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

Haoran Li<sup>a</sup>, Hai-Yun Huang<sup>a</sup>, Thierry Roisnel<sup>a</sup> and Henri Doucet<sup>a,\*</sup>

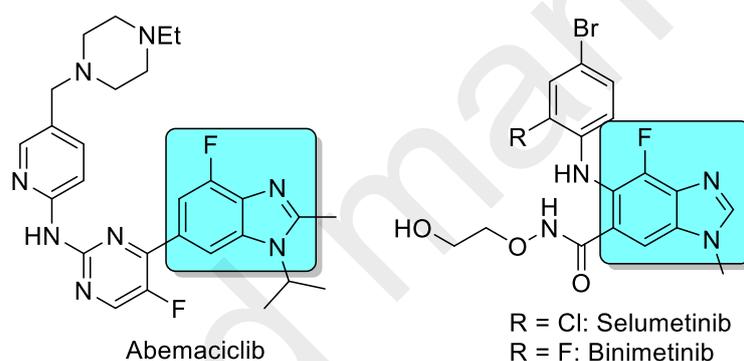
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## ABSTRACT

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.

## 1. Introduction

Fluoro-substituted benzimidazole units can be found in several important drugs (Fig. 1).<sup>1</sup> 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<sup>1a</sup> and Binimetinib<sup>1b</sup> are also anti-cancer drugs developed to treat various cancers.

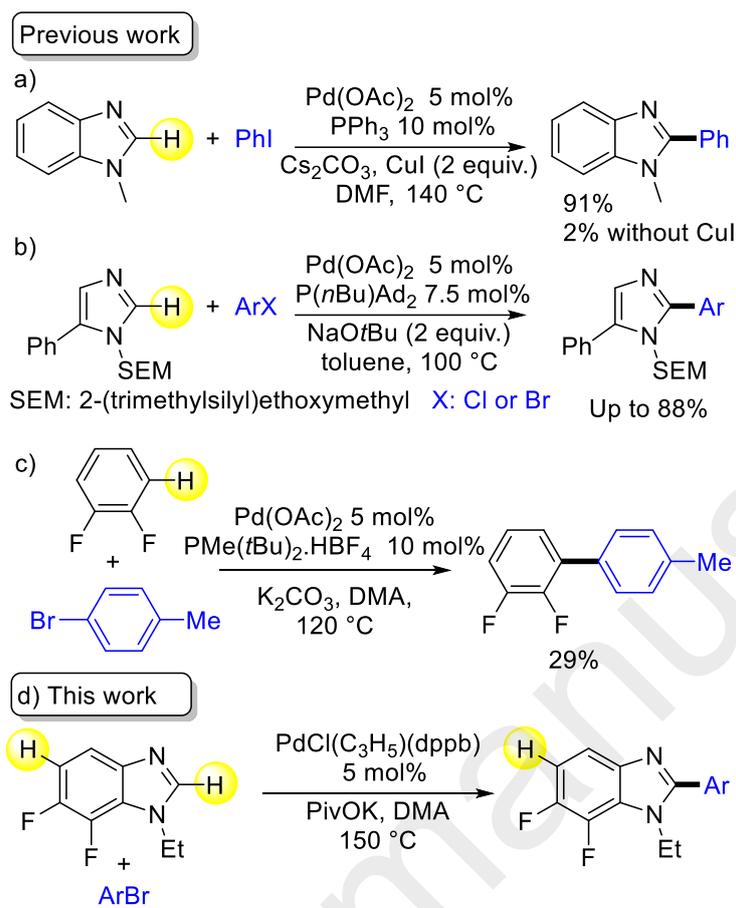


**Figure 1.** Representative examples of drugs containing a fluorobenzimidazole unit.

Since the seminal work by Ohta et al. in 1990 on the Pd-catalyzed arylation of a wide range of 5-membered ring heteroarenes such as pyrroles, indoles or thiophenes, *via* a C-H bond functionalization,<sup>2</sup> the so-called direct arylation of heteroarenes has been demonstrated to be a very effective tool to access (hetero)biaryls.<sup>3,4</sup> 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.

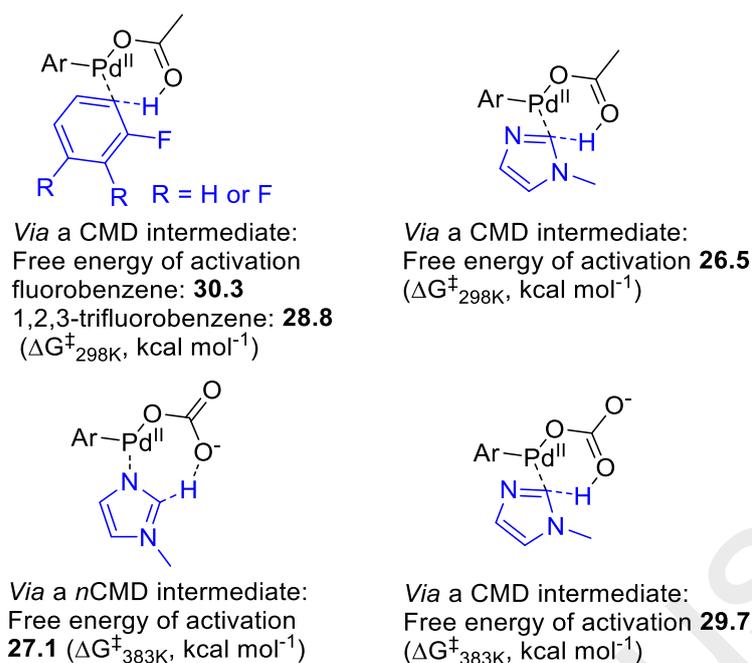
The first example of Pd-catalyzed direct arylation of a benzimidazole<sup>5</sup> was reported by Miura and co-workers who obtained 2-phenylbenzimidazole from 1-methylbenzo[*d*]imidazole and iodobenzene using Pd(OAc)<sub>2</sub> as the catalyst (Scheme 1, a).<sup>5a</sup> In 2010, Sames et al. described a general Pd-catalyzed approach to arylated imidazoles (Scheme 1, b).<sup>5f</sup> For the C2-arylation of imidazoles, they employed Pd(OAc)<sub>2</sub>/P(*n*Bu)Ad<sub>2</sub> associated to NaOtBu 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.<sup>6-8</sup> Even 1,2-difluorobenzene was found to afford the corresponding difluorobiaryl using Pd(OAc)<sub>2</sub>/PMe(*t*Bu)<sub>2</sub> and K<sub>2</sub>CO<sub>3</sub> as the catalytic system with 4-bromotoluene as coupling partner (Scheme 1, c).<sup>8a</sup>

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

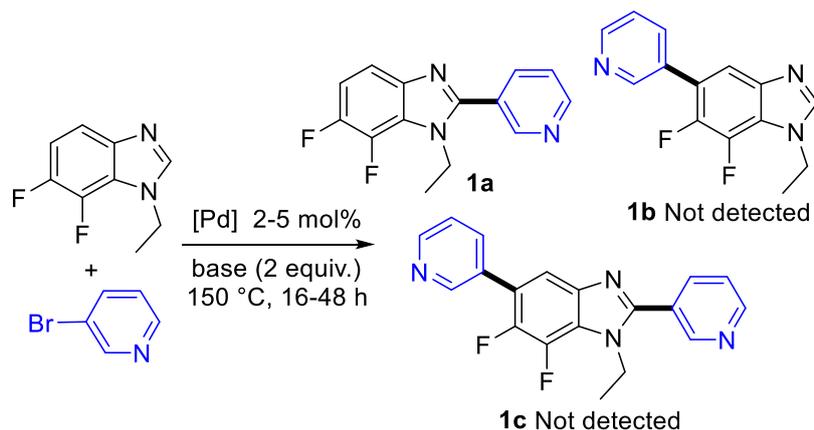
According to Gorelsky calculations, the arylation of polyfluorobenzene rings using aryl halides as the aryl source likely proceed *via* a concerted metallation deprotonation (CMD) mechanism.<sup>9</sup> The energy of activation of C-H bonds flanked by a fluoro substituent is higher for fluorobenzene (30.3 kcal mol<sup>-1</sup>), than for 1,2,3-trifluorobenzene (28.8 kcal mol<sup>-1</sup>) (Fig. 2, top left). Therefore, for 1,2-difluorobenzene it should be located between these two values.<sup>9b</sup> Gorelsky also calculated the energy of activation for C2-arylation of 1-methylimidazole *via* a CMD mechanism (26.5 kcal mol<sup>-1</sup>) (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.<sup>10</sup> 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.<sup>10</sup> 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).



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

## 2. Results and Discussion

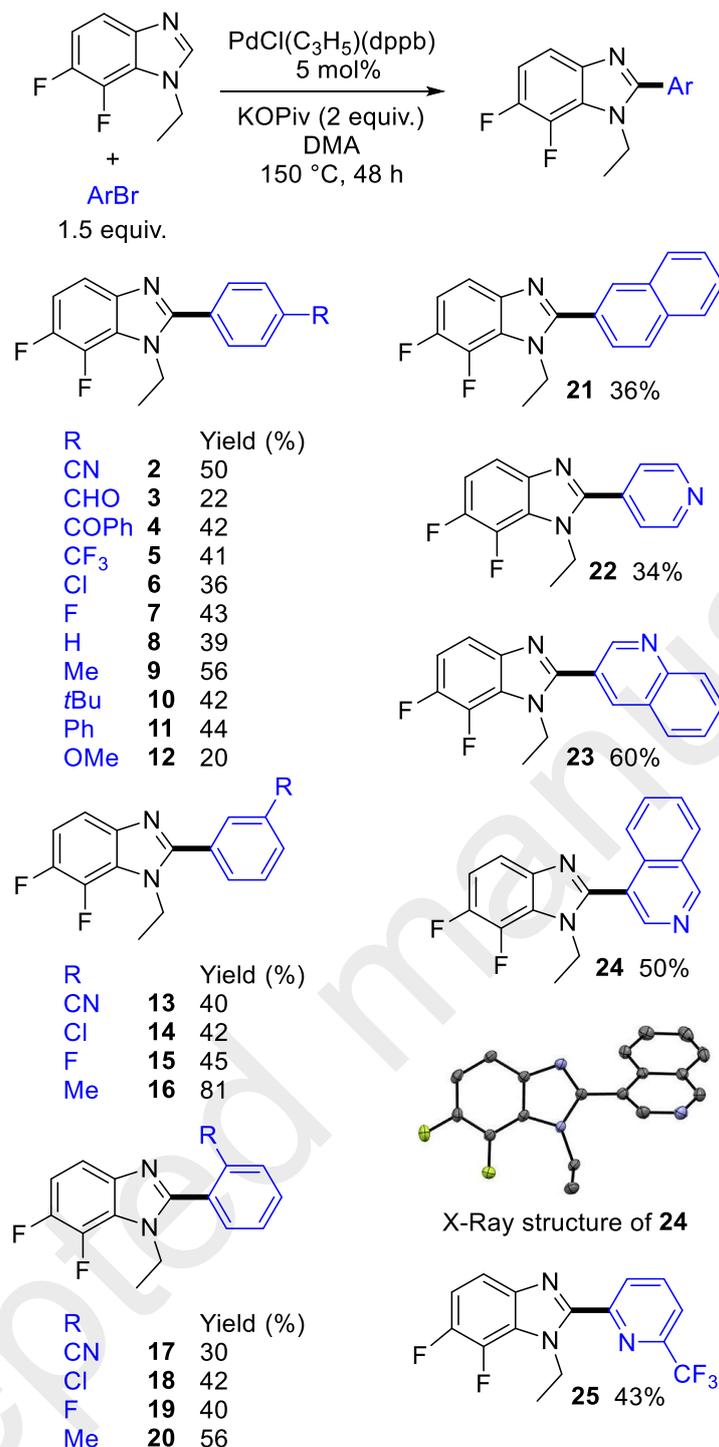
Based on our previous results on palladium-catalyzed direct arylation,<sup>11</sup> we first examined the regioselectivity of the arylation of 1-ethyl-6,7-difluorobenzodimidazole with 1.5 equiv. of 3-bromopyridine. In the presence of 2 mol% PdCl(C<sub>3</sub>H<sub>5</sub>)(dppb)<sup>12</sup> catalyst 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<sub>2</sub>CO<sub>3</sub> 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)<sub>2</sub> (2 mol%) gave **1a** in only 32%, but a higher loading of PdCl(C<sub>3</sub>H<sub>5</sub>)(dppb) catalyst (5 mol%) afforded **1a** in 53% yield (Table 1, entries 8 and 9). The use CuI as additive or of KOAc and Cs<sub>2</sub>CO<sub>3</sub> as a mixture of bases did not improve the reaction 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.

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

Entry	Catalyst (mol %)	Base	Solvent	Time (h)	Yield in <b>1a</b> (%)
1	PdCl(C <sub>3</sub> H <sub>5</sub> )(dppb) (2)	KOAc	DMA	16	22
2	PdCl(C <sub>3</sub> H <sub>5</sub> )(dppb) (2)	Cs <sub>2</sub> CO <sub>3</sub>	DMA	16	<5
3	PdCl(C <sub>3</sub> H <sub>5</sub> )(dppb) (2)	KOPiv	DMA	16	25
4	PdCl(C <sub>3</sub> H <sub>5</sub> )(dppb) (2)	KOPiv	DMA	48	40
5	PdCl(C <sub>3</sub> H <sub>5</sub> )(dppb) (2)	KOPiv	xylene	48	15
6	PdCl(C <sub>3</sub> H <sub>5</sub> )(dppb) (2)	KOPiv	NMP	48	20
7	PdCl(C <sub>3</sub> H <sub>5</sub> )(dppb) (2)	KOPiv	DMF	48	34
8	Pd(OAc) <sub>2</sub> (2)	KOPiv	DMA	48	32
9	PdCl(C <sub>3</sub> H <sub>5</sub> )(dppb) (5)	KOPiv	DMA	48	53
10	PdCl(C <sub>3</sub> H <sub>5</sub> )(dppb) (5)	KOPiv (2 equiv.) + CuI (2 equiv.)	DMA	48	42 <sup>a</sup>
11	PdCl(C <sub>3</sub> H <sub>5</sub> )(dppb) (5)	KOPiv + Cs <sub>2</sub> CO <sub>3</sub>	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. <sup>a</sup> The formation of a large amount of insoluble salt was also 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<sub>3</sub>H<sub>5</sub>)(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.<sup>15</sup> 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.<sup>16</sup> 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.



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

Based on our experimental results – e.g. better yields using PivOK base which is a base of choice for CMD mechanism than with  $\text{Cs}_2\text{CO}_3$  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 regioselectively 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.

## Acknowledgments

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## References and notes

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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<sub>3</sub>H<sub>5</sub>)(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. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 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). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 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<sup>+</sup> C<sub>14</sub>H<sub>11</sub>F<sub>2</sub>N<sub>3</sub> 259, found 259.
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16. X-ray structure of **24**: CCDC: 2049511

## Supplementary Material

Experimental procedures, products characterizations and copies of the <sup>1</sup>H, <sup>13</sup>C NMR, LRMS and HRMS for all compounds.