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Synthesis of Fused Imidazole-Containing Ring Systems via Dual Oxidative Amination of C(sp^3)−H Bonds

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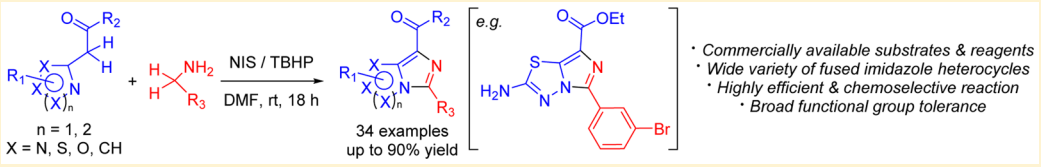
Supporting Information



ABSTRACT: A general and efficient method for a metal-free one-pot synthesis of highly substituted fused imidazole-containing 5,5- and 5,6-fused bicyclic heterocycles is described. Starting from commercially available substrates and reagents, the reaction proceeds through two C−N bond formations and an oxidative dehydrogenation to form highly substituted products in good to excellent yield.

Fused heterocyclic ring systems containing bridgehead nitrogens not only are biologically relevant but also are valuable building blocks in medicinal chemistry and present a persistent synthetic challenge (Figure 1).[1] Typical approaches

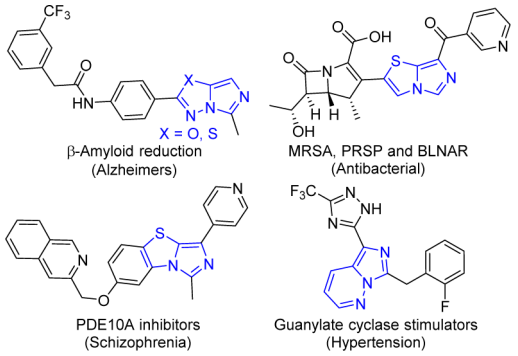
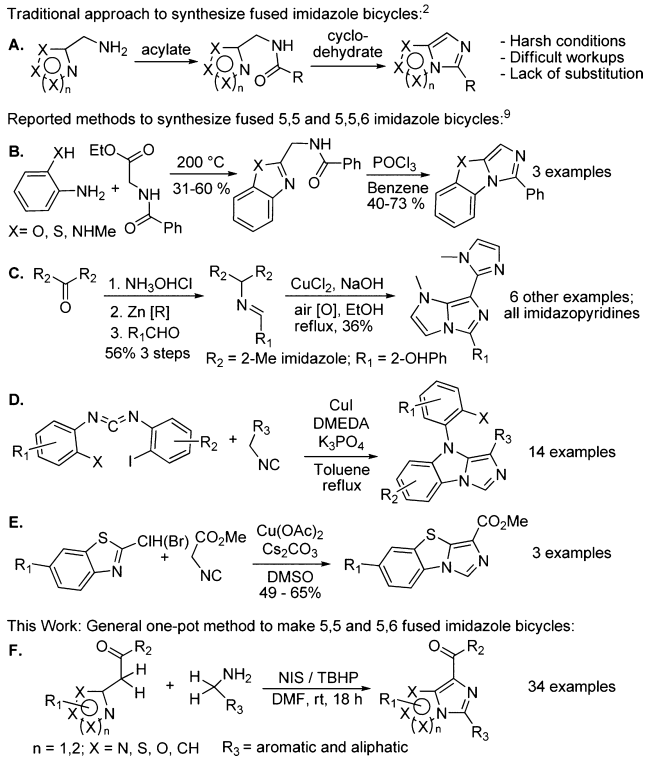


Figure 1. Examples of fused imidazole-containing rings in medicinal chemistry.[1]

to their synthesis involve acylation of *o*-nitrogen-containing arylmethylamines and subsequent cyclodehydration (Scheme 1A).[2] Several recent publications have reported routes to polysubstituted 5,6-fused imidazo[1,5-*a*]pyridines in one pot through CH arylation,[3] multicomponent condensation,[4] and C(sp^3)−H amination;[5−8] however, methods for accessing 5,5- and 5,5,6-fused ring systems remain scarce and often suffer from limitations such as a lack of commercial availability of starting materials, long synthetic routes, harsh reaction conditions, complex isolation procedures, and limitations in scope (Scheme 1B−E).[9]

In the course of one of our medicinal chemistry programs, we became interested in testing the effect of replacing an imidazo[1,5-*a*]pyridine core with a variety of 5,5-fused bridgehead nitrogen-containing heterocycles. In studying the

Scheme 1. Summary of Methods for Synthesizing Fused Imidazole Ring Systems



existing methods, we found a number of inadequacies, including the aforementioned drawbacks. We envisioned that a general method for synthesizing 5,5-imidazole-containing

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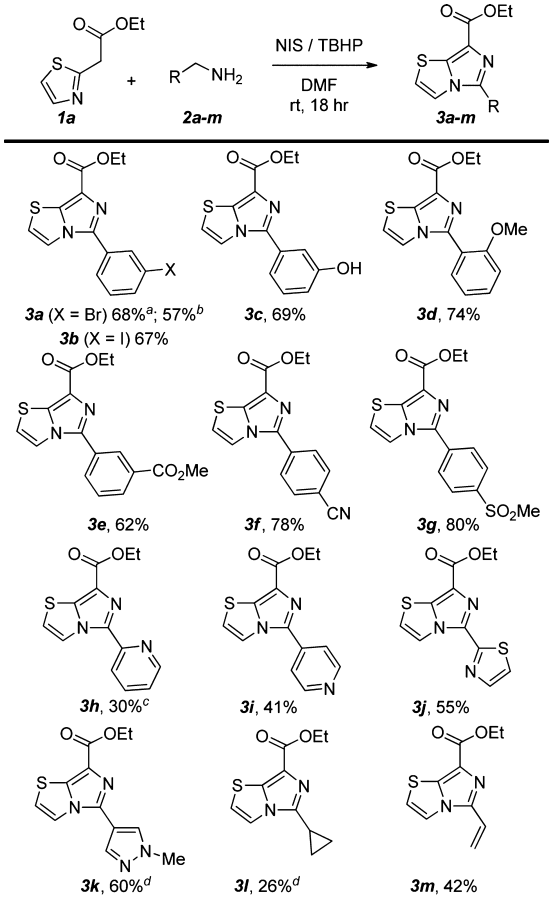
fused ring systems would be valuable from a synthetic and medicinal chemistry perspective. Herein, we report a robust and chemoselective method for their synthesis in a one-pot fashion from commercially available starting materials (Scheme 1F).

Pioneering work by Yan et al. demonstrated the first example of a metal-free sequential dual oxidative amination of C(sp^3)–H bonds for synthesizing imidazo[1,5-*a*]pyridines.[5] With this as a foundation, we sought to optimize the transformation to be applicable for the synthesis of a broad range of fused ring systems. At the outset of our investigation, we were able to demonstrate that the reaction could be performed in standard vials, negating the requirement for a Schlenk tube and making it more experimentally convenient.[5] We found that the order of addition was also important, with the best results obtained when the iodine source and oxidant were added to a solution of heteroaromatic substrate and amine in solvent.[10] With these adjustments in place, we began our evaluation of the reaction conditions (see the Supporting Information and Table 1). Beginning with ethyl 2-(thiazol-2-yl)acetate (**1a**, 1.0 equiv), 3-bromobenzylamine (**2a**, 2.0 equiv), an iodine source (1.0 equiv), and TBHP (3.0 equiv) in DMA (0.5 M), we were pleased to observe formation of ethyl 5-(3-bromophenyl)-imidazo[5,1-*b*]thiazole-7-carboxylate **3a** as the primary product. Furthermore, NIS appeared to be the best iodine source of

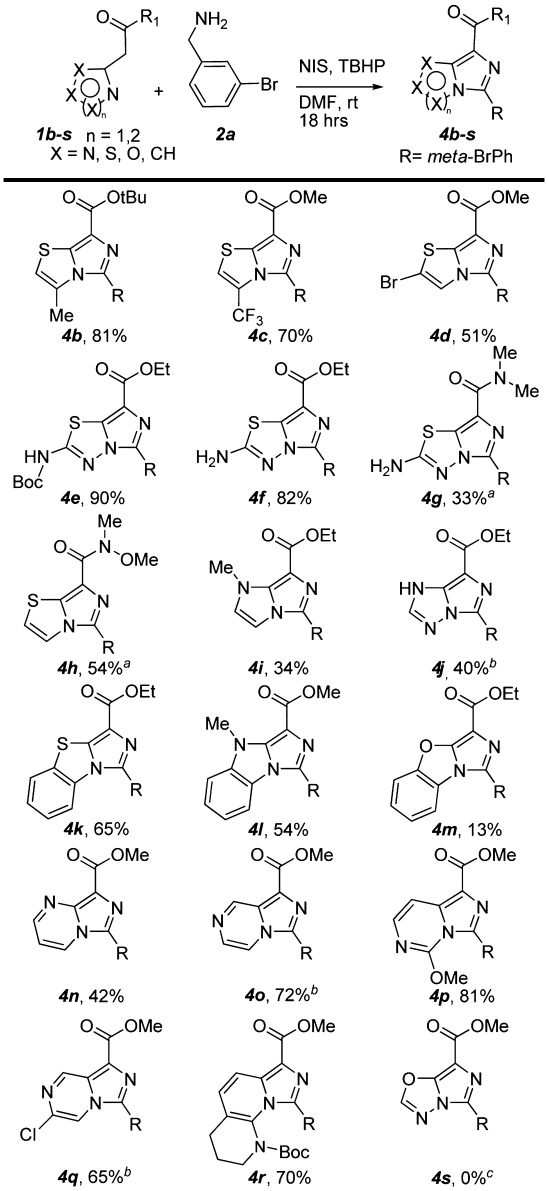
Table 1. Amine Scope of the Imidazo[5,1-*b*]thiazole Core[e]



[a]ACN as the solvent. [b]The 0.5 and 6.0 mmol scales in DMF gave the same yield. [c]With 1.1 equiv of amine. [d]Reaction mixture heated at 80 °C for 18 h. [e]Isolated percent yields reported. Reaction conditions: **1a** (0.5 mmol), **2** (1.0 mmol), NIS (0.5 mmol), TBHP (1.5 mmol), solvent (0.5 M), rt, 18 h.

those screened for 5,5-fused ring formation. In our examination of the effect of solvent (see the Supporting Information and Table 2), we found that ACN was marginally better in terms of

Table 2. Heteroaromatic Substrate Scope[d]



[a]Reaction mixture heated at 80 °C for 18 h. [b]Here 1.1 equiv of amine used. [c]Product observed but not isolated because of rapid decomposition. [d]Isolated percent yields reported. Reaction conditions: **1** (0.5 mmol), **2a** (1.0 mmol), NIS (0.5 mmol), TBHP (1.5 mmol), solvent (0.5 M), rt, 18 h.

yield of **3a**, but DMF was ultimately selected because of its superior solubilizing ability. With our newly optimized conditions in hand, we proceeded to probe the amine scope (Table 1).

Compound **3a** was isolated in 68% yield in ACN and 57% yield in DMF with no column purification, with the product isolated following trituration of the reaction mixture.[11] We were able to demonstrate the scalability of the reaction by achieving the same yield (57%) at 1 g (6 mmol) scale in DMF. The method tolerates both electron-donating (hydroxy **2c**, methoxy **2d**) and electron-withdrawing groups on the amine (halogens

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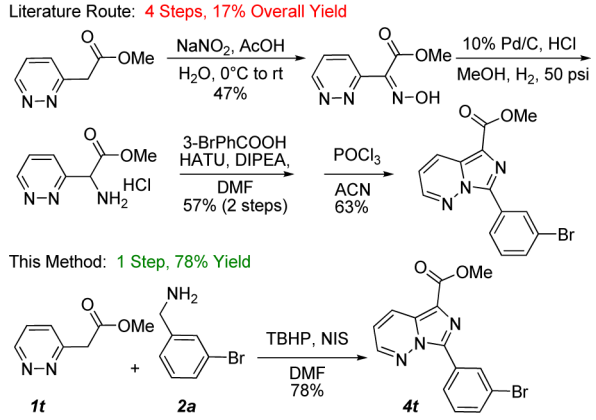
2a and **2b**, ester **2e**, nitrile **2f**, and sulfone **2g**). Examples **3a** and **3b** contain halogens that can act as a synthetic handle for further elaboration. We were very gratified to see that the free hydroxyl group in **3c** was benign under the reaction conditions.[12] The *o*-methoxy substituent in **3d** demonstrated that the reaction can also tolerate increased steric demand on the amine substrate.[13] The exceptional chemoselectivity and functional group tolerability of the reaction were further evidenced by examples **3e−g**, where an ester, nitrile, and sulfone were not affected under these reaction conditions. Interestingly, amine substrates **2h−k** with additional potentially reactive nitrogens were also tolerated in the reaction (examples **3h−k**). Although pyridin-2-ylmethanamine had not been shown to be a viable amine substrate on prior occasions with similarly proposed mechanisms,[6,8,14] the corresponding product, **3h**, was obtained, albeit in low yield, through adjustment of the number of equivalents of the amine substrate from 2.0 to 1.1. The scope was further expanded to include aliphatic amines as in **3l** and **3m**. In addition, the allylic moiety in **3m** is a multifaceted group that is poised to undergo further functionalization. Although the isolated yields were somewhat low for several of the examples in this table, we were delighted to synthesize a wide variety of highly complex, polysubstituted imidazo[5,1-*b*]thiazoles with exceptional chemoselectivity and diversity in one step with broad functional group tolerance.[15]

Our attention then turned to investigating the scope of the heteroaromatic substrate (Table 2). Electron-donating and -withdrawing groups (Me, CF_3, and Br) were tolerated at multiple positions on the imidazo[5,1-*b*]thiazole as seen in examples **4b−d**. Initially, we chose to mask the free amino group of the heteroaromatic substrate in **4e** with a *tert*-butoxycarbonyl (Boc) group as we were concerned that it might hinder product formation. We were subsequently able to show that this is not the case, as the free amino group was tolerated under the reaction conditions as shown by **4f** and **4g**. Additionally, we were unable to find any prior instances of this imidazo[5,1-*b*][1,3,4]thiadiazol-2-amine core in the literature. The Weinreb amide was also a competent substrate in this reaction shown by **4h** in 54% yield and is a versatile handle for additional manipulation. Furthermore, tertiary amide **4g** can potentially be readily converted to an aldehyde.[16] Imidazo[1,5-*a*]imidazole **4i** gave lower yields of 34%, but our one-step synthesis, which allowed for more structural diversification, offered advantages over the previously reported four-step method for making this ring system.[9e] Similarly, the polysubstituted imidazo[1,5-*b*][1,2,4]triazole **4j**, whose starting material and subsequent product contains a free NH, has been poorly examined in the literature but was easily prepared in 40% yield with this method.[17] As demonstrated by **4k−m**, benzothiazole, benzimidazole, and benzoxazole were all competent substrates in the reaction for the formation of the corresponding 5,5,6-fused ring systems. In some cases, low yields can be potentially be explained by the pK_a of the nitrogen in the heteroaromatic substrate, which offers a relative estimation of its nucleophilicity. In particular, for methyl 2-(benzo[*d*]oxazol-2-yl)acetate (**1m**), used to synthesize **4m** in 13% yield, the pK_a is on the order of 0.5.[18] Several other examples of heteroaromatic substrates whose nitrogen atom has a negative or unknown pK_a value failed to yield any product (such as isoxazole, 1,2,4-oxadiazole, and benzo[*d*]isothiazole).[19] We were able to observe formation of imidazo[5,1-*b*][1,3,4]-oxadiazole **4s**, but it rapidly decomposed during isolation, presumably because of the instability of the product.[20]

After demonstrating the successful synthesis of a variety of complex 5,5- and 5,5,6-fused imidazole-containing bicycles, we wanted to further demonstrate the robustness of the method through extension to fused 5,6 systems.[21] To that end, with examples **4n−r**, we were able to show that highly substituted 5,6-fused imidazole ring systems, including imidazo[1,5-*a*]pyrimidine, imidazo[1,5-*a*]pyrazine, imidazo[1,5-*c*]-pyrimidine, and 1,2,3,4-tetrahydroimidazo[1,5-*a*][1,8]-naphthyridine, could all be accessed using this method. Although the one-pot synthesis of the imidazo[1,5-*c*]pyrimidine core was not compatible with a prior method,[14] we were gratified to isolate **4p** in 81% yield. In addition, **4q** demonstrated that a reactive functional group (chlorine) on the pyrazine substrate remained undisturbed and offered an option for further elaboration if necessary.

In addition to displaying the broad scope of the amine and heteroaromatic substrates, we were able to use this methodology to improve upon a synthesis of an imidazo[1,5-*b*]pyridazine intermediate that had been employed in the synthesis of NF-$\kappa\beta$-inducing kinase (NIK) inhibitors (Scheme 2).[1d] Using (methyl-2-pyridazin-3-yl)acetate **1t** as a common

Scheme 2. Improved Route to the Literature Intermediate (example 4t)[1d]



starting material, **4t** was synthesized in 78% yield following a trituration, avoiding any column chromatography, rather than in four steps, and in 17% overall yield with the previous literature route.

With the objective of further elucidating the reaction mechanism, we isolated and characterized several reaction intermediates encountered during our scope investigations. Imine intermediate **5** was obtained in 50% yield when the reaction was performed at room temperature (Scheme 3A), but conversion to product **3k** (Table 1) could be effected with heating to 80 °C from the outset. Similarly, secondary amine **6** was isolated in 43% yield (Scheme 3B), while formation of product **4g** (Table 2) was realized when the reaction mixture was heated to 80 °C.[22] The isolation of both imine **5** and secondary amine **6** as reaction intermediates supports the previously proposed mechanistic pathways.[5,8,14,23] We also observed when the heteroaromatic substrate was a ketone and the starting material was primarily in the enol form (as indicated by NMR), preferential and unexpected formation of a 2,4,5-substituted oxazole **7** was seen in 44% yield over our desired imidazobenzimidazole **4u**, obtained in 22% yield (Scheme 3C). We are currently investigating whether we can alter the conditions to bias the reaction outcome. In addition,

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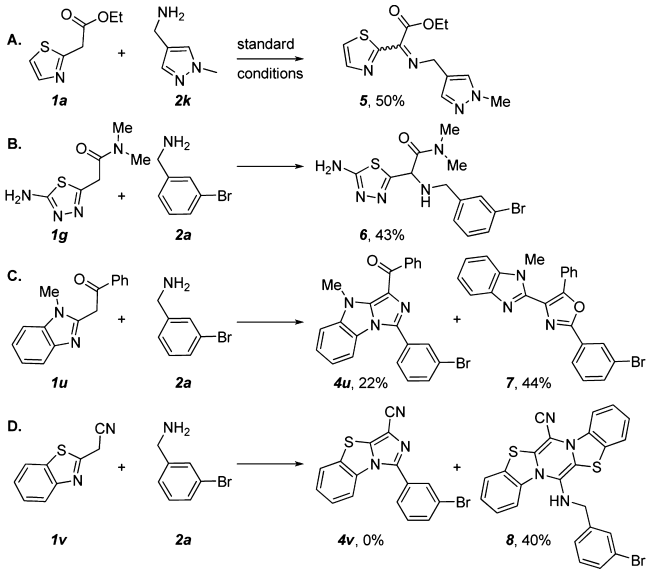
Scheme 3. Isolated Potential Reaction Intermediates and Byproducts[a]



[a]Isolated percent yields reported. Standard reaction conditions: **1** (0.5 mmol), **2** (1 mmol), NIS (0.5 mmol), TBHP (1.5 mmol), solvent (0.5 M), rt, 18 h.

mechanistic studies are underway in an attempt to elucidate the reaction mechanism beyond what has been previously reported.

Attempts to expand the scope beyond ester, ketone, amide, and Weinreb amide moieties at C-4 of the imidazole ring were met with some limitations. In the case of the nitrile, instead of **4v**, we saw the benzo[*d*]thiazole ring nitrogens react preferentially over the secondary amine nitrogen to give **8** in 40% yield (Scheme 3D).[24] Additional heteroaromatic substrates containing electron-withdrawing groups such as CF_3, SO_2Ph, and symmetrical benzo[*d*]thiazole rings (with CH_2 between them) also failed to give product, which we attributed to insufficient captodative resonance stabilization of the proposed radical reaction intermediate.[5,8,14]

In summary, we were able to develop a highly chemoselective, robust, and general method for synthesizing a variety of historically difficult to access, complex polysubstituted 5,5- and 5,6-fused imidazole-containing heterocycles in moderate to excellent yields. A wide array of functional group tolerance on both the heteroaromatic and amine substrates was demonstrated. Additionally, our method allowed access to fused heterocycles that had not been previously reported in the literature. We believe this method has the capability of having an impact in fields such as medicinal chemistry, agrochemicals, and materials as it allows for rapid synthesis of a diverse range of fused heterocycles.

EXPERIMENTAL SECTION

General Information. Unless otherwise indicated, all commercial reagents and solvents were used without additional purification. Anhydrous solvents were used in reaction optimization and scope. ^{1}H NMR spectra were recorded with a 400 or 500 MHz spectrometer. Chemical shifts (in parts per million) were referenced to tetramethylsilane (δ 0) in DMSO-d_6 (δ 2.5) or $CDCl_3$ (δ 7.26) as an internal standard. ^{13}C NMR spectra were obtained with the same NMR spectrometer and were calibrated with DMSO-d_6 (δ 39.51) or $CDCl_3$ (δ 77.2). HRMS spectra were recorded on an Orbitrap Q Exactive mass spectrometer. In situations in which final compounds contain bromine, ^{79}Br with an exact mass of 78.9183 was used in the calculation. Thin-layer chromatograms were performed on Silica gel 60 F254 aluminum-backed plates and visualized with UV light. Reactions were monitored by a walkup LCMS/UV system using 2 to 98% acetonitrile with 0.1% formic acid (or 0.01% ammonia) over 2.5 min (short method) or 5.5 min (long method). Flash column chromatography purifications were performed on automated systems equipped with wavelengths of 254 and 280 nm. Reverse phase purification of compound **4m** was achieved by HPLC with a gradient of 5 to 95% acetonitrile/water (with 0.1% formic acid or 0.1% NH_4OH) over 10 min at a rate of 60 mL/min. The starting materials were commercially available with the exception of **1e**, **1h**, **1p**, and **1q**. Ethyl 2-(1-methyl-1*H*-benzo[*d*]imidazol-2-yl)acetate used in the synthesis of compound **4l** was prepared as described in ref 25.

General Procedure A. To a stirring solution of the heteroaromatic substrate (0.5 mmol) in *N*,*N*-dimethylformamide (2 mL/mmol, 0.5 M) were added dropwise the benzylamine derivative (1.0 mmol, 2.0 equiv), NIS (0.5 mmol, 1.0 equiv), and finally TBHP (70% aq, 1.5 mmol, 3.0 equiv). The reaction mixture was subsequently stirred overnight (18 h), and then the reaction was quenched with a saturated $Na_2S_2O_3$ solution (2.0 mL) to reduce any excess iodine followed by addition of a saturated ammonium chloride solution (10 mL) and extraction with dichloromethane (10 mL). The organic layer was dried with magnesium sulfate, filtered, and concentrated to afford the crude fused imidazole bicyclic product that was purified via flash column chromatography using a heptanes/iPrOAc or 3:1 iPrOAc:MeOH to heptanes gradient.

General Procedure B. The differences from procedure A are as follows. After the reaction had been quenched with a saturated $Na_2S_2O_3$ solution, a solid precipitated from the aqueous solution that was further diluted with water (10 mL), collected by filtration, and triturated by sonicating or rinsing the solid in a slurry of methanol. The solid was re-collected by filtration and dried under vacuum to afford the pure fused imidazole bicyclic product without the necessity of column purification.

*Ethyl 2-[5-(tert-Butoxycarbonylamino)-1,3,4-thiadiazol-2-yl]-acetate (**1e**).* To a suspension of ethyl 2-(5-amino-1,3,4-thiadiazol-2-yl)acetate (500 mg, 2.67 mmol, 1.0 equiv) in dichloromethane (0.25 M, 10.7 mL) at room temperature were added di-*tert*-butyl dicarbonate (661 mg, 1.1 equiv) and 4-dimethylaminopyridine (34 mg, 0.1 equiv). After being stirred for 18 h at rt, the reaction mixture was washed with 1 N HCl, and the organic layer was dried with magnesium sulfate, filtered, and concentrated. The crude was purified via flash column chromatography using a heptanes/iPrOAc gradient to afford 430 mg (56%) of ethyl 2-[5-(*tert*-butoxycarbonylamino)-1,3,4-thiadiazol-2-yl]acetate as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.81 (s, 1H), 4.19−4.11 (m, 4H), 1.49 (s, 9H), 1.21 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.8, 161.6, 156.2, 152.7, 81.9, 61.1, 35.0, 27.8, 14.0; HRMS (ESI) [M + H]$^+$ calcd $C_{11}H_{18}N_3O_4S$ 288.1018, found 288.1013.

*N-Methoxy-N-methyl-2-thiazol-2-yl-acetamide (**1h**).* To a solution of 2-thiazoleacetic acid (400 mg, 2.68 mmol, 1.0 equiv) in DMF (0.5 M) were added *N*,*O*-dimethylhydroxylamine hydrochloride (2.0 equiv), HATU (1.1 equiv), and DIPEA (4.0 equiv). The reaction mixture was stirred for 30 min, the reaction quenched with a saturated ammonium chloride solution, and the mixture extracted with DCM. The organic layer was dried with magnesium sulfate, filtered, concentrated, and purified by column chromatography using a heptanes/iPrOAc gradient to afford 450 mg (90%) of *N*-methoxy-*N*-methyl-2-thiazol-2-yl-acetamide: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 3.4 Hz, 1H), 7.30 (d, J = 3.3 Hz, 1H), 4.24 (s, 2H), 3.74 (s, 3H), 3.25 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.4, 162.8, 142.1, 120.0, 61.7, 36.6, 32.4; HRMS (ESI) [M + H]$^+$ calcd $C_7H_{11}N_2O_2S$ 187.0541, found 187.0536.

*Methyl 2-(2-Methoxypyrimidin-4-yl)acetate (**1p**).* To a 0.5 M solution of methyl 2-(2-chloropyrimidin-4-yl)acetate (460 mg, 2.5 mmol, 1.0 equiv) in MeOH (0.5 M) was added sodium methoxide (2.0 equiv, 30% mass in MeOH). The reaction mixture was stirred for 24 h at room temperature, then diluted with a saturated ammonium chloride solution (20 mL), and extracted with DCM (20 mL). The

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organic layer was dried with magnesium sulfate, filtered, concentrated, and purified by column chromatography using a heptanes/iPrOAc gradient to afford 100 mg (22%) of methyl 2-(2-methoxypyrimidin-4-yl)acetate as an oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, J = 5.0 Hz, 1H), 6.96 (d, J = 5.0 Hz, 1H), 4.01 (s, 3H), 3.76 (s, 2H), 3.74 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7, 165.7, 165.3, 159.4, 114.8, 54.9, 52.4, 43.2; HRMS (ESI) $[M + H]^+$ calcd $C_8H_{11}N_2O_3$ 183.0770, found 183.0764.

*Methyl 2-(5-Chloropyrazin-2-yl)acetate (**1q**).* To a solution of 2-(5-chloropyrazin-2-yl)acetic acid (509 mg, 3.0 mmol, 1.0 equiv) in DMF (0.5 M) were added potassium carbonate (3.0 equiv) and iodomethane (1.1 equiv). The reaction mixture was stirred at room temperature for 1 h, and then the reaction was quenched with a saturated solution of ammonium chloride and DCM. The organic layer was dried with magnesium sulfate, filtered, and concentrated. The crude was purified via flash column chromatography using a heptanes/iPrOAc gradient to afford 290 mg (53%) of methyl 2-(5-chloropyrazin-2-yl)acetate as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (s, 1H), 8.51 (s, 1H), 3.88 (s, 2H), 3.75 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.6, 150.0, 148.7, 143.2, 143.0, 52.7, 40.6; HRMS (ESI) $[M + H]^+$ calcd $C_7H_8ClN_2O_2$ 187.0274, found 187.0269.

*Ethyl 5-(3-Bromophenyl)imidazo[5,1-b]thiazole-7-carboxylate (**3a**).* Ethyl 2-thiazol-2-ylacetate **1a** (0.5 mmol) was reacted with 3-bromobenzylamine **2a** (2.0 equiv) according to general procedure B. The reaction was performed in acetonitrile on a 0.5 mmol scale to give a 68% yield and in DMF on a 0.5 and 6 mmol scale to give a 57% yield: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.37 (d, J = 4.2 Hz, 1H), 8.07−8.04 (m, 1H), 7.95−7.91 (m, 1H), 7.68−7.64 (m, 1H), 7.59 (d, J = 4.2 Hz, 1H), 7.52−7.46 (m, 1H), 4.32 (q, J = 7.1 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.3, 141.1, 136.5, 131.5, 131.2, 130.9, 128.7, 125.0, 122.1, 120.5, 120.2, 119.9, 59.7, 14.2; HRMS (ESI) $[M + H]^+$ calcd $C_{14}H_{12}BrN_2O_2S$ 350.9803, found 350.9808.

*Ethyl 5-(3-Iodophenyl)imidazo[5,1-b]thiazole-7-carboxylate (**3b**).* Ethyl 2-thiazol-2-ylacetate **1a** (0.5 mmol) was reacted with 3-iodobenzylamine **2b** (2.0 equiv) according to general procedure B to give 133 mg (67%) of a light tan solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 (d, J = 4.2 Hz, 1H), 8.24−8.22 (m, 1H), 7.97−7.93 (m, 1H), 7.86−7.82 (m, 1H), 7.60 (d, J = 4.2 Hz, 1H), 7.36−7.31 (m, 1H), 4.31 (q, J = 7.1 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.5, 141.2, 137.5, 136.5, 134.7, 131.2, 131.0, 125.5, 120.5, 120.5, 120.2, 95.4, 60.0, 14.4; HRMS (ESI) $[M + H]^+$ calcd $C_{14}H_{12}IN_2O_2S$ 398.9664, found 398.9659.

*Ethyl 5-(3-Hydroxyphenyl)imidazo[5,1-b]thiazole-7-carboxylate (**3c**).* Ethyl 2-thiazol-2-ylacetate **1a** (0.5 mmol) was reacted with 3-hydroxybenzylamine **2c** (2.0 equiv) according to general procedure A to give 100 mg (69%) of a light orange solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.75 (s, 1H), 8.30 (d, J = 4.1 Hz, 1H), 7.58 (d, J = 4.2 Hz, 1H), 7.40−7.30 (m, 3H), 6.94−6.83 (m, 1H), 4.31 (q, J = 7.1 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.6, 157.8, 140.8, 138.3, 130.3, 130.2, 120.3, 120.2, 120.0, 117.0, 116.3, 113.2, 59.9, 14.5; HRMS (ESI) $[M + H]^+$ calcd $C_{14}H_{13}N_2O_3S$ 289.0647, found 289.0641.

*Ethyl 5-(2-Methoxyphenyl)imidazo[5,1-b]thiazole-7-carboxylate (**3d**).* Ethyl 2-thiazol-2-ylacetate **1a** (0.46 mmol) was reacted with 2-methoxybenzylamine **2d** (2.0 equiv) according to general procedure A to give 102 mg (74%) of a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (dd, J = 7.6, 1.8 Hz, 1H), 7.44 (ddd, J = 8.3, 7.5, 1.8 Hz, 1H), 7.38 (d, J = 4.2 Hz, 1H), 7.10−7.05 (m, 1H), 7.01 (dd, J = 8.4, 1.0 Hz, 1H), 6.96 (d, J = 4.2 Hz, 1H), 4.45 (q, J = 7.1 Hz, 2H), 3.83 (s, 3H), 1.42 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.7, 156.7, 139.8, 137.2, 132.2, 131.1, 121.4, 121.2, 120.2, 118.7, 117.1, 111.2, 60.5, 55.6, 14.7; HRMS (ESI) $[M + H]^+$ calcd $C_{15}H_{15}N_2O_3S$ 303.0798, found 303.0792.

*Ethyl 5-[3-(Methoxycarbonyl)phenyl]imidazo[5,1-b]thiazole-7-carboxylate (**3e**).* To a solution of the HCl salt of methyl 4-(aminomethyl)benzoate hydrochloride **2e** (1.0 mmol, 200 mg) in acetonitrile was added Amberlyst 21 (380 mg). The suspension was stirred at room temperature for 30 min, then filtered, and washed with CH_2Cl_2 to remove the resin. The filtrant was collected and concentrated in vacuo. The residue was then redissolved in DMF (1 mL) and reacted with ethyl 2-(thiazol-2-yl)acetate **1a** (0.5 mmol, 90 mg) according to general procedure A to give 103 mg (62% yield) of a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (t, J = 1.8 Hz, 1H), 8.19−8.07 (m, 2H), 7.85 (d, J = 4.2 Hz, 1H), 7.59 (td, J = 7.8, 0.6 Hz, 1H), 7.13 (d, J = 4.2 Hz, 1H), 4.47 (q, J = 7.1 Hz, 2H), 3.96 (s, 3H), 1.45 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.5, 162.6, 132.1, 131.7, 131.1, 130.3, 130.1, 129.4, 127.4, 119.5, 118.6, 61.0, 52.5, 14.8; HRMS (ESI) $[M + H]^+$ calcd $C_{16}H_{15}N_2O_4S$ 331.0753, found 331.0747.

*Ethyl 5-(4-Cyanophenyl)imidazo[5,1-b]thiazole-7-carboxylate (**3f**).* Ethyl 2-(thiazol-2-yl)acetate **1a** (0.5 mmol, 90 mg) was reacted with 4-(aminomethyl)benzonitrile **2f** (1.0 mmol, 130 μL) according to general procedure A to give 116 mg (78% yield) of a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01−7.99 (m, 2H), 7.85 (d, J = 4.2 Hz, 1H), 7.79−7.77 (m, 2H), 7.19 (d, J = 4.2 Hz, 1H), 4.47 (q, J = 7.1 Hz, 2H), 1.45 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.3, 141.5, 137.0, 133.8, 133.0, 127.1, 122.9, 120.3, 118.4, 112.6, 61.2, 14.7; HRMS (ESI) $[M + H]^+$ calcd $C_{15}H_{12}N_3O_2S$ 298.0650, found 298.0645.

*Ethyl 5-[4-(Methylsulfonyl)phenyl]imidazo[5,1-b]thiazole-7-carboxylate (**3g**).* To a solution of the HCl salt of (4-methylsulfonylphenyl)methanamine **2g** (1.0 mmol, 220 mg) in acetonitrile was added Amberlyst 21 (380 mg). The suspension was stirred at room temperature for 30 min, then filtered, and washed with DCM to remove the resin. The filtrant was collected and concentrated in vacuo. The residue was then redissolved in DMF (1 mL) and reacted with ethyl 2-(thiazol-2-yl)acetate **1a** (0.5 mmol, 90 mg) according to general procedure A to give 140 mg (80% yield) of a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11−8.05 (m, 4H), 7.87 (d, J = 4.2 Hz, 1H), 7.20 (d, J = 4.2 Hz, 1H), 4.48 (q, J = 7.1 Hz, 2H), 3.11 (s, 3H), 1.45 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.2, 141.4, 140.6, 136.8, 134.6, 128.2, 127.3, 122.8, 120.2, 118.3, 61.0, 44.5, 14.6; HRMS (ESI) $[M + H]^+$ calcd $C_{15}H_{15}N_2O_4S_2$ 351.0473, found 351.0468.

*Ethyl 5-(Pyridin-2-yl)imidazo[5,1-b]thiazole-7-carboxylate (**3h**).* Ethyl 2-thiazol-2-ylacetate **1a** (0.5 mmol) was reacted with 4-pyridylmethanamine **2h** (1.1 equiv) according to general procedure A to give 45 mg (30%) of a red solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.84 (d, J = 4.2 Hz, 1H), 8.71−8.68 (m, 1H), 8.17−8.14 (m, 1H), 8.00−7.95 (m, 1H), 7.63 (d, J = 4.0 Hz, 1H), 7.47−7.43 (m, 1H), 4.33 (q, J = 7.1 Hz, 2H), 1.35 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.4, 149.1, 148.1, 141.6, 137.5, 136.7, 123.4, 122.1, 120.5, 120.3, 120.2, 60.0, 14.4; HRMS (ESI) $[M + H]^+$ calcd $C_{13}H_{12}N_3O_2S$ 274.0650, found 274.0645.

*Ethyl 5-(Pyridin-4-yl)imidazo[5,1-b]thiazole-7-carboxylate (**3i**).* Ethyl 2-thiazol-2-ylacetate **1a** (0.5 mmol) was reacted with 4-pyridylmethanamine **2i** (2.0 equiv) according to general procedure A to give 56 mg (41%) of a light yellow solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.73−8.70 (m, 2H), 8.57 (d, J = 4.1 Hz, 1H), 7.94−7.91 (m, 2H), 7.69 (d, J = 4.2 Hz, 1H), 4.33 (q, J = 7.1 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.4, 150.4, 142.1, 135.9, 135.7, 121.1, 121.0, 120.6, 120.0, 60.0, 14.4; HRMS (ESI) $[M + H]^+$ calcd $C_{13}H_{12}N_3O_2S$ 274.0650, found 274.0645.

*Ethyl 5-(Thiazol-2-yl)imidazo[5,1-b]thiazole-7-carboxylate (**3j**).* Ethyl 2-(thiazol-2-yl)acetate **1a** (0.5 mmol, 90 mg) was reacted with thiazol-2-ylmethanamine **2j** (1.0 mmol, 110 mg) according to general procedure A to give 77 mg (55% yield) of a yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, J = 4.2 Hz, 1H), 7.86 (d, J = 3.2 Hz, 1H), 7.39 (d, J = 3.2 Hz, 1H), 7.13 (d, J = 4.2 Hz, 1H), 4.66 (s, 2H), 4.46 (q, J = 7.1 Hz, 2H), 1.45 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.2, 157.9, 143.4, 141.1, 133.5, 122.1, 121.4, 119.9, 119.0, 61.1, 14.7; HRMS (ESI) $[M + H]^+$ calcd $C_{11}H_{10}N_3O_2S_2$ 280.0214, found 280.0209.

*Ethyl 5-(1-Methyl-1H-pyrazol-4-yl)imidazo[5,1-b]thiazole-7-carboxylate (**3k**).* Ethyl 2-(thiazol-2-yl)acetate **1a** (0.5 mmol) was reacted with (1-methylpyrazol-4-yl)methanamine **2k** (2.0 equiv) according to general procedure A but instead of room temperature was heated to 80 °C for 18 h to give 83 mg (60% yield) of an orange

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oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.89 (s, 1H), 7.63 (d, J = 4.2 Hz, 1H), 7.08 (d, J = 4.2 Hz, 1H), 4.44 (q, J = 7.1 Hz, 2H), 3.98 (s, 3H), 1.43 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.5, 139.2, 136.7, 133.2, 129.2, 121.1, 119.1, 117.8, 112.5, 60.8, 39.4, 14.7; HRMS (ESI) $[M + H]^+$ calcd $C_{12}H_{13}N_4O_2S$ 277.0759, found 277.0754.

*Ethyl 5-Cyclopropylimidazo[5,1-b]thiazole-7-carboxylate (**3l**).* Ethyl 2-(thiazol-2-yl)acetate **1a** (1.5 mmol) was reacted with cyclopropylamine **2l** (2.0 equiv) according to general procedure A but instead of room temperature was heated to 80 °C for 18 h to give 110 mg of an inseparable mixture of product and succinimide (31% yield, adjusted to 26% based on NMR) of a red-orange oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ *8.41 (bs, 1H), 7.51 (d, J = 4.2 Hz, 1H), 6.99 (d, J = 4.2 Hz, 1H), 4.40 (q, J = 7.1 Hz, 2H), *2.76 (s, 2H), 2.01 (tt, J = 8.3, 5.0 Hz, 1H), 1.40 (t, J = 7.1 Hz, 3H), 1.20−1.05 (m, 2H), 1.08−0.90 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ *177.3, 162.6, 141.4, 138.6, 119.9, 118.2, 117.0, 60.6, *29.7, 14.8, 8.1, 7.0; HRMS (ESI) $[M + H]^+$ calcd $C_{11}H_{13}N_2O_2S$ 237.0698, found 237.0691.

*Ethyl 5-Vinylimidazo[5,1-b]thiazole-7-carboxylate (**3m**).* Ethyl 2-(thiazol-2-yl)acetate **1a** (1.5 mmol) was reacted with allylamine **2m** (2.0 equiv) according to general procedure A to give 140 mg (42% yield) of an orange amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 4.2 Hz, 1H), 7.09 (d, J = 4.1 Hz, 1H), 6.80 (dd, J = 17.7, 11.6 Hz, 1H), 6.10 (d, J = 17.8 Hz, 1H), 5.55 (d, J = 11.6 Hz, 1H), 4.44 (q, J = 7.1 Hz, 2H), 1.43 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.5, 139.9, 137.5, 123.9, 121.6, 119.2, 118.0, 117.9, 60.9, 14.7; HRMS (ESI) $[M + H]^+$ calcd $C_{10}H_{11}N_2O_2S$ 223.0541, found 223.0533.

*tert-Butyl 5-(3-Bromophenyl)-3-methylimidazo[5,1-b]thiazole-7-carboxylate (**4b**).* *tert*-Butyl 2-(4-methylthiazol-2-yl)acetate **1b** (0.5 mmol) was reacted with 3-bromobenzylamine **2a** (2.0 equiv) according to general procedure A to give 160 mg (81%) of an orange solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.86−7.84 (m, 1H), 7.74−7.70 (m, 1H), 7.66−7.62 (m, 1H), 7.48−7.43 (m, 1H), 7.08−7.06 (m, 1H), 2.08 (d, J = 1.2 Hz, 3H), 1.55 (s, 9H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 160.7, 140.6, 137.3, 132.5, 132.2, 132.0, 129.8, 129.3, 129.1, 120.8, 114.1, 79.9, 28.0, 14.3; HRMS (ESI) $[M + H]^+$ calcd $C_{17}H_{18}BrN_2O_2S$ 393.0272, found 393.0267.

*Ethyl 5-(3-Bromophenyl)-3-(trifluoromethyl)imidazo[5,1-b]thiazole-7-carboxylate (**4c**).* Ethyl 2-[4-(trifluoromethyl)thiazol-2-yl]acetate **1c** (0.5 mmol, 120 mg) was reacted with 3-bromobenzylamine **2a** (1.0 mmol, 130 μL) according to general procedure A to give 145 mg (69% yield) of a yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (brs, 1H), 7.63 (dd, J = 8.1, 3.1 Hz, 1H), 7.60−7.58 (m, 1H), 7.48−7.45 (m, 1H), 7.31 (t, J = 7.9 Hz, 1H), 4.46 (q, J = 7.1 Hz, 2H), 1.43 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.2, 140.2, 138.7, 133.5, 133.4, 131.6, 129.6, 129.0 (q, J = 1.8 Hz), 124.6 (q, J = 4.9 Hz), 122.8, 122.6, 122.1, 118.6 (q, J = 270.4 Hz), 61.3, 14.7; HRMS (ESI) $[M + H]^+$ calcd $C_{15}H_{11}BrF_3N_2O_2S$ 418.9677, found 418.9673.

*Methyl 2-Bromo-5-(3-bromophenyl)imidazo[5,1-b]thiazole-7-carboxylate (**4d**).* Methyl 2-(5-bromo-1,3-thiazol-2-yl)acetate **1d** (0.5 mmol) was reacted with 3-bromobenzylamine **2a** (2.0 equiv) according to general procedure B to give 106 mg (51%) of an orange solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.83−8.82 (m, 1H), 8.06−8.05 (m, 1H), 7.96−7.92 (m, 1H), 7.70−7.67 (m, 1H), 7.51−7.46 (m, 1H), 3.85 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.6, 139.1, 137.5, 132.0, 131.1, 130.8, 129.0, 125.6, 122.3, 122.1, 120.8, 107.2, 51.6; HRMS (ESI) $[M + H]^+$ calcd $C_{13}H_9Br_2N_2O_2S$ 414.8751, found 414.8743.

*Ethyl 5-(3-Bromophenyl)-2-[(tert-butoxycarbonyl)amino]-imidazo[5,1-b][1,3,4]thiadiazole-7-carboxylate (**4e**).* Ethyl 2-[5-(*tert*-butoxycarbonylamino)-1,3,4-thiadiazol-2-yl]acetate **1e** (0.5 mmol) was reacted with 3-bromobenzylamine **2a** (2.0 equiv) according to general procedure B to give 210 mg (90%) of a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.56 (s, 1H), 8.43−8.37 (m, 1H), 8.23−8.16 (m, 1H), 7.67−7.60 (m, 1H), 7.54−7.45 (m, 1H), 4.31 (q, J = 7.1 Hz, 2H), 1.53 (s, 9H), 1.33 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 160.9, 160.7, 152.8, 135.1, 134.5, 131.6, 130.9, 130.4, 127.9, 124.6, 122.0, 118.5, 83.2, 60.2, 27.7, 14.4; HRMS (ESI) $[M + H]^+$ calcd $C_{18}H_{20}BrN_4O_4S$ 467.0389, found 467.0383.

*Ethyl 2-Amino-5-(3-bromophenyl)imidazo[5,1-b][1,3,4]-thiadiazole-7-carboxylate (**4f**).* Ethyl 2-(5-amino-1,3,4-thiadiazol-2-yl)acetate **1f** (0.5 mmol) was reacted with 3-bromobenzylamine **2a** (2.0 equiv) according to general procedure A to give 150 mg (82%) of a yellow solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.44−8.40 (m, 1H), 8.23−8.19 (m, 1H), 8.01 (s, 2H), 7.64−7.59 (m, 1H), 7.51−7.45 (m, 1H), 4.28 (q, J = 7.1 Hz, 2H), 1.32 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.0, 161.2, 135.1, 133.3, 131.3, 130.9, 130.8, 127.8, 124.5, 122.0, 119.0, 60.1, 14.4; HRMS (ESI) $[M + H]^+$ calcd $C_{13}H_{12}BrN_4O_2S$ 366.9864, found 366.9846.

*2-Amino-5-(3-bromophenyl)-N,N-dimethylimidazo[5,1-b][1,3,4]-thiadiazole-7-carboxamide (**4g**).* 2-(5-Amino-1,3,4-thiadiazol-2-yl)-*N*,*N*-dimethylacetamide **1g** was reacted with 3-bromobenzylamine **2a** (2.0 equiv) according to general procedure A but instead of room temperature was heated to 80 °C for 18 h to give 60 mg (33%) of a yellow solid: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.40 (t, J = 1.9 Hz, 1H), 8.20 (dt, J = 1.4, 7.9 Hz, 1H), 7.76 (s, 2H), 7.56 (dt, J = 1.5, 8.1 Hz, 1H), 7.45 (t, J = 7.9 Hz, 1H), 3.18 (s, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.8, 161.0, 133.1, 132.8, 131.3, 131.0, 130.9, 127.5, 124.5, 124.3, 122.1, 37.6, 36.1; HRMS (ESI) $[M + H]^+$ calcd $C_{13}H_{13}BrN_5OS$ 366.0024, found 366.0019.

*5-(3-Bromophenyl)-N-methoxy-N-methylimidazo[5,1-b]thiazole-7-carboxamide (**4h**).* *N*-Methoxy-*N*-methyl-2-thiazol-2-yl-acetamide **1h** (80 mg, 0.43 mmol) was reacted with 3-bromobenzylamine **2a** (2.0 equiv) according to general procedure A but instead of room temperature was heated to 80 °C for 18 h to afford 85 mg (54%) of an off-white amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03−7.98 (m, 1H), 7.80 (d, J = 4.3 Hz, 1H), 7.78−7.74 (m, 1H), 7.57−7.52 (m, 1H), 7.40−7.33 (m, 1H), 7.10 (d, J = 4.2 Hz, 1H), 3.91 (s, 3H), 3.62 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.6, 141.2, 136.3, 132.1, 132.0, 130.6, 129.7, 125.1, 124.2, 123.3, 120.0, 118.0, 61.9, 35.1; HRMS (ESI) $[M + H]^+$ calcd $C_{14}H_{13}BrN_3O_2S$ 365.9912, found 365.9908.

*Ethyl 5-(3-Bromophenyl)-1-methyl-1H-imidazo[1,5-a]imidazole-7-carboxylate (**4i**).* Methyl 2-(1-methylimidazol-2-yl)acetate hydrochloride **1i** (0.45 mmol) was reacted with 3-bromobenzylamine **2a** (2.0 equiv) according to general procedure A to give 54 mg (34%) of an orange solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.05−8.01 (m, 2H), 7.91−7.87 (m, 1H), 7.56−7.52 (m, 1H), 7.50 (d, J = 2.3 Hz, 1H), 7.47−7.41 (m, 1H), 4.26 (q, J = 7.1 Hz, 2H), 3.99 (s, 3H), 1.32 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.9, 142.4, 132.0, 131.1, 130.1, 127.8, 127.2, 126.9, 123.1, 122.3, 106.4, 104.6, 59.0, 35.1, 14.5; HRMS (ESI) $[M + H]^+$ calcd $C_{15}H_{15}BrN_3O_2$ 348.0348, found 348.0342.

*Ethyl 5-(3-Bromophenyl)-1H-imidazo[5,1-c][1,2,4]triazole-7-carboxylate (**4j**).* Ethyl 2-(4*H*-1,2,4-triazol-3-yl)acetate **1j** (0.5 mmol) was reacted with 3-bromobenzylamine **2a** (1.1 equiv) according to general procedure A to give 67 mg (40%) of a yellow solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.74 (s, 1H), 8.41−8.35 (m, 1H), 8.25−8.17 (m, 1H), 7.59−7.52 (m, 1H), 7.52−7.43 (m, 1H), 4.28 (q, J = 7.1 Hz, 2H), 1.32 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.4, 147.3, 131.3, 131.1, 130.3, 127.2, 126.6, 123.2, 122.1, 102.7, 59.1, 14.6; HRMS (ESI) $[M + H]^+$ calcd $C_{13}H_{12}BrN_4O_2$ 335.0144, found 335.0138.

*Ethyl 5-(3-Bromophenyl)imidazo[5,1-b]benzo[d]thiazole-7-carboxylate (**4k**).* Methyl 2-(benzo[*d*]thiazol-2-yl)acetate **1k** (0.5 mmol) was reacted with 3-bromobenzylamine **2a** (2.0 equiv) according to general procedure B to give 130 mg (65%) of a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.08−8.04 (m, 1H), 8.00−7.97 (m, 1H), 7.85−7.79 (m, 2H), 7.62−7.56 (m, 1H), 7.51−7.41 (m, 2H), 7.39−7.35 (m, 1H), 4.34 (q, J = 7.1 Hz, 2H), 1.36 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.4, 139.3, 138.5, 133.0, 132.7, 132.0, 131.7, 131.5, 130.7, 128.1, 126.3, 126.1, 121.7, 121.2, 114.1, 59.9, 14.2; HRMS (ESI) $[M + H]^+$ calcd $C_{18}H_{14}BrN_2O_2S$ 400.9959, found 400.9960.

*Ethyl 5-(3-Bromophenyl)-1-methyl-1H-benzo[d]imidazole[1,5-a]-imidazole-7-carboxylate (**4l**).* Ethyl 2-(1-methylbenzimidazol-2-yl)-acetate **1l** was reacted with 3-bromobenzylamine **2a** (2.0 equiv)

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according to general procedure A to give 108 mg (54%) of a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.00−7.97 (m, 1H), 7.88−7.84 (m, 1H), 7.74−7.71 (m, 1H), 7.65−7.60 (m, 2H), 7.59−7.54 (m, 1H), 7.52−7.47 (m, 1H), 7.28−7.23 (m, 1H), 4.31 (q, J = 7.1 Hz, 2H), 4.12 (s, 3H), 1.34 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.1, 144.3, 139.0, 132.2, 131.6, 131.0, 130.8, 130.1, 126.3, 125.3, 123.1, 121.8, 120.6, 112.1, 110.9, 104.9, 59.1, 31.4, 14.3; HRMS (ESI) [M + H]$^+$ calcd $C_{19}H_{17}BrN_3O_2$ 398.0504, found 398.0499.

*Methyl 1-(3-Bromophenyl)benzo[d]imidazo[5,1-b]oxazole-3-carboxylate (**4m**).* Methyl 2-(benzo[*d*]oxazol-2-yl)acetate **1m** (1.5 mmol) was reacted with 3-bromobenzylamine **2a** (2.0 equiv) according to general procedure A to give 75 mg (13%) of a white solid following reverse phase HPLC purification: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.05−8.02 (m, 1H), 7.94−7.88 (m, 2H), 7.81−7.75 (m, 1H), 7.75−7.70 (m, 1H), 7.63−7.53 (m, 2H), 7.51−7.45 (m, 1H), 3.86 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.1, 153.7, 152.5, 132.4, 131.9, 131.4, 131.3, 130.0, 126.7, 126.3, 126.3, 125.0, 124.8, 122.2, 113.4, 113.3, 104.8, 51.2; HRMS (ESI) [M + H]$^+$ calcd $C_{17}H_{12}BrN_2O_3$ 371.0031, found 371.0026.

*Methyl 6-(3-Bromophenyl)imidazo[1,5-a]pyrimidine-8-carboxylate (**4n**).* Methyl 2-(2-pyrimidyl)acetate **1n** (0.5 mmol) was reacted with 3-bromobenzylamine **2a** (2.0 equiv) according to general procedure A to give 70 mg (42%) of a light yellow solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.96 (dd, J = 7.3, 1.8 Hz, 1H), 8.65−8.59 (m, 1H), 8.07−8.01 (m, 1H), 7.95−7.84 (m, 1H), 7.78−7.70 (m, 1H), 7.59−7.50 (m, 1H), 7.07 (dd, J = 7.3, 3.8 Hz, 1H), 3.87 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.0, 151.4, 140.8, 134.0, 132.1, 131.5, 130.9, 130.6, 130.5, 126.9, 122.0, 119.1, 110.3, 50.8; HRMS (ESI) [M + H]$^+$ calcd $C_{14}H_{11}BrN_3O_2$ 332.0035, found 332.0029.

*Methyl 3-(3-Bromophenyl)imidazo[1,5-a]pyrazine-1-carboxylate (**4o**).* Methyl 2-pyrazineacetate **1o** (0.5 mmol) was reacted with 3-bromobenzylamine **2a** (1.1 equiv) according to general procedure B to give 120 mg (72%) of a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.52 (d, J = 1.7 Hz, 1H), 8.59 (dd, J = 5.0, 1.6 Hz, 1H), 8.07−8.05 (m, 1H), 7.95−7.91 (m, 1H), 7.90 (d, J = 5.0 Hz, 1H), 7.81−7.77 (m, 1H), 7.60−7.55 (m, 1H), 3.95 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.1, 146.0, 138.0, 132.7, 131.2, 130.9, 130.6, 130.2, 128.7, 127.3, 124.5, 122.2, 116.3, 51.7; HRMS (ESI) [M + H]$^+$ calcd $C_{14}H_{11}BrN_3O_2$ 332.0035, found 332.0030.

*Methyl 3-(3-Bromophenyl)-5-methoxyimidazo[1,5-c]pyrimidine-1-carboxylate (**4p**).* Methyl 2-(2-methoxypyrimidin-4-yl)acetate **1p** (0.27 mmol) was reacted with 3-bromobenzylamine **2a** (2.0 equiv) according to general procedure A to give 80 mg (81%) of a light yellow solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.94−7.90 (m, 1H), 7.74−7.68 (m, 2H), 7.65 (d, J = 6.4 Hz, 1H), 7.60 (d, J = 6.4 Hz, 1H), 7.47−7.40 (m, 1H), 3.96 (s, 3H), 3.87 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.7, 147.8, 138.5, 137.6, 137.2, 133.3, 133.1, 131.6, 129.5, 129.3, 120.9, 120.3, 106.5, 55.6, 51.3; HRMS (ESI) [M + H]$^+$ calcd $C_{15}H_{13}BrN_3O_3$ 362.0140, found 362.0135.

*Methyl 3-(3-Bromophenyl)-6-chloroimidazo[1,5-a]pyrazine-1-carboxylate (**4q**).* Methyl 2-(5-chloropyrazin-2-yl)acetate **1q** (0.5 mmol) was reacted with 3-bromobenzylamine **2a** (1.1 equiv) according to general procedure B to give 120 mg (65%) of a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.51 (s, 1H), 8.02 (s, 1H), 7.91−7.89 (m, 1H), 7.80−7.76 (m, 1H), 7.71−7.67 (m, 1H), 7.50−7.45 (m, 1H), 3.95 (s, 3H); ^{13}C NMR (101 MHz, DMSO) δ 161.8, 144.5, 139.0, 133.7, 132.7, 132.6, 130.8, 130.3, 130.0, 129.4, 124.6, 121.8, 120.4, 51.9; HRMS (ESI) [M + H]$^+$ calcd $C_{14}H_{10}BrClN_3O_2$ 365.9645, found 365.9639.

*1-(tert-Butyl) 7-Methyl 9-(3-bromophenyl)-3,4-dihydroimidazo[1,5-a][1,8]naphthyridine-1,7(2H)-dicarboxylate (**4r**).* (8-Boc-5,6,7,8-tetrahydro[1,8]naphthyridin-2-yl)acetic acid methyl ester **1r** (0.5 mmol) was reacted with 3-bromobenzylamine **2a** (2.0 equiv) according to general procedure B to give 170 mg (70%) of a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.01 (d, J = 9.0 Hz, 1H), 7.72 (s, 1H), 7.61−7.53 (m, 2H), 7.38−7.31 (m, 1H), 7.19 (d, J = 9.1 Hz, 1H), 4.16−4.05 (m, 1H), 3.87 (s, 3H), 3.49−3.36 (m, 1H), 2.93−2.84 (m, 1H), 2.81−2.70 (m, 1H), 2.06−1.85 (m, 2H), 1.02 (s, 9H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 163.6, 152.2, 138.5, 136.7, 133.8, 132.8, 132.1, 131.2, 129.2, 128.2, 121.0, 120.6, 118.7, 115.8, 81.8, 51.3, 45.0, 27.8, 24.9, 23.0; HRMS (ESI) [M + H]$^+$ calcd $C_{23}H_{25}BrN_3O_4$ 486.1028, found 486.1010.

*Methyl 7-(3-Bromophenyl)imidazo[1,5-b]pyridazine-5-carboxylate (**4t**).* Methyl pyridazin-3-yl-acetate **1t** (0.5 mmol) was reacted with 3-bromobenzylamine **2a** (2.0 equiv) according to general procedure B to give 130 mg (78%) of a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.68 (d, J = 4.2 Hz, 1H), 8.61−8.50 (m, 2H), 8.41 (d, J = 7.9 Hz, 1H), 7.69 (d, J = 7.9 Hz, 1H), 7.57−7.48 (m, 1H), 7.27 (dd, J = 9.3, 4.4 Hz, 1H), 3.92 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.3, 146.5, 137.9, 131.9, 130.8, 130.6, 129.9, 129.7, 128.0, 126.4, 121.7, 120.8, 117.7, 51.5; HRMS (ESI) [M + H]$^+$ calcd $C_{14}H_{11}BrN_3O_2$ 332.0035, found 332.0029. Intermediate **4t** was previously synthesized and claimed in a patent (ref 1d), but no characterization data were reported.

*Ethyl 2-{[(1-Methyl-1H-pyrazol-4-yl)methyl]imino}-2-(thiazol-2-yl)acetate (**5**).* Ethyl 2-(thiazol-2-yl)acetate **1a** (0.5 mmol, 90 mg) was reacted with (1-methylpyrazol-4-yl)methanamine **2k** (2.0 equiv, 110 mg) according to general procedure A to give 70 mg (51% yield) of a white solid (*E*/*Z* geometry not determined): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 3.2 Hz, 1H), 7.48 (s, 1H), 7.44 (d, J = 3.2 Hz, 1H), 7.37 (s, 1H), 4.66 (s, 2H), 4.51 (q, J = 7.1 Hz, 2H), 3.88 (s, 3H), 1.42 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.5, 163.4, 155.6, 144.3, 138.7, 129.3, 122.4, 117.9, 62.3, 49.2, 39.0, 14.3; HRMS (ESI) [M + H]$^+$ calcd $C_{12}H_{15}N_4O_2S$ 279.0916, found 279.0919.

*2-(5-Amino-1,3,4-thiadiazol-2-yl)-2-[(3-bromobenzyl)amino]-N,N-dimethylacetamide (**6**).* 2-(5-Amino-1,3,4-thiadiazol-2-yl)-*N*,*N*-dimethylacetamide **1g** (0.5 mmol) was reacted with 3-bromobenzylamine **2a** (2.0 equiv) according to general procedure A to give 80 mg (43%) of an off-white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.57−7.52 (m, 1H), 7.46−7.41 (m, 1H), 7.34−7.24 (m, 2H), 7.11 (s, 2H), 4.88 (d, J = 9.1 Hz, 1H), 3.70−3.64 (m, 2H), 3.21−3.11 (m, 1H), 2.98 (s, 3H), 2.85 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 169.2, 169.0, 159.1, 143.0, 130.6, 130.3, 129.6, 127.0, 121.6, 57.0, 50.0, 36.5, 35.4; HRMS (ESI) [M + H]$^+$ calcd $C_{13}H_{17}BrN_5OS$ 370.0337, found 370.0334.

*1-(3-Bromophenyl)-4-methyl-4H-benzo[d]imidazo[1,5-a]-imidazol-3-yl (Phenyl)methanone (**4u**) and 2-(3-Bromophenyl)-4-(1-methyl-1H-benzo[d]imidazol-2-yl)-5-phenyloxazole (**7**).* 2-(1-Methylbenzimidazol-2-yl)-1-phenyl-ethanone **1u** (0.46 mmol) was reacted with 3-bromobenzylamine **2a** (2.0 equiv) according to general procedure A, followed by trituration from a MeOH/DCM mixture for the ketone product, to give **4u** [43 mg (22%) of a yellow solid] and **7** [88 mg (44%) of a white solid].

*Data for **4u**.* ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.28−8.23 (m, 2H), 8.05 (t, J = 1.9 Hz, 1H), 7.93 (dt, J = 1.3, 7.8 Hz, 1H), 7.77 (ddd, J = 0.9, 2.1, 7.9 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.67 (d, J = 8.2 Hz, 1H), 7.62−7.50 (m, 5H), 7.34 (ddd, J = 1.1, 7.4, 8.4 Hz, 1H), 4.33 (s, 3H); ^{13}C NMR (101 MHz, DMSO) δ 184.0, 146.0, 139.0, 138.8, 132.1, 132.0, 131.1, 131.0, 131.0, 130.3, 130.0, 127.7, 126.8, 125.6, 123.1, 122.0, 121.4, 115.5, 112.4, 111.6, 32.2; HRMS (ESI) [M + H]$^+$ calcd $C_{23}H_{17}ON_3Br$ 430.0550, found 430.0541.

*Data for **7**.* ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.36 (t, J = 1.9 Hz, 1H), 8.21 (dt, J = 1.3, 7.8 Hz, 1H), 8.19−8.15 (m, 2H), 7.90−7.80 (m, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.69 (d, J = 8.1 Hz, 1H), 7.60 (t, J = 7.9 Hz, 1H), 7.53−7.44 (m, 3H), 7.38 (ddd, J = 1.2, 7.1, 8.2 Hz, 1H), 7.34−7.26 (m, 1H), 3.98 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 158.3, 150.8, 145.5, 142.6, 136.4, 134.4, 132.0, 130.3, 129.3, 129.2, 128.7, 127.8, 127.3, 127.0, 125.9, 123.6, 122.9, 122.8, 119.9, 111.1, 31.9; HRMS (ESI) [M + H]$^+$ calcd $C_{23}H_{17}ON_3Br$ 430.0550, found 430.0547.

*13-[(3-Bromobenzyl)amino]benzo[4,5]thiazolo[3,2-a]benzo[4,5]-thiazolo[3,2-d]pyrazine-6-carbonitrile (**8**).* 2-(1,3-Benzothiazol-2-yl)-acetonitrile **1v** (0.5 mmol) was reacted with 3-bromobenzylamine **2a** (1.1 equiv) according to general procedure B to give 100 mg of a yellow solid containing **8** and an inseparable unknown byproduct in a 6.7:1 molar ratio for a 40% combined yield: ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.53 (t, J = 6.4 Hz, 1H), 8.32 (dd, J = 8.0, 1.3 Hz, 1H), 8.26−8.22 (m, 1H), 8.12 (dd, J = 8.2, 1.2 Hz, 1H), 7.95 (dd, J = 8.0, 0.9 Hz, 1H), 7.69 (td, J = 8.1, 7.7, 1.4 Hz, 1H), 7.64 (ddd, J = 8.6, 7.2,

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1.3 Hz, 1H), 7.56 (ddd, J = 8.3, 7.4, 1.4 Hz, 1H), 7.51−7.46 (m, 2H), 7.46−7.41 (m, 1H), 7.34−7.28 (m, 2H), 4.66 (d, J = 6.4 Hz, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 164.9, 157.2, 155.5, 152.6, 152.1, 140.3, 135.6, 131.9, 130.8, 130.4, 130.0, 127.3, 127.1, 126.8, 126.2, 125.0, 124.1, 123.0, 122.2, 121.8, 121.3, 118.7, 77.3, 48.1; HRMS (ESI) $[M + H]^+$ calcd $C_{24}H_{16}BrN_4S_2$ 503.0000, found 502.9994.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01517.

Typical experimental procedure and characterization of all products (PDF)

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Notes

The authors declare no competing financial interest.

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(10) With methyl 2-(pyrazin-2-yl)acetate as a test substrate, purity enhancements were seen by LC/MS when the order of addition was changed from adding solvent last to all reagents to adding catalyst/oxidant last to heteroaromatic substrate/amine/DMA.

(11) In cases in which isolation and purification by trituration were not possible, compounds were isolated by silica gel column chromatography.

(12) No formation of aryl iodide was observed when reactions were monitored by LC.MS.

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(22) Compounds **5** and **6** were also again subjected to the reaction conditions (heated to 80 °C from the beginning because **3k** and **4g** are not formed at rt), following isolation, to afford clean conversion to products **3k** and **4g**.

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(24) Complex fragmentation patterns suggesting possible dimers were observed by LC/MS for reactions involving heteroaromatic substrates (**1i**, **1j**, **1n**, **1o**, **1q**, and **1v**). We isolated a dimer in one case (example **8**) as **4v** was not seen and **8** was the major byproduct. In other cases in which the product was one of the major peaks as determined by LC/MS (**4i**, **4j**, **4n**, **4o**, and **4q**), we attribute reduced yields to these dimers. The reduction of the number of amine equivalents from 2 to 1.1 worked well to reduce the level of dimer formation for isolation of **4j**, **4o**, and **4q** but did not appear to make a difference for **4i** or **4n**. All attempts to isolate and characterize any other putative dimers observed by LC/MS via silica gel chromatography were unsuccessful.

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