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C2-Selective Branched Alkylation of Benzimidazoles by Rhodium(I)-Catalyzed C−H Activation

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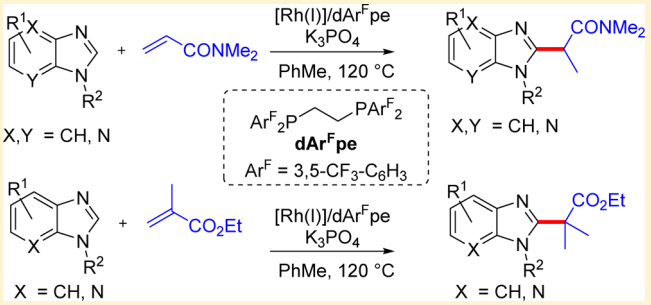
Supporting Information

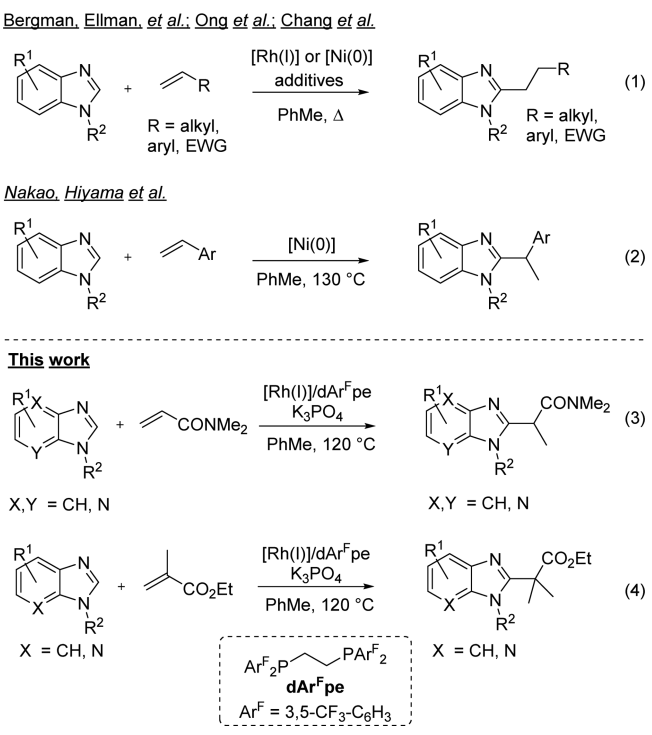
ABSTRACT: Herein, we report a Rh(I)/bisphosphine/K_3PO_4 catalytic system allowing for the first time the selective branched C−H alkylation of benzimidazoles with Michael acceptors. Branched alkylation with *N*,*N*-dimethyl acrylamide was successfully applied to the alkylation of a broad range of benzimidazoles incorporating a variety of *N*-substituents and with both electron-rich and -poor functionality displayed at different sites of the arene. Moreover, the introduction of a quaternary carbon was achieved by alkylation with ethyl methacrylate. The method was also shown to be applicable to the C2-selective branched alkylation of azabenzimidazoles.



The benzimidazole framework is among the most extensively used scaffolds in the pharmaceutical industry,[1] and the synthesis and functionalization of benzimidazoles have been the subject of a considerable number of studies.[2] Among them, the regioselective transition metal-catalyzed C−H functionalization of benzimidazoles has elicited significant interest because it allows rapid access to elaborated substrates from simple precursors.[3] In particular, the direct C−H alkylation of C2-unsubstituted benzimidazoles with alkenes proceeds with complete atom economy.[4] Both Rh and Ni catalyst systems have been reported to promote intermolecular benzimidazole C−H alkylations with very high *linear* selectivity, and depending on the reaction conditions and catalyst used, a vinyl group can be substituted with alkyl,[5] aryl,[6] or electron-withdrawing[7] groups (Scheme 1, eq 1). In contrast, *branched*-selective intermolecular alkylation of benzimidazoles is limited to a single report, which employs styrenes with a Ni catalyst system (Scheme 1, eq 2).[8,9] We have recently demonstrated that a Rh(I) precatalyst combined with the electron-poor ligand dAr^Fpe and K_3PO_4 enables the completely branched selective alkylation of pyridines in high yields.[10] Herein, we report that this catalyst system can be extended to the *branched* selective alkylation of a wide range of benzimidazole and azabenzimidazole derivatives with *N*,*N*-dimethylacrylamide (eq 3) and to the first examples of branched-selective C−H alkylation to introduce a quaternary carbon with ethyl methacrylate (eq 4).

After reevaluation of a broad range of reaction parameters, it was found that the optimal conditions previously reported for the branched alkylation of pyridines were also the most effective for the branched alkylation of *N*-methylbenzimidazole **1a** with *N*,*N*-dimethylacrylamide **2**. Under these conditions, product **3a** was obtained in 71% yield with exclusive regioselectivity in favor of the C2-position and with complete

Scheme 1. C2-Selective Alkylations of Benzimidazoles



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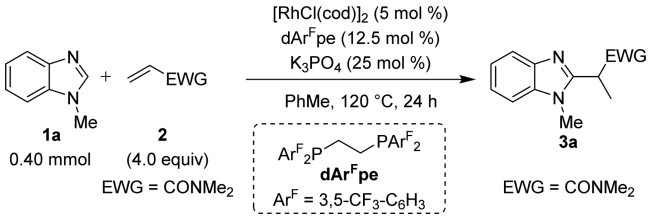
branched selectivity (Table 1, entry 1). K_3PO_4 was the base of choice as other inorganic bases either led to complete shut-

Table 1. Key Reaction Parameters



entry	change from optimal conditions	yield[a]
1	none	71% (68%)
2	K_2HPO_4 instead of K_3PO_4	0%
3	K_2CO_3 instead of K_3PO_4	15%
4	KOPiv instead of K_3PO_4	0%
5	dppe instead of dArFpe	13%
6	100 °C instead of 120 °C	14%
7	EWG = CO_2tBu instead of $CONMe_2$	12%
8	EWG = CO_2Et instead of $CONMe_2$	14%[b]
9	Mesitylene instead of PhMe	74%
10	THF instead of PhMe	41%

[a]Determined from the crude reaction mixture by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. Isolated yields in parentheses. [b]^{1}H NMR also showed the presence of 17% yield of the linear product.

down of the reaction or drastically reduced yields (Table 1, entries 2–4). The electron-deficient bisphosphine dArFpe ((3,5-CF_3Ph)pe) was also a critical element of the catalytic system, and the use of its more electron-rich analogue dppe only led to a 13% yield (Table 1, entry 5). Reducing the temperature to 100 °C seemed to promote competitive polymerization of the alkene partner (Table 1, entry 6), as did the replacement of acrylamide **2** by *tert*-butyl acrylate and ethyl acrylate (Table 1, entries 7 and 8). Mesitylene was evaluated in place of toluene as solvent because its boiling point of 165 °C is well above the reaction temperature of 120 °C and gave a comparable reaction yield (Table 1, entry 9). However, toluene was employed for evaluating reaction scope because it can be readily purchased in anhydrous form. Other common solvents such as THF could be used in the reaction, but the yield was significantly lower (Table 1, entry 10).

The optimized conditions proved to be very general, and a broad scope was observed for the benzimidazole coupling partner (Scheme 2). Substitution at the N1-position with a methyl, phenyl or benzyloxymethyl (BOM) protecting group led to excellent yields of the corresponding benzimidazoles **3a–c**, and scale-up of the alkylation of benzimidazole **1a** from 0.4 to 7.6 mmol did not lead to a significant change in yield. Benzimidazoles substituted at the C5, C6, or C7 positions with a wide range of electron-withdrawing groups such as esters (**3d** and **3e**), sulfonyl (**3f**), chloro (**3g**), nitrile (**3h**), or trifluoromethyl (**3i–l**) provided alkylation products in good to excellent yields. Only benzimidazole **3l**, bearing a trifluoromethyl substituent at the C4-position, was obtained in a low yield of 12%. Electron-donating group such as methoxy or methyl were also very well tolerated when used in conjunction with a BOM-protecting group (**3m–o**). Because we previously reported that azines could be efficiently alkylated using the present method, it was a surprise for us to see that azine-fused imidazoles **1p** and **1q** could be selectively alkylated at the C2 position without any undesired alkylation on the azine ring. Electron-withdrawing and -donating substituents were well tolerated in these cases as well (**3r** and **3s**). In very preliminary studies, an *N*-methyl and an *N*-BOM-substituted imidazole were evaluated under the standard reaction conditions, but starting material was primarily recovered (**3t** and **3u**). It is possible that alkylation might occur under different reaction conditions or with imidazoles having alternative substitution patterns.

Although broad in scope with respect to the benzimidazole substituents, this method is primarily restricted to *N,N*-disubstituted acrylamides as the Michael acceptor. We therefore demonstrated that the amide products can be easily transformed to the corresponding aldehydes by treatment with Schwartz reagent (Scheme 3).[11] Owing to the instability of the aldehyde products to long-term storage, they were isolated and characterized as their *O*-methyl oximes derivatives **4** after treatment with NH_2–OMe·HCl. Given that aldehydes are among the most versatile functional handles in organic chemistry, this method can potentially be used to access a very broad range of branched benzimidazole derivatives.

The introduction of a quaternary carbon center by Rh(I)-catalyzed C–H bond additions to methacrylate derivatives was also investigated (Scheme 4). Although *N,N*-dimethyl methacrylamide did not provide any desired product, ethyl methacrylate (**5**) proved to be a suitable alkene partner, thus allowing the direct incorporation of a quaternary center (Scheme 4). However, in contrast to what was observed in the scope exploration using *N,N*-dimethylacrylamide, we found that the branched to linear alkylation selectivity of this reaction is dependent upon the substitution pattern of nitrogen heterocycle **1**. Indeed, although the use of *N*-BOM-benzimidazole (**1c**) led to both branched and linear products in 32% (**6c**) and 34% (**6c′**) yields, respectively, electron-poor heterocycles provided the branched products such as **6j** and **6q** with high selectively and in excellent yields. We also found that the reaction was very sensitive to any adventitious water, which resulted in low yields of product. The greater sensitivity of the alkylation reaction to water when ethyl methacrylate (**5**) is used instead of *N,N*-dimethylacrylamide (**2**) potentially arises from the higher propensity of ethyl methacrylate to oligomerize under basic conditions.

In summary, we have developed a Rh(I)-catalyzed C2-selective alkylation of benzimidazole derivatives with *N,N*-dimethylacrylamide with complete branched selectivity. This transformation complements the previously reported branched alkylation of benzimidazoles by styrenes and the linear alkylation of benzimidazoles by Michael acceptors. Alkylated benzimidazoles featuring a broad range of different electronic properties can be accessed in good to excellent yields, and the amide products can be easily converted to aldehydes as versatile synthetic intermediates, thereby making the reported method useful for drug discovery applications. Moreover, the branched alkylation of benzimidazole derivatives with ethyl methacrylate was achieved for the preparation of products incorporating a quaternary carbon.

EXPERIMENTAL SECTION

General Experimental. Unless otherwise indicated, all reactions were performed under a nitrogen gas atmosphere in oven-dried glassware cooled under nitrogen gas. Toluene, diethyl ether, dichloromethane, and THF were degassed by argon sparging and purified by elution through a column of activated alumina under an

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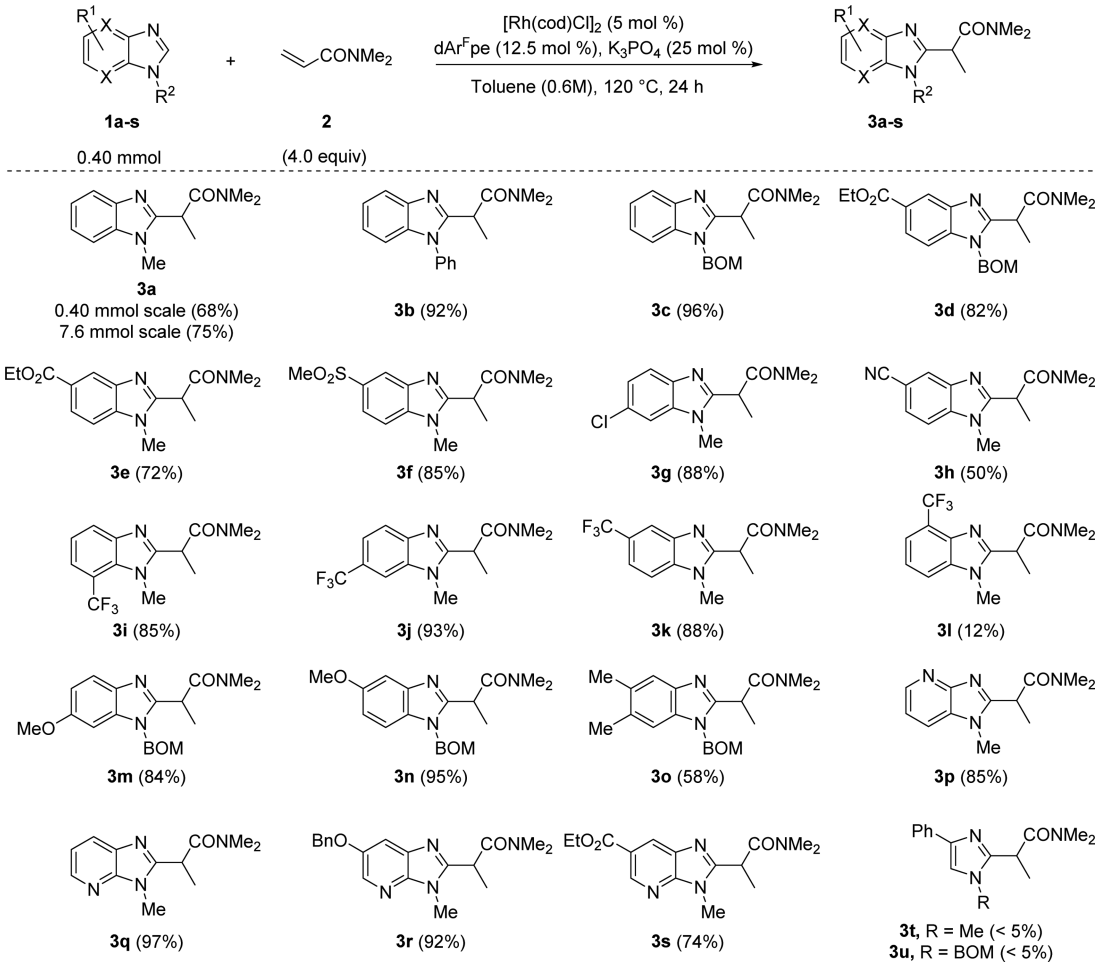
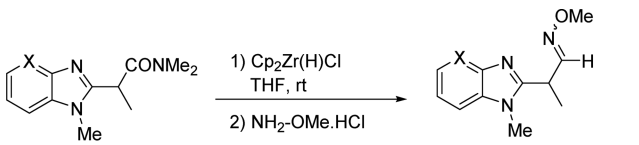
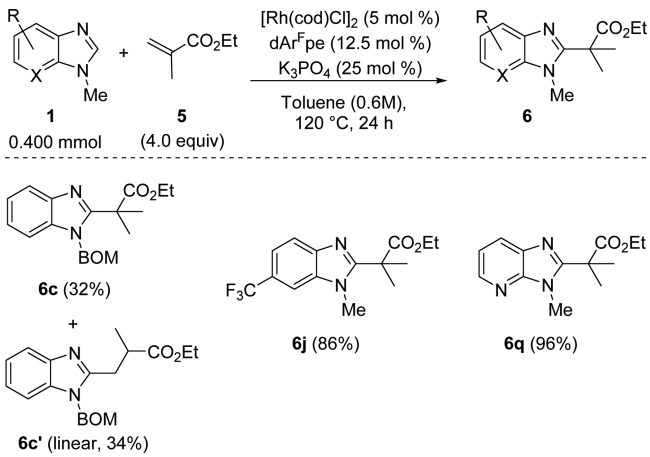
Scheme 2. Scope of the Reaction Using *N,N*-Dimethylacrylamide



Scheme 3. Transformations of Product Amide



Scheme 4. Direct Incorporation of Quaternary Centers with Ethyl Methacrylate



argon atmosphere prior to use. Mesitylene was dried and distilled under nitrogen from CaH_2 and then degassed by sparging with N_2. 1,2-Bis(bis(3,5-bis(trifluoromethyl)phenyl)phosphino)ethane (dAr^Fpe) was synthesized according to a modified literature procedure. All other catalyst and ligands were purchased from Strem Chemical and used without further purification. Potassium phosphate was dried at 160 °C under high vacuum prior to use. *N*-Methylbenzimidazole **1a** was recrystallized from Et_2O/pentane prior to use. All liquid azoles and *N,N*-dimethylacrylamide **2** were dried by elution through a small column of activated basic alumina and degassed by nitrogen sparging prior to use. Ethyl methacrylate **4** was dried over $CaCl_2$, distilled under reduced pressure under nitrogen and then degassed by nitrogen sparging prior to use. All other reagents were purchased from commercial sources and used without further purification. All microwave-heated reactions were performed in a Biotage Initiator+ microwave reactor, which employs an external IR sensor. Flash column chromatography was performed over grade 60 silica gel (230−400 mesh). Preparative TLC was performed over silica gel-coated glass plates (20 × 20 cm, 1000 or 2000 μm). Reverse-phase column chromatography was performed on prepacked cartridges of C18 silica gel using an automated purification system. NMR chemical shifts (δ) are reported in ppm relative to $CHCl_3$ (δ = 7.26 ppm), acetone (δ = 2.05 ppm), H_2O (δ = 4.79 ppm), or $(CH_3)_2SO$ (δ = 2.50 ppm) for ^{1}H NMR, $CDCl_3$ (δ = 77.16 ppm) or $(CD_3)_2CO$ (δ = 29.8 ppm), for ^{13}C NMR, 85% aqueous H_3PO_4 for ^{31}P NMR (external reference, δ = 0 ppm), and trifluoroacetic acid for ^{19}F-NMR (external reference, δ = −76.55 ppm). All ^{13}C NMR are proton decoupled. All ^{19}F and ^{31}P NMR are carbon decoupled. The multiplicity and shape of NMR signals are designated by the following abbreviations: s, singlet; d,

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doublet; t, triplet; q, quartet; m, multiplet; app, apparent. Coupling constants (*J* values) are reported in hertz (Hz). High-resolution mass spectra (HRMS) were recorded on a quadrupole time-of-flight mass spectrometer after electrospray ionization. Melting points (mp) are reported uncorrected.

1,2-Bis(bis(3,5-bis(trifluoromethyl)phenyl)phosphino)ethane (dAr^{F}pe). A freshly titrated solution of *i*PrMgBr (1.10 M in THF, 26.3 mL, 28.9 mmol, 6.7 equiv)[12] was charged in an oven-dried round-bottom flask previously flushed with nitrogen. Additional dry diethyl ether (30 mL) was added, and the resulting solution was cooled to −10 °C. Neat 1-bromo-3,5-bis(trifluoromethyl)benzene (5.20 mL, 30.2 mmol, 7.0 equiv) was added dropwise over 20 min; the reaction mixture was stirred at −10 °C for 1 h, and then allowed to warm to room temperature and stirred for 3 h. The resulting clear brown solution was cooled to 0 °C, and neat 1,2-bis(dichlorophosphino)-ethane (0.65 mL, 4.3 mmol, 1.0 equiv) was added dropwise over 5 min. The resulting suspension was allowed to warm to room temperature and stirred for 16 h. The resulting suspension was cooled to 0 °C and quenched with an aqueous saturated NH_4Cl solution. The organic solvents were removed in vacuo, and water and ethyl acetate were added to the resulting slurry until two clear phases were obtained. The phases were separated, and the aqueous phase was extracted twice with EtOAc. The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo to give an orange solid. This solid was then washed with small amounts of peroxide-free and BHT-free diethyl ether until a white powder was obtained, which was then dried under high vacuum to give the desired product (3.96 g, 4.20 mmol, 97% yield). ^1H and ^{19}F NMR matched the reported data.[13] ^1H NMR (600 MHz, acetone-d_6) δ 8.11 (s, 8H), 8.05 (s, 4H), 2.73 (t, J = 5.3 Hz, 4H); ^{19}F NMR (150 MHz, acetone-d_6) δ −63.5; ^{31}P NMR (200 MHz, acetone-d_6) δ −9.4.

*1-Phenyl-1H-benzo[d]imidazole (**1b**).* 1*H*-Benzimidazole (236 mg, 2.00 mmol, 1.0 equiv) and Cs_2CO_3 (3.26 g, 10.0 mmol, 5.0 equiv) were weighed in a 20 mL Biotage microwave vial (#354833, HxD = 8 × 2.8 cm), followed by dry DMA (20 mL) and fluorobenzene (0.88 mL, 9.3 mmol, 4.7 equiv). The vial was sealed with a Teflon-lined cap and heated at 190 °C in a Biotage Initiator+ microwave reactor for 16 h. The reaction mixture was poured on water and Et_2O; the phases were separated, and the aqueous phase was extracted three times with Et_2O. The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo to give the crude product. Purification by flash chromatography over silica gel (60% EtOAc/petroleum ether) gave desired product **1b** as a colorless oil (370 mg, 1.90 mmol, 95% yield). ^1H NMR spectra matched the reported data.[14] ^1H NMR (600 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.93−7.84 (m, 1H), 7.62−7.50 (m, 5H), 7.50−7.43 (m, 1H), 7.39−7.29 (m, 2H).

*1-((Benzyloxy)methyl)-1H-benzo[d]imidazole (**1c**).* Under N_2 at 0 °C, to a solution of 1*H*-benzimidazole (1.00 g, 8.46 mmol, 1.0 equiv) in dry DMF (20 mL) was added NaH (60% w/w in oil, 340 mg, 8.87 mmol, 1.05 equiv) in one portion. The reaction mixture was stirred at 0 °C for 10 min, then neat BOM-Cl (90% purity, 1.38 mL, 8.90 mmol, 1.05 equiv) was added dropwise. The resulting solution was stirred at rt for 16 h. The reaction mixture was then poured onto a 10% w/w LiCl aqueous solution. EtOAc was added; the phases were separated, and the organic phase was washed three more times with a 10% w/w LiCl solution. The organic phase was dried over Na_2SO_4 and concentrated in vacuo to give a yellow oil. Purification by flash chromatography over silica gel (60−100% EtOAc/petroleum ether) gave desired product **1c** as a white amorphous solid (1.27 g, 5.33 mmol, 63% yield). ^1H NMR spectra matched the reported data.[15] ^1H NMR (600 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.86−7.82 (m 1H), 7.56−7.53 (m, 1H), 7.38−7.31 (m, 5H), 7.30−7.26 (m, 2H), 5.60 (s, 2H), 4.47 (s, 2H).

Benzimidazole-5-carboxylic Acid Ethyl Ester. Benzimidazole-5-carboxylic acid (1.00 g, 6.17 mmol, 1.0 equiv) was dissolved in EtOH (15.5 mL), treated with concentrated H_2SO_4 (0.36 mL, 6.9 mmol, 1.1 equiv), and heated to reflux for 24 h. After cooling to room temperature, the mixture was poured onto ice, and 5 N aqueous NaOH was added until pH ∼9 was reached. The mixture was extracted with EtOAc (3 × 30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography over silica gel (100% EtOAc) gave desired product benzimidazole-5-carboxylic acid ethyl ester as a cream-colored amorphous solid (751 mg, 3.95 mmol, 64% yield). ^1H NMR matched the reported data.[16] ^1H NMR (500 MHz, DMSO-d6) δ 12.79 (s, 1H), 8.40 (s, 1H), 8.23 (s, 1H), 7.84 (d, J = 7.9 Hz, 1H), 7.67 (s, 1H), 4.32 (q, J = 7.1 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H).

*Ethyl 1-((Benzyloxy)methyl)-1H-benzo[d]imidazole-5-carboxylate (**1d**).* Benzimidazole-5-carboxylic acid ethyl ester (0.50 g, 2.6 mmol, 1 equiv) was dissolved in DMF (2.5 mL), and the reaction solution was cooled to 0 °C. Sodium hydride (60% w/w in oil, 91 mg, 3.9 mmol, 1.5 equiv) was added, and the reaction mixture was stirred for 15 min followed by the addition of BOM-Cl (90% purity, 0.41 mL, 2.6 mmol, 1.0 equiv). The reaction mixture was then stirred for 45 min at room temperature, and the reaction was quenched with 0.25 mL of 30% w/w aqueous NH_3. The solvents were removed in vacuo, and the residue was partitioned between water and dichloromethane. The aqueous phase was extracted with dichloromethane (3 × 5 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography over silica gel (65% EtOAc/hexanes) gave desired product **1d** as a white amorphous solid (220 mg, 0.71 mmol, 27% yield). Mp 82−85 °C; IR (neat) 3066, 2982, 2937, 1709, 1622, 1461, 1278, 1245, 1193, 1058, 748, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H), 8.08 (d, J = 8.5 Hz, 1H), 8.02 (s, 1H), 7.55 (d, J = 8.5 Hz, 1H), 7.38−7.32 (m, 3H), 7.26−7.28 (m, 2H), 5.61 (s, 2H), 4.47 (s, 2H), 4.42 (q, J = 7.1 Hz, 2H), 1.43 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0, 144.7, 143.9, 136.8, 136.0, 128.9, 128.6, 128.2, 125.7, 125.3, 123.0, 110.2, 73.6, 70.5, 61.1, 14.6; HRMS (ESI+, m/z) $[M + H]^+$ calcd for $C_{18}H_{19}N_2O_3^+$ 311.1390, found 311.1410.

*1-Methyl-5-methylsulfonyl-benzimidazole (**1f**).* 1-Fluoro-4-methylsulfonyl-2-nitrobenzene (1.00 g, 4.57 mmol, 1.0 equiv) was weighed in a 20 mL Biotage microwave vial (#354833, HxD = 8 × 2.8 cm) followed by a 2 M solution of $MeNH_2$ in THF (11.4 mL, 22.8 mmol, 5 equiv). The vial was sealed with a Teflon-lined cap, and the mixture was stirred at room temperature for 30 min. The reaction mixture was then concentrated in vacuo, and the resulting residue was suspended in Et_2O and filtered to give crude *N*-methyl-4-(methylsulfonyl)-2-nitroaniline. This solid was then transferred to a 250 mL Morton flask, to which was added Pd/C (1.06 g, 10 mol %), and the solids were suspended in EtOH (100 mL), placed under an atmosphere of H_2, and stirred at room temperature for 2.5 h. The reaction mixture was then filtered through pad of Celite, rinsed with MeOH, and concentrated to give crude *N*-methyl-4-(methylsulfonyl)benzene-1,2-diamine. The crude reaction product was transferred into a 20 mL Biotage microwave vial (#354833, HxD = 8 × 2.8 cm), to which was added formic acid (90% w/w in water, 17.1 mL, 407 mmol, 90 equiv). The vial was sealed with a Teflon-lined cap and heated at 150 °C in a Biotage Initiator+ microwave reactor for 1 h. The solution was made basic with 2 M NaOH followed by concentrated NaOH until pH ∼9 was reached. The mixture was extracted with CH_2Cl_2 (3 × 50 mL), and the organic layers were combined, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography over silica gel (100% EtOAc) gave desired product **1f** as a pale orange amorphous solid (711 mg, 3.40 mmol, 68% yield). Mp 162−164 °C; IR (neat) 3081, 2995, 2904, 1612, 1501, 1329, 1284, 1259, 1136, 1061, 769, 637 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.42 (s, 1H), 8.04 (s, 1H), 7.90 (d, J = 8.5 Hz, 1H), 7.54 (d, J = 8.5 Hz, 1H), 3.92 (s, 3H), 3.09 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 146.4, 143.5, 138.0, 134.7, 121.9, 121.0, 110.4, 45.3, 31.6; HRMS (ESI+, m/z) $[M + H]^+$ calcd for $C_9H_{11}N_2O_2S^+$ 211.0536, found 211.0528.

*1-Methyl-6-chloro-1H-benzo[d]imidazole (**1g**).* 4-Chloro-2-fluoro-1-nitro-benzene (1.00 g, 5.70 mmol, 1.0 equiv) was weighed in a 20 mL Biotage microwave vial (#354833, HxD = 8 × 2.8 cm), followed by a 2 M solution of $MeNH_2$ in THF (14.2 mL, 28.5 mmol, 5 equiv). The vial was sealed with a Teflon-lined cap, and the reaction mixture was stirred at room temperature for 1 h. The resulting suspension was filtered over a sintered glass funnel, and the filtrate was concentrated in vacuo to give crude 5-chloro-*N*-methyl-2-nitroaniline as an orange solid. A slurry of Raney nickel in water was then charged in a 100 mL

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round-bottom flask; the water was evaporated in vacuo to give ~1.8 g of dry Raney nickel (30.7 mmol, 4.8 equiv). Crude 5-chloro-*N*-methyl-2-nitroaniline was then added to the Raney nickel as a solution in MeOH (50 mL), and the resulting suspension was vigorously stirred under a hydrogen atmosphere for 2 h. The resulting colorless suspension was filtered over a bed of Celite (Et_2O washings) and then concentrated in vacuo to give crude 5-chloro-*N*1-methylbenzene-1,2-diamine as a black oil. This oil was then transferred into a 20 mL Biotage microwave vial (#354833, HxD = 8 × 2.8 cm) to which was added formic acid (90% w/w in water, 20.4 mL, 486 mmol, 85 equiv). The vial was sealed with a Teflon-lined cap and heated at 150 °C for 2.5 h in a Biotage Initiator+ microwave reactor. The reaction mixture was concentrated in vacuo to give a bright pink solid. Purification by reverse-phase flash chromatography over C18 silica gel (20−40% MeCN + 0.1% TFA/H_2O + 0.1% TFA) gave the desired product as its TFA salt, which was then treated with an aqueous saturated solution of $NaHCO_3$. Extraction with EtOAc, followed by drying with Na_2SO_4 and in vacuo concentration led to desired product **1g** as a white amorphous solid (720 mg, 4.32 mmol, 76% overall yield). ^{1}H NMR spectra matched the reported data.[17] ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.70 (d, J = 8.7 Hz, 1H), 7.38 (d, J = 2.0 Hz, 1H), 7.25 (dd, J = 8.7, 2.0 Hz, 1H), 3.81 (s, 3H).

*1-Methyl-1H-benzo[d]imidazole-5-carbonitrile (**1h**).* 4-Chloro-3-nitro-benzonitrile (1.00 g, 5.48 mmol, 1.0 equiv) was weighed in a 20 mL Biotage microwave vial (#354833, HxD = 8 × 2.8 cm) followed by a 2 M solution of $MeNH_2$ in THF (13.7 mL, 2 M in THF, 5 equiv). The vial was sealed with a Teflon-lined cap, and the reaction mixture was stirred at room temperature for 30 min. The reaction mixture was then concentrated in vacuo. The resulting residue was suspended in Et_2O and filtered to give crude 4-methylamino-3-nitro-benzonitrile, which was then suspended in EtOH/H_2O (10:1, 19 mL) under N_2 at room temperature. Iron powder (1.00 g, 1.79 mmol, 3.3 equiv) and $CaCl_2$ (0.45 g, 4.1 mmol, 0.7 equiv) were added to the reaction mixture, and the mixture was heated at reflux for 2 h. The reaction mixture was cooled to room temperature and filtered through a pad of Celite. The filtrate was concentrated in vacuo, and the residue was redissolved in CH_2Cl_2, washed with water and brine, and dried over Na_2SO_4. The solvent was removed in vacuo to give crude 3-amino-4-methylamino-benzonitrile. To trimethyl orthoformate (15.8 mL) were added 3-amino-4-methylamino-benzonitrile and *p*-toluenesulfonic acid monohydrate (17 mg, 0.089 mmol, 0.016 equiv). The reaction mixture was stirred at 100 °C for 2.5 h, after which time the mixture was cooled and water (60 mL) was added. The solution was partitioned with EtOAc (2 × 90 mL), and the organic layers were combined, dried with $MgSO_4$ and concentrated. Purification by flash chromatography over silica gel (100% EtOAc) gave desired product **1h** as a light brown amorphous solid (339 mg, 2.15 mmol, 39% overall yield). Mp 136−137 °C; IR (neat) 3090, 3030, 2955, 2223, 1614, 1503, 1470, 1332, 1260, 877, 825, 646 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.14 (s, 1H), 8.00 (s, 1H), 7.58 (d, J = 8.4 Hz, 1H), 7.47 (d, J = 8.4 Hz, 1H), 3.90 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 146.0, 143.5, 137.3, 126.5, 125.7, 119.9, 110.7, 105.8, 31.5; HRMS (ESI+, m/z) $[M + H]^+$ calcd for $C_9H_8N_3^+$ 158.0713, found 158.0719.

*1-Methyl-7-(trifluoromethyl)-1H-benzo[d]imidazole (**1i**).* 2-Chloro-1-nitro-3-(trifluoromethyl)benzene (1.20 g, 5.32 mmol, 1.0 equiv) was weighed in a 20 mL Biotage microwave vial (#354833, HxD = 8 × 2.8 cm) followed by a 2 M solution of $MeNH_2$ in THF (12 mL, 24 mmol, 4.5 equiv). The vial was sealed with a Teflon-lined cap and heated at 150 °C for 15 min in a Biotage Initiator+ microwave reactor. The resulting suspension was filtered over a sintered glass funnel, and the filtrate was concentrated in vacuo to give crude *N*-methyl-2-nitro-6-(trifluoromethyl)aniline as a yellow solid. This solid was then transferred to a 250 mL Morton flask to which were added PtO_2 (134 mg, 0.591 mmol, 0.11 equiv) and absolute ethanol (50 mL). This suspension was vigorously stirred under a hydrogen atmosphere for 2 h. The resulting colorless suspension was filtered over a bed of Celite (Et_2O washings) and then concentrated in vacuo to give crude *N*1-methyl-6-(trifluoromethyl)benzene-1,2-diamine as an orange oil. This oil was then transferred into a 20 mL Biotage microwave vial (#354833, HxD = 8 × 2.8 cm) to which was added formic acid (90% w/w in water, 15.0 mL, 358 mmol, 67 equiv). The vial was sealed with a Teflon-lined cap and heated at 150 °C for 10 min in a Biotage Initiator+ microwave reactor. The reaction mixture was concentrated in vacuo to give a red oil. Purification by flash chromatography over silica gel (80% EtOAc/petroleum ether) gave desired product **1i** as a pale yellow amorphous solid (702 mg, 3.51 mmol, 66% overall yield). ^{1}H NMR spectra matched the reported data.[18] ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.01 (d, J = 8.2 Hz, 1H), 7.94 (s, broad, 1H), 7.64 (d, J = 7.6 Hz, 1H), 7.35 (t_{app}, J = 7.9 Hz, 1H), 4.00 (q, J = 1.8 Hz, 3H); ^{19}F NMR (470 MHz, $CDCl_3$) δ −55.02.

*1-Methyl-6-(trifluoromethyl)-1H-benzo[d]imidazole (**1j**).* 2-Chloro-1-nitro-4-(trifluoromethyl) benzene (1.00 g, 4.43 mmol, 1.0 equiv) was weighed in a 20 mL Biotage microwave vial (#354833, HxD = 8 × 2.8 cm) followed by a 2 M solution of $MeNH_2$ in THF (11.0 mL, 22.2 mmol, 5 equiv). The vial was sealed with a Teflon-lined cap and heated at 150 °C for 30 min in a Biotage Initiator+ microwave reactor. The resulting suspension was filtered over a sintered glass funnel, and the filtrate was concentrated in vacuo to give crude *N*-methyl-2-nitro-5-(trifluoromethyl)aniline as a bright orange solid. This solid was then transferred to a 250 mL Morton flask to which were added PtO_2 (113 mg, 0.500 mmol, 0.11 equiv) and absolute ethanol (50 mL). This suspension was vigorously stirred under a hydrogen atmosphere for 2 h. The resulting colorless suspension was filtered over a bed of Celite (Et_2O washings) and then concentrated in vacuo to give crude *N*1-methyl-5-(trifluoromethyl)benzene-1,2-diamine as an orange oil. This oil was then transferred into a 20 mL Biotage microwave vial (#354833, HxD = 8 × 2.8 cm) to which was added formic acid (90% w/w in water, 15.0 mL, 358 mmol, 80 equiv). The vial was sealed with a Teflon-lined cap and heated at 150 °C for 10 min in a Biotage Initiator+ microwave reactor. The reaction mixture was concentrated in vacuo to give a red oil. Purification by flash chromatography over silica gel (50% acetone/petroleum ether) gave desired product **1j** as a white amorphous solid (745 mg, 3.72 mmol, 84% overall yield). Mp 96−98 °C; IR (neat) 3031, 1507, 1338, 1302, 1160, 1093, 1063, 901, 814, 663 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.87 (d, J = 8.5 Hz, 1H), 7.67 (s, 1H), 7.53 (dd, J = 8.5, 1.2 Hz, 1H), 3.88 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 146.0, 145.9, 134.1, 125.4 (q, J = 32 Hz), 124.9 (q, J = 272 Hz), 120.9, 119.2 (q, J = 4 Hz), 107.4 (q, J = 5 Hz), 31.4; ^{19}F NMR (470 MHz, $CDCl_3$) δ −60.67; HRMS (ESI+, m/z) $[M + H]^+$ calcd for $C_9H_8F_3N_2^+$ 201.0634, found 201.0633.

*1-Methyl-5-(trifluoromethyl)-1H-benzo[d]imidazole (**1k**).* 1-Chloro-2-nitro-4-(trifluoromethyl) benzene (1.00 g, 4.43 mmol, 1.0 equiv) was weighed in a 20 mL Biotage microwave vial (#354833, HxD = 8 × 2.8 cm) followed by a 2 M solution of $MeNH_2$ in THF (11.0 mL, 22.2 mmol, 5 equiv). The vial was sealed with a Teflon-lined cap and heated at 150 °C for 15 min in a Biotage Initiator+ microwave reactor. The resulting suspension was filtered over a sintered glass funnel, and the filtrate was concentrated in vacuo to give crude *N*-methyl-2-nitro-4-(trifluoromethyl)aniline as a bright orange solid. This solid was then transferred to a 250 mL Morton flask to which were added PtO_2 (113 mg, 0.500 mmol, 0.11 equiv) and absolute ethanol (50 mL). This suspension was vigorously stirred under a hydrogen atmosphere for 2 h. The resulting colorless suspension was filtered over a bed of Celite (Et_2O washings) and then concentrated in vacuo to give crude *N*1-methyl-4-(trifluoromethyl)benzene-1,2-diamine as an orange oil. This oil was then transferred into a 20 mL Biotage microwave vial (#354833, HxD = 8 × 2.8 cm) to which was added formic acid (90% w/w in water, 15.0 mL, 358 mmol, 80 equiv). The vial was sealed with a Teflon-lined cap and heated at 150 °C for 10 min in a Biotage Initiator+ microwave reactor. The reaction mixture was concentrated in vacuo to give a red oil. Purification by flash chromatography over silica gel (50% acetone/petroleum ether) gave desired product **1k** as a white amorphous solid (676 mg, 3.38 mmol, 76% overall yield). ^{1}H NMR spectra matched the reported data.[19] ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.96 (s, 1H), 7.56 (dd, J = 8.5, 1.2 Hz, 1H), 7.46 (d, J = 8.5 Hz, 1H), 3.88 (s, 3H); ^{19}F NMR (470 MHz, $CDCl_3$) δ −60.60.

*1-Methyl-4-(trifluoromethyl)-1H-benzo[d]imidazole (**1l**).* 1-Chloro-2-nitro-4-(trifluoromethyl) benzene (1.15 g, 5.10 mmol, 1.0

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equiv) was weighed in a 20 mL Biotage microwave vial (#354833, HxD = 8 × 2.8 cm) followed by powdered silicon carbide (1.15 g) and a 2 M solution of $MeNH_2$ in THF (12.0 mL, 24.0 mmol, 4.7 equiv). The vial was sealed with a Teflon-lined cap and heated at 190 °C for 30 min in a Biotage Initiator+ microwave reactor. The resulting suspension was filtered over a sintered glass funnel, and the filtrate was concentrated in vacuo to give a bright orange solid. This solid was then purified by flash chromatography over silica gel (10% diethyl ether/petroleum ether) to give pure 2-chloro-*N*-methyl-6-trifluoromethyl-aniline as a bright orange solid (450 mg, 2.15 mmol, 42% yield). This solid was then transferred to a 50 mL Morton flask to which were added PtO_2 (46 mg, 0.20 mmol, 0.1 equiv) and absolute ethanol (16 mL). This suspension was vigorously stirred under a hydrogen atmosphere for 2 h. The resulting colorless suspension was filtered over a bed of Celite (Et_2O washings) and then concentrated in vacuo to give crude *N*1-methyl-3-(trifluoromethyl)benzene-1,2-diamine as an orange oil. This oil was then transferred into a 20 mL Biotage microwave vial (#354833, HxD = 8 × 2.8 cm) to which was added formic acid (90% w/w in water, 5.50 mL, 131 mmol, 60 equiv). The vial was sealed with a Teflon-lined cap and heated at 150 °C for 10 min in a Biotage Initiator+ microwave reactor. The reaction mixture was concentrated in vacuo to give a red oil. Purification by flash chromatography over silica gel (80% EtOAc/petroleum ether) gave desired product **1l** as a pale yellow amorphous solid (208 mg, 1.04 mmol, 20% overall yield). ^{1}H NMR spectra matched the reported data.[18] ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.58 (dd_{app}, J = 7.7, 2.3 Hz, 2H), 7.38 (t_{app}, J = 7.7 Hz, 1H), 3.90 (s, 3H); ^{19}F NMR (470 MHz, $CDCl_3$) δ −60.96.

*1-((Benzyloxy)methyl)-6-methoxy-1H-benzo[d]imidazole (**1m**) and 1-((Benzyloxy)methyl)-5-methoxy-1H-benzo[d]imidazole (**1n**).* Under N_2 at 0 °C, to a solution of 5-methoxy-1*H*-benzo[*d*]imidazole (1.00 g, 6.76 mmol, 1.0 equiv) in dry DMF (15 mL) was added NaH (60% w/w in oil, 405 mg, 10.1 mmol, 1.50 equiv) in one portion. The reaction mixture was stirred at 0 °C for 1 h, and then neat BOM-Cl (90% pure, 1.25 mL, 8.10 mmol, 1.2 equiv) was added dropwise. The resulting solution was stirred at rt for 16 h. The reaction mixture was then poured onto a 10% w/w LiCl aqueous solution. EtOAc was added; the phases were separated, and the organic phase was washed three more times with a 10% w/w LiCl solution. The organic phase was dried over Na_2SO_4 and concentrated in vacuo to give a yellow oil. Purification by flash chromatography over silica gel (60−100% EtOAc/CH_2Cl_2) gave, by order of elution, desired products **1m** (325 mg, 1.21 mmol, 18% yield) as a pale yellow amorphous solid and **1n** (175 mg, 0.652 mmol, 10% yield) as a pale yellow oil. (**1m**): mp 67−70 °C; IR (neat) 3099, 2836, 1627, 1587, 1505, 1453, 1361, 1279, 1092, 1022, 955, 817, 733 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.69 (d, J = 8.6 Hz, 1H), 7.38−7.30 (m, 3H), 7.30−7.24 (m, 2H), 6.99−6.90 (m, 2H), 5.53 (s, 2H), 4.45 (s, 2H), 3.86 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.3, 142.3, 138.6, 136.3, 134.4, 128.8, 128.5, 128.2, 121.1, 112.5, 93.8, 73.4, 70.0, 56.0; HRMS (ESI+, m/z) [M + H]$^+$ calcd for $C_{16}H_{17}N_2O_2^+$ 269.1285, found 269.1285. (**1n**): IR (neat) 2939, 1623, 1593, 1487, 1442, 1349, 1218, 1142, 1071, 941, 829, 697 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.40 (d, J = 8.8 Hz, 1H), 7.37−7.28 (m, 4 H), 7.27−7.24 (m, 2H), 6.98 (dd, J = 8.8, 1.7 Hz, 1H), 5.53 (s, 2H), 4.43 (s, 2H), 3.87 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.7, 145.1, 143.4, 136.2, 128.8, 128.4, 128.2, 128.1, 113.8, 110.9, 102.6, 73.6, 70.1, 55.9; HRMS (ESI+, m/z) [M + H]$^+$ calcd for $C_{16}H_{17}N_2O_2^+$ 269.1285, found 269.1281.

*1-((Benzyloxy)methyl)-5,6-dimethyl-1H-benzo[d]imidazole (**1o**).* 5,6-Dimethylbenzimidazole (0.500 g, 3.42 mmol, 1.0 equiv) was dissolved in DMF (2.5 mL), and the reaction solution was cooled to 0 °C. Sodium hydride (60% w/w oil oil, 118 mg, 5.13 mmol, 1.5 equiv) was added, and the reaction mixture was stirred for 15 min before the addition of BOM-Cl (90% purity, 0.53 mL, 3.42 mmol, 1.0 equiv). The reaction mixture was stirred for 45 min at room temperature, and the reaction was quenched with 0.25 mL of a 30% w/w aqueous NH_3. The solvents were removed in vacuo, and the residue was partitioned between water and dichloromethane. The aqueous phase was extracted with dichloromethane (3 × 5 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography over silica gel (90% EtOAc/hexanes) gave desired product **1o** as a pale yellow amorphous solid (778 mg, 2.92 mmol, 85% yield). Mp 98−99 °C; IR (neat) 3089, 2970, 2883, 1704, 1495, 1356, 1215, 1093, 1001, 844, 742, 697 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.59 (s, 1H), 7.38−7.26 (m, 6H), 5.52 (s, 2H), 4.43 (s, 2H), 2.40 (s, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 142.8, 142.5, 136.3, 132.9, 132.2, 131.8, 128.7, 128.4, 128.1, 120.5, 110.6, 73.3, 70.0, 20.7, 20.4; HRMS (ESI+, m/z) [M + H]$^+$ calcd for $C_{17}H_{19}N_2O^+$ 267.1492, found 267.1512.

*1-Methyl-1H-imidazo[4,5-b]pyridine (**1p**).* 3-Fluoro-2-nitro-pyridine (1.00 g, 7.04 mmol, 1.0 equiv) was weighed in a 20 mL Biotage microwave vial (#354833, HxD = 8 × 2.8 cm) followed by a 2 M solution of $MeNH_2$ in THF (17.6 mL, 35.2 mmol, 5 equiv). The vial was sealed with a Teflon-lined cap and stirred at rt for 30 min. The resulting suspension was filtered over a sintered glass funnel, and the filtrate was concentrated in vacuo to give crude *N*-methyl-2-nitropyridin-3-amine as a bright yellow solid. This solid was then transferred to a 250 mL Morton flask to which were added 5% w/w Pd/C (749 mg, 0.352 mmol, 0.05 equiv) and absolute ethanol (50 mL). This suspension was vigorously stirred under a hydrogen atmosphere for 2 h. The resulting colorless suspension was filtered over a bed of Celite (Et_2O washings) and then concentrated in vacuo to give crude *N*3-methylpyridine-2,3-diamine as a beige solid. This oil was then transferred into a 20 mL Biotage microwave vial (#354833, HxD = 8 × 2.8 cm) to which was added formic acid (90% w/w in water, 23.6 mL, 564 mmol, 80 equiv). The vial was sealed with a Teflon-lined cap and heated at 150 °C for 20 min in a Biotage microwave Initiator+ reactor. The reaction mixture was concentrated in vacuo to give a red oil. Purification by flash chromatography over silica gel (100% acetone) gave desired product **1p** as beige crystals (560 mg, 4.21 mmol, 60% overall yield). ^{1}H NMR spectra matched the reported data.[20] ^{1}H NMR (600 MHz, D_2O) δ 8.24 (d, J = 4.9 Hz, 1H), 8.10 (s, 1H), 7.75 (d, J = 8.1 Hz, 1H), 7.26−7.07 (m, 1H), 3.72 (s, 3H).

*3-Methyl-3H-imidazo[4,5-b]pyridine (**1q**).* Under N_2 at 0 °C, to a solution of 1*H*-imidazo[4,5-*b*]pyridine (500 mg, 4.20 mmol, 1.0 equiv) in dry DMF (2 mL) was added NaH (60% w/w in oil, 252 mg, 6.30 mmol, 1.50 equiv) in one portion. The reaction mixture was stirred at 0 °C for 10 min, and then neat MeI (0.40 mL, 6.30 mmol, 1.5 equiv) was added dropwise. The resulting solution was stirred at rt for 16 h. The reaction mixture was then poured onto water. EtOAc was added; the phases were separated, and the organic phase was washed twice more with water. The organic phase was dried over Na_2SO_4 and concentrated in vacuo to give a red oil. Purification by flash chromatography over silica gel (80% acetone/petroleum ether) gave desired product **1q** as a pale yellow amorphous solid (275 mg, 2.07 mmol, 49% yield). ^{1}H NMR matched the reported data.[20] ^{1}H NMR (600 MHz, D_2O) δ 8.13 (d, J = 5.0 Hz, 1H), 8.09 (s, 1H), 7.87 (d, J = 8.1 Hz, 1H), 7.19 (dd, J = 7.6, 5.0 Hz, 1H), 3.70 (s, 3H).

*6-(Benzyloxy)-3-methyl-3H-imidazo[4,5-b]pyridine (**1r**).* 3-Methyl-3*H*-imidazo[4,5-*b*]pyridin-6-ol (250 mg, 1.68 mmol, 1.0 equiv) and K_2CO_3 (394 mg, 2.85 mmol, 1.7 equiv) were weighed in a 20 mL Biotage microwave vial (#354833, HxD = 8 × 2.8 cm), followed by MeCN (12 mL). Benzyl bromide (0.30 mL, 2.5 mmol, 1.5 equiv) was added. the vial was sealed with a Teflon-lined cap and heated at 80 °C in a Biotage Initiator+ microwave reactor for 5 h. The reaction mixture was filtered over cotton-wool, and the filtrate was concentrated in vacuo. Purification by flash chromatography over silica gel (60% acetone/petroleum ether) gave desired product **1r** as a white amorphous solid (170 mg, 0.710 mmol, 42% yield). Mp 119−120 °C; IR (neat) 3079, 2922, 1595, 1512, 1453, 1321, 1221, 1116, 1009, 898, 743, 701 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.26 (d, J = 2.5 Hz, 1H), 7.96 (s, 1H), 7.64 (d, J = 2.5 Hz, 1H), 7.46 (d, J = 7.4 Hz, 2H), 7.39 (t, J = 7.4 Hz, 2H), 7.33 (t, J = 7.4 Hz, 1H), 5.15 (s, 2H), 3.89 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.4, 145.0, 142.5, 136.5, 136.0, 135.6, 128.8, 128.3, 127.8, 112.4, 71.5, 30.0; HRMS (ESI+, m/z) [M + H]$^+$ calcd for $C_{14}H_{14}N_3O^+$ 240.1131, found 240.1132.

*Ethyl 3-Methyl-3H-imidazo[4,5-b]pyridine-6-carboxylate (**1s**).* 3-Methylimidazo[4,5-*b*]pyridine-6-carboxylic acid (0.126 g, 0.710 mmol, 1.0 equiv) was heated in $SOCl_2$ (15 mL) at 80 °C for 2 h. The excess

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$SOCl_2$ was removed in vacuo. The remaining residue was dissolved in EtOH (10 mL) and heated at reflux for 1 h. EtOH was then removed in vacuo. Purification by flash chromatography over silica gel (100% EtOAc) gave desired product **1s** as a white amorphous solid (79 mg, 0.38 mmol, 54% yield). Mp 89−90 °C; IR (neat) 3058, 2993, 2928, 1700, 1603, 1403, 1297, 1240, 1180, 1026, 784, 637 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 9.10 (s, 1H), 8.69 (s, 1H), 8.13 (s, 1H), 4.44 (q, J = 7.1 Hz, 2H), 3.95 (s, 3H), 1.43 (t, J = 7.1 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 166.1, 150.1, 146.7, 146.5, 134.8, 129.7, 121.6, 61.4, 30.1, 14.5; HRMS (ESI+, m/z) $[M + H]^+$ calcd for $C_{10}H_{12}N_3O_2^+$ 206.0924, found 206.0930.

General Procedure for Branched Alkylation. In a N_2-filled glovebox, an oven-dried Biotage microwave vial (#352016, HxD = 8 × 1.5 cm) was charged with $[Rh(cod)Cl]_2$ (0.05 equiv), 1,2-bis(bis(3,5-bis(trifluoromethyl)phenyl)phosphino)ethane (dAr^Fpe) (0.125 equiv), potassium phosphate (0.25 equiv), and the azole (1.0 equiv). Toluene was then added (c = 0.6 M), and the reaction mixture was stirred for 5 min to give a yellow-red suspension. The alkene was then added (4.0 equiv). The vial was sealed with a Teflon-lined septum, taken out of the glovebox, and heated for 24 h at 120 °C in a pre-equilibrated oil bath. The reaction mixture was then filtered over a short pad of silica gel (∼2 cm) in a pasteur pipet followed by washing with acetone until the filtrate came out clear. The filtrate was then concentrated in vacuo, and the products were purified by the indicated chromatography techniques.

*N,N-Dimethyl-2-(1-methyl-1H-benzo[d]imidazol-2-yl)-propanamide (**3a**).* Scale of 0.4 mmol: Prepared according to the general procedure from 1-methyl-1*H*-benzo[*d*]imidazole **1a** (53 mg, 0.40 mmol, 1.0 equiv) and *N,N*-dimethylacrylamide **2** (0.17 mL, 1.6 mmol, 4.0 equiv). Purification by flash chromatography over silica gel (50% acetone/CH_2Cl_2) followed by further purification by preparative TLC (5% MeOH/CH_2Cl_2) gave desired product **3a** as an off-white solid (63 mg, 0.27 mmol, 68% yield). Scale of 7.6 mmol: Prepared according to the general procedure from 1-methyl-1*H*-benzo[*d*]-imidazole **1a** (1.00 g, 7.57 mmol, 1.0 equiv) and *N,N*-dimethylacrylamide **2** (0.17 mL, 1.6 mmol, 4.0 equiv) using a 10−20 mL Biotage vial (#354833, HxD = 8 × 2.8 cm). Purification by flash chromatography over silica gel (20% acetone/CH_2Cl_2 + 1% aqueous NH_4OH) followed by trituration with 10% Et_2O/pentane gave desired product **3a** as an off-white amorphous solid (1.32 g, 5.71 mmol, 75% yield). Mp 104−105 °C; IR (neat) 2941, 1631, 1495, 1458, 1432, 1390, 1369, 1305, 1283, 1261, 1132, 1072, 769 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.73 (m, 1H), 7.37−7.22 (m, 3H), 4.44 (q, J = 7.2 Hz, 1H), 3.80 (s, 3H), 3.01 (s, 3H), 2.98 (s, 3H), 1.68 (d, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.5, 153.2, 142.2, 136.6, 122.7, 122.2, 119.7, 109.3, 39.4, 37.4, 36.4, 30.5, 16.1; HRMS (ESI+, m/z) $[M + H]^+$ calcd for $C_{13}H_{18}N_3O^+$ 232.1444, found 232.1449.

*N,N-Dimethyl-2-(1-phenyl-1H-benzo[d]imidazol-2-yl)-propanamide (**3b**).* Prepared according to the general procedure from **1b** (78.0 mg, 0.400 mmol, 1.0 equiv) and *N,N*-dimethylacrylamide **2** (0.17, 1.6 mmol, 4.0 equiv). Purification by flash chromatography over silica gel (30% acetone/CH_2Cl_2) gave desired product **3b** as a pale yellow amorphous solid (108 mg, 0.368 mmol, 92% yield). Mp 135−137 °C. IR (neat) 3059, 2937, 1642, 1595, 1501, 1454, 1395, 1267, 1148, 1089, 752, 699 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.84 (d, J = 7.9 Hz, 1H), 7.63−7.50 (m, 3H), 7.39−7.31 (m, 2H), 7.31−7.22 (m, 1H), 7.19 (td, J = 7.7, 1.1 Hz, 1H), 7.03 (d, J = 7.9 Hz, 1H), 4.10 (q, J = 7.0 Hz, 1H), 2.80 (s, 3H), 2.66 (s, 3H), 1.66 (d, J = 7.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.0, 153.8, 142.5, 137.2, 135.8, 130.0, 129.5, 128.1, 123.1, 122.4, 120.0, 110.0, 37.1, 37.0, 36.0, 16.4; HRMS (ESI+, m/z) $[M + H]^+$ calcd for $C_{18}H_{20}N_3O^+$ 294.1601, found 294.1609.

*2-(1-((Benzyloxy)methyl)-1H-benzo[d]imidazol-2-yl)-N,N-dimethylpropanamide (**3c**).* Prepared according to the general procedure from **1c** (95.0 mg, 0.400 mmol, 1.0 equiv) and *N,N*-dimethylacrylamide **2** (0.17, 1.6 mmol, 4.0 equiv). Purification by flash chromatography over silica gel (30% acetone/CH_2Cl_2) gave desired product **1c** as a yellow amorphous solid (129 mg, 0.382 mmol, 96% yield). Mp 55−56 °C; IR (neat) 2934, 1648, 1507, 1454, 1394, 1358, 1298, 1137, 1052, 768 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.77 (m, 1H), 7.39−7.31 (m, 4H), 7.30−7.26 (m, 4H), 5.67 (d, J = 11.0 Hz, 1H), 5.56 (d, J = 11.0 Hz, 1H), 4.51 (s, 2H), 4.44 (q, J = 7.1 Hz, 1H), 2.96 (s, 3H), 2.93 (s, 3H), 1.69 (d, J = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.7, 153.9, 142.4, 136.8, 135.9, 128.7, 128.3, 127.9, 123.3, 122.7, 120.0, 109.8, 72.5, 70.6, 38.6, 37.4, 36.3, 16.7; HRMS (ESI+, m/z) $[M + H]^+$ calcd for $C_{20}H_{24}N_3O_2^+$ 338.1863, found 338.1869.

*Ethyl 1-((Benzyloxy)methyl)-2-(1-(dimethylamino)-1-oxopropan-2-yl)-1H-benzo[d]imidazole-5-carboxylate (**3d**).* Prepared according to the general procedure from **1d** (124 mg, 0.400 mmol, 1.0 equiv) and *N,N*-dimethylacrylamide **2** (0.17 mL, 1.6 mmol, 4.0 equiv). Purification by flash chromatography over silica gel (30% acetone/CH_2Cl_2) gave desired product **3d** as a cream-colored amorphous solid (134 mg, 0.330 mmol, 82% yield). Mp 93−94 °C; IR (neat) 3064, 2976, 2939, 1700, 1643, 1618, 1420, 1277, 1216, 1112, 1013, 774, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.49 (s, 1H), 8.00 (d, J = 9.5 Hz, 1H), 7.39−7.30 (m, 4H), 7.27−7.21 (m, 2H), 5.67 (d, J = 11.0 Hz, 1H), 5.55 (d, J = 11.0 Hz, 1H), 4.49 (s, 2H), 4.44 (q, J = 7.2 Hz, 1H), 4.39 (q, J = 7.1 Hz, 2H), 2.98 (s, 3H), 2.93 (s, 3H), 1.71 (d, J = 7.2 Hz, 3H), 1.40 (t, J = 7.1 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.6, 167.1, 155.5, 142.0, 139.1, 136.4, 128.8, 128.5, 128.0, 125.3, 124.8, 122.3, 109.5, 72.6, 70.6, 61.0, 38.6, 37.4, 36.3, 16.4, 14.5; HRMS (ESI+, m/z) $[M + H]^+$ calcd for $C_{23}H_{28}N_3O_4^+$ 410.2074, found 410.2074.

*2-(1-(Dimethylamino)-1-oxopropan-2-yl)-1-methyl-1H-benzo[d]-imidazol-5-yl propionate (**3e**).* Prepared according to the general procedure from ethyl 1-methyl-1*H*-benzo[d]imidazole-5-carboxylate **1e** (82.0 mg, 0.400 mmol, 1.0 equiv) and *N,N*-dimethylacrylamide **2** (0.17, 1.6 mmol, 4.0 equiv). Purification by flash chromatography over silica gel (5−20% acetone/CH_2Cl_2) gave desired product **3e** as an orange amorphous solid (87 mg, 0.287 mmol, 72% yield). Mp 108−110 °C; IR (neat) 2982, 1705, 1636, 1618, 1453, 1392, 1296, 1247, 1205, 1102, 1083, 907, 773 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.46 (s, 1H), 8.01 (dd, J = 8.6, 1.2 Hz, 1H), 7.31 (d, J = 8.6 Hz, 1H), 4.44 (q, J = 7.2 Hz, 1H), 4.39 (q, J = 7.1 Hz, 2H), 3.81 (s, 3H), 3.03 (s, 3H), 2.99 (s, 3H), 1.70 (d, J = 7.2 Hz, 3H), 1.40 (t, J = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.3, 167.3, 155.0, 141.8, 139.7, 124.8, 124.3, 122.0, 108.9, 61.0, 39.3, 37.5, 36.4, 30.7, 15.9, 14.5; HRMS (ESI+, m/z) $[M + H]^+$ calcd for $C_{16}H_{22}N_3O_3^+$ 304.1656, found 304.1673.

*N,N-Dimethyl-2-(1-methyl-5-methylsulfonyl-benzimidazol-2-yl)-propanamide (**3f**).* Prepared according to the general procedure from **1f** (84.0 mg, 0.400 mmol, 1.0 equiv) and *N,N*-dimethylacrylamide **2** (0.17 mL, 1.6 mmol, 4.0 equiv). Purification by flash chromatography over silica gel (0−5% methanol/EtOAc) followed by trituration with 10% Et_2O/pentane gave desired product **3f** as a cream-colored solid (105 mg, 0.34 mmol, 85% yield). Mp 176−178 °C; IR (neat) 3012, 2997, 2933, 1635, 1421, 1292, 1246, 1143, 974, 774, 620 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.87 (d, J = 8.5 Hz, 1H), 7.45 (d, J = 8.5 Hz, 1H), 4.47 (q, J = 7.2 Hz, 1H), 3.85 (s, 3H), 3.07 (s, 3H), 3.07 (s, 3H), 3.00 (s, 3H), 1.72 (d, J = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.1, 156.5, 142.0, 139.9, 134.4, 121.5, 120.1, 110.1, 45.3, 39.1, 37.5, 36.4, 30.9, 15.8; HRMS (ESI+, m/z) $[M + H]^+$ calcd for $C_{14}H_{20}N_3O_3S^+$ 310.1220, found 310.1217.

*2-(6-Chloro-1-methyl-1H-benzo[d]imidazol-2-yl)-N,N-dimethyl-propanamide (**3g**).* Prepared according to the general procedure from **1g** (82.0 mg, 0.400 mmol, 1.0 equiv) and *N,N*-dimethylacrylamide **2** (0.17, 1.6 mmol, 4.0 equiv). Purification by flash chromatography over silica gel (5−20% acetone/CH_2Cl_2) gave desired product **3g** as a pale yellow amorphous solid (94 mg, 0.354 mmol, 88% yield. Mp 139−140 °C; IR (neat) 3065, 2950, 1644, 1502, 1474, 1392, 1270, 1133, 1052, 922, 821, 671 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.62 (d, J = 8.6 Hz, 1H), 7.30 (d, J = 1.9 Hz, 1H), 7.21 (dd, J = 8.6, 1.9 Hz, 1H), 4.40 (q, J = 7.2 Hz, 1H), 3.75 (s, 3H), 3.02 (s, 3H), 2.99 (s, 3H), 1.68 (d, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.3, 154.1, 140.9, 137.2, 128.5, 122.8, 120.5, 109.5, 39.3, 37.4, 36.4, 30.6, 16.0; HRMS (ESI+, m/z) $[M + H]^+$ calcd for $C_{13}H_{17}ClN_3O^+$ 266.1055, found 266.1055.

*2-(5-Cyano-1-methyl-1H-benzo[d]imidazol-2-yl)-N,N-dimethyl-propanamide (**3h**).* Prepared according to the general procedure from

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1h (63 mg, 0.40 mmol, 1.0 equiv) and *N,N*-dimethylacrylamide **2** (0.17 mL, 1.6 mmol, 4.0 equiv). Purification by reverse-phase flash chromatography over C18 silica gel (10−20% MeCN + 0.1% TFA/H_2O + 0.1% TFA) gave the desired product as its TFA salt, which was treated with an aqueous saturated solution of $NaHCO_3$. Extraction with EtOAc followed by drying with Na_2SO_4 and in vacuo concentration led to desired product **3h** as a white amorphous solid (51 mg, 0.20 mmol, 50% yield). Mp 150 °C (decomp); IR (neat) 3083, 2994, 2945, 2216, 1634, 1615, 1483, 1388, 1297, 1075, 915, 823, 636 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.53 (dd, J = 8.4, 1.5 Hz, 1H), 7.37 (d, J = 8.4 Hz, 1H), 4.44 (q, J = 7.2 Hz, 1H), 3.82 (s, 3H), 3.06 (s, 3H), 3.00 (s, 3H), 1.71 (d, J = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.0, 156.1, 141.9, 139.3, 126.2, 124.7, 120.1, 110.4, 105.5, 39.9, 37.5, 36.4, 30.8, 15.8; HRMS (ESI+, m/z) $[M + H]^+$ calcd for $C_{14}H_{17}N_4O^+$ 257.1397, found 257.1405.

*N,N-Dimethyl-2-(1-methyl-7-(trifluoromethyl)-1H-benzo[d]-imidazol-2-yl)propanamide (**3i**).* Prepared according to the general procedure from **1i** (80.0 mg, 0.400 mmol, 1.0 equiv) and *N,N*-dimethylacrylamide **2** (0.17, 1.6 mmol, 4.0 equiv). Purification by flash chromatography over silica gel (35% acetone/CH_2Cl_2) gave desired product **3i** as a pale yellow amorphous solid (101 mg, 0.337 mmol, 85% yield). Mp 112−114 °C; IR (neat) 2993, 1641, 1528, 1461, 1388, 1284, 1215, 1169, 1108, 1089, 957, 805, 750 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.94 (d, J = 8.1 Hz, 1H), 7.59 (d, J = 7.7 Hz, 1H), 7.29 (t_{app}, J = 7.9 Hz, 1H), 4.40 (q, J = 7.2 Hz, 1H), 3.88 (q, J = 1.7 Hz, 3H), 3.023 (s, 3H), 3.02 (s, 3H), 1.72 (d, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.4, 155.6, 144.4, 132.2, 124.3, 124.0 (q, J = 271 Hz), 121.22 (q, J = 6 Hz), 121.18, 113.7 (q, J = 33 Hz), 39.1, 37.4, 36.5, 32.5 (q, J = 6 Hz), 16.0; ^{19}F NMR (470 MHz, $CDCl_3$) δ −53.94; HRMS (ESI+, m/z) $[M + H]^+$ calcd for $C_{14}H_{17}F_3N_3O^+$ 300.1318, found 300.1324

*N,N-Dimethyl-2-(1-methyl-6-(trifluoromethyl)-1H-benzo[d]-imidazol-2-yl)propanamide (**3j**).* Prepared according to the general procedure from **1j** (80.0 mg, 0.400 mmol, 1.0 equiv) and *N,N*-dimethylacrylamide **2** (0.17, 1.6 mmol, 4.0 equiv). Purification by flash chromatography over silica gel (35% acetone/CH_2Cl_2) gave desired product **3j** as a pale yellow oil (111 mg, 0.371 mmol, 93% yield). Mp 128−130 °C; IR (neat) 2945, 1647, 1471, 1391, 1341, 1307, 1278, 1154, 1107, 1048, 923, 832, 666 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.80 (d, J = 8.3 Hz, 1H), 7.60 (s, 1H), 7.51 (d, J = 8.3 Hz, 1H), 4.45 (q, J = 7.1 Hz, 1H), 3.84 (s, 3H), 3.03 (s, 3H), 3.00 (s, 3H), 1.71 (d, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.1, 155.9, 144.5, 136.0, 125.0 (q, J = 32 Hz), 124.9 (q, J = 272 Hz), 120.0, 119.2 (q, J = 4 Hz), 107.1 (q, J = 4 Hz), 39.3, 37.5, 36.4, 30.7, 15.9; ^{19}F NMR (470 MHz, $CDCl_3$) δ −60.66; HRMS (ESI+, m/z) $[M + H]^+$ calcd for $C_{14}H_{17}F_3N_3O^+$ 300.1318, found 300.1313.

*N,N-Dimethyl-2-(1-methyl-5-(trifluoromethyl)-1H-benzo[d]-imidazol-2-yl)propanamide (**3k**).* Prepared according to the general procedure from **1k** (80.0 mg, 0.400 mmol, 1.0 equiv) and *N,N*-dimethylacrylamide **2** (0.17, 1.6 mmol, 4.0 equiv). Purification by flash chromatography over silica gel (35% acetone/CH_2Cl_2) gave desired product **3k** as a pale yellow oil (105 mg, 0.351 mmol, 88% yield). Mp 148−149 °C; IR (neat) 2944, 1646, 1629, 1495, 1391, 1326, 1256, 1228, 1098, 1049, 925, 816, 707 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.53 (d, J = 8.3 Hz, 1H), 7.39 (d, J = 8.3 Hz, 1H), 4.46 (q, J = 7.1 Hz, 1H), 3.83 (s, 3H), 3.04 (s, 3H), 2.99 (s, 3H), 1.70 (d, J = 7.1 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.2, 155.3, 141.7, 138.5, 125.0 (q, J = 272 Hz), 124.8 (q, J = 32 Hz), 119.7 (q, J = 4 Hz), 117.4 (q, J = 4 Hz), 109.7, 39.3, 37.5, 36.4, 30.8, 15.9; ^{19}F NMR (470 MHz, $CDCl_3$) δ −60.66; HRMS (ESI+, m/z) $[M + H]^+$ calcd for $C_{14}H_{17}F_3N_3O^+$ 300.1318, found 300.1331.

*N,N-Dimethyl-2-(1-methyl-4-(trifluoromethyl)-1H-benzo[d]-imidazol-2-yl)propanamide (**3l**).* Prepared according to the general procedure from **1l** (80.0 mg, 0.400 mmol, 1.0 equiv) and *N,N*-dimethylacrylamide **2** (0.17, 1.6 mmol, 4.0 equiv). Purification by flash chromatography over silica gel (5−20% acetone/CH_2Cl_2) gave desired product **3l** as a pale yellow oil (15 mg, 0.050 mmol, 12% yield). IR (neat) 2926, 1642, 1464, 1428, 1393, 1318, 1212, 1119, 1101, 936, 754 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.53 (d, J = 7.6 Hz, 1H), 7.50 (d, J = 8.1 Hz, 1H), 7.33 (t_{app}, J = 7.8 Hz, 1H), 4.65 (q, J = 7.2 Hz, 1H), 3.87 (s, 3H), 3.08 (s, 3H), 2.97 (s, 3H), 1.68 (d, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.2, 154.7, 139.0 (q, J = 1 Hz), 137.8, 124.1 (q, J = 273 Hz), 121.8, 120.7 (q, J = 32 Hz), 119.6 (q, J = 5 Hz), 113.2, 39.8, 37.6, 36.5, 31.0, 16.0; ^{19}F NMR (470 MHz, $CDCl_3$) δ −60.77; HRMS (ESI+, m/z) $[M + H]^+$ calcd for $C_{14}H_{17}F_3N_3O^+$ 300.1318, found 300.1324.

*2-(1-((Benzyloxy)methyl)-6-methoxy-1H-benzo[d]imidazol-2-yl)-N,N-dimethylpropanamide (**3m**).* Prepared according to the general procedure from **1m** (107 mg, 0.400 mmol, 1.0 equiv) and *N,N*-dimethylacrylamide **2** (0.17, 1.6 mmol, 4.0 equiv). Purification by flash chromatography over silica gel (20−40% acetone/CH_2Cl_2) gave desired product **3m** as a pale yellow oil (124 mg, 0.337 mmol, 84% yield). IR (neat) 2936, 1644, 1486, 1454, 1393, 1207, 1139, 1074, 1056, 816, 733 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.63 (d, J = 8.7 Hz, 1H), 7.38−7.27 (m, 5H), 6.89 (dd, J = 8.7, 2.3 Hz, 1H), 6.79 (d, J = 2.3 Hz, 1H), 5.61 (d, J = 11.0 Hz, 1H), 5.50 (d, J = 11.0 Hz, 1H), 4.50 (s, 2H), 4.40 (q, J = 7.2 Hz, 1H), 3.81 (s, 3H), 2.96 (s, 3H), 2.93 (s, 3H), 1.67 (d, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.8, 157.0, 152.8, 136.8 (2C), 136.5, 128.7, 128.3, 128.0, 120.4, 111.7, 93.8, 72.4, 70.3, 56.0, 38.7, 37.3, 36.3, 16.6; HRMS (ESI+, m/z) $[M + H]^+$ calcd for $C_{21}H_{26}N_3O_3^+$ 368.1969, found 368.1970.

*2-(1-((Benzyloxy)methyl)-5-methoxy-1H-benzo[d]imidazol-2-yl)-N,N-dimethylpropanamide (**3n**).* Prepared according to the general procedure from **1n** (107 mg, 0.400 mmol, 1.0 equiv) and *N,N*-dimethylacrylamide **2** (0.17, 1.6 mmol, 4.0 equiv). Purification by flash chromatography over silica gel (20−40% acetone/CH_2Cl_2) gave desired product **3n** as a pale yellow oil (139 mg, 0.378 mmol, 95% yield). IR (neat) 2938, 1643, 1487, 1441, 1394, 1276, 1197, 1151, 1057, 949, 736 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.38−7.29 (m, 3H), 7.28−7.26 (m, 3H), 7.22 (d, J = 8.8 Hz, 1H), 6.91 (dd, J = 8.8, 2.3 Hz, 1H), 5.62 (d, J = 11.0 Hz, 1H), 5.52 (d, J = 11.0 Hz, 1H), 4.49 (s, 2H), 4.39 (q, J = 7.2 Hz, 1H), 3.85 (s, 3H), 2.95 (s, 3H), 2.93 (s, 3H), 1.68 (d, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.6, 156.3, 154.0, 143.0, 136.5, 130.1, 128.5, 128.1, 127.8, 112.8, 110.0, 102.2, 72.3, 70.3, 55.7, 38.2, 37.1, 36.1, 16.5; HRMS (ESI+, m/z) $[M + H]^+$ calcd for $C_{21}H_{26}N_3O_3^+$ 368.1969, found 368.1959.

*2-(1-((Benzyloxy)methyl)-5,6-dimethyl-1H-benzo[d]imidazol-2-yl)-N,N-dimethylpropanamide (**3o**).* Prepared according to the general procedure from **1o** (107 mg, 0.400 mmol, 1.0 equiv) and *N,N*-dimethylacrylamide **2** (0.17 mL, 1.6 mmol, 4.0 equiv). Purification by flash chromatography over silica gel (30% acetone/CH_2Cl_2) gave desired product **3o** as a cream-colored amorphous solid (85 mg, 0.23 mmol, 58% yield). Mp 121−123 °C; IR (neat) 2982, 2948, 2844, 1651, 1466, 1382, 1069, 1026, 852, 743, 697 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.38−7.27 (m, 5H), 7.08 (s, 1H), 5.62 (d, J = 11.0 Hz, 1H), 5.51 (d, J = 11.0 Hz, 1H), 4.50 (s, 2H), 4.39 (q, J = 7.2 Hz, 1H), 2.93 (s, 3H), 2.92 (s, 3H), 2.36 (s, 6H), 1.66 (d, J = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.8, 153.0, 141.0, 136.9, 134.4, 132.3, 131.5, 128.7, 128.3, 128.0, 120.1, 110.1, 72.4, 70.4, 38.8, 37.3, 36.4, 20.7, 20.4, 16.8; HRMS (ESI+, m/z) $[M + H]^+$ calcd for $C_{22}H_{28}N_3O_2^+$ 366.2176, found 366.2186.

*N,N-Dimethyl-2-(3-methyl-3H-imidazo[4,5-b]pyridin-2-yl)-propanamide (**3p**).* Prepared according to the general procedure from **1p** (100 mg, 0.751 mmol, 1.0 equiv) and *N,N*-dimethylacrylamide **2** (0.31, 3.0 mmol, 4.0 equiv). Purification by flash chromatography over silica gel (5−10% MeOH/CH_2Cl_2) gave desired product **3p** as a beige amorphous solid (148 mg, 0.637 mmol, 85% yield). Mp 141−143 °C; IR (neat) 2940, 1637, 1612, 1506, 1445, 1408, 1389, 1274, 1142, 1081, 781, 755, 581 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.52 (dd, J = 4.8, 1.2 Hz, 1H), 7.61 (dd, J = 7.9, 1.2 Hz, 1H), 7.19 (dd, J = 7.9, 4.8 Hz, 1H), 4.55 (q, J = 7.2 Hz, 1H), 3.83 (s, 3H), 3.07 (s, 3H), 2.97 (s, 3H), 1.71 (d, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.2, 155.6, 155.2, 144.9, 128.9, 117.8, 117.2, 39.7, 37.6, 36.4, 30.8, 15.8; HRMS (ESI+, m/z) $[M + H]^+$ calcd for $C_{12}H_{17}N_4O^+$ 233.1397, found 233.1397.

*N,N-Dimethyl-2-(3-methyl-3H-imidazo[4,5-b]pyridin-2-yl)-propanamide (**3q**).* Prepared according to the general procedure from **1q** (53.0 mg, 0.400 mmol, 1.0 equiv) and *N,N*-dimethylacrylamide **2** (0.17, 1.6 mmol, 4.0 equiv). Purification by flash chromatography over silica gel (60% acetone/CH_2Cl_2) gave desired product **3q** as a pale

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yellow amorphous solid (90 mg, 0.387 mmol, 97% yield). Mp 105−106 °C; IR (neat) 3029, 2977, 1636, 1601, 1509, 1475, 1448, 1399, 1281, 1132, 1076, 806, 782, 702 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.35 (dd, J = 4.8, 1.4 Hz, 1H), 7.99 (dd, J = 8.0, 1.4 Hz, 1H), 7.21 (dd, J = 8.0, 4.8 Hz, 1H), 4.39 (q, J = 7.2 Hz, 1H), 3.86 (s, 3H), 3.02 (s, 3H), 3.00 (s, 3H), 1.71 (d, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.1, 154.7, 148.9, 143.7, 134.5, 127.1, 118.3, 39.3, 37.4, 36.4, 29.0, 15.7; HRMS (ESI+, m/z) $[M + H]^+$ calcd for $C_{12}H_{17}N_4O^+$ 233.1397, found 233.1406.

*2-(6-(Benzyloxy)-3-methyl-3H-imidazo[4,5-b]pyridin-2-yl)-N,N-dimethylpropanamide (**3r**).* Prepared according to the general procedure from **1r** (96.0 mg, 0.400 mmol, 1.0 equiv) and *N,N*-dimethylacrylamide **2** (0.17, 1.6 mmol, 4.0 equiv). Purification by flash chromatography over silica gel (40% acetone/CH_2Cl_2) gave desired product **3r** as an off-white amorphous solid (125 mg, 0.369 mmol, 92% yield). Mp 128−129 °C; IR (neat) 2941, 1636, 1498, 1453, 1393, 1258, 1174, 1028, 869, 731, 692 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.19 (d, J = 2.4 Hz, 1H), 7.56 (d, J = 2.4 Hz, 1H), 7.45 (d, J = 7.2 Hz, 2H), 7.38 (t_{app}, J = 7.3 Hz, 2H), 7.32 (m, 1H), 5.13 (s, 2H), 4.33 (q, J = 7.2 Hz, 1H), 3.81 (s, 3H), 3.00 (s, 6H), 1.67 (d, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.1, 155.0, 152.4, 143.8, 136.6, 134.9, 134.6, 128.8, 128.3, 127.7, 112.0, 71.6, 39.3, 37.4, 36.4, 29.0, 15.7; HRMS (ESI+, m/z) $[M + H]^+$ calcd for $C_{19}H_{23}N_4O_2^+$ 339.1816, found 339.1821.

*Ethyl 2-(1-(Dimethylamino)-1-oxopropan-2-yl)-3-methyl-3H-imidazo[4,5-b]pyridine-6-carboxylate (**3s**).* Prepared according to the general procedure from **1s** (82 mg, 0.40 mmol, 1.0 equiv) and *N,N*-dimethylacrylamide **2** (0.17 mL, 1.6 mmol, 4.0 equiv). Purification by flash chromatography over silica gel (20% acetone/CH_2Cl_2) gave desired product **3s** as a pale yellow solid (90 mg, 0.30 mmol, 74% yield). Mp 137−138 °C; IR (neat) 3041, 2987, 2942, 1715, 1636, 1602, 1481, 1371, 1293, 1197, 1086, 1009, 789, 621 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.04 (d, J = 1.8 Hz, 1H), 8.61 (d, J = 1.8 Hz, 1H), 4.46−4.37 (m, 3H), 3.88 (s, 3H), 3.05 (s, 3H), 3.01 (s, 3H), 1.73 (d, J = 7.2 Hz, 3H), 1.42 (t, J = 7.1 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.9, 166.2, 156.7, 151.5, 146.0, 133.8, 128.6, 121.6, 61.3, 39.3, 37.5, 36.4, 29.3, 15.5, 14.5; HRMS (ESI+, m/z) $[M + H]^+$ calcd for $C_{15}H_{21}N_4O_3^+$ 305.1608, found 305.1624.

*2-(1-Methyl-1H-benzo[d]imidazol-2-yl)propanal O-Methyl Oxime (**4a**).* In a N_2-filled glovebox, a flame-dried Biotage microwave vial (#351521, HxD = 8 × 1.5 cm) was charged with bis-(cyclopentadienyl)zirconium(IV) chloride hydride (62 mg, 0.24 mmol, 1.2 equiv) followed by THF (3 mL). To this suspension was added **3a** (46 mg, 0.2 mmol, 1.0 equiv) in THF (2.1 mL), and the vial was sealed with a Teflon-lined septum. The mixture was stirred at room temperature for 1.5 h, after which time NH_2−OMe·HCl (50 mg, 0.6 mmol, 3 equiv) was added, and the reaction mixture was stirred for an additional 2 h. The reaction mixture was then concentrated in vacuo. An aqueous saturated solution of $NaHCO_3$ was added until pH ∼8 was reached, and the resulting mixture was then extracted with EtOAc (3 × 25 mL). The organic phase was dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography over silica gel (15% EtOAc/hexanes + 1% Et_3N) gave a mixture of oxime isomers as a clear oil (38 mg, 0.176 mmol, 88% yield, 3:1 dr). For characterization purposes, stereoisomerically pure samples of each of the isomers were obtained by chromatography over silica gel (1% acetone/CH_2Cl_2 + 1% Et_3N) followed by a second silica gel column (10% EtOAc/Hexanes +1% Et_3N). (Major isomer of **4a**): IR (neat) 2991, 2937, 2824, 1615, 1500, 1473, 1279, 1048, 1031, 840, 748 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 6.8 Hz, 1H), 7.50 (d, J = 7.6 Hz, 1H), 7.36−7.23 (m, 3H), 4.03 (p, J = 7.1 Hz, 1H), 3.84 (s, 3H), 3.78 (s, 3H), 1.68 (d, J = 7.0 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 153.9, 150.6, 142.5, 136.0, 122.7, 122.2, 119.7, 109.2, 61.8, 33.7, 30.0, 17.3; HRMS (ESI+, m/z) $[M + H]^+$ calcd for $C_{12}H_{16}N_3O^+$ 218.1288, found 218.1310. (Minor isomer of **4a**): IR (neat) 2976, 2938, 2833, 1616, 1504, 1468, 1279, 1050, 1031, 872, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 6.6 Hz, 1H), 7.34−7.23 (m, 3H), 6.91 (d, J = 7.4 Hz, 1H), 4.67 (p, J = 7.1 Hz, 1H), 3.94 (s, 3H), 3.74 (s, 3H), 1.61 (d, J = 7.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 154.5, 150.5, 142.6, 135.8, 122.6, 122.2, 119.8, 109.3, 62.1, 29.7, 28.8, 16.7; HRMS (ESI+, m/z) $[M + H]^+$ calcd for $C_{12}H_{16}N_3O^+$ 218.1288, found 218.1289.

*2-(1-Methyl-1H-imidazo[4,5-b]pyridin-2-yl)propanal O-Methyl Oxime (**4p**).* In a N_2-filled glovebox, a flame-dried Biotage microwave vial (#351521, HxD = 8 × 1.5 cm) was charged with bis-(cyclopentadienyl)zirconium(IV) chloride hydride (62 mg, 0.24 mmol, 1.2 equiv) followed by THF (3 mL). To this suspension was added **3p** (47 mg, 0.2 mmol, 1.0 equiv) suspended in THF (3.1 mL), and the vial was sealed with a Teflon-lined septum. The mixture was stirred at room temperature for 2.5 h, after which time NH_2−OMe·HCl (50 mg, 0.6 mmol, 3 equiv) was added, and the reaction mixture was stirred for an additional 2.5 h. The reaction mixture was concentrated in vacuo. An aqueous saturated solution of $NaHCO_3$ was added until pH ∼8 was reached, and the resulting mixture was extracted with EtOAc (3 × 25 mL). The organic phase was dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography over silica gel (80% EtOAc/hexanes + 1% Et_3N) gave a mixture of *E*- and *Z*-isomers as a pale yellow oil (29 mg, 0.131 mmol, 66% yield, 3:1 dr). IR (neat) 2987, 2939, 2819, 1612, 1503, 1454, 1408, 1279, 1050, 888, 778, 731 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.51 (d, J = 4.7 Hz, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.52 (d, J = 7.6 Hz, 0.75H), 7.19 (t, J = 8.0, 4.8 Hz, 1H), 6.96 (d, J = 7.3 Hz, 0.25H), 4.68 (p, J = 7.0 Hz, 0.25H), 4.03 (p, J = 7.1 Hz, 0.75H), 3.93 (s, 0.75H), 3.83 (s, 2.25H), 3.80 (s, 2.25H), 3.77 (s, 0.75H), 1.69 (d, J = 7.0 Hz, 2.25H), 1.62 (d, J = 7.0 Hz, 0.75H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 156.9, 156.4, 155.4, 155.3, 150.2, 149.9, 144.6, 144.6, 128.1, 127.9, 117.7, 117.6, 116.99, 116.97, 62.0, 61.7, 33.7, 29.9, 29.7, 28.8, 17.1, 16.6; HRMS (ESI+, m/z) $[M + H]^+$ calcd for $C_{11}H_{15}N_4O^+$ 219.1240, found 219.1247.

*Ethyl 2-(1-((Benzyloxy)methyl)-1H-benzo[d]imidazol-2-yl)-2-methylpropanoate (**6c**) and Ethyl 3-(1-((Benzyloxy)methyl)-1H-benzo[d]imidazol-2-yl)-2-methylpropanoate (**6c′**).* Prepared according to the general procedure from **1c** (95 mg, 0.400 mmol, 1.0 equiv) and ethyl methacrylate **5** (0.190 mL, 1.6 mmol, 4.0 equiv). Purification by flash chromatography over silica gel (5−10% diethyl ether/CH_2Cl_2) gave, by order of elution, desired products **6c** as a pale yellow oil (45 mg, 0.128 mmol, 32% yield) and **6c′** as a pale yellow oil (48 mg, 0.136 mmol, 34% yield). (**6c**): IR (neat) 2985, 1728, 1457, 1361, 1247, 1147, 1064, 1025, 909, 728 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.88−7.74 (m, 1H), 7.43−7.19 (m, 8H), 5.46 (s, 2H), 4.56 (s, 2H), 4.10 (q, J = 7.1 Hz, 2H), 1.81 (s, 6H), 1.13 (t, J = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.1, 156.1, 141.7, 136.6, 136.4, 128.7, 128.3, 127.9, 123.4, 122.6, 120.0, 110.1, 73.0, 70.8, 61.7, 44.7, 26.1, 14.1; HRMS (ESI+, m/z) $[M + H]^+$ calcd for $C_{21}H_{25}N_2O_3^+$ 353.1860, found 353.1851. (**6c′**): IR (neat) 2979, 1725, 1519, 1456, 167, 1281, 1178, 1066, 906, 736, 697 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.87−7.61 (m, 1H), 7.40−7.21 (m, 8H), 5.65 (d, J = 11.3 Hz, 1H), 5.54 (d, J = 11.3 Hz, 1H), 4.49 (s, 2H), 4.17−4.04 (m, 2H), 3.39−3.28 (m, 2H), 2.93 (q_{app}, J = 9.6 Hz, 1H), 1.33 (d, J = 6.7 Hz, 3H), 1.20 (t, J = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.7, 153.7, 142.7, 136.7, 135.3, 128.7, 128.3, 127.9, 122.8, 122.5, 119.5, 109.5, 71.9, 70.3, 60.7, 38.3, 30.8, 17.7, 14.2; HRMS (ESI+, m/z) $[M + H]^+$ calcd for $C_{21}H_{25}N_2O_3^+$ 353.1860, found 353.1847.

*Ethyl 2-Methyl-2-(1-methyl-6-trifluoromethyl-1H-benzo[d]-imidazol-2-yl)propanoate (**6j**).* Prepared according to the general procedure from **1j** (80.0 mg, 0.400 mmol, 1.0 equiv) and ethyl methacrylate **5** (0.190 mL, 1.6 mmol, 4.0 equiv). Purification by flash chromatography over silica gel (10% acetone/CH_2Cl_2) gave desired product **6j** as a pale yellow oil (108 mg, 0.344 mmol, 86% yield). IR (neat) 2987, 1732, 1509, 1469, 1335, 1279, 1151, 1010, 1049, 822, 732 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.85 (d, J = 8.4 Hz, 1H), 7.59 (s, 1H), 7.52 (d, J = 8.5 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 3.69 (s, 3H), 1.78 (s, 6H), 1.22 (t, J = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.8, 158.7, 144.0, 136.3, 125.0 (q, J = 32 Hz), 124.9 (d, J = 272 Hz), 120.2, 119.2 (q, J = 3 Hz), 107.0 (q, J = 4 Hz), 62.0, 44.6, 31.1, 25.5, 14.3; ^{19}F NMR (470 MHz, $CDCl_3$) δ −60.63. HRMS (ESI+, m/z) $[M + H]^+$ calcd for $C_{15}H_{18}F_3N_2O_2^+$ 315.1315, found 315.1310.

*Ethyl 2-Methyl-2-(3-methyl-3H-imidazo[4,5-b]pyridin-2-yl)-propanoate (**6q**).* Prepared according to the general procedure from

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1q (53.0 mg, 0.400 mmol, 1.0 equiv) and ethyl methacrylate **5** (0.190 mL, 1.6 mmol, 4.0 equiv). Purification by flash chromatography over silica gel (10% acetone/CH_2Cl_2) gave desired product **4q** as a pale yellow oil (95 mg, 0.384 mmol, 96% yield). IR (neat) 2982, 1731, 1602, 1500, 1464, 1407, 1387, 1283, 258, 1229, 1147, 1021, 774 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.36 (dd, J = 4.8, 1.4 Hz, 1H), 8.03 (dd, J = 7.9, 1.4 Hz, 1H), 7.22 (dd, J = 7.9, 4.8 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 3.75 (s, 3H), 1.78 (s, 6H), 1.22 (t, J = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.7, 157.3, 149.3, 143.8, 134.0, 127.2, 118.3, 61.9, 44.8, 29.5, 25.2, 14.3; HRMS (ESI+, m/z) $[M + H]^+$ calcd for $C_{13}H_{18}N_3O_2^+$ 248.1394, found 248.1400.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b01723.

^1H, ^{13}C, and ^{19}F NMR spectra for all new compounds and ^1H NMR spectra for previously reported compounds (PDF)

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Notes

The authors declare no competing financial interest.

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