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Synthesis of 3-Aminoimidazo[1,2-*a*]pyridines from α-Aminopyridinyl Amides

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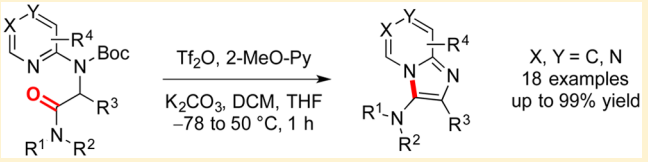
Supporting Information

ABSTRACT: 3-Aminoimidazo[1,2-*a*]pyridines are rapidly synthesized via a facile and mild cyclodehydration-aromatization reaction starting from readily available amides. The cyclodehydration step is mediated by the activation of *N*-Boc-protected 2-aminopyridine-containing amides by triflic anhydride (Tf_2O) in the presence of 2-methoxypyridine (2-MeO-Py). Subsequently, the addition of K_2CO_3 in THF ensured a clean deprotection-aromatization sequence to afford the desired heterocycle. A wide variety of functional groups and substitution patterns were tolerated under the optimized procedure, and good to excellent yields were obtained for the fused bicyclic 3-aza-heterocycles. In addition, the reaction was found to be scalable to gram-scale and could be performed with unprotected acyclic amide precursors. We also found that the resulting products were valuable intermediates for both Pd- and Ru-catalyzed C−H arylation reactions, allowing for the elaboration to diversely functionalized building blocks.



INTRODUCTION

Nitrogen-containing heterocycles are omnipresent in contemporary medicinal chemistry.[1] They encompass a large number of natural and commercialized synthetic products, exhibiting a remarkably diverse array of biological activities. For instance, the bicyclic imidazo[1,2-*a*]pyridine scaffold, a pertinent nitrogen-containing heterocycle, is increasingly reported to be a valuable drug template and building block.[2] Notably, it is present in various clinically approved drugs, such as zolpidem,[3] alpidem,[4] olprinone,[5] and zolimidine.[6] Moreover, imidazo[1,2-*a*]pyridines are ideal and well-known precursors of both abnormal *N*-heterocyclic carbene (NHC) ligands[7] and organic functional material, playing a critical role in the properties of certain optoelectronic materials.[8]

The C-3 position of imidazo[1,2-*a*]pyridines is an adjustable and metabolically important branching point for several therapeutics, whereby the judicious choice of a substituent at this position has been shown to determine whether a clinical candidate is poorly active or a lead molecule.[9] Consequently, imidazo[1,2-*a*]pyridines substituted at C-3 with an amino group have attracted increasing interest from the pharmaceutical industry. They are included in the structure of potent anti-inflammatory (**I**),[10] anticancer (**II**),[11] and antifibrosis (**III**)[12] targets (examples highlighted in blue, Figure 1). In parallel to medicinal chemistry, recent discoveries in material sciences showcase a different flavor to the potential applications of 3-aminoimidazo[1,2-*a*]pyridines, as they were implicated in the design of a class of fluorescent dyes.[13]

Given the existence of a variety of functions of 3-aminoimidazo[1,2-*a*]pyridines, there comes a need for new and convergent synthetic methods applicable toward the elaboration of these heterocyclic derivatives.[14] Many contemporary approaches rely on the Groebke−Blackburn−Bienaymé (GBB) multicomponent condensation (Scheme 1a).[15] This three-component reaction consists of a one-pot coupling of aldehydes, 2-aminopyridines (or amidines), and isocyanides. The transformation of these reagents to the titled heterocycles is often catalyzed by Brønsted acids (e.g., NH_4Cl,[16] AcOH,[15a] $HClO_4$,[15b] or PTSA[17]) or Lewis acids (e.g., $Sc(OTf)_3$,[15c,18]

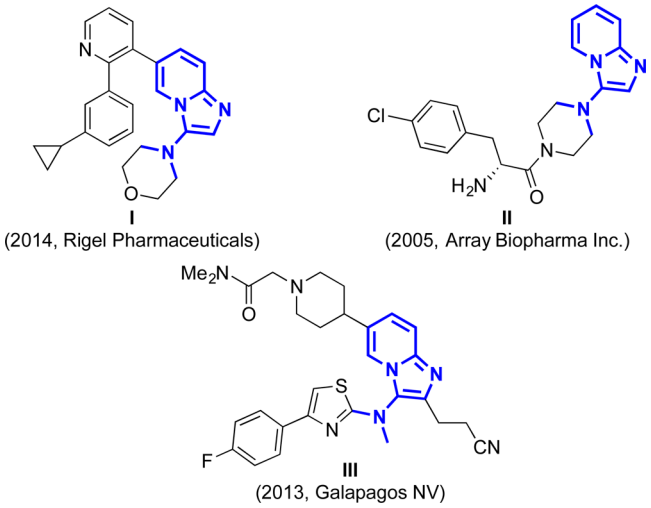


Figure 1. Bioactive pharmaceutical leads bearing substituted 3-aminoimidazo[1,2-*a*]pyridines.

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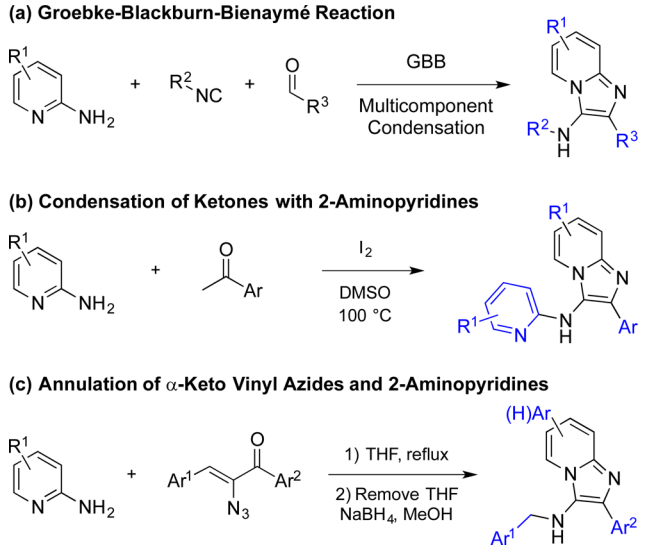
Scheme 1. Strategies for the Synthesis of 3-Aminoimidazo[1,2-*a*]pyridines

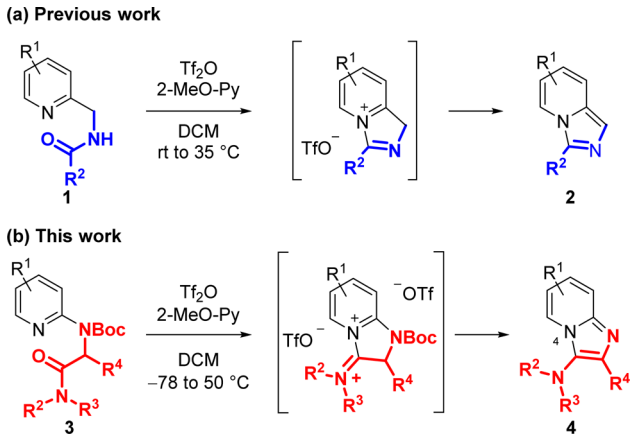


$BiCl_3$,[19] $ZnCl_2$,[20] or $SnCl_2{\cdot}2H_2O$[21]). Recent improvements to GBB heterocyclizations have disclosed the ability to use water,[22] ionic liquids,[23] solvent-free conditions,[24] as well as microwave irradiation, which increasingly provide shorter and cleaner reactions overall.[18a,25] Multicomponent condensations often constitute attractive synthetic strategies for the rapid and efficient combinatorial generation of libraries of nitrogen-containing heterocycles. However, this advantage is not necessarily well-represented with GBB heterocyclization methods, as they suffer from various drawbacks. For instance, they are limited to toxic, costly, and/or scarcely available isocyanide partners, which classically exhibit short half-lives at ambient temperatures.[26] Additionally, the scope of these methods is somewhat limited; the synthesis of trisubstituted amines at the C-3 position can be troublesome; and C-2 unsubstituted 3-aminoimidazo[1,2-*a*]pyridines are rarely synthesized following typical GBB procedures.[15−25,27]

An alternative method for the synthesis 3-aminoimidazo[1,2-*a*]pyridines relies on the condensation of aromatic ketones with 2 equiv of 2-aminopyridines (Scheme 1b).[28] This strategy is also not general, and the scope is inherently limited to preparing 2-aminopyridyls with substituents at the C-3 position and the use of acetophenone precursors. A complementary strategy for the synthesis of 3-aminoimidazo[1,2-*a*]pyridines is reported to proceed via sequential annulation of *α*-keto vinyl azide units and 2-aminopyridines followed by reduction of the corresponding imine, allowing for the formation of products with monosubstituted C-3-amino groups (Scheme 1c). The methodology is practical, but the scope is limited to aryl substitutions on the *α*-keto vinyl azide partner.[29] The development of a robust, general synthetic method for synthesizing structurally diverse imidazo[1,2-*a*]pyridines with high levels of chemoselectivity is a desirable yet currently unrealized goal. Our previous work with triflic anhydride (Tf_2O)-mediated activation of amides inspired us to pursue a complementary strategy toward these heterocycles.[30] We aimed to develop operationally simple conditions that may be used to introduce a wide variety of substitution patterns within the 3-aminoimidazo[1,2-*a*]pyridines scaffold.

Various methods based on the chemoselective electrophilic activation of amides in the presence of Tf_2O have found broad applications in the synthesis of valuable building blocks.[30,31] An example of such strategy can be found in our recently reported intramolecular cyclodehydration-aromatization work toward the synthesis of imidazo[1,5-*a*]pyridines (**2**), a constitutional isomer, from activated secondary amides (**1**) (Scheme 2a).[32] In

Scheme 2. Synthesis of Imidazo[1,5-*a*]azines and 3-Aminoimidazo[1,2-*a*]pyridines by Tf_2O-Mediated Activation of Amides

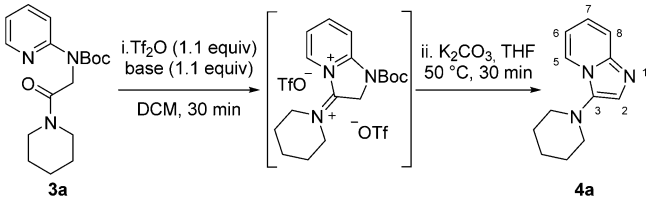


these earlier studies, we determined that the use of 2-methoxypyridine (2-MeO-Py), a slightly basic additive, is required for the activation step to obtain an efficient conversion to the desired target.[33,30a] Inspired by these results, we envisioned developing an analogous route that would allow the synthesis of 3-aminoimidazo[1,2-*a*]pyridines (**4**) from both tertiary and secondary amides (**3**) (Scheme 2b).

RESULTS AND DISCUSSION

We initially investigated the synthesis of **4a** by applying the previously reported activation conditions to **3a**, a simple amide bearing a *tert*-butoxycarbonyl (Boc) protecting group accessed in two steps from commercially available 2-Boc-aminopyridine. In the presence of 2-MeO-Py in DCM (DCM) at ambient temperature, desired product **4a** was obtained in 85% yield before optimization (Table 1, entry 1). On the basis of our

Table 1. Optimization of the Activation-Cyclodehydration Reaction Sequence



entry	base	temp (°C)	time (h)	concn (M)	yield **4a** (%)[a]
1	2-MeO-Py	rt	1	0.2	85
2	2-MeO-Py	rt	0.5	0.6	80
3	2-MeO-Py	0 °C to rt	0.5	0.6	86
4	2-MeO-Py	−78 °C to rt	0.5	0.6	99
5	2-F-Py	rt	0.5	0.6	90
6	none	rt	0.5	0.6	53

[a]Yields determined from the crude reaction mixture by ^{1}H NMR analysis using Ph_3CH as an internal standard.

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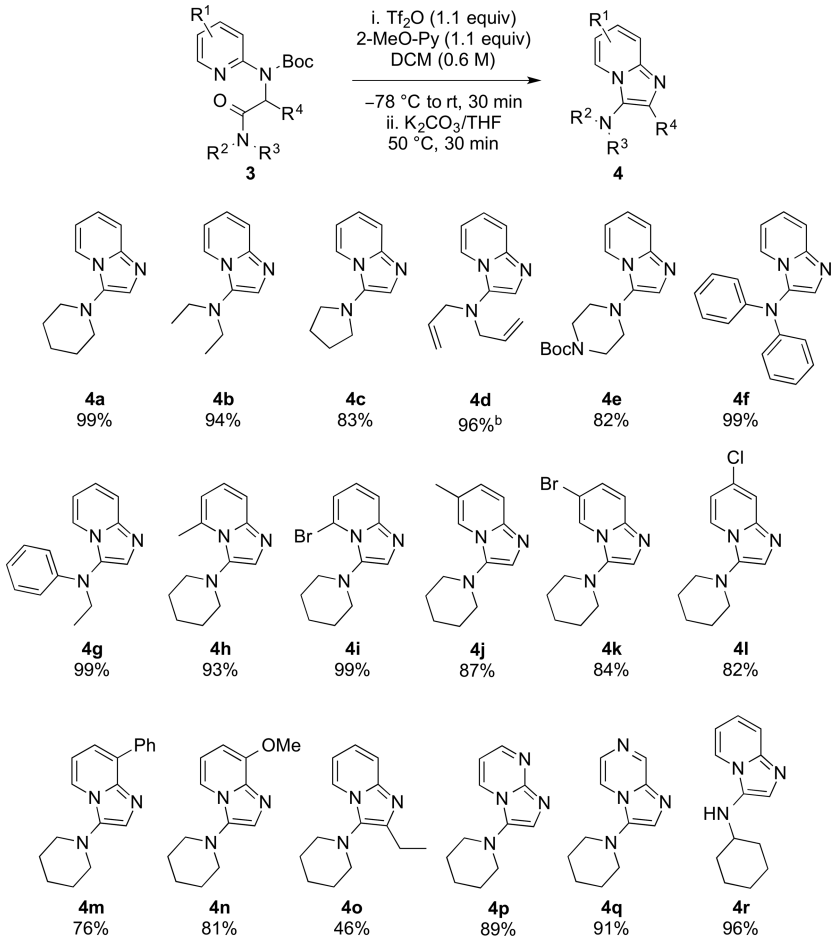
Scheme 3. Synthesis of 3-Aminoimidazo[1,2-*a*]pyridines from the Optimized Cyclodehydration-Aromatization Conditions[a]



[a]Isolated yields. [b]Yield obtained from 4.2 mmol of the corresponding amide precursor.

previous experience with heterocycles, such as **2**, we rapidly and efficiently optimized the overall transformation toward **4a** by fine-tuning various parameters of the reaction. Improved conditions for the activation-cyclodehydration sequence were readily obtained by employing 1.1 equiv of 2-MeO-Py in DCM (0.6 M) while warming the reaction mixture from −78 °C to room temperature (rt) over 30 min to ensure complete activation of the amide. As exemplified in different methodologies involving Tf_2O-mediated electrophilic activation of amides, the addition of 2-substituded pyridines as non-nucleophilic and slightly basic additives in the reaction was found to be crucial to achieve an appreciable level of efficiency.[34] Commonly used 2-F-Py also works well in the activation step, although less expensive 2-MeO-Py was the base of choice in this methodology. Consecutively, we screened different acidic and basic conditions for the deprotection-aromatization step and found that the transformation was very clean when performed in the presence of K_2CO_3 in tetrahydrofuran (THF) at 50 °C for an additional 30 min. Both transformations were run in the same pot, facilitating both the workup and purification procedures.

To explore the scope of the cyclodehydration-aromatization sequence, various amides (**3**) were evaluated under the optimized conditions (Scheme 3). All of these amides can be obtained similarly to **3a** from commercially available *N*-Boc-aminopyridines, bromoacetyl bromide, and an equivalent of amine. To our delight, the overall process toward the synthesis of 3-aminoimidazo[1,2-*a*]pyridines **4** was shown to be effective in the presence of a variety of tertiary amide substrates, tolerating different substitution patterns on both the pyridine and amide components. More precisely, cyclic and acyclic amines can be incorporated at the C-3 position of the imidazo[1,2-*a*]pyridines while consistently affording high yields (Scheme 3, **4a**−**4e**). *N*-Aryl-substituted 3-aminoimidazo[1,2-*a*]pyridines **4f** and **4g** are also efficiently synthesized in excellent yields. The variation of the electronic and steric properties in all positions of the aminoimidazo[1,2-*a*]pyridine (C-5, C-6, C-7 and C-8) is also well tolerated, as good to excellent yields were obtained in the presence of various functional groups (compounds **4h**−**4n**). Interestingly, product **4o**, with an alkyl substitution at the C-2 position, is accessible in moderate yield under our optimized conditions. Notably, the described method tolerates the replacement of the pyridine ring by other heterocycles, such as pyrimidine (**4p**) and pyrazine (**4q**). The procedure can be efficiently extended to secondary amides, affording monosubstituted 3-aminoimidazo[1,2-*a*]-pyridine **4r** in excellent yield (96%). Finally, the transformation was shown to be amenable to gram-scale, as product **4d** was isolated with 96% yield.

Following our success with Boc-protected substrates, we decided to further expand the scope of the current methodology by starting from an unprotected amide (Scheme 4). The treatment of amide **3s** with 2.0 equiv of Tf_2O instead of 1.0 equiv under the optimized conditions led to the corresponding

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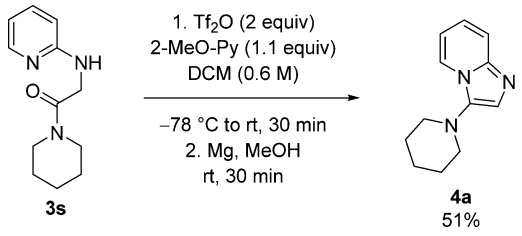
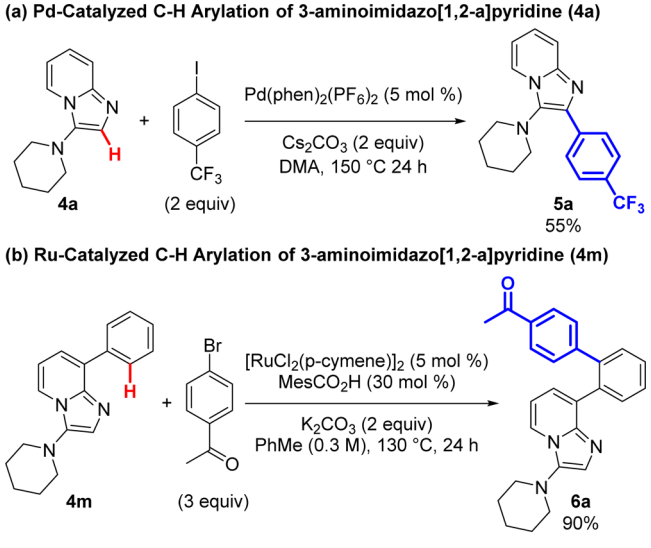
Scheme 4. Synthesis of 3-Aminoimidazo[1,2-*a*]pyridine from an Unprotected Amide (3s)



3-aminoimidazo[1,2-*a*]pyridine (**4a**) in a reasonable 51% yield following full conversion of starting amide. In this case, the additional equivalent of Tf_2O is required because of initial triflation of the N-1 moiety, which is ultimately cleaved in the presence of Mg(0) in MeOH at the aromatization step.

Inspired by the plethora of methodologies that exploit nitrogen-based directing groups for transition metal-catalyzed C−H arylations,[35] we sought to take advantage of the nitrogen atom at the *N*-1 position of 3-aminoimidazo[1,2-*a*]pyridine **4a** to perform divergent Pd- and Ru-catalyzed C−H functionalization reactions. The introduction of an aryl substituent at the C-2 position was achieved by an intermolecular Pd-catalyzed direct C−H arylation reaction (Scheme 5a). Using reported

Scheme 5. Novel Metal-Catalyzed C−H Functionalization of 3-Aminoimidazo[1,2-*a*]pyridines



conditions developed by the Murai group with 4-iodobenzotrifluoride as the coupling partner, this C−H activation reaction provided the desired polysubstituted 3-aminoimidazo[1,2-*a*]pyridine **5a** in 55% yield.[36] Although our approach to 3-aminoimidazo[1,2-*a*]pyridine (Scheme 2) allows the incorporation of an alkyl group at the C-2 position of these scaffolds (Scheme 3, compound **4o**), this Pd-catalyzed postfunctionalization complements the initial strategy by allowing the addition of aryl groups at the same position at a later stage. The latter approach may be advantageous for generating various C-2-substituted heterocycles using a combinatorial approach.

Considering the ability of the nitrogen atom at the N-1 position to chelate palladium species, we further pursued the polyfunctionalization of the 3-aminoimidazo[1,2-*a*]pyridine scaffold by performing a Ru-catalyzed C−H arylation at the ortho position of the phenyl group in **4m** (Scheme 5b).[37] When imidazo[1,2-*a*]pyridine **4m** was subjected to non-optimized Ackermann C−H arylation conditions, employing $[RuCl_2(p\text{-cymene})]_2$ complex as the catalyst in the presence of 4-bromoacetophenone, monoarylated product **6a** was obtained in 90% yield with the remaining 10% stemming from the diarylated product. A distinguished feature of such ruthenium-catalyzed transformation is exemplified by its site selectivity being complementary to traditional Pd-catalyzed C−H bond arylation reactions.

Overall, we have successfully developed a mild cyclodehydration-aromatization process that is effective using short reaction times while using minimal amounts of an activating reagent. These conditions were applied to a large panel of tertiary amides with various substitution patterns. The methodology is also shown to be effective in the presence of an unprotected substrate (**3s**) or with a secondary amide (**3r**). The 3-aminoimidazo[1,2-*a*]pyridine products readily engage in versatile transition metal-catalyzed C−H arylation reactions for the synthesis of more complex scaffolds. These include intermolecular Pd- and Ru-catalyzed C−H functionalizations, demonstrating the efficiency of the 3-aminoimidazo[1,2-*a*]-pyridine motif as a directing group under contemporary C−H arylation methodologies. We expect this methodology and postmodification strategies to be useful in medicinal chemistry toward the synthesis of novel drug candidates.

EXPERIMENTAL SECTION

General Information. Unless otherwise stated, all glassware was stored in the oven and/or was flame-dried prior to use. All reactions were set up under an argon atmosphere[38] while adding reagents and were run with the exclusion of moisture. All reaction flasks were kept closed with a septum during the reaction time. Anhydrous solvents were obtained either by filtration through drying columns (THF, DCM, toluene) or by distillation over CaH_2 (MeOH) or BaO (DMA). Analytical thin-layer chromatography (TLC) was performed on precoated, glass-backed silica gel. Visualization of the developed chromatogram was performed by UV absorbance (254 nm), UV fluorescence (350 nm), or aqueous potassium permanganate ($KMnO_4$). Flash column chromatography was performed on an automatic purification system. Prepacked normal phase silica gel columns (12, 24, 40, 80, and 120 g) were used for separation of products. Melting points were obtained on a melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra (^{1}H NMR, ^{13}C NMR, and ^{19}F NMR) were recorded on 400 and 500 MHz spectrometers. Chemical shifts for ^{1}H NMR spectra are recorded in parts per million from tetramethylsilane using the central peak of chloroform ($CHCl_3$) (δ = 7.26 ppm), MeOH (δ = 3.31 ppm), or HDO (δ = 4.79 ppm) as the internal standard. Chemical shifts for ^{13}C NMR spectra are recorded in parts per million from tetramethylsilane using the central peak of $CDCl_3$ (δ = 77.23 ppm) as the internal standard. All ^{13}C NMR spectra were obtained with complete proton decoupling. Chemical shifts for ^{19}F NMR spectra are recorded in parts per million from trichlorofluoromethane using the central peak of trifluorotoluene (δ = −63.72 ppm) as the internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad), coupling constant in Hz, and integration. Infrared spectra are reported in reciprocal centimeters (cm^{-1}). High resolution mass spectra were performed by positive electrospray ionization on a TOF analyzer.

Reagents. Unless otherwise stated, commercial reagents were used without purification. Trifluoromethanesulfonic anhydride (Tf_2O) was made by heating TfOH on P_4O_{10}, distilled, and kept under argon in a Schlenk flask before use. 2-Methoxypyridine was distilled over 4 Å molecular sieves and kept under argon before use. $[Pd(phen)_2][PF_6]_2$[39] was synthesized according to previously reported procedures.

Experimental Procedures and Characterization Data. *Synthesis of Carbamates. Procedure A.* To a 50 mL round-bottom flask

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equipped with a magnetic stirrer was added 2-aminopyridine (25 mmol, 1 equiv) in THF (12.5 mL, 2 M). Boc_2O (27.5 mmol, 1.1 equiv) was added in one portion, and the resulting mixture was stirred at rt for 16 h. Solvents were then removed under reduced pressure, and the residue was dissolved in DCM and washed with sat. $NaHCO_3$ and brine. The combined organic layers were dried on Na_2SO_4, filtered, and concentrated under reduced pressure. The residue thus obtained was purified by automated flash chromatography over high performance silica gel (40 g column) using a gradient of 0−30% EtOAc/hexanes with a flow of 45 mL/min. The crude amide was injected using a dry pack of silica gel. Fractions containing the carbamate were concentrated to dryness.

Procedure B. To a flame-dried 50 mL round-bottom flask equipped with a magnetic stirrer were added NaHMDS (4.2 mmol, 2.1 equiv) and THF (10 mL, 0.2 M). The aminopyridine was added slowly at 0 °C, and the resulting mixture was stirred at this temperature for 30 min before the dropwise addition of Boc_2O (2.4 mmol, 1.2 equiv). The reaction mixture was then allowed to warm to rt and was stirred for 16 h. Excess NaHMDS was quenched with methanol at 0 °C, and the solvents were removed under reduced pressure. DCM was added, and the mixture was washed with sat. $NaHCO_3$ and brine. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue thus obtained was purified by automated flash chromatography over high performance silica gel (40 g column) using a gradient of 0−30% EtOAc/hexanes with a flow of 45 mL/min. The crude amide was injected using a dry pack of silica gel. Fractions containing the carbamate were concentrated to dryness.

Characterization Data of Carbamates. tert-Butyl (3-Methoxypyridin-2-yl)carbamate. Following general procedure B, the crude aminopyridine was purified by flash chromatography over silica gel using a gradient of 0−30% EtOAc/hexanes. The crude amide was injected using a dry pack of silica gel over a 24 g column, and a flow of 35 mL/min was used. Fractions containing desired carbamate were obtained as a yellow oil (1.5 mmol, 334 mg, 37% yield). R_f = 0.30 (30% acetone/petroleum ether); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.06 (d, J = 4.8 Hz, 1 H), 7.37 (br s, 1 H), 7.09 (dd, J = 8.0, 1.2 Hz, 1 H), 6.93 (dd, J = 8.0, 5.0 Hz, 1 H), 3.88 (s, 3 H), 1.54 (s, 9 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 150.8, 143.7, 142.3, 139.3, 118.0, 116.6, 80.9, 55.5, 28.2; HRMS (ESI-pos, m/z) calcd for $C_{11}H_{17}N_2O_3$ $[M + H]^+$ 225.1234, found 225.1224; FTIR (neat, cm^{-1}) 3435, 2977, 2934, 1743, 1597, 1499, 1147, 1120, 1017, 727.

tert-Butyl (5-Methylpyridin-2-yl)carbamate. Following general procedure A, the crude aminopyridine was purified by flash chromatography over silica gel using a gradient of 0−30% EtOAc/hexanes. The crude amide was injected using a dry pack of silica gel over a 24 g column, and a flow of 35 mL/min was used. Fractions containing desired carbamate were obtained as a white solid (9.6 mmol, 2 g, 96% yield). R_f = 0.46 (20% ether/petroleum ether); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.19 (br s, 1 H), 8.07 (d, J = 2.2 Hz, 1 H), 7.91 (d, J = 8.6 Hz, 1 H), 7.54 (dd, J = 8.6, 2.2 Hz, 1 H), 2.29 (s, 3 H), 1.54 (s, 9 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 152.4, 149.6, 146.1, 139.8, 127.6, 112.2, 81.1, 28.3, 17.6; HRMS (ESI-pos, m/z) calcd for $C_{11}H_{17}N_2O_2$ $[M + H]^+$ 209.1285, found 209.1291; mp 138−140 °C; FTIR (neat, cm^{-1}) 3169, 2973, 2924, 1716, 1523, 1155, 1053, 1026, 766.

tert-Butyl Pyrazin-2-ylcarbamate. Following general procedure A. The crude aminopyridine was purified by flash chromatography over silica gel using a gradient of 0−30% EtOAc/hexanes. The crude amide was injected using a dry pack of silica gel over a 24 g column, and a flow of 35 mL/min was used. Fractions containing desired carbamate were obtained as a white solid (6.7 mmol, 1.31 g, 67% yield). R_f = 0.43 (30% EtOAc/petroleum ether); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.33 (s, 1 H), 8.27 (d, J = 2.6 Hz, 1 H), 8.22−8.25 (m, 1 H), 8.20 (br s, 1 H), 1.57 (s, 9 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 151.8, 148.8, 141.6, 138.8, 135.9, 81.9, 28.2; HRMS (ESI-pos, m/z) calcd for $C_9H_{14}N_3O_2$ $[M + H]^+$ 196.1081, found 196.1084; mp 112−114 °C; FTIR (neat, cm^{-1}) 3208, 2976, 1726, 1554, 1417, 1243, 1151, 1078, 1011.

Other carbamates used for the synthesis of amides **3a−r** are commercially available

*General Procedures for the Synthesis of Amides **3a−r**.* To a 50 mL round-bottom flask equipped with a magnetic stirrer was added the Boc-protected aminopyridine (21 mmol, 1 equiv) in THF (106 mL, 0.2 M). The mixture was cooled to 0 °C, and NaH (23.3 mmol, 1.1 equiv) was added. The reaction mixture was stirred at this temperature for 30 min, and the amide (21 mmol, 1 equiv) was added slowly. The mixture was then stirred at rt for another 16 h before quenching the excess NaH with MeOH at 0 °C. Solvents were removed under reduced pressure, and the residue was dissolved in DCM. The resulting solution was washed with sat. $NaHCO_3$ and brine. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue thus obtained was purified by automated flash chromatography over high performance silica gel (24 g column) using a gradient of 0−30% EtOAc/hexanes with a flow of 35 mL/min. The crude amide was injected using a dry pack of silica gel. Fractions containing amide (**3**) were concentrated to dryness.

*Characterization Data of Amides **3a−r**. tert-Butyl (2-Oxo-2-(piperidin-1-yl)ethyl)(pyridin-2-yl)carbamate (**3a**).* Following the general procedure, **3a** was obtained as a white solid (12.2 mmol, 3.9 g, 62% yield). R_f = 0.27 (30% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.28 (ddd, J = 4.9, 2.0, 0.8 Hz, 1 H), 7.82 (br s, 1 H), 7.55−7.70 (m, 1 H), 6.96 (ddd, J = 7.3, 4.9, 1.0 Hz, 1 H), 4.82 (s, 2 H), 3.30−3.68 (m, 4 H), 1.42−1.75 (m, 15 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 166.7, 154.3, 154.0, 147.0, 136.9, 119.2, 81.4, 47.6, 45.7, 43.1, 28.2, 26.3, 25.5, 24.5; HRMS (ESI-pos, m/z) calcd for $C_{17}H_{25}N_3O_3$ $[M + H]^+$ 320.1969, found 320.1984; mp 84−86 °C; FTIR (neat, cm^{-1}) 2973, 2929, 2855, 1712, 1659, 1385, 1240, 1153, 786.

*tert-Butyl (2-(Diethylamino)-2-oxoethyl)(pyridin-2-yl)carbamate (**3b**).* Following the general procedure, **3b** was obtained as an off-white solid (7.2 mmol, 2.2 g, 46% yield). R_f = 0.56 (30% acetone/petroleum ether); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.28 (ddd, J = 4.9, 2.0, 0.8 Hz, 1 H), 7.86 (br s, 1 H), 7.56−7.71 (m, 1 H), 6.97 (ddd, J = 7.3, 4.9, 1.0 Hz, 1 H), 4.82 (s, 2 H), 3.37 (dd, J = 14.6, 7.2 Hz, 4 H), 1.51 (s, 9 H), 1.01−1.35 (m, 6 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 167.6, 154.4, 154.0, 147.0, 137.0, 119.2, 81.5, 47.5, 41.3, 40.6, 28.2, 14.3, 13.1; HRMS (ESI-pos, m/z) calcd for $C_{16}H_{25}N_3O_3$ $[M + H]^+$ 308.1969, found 308.1981; mp 68−70 °C; FTIR (neat, cm^{-1}) 2971, 2931, 1715, 1645, 1470, 1363, 1226, 1144, 781.

*tert-Butyl (2-Oxo-2-(pyrrolidin-1-yl)ethyl)(pyridin-2-yl)carbamate (**3c**).* Following the general procedure, **3c** was obtained as a pink oil (1.62 mmol, 495 mg, 65% yield). R_f = 0.39 (30% acetone/petroleum ether); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.31 (ddd, J = 5.0, 1.9, 0.8 Hz, 1 H), 7.84 (br s, 1 H), 7.68 (t, J = 7.1 Hz, 1 H), 6.92−7.10 (m, 1 H), 4.79 (s, 2 H), 3.49 (dt, J = 10.0, 6.9 Hz, 4 H), 1.75−2.09 (m, 4 H), 1.51 (s, 9 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 166.5, 153.7, 153.3, 146.5, 136.4, 118.6, 80.8, 47.7, 45.2, 44.9, 27.6, 25.6, 23.4; HRMS (ESI-pos, m/z) calcd for $C_{16}H_{24}N_3O_3$ $[M + H]^+$ 306.1812, found 306.1823; FTIR (neat, cm^{-1}) 2973, 2874, 1708, 1656, 1435, 1366, 1226, 1148, 1061.

*tert-Butyl (2-(Diallylamino)-2-oxoethyl)(pyridin-2-yl)carbamate (**3d**).* Following the general procedure, **3d** was obtained as a colorless oil (1.34 mmol, 445 mg, 67% yield). R_f = 0.28 (30% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.21−8.33 (m, 1 H), 7.83 (br s, 1 H), 7.54−7.66 (m, 1 H), 6.94 (ddd, J = 7.2, 4.9, 0.9 Hz, 1 H), 5.63−5.94 (m, 2 H), 5.05−5.35 (m, 4 H), 4.82 (s, 2 H), 3.85−4.08 (m, 4 H), 1.50 (s, 9 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 168.5, 154.2, 153.9, 146.9, 136.9, 133.1, 132.5, 119.2, 119.1, 117.3, 116.9, 81.5, 48.5, 48.3, 47.4, 28.1; HRMS (ESI-pos, m/z) calcd for $C_{18}H_{26}N_3O_3$ $[M + H]^+$ 332.1969, found 332.1971; FTIR (neat, cm^{-1}) 2978, 1712, 1664, 1590, 1469, 1367, 1223, 1151, 730.

*tert-Butyl 4-(N-(tert-Butoxycarbonyl)-N-(pyridin-2-yl)glycyl)-piperazine-1-carboxylate (**3e**).* Following the general procedure, **3e** was obtained as a white solid (2.16 mmol, 911 mg, 89% yield). R_f = 0.25 (10% acetone/petroleum ether); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.22−8.34 (m, 1 H), 7.82 (br s, 1 H), 7.64 (td, J = 7.8, 1.9 Hz, 1 H), 6.99 (dd, J = 6.8, 5.3 Hz, 1 H), 4.85 (s, 2 H), 3.35−3.67 (m, 8 H), 1.50 (d, J = 16.5 Hz, 18 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 167.2, 154.3, 153.9, 153.6, 146.9, 136.9, 119.0, 119.0, 81.5, 80.1, 47.3, 44.4, 41.6, 28.2, 28.0; HRMS (ESI-pos, m/z) calcd for $C_{21}H_{32}N_4O_5$ $[M + H]^+$

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J. Org. Chem. 2016, 81, 10348−10356

421.2446, found 421.2448; mp 124−126 °C; FTIR (neat, cm^{-1}) 2973, 2931, 1682, 1413, 1365, 1235, 1151, 1019, 779.

*tert-Butyl (2-(Diphenylamino)-2-oxoethyl)(pyridin-2-yl)-carbamate (**3f**).* Following the general procedure, **3f** was obtained as a white solid (1.02 mmol, 410 mg, 51% yield). R_f = 0.29 (30% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.34 (dd, J = 4.9, 1.0 Hz, 1 H), 7.84 (br s, 1 H), 7.57−7.68 (m, 1 H), 7.31 (br s, 10 H), 6.98 (ddd, J = 7.2, 4.9, 0.7 Hz, 1 H), 4.65 (s, 2 H), 1.56 (s, 9 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 168.6, 154.0, 153.8, 147.0, 141.9, 136.9, 129.4, 128.8, 125.7, 119.1, 119.0, 81.6, 49.5, 28.2; HRMS (ESI-pos, m/z) calcd for $C_{24}H_{26}N_3O_3$ $[M + H]^+$ 404.1969, found 404.1987; mp 46−52 °C; FTIR (neat, cm^{-1}) 2974, 1687, 1589, 1469, 1366, 1227, 1147, 755, 692.

*tert-Butyl (2-(Ethyl(phenyl)amino)-2-oxoethyl)(pyridin-2-yl)-carbamate (**3g**).* Following the general procedure, **3g** was obtained as an off-white solid (2.25 mmol, 800 mg, 99% yield). R_f = 0.40 (30% EtOAc/petroleum ether); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.30 (d, J = 3.5 Hz, 1 H), 7.80 (br s, 1 H), 7.57−7.67 (m, 1 H), 7.42−7.51 (m, 2 H), 7.34−7.41 (m, 1 H), 7.29 (d, J = 7.3 Hz, 2 H), 6.93−7.01 (m, 1 H), 4.44 (s, 2 H), 3.77 (q, J = 7.2 Hz, 2 H), 1.53 (s, 9 H), 1.13 (t, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 168.0, 154.2, 153.8, 146.9, 141.2, 137.1, 129.8, 128.5, 128.2, 119.4, 119.2, 81.5, 48.9, 44.2, 28.2, 13.1; HRMS (ESI-pos, m/z) calcd for $C_{20}H_{26}N_3O_3$ $[M + H]^+$ 356.1969, found 356.1976; mp 118−120 °C; FTIR (neat, cm^{-1}) 3058, 2971, 2930, 1713, 1666, 1376, 1149, 786, 697.

*tert-Butyl (6-Methylpyridin-2-yl)(2-oxo-2-(piperidin-1-yl)ethyl)-carbamate (**3h**).* Following the general procedure, **3h** was obtained as a white solid (3.6 mmol, 1.2 g, 75% yield). R_f = 0.30 (30% EtOAc/petroleum ether); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.59 (br s, 1 H), 7.47−7.55 (m, 1 H), 6.83 (d, J = 7.3 Hz, 1 H), 4.81 (s, 2 H), 3.24−3.74 (m, 4 H), 2.44 (s, 3 H), 1.39−1.8 (m, 15 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 166.9, 155.9, 154.1, 153.6, 137.4, 118.7, 116.8, 81.3, 47.7, 45.8, 43.1, 30.9, 28.2, 26.3, 25.5, 24.6, 24.1; HRMS (ESI-pos, m/z) calcd for $C_{18}H_{28}N_3O_3$ $[M + H]^+$ 334.2125, found 334.2135; mp 78−80 °C; FTIR (neat, cm^{-1}) 2974, 2933, 2856, 1710, 1657, 1455, 1364, 1223, 1152.

*tert-Butyl (6-Bromopyridin-2-yl)(2-oxo-2-(piperidin-1-yl)ethyl)-carbamate (**3i**).* Following the general procedure, **3i** was obtained as an off-white solid (0.74 mmol, 294 mg, 74% yield). R_f = 0.28 (30% EtOAc/petroleum ether); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.86 (br s, 1 H), 7.46 (dd, J = 8.3, 7.7 Hz, 1 H), 7.12 (dd, J = 7.5, 0.6 Hz, 1 H), 4.78 (s, 2 H), 3.30−3.73 (m, 4 H), 1.38−1.91 (m, 15 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 166.3, 154.2, 153.5, 139.2, 138.2, 122.7, 117.3, 82.1, 47.3, 46.0, 43.3, 28.1, 26.2, 25.5, 24.6; HRMS (ESI-pos, m/z) calcd for $C_{17}H_{25}BrN_3O_3$ $[M + H]^+$ 398.1074, found 398.1090; mp 96−100 °C; FTIR (neat, cm^{-1}) 2974, 2934, 2856, 1654, 1437, 1364, 1229, 1149, 1127.

*tert-Butyl (5-Methylpyridin-2-yl)(2-oxo-2-(piperidin-1-yl)ethyl)-carbamate (**3j**).* Following the general procedure, **3j** was obtained as an off-white solid (1.43 mmol, 477 mg, 72% yield). R_f = 0.47 (30% acetone/petroleum ether); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.08 (dd, J = 1.7, 0.7 Hz, 1 H), 7.66 (br s, 1 H), 7.35−7.50 (m, 1 H), 4.77 (s, 2 H), 3.23−3.68 (m, 4 H), 2.24 (s, 3 H), 1.39−1.77 (m, 15 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 166.7, 154.0, 152.1, 146.9, 137.7, 128.6, 119.3, 81.1, 47.7, 45.6, 43.0, 28.1, 26.2, 25.4, 24.4, 17.6; HRMS (ESI-pos, m/z) calcd for $C_{18}H_{28}N_3O_3$ $[M + H]^+$ 334.2125, found 334.2112; mp 82−84 °C; FTIR (neat, cm^{-1}) 2975, 2921, 2857, 1702, 1651, 1482, 1384, 1229, 1154.

*tert-Butyl (5-Bromopyridin-2-yl)(2-oxo-2-(piperidin-1-yl)ethyl)-carbamate (**3k**).* Following the general procedure, **3k** was obtained as an off-white solid (0.50 mmol, 200 mg, 50% yield). R_f = 0.43 (30% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.23−8.40 (m, 1 H), 7.80 (br s, 1 H), 7.72 (m, 2.5 Hz, 1 H), 4.81 (s, 2 H), 3.27−3.71 (m, 4 H), 1.43−1.80 (m, 15 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 166.4, 153.6, 153.0, 147.6, 139.6, 82.0, 47.5, 45.8, 43.2, 28.2, 26.3, 25.5, 24.5; HRMS (ESI-pos, m/z) calcd for $C_{17}H_{25}BrN_3O_3$ $[M + H]^+$ 398.1074, found 398.1077; mp 104−108 °C; FTIR (neat, cm^{-1}) 2934, 2855, 1702, 1652, 1464, 1365, 1223, 1152, 836.

*tert-Butyl (4-Chloropyridin-2-yl)(2-oxo-2-(piperidin-1-yl)ethyl)-carbamate (**3l**).* Following the general procedure, **3l** was obtained as a yellow oil (0.70 mmol, 248 mg, 64% yield). R_f = 0.28 (30% EtOAc/petroleum ether); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.16 (d, J = 5.3 Hz, 1 H), 7.99 (br s, 1 H), 6.96 (dd, J = 5.5, 1.8 Hz, 1 H), 4.84 (s, 2 H), 3.33−3.68 (m, 4 H), 1.46−1.83 (m, 15 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 166.4, 155.2, 153.6, 147.5, 144.5, 119.4, 118.8, 82.1, 47.3, 45.8, 43.2, 28.1, 26.3, 25.5, 24.5; HRMS (ESI-pos, m/z) calcd for $C_{17}H_{25}ClN_3O_3$ $[M + H]^+$ 354.1579, found 354.1593; FTIR (neat, cm^{-1}) 2975, 2936, 2851, 1703, 1645, 1384, 1233, 1149, 843.

*tert-Butyl (2-Oxo-2-(piperidin-1-yl)ethyl)(3-phenylpyridin-2-yl)-carbamate (**3m**).* Following the general procedure, **3m** was obtained as a colorless oil (0.71 mmol, 281 mg, 99% yield). R_f = 0.51 (10% MeOH/DCM); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.35 (dd, J = 4.7, 1.6 Hz, 1 H), 7.63−7.94 (m, 3 H), 7.43 (t, J = 7.6 Hz, 2 H), 7.32 (d, J = 7.0 Hz, 1 H), 7.19 (dd, J = 7.5, 4.8 Hz, 1 H), 4.59−5.11 (m, 2 H), 3.38−3.74 (m, 4 H), 1.52−1.71 (m, 6 H), 0.99 (br s, 9 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 166.7, 153.8, 152.1, 146.5, 139.3, 139.2, 133.6, 128.6, 128.4, 127.4, 121.5, 81.1, 49.4, 46.1, 43.1, 27.4, 26.3, 25.5, 24.6; HRMS (ESI-pos, m/z) calcd for $C_{23}H_{30}N_3O_3$ $[M + H]^+$ 396.2287, found 396.2283; FTIR (neat, cm^{-1}) 3059,2978, 2934, 2856, 1657, 1365, 1236, 1153, 701.

*tert-Butyl (3-Methoxypyridin-2-yl)(2-oxo-2-(piperidin-1-yl)ethyl)-carbamate (**3n**).* Following the general procedure, **3n** was obtained as a brown oil (1.06 mmol, 371 mg, 72% yield). R_f = 0.30 (30% acetone/petroleum ether); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.92 (dd, J = 4.8, 1.5 Hz, 1 H), 7.16 (dd, J = 8.2, 1.4 Hz, 1 H), 7.07 (dd, J = 8.3, 4.8 Hz, 1 H), 4.64 (s, 2 H), 3.87 (s, 3 H), 3.31−3.55 (m, 4 H), 1.43−1.68 (m, 6 H), 1.37 (s, 9 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 166.4, 153.8, 150.6, 145.0, 138.7, 122.1, 118.8, 80.4, 55.4, 53.3, 49.1, 45.7, 42.9, 27.9, 26.1, 25.3, 24.4; HRMS (ESI-pos, m/z) calcd for $C_{18}H_{28}N_3O_4$ $[M + H]^+$ 350.2074, found 350.2080; FTIR (neat, cm^{-1}) 2977, 2935, 2856, 1699, 1659, 1451, 1365, 1157, 727.

*tert-Butyl (1-Oxo-1-(piperidin-1-yl)butan-2-yl)(pyridin-2-yl)-carbamate (**3o**).* Following the general procedure, **3o** was obtained as a colorless oil (0.36 mmol, 126 mg, 36% yield). R_f = 0.63 (30% acetone/petroleum ether); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.34−8.45 (m, 1 H), 7.59−7.69 (m, 1 H), 7.40 (d, J = 8.3 Hz, 1 H), 7.08 (ddd, J = 7.3, 4.8, 0.9 Hz, 1 H), 5.16 (t, J = 7.2 Hz, 1 H), 3.34−3.68 (m, 4 H), 1.70−2.06 (m, 2 H), 1.45−1.67 (m, 6 H), 1.41 (s, 9 H), 0.92 (t, J = 7.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 168.8, 154.1, 153.0, 147.9, 137.1, 122.2, 121.1, 81.2, 58.0, 46.2, 43.4, 28.1, 26.2, 25.5, 24.6, 24.0, 11.0; HRMS (ESI-pos, m/z) calcd for $C_{19}H_{30}N_3O_3$ $[M + H]^+$ 348.2282, found 348.2296; FTIR (neat, cm^{-1}) 2974, 2934, 2855, 1698, 1649, 1367, 1243, 1153, 730.

*tert-Butyl (2-Oxo-2-(piperidin-1-yl)ethyl)(pyrimidin-2-yl)-carbamate (**3p**).* Following the general procedure, **3p** was obtained as an off-white solid (1.42 mmol, 456 mg, 79% yield). R_f = 0.36 (50% acetone/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.57 (d, J = 4.8 Hz, 2 H), 6.91 (t, J = 4.8 Hz, 1 H), 4.75 (s, 2 H), 3.28−3.76 (m, 4 H), 1.40−1.83 (m, 15 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 166.2, 160.4, 157.4, 153.0, 115.8, 81.7, 48.4, 45.7, 43.1, 28.0, 26.2, 25.5, 24.4; HRMS (ESI-pos, m/z) calcd for $C_{16}H_{25}N_4O_3$ $[M + H]^+$ 321.1921, found 321.1935; mp 134−136 °C; FTIR (neat, cm^{-1}) 2978, 2963, 2936, 2861, 1731, 1657, 1413, 1152, 794.

*tert-Butyl (2-Oxo-2-(piperidin-1-yl)ethyl)(pyrazin-2-yl)carbamate (**3q**).* Following the general procedure, **3q** was obtained as a white solid (1.97 mmol, 631 mg, 98% yield). R_f = 0.28 (30% acetone/petroleum ether); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.19 (br s, 1 H), 8.02−8.40 (m, 2 H), 4.77 (s, 2 H), 3.20−3.76 (m, 4 H), 1.44−1.82 (m, 15 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 166.0, 153.2, 151.1, 141.2, 140.9, 138.2, 82.6, 46.9, 45.8, 43.2, 28.1, 26.3, 25.5, 24.5; HRMS (ESI-pos, m/z) calcd for $C_{16}H_{25}N_4O_3$ $[M + H]^+$ 321.1921, found 321.1913; mp 98−100 °C; FTIR (neat, cm^{-1}) 2974, 2933, 2859, 1714, 1650, 1408, 1238, 1154, 1006.

*tert-Butyl (2-(Cyclohexylamino)-2-oxoethyl)(pyridin-2-yl)-carbamate (**3r**).* Following the general procedure, **3r** was obtained as a white solid (4.05 mmol, 1.35 g, 79% yield). R_f = 0.56 (30% acetone/petroleum ether); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.32−8.40 (m, 1 H), 7.68−7.74 (m, 1 H), 7.61−7.67 (m, 1 H), 7.10 (ddd, J = 7.2, 5.0, 1.1 Hz, 1 H), 6.93 (d, J = 6.6 Hz, 1 H), 4.37 (s, 2 H), 3.74−3.94 (m, 1 H), 1.55−1.95 (m, 5 H), 1.51 (s, 9 H), 1.07−1.44 (m, 5 H); ^{13}C

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NMR ($CDCl_3$, 126 MHz) δ 169.1, 154.4, 153.8, 147.6, 137.6, 120.5, 119.8, 82.3, 52.2, 47.8, 32.9, 28.1, 25.5, 24.5; HRMS (ESI-pos, m/z) calcd for $C_{18}H_{28}N_3O_3$ $[M + H]^+$ 334.2125, found 334.2130; mp 102−104 °C; FTIR (neat, cm^{-1}) 3296, 2976, 2930, 2854, 1713, 1655, 1366, 1224, 1149.

*General Procedure for the Synthesis of 3-Aminoimidazo[1,2-a]pyridines **4a−r**.* To a flame-dried and argon-flushed 10 mL glass microwave vial equipped with a magnetic stirrer and a rubber septum was added the amide (0.3 mmol, 1.0 equiv) in anhydrous DCM (0.5 mL, 0.60 M). 2-Methoxypyridine (2-MeOPyr) (35 μL, 0.33 mmol, 1.1 equiv) was added via syringe, and the reaction mixture was cooled to −78 °C. Triflic anhydride (55 μL, 0.33 mmol, 1.1 equiv) was added dropwise via syringe, and the reaction mixture was stirred at −78 °C for 10 min and at rt for another 20 min. The reaction was quenched by the addition of K_2CO_3 (3.0 mmol, 10.0 equiv) and THF (2.0 mL, 0.15 M) and then stirred at 50 °C for 30 min. The residue thus obtained was purified by automated flash chromatography over high performance silica gel (24 g column) using a gradient of 0−50% acetone/hexanes with a flow of 35 mL/min. The crude amide was injected using a dry pack of silica gel. Fractions containing 3-aminoimidazo[1,2-*a*]pyridines (**3**) were concentrated to dryness.

*Characterization Data of 3-Aminoimidazo[1,2-a]pyridines. 3-(Piperidin-1-yl)imidazo[1,2-a]pyridine (**4a**).* Following the general procedure, **4a** was obtained as a pale brown solid (0.25 mmol, 50 mg, 99% yield). R_f = 0.31 (10% MeOH/DCM); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.96 (dt, J = 6.8, 1.2 Hz, 1 H), 7.55 (dt, J = 9.0, 1.0 Hz, 1 H), 7.24 (s, 1 H), 7.12 (ddd, J = 9.1, 6.6, 1.3 Hz, 1 H), 6.79 (td, J = 6.7, 1.0 Hz, 1 H), 2.87−3.06 (m, 4 H), 1.57−1.91 (m, 6 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 141.6, 136.4, 123.4, 122.4, 120.5, 117.8, 111.6, 53.0, 26.1, 24.1; HRMS (ESI-pos, m/z) calcd for $C_{12}H_{16}N_3$ $[M + H]^+$ 202.1339, found 202.1330; mp 68−70 °C; FTIR (neat, cm^{-1}) 3035, 2945, 2913, 2793, 1503, 1304, 1250, 750, 739.

*N,N-Diethylimidazo[1,2-a]pyridin-3-amine (**4b**).* Following the general procedure, **4b** was obtained as a brown oil (47 mg, 83% yield). R_f = 0.33 (10% MeOH/DCM); ^1H NMR ($CDCl_3$, 500 MHz) δ 8.10 (d, J = 7.0 Hz, 1 H), 7.57 (d, J = 9.0 Hz, 1 H), 7.35 (s, 1 H), 7.15 (ddd, J = 9.1, 6.6, 1.3 Hz, 1 H), 6.81 (td, J = 6.7, 1.0 Hz, 1 H), 3.08 (q, J = 7.2 Hz, 4 H), 1.03 (t, J = 7.1 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 141.7, 133.1, 124.1, 123.9, 122.7, 117.5, 111.8, 48.5, 12.6; HRMS (ESI-pos, m/z) calcd for $C_{11}H_{16}N_3$ $[M + H]^+$ 190.1339, found 190.1330; FTIR (neat, cm^{-1}) 2969, 2932, 2870, 1545, 1304, 1251, 1134, 1077, 739.

*3-(Pyrrolidin-1-yl)imidazo[1,2-a]pyridine (**4c**).* Following the general procedure, a [1,2-*a*]pyridine g column with a flow of 35 mL/min was used. Fractions containing **4c** were obtained as a brown oil (0.43 mmol, 81 mg, 94% yield). R_f = 0.28 (10% MeOH/DCM); ^1H NMR ($CDCl_3$, 500 MHz) δ 8.00 (d, J = 7.0 Hz, 1 H), 7.57 (d, J = 9.0 Hz, 1 H), 7.23 (s, 1 H), 7.12 (ddd, J = 9.0, 6.6, 1.2 Hz, 1 H), 6.80 (td, J = 6.7, 0.8 Hz, 1 H), 3.15−3.27 (m, 4 H), 2.0 (dt, J = 6.9, 3.2 Hz, 4 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 141.2, 134.8, 123.6, 122.9, 118.4, 117.4, 111.8, 52.1, 24.5; HRMS (ESI-pos, m/z) calcd for $C_{11}H_{14}N_3$ $[M + H]^+$ 188.1182, found 188.1185; FTIR (neat, cm^{-1}) 2963, 2927, 2873, 2826, 1548, 1299, 1132, 745, 733.

*N,N-Diallylimidazo[1,2-a]pyridin-3-amine (**4d**).* Following the general procedure, **4d** was obtained as a colorless oil (4.06 mmol, 867 mg, 96% yield). R_f = 0.36 (10% MeOH/DCM); ^1H NMR ($CDCl_3$, 500 MHz) δ 8.08 (dd, J = 6.8, 1.1 Hz, 1 H), 7.59 (d, J = 9.2 Hz, 1 H), 7.33 (s, 1 H), 7.10−7.22 (m, 1 H), 6.83 (t, J = 6.8 Hz, 1 H), 5.85 (ddt, J = 17.0, 10.3, 6.3 Hz, 2 H), 5.09−5.31 (m, 4 H), 3.64 (d, J = 6.2 Hz, 4 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 141.8, 134.0, 133.1, 124.8, 123.2, 122.4, 118.2, 117.8, 111.5, 56.2; HRMS (ESI-pos, m/z) calcd for $C_{13}H_{16}N_3$ $[M + H]^+$ 214.1339, found 214.1339; FTIR (neat, cm^{-1}) 3080, 2979, 2924, 2849, 1261, 1150, 1030, 753, 636.

*tert-Butyl 4-(Imidazo[1,2-a]pyridin-3-yl)piperazine-1-carboxylate (**4e**).* Following the general procedure, **4e** was obtained as a yellow oil (0.27 mmol, 82 mg, 82% yield). R_f = 0.38 (20% MeOH/DCM); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.99 (dt, J = 6.9, 1.1 Hz, 1 H), 7.50−7.60 (m, 1 H), 7.29 (s, 1 H), 7.14 (ddd, J = 9.1, 6.6, 1.3 Hz, 1 H), 6.81 (td, J = 6.8, 0.9 Hz, 1 H), 3.57−3.71 (m, 4 H), 2.93−3.07 (m, 4 H), 1.50 (s, 9 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 154.6, 142.2, 134.8, 123.5, 122.1, 121.7, 118.1, 111.8, 80.0, 51.7, 44.0, 28.4; HRMS (ESI-pos, m/z) calcd for $C_{16}H_{22}N_4O_2$ $[M + H]^+$ 303.1816, found 303.1824; FTIR (neat, cm^{-1}) 2975, 2928, 2829, 1688, 1418, 1244, 1165, 1125, 729.

*N,N-Diphenylimidazo[1,2-a]pyridin-3-amine (**4f**).* Following the general procedure, **4f** was obtained as a brown solid (0.38 mmol, 108 mg, 99% yield). R_f = 0.42 (10% MeOH/DCM); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.77−7.89 (m, 1 H), 7.72 (d, J = 9.2 Hz, 1 H), 7.58 (s, 1 H), 7.20−7.35 (m, 5 H), 6.99−7.14 (m, 5 H), 6.79 (td, J = 6.8, 0.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 145.5, 142.8, 129.5, 129.1, 127.6, 124.8, 123.1, 122.4, 120.8, 118.1, 112.7; HRMS (ESI-pos, m/z) calcd for $C_{19}H_{16}N_3$ $[M + H]^+$ 286.1339, found 286.1326; mp 136−140 °C; FTIR (neat, cm^{-1}) 3059, 3033, 1585, 1548, 1481, 1288, 1137, 752, 690.

*N-Ethyl-N-phenylimidazo[1,2-a]pyridin-3-amine (**4g**).* Following the general procedure, **4g** was obtained as a yellow oil (0.74 mmol, 175 mg, 99% yield). R_f = 0.2 (50% acetone/petroleum ether); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.73 (dt, J = 6.8, 1.2 Hz, 1 H), 7.66 (d, J = 8.8 Hz, 1 H), 7.55 (s, 1 H), 7.16−7.24 (m, 3 H), 6.82 (tt, J = 7.3, 1.0 Hz, 1 H), 6.77 (td, J = 6.7, 0.9 Hz, 1 H), 6.52−6.62 (m, 2 H), 3.77 (q, J = 7.2 Hz, 2 H), 1.29 (t, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 146.5, 143.1, 129.4, 129.2, 127.4, 124.4, 122.5, 118.8, 118.2, 113.3, 112.1, 46.1, 13.3; HRMS (ESI-pos, m/z) calcd for $C_{15}H_{15}N_3$ $[M + H]^+$ 238.1339, found 238.1340; FTIR (neat, cm^{-1}) 2972, 2932, 1596, 1494, 1344, 1254, 1138, 738, 692.

*5-Methyl-3-(piperidin-1-yl)imidazo[1,2-a]pyridine (**4h**).* Following the general procedure, **4h** was obtained as a brown oil (0.32 mmol, 68 mg, 93% yield). R_f = 0.29 (10% MeOH/DCM); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.31−7.41 (m, 2 H), 6.96 (dd, J = 9.0, 6.6 Hz, 1 H), 6.40 (d, J = 6.8 Hz, 1 H), 3.18 (dt, J = 11.2, 3.5 Hz, 2 H), 2.89 (s, 3 H), 2.70−2.81 (m, 2 H), 1.59−1.92 (m, 5 H), 1.27−1.45 (m, 1 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 143.3, 139.1, 136.4, 124.3, 123.5, 115.9, 112.9, 56.1, 25.6, 23.9, 19.3; HRMS (ESI-pos, m/z) calcd for $C_{13}H_{18}N_3$ $[M + H]^+$ 216.1495, found 216.1502; FTIR (neat, cm^{-1}) 2931, 2850, 2805, 1507, 1290, 1251, 1143, 774, 732.

*5-Bromo-3-(piperidin-1-yl)imidazo[1,2-a]pyridine (**4i**).* Following the general procedure, **4i** was obtained as a brown oil (0.42 mmol, 119 mg, 99% yield). R_f = 0.47 (10% MeOH/DCM); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.49 (dd, J = 8.7, 1.4 Hz, 1 H), 7.37 (s, 1 H), 6.79−7.03 (m, 2 H), 3.14−3.39 (m, 2 H), 2.73 (td, J = 11.5, 2.7 Hz, 2 H), 1.58−1.94 (m, 5 H), 1.28−1.49 (m, 1 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 144.0, 139.3, 124.5, 123.5, 118.5, 117.2, 112.4, 55.5, 25.3, 23.9; HRMS (ESI-pos, m/z) calcd for $C_{12}H_{15}BrN_3$ $[M + H]^+$ 280.0444, found 280.0433; FTIR (neat, cm^{-1}) 2932, 2849, 2803, 1543, 1477, 1275, 1250, 1148, 770.

*6-Methyl-3-(piperidin-1-yl)imidazo[1,2-a]pyridine (**4j**).* Following the general procedure, **4j** was obtained as a brown oil (0.22 mmol, 47 mg, 87% yield). R_f = 0.24 (10% MeOH/DCM); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.72 (s, 1 H), 7.46 (d, J = 9.4 Hz, 1 H), 7.20 (s, 1 H), 6.97 (dd, J = 9.2, 1.7 Hz, 1 H), 2.90−3.07 (m, 4 H), 2.35 (s, 3 H), 1.57−1.8 (m, 6 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 139.5, 136.2, 128.7, 122.6, 120.2, 117.7, 116.1, 53.0, 26.0, 24.0, 18.4; HRMS (ESI-pos, m/z) calcd for $C_{13}H_{18}N_3$ $[M + H]^+$ 216.1495, found 216.1506; FTIR (neat, cm^{-1}) 2934, 2852, 2811, 1653, 1525, 1250, 894, 796, 725.

*6-Bromo-3-(piperidin-1-yl)imidazo[1,2-a]pyridine (**4k**).* Following the general procedure, **4k** was obtained as a yellow oil (0.21 mmol, 59 mg, 84% yield). R_f = 0.30 (50% acetone/hexanes); ^1H NMR ($CDCl_3$, 500 MHz) δ 8.07 (dd, J = 1.8, 0.7 Hz, 1 H), 7.45 (dd, J = 9.5, 0.7 Hz, 1 H), 7.25 (s, 1 H), 7.17 (dd, J = 9.4, 1.9 Hz, 1 H), 2.89−3.05 (m, 4 H), 1.52−1.86 (m, 6 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 140.0, 136.6, 126.8, 122.5, 121.7, 118.5, 106.7, 53.0, 26.1, 24.0; HRMS (ESI-pos, m/z) calcd for $C_{12}H_{14}BrN_3$ $[M + H]^+$ 280.0444, found 280.0455; FTIR (neat, cm^{-1}) 2935, 2851, 2811, 2185, 1381, 1155, 901, 791, 727.

*7-Chloro-3-(piperidin-1-yl)imidazo[1,2-a]pyridine (**4l**).* Following the general procedure, **4l** was obtained as a colorless oil (0.12 mmol, 27 mg, 82% yield). R_f = 0.35 (10% MeOH/DCM); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.88 (d, J = 7.2 Hz, 1 H), 7.53 (d, J = 1.1 Hz, 1 H), 7.24 (br s, 1 H), 6.76 (dd, J = 7.2, 1.7 Hz, 1 H), 2.92−3.02 (m, 4 H), 1.58−1.82 ppm (m, 6 H); ^{13}C NMR ($CDCl_3$, 176 MHz) δ 148.9, 136.9, 132.5, 123.0, 118.5, 115.8, 114.6, 53.0, 26.0, 23.9; HRMS (ESI-pos, $m/$

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J. Org. Chem. 2016, 81, 10348−10356

z) calcd for $C_{12}H_{15}ClN_3$ $[M + H]^+$ 236.0949, found 236.0939; FTIR (neat, cm^{-1}) 2936, 2852, 2817, 1650, 1626, 1443, 1281, 793, 731.

*8-Phenyl-3-(piperidin-1-yl)imidazo[1,2-a]pyridine (**4m**).* Following the general procedure, **4m** was obtained as an off-white solid (0.48 mmol, 134 mg, 76% yield). R_f = 0.32 (30% EtOAc/petroleum ether); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.92−8.03 (m, 3 H), 7.45−7.55 (m, 2 H), 7.37−7.44 (m, 1 H), 7.31 (s, 1 H), 7.23 (dd, J = 6.9, 1.2 Hz, 5 H), 6.88 (t, J = 6.9 Hz, 1 H), 2.95−3.09 (m, 4 H), 1.60−1.89 (m, 6 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 140.5, 136.7, 136.7, 130.6, 128.9, 128.4, 128.0, 121.7, 121.4, 121.2, 111.6, 53.1, 26.2, 24.2; HRMS (ESI-pos, m/z) calcd for $C_{18}H_{19}N_3$ $[M + H]^+$ 278.1652, found 278.1663; mp 96−98 °C; FTIR (neat, cm^{-1}) 2929, 2829, 1450, 1367, 1300, 1147, 748, 693, 573.

*8-Methoxy-3-(piperidin-1-yl)imidazo[1,2-a]pyridine (**4n**).* Following the general procedure, **4n** was obtained as an off-white solid (0.28 mmol, 64 mg, 81% yield). R_f = 0.37 (10% MeOH/DCM); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.60 (dd, J = 6.8, 0.7 Hz, 1 H), 7.17 (s, 1 H), 6.67 (t, J = 7.2 Hz, 1 H), 6.33−6.43 (m, 1 H), 3.99 (s, 3 H), 2.90−3.05 (m, 4 H), 1.54−1.83 (m, 6 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 149.3, 137.3, 136.1, 120.0, 115.4, 111.3, 99.3, 55.7, 53.1, 26.1, 24.1; HRMS (ESI-pos, m/z) calcd for $C_{13}H_{18}N_3O$ $[M + H]^+$ 232.1444, found 232.1453; mp 106−110 °C; FTIR (neat, cm^{-1}) 3038, 2927, 2915, 2847, 2805, 1542, 1275, 1069, 737.

*2-Ethyl-3-(piperidin-1-yl)imidazo[1,2-a]pyridine (**4o**).* Following the general procedure, **4o** was obtained as a brown solid (0.17 mmol, 38 mg, 46% yield). R_f = 0.32 (10% MeOH/DCM); ^1H NMR ($CDCl_3$, 500 MHz) δ 8.02 (dt, J = 6.8, 1.2 Hz, 1 H), 7.47 (d, J = 9.0 Hz, 1 H), 7.08 (ddd, J = 9.0, 6.7, 1.4 Hz, 1 H), 6.74 (td, J = 6.7, 1.0 Hz, 1 H), 3.00−3.15 (m, 4 H), 2.84 (q, J = 7.6 Hz, 2 H), 1.74 (br s, 6 H), 1.36 (t, J = 7.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 140.8, 140.0, 129.8, 123.3, 122.4, 116.7, 111.1, 52.4, 27.2, 24.1, 21.6, 14.7; HRMS (ESI-pos, m/z) calcd for $C_{14}H_{19}N_3$ $[M + H]^+$ 230.1652, found 230.1654; FTIR (neat, cm^{-1}) 2932, 2850, 2812, 1557, 1501, 1347, 1223, 753, 738.

*3-(Piperidin-1-yl)imidazo[1,2-a]pyrimidine (**4p**).* Following the general procedure, **4p** was obtained as a dark green solid (0.27 mmol, 54 mg, 89% yield). R_f = 0.29 (10% MeOH/DCM); ^1H NMR ($CDCl_3$, 500 MHz) δ 8.48 (dd, J = 3.9, 2.1 Hz, 1 H), 8.25 (dd, J = 6.8, 2.0 Hz, 1 H), 7.40 (s, 1 H), 6.84 (dd, J = 6.8, 4.0 Hz, 1 H), 2.86−3.12 (m, 4 H), 1.55−1.89 (m, 6 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 148.4, 144.7, 134.6, 130.0, 122.7, 107.7, 52.9, 26.0, 24.0; HRMS (ESI-pos, m/z) calcd for $C_{11}H_{15}N_4$ $[M + H]^+$ 203.1291, found 203.1301; mp 112−116 °C; FTIR (neat, cm^{-1}) 3060, 2929, 2856, 2793, 2755, 1496, 839, 779, 762.

*3-(Piperidin-1-yl)imidazo[1,2-a]pyrazine (**4q**).* Following the general procedure, **4q** was obtained as a brown solid (0.17 mmol, 34 mg, 91% yield). R_f = 0.29 (10% MeOH/DCM); ^1H NMR ($CDCl_3$, 500 MHz) δ 8.99 (d, J = 1.1 Hz, 1 H), 7.75−7.94 (m, 2 H), 7.41 (s, 1 H), 2.93−3.10 (m, 4 H), 1.56−1.91 (m, 6 H); ^{13}C NMR (CDCl3, 126 MHz) δ 143.8, 137.2, 137.1, 128.6, 123.5, 115.4, 52.5, 25.9, 23.9; HRMS (ESI-pos, m/z) calcd for $C_{11}H_{15}N_4$ $[M + H]^+$ 203.1291, found 203.1301; mp 64−66 °C; FTIR (neat, cm^{-1}) 2935, 2844, 2805, 1528, 1315, 1242, 891, 792, 610.

*N-Cyclohexylimidazo[1,2-a]pyridin-3-amine (**4r**).* Following the general procedure, **4r** was obtained as a brown solid (0.29 mmol, 62 mg, 96% yield). R_f = 0.18 (10% MeOH/DCM); ^1H NMR ($CDCl_3$, 400 MHz) δ 8.03 (d, J = 7.0 Hz, 1 H), 7.51 (d, J = 9.0 Hz, 1 H), 7.21 (s, 1 H), 7.09 (ddd, J = 9.0, 6.7, 1.1 Hz, 1 H), 6.70−6.86 (m, 1 H), 2.88−3.08 (m, 1 H), 1.98 (d, J = 9.7 Hz, 2 H), 1.55−1.85 (m, 3 H), 1.07−1.39 (m, 6 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 140.3, 130.2, 124.9, 122.9, 118.6, 116.3, 112.5, 56.1, 33.5, 25.7, 24.8; HRMS (ESI-pos, m/z) calcd for $C_{13}H_{18}N_3$ $[M + H]^+$ 216.1495, found 216.1486; mp 100−106 °C; FTIR (neat, cm^{-1}) 3174, 2995, 2921, 2852, 1565, 1365, 1120, 735, 724.

*General Procedure for the Pd-Catalyzed C−H Arylation of 3-Aminoimidazo[1,2-a]pyridine **4a**.* To a flame-dried 10 mL microwave vial equipped with a magnetic stirrer was added dry cesium carbonate (0.8 mmol, 2 equiv). The vial was dried in a vacuum oven at 200 °C for 16 h. After cooling said vial, 3-(piperidin-1-yl)imidazo[1,2-*a*]pyridine (0.4 mmol, 1 equiv) was added in the glovebox. The vial was sealed in the glovebox, and 1-iodo-4-(trifluoromethyl)benzene (0.8 mmol, 2 equiv) and freshly distilled DMA (1 mL, 0.5 M) were added to the reaction vessel. The resulting mixture was then heated to 150 °C for 24 h, after which the reaction was cooled to rt and the solids were filtered over a pad of Celite. The residue was purified using flash chromatography (0−50% acetone/hexanes, 24 g column) to afford 3-(piperidin-1-yl)-2-(4-(trifluoromethyl)phenyl)imidazo[1,2-*a*]-pyridine (**5a**) (75 mg, 55% yield) as a bright yellow oil. R_f = 0.49 (40% acetone/petroleum ether); ^1H NMR ($CDCl_3$, 500 MHz) δ 8.11 (d, J = 7.0 Hz, 1 H), 8.06 (d, J = 7.9 Hz, 2 H), 7.65−7.77 (m, 3 H), 7.23−7.31 (m, 1 H), 6.90 (t, J = 6.7 Hz, 1 H), 3.14 (t, J = 5.0 Hz, 4 H), 1.55−1.88 (m, 6 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 141.6, 138.3, 135.2, 130.9, 130.1, 129.6, 128.5, 125.1, 124.5, 123.3, 117.9, 111.9, 51.2, 26.9, 24.0; ^{19}F NMR ($CDCl_3$, 471 MHz) δ −62.5; HRMS (ESI-pos, m/z) calcd for $C_{19}H_{18}F_3N_3$ $[M + H]^+$ 346.1526, found 346.1530; FTIR (neat, cm^{-1}) 2937, 2851, 1319, 1162, 1115, 1063, 847, 753, 730.

*General Procedure for the Ru-Catalyzed C−H Arylation of 3-Aminoimidazo[1,2-a]pyridine **4m**.* To a flame-dried 10 mL microwave vial equipped with a magnetic stirrer and charged with **2m** (0.1 mmol, 1 equiv) were added, in the glovebox, dry potassium carbonate (0.2 mmol, 2 equiv), 2,4,6-trimethylbenzoic acid (0.03 mmol, 0.3 equiv), $[RuCl_2(p\text{-cymene})]_2$ (0.005 mmol, 0.05 equiv), and 4-bromoacetophenone (0.3 mmol, 3 equiv). The vial was sealed with a septum, and toluene (0.5 mL, 0.2 M) was added. The resulting mixture was then heated at 150 °C for 15 h, after which ethyl acetate was added, and the mixture was filtered over a pad of Celite and concentrated under reduced pressure. The residue was purified using flash chromatography (0−50% EtOAc/hexanes, 24 g column) to afford 1-(2′-(3-(piperidin-1-yl)imidazo[1,2-*a*]pyridin-8-yl)-[1,1′-biphenyl]-4-yl)ethan-1-one (**6a**) (0.091 mmol, 36 mg, 91% yield) as a brown solid. R_f = 0.41 (40% acetone/petroleum ether); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.86 (dd, J = 6.1, 1.9 Hz, 1 H), 7.69−7.80 (m, 3 H), 7.45−7.55 (m, 3 H), 7.27−7.32 (m, 2 H), 7.24 (s, 1 H), 6.28−6.82 (m, 2 H), 2.94−3.09 (m, 4 H), 2.54 (s, 3 H), 1.55−1.89 (m, 6 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 197.9, 146.5, 140.9, 140.2, 136.5, 135.1, 135.0, 131.2, 130.3, 130.0, 129.5, 128.4, 127.9, 127.9, 124.9, 121.3, 121.0, 111.3, 53.0, 26.5, 26.1, 24.1; HRMS (ESI-pos, m/z) calcd for $C_{26}H_{25}N_3O$ $[M + H]^+$ 396.2070, found 396.2074; mp 70−72 °C; FTIR (neat, cm^{-1}) 2931, 2853, 2810, 2214, 1677, 1259, 917, 721, 594.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01324.

NMR spectra and compound characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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