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Direct Sequential C3 and C1 Arylation Reaction of Imidazo[1,5-*a*]pyridine Catalyzed by a 1,10-Phenanthroline–Palladium Complex

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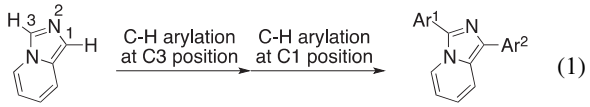
The direct sequential arylation reaction at the C3 and C1 positions of imidazo[1,5-*a*]pyridines with a variety of aryl iodides catalyzed by $[Pd(phen)_2](PF_6)_2$ is described. The reaction of unsubstituted imidazo[1,5-*a*]pyridine with various aryl iodides proceeded selectively at the C3 position to exclusively give the corresponding C3-arylated products. The one-pot double-arylation reaction at the C3 and C1 positions of unsubstituted imidazo[1,5-*a*]pyridine with different aryl groups was also achieved.

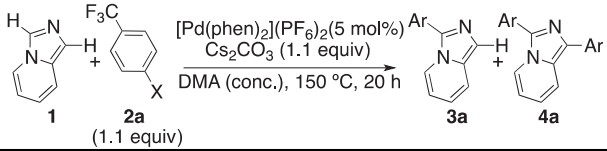
Imidazo[1,5-*a*]pyridines are an attractive class of compounds due to their potential for application in electronic- and photofunctional materials such as organic thin-layer field effect transistors (FETs)[1] and organic light-emitting diodes (OLEDs),[2] and as precursors of *N*-heterocyclic carbenes (NHCs).[3] In addition, due to their bioactive properties, imidazo[1,5-*a*]pyridines have been used in pharmaceuticals such as HIV-protease inhibitors,[4] cardiotonic agents,[5] aromatase inhibitors in estrogen-dependent diseases,[6] and thromboxane A2 synthetase inhibitors.[7] Hence, synthesis of imidazo[1,5-*a*]pyridine derivatives has recently attracted increasing attention. Several methods for the synthesis of substituted imidazo[1,5-*a*]pyridines, where the imidazo[1,5-*a*]pyridine ring is constructed via the condensation–cyclization of 2-pyridylmethylamine, have been reported.[8–10] However, these reactions require stoichiometric amounts of metal salts and/or oxidants that are not incorporated into the products. Therefore, more straightforward methods that lead to substituted imidazo[1,5-*a*]pyridines are still needed. In addition, from the perspective of green chemistry, new reactions with by-products that pose less of an environmental burden are desired.



(1)

Recently, direct C–H arylation has emerged as an alternative to cross-coupling reactions of organometallic reagents and aryl halides since it does not require the preparation of these substrates.[11] In this context, we have also reported that Pd–phenanthroline complexes such as $[Pd(phen)_2](PF_6)_2$ (phen: 1,10-phenanthroline) catalyzed multiple arylation reactions of imid-, ox-, and thiazoles.[12] We then speculated on the applicability of this direct C–H arylation to unsubstituted imidazo[1,5-*a*]pyridine (**1**), which is prepared by phosphoryl trichloride-mediated condensation–cyclization of *N*-formyl-2-pyridylmethylamine. However, **1** possesses several C–H bonds, which can participate in direct arylation reactions. We report herein the selective C3 arylation reaction of **1** catalyzed by $[Pd(phen)_2](PF_6)_2$ (eq 1). The one-pot double-arylation reaction of **1** with different aryl groups is also described.

Table 1. Pd-Catalyzed C3 arylation of imidazo[1,5-*a*]pyridine: Screening of the reaction conditions[a]



1 **2a** (1.1 equiv) **3a** **4a**

Entry	X	Conc./M	**3a**/%[b]	**4a**/%[b]
1	I	1	86	10
2	Br	1	74	10
3	Br	0.5	59	3
4	I	0.5	98	trace

[a]Reactions were carried out using imidazo[1,5-*a*]pyridine (**1**) (0.5 mmol) and aryl iodide (1.1 equiv) in the presence of $[Pd(phen)_2](PF_6)_2$ (5 mol %) and Cs_2CO_3 (1.1 equiv) in DMA at 150 °C for 20 h. [b]Isolated yield.

First, the efficiency and selectivity of the $[Pd(phen)_2](PF_6)_2$-catalyzed reaction between **1** and 4-iodo(trifluoromethyl)benzene (**2a**) were examined (Table 1). The reaction in 1 M solution gave **3a** and **4a** in respective yields of 86% and 10% (Entry 1). Products derived from the cleavage of other C–H bonds in **1** were not observed. These results clearly indicated that the arylation that was accompanied by C–H bond cleavage takes place initially at the C3 position, and then at the C1 position of C3-arylated imidazo[1,5-*a*]pyridine **3a**. To improve the selectivity of the reaction, the use of bromide and/or a diluted solution was examined. Finally, C3 arylation took place exclusively with **2aI** under low-concentration conditions to give **3a** in 98% yield (Entry 4).

With the optimum reaction conditions in hand, the direct arylation reaction of **1** and a variety of aryl halides was examined. The results are summarized in Table 2. When $[Pd(phen)_2](PF_6)_2$ was used as a catalyst, the desired arylated products **3** were obtained in moderate to high yields regardless of the aryl iodides **2**. The reaction proceeded smoothly with both electron-rich (Entries 3–5) and -poor (Entries 1 and 6–8) aryl iodides **2** to give the monoarylated products **3** in good to high yields. In the reactions with 4-nitro- (**2g**) and 4-ethoxycarbonylphenyl iodide (**2h**) as coupling partners, K_2CO_3 worked as a suitable base (Entries 7 and 8). The reactions of **1** with sterically hindered 2-iodotoluene (**2i**) and 1-iodo-2,4-dimethylbenzene (**2k**) also took place to give the corresponding products **3i** and **3k** in good yields, whereas those with 2-iodoanisole (**2j**) gave **3j** in a lower yield (Entries 9–11). 2-Iodopyridine (**2l**) was a sluggish substrate, and the reaction afforded the product **3l** in only moderate yield (Entry 12). The reaction with diiodofluorene **2m** gave the bis(imidazopyridine) **3m** in 90% yield (Entry 13). Finally, the use of *m*-diiodobenzene (**2n**) as a coupling partner led to 1,3-bis(3-imidazopyridyl)benzene **3n**,

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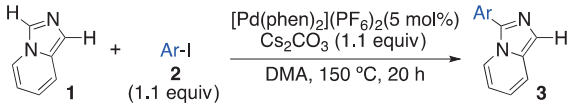
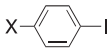
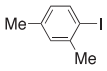
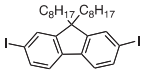
Table 2. Direct C1 arylation reaction of imidazopyridine **1**

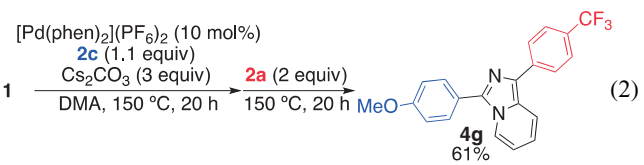


Entry	I–Ar (**2**)		Yield/%[a]
1		X = CF_3: **2a**	**3a**: 98
2		X = H: **2b**	**3b**: 86
3		X = OMe: **2c**	**3c**: 68
4		X = Me: **2d**	**3d**: 74
5		X = NMe_2: **2e**	**3e**: 98
6		X = F: **2f**	**3f**: 74
7		X = NO_2: **2g**	**3g**: 73[b]
8		X = COOEt: **2h**	**3h**: 63[b]
9		X = Me: **2i**	**3i**: 73
10		X = OMe: **2j**	**3j**: 50
11		**2k**	**3k**: 70
12		**2l**	**3l**: 49
13		**2m**	**3m**: 90[c]
14		**2n**	**3n**: 82[c,d]

[a]Isolated yield. [b]K_2CO_3 was used instead of Cs_2CO_3. [c]The reaction was carried out with 2.5 equiv of **1**. [d]The reaction was performed for 40 h.

which may be useful as an NCN pincer ligand, in 82% yield (Entry 14).

Previously, we reported the direct C1 arylation of 3-arylimidazo[1,5-*a*]pyridines under similar conditions.[13] Therefore, we considered that we could achieve the one-pot sequential C3 and C1 diarylation reaction of unsubstituted imidazopyridine **1** with two different aryl iodides. After an initial screening of the reaction conditions, the use of 10 mol % of $[Pd(phen)_2](PF_6)_2$ and 3 equiv of Cs_2CO_3 as initial quantities was found to be effective for the sequential reactions, and no additional catalyst or base was necessary in the second reaction under the reaction conditions. In fact, the reaction of unsubstituted imidazopyridine **1** and 1.1 equiv of *p*-iodoanisole (**2c**) at 150 °C was complete within 20 h and selectively gave the C3-monoarylated product **3c** based on the results of a TLC analysis. The second arylation was achieved by the simple addition of 4-iodo(trifluoromethyl)-benzene (**2a**) (2 equiv) to the mixture at 150 °C to give the target diarylated imidazopyridine **4g** in 61% yield after 20 h (eq 2).



(2)

In conclusion, we have demonstrated the Pd–phenanthroline-complex-catalyzed selective C3-arylation of unsubstituted imidazo[1,5-*a*]pyridine (**1**) with aryl iodides. The one-pot sequential arylation reaction of unsubstituted imidazopyridine was further achieved under this catalytic system for the first time. These reactions provide an attractive method for synthesizing various disubstituted imidazopyridines and a library of 1,3-diarylimidazopyridines with high efficiency. Further investigations of the direct one-pot sequential arylation reaction of simple heteroarenes with a Pd–phenanthroline catalyst are underway in our laboratory.

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13 For further details on the direct C1 arylation reaction of 3-aryl-imidazopyridines, Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html. Also see ref. 12a.

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