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Phosphine-free palladium-catalysed direct 5-arylation of imidazole derivatives at low catalyst loading

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ABSTRACT

The regioselective 5-arylation of imidazole derivatives with aryl bromides using a low loading of a phosphine-free palladium catalyst gives a simple and economic access to the corresponding 5-arylimidazoles. The choice of the base and of the solvent was found to be crucial to form these products in high yields. Using KOAc as the base, DMAc as the solvent and only 0.5–0.01 mol % $Pd(OAc)_2$ as the catalyst, the target products were obtained in moderate to good yields with a wide variety of aryl bromides. Substituents such as fluoro, trifluoromethyl, formyl, acetyl, propionyl, ester or nitrile on the aryl bromide are tolerated. Sterically congested aryl bromides or heteroaryl bromides can also be employed. The nature of the substituents on the imidazole derivative has an important influence on the yields.

1. Introduction

5-Arylimidazoles are important building blocks in organic synthesis due to their biological properties. Suzuki, Stille or Negishi palladium-catalysed cross-coupling reactions are among the most efficient methods to prepare such compounds.[1] However, they require the preliminary preparation of a requisite organometallic. Ohta and co-workers reported in 1990 that the direct 2- or 5-arylation of several heteroaromatics with aryl halides via a C–H bond activation proceed in moderate to good yields using $Pd(PPh_3)_4$ as the catalyst.[2] Since these exciting results, the palladium-catalysed direct arylation of heteroaryl derivatives with aryl halides or triflates has proved to be a very powerful method for the synthesis of a wide variety of arylated heterocycles.[3–10] This reaction provides a cost-effective and environmentally attractive access for the preparation of such compounds. Indeed, the major by-products of the reaction are a base associated to HX, instead of metallic salts produced under more classical cross-coupling procedures such as Suzuki, Negishi or Stille reactions. Moreover, the method avoids the preliminary preparation of an organometallic derivative, reducing then the number of steps to prepare these compounds. However, so far, most of the results have been described using thiophenes,[5] furans,[7] thiazoles[8] or oxazole[9] derivatives. Several methods for the 2-arylation of imidazoles have also been reported.[11] On the other hand, the 5-arylation of imidazoles has attracted less attention and led in several cases to poor yields and to mixtures of products. The first example of direct 5-arylation of imidazoles was reported by Ohta and co-workers in 1992.[12] The arylation of 1-methylimidazole or 1,2-dimethylimidazole with three chloropyrazines using 5 mol % $Pd(PPh_3)_4$ as the catalyst gave the 5-arylation products in 40–83% yields. Since these results, four other groups have reported the direct 5-arylation of imidazoles using 5–10 mol % $Pd(OAc)_2$ associated to 10–20 mol % of phosphine or arsine ligands as the catalytic systems.[13] A SEM-protected 2-phenylimidazole has also been arylated on C5 using iodobenzene as reactant and 2.5 mol % of palladium complexes containing imidazolyl carbene ligands as the catalysts. The coupling product was obtained in 54% yield.[14] Very recently, Fagnou and co-workers described the 5-arylation of 1-methylimidazole or 1,2-dimethylimidazole using 2 mol % of $Pd(OAc)_2$ associated with 4 mol % PCy_3 as the catalytic system. Using this relatively low catalyst loading, the 5-arylation products were obtained in only 32–40% yields.[15] Finally, a few examples of direct 5-arylations of imidazoles via intramolecular cyclisation have also been described.[16]

So far, to our knowledge, all the procedures reported for the 5-arylation via C–H bond activation of imidazoles required 2–10 mol % of palladium and 4–20 mol % of ligand.[13–15] Therefore, the discovery of more effective conditions, for the direct coupling of imidazole derivatives with aryl halides under lower catalyst loading conditions, would be a considerable advantage for industrial applications and for sustainable development. Moreover, the scope of the reaction needs to be largely extended to a wider variety of aryl halides and imidazoles. Here, we wish to report on the reaction of a set of electronically and sterically diverse aryl bromides using mono- or disubstituted imidazoles at low catalyst loadings using a ligand-free palladium catalyst.

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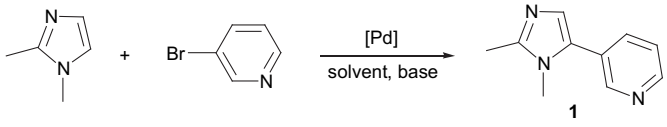
Recently, Heck and Suzuki reactions under low catalyst loading (0.1–0.01 mol %) using ligand-free catalyst $Pd(OAc)_2$ have been described by de Vries and co-workers.[17] They have demonstrated that, at elevated temperature, when $Pd(OAc)_2$ is employed as catalyst precursor, soluble palladium(0) colloids or nanoparticles are formed, and that these reactions take place via the interaction of the arylating agent with the palladium atoms in the outer rim of the nanoparticles. This leads to the formation of monomeric or dimeric anionic palladium complexes that undergo the usual steps of the Heck or Suzuki mechanisms.

We have already reported the direct 5-arylation of a range of thiazole, furans, pyrroles or thiophene derivatives using a phosphine-free palladium catalyst.[18] Here, we wish to report on the reaction of a set of imidazoles using a very wide variety of electronically and sterically diverse aryl or heteroaryl bromides at low catalyst loadings using such phosphine-free palladium catalyst.

2. Results and discussion

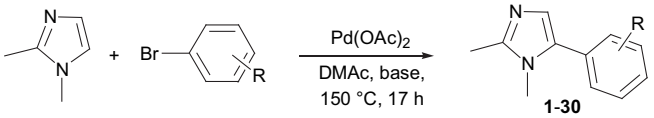
For this study, based on previous results,[18] DMAc was initially chosen as the solvent and KOAc as the base. The reactions were performed at 150 °C under argon in the presence 0.01 mol % $Pd(OAc)_2$ as the catalyst. Using these conditions, the coupling of 3-bromopyridine with 1,2-dimethylimidazole gave **1** in a moderate 44% yield (Table 1, entry 1). First, we examined the influence of the solvent for this reaction (Scheme 1, Table 1, entries 1–5). No conversion of 3-bromopyridine was observed in toluene or dioxane, when using 0.01 mol % catalyst (Table 1, entries 3 and 4). On the other hand, the use of NMP or DMF led to partial conversion of this aryl bromide, but did not allow to improve the yield of the reaction (Table 1, entries 2 and 5). A very important effect of the nature of the base was also observed. Carbonates, KF or *t*BuOK gave no target product **1**; whereas, NaOAc and KOAc led to **1** in 12% and 44% yields, respectively (Table 1, entries 1, 7–11).



Scheme 1.

Then, we examined the influence of the palladium source using 0.01 mol % catalyst. $PdCl_2$ and $[PdCl(C_3H_5)]_2$ led to lower conversions of 3-bromopyridine and lower yield of **1** than $Pd(OAc)_2$ (Table 1, entries 1, 12 and 17). For this reaction, the presence of bidentate phosphine ligands such as dppe or dppb did not allowed to increase the yields of **1** (Table 1, entries 13–16, 18 and 19). In order to obtain a high isolated yield of **1**, we also optimised the substrate/catalyst ratio of the reaction. In the presence of 0.1 mol % catalyst, **1** was obtained in 90% isolated yield (Table 1, entry 22).

Then, using the most efficient reaction condition (DMAc, KOAc, $Pd(OAc)_2$, 150 °C), we explored the scope and limitations of this reaction using *para*-, *meta*- and *ortho*-substituted aryl bromides and also some heteroaryl bromides employing 1,2-dimethylimidazole as coupling partner (Scheme 2, Tables 2–5).



Scheme 2.

First, we have investigated the reaction of 1,2-dimethylimidazole with several *para*-substituted aryl bromides (Scheme 2, Table 2). In most cases, the reaction proceeds very smoothly in the presence of 0.1–0.5 mol % $Pd(OAc)_2$ as the catalyst. We observed that yields of 73–81% can be obtained for activated substrates such as 4-bromopropiophenone, 4-bromobenzaldehyde, 4-bromobenzonitrile or 4-trifluoromethylbromobenzene (Table 2, entries 1–11). We also obtained satisfactory results using 4-fluorobromobenzene (Table 1, entries 13 and 14).

On the other hand, with 4-*t*-butylbromobenzene or 4-bromo-*N*,*N*-dimethylaniline, moderate yields of **11** and **13** were obtained using KOAc as the base (Table 2, entries 19 and 23). Surprisingly, with these deactivated aryl bromides, good yields were obtained using K_2CO_3 as the base and 0.5 mol % catalyst (Table 2, entries 20 and 24). These results reveal that, as expected, the stability of this

Table 1
Influence of the reaction conditions for palladium catalysed arylation of 1,2-dimethylimidazole with 3-bromopyridine (Scheme 1)

Entry	Catalyst	Base	Solvent	Temperature (°C)	Substrate/catalyst ratio	Conversion of 3-bromopyridine (%)
1	$Pd(OAc)_2$	KOAc	DMAc	150	10,000	53 (44)
2	$Pd(OAc)_2$	KOAc	NMP	150	10,000	28
3	$Pd(OAc)_2$	KOAc	toluene	150	10,000	0
4	$Pd(OAc)_2$	KOAc	dioxane	150	10,000	0
5	$Pd(OAc)_2$	KOAc	DMF	150	10,000	32
6	$Pd(OAc)_2$	NaOAc	DMAc	150	10,000	17 (12)
7	$Pd(OAc)_2$	Na_2CO_3	DMAc	150	10,000	0
8	$Pd(OAc)_2$	K_2CO_3	DMAc	150	10,000	0
9	$Pd(OAc)_2$	Cs_2CO_3	DMAc	150	10,000	0
10	$Pd(OAc)_2$	KF	DMAc	150	10,000	0
11	$Pd(OAc)_2$	*t*BuOK	DMAc	150	10,000	0
12	$PdCl_2$	KOAc	DMAc	150	10,000	33
13	$Pd(OAc)_2$/2 PPh_3	KOAc	DMAc	150	10,000	10
14	$Pd(OAc)_2$/dppb	KOAc	DMAc	150	10,000	37
15	$Pd(OAc)_2$/dppe	KOAc	DMAc	150	10,000	49
16	$Pd(OAc)_2$/dppm	KOAc	DMAc	150	10,000	7
17	$^1/_2$ $[PdCl(C_3H_5)]_2$	KOAc	DMAc	150	10,000	16
18	$^1/_2$ $[PdCl(C_3H_5)]_2$/dppb	KOAc	DMAc	150	10,000	45
19	$^1/_2$ $[PdCl(C_3H_5)]_2$/dppe	KOAc	DMAc	150	10,000	28
20	$Pd(OAc)_2$	KOAc	DMAc	130	10,000	2
21	$Pd(OAc)_2$	KOAc	DMAc	150	2000	86 (78)
22	$Pd(OAc)_2$	KOAc	DMAc	150	1000	97 (90)
23	$Pd(OAc)_2$	KOAc	DMAc	150	200	100

Conditions: [Pd], 3-bromopyridine (1 equiv), 1,2-dimethylimidazole (2 equiv), base (2 equiv), 17 h, GC and NMR conversion of 3-bromopyridine, yields in parenthesis are isolated.