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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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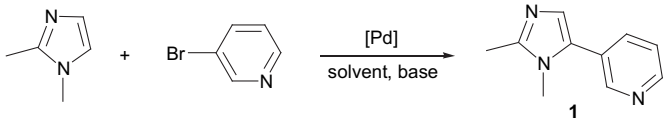
Recently, Heck and Suzuki reactions under low catalyst loading (0.1–0.01 mol %) using ligand-free catalyst $Pd(OAc)_2$ have been described by de Vries and co-workers.[17] They have demonstrated that, at elevated temperature, when $Pd(OAc)_2$ is employed as catalyst precursor, soluble palladium(0) colloids 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

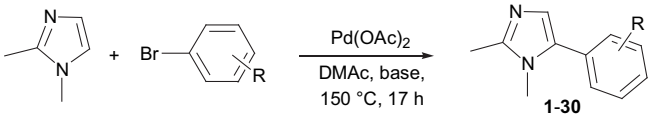
For this study, based on previous results,[18] DMAc was initially chosen as the solvent and KOAc as the base. The reactions were performed at 150 °C under argon in the presence 0.01 mol % $Pd(OAc)_2$ as the catalyst. Using these conditions, the coupling of 3-bromopyridine with 1,2-dimethylimidazole gave **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).

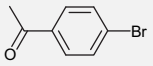
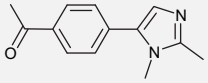
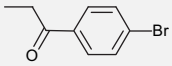
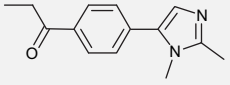
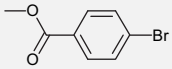
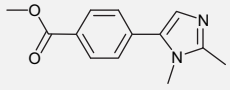
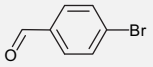
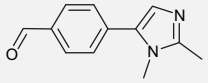
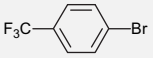
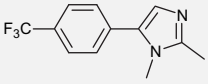
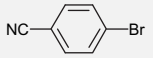
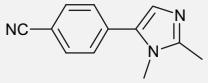
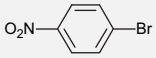
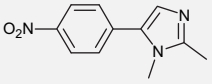
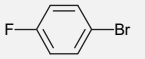
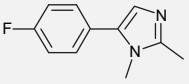
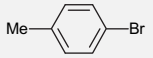
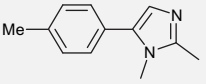
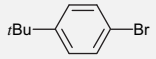
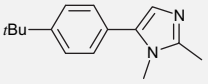
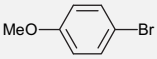
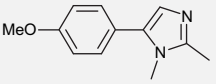
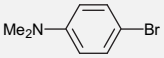
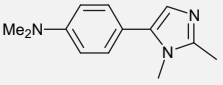
On the other hand, with 4-*t*-butylbromobenzene or 4-bromo-*N*,*N*-dimethylaniline, moderate yields of **11** and **13** were obtained using KOAc as the base (Table 2, entries 19 and 23). Surprisingly, with these deactivated aryl bromides, good yields were obtained using K_2CO_3 as the base and 0.5 mol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

Table 2
Palladium catalysed reaction of 1,2-dimethylimidazole with *para*-substituted aryl bromides (Scheme 2)

Entry	Aryl bromide	Product	Base	Substrate/cat. ratio	Yield (%)
1		 **2**	KOAc	200	79
2			KOAc	1000	65
3		 **3**	KOAc	200	78
4			KOAc	1000	62
5		 **4**	KOAc	200	73
6			KOAc	1000	44
7		 **5**	KOAc	1000	77
8		 **6**	KOAc	1000	80
9			KOAc	10,000	17
10		 **7**	KOAc	1000	81[a]
11			KOAc	10,000	12
12		 **8**	KOAc	1000	25
13		 **9**	KOAc	200	75
14			KOAc	1000	54
15		 **10**	KOAc	200	70
16			KOAc	1000	31
17			K_2CO_3	200	78
18			K_2CO_3	1000	10
19		 **11**	KOAc	200	50
20			K_2CO_3	200	77
21		 **12**	KOAc	200	50
22			K_2CO_3	200	31
23		 **13**	KOAc	200	22
24			K_2CO_3	200	70

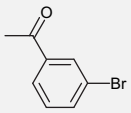
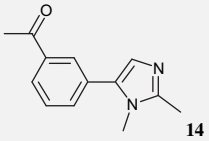
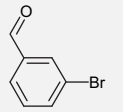
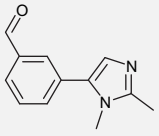
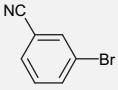
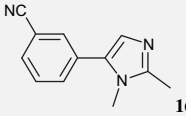
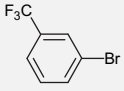
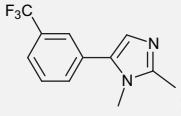
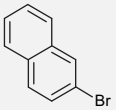
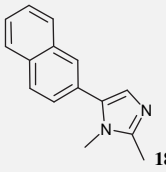
Conditions: $Pd(OAc)_2$, ArBr (1 equiv), 1,2-dimethylimidazole (2 equiv), base (2 equiv), DMAc, 150 °C, 17 h, isolated yields.
[a] Traces of homo-coupling of 4-trifluoromethylbromobenzene were also observed.

phosphine-free palladium active species largely depend on the palladium concentration. However, it also depends on the nature of the base. In general, when 0.01–0.1 mol % catalyst was employed, the use of KOAc as the base gave higher conversions of the aryl bromides than with K_2CO_3 (Table 1, entries 1 and 8). Under such low palladium concentration, the aggregation of palladium into 'palladium black' seems relatively slow. On the other hand, when 0.5 mol % of catalyst was employed, the use of K_2CO_3 led in some cases to similar or higher yields than KOAc for the reactions performed with deactivated aryl bromides. We believe that K_2CO_3 is a more suitable base for stabilising palladium species; whereas, KOAc associated to palladium gives less stable but more active palladium species.

The influence of the presence of *meta*-substituents on the aryl bromide is reported in the Table 3. As expected, relatively similar yields than in the presence of the *para*-substituted substrates were obtained for the reactions performed with 3-bromoacetophenone, 3-bromobenzaldehyde, 3-bromobenzonitrile or 3-trifluoromethylbromobenzene using 0.5 mol % catalyst (Table 3, entries 1–8). With 2-bromonaphthalene, a yield of 77% in **18** was obtained (Table 3, entries 9 and 10).

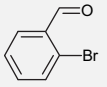
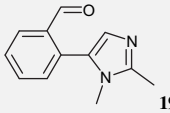
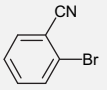
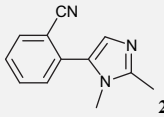
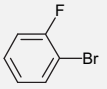
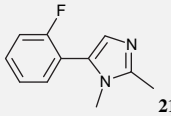
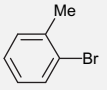
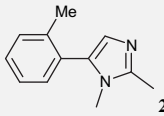
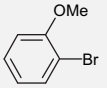
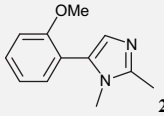
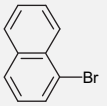
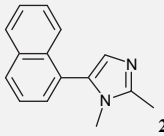
Then, we examined the reactivity of 1,2-dimethylimidazole with a set of *ortho*-substituted aryl bromides using the same reaction conditions (Scheme 2, Table 4). *ortho*-Substituents on the aryl bromides generally have a more important effect on the reaction rates of palladium-catalysed reactions due to their steric or

Table 3
Palladium catalysed reaction of 1,2-dimethylimidazole with *meta*-substituted aryl bromides (Scheme 2)

Entry	Aryl bromide	Product	Substrate/ cat. ratio	Yield (%)
1		 **14**	200	79
2			1000	25
3		 **15**	200	58
4			1000	76
5		 **16**	1000	78
6			200	32
7		 **17**	1000	75
8			200	41
9		 **18**	1000	77
10			200	33

Conditions: $Pd(OAc)_2$, ArBr (1 equiv), 1,2-dimethylimidazole (2 equiv), KOAc (2 equiv), DMAc, 150 °C, 17 h, isolated yields.

Table 4
Palladium catalysed reaction of 1,2-dimethylimidazole with *ortho*-substituted aryl bromides (Scheme 2)

Entry	Aryl bromide	Product	Substrate/ cat. ratio	Yield (%)
1		 **19**	200	38
2		 **20**	200	74
3			1000	28
4		 **21**	200	72
5		 **22**	200	65
6			200	79[a]
7		 **23**	200	0
8			200	0[a]
9		 **24**	200	76
10			1000	33

Conditions: $Pd(OAc)_2$, ArBr (1 equiv), 1,2-dimethylimidazole (2 equiv), KOAc (2 equiv), DMAc, 150 °C, 17 h, isolated yields.
[a] K_2CO_3 (2 equiv) was used as the base.

coordination properties. The expected 5-aryl-1,2-dimethylimidazoles **19**–**24** were obtained in moderate to good yields. In some cases, similar yields than in the presence of the *para*-substituted aryl bromides were obtained. For example, we observed that the coupling of 2-bromobenzonitrile or 2-fluorobromobenzene proceeds nicely to give **20** and **21** in 74 and 72% yields, respectively (Table 4, entries 2 and 4).

On the other hand, 2-bromobenzaldehyde gave **19** in a lower yield of 38%, due to the formation of unidentified side-products (Table 4, entry 1). 1-Bromonaphthalene gave **24** in 76% yield (Table 4, entries 9 and 10). Even slightly deactivated and congested aryl bromide, 2-bromotoluene led to the 5-arylated imidazole **22** in good yield. However, with this substrate, a higher yield was obtained using K_2CO_3 as the base (Table 4, entries 5 and 6). In the presence of this phosphine-free catalyst, congested and deactivated aryl bromide, 2-bromoanisole was recovered unreacted (Table 4, entries 7 and 8).

Heteroaryl bromides are also suitable reactants (Table 5). Pyridines or quinolines are π-electron deficient heterocycles and therefore, their oxidative addition to palladium is, in general, relatively easy. Using 3- or 4-bromopyridines, 3-bromoquinoline, 4-bromoisoquinoline or 5-bromopyrimidine and 1,2-dimethylimidazole as reactants, **1** and **26**–**29** were obtained in high yields using 0.1–0.5 mol % catalyst (Table 5, entries 2–10). On the other hand, in the presence of 2-bromopyridine or 2-bromopyrimidine, the formation of the expected products **25** and **30** was not detected (Table 5, entries 1 and 11).

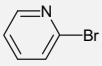
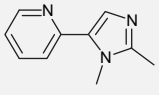
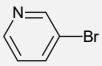
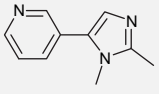
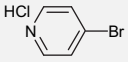
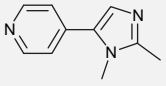
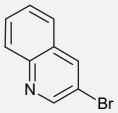
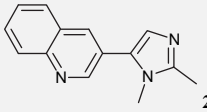
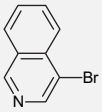
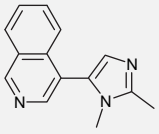
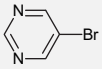
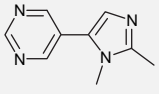
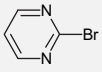
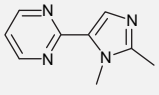
This might be due to some coordination of the nitrogen atoms of 2-bromopyridine or 2-bromopyrimidine to palladium. Such coordination could poison the catalyst. We had previously observed a similar phenomenon with such reactants for Heck reaction.[19]

Next, we examined the influence of the nature of the imidazole substituent on nitrogen (Table 6). Surprisingly, in the presence of 1-decyl-2-methylimidazole or 1-benzyl-2-methylimidazole, low yields of **31** and **33** were obtained (Table 6, entries 1 and 3). The reaction of 4-bromoacetophenone with an imidazole substituted by a propionitrile on nitrogen gave no coupling product (Table 6, entry 4). On the other hand, a yield of 71% of **32** was obtained when using 1-isobutyl-2-methylimidazole as coupling partner (Table 6, entry 2). This difference of reactivity might partially come from the presence of some impurities in the reactants. In the presence of 1-isobutyl-2-methylimidazole, the formation of a moderate amount of the 4-arylated imidazole was also detected by GC/MS (Scheme 2).

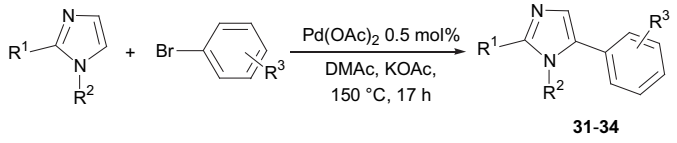
Then, using Bellina and Rossi procedure,[11e] we prepared 1-methyl-2-(4-trifluoromethylphenyl)-imidazole. Using this reactant and 4-bromobenzonitrile with 0.5 mol % $Pd(OAc)_2$, **35** was obtained in 54% yield (Scheme 4). This method should allow the synthesis of a very wide variety of 2,5-diarylimidazoles in only two steps.

The reactivity of an imidazole substituted on position 2 by a formyl group was also examined (Scheme 5). Using 4-bromobenzonitrile or 4-bromobenzaldehyde, the coupling products **36** and **37** were obtained in 52 and 69% yields, respectively. The presence of such electron-withdrawing function on the imidazole ring seems to slow down the arylation rate.

Table 5
Palladium catalysed reaction of 1,2-dimethylimidazole with heteroaryl bromides (Scheme 2)

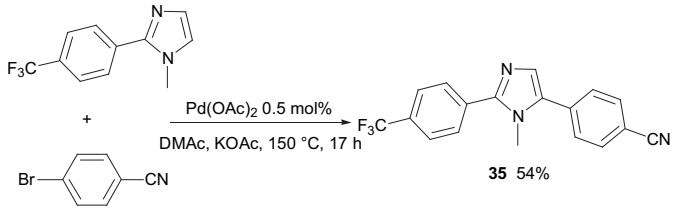
Entry	Aryl bromide	Product	Substrate/ cat. ratio	Yield (%)
1		 **25**	200	0
2		 **1**	1000	90
3		 **26**	200	84[a]
4			1000	54[a]
5		 **27**	200	85
6			1000	40
7		 **28**	200	87
8			1000	50
9		 **29**	200	85
10			1000	78
11		 **30**	200	0

Conditions: $Pd(OAc)_2$, ArBr (1 equiv), 1,2-dimethylimidazole (2 equiv), KOAc (2 equiv), DMAc, 150 °C, 17 h, isolated yields.
[a] KOAc (3 equiv) was used as the base.



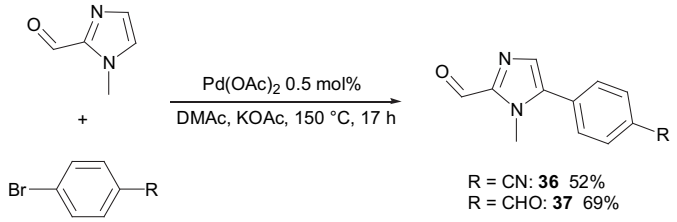
31-34

Scheme 3.



35 54%

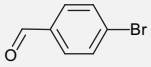
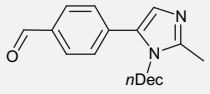
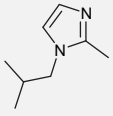
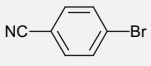
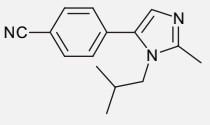
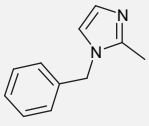
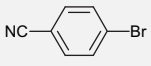
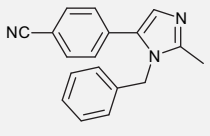
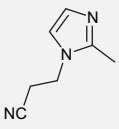
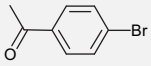
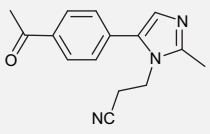
Scheme 4.



Scheme 5.

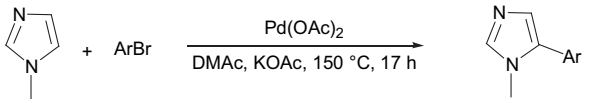
can be arylated. Bellina, Rossi and co-workers have extensively studied the arylation of such compounds. They have reported that using 1-methyl, 1-benzyl or 1-phenylimidazoles, 5 mol % $Pd(OAc)_2$, 10 mol % $AsPh_3$ or P(2-furyl)$_3$, CsF or K_2CO_3 as the bases and DMF as the solvent, the 5-arylated imidazoles were obtained in 22–80% yields.[13c–13e] Using our procedure, in the presence of 1-methylimidazole and 0.5 mol % $Pd(OAc)_2$, the regioselectivity in favour of

Table 6
Palladium catalysed reaction of 1-alkyl-2-methylimidazole with aryl bromides (Scheme 3)

Entry	Imidazole derivative	Aryl bromide	Product	Yield (%)
1			 **31**	21
2			 **32**	71
3			 **33**	34
4			 **34**	0

Conditions: $Pd(OAc)_2$ (0.005 equiv), ArBr (1 equiv), 1-alkyl-2-methylimidazole (2 equiv), KOAc (2 equiv), DMAc, 150 °C, 17 h, isolated yields.

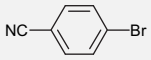
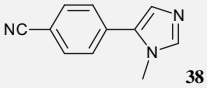
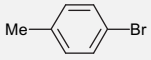
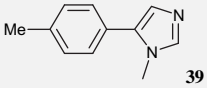
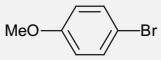
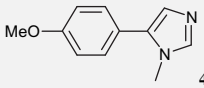
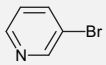
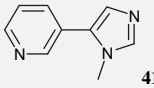
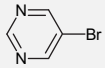
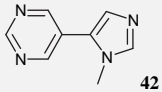
Finally, we explored the direct arylation of 1-methylimidazole using our low catalyst loading procedure (Scheme 6, Table 7). In the course of this reaction, both the positions 2 and 5 of this reactant the 5-arylation was high (Table 7). Moreover, good yields of target compounds **38**, **41** and **42** were obtained using activated aryl bromides such as 4-bromobenzonitrile, 3-bromopyridine or



38-42

Scheme 6.

Table 7
Palladium catalysed reaction of 1-methylimidazole with aryl bromides (Scheme 6)

Entry	Aryl bromide	Product	Substrate/ cat. ratio	Yield (%)
1		 **38**	200	76
2			1000	47
3		 **39**	200	40
4		 **40**	200	42
5		 **41**	200	81
6			1000	31
7		 **42**	200	67

Conditions: $Pd(OAc)_2$, ArBr (1 equiv), 1-methylimidazole (2 equiv), KOAc (2 equiv), DMAc, 150 °C, 17 h, isolated yields.

5-bromopyrimidine. On the other hand, in the presence of the deactivated aryl bromides, 4-bromotoluene or 4-bromoanisole, **39** and **40** were obtained in moderate yields (Table 7, entries 3 and 4). Fagnou and co-workers had also obtain a low yield of **40** using 2 mol % of $Pd(OAc)_2$ associated with 4 mol % PCy_3 as the catalyst.[16] Therefore, the procedures described by Bellina and Rossi should be preferred for the reactions in the presence of such challenging substrates.[13c–13e]

In summary, we report here a simple and atom-economical method for the synthesis of 5-arylimidazoles. We have established that, using appropriate reaction conditions, ligand-free $Pd(OAc)_2$ provides an efficient catalyst for the direct coupling of aryl bromides with some imidazole derivatives. The reaction is highly regioselective, as in most cases, only the 5-arylated imidazoles were formed. In the presence of 1,2-dimethylimidazole as coupling partner, a wide range of functions such as fluoro, acetyl, formyl, benzoyl, carboxylate or nitrile on the aryl bromide are tolerated. Some sterically hindered aryl bromides and several heteroaromatic substrates such as bromopyridines have also been employed successfully. The substituents on imidazole have a very important influence on the reaction rates and yields. It should be noted that, despite their interest, most of the products prepared by this method are new, indicating a relatively limited access to such compounds using more traditional cross-coupling procedures. This procedure employs a relatively low loading (0.5–0.01 mol %) of a commercially available, phosphine-free and air stable palladium source. Therefore, there is no need to eliminate phosphine derivatives at the end of the reaction. Moreover, a very wide variety of aryl bromides are commercially available. These are practical advantages of this reaction.

3. Experimental

3.1. General remarks

All reactions were run under argon in Schlenk tubes using vacuum lines. DMAc analytical grade was not distilled before use. KOAc or K_2CO_3 (99%) was used. Commercial aryl bromides and imidazoles were used without purification. The reactions were followed by GC and NMR. ^1H and ^{13}C spectra were recorded with a Bruker 200 MHz spectrometer in $CDCl_3$ solutions. Chemical shifts are reported in ppm relative to $CDCl_3$ (7.25 for ^1H NMR and 77.0 for ^{13}C NMR). Flash chromatography was performed on silica gel (230–400 mesh).

3.2. General procedure

In a typical experiment, the aryl halide (1 mmol), imidazole derivative (2 mmol), KOAc (0.196 g, 2 mmol) or K_2CO_3 (0.276 g, 2 mmol) (see tables) and $Pd(OAc)_2$ (see tables), were dissolved in DMAc (5 mL) under an argon atmosphere. The reaction mixture was stirred at 150 °C for 17 h. After evaporation of the solvent, the product was purified by silica gel column chromatography.

*3.2.1. 5-(3-Pyridyl)-1,2-dimethylimidazole (**1**)*[20]. From 3-bromopyridine (0.158 g, 1 mmol), 1,2-dimethylimidazole (0.192 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (0.22 mg, 0.001 mmol), product **1** was obtained in 90% (0.156 g) yield.

^1H NMR (200 MHz, $CDCl_3$) δ 8.50 (s, 1H), 8.48 (d, J=4.8 Hz, 1H), 7.62 (d, J=7.8 Hz, 1H), 7.34 (dd, J=4.8, 7.8 Hz, 1H), 6.97 (s, 1H), 3.48 (s, 3H), 2.42 (s, 3H).

*3.2.2. 5-(4-Acetylphenyl)-1,2-dimethylimidazole (**2**).* From 4-bromoacetophenone (0.199 g, 1 mmol), 1,2-dimethylimidazole (0.192 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), product **2** was obtained in 79% (0.169 g) yield.

^1H NMR (200 MHz, $CDCl_3$) δ 7.91 (d, J=8.4 Hz, 2H), 7.37 (d, J=8.4 Hz, 2H), 6.96 (s, 1H), 3.50 (s, 3H), 2.52 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 197.1, 146.9, 135.5, 134.7, 132.3, 128.5, 127.7, 126.6, 31.4, 26.3, 13.3; $C_{13}H_{14}N_2O$: calcd C 72.87, H 6.59; found C 73.00, H 6.55.

*3.2.3. 5-(4-Propionylphenyl)-1,2-dimethylimidazole (**3**).* From 4-bromopropiophenone (0.213 g, 1 mmol), 1,2-dimethylimidazole (0.192 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), product **3** was obtained in 78% (0.178 g) yield.

^1H NMR (200 MHz, $CDCl_3$) δ 7.90 (d, J=8.4 Hz, 2H), 7.35 (d, J=8.4 Hz, 2H), 6.92 (s, 1H), 3.47 (s, 3H), 2.89 (q, J=7.7 Hz, 2H), 2.34 (s, 3H), 1.10 (t, J=7.7 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 199.7, 146.6, 135.2, 134.3, 132.2, 128.1, 127.6, 126.1, 31.4, 31.3, 13.1, 7.8; $C_{14}H_{16}N_2O$: calcd C 73.66, H 7.06; found C 73.45, H 7.15.

*3.2.4. Methyl 4-(2,3-dimethylimidazol-4-yl)-benzoate (**4**).* From methyl 4-bromobenzoate (0.215 g, 1 mmol), 1,2-dimethylimidazole (0.192 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), product **4** was obtained in 73% (0.168 g) yield.

^1H NMR (200 MHz, $CDCl_3$) δ 8.10 (d, J=8.4 Hz, 2H), 7.44 (d, J=8.4 Hz, 2H), 7.13 (s, 1H), 3.94 (s, 3H), 3.59 (s, 3H), 2.56 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 166.5, 146.7, 133.8, 131.3, 130.0, 129.6, 128.2, 124.5, 52.2, 31.6, 12.9; $C_{13}H_{14}N_2O_2$: calcd C 67.81, H 6.13; found C 67.68, H 6.40.

*3.2.5. 5-(4-Formylphenyl)-1,2-dimethylimidazole (**5**).* From 4-bromobenzaldehyde (0.185 g, 1 mmol), 1,2-dimethylimidazole (0.192 g,

2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (0.22 mg, 0.001 mmol), product **5** was obtained in 77% (0.154 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$) δ 9.94 (s, 1H), 7.85 (d, J=8.4 Hz, 2H), 7.46 (d, J=8.4 Hz, 2H), 7.02 (s, 1H), 3.54 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 191.0, 146.9, 135.7, 134.4, 131.8, 129.6, 127.6, 126.7, 31.2, 13.1; $C_{12}H_{12}N_2O$: calcd C 71.98, H 6.04; found C 72.07, H 6.13.

*3.2.6. 5-(4-Trifluoromethylphenyl)-1,2-dimethylimidazole (**6**).* From 4-trifluoromethylbromobenzene (0.225 g, 1 mmol), 1,2-dimethylimidazole (0.192 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (0.22 mg, 0.001 mmol), product **6** was obtained in 80% (0.192 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.64 (d, J=8.4 Hz, 2H), 7.44 (d, J=8.4 Hz, 2H), 7.00 (s, 1H), 3.53 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 146.7, 133.8, 132.0, 129.3 (q, J=32.5 Hz), 128.2, 126.2, 125.5 (q, J=3.8 Hz), 124.0 (q, J=272.0 Hz), 31.2, 13.2; $C_{12}H_{11}F_3N_2$: calcd C 60.00, H 4.62; found C 59.97, H 4.54.

*3.2.7. 4-(2,3-Dimethylimidazol-4-yl)-benzonitrile (**7**).* From 4-bromobenzonitrile (0.182 g, 1 mmol), 1,2-dimethylimidazole (0.192 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (0.22 mg, 0.001 mmol), product **7** was obtained in 81% (0.160 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.61 (d, J=8.4 Hz, 2H), 7.39 (d, J=8.4 Hz, 2H), 6.98 (s, 1H), 3.51 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 147.0, 134.3, 131.9, 131.2, 127.7, 126.7, 118.0, 110.1, 31.1, 13.0; $C_{12}H_{11}N_3$: calcd C 73.07, H 5.62; found C 73.14, H 5.44.

*3.2.8. 5-(4-Nitrophenyl)-1,2-dimethylimidazole (**8**).* From 4-bromonitrobenzene (0.202 g, 1 mmol), 1,2-dimethylimidazole (0.192 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (0.22 mg, 0.001 mmol), product **8** was obtained in 25% (0.054 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$) δ 8.27 (d, J=8.4 Hz, 2H), 7.53 (d, J=8.4 Hz, 2H), 7.12 (s, 1H), 3.62 (s, 3H), 2.48 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 148.0, 146.6, 136.9, 131.5, 128.3, 128.1, 124.1, 31.7, 13.7; $C_{11}H_{11}N_3O_2$: calcd C 60.82, H 5.10; found C 61.02, H 5.01.

*3.2.9. 5-(4-Fluorophenyl)-1,2-dimethylimidazole (**9**).* From 4-bromofluorobenzene (0.175 g, 1 mmol), 1,2-dimethylimidazole (0.192 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), product **9** was obtained in 75% (0.143 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.31 (dd, J=8.4, 5.5 Hz, 2H), 7.12 (t, J=8.4 Hz, 2H), 6.93 (s, 1H), 3.50 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 162.4 (d, J=248 Hz), 145.7, 132.5, 130.5 (d, J=8.2 Hz), 126.3, 125.0, 115.7 (d, J=21.6 Hz), 31.1, 13.4; $C_{11}H_{11}FN_2$: calcd C 69.46, H 5.83; found C 69.44, H 5.74.

*3.2.10. 5-(4-Tolyl)-1,2-dimethylimidazole (**10**).* From 4-bromotoluene (0.171 g, 1 mmol), 1,2-dimethylimidazole (0.192 g, 2 mmol) and K_2CO_3 (0.276 g, 2 mmol) with $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), product **10** was obtained in 78% (0.145 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.22 (m, 4H), 6.91 (s, 1H), 3.49 (s, 3H), 2.42 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 145.4, 137.4, 133.3, 129.2, 128.4, 127.3, 125.0, 31.1, 21.0, 13.4; $C_{12}H_{14}N_2$: calcd C 77.38, H 7.58; found C 77.49, H 7.64.

*3.2.11. 5-(4-tert-Butylphenyl)-1,2-dimethylimidazole (**11**).* From 4-*tert*-butylbromobenzene (0.213 g, 1 mmol), 1,2-dimethylimidazole (0.192 g, 2 mmol) and K_2CO_3 (0.276 g, 2 mmol) with $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), product **11** was obtained in 77% (0.176 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.46 (d, J=8.4 Hz, 2H), 7.29 (d, J=8.4 Hz, 2H), 6.94 (s, 1H), 3.54 (s, 3H), 2.46 (s, 3H), 1.36 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 150.7, 145.7, 133.5, 128.3, 127.6, 125.6, 125.5, 34.6, 31.4, 31.3, 13.7; $C_{15}H_{20}N_2$: calcd C 78.90, H 8.83; found C 78.81, H 8.91.

*3.2.12. 5-(4-Methoxyphenyl)-1,2-dimethylimidazole (**12**)*[15]. From 4-bromoanisole (0.187 g, 1 mmol), 1,2-dimethylimidazole (0.192 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), product **12** was obtained in 50% (0.101 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.25 (d, J=8.4 Hz, 2H), 6.94 (d, J=8.4 Hz, 2H), 6.87 (s, 1H), 3.81 (s, 3H), 3.47 (s, 3H), 2.43 (s, 3H).

*3.2.13. 5-(4-Dimethylaminophenyl)-1,2-dimethylimidazole (**13**).* From 4-bromo-*N*,*N*-dimethylaniline (0.200 g, 1 mmol), 1,2-dimethylimidazole (0.192 g, 2 mmol) and K_2CO_3 (0.276 g, 2 mmol) with $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), product **13** was obtained in 70% (0.151 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.25 (d, J=8.2 Hz, 2H), 6.84 (s, 1H), 6.78 (d, J=8.2 Hz, 2H), 3.47 (s, 3H), 2.95 (s, 6H), 2.41 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 149.7, 144.6, 133.7, 129.4, 123.9, 117.7, 112.0, 40.1, 30.8, 13.3; $C_{13}H_{17}N_3$: calcd C 72.52, H 7.96; found C 72.52, H 7.87.

*3.2.14. 5-(3-Acetylphenyl)-1,2-dimethylimidazole (**14**).* From 3-bromoacetophenone (0.199 g, 1 mmol), 1,2-dimethylimidazole (0.192 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), product **14** was obtained in 79% (0.169 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.85–7.80 (m, 2H), 7.45–7.40 (m, 2H), 6.89 (s, 1H), 3.45 (s, 3H), 2.51 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 197.1, 145.8, 136.9, 132.3, 132.0, 130.2, 128.5, 127.4, 127.0, 125.0, 30.9, 26.1, 12.8; $C_{13}H_{14}N_2O$: calcd C 72.87, H 6.59; found C 73.02, H 6.50.

*3.2.15. 5-(3-Formylphenyl)-1,2-dimethylimidazole (**15**).* From 3-bromobenzaldehyde (0.185 g, 1 mmol), 1,2-dimethylimidazole (0.192 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), product **15** was obtained in 76% (0.152 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$) δ 9.89 (s, 1H), 7.80–7.65 (m, 2H), 7.55–7.45 (m, 2H), 6.87 (s, 1H), 3.43 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 191.5, 146.2, 136.3, 133.7, 131.7, 131.0, 129.1, 128.6, 128.5, 125.7, 31.1, 13.1; $C_{12}H_{12}N_2O$: calcd C 71.98, H 6.04; found C 72.17, H 6.12.

*3.2.16. 3-(2,3-Dimethylimidazol-4-yl)-benzonitrile (**16**).* From 3-bromobenzonitrile (0.182 g, 1 mmol), 1,2-dimethylimidazole (0.192 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), product **16** was obtained in 78% (0.154 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40–7.20 (m, 4H), 6.94 (s, 1H), 3.49 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 146.8, 132.3, 131.5, 131.2, 131.0, 130.7, 129.4, 126.5, 118.1, 112.7, 31.2, 13.3; $C_{12}H_{11}N_3$: calcd C 73.07, H 5.62; found C 73.18, H 5.42.

*3.2.17. 5-(3-Trifluoromethylphenyl)-1,2-dimethylimidazole (**17**).* From 3-trifluoromethylbromobenzene (0.225 g, 1 mmol), 1,2-dimethylimidazole (0.192 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), product **17** was obtained in 75% (0.180 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.62–7.45 (m, 4H), 7.00 (s, 1H), 3.53 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 146.6, 132.0, 131.5, 131.3, 131.1 (q, J=32.2 Hz), 129.1, 126.6, 124.9 (q, J=3.8 Hz), 124.1 (q, J=3.7 Hz), 123.8 (q, J=272.4 Hz), 31.2, 13.5; $C_{12}H_{11}F_3N_2$: calcd C 60.00, H 4.62; found C 60.10, H 4.71.

*3.2.18. 1,2-Dimethyl-5-naphthalen-2-ylimidazole (**18**)*[13a]. From 2-bromonaphthalene (0.207 g, 1 mmol), 1,2-dimethylimidazole (0.192 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), product **18** was obtained in 77% (0.171 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.95–7.70 (m, 4H), 7.50–7.30 (m, 3H), 7.03 (s, 1H), 3.45 (s, 3H), 2.40 (s, 3H).

*3.2.19. 5-(2-Formylphenyl)-1,2-dimethylimidazole (**19**).* From 2-bromobenzaldehyde (0.185 g, 1 mmol), 1,2-dimethylimidazole (0.192 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with

$Pd(OAc)_2$ (1.1 mg, 0.005 mmol), product **19** was obtained in 38% (0.076 g) yield.

^1H NMR (200 MHz, $CDCl_3$) δ 9.91 (s, 1H), 7.98 (d, J=7.8 Hz, 1H), 7.64 (t, J=7.5 Hz, 1H), 7.51 (t, J=7.5 Hz, 1H), 7.34 (d, J=7.6 Hz, 1H), 6.90 (s, 1H), 3.36 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 191.4, 146.5, 134.9, 134.8, 133.6, 132.8, 131.6, 128.8, 128.5, 128.1, 30.9, 13.3; $C_{12}H_{12}N_2O$: calcd C 71.98, H 6.04; found C 71.87, H 6.10.

*3.2.20. 2-(2,3-Dimethylimidazol-4-yl)-benzonitrile (**20**).* From 2-bromobenzonitrile (0.182 g, 1 mmol), 1,2-dimethylimidazole (0.192 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), product **20** was obtained in 74% (0.146 g) yield.

^1H NMR (200 MHz, $CDCl_3$) δ 7.65 (d, J=8.0 Hz, 1H), 7.56 (t, J=7.8 Hz, 1H), 7.38 (t, J=7.8 Hz, 1H), 7.31 (d, J=8.0 Hz, 1H), 6.98 (s, 1H), 3.38 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 146.7, 134.9, 133.2, 132.5, 130.6, 128.9, 128.1, 127.7, 117.6, 112.4, 31.0, 13.2; $C_{12}H_{11}N_3$: calcd C 73.07, H 5.62; found C 73.10, H 5.54.

*3.2.21. 5-(2-Fluorophenyl)-1,2-dimethylimidazole (**21**).* From 2-bromofluorobenzene (0.175 g, 1 mmol), 1,2-dimethylimidazole (0.192 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), product **21** was obtained in 72% (0.137 g) yield.

^1H NMR (200 MHz, $CDCl_3$) δ 7.42–7.25 (m, 2H), 7.18 (t, J=7.8 Hz, 1H), 7.13 (t, J=7.8 Hz, 1H), 6.95 (s, 1H), 3.42 (s, 3H), 2.49 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 159.3 (d, J=247.6 Hz), 146.0, 131.8, 130.1 (d, J=8.2 Hz), 127.5, 126.4, 124.3 (d, J=3.8 Hz), 118.1 (d, J=15.4 Hz), 115.7 (d, J=22.0 Hz), 31.0, 13.3; $C_{11}H_{11}FN_2$: calcd C 69.46, H 5.83; found C 69.34, H 5.90.

*3.2.22. 5-(2-Tolyl)-1,2-dimethylimidazole (**22**).* From 2-bromotoluene (0.171 g, 1 mmol), 1,2-dimethylimidazole (0.192 g, 2 mmol) and K_2CO_3 (0.276 g, 2 mmol) with $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), product **22** was obtained in 79% (0.147 g) yield.

^1H NMR (200 MHz, $CDCl_3$) δ 7.20–7.05 (m, 4H), 6.81 (s, 1H), 3.27 (s, 3H), 2.43 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 144.8, 138.1, 131.9, 131.1, 130.1, 129.8, 128.5, 125.6, 125.5, 30.5, 19.9, 13.4; $C_{12}H_{14}N_2$: calcd C 77.38, H 7.58; found C 77.20, H 7.57.

*3.2.23. 1,2-Dimethyl-5-naphthalen-1-ylimidazole (**24**)[13a].* From 1-bromonaphthalene (0.207 g, 1 mmol), 1,2-dimethylimidazole (0.192 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), product **24** was obtained in 76% (0.169 g) yield.

^1H NMR (200 MHz, $CDCl_3$) δ 7.96–7.90 (m, 2H), 7.65 (d, J=8.0 Hz, 1H), 7.60–7.30 (m, 4H), 7.03 (s, 1H), 3.26 (s, 3H), 2.52 (s, 3H).

*3.2.24. 5-(4-Pyridyl)-1,2-dimethylimidazole (**26**)[20].* From 4-bromopyridine hydrochloride (0.194 g, 1 mmol), 1,2-dimethylimidazole (0.192 g, 2 mmol) and KOAc (0.294 g, 3 mmol) with $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), product **26** was obtained in 84% (0.146 g) yield.

^1H NMR (200 MHz, $CDCl_3$) δ 8.61 (d, J=6.0 Hz, 2H), 7.26 (d, J=6.0 Hz, 2H), 7.11 (s, 1H), 3.61 (s, 3H), 2.45 (s, 3H).

*3.2.25. 5-(3-Quinolyl)-1,2-dimethylimidazole (**27**).* From 3-bromoquinoline (0.208 g, 1 mmol), 1,2-dimethylimidazole (0.192 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), product **27** was obtained in 85% (0.190 g) yield.

^1H NMR (200 MHz, $CDCl_3$) δ 8.81 (s, 1H), 8.01 (d, J=8.0 Hz, 1H), 7.97 (s, 1H), 7.71 (d, J=8.0 Hz, 1H), 7.61 (t, J=7.8 Hz, 1H), 7.45 (t, J=7.8 Hz, 1H), 7.03 (s, 1H), 3.48 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 149.8, 146.7, 146.6, 134.0, 129.8, 129.4, 128.8, 127.5, 127.2, 126.9, 126.5, 123.3, 31.1, 13.2; $C_{14}H_{13}N_3$: calcd C 75.31, H 5.87; found C 75.22, H 5.80.

*3.2.26. 5-(4-Isoquinolyl)-1,2-dimethylimidazole (**28**).* From 4-bromoisoquinoline (0.208 g, 1 mmol), 1,2-dimethylimidazole (0.192 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), product **28** was obtained in 87% (0.194 g) yield.

^1H NMR (200 MHz, $CDCl_3$) δ 9.17 (s, 1H), 8.35 (s, 1H), 7.93 (d, J=8.0 Hz, 1H), 7.62–7.40 (m, 3H), 6.97 (s, 1H), 3.22 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 152.7, 146.0, 144.1, 134.9, 130.9, 127.9, 127.7, 127.5, 127.3, 127.2, 124.1, 121.4, 30.8, 13.2; $C_{14}H_{13}N_3$: calcd C 75.31, H 5.87; found C 75.40, H 5.99.

*3.2.27. 5-(5-Pyrimidyl)-1,2-dimethylimidazole (**29**).* From 5-bromopyrimidine (0.159 g, 1 mmol), 1,2-dimethylimidazole (0.192 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), product **29** was obtained in 85% (0.148 g) yield.

^1H NMR (200 MHz, $CDCl_3$) δ 9.12 (s, 1H), 8.72 (s, 2H), 7.05 (s, 1H), 3.54 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 157.2, 155.3, 147.7, 127.7, 126.3, 124.9, 31.3, 13.4; $C_9H_{10}N_4$: calcd C 62.05, H 5.79; found C 62.20, H 5.78.

*3.2.28. 4-(3-Decyl-2-methylimidazol-4-yl)-benzaldehyde (**31**).* From 4-bromobenzaldehyde (0.185 g, 1 mmol), 1-decyl-2-methylimidazole (0.444 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), product **31** was obtained in 21% (0.069 g) yield.

^1H NMR (200 MHz, $CDCl_3$) δ 10.04 (s, 1H), 7.94 (d, J=8.4 Hz, 2H), 7.51 (d, J=8.4 Hz, 2H), 7.45 (s, 1H), 3.93 (t, J=7.5 Hz, 2H), 2.46 (s, 3H), 1.50–1.00 (m, 16H), 0.85 (t, J=7.5 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 191.4, 137.0, 135.1, 131.4, 131.3, 130.1, 128.5, 127.4, 44.3, 31.7, 30.4, 29.4, 29.3, 29.2, 29.1, 28.9, 26.4, 22.5, 14.0; $C_{21}H_{30}N_2O$: calcd C 77.26, H 9.26; found C 77.17, H 9.34.

*3.2.29. 4-(3-Isobutyl-2-methylimidazol-4-yl)-benzonitrile (**32**).* From 4-bromobenzonitrile (0.182 g, 1 mmol), 1-isobutyl-2-methylimidazole (0.276 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), product **32** was obtained in 71% (0.170 g) yield.

^1H NMR (200 MHz, $CDCl_3$) δ 7.70 (d, J=8.4 Hz, 2H), 7.45 (d, J=8.4 Hz, 2H), 7.01 (s, 1H), 3.78 (d, J=7.6 Hz, 2H), 2.46 (s, 3H), 1.67 (m, 1H), 0.69 (d, J=6.6 Hz, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 147.5, 135.8, 132.4, 131.2, 128.5, 128.2, 118.5, 110.9, 51.4, 29.4, 19.6, 14.0; $C_{15}H_{17}N_3$: calcd C 75.28, H 7.16; found C 75.30, H 7.14.

*3.2.30. 4-(3-Benzyl-2-methylimidazol-4-yl)-benzonitrile (**33**).* From 4-bromobenzonitrile (0.182 g, 1 mmol), 1-benzyl-2-methylimidazole (0.344 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), product **33** was obtained in 34% (0.093 g) yield.

^1H NMR (200 MHz, $CDCl_3$) δ 7.58 (d, J=8.2 Hz, 2H), 7.40–7.20 (m, 5H), 7.16 (s, 1H), 6.94 (d, J=8.2 Hz, 2H), 5.15 (s, 2H), 2.35 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 147.8, 136.0, 134.7, 132.4, 132.0, 129.1, 128.3, 128.0, 127.8, 125.3, 118.4, 110.9, 47.4, 13.5; $C_{18}H_{15}N_3$: calcd C 79.10, H 5.53; found C 79.31, H 5.54.

*3.2.31. 4-[3-Methyl-2-(4-trifluoromethylphenyl)-imidazol-4-yl]-benzonitrile (**35**).* From 4-bromobenzonitrile (0.182 g, 1 mmol), 1-methyl-2-(4-trifluoromethylphenyl)-imidazole (0.452 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), product **35** was obtained in 54% (0.177 g) yield.

^1H NMR (200 MHz, $CDCl_3$) δ 7.83 (d, J=8.2 Hz, 2H), 7.80–7.72 (m, 4H), 7.58 (d, J=8.2 Hz, 2H), 7.33 (s, 1H), 3.74 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 149.3, 134.2, 134.3, 133.6, 132.7, 131.3 (q, J=32.5 Hz), 129.6, 129.1, 128.6, 125.6 (q, J=3.8 Hz), 124.0 (q, J=272.0 Hz), 118.4, 111.5, 34.1; $C_{18}H_{12}F_3N_3$: calcd C 66.05, H 3.70; found C 66.21, H 3.87.

*3.2.32. 4-(2-Formyl-3-methylimidazol-4-yl)-benzonitrile (**36**).* From 4-bromobenzonitrile (0.182 g, 1 mmol), 1-methyl-2-formylimidazole

(0.220 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), product **36** was obtained in 52% (0.110 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$) δ 9.85 (s, 1H), 7.78 (d, J=8.4 Hz, 2H), 7.55 (d, J=8.4 Hz, 2H), 7.39 (s, 1H), 3.98 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 182.4, 145.1, 137.6, 132.8, 132.4, 131.7, 129.5, 118.1, 113.0, 33.4;; $C_{12}H_9N_3O$: calcd C 68.24, H 4.29; found C 68.31, H 4.19.

*3.2.33. 5-(4-Formylphenyl)-1-methylimidazole-2-carbaldehyde (**37**).* From 4-bromobenzaldehyde (0.185 g, 1 mmol), 1-methyl-2-formylimidazole (0.220 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), product **37** was obtained in 69% (0.148 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$) δ 10.06 (s, 1H), 9.84 (s, 1H), 7.99 (d, J=8.4 Hz, 2H), 7.60 (d, J=8.4 Hz, 2H), 7.40 (s, 1H), 4.00 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 190.8, 181.8, 144.5, 137.8, 135.9, 133.1, 131.2, 129.6, 128.9, 32.9; $C_{12}H_{10}N_2O_2$: calcd C 67.28, H 4.71; found C 67.39, H 4.61.

*3.2.34. 4-(3-Methylimidazol-4-yl)-benzonitrile (**38**).* From 4-bromobenzonitrile (0.182 g, 1 mmol), 1-methylimidazole (0.164 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), product **38** was obtained in 76% (0.139 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.64 (d, J=8.0 Hz, 2H), 7.49 (d, J=8.0 Hz, 2H), 7.28 (s, 1H), 7.13 (s, 1H), 3.67 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 140.0, 133.8, 132.0, 131.1, 129.2, 127.7, 118.1, 110.5, 32.4; $C_{11}H_9N_3$: calcd C 72.11, H 4.95; found C 72.20, H 4.98.

*3.2.35. 5-(4-Tolyl)-1-methylimidazole (**39**)*[21]. From 4-bromotoluene (0.171 g, 1 mmol), 1-methylimidazole (0.164 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), product **39** was obtained in 40% (0.069 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.29 (d, J=8.2 Hz, 2H), 7.25 (d, J=8.2 Hz, 2H), 7.08 (s, 1H), 3.65 (s, 3H), 2.40 (s, 3H).

*3.2.36. 5-(4-Methoxyphenyl)-1-methylimidazole (**40**)*[15]. From 4-bromoanisole (0.187 g, 1 mmol), 1-methylimidazole (0.164 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), product **40** was obtained in 42% (0.079 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.32 (d, J=8.0 Hz, 2H), 7.05 (s, 1H), 6.99 (d, J=8.0 Hz, 2H), 3.87 (s, 3H), 3.65 (s, 3H).

*3.2.37. 3-(3-Methylimidazol-4-yl)-pyridine (**41**)*[13d]. From 3-bromopyridine (0.158 g, 1 mmol), 1-methylimidazole (0.164 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), product **41** was obtained in 81% (0.129 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$) δ 8.61 (s, 1H), 8.54 (d, J=4.8 Hz, 1H), 7.66 (d, J=7.8 Hz, 1H), 7.53 (s, 1H), 7.33 (dd, J=4.8, 7.8 Hz, 1H), 7.10 (s, 1H), 3.63 (s, 3H).

*3.2.38. 5-(3-Methylimidazol-4-yl)-pyrimidine (**42**).* From 5-bromopyrimidine (0.159 g, 1 mmol), 1-methylimidazole (0.164 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), product **42** was obtained in 67% (0.107 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$) δ 9.20 (s, 1H), 8.80 (s, 2H), 7.61 (s, 1H), 7.24 (s, 1H), 3.72 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 157.6, 155.4, 140.7, 130.1, 126.4, 124.5, 32.6; $C_8H_8N_4$: calcd C 59.99, H 5.03; found C 60.10, H 5.08.

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