JOC The Journal of Organic Chemistry

Article

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Zinc Acetate-Promoted Buchwald–Hartwig Couplings of Heteroaromatic Amines

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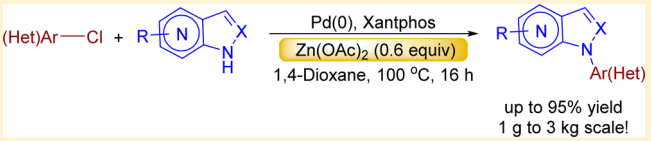
Supporting Information

ABSTRACT: Zinc salts have been shown to promote the Buchwald–Hartwig coupling of azaindoles and azaindazoles with heteroaryl chlorides to provide the corresponding 1-aryl-1*H*-azaindoles and 1-aryl-1*H*-azaindazoles. The substrate scope and mechanistic aspects of this reaction were explored.



INTRODUCTION

The construction of C–N bonds by Pd-catalyzed cross coupling of amines with aryl halides, pseudohalides, and aryl ethers has emerged as a powerful tool for the synthesis of functionalized diaryl amines,[1] an important class of compounds with wide utility in pharmaceuticals, natural products, and organic materials.[2] This area has witnessed tremendous growth over the past two decades ever since the initial reports by Buchwald and Hartwig[3] with the continuous development of a variety of ligands and precatalysts to synthesize novel classes of increasingly complex molecules.

The 1-aryl-1*H*-azaindazole motif and its variants are present in several pharmaceutically active ingredients[4] and herbicides (compounds **1**–**4**, Figure 1).[5] Our interest in this class of compounds stemmed from the need to synthesize large quantities of **8** (Scheme 2), an intermediate in the synthesis of a potential drug candidate under development within Bristol-Myers Squibb. A survey of the literature revealed that compounds of this type were assembled via annulation strategies that formed the indazole ring from the appropriate open-chain precursors (Scheme 1).[6] In an effort to develop a more convergent synthesis, we envisioned that the key intermediate **8** could be synthesized via a Buchwald–Hartwig coupling reaction between 5-cyano-7-azaindazole **6** (derived from bromide **5**) and chloropyridine **7** (Scheme 2).[7]

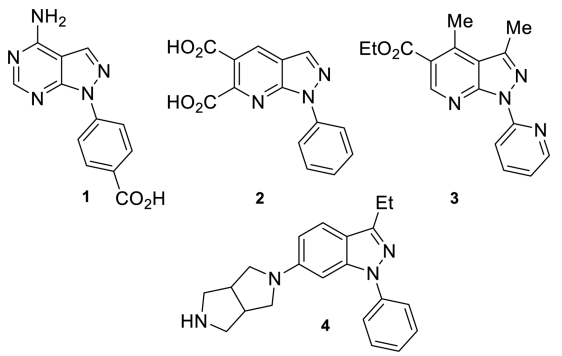
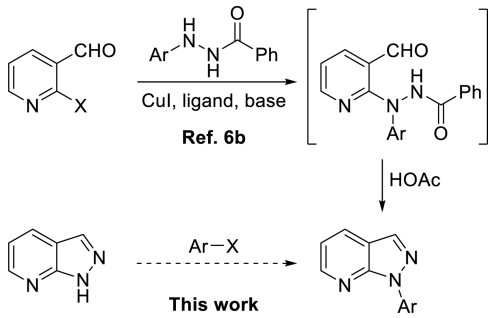


Figure 1. Substituted azaindazoles of biological interest.

Scheme 1



RESULTS AND DISCUSSION

Our initial attempts at the Pd-mediated coupling reaction provided low conversions (38 area % by HPLC) with an isolated yield of ca. 25%.[8] We attributed the low conversions to possible contaminants in the batch of **6** utilized for this transformation (which was isolated via an unoptimized crystallization) and theorized that a column chromatography would provide material of higher purity and consequently lead to a better performance in the Buchwald coupling. However, we were surprised to discover that the purified material led to a lower conversion (Scheme 2, entries 1 and 2), suggesting that

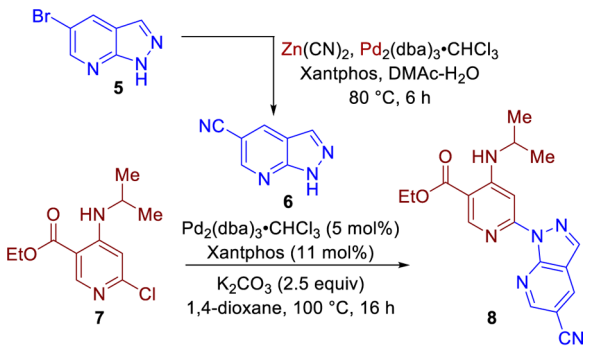
Received: May 6, 2017

DOI: 10.1021/acs.joc.7b01101
J. Org. Chem. XXXX, XXX, XXX–XXX

one of the contaminants actually had a beneficial rather than deleterious impact on the coupling reaction.

Cyanoazaindazole **6** was synthesized from the corresponding bromide **5** via a Pd-mediated cyanation using $Zn(CN)_2$ as the cyanide source (Scheme 2).[9] Although the crystallized and column purified batches were of comparable purity by the HPLC analysis, an inductively coupled plasma-mass spectrometry (ICP-MS) analysis revealed that, as anticipated, the former contained much higher levels of residual Zn and Pd than the latter (Scheme 2, entries 1 and 2). This led us to postulate that

Scheme 2



entry	**8** (HPLC area %)	comments	Zn (ppm)	Pd (ppm)
1	38	**6** isolated by crystallization	48066	56
2	16	**6** isolated after chromatography	42	11

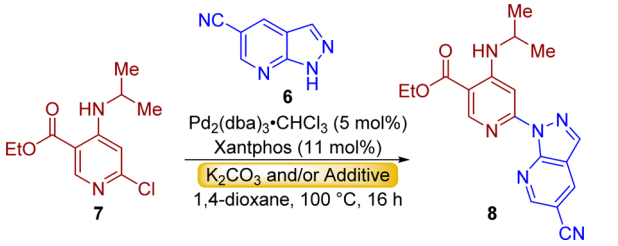
the addition of zinc or perhaps other Lewis acids would lead to enhanced conversions in the Buchwald–Hartwig reaction, and we sought to probe this further.

It is well-recognized that amines contained in a heteroaromatic ring system and heteroaryl halides[10] are often poor partners in the Buchwald–Hartwig reaction, partially due to catalyst deactivation through the binding of the heteroatom to the metal. Hartwig et al. have demonstrated that the addition of a stoichiometric Lewis acid can significantly accelerate the reductive elimination and thus promote the palladium catalyzed coupling of amines with unactivated heteroaryl halides.[11]

On the basis of our own results and literature precedent, we screened several additives (zinc salts as well as other Lewis acids) in the coupling of **6** with **7**.[12] While all of the "non-zinc" Lewis acids afforded very little conversion in the presence of 2.5 equiv of K_2CO_3 as a base (Table 1, entries 1–7), zinc salts provided tangible conversions (entries 8–11). Of the salts screened, zinc acetate gave the highest conversion (entry 11), albeit with 7–15% ester hydrolysis (presumably due to added K_2CO_3 and adventitious moisture). We rationalized that a counterion of the appropriate pK_a in the zinc species could function as a base (instead of K_2CO_3) and also potentially suppress the ester hydrolysis. It was gratifying to note that the use of 1.1 equiv of zinc acetate (without an additional base) led to 91% conversion (entry 12), and more importantly, even 0.6 equiv of zinc acetate and pivalate provided virtually quantitative conversions (entries 13 and 14). Of these, $Zn(OAc)_2$ emerged as the additive of choice primarily due to its low molecular weight, lower cost, and wider availability on a large scale. After further fine-tuning, the zinc acetate process was scaled up to furnish **8** in ca. 80% yield on a 3 kg scale.

Our results using zinc acetate suggested that further investigation was warranted in order to understand the

Table 1. Screening of Various Lewis Acids and Zinc Salts in the Coupling of 7 with 6[a]



entry	additive (equiv)	K_2CO_3 (equiv)	**8** (HPLC area %)
1	none	2.5	3
2	$Cu(OAc)_2$ (1.1)	2.5	<1
3	anhydrous $AlCl_3$ (1.1)	2.5	<1
4	$CeCl_3·7H_2O$ (1.1)	2.5	<1
5	$FeCl_3·6H_2O$ (1.1)	2.5	<1
6	$Co(OAc)_2$ (1.1)	2.5	15
7	BEt_3 (1.1)	2.5	<1
8[b]	anhydrous $ZnCl_2$ (1.1)	2.5	51
9[b]	anhydrous $ZnBr_2$ (1.1)	2.5	17
10[b]	$Zn(OTf)_2$ (1.1)	2.5	34
11[b]	$Zn(OAc)_2$ (1.1)	2.5	88
12	$Zn(OAc)_2$ (1.1)		91
13	$Zn(OAc)_2$ (0.6)		98
14	$Zn(OPiv)_2$ (0.6)		99
15[c]	$Zn(OAc)_2$ (0.6)		<1

[a]All reactions were carried out on a 0.18 mmol scale. [b]Between 7 and 15% of ester hydrolysis product was observed. [c]Control experiment in the absence of $Pd_2(dba)_3·CHCl_3$ and Xantphos.

substrate scope of this reaction. We wished to determine the effect of nitrogen on the six-membered ring on both the selectivity and the yield of the cross-coupling reaction. To this end, a series of reactions was carried out using 7-, 6-, 5-, and 4-azaindazoles (**9a–d**) as well as indazole (**9e**) as the amine partner and **7** as the aryl halide partner (Scheme 3).

In all of these cases, the reactions with K_2CO_3 failed to yield any product, while those with $Zn(OAc)_2$ afforded moderate to excellent yields and selectivities. Specifically, N1 adducts **10a**, **10d**, and **10e** were formed exclusively, while reactions of **9b** and **9c** preferentially afforded the N1 adducts **10b** and **10c** in addition to the corresponding N2 adducts **11b** and **11c**, respectively. Furthermore, the reactions with **9a–c** gave almost quantitative conversions, whereas those with **9d** and **9e** were relatively sluggish leading to 73% and 55% conversions, respectively. These results suggested that the nitrogen on the six-membered ring of the amine coupling partner plays a pivotal role in influencing both selectivity and reactivity; its presence is required for reactivity (as evidenced by the relatively low conversion to the indazole-coupled product **10e**), and its position possibly influences selectivity (as implied by the exclusive formation of **10a** as opposed to mixtures obtained in other cases with high conversions, i.e., **10b**/**11b** and **10c**/**11c**).

We then examined the reactions of several azaindazoles and azaindoles with a variety of heteroaryl chlorides under the $Zn(OAc)_2$-mediated conditions (Scheme 4). In almost all instances, the reactions with K_2CO_3 yielded very little product in contrast to the $Zn(OAc)_2$-mediated protocol where excellent conversions were achieved. While the reaction of 2-chloropyridine with 7-azaindazole and its 5-cyano analog afforded **14a** and **14e**, respectively, in virtually quantitative yields, the reactions with the corresponding 7-azaindoles furnished **14b**

DOI: 10.1021/acs.joc.7b01101
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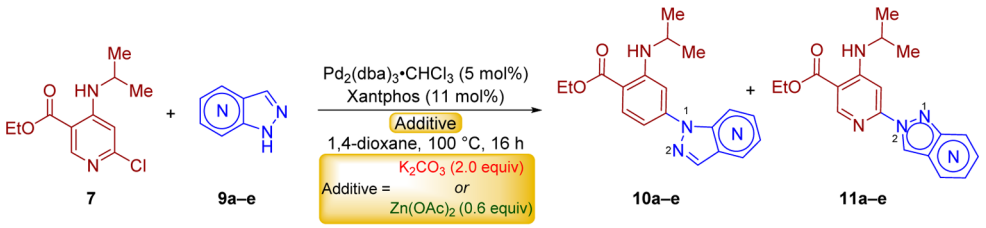
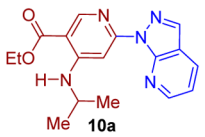
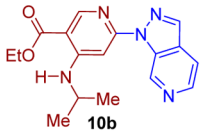
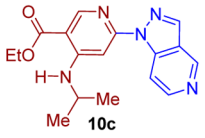
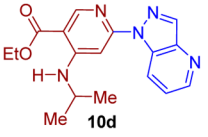
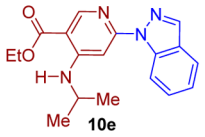
Scheme 3



major product	% conv with K_2CO_3	% conv with $Zn(OAc)_2$	**10/11** (N1/N2) ratio with $Zn(OAc)_2$
 **10a**	Trace	100	100/0
 **10b**	Trace	100	4/1
 **10c**	Trace	100	5/1
 **10d**	Trace	73	100/0
 **10e**	Trace	55	100/0

and **14f** in 68% and 50% yields, respectively. Interestingly, in cases where only modest yields were attained with the $Zn(OAc)_2$ protocol (reactions with azaindoles to furnish **14b**, **14k**, **14o**, and **14p**), the use of K_2CO_3 and $Zn(OAc)_2$ gave substantially higher yields, implying that the presence of zinc and a base of the appropriate pK_a were essential. Analogous to its reaction with **7** to provide **10e** (Scheme 3), the reaction of indazole with 2-chloropyridine afforded **14c** in only 23% yield (Scheme 4). Importantly, the $Zn(OAc)_2$ conditions were tolerant of ester and nitrile functionalities (which are generally prone to hydrolysis under basic conditions) as evidenced by the high yields obtained with **14d**, **14e**, and **14m**. Other heteroaryl chlorides such as 2-pyrazyl (**14g**) and 2-pyrimidyl (**14h**) chlorides worked well under the reaction conditions, as did the 4-pyridyl (**14n**, **14o**) and 4-quinolinyl (**14i**) analogs. Intriguingly, the reactions of chlorobenzene, 3-chloropyridine, and their iodo analogs with 7-azaindazole did not lead to any product. These results reinforced the fact that the presence and position of the nitrogen atoms in both of the coupling partners were important for the success of the zinc-mediated protocol.

Since the reactions progressed extremely well with substoichiometric amounts of "zinc" (0.6 equiv) and stoichiometric amounts of "acetate" (1.2 equiv), our next step was to investigate if similar conversions could be achieved with catalytic $Zn(OAc)_2$ and a stoichiometric base. Indeed, the reaction between **7** and **6** using 0.1 equiv of $Zn(OAc)_2$ and 1 equiv of NaOAc proceeded almost as fast as the reaction with 0.6 equiv of $Zn(OAc)_2$, validating our hypothesis on the catalytic nature of zinc. The reaction with sodium acetate alone was much slower reaching <20% conversion after 12 h (Figure 2).

In an effort to elucidate the role of zinc and to garner an understanding of the reaction pathway and intermediates, we mixed 1 equiv of 7-azaindole (**17**) with 1 equiv of $Zn(OAc)_2$ in dioxane and determined the structure of the resultant solid after recrystallization by single crystal X-ray analysis.[13] This revealed a dimeric structure in the solid state, where the pyridine nitrogens coordinate to the zinc atoms and the oxygen atoms of the acetate ligands form a hydrogen bond with the N–H proton of the pyrrole ring (**15**, Figure 3). Presumably, both of these phenomena would increase the acidity of the proton on the five-membered ring nitrogen, facilitating deprotonation; this could also lead to an azazincate-type species (**A**/**B**, Figure 4),[14] which would undergo a fast transmetalation with **C** to give **D**.[15] The binding of zinc to the nitrogen atoms in **D** can also accelerate the reductive elimination step as demonstrated by Shen and Hartwig.[11] The addition of 10 mol % of **15** to an equimolar mixture of 7-azaindole (**17**), 2-chloropyridine (**16**),

DOI: 10.1021/acs.joc.7b01101
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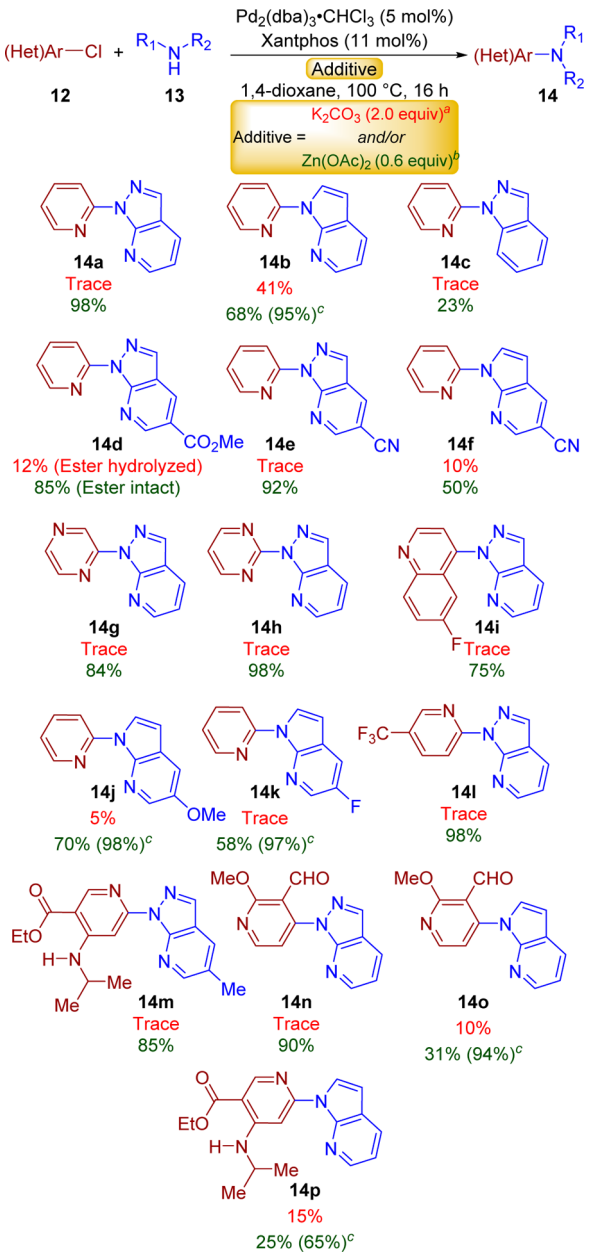
Scheme 4



[a]Numbers in red represent conversions (HPLC area %) in the presence of K_2CO_3 (without $Zn(OAc)_2$). [b]Numbers in green are isolated yields using $Zn(OAc)_2$ (without K_2CO_3). [c]Numbers in parentheses refer to isolated yields in the presence of K_2CO_3 and $Zn(OAc)_2$.

Pd_2dba_3·$CHCl_3$, Xantphos, and K_2CO_3 (used as an external base in the absence of a stoichiometric amount of zinc acetate) furnished **14b** in >99% conversion (Scheme 5), lending credence to the intermediacy of **15** in the reaction pathway and reinforcing our observation that the reaction could be carried out with catalytic zinc salts in the presence of a stoichiometric base.

SUMMARY

In summary, we have discovered the ability of zinc salts to mediate the Buchwald–Hartwig coupling of heteroaryl chlorides with azaindazoles and azaindoles to provide the

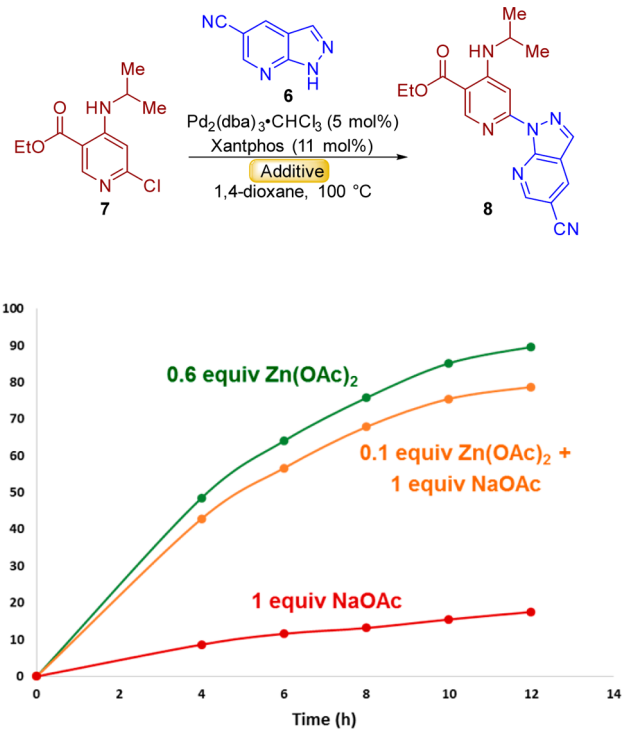


Figure 2. Comparison of reaction rates using 0.6 equiv of $Zn(OAc)_2$, 0.1 equiv of $Zn(OAc)_2$ plus 1 equiv of NaOAc, and NaOAc alone.

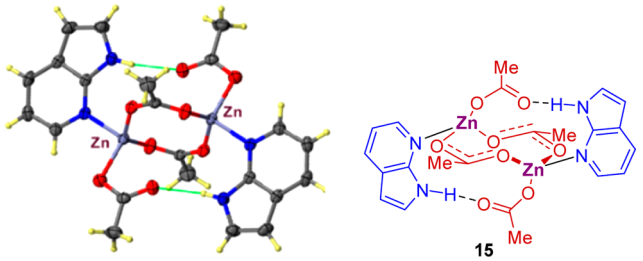


Figure 3. X-ray crystal structure (ORTEP with 30% probability ellipsoids) of the adduct of 7-azaindole with $Zn(OAc)_2$.

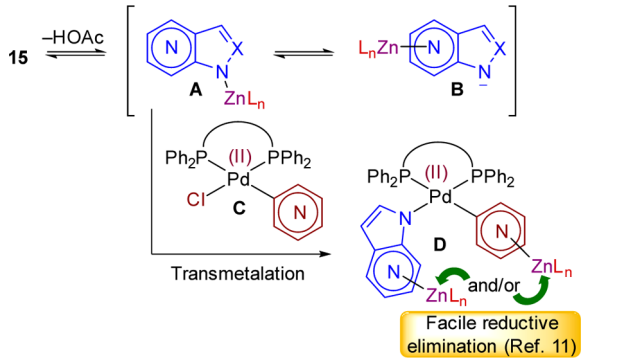
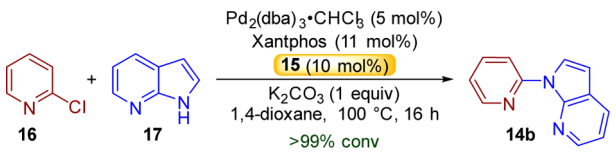


Figure 4. Plausible reaction pathway.

Scheme 5



DOI: 10.1021/acs.joc.7b01101
J. Org. Chem. XXXX, XXX, XXX–XXX

corresponding 1-aryl-substituted analogs. These compounds were hitherto accessible primarily via annulation approaches to form the five-membered rings, and the protocol described herein provides a rapid and convergent entry into these systems. This methodology exhibits significant functional group tolerance and was demonstrated successfully on a multikilogram scale.

EXPERIMENTAL SECTION

General Experimental Procedures. All reactions were performed under a nitrogen atmosphere. All products were purified by flash chromatography using silica gel (5−20 μm) as needed. Thin layer chromatography (TLC) was performed on glass plates coated with silica gel 60 with F254 indicator. Commercial reagents were purchased from Sigma-Aldrich, Acros, Fisher, Strem, TCI, Combi Blocks, Alfa Aesar, or Cambridge Isotopes Laboratories and used as received. 1,4-Dioxane was degassed by sparging with N_2 and stored over activated 4 Å MS under a nitrogen atmosphere in a glovebox. Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ($CHCl_3$ = δ 7.28; $(CD_3)_2SO$ = δ 2.07). Chemical shifts for carbons are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent ($CDCl_3$ = δ 77.07; $(CD_3)_2SO$ = δ 28.94). Mass spectral data were obtained using an Orbitrap mass spectrometer. Melting points were obtained using a Stuart SMP10 instrument.

*5-Bromo-1H-pyrazolo[3,4-b]pyridine (**5**).* To an oven-dried 500 mL three-neck round-bottomed flask fitted with a thermo-jacket and reflux condenser was added 200 mL of ethanol followed by 5-bromo-2-fluoronicotinaldehyde (20 g, 1.0 equiv), 65% hydrazine hydrate (40 mL), and water (40 mL). The reaction mixture was stirred for 15 h at 65 °C. After completion of the reaction, the mass was cooled to room temperature, diluted with water (400 mL), and stirred for 30 min. The resultant brown solid was filtered and dried under vacuum to afford 16 g (82%) of compound **5** (mp 201−203 °C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.88 (bs, 1H), 8.59 (d, J = 2.4 Hz, 1H), 8.53 (d, J = 2.0 Hz, 1H), 8.14 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 150.5, 149.5, 133.3, 132.5, 116.6, 112.0. HRMS (ESI-Orbitrap), m/z: [M + H]$^+$ calcd for $C_6H_5BrN_3$, 197.9667; found, 197.9667.

*1H-Pyrazolo[3,4-b]pyridine-5-carbonitrile (**6**).* To an oven-dried 500 mL three-neck round-bottomed flask fitted with a thermo-jacket and reflux condenser was added 250 mL of dimethylacetamide and 9 mL of water (2.0 equiv) followed by 5-bromo-1*H*-pyrazolo[3,4-*b*]pyridine (**5**) (50 g, 1.0 equiv), zinc cyanide (20.8 g, 0.7 equiv), $Pd_2(dba)_3$·$CHCl_3$ (2.6 g, 10 mol %), and Xantphos (1.46 g, 10 mol %). The reaction mixture was stirred for 6 h at 80 °C. Upon completion of the reaction, the mass was cooled to room temperature and filtered through Celite. The filtrate was treated with 10% aqueous trisodium citrate (300 mL). The biphasic solution was again filtered through Celite. The organic layer was separated and concentrated in vacuo. The residue was recrystallized using a mixture of acetic acid (250 mL) and water (500 mL). The product was dried under vacuum to afford 30 g (82%) of compound **6** as a brownish solid (mp 247−249 °C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 14.25 (bs, 1H), 8.89 (s, 2H), 8.36 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 152.4, 151.9, 136.5, 135.2, 118.5, 114.0, 101.6.

*Ethyl 6-Chloro-4-(isopropylamino)nicotinate (**7**).* A solution of 20 g of ethyl 4,6-dichloronicotinate in 300 mL of acetonitrile was added to an oven-dried 500 mL three-neck round-bottomed flask fitted with thermo-jacket and reflux condenser. Isopropylamine (23 mL) was added to the flask, and the mixture was stirred for 8 h at 65 °C. After completion of the reaction, the reaction mixture was cooled to room temperature. Water (500 mL) was added, and the resultant slurry was stirred for 1 h. The solid was isolated by filtration and dried under vacuum to afford 19.5 g (88%) of compound **7** as an off-white solid (mp 58−60 °C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.54 (s, 1H), 7.99 (d, J = 7.6 Hz, 1H), 6.84 (s, 1H), 4.33−4.28 (q, J = 7.0 Hz, 2H), 3.89−3.84 (m, 1H), 1.32 (t, J = 7.0 Hz, 3H), 1.20 (d, J = 6.4 Hz, 6H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.2, 155.2, 154.9, 152.9, 106.7, 105.4, 61.2, 43.5, 22.4, 14.4. HRMS (ESI-Orbitrap), m/z: [M + H]$^+$ calcd for $C_{11}H_{16}ClN_2O_2$, 243.0900; found, 243.0889.

*Ethyl 6-(5-Cyano-1H-pyrazolo[3,4-b]pyridine-1-yl)-4-(isopropylamino)nicotinate (**8**).* To a dried 300 L stainless steel reactor was added 60 L of 1,4-dioxane (20 vol with respect to **7**) under a nitrogen atmosphere. Ethyl 6-chloro-4-(isopropylamino)nicotinate (**7**) (3.0 kg, 1.0 equiv), 1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (**6**) (1.8 kg, 1.0 equiv), and $Zn(OAc)_2$ (1.4 kg, 0.6 equiv) were added into the reactor, and nitrogen was sparged through the mixture for 30 min followed by the addition of 729 g of $Pd(dba)_2$ (10 mol %)[16] and 800 g of Xantphos (11 mol %). The mixture was stirred for 16 h at 100 °C. After completion of the reaction, the mass was cooled to room temperature, 150 L of cold water was added into the reactor, and was stirred for 1 h. The resultant solid was filtered and dissolved in 60 L of CH_2Cl_2. Activated carbon and Siliabond thiol (900 g each) were added into the CH_2Cl_2 solution, the combined mass was stirred for 2 h at 20−30 °C and filtered, and the filtrate was concentrated to 9−10 L. After solvent exchange into THF (2 × 30 L) and concentration to ∼10 L, 4 M ethanolic HCl solution (6 L) was added slowly into the solution to give a brownish solid, which was filtered and dried at 60−65 °C for 16 h under vacuum to afford 3.3 kg (76%) of compound **8** (mp 184−186 °C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.08 (s, 1H), 8.83 (s, 1H), 8.60 (s, 1H), 8.43 (d, J = 5.5 Hz, 1H), 8.09 (d, J = 7.5 Hz, 1H), 7.89 (dd, J = 5.3, 1.3 Hz, 1H), 7.22 (s, 1H), 4.33 (q, J = 7.2 Hz, 2H), 3.89 (dd, J = 13.3, 6.8 Hz, 1H), 1.35 (t, J = 7.0 Hz, 3H), 1.32−1.23 (m, 6H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.8, 154.5, 153.1, 152.2, 151.8, 150.0, 136.9, 136.8, 117.5, 116.4, 105.8, 103.1, 60.66, 43.3, 29.6, 21.9, 14.0. HRMS (ESI-Orbitrap), m/z: [M + H]$^+$ calcd for $C_{18}H_{19}N_6O_2$, 351.1569; found, 351.1550.

General Procedures for Buchwald−Hartwig Coupling of Aryl Chlorides with Azaindoles and Azaindazoles (Schemes 3 and 4). *Procedure A (with Zinc Acetate).* To an oven-dried three-neck round-bottomed flask fitted with a thermo-jacket and reflux condenser was added degassed 1,4-dioxane (20 vol with respect to the aryl chloride) under a N_2 atmosphere. The aryl chloride (limiting reagent, 1.0 equiv), amine (1.0 equiv), and $Zn(OAc)_2$ (0.6 equiv) were added into the round-bottomed flask, and nitrogen was sparged through the mixture for 10 min followed by the addition of $Pd_2(dba)_3$·$CHCl_3$ (5 mol %) and Xantphos (11 mol %). The mixture was stirred for 16 h at 100 °C. After completion of the reaction, the mass was cooled to room temperature, diluted with CH_2Cl_2 (10 vol with respect to the aryl chloride), and filtered through a plug of silica gel. The filtrate was concentrated in vacuo and then purified by column chromatography to give the desired product.

Procedure B (with Zinc Acetate and K_2CO_3). To an oven-dried three-neck round-bottomed flask fitted with a thermo-jacket and reflux condenser was added degassed 1,4-dioxane (20 vol with respect to the aryl chloride) under a N_2 atmosphere. The aryl chloride (limiting reagent, 1.0 equiv), amine (1.0 equiv), $Zn(OAc)_2$ (0.6 equiv), and K_2CO_3 (2.0 equiv) were added into the round-bottomed flask, and nitrogen was sparged through the mixture for 10 min followed by the addition of $Pd_2(dba)_3$·$CHCl_3$ (5 mol %) and Xantphos (11 mol %). The mixture was stirred for 16 h at 100 °C. After completion of the reaction, the mass was cooled to room temperature, diluted with CH_2Cl_2 (10 vol with respect to the aryl chloride), and filtered through a plug of silica gel. The filtrate was concentrated in vacuo and then purified by column chromatography to give the desired product.

*Ethyl 4-(Isopropylamino)-6-(1H-pyrazolo[3,4-b]pyridin-1-yl)-nicotinate (**10a**).* The reaction was carried out on a 1.00 g scale using Procedure A. The product was purified by column chromatography using EtOAc/*n*-heptane (2:1) as the eluent to afford 1.32 g (98%) of compound **10a** as a pale yellowish solid (mp 97−99 °C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.79 (s, 1H), 8.70 (d, J = 4.4 Hz, 1H), 8.49 (s, 1H), 8.40 (d, J = 7.5 Hz, 1H), 8.04 (d, J = 7.5 Hz, 1H), 7.70 (s, 1H), 7.40 (dd, J = 7.8, 4.8 Hz, 1H), 4.33 (q, J = 7.0 Hz, 2H), 3.93−3.80 (m, 1H), 1.35 (t, J = 7.0 Hz, 3H), 1.31 (d, J = 6.5 Hz, 6H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.4, 155.0, 154.2, 152.7, 150.7, 150.1, 136.5, 131.6, 119.1, 117.9, 105.7, 97.3, 61.0, 43.8, 22.5, 14.6. HRMS (ESI-Orbitrap), m/z: [M + H]$^+$ calcd for $C_{17}H_{20}N_5O_2$, 326.1617; found, 326.1592.

DOI: 10.1021/acs.joc.7b01101
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*Ethyl 4-(Isopropylamino)-6-(1H-pyrazolo[3,4-c]pyridin-1-yl)-nicotinate (**10b**).* The reaction was carried out on a 500 mg scale using Procedure A. The product was purified by column chromatography using EtOAc/*n*-heptane (2:1) as the eluent to afford 302 mg (45%) of compound **10b** as an off-white solid (mp 149−151 °C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.09 (s, 1H), 8.84 (s, 1H), 8.60 (d, J = 0.8 Hz, 1H), 8.43 (d, J = 5.2 Hz, 1H), 8.09 (d, J = 7.6 Hz, 1H), 7.89 (dd, J = 5.3, 1.3 Hz, 1H), 7.22 (s, 1H), 4.33 (q, J = 7.2 Hz, 2H), 3.89 (dd, J = 13.3, 6.8 Hz, 1H), 1.35 (t, J = 7.0 Hz, 3H), 1.32−1.23 (m, 6H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.4, 156.1, 155.1, 152.9, 141.3, 139.3, 137.9, 135.7, 130.3, 115.7, 105.6, 92.7, 61.1, 43.7, 22.5, 14.6. HRMS (ESI-Orbitrap), m/z: [M + H]$^+$ calcd for $C_{17}H_{20}N_5O_2$, 326.1617; found, 326.1596.

*Ethyl 4-(Isopropylamino)-6-(1H-pyrazolo[4,3-c]pyridin-1-yl)-nicotinate (**10c**).* The reaction was carried out on a 250 mg scale using Procedure A. The product was purified by column chromatography using EtOAc/*n*-heptane (2:1) as the eluent to afford 288 mg (86%) of compound **10c** as an off-white solid (mp 128−130 °C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.22 (d, J = 0.8 Hz, 1H), 8.80 (s, 1H), 8.68 (s, 1H), 8.59−8.54 (m, 2H), 8.09 (d, J = 7.6 Hz, 1H), 7.23 (s, 1H), 4.35−4.30 (q, J = 7.2 Hz, 2H), 3.91−3.86 (m, 1H), 1.37−1.33 (t, J = 7.2 Hz, 3H), 1.29−1.28 (d, J = 6.4 Hz, 6H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.8, 155.9, 154.6, 152.2, 145.9, 145.5, 141.4, 137.8, 122.8, 109.9, 105.0, 92.7, 60.6, 43.1, 21.9, 14.0. HRMS (ESI-Orbitrap), m/z: [M + H]$^+$ calcd for $C_{17}H_{20}N_5O_2$, 326.1617; found, 326.1590.

*Ethyl 4-(Isopropylamino)-6-(1H-pyrazolo[4,3-b]pyridin-1-yl)-nicotinate (**10d**).* The reaction was carried out on a 250 mg scale using Procedure A. The product was purified by column chromatography using EtOAc/*n*-heptane (2:1) as the eluent to afford 204 mg (61%) of compound **10d** as a pale pinkish solid (mp 140−142 °C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.05−9.03 (d, J = 8.4 Hz, 1H), 8.77 (s, 1H), 8.68−8.67 (m, 2H), 8.08−8.06 (d, J = 7.2 Hz, 1H), 7.58−7.55 (dd, J = 8.4, 4.4 Hz, 1H), 7.22 (s, 1H), 4.35−4.29 (q, J = 6.8 Hz, 2H), 3.91−3.86 (m, 1H), 1.37−1.33 (t, J = 7.2 Hz, 3H), 1.29−1.28 (d, J = 6.4 Hz, 6H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.8, 156.0, 154.5, 152.2, 147.1, 143.2, 138.0, 131.9, 123.4, 122.5, 104.9, 92.0, 60.5, 43.1, 21.9, 14.0. HRMS (ESI-Orbitrap), m/z: [M + H]$^+$ calcd for $C_{17}H_{20}N_5O_2$, 326.1617; found, 326.1603.

*Ethyl 6-(1H-Indazol-1-yl)-4-(isopropylamino)nicotinate (**10e**).* The reaction was carried out on a 500 mg scale using Procedure A. The product was purified by column chromatography using EtOAc/*n*-heptane (1:3) as the eluent to afford 268 mg (40%) of compound **10e** as an off-white solid (mp 91−93 °C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.79−8.76 (m, 2H), 8.47 (s, 1H), 8.03 (d, J = 7.2 Hz, 1H), 7.90−7.88 (d, J = 8.0 Hz, 1H), 7.57−7.53 (m, 1H), 7.34−7.30 (m, 1H), 7.22 (s, 1H), 4.36−4.23 (q, J = 6.8 Hz, 2H), 3.89−3.84 (m, 1H), 1.37−1.30 (t, J = 7.2 Hz, 3H), 1.30−1.22 (d, J = 6.4 Hz, 6H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.9, 156.5, 154.4, 152.2, 138.5, 137.9, 128.1, 125.8, 122.7, 121.2, 115.5, 104.6, 92.2, 60.4, 43.0, 21.9, 14.0. HRMS (ESI-Orbitrap), m/z: [M + H]$^+$ calcd for $C_{18}H_{21}N_4O_2$, 325.1665; found, 325.1638.

*1-(Pyridin-2-yl)-1H-pyrazolo[3,4-b]pyridine (**14a**).* The reaction was carried out on a 1.00 g scale using Procedure A. The product was purified by column chromatography using EtOAc/*n*-heptane (3:1) as the eluent to afford 1.69 g (98.0%) of compound **14a** as a brownish oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.69−8.64 (dd, J = 4.4, 1.6 Hz, 1H), 8.64 (s, 1H), 8.49 (s, 1H), 8.39 (dd, J = 8.0, 1.6 Hz, 1H), 8.23−8.21 (m, 1H), 8.09−8.05 (m, 1H), 7.46−7.39 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 150.7, 149.9, 149.6, 148.7, 138.7, 135.6, 131.1, 122.2, 118.5, 117.0, 116.7. HRMS (ESI-Orbitrap), m/z: [M + H]$^+$ calcd for $C_{11}H_9N_4$, 197.0827; found, 197.0816.

*1-(Pyridin-2-yl)-1H-pyrrolo[2,3-b]pyridine (**14b**).* The reaction was carried out on a 1.00 g scale using Procedure A. The product was purified by column chromatography using EtOAc/*n*-heptane (1:5) as the eluent to afford 1.17 g (68%) of compound **14b** as a white solid.

The reaction was carried out on a 1.00 g scale using Procedure B. The product was purified by column chromatography using EtOAc/*n*-heptane (1:5) as the eluent to afford 1.63 g (95%) of compound **14b** (mp 64−66 °C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.48−8.47 (dd, J = 8.0, 0.8 Hz, 1H), 8.46 (d, J = 0.8 Hz, 1H), 8.46−8.37 (m, 2H), 7.95−7.92 (dd, J = 8.0, 2 Hz, 1H), 7.86−7.82 (m, 1H), 7.16−7.12 (m, 2H), 6.64−6.63 (d, J = 4.0 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 150.8, 148.2, 147.5, 143.1, 138.2, 129.1, 126.4, 123.3, 120.3, 117.2, 115.7, 102.6. HRMS (ESI-Orbitrap), m/z: [M + H]$^+$ calcd for $C_{12}H_{10}N_3$, 196.0875; found, 196.0861.

*1-(Pyridin-2-yl)-1H-indazole (**14c**).* The reaction was carried out on a 1.00 g scale using Procedure A. The product was purified by column chromatography using EtOAc/*n*-heptane (1:5) as the eluent to afford 395 mg (23%) of compound **14c** as a white solid (mp 81−83 °C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.78−8.76 (d, J = 8.8 Hz, 1H), 8.59−8.58 (d, J = 4.8 Hz, 1H), 8.46 (s, 1H), 8.04−8.01 (m, 2H), 7.92−7.90 (d, J = 8.0 Hz, 1H), 7.59−7.55 (m, 1H), 7.35−7.31 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 153.6, 147.9, 139.1, 138.1, 137.3, 128.1, 125.7, 122.6, 121.2, 120.4, 114.8, 112.9. HRMS (ESI-Orbitrap), m/z: [M + H]$^+$ calcd for $C_{12}H_{10}N_3$, 196.0875; found, 196.0859.

*Methyl 1-(Pyridin-2-yl)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate (**14d**).* The reaction was carried out on a 500 mg scale using Procedure A.[17] The product was purified by column chromatography using EtOAc/*n*-heptane (1:2) as the eluent to afford 952 mg (85%) of compound **14d** as a pale brownish solid (mp 134−136 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.34 (d, J = 2.0 Hz, 1H), 8.83−8.82 (d, J = 2.4 Hz, 1H), 8.72 (m, 1H), 8.40 (m, 2H), 7.96−7.92 (m, 1H), 7.34−7.30 (m, 1H), 4.01 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.7, 151.5, 151.1, 149.0, 139.2, 138.5, 136.3, 132.7, 122.0, 120.9, 117.1, 116.2, 52.5. HRMS (ESI-Orbitrap), m/z: [M + H]$^+$ calcd for $C_{13}H_{11}N_4O_2$, 255.0882; found, 255.0863.

*1-(Pyridin-2-yl)-1H-pyrazolo[3,4-b]pyridine-5-carbonitrile (**14e**).* The reaction was carried out on a 1.00 g scale using Procedure A. The product was purified by column chromatography using EtOAc/*n*-heptane (2:1) as the eluent to afford 1.79 g (92%) of compound **14e** as an off-white solid (mp 193−195 °C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.06−9.03 (m, 2H), 8.67−8.65 (m, 2H), 8.12−8.10 (m, 2H), 7.53−7.50 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 151.7, 150.1, 149.7, 148.1, 139.0, 136.9, 136.6, 123.1, 117.6, 117.3, 116.1, 103.0. HRMS (ESI-Orbitrap), m/z: [M + H]$^+$ calcd for $C_{12}H_8N_5$, 222.0780; found, 222.0771.

*1-(Pyridin-2-yl)-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (**14f**).* The reaction was carried out on a 500 mg scale using Procedure A. The product was purified by column chromatography using EtOAc/*n*-heptane (1:4) as the eluent to afford 485 mg (50%) of compound **14f** as an off-white solid (mp 191−193 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.81−8.79 (d, J = 8.4 Hz, 1H), 8.65 (s, 1H), 8.64−8.51 (m, 2H), 8.25−8.24 (d, J = 2.0 Hz, 1H), 7.93−7.89 (m, 1H), 7.26−7.23 (m, 1H), 6.74−6.73 (d, J = 4.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.5, 145.8, 141.2, 138.5, 132.7, 129.3, 122.5, 121.5, 118.4, 112.4, 116.2, 102.9, 102.5. HRMS (ESI-Orbitrap), m/z: [M + H]$^+$ calcd for $C_{13}H_9N_4$, 221.0827; found, 221.0816.

*1-(Pyrazin-2-yl)-1H-pyrazolo[3,4-b]pyridine (**14g**).* The reaction was carried out on a 1.00 g scale using Procedure A. The product was purified by column chromatography using EtOAc/*n*-heptane (2:1) as the eluent to afford 1.45 g (84%) of compound **14g** as a pale brownish solid (mp 94−96 °C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.58 (m, 1H), 8.75−8.73 (m, 2H), 8.70−8.69 (m, 1H), 8.61 (s, 1H), 8.46−8.43 (dd, J = 8.0, 1.6 Hz, 1H), 7.48−7.45 (dd, J = 8.0, 4.8 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 150.2, 149.9, 147.3, 143.1, 142.2, 138.0, 137.2 131.4, 118.9, 117.2. HRMS (ESI-Orbitrap), m/z: [M + H]$^+$ calcd for $C_{10}H_8N_5$, 198.0780; found, 198.0771.

*1-(Pyrimidin-2-yl)-1H-pyrazolo[3,4-b]pyridine (**14h**).* The reaction was carried out on a 1.00 g scale using Procedure A. The product was purified by column chromatography using EtOAc/*n*-heptane (2:1) as the eluent to afford 1.69 g (98%) of compound **14h** as a brownish solid (mp 90−92 °C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.02 (d, J = 4.8 Hz, 2H), 8.71−8.70 (dd, J = 4.8, 1.6 Hz, 1H), 8.53 (s, 1H), 8.41−8.39 (dd, J = 8.0, 1.6 Hz, 1H), 7.60−7.58 (t, J = 4.8 Hz, 1H), 7.44−7.41 (dd, J = 8.0, 4.4 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.3, 156.3, 150.5, 149.9, 136.6, 130.9, 119.8, 118.9, 117.1. HRMS (ESI-Orbitrap), m/z: [M + H]$^+$ calcd for $C_{10}H_8N_5$, 198.0780; found, 198.0766.

DOI: 10.1021/acs.joc.7b01101
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*6-Fluoro-4-(1H-pyrazolo[3,4-b]pyridin-1-yl)quinolone (**14i**).* The reaction was carried out on a 500 mg scale using Procedure A. The product was purified by column chromatography using EtOAc/*n*-heptane (2:1) as the eluent to afford 546 mg (75%) of compound **14i** as an off-white solid (mp 178−180 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.06 (d, J = 3.2 Hz, 1H), 8.64−8.63 (dd, J = 2.8, 1.6 Hz, 1H), 8.40 (d, J = 1.6 Hz, 1H), 8.26−8.21 (m, 2H), 7.90−7.83 (m, 2H), 7.58−7.54 (m, 1H), 7.34−7.30 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.1, 151.5, 149.8, 149.5, 147.4, 141.7, 141.6, 135.6, 132.5 (d, J_{C-F} = 9.1 Hz), 130.6, 124.7, 120.4 (d, J_{C-F} = 25.7 Hz), 118.5 (d, J_{C-F} = 60.9 Hz), 116.8, 108.5 (d, J_{C-F} = 24.2 Hz). HRMS (ESI-Orbitrap), m/z: $[M + H]^+$ calcd for $C_{15}H_{10}FN_4$, 265.0889; found, 265.0869.

*5-Methoxy-1-(pyridin-2-yl)-1H-pyrrolo[2,3-b]pyridine (**14j**).* The reaction was carried out on a 100 mg scale using Procedure A. The product was purified by column chromatography using EtOAc/*n*-heptane (1:5) as the eluent to afford 138 mg (70% yield) of compound **14j** as a colorless oil.

The reaction was carried out on a 100 mg scale using Procedure B. The product was purified by column chromatography using EtOAc/*n*-heptane (1:5) as the eluent to afford 194 mg (98%) of compound **14j**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.87−8.85 (d, J = 8.4, 1H), 8.47−8.45 (m, 1H), 8.35 (d, J = 4.0 Hz, 1H), 8.16 (d, J = 2.8 Hz, 1H), 7.87−7.82 (m, 1H), 7.46 (d, J = 2.8 Hz, 1H), 7.15−7.12 (m, 1H), 6.57 (d, J = 4.0 Hz, 1H), 3.91 (s, 3H), 1.38 (s, 1H), 1.32−1.19 (m, 2H), 0.89 (t, J = 6.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.9, 150.8, 148.2, 142.8, 138.2, 133.0, 127.1, 123.4, 120.1, 115.1, 112.0, 102.2, 56.2. HRMS (ESI-Orbitrap), m/z: $[M + H]^+$ calcd for $C_{13}H_{12}N_3O$, 226.0980; found, 226.0964.

*5-Fluoro-1-(pyridin-2-yl)-1H-pyrrolo[2,3-b]pyridine (**14k**).* The reaction was carried out on a 100 mg scale using Procedure A. The product was purified by column chromatography using EtOAc/*n*-heptane (1:5) as the eluent to afford 109 mg (58%) of compound **14k** as an off-white solid (mp 87−89 °C).

The reaction was carried out on a 100 mg scale using Procedure B. The product was purified by column chromatography using EtOAc/*n*-heptane (1:5) as the eluent to afford 182 mg (97%) of compound **14k**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.85 (dt, J = 8.4, 0.9 Hz, 1H), 8.53−8.47 (m, 1H), 8.44 (d, J = 3.8 Hz, 1H), 8.28 (dd, J = 2.6, 1.4 Hz, 1H), 7.88 (ddd, J = 8.3, 7.3, 2.0 Hz, 1H), 7.65 (dd, J = 8.8, 2.8 Hz, 1H), 7.19 (ddd, J = 7.3, 4.9, 1.0 Hz, 1H), 6.66−6.59 (m, 1H), 1.38 (s, 1H), 1.32−1.23 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.1 (d, J_{C-F} = 242.6 Hz), 150.5, 148.3, 144.1, 138.3, 131.5 (d, J_{C-F} = 28.5 Hz), 128.5, 123.7 (d, J_{C-F} = 7.0 Hz), 120.5, 115.3, 114.9 (d, J_{C-F} = 20.5 Hz), 102.3 (d, J_{C-F} = 3.7 Hz). HRMS (ESI-Orbitrap), m/z: $[M + H]^+$ calcd for $C_{12}H_9FN_3$, 214.0781; found, 214.0761.

*1-(4-(Trifluoromethyl)pyridin-2-yl)-1H-pyrazolo[3,4-b]pyridine (**14l**).* The reaction was carried out on a 1.00 g scale using Procedure A. The product was purified by column chromatography using EtOAc/*n*-heptane (5:1) as the eluent to afford 1.42 g (98%) of compound **14l** as a white solid (mp 129−131 °C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.02 (m, 1H), 8.76−8.74 (dd, J = 4.8, 1.6 Hz, 1H), 8.63−8.60 (m, 2H), 8.48−8.43 (m, 2H), 7.49−7.45 (dd, J = 8.0, 4.8 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 150.3, 146.3 (q, J_{C-F} = 297 Hz), 146.5, 146.4, 146.4, 137.8, 136.8, 131.9, 122.9 (q, J_{C-F} = 7.3 Hz), 119.6, 118.2, 115.6. HRMS (ESI-Orbitrap), m/z: $[M + H]^+$ calcd for $C_{12}H_8F_3N_4$, 265.0701; found, 265.0686.

*Ethyl 4-(Isopropylamino)-6-(5-methyl-1H-pyrazolo[3,4-b]pyridin-1-yl)nicotinate (**14m**).* The reaction was carried out on a 500 mg scale using Procedure A. The product was purified by column chromatography using EtOAc/*n*-heptane (2:1) as the eluent to afford 594 mg (85%) of compound **14m** as an off-white solid (mp 124−126 °C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.78 (s, 1H), 8.55 (s, 1H), 8.39 (s, 1H), 8.14 (bs, 1H), 8.03−8.01 (d, J = 6.8 Hz, 1H), 7.69 (s, 1H), 4.36−4.31 (q, J = 6.8 Hz, 2H), 3.87−3.82 (m, 1H), 2.46 (s, 3H), 1.42−1.14 (m, 9H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.9, 154.5, 153.7, 152.2, 150.7, 149.0, 135.4, 130.0, 127.7, 117.4, 105.0, 96.2, 60.5, 43.2, 21.9, 17.7, 14.1. HRMS (ESI-Orbitrap), m/z: $[M + H]^+$ calcd for $C_{18}H_{22}N_5O_2$, 340.1773; found, 340.1757.

*2-Methoxy-4-(1H-pyrazolo[3,4-b]pyridin-1-yl)nicotinaldehyde (**14n**).* The reaction was carried out on a 500 mg scale using Procedure A. The product was purified by column chromatography using EtOAc/*n*-heptane (2:1) as the eluent to afford 667 mg (90%) of compound **14n** as an off-white solid (mp 158−160 °C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.12 (s, 1H), 8.67−8.65 (dd, J = 4.8, 1.6 Hz, 1H), 8.59 (s, 1H), 8.52−8.51 (d, J = 5.6 Hz, 1H), 8.44−8.42 (dd, J = 8.0, 1.6 Hz 1H), 7.75−7.74 (d, J = 5.6 Hz, 1H), 7.45−7.42 (dd, J = 8.0, 4.8 Hz, 1H), 4.02 (m, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 189.0, 163.1, 151.5, 150.6, 150.3, 146.3, 137.7, 132.2, 119.6, 117.7, 113.2, 112.7, 54.7. HRMS (ESI-Orbitrap), m/z: $[M + H]^+$ calcd for $C_{13}H_{11}N_4O_2$, 255.0882; found, 255.0860.

*2-Methoxy-4-(1H-pyrrolo[2,3-b]pyridin-1-yl)nicotinaldehyde (**14o**).* The reaction was carried out on a 500 mg scale using Procedure A. The product was purified by column chromatography using EtOAc/*n*-heptane (1:5) as the eluent to afford 228 mg (31% yield) of compound **14o** as a brownish solid.

The reaction was carried out on a 500 mg scale using Procedure B. The product was purified by column chromatography using EtOAc/*n*-heptane (1:5) as the eluent to afford 694 mg (94%) of compound **14o** (mp 97−99 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.20 (s, 1H), 8.42−8.41 (d, J = 5.6 Hz, 1H), 8.32−8.31 (dd, J = 4.8, 1.2 Hz, 1H), 7.98−7.95 (dd, J = 8.0, 1.6 Hz 1H), 7.39−7.38 (d, J = 4.0 Hz, 1H), 7.17−7.12 (m, 2H), 6.71−6.70 (d, J = 3.6 Hz, 1H), 4.13 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.0, 164.7, 151.7, 147.5, 146.8, 143.8, 129.4, 128.4, 121.6, 117.6, 115.3, 113.9, 103.4, 54.4. HRMS (ESI-Orbitrap), m/z: $[M + H]^+$ calcd for $C_{14}H_{11}N_3O_2$, 254.0930; found, 254.0904.

*Ethyl 4-(Isopropylamino)-6-(1H-pyrrolo[2,3-b]pyridin-1-yl)-nicotinate (**14p**).* The reaction was carried out on a 500 mg scale using Procedure A. The product was purified by column chromatography using EtOAc/*n*-heptane (1:4) as the eluent to afford 167 mg (25%) of compound **14p** as a white solid.

The reaction was carried out on a 500 mg scale using Procedure B. The product was purified by column chromatography using EtOAc/*n*-heptane (1:4) as the eluent to afford 434 mg (65%) of compound **14p** as a white solid (mp 90−92 °C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.71 (d, J = 3.2 Hz, 1H), 8.47 (s, 1H), 8.43−8.41 (m, 2H), 8.12−8.10 (dd, J = 6.8, 1.6 Hz, 1H), 8.03−8.01 (d, J = 7.2 Hz, 1H), 7.29−7.27 (dd, J = 8.0, 4.8 Hz, 1H), 6.76−6.75 (d, J = 4.0 Hz, 1H), 4.34−4.28 (q, J = 6.8 Hz, 2H), 3.88−3.83 (m, J = 6.5 Hz, 1H), 1.36−1.32 (m, 9H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.4, 155.2, 153.1, 152.4, 147.6, 143.8, 130.0, 126.7, 123.7, 118.2, 104.7, 103.5, 95.6, 60.8, 43.9, 22.4, 14.6. HRMS (ESI-Orbitrap), m/z: $[M + H]^+$ calcd for $C_{18}H_{21}N_4O_2$, 325.1665; found, 325.1639.

*Compound **15**.* In a glovebox under a nitrogen atmosphere, 7-azaindole (**17**, 500 mg, 4.23 mmol, 1.0 equiv), $Zn(OAc)_2$ (776.5 mg, 4.23 mmol, 1.0 equiv), and toluene (7 mL) were combined in a 20 mL vial. The vial was capped with a Teflon-lined cap and heated at 100 °C for 4 h to get a colorless solution. The vial was then cooled to room temperature to give X-ray quality crystals of compound **15** (1.2 g, 95%).

*Catalytic Activity of **15**.* In a glovebox under a nitrogen atmosphere, complex **15** (60 mg, 0.1 mmol), 2-chloropyridine (**16**) (114 mg, 1 mmol, 1.0 equiv), 7-azaindole (**17**) (118 mg, 1 mmol, 1.0 equiv), $Pd_2(dba)_3{\cdot}CHCl_3$ (51.8 mg, 5 mol %), Xantphos (63.5 mg, 11 mol %), and K_2CO_3 (138 mg, 1 mmol, 1.0 equiv) were added to a 20 mL vial. Dioxane (10 mL) was added, and the vial was capped with a Teflon-lined cap and removed from the glovebox. The mixture was heated at 100 °C for 16 h. The reaction mixture was then diluted with CH_2Cl_2 (10 mL) and filtered through a plug of silica gel, which was rinsed with CH_2Cl_2 (20 mL). The filtrate was concentrated, and the crude material was purified by column chromatography using EtOAc/*n*-heptane (1:5) as the eluent to afford 191 mg (98%) of compound **14b** as a white solid. The spectral data for this product match those reported, vide supra.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b01101.

DOI: 10.1021/acs.joc.7b01101
J. Org. Chem. XXXX, XXX, XXX−XXX

Crystal data (CIF)
Starting material preparation, ^{1}H and ^{13}C NMR spectra of new compounds, and X-ray crystallographic analysis of **15** (PDF)

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank Lopa Bakrania, Yi Xiao, Sathish Kumar Chandrasekaran, and Sravankumar Gangisetty for their contributions. Analytical support from Naresh Marella, Saravanan Natarajan, and Nadarajan Manikandan is gratefully acknowledged. Single crystal X-ray analysis was performed by Amol Dikundwar and Meenakshi Sundaram. We thank Rajgopal Sharma and Prof. Scott Rychnovsky for the helpful suggestions during the preparation of this manuscript. Our sincere thanks to David Kronenthal, Rajendra Deshpande, and Robert Waltermire for their support of this work.

REFERENCES

(1) Ruiz-Castillo, P.; Buchwald, S. L. *Chem. Rev.* **2016**, *116*, 12564.
(2) (a) Torborg, C.; Beller, M. *Adv. Synth. Catal.* **2009**, *351*, 3027. (b) Corbet, J.-P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651. (c) Schlummer, B.; Scholz, U. *Adv. Synth. Catal.* **2004**, *346*, 1599. (d) Surry, D. S.; Buchwald, S. L. *Chem. Sci.* **2011**, *2*, 27. (e) Hartwig, J. F. *Nature* **2008**, *455*, 314. (f) Bariwal, J.; Van der Eycken, E. *Chem. Soc. Rev.* **2013**, *42*, 9283.
(3) (a) Paul, F.; Patt, J.; Hartwig, J. *J. Am. Chem. Soc.* **1994**, *116*, 5969. (b) Guram, A.; Buchwald, S. *J. Am. Chem. Soc.* **1994**, *116*, 7901.
(4) (a) Gupta, S.; Rodrigues, L. M.; Esteves, A. P.; Oliveira-Campos, A. M. F.; Nascimento, M. S. J.; Nazareth, N.; Cidade, H.; Neves, M. P.; Fernandes, E.; Pinto, M. *Eur. J. Med. Chem.* **2008**, *43*, 771. (b) Coulter, T. S.; Taylor, S.; Murfin, S.; Thammalaksa, V.; Aicher, B.; Jaekel, S.; Reuter, T. PCT Int. Appl. WO 2006066937 A2 20060629, 2006. (c) Zhang, X. Q.; Song, F. B.; Kuo, G. H.; Xiang, A.; Gibbs, A. C.; Abad, M. C.; Sun, W. M.; Kuo, L. C.; Sui, Z. H. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4762. (d) Uchikawa, O.; Mitsui, K.; Asakawa, A.; Morimoto, S.; Yamamoto, M.; Kimura, H.; Moriya, T.; Mizuno, M. PCT Int. Appl. WO 2001072749 A1 20011004, 2001.
(5) Nordhoff, E.; Franke, W.; Arndt, F.; Koetter, C. Ger. Offen. DE 3616849 A1 19871119, 1987.
(6) (a) Wray, B. C.; Stambuli, J. P. *Org. Lett.* **2010**, *12*, 4576. (b) Xiong, X.; Jiang, Y.; Ma, D. *Org. Lett.* **2012**, *14*, 2552. (c) An, J.; Alper, H.; Beauchemin, A. M. *Org. Lett.* **2016**, *18*, 3482.
(7) Anderson, K. W.; Tundel, R. E.; Ikawa, T.; Altman, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 6523.
(8) Reactions with Cu under Ullman-type conditions did not afford any product.
(9) Maligres, P. E.; Waters, M. S.; Fleitz, F.; Askin, D. *Tetrahedron Lett.* **1999**, *40*, 8193.
(10) (a) Burton, G.; Cao, P.; Li, G.; Rivero, R. *Org. Lett.* **2003**, *5*, 4373. (b) Alcaraz, L.; Bennion, C.; Morris, J.; Meghani, P.; Thom, S. M. *Org. Lett.* **2004**, *6*, 2705. (c) Ji, J.; Li, T.; Bunnelle, W. H. *Org. Lett.* **2003**, *5*, 4611. (d) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421.
(11) Shen, Q.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 7734.
(12) The isolation of compound **6** was subsequently streamlined to provide material containing <50 ppm Zn. See the Experimental Section.
(13) Attempts to obtain a crystal structure of adducts of $Zn(OAc)_2$ with 7-azaindazole and its substituted analogs were hampered by the poor solubility of these adducts, which precluded isolation of single crystals.
(14) Structure **B** is depicted as a monoamidozinc species. It is also likely to exist as a diamidozinc in solution (L_n = azaindole), which can undergo faster transmetalation, analogous to diarylzinc. See: McCann, L. C.; Organ, M. G. *Angew. Chem., Int. Ed.* **2014**, *53*, 4386.
(15) Lee, D.-Y.; Hartwig, J. F. *Org. Lett.* **2005**, *7*, 1169.
(16) During the laboratory development studies and all the experiments described in the manuscript, $Pd_2(dba)_3{\cdot}CHCl_3$ was used as the Pd source. However, for scaleup, $Pd(dba)_2$ was used because of its ready availability at the time.
(17) For the preparation of the starting material for this experiment, please see the Supporting Information.

DOI: 10.1021/acs.joc.7b01101
J. Org. Chem. XXXX, XXX, XXX−XXX