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Direct arylation and Suzuki-Miyaura coupling of imidazo [1,2-*a*]pyridines catalyzed by (SIPr)Pd(allyl)Cl complex under microwave-irradiation

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Abstract: A short and practical arylation of imidazo[1,2-*a*]pyridine and imidazole derivatives with aryl halides or aryl boronic acids as coupling partners was successfully carried out using phosphine-free (SIPr)Pd(allyl)Cl as the catalyst [SIPr: (*N*,*N*'-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene)] ((SIPr)Pd(allyl)Cl complex). 3,6-disubstituted imidazo[1,2-*a*]pyridine and 5-substituted imidazole compounds were obtained in good to excellent yields in only 1h under microwave-assisted C-H arylation and Suzuki-Miyaura coupling reaction conditions.

Keywords: Direct arylation; Suzuki-Miyaura coupling; Imidazo[1,2-*a*]pyridine; Microwave-irradiation.

1. Introduction

Over the last decades, many substituted imidazo [1,2-*a*] pyridine compounds are found to be biologically active [1-5]. For example, this heterocyclic system has been reported as melatonin receptor ligands [6], antiviral [7], antiulcer [8], antibacterial [9], antifungal compounds [10], agonist of benzodiazepine receptor [11], calcium channel blocker [12], β-amyloid formation inhibitor [13], ligand for detecting β-amyloid [14], herbicidal [15], cyclin-dependent kinase (CDK) inhibitors [16], GABAA receptor modulator [17] and constitute a novel class of orally active nonpeptide bradykinin B2 receptor antagonists [18]. Moreover, it possesses inhibitory activity against cyclooxigenase-2 (COX-2) with high selectivity in relation to COX-1. The imidazo[1,2-a] pyridine is also present in pharmacologically important drugs such as Alpidem [19], Zolpidem [20] and Olprinone [21].

During the last fifteen years, several methods for the formation of carbon–carbon bonds on imidazo[1,2-a] pyridine derivatives using transition metal catalysts have been reported [22] such as Sonogashira, Heck, Negishi, Suzuki–Miyaura and Stille cross-coupling. In addition, C-H arylation has proved extremely versatile and has found extensive use in natural products and heterocyclic synthesis [22,23] and is considered nowadays as a powerful addition to the classic palladium cross-coupling reactions.

N-Heterocyclic carbenes (NHCs) have received a great deal of attention from a number of researchers over the past few decades. These ligands have been employed in a broad range of fields, including organocatalysis[24] and organometallic chemistry [25]. Many reports described the applications of the [Pd(NHC)] complexes as catalysts for Suzuki-Miyaura coupling, Buchwald-Hartwig amination reaction, Kumada coupling, Sonogashira coupling, Heck reaction, Stille coupling, dehalogenation reactions as well as ketone arylation reactions [26].

In contrast, they have been weakly applied in C-H arylation reactions [27]. In this area, our group has a long-standing interest in C-H activation of 6,5-fused heterocyclic system in general [28] and imidazo[1,2-a] pyridine derivatives in particular [29]. In previous published works, we have reported a regioselective palladium-catalyzed C-3 (hetero)arylation [30a] and C-3 alkenylation [31] of imidazo[1,2-*a*] pyridines. We have developed also a one-pot C-3/C-6 di-functionalization of imidazo[1,2-*a*] pyridines using sequential Suzuki/direct (hetero)arylation, Suzuki/Suzuki and Sonogashira/ Sonogashira cross-coupling reactions [30b,32].

Herein, we wish to describe the efficacy and the ability of the allyl-[1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazolidin-2-ylidene] chloropalladium (II) [(SIPr)Pd(allyl)Cl] catalytic system (Fig. 1) to

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catalyze direct arylation and Suzuki-Miyaura coupling reactions for the functionalization of imidazo[1,2-a] pyridine derivatives. Reactions were developed under microwave irradiation using aryl bromides to achieve direct arylation at position C-3 and boronicacids as coupling partners to introduce aryls at position C-6. In is noticed that (SIPr)Pd(allyl)Cl complex which is an air stable commercially available catalyst has proven a good efficiency in Buchwald–Hartwig amination [33] as well as in ketone arylation reactions [34].

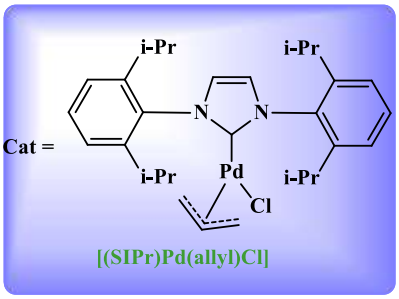
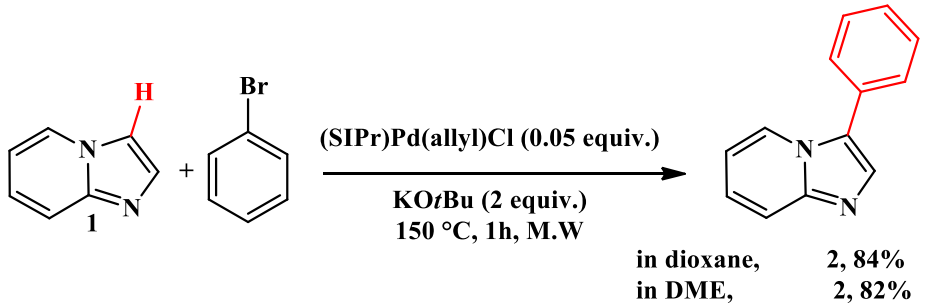


Figure 1. (SIPr)Pd(allyl)Cl complex

2. Results and Discussion

At the outset of this investigation, the C-H arylation reaction was carried out under the previously published conditions used for $Pd(OAc)_2$-catalyzed direct arylation and heteroarylation of imidazo[1,2-a] pyridines at the C3-position [130°C for 1 hour] [30a]. Thus, under microwaves irradiation, the reaction of imidazo[1,2-a] pyridine **1** (1 equiv.) with bromobenzene (1.2 equiv.) catalyzed by phosphine-free (SIPr)Pd(allyl)Cl complex [33,34] (5 mol%) in the presence of KO*t*Bu (2 equiv.) as base at 150°C for 1 h was achieved in different solvents. Among the solvents screened, dioxane and DME gave the best yield (Scheme 1).

The optimized reaction conditions were then established as follow: imidazo[1,2-a] pyridine **1** (1 equiv.), bromobenzene (1.2 equiv.), KO*t*Bu (2 equiv.), (SIPr)Pd(allyl)Cl complex (5 mol%) in dioxane or DME (2 ml) at 150°C for 1 h under MW (Scheme 1). Under these conditions, either dioxane or DME as solvent led to the expected product **2** [30a] in 84 and 82% yield, respectively (Scheme 1).



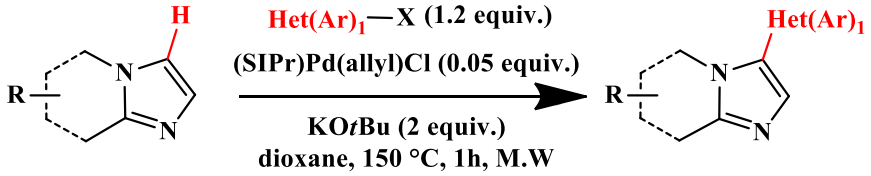
Scheme 1. Optimization of C-H arylation of imidazo[1,2-a] pyridine under microwave-irradiation with bromobenzene

With these reaction conditions in hand, we evaluated then the scope and limitations of our method using various imidazo[1,2-a] pyridine analogues (Table 1). When 4-bromotoluene, 3-bromotulene or 2-bromotoluene were used as coupling partners, the desired products **3-5** were obtained in 78 [35], 81[30a] and 75% [35] yields, respectively (entries 2-4, Table 1). This result shows no real impact of the position of the methyl group on the reaction yield. We also proved that the use of 2-iodotoluene instead of 2-bromotoluene did not improve significantly the reaction yield (76% instead of 75%, entries 4 and 5, Table 1). The same result was observed when using either 4-iodonitrobenzene or 4-bromonitrobenzene as coupling partners (entries 6 and 7, Table 1). In these cases, the expected product **6** was isolated in 82 and 80% yield [36], respectively.

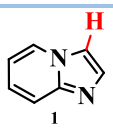
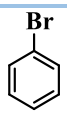
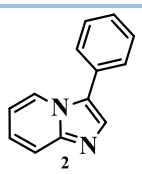
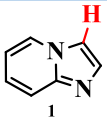
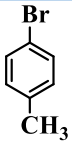
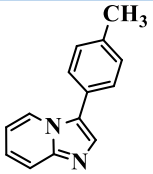
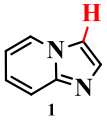
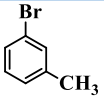
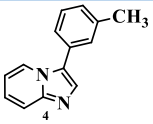
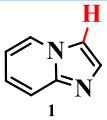
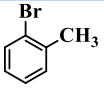
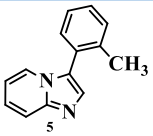
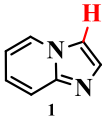
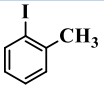
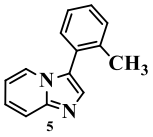
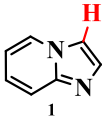
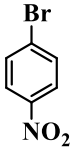
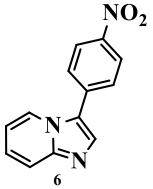
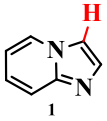
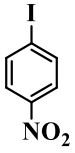
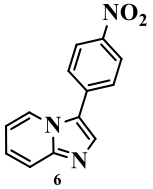
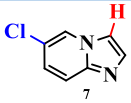
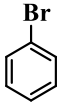
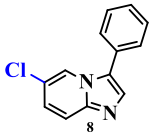
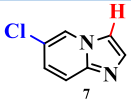
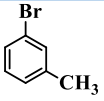
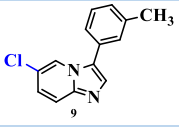
Then, we decided to use 5-chloroimidazo[1,2-a] pyridine **7** as starting material. In this case, the reaction between **7** and bromobenzene led to the desired product **8** [30a] in 77% yield showing very good tolerance to the presence of the choro group on the six membered ring (entry 8**,** Table 1). Good reaction yields were obtained using either 3-bromotoluene or 4-methoxybromobenzene as coupling partners which demonstrated that no effect of the use of electron with donating group or electron with drawing group on the reaction yield (compounds **9** [30a] and **10** [37], entries 9 and 10, Table 1). We also showed that the reaction is feasible when using bromoheteroaryls as coupling partners. Thus, the reaction between **1** and either 3-bromopyridine or 2-bromothiophene led to expected products **11**[30a] and **12** [38] in 69 and 60% yields, respectively (entries 11 and 12, Table 1).

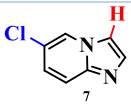
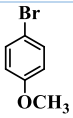
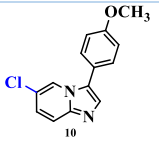
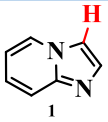
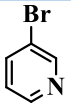
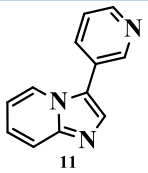
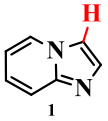
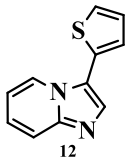
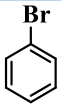
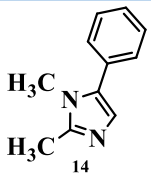
Finally, we showed that the reaction conditions can be applied to achieve the direct arylation of imidazoles. In this case, 1,2-dimethyl-*1H*-imidazole **13** was selected as starting material and bromobenzene as coupling partner which led to the expected arylated product **14** [39] in 63% yield (entry 13, Table 1).

Table 1. Direct arylation of imidazo[1,2-*a*] pyridines and imidazole [a]



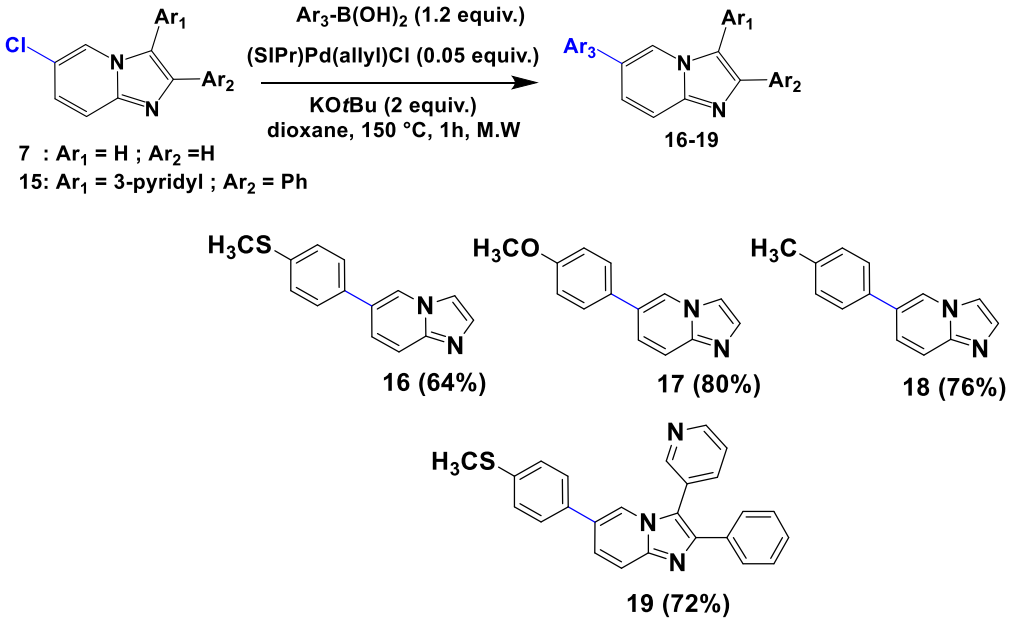
R= H, Cl, X= Br or I
Het(Ar)$_1$= Phenyl, tolyl, thienyl, pyridin-3-yl

Entry	Substrates	Reactants	Products	Yield[b]
1				84%
2				78%
3				81%
4				75%
5				76%
6				80%
7				82%
8				77%
9				83%

10				**74%**
11				**69%**
12				**60%**
13				**63%**

[a] Reaction conditions: (SIPr)Pd(allyl)Cl (0.05 equiv.), Ar_1-Br (1.2 equiv.), KO*t*Bu (2 equiv.), 2 ml of dioxane 150°C, 1h, M.W. [b] Isolated yields

Under the optimized reaction conditions for direct arylation, we next examined Pd-catalyzed Suzuki-Miyaura cross-coupling of 6-chloroimidazo [1,2-a] pyridine derivatives. Gratifyingly, the starting materials **7** and **15**[30a] could be efficiently functionalized at 6-position using boronic acids as coupling partners under following conditions [(SIPr)Pd(allyl)Cl (5 mol%), KOtBu (2 equiv.), dioxane at 150°C for 1 hour under M.W. This procedure allowed to isolate the desired products **16** [30b,32], **17** [30b,32], **18** and **19** [30b] in good yields (64-80 %, Scheme 2).



Scheme 2. Suzuki-Miyaura coupling of 6-chloroimidazo[1,2-*a*] pyridine.

3. Conclusion

In summary, we have reported a new catalytic system that provides a direct access to a wide range of 3-aryl-imidazo[1,2-*a*]pyridines C-H direct arylation under microwave-irradiation. The developed reaction conditions were also successfully applied to the direct arylation of 1, 2-dimethyl-1*H*-imidazole. Moreover, the catalyst system based on (SIPr)Pd(allyl)Cl complex was highly effective for Suzuki-Miyaura coupling reaction of 6-chloroimidazo[1,2-*a*] pyridines with boronic acids

under the same reaction conditions developed for direct arylation.

4. Experimental

Microwaves-assisted reactions were carried out in a CEM Initiator microwave synthesis instrument. Melting points were determined with Büchi SMP-20 melting point apparatus and were uncorrected. ^{1}H NMR and ^{13}C NMR were recorded on a Bruker Avance DPX250 spectrometer (^{1}H, 250MHz, ^{13}C, 63MHz) using tetramethylsilane as the internal standard, multiplicities were determined by the DEPT 135 sequence. Chemical shifts were reported in parts per million (ppm, δ units). Coupling constants were reported in units of hertz (Hz). Splitting patterns were designated as s, singlet; d, doublet, t, triplet, m, multiplet. All commercial solvents were used without further purification. The following solvents and reagents have been abbreviated: ethyl acetate (EtOAc), ethanol (EtOH), and petroleum ether (PE). Column chromatography was carried out using Silica gel 60N (spherical, neutral, 40-63 µm, Merck). Thin layer chromatography (TLC) was carried out on Merck silica gel 60F_{254} percolated plates. Visualization was made with ultraviolet light. Allyl[1,3-bis(2,6-diisopropylphenyl)-2-imidazolidinylidene] chloro palladium (II), 97%, Synonym: (SIPr)Pd(allyl)Cl, (Sigma-Aldrich). All reported yields were isolated.

General Procedure for Palladium-Catalyzed Direct (Hetero)Arylation under Microwave Irradiation (Scheme 1, Table 1).

Typically, to a solution of imidazo[1,2-a] pyridine derivatives (100 mg) dissolved in 2 mL of dioxane in a vial microwave tube with a stir bar were added, aryl halide (1.2 equiv.), potassium *tert*-butoxide (KO*t*Bu) (2 equiv.) and (SIPr)Pd(allyl)Cl (5 mol%). The vial was sealed with a silicon septum and subjected to microwave irradiation at 150°C for 1 h with stirring. The reaction mixture was allowed to cool to room temperature, and the solution was diluted with H_2O then extracted with (3x15 mL of dichloromethane. The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated under vacuum. The residue was purified by column chromatography on silica gel (EtOAc/ hexane) to give the desired products **2-6**, **8-12** and **14**.

3-Phenyl-imidazo[1,2-a]pyridine2 [30a,35,36].
The generale procedure afforded 138 mg (84% yield) of the title compound. ^{1}H NMR and ^{13}C NMR spectrum matched that of the literature.

3-(p-Tolyl)imidazo[1,2,a]pyridine 3 [35,36].
The generale afforded 138 mg (78% yield) of the title compound. Compound **3**was identified by comparison of NMR data with those reported in the literature.

3-(m-Tolyl)imidazo[1,2,a]pyridine 4 [30a,35].
The generale procedure afforded 143 mg (81% yield) of the title compound. ^{1}H NMR and ^{13}C NMR spectrum matched that of the literature.

3-*(o-Tolyl)imidazo[1,2,a]pyridine 5* [35].
The generale procedure afforded (133 mg 75% yield and 134 mg 76% yield) of the title compound. ^{1}H NMR and ^{13}C NMR spectrum matched that of the literature.

3-(4-Nitrophenyl)-imidazo[1,2-a] pyridine 6 [36].
The generale procedure afforded (163 mg 80% yield and 167 mg 82% yield) of the title compound. ^{1}H NMR and ^{13}C NMR spectrum matched that of the literature.

6-Chloro-3-phenyl-imidazo[1,2-a] pyridine 8 [30a].

The generale procedure afforded 115 mg (77% yield) of the title compound. ^{1}H NMR and ^{13}C NMR spectrum matched that of the literature.

6-Chloro-3-(m-tolyl)-imidazo[1,2-a] pyridine 9 [30a].
The generale procedure for formation reaction afforded 132 mg (83% yield) of the title compound. ^{1}H NMR and ^{13}C NMR spectrum matched that of the literature.

6-Chloro-3-(4-methoxyphenyl) imidazo[1,2,a] pyridine 10 [37].
The generale procedure afforded 125 mg (74% yield) of the title compound. ^{1}H NMR and ^{13}C NMR spectrum matched that of the literature.

3-Pyridin-3-ylimidazo[1,2-a] pyridine 11 [30a,b,36,38].
The generale procedure afforded 114 mg (69% yield) of the title compound. ^{1}H NMR and ^{13}C NMR spectrum matched that of the literature.

3-(Thiophen-2-yl)imidazo[1,2-a] pyridine 12 [38].
The generale procedure afforded 102 mg (60% yield) of the title compound. ^{1}H NMR and ^{13}C NMR spectrum matched that of the literature.

1,2-Dimethyl-5-phenyl-1H-imidazole 14 [36,39].
The generale procedure afforded 112 mg (63% yield) of the title compound. ^{1}H NMR and ^{13}C NMR spectrum matched that of the literature.

General Procedure for Palladium-Catalyzed Suzuki Coupling Reaction under Microwave Irradiation (Scheme 2).

Typically, to a solution of 6-chloroimidazo[1,2-a] pyridine (100 mg, 0.66 mmol) dissolved in 2 ml of dioxane in a vial microwave tube with a stir bar were added, aryl boronic acid (1.2 equiv.), potassium *tert*-butoxide (KO*t*Bu) (2 equiv.) and (SIPr)Pd(allyl)Cl (5 mol%). The vial was sealed with a silicon septum and subjected to microwave irradiation at 150°C for 1h with stirring. The reaction mixture was allowed to cool to room temperature and the solution was

diluted with H_2O then extracted with (3x15 mL of dichloromethane. The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated under vacuum. The residue was purified by column chromatography on silica gel (EtOAc/ Hexane) to give the desired products **16-19**.

6-p-Tolylimidazo[1,2-a] pyridine 18.

The general procedure for Suzuki-Miyaura afforded 180 mg (76% yield) as an oil of the title compound. ^{1}H NMR (250 MHz, $CDCl_3$) δ= 2.43 (s, 3H), 7.30 (d, *J* = 7.5 Hz, 2H), 7.52-7.38 (m, 3H), 7.74-7.60 (m, 3H), 8.29 (s, 1H). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 21.1 (CH_3), 112.6 (CH), 117.6 (CH), 122.7 (CH), 125.2 (CH), 126.7 (2xCH), 129.8 (2xCH), 133.9 (CH), 134.3 (C), 137.7 (2C), 144.7 (C). IR: 1512 (C=C), 1669 (C=N). HRMS (+ESI) m/z: $[M+H]^+$ calculated for $C_{14}H_{12}N_2$: 209.1069, found, 209.1073.

Compounds **16** [30b], **17** [32a] and **19** [30b] were identified by comparison of their NMR data with those reported in the literature.

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