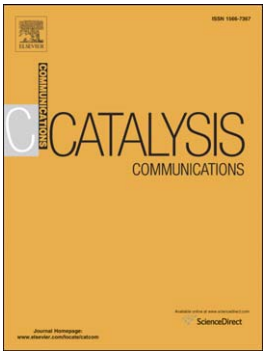

Highly Regioseletive Palladium-Catalyzed Direct Cross-coupling of Imidazo[1,2-a]pyridines with Arylboronic Acids

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Highly Regioseletive Palladium-Catalyzed Direct Cross-coupling of Imidazo[1,2-a]pyridines with Arylboronic Acids

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Abstract

A highly regioselective method for the palladium-catalyzed direct cross-coupling of imidazo[1,2-a]pyridines with arylboronic acids has been developed by using O_2 as oxidant. This process can be applied to a wide range of imidazo[1,2-a]pyridines and arylboronic acids with excellent C-3-regioselectivity. It provides a new way for developing C-C bond-forming processes of multisubstituted imidazo[1,2-a]pyridines, which are common structural motifs in natural products and pharmaceuticals.

Keywords: Regioseletive; Palladium-Catalyzed; Imidazo[1,2-a]pyridines; Cross-coupling; Arylboronic Acids

Introduction

Transition metal-mediated cross-coupling reactions are one of the most powerful tools for the formation of carbon-carbon bonds via C-H bonds activation.[1-13] Among transition metals, Pd-catalyzed[14-21] cross-coupling reactions have become one of the most widely and versatile used processes for the formation of carbon-carbon bonds due to its high synthetic efficiency. With the development of chemistry, organic chemists are expected not only to design elegant transformations for formation of carbon-carbon bonds but also to improve the catalyst system to maximize resource utilization, especially for environmental benign and safety. Therefore, the discovery of direct cross-coupling for the formation of C-C bonds has attracted great attention of organic chemists. Achieving selective transition-metal-catalyzed direct cross-coupling for the formation of C-C bonds continues to attract research groups worldwide huge attention, especially in synthesizing bioactive motifs.

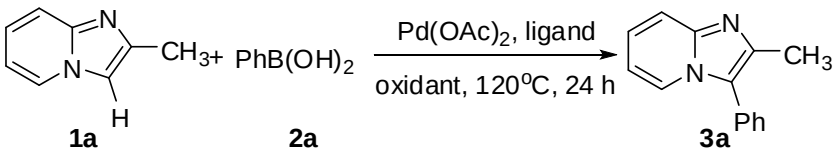
On the other hand, imidazo[1,2-a]pyridine derivatives are one of the important class of heterocyclic compound[22] and exhibit a wide range of biological activities, such as antiviral,[23] antiprotozoal,[24] antiherpes[25] and anti-apoptotic properties.[26] During the last years, significant efforts have been made to develop the conventional methods[27-29] for the synthesis of

these compounds typically containing the condensation of 2-aminopyridines with α-halo ketones[30-31] , multicomponent reaction[32] ,transition metal-mediated cross-coupling [33-34] , cyclization reactions and so on.[35] Despite facile transformations for their preparation have been developed, arylation of imidazo[1,2-a]pyridine is still highly favourable by using arylboronic acids as substrates. Herein, we report the development of a general, regiospecific Pd-catalyzed direct arylation of imidazo[1,2-a]pyridines with arylboronic acids.

Results and discussion

At the outset of our studies, we chose 2-methylimidazo[1,2-a]pyridine **1a** and phenylboronic acid **2a** as initial substrates to optimize the reaction conditions. And the results are summarized in Table1. Interestingly, the reaction of **1a** with **2a** afforded the desired 2-methyl-3-phenylimidazo[1,2-a]pyridine (**3a**) in 59% yield (entry 1, Table 1) by using $Pd(OAc)_2$ (5 mol %) as catalyst and $Cu(OAc)_2$ as oxidant in 1,4-dioxane at 120 ℃ for 24 h. Other oxidants, such as $CuCl_2$ (entry 2, Table 1), AgOAc (entry 3, Table 1), Ag_2CO_3 (entry 4, Table 1) and O_2 (entry 7, Table 1) afforded the desired product **3a** in 33-39% yields, respectively. No product was observed when BQ (entry 5, Table 1) or Oxone (entry 6, Table 1) was used as oxidant or in the absence of oxidant (entry 8, Table 1). To our delight, a good yield of 85% was obtained, when the reaction was carried out by using $Cu(OAc)_2$ (10 mol%) and O_2 (with oxygen balloon) as co-oxidant (entry 9, Table 1). Subsequently, our study focused on the arylation of **1a** by testing various ligands, such as pyridine, bipy, DMEDA (Dimethylethylenediamine)(entries 10-12, Table 1). However, the yield was lower than expected. We further explored the reaction in various solvents (entries 13-17, Table 1), and 1,4-dioxane was demonstrated as the best choice.

Table 1. Optimization of Reaction Conditions. [a]



1a **2a** **3a**

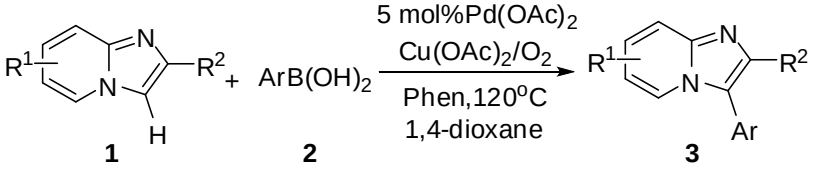
Entry	Oxidant	Ligand	Solvent	Yield (%)[b]
1	$Cu(OAc)_2$	Phen	Dioxane	59%
2	$CuCl_2$	Phen	Dioxane	37

3	AgOAc	Phen	Dioxane	33
4	Ag_2CO_3	Phen	Dioxane	39
5	BQ	Phen	Dioxane	Trace
6	Oxone	Phen	Dioxane	Trace
7[c]	O_2[c]	Phen	Dioxane	36
8	-	Phen	Dioxane	-
9	$Cu(OAc)_2/O_2$	Phen	Dioxane	85
10	$Cu(OAc)_2/O_2$	pyridine	Dioxane	21
11	$Cu(OAc)_2/O_2$	Bipy	Dioxane	44
12	$Cu(OAc)_2/O_2$	DMEDA	Dioxane	17
13	$Cu(OAc)_2/O_2$	Phen	Toluene	78
14	$Cu(OAc)_2/O_2$	Phen	DMA	67
15	$Cu(OAc)_2/O_2$	Phen	NMP	60
16	$Cu(OAc)_2/O_2$	Phen	DMSO	10
17	$Cu(OAc)_2/O_2$	Phen	DMF	13

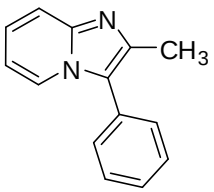
[a] Reaction conditions: 2-methylimidazo[1,2-a]pyridine **1a** (0.5 mmol), phenylboronic acid (**2a)** (1.2 mmol), $Pd(OAc)_2$ (5 mol%), O_2 (600 mL), other oxidant (10 mol%), ligand (10 mol%) in 3 mL of solvent at 120 °C for 24 h. [b] GC yield. [c] oxygen balloon

Under optimized reaction conditions, the scope of this direct arylation of imidazo[1,2-a]pyridines with arylboronic acids were further explored. Various 2-sustituted imidazo[1,2-a]pyridines with different arylboronic acids were firstly examined and the results are described in Table 2. As shown in Table 2, different substituents on the aromatic ring of arylboronic acids were suitable partners and gave corresponding products in moderate to good yields in this process. The position of the substituents on the phenyl ring of arylboronic acids played a critical role and meta or para substituents gave the good yields, while *ortho*-substituted arylboronic acid give **3d** in moderate yield. It is noteworthy that this strategy also tolerated electron-rich and electron-poor groups on the aromatic of boronic acids. As expected, a variety of 2-sustituted imidazo[1,2-a]pyridines were compatible with the direct arylation. Notably, the substrate containing strong electron-withdrawing group 2-(trifluoromethyl)imidazo[1,2-a]pyridine was also tested and afforded corresponding products **3f** and **3u** in moderate yield.

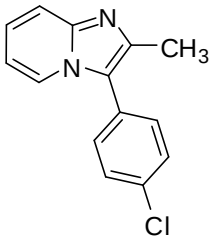
Table 2. Pd-catalyzed Arylation of 2-substituted Imidazo[1,2-a]pyridines [a]



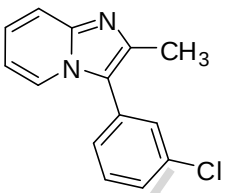
1 **2** **3**



3a 79%



3b 73%



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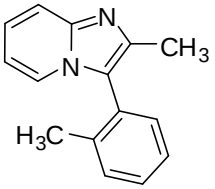
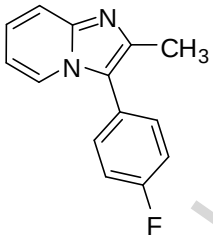
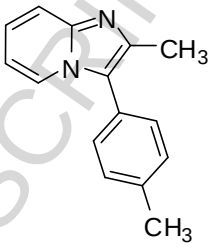


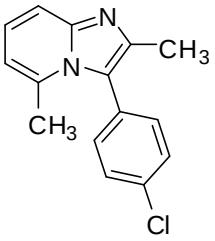
3d 50%



3e 75 %



3f 78 %



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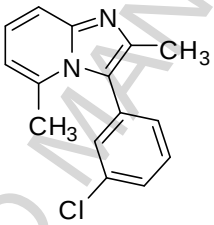
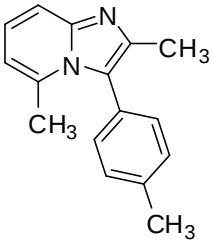
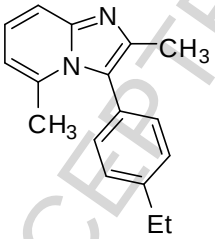


3h 78%



3i 82%



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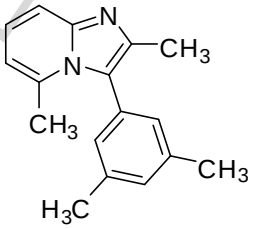

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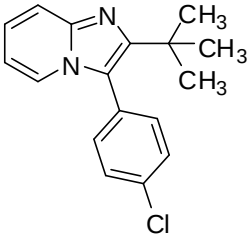
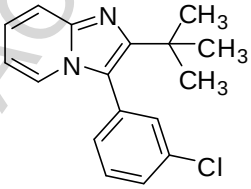
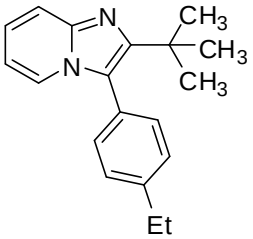


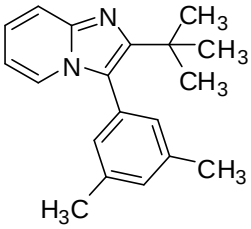
3l 74%



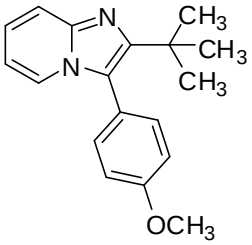
3m 75%



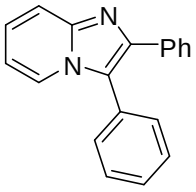
3n 78%



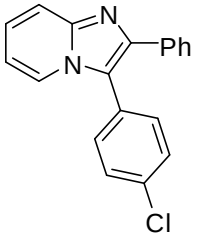
3o 77%



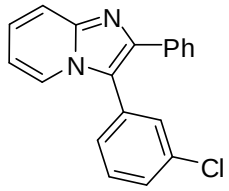
3p 79%



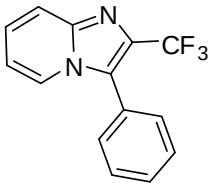
3q 75%



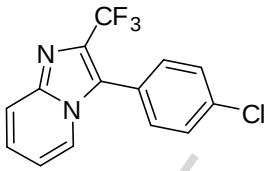
3r 78%



3s 78%



3t 55%

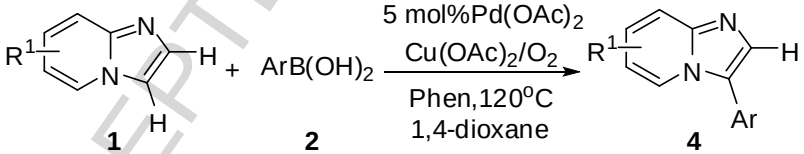


3u 65%

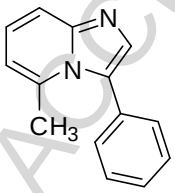
[a] Isolated yields;

Subsequently, regioselective Pd-catalyzed direct arylation was investigated. And the results were outlined in Table 3. The effect of substituents on the arylboronic acids and imidazo[1,2-a]pyridine was tested. Seen from Table 3, moderate to good isolated yields could be achieved under optimized reaction conditions. The results indicated arylboronic acids with different substituent groups presented on the aromatic ring could react smoothly, and the resulting corresponding products were obtained in good yields. It should be noted that the present arylation performed highly regioselectively and the products were obtained as the sole product. All those cases clearly showed that an efficient and highly regioselective arylation has been developed.

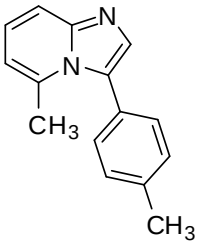
Table 3. Regioselective Pd-catalyzed Direct Arylation of Imidazo[1,2-a]pyridines [a]



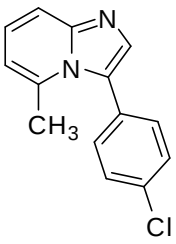
1 **2** **4**



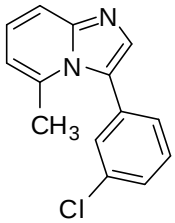
4a 75%



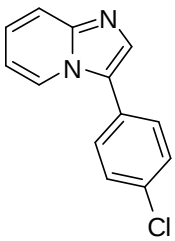
4b 80%



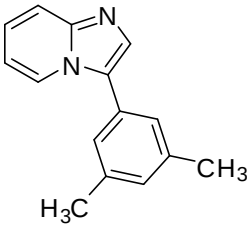
4c 83%



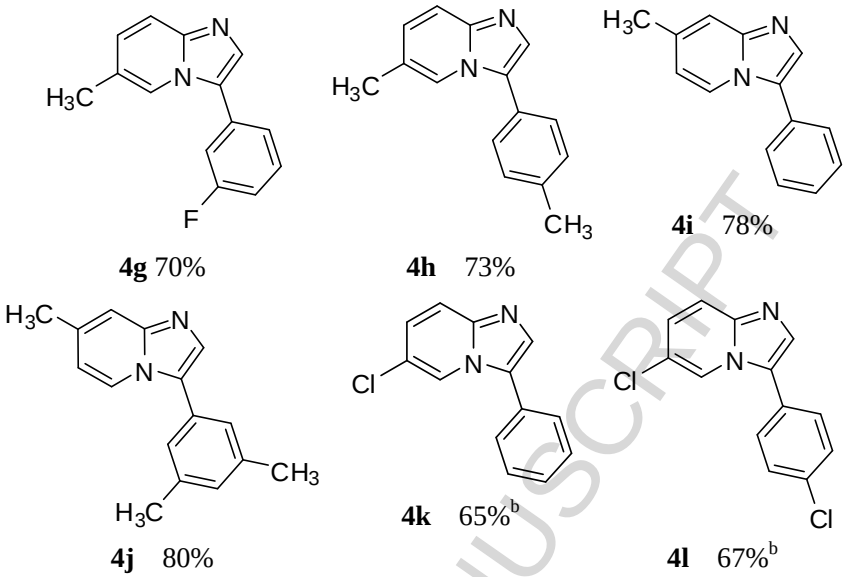
4d 76%



4e 75%

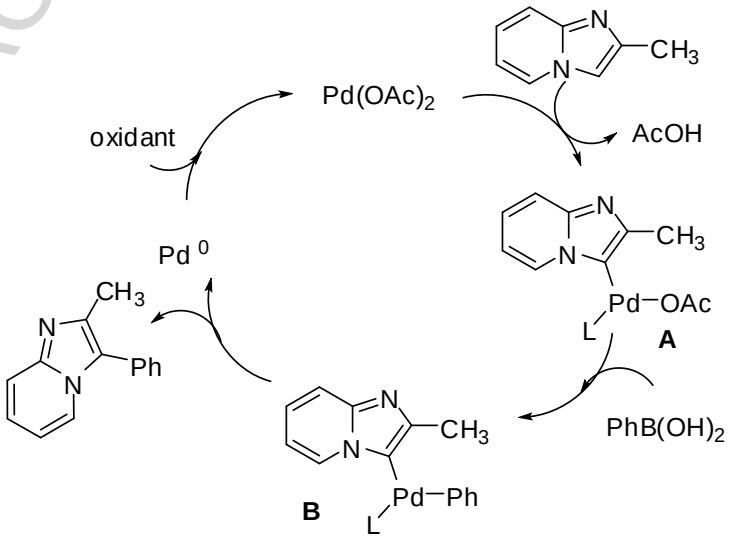


4f 78 %



[a] Isolated yields; [b]The yields of 4k and 4l are only moderate because part of the substrate 6-chloroimidazo[1,2-a]pyridine not been fully converted.

A plausible mechanism of Pd-catalyzed direct arylation of imidazo[1,2-a]pyridine with arylboronic acids has been described in Scheme 1. The mechanism was in consistence with previous studies on the arylation of heterocycles. First, The C-H bond at 3-position of **1a** was cleaved by $Pd(OAc)_2$ to give the intermediate **A**. And then the key intermediate **B** was formed from immediate **A** coordinated with **2a**, which would then undergo reductive elimination to give the product **3a** and regenerated the palladium catalyst so that it could participate again in the catalytic cycle.



Scheme 1. Proposal Mechanism

Conclusions

In summary, we have described an efficient and highly regioselective Pd-catalyzed direct cross-coupling of imidazo[1,2-a]pyridine with arylboronic acids for the formation of C-C bonds. This transformation is applicable to a variety of imidazo[1,2-a]pyridines and arylboronic acids and gives the corresponding products in moderate to good yields. It also provides a new approach to construct various functionalized imidazo[1,2-a]pyridines core π systems which is broadly applicable for the synthesis of biologically active molecules. This process has two advantages over our previous arylation of imidazo[1,2-a]pyridines: 1) no need for pre-functionalization of the substrate; 2) non-toxic oxygen as oxidant.

Acknowledgments

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Highlights

Pd-catalyzed cross-coupling of imidazo[1,2-a]pyridines with aryl boronic acids;

It represents excellent C-3-regioselectivity direct arylation;

A new method for the formation of C-C bond to prepare imidazo[1,2-a]pyridines;