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Note

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Palladium-Catalyzed C3 Arylations of 1*H* and 2*H* Pyrazolo[4,3-b]pyridines on Water

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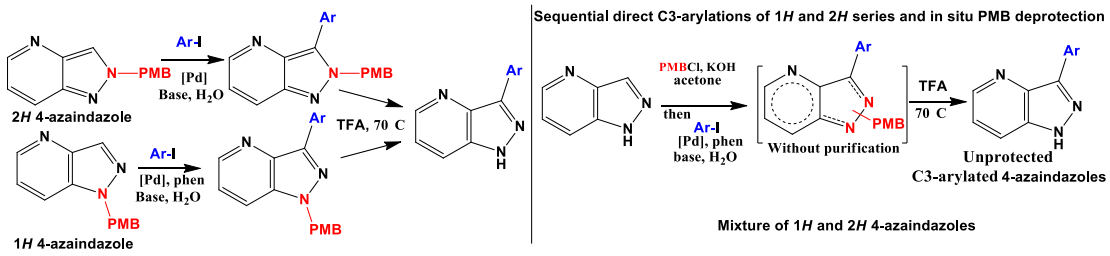
Supporting Information Placeholder

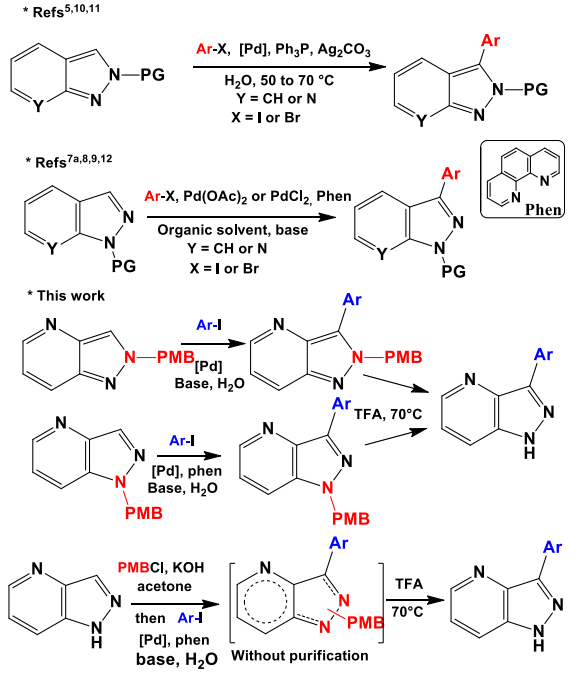


ABSTRACT: Direct C3-arylation of 1*H*-pyrazolo[4,3-b]pyridines and direct C3-arylation of 2*H*-pyrazolo[4,3-b]pyridines in water have been developed. New protocol for sequential C3-arylation procedure on a mixture of 1*H*- and 2*H*-pyrazolo[4,3-b]pyridines followed by in situ PMB cleavage has also been achieved. This procedure led to unprotected (*NH*) C3-arylated 1*H*-pyrazolo[4,3-b]pyridines in good yields.

Direct arylation is nowadays a very good alternative to traditional cross-coupling reactions such as Suzuki-Miyaura[1], Stille[2] and Negeshi[3]. This C-H activation method doesn't require the use of pre-functionalized starting materials and allows the rapid and atom-economical formation of inter or intra carbone-carbone bond[4]. Although the effort made for the development of this filed, the need of specific conditions to functionalize each heterocyclic system is still required. It is even necessary to develop specific conditions for each positional isomer. For example, in the case of indazoles and azaindazoles, the arylation of 2*H* isomer doesn't required the use of ligand in contrast to 1*H* isomer because of the lack of the reactivity of 1*H* series compared to 2*H* series[5-7].

Graney et al. reported the first example of intermolecular direct arylation of 2*H* indazole series in water using $Pd(dppf)Cl_2$ (5 mol %) and 10 mol % of Ph_3P as ligand[5]. Two years later, our group[7a] in along with Itami group[8] developed conditions to achieve direct arylation of 1*H* indazole series. The key of this success was the use of bidentate ligand (1,10-phenanthroline in both cases). Later, the reaction conditions have been optimized by Yu group by reducing catalyst and ligand loading[9]. Recently, we reported C3-direct arylation of 2*H* 7-azaindazoles in water using $Pd(PPh_3)_2Cl_2$ as catalyst and PPh_3 as ligand[10] (Scheme 1). Later, Doucet and his group reported a phosphine free C3-arylation of 2*H*-indazoles in DMA using 5 mol% of $Pd(OAc)_2$ as catalyst[11]. Very recently, Popowycz and Lavrard reported C3-arylation of 1*H* 7-azaindazoles under similar conditions previously developed by Yu group[9] using $Pd(phen)_2(PF_6)_2$ as catalyst in the presence of Cs_2CO_3 in toluene at 160°C for 72h[12].

In continuation of our research program on indazoles and azaindazoles functionalization by CH and CH/CH activation,[7,10,13] we wish to report herein the first examples of direct C3-arylation on both 1*H*-pyrazolo[4,3-b]pyridines and 2*H*-pyrazolo[4,3-b]pyridines (1*H* and 2*H* 4-azaindazoles). In the case of 1*H*-pyrazolo[4,3-b]pyridines, the procedure was developed under mild conditions using water as the sole solvent and 5 mol% of $Pd(PPh_3)_4$ catalyst and 10 mol% of 1,10-phenanthroline as ligand. In the case of 2*H*-pyrazolo[4,3-b]pyridines, the reaction was conducted in water and with a low catalyst loading (2.5 mol %).

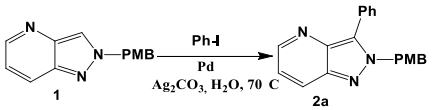


Scheme 1. Reported methods for direct arylation of indazoles and azaindazoles compared to this work.

We developed also an original sequential direct C3-arylations directly on 1*H* and 2*H* pyrazolo[4,3-b]pyridines in mixture (obtained by alkylation of starting material pyrazolo[4,3-b]pyridine by PMBCl). Then, without purification of C3-arylated intermediates, the cleavage of PMB protecting group allowed the synthesis of *NH* C3-arylated pyrazolo[4,3-b]pyridines in good yields (Scheme 1).

Inspired by our previous report[10], we selected pyrazolo[4,3-b]pyridine **1**[14,15] (see supporting information) as starting material and 1-iodo-benzene as coupling partner to optimize reaction conditions. With 5 mol% $Pd(PPh_3)_2Cl_2$ as catalyst, 10 mol% PPh_3 as ligand and 1 equiv. of Ag_2CO_3 as base, the reaction proceeded in H_2O at 70 °C for 24h and led, regioselectively, to the desired C3-arylated product **2** in 90% isolated yield (entry 1, Table 1). The reaction yield was slightly improved when $Pd(PPh_3)_4$ was used instead of $Pd(PPh_3)_2Cl_2$, (entry 2, Table 1). 1,10-Phenanthroline used as ligand instead of PPh_3 was much less effective (40%, entry 3, Table 1). Very interestingly, without additional PPh_3 (entry 4, Table 1) the desired product was isolated in good yield (80%). Additional optimizations using of $Pd(PPh_3)_4$ as catalyst led to improved yield (85%, entry 5, Table 1). Lastly, the reduction of both $Pd(PPh_3)_4$ (2.5 mol%) and PPh_3 (5 mol%) loading did not affect reaction yield and led to compound **2** in 82% yield (entry 6, Table 1). Again, under $Pd(PPh_3)_4$ as catalyst conditions (entry 7, Table 1), the expected product **2** was obtained in 80% yield. Almost similar results were obtained when $Pd(PPh_3)_2Cl_2$ was used instead of $Pd(PPh_3)_4$ under either conditions with or without ligand (entries 8 and 9, Table 1). When $Pd(PPh_3)_4$ loading was reduced to 1.5 mol%, the reaction required adding PPh_3 to achieve total reaction conversion (entries, 10 and 11, Table 1). Low conversion was also obtained when 1.5 mol% of $Pd(PPh_3)_2Cl_2$ was employed under conditions using $Pd(PPh_3)_4$ as catalyst (38%, entry 12, Table 1). After the screening of various reaction conditions we decided to use the following ones to study the scope and limitations of this method [$Pd(PPh_3)_2Cl_2$ (2.5), Ag_2CO_3 (1 equiv.), H_2O, 70°C, 24h (entry 9, table 1)].

Table 1. Optimization of C3 arylation of 2*H* pyrazolo[4,3-b]pyridine **1**.

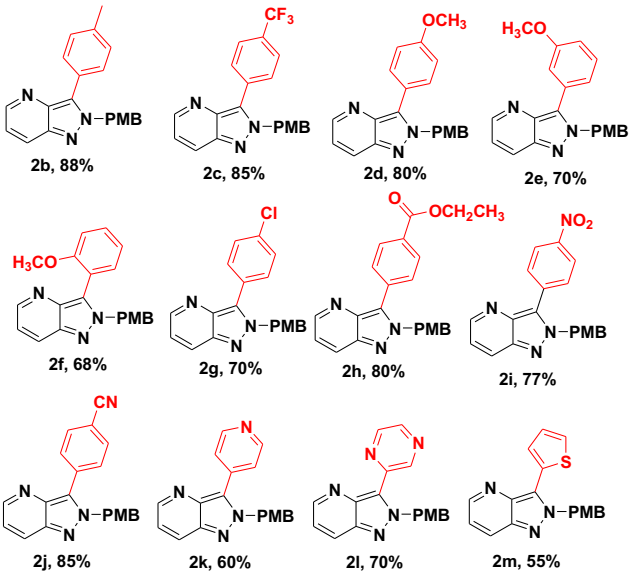


Entry	Pd (mol%)	Ligand (%)	Con. % [b]	Yield % [a]
1	$Pd(PPh_3)_2Cl_2$(5)	PPh_3(10)	100	90
2	$Pd(PPh_3)_4$(5)	PPh_3(10)	100	92
3	$Pd(PPh_3)_4$(5)	Phen(10)	53	40 (45)[c]
4	$Pd(PPh_3)_2Cl_2$(5)	none	100	80
5	$Pd(PPh_3)_4$(5)	none	100	85
6	$Pd(PPh_3)_4$(2.5)	PPh_3(5)	100	82
7	$Pd(PPh_3)_4$(2.5)	none	100	80
8	$Pd(PPh_3)_2Cl_2$(2.5)	PPh_3 (5)	100	80
9	$Pd(PPh_3)_2Cl_2$(2.5)	none	100	80
10	$Pd(PPh_3)_4$(1.5)	PPh_3(5)	100	80
11	$Pd(PPh_3)_4$(1.5)	none	62	NI
12	$Pd(PPh_3)_2Cl_2$(1.5)	none	38	NI

Reaction conditions: iodobenzene (1 equiv.), Pd, Ligand, Base, H_2O, 70 °C, 24h. [a] isolated yield of **2a**, [b] conversion based on ^1H NMR, [c] yield of isolated starting material **1**. NI : note isolated.

With the optimized reaction conditions in hand, we decided to study the scope and limitations by using various iodo-aryls and iodo-heteroaryls as coupling partners. The results set out in Table 2 show that all the expected C3-arylated products were regioselectively obtained in good to excellent yields (55 to 88%). This study revealed also that under the reaction conditions various functionalities were tolerated (ester, CN, NO_2). Pyridine, pyridazine and thiophene were efficiently coupled in 60, 70 and 55% yield, respectively (compounds **2k**, **2l** and 2**m**, Table 2).

Table 2. Scope and limitations of C3-arylation of 2*H* pyrazolo[4,3-b]pyridine **1**.



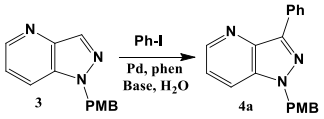
Reaction conditions: iodobenzene (1 equiv.), $Pd(PPh_3)_2Cl_2$ (2.5 mol%), Ag_2CO_3 (1 equiv.), H_2O, 70 °C, 24h.

Then, we turned our attention to study C3-direct arylation of 1*H*-pyrazolo[4,3-b]pyridine isomers. For this aim, we selected the starting material **3**[14,15] (see supporting information) and iodobenzene as coupling partners for the optimization study. Using the best reaction conditions in 1*H* series and in 2*H* series of 7-azaindazoles[10] [5 mol% of $Pd(PPh_3)_2Cl_2$ as metal, 10 mol% of PPh_3 as ligand and 1 equiv. of Ag_2CO_3 as base in H_2O at 70 °C for 24h,], the expected C3-arylated product **4** was isolated in low yield (30%) (entry 1, Table 3). The use of 1,10-phenanthroline instead of PPh_3 did not improved the reaction yield (entry 2, Table 3). The same result was observed using $Pd(PPh_3)_4$ with either 1 or 2 equiv. of Ag_2CO_3 (entries 3 and 4, Table 3).

The screening of other bases such as K_2CO_3, Cs_2CO_3, K_3PO_4, resulted in a complete loss of the reactivity (entries 5-7, Table 3). Improved yields were observed when the reaction time was prolonged to 36h at 70°C (entry 8 compared to 4, Table 3). When the reaction mixture was heated to 90°C, the expected product was obtained in a very good 80% yield in 24h (entry 9).

All the other attempts to improve the reaction conditions and yield by using 1 equiv. of Ag_2CO_3 instead of 2 equiv. (entry 10), Ph_3P instead of 1,10-phenanthroline (entry 11), without additional PPh_3 conditions (entry 12) or the use of 5 mol% of 1,10-phenanthroline instead of 10 mol% (entry 13), offered lower yields. Finally, the flowing conditions [$Pd(PPh_3)_4$ (5), Phen 10 mol%, Ag_2CO_3 (1.3 equiv.), H_2O, 90°C, 24h, entry 14] were found to be the optimum and were used to study the scope and limitations of C3 direct arylation of 1*H*-4 azaindazoles.

Table 3. Optimization of C3 arylation of 1*H*-pyrazolo[4,3-b]pyridine **3**.

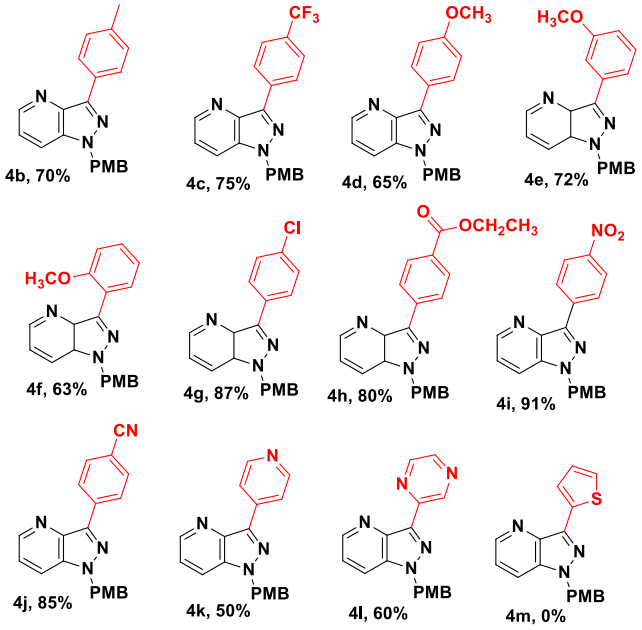


entry	Pd	L	base (equiv.)	T °C	Con.%[b]	yields% [a]
1	$Pd(PPh_3)_2Cl_2$	PPh_3	Ag_2CO_3 (1)	70	40	30(60)[c]
2	$Pd(PPh_3)_2Cl_2$	Phen	Ag_2CO_3 (1)	70	40	NI
3	$Pd(PPh_3)_4$	Phen	Ag_2CO_3 (1)	70	40	NI
4	$Pd(PPh_3)_4$	Phen	Ag_2CO_3 (2)	70	49	NI
5	$Pd(PPh_3)_4$	Phen	K_2CO_3(2)	70	0	0
6	$Pd(PPh_3)_4$	Phen	Cs_2CO_3 (2)	70	0	0
7	$Pd(PPh_3)_4$	Phen	K_3PO_4(2)	70	0	0
8	$Pd(PPh_3)_4$	Phen	Ag_2CO_3 (2)	70	87	70(13)[c,d]
9	$Pd(PPh_3)_4$	Phen	Ag_2CO_3 (2)	90	100	80
10	$Pd(PPh_3)_4$	Phen	Ag_2CO_3 (1)	90	82	75 (10)[d]
11	$Pd(PPh_3)_4$	PPh_3	Ag_2CO_3 (2)	90	53	40 (38)[d]
12	$Pd(PPh_3)_4$	none	Ag_2CO_3 (2)	90	54	45(30)[c]
13	$Pd(PPh_3)_4$	Phen	Ag_2CO_3 (1.3)	90	48[e]	NI
14	$Pd(PPh_3)_4$	Phen	Ag_2CO_3 (1.3)	90	100	80

Reaction conditions: iodobenzene (2 equiv.), Pd (5 mol%), Ligand (10 mol%), Base, H_2O, 70 to 90°C, 24h. [a] isolated yields, [b] conversion based on ^1H NMR, [c] t = 36h, [d] isolated yields of **3**. [e] in this case 5 mol% instead of 10 mol% of Phen was used. NI : note isolated.

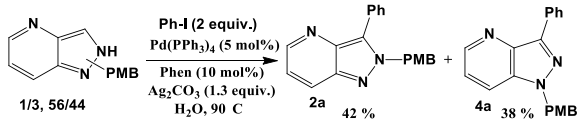
Then, we surveyed substrate scope with various iodo-aryls and iodo-heteroaryls as coupling partners (Table 4). These reactions afforded the corresponding C3-arylated products **4a-l** in moderate to excellent yields (50 to 91%). Again, pyridine and pyridazine were efficiently coupled with 50 and 60% yield, respectively (compounds **4k** and **4l**, Table 4). Surprisingly, the reaction using 2-iodothiophene as coupling partner did not lead to expected product 2**m**. In this case only starting material was recovered.

Table 4. Scope and limitations of C3-arylation of pyrazolo[4,3-b]pyridine **3**.



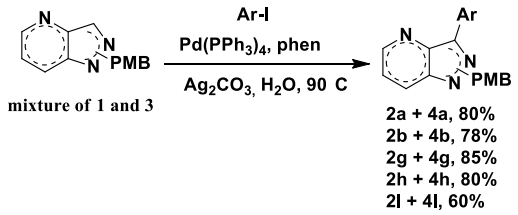
Reaction conditions: iodoaryl (2 equiv.), $Pd(PPh_3)_4$ (5 mol%), Phen (10 mol%), Ag_2CO_3 (1.3 equiv.), H_2O, 90°C, 24h.

Then, we decided to develop a sequential C3 direct arylation on *1H* and *2H* series. For this reason, we decided to find reaction conditions adapted for the arylation of both the isomers. After screening of reaction conditions, we finally found that the mixture of compounds **1/3** (obtained as a mixture (ratio of **1/3**, 56/44) by *N*-alkylation of the pyrazolo[4,3-b]pyridine by PMBCl) react smoothly with iodobenzene (2 equiv.) in the presence of $Pd(PPh_3)_4$ (5 mol%), 1,10-phenanthroline (10 mol%) and Ag_2CO_3 (1.3 equiv.) in H_2O at 90°C for 24h. Under these reaction conditions, C3 arylated products **2a** and **4a** were isolated as pure compounds in 42 and 38 % yields, respectively (80 % global yield) (Scheme 2).



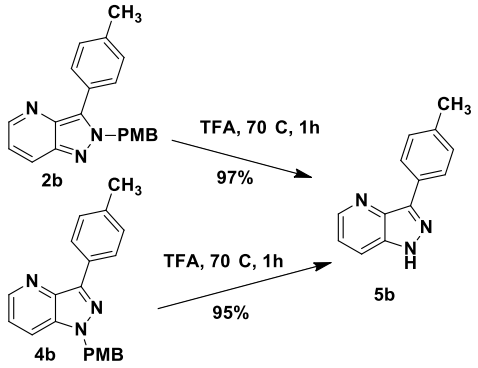
Scheme 2. Sequential C3-arylation on **3** and **1** mixture.

The scope was then extended to iodobenzene, iodotoluene, 1-chloro-4-iodobenzene, ethyl 4-iodobenzoate or 2-iodopyrazine as coupling partners. As expected, C3-arylated products **2a/4a**, **2b/4b**, **2g/4g**, **2h/4h** and **3l/4l** as 1*H* and 2*H* isomer mixtures were obtained in 80, 78, 85, 80 and 60% global yields, respectively (Scheme 3).



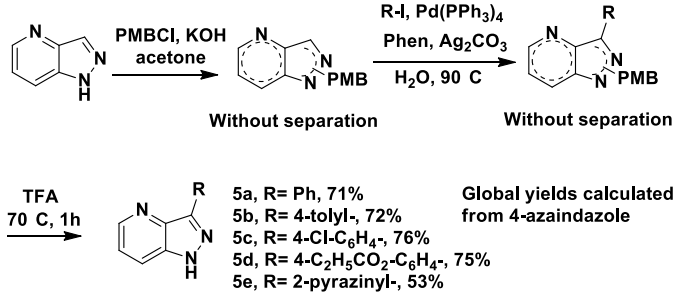
Scheme 3. Sequential C3-arylation on **3** and **1** mixture using various iodoaryls.

Deprotection of the PMB protecting group to generate NH unprotected C3-arylated products was investigated. For this purpose, we found, that the treatment of isolated isomers **2b** and **4b** with TFA at 70°C for 1h[15] led to the only expected NH unprotected C3-arylated product **5b** in 97 and 95% yields, respectively (Scheme 4).



Scheme 4. Cleavage of PMB protecting group.

Encouraged by these results (Schemes 3 and 4), we decided to directly run the reaction on the mixture of compound **1** and **3** with various iodoaryls in the presence of $Pd(PPh_3)_4$ (5 mol%), 1,10-phenanthroline (10 mol%) and Ag_2CO_3 (1.3 equiv.) in H_2O at 90°C for 24h. The expected C3-arylated products were obtained as 1*H* and 2*H* isomer mixtures. After a simple filtration, without any column chromatography separation, the crude (1*H* and 2*H* isomer mixtures) was treated with TFA at 70°C for 1h and led to the expected C3-arylated unprotected *NH* pyrazolo[4,3-b]pyridines **5a-e** in good to excellent global yields (over three steps starting from 1*H*-pyrazolo[4,3-b]pyridine) (Scheme 5).



Scheme 5. Sequential C3-arylation of 1*H* and 2*H* series of pyrazolo[4,3-b]pyridines and cleavage of the PMB protecting group.

Conclusion

In summary, we have reported the first palladium catalyzed direct C3 arylation of both 1*H* and *2H* pyrazolo[4,3-b]pyridine series under mild reaction conditions. Low catalyst loading and water conditions have been applied in the cases of 1*H* pyrazolo[4,3-b]pyridines and *2H* pyrazolo[4,3-b]pyridines. We developed also conditions to achieve unprotected C3-arylated *1H* pyrazolo[4,3-b]pyridines using a three steps sequence including an original sequential C3-arylation on 1*H* and *2H* pyrazolo[4,3-b]pyridine mixtures followed by in situ cleavage of the PMB protecting group. The development of new cross-coupling reactions and their mechanistic investigations are ongoing in our laboratories.

Experiment section

General information

The reactions were monitored by thin-layer chromatography (TLC) using aluminum sheets coated with silica gel 60 F254. Flash column chromatography was carried out using silica gel 60 Å (0.04–0.06 mm). ^1H and ^{13}C NMR spectra were recorded with a 250 MHz (^1H: 250 and ^{13}C: 63 MHz) or 400 MHz (^1H: 400 and ^{13}C: 101 MHz) Bruker spectrometer. Using $CDCl_3$, MeOH, Acetone and DMSO as solvent. Chemical shifts of ^1H NMR and ^{13}C NMR were recorded in parts per million (ppm, δ) relative to tetramethylsilane (δ = 0.00 ppm) calibrated to the residual solvent peak as an internal standard [($CDCl_3$: δ_H = 7.26 ppm and δ_C = 77.0 ppm) (CD_3OD: δ_H = 3.31 and 4.84 ppm and δ_C = 49.0 ppm); (DMSO-d6: δ_H = 2.50 ppm and δ_C = 39.4 ppm)]. Data are reported as follow: chemical shift in ppm (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (Hz). High-resolution mass spectra (HRMS) were recorded with a Maxis Bruker 4G instrument and were performed in positive mode with an ESI source on a Q-TOF mass spectrometer with an accuracy tolerance of 2 ppm.

Materials: Unless otherwise noted, all reagent-grade chemicals and solvents commercially available were used without further purification. All aryl iodides, silver carbonate, 1,10-phenanthroline and triphenylphosphine were stored in sealed, cool and dry conditions.

Synthetic procedures:

Synthesis of 1*H*-pyrazolo[4,3-*b*] pyridine:

Hydrazine hydrate (10 mL) was added to a mixture of 3-fluoro-2-formylpyridine **1 (**3.00 g, 24 mmol) and *p*-TsOH (2.06 g, 12 mmol). The reaction mixture was stirred for 3 h at 130 C°. Upon cooling with cold water, the mixture was extracted three times with EtOAc. The combined organic extracts were dried over anhydrous $MgSO_4$. After filtration, the solvent was removed in vacuum. The residue was purified by flash chromatography to give compound **2g** in 70% yield as a white solid.

***N*-Alkylation of 1*H*-pyrazolo[4,3-*b*] pyridine:**

Potassium hydroxide (1.4 g, 25.21 mmol) was added to a solution of 1*H*-pyrazolo [4,3-*b*] pyridine (1 g, 8.40 mmol) in acetone (30 mL), and the mixture was maintained for 60 min at 0 °C. Then, 4-methoxybenzyl chloride (1.9 g, 12.6 mmol, 1.5 equiv) was added. The reaction mixture was warmed to room temperature and maintained for 4 h. The reaction mixture was quenched with water and extracted with EtOAc. The combined organic extracts were dried over anhydrous $MgSO_4$. After filtration, the solvent was removed in vacuum. The desired products were purified by column chromatography (petroleum ether/ ethyl acetate, 6:4) which led to para-methoxybenzylated products **1**-**3** (50%-43% yield).

General procedure for direct arylation of iodoarenes with 1-para-methoxybenzy-pyrazolo[4,3-b]pyridine on water:

A sealed tube was charged with 1-para-methoxybenzy-pyrazolo[4,3-b]pyridine (100 mg, 0,41 mmol, 1 equiv), iodobenzene (0,83 mmol, 2 equiv), $Pd(PPh_3)_4$ (24,17 mg, 0,020mmol, 5 mol%), Ag_2CO_3 (150 mg, 0,54 mmol, 1,3 equiv) and phenanthroline (7,5 mg, 0,041 mmol, 10 mol%). A magnetic stirrer bar was added and the mixture of solids was gently shaken for a few seconds to ensure all solids were well mixed. Distilled water (3 ml) was added and the tube was covered with a cap. The tube and its contents were then heated and stirred 90 °C for 24 h. After this time the reaction mixture was cooled down to rt. CH_2Cl_2 (5 ml) was added and the contents of the tube were filtered through a short pad of celite. The tube was rinsed once with an additional 2 ml of CH_2Cl_2. The organic layer was separated, and the aqueous phase extracted once with CH_2Cl_2. The organic layers were combined and concentrated *in vacuo*. The residue was purified by flash chromatography (silica; petroleum ether/ ethyl acetate, 4:1, the same system was used to purify all synthesized products) to provide the title compound as a white solid in 80% yield.

General procedure for direct arylation of iodoarenes with 2-para-methoxybenzy-pyrazolo[4,3-b]pyridine on water:

A sealed tube was charged with 2-para-methoxybenzy-pyrazolo [4,3-b]pyridine (100 mg, 0,41 mmol, 1 equiv), iodobenzene (0,41 mmol, 1 equiv), $Pd(PPh_3)_2Cl_2$ (7,34 mg, 0.010mmol, 2,5 mol%), and Ag_2CO_3 (115 mg, 0,41 mmol, 1 equiv). A magnetic stirrer bar was added and the mixture of solids was gently shaken for a few seconds to ensure all solids were well mixed. Distilled water (3 ml) was added and the tube was covered with a cap. The tube and its contents were then heated and stirred at 70 °C for 24 h. After this time the reaction mixture was cooled down to rt. CH_2Cl_2 (5 ml) was added and the contents of the tube were filtered through a short pad of celite. The tube was rinsed once with an additional 2 ml of CH_2Cl_2. The organic layer was separated, and the aqueous phase extracted once with CH_2Cl_2. The organic layers were combined and concentrated *in vacuo*. The residue was purified by flash chromatography (silica; petroleum ether/ ethyl acetate, 1:1, the same system was used to purify all synthesized products) to provide the title compound as a white solid in 80% yield

Sequential C3-arylation

100 mg of the mixture [**1**+**3**/56%+44%], 1equiv) was put in a tube, iodobenzene (2 equiv), $Pd(PPh_3)_4$ (5 mol%), Ag_2CO_3 (1,3 equiv) and phenanthroline (10 mol%). A magnetic stirrer bar was added and the mixture of solids was gently shaken for a few seconds to ensure all solids were well mixed. Distilled water (3 ml) was added and the tube was covered with a cap. The tube and its contents were then heated and stirred at 90 °C for 24 h. After this time the reaction mixture was cooled down to room temperature. CH_2Cl_2 (10 ml) was added and the contents of the tube were filtered through a short pad of celite. The tube was rinsed once with an additional 5 ml of CH_2Cl_2. The organic layer was separated, and the aqueous phase extracted once with CH_2Cl_2. The organic layers were combined and concentrated in vacuo The residue was purified by flash chromatography (silica; petroleum ether/ ethyl acetate, 1:1, the same system was used to purify all synthesized products) to provide the C3 arylated products **2a** and **4a** were isolated as pure compounds in 42 and 38 % yields, respectively (80 % global yield).

General protocol for deprotection sequence:

To a 50 mg of **2b** or (**4b**) was added TFA (3 ml). The reaction mixture was stirred at 70 °C for 2 h, after concentration, the residue was dissolved in EtOAc (10 ml) and washed with $NaHCO_3$ (10 ml), brine (10 ml), dried ($MgSO_4$) and concentrated in vacuo. Residue was purified by flash chromatography (silica; ethyl acetate) to provide the product **5b** in 97% yield.

General protocol for arylation/deprotection sequences:

1*H*-Pyrazolo [4,3-b] pyridine (100 mg, 0.84 mmol) was dissolved in 3 ml acetone and cooled to 0 °C then, KOH (141 mg, 2.52 mmol, 3 equiv) was added at 0 °C and the resulting mixture was allowed to stir for 60 minutes. 4-Methoxybenzyl chloride (197 mg, 1.26 mmol, 1.5 equiv) was added and the reaction allowed to warm to room temperature and stirred for an additional 4 hours. The reaction mixture was quenched with water and extracted with EtOAc. The combined organic extracts were dried over anhydrous $MgSO_4$. After filtration, the solvent was removed in vacuum. The desired products (**1**+**3**) were filtered by simple filtration. Then, the mixture was put in a tube [**1**+**3**/56%+44%], 1 equiv), iodo heteroaryl (2 equiv), $Pd(PPh_3)_4$ (5 mol%), Ag_2CO_3 (1,3 equiv) and phenanthroline (10 mol%). A magnetic stirrer bar was added and the mixture of solids was gently shaken for a few seconds to ensure all solids were well mixed. Distilled water (3 ml) was added and the tube was covered with a cap. The tube and its contents were then heated and stirred at 90 °C for 24 h. After this time the reaction mixture was cooled down to room tem-

perature. CH_2Cl_2 (10 ml) was added and the contents of the tube were filtered through a short pad of celite. The tube was rinsed once with an additional 5 ml of CH_2Cl_2. The organic layer was separated and the aqueous phase extracted once with CH_2Cl_2. The organic layers were combined and concentrated in vacuo, then after a simple filtration of the crude product, TFA (3 ml) was added and the mixture was stirred at 70 ° C for 2 hours. After concentration, the residue was dissolved in EtOAc (10 ml) and washed with $NaHCO_3$ (10 ml), brine (10 ml), dried ($MgSO_4$) and concentrated in vacuo. Residue was purified by flash chromatography (silica; petroleum ether/ ethyl acetate, 1:1) to provide the desired product.

Characterization data

1*H*-Pyrazolo[4,3-b]pyridine:

White solid (2g, 16.80 mmol, 70%), **mp** = 95-97 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 13.00 (s, 1H), 8.61 (d, J = 4.1 Hz, 1H), 8.38 (s, 1H), 7.88 (d, J = 8.5 Hz, 1H), 7.29 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 145.5, 140.8, 134.6, 133.1, 121.1, 118.6; **HRMS** (calcd for $C_6H_6N_3$ ([M+H]$^+$): 120.0555; Found: 120.0556. **IR** (neat) $\tilde{\nu}$= 3440, 3089, 1430 cm^{-1}.

1-(4-Methoxybenzyl)-1*H*-pyrazolo[4,3-b]pyridine 3:

Red oil (860 mg, 3.59 mmol, 43%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.55 (dd, J = 4.4, 0.9 Hz, 1H), 8.26 (s, 1H), 7.63 (d, J = 8.6 Hz, 1H), 7.21 (dd, J = 8.6, 4.4 Hz, 1H), 7.16 (d, J = 8.6 Hz, 2H), 6.84 (d, J = 8.6 Hz, 2H), 5.53 (s, 2H), 3.76 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 159.5, 145.6, 142.4, 134.2, 132.3, 128.8, 128.2, 120.6, 117.4, 114.3, 55.4, 53.4; **HRMS** (calcd for $C_{14}H_{14}N_3O$ ([M+H]$^+$): 240.1332; Found: 240.1331. **IR** (neat) $\tilde{\nu}$= 3417, 2964, 2840, 1601, 1175 cm^{-1}

2-(4-Methoxybenzyl)-2*H*-pyrazolo[4,3-b]pyridine 1:

Red oil (1 g, 4.1 mmol, 50%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.52 (d, J = 4.1 Hz, 1H), 8.20 (s, 1H), 8.00 (d, J = 8.7 Hz, 1H), 7.21 (d, J = 8.7 Hz, 2H), 7.10 (dd, J = 8.7, 4.1 Hz, 1H), 6.82 (d, J = 8.7 Hz, 2H), 5.46 (s, 2H), 3.67 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 159.2, 147.4, 141.1, 138.6, 129.1, 126.8, 125.0, 123.2, 120.5, 113.7, 57.0, 54.6; **HRMS** calcd for $C_{14}H_{14}N_3O$ [M+H]$^+$): 240.1131; Found: 240.1131. **IR** (neat) $\tilde{\nu}$= 3410, 2836, 1511, 1246 cm^{-1}

2-(4-Methoxybenzyl)-3-phenyl-2*H*-pyrazolo[4,3-b]pyridine 2a:

Yellow solid (104 mg, 0.33 mmol, 80%), **mp** = 90-92 °C. **^{1}H NMR** (250 MHz, $CDCl_3$) δ_H 8.62 (d, J = 4.3 Hz, 1H), 8.10 (d, J = 9.0 Hz, 1H), 7.71 – 7.43 (m, 5H), 7.26 (dd, J = 9.0, 4.3 Hz, 1H), 7.09 (d, J = 8.7 Hz, 2H), 6.84 (d, J = 8.7 Hz, 2H), 5.66 (s, 2H), 3.79 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 159.4, 148.4, 141.4, 137.4, 136.8, 130.1, 129.2, 129.1, 128.6, 128.6, 128.5, 125.7, 121.72, 114.3, 55.4, 54.7; **HRMS** calcd for $C_{20}H_{18}N_3O$ ([M+H]$^+$): 316.1444; Found: 316.1444. **IR** (neat) $\tilde{\nu}$= 3410, 2928, 1173 cm^{-1}

2-(4-Methoxybenzyl)-3-p-tolyl-2*H*-pyrazolo[4,3-b]pyridine 2b:

Yellow solid (118 mg, 0.35 mmol, 88%), **mp** = 85-87 °C. **^{1}H NMR** (250 MHz, $CDCl_3$) δ_H 8.58 (dd, *J* = 4.0, 2.6 Hz, 1H), 8.07 (dd, *J* = 8.7, 2.6 Hz, 1H), 7.48 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8 Hz, 2H), 7.2 (dd, *J* = 8.7, 4.0 Hz, 1H), 7.08 (d, *J* = 8.5 Hz, 2H), 6.82 (d, *J* = 8.5 Hz, 2H), 5.63 (s, 2H), 3.77 (s, 3H), 2.44 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 159.4, 148.2, 141.4, 139.3, 137.4, 137.0, 130.0, 129.8, 128.7, 128.7, 125.6, 125.5, 121.6, 114.3, 55.4, 54.6, 21.5; **HRMS** calcd for $C_{21}H_{20}N_3O$ ([M+H]$^+$): 330.1599; Found: 330.1600. **IR** (neat) $\tilde{\nu}$= 3031, 1609.1337 cm^{-1}.

2-(4-Methoxybenzyl)-3-(4-(trifluoromethyl)phenyl)-2*H*-pyrazolo[4,3-b]pyridine 2c:

Yellow solid (133 mg, 0.34 mmol, 85%), **mp** = 113-115°C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.60 (dd, *J* = 4.1, 1.5 Hz, 1H), 8.10 (dd, *J* = 8.8, 1.5 Hz, 1H), 7.77(q, *J* = 8.6 Hz, 4H), 7.27 (dd, *J* = 8.8, 4.1 Hz, 1H), 7.06 (d, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 8.6 Hz, 2H), 5.65 (s, 2H), 3.76 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 159.5, 148.9, 141.4, 137.5, 135.0, 132.1, 131.0 (q, J = 32.9 Hz), 130.3, 128.4, 128.1, 126.0 (q, J = 3.7 Hz), 125.9, 124.0 (q, J = 272.3 Hz), 121.9, 114.3, 55.3, 55.0; **HRMS** calcd for $C_{21}H_{17}F_3N_3O$ ([M+H]$^+$): 384.1317; Found: 384.1318. **IR** (neat) $\tilde{\nu}$= 3030, 1600, 1400, 1330 cm^{-1}.

2-(4-Methoxybenzyl)-3-(4-methoxyphenyl)-2*H*-pyrazolo[4,3-b]pyridine 2d:

Yellow solid (113 mg, 0.32 mmol, 80%), **mp** = 106-108 °C**. ^{1}H NMR** (250 MHz, $CDCl_3$) δ_H 8.57 (dd, *J* = 4.1, 1.5 Hz, 1H), 8.06 (dd, *J* = 8.8, 1.5 Hz, 1H), 7.52 (d, *J* = 8.8 Hz, 2H), 7.22 (dd, *J* = 8.8, 4.1 Hz, 1H), 7.13 – 7.01 (m, 4H), 6.82 (d, *J* = 8.8 Hz, 2H), 5.62 (s, 2H), 3.87 (s, 3H), 3.76 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 160.3, 159.3, 148.1, 141.3, 137.4, 136.7, 131.4, 128.7, 128.5, 125.6, 121.6, 120.7, 114.6, 114.2, 55.5, 55.3, 54.5; **HRMS** calcd for $C_{21}H_{20}N_3O_2$ ([M+H]$^+$): 346.1547; Found: 346.1550. **IR** (neat) $\tilde{\nu}$= 3007, 2961, 1606, 1250 cm^{-1}

2-(4-Methoxybenzyl)-3-(3-methoxyphenyl)-2*H*-pyrazolo[4,3-b]pyridine 2e:

Orange oil (99 mg, 0.28 mmol, 70%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.58 (dd, *J* = 4.3, 1.5 Hz, 1H), 8.07 (dd, *J* = 8.8, 1.5 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.22 (dd, *J* = 8.8, 4.3 Hz, 1H), 7.18 (d, *J* = 7.6 Hz, 1H), 7.11 – 7.05 (m, 3H), 7.01 (dd, *J* = 8.8, 2.6 Hz, 1H), 6.81 (d, *J* = 8.8 Hz, 2H), 5.63 (s, 2H), 3.76 (s, 3H), 3.74 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 159.8, 159.3, 148.2, 141.2, 137.3, 136.5, 130.0, 129.5, 128.5, 128.5, 125.5, 122.3, 121.5, 115.3, 115.1, 114.1, 55.2, 55.2, 54.6; **HRMS** calcd for $C_{21}H_{20}N_3O_2$ ([M+H]$^+$): 346.1548; Found: 346.1550. **IR** (neat) $\tilde{\nu}$= 3059, 2938, 1604, 1283 cm^{-1}

2-(4-Methoxybenzyl)-3-(2-methoxyphenyl)-2*H*-pyrazolo[4,3-b]pyridine 2f:

Yellow solid (96 mg, 0.27 mmol, 68%), **mp** = 106-108 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.54 (dd, *J* = 4.1, 1.5 Hz, 1H), 8.06 (dd, *J* = 8.8, 1.5 Hz, 1H), 7.49 (t, *J* = 8.7 Hz, 1H), 7.37 (dd, *J* = 7.5, 1.5 Hz, 2H), 7.20 (dd, *J* = 8.8, 4.1 Hz, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 7.05 (d, *J* = 8.7 Hz, 1H), 7.00 (d, *J* = 8.7 Hz, 2H), 6.75 (d, *J* = 8.7 Hz, 2H), 5.46 (s, 2H), 3.74 (s, 3H), 3.72 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 159.3, 157.3, 148.0, 141.4, 138.0, 133.8, 132.9, 131.3, 129.3, 128.5, 125.7, 121.3, 121.3, 117.4, 113.9, 111.5, 55.6, 55.3, 55.3; **HRMS** calcd for $C_{21}H_{20}N_3O_2$ ($[M+H]^+$): 346.1550; Found: 346.1550. **IR** (neat) ν̃= 3058, 2960, 1615, 1495 cm^{-1}

2-(4-Methoxybenzyl)-3-(4-chlorophenyl)-2*H*-pyrazolo[4,3-b]pyridine 2g:

White solid (100 mg, 0.28 mmol, 70%), **mp** = 119-121 °C**. ^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.58 (dd, *J* = 4.1, 1.4 Hz, 1H), 8.08 (dd, *J* = 8.8, 1.4 Hz, 1H), 7.51 (q, *J* = 8.7 Hz, 4H), 7.24 (dd, *J* = 8.8, 4.1 Hz, 1H), 7.06 (d, *J* = 8.7 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 5.62 (s, 2H), 3.76 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 159.5, 148.6, 141.4, 137.4, 135.4, 135.4, 131.3, 129.4, 128.5, 128.3, 126.9, 125.8, 121.8, 114.3, 55.3, 54.8; **HRMS** calcd for $C_{20}H_{17}ClN_3O$ ($[M+H]^+$): 350.1052; Found: 350.1054. **IR** (neat) ν̃= 3059, 1500, 706 cm^{-1}.

Ethyl 4-(2-(4-methoxybenzyl)-2*H*-pyrazolo[4,3-b]pyridin-3-yl)benzoate 2h:

White solid (126 mg, 0.32 mmol, 80%), **mp** = 117-119 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.61 (dd, *J* = 4.1, 1.4 Hz, 1H), 8.20 (d, *J* = 8.3 Hz, 2H), 8.10 (dd, *J* = 8.8, 1.4 Hz, 1H), 7.71 (d, *J* = 8.3 Hz, 2H), 7.27 (dd, *J* = 8.8, 4.1 Hz, 1H), 7.07 (d, *J* = 8.7 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 5.66 (s, 2H), 4.42 (q, *J* = 7.1 Hz, 2H), 3.76 (s, 3H), 1.42 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 166.1, 159.4, 148.7, 141.4, 137.5, 135.5, 132.8, 130.8, 130.1, 129.9, 128.5, 128.2, 125.8, 121.8, 114.3, 61.3, 55.3, 55.0, 14.4; **HRMS** calcd for $C_{23}H_{22}N_3O_3$ ($[M+H]^+$): 388.1658; Found: 388.1655. **IR** (neat) ν̃= 2977, 1712, 1606, 1162 cm^{-1}

2-(4-Methoxybenzyl)-3-(4-nitrophenyl)-2*H*-pyrazolo[4,3-b]pyridine 2i:

Yellow solid (113 mg, 0.31 mmol, 77%), **mp** = 130-132 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.64 (dd, J = 4.1, 1.4 Hz, 1H), 8.38 (d, J = 8.8 Hz, 2H), 8.13 (dd, J = 8.8, 1.4 Hz, 1H), 7.83 (d, J = 8.8 Hz, 2H), 7.31 (dd, J = 8.8, 4.1 Hz, 1H), 7.06 (d, J = 8.8 Hz, 2H), 6.83 (d, J = 8.8 Hz, 2H), 5.69 (s, 2H), 3.78 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 159.6, 149.3, 147.8, 141.5, 137.7, 134.9, 134.0, 130.7, 128.4, 127.9, 126.1, 124.2, 122.1, 114.5, 55.4, 55.4; **HRMS** calcd for $C_{20}H_{17}N_4O_3$ ($[M+H]^+$): 361.1292; Found: 361.1295. **IR** (neat) ν̃= 3059, 1576, 1541, 1328 cm^{-1}

4-(2-(4-Methoxybenzyl)-2*H*-pyrazolo[4,3-b]pyridin-3-yl)benzonitrile 2j:

White solid (118 mg, 0.34 mmol, 85%), **mp** = 190-192 °C. **^{1}H NMR** (250 MHz, CDCl3) δ_H 8.62 (dd, J = 4.1, 1.4 Hz, 1H), 8.12 (dd, J = 8.8, 1.4 Hz, 1H), 7.78 (q, J = 8.8 Hz, 4H), 7.29 (dd, J = 8.8, 4.1 Hz, 1H), 7.05 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.6 Hz, 2H), 5.67 (s, 2H), 3.77 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 159.6, 149.2, 141.4, 137.5, 134.4, 133.1, 132.7, 130.5, 128.4, 127.9, 126.1, 122.0, 118.5, 114.4, 112.6, 55.4, 55.3; **HRMS** calcd for $C_{21}H_{17}N_4O$ ($[M+H]^+$): 341.1395; Found: 341.1396. **IR** (neat) ν̃= 3350, 3187, 2221, 1608 cm^{-1}

2-(4-Methoxybenzyl)-3-(pyridin-4-yl)-2*H*-pyrazolo[4,3-b]pyridine 2k:

Yellow solid (77 mg, 0.24 mmol, 60%), **mp** = 97-99 °C**. ^{1}H NMR** (400 MHz, CDCl3) δ_H 8.77 (d, J = 5.9 Hz, 2H), 8.64 (dd, J = 4.1, 1.4 Hz, 1H), 8.12 (dd, J = 8.8, 1.4 Hz, 1H), 7.58 (d, J = 8.8 Hz, 2H), 7.29 (dd, J = 8.8, 4.1 Hz, 1H), 7.06 (d, J = 8.8 Hz, 2H), 6.83 (d, J = 8.8 Hz, 2H), 5.70 (s, 2H), 3.77 (s, 3H). **^{13}C NMR** (101 MHz, CDCl3) δ_C 159.6, 150.6, 149.3, 141.5, 137.6, 136.2, 133.5, 128.4, 128.0, 126.1, 124.0, 122.0, 114.5, 55.4, 55.4; **HRMS** calcd for $C_{19}H_{17}N_4O$ ($[M+H]^+$): 317.1395; Found: 317.1396. **IR** (neat) ν̃= 3369, 2849, 1398, 1275 cm^{-1}

2-(4-Methoxybenzyl)-3-(pyrazin-2-yl)-2*H*-pyrazolo[4,3-b]pyridine 2l:

Yellow solid (90 mg, 0.28 mmol, 70%), **mp** = 128-130 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.98 (d, *J* = 1.6 Hz, 1H), 8.67 (m, 2H), 8.54 (d, *J* = 2.5 Hz, 1H), 8.12 (dd, *J* = 8.7, 1.6 Hz, 1H), 7.28 (dd, *J* = 8.7, 4.1 Hz, 1H), 7.23 (d, *J* = 8.6 Hz, 2H), 6.77 (d, *J* = 8.6 Hz, 2H), 6.26 (s, 2H), 3.72 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 159.3, 149.1, 146.1, 144.8, 143.3, 143.0, 141.1, 138.1, 129.7, 129.3, 128.7, 126.2, 121.7, 114.0, 56.5, 55.2; **HRMS** calcd for $C_{18}H_{16}N_5O$ ($[M+H]^+$): 318.1349; Found: 318.1349. **IR** (neat) ν̃= 3057, 2919, 1603, 1395, 1187 cm^{-1}.

2-(4-Methoxybenzyl)-3-(thiophen-2-yl)-2*H*-pyrazolo[4,3-b]pyridine 2m:

Orange oil (72 mg, 0.22 mmol, 55%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.64 (dd, J = 4.1, 1.4 Hz, 1H), 8.07 (dd, J = 8.7, 1.4 Hz, 1H), 7.55 (dd, J = 5.1, 1.1 Hz, 1H), 7.47 (dd, J = 3.6, 1.1 Hz, 1H), 7.27 (dd, J = 8.7, 4.1 Hz, 1H), 7.20 (dd, J = 5.1, 3.6 Hz, 1H), 7.10 (d, J = 8.7 Hz, 2H), 6.83 (d, J = 8.7 Hz, 2H), 5.78 (s, 2H), 3.77 (s, 3H). **^{13}C NMR** (101 MHz, CDCl3) δ_C 159.5, 148.5, 141.4, 137.6, 130.4, 129.0, 128.4, 128.4, 128.3, 128.2, 127.9, 125.9, 121.9, 114.3, 55.4, 55.2; **HRMS** calcd for $C_{18}H_{16}N_3OS$ ($[M+H]^+$): 322.1008; Found: 322.1008. **IR** (neat) ν̃= 3057, 2600, 1350, 1080 cm^{-1}

1-(4-Methoxybenzyl)-3-phenyl-1*H*-pyrazolo[4,3-b]pyridine 4a:

White solid (104 mg, 0.33 mmol, 80%), **mp** = 80-82 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.64 (d, J = 4.3 Hz, 1H), 8.52 (d, J = 7.7 Hz, 2H), 7.61 (d, J = 8.5 Hz, 1H), 7.51 (t, J = 7.7 Hz, 2H), 7.39 (t, J = 7.7 Hz, 1H), 7.28 – 7.17 (m, 3H), 6.84 (d, J = 8.5 Hz, 2H), 5.59 (s, 2H), 3.77 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 159.5, 145.5, 143.1, 140.2, 133.8, 132.5, 128.8, 128.7, 128.3, 128.2, 127.3, 120.6, 117.5, 114.3, 55.4, 53.5; **HRMS** calcd for $C_{20}H_{18}N_3O$ ($[M+H]^+$): 316.1441; Found: 316.1444. **IR** (neat) ν̃= 3410, 2930, 1170 cm^{-1}

1-(4-Methoxybenzyl)-3-p-tolyl-1*H*-pyrazolo[4,3-b]pyridine 4b:

Yellow solid (94 mg, 0.28 mmol, 70%), **mp** = 60-62 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.62 (dd, *J* = 4.3, 1.4 Hz, 1H), 8.44 (d, *J* = 8.2 Hz, 2H), 7.57 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.33 (d, *J* = 7.9 Hz, 2H), 7.21 – 7.16 (m, 3H), 6.83 (d, *J* = 8.2 Hz, 2H), 5.55 (s, 2H), 3.75 (s, 3H), 2.42 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 159.4, 145.2, 143.1, 140.1, 138.0, 133.6, 129.6, 129.4, 128.7, 128.4, 127.1, 120.4, 117.4, 114.2, 55.3, 53.3, 21.5; **HRMS** for $C_{21}H_{20}N_3O$ ($[M+H]^+$): 330.1601; Found: 330.1600. IR (neat) ν̃= 3030, 1605, 1340 cm^{-1}.

1-(4-Methoxybenzyl)-3-(4-(trifluoromethyl)phenyl)-1*H*-pyrazolo[4,3-b]pyridine 4c:

White solid (117 mg, 0.30 mmol, 75%), **mp** = 100-102 °C.**^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.72 – 8.61 (m, 3H), 7.74 (d, *J* = 7.8 Hz, 2H), 7.63 (d, *J* = 8.5 Hz, 1H), 7.27 – 7.17 (m, 3H), 6.84 (d, *J* = 7.8 Hz, 2H), 5.58 (s, 2H), 3.76 (s, 3H). **^{13}C NMR** (101 MHz, CDCl3) δC 159.5, 145.7, 141.4, 140.1, 135.9, 133.7, 129.6 (q, J = 32.3 Hz), 128.7, 128.4, 127.8, 127.1, 125.4 (q, J = 3.8 Hz), 124.4 (q, J = 270 Hz), 120.7, 117.6, 55.2, 53.5; **HRMS** calcd for $C_{21}H_{17}F_3N_3O$ ($[M+H]^+$): 384.1315; Found: 384.1318. **IR** (neat) ν̃= 3030, 1500, 1300, 1330 cm^{-1}.

1-(4-Methoxybenzyl)-3-(4-methoxyphenyl)-1*H*-pyrazolo[4,3-b]pyridine 4d:

White solid (91 mg, 0.263 mmol, 65%), **mp** = 113-115 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.61 (dd, *J* = 4.4, 1.4 Hz, 1H), 8.47 (d, *J* = 8.8 Hz, 2H), 7.58 (dd, *J* = 8.8, 1.4 Hz, 1H), 7.20 (m, 3H), 7.05 (d, *J* = 8.8 Hz, 2H), 6.83 (d, *J* = 8.8 Hz, 2H), 5.55 (s, 2H), 3.87 (s, 3H), 3.76 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 159.7, 159.4, 145.1, 143.0, 140.0, 133.7, 128.7, 128.6, 128.4, 125.3, 120.5, 117.3, 114.3, 114.2, 55.4, 55.3, 53.3; **HRMS** calcd for $C_{21}H_{20}N_3O_2$ ($[M+H]^+$): 346.1546; Found: 346.1550. **IR** (neat) ν̃= 3000, 2955, 1606, 1250 cm^{-1}.

1-(4-Methoxybenzyl)-3-(3-methoxyphenyl)-1*H*-pyrazolo[4,3-b]pyridine 4e:

Yellow solid (101 mg, 0.29 mmol, 72%), **mp** = 90-92 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.61 (dd, *J* = 4.3, 1.4 Hz, 1H), 8.19 (d, *J* = 7.7 Hz, 1H), 8.14 (s, 1H), 7.57 (dd, *J* = 8.7, 1.4 Hz, 1H), 7.43 (t, *J* = 8.0 Hz, 1H), 7.18 (m, 3H), 6.95 (dd, *J* = 7.7, 3.0 Hz, 1H), 6.82 (d, *J* = 8.7 Hz, 2H), 5.54 (s, 2H), 3.92 (s, 3H), 3.74 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 159.9, 159.4, 145.4, 142.7, 140.1, 133.8, 133.6, 129.7, 128.75, 128.2, 120.5, 119.9, 117.4, 114.3, 114.2, 112.1, 55.4, 55.3, 53.3; **HRMS** calcd for $C_{21}H_{20}N_3O_2$ ($[M+H]^+$): 346.1549; Found:,346.1550. **IR** (neat) ν̃= 3050, 2934, 1601, 1280cm^{-1}.

1-(4-Methoxybenzyl)-3-(2-methoxyphenyl)-1*H*-pyrazolo[4,3-b]pyridine 4f:

Orange oil (90 mg, 0.260 mmol, 63%). **^{1}H NMR** (250 MHz, $CDCl_3$) δ_H 8.58 (d, *J* = 4.3 Hz, 1H), 7.80 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.60 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.45 – 7.33 (m, 1H), 7.24 (d, *J* = 9.2 Hz, 2H), 7.24 – 7.02 (m, 3H), 6.84 (d, *J* = 9.2 Hz, 2H), 5.61 (s, 2H), 3.86 (s, 3H), 3.77 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 159.4, 157.8, 145.4, 142.6, 141.0, 133.0, 132.0, 130.0, 128.9, 128.5, 120.9, 120.9, 120.5, 117.4, 114.2, 112.0, 56.2, 55.4, 53.5; **HRMS** calcd for $C_{21}H_{20}N_3O_2$ ($[M+H]^+$): 346.1549; Found: 346.1550. **IR** (neat) ν̃= 3055, 2962, 1610, 1490 cm^{-1}.

1-(4-Methoxybenzyl)-3-(4-chlorophenyl)-1*H*-pyrazolo[4,3-b]pyridine 4g:

White solid (124 mg, 0.35 mmol, 87%), **mp** = 104-106 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.59 (dd, *J* = 4.3, 1.4 Hz, 1H), 8.49 (d, *J* = 8.5 Hz, 2H), 7.57 (d, *J* = 8.5 Hz, 1H), 7.45 (d, *J* = 8.5 Hz, 2H), 7.17 (m, 3H), 6.81 (d, *J* = 8.5 Hz, 2H), 5.52 (s, 2H), 3.73 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 159.5, 145.5, 141.8, 139.9, 133.8, 133.7, 131.0, 128.8, 128.7, 128.4, 128.1, 120.6, 117.5, 114.3, 55.3, 53.4; **HRMS** calcd for $C_{20}H_{17}ClN_3O$ ($[M+H]^+$): 350.1051; Found: 350.1054. **IR** (neat) ν̃= 3060, 1501, 701 cm^{-1}.

Ethyl 4-(1-(4-methoxybenzyl)-1*H*-pyrazolo[4,3-b]pyridin-3-yl)benzoate 4h:

White solid (126 mg, 0.32 mmol, 80%), **mp** = 111-113 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.65 (m, 3H), 8.17 (d, *J* = 8.3 Hz, 2H), 7.61 (d, *J* = 8.3 Hz, 1H), 7.22 (m, 3H), 6.83 (d, *J* = 8.3 Hz, 1H), 5.57 (s, 2H), 4.41 (q, *J* = 7.1 Hz, 2H), 3.75 (s, 3H), 1.42 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 166.7, 159.5, 145.8, 141.8, 140.3, 136.8, 133.8, 129.9, 129.7, 128.8, 128.0, 126.8, 120.7, 117.7, 114.3, 61.0, 55.3, 53.6, 14.4; **HRMS** calcd for $C_{23}H_{22}N_3O_3$ ($[M+H]^+$): 388.1656; Found: 388.1655. **IR** (neat) ν̃= 2975, 1710, 1606, 1161 cm^{-1}.

1-(4-Methoxybenzyl)-3-(4-nitrophenyl)-1*H*-pyrazolo[4,3-b]pyridine 4i:

Yellow oil (135 mg, 0.37 mmol, 91%), **mp** = 160-162 °C. **^{1}H NMR** (250 MHz, $CDCl_3$) δ_H 8.77 (d, *J* = 9.0 Hz, 2H), 8.68 (dd, *J* = 4.3, 1.2 Hz, 1H), 8.33 (d, *J* = 9.0 Hz, 2H), 7.68 (dd, *J* = 8.6, 1.2 Hz, 1H), 7.34 – 7.17 (m, 3H), 6.86 (d, *J* = 8.6 Hz, 2H), 5.61 (s, 2H), 3.77 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 159.7, 147.2, 146.3, 140.6, 140.3, 139.0, 133.9, 128.9, 127.7, 127.5, 124.0, 121.0, 118.0, 114.4, 55.4, 53.9; **HRMS** calcd for $C_{20}H_{17}N_4O_3$ ($[M+H]^+$): 361.1295; Found: 361.1295. **IR** (neat) ν̃= 3050, 1573, 1540, 1320 cm^{-1}.

4-(1-(4-Methoxybenzyl)-1*H*-pyrazolo[4,3-b]pyridin-3-yl)benzonitrile 4j:

White solid (118 mg, 0.34 mmol, 85%), **mp** = 178-180 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.65 (m, 3H), 7.95 (d, J = 8.8 Hz, 2H), 7.64 (dd, J = 8.8, 1.2 Hz, 1H), 7.25 (m, 3H), 6.85 (d, J = 8.8 Hz, 2H), 5.59 (s, 2H), 3.76 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 169.4, 159.6, 145.8, 141.8, 140.3, 136.1, 133.8, 132.5, 128.8, 128.0, 127.8, 127.2, 120.8, 117.7, 114.4, 55.4, 53.6; **HRMS** calcd for $C_{21}H_{17}N_4O$ ($[M+H]^+$): 341.1503; Found: 341.1502. **IR** (neat) $\tilde{\nu}$= 3350, 3180, 2218, 1605 cm^{-1}

1-(4-Methoxybenzyl)-3-(pyridin-4-yl)-1*H*-pyrazolo[4,3-b]pyridine 4k:

Yellow solid (64 mg, 0.20 mmol, 50%), **mp** = 123-125 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.77 (dd, *J* = 4.5, 1.6 Hz, 2H), 8.64 (dd, *J* = 4.5, 1.4 Hz, 1H), 8.12 (dd, *J* = 8.8, 1.6 Hz, 1H), 7.59 (dd, *J* = 4.5, 1.6 Hz, 2H), 7.30 (dd, *J* = 8.8, 4.1 Hz, 1H), 7.06 (d, *J* = 8.8 Hz, 2H), 6.83 (d, *J* = 8.8 Hz, 2H), 5.70 (s, 2H), 3.77 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 159.6, 150.6, 149.2, 141.5, 137.6, 136.2, 133.5, 128.4, 127.9, 126.1, 124.0, 122.0, 114.4, 55.4, 55.3; **HRMS** calcd for $C_{19}H_{17}N_4O$ ($[M+H]^+$): 317.1394; Found: 317.1396. **IR** (neat) $\tilde{\nu}$= 3369, 2850, 1395, 1270 cm^{-1}.

1-(4-Methoxybenzyl)-3-(pyrazin-2-yl)-1*H*-pyrazolo[4,3-b]pyridine 4l:

Yellow solid (77 mg, 0.24 mmol, 60%), **mp** = 80-82 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) 9.93 (d, *J* = 1.1 Hz, 1H), 8.78 (s, 1H), 8.73 (d, *J* = 2,4Hz, 1H), 8.58 (d, *J* = 2.4 Hz, 1H), 7.67 (dd, *J* = 8.4, 1.1 Hz, 1H), 7.28 (dd, *J* = 8.4, 3.1 Hz, 1H), 7.24 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 5.68 (s, 2H), 3.76 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 159.6, 147.5, 146.8, 144.6, 144.6, 143.4, 140.2, 140.1, 133.7, 128.9, 127.6, 121.0, 118.1, 114.3, 55.3, 54.1; **HRMS** calcd for $C_{18}H_{16}N_5O$ ($[M+H]^+$): 318.1346; Found: 318.1349. **IR** (neat) $\tilde{\nu}$= 3050, 2920, 1603, 1392, 1183 cm^{-1}.

3-Phenyl-1*H*-pyrazolo[4,3-b]pyridine 5a:

White solid (116 mg, 0.32 mmol, 71%), **mp** = 168-169°C. **^{1}H NMR** (400 MHz, MeOD) δH 8.62 (dd, J = 4.4, 1.3 Hz, 1H), 8.39 (d, J = 7.5 Hz, 2H), 8.03 (dd, J = 8.5, 1.3 Hz, 1H), 7.52 (t, J = 7.5 Hz, 2H), 7.47 – 7.36 (m, 2H). **^{13}C NMR** (101 MHz, MeOD) δ_C 146.6, 144.8, 139.4, 135.9, 133.7, 129.5, 129.3, 128.4, 122.3, 120.0; **HRMS** calcd for $C_{12}H_{10}N_3$ ($[M+H]^+$): 196.0869; Found: 196.0870. **IR** (neat) $\tilde{\nu}$= 3209, 3146, 3055, 1600, 1292 cm^{-1}.

3-p-Tolyl-1*H*-pyrazolo[4,3-b]pyridine 5b:

Green solid (125 mg, 0.39 mmol, 72%), **mp** = 191-193 °C. **^{1}H NMR** (250 MHz, Acetone) δ_H 12.42 (s, 1H), 8.63 (dd, J = 4.3, 1.3 Hz, 1H), 8.54 (d, J = 8.5 Hz, 2H), 8.03 (dd, J = 8.5, 1.3 Hz, 1H), 7.39 (dd, J = 8.5, 4.3 Hz, 1H), 7.32 (d, J = 8.5 Hz, 2H), 2.39 (s, 3H). **^{13}C NMR** (101 MHz, CDCl3) δ_C 145.6, 144.8, 139.1, 138.3, 134.2, 129.4, 129.3, 127.2, 121.0, 117.9, 21.4; **HRMS** calcd for $C_{13}H_{12}N_3$ ($[M+H]^+$): 210.1024; Found: 210.1025. **IR** (neat) $\tilde{\nu}$= 3057, 2919, 1603, 1395 cm^{-1}.

3-(4-Chlorophenyl)-1*H*-pyrazolo[4,3-b]pyridine 5c:

Yellow solid (147 mg, 0.39 mmol, 76%), **mp** = 230-232 °C. **^{1}H NMR** (400 MHz, DMSO) δ_H 13.52 (s, 1H), 8.63 (dd, J = 4.3, 1.4 Hz, 1H), 8.55 (d, J = 8.7 Hz, 2H), 8.07 (dd, J = 8.7, 1.4 Hz, 1H), 7.58 (d, J = 8.7 Hz, 2H), 7.44 (dd, J = 8.7, 4.3 Hz, 1H). **^{13}C NMR** (101 MHz, DMSO) δ_C 145.6, 140.6, 138.1, 134.0, 132.4, 131.5, 128.6, 127.8, 121.0, 118.9; **HRMS** calcd for $C_{12}H_9ClN_3$ ($[M+H]^+$): 230.0479; Found: 230.0479. **IR** (neat) $\tilde{\nu}$= 3067, 2919, 1603, 1395, 706 cm^{-1}.

Ethyl 4-(1*H*-pyrazolo[4,3-b]pyridin-3-yl)benzoate 5d:

White solid (167 mg, 0.40 mmol, 75%), **mp** = 184-186 °C**. ^{1}H NMR** (250 MHz, CDCl3) δ_H 10.55 (s, 1H), 8.73 (dd, J = 4.3, 1.1 Hz, 1H), 8.64 (d, J = 8.5 Hz, 1H), 8.19 (d, J = 8.5 Hz, 2H), 7.84 (d, J = 8.5 Hz, 1H), 7.36 (dd, J = 8.5, 4.3 Hz, 1H), 4.42 (q, J = 7.1 Hz, 2H), 1.43 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, MeOD) δ_C 167.9, 147.0, 143.3, 139.7, 138.4, 135.9, 130.8, 130.6, 127.9, 122.4, 120.1, 62.1, 14.6; **HRMS** calcd for $C_{15}H_{14}N_3O_2$ ($[M+H]^+$): 268.1081; Found: 268.1080. **IR** (neat) $\tilde{\nu}$= 3369, 3031, 1710, 1603, 1161 cm^{-1}.

3-(Pyrazin-2-yl)-1*H*-pyrazolo[4,3-b]pyridine 5e:

White solid (87 mg, 0.38 mmol, 53%), **mp** = 180-182 °C**. ^{1}H NMR** (400 MHz, MeOD) δ_H 9.76 (d, J = 1.3 Hz, 1H), 8.75 (dd, J = 2.3, 1.3 Hz, 1H), 8.69 (d, J = 3.6 Hz, 1H), 8.60 (d, J = 2.3 Hz, 1H), 8.10 (dd, J = 8.6, 1.3 Hz, 1H), 7.48 (dd, J = 8.6, 4.4 Hz, 1H). **^{13}C NMR** (101 MHz, MeOD) δ_C 147.5, 146.5, 144.3, 143.4, 143.1, 121.3, 121.0, 118.1, 115.2, 112.3; **HRMS** calcd for $C_{10}H_8N_5$ ($[M+H]^+$): 198.0774; Found: 198.0774. **IR** (neat) $\tilde{\nu}$= 3057, 2850, 1600, 1390, 1187 cm^{-1}.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02136.
Characterization data for all new Compounds (PDF).

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