 (s, 3H), 2.74 (s, 3H); **^{13}C{^{1}H} NMR (126 MHz, DMSO-*d*$_6$/D$_2$O/TFA) δ** 150.0, 148.5, 147.3, 146.0, 142.1, 141.5, 139.7, 139.5, 135.9, 135.5, 133.8, 132.5, 131.0, 130.8, 130.2, 130.2, 129.3, 125.2, 124.1, 123.3, 122.0, 44.1, 21.5; **ν_{max} (cm^{-1}, thin film, ATR):** 2922 (w), 2845 (w), 1614 (w), 1584 (w), 1509 (w), 1490 (w), 1449 (w), 1303 (s), 1210 (w), 1155 (m), 1141 (s), 1104 (m), 1073 (w), 975 (w), 958 (w), 880 (m), 837 (s), 765 (s), 742 (m); **HRMS**

(ESI+/TOF) m/z: $[M+H]^+$ Calcd for $C_{25}H_{21}N_4O_2S$ 441.1385; Found 441.1372; **mp:** 300.0 °C (dec.).

tert-Butyl 4-(4-bromo-5-(pyridin-4-yl)-1H-imidazol-2-yl)piperidine-1-carboxylate (**69**) Following a modified literature procedure[24], a 25 mL round-bottom flask was charged with **36** (437 mg, 1.33 mmol, 1.00 equiv.), dry DCM (5.9 mL), dry pyridine (1.5 mL) and a magnetic stirrer bar under inert atmosphere. The RBF was covered with aluminum foil and the reaction mixture was cooled to 0 ºC in an ice/water bath and stirred for 15 minutes. Solid Py•HBr•Br_2 (pyridinium hydrobromide perbromide, 520 mg, 1.46 mmol, 1.10 equiv.) was added in portions, by briefly removing the Suba seal, and the reaction mixture was stirred at 0 ºC for 1 hour. After consumption of the starting material, indicated by TLC analysis (100% EtOAc, Dragendorff), the solvent was removed in the rotaevaporator. The residue was partitioned between 1M aq. $NaHSO_3$ (1x 30 mL) and $CHCl_3$ (1x 30 mL). The phases were separated and the aqueous layer was extracted with $CHCl_3$ (3x 15 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated in the rotaevaporator. Purification by silica gel chromatography, eluting with MeOH in $CHCl_3$ (13 cm x 30 mm, gradient elution, 4% → 6%, 0.5% increases, 80 mL runs, 20 mL fractions) followed by repurification in silica gel using EtOAc:EtOH (3:1) in hexanes (13 cm x 30 mm, isocratic elution, 50% EtOAc:EtOH (3:1)/Hex, 400 mL run, 20 mL fractions) yielded a light yellow gum to which precipitation was induced with pentane to afford **69** as pale yellow solid (95% yield, 513 mg, 1.26 mmol). $\mathbf{R_f}$ = 0.37 (50% EtOAc:EtOH (3:1)/Hexanes, UV, Dragendorff). $\mathbf{R_f}$ = 0.17 (5% MeOH/DCM, UV, Dragendorff). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 12.10 (br. s, 1H), 8.52 (s, 2H), 7.76 (s, 2H), 4.14 (d, J = 11.4 Hz, 2H), 2.97 – 2.88 (m, 1H), 2.88 – 2.68 (m, 2H), 1.92 (d, J = 11.5 Hz, 2H), 1.84 – 1.64 (m, 2H), 1.43 (s, 9H). **^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ** 154.8, 153.2, 149.6, 120.4, 80.3, 43.9, 36.7, 30.8, 28.6 **Note:** Due to slow relaxation, some $^{13}C\{^1H\}$ NMR signals were not identified in the spectra[28]. Specifically, the $^{13}C\{^1H\}$ NMR data for compound **69** lacks three of the twelve expected signals. **ν_{max} (cm^{-1}, thin film, ATR):** 2875 (br), 1679 (s), 1603 (s), 1580 (w), 1519 (w), 1367 (m), 1276 (m), 1233 (s), 1164 (s), 1125 (m), 1063 (w), 1045 (w), 1003 (m), 981 (m), 935 (m), 874 (w), 821 (m), 723 (w), 693 (m). **HRMS (ESI+/TOF) m/z:** $[M+H]^+$ Calcd for $C_{18}H_{24}BrN_4O_2$ 407.1083, 409.1064; Found 407.1051, 409.1126. **mp:** 197.0 °C (dec.).

*tert-Butyl 4-(4-(6-methoxynaphthalen-2-yl)-5-(pyridin-4-yl)-1H-imidazol-2-yl)piperidine-1-carboxylate (**71**).* The title compound was prepared according to general

procedure C, using **69** (41.0 mg, 0.10 mmol, 1.00 equiv.), 2-(6-methoxynaphthalen-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**S16**) (52.0 mg, 0.175 mmol, 1.75 equiv.), $Pd(OAc)_2$ (2.3 mg, 10 mol%) and Aphos (6.7 mg, 24 mol%). Purification by silica gel chromatography, eluting with EtOH in $CHCl_3$ (20 cm x 15 mm, gradient elution, 0% → 4.5%, 0.5% increases, 25 mL runs, 5 mL fractions then isocratic elution, 4.5% EtOH/$CHCl_3$, 50 mL run, 5 mL fractions) yielded **71** as a pale yellow solid (89% yield, 43.0 mg, 0.89 mmol). **R_f =** 0.40 (7% EtOH/$CHCl_3$, UV, Dragendorff stain). **^{1}H NMR (250 MHz, $CDCl_3$) δ** 10.07 (br. s, 1H), 8.41 (d, *J* = 5.2 Hz, 2H), 7.90 – 7.77 (m, 1H), 7.72 (d, *J* = 8.6 Hz, 1H), 7.67 (d, *J* = 8.8 Hz, 1H), 7.59 – 7.36 (m, 3H), 7.21 – 7.11 (m, 2H), 4.30 – 4.12 (m, 2H), 3.93 (s, 3H), 3.00 (tt, *J* = 11.7, 3.6 Hz, 1H), 2.92 – 2.73 (m, 2H), 2.11 – 1.95 (m, 2H), 1.77 (dq, *J* = 3.7, 12.4 Hz, 1H), 1.45 (s, 9H). **^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ** 158.5, 154.8, 151.3, 150.2, 149.8, 142.8, 134.4, 133.6, 129.6, 129.4, 129.0, 127.7, 127.2, 127.1, 126.8, 125.8, 121.5, 121.3, 119.8, 105.9, 79.9, 55.5, 36.5, 31.0, 29.8, 28.6. **ν_{max} (cm^{-1}, thin film, ATR):** 2930 (br), 1693 (s), 1601 (s), 1536 (w), 1418 (m), 1391 (w), 1366 (w), 1273 (m), 1249 (w), 1210 (m), 1165 (s), 1123 (m), 1085 (m), 1030 (w), 1007 (w), 99 (w), 857 (w), 831 (m), 693 (w), 667 (w). **HRMS (ESI+/TOF) m/z:** $[M+H]^+$ Calcd for $C_{29}H_{33}N_4O_3$ 485.2553; Found 485.2537. **mp:** 193.0 °C (dec.). Spectroscopic data are in accordance with the literature[11].

Synthesis of GSK3037619A (**72**)**:** *N*-Boc piperidine substituted imidazole **71** (12.0 mg, 0.03 mmol, 1.0 equiv.) was dissolved in DCM (0.25 mL, 0.1 M) under nitrogen atmosphere. Trifluoroacetic acid (39 µL, 0.50 mmol, 20 equiv.) was added and the reaction mixture was allowed to stir for 1h and was followed by TLC (10% MeOH:NH_4OH (10:1)/DCM). After consumption of starting material, the solvent and excess trifluoroacetic acid was removed in vacuo and the residue was dissolved in anhydrous MeCN (1 mL, 0.03 M) under nitrogen atmosphere. Then Et_3N (5.3 µL, 0.04 mmol, 1.5 equiv.) was added followed by a 37 % aqueous formaldehyde solution (14 µL, 0.19 mmol, 7.5 equiv.) and the reaction mixture was left to stir for 1h at room temperature. $Na(OAc)_3BH$ (14.0 mg, 0.06 mmol, 2.5 equiv.) was added and the reaction mixture stirred for 18h. The solvent was removed under reduced pressure and the residue was diluted in 10% MeOH:NH_4OH (10:1)/$CHCl_3$, filtered through a short (1 cm x 15 mm) pad of silica gel, which was washed with 10% MeOH:NH_4OH (10:1)/$CHCl_3$ until product has eluted completely, the solvent was concentrated resulting in a yellow residue. Purification by silica gel chromatography, eluting with MeOH:NH_4OH (10:1) in $CHCl_3$ (4 cm x 15 mm,

isocratic elution, 10% MeOH:NH_4OH (10:1)/$CHCl_3$, 50 mL run, 2 mL fractions) yielded a white solid which was triturated with Et_2O:Hexanes (2:8) (3x 5 mL) to afford **72** as a white solid (80% yield, 8 mg, 0.02 mmol). **R_f =** 0.40 (10% MeOH:NH_4OH (10:1)/$CHCl_3$, UV, Dragendorff stain). **^{1}H NMR (600 MHz, CD_3OD) δ** 8.36 (d, *J* = 6.2 Hz, 2H), 7.88 (s, 1H), 7.82 (d, *J* = 8.5 Hz, 1H), 7.75 (d, *J* = 8.9 Hz, 1H), 7.49 (d, *J* = 6.2 Hz, 2H), 7.43 (dd, *J* = 1.7, 8.6 Hz, 1H), 7.28 (d, *J* = 2.5 Hz, 1H), 7.17 (dd, *J* = 9.0, 2.7 Hz, 1H), 3.93 (s, 3H), 3.02 (d, *J* = 11.8 Hz, 2H), 2.87 (tt, *J* = 12.0, 3.9, Hz, 1H), 2.34 (s, 3H), 2.19 (dt, *J* = 11.9, 2.0 Hz, 2H), 2.06 (d, *J* = 11.1 Hz, 2H), 1.97 (dq, *J* = 12.6, 3.4 Hz, 2H). **^{13}C{^{1}H} NMR (151 MHz, CD_3OD) δ** 159.9, 154.1, 150.0, 136.0, 130.6, 130.3, 128.6, 128.6, 127.9, 123.0, 120.6, 106.8, 56.4, 55.8, 46.4, 36.9, 31.7. **ν_{max} (cm^{-1}, thin film, ATR):** 3010 (br), 2939 (w), 2848 (w), 2792 (w), 1630 (w), 1601 (s), 1535 (w), 1493 (w), 1465 (w), 1379 (w), 1270 (m), 1209 (w), 1181 (w), 1164 (w), 1127 (w), 1066 (w), 1029 (w), 994 (w), 832 (w), 753 (w), 695 (w). **HRMS (ESI+/TOF) m/z:** $[M+H]^+$ Calcd for $C_{25}H_{27}N_4O$ 399.2185; Found 399.2201**. mp:** 262.0 °C (dec.)

2. Associated Content

The Supporting Information is available free of charge on the ACS Publications website at DOI: XX.XXXX/XXX.XXX.XXXXXXX

^{1}H and ^{13}C{^{1}H} NMR spectra for compounds 5-31, 32, 36, 43, 44, 46-64, 67, 69, 71, 72. Optimization tables (Table S1 and Table S2). Synthetic procedures for compounds S1-S16.

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Notes

The authors declare no competing financial interest

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