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Pd(0)-Catalyzed Direct Inter- and Intramolecular C–H Functionalization of 4-Carboxyimidazoles

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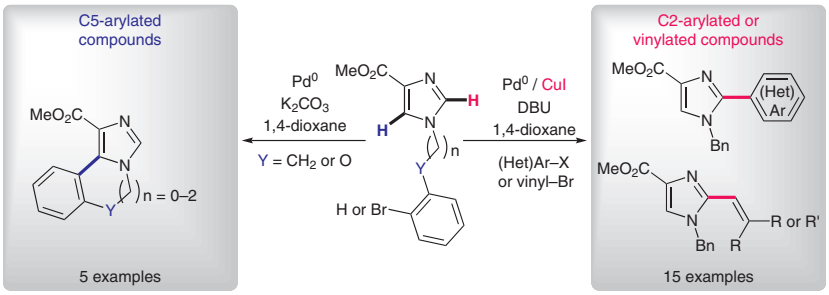

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Abstract The palladium-catalyzed arylation and alkenylation of *N*-substituted methyl imidazole-4-carboxylates are described through inter- and intramolecular pathways. Both direct C2–H and C5–H arylation and alkenylation proceed under Pd(0)/Cu(I) cooperative catalysis and Pd(0) catalysis, respectively, in low-polarity 1,4-dioxane solvent. The methodology gives access to C2 (hetero)aryl or alkenyl imidazoles as well as innovative C2- and C5-arylated fused imidazoles tricycles with a five- to seven-membered middle ring.

Key words C–H functionalization, palladium catalysis, imidazole, arylation, alkenylation

Imidazoles are abundantly present in various naturally occurring and biologically active compounds,[1] pharmaceuticals,[2] and materials.[3] This class of azaheterocycle is employed to produce *N*-heterocyclic carbenes (NHC) used as ligands in various transition-metal complexes in homogeneous catalysis[4] and organocatalysis.[5] Imidazolium-based ionic liquids are also often considered as green reaction media due to their unique chemical and physical properties.[6]

In this context, a concise synthetic access towards imidazole cores is of high importance. Since the last decades, the synthesis of imidazoles over numerous standard condensation reactions has been intensively reported.[7] The main drawback arises from the introduction at an early stage of the adequate functional group that compromises the subsequent cyclization sequence.

One modern synthetic alternative is focused on the late-stage palladium-catalyzed C–H functionalization reactions from C2, C4, and C5 unsubstituted imidazoles.[8–12] In particular, Pd(0)-catalyzed C–H (hetero)arylation of *N*-substituted imidazoles with aryl halides at C2 and/or C5 positions has been widely studied by Bellina and Rossi group.[12] As some remarkable progresses, the orthogonal C2–H versus C5–H arylation of *N*-substituted imidazoles have been developed, respectively, under base-assisted Pd(0)/Cu(I) cooperative catalysis and Pd(0)-catalyzed concerted metalation–deprotonation (CMD), taking advantage of the acidic and the nucleophilic specific characters of the C2 and C5 sites, respectively.[12b,i] Although less reactive, the C4 position of the imidazole ring can also be functionalized through specific C–H activation methodology.[13] Inspired by the pioneering work of Suzuki on intramolecular C–H arylation of *N*-bromophenyl imidazole-4-carboxamide,[14] and in line with our ongoing interest into the regioselective Pd(0)-catalyzed C–H arylation and alkenylation with halides of (oxa)thiazole-4-carboxylates,[15] as well as imidazole-5-carboxylates,[16] we turned our attention to the 4-carboxyimidazole series. Unlike the parent imidazole, the presence of an ester function at C-4 offers several new synthetic and methodological opportunities. Indeed, the carboxylate group may be easily removed by catalytic extrusion of volatile CO_2 or converted into a wealth of other moieties and can be used as leaving group in various decarboxylative couplings with formation of C–C or C–heteroatom bonds.[17]

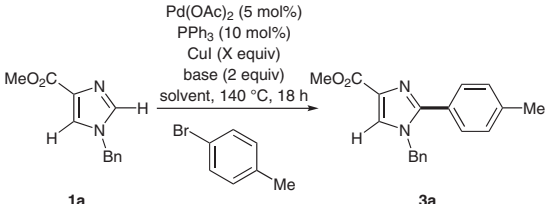
Herein, we have turned our attention to an exhaustive study of selective C2–H and C5–H arylations of methyl *N*-substituted imidazole-4-carboxylates with aryl halides under Pd(0) catalysis through both inter- and intramolecular pathways. The latter approach provides access to innovative nonaromatic imidazoles based tricycles offering potential for applications in the pharmaceutical area.

We started our investigations by selecting methyl *N*-benzylimidazole-4-carboxylate (**1a**) as substrate, which was readily prepared by *N*-benzylation of commercially available methyl imidazole-4-carboxylate under S_N2-type nucleophilic substitution using NaH as base and benzyl bromide as electrophile.[18,19] The first study of Pd(0)-catalyzed C–H arylation of **1a** with of 4-bromotoluene (1.2 equiv) was carried out using $Pd(OAc)_2$ as catalyst, PPh_3 as ligand (Table 1), and Cu(I) to functionalize selectively the C-2 site in accordance with the work reported by Bellina and Rossi.[12i] In our hands, the reaction was found to be inefficient in the standard highly polar DMF solvent with both potassium and cesium carbonates leading mainly to degradation of starting material **1a** (Table 1, entry 1). However, in the less polar solvent 1,4-dioxane, the Pd(0)-catalyzed and CuI-assisted C–H arylation of **1a** with bromotoluene provided selectively the C2–H arylated imidazole-4-carboxylate **3a** in 34% yield (Table 1, entry 2).

Three additional bases, Cs_2CO_3, CsF, and DBU, were then evaluated. Cs_2CO_3 proved to be deleterious to the C–H arylation process leading mainly to degradation of the starting material **1a** (Table 1, entry 3). On the other hand, CsF and DBU were found more efficient than K_2CO_3, since the C2-arylated imidazole-4-carboxylate **3a** was produced in 51% and 76% yields, respectively (Table 1, entries 4 and 5). Changing the electrophile to *p*-iodotoluene, keeping DBU as base, led to the production of **3a** in an excellent 95% isolated yield (Table 1, entry 6). Then, the C–H arylation of the methyl imidazole-4-carboxylate **1a** with *p*-iodotoluene was carried out under microwave irradiation, using the optimized conditions. However, in this case, the use of PPh_3 as ligand, which is prone to C–P cleavage reactions,[20,21] led to the introduction of a phenyl group into C-2 of the imidazole **1a** as a side product. A replacement $PCy_3{\cdot}HBF_4$ ligand was then employed and in this case, the C-2-arylated imidazole-4-carboxylate **3a** was obtained as a single product in 66% yield after 20 min irradiation (Table 1, entry 7). Lower amounts of CuI reduced the efficiency of the C–H arylation process with *p*-bromotoluene (Table 1, entry 8). More importantly, without the copper additive, very poor reactivity was observed (Table 1, entries 9–11) using DBU, Cs_2CO_3, and K_2CO_3 as bases, suggesting that the standard carbonate-assisted palladium-catalyzed C–H arylation process is not operative.

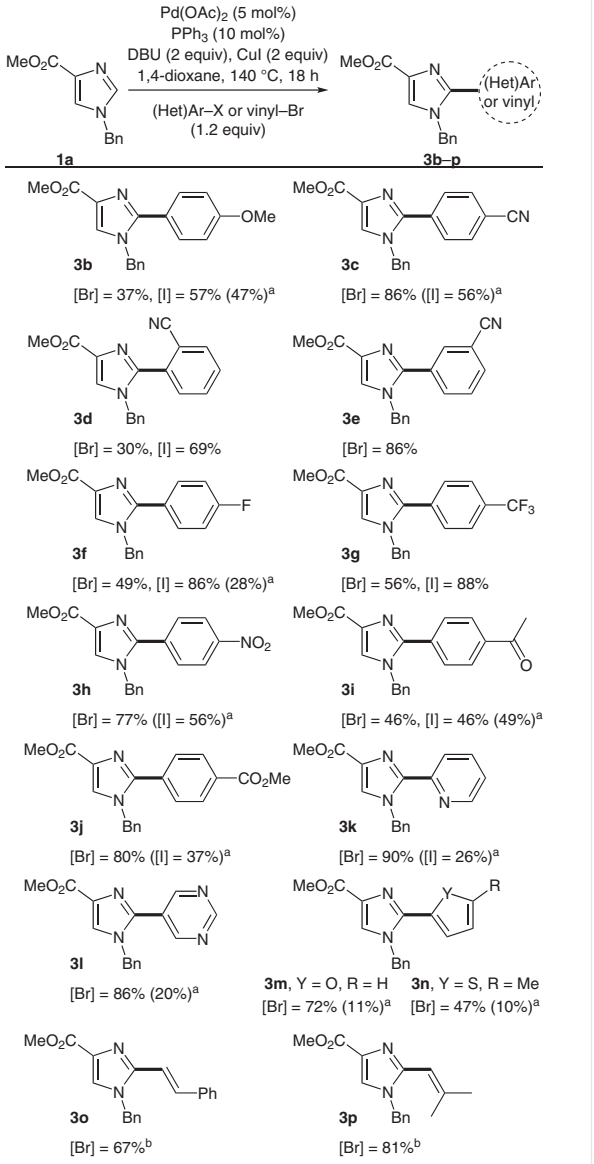
With these optimal catalytic conditions, the scope of the intermolecular arylation of the imidazole **1a** with different bromo- and iodoarene electrophiles was investigated.[22,23] Interestingly, the methodology was found to be effective over a wide range of aryl bromides incorporating electron-withdrawing and electron-donating groups. Notably, a broad series of C2-arylated imidazoles flanked with methyl (**3a**), methoxy (**3b**), cyano (**3c–e**), fluoro (**3f**), trifluoromethyl (**3g**), nitro (**3h**), methyl ketone (**3i**), and methyl ester (**3j**) groups was successfully isolated in moderate to good yields (Scheme 1). The yields could be significantly improved by using aryl iodides as electrophiles, as exemplified by methyl C2-arylated imidazole-4-carboxylates **3b**, **3d**, **3g**, and **3f**. Importantly, the protocol was also efficient with bromoheterocycles as electrophiles. Indeed, several methyl C2-heteroarylated-imidazole-4-carboxylates were synthetized in the presence of representative heterocycles such as pyridine (**3k**), pyrimidine (**3l**), furan (**3m**), and 5-methylthiophene (**3n**). In additional studies, reactions were performed under microwave irradiation using iodoarenes. Although the time of the reaction was reduced to 20 min compared to conventional heating, in most of cases, lower yields were observed, with methyl imidazole-4-carboxylates **3b**,**c**,**f**,**h–n** being obtained in a range of poor to moderate yields (10–56%).

Table 1 Optimization of the Palladium-Catalyzed Intermolecular Direct C–H Arylation of **1a**



Entry	Base	Solvent	CuI (n equiv)	Yield (%)[b]
1	K_2CO_3	DMF	2	< 5
2	K_2CO_3	1,4-dioxane	2	34
3	Cs_2CO_3	1,4-dioxane	2	4
4	CsF	1,4-dioxane	2	51
5	DBU	1,4-dioxane	2	76
6	DBU	1,4-dioxane	2	95[a]
7	DBU	1,4-dioxane	2	66[c]
8	DBU	1,4-dioxane	1	65
9	DBU	1,4-dioxane	–	<5
10	Cs_2CO_3	1,4-dioxane	–	< 5
11	K_2CO_3	1,4-dioxane	–	< 5

[a] Using 4-iodotoluene (1.2 equiv) as electrophile instead of 4-bromotoluene.
[b] Yield of isolated compound.
[c] Reaction conditions: **1a** (1 equiv), 4-iodotoluene (1 equiv), $Pd(OAc)_2$ (5 mol%), $PCy_3{\cdot}HBF_4$ (10 mol%), DBU (2 equiv), CuI (2 equiv), in 1,4-dioxane ([**1a**] = 0.16 M), 210 °C, 20 min under microwave irradiation.

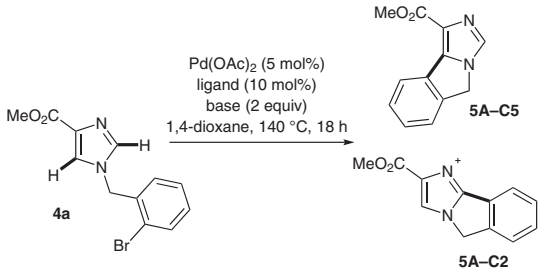


Scheme 1 Scope of (hetero)aryl and alkenyl halide substrates. [a] Yields obtained under microwave irradiation conditions (Table 1, entry 7) are given in brackets. [b] P(*o*-tolyl)$_3$ phosphine ligand was used instead of PPh_3.

As previously mentioned, regioselective direct arylation to afford the C-2- or C-5-arylated imidazole compounds has attracted a lot of attention during the past decades. However, the C2–H alkenylation of unsubstituted imidazoles has been less successful in contrast to benzofused azole derivatives such as benzimidazole under Pd (with or without copper co-catalysis) from the corresponding alkenyl bromides.[24,25] Nevertheless, a Pd-catalyzed cross-dehydrogenative coupling reaction was successfully developed by Ong in 2014 to afford the corresponding C2-alkenylated imidazoles.[26] In this context, C–H alkenylation of **1a** with alkenyl halides was then examined. However, applying the above-optimized protocol, the direct alkenylation of **1a** with the 2-bromostyrene failed. Meanwhile, in accordance with our previous observations in C–H alkenylation of 4,4′-dialkylimidazolone series,[27] the direct C–H alkenylation reaction of **1a** with the 2-bromostyrene was found to be effective when simply replacing PPh_3 by P(*o*-tolyl)$_3$ as ligand. In this case, the expected alkenylated imidazoles **3o**–**p** were produced in 67% and 81% yields, respectively, from the corresponding bromoalkene coupling partners (Scheme 1).

In continuation of this selective intermolecular C2–H (hetero)arylation of compound **1a**, we then turned our attention to the development of an intramolecular C–H arylation protocol starting from methyl 1-(2-bromobenzyl)-1*H*-imidazole-4-carboxylate (**4a**). Surprisingly, the optimized protocol used for intermolecular C2–H arylation of **1a** was ineffective. Furthermore, using the same biscatalytic mode, but using carbonate bases was also found to be ineffective.[21] However, on the basis of our previous investigations into regioselective copper-free Pd(0)-catalyzed and carbonate-assisted arylation of oxa(thia)zole-4-carboxylates,[15f,g] intramolecular C–H arylation of **4a** was achieved under standard catalysis, using $Pd(OAc)_2$, carbonate bases, and various phosphines in 1,4-dioxane. The results are summarized in Table 2 and show clearly that under these conditions a mixture of 4-carboxyimidazole-based tricyclic heterocycles possessing both imidazol-2-yl-aryl (**5A–C2**) and imidazole-5-yl-aryl (**5A–C5**) systems could be identified, with isomer **5A–C5** being the major product. Good performance in the direct C5–H arylation was observed using K_2CO_3 as base and PPh_3 as well as electron-rich $PCy_3{\cdot}HBF_4$ and electron-poor P(4-FC_6H_4)$_3$ as ligand, providing the 4-carboxyimidazole-based tricyclic heterocycle **5A–C5** in a range of 70–81% isolated yields (Table 2, entries 1–3). Only the bidendate ligand dppb proved to be less effective (Table 2, entry 4). The observed C5–H selectivity using K_2CO_3 and electron-rich or electron-poor phosphines as optimal reagents indicate a carbonate-assisted CMD-based process which, probably due to steric hindrance, was not appropriate for the intramolecular arylation of imidazole **1a** reported above. In accordance with our observations in the (oxa)thiazole-4-carboxylate series, the acetate-assisted metalation–deprotonation process was also found to be ineffective with compound **4a** (Table 2, entry 5). In addition, with stronger bases such as Cs_2CO_3, the intramolecular C–H arylation of **4a** proceeded less efficiently, as the 4-carboxyimidazole-based tricyclic heterocycle **5A–C5** was still isolated, as the main product, although in a poor 35% yield (Table 2, entry 6).

Table 2 Optimization of the Reaction Conditions of Palladium-Catalyzed Intramolecular C–H Arylation of **4a**

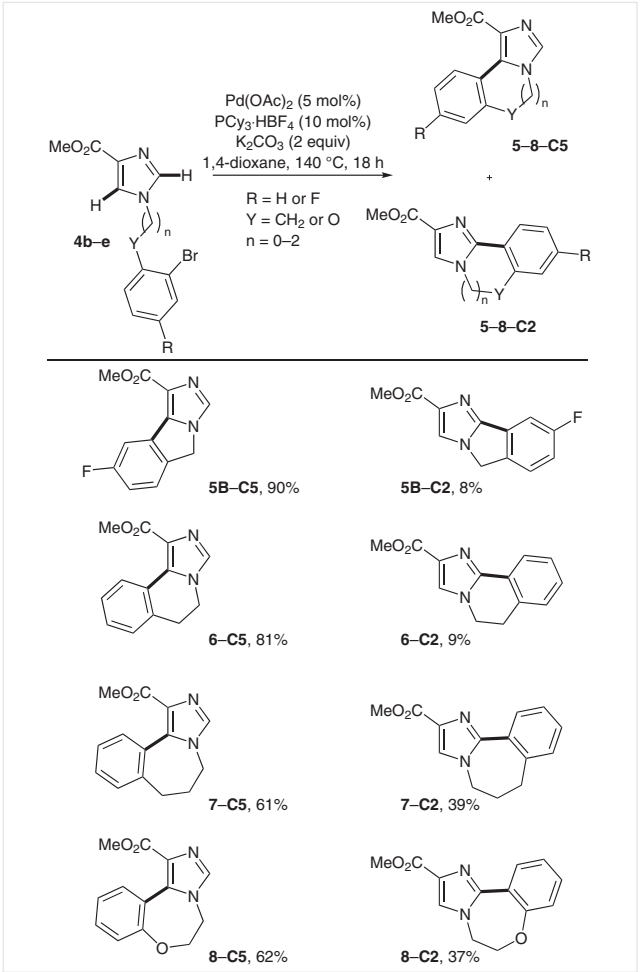


Entry	Ligand	Base	Yield (%)[a,b] **5A–C5**	Yield (%)[a,b] **5A–C2**
1	PPh_3	K_2CO_3	70	3
2	$PCy_3{\cdot}HBF_4$	K_2CO_3	81	9
3	$P(4\text{-}FC_6H_4)_3$	K_2CO_3	81	17
4	dppb	K_2CO_3	42	nd
5	$PCy_3{\cdot}HBF_4$	KOAc	nd	nd
6	$PCy_3{\cdot}HBF_4$	Cs_2CO_3	35	3
7	P*t*-$Bu_2Me{\cdot}HBF_4$	K_2CO_3	79	7
8	P*t*-$Bu_3{\cdot}HBF_4$	K_2CO_3	23	27

[a] Reaction conditions: **4a** (1 equiv), $Pd(OAc)_2$ (5 mol%), ligand (10 mol%), base (2 equiv), 1,4-dioxane (0.16 M), 140 °C, 18 h.
[b] Yield of isolated product.

Having previously highlighted the shift of selectivity from the more sterically hindered C-5 site to the less sterically hindered C-2 site through K_2CO_3-assisted CMD in oxazole and thiazole-4-carboxylate series by using bulky ligands,[15f,g] the behavior of the intramolecular C–H arylation of **4a** regarding the regioselectivity was examined with increasing phosphine bulk. Firstly, P*t*-Bu_2Me gave predominantly the same **5A–C5** isomer ratio in a good 79% yield (Table 2, entry 7). However, on further increasing the bulk of the phosphine, and using the most sterically hindered P*t*-$Bu_3{\cdot}HBF_4$, the imidazole-based tricyclic heterocycle **5A–C2** was formed in a slight excess compared to its regioisomer **5A–C5** (Table 2, entry 8). Overall, full inversion of the regioselectivity was not observed as anticipated.

The production of 4-carboxyimidazole-based tricyclic heterocycles **5–8** embedding with five- to seven-membered central rings was finally investigated starting from various methyl *N*-alkylated imidazole-4-carboxylates **4b–g** using the optimized $PCy_3{\cdot}HBF_4$ ligand. Results are depicted in Scheme 2. The *para*-fluorinated imidazole-based tricyclic heterocycle **5B–C5** was produced in an excellent 90% yield, the **5B–C2** isomer being isolated in a very small amount (8%). Similarly, for the preparation of five-membered medium-ring models, the imidazole-based six-membered tricyclic heterocyclic **6–C5** was also successfully obtained as the major product in an excellent 81% yield. Again, the alternative isomer **6–C2** was produced as the only side product in 9% yield. Formation of compounds **6–C5** and **6–C2** has already been reported via a radical cyclization, although with lower yield and selectivity.[18a] With these promising results in hand, the preparations of imidazole-based seven-membered tricyclic heterocycles **7** and **8** were next investigated. However, in this case, we found that the ring-closing reaction occurred mainly at the **C5** site of the imidazole ring leading to the **7–C5** and **8–C5** isomers in moderate 61% and 62% yields, a significant reduction of selectivity in favor of the less steric hindered C2–H site were observed and the **7–C2** and **8-C2** isomers were isolated in more significant yields (39% and 37%, respectively). Unfortunately, this methodology failed to prepare the imidazole-based eight-membered tricyclic heterocycles.



Scheme 2 Synthesis of 4-carboxyimidazole-based tricyclic heterocycles

Finally, regarding the reactivity and the regioselectivity observed within this direct intramolecular and intermolecular C–H arylation in the imidazole-4-carboxylate series, using both Pd(0)- or Pd(0)/CuI-cooperative catalysis, some observations about the modes of carbonate-assisted metalation–deprotonation can be proposed (Figure 1). First, we assumed that the standard K_2CO_3-assisted CMD-based reac-

tivity could not proceed at both the highly sterically hindered C2–H and C5–H sites of **1a** (model A and B) whilst, for the intramolecular pathway from compound **4a**, the reactivity could be recovered due to a decrease of steric constraints. In that case, the C5–H *vs* C2–H competition was observed, showing that the energetic barriers might be very close (mode C and D). Naturally, the intramolecular direct C2–H arylation pathway under Pd(0)/CuI-cooperative catalysis is disfavored by the difficulty of achieving consecutive generation of imidazole-2-yl copper as well as the oxidative addition of Pd(0) to the aryl halide moiety within the same molecule, prior to the key intramolecular transmetalation. On the other hand, the CuI co-catalyst, only being efficient for intermolecular C2–H arylation of **1a**, the CMD mode from the *N*-(CuI)-chelated imidazole-4-carboxylate complex reported by the Gorelsky group (model E and G),[28] might be discarded here in favor of the generation of a imidazole-2-yl copper intermediate (model F), in accordance to the suggestion by Bellina and Rossi.[12f]

In summary, this work reports the first full investigation of palladium-catalyzed direct C–H functionalization of *N*-substituted imidazole-4-carboxylates. In particular, the first selective direct C2–H (het)arylation and alkenylation of *N*-benzyl imidazole-4-carboxylates with bromo- and iodo(het)arenes and bromoalkenes under Pd(0)/Cu(I)-cooperative catalysis has been described giving an efficient access to a broad library of C-2-functionalized methyl imidazole-4-carboxylate compounds. In contrast to previous observations in *N*-substituted 4-nitroimidazole-4-carboxylates,[29] in our case the intermolecular CMD-based reactivity does not operate at C5 when both C4 and the imidazole nitrogen are substituted. Conversely, using *N*-(*o*-halogenobenzyl) imidazole-4-carboxylates as starting materials, arylation occurred under K_2CO_3-assisted CMD-based conditions to produce novel C-5-arylated fused imidazoles with five- to seven-membered central rings as major products. The standard cooperative Pd(0)/Cu(I) catalysis proved inoperative in the intramolecular pathway, possibly due to the difficulty of forming the imidazole-2-yl copper intermediate followed by the oxidative addition of Pd(0) to the aryl halide moiety. Moreover, a loss of C-5–H *vs* C2–H selectivity was clearly observed during the preparation of seven-membered tricyclic imidazole-based heterocycles, probably due to the increased size of the linker. Additional studies are currently ongoing further functionalize these tricyclic scaffolds further in order to generate chemical diversity.

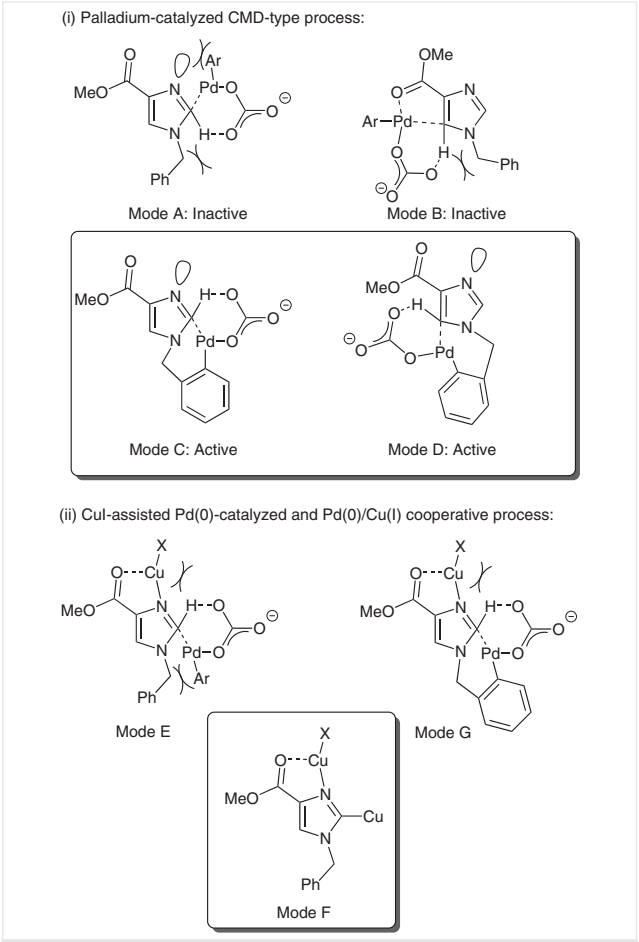


Figure 1 Plausible intermediates in the catalytic C–H arylation

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1708003.

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(21) See the Supporting Information for more details.

(22) **General Procedure for Pd-Catalyzed Intermolecular Direct C2–H Arylation of Methyl *N*-Benzyl-1*H*-imidazole 4-carboxylate under Thermic Conditions**
Methyl 1-benzyl-1*H*-imidazole-4-carboxylate (**1a**, 80 mg, 0.37 mmol, 1 equiv), the requisite halide **2** (1.2 equiv), $Pd(OAc)_2$ (18 µmol, 5 mol%), PPh_3 (37 µmol, 10 mol%), CuI (0.74 mmol, 2 equiv), and anhydrous DBU (0.74 mmol, 2 equiv) were placed in a dry sealed tube containing a magnetic stir bar. The tube was evacuated and back-filled with nitrogen three times before adding anhydrous 1,4-dioxane (2.5 mL). The tube was sealed and heated to 140 °C for 18 h. The reaction was filtered through a Celite® pad (washing with DCM and EtOAc). The solvents were removed under reduced pressure, and the crude product was then purified by column chromatography (DCM to DCM/EtOAc, 9:1).

(23) Compound **3a** was prepared according to the general procedure. The crude product was purified by flash chromatography to afford **3a** in 76% yield using the aryl bromide and 95% yield using the aryl iodide as a pale yellow solid; mp 89–90 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.64 (s, 1 H_{im}, H5), 7.46 (d, *J* = 8.0 Hz, 2 H_{arom}), 7.35–7.33 (m, 3 H_{benzyl}), 7.22 (d, *J* = 8.0 Hz, 2 H_{arom}), 7.09–7.07 (m, 2 H_{benzyl}), 5.19 (s, 2 H), 3.89 (s, 3 H, OMe), 2.38 (s, 3 H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.5 (C=O), 149.5 (C2, Cq_{im}), 139.7 (C4′, Cq_{arom}), 135.9 (C1′, Cq_{benzyl}), 132.9 ($C4_{im}$, Cq), 129.3 (2 × CH), 129.2 (2 × CH), 129.1 (2 × CH), 128.4 (CH_{benzyl}), 127.1 (C5, CH_{im}), 126.9 (2 × CH_{benzyl}), 126.5 (Cq), 51.8 (OCH_3), 51.0 (NCH_2), 21.4 (CH_3). IR (ATR): 3125, 3079, 2920, 2850, 1689, 1549, 1330, 1227, 1004, 725 cm^{-1}. HRMS: Anal. Calcd for $C_{19}H_{19}N_2O_2$ $[M + H]^+$: 307.1447; found: 307.1455.

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