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Palladium-catalyzed Highly Regioselective C-3 Arylation of Imidazo[1,5-*a*]pyridine

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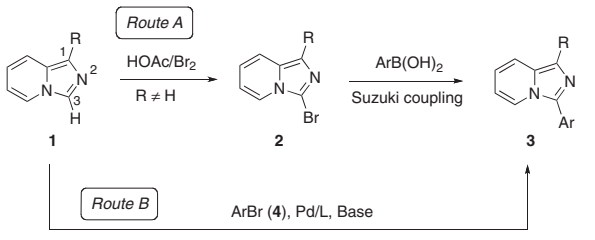
A direct palladium-catalyzed highly regioselective C-3 arylation of imidazo[1,5-*a*]pyridine with aryl bromides has been developed. This reaction is quite general with respect to the aryl or hetaryl bromide.

N-Fused bicyclic heteroarenes have attracted increasing attention due to their unique biological activities and photophysical properties.[1] Among them, imidazo[1,5-*a*]pyridines (2-azaindolizines) have been actively investigated as photofunctional materials,[2] precursors of *N*-heterocyclic carbenes,[3] as well as versatile pharmaceuticals[4] (e.g., cardiotonic agents,[5] corticotropin releasing hormone receptors,[6] and HIV-protease inhibitors[7]). Therefore, efficient assembly of functionalized imidazo[1,5-*a*]pyridine derivatives is of high demand. To date, most synthetic efforts have been devoted to building the imidazole ring of imidazo[1,5-*a*]pyridine,[8] largely relying on the Vilsmeier-type cyclization of *N*-(2-pyridylmethyl)amides.[9] However, these methods either require multistep syntheses of starting materials or are limited to the particular types of substrates. In contrast, a direct, late-stage modification of imidazo[1,5-*a*]pyridine core is much less studied. Precedented two-step C-3 arylation of imidazo[1,5-*a*]pyridine (**1**) involves its electrophilic bromination in the presence of $HOAc/Br_2$, followed by the Suzuki cross-coupling reaction of the formed hetaryl bromide **2** with arylboronic acids to produce **3** in good yields (eq 1, route A).[4a,10]

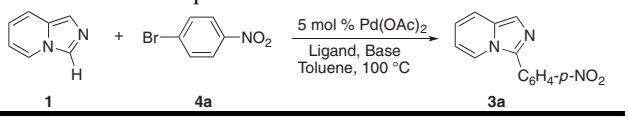
Recently, aryl–aryl bond formation via transition-metal-catalyzed C–H bond arylation approach achieved enormous progress in both aromatic and heteroaromatic systems.[11] However, direct C–H bond arylation of imidazopyridine **1** is limited to a few examples of cationic Pd-catalyzed C-1 arylation of C-3-substituted imidazo[1,5-*a*]pyridines.[12] To the best of our knowledge, there are no reports on a direct C-3 C–H arylation of **1**. Based on our previous regioselective Pd-catalyzed electrophilic arylation of indolizines,[13] we envisioned that the structural similarity of imidazo[1,5-*a*]pyridine and indolizine might allow the same type of transformations to occur. Herein, we report an efficient and practical approach toward regioselective C-3 arylation of imidazo[1,5-*a*]pyridine (eq 1, route B).



(1)

First, we tested the cross-coupling reaction of unsubstituted imidazo[1,5-*a*]pyridine (**1**) and 4-bromonitrobenzene (**4a**). Promisingly, the C-3-arylated product **3a** was formed in 18% NMR yield by using $Pd(OAc)_2$ catalyst (5 mol %) and Bu_4NOAc (2 equiv) as the base in toluene at 100 °C (Table 1, Entry 1). A brief screening of various bases resulted in no improvement of the reaction efficiency (Entries 2–4). Remarkably, addition of phosphine ligands, such as triphenylphosphine or tricyclohexylphosphine, dramatically increased the efficiency of the reaction producing **3a** in 86% and 71% yield, respectively (Entries 5 and 6). Employment of more electron-rich and sterically bulkier ligands was not beneficial for this transformation (Entries 7 and 8). Remarkably, in all cases, no traces of the regioisomeric C-1-arylated product were detected by the GC/MS analyses of crude reaction mixtures.

Table 1. Optimization of reaction conditions[a]



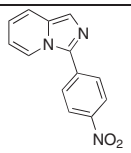
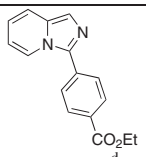
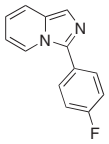
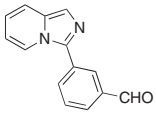
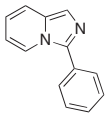
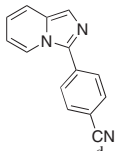
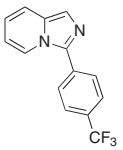
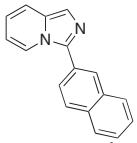
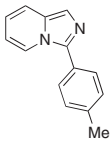
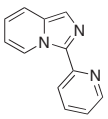
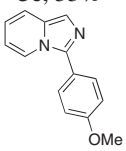
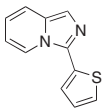
Entry	Ligand	Base	Yield/%[b]
1	N/A	Bu_4NOAc	18
2	N/A	Cs_2CO_3	6
3	N/A	AgOAc	17
4	N/A	KOAc	4
5	**PPh_3**	**Bu_4NOAc**	**86**
6	PCy_3	Bu_4NOAc	71
7	TDMPP[c]	Bu_4NOAc	7
8	*t*-$Bu_2MeP \cdot HBF_4$	Bu_4NOAc	28

[a]Conditions: imidazo[1,5-*a*]pyridine (**1**) (1 equiv), *p*-$NO_2C_6H_4Br$ (1 equiv), $Pd(OAc)_2$ (5 mol %), ligand (10 mol %), base (2 equiv), toluene, 100 °C, 8 h. [b]NMR yield. [c]TDMPP: Tris(2,6-dimethoxyphenyl)phosphine.

Next, the scope of the regioselective C-3 arylation[14] of **1** was examined (Table 2). Gratifyingly, it was found that this method is quite efficient and very general. A variety of functional groups, such as nitro (**3a**), F (**3b**), CF_3 (**3d**), OMe (**3f**), ester (**3g**), aldehyde (**3h**), and nitrile (**3i**), were perfectly tolerated under these reaction conditions, producing the corresponding biaryls in good to excellent yields. Remarkably, in all cases, the arylation reactions uniformly gave C-3-arylated imidazo[1,5-*a*]pyridines. Of note, 2-bromonaphthalene (**4j**), as well as heteroaromatic bromides such as 2-bromopyridine (**4k**) and 2-bromothiophene (**4l**), were competent in this reaction to produce C-3-naphthyl- and hetaryl-substituted imidazo[1,5-*a*]pyridines in moderate yields. Interestingly, **3k** was shown to be a good ligand for C-1 arylation of **3f**.[12]

At this point, the exact mechanism of this transformation is unclear. The lack of the kinetic isotope effect ($k_H/k_D = 1.0$ for arylation of **1** and C-3-deuterated analog **1-*d***)[15] could suggest an electrophilic pathway.[13,16] However, since arylation did not occur at the most nucleophilic C-1 position of this heterocycle,[9,17] a concerted metalation–deprotonation (CMD)[18] pathway could be responsible for the observed regiochemistry.

Table 2. Arylation scope of imidazo[1,5-*a*]pyridine[a,b]

Entry	Product	Entry	Product
1	 **3a**, 90%	7	 **3g**, 50%[d]
2	 **3b**, 88%	8	 **3h**, 51%[d]
3	 **3c**, 99%	9	 **3i**, 71%[d]
4	 **3d**, 86%	10	 **3j**, 46%[d]
5	 **3e**, 55%[c]	11	 **3k**, 48%
6	 **3f**, 56%	12	 **3l**, 78%

[a]Conditions: imidazo[1,5-*a*]pyridine (**1**) (0.4 mmol), aryl bromide **4** (1.05 equiv), $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), Bu_4NOAc (2 equiv), toluene (1 mL), 100 °C. [b]Isolated yield. [c]PCy_3 was used. [d]$Pd(OAc)_2$ (10 mol %) and PPh_3 (20 mol %) were used.

In summary, we developed a highly regioselective Pd-catalyzed C-3 arylation of imidazopyridine **1** with aryl- and hetaryl bromides. This method allows for rapid preparation of C-3-arylated imidazo[1,5-*a*]pyridines.[19]

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14 The C-3 regioselectivity was further proved by the reaction of 3-deuteroimidazo[1,5-*a*]pyridine (**1-*d***) with **4d**. **3d** was the only product.

15 See Supporting Information for details.[19]

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