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One pot $Pd(OAc)_2$-catalysed 2,5-diarylation of imidazoles derivatives

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ABSTRACT

The regioselective 2- or 5-arylation of imidazole derivatives with aryl halides using palladium catalysts has been described in recent years; whereas the arylation at both C2 and C5 carbons of imidazoles in high yields has not been performed. We found conditions allowing the access to these 2,5-diarylimidazoles via a one pot reaction. The choice of the base was found to be crucial to obtain these products in high yields. Using CsOAc as the base, DMA as the solvent and only 2 mol % of the phosphine-free $Pd(OAc)_2$ the catalyst, the target 2,5-diarylated imidazoles were obtained in moderate to good yields with a wide variety of aryl bromides. Substituents such as fluoro, trifluoromethyl, formyl, acetyl, propionyl, ester, nitro or nitrile on the aryl bromide were tolerated. Sterically congested aryl bromides or heteroaryl bromides can also be employed. Surprisingly the nature of the substituent at position 1 on the imidazole derivative exhibits a huge influence on the reaction.

1. Introduction

Aryl-substituted imidazoles including 2,5-diarylimidazoles are important structures due to their biological properties. For example, Fenflumizol and Trifenagrel are platelet aggregation inhibitors (Fig. 1).

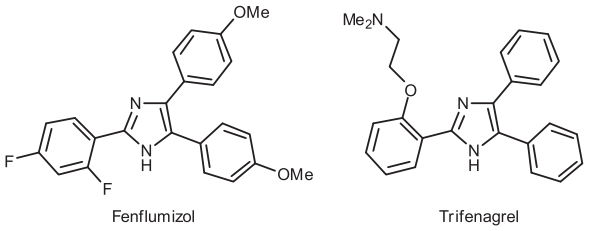

Fig. 1. Examples of bioactive 2,5-diarylimidazoles.

Suzuki, Stille or Negishi palladium-catalysed cross-coupling reactions are among the most efficient methods to prepare 2,5-diarylimidazoles.[1] However, they require the previous preparation of an organometallic derivative. As early as 1990, Ohta et al. reported that the direct arylation of 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 Pd-catalysed direct arylation of heteroaryls using aryl halides as coupling partners has proved to be a very powerful method for a simpler and greener access to a wide variety of arylated heterocycles, as the major by-products of the reaction are a base associated to HX, instead of metallic salts produced under more classical cross-coupling procedures.[3] Moreover, the method avoids the preliminary preparation of an organometallic derivative. However, so far, the direct arylation of imidazoles has attracted less attention than the arylation of thiophenes or thiazoles, and in most cases mono-arylations have been described.[4–6] The first example of direct 5-arylation of imidazoles using chloropyrazines as coupling partners and 5 mol % $Pd(PPh_3)_4$ as the catalyst was reported by Ohta and co-workers in 1992.[4] Since these results, several groups described conditions allowing the intermolecular Pd-catalysed direct 2- or 5-arylation of imidazoles.[5,6]

So far, to our knowledge, only a few examples of Pd-catalysed arylations at both C2 and C5 carbons of imidazoles in one pot have been described.[7–9] In 1998, Miura et al. reported the regioselectivity of the arylation of 1-methylimidazole using various reaction conditions.[8a] In the presence of bromobenzene, they observed the formation of a mixture of 5-arylation and 2,5-diarylation products in a 54:24 ratio (Scheme 1, top). They also

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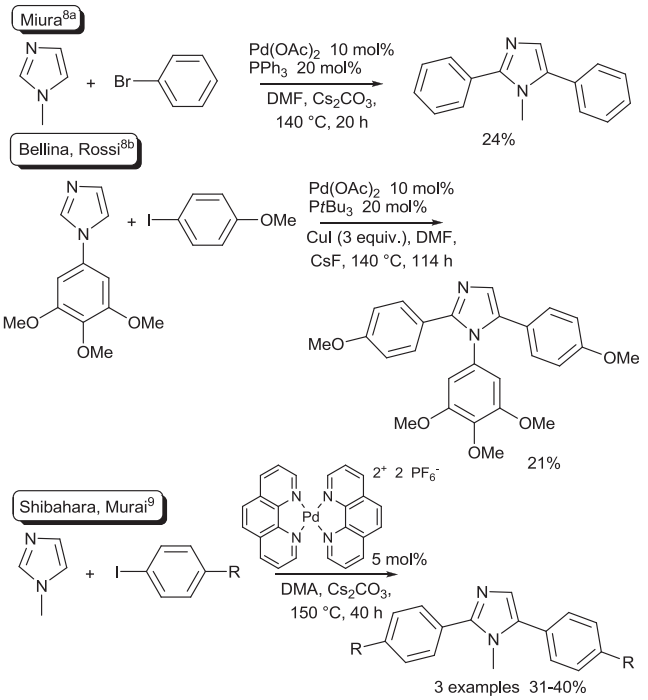


Scheme 1. Reported examples of Pd-catalysed one pot access to 2,5-diarylimidazoles.

reported that the addition of 2 equiv of CuI to the reaction mixture, using iodobenzene as the coupling partner, drastically modify the selectivity of the reaction, as a mixture of C2 and C2,C5 arylation products in a 37:40 ratio was obtained. It should be noted that CuI itself promotes the C2 arylation of imidazole. Bellina, Rossi and co-workers also studied the influence of several parameters for the arylation of imidazoles, and succeeded in a few cases to obtain directly the 2,5-diarylated imidazoles although in moderate yields.[8b] A few 2,5-diarylimidazoles have also been prepared by Shibahara, Murai et al. using a 1,10-phenanthroline containing Pd catalyst and aryl iodides as coupling partners.[9] However, so far sequential Pd-catalysed direct arylations remains the most reliable method to prepare 2,5-diarylimidazoles in good yields.[10]

Therefore, the discovery of effective conditions, for the direct coupling of aryl halides at both C2 and C5 positions of imidazole derivatives in one pot, would constitute a considerable advantage allowing a simpler access to 2,5-diarylimidazoles.

Here, we wish to (i) report that $Pd(OAc)_2$ catalyst without any additional ligand promotes the direct access to 2,5-diarylimidazoles in one pot, (ii) report on the reaction scope using a large set of electronically and sterically diverse aryl bromides, (iii) reveal the influence of the imidazole *N*-substituent.

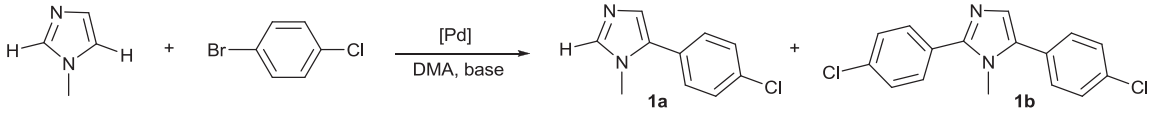
2. Results and discussion

We have recently reported the direct 5-arylation of a range of imidazole derivatives using a phosphine-free palladium catalyst.[11] Based on these results, for this study DMA was initially chosen as the solvent and KOAc as the base. The reactions were performed at 150 °C under argon in the presence of $Pd(OAc)_2$ catalyst. Using only 0.5 mol% $Pd(OAc)_2$, the reaction of 3 equiv of 4-bromochlorobenzene with 1 equiv of 1-methylimidazole affords the mono- and di-arylation products **1a**:**1b** in a 73:27 ratio and the target product **1b** was isolated in a low yield of 18% (Table 1, entry 1). Then, we examined the influence of the amount of catalyst and base for this reaction (Scheme 2, Table 1, entries 2–5). A larger excess (4 equiv) of KOAc base affords the products **1a**:**1b** in a 68:32 ratio. In the presence of 1 or 2 mol-% $Pd(OAc)_2$ instead of 0.5 mol%, an almost equimolar mixture of **1a**:**1b** was obtained. A longer reaction time (48 h instead on 20 h) led to products **1a**:**1b** in 23:77 ratio and **1b** was isolated in 62% yield (Table 1, entry 5). An important effect of the acetate countercations was observed. The use of CsOAc instead of KOAc in the presence of 2 mol% $Pd(OAc)_2$ gave **1a**:**1b** in 12:88 ratio and **1b** in 70% yield; whereas, NaOAc (2 equiv) led to products **1a**:**1b** in 89:11 ratio and allowed to isolate **1a** in 64% yield (Table 1, entries 8 and 10). A lower reaction temperature (120 °C) affords products **1a**:**1b** in 92:8 ratio (Table 1, entry 9).

Table 1
Influence of the reaction conditions for palladium catalysed arylation of 1-methylimidazole with 4-bromochlorobenzene (Scheme 2)

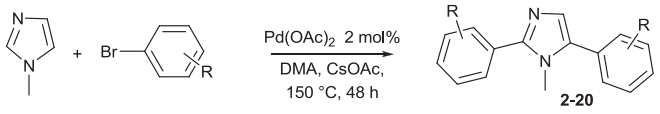
Entry	Catalyst (mol%)	Base (equiv)	Time (h)	Ratio **1a**:**1b**	Yield in **1b** (%)
1	0.5	KOAc (3)	20	73:27	18
2	0.5	KOAc (4)	20	68:32	
3	1	KOAc (4)	20	52:48	
4	2	KOAc (4)	20	52:48	
5	1	KOAc (4)	48	23:77	62
6	1	KOAc (3) Cs_2CO_3 (3)	20	44:56	
7	1	CsOAc (4)	48	15:85	
8	2	CsOAc (4)	48	**12:88**	70
9	2	CsOAc (4)	48	92:8[a]	
10	0.5	NaOAc (2)	20	**89:11**[b]	64

Conditions: $Pd(OAc)_2$ 0.5–2 mol%, 4-bromochlorobenzene (3 equiv), 1-methylimidazole (1 equiv), DMA, 150 °C, 20 h, isolated yields.
[a] 120 °C.
[b] 4-Bromochlorobenzene (1.2 equiv), 1-methylimidazole (1 equiv), yield in **1a**.



Scheme 2. Pd-catalysed direct diarylation of 1-methylimidazole with 4-bromobenzonitrile.

Then, using the most effective reaction conditions (DMA, CsOAc, $Pd(OAc)_2$, 150 °C, 48 h) we explored the scope of this reaction using *para*-, *meta*- and *ortho*-substituted aryl bromides and also some heteroaryl bromides employing 1-methylimidazole as the coupling partner (Scheme 3, Table 2).



Scheme 3. Scope of the Pd-catalysed direct diarylation of 1-methylimidazole.

First, we investigated the reaction of 1-methylimidazole with several *para*-substituted aryl bromides (Scheme 3, Table 2). In most cases, the reaction proceeds very smoothly in the presence of 2 mol% $Pd(OAc)_2$ catalyst. With electron deficient aryl bromides such as 4-bromoacetophenone, 4-bromopropiophenone, ethyl