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Regiocontrolled palladium-catalyzed direct C2-arylation of a difluorobenzo[*d*]imidazole

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ABSTRACT

Conditions for the regioselective palladium-catalyzed direct arylation of a 6,7-difluorobenzo[*d*]imidazole using aryl bromides as the coupling partners are described. The site selectivity of the arylation was found to be in favor of the C2-carbon of the difluorobenzo[*d*]imidazole; whereas the difluoro-substituted ring remained untouched, even in the presence of an excess of aryl bromide. This method tolerates a variety of substituents at *para*-, *meta*- and *ortho*-positions on the aryl bromide and also *N*-containing heteroaryl bromides.

Introduction

Fluoro-substituted benzimidazole units can be found in several important drugs (Fig. 1).[1] For example, Abemaciclib is a drug for the treatment of advanced or metastatic breast cancers which was designated as a "breakthrough therapy" for breast cancer by the U. S. Food and Drug Administration in October 2015 (Fig. 1, left). Selumetinib[1a] and Binimetinib[1b] are also an anti-cancer drugs developed to treat various cancers.

Since the seminal work by Ohta et al. in 1990 on the Pd-catalyzed arylation of a wide range of 5-membered ring heteroaromatics such as pyrroles, indoles or thiophenes, *via* a C—H bond functionalization,[2] the so-called direct arylation of heteroarenes has been demonstrated to be a very effective tool to access (hetero)biaryls.[3,4] When this methodology can be employed to the late-stage functionalization of drugs, it provides a very convenient method for the access to a library of compounds in only a few steps allowing an easier screening of the biological properties of a family of compounds with a specific unit.

The first example of Pd-catalyzed direct arylation of a benzimidazole[5] was reported by Miura and co-workers who obtained 2-phenylbenzimidazole from 1-methylbenzo[*d*]imidazole and iodobenzene using $Pd(OAc)_2$ as the catalyst (Scheme 1, a).[5a] In 2010, Sames et al. described a general Pd-catalyzed approach to arylated imidazoles (Scheme 1, b).[5f] For the C2-arylation of imidazoles, they employed $Pd(OAc)_2/P(n\text{Bu})Ad_2$ associated to NaO*t*Bu as the base. Polyfluorobenzenes are also a very important class of substrates in Pd-catalyzed direct arylation, as many of them allow to obtain the corresponding biaryls in good yields.[6–8] Even 1,2-difluorobenzene was found to afford the corresponding difluorobiaryl using $Pd(OAc)_2/PMe(t\text{Bu})_2$ and K_2CO_3 as the catalytic system with 4-bromotoluene as coupling partner (Scheme 1, c).[8a]

According to Gorelsky calculations, the arylation of polyfluorobenzene rings using aryl halides as the aryl source likely proceed *via* a concerted metallation deprotonation (CMD) mechanism.[9] The energy of activation of C—H bonds flanked by a fluoro substituent is higher for fluorobenzene (30.3 kcal mol^{-1}), than for 1,2,3-trifluorobenzene (28.8 kcal mol^{-1}) (Fig. 2, top left). Therefore,

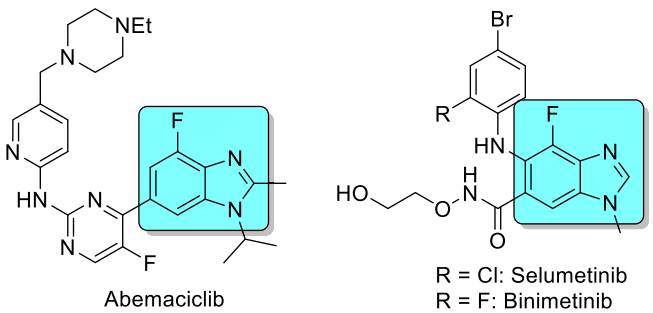

Figure 1. Representative examples of drugs containing a fluorobenzimidazole unit.

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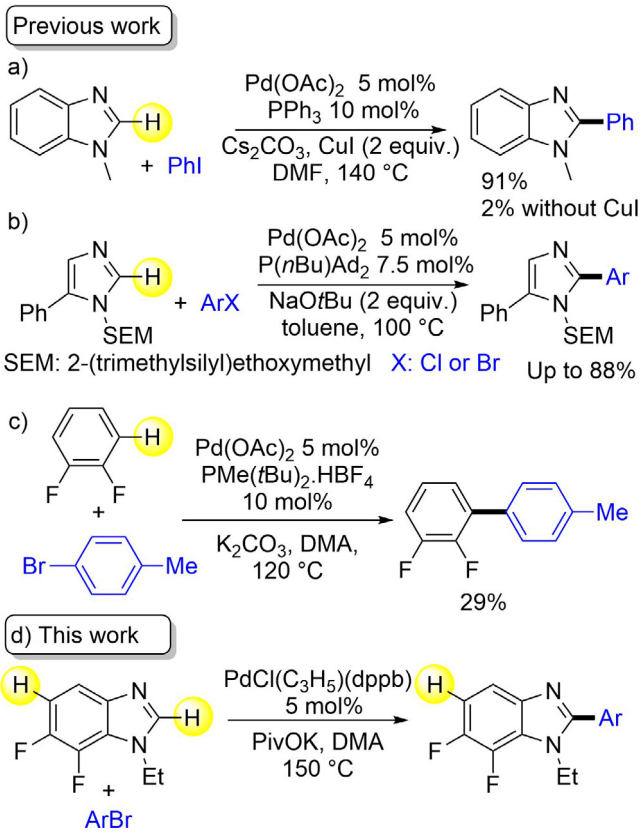


Scheme 1. Pd-catalyzed direct arylations of benzimidazoles and difluorobenzenes with aryl halides.

for 1,2-difluorobenzene it should be located between these two values.[9b] Gorelsky also calculated the energy of activation for C2-arylation of 1-methylimidazole via a CMD mechanism (26.5 kcal mol^{-1}) (Fig. 2, top right). Conversely, for (benzo) imidazoles, according to Gandon and Hoarau computational study the presence of a coordinating nitrogen atom may be involved in the mechanism.[10] The azole coordination on palladium would strongly favor a non-concerted metallation deprotonation (*n*CMD) mechanism (Fig. 2, bottom right). Their calculations using a carbonate as base/ligand gives an energy of activation of 27.1 for the *n*CMD and 29.7 for the CMD mechanisms.[10] Therefore, from a polyfluoro-substituted benzimidazole, a regioselective arylation at the C2-position was conceivable. However, to the best of our knowledge, the Pd-catalyzed direct arylation methodology has not been applied to the synthesis of fluoro-substituted imidazoles yet. Herein, we report on the site-selectivity of the Pd-catalyzed direct arylation of a difluorobenzo[*d*]imidazole and on the scope of the reaction (Scheme 1, d).

Results and discussion

Based on our previous results on palladium-catalyzed direct arylation,[11] we first examined the regioselectivity of the arylation of 1-ethyl-6,7-difluorobenzo[*d*]imidazole with 1.5 equiv. of 3-bromopyridine. In the presence of 2 mol% $PdCl(C_3H_5)(dppb)$ [12] catalyst and KOAc base at 150 °C in DMA, the C2-arylated imidazole **1a** was regioselectively obtained in 22% yield (Table 1, entry 1). Under these conditions, the difluorobenzene ring remained untouched. The use of Cs_2CO_3 as the base instead of KOAc provided **1a** in a very low yield; whereas, the use of PivOK using a longer reaction time improved to yield to 40% (Table 1, entries 2–4). The yield in **1a** was not improved by using xylene, DMF or NMP as the solvents (Table 1, entries 5–7). Phosphine-free catalyst Pd $(OAc)_2$ (2 mol%) gave **1a** in only 32%, but a higher loading of $PdCl(C_3H_5)(dppb)$ catalyst (5 mol%) afforded **1a** in 53% yield (Table 1, entries 8 and 9). The use CuI as additive or of KOPiv and Cs_2CO_3 as a mixture of bases did not improved the reaction

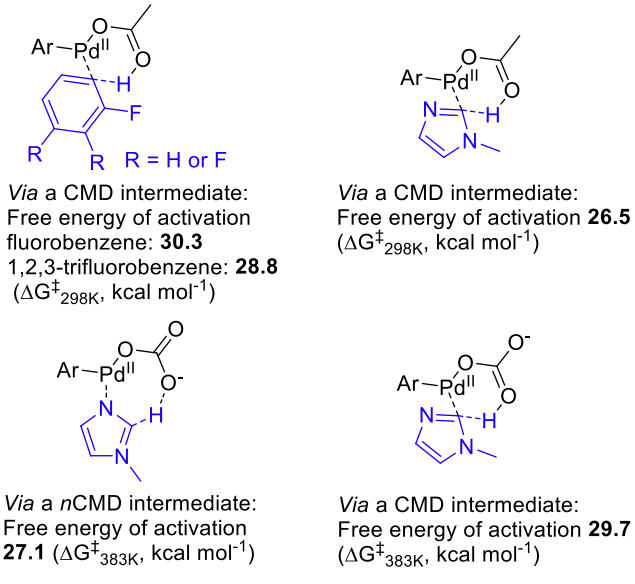
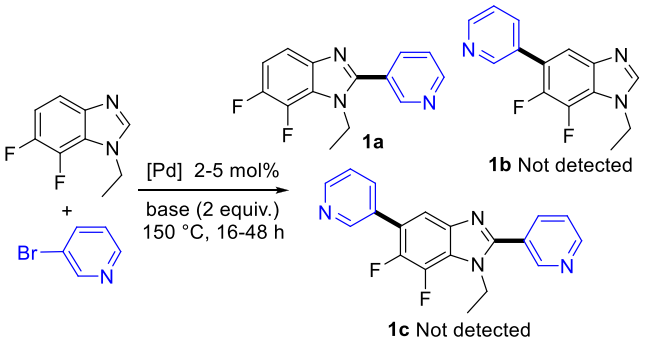


Figure 2. DFT calculated intermediates and energies of activation for the direct arylation of (poly)fluorobenzenes and imidazoles.

Table 1
Influence of the reaction conditions for the palladium-catalysed direct coupling of 1-ethyl-6,7-difluorobenzo[*d*]imidazole with 3-bromopyridine [13,14]



Entry	Catalyst (mol %)	Base	Solvent	Time (h)	Yield in **1a** (%)
1	$PdCl(C_3H_5)(dppb)$ (2)	KOAc	DMA	16	22
2	$PdCl(C_3H_5)(dppb)$ (2)	Cs_2CO_3	DMA	16	<5
3	$PdCl(C_3H_5)(dppb)$ (2)	KOPiv	DMA	16	25
4	$PdCl(C_3H_5)(dppb)$ (2)	KOPiv	DMA	48	40
5	$PdCl(C_3H_5)(dppb)$ (2)	KOPiv	xylene	48	15
6	$PdCl(C_3H_5)(dppb)$ (2)	KOPiv	NMP	48	20
7	$PdCl(C_3H_5)(dppb)$ (2)	KOPiv	DMF	48	34
8	$Pd(OAc)_2$ (2)	KOPiv	DMA	48	32
9	$PdCl(C_3H_5)(dppb)$ (5)	KOPiv	DMA	48	53
10	$PdCl(C_3H_5)(dppb)$ (5)	KOPiv (2 equiv.) + CuI (2 equiv.)	DMA	48	42[a]
11	$PdCl(C_3H_5)(dppb)$ (5)	KOPiv + Cs_2CO_3	DMA	48	41

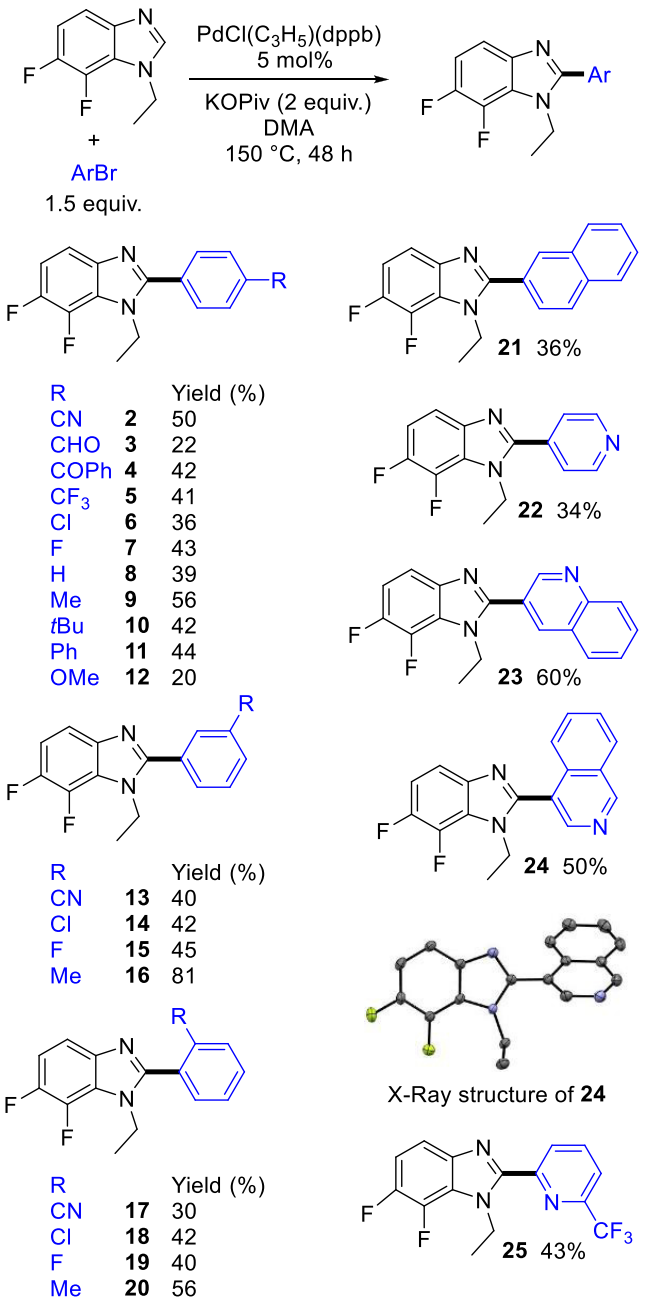
Conditions: 1-Ethyl-6,7-difluorobenzo[*d*]imidazole (1 mmol), 3-bromopyridine (1.5 mmol), base (2 mmol), 150 °C, isolated yields. [a] The formation of a large amount of insoluble salt was also observed.

yield (Table 1, entries 10 and 11). Although an excess of 3-bromopyridine was employed (1.5 equiv.), in the course of these reactions no formation of C5-arylated or C2,C5-diarylated products **1b** and **1c** was observed.

Then, the influence of substituents on the aryl bromide for the C2-arylation of 1-ethyl-6,7-difluorobenzo[*d*]imidazole was studied using 5 mol% $PdCl(C_3H_5)(dppb)$ catalyst and PivOK in DMA at 150 °C (Scheme 2). We first employed electron-deficient *para*-substituted aryl bromides. A cyano substituent at the C4-position afforded product **2** in 50%; whereas, 4-bromobenzaldehyde gave the expected C2-arylated benzimidazole **3** in only 22% yield due to the formation of degradation products. Benzoyl, trifluoromethyl, chloro and fluoro *para*-substituents on the aryl bromide were tolerated giving rise to products **4**–**7** in 36–43% yields. Under these reaction conditions, no cleavage of the C-Cl bond was observed. The electron-neutral bromobenzene and slightly electron-rich 4-bromotoluene and 4-*tert*-butylbromobenzene gave the desired coupling products **8**–**10** in 39–56% yields revealing that with these aryl bromides, the oxidative addition step is not the rate limiting step of the catalytic cycle. Conversely, the use of more electron-rich 4-bromoanisole led to the C2-arylated benzimidazole **12** in only 20% yield, due to a poor conversion. We also studied the influence of *meta*-substituents on the aryl bromide. With Cyano-, chloro or fluoro-substituted aryl bromides, moderate yields in the expected products **13**–**15** were obtained; whereas more electron-rich 3-bromotoluene gave **16** in 81% yield. With more sterically hindered *ortho*-substituted aryl bromides, such as 2-bromobenzonitrile and 2-bromochlorobenzene, the arylated benzimidazole derivatives **17** and **18** were obtained in 30% and 42% yield, respectively. Again the use of more-electron rich 2-bromotoluene gave the target product **20** in a higher yield of 56%. The *N*-containing 6-membered ring heterocycles are present in many very important drugs. [15] Therefore, the reactivity of 4-bromopyridine, 3-bromoquinoline and also 4-bromoisoquinoline was also studied. In all cases, the desired coupling products **22**–**24** were obtained. The structure of **24** was confirmed by X-ray analysis.[16] 2-Bromo-6-(trifluoromethyl)pyridine was also found to be reactive leading to the desired arylation product **25** in 43% yield. It should be mentioned that in all cases, no other regioisomers were detected by GC/MS analysis of the crude mixtures confirming that the difluoro-substituted ring is unreactive under these conditions.

Based on our experimental results – e.g. better yields using PivOK base which is a base of choice for CMD mechanism than with Cs_2CO_3 usually employed for *n*CMD process - and on the energies of activation of the figure 2, a CMD mechanism seems to be slightly favored. However, the coordination of the imidazole unit to palladium cannot be excluded.

In summary, we report herein the first examples of metal-catalyzed C—H bond functionalizations of a fluoro-substituted benzimidazole. The arylation occurred regiospecifically at the C2-position of benzimidazole; whereas, the C—H bond flanked by a fluorine atom remained untouched. This selectivity might be due to the coordination of one of the nitrogen atoms of difluorobenzo[*d*]imidazole to palladium. Low to moderate yields for C2-arylated difluorobenzimidazole were obtained using aryl bromides bearing useful functional groups such as nitrile, benzoyl, formyl, chloro, fluoro, trifluoromethyl or methoxy. Nitrogen-containing heteroaryl bromides were also tolerated. Therefore, this direct arylation methodology which employs easily available reactants, catalyst and base, provides a straightforward access to fluoro-substituted 2-arylbenzimidazoles allowing to tune or modify easily their properties.



Scheme 2. Scope of the Pd-catalyzed direct C2-arylations of 1-ethyl-6,7-difluorobenzo[*d*]imidazole using various aryl bromides.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Experimental procedures, products characterizations and copies of the ^{1}H, ^{13}C NMR LRMS and HRMS for all compounds. Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.153112.

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[13] Synthesis of C2-arylated 1-ethyl-6,7-difluorobenzo[d]imidazoles (Scheme 2): To a 25 mL oven dried Schlenk tube, aryl bromide (1.5 mmol), 1-ethyl-6,7-difluoro-benzo[d]imidazole (0.182 g, 1 mmol), KOPiv (0.280 g, 2 mmol), DMA (2 mL) and $PdCl(C_3H_5)$(dppb) (30.5 mg, 0.05 mmol) were successively added. The reaction mixture was evacuated by vacuum-argon cycles (5 times) and stirred at 150 °C (oil bath temperature) for 48 hours. After cooling the reaction at room temperature and concentration, the crude mixture was purified by silica column chromatography to afford the C2-arylated 1-ethyl-6,7-difluorobenzo[d]imidazoles **1a** and **2-25**.

[14] 1-Ethyl-6,7-difluoro-2-(pyridin-3-yl)benzo[*d*]imidazole **1a**: Following the procedure of reference 13, 3-bromopyridine (0.237 g, 1.5 mmol) and 1-ethyl-6,7-difluoro-benzo[*d*]imidazole (0.182 g, 1 mmol), affords **1a** in 53% (0.137 g) yield as a white solid: mp 96-98 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 8.96 (s, 1H), 8.78 (d, *J* = 4.3 Hz, 1H), 8.05 (d, *J* = 6.2 Hz, 1H), 7.55-7.49 (m, 2H), 7.13 (ddd, *J* = 11.1, 8.8, 7.4 Hz, 1H), 4.38 (q, *J* = 7.6 Hz, 2H), 1.52 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 151.9 (d, *J* = 2.2 Hz), 151.2, 149.7, 147.1 (dd, *J* = 241.4, 10.9 Hz), 141.6 (d, *J* = 2.1 Hz), 137.2 (dd, *J* = 239.7, 17.7 Hz), 137.0, 126.1, 124.4 (dd, *J* = 5.9, 5.2 Hz), 123.7, 115.5 (dd, *J* = 7.9, 4.2 Hz), 112.2 (d, *J* = 21.0 Hz), 41.7 (d, *J* = 3.5 Hz), 16.9 (d, *J* = 3.3 Hz). LRMS calcd for M^+ $C_{14}H_{11}F_2N_3$ 259, found 259.

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