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Ni-Catalyzed C−H Functionalization in the Formation of a Complex Heterocycle: Synthesis of the Potent JAK2 Inhibitor BMS-911543

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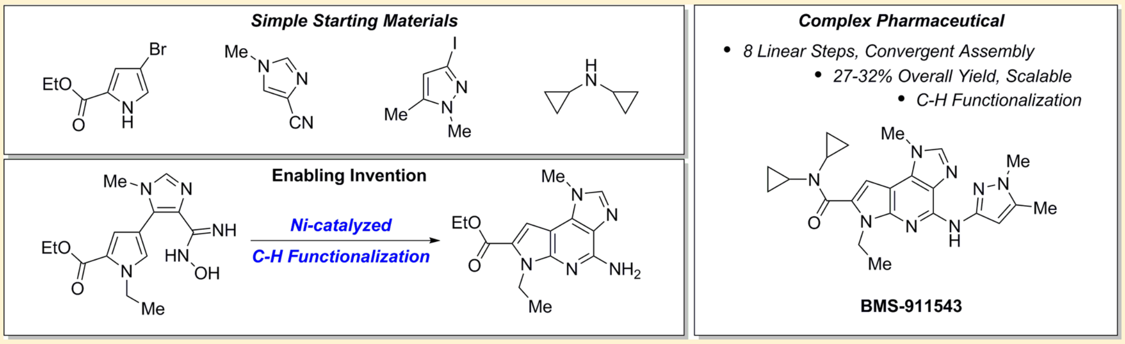
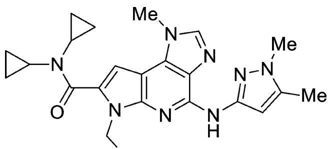
Ⓢ *Supporting Information*



ABSTRACT: BMS-911543 is a complex pyrrolopyridine investigated as a potential treatment for myeloproliferative disorders. The development of a short and efficient synthesis of this molecule is described. During the course of our studies, a Ni-mediated C−N bond formation was invented, which enabled the rapid construction of the highly substituted 2-aminopyridine core. The synthesis of this complex, nitrogen-rich heterocycle was accomplished in only eight steps starting from readily available materials.

■ INTRODUCTION

Myeloproliferative disorders (MPDs) [or myeloproliferative neoplasms (MPNs)] are a group of diseases of the bone marrow in which myeleosites, or young blood cells, grow abnormally producing excessive concentrations of mature cells (i.e., red blood cells, white blood cells, or platelets).[1] These hematological neoplasms are classified into four main diseases, chronic myelogenous leukemia,[2] essential thrombocytopenia,[3] polythemia vera,[4] and myelofibrosis.[5] In 2005, a strong correlation between these diseases and a mutation of the 617 codon of the JAK2 kinase was described, providing evidence of a commonality across a subset of patients.[6] Approaches to the treatment of MPDs have focused on the development of small molecules that selectively inhibit this mutated pathway,[7] with the first compound in this class, ruxolitinib[8] (Jakafi), gaining FDA approval in 2011.[9] BMS-911543[10] **1** (Figure 1) was recently identified as a potent and selective inhibitor, showing excellent specificity with respect to other members of the JAK-family of kinases, the potential for improved efficacy and reduced off-target liabilities versus other MPD treatment options.[11]



BMS-911543, **1**

Figure 1. BMS-911543.

The initial synthesis of BMS-911543 (**1**) relied on a retrosynthetic strategy disconnecting the molecule to 2,6-dichloropyridine (Figure 2).[11] While this synthesis was optimal for supporting initial target identification, 19 linear steps were required to prepare the selected compound. The high step count was due to stepwise functionalization of the pyridine ring system. Multiple functional group manipulations were utilized to regioselectively advance the 2,6-dichloropyridine and install the required substituents on the pyridine nucleus, especially with respect to the required nitrogen substitution pattern. Indeed, functionalizing the periphery of pyridine is a long-standing problem, and the synthesis of pentasubstituted pyridines is particularly challenging.[12]

When devising a new synthetic strategy for the synthesis for BMS-911543 (**1**), and in contrast to the prior approach, we surmised that a disconnection through the central ring of the molecule, via one of three potential bonds, would allow us to start from simpler heterocycles and deliver a more convergent synthesis of this complex structure (Figure 3). Retrosynthetically, we envisioned that the dicyclopropylamine (DCPA) and pyrazole moieties could be installed at the end of the synthesis through standard amidation and C−N bond coupling reactions (Figure 3). Next, we sought to separate the two external

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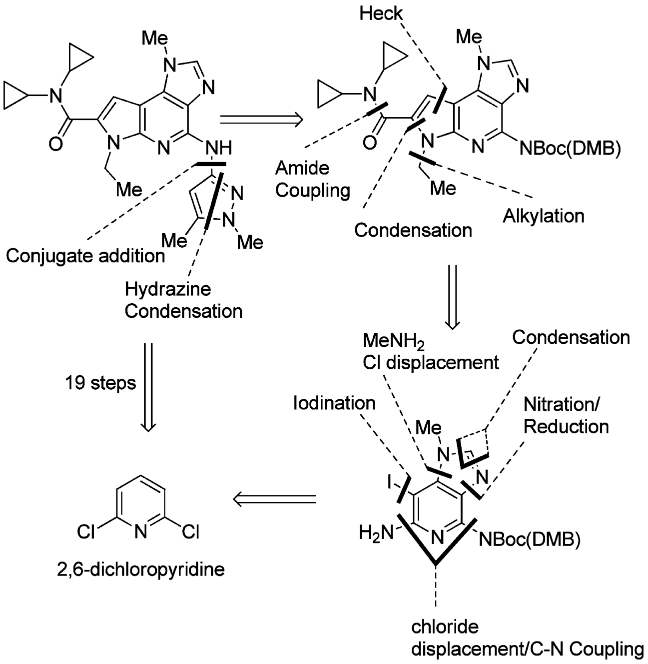


Figure 2. Original disconnection strategy to prepare BMS-911543.[11]

heterocycles (i.e., a pyrrole and an imidazole), building the central pyridine through the union of the smaller systems. It was hoped that the construction of the pyridine in this manner would obviate many of the challenges present in the original synthesis, minimize functional group interconversions, and result in a simpler and more efficient approach to our desired heterocycle **1**. Out of the three potential "ring-forming" bond formations within this strategy, we focused on disconnecting the 1,2-C−N bond via a proposed 6π-cyclization[13] of amidine **2**. The synthesis of this key intermediate would come from coupling a C5-activated cyanoimidazole **3** with the known bromopyrrole **4**.[14] Despite the lack of solid precedent for amidine electrocyclizations of this type, we felt that the ease of many electrocyclizations,[15] coupled with the potential for multiple conditions to mediate this key cyclization, supported the exploration of this strategy. Herein we describe the realization of this approach and the development of a Ni-mediated cyclization, which enabled the efficient construction of this highly functionalized pyrrolopyridine in just 8 steps and 29% overall yield.[16]

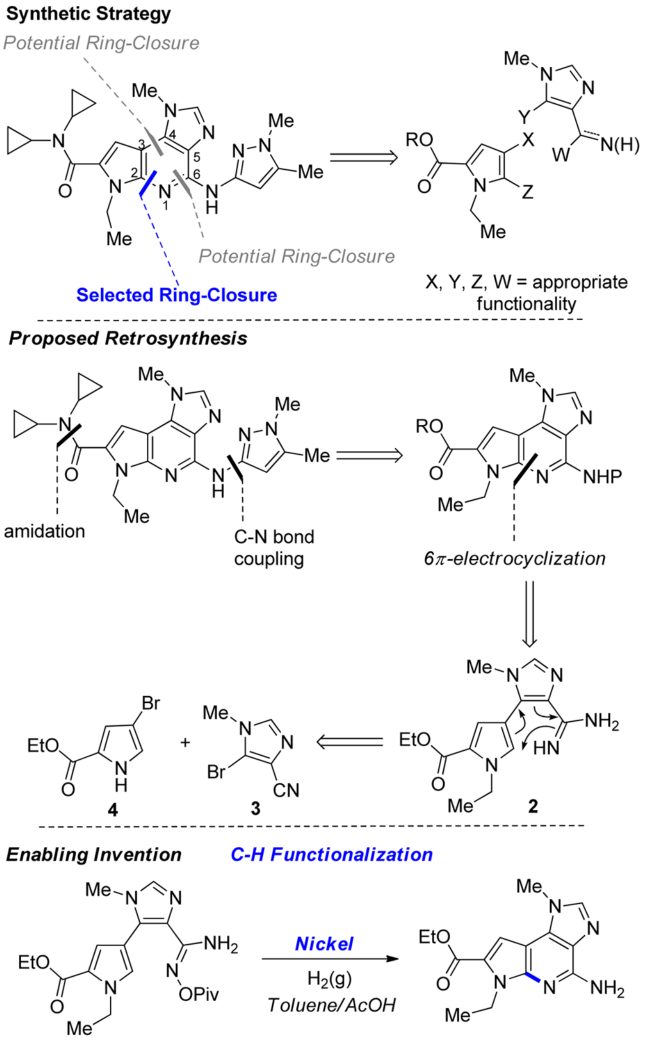
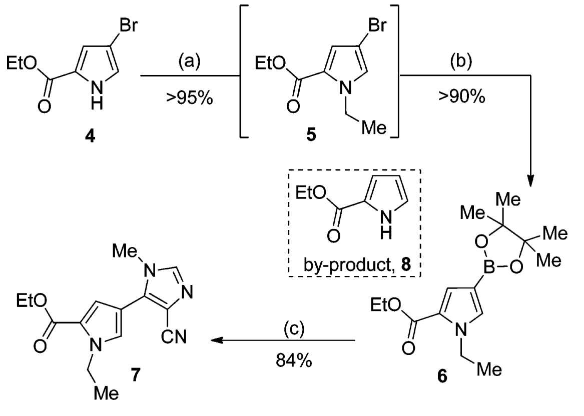


Figure 3. Disconnection strategy and key transformations for the proposed synthesis of BMS-911543, **1**.

Scheme 1. Synthesis of Nitrile 7^a

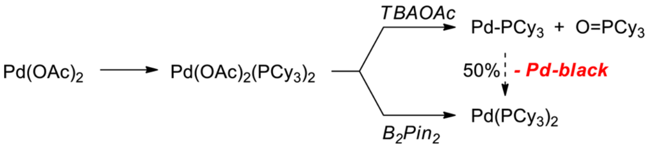


^{a}Conditions: (a) EtI (1.2 equiv), K_2CO_3 (1.5 equiv), DMF, 25 °C, 16 h; (b) $Pd(OAc)_2$ (1 mol %), PCy_3HBF_4 (2.5 mol %), B_2Pin_2 (1.2 equiv), $N(Me)_4OAc$ (3.0 equiv), toluene, 80 °C, 2 h; (c) $Pd(OAc)_2$ (1 mol %), PPh_3 (2.5 mol %), **3** (0.9 equiv), K_2CO_3 (1.5 equiv), DMAc/H_2O (5:1), 80 °C, 2 h.

RESULTS AND DISCUSSION

In order to evaluate the proposed 6π-electrocyclization, it was necessary to synthesize the pyrrole−imidazole **7** (Scheme 1). We proposed to accomplish this via a Suzuki coupling, starting from the C4-brominated pyrrole **4**. Preparation of the known 4-bromopyrrole **4** was accomplished in two steps from trichloroacetylpyrrole,[17] which was followed by *N*-ethylation to give the *N*-ethylpyrrole **5** (Scheme 1). The borylation of electron-rich heteroaromatic compounds can be difficult due to the general lack of stability of the resulting electron-rich boronates;[18] indeed, the formation of pyrrole **6** proved challenging. Initial screening results indicated that a combination of KOAc/$Pd(OAc)_2$/Cy_3P in toluene was capable of giving high yields of the desired boronate **6** (>95% conversion with ~99:1 selectivity for Miyaura borylation over proto-dehalogenation). However, these conditions proved to be extremely capricious in a laboratory setting, with significant amounts of the proto-dehalogenated pyrrole **8** being produced as the scale of the reaction increased (up to 50% proto-dehalogenation could be observed on gram scale). During our development of this palladium-mediated borylation, several key observations were made that proved to be important for achieving high yields and reproducibility: (a) A soluble base, such as NMe_4OAc, was critical. The use of insoluble bases (such as KOAc in toluene) can result in base starvation and significantly impact both catalyst turnover and stability. (b) Formation of unligated palladium during catalyst activation (and associated formation of Pd-black) was the main source of proto-debromination; ensuring controlled reduction of the metal center to a ligated species was critical to maintain high selectivity for borylation over reductive dehalogenation. (c) Reduction of $Pd(OAc)_2$ was smoothly mediated (either pre- or postphosphine ligation) by B_2Pin_2. This finding represents an alternate mode of palladium reduction which, in contrast to the base/water-mediated pathway,[19] does not result in phosphine oxidation. Based on this finding, we discovered that the order of reagent addition could impact the identity (and therefore activity and stability) of the catalyst complex. In the absence of a reducing agent, such as B_2pin_2, the $[(PCy_3)_2Pd(OAc)_2]$ species formed from $Pd(OAc)_2/PCy_3$ could be reduced by the ligated PCy_3 to form an unstable, monoligated $[(PCy_3)Pd(0)]$ complex and the corresponding phosphine oxide. In contrast, addition of the ligated palladium complex $[(PCy_3)_2Pd(OAc)_2]$ to a solution containing B_2Pin_2 resulted in formation of a stable, though less active Pd(0) complex, $Pd(PCy_3)_2$. Thus, *without any change in stoichiometry*, two distinct catalysts could be formed. (d) It was also demonstrated that the monoligated palladium tricyclohexylphosphine was unstable in solution in the absence of Ar−Br, disproportionating to L_2Pd and Pd-black, the root cause of proto-dehalogenation (Scheme 2).

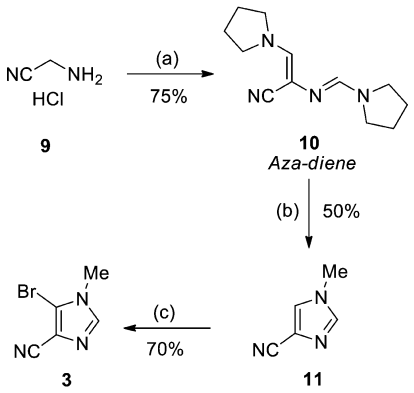
Scheme 2. Controlled Palladium Reduction[20]



Thus, ensuring full Pd-ligation prior to reduction, with reduction occurring in the presence of the aryl bromide, were both critical factors for reproducibly conducting this borylation. Our work elucidating these factors, establishing the source of palladium reduction, and its corresponding impact on catalyst structure was recently published.[20]

With the borylated pyrrole **6** in hand, a Suzuki coupling was envisioned to join the key heterocycles. However, the cyanoimidazole coupling partner **3** proved difficult to obtain. The reported regioselective synthesis of this small molecule required an extraordinary number of steps, proceeding via two steps from the corresponding carboxylic acid,[21] itself prepared in four steps from maleonitrile.[22] Thus, we chose to develop an alternate approach, exploring a conjugate bisaminomethylenation/cyclization based strategy, originally reported by Biere et al. (Scheme 3).[23] After significant optimization, an efficient two-step protocol involving condensation of amino acetonitrile **9** with DMF·DMA to give azadiene **10**, followed by an *N*-methylaniline-catalyzed addition of methylamine, prepared imidazole **11** in good overall yield and excellent purity. This approach was found to be general for preparing 1,4-*N*-substituted imidazoles, providing complete regiochemical control in the formation of a wide range of 1-*N*-substituted-4-carboxy imidazoles.[24] Finally, regioselective bromination was accomplished using *N*-bromosuccinimide (NBS) in DMF, producing the C5 regioisomer **3** with >90:10 (C5:C2) selectivity. C5-Bromoimidazole **3** could be isolated as a single isomer by direct crystallization.[25] With both coupling partners in hand, the Suzuki coupling of boronic ester **6** with C5-bromoimidazole **3** proceeded under standard conditions using $Pd(OAc)_2/PPh_3$, delivering the biaryl compound **7** without issue (Scheme 1).[26]

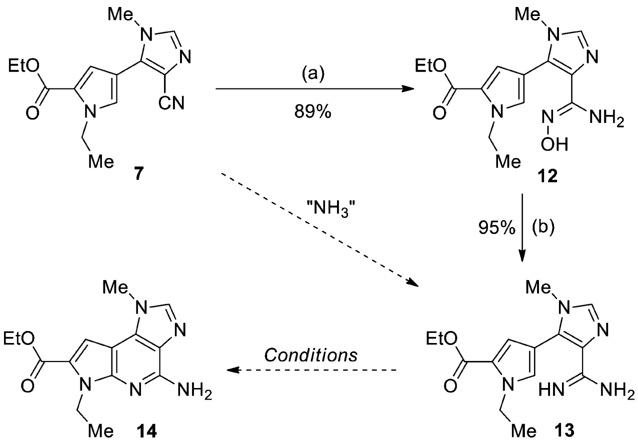
Scheme 3. Imidazole Synthesis[24],[a]



[a] Conditions: (a) DMF.DMA (4 equiv), pyrrolidine (5 equiv), 70 °C; (b) $MeNH_2$.HCl (2.25 equiv), *N*-methylaniline (10 mol %), AcOH (5 mL/g), 100 °C; (c) NBS (1.1 equiv), DMF (5 mL/g).

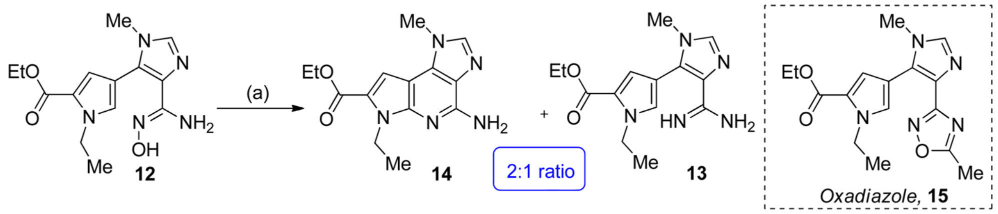
In order to test our proposed 6*π*-electrocyclization, we required the conversion of the nitrile in pyrrole **7** to the corresponding amidine **13** (Scheme 4). However, the desired amidine **13** proved surprisingly challenging to prepare, with direct aminolysis of nitrile **7** returning only unreacted starting material. This lack of reactivity was circumvented by converting nitrile **7** to hydroxyamidine **12** (by treatment with ethanolic NH_2OH, Scheme 4), followed by reduction under standard conditions (Pd/C),[27] providing the desired amidine **13** in excellent overall yield. As described (vide supra), it was hoped that amidine **13** would undergo a 6*π* electrocyclization either spontaneously or under basic, acidic, or thermal conditions. Unfortunately, initial efforts to affect cyclization failed. At the time of this work, limited examples of such cyclizations had been reported, the most relevant being a highly conjugated *π*-

Scheme 4. Formation of Amidine 13[a]



[a] Conditions: (a) NH_2OH HCl, Et_3N, EtOH; (b) 10 wt % of Pd/C, Ac_2O, AcOH/MeOH, 80 psig.

Scheme 5. Discovery of a Ni-Catalyzed Cyclization[a]



[a]Conditions: (a) 50 wt % Raney-Ni; Ac_2O, AcOH, MeOH, 25 °C.

Scheme 6. Reaction Concept Leveraged for Optimization

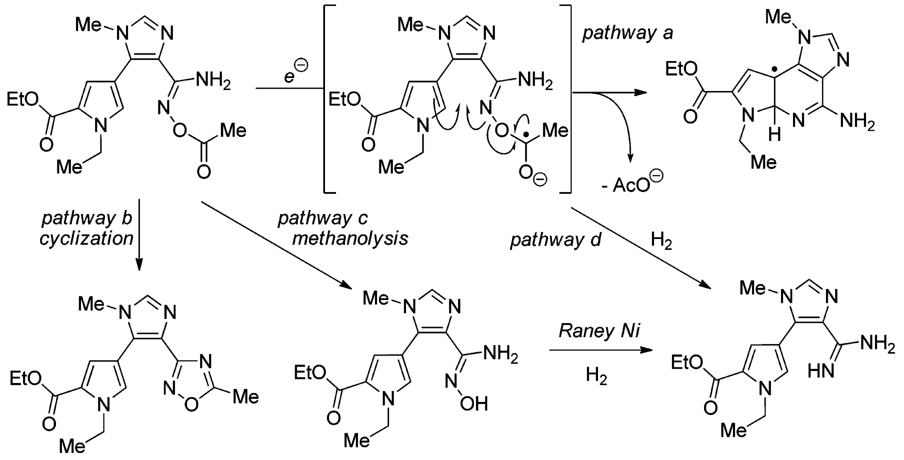
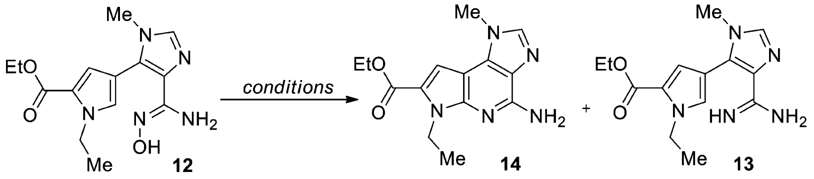


Table 1. Optimization of the Ni-Catalyzed Cyclization



entry	conditions[a]	ratio (**14**:**13**)
1	50 wt % of Raney-Ni, 10 equiv of Ac_2O, MeOH/AcOH	8:1
2	50 wt % of Raney-Ni, no Ac_2O, MeOH/AcOH	1:99
3	50 wt % of Raney-Ni, 2.5 equiv of Piv_2O, MeOH/AcOH	11:1
4	50 wt % of Raney-Ni, 1 equiv of Piv_2O, toluene/AcOH	13:1
5	20 wt % of PRICAT, 1 equiv of Piv_2O, toluene/AcOH	16:1[b]

[a]3 psig H_2, 25 °C, 12 h; [b]Isolated in >99:1 14:13 ratio and 77% yield of 14.

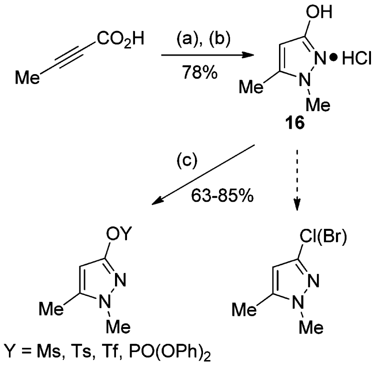
system cyclizing with aerobic oxidation.[28] Re-evaluating our conceptualization of this approach led us to consider the pyrrole acting as a nucleophilic component. We therefore began studying activated forms of the hydroxylamine **12**. Unfortunately, activation of the hydroxyamidine through tosylation, acylation, or phosphorylation failed to yield the desired product, resulting only in nonproductive reactivity. We therefore considered a radical-based approach and surveyed the hydroxyamidine **12** and several analogues (*O*-acetylation, tosylation, etc.) in the presence of various mediators (CAN, $NaNO_2$, Cu salts, Fe, Sm, etc.). After screening a wide variety of conditions, Raney Ni was shown to be singularly effective, mediating the desired cyclization under reductive conditions (Scheme 5). In our initial experiments, only a modest ~2:1 ratio of the desired cyclized pyridine **14** and the reduced amidine **13** was obtained, cyclization to the C3-position of the pyrrole was not observed. Encouraged by these results, we sought to further optimize this transformation.

The desired product **14** and amidine **13** were formed along with a significant amount of oxadiazole **15** (formed through condensative self-cyclization of the *O*-acylated amidine, Scheme 6, pathway b). In seeking to optimize this transformation, we quickly determined that hydrogen and *O*-acylation were critical; control experiments showed that exposure of the hydroxyamidine **12** to the reaction conditions resulted in quantitative conversion to the amidine **13**. While no mechanistic studies were performed, we rationalized the reaction coordinate as shown (Scheme 6); this proposal helped guide our optimization, though other mechanisms could easily be proposed. We presumed that the amidine was formed by two pathways, methanolysis of the acetate (returning the hydroxyamidine, pathway c, which would then reduce) along with a competitive reduction of the acetylated intermediate (pathway d); thus, the stability and activity of the *O*-acylated amidine of **12** were critical. In order to optimize this reaction, we needed to limit self-condensation of the *O*-acylated amidine (pathway b), ensure stability of the *O*-acylated species (i.e., limit methanolysis, pathway c), and enhance the productive cyclization (pathway a) over competitive reduction (pathway d). Given the requirement for reducing conditions, we hypothesized that the desired transformation occurs through a radical process mediated by a low-valent form of nickel; single-electron transfer from a nickel species into the acetate carbonyl would yield a radical anion. N−O bond cleavage with addition of the single electron into the pyrrole would form the desired C−N bond with loss of acetate anion. The resulting radical would then aromatize to yield the observed product (Scheme 6).

To optimize the transformation, we systematically varied parameters which could contribute to the rate of each side reaction noted above. To reduce the rate of direct reduction (pathway d), the hydrogen pressure was reduced from 80 to 3 psig (Table 1, entry 1), which increased the ratio to 8:1 in favor of the ring-closed product. The propensity for self-cyclization (pathway b) was reduced by using a more sterically demanding acylating agent, pivalic anhydride. This also resulted in a small improvement in the product:amidine ratio, potentially through limiting the amount of *O*-acetate methanolysis, pathway c (Table 1, entry 3). Substituting MeOH for toluene removed the possibility of methanolysis all together, further improving the observed selectivity to 13:1 (cyclization/reduction **14**:**13**). Finally, we focused on the source of low-valent nickel, both to continue optimization and in an attempt to remove Raney-Ni from the reaction. Several alternate nickel complexes were surveyed [such as $Ni(acac)_2(H_2O)_2$] with nickel oxide supported on silica (PRICAT)[29] being found to be highly active in the desired transformation. This new system resulted in a further improvement in selectivity to ~16:1 ratio (Table 1, entry 5). Interestingly, unsupported Ni sources (such as $Ni(acac)_2(H_2O)_2$) proved unreactive even under the reductive conditions ($H_{2(g)}$). The pyridine **14** was easily isolated from these reactions in good yield (ca. 64−77%) and excellent purity (>99:1 **14**:**13**) through azeotropic removal of acetic acid and direct precipitation from toluene. It is worth noting that since this work was completed some examples of this style of cyclization have been reported, though they appear to operate through thermal dehydration under harsh reaction conditions (ca. >200 °C).[30] An interesting copper-mediated amino-bromination of indoles, leveraging N−O cleavage of oxime esters, was also recently reported.[31]

We next focused our attention on attaching the final pyrazole heterocycle. The prior synthesis leveraged a condensation-based strategy, which required several steps and the use of Boc-protected methyl hydrazine, to obtain regiochemical control (with respect to the *N*-methyl substituent). We envisioned a more convergent approach utilizing a C−N coupling, which would allow us to couple a regiochemically pure 3-halopyrazole and obviate any concerns of isomer formation.

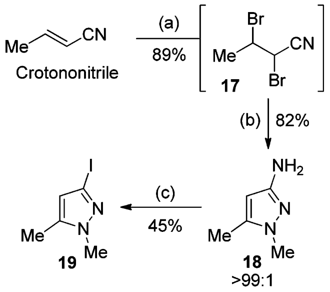
Scheme 7. Formation of Pyrazole 16[a]



[a]Conditions: (a) EDAC, DMAP, $BocNMeNH_2$, DCM (10 mL/g); (b) HCl, IPA (12.5 mL/g); (c) either MsCl, TsCl, Tf_2O or $(PhO)_2POCl$.

Unfortunately, our ability to develop this C−N coupling was limited by the synthesis of the pyrazole component. While the pyrazolone **16** was easy to prepare in good yield and selectivity from butynoic acid, the subsequent dehydrative halogenation proved difficult to accomplish (Scheme 7). For example, classic conditions ($POCl_3$ or $POBr_3$ either neat or in toluene, with or without various additives) failed to yield the desired chloride (or bromide).[32] Subsequent NMR studies indicated that while activation of the amide carbonyl was occurring, the S_NAr with chloride was not, even under the most forcing conditions (neat $POCl_3$ at 120 °C). However, since pyrazolone **16** was easily prepared, we examined its reactivity to electrophilic reagents to form potential coupling partners; thus, the pyrazole *O*-mesylate, *O*-triflate, *O*-phosphate, and *O*-tosylate were prepared. However, palladium-mediated couplings of these compounds proved difficult to develop, with little to no product being observed under most conditions. Thus, we turned to a Sandmeyer halogenation to prepare the iodopyrazole **19**,[33] hoping that alternate metals (such as copper) would effectively mediate the desired coupling. The synthesis of aminopyrazole **18** was known, starting from crotononitrile (Scheme 8).[34] We found that while the initial addition of bromine to crotononitrile was extremely slow, catalytic amounts of HBr could be employed to improve the reaction rate; thus HBr was added to the bromination reaction providing good yields of dibromide **17**. Significant optimization was then required to obtain high regioselectivity in the hydrazine addition/cyclization. Highly basic reaction conditions were necessary to obtain the desired regioisomer with good selectivity (>95:5); under acidic conditions the opposite regiochemical outcome was obtained. The Sandmeyer reaction, converting aminopyrazole **18** to iodopyrazole **19**, occurred smoothly albeit in modest yield.[35]

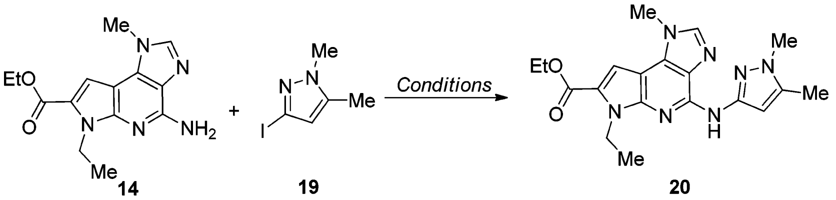
Scheme 8. Formation of Pyrazole 19[a]



[a]Conditions: (a) Br_2 (1.0 equiv), HBr (0.5 mol %), DCM (15 mL/g); (b) $MeNHNH_2{\cdot}H_2SO_4$ (1.0 equiv), NaOH (3.0 equiv), H_2O (5 mL/g); (c) *i*-amylNO (1.5 equiv), CH_2I_2 (1.75 equiv), *i*-PrOH (5 mL/g).

With iodopyrazole **19** in hand, we focused on developing a copper-mediated Ullmann−Goldberg−Buchwald coupling (Table 2).[36] An initial screen of ligand types focused on the use of diamine,[37] diketone,[38] and phenanthroline ligands.[39] It

Table 2. Optimization of the Ullmann−Goldberg−Buchwald Coupling



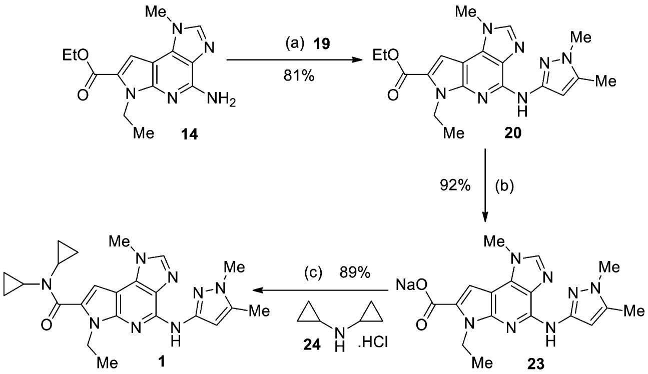
entry	scale	base	base (equiv)	DMEDA (equiv)	alcohol (equiv)	conv[a] (%)
1	mg	Cs_2CO_3	3.0	1.5		64
2	mg	Ag_2CO_3	3.0	1.5		31.1
3	mg	Ag_3PO_4	3.0	1.5		5.8
4	mg	K_3PO_4	2.5	1.5		60
5	mg	K_3PO_4	5.0	1.5		85
6	mg	K_3PO_4	5.0	3.0		84.3
7	g	K_3PO_4	3.0	1.2[c]		58[b]
8	g	K_3PO_4	3.0	1.5	*i*-BuOH (0.1)	72
9	g	K_3PO_4	3.0	1.5	*t*-BuOH (1.0)	71
10	g	KO*t*-Bu	3.0	1.5		79
11	**g**	**NaO*t*-Bu**	**3.0**	**1.5**		**97.6**
12	g	NaO*t*-amyl	3.0	1.5		88.9

[a] Conversion after 20 h. [b] Additional 0.6 equiv of CuI/DMEDA and 20 h resulted in an improvement to 75% conversion, though the reaction was much slower than the screening scale, with significantly more deiodination observed. [c] Further optimization on the screening scale (mg) suggested 1.2 equiv of DMEDA was sufficient.

was quickly found that diamine ligands offered unique reactivity in this transformation, with dimethylethylenediamine (DMEDA) appearing optimal. Additionally, it was determined that stoichiometric amounts of copper were needed to drive the reaction to completion, with CuI being the best metal source. We felt that the need for the high Cu loadings may have been due to competitive coordination of the product pyridine−pyrazole system, competing with the active ligand. Indeed, the coupled product **20**, which precipitated from the reaction mixture, contained an almost 1:1 mol ratio of copper.

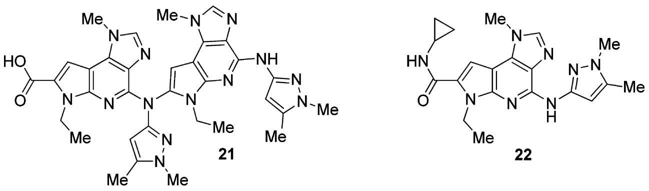
With DMEDA and CuI selected as our best conditions, we focused on optimizing the other parameters of the reaction, specifically the base and ligand loadings (Table 2). We surveyed a wide variety of inorganic bases, varying both the cationic and anionic components, and found that both carbonate and phosphate bases showed promise, with Cs_2CO_3 providing a good level of reactivity (Table 2, entries 1 and 4). Interestingly, halide-extracting counterions such as Ag (entries 2 and 3) resulted in diminished yields. Increasing the equivalents of base gave higher conversion (entry 5) while increasing the ratio of diamine to Cu had only a minimal effect (entry 6). After additional experimentation, we initially settled on conditions of 1.2 equiv DMEDA with 3.0 equiv of K_3PO_4, which reliably gave full conversion on screening (mg) scale. However, in performing these conditions on laboratory (gram) scale, great variability was observed, with very low conversion often being observed (for example, entry 7). After exploring a variety of parameters, we traced this variability to contamination of iodopyrazole **19**. Isoamyl alcohol, leftover from the Sandmeyer reaction (Scheme 8), was found to be critical in achieving good rates and reactivity in the Ullmann process. We proposed that the alcohol was acting as a proton-shuttle, negating the low solubility of K_3PO_4 in toluene. Indeed, the addition of alcohol (isoamyl or *tert*-butyl, entries 8 and 9) restored the reactivity seen during screening. With this data, we refocused our efforts on more soluble organic bases, quickly finding that sodium *tert*-butoxide provided excellent conversion and reaction rates, being slightly more effective than the corresponding *tert*-amylate (entries 11 and 12). With these optimized conditions in hand, the coupling of the aniline **14** with iodopyrazole **19** proceeded smoothly; the Cu-containing product precipitated from the reaction mixture and was isolated by filtration. Treatment of this crude product with ammonium hydroxide removed the copper and enabled the isolation of the ester in good yield and purity (ca. 80%, Scheme 9).

Scheme 9. End game to BMS-911543[a]



[a] (a) CuI (1.5 equiv), **19** (1.3 equiv), NaO*t*-Bu (3.0 equiv), DMEDA (1.5 equiv), toluene, 100 °C, 20 h; (b) NaOH (1.75 equiv), EtOH, H_2O, 70 °C, 4 h; (c) DMC (1.15 equiv), **24** (1.2 equiv), DIPEA (3.0 equiv), CH_2Cl_2, 25 °C, 2 h.

With ester **20** in hand, completion of the synthesis appeared trivial: ester saponification followed by amide bond formation. In actuality, both steps proved challenging. The saponification of ester **20** in EtOH was extremely sensitive to trace copper and oxygen with rapid formation of an impurity, which could occur in near quantitative levels if neither parameter was controlled (Figure 4). Given the challenges observed with the pyrazole coupling (vide supra), it was surprising when this impurity was



21 22

Figure 4. Main impurities formed in the last two steps.

identified as the product of a decarboxylative coupling, forming heterocycle **21** (Figure 4); presumably **21** is formed through copper mediated C2-indole decarboxylation and C−N coupling of the resulting C2-cuprate. To control this impurity, the Cu levels in ester **20** needed to be controlled below 50 ppm and oxygen rigorously excluded from the system. With control over both of these parameters, smooth saponification was observed, giving the Na salt **23** in high yield (Scheme 9).

The amide bond formation also proved complex, due in no small part to the lack of availability of high quality dicyclopropylamine (DCPA, **24**); indeed, during the course of our studies we developed three procedures to prepare this challenging small molecule.[40] Surprisingly, standard methods of amide bond formation (EDAc/HOBt,[41] HATU,[42] CDI,[43] etc.) failed to cleanly convert acid **23** to amide **1**. Significant levels of the monocyclopropyl compound **22** were often observed (Figure 4). This was attributed to the inherent instability of DCPA, which is known to convert to cyclopropylamine under basic conditions.[39a] After screening a variety of more unusual conditions, we found that DMC (2-chloro-1,3-dimethylimidazolidinium chloride)[44] was able to cleanly and quantitatively form the acid chloride of carboxylate **23**. With this reagent, the acid chloride formed directly from the Na salt (therefore under basic to neutral conditions) which was critical to avoiding precipitation of an insoluble form of carboxylate **23**. With the higher reactivity of the acid chloride, smooth coupling with DCPA (in the presence of DIPEA) was observed, completing the synthesis of BMS-911543 (**1**) in only eight steps and high overall yield.

■ CONCLUSION

In summary, we have developed a short and highly convergent route to the complex pyrrolopyridine, BMS-911543 (**1**), that proceeds in eight steps from the known bromopyrrole **4** in an overall yield of 27−32%. Invention of a Ni-mediated C−H functionalization enabled the key cyclization, providing the desired highly substituted pyridine in excellent yield and selectivity. Optimization of this reaction leveraged rational, stepwise improvements in conditions, based on a core mechanistic hypothesis. Additionally, a new and broadly impactful palladium reduction/activation pathway was elucidated, along with its impact to catalyst identity, reactivity, and stability in the Miyaura borylation of pyrrole **4**. New synthetic routes to three of the four key building blocks were also developed, significantly improving upon the known syntheses of these important fragments.

■ EXPERIMENTAL SECTION

General Methods. All procedures were conducted under an inert (N_2) atmosphere in standard laboratory equipment using standard techniques (unless otherwise noted). Commercial solvents (reagent grade), reagents, and catalysts were used directly as supplied from commercial sources and without further purification. Reactions were monitored by standard analytical techniques and the products characterized by ^{1}H NMR (at either 500 or 400 MHz as noted) and ^{13}C NMR (100 MHz) in the appropriate deuterated solvent (listed). Chemical shifts are quoted in parts per million. All compounds were isolated by crystallization, unless otherwise noted, with reported yields corrected for both starting material and product potencies (as determined either by quantitative NMR or HPLC analysis). NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant, integration. High resolution mass-spectra were obtained using electro-spray ionization (ESI+) with an LTQ-Oribtrap mass analyzer.

1-(4-Bromo-1*H*-pyrrol-2-yl)-2,2,2-trichloroethanone. To a cooled solution (0 °C) of trichloroacetylpyrrole (200 g, 0.94 mol, 1.00 equiv) in CH_3CN (1.0 L, 5.0 mL/g) was added NBS (168 g, 0.94 mol, 1.00 equiv) slowly portionwise. The reaction was stirred at 23 °C for 1.5 h. The reaction mixture was quenched by the slow addition of water (3.0 L, 15.0 mL/g) and cooled to 0 °C, and the solids were allowed to desaturate for an additional 1 h. The solids were filtered, washed with water (1.0 L, 5.0 mL/g), and dried in vacuo to yield bromopyrrole (264 g, 96% yield) as tan plates (mp 140−143 °C): ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.84 (br s, 1H), 7.53 (br s, 1H), 7.31 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.6, 129.0, 122.0, 121.5, 97.5, 94.5; HRMS-ESI (m/z) calcd for $C_6H_2BrCl_3NO$ $[M - H]^-$ 287.8380 and 289.8365, found 287.8374 and 289.8346

Ethyl 4-Bromo-1*H*-pyrrole-2-carboxylate, 4. To a cooled solution (0 °C) of 1-(4-bromo-1*H*-pyrrol-2-yl)-2,2,2-trichloroethanone (261.3 g, 896.8 mmol, 1.0 equiv) in EtOH (914.6 mL, 3.5 mL/g) was slowly added a 25 wt % solution of NaOEt in EtOH (0.1 equiv) over 45 min while an internal temperature below 5 °C was maintained. The reaction was stirred at 25−30 °C for an additional 1 h before being concentrated to approximately 340 or 1.3 mL/g with respect to starting material. To a separate flask containing water at 0 °C was slowly added the concentrated reaction mixture over 1 h to precipitate the product. The slurry was held at 0 °C for an additional 1 h to complete the desaturation, and then the solids were filtered, washed with water (1.3 L, 5.0 mL/g), and dried in vacuo to yield ethyl ester **4** (181.9 g, 92% yield) as a semicrystalline to amorphous solid (mp 60−63 °C):[15] ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.25 (br s, 1H), 7.15 (s, 1H), 6.79 (s, 1H), 4.23 (q, J = 7.1 Hz, 2H), 1.26 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.5, 123.7, 122.8, 115.9, 95.8, 59.9, 14.2; HRMS-ESI (m/z) calcd for $C_7H_7BrNO_2$ $[M - H]^-$ 215.9660 and 217.9640, found 215.9647 and 217.9621

Ethyl 1-Ethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrrole-2-carboxylate, 6. To a solution of pyrrole **4** (207 g, 0.951 mol, 1.00 equiv) in DMF (2.07 L, 10.0 mL/g) was added K_2CO_3 (325 mesh, 197 g, 1.43 mol, 1.50 equiv) portionwise while maintaining an internal temperature below 25 °C. To this mixture was added dropwise ethyl iodide (178 g, 1.14 mol, 1.20 equiv). The reaction mixture was allowed to stir for 16 h before being quenched by the slow addition of water (2.07 L, 10 mL/g). MTBE (1.24 L, 6.00 mL/g) was added, and the biphasic mixture was stirred for 10 min. The phases were separated, and the aqueous layer was extracted with MTBE (3 × 1.2 L, 6.0 mL/g). The combined organic layers were washed with water (3 × 1.04 L, 5.00 mL/g) and then concentrated under reduced pressure to provide ethylated pyrrole **5** (203.9 g) as a reddish brown oil. The oil was diluted 3× with PhMe (1.7 L, 8.0 mL/g) and concentrated. The residue was redissolved in PhMe (725 mL, 3.5 mL/g) and added activated carbon (10.4 g, 5.0 wt %). The solution was stirred for 30 min, filtered through Celite, and used directly without further purification.

To a flask was charged $Pd(OAc)_2$ (0.912 g, 4.06 mmol, 0.01 equiv), tricyclohexylphosphine tetrafluoroborate (3.74 g, 10.2 mmol, 0.025 equiv), tetramethylammonium acetate (5.41 g, 40.6 mmol, 0.10 equiv), and dry, degassed PhMe (50 mL, 0.5 mL/g). The solution was stirred at 23 °C for 2 h and filtered under nitrogen. A separate flask charged with tetramethylammonium acetate (157 g, 1.18 mol, 2.9 equiv) and water (22.0 mL, 1.22 mol, 3.00 equiv) and degassed PhMe (0.750 L, 7.5 mL/g) was warmed to 80 °C for 30 min. The solution was cooled to 23 °C, and the solution of pyrrole **5** (100 g, 0.406 mol, 1.0 equiv, limiting reagent) in PhMe (20−25 wt %) from the previous step and bis(pinacolato)borane (124 g, 0.487 mol, 1.2 equiv) were added followed by the solution of catalyst. The reaction mixture was warmed to 80 °C and stirred for 4 h. The reaction was cooled to 23 °C, quenched by the addition of aqueous sodium thiosulfate (5 wt %, 1.00 L, 10 mL/g), and stirred for 3 h. The heterogeneous black solution was filtered through a pad of Celite and washed with PhMe (0.3 L, 3.0 mL/g). The layers were separated, and the organics were washed with aqueous sodium thiosulfate (5 wt %, 1.00 L, 10 mL/g). The heterogeneous solution was stirred for 1 h at 25 °C and filtered again through a pad of Celite. The layers were separated and the organic layer was concentrated under reduced pressure. The residue was dissolved 3× in EtOH (0.7 L, 7.0 mL/g) and concentrated in vacuo. The residue was redissolved in EtOH (0.7 L, 7.0 mL/g) and cooled to 0 °C, and water (1.4 L, 14 mL/g) was slowly added dropwise over 2 h. The slurry was stirred at 0 °C for an additional 2 h and filtered. The solids were washed with water (0.4 L, 4.0 mL/g) and dried in vacuo to afford boronate **6** (112 g, 95.3 wt %, 90% yield) as light tan plates (mp 44−49 °C): ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.42 (d, J = 1.8 Hz, 1H), 7.02 (d, J = 1.8 Hz, 1H), 4.29 (q, J = 7.1 Hz, 2H), 4.19 (q, J = 7.2 Hz, 2H), 1.26 (t, J = 7.2 Hz, 3H), 1.27 (t, J = 7.1 Hz, 3H), 1.23 (s, 12H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.0, 136.4, 123.8, 122.3, 117.6, 82.8, 59.4, 43.4, 24.6, 16.8, 14.1; HRMS-ESI (m/z) calcd for $C_{15}H_{25}BNO_4$ [M + H]$^+$ 294.1871, found 294.1863

1-Methyl-4-cyanoimidazole, 11.[45] To a flask were added methylammonium chloride (86.93 g, 2.25 equiv), AcOH (396 mL, 3 mL/g), and *N*-methylaniline (6.12 mL, 0.10 equiv). The mixture was heated to an internal temperature of 105 °C. Separately, the azadiene **10** (prepared using the reported procedure, 123.05 g)[22] was dissolved in AcOH (246 mL, 2 mL/g, minor exotherm) and was added over 30 min maintaining an internal temperature of 99−105 °C. The mixture was held at 100−105 °C until the azadiene was consumed. The reaction mixture was cooled to 50 °C, diluted 3× with toluene (615 mL), and concentrated to approximately 200 mL. The mixture was diluted with water (615 mL) and brought to pH 6.5 by the addition of 50 wt % NaOH, keeping the internal temperature below 30 °C. Activated carbon (Darco G-60, 40.6 g, 33 wt % with respect to azadiene starting material) was added, and the mixture stirred for 30 min, filtered, and rinsed with water (40 mL) and then dichloromethane (615 mL, 5 mL/g). The layers were separated, and the aqueous layer was extracted with dichloromethane (2 × 615 mL, 2 × 5 mL/g). The combined organic layers were concentrated to approximately 2 mL/g, and then petroleum ether (bp 30−60 °C, 1.23 L, 10 mL/g) was slowly added over 1 h to precipitate the desired imidazole **11** as light orange needles (73−75 °C) which were used without further purification. Typical isolated yield ∼50%. All spectroscopic data matched prior literature.[43]

5-Bromo-1-methyl-1*H*-imidazole-4-carbonitrile, 3. To a solution of cyanoimidazole **11** (200 g, 1.87 mol, 1.0 equiv) in DMF (1.0 L, 5.0 mL/g) at 30−35 °C was added NBS (365 g, 2.05 mol, 1.1 equiv) slowly portionwise. The reaction mixture was stirred at 30−35 °C for 5 h. The reaction mixture was cooled to 10 °C, quenched by the slow addition of water (4.0 L, 20 mL/g), and stirred for an additional 5 h. The solids were filtered, washed with water (0.8 L, 4.0 mL/g) and dried in vacuo to yield bromocyanoimidazole **3** (250.2 g, 70% yield) as a white plates (mp 140−147 °C): ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.05 (s, 1H), 3.66 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 141.4, 115.0, 114.3, 113.4, 33.4; HRMS-ESI (m/z) calcd for $C_5H_5N_3Br$ [M + H]$^+$ 185.9664, found 185.9660

Ethyl 4-(4-Cyano-1-methyl-1*H*-imidazol-5-yl)-1-ethyl-1*H*-pyrrole-2-carboxylate, 7. To a flask charged with Pd(OAc)$_2$ (0.574 g, 2.56 mmol, 0.01 equiv) and PPh$_3$ (1.34 g, 5.12 mmol, 0.025 equiv) was added DMAc (12.8 mL, 0.17 mL/g). The solution was degassed and stirred at ambient temperature for 10 min. To a separate flask charged with boronate **6** (75.0 g, 0.256 mol, 1.00 equiv) as a solution in DMAc (375 mL, 5 mL/g) were added bromocyanoimidazole **3** (42.8 g, 0.230 mol, 0.9 equiv) and potassium carbonate (53.0 g, 0.384 mmol, 1.5 equiv) followed by DMAc (750 mL, 10 mL/g) and water (375 mL, 5.0 mL/g). The slurry was degassed, and the palladium catalyst solution was added, held for 10 min at ambient temperature, and then warmed to 80 °C for an additional 2 h. The reaction mixture was quenched by the slow addition of water (2.18 L, 29 mL/g) while maintaining an internal temperature below 35 °C and stirred for an additional 2 h. The solids were filtered, washed with water (975 mL, 13 mL/g), and dried in vacuo to provide imidazolpyrrole **7** (58.6 g, 84% yield) as white plates (mp 208−216 °C): ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.85 (s, 1H), 7.68 (d, J = 1.8 Hz, 1H), 7.21 (d, J = 1.8 Hz, 1H), 4.39 (q, J = 7.1 Hz, 2H), 4.27 (q, J = 6.9 Hz, 2H), 3.72 (s, 3H), 1.35 (t, J = 7.1 Hz, 3H), 1.29 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.7, 140.4, 136.2, 127.9, 122.2, 116.5, 116.1, 108.9, 108.2, 59.9, 43.9, 33.0, 16.8, 14.2; HRMS-ESI (m/z) calcd for $C_{14}H_{17}N_4O_2$ [M + H]$^+$ 273.1346, found 273.1342.

Ethyl 1-Ethyl-4-(4-(*N*-hydroxycarbamimidoyl)-1-methyl-1*H*-imidazol-5-yl)-1*H*-pyrrole-2-carboxylate, 12. To a solution of pyrrole **7** (58.6 g, 0.215 mol, 1.00 equiv) in EtOH (762 mL, 13.0 mL/g) at 40 °C was added NH$_2$OH·HCl (59.8 g, 0.861 mol, 4.00 equiv) followed by EtOH (117 mL, 2.0 mL/g). The reaction mixture was stirred at 40 °C for 10 min followed by the slow addition of Et$_3$N (123 mL, 0.882 mol, 4.1 equiv) over 1 h while maintaining an internal temperature below 40 °C and then was stirred at 40 °C for an additional 16 h. The reaction mixture was cooled to ambient temperature and stirred for an additional 1 h. The solids were filtered, washed with water (234 mL, 4.0 mL/g), and dried in vacuo to provide hydroxyamidine **12** (58.2 g, 0.191 mol, 89% yield) as off-white plates (mp 226−229 °C): ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.15 (s, 1H), 7.67 (s, 1H), 7.50 (d, J = 1.8 Hz, 1H), 7.04 (d, J = 1.8 Hz, 1H), 5.33 (s, 2H), 4.32 (q, J = 7.1 Hz, 2H), 4.23 (q, J = 7.1 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H), 1.28 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.1, 148.0, 137.2, 130.9, 129.8, 123.8, 120.5, 118.8, 110.5, 59.5, 43.5, 32.2, 16.8, 14.3; HRMS-ESI (m/z) calcd for $C_{14}H_{20}N_5O_3$ [M + H]$^+$ 306.1561, found 306.1551.

Ethyl 4-Amino-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-*d*]-pyrrolo[2,3-*b*]pyridine-7-carboxylate Acetic Acid Salt 14. To a pressure vessel charged with hydroxyamidine **12** (50.0 g, 0.164 mol, 1.0 equiv) in AcOH (0.650 L, 13.0 mL/g) and PhMe (0.500 L, 10.0 mL/g) was added Piv$_2$O (30.5 g, 0.164 mol, 1.0 equiv) followed by PhMe (0.150 L, 3.0 mL/g). The pressure vessel was degassed with N$_2$, and the reaction mixture was stirred at 20−30 °C for 0.5 h. PRICAT (9.00 g, 18−20 wt %) as a slurry in AcOH (0.100 L, 2.0 mL/g) and PhMe (0.1 L, 2.0 mL/g) was added and the pressure vessel degassed with nitrogen and then pressurized with hydrogen (3 psig). The reaction mixture was stirred at 20−30 °C for 20 h. Upon completion, the hydrogen was purged from the pressure vessel with nitrogen. The reaction mixture was filtered through a plug of Celite, and the cake was washed with PhMe (2 × 0150 L, 2 × 3.0 mL/g). The reaction mixture was concentrated, dissolved 3× in PhMe (0.250 L, 5.0 mL/g), and concentrated to remove excess AcOH. To the residue was added PhMe (0.200 L, 4.0 mL/g), and the mixture was warmed to 50 °C for 2−5 h to effect crystallization. The mixture was cooled to 0 °C and stirred for an additional 2−5 h. The solids were filtered, washed with PhMe (2 × 0.100 L, 2 × 2.0 mL/g), and dried in vacuo to provide the AcOH salt of aminopyridine **14** (36.4 g, 64% yield) as white rods: mp 208−210 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.00 (br s, 1H), 7.96 (br s, 1H), 7.38 (s, 1H), 6.57 (br s, 2H), 4.59 (q, J = 6.8 Hz, 2H), 4.28 (q, J = 7.1 Hz, 2H), 3.99 (s, 3H), 1.91 (br s, 3H), 1.32 (t, J = 7.1 Hz, 3H), 1.25 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.8, 151.4, 145.5, 140.2, 133.2, 119.3, 106.1, 98.0, 59.5, 37.7, 32.2, 21.0, 15.8, 14.3; HRMS-ESI (m/z) calcd for $C_{14}H_{18}N_5O_2$ [M + H]$^+$ 288.1455, found 288.1448

1,5-Dimethyl-1*H*-pyrazol-3-ol Hydrochloride, 16. To a solution of 2-butynoic acid (10.0 g, 118 mmol, 1.00 equiv) and DMAP (1.45 g, 11.9 mmol, 0.1 equiv) in dichloromethane (100 mL, 10 mL/g) was charged *N*-Boc methyl hydrazine (18.5 g, 126 mmol, 1.06 equiv) over 1 min. The reaction mixture was cooled to 0 °C, and EDAC (25.1 g, 131 mmol, 1.10 equiv) was charged in five equal portions over 50 min. The resulting pale yellow solution was then allowed to warm to ambient temperature, stirred an additional 1.5 h, diluted with 1 N aqueous HCl (100 mL, 10 mL/g), and agitated for 5 min. The organic layer was separated and washed with 1 N aqueous HCl (100 mL, 10 mL/g) and then water (100 mL, 10 mL/g). The solution was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was then charged with 2-propanol (125 mL, 12.5 mL/g) followed by concentrated HCl (25.9 g, 261 mmol, 2.20 equiv) over 1 min. The reaction mixture was then warmed to 63 °C, at which point gas evolution was observed. After 30 h, the reaction mixture was cooled to ambient temperature and concentrated in vacuo. The resulting residue was then charged with CH_3CN (100 mL, 10 mL/g) and concentrated in vacuo. This process with repeated 3× more. The final residue was then charged with CH_3CN (40 mL, 4 mL/g) and warmed to 75 °C. The resulting slurry was then cooled to ambient temperature over 1 h and allowed to continue to desaturate overnight. The solids were filtered, washed with CH_3CN (2 × 40 mL, 2 × 4 mL/g), and then dried under vacuum at ambient temperature to afford salt **16** (13.7 g, 78% yield) as a white crystalline solid: mp 178−182 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 5.72 (s, 1 H); 3.65 (s, 3 H); 2.24 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 146.0, 90.6, 34.1, 10.8; HRMS-ESI (m/z) calcd for $C_5H_9N_2O$ $[M + H]^+$ 113.0709, found 113.0712.

1,5-Dimethyl-1*H*-pyrazol-3-yl Methanesulfonate. To a mixture of 1,5-dimethyl-1*H*-pyrazol-3-ol hydrochloride **16** (0.400 g, 2.69 mmol, limiting reagent), potassium carbonate (0.930 g, 6.73 mmol, 2.5 equiv), and tetraethylammonium bromide (0.170 g, 0.809 mmol, 0.3 equiv) in CH_3CN (8 mL, 20 mL/g) at ambient temperature was charged methanesulfonyl chloride (0.460 g, 4.02 mmol, 1.5 equiv). The resulting white slurry was warmed to 45 °C and, after 2.5 h, was cooled to ambient temperature and concentrated in vacuo. Purification by SiO_2 [40 g ISCO column, flow rate 30 mL/min, gradient 10% to 65% EtOAc in hex; R_f = 0.31 (1:1 hex:EtOAc)] afforded 0.410 g (80% yield) as a white crystalline solid (mp 88−89 °C) after drying in a vacuum oven: ^1H NMR (400 MHz, $CDCl_3$) δ 5.85 (s, 1 H); 3.68 (s, 3 H); 3.25 (s, 3 H), 2.23 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 140.7, 96.3, 37.9, 36.1, 11.3; HRMS-ESI (m/z) calcd for $C_6H_{11}N_2O_3S$ $[M + H]^+$ 191.0485, found 191.0483.

1,5-Dimethyl-1*H*-pyrazol-3-yl 4-Methylbenzenesulfonate. To a mixture of 1,5-dimethyl-1*H*-pyrazol-3-ol hydrochloride **16** (0.400 g, 2.69 mmol, limiting reagent), potassium carbonate (0.930 g, 6.73 mmol, 2.5 equiv), and tetraethylammonium bromide (0.170 g, 0.809 mmol, 0.3 equiv) in CH_3CN (8 mL, 20 mL/g) at ambient temperature was charged *p*-toluenesulfonyl chloride (0.770 g, 4.04 mmol, 1.5 equiv). The resulting white slurry was warmed to 45 °C and after 2.5 h was cooled to ambient temperature and concentrated in vacuo. Purification by SiO_2 [40 g ISCO column, flow rate 30 mL/min, gradient 10% to 50% EtOAc in hex; R_f = 0.24 (2:1 hex:EtOAc)] afforded 0.612 g (85% yield) as a white crystalline solid (mp 93−94 °C) after drying in a vacuum oven: ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8 Hz, 2 H); 7.31 (d, J = 8 Hz, 2 H); 5.70 (s, 1 H), 3.59 (s, 3 H), 2.43 (s, 3 H), 2.18 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.8, 145.2, 140.2, 132.5, 129.6, 128.4, 95.9, 36.0, 21.6, 11.3; HRMS-ESI (m/z) calcd for $C_{12}H_{15}N_2O_3S$ $[M + H]^+$ 267.0797, found 267.0795.

1,5-Dimethyl-1*H*-pyrazol-3-yl Trifluoromethanesulfonate. To a mixture of 1,5-dimethyl-1*H*-pyrazol-3-ol hydrochloride **16** (5.00 g, 33.65 mmol, limiting reagent) and DCM (100 mL, 20 mL/g) was charged DIPEA (10.5 g, 81.24 mmol, 2.4 equiv). The resulting clear, colorless solution was cooled to −7 °C and treated with trifluoromethanesulfonic anhydride (10.7 g, 37.92 mmol, 1.13 equiv) dropwise over ∼30 min, maintaining the internal temperature below 0 °C. The resulting yellow solution was then aged between −5 and 0 °C for 1 h. The reaction mixture was then charged with 50% saturated aqueous $NaHCO_3$ (100 mL, 20 vol) over ∼5 min, maintaining the internal temperature <10 °C. The biphasic mixture was then warmed to ambient temperature, and the resulting lower DCM layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by SiO_2 (160 g ISCO column, flow rate 40 mL/min, gradient 0% to 35% EtOAc in hex) afforded 5.17 g (63% yield) of the triflate as a pale yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 5.90 (s, 1 H), 3.70 (s, 3 H), 2.23 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.8, 141.2, 118.6 (q, J = 1020 Hz), 95.5, 36.2, 11.3; HRMS-ESI (m/z) calcd for $C_6H_8F_3N_2O_3S$ $[M + H]^+$ 245.0208, found 245.0200.

1,5-Dimethyl-1*H*-pyrazol-3-yl Diphenyl Phosphate. To a mixture of 1,5-dimethyl-1*H*-pyrazol-3-ol hydrochloride **16** (0.400 g, 2.69 mmol, limiting reagent), potassium carbonate (0.930 g, 6.73 mmol, 2.5 equiv), and tetraethylammonium bromide (0.170 g, 0.809 mmol, 0.3 equiv) in CH_3CN (8 mL, 20 mL/g) at ambient temperature was charged diphenyl chlorophosphate (0.800 g, 2.98 mmol, 1.1 equiv). The resulting slurry was warmed to 45 °C and, after 4 h, was filtered, rinsed with DCM (3 × 8 mL), and concentrated in vacuo. Purification by SiO_2 [12 g ISCO column, flow rate 15 mL/min, gradient 0% to 66% EtOAc in hex; R_f = 0.29 (1:1 hex:EtOAc)] afforded 728 g (79% yield) as an oil which solidified upon standing: ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (m, 4 H), 7.28 (m, 4 H), 7.19 (m, 2 H), 5.81 (s, 1 H), 3.65 (s, 3 H), 2.19 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5, 150.4, 140.2, 129. 7, 125. 5, 120.1, 93.7, 35.8, 11.3; HRMS-ESI (m/z) calcd for $C_{17}H_{18}N_2O_4P$ $[M + H]^+$ 345.0998, found 345.0987.

2,3-Dibromobutanenitrile 17. To a solution of crotononitrile (500 g, 7.45 mol, 1.0 equiv) in dichloromethane (6.5 L, 13 mL/g) at 5−7 °C was added bromine (1.19 kg, 7.45 mol, 1.0 equiv) as a solution in dichloromethane (1.0 L, 2.0 mL/g based on nitrile) via an addition funnel over a period of 60 min while the internal temperature was maintained at 5−10 °C. HBr in acetic acid (33%, 9.0 g, 0.0373 mol, 0.005 equiv) was then added at 10−12 °C, and the reaction was stirred for 30 min at 10−12 °C, raised to 18−20 °C, and held for 2 to 4 h. (Note: an exotherm was observed that increased the internal temperature to 28 °C). The reaction mixture was then concentrated in vacuo, and the crude material was used directly without purification (1.510 kg, 89% yield.)

1,5-Dimethyl-1*H*-pyrazol-3-amine, 18.[46] Dibromide **17** (250 g, 1.10 mol, 1.00 equiv) was added dropwise to a solution of NaOH (132.2 g, 3.30 mol, 3.00 equiv) and methyl hydrazine hydrogen sulfate (50.7 g, 1.10 mol, 1.0 equiv) in water (1.25 L, 5 mL/g). Once the addition was complete, the aqueous mixture was extracted with toluene (250 mL, 1.0 mL/g) to remove organic impurities (the product remained in the aqueous phase), and then the aqueous layer was washed with DCM (3 × 2−2.5 mL/g) to extract the product. The dichloromethane phases were combined, dried over Na_2SO_4, and concentrated in vacuo to give pyrazole **18** (196 g, 82%, 69:1 *N*-Me isomer ratio) as a light yellow solid. The spectral data were consistent with previous reports.[44]

Ethyl 4-((1,5-Dimethyl-1*H*-pyrazol-3-yl)amino)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridine-7-carboxylate, 20. *Preparation of 3-Iodo-1,5-dimethyl-1H-pyrazole, 19.* To a solution of pyrazole **18** (41.6 g, 374.28 mmol, 1.00 equiv) in isopropyl alcohol (0.21 L, 5 mL/g) were added isobutyl nitrite (74.19 mL, 561.42 mmol, 1.50 equiv) and diiodomethane (52.79 mL, 654.99 mmol, 1.75 equiv) at ambient temperature. After completion of the addition, the mixture was slowly heated to 55 °C over 1 h and stirred for 5−6 h. The mixture was then cooled to ambient temperature, a 6 N aqueous solution of HCl (420 mL, 10 mL/g) was added, and the resulting solution was washed with heptane (420 mL, 10 mL/g). The aqueous phase was then neutralized with a 10 N aqueous solution of NaOH (260 mL, 6.25 mL/g) to pH 8−10, and the product was extracted with toluene (420 mL, 10.0 mL/g). The resulting toluene layer was washed with a 0.5 N aqueous solution of HCl (210 mL, 5.0 mL/g) and a 5 wt % aqueous solution of K_3PO_4 (210 mL, 5.0 mL/g). The solution was then concentrated in vacuo to afford iodopyrazole **19** (43.8 g, 84.1 wt %; 45% corrected yield) as a brown solid, which was used directly without further purification.

To a flask under a nitrogen blanket was charged amine **14** (62.0 g, 179 mmol, 1.00 equiv), iodopyrazole **19** (75.5 g, 253.2 mmol, 1.40 equiv), copper(I) iodide (51.7 g, 271.3 mmol, 1.50 equiv), sodium *tert*-butoxide (52.6 g, 539.2 mmol, 3.00 equiv), and toluene (1.24 L, 20 mL/g). *sym*-Dimethylethylene diamine (24 g, 271 mmol, 1.50 equiv) was charged, and the batch was heated to 95−100 °C and held for 20 h. The reaction mixture was then cooled to 30 °C and filtered. The cake was rinsed with THF, followed by dichloromethane. The cake was charged back to the flask, and water (620 mL, 10.0 mL/g) and ammonium hydroxide 28 wt % solution (620 mL, 10.0 mL/g) were added. The slurry was stirred for 2 h and then filtered, and the cake was washed with water. The cake was then transferred to a flask containing acetic acid (309 mL, 5.00 mL/g) and dichloromethane

(180 mL, 2.90 mL/g) and stirred to dissolve. The solution was then transferred *slowly* (gas evolution, exothermic) to a flask containing a biphasic solution of dichloromethane (1.86 L, 30.0 mL/g) and 28 wt % aqueous ammonium hydroxide (1.61 L, 26.0 mL/g). The layers were separated, and the organic phase was washed with brine and concentrated in vacuo. The residue was stirred in a solution of THF (868 mL, 14.0 mL/g) and water (434 mL, 7.0 mL/g) at 58 °C for 1−2 h. The solids were filtered, washed with THF/water 1:3, and then dried in vacuo at 55 °C to afford ester **20** (58.2 g, 81% yield) as off-white plates: mp 262−266 °C; ^{1}H NMR (400 MHz, CD$_2$Cl$_2$) δ 8.04 (s, 1 H), 7.66 (s, 1 H), 7.39 (s, 1 H), 6.90 (s, 1 H), 4.80 (q, *J* = 7.1 Hz, 2 H), 4.35 (q, *J* = 7.2 Hz, 2 H), 4.02 (s, 3 H), 3.69 (s, 3 H), 2.32 (s, 3 H), 1.44 (t, *J* = 6.9 Hz, 3 H); 1.41 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 162.0, 147.6, 146.1, 140.2, 139.5, 134.1, 125.6, 122.0, 105.7, 99.5, 96.6, 60.6, 51.0, 39.6, 36.0, 33.2, 16.0, 14.9, 11.9; HRMS-ESI (*m*/*z*) calcd for C$_{19}$H$_{24}$N$_7$O$_2$ [M + H]$^+$ 382.1986, found 382.1977.

Sodium 4-((1,5-Dimethyl-1*H*-pyrazol-3-yl)amino)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridine-7-carboxylate, 23. To a flask under a nitrogen blanket was charged ester **20** (8.0 g, 21.0 mmol, 1.0 equiv) followed by absolute ethanol (132 mL, 16.5 mL/g) and 2 M aqueous sodium hydroxide (18.4 mL, 36.76 mmol, 1.75 equiv). The resulting mixture was then degassed by reducing the pressure to 200 Torr and backfilling with nitrogen. This degassing process was performed a total of five times. The reaction was then warmed to 70 °C and held for an additional 4 h. The resulting slurry was then charged with absolute ethanol (120 mL, 15 mL/g) via addition funnel over 0.5 h, maintaining an internal temperature between 65 and 70 °C. The reaction mixture was then cooled to 55 °C over 0.5 h, held at 55 °C for 1 h, and then cooled to 20 °C over 2 h. After an additional 1.5 h, the slurry was filtered and the solids were washed with a solution of absolute ethanol (43.2 mL, 5.4 mL/g) and water (4.8 mL, 0.6 mL/g), then with THF (64.3 mL, 8 mL/g), and dried in vacuo at 80 °C to afford sodium salt **23** (7.24 g, 92% yield) as white to pale-pink rods (mp 290−300 °C): ^{1}H NMR (400 MHz, D$_2$O) δ 7.28 (s, 1H), 6.71 (s, 1H), 6.17 (s, 1H), 4.18 (m, 2H), 3.46 (s, 3H), 3.42 (s, 3H), 2.01 (s, 3H), 1.09 (t, *J* = 4 Hz, 3H); ^{13}C NMR (100 MHz, D$_2$O) δ 169.2, 146.9, 142.9, 142.2, 140.4, 139.7, 132.8, 128.0, 121.7, 102.3, 97.7, 95.0, 38.2, 34.3, 31.9, 15.2, 10.3; HRMS-ESI (*m*/*z*) calcd for C$_{17}$H$_{19}$N$_7$O$_2$ [M + H]$^+$ 354.1673, found 354.1667.

***N*,*N*-Dicyclopropyl-4-((1,5-dimethyl-1*H*-pyrazol-3-yl)amino)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridine-7-carboxamide, 1.** A solution of 2-chloro-1,3-dimethylimidazolinium chloride (104.9 g, 620.6 mmol, 1.15 equiv) in dichloromethane (1.00 L, 5.0 mL/g) was quickly added to a stirred slurry of sodium salt **23** (200 g, 517.1 mmol, 1.00 equiv) in dichloromethane (5.00 L, 25.0 mL/g) over approximately 2 min under nitrogen. The reaction was held at 20 °C for 1 h, and then dicyclopropylamine hydrochloride (**24**, 87.26 g, 646.4 mmol, 1.2 equiv) and diisopropylethylamine (200.5 g, 1.55 mol, 3.00 equiv) were added followed by a rinse of dichloromethane (1.00 L, 5.00 mL/g). The reaction was held at 20−25 °C for 3 h, washed with water (3 × 2.40 L, 3 × 12.0 mL/g), and concentrated in vacuo to 1.00 L. The solution was brought to 35 °C and then seeded with a slurry of amide **1** (2.0 g, 1 wt %/wt) in tetrahydrofuran (400 mL, 2.0 mL/g). After 30 min, the solvent was exchanged to tetrahydrofuran by constant volume distillation until dichloromethane was <3% v/v. The slurry was then cooled to 0 °C, aged for 1 h, filtered, and washed with cold tetrahydrofuran (400 mL, 2.0 mL/g). The solids were dried in vacuo at 50 °C to obtain amide **1** (198.3 g, 89% yield) as off-white plates (mp 271−274 °C), which contained 0.13 wt % water by Karl Fisher analysis: ^{1}H NMR (600 MHz, DMF-d_7) δ 8.15 (br s, 1H), 8.07 (s, 1H), 7.30 (s, 1H), 6.96 (s, 1H), 4.66 (q, *J* = 7.1 Hz, 2H), 4.11 (s, 3H), 3.72 (s, 3H), 2.35 (s, 3H), 3.01 (m, 2H), 1.43 (t, *J* = 7.1 Hz, 3H), 0.81−0.73 (m, 8H); ^{13}C NMR (125 MHz, DMF-d_7) δ 167.6, 148.5, 145.4, 144.7, 141.7, 139.7, 134.9, 128.0, 125.4, 102.9, 99.5, 96.9, 39.4, 36.0, 33.1, 32.0, 16.5, 11.6, 9.6; HRMS-ESI (*m*/*z*) calcd for C$_{23}$H$_{29}$N$_8$O [M + H]$^+$ 433.2464, found 433.2457.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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