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Pd-catalyzed coupling reaction of fluorinated propargyl amidines with aryl iodides†

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Catalyzed by ligand free $Pd(OAc)_2$, 2,5-disubstituted imidazole was prepared in good yield by the reaction of fluorinated propargyl amidines with iodoarene. Mechanistic studies indicated that this transformation occurs through a nitropalladation–reductive elimination pathway.

Imidazoles as five-membered N-heterocyclic compounds occur in a number of natural products, in particular alkaloids.[1] Owing to their biological properties, many of these are important ingredients for antibacterial, antiviral, antitumor, anticardiovascular, and antiinflammatory agents.[2,3] Recently, imidazoles with fluorinated groups have received significant attention based on the fact that the physicochemical properties of organic compounds can be greatly affected by introducing fluorinated groups.[4,5] With CF_3I and CF_3SiMe_3 as the fluorinating reagents, direct trifluoromethylation has become an important approach to access these compounds.[6] However, this method suffers from the use of expensive or hazardous reagents, harsh reaction conditions, and poor yield. Alternatively, imidazoles bearing fluorinated groups can be prepared from fluorinated building blocks. For example, treatment of fluorocarboxylic acid or fluorinated 1,3-dicarbonyl compounds with 1,2-diaminobenzene successfully formed 2-fluoroalkyl benzimidazoles.[7] Multi-substituted imidazoles are also accessible by applying other fluorinated building blocks.[8] Fluorinated propargyl amidines presented some unique properties in our work.[10b] Considering the reaction pattern, propargyl amidine was suitable for the preparation 2,5-disubstituted imidazoles. Herein, we disclose the synthesis of 2-fluoroalkyl-5-benzyl imidazoles from fluorinated propargyl amidines and aryl iodides using ligand free palladium acetate as the catalytic source.

In our initial study, 2-trifluoromethyl *N*-(*p*-methoxyphenyl-*N*-propargyl amidine **1aa** was treated with *p*-methoxyl iodobenzene **2a** (1.2 equiv.) in the presence of K_2CO_3 (1.5 equiv.) and $Pd(OAc)_2$ (10 mol%) in CH_3CN at room temperature. The desired product, 5-benzyl imidazole **3aaa** was obtained in 26% yield. In an effort to optimize the reaction, reaction conditions were investigated by varying the temperature, base, solvent and catalyst. The outcome, however, was not promising (Table 1 in ESI†). In these reactions, 5-benzyl imidazole as the only product was obtained in low yield, no byproduct such as 5-methyl imidazole or 3-(*p*-methoxphenyl) prop-2-ynyl amidine was detected. The presence of the fluoroalkyl group increases the acidity of the hydrogen atom on the amidinoyl group, which leads to deprotonation under strong basic conditions, and the increased amount of propargyl amidine anion will promote the reaction. By using a 1.0 : 0.7 : 1.2 molar ratio of **1aa** : **2a** : K_2CO_3, an improved yield of 76% was obtained when the reaction was carried out in CH_3CN at 80 °C, in the presence of 10 mol% $Pd(OAc)_2$ (Table 1, entry 1). A similar result was obtained when K_3PO_4 was used as the base (Table 1, entry 2). The yield of 5-benzyl imidazole **3aaa** was increased to 84% when DMF was chosen as the solvent (Table 1, entry 5). The concentration of propargyl amidine was found to affect the yield of **3aaa**, a lower yield was obtained with a higher concentration of **1aa** (Table 1, entries 12, 13).

The scope of the palladium-catalyzed coupling of fluorinated propargyl amidines with aryl iodides by this procedure is summarized in Table 2. To our delight, this reaction shows good compatibility towards aryl iodides containing many functional groups, such as ester and acetyl groups (Table 2, entries 5, 6). Iodoarenes with both electron-donating and electron-withdrawing groups gave moderate to good yields of the corresponding products (Table 2, entries 1–7). Iodoarenes with an electron-withdrawing group give a lower yield (Table 2, entries 5–7). Steric hindrance of iodoarene imposed by *ortho*-substitution has little impact on the yield except for the substrate with *ortho*-fluorine (Table 2, entries 8, 9, entry 10). Steric and electronic effects of propargyl amidines were also negligible for the coupling reaction (Table 2, entries 11–13). Substrates

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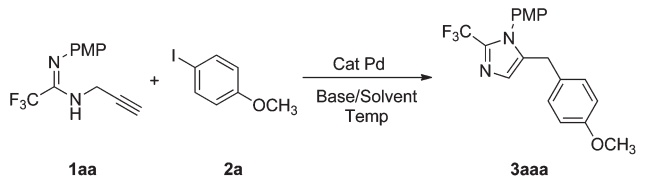
Table 1 Optimized condition for the synthesis of **3aaa**

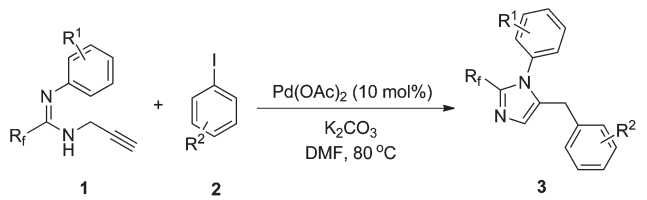


1aa **2a** **3aaa**

Entry	Catalyst	Solvent	Base	Temp/°C	Yield/%[a]
1	$Pd(OAc)_2$	CH_3CN	K_2CO_3	80	76
2	$Pd(OAc)_2$	CH_3CN	K_3PO_4	80	71
3	$Pd(OAc)_2$	CH_3CN	Na_2CO_3	80	65[b]
4	$Pd(OAc)_2$	CH_3CN	Py	80	58[b]
5	$Pd(OAc)_2$	DMF	K_2CO_3	80	84
6	$Pd(OAc)_2$	DMF	K_3PO_4	80	75
7	$Pd(OAc)_2$	DMF	Py	80	46[b]
8	$Pd(OAc)_2$	DMF	K_2CO_3	60	70
9	$Pd(PPh_3)_2Cl_2$	CH_3CN	K_2CO_3	80	68
10	$Pd(PPh_3)_2Cl_2$	DMF	K_2CO_3	80	77
11	$Pd(PPh_3)_2Cl_2$	DMF	K_3PO_4	80	62
12	$Pd(OAc)_2$	DMF	K_2CO_3	80	74[c]
13	$Pd(OAc)_2$	DMF	K_2CO_3	80	55[b,d]

[a] Isolated yield. [b] Calculated by ^{19}F NMR. [c] The molar ratio of **1aa** : **2a** = 1 : 0.8. [d] The molar ratio of **1aa** : **2a** = 1 : 1.

Table 2 Pd-catalyzed formation of 2-fluoroalkyl-5-benzyl imidazole **3**



1 **2** **3**

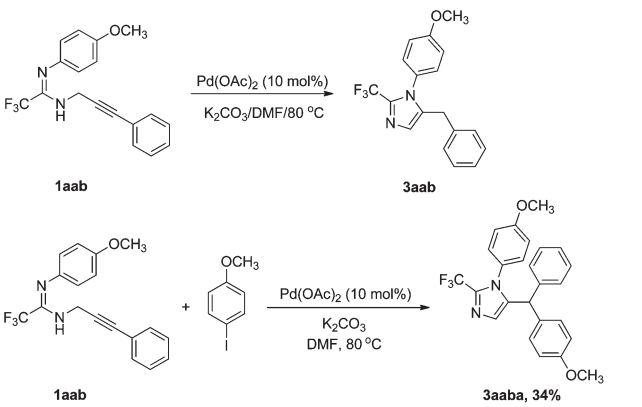
Entry	R_f	R^1	R^2	Yield/%[a]
1	$-CF_3$	*p*-OCH_3	*p*-OCH_3	**3aaa**/84
2	$-CF_3$	*p*-OCH_3	H	**3aab**/80
3	$-CF_3$	*p*-OCH_3	*p*-Cl	**3aac**/85
4	$-CF_3$	*p*-OCH_3	*m*-CH_3	**3aad**/74
5	$-CF_3$	*p*-OCH_3	*p*-COOEt	**3aae**/61
6	$-CF_3$	*p*-OCH_3	*p*-$COCH_3$	**3aaf**/68
7	$-CF_3$	*p*-OCH_3	*p*-CF_3	**3aag**/79
8	$-CF_3$	*p*-OCH_3	*o*-OCH_3	**3aah**/81
9	$-CF_3$	*p*-OCH_3	*o*-CF_3	**3aai**/75
10	$-CF_3$	*p*-OCH_3	*o*-F	**3aaj**/42
11	$-CF_3$	*p*-Cl	*p*-OCH_3	**3aba**/72
12	$-CF_3$	*o*-OCH_3	*p*-OCH_3	**3aca**/86
13	$-CF_3$	Naphth	*p*-OCH_3	**3ada**/80
14	$-CF_2Br$	*p*-OCH_3	*p*-OCH_3	—
15	$-CF_2H$	H	*p*-OCH_3	**3cea**/77

[a] Isolated yield.

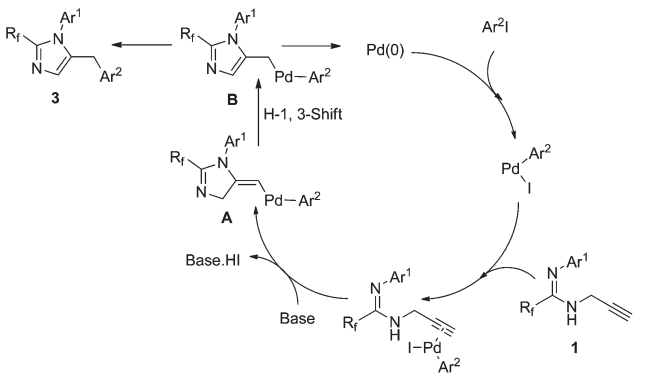
with $-CF_2Br$ are too unstable under the reaction condition to afford any product (Table 1, entry 14), while good yield was obtained from substrates with $-CF_2H$ (Table 1, entry 15).

This transformation may proceed through two pathways.[9] In path I, the C–C triple bond in the propargyl amidine coordinates to the σ-aryl palladium complex. A nitrogen atom attacks the activated C–C triple bond and the propargyl amidine accepts the attack of the nitrogen atom to afford a σ-aryl-σ-(5-imidazolymethyl) palladium intermediate, which then undergoes reductive elimination to form 5-benzyl imidazole (path I). Alternatively, 3-aryl prop-2-yne amidine would be produced first from the σ-aryl palladium complex with a terminal alkyne, and then it undergoes 5-*exo-dig* cyclization to give the desired product (path II).

With the inductive electron-withdrawing effect of fluoroalkyl, deprotonation of amidinolyl readily takes place under basic conditions, and then undergoes intramolecular nucleophilic reaction with the activated alkyne to give the desired product. In our system, 5-benzyl imidazole was found to be the sole product. To distinguish these two pathways, we prepared *N*-(3-phenyl) prop-2-ynyl amidine **1aab**. Under the same conditions, only a low yield (63%) of 5-benzyl imidazole **3aab** was detected by ^{19}F NMR, which was lower than from the reaction of fluorinated proparygyl amidine with iodobenzene (Table 2, entry 2). In the presence of an iodoarene, **1aab** underwent a cyclization–arylation to give 5-diarymethyl imidazole **3aaba** in very low yield due to large steric hindrance. Judging from these observations, it is very likely that the transformation proceeds through path I. The proposed mechanism is shown in Scheme 1. 5-Benzyl imidazole **3** is most likely generated by reductive elimination from the intermediate **B**, which is more stable than the σ-vinyl-σ-aryl palladium species **A** (Scheme 2).[10]



Scheme 1 Transformations of **1aab** catalyzed by $Pd(OAc)_2$.



Scheme 2 Proposed mechanism for the formation of 2,5-disubstituted imidazoles.

In conclusion, a convenient protocol to generate 2,5-disubstituted imidazoles has been developed. With ligand free Pd-$(OAc)_2$ as the catalyst, 2-fluoroalkyl-5-benzyl imidazoles can be obtained in moderate to good yields from the reaction of fluorinated propargyl amidines with aryl iodides. This transformation is compatible with a wide range of functional groups. Mechanistic investigations revealed that the reaction most likely proceeds *via* a nitropalladation–reductive elimination pathway.

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