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"On Water" Direct C-3 Arylation of 2H-Pyrazolo[3,4-b]pyridines

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ABSTRACT. An "on water" palladium catalyzed direct (hetero)arylation of 2*H*-pyrazolo[3,4-b]pyridines has been developed. The reactions proceeds smoothly with at low catalytic loading at low temperature providing the C3 (hetero)arylated products in good to excellent isolated yields. *NH* Free 3-arylated 7-azaindazoles were also prepared by simple cleavage of the *N*-protected groups.

INTRODUCTION

Direct arylation is considered nowadays as one of the most important achievements in organic chemistry[1-10]. This method, in contrast to classical cross-coupling reactions (for example Suzuki-Miyaura and Stille), avoids the use of stoichiometric organometallics, which are often expensive, need time-consuming preparation and may

produce toxic by-products. Although the advances made in direct arylation, this method still suffers from some drawbacks such as the use of drastic reaction conditions including high temperatures, organic solvents, and high metal catalyst loading.

2*H*-Pyrazolo[3,4-b]pyridines (2*H*-7-azaindazoles) are quite rare in nature. 7-Azaindazole analogues have been reported with a broad range of biological activities. In recent examples, they have shown activities such as potent and selective FGFR kinase inhibitors[11], c-Met inhibitors[12], anticancer agents[13-15], inhibitors of human nicotinamide phosphoribosyltransferase (NAMPT)[16], dual orexin receptor antagonists (DORAs)[17]. Moreover, 3-arylated 7-azaindazoles are present in drugs such as BAY 41-2272[18], BAY 63-2521[19] (Riociguat, Adempas®) and BAY 41-8543[20] known as stimulators of soluble guanylate cyclase (sGC) through a NO-independent mechanism. This Bay drugs family inhibit platelet aggregation, induce vasorelaxation and are used for the treatment of chronic thromboembolic pulmonary hypertension and pulmonary arterial hypertension (Figure 1).

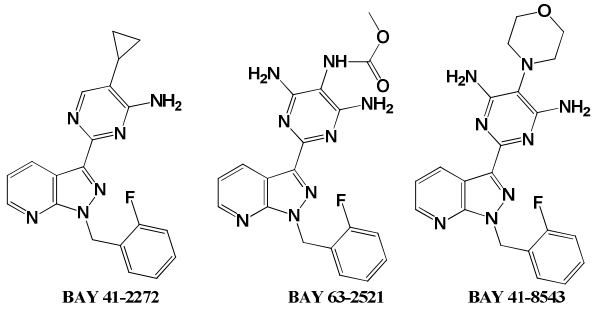
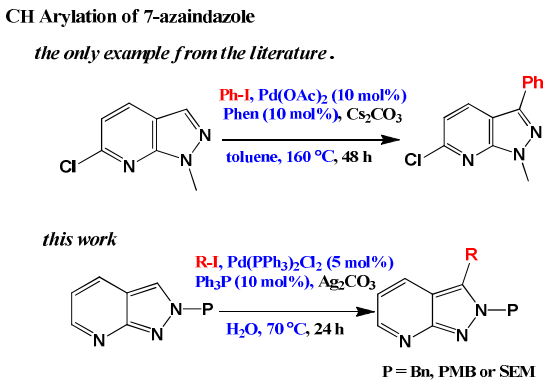


Fig. 1. Representative examples of drugs containing 3-arylated 7-azaindazoles.

Despite these important biological properties, only one example on the direct arylation of 1*H*-pyrazolo[3,4-b]pyridine emerged from the elegant study reported by Yu et al.[21] In this case, the cross-coupling reaction was achieved via palladium direct arylation using 10 mol% of $Pd(OAc)_2$ in organic solvent at high temperature (toluene at 160 °C, Scheme 1).

Water, a non-toxic liquid, is the solvent of choice for green chemistry. However, working with water is still challenging because of its limited chemical compatibility as well as the low aqueous solubility of large number of reactants.

Herein we wish to report the direct (hetero)arylation of 2*H*-7-azaindazoles under "on water" conditions at low temperature (70 °C) using a low amount of palladium catalyst (Scheme 1). It is noteworthy that the use of "on water" conditions in direct C-H arylation is still challenging [22-33].



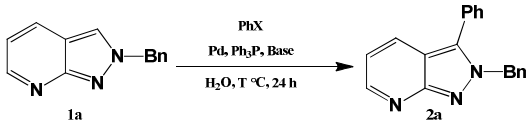
Scheme 1. Reported method on 1*H*-7-azaindazole *versus* our procedure on the 2*H*-7-azaindazole series.

Results and discussion

We started our investigation using 2*H*-7-azaindazole **1a** and benzene iodide as model substrates. In an initial attempt, **1a** was treated by benzene iodide (2 equiv.) in the presence of 10 mol% of $Pd(OAc)_2$ as catalyst, 20 mol% of PPh_3 and 1 equiv. of Ag_2CO_3 as base in H_2O at 60 °C. This sequence did not give the expected product but only the starting 2*H*-7-azaindazole **1a** which was quantitatively recovered (entry 1, Table 1). The same result was observed when $PdCl_2$ was used instead of $Pd(OAc)_2$ (entry 2, Table 1). However, the use of $Pd(PPh_3)_2Cl_2$ as catalyst led to the desired product in very good yield (entry 3, Table 1). When the reaction mixture was heated at 70 °C the yield was slightly enhanced without any traces of starting

material (entry 4, Table 1). Then, the amount of both the catalyst and the ligand were reduced to 10 mol% without any decrease in the reaction yield (entry 5, Table 1). More interestingly, the amount of catalyst could be reduced to 5 mol% and the desired product was isolated in 92% yield (entry 6, Table 1). Further attempts to reduce the amount of both the catalyst and the ligand did not induce coupling (entries 7 and 8, Table 1). We also tested the effect of the ligand by carrying out the reaction without Ph_3P. Although the desired product was obtained in 50% isolated yield, a large amount of starting material was also recovered (entry 9, Table 1). When $Pd(dppf)Cl_2.DCM$ was used instead of $Pd(PPh_3)_2Cl_2$ under the optimised reaction conditions, the expected product was obtained in a 87/13 ratio with the starting material (based on ^1H NMR, entry 10, Table 1). We also found that bromobenzene was less reactive than benzene iodide. The mixture needed to be heated to 110 °C to achieve a good reaction yield, and nevertheless, 15% of starting material **1a** was recovered (entry 11, Table 1). The replacement of Ag_2CO_3 by either K_3PO_4, Cs_2CO_3 or K_2CO_3 bases led to a total loss of the reactivity. Thus, only starting material was recovered in the cases of K_3PO_4 and K_2CO_3 (entries 12 and 13, Table 1), while, a very low yield of desired product **2a** was obtained with Cs_2CO_3 (entry 14, Table 1).

Table 1. Optimisation of the "on water" palladium catalysed direct (hetero)arylation of 2*H*-pyrazolo[3,4-b]pyridine **1a**.



entry	X	Pd (mol %)	PPh_3 (%)	Base(2éq)	T (°C)	yield (%)
1	I	$Pd(OAc)_2$ (10)	20	Ag_2CO_3	60	(100)[a]
2	I	$Pd(Cl)_2$ (10)	20	Ag_2CO_3	60	(100)[a]
3	I	$Pd(PPh_3)_2Cl_2$ (10)	20	Ag_2CO_3	60	92[b] (traces)[a]
4	I	$Pd(PPh_3)_2Cl_2$ (10)	20	Ag_2CO_3	70	94[b]
5	I	$Pd(PPh_3)_2Cl_2$ (10)	10	Ag_2CO_3	70	94[b]
6	I	$Pd(PPh_3)_2Cl_2$ (5)	10	Ag_2CO_3	70	92[b]

7	I	$Pd(PPh_3)_2Cl_2$ (5)	5	Ag_2CO_3	70	77[c] (23)[a]
8	I	$Pd(PPh_3)_2Cl_2$ (2.5)	5	Ag_2CO_3	70	63[c] (37)[a]
9	I	$Pd(PPh_3)_2Cl_2$ (5)	0	Ag_2CO_3	70	50[b] (42)[d]
10	I	$Pd(dppf)Cl_2$.DCM (5)	10	Ag_2CO_3	70	87[c] (13)[a]
11	Br	$Pd(PPh_3)_2Cl_2$ (5)	10	Ag_2CO_3	110	80[c] (15)[d]
12	I	$Pd(PPh_3)_2Cl_2$ (5)	10	K_3PO_4	70	(100)[a]
13	I	$Pd(PPh_3)_2Cl_2$ (5)	10	K_2CO_3	70	(100)[a]
14	I	$Pd(PPh_3)_2Cl_2$ (5)	10	Cs_2CO_3	70	10[b] (80)[d]

[a] % of recovered starting material **1a** based on ^{1}H NMR, [b] yield of isolated product **2a**, [c] % of product **2a** based on ^{1}H NMR. [d] yield of recovered starting material **1a**.

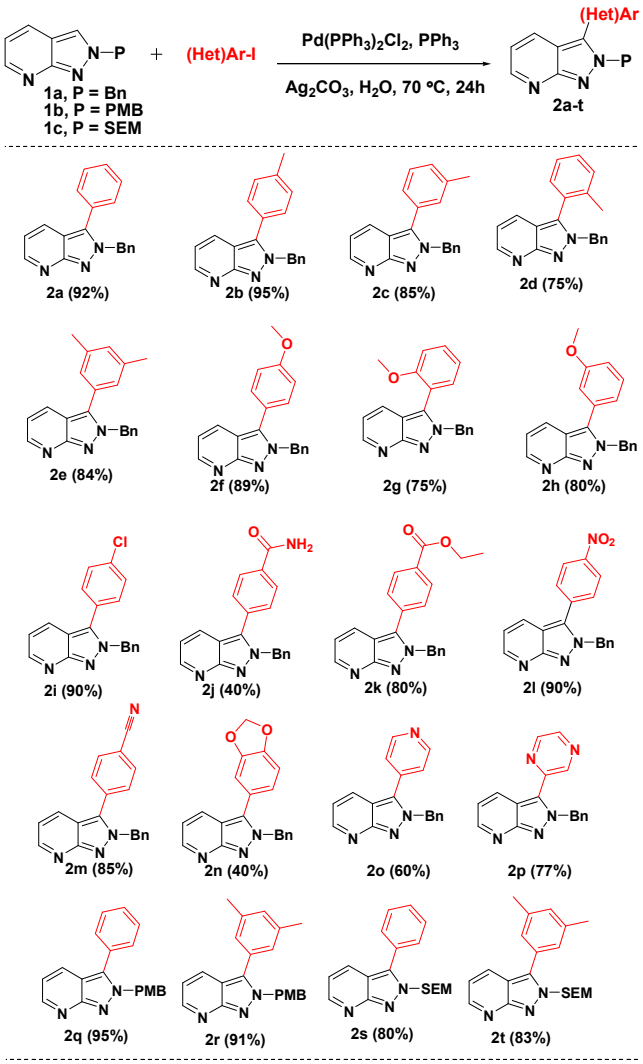
The scope and limitation of the "on water" palladium catalysed direct (hetero)arylation were investigated from the starting 2*H*-7-azaindazole **1a** and **1b** with various aryl and heteroaryl iodides (Table 2). It was found that the nature of the substituents (electron-donating or electron-withdrawing groups) or steric hindrance (methoxy group at the 2-position of the aromatic ring) on the iodoaryl ring did not affect the reaction yields (compounds **2a-i** and **2k-m**). This procedure also showed a very high tolerance to various substituents on the aryl rings (methoxy, chlorine, amide, ester, nitro, cyano and ether groups). In only two cases were low yields obtained (compounds **2j** and **2n**). We were also able to introduce heteroaryl groups such as pyridyl and pyrazyl groups in good yields (compounds **2o** and **2p**).

Very recently, free (*NH*) 7-azaindazoles were reported with very interesting biological applications such as metabotropic glutamate receptor 5 positive allosteric modulators[34], CDK8 Inhibitors[35], FGFR Kinase Inhibitors[11], or analgesic and anti-inflammatory activities[36]. In order to generate 3-arylated free (*NH*) 7-azaindazoles, we decided to use either *p*-methoxybenzyl (PMB) or trimethylsilyl ethoxymethyl chloride (SEM)[37] as protecting groups instead of Bn. This choice was mandatory because the cleavage of the Bn protecting group led to various by-products.

The treatment of starting materials **1b** containing PMB or **1c** containing SEM (the preparation of starting materials **1b** and **1c** is described in the supporting information)

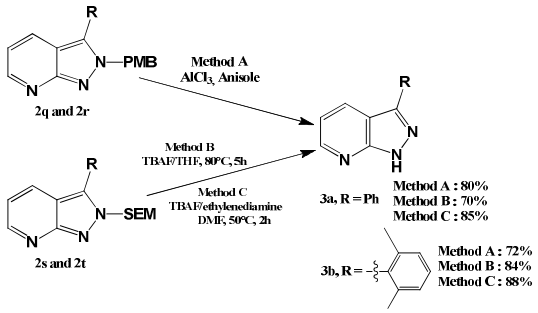
by either benzene iodide or 1-iodo-3,5-dimethylbenzene as coupling partner under the optimised reaction conditions led to the expected 3-arylated compounds **2q** **2r**, **2s** and **2t** in good yields (Table 2).

Table 2. Scope and limitation of the "on water" palladium catalysed direct (hetero)arylation of 2*H*-pyrazolo[3,4-b]pyridines **1a-c**.



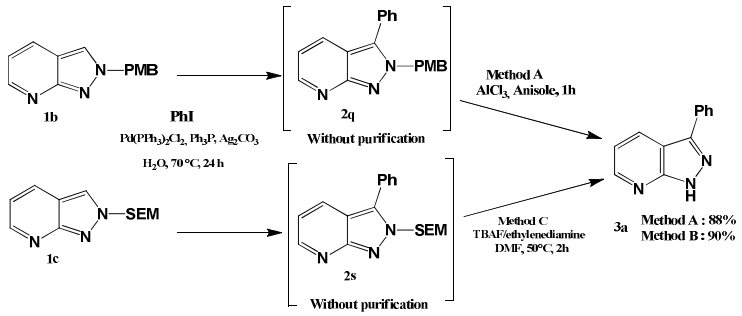
Then, to produce 3-arylated free *(NH)* 7-azaindazole derivatives, we treated compounds **2q** and **2r** with $AlCl_3$ in anisole (Method A). This procedure furnished the expected 3-arylated free (*NH)* 7-azaindazoles **3a** and **3b** in 80 and 72% yield, respectively. In the case of 3-arylated indazoles containing a SEM protecting group (derivatives **2s** and **2t)**, the expected 3-arylated

free (*NH)* 7-azaindazoles **3a** and **3b** were obtained using two different methods B and C. Following method B[37], **2s** and **2t** were treated with TBAF in THF at 80°C for 5h leading to **3a** and **3b** in 70 and 84% yield, respectively. Using method C[38] (TBAF /ethylenediamine in DMF at 50°C for 2h), the expected 3-arylated free *(NH)* 7-azaindazoles **3a** and **3b** were isolated in 85 and 88% yield, respectively (Scheme 2).



Scheme 2. Preparation of 3-arylated free *NH* 7-azaindazoles **3a-b**.

To produce 3-arylated free *(NH)* 7-azaindazole derivatives with limiting time-consuming purifications, we proposed an arylation/deprotection sequence directly from staring materials **1b** and **1c**, without any gel chromatography of the intermediates **2q** and **2s**. Thus, **1b** was arylated under optimized "on water" reaction conditions, then, after filtration, extraction and removal of solvent, crude product **2q** was treated by $AlCl_3$ in anisole (Method A). This procedure furnished the expected 3-arylated free (*NH)* 7-azaindazoles **3a** in 88% yield, (two steps yield). In the case of starting material **1c**, the treatment under similar arylation conditions led to intermediate **2s**, then, the expected 3-arylated free (*NH)* 7-azaindazoles **3a** was achieved by treatment of crude intermediate **2s** by TBAF /ethylenediamine in DMF at 50°C for 2h[38]. The expected 3-arylated free *(NH)* 7-azaindazoles **3a** was isolated in 90% yield (two steps yield) (Scheme 3).



Scheme 3. Arylation/deprotection route to 3-arylated free *NH* 7-azaindazole **3a**.

CONCLUSIONS

In conclusion, we have reported an original direct (hetero)arylation of 2*H*-pyrazolo[3,4-b]pyridines in good to excellent yields under "on water" conditions at 70 °C using only 5 mol% of palladium catalyst. This procedure tolerates a wide variety of functional groups. Under mild reaction conditions, we have also shown the possibility of generating free (*NH)* pyrazolo[3,4-*b*]pyridines by the cleavage of the PMB or SEM protecting groups. Improved yields were obtained using an (hetero)arylation/deprotection sequence avoiding gel chromatography purification of crude intermediates.

EXPERIMENTAL 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). ^{1}H and ^{13}C NMR spectra were recorded with a 250 MHz (^{1}H: 250 and ^{13}C: 63 MHz) or 400 MHz (^{1}H: 400 and ^{13}C: 100.7 MHz) Bruker spectrometer using $CDCl_3$ as solvent. Chemical shifts of ^{1}H 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 = 7.26 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), and integration. Chemical shifts of ^{13}C NMR were reported in ppm and calibrated to the residual solvent peak as an internal standard ($CDCl_3$: δ = 77.0 ppm). 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 by the "Federation de Recherche" ICOA/CBM (FR2708) platform.

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

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

Hydrazine hydrate (10 mL) was added to a mixture of 2-chloro-3-formylpyridine **(**5.00 g, 35 mmol) and *p*-TsOH (3.50 g, 18 mmol). The reaction mixture was stirred for 3 h at 130 °C. Upon cooling with cold water, the mixture was extracted with EtOAc. The combined organic extracts were dried over anhydrous $MgSO_4$. After filtration, the solvent was removed in vacuum to give 1*H*-pyrazolo [3,4-b] pyridine (3.74 g, 90%) as a yellow solid.

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

Yield: (3,8 g, 90%) White solid, mp 98-99 °C. (literature, 88-90°C[39], 97-98°C[40]), IR (neat): ν̃ = 3450, 3089 , 2958, 1429 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = δ13.65 (s, 1H), 8.66 (dd, J = 4.6, 1.6 Hz, 1H), 8.13 (s, 1H), 8.12 (d, J = 1.6 Hz, 1H), 7.16 (dd, J = 8.0, 4.6 Hz, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 151.8, 148.7, 133.7, 130.6, 117.0, 115.4 ppm. HRMS: calcd. for $C_6H_6N_3[M+H]^+$: 120.0555, found 120.0556.

_N_-Alkylation of 1_H_-pyrazolo [3,4-_b_] pyridine

Potassium hydroxide (1.4 g, 25.21 mmol) was added to a solution of 1*H*-pyrazolo [3,4-*b*] pyridine (1 g, 8.40 mmol) in acetone (10 mL), and the mixture was maintained for 60 min at 0 °C. Then, benzyl chloride (1.5 g, 12.6 mmol, 1.5 equiv) or 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 7 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 /AcOEt, 8:2) for the benzylated product **1a** (50% yield) and (petroleum ether /AcOEt, 1:1) for the para-methoxybenzylated product **1b** (51% yield).

2-Benzyl-2*H*-pyrazolo[3,4-*b*]pyridine 1a.

Yield: (875 mg, 50%) yellow solid, mp 142-143 °C (literature 142-144 C°[40]). IR (neat): ν̃ = 3088, 2943, 1615, 1157, cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.69 (dd, J = 4.2, 1.8 Hz, 1H), 7.98 (dd, J = 8.3, 1.8 Hz, 1H), 7.86 (s, 1H), 7.41 – 7.30 (m, 5H), 7.03 (dd, J = 8.3, 4.2 Hz, 1H), 5.63 (s, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.5, 151.6, 135.2, 129.7, 129.1, 128.7, 128.5, 122.5, 117.9, 114.4, 58.2 ppm. HRMS: calcd. for $C_{13}H_{12}N_3[M+H]^+$: 210.1025, found 210.1025.

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

Yield: (1,02 g, 51%) red liquid. IR (neat): ν̃ = 3417, 2935, 1667, 1176, cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.65 (d, J = 4.2 Hz, 1H), 7.95 (d, J = 8.3 Hz, 1H), 7.83 (s, 1H), 7.30 (d, J = 8.3 Hz, 2H), 6.98 (dd, J = 8.3, 4.2 Hz, 1H), 6.87 (d, J = 8.3 Hz, 2H), 5.52 (s, 2H), 3.77 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 159.8, 158.3, 151.2, 130.0, 129.6, 127.0, 122.2, 117.6,

114.2, 114.2, 57.5, 55.2 ppm. HRMS: calcd. for $C_{14}H_{14}N_3O[M+H]^+$: 240.1133, found 240.1131.

Procedure of 1*H*-pyrazolo [3,4-*b*]pyridine protection by SEM[6]

To a cold, stirred solution of 1*H*-pyrazolo [3,4-*b*]pyridine (150 mg, 1.26 mmol) in dry THF (5 mL), *N*,*N*-dicyclohexylmethylamine (1.5 mmol) was added dropwise over a period of 15 min. Then a solution of 2-(trimethylsilyl)ethoxymethyl chloride (1.26 mmol) in THF (1 mL) was added over a period of 45 min. The reaction mixture was slowly warmed to room temperature and stirred for 36 hours. The reaction was then diluted with pentane and the resulting suspension was stirred at 20 °C for 30 min. The reaction mixture was filtered through a pad of celite and the solid was washed with of pentane. The filtrate was concentrated under vacuum and purified by column chromatography on silica gel (elution with DCM/AcOEt, 1:1) to yield compound **1c** in 60% as a white solid.

2-((2-(Trimethylsilyl)ethoxy)methyl)-2*H*-pyrazolo[3,4-*b*]pyridine 1c.

Yield: (188 mg, 60%) White solid, mp 75-77 °C. IR (neat): $\tilde{\nu}$ = 3103, 2952, 1615, cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ = 8.66 (dd, J = 4.2, 1.7 Hz, 1H), 8.09 (s, 1H), 8.01 (dd, J = 8.4, 1.7 Hz, 1H), 7.00 (dd, J = 8.4, 4.2 Hz, 1H), 5.71 (s, 2H), 3.59 (t, J = 8.0 Hz, 2H), 0.87 (t, J = 8.0 Hz, 2H), -0.09 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.2, 152.2, 130.1, 122.3, 118.3, 114.5, 82.5, 68.1, 18.0, -1.2. HRMS: calcd. for $C_{12}H_{20}N_3OSi[M+H]^+$: 250.1368, found 250.1370.

Procedure for on water direct arylation of 2-benzyl-2*H*-pyrazolo [3,4-*b*]pyridine with benzene iodide :

A sealed tube was charged with 2-benzyl-2*H*-pyrazolo[3,4-*b*]pyridine (50 mg, 0.23 mmol, 1equiv), benzene iodide (93.84 mg, 0.46 mmol, 2 equiv), $Pd(PPh_3)_2Cl_2$ (8.39 mg, 0.011 mmol, 5 mol%), Ag_2CO_3 (63.42 mg, 0,23 mmol, 1 equiv) and PPh_3 (6.03 mg, 0,023 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 in a preheated oil bath at 70 °C for 24 h. After this time the reaction mixture was cooled down to room temperature. 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) to provide the title compound as a white solid in 92% yield.

2-Benzyl-3-phenyl-2*H*-pyrazolo [3,4-*b*] pyridine 2a.

Yield: (60 mg, 92%) White solid, mp 135-136 °C. IR (neat): ν̃ = 3048, 3033, 1614, 1336, cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.73 (dd, J = 4.2, 1.7 Hz, 1H), 7.93 (dd, J = 8.3, 1.7 Hz, 1H), 7.59 – 7.16 (m, 10H), 7.04 (dd, J = 8.3, 4.2 Hz, 1H), 5.66 (s, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.9, 152.0, 136.4, 136.4, 129.9, 129.7, 129.46, 129.2, 129.0, 128.7, 128.0, 127.4, 118.0, 113.8, 54.9 ppm. HRMS: calcd. for $C_{19}H_{16}N_3$ $[M+H]^+$: 286.1337, found 286.1338.

2-Benzyl-3-*p*-tolyl-2*H*-pyrazolo [3,4-*b*] pyridine 2b.

Yield: (65 mg, 95%) yellow liquid. IR (neat): ν̃ = 3031, 1609, 1337 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.73 (dd, J = 4.1, 1.8 Hz, 1H), 7.92 (dd, J = 8.3, 1.8 Hz, 1H), 7.41 – 7.12 (m, 9H), 7.03 (dd, J = 8.3, 4.1 Hz, 1H), 5.65 (s, 2H), 2.45 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.0, 152.0, 139.6, 136.6, 130.1, 130.0, 129.9, 129.7, 128.8, 128.0, 127.5, 126.0, 117.9, 113.8, 54.8, 21.5 ppm. HRMS: calcd. for $C_{20}H_{18}N_3$ $[M+H]^+$: 300.1495, found 300.1496.

2-Benzyl-3-*m*-tolyl-2*H*-pyrazolo[3,4-*b*]pyridine 2c.

Yield: (58 mg, 85%) yellow solid, mp 110-111 °C. IR (neat): ν̃ = 3051, 1615, 1337, cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.72 (d, J = 4.0 Hz, 1H), 7.92 (d, J = 8.3 Hz, 1H), 7.39 (t, J = 7.5 Hz, 1H), 7.34 – 7.14 (m, 8H), 7.02 (dd, J = 8.3, 4.0 Hz, 1H), 5.64 (s, 2H), 2.39 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.9, 152.0, 138.9, 136.6, 136.5, 130.4, 130.1, 130.0, 129.0, 128.8, 128.7, 127.9, 127.5, 126.8, 117.8, 113.8, 54.9, 21.4 ppm. HRMS: calcd. for $C_{20}H_{18}N_3[M+H]^+$: 300.1497, found 300.1495.

2-Benzyl-3-*o*-tolyl-2*H*-pyrazolo [3,4-*b*] pyridine 2d.

Yield: (51 mg, 75%) yellow liquid. IR (neat): ν̃ = 3056, 1494, 1337, cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.72 (dd, J = 4.1, 1.5 Hz, 1H), 7.71 (dd, J = 8.3, 1.5 Hz, 1H), 7.51 – 7.03 (m, 9H), 7.00 (dd, J = 8.3, 4.1 Hz, 1H), 5.45 (q, J = 14.4 Hz, 2H), 1.85 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.7, 151.9, 138.6, 135.7, 135.5, 131.0, 130.7, 130.1, 129.8, 128.6, 128.3, 128.2, 128.1, 126.2, 117.7, 114.3, 55.2, 19.7 ppm. HRMS: calcd. for $C_{20}H_{18}N_3$ $[M+H]^+$: 300.1495, found 300.1497.

2-Benzyl-3-(3,5-dimethylphenyl)-2H-pyrazolo[3,4-*b*]pyridine 2e.

Yield: (60 mg, 84%) yellow solid, mp 111-112 °C. IR (neat): ν̃ = 3032, 2946, 1395, cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.74 (dd, J = 4.2, 1.3 Hz, 1H), 7.95 (dd, J = 8.3, 1.3 Hz, 1H), 7.28 (m, 5H), 7.15 (s, 1H), 7.04 (dd, J = 8.3, 4.2 Hz, 1H), 7.01 (s, 2H), 5.65 (s, 2H), 2.37 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.9, 151.9 138.8, 136.8, 136.7, 131.0, 130.1, 128.7, 128.6, 127.9, 127.6, 127.5, 117.7, 113.7, 54.9, 21.3 ppm. HRMS: calcd. for $C_{21}H_{20}N_3[M+H]^+$: 314.1652, found 314.1651.

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

Yield: (64 mg, 89%) White solid, mp 134-135 °C. IR (neat): ν̃ = 3007, 2961, 1606, 1250 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.72 (dd, J = 4.2, 1.7 Hz, 1H), 7.91 (dd, J = 8.3, 1.7 Hz, 1H), 7.43 – 7.13 (m, 7H), 7.08 – 6.96 (m, 3H), 5.63 (s, 2H), 3.88 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.5, 158.0, 152.0, 136.6, 136.4, 131.1, 130.0, 128.7, 127.9, 127.4, 121.1,

117.7, 114.7, 113.8, 55.5, 54.7 ppm. HRMS: calcd. for $C_{20}H_{18}N_3O[M+H]^+$: 316.1444, found 316.1446.

2-Benzyl-3-(2-methoxyphenyl)-2*H*-pyrazolo[3,4-*b*] pyridine 2g.

Yield: (54 mg, 75%) yellow liquid. IR (neat): ν˜ = 3058, 2960, 1615, 1495, cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ= 8.70 (d, J = 8.3, 1H), 7.80 (dd, J = 8.3, 1.4 Hz, 1H), 7.49 (td, J = 8.3, 1.4 Hz, 1H), 7.22 – 7.04 (m, 8H), 7.92 (dd, J = 8.3, 1.4 Hz, 1H), 5.52 (s, 2H), 3.66 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.0, 157.4, 151.7, 136.3, 133.1, 132.2, 131.4, 130.1, 128.4, 127.9, 127.7, 121.0, 117.8, 117.5, 114.6, 111.5, 55.5, 55.5 ppm. HRMS: calcd. for $C_{20}H_{18}N_3O$ $[M+H]^+$: 316.1444, found 316.1442.

2-Benzyl-3-(3-methoxyphenyl)-2*H*-pyrazolo[3,4-*b*] pyridine 2h.

Yield: (58 mg, 80%) White solid, mp 88-89 °C. IR (neat): ν˜ = 3059, 2938, 1604, 1283, cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ= 8.74 (dd, J = 4.3, 1.7 Hz, 1H), 7.95 (dd, J = 8.3, 1.7 Hz, 1H), 7.48 – 7.34 (m, 1H), 7.34 – 7.15 (m, 5H), 7.09 – 6.95 (m, 3H), 6.88 (dd, J = 8.3, 4.3 Hz, 1H), 5.67 (s, 2H), 3.73 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.0, 158.0, 152.1, 136.6, 136.3, 130.3, 130.1, 130.0, 128.8, 128.0, 127.4, 122.1, 118.0, 115.3, 115.0, 113.8, 55.4, 55.0 ppm. HRMS: calcd. for $C_{20}H_{18}N_3O[M+H]^+$: 316.1444, found 316.1444.

2-Benzyl-3-(4-chlorophenyl)-2*H*-pyrazolo[3,4-*b*]pyridine 2i.

Yield: (66 mg, 90%) yellow liquid. IR (neat): ν˜ = 3059, 1500, 706 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.74 (dd, J = 4.3, 1.7 Hz, 1H), 7.89 (dd, J = 8.4, 1.7 Hz, 1H), 7.49 (d, J = 7.2 Hz, 2H), 7.37 – 7.23 (m, 5H), 7.16 (d, J = 7.2 Hz, 2H), 7.06 (dd, J = 8.4, 4.3 Hz, 1H), 5.64 (s, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.9, 152.2, 136.3, 135.8, 135.1, 131.0, 129.6, 129.6, 128.9, 128.2, 127.4, 127.3, 118.3, 114.0, 55.0 ppm. HRMS: calcd. for $C_{19}H_{15}ClN_3$ $[M+H]^+$: 320.0949, found 320.0948.

4-(2-Benzyl-2*H*-pyrazolo[3,4-*b*]pyridin-3-yl) benzamide 2j.

Yield: (30 mg, 40%) Colorless liquid. IR (neat): ν̃ = 3351, 3200, 1611, cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ= 8.76 (dd, J = 4.2, 1.7 Hz, 1H), 7.97 (d, J = 8.2 Hz, 2H), 7.92 (dd, J = 8.2, 1.7 Hz, 1H), 7.50 (d, J = 8.2 Hz, 2H), 7.36 – 7.13 (m, 7H), 7.09 (dd, J = 8.2, 4.2 Hz, 1H), 5.67 (s, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.3, 157.9, 152.3, 136.2, 135.1, 134.1, 132.5, 130.0, 129.6, 128.9, 128.3, 128.2, 127.3, 118.6, 114.2, 55.2 ppm. HRMS: calcd. for $C_{20}H_{17}N_4O[M+H]^+$: 329.1396, found 329.1397.

Ethyl 4-(2-benzyl-2*H*-pyrazolo[3,4-*b*]pyridin-3-yl)benzoate 2k.

Yield: (65 mg, 80%) yellow solid, mp 112-113 °C. IR (neat): ν̃ = 2977, 1712, 1606, 1162, cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ= 8.75 (dd, J = 4.2, 1.4 Hz, 1H), 8.18 (d, J = 8.2 Hz, 2H), 7.93 (dd, J = 8.2, 1.4 Hz, 1H), 7.50 (d, J = 8.2 Hz, 2H), 7.30 – 7.13 (m, 5H), 7.08 (dd, J = 8,2, 4.2 Hz, 1H), 5.68 (s, 2H), 4.44 (q, J = 7.1 Hz, 2H), 1.43 (t, J = 7.1 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.9, 157.9, 152.2, 136.1, 135.2, 133.2, 131.2, 130.3, 129.6, 129.6, 128.8, 128.1, 127.3, 118.5, 114.0, 61.5, 55.2, 14.4 ppm. HRMS: calcd. for $C_{22}H_{20}N_3O_2[M+H]^+$: 358.1550, found 358.1550.

2-Benzyl-3-(4-nitrophenyl)-2*H*-pyrazolo[3,4-*b*] pyridine 2l.

Yield: (68 mg, 90%) yellow solid, mp 150-151 °C. IR (neat): ν̃ = 3059, 1576, 1541, 1328, cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ= 8.78 (dd, J = 4.2, 1.7 Hz, 1H), 8.36 (d, J = 8.4 Hz, 2H), 7.93 (dd, J = 8.4, 1.7 Hz, 1H), 7.60 (d, J = 8.4 Hz, 2H), 7.32 – 7.24 (m, 3H), 7.18 – 7.10 (m, 3H), 5.70 (s, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.8, 152.4, 148.1, 135.8, 135.3, 133.7, 130.5, 129.1, 129.0, 128.4, 127.2, 124.4, 119.1, 114.2, 55.5 ppm. HRMS: calcd. for $C_{19}H_{15}N_4O_2[M+H]^+$: 331.1189, found 331.1190.

4-(2-Benzyl-2*H*-pyrazolo[3,4-*b*]pyridin-3-yl) benzonitrile 2m.

Yield: (60 mg, 85%) Colorless liquid. IR (neat): ν̃ = 3350, 3187, 2221, 1608, cm^1. ^1H NMR (400 MHz, $CDCl_3$): δ= 8.76 (dd, J = 4.2, 1.3 Hz, 1H), 7.96 (d, J = 8.3 Hz, 2H), 7.92 (dd, J = 8.3, 1.3 Hz, 1H), 7.50 (d, J = 8.3 Hz, 2H), 7.36 – 7.22 (m, 3H), 7.20 – 7.14 (m, 2H), 7.09 (dd,

J = 8.3, 4.2 Hz, 1H), 5.67 (s, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.6, 158.2, 157.1, 152.6, 136.5, 134.4, 132.9, 130.3, 129.9, 129.2, 128.6, 128.5, 127.6, 118.9, 114.4, 55.5 ppm. HRMS: calcd. for $C_{20}H_{15}N_4[M+H]^+$: 311.1396, found 311.1397.

3-(Benzo[d][1,3]dioxol-5-yl)-2-benzyl-2*H* pyrazolo[3,4-*b*]pyridine 2n.

Yield: (30 mg, 40%) yellow solid, mp 151-152 °C. IR (neat): ν̃ = 3057, 2916, 1602, 1035,cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.72 (dd, J = 4.3, 1.7 Hz, 1H), 7.91 (dd, J = 8.4, 1.7 Hz, 1H), 7.33 – 7.11 (m, 5H), 7.03 (dd, J = 8.4, 4.3 Hz, 1H), 6.96 – 6.80 (m, 2H), 6.06 (s, 2H), 5.64 (s, 2H)). ^{13}C NMR (101 MHz, $CDCl_3$): δ= 157.9, 152.0, 148.7, 148.3, 136.4, 136.1, 129.9, 129.1, 128.8, 128.3, 128.0, 127.4, 117.9, 113.8, 109.9, 109.0, 101.7, 54.8 ppm. HRMS: calcd. for $C_{20}H_{16}N_3O_2[M+H]^+$: 330.1237, found 330.1237.

2-Benzyl-3-(pyridin-4-yl)-2*H*-pyrazolo[3,4-*b*] pyridine 2o.

Yield: (40 mg, 60%) yellow solid, mp 138-139 °C. IR (neat): ν̃ = 3369, 2849, 1398, 1275 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.83 – 8.73 (m, 3H), 7.97 (dd, J = 8.4, 1.7 Hz, 1H), 7.37 – 7.27 (m, 5H), 7.17 – 7.10 (m, 2H), 7.13 (dd, J = 8.4, 4.3 Hz, 1H), 5.71 (s, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.0, 152.4, 150.8, 136.8, 135.9, 133.3, 129.2, 129.0, 128.3, 127.2, 123.8, 119.0, 114.0, 55.3 ppm. HRMS: calcd. for $C_{18}H_{15}N_4$ $[M+H]^+$: 287.1291, found 287.1290.

2-Benzyl-3-(pyrazin-2-yl)-2*H*-pyrazolo[3,4-*b*]pyridine 2p.

Yield: (51 mg, 77%) White solid, mp 148-149 °C. IR (neat): ν̃ = 3057, 2919, 1603, 1395, 1187 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.94 (d, J = 1.7 Hz, 1H), 8.84 – 8.68 (m, 2H), 8.59 (dd, J = 2.5, 0.3 Hz, 1H), 8.20 (dd, J = 8.4, 1.7 Hz, 1H), 7.32 – 7.07 (m, 6H), 6.15 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ= 157.4, 151.7, 144.5, 144.1, 144.1, 143.3, 135.8, 129.8, 128.9, 128.3, 127.7, 127.5, 119.2, 113.7, 55.9 ppm. HRMS: calcd. for $C_{17}H_{14}N_5[M+H]^+$: 288.1243, found 288.1243.

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

Yield: (60 mg, 95%) Colorless liquid. IR (neat): ν̃ = 3410, 2928, 1173 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.73 (d, J= 8.3 Hz, 1H), 7.92 (d, J = 8.3 Hz, 1H), 7.52 (d, J = 5.2 Hz, 3H), 7.45 – 7.37 (m, 2H), 7.14 (d, J = 8.3 Hz, 2H), 7.04 (dd, J = 8.3, 3.7 Hz, 1H), 6.79 (d, J = 8.3 Hz, 2H), 5.59 (s, 2H), 3.76 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.1, 157.7, 151.7, 136.1, 129.8, 129.7, 129.3, 129.1, 129.0, 128.9, 128.5, 128.4, 117.8, 114.0, 55.2, 54.3 ppm. HRMS: calcd. for $C_{20}H_{18}N_3O$ $[M+H]^+$: 316.1443, found 316.1444.

2-(4-Methoxybenzyl)-3-(3,5-dimethylphenyl)-2*H*-pyrazolo[3,4-*b*]pyridine 2r.

Yield: (62 mg, 91%) Colorless liquid. IR (neat): ν̃ = 3201, 3088, 2818 , 1290 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.70 (dd, J = 5.2, 1.4 Hz, 1H), 7.91 (dd, J = 8.4, 1.4 Hz, 1H), 7.21 – 7.12 (m, 3H), 7.01 (d, J = 5.2 Hz, 3H), 6.80 (d, J = 8.4 Hz, 2H), 5.56 (s, 2H), 3.76 (s, 3H), 2.37 (s, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ= 159.7, 158.2, 152.1, 139.1, 136.9, 131.3, 130.4, 129.5, 129.2, 129.0, 127.9, 118.0, 114.3, 114.1, 55.6, 54.7, 21.7 ppm. HRMS: calcd. for $C_{22}H_{22}N_3O$ $[M+H]^+$: 344.1756, found 344.1757.

3-Phenyl-2-((2-(trimethylsilyl) ethoxy) methyl)-2*H*-pyrazolo[3,4-*b*]pyridine 2s.

Yield: (52 mg, 80%) White solid, mp 79-81 °C. IR (neat): ν̃ = 3105, 2953, 2927, 1600 cm^{-1}. ^{1H} NMR (250 MHz, $CDCl_3$) δ 8.75 (dd, J = 4.1, 1.6 Hz, 1H), 8.05 (dd, J = 8.4, 1.6 Hz, 1H), 7.74 (d, J = 7.1 Hz, 2H), 7.60 – 7.44 (m, 3H), 7.07 (dd, J = 8.4, 4.1 Hz, 1H), 5.74 (s, 2H), 3.93 (t, J = 8.0 Hz, 2H), 0.98 (t, J = 8.0 Hz, 2H), -0.01 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.7, 152.7, 137.1, 130.5, 129.8, 129.3, 129.2, 128.9, 118.3, 113.6, 79.6, 68.2, 18.2, -1.2 ppm. HRMS: calcd. for $C_{18}H_{24}N_3OSi$$[M+H]^+$: 326.1680, found 326.1683.

3-(3,5-Dimethylphenyl)-2-((2-(trimethylsilyl)ethoxy)methyl)-2*H*-pyrazolo[3,4-*b*]pyridine 2t.

Yield: (58 mg, 83%) Colorless liquid IR (neat): ν̃ = 3137, 2913, 1604 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.75 (dd, J = 4.1, 1.8 Hz, 1H), 8.04 (dd, J = 8.4, 1.8 Hz, 1H), 7.33 (s, 2H), 7.15 (s, 1H), 7.05 (dd, J = 8.4, 4.1 Hz, 1H), 5.73 (s, 2H), 3.9 (t, J = 8.0 Hz, 2H), 2.42 (s, 6H),

0.87 (t, J = 8.0 Hz, 2H), -0.01 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.7, 152.6, 138.9, 137.5, 131.1, 130.7, 128.7, 127.5, 118.1, 113.5, 79.6, 68.1, 21.5, 18.1, -1.1 ppm. HRMS: calcd. for $C_{20}H_{28}N_3OSi[M+H]^+$: 354.1993, found 354.1996.

General protocol for arylation/deprotection sequence

A sealed tube was charged with 2-R-2*H*-pyrazolo[3,4-*b*]pyridine **1b** or **1c** (1equiv), benzene iodide (2 equiv), $Pd(PPh_3)_2Cl_2$ (5 mol%), Ag_2CO_3 (1 equiv) and PPh_3 (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 in a preheated oil bath at 70 °C for 24 h. After this time the reaction mixture was cooled down to room temperature. 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*. For the gross of 2-PMB-3-phenyl-2*H*-pyrazolo [3,4-*b*] pyridine **2q**, 3 mL of anisole was added with 10 equiv of aluminum chloride. The mixture was then stirred at 0°C for 1 hour then poured into ice. The precipitate was filtered off, washed with water, to afford compound **3a** in 90% yield. For the gross of 2-SEM-3-phenyl-2*H*-pyrazolo [3,4-*b*] pyridine **2s**, tetrabutylammonium fluoride (1M in THF, 3 equiv) and ethylenediamine (6 equiv) were added in *N*,*N*-dimethylformamide (2 mL). The mixture was then stirred at 50°C for 2h. After cooling, the volatiles were removed by evaporation in vacuo and co-evaporation with toluene. The residue was purified by column chromatography on silica to afford compound **3a** in 88% yield.

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

Yield: (34 mg, 88%) green solid, mp 164-165 °C. IR (neat): ν˜ = 3209, 3146, 3055, 1600, 1292 cm–1. ^{1}H NMR (400 MHz, $CDCl_3$): δ= 12.83 (s, 1H), 8.69 (d, J = 4.5 Hz, 1H), 8.43 (d, J

= 8.1 Hz, 1H), 8.01 (d, J = 8.1 Hz, 2H), 7.54 (t, J = 7.6 Hz, 2H), 7.46 (t, J = 7.6 Hz, 1H), 7.26 (dd, J = 8.1, 4.5 Hz, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ= 153.0, 148.7, 144.7, 133.1, 130.9, 129.0, 128.5, 127.2, 117.2, 113.4 ppm. HRMS: calcd. for $C_{12}H_{10}N_3$ $[M+H]^+$: 196.0871, found 196.0869.

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

Yield: (23 mg, 72%) White solid, mp 172-173 °C. IR (neat): ν˜ = 3206, 3090, 1604, 1289 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ= 13.42 (s, 1H), 8.69 (dd, J = 4.7, 1.5 Hz, 1H), 8.42 (dd, J = 8.0, 1.5 Hz, 1H), 7.62 (s, 2H), 7.23 (dd, J = 8.0, 4.7 Hz, 1H), 7.08 (s, 1H), 2.43 (s, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ= 153.0, 148.5, 144.8, 138.5, 133.0, 131.1, 130.2, 125.0, 117.0, 113.5, 21.4 ppm. HRMS: calcd. for $C_{14}H_{14}N_3$ $[M+H]^+$: 224.1184, found 224.1182.pectra of

Associated Content

Figures giving proton and carbon NMR spectra of the reported compounds, NOESY NMR of **1b** and **1c compounds**. This material is available free of charge via the internet at http://pubs.acs.org.

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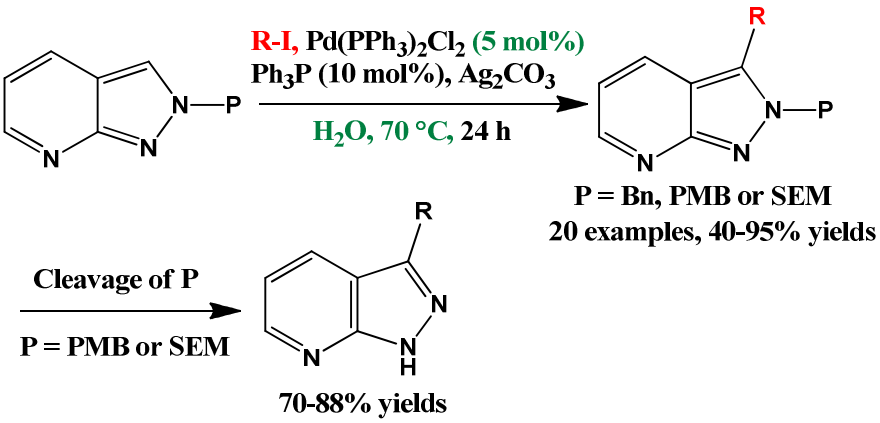
TOC graphic


R-I, Pd(PPh3)2Cl2 (5 mol%)
Ph3P (10 mol%), Ag2CO3
H2O, 70 °C, 24 h
N—P
R
P = Bn, PMB or SEM
20 examples, 40-95% yields
Cleavage of P
P = PMB or SEM
70-88% yields