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COMMUNICATION

Controllable access to multi-substituted imidazoles via palladium(II)-catalyzed C-C coupling and C-N condensation cascade reaction

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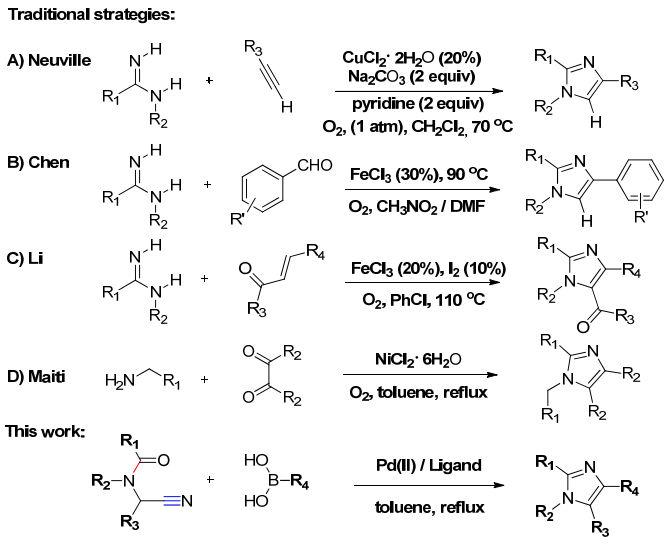
A novel and efficient protocol for the synthesis of various 2, 4-disubstituted, 1, 2,4-trisubstituted and 1, 2, 4, 5-tetra-substituted imidazoles *via* cascade palladium catalyzed C-C coupling followed by intramolecular C-N bond formation was developed. Readily accessible boronic acids and N-substituted-2-amino-acetonitriles were firstly reported as starting materials to construct *di-*, *tri-*, and *tetra-* substituted imidazoles in good to excellent yield.

Multi-substituted imidazoles are common motifs in many drug molecules with interesting bioactivities.[1] By introducing different substituents to the imidazole ring, binding affinity and characteristics of the molecule could be modified. In recent years, various synthetic methods have been developed for di-substituted[2] and tri-substituted[3] imidazoles while the synthesis of tetra-substituted imidazole has received relatively less attention.[4] Neuville's group developed an efficient copper-catalyzed synthesis of 1, 2, 4-trisubstituted imidazoles using amidines and terminal alkynes (Scheme 1A).[5] Chen's group reported iron(III)-catalyzed synthesis of 1, 2, 4-trisubstituted imidazoles with amidines and aldehydes (Scheme 1B).[6] Li's group published iron(III)-catalyzed synthesis of 1, 2, 4, 5-tetrasubstituted imidazoles with amidines and chalcones (Scheme 1C).[7] Maiti's group took primary amine and 1, 2-diketone as the starting materials to synthesize tetra-substituted imidazoles with Ni catalyst (Scheme 1D).[8] Reissig and co-workers also developed a four-component multisteps reaction of alkoxyallenes, imines, iodine, and nitriles to prepare tetra-substituted imidazoles.[4c, 4d] In the protocols mentioned above, researchers focused on only one specific substitution pattern, either tri-substituted imidazoles (Neuville and Chen) or tetra-substituted imidazoles (Li, Maiti and Reissig). To the best of our knowledge, no method which is capable of synthesizing *di-*, *tri-* and *tetra-* substituted imidazoles has been developed. In addition, further oxidant such as O_2 was required in all previously published cases. In order to complete the existing arsenal, we set out the goal to develop a method which can construct 2, 4-disubstituted, 1, 2, 4-trisubstituted and 1, 2, 4, 5-tetrasubstituted imidazoles at will without further oxidant.

Palladium catalyzed synthesis of arylketone through addition of arylboronic acid to nitrile has been developed by Lacrock's group[9, 10] and others[11]. Inspired by these previous examples, we proposed a palladium (II) catalyzed tandem reaction for the synthesis of *di-*, *tri-*, and *tetra-* substituted imidazoles through the addition of arylboronic acids to nitriles followed by an intramolecular cyclization. As a starting point, N-substituted-2-amino-acetonitrile and phenylboronic acid were used to test the concept. As shown in Table 1, the reaction was carried out between N-(cyanomethyl)-N-phenylacetamide **1a** (0.5 mmol) and phenylboronic acid **2a** (0.75 mmol) in anhydrous toluene (2.0 mL) at 130 ˚C under microwave irradiation for 2.5 h, in the presence of catalyst $Pd(TFA)_2$ (10 mol %) or $Pd(OAc)_2$ (10 mol%) and ligand **L1** (10 mol%). The desired product **3a** was obtained in 43% and 17% yields, respectively (Table 1, entries 1-2). We chose $Pd(TFA)_2$ as the metal source and screened



Scheme 1 Synthetic strategies of 1, 2, 4-trisubstituted and 1, 2, 4, 5-tetrasubstituted imidazoles.

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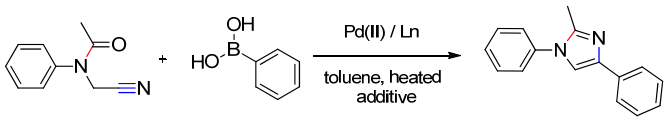
a variety of bipyridyl ligands (**L2**-**L9**, Fig. 1). The results showed that **L2** was the optimal ligand for the model reaction with yield up to 56% (Table 1, entry 4).

In order to improve the reaction conversion, additives were employed. Trifluoroacetic acid was first considered as the additive, with the assumption that CF_3COO^- may play an important role in the catalytic cycle (Table 1, entry 12). Although a promising increase on the conversion was observed, higher ratio of hydrolyzed byproduct formed at the same time (Table 1, ESI†). Thus, $CF_3CO_2NH_4$ (1.0 equiv) was tested alternatively. The result showed that not only the reaction yield was increased dramatically, but also the ketimine hydrolysis byproduct was restrained completely (Table 1, entry 13). In order to further optimize the reaction condition, reduced Pd loading to 5 mol% was also tested. However, a decreased yield to 52% was rendered (Table 1, entry 14).

With the optimized condition, the scope of boronic acids was then explored (Scheme 2). In terms of electronic effect, both electron-rich substrates (**2a**-**2d**) and electron-deficient substrates (**2e**-**2h**) could be tolerated (yield from 64% to 90%, Scheme 2). Substitution at the ortho position such as methyl (**2i**, 60%), methoxy (**2j**, 31%) and isopropyl (**3k**, 47%) indicated that the reaction is sensitive to steric effect. In order to further install different functional groups, halogens containing boronic acids were screened (**2l**-**2n**, 45%-68%). Heterocycle such as 6-indole boronic acid (**2o**) was examined and

Table 1 Screening of the reaction conditions for synthesis of 1, 2, 4-trisubstituted imidazoles.



1a 2a 3a

Entry[a]	Pd(II)	L	Additive	Yield[b] (%)
1	$Pd(TFA)_2$	L1		43
2	$Pd(OAc)_2$	L1		17
3	$Pd(OAc)_2$	L2		37
4	$Pd(TFA)_2$	L2		56
5	$Pd(TFA)_2$	L3		36
6	$Pd(TFA)_2$	L4		34
7	$Pd(TFA)_2$	L5		29
8	$Pd(TFA)_2$	L6		13
9	$Pd(TFA)_2$	L7		23
10	$Pd(TFA)_2$	L8		26
11	$Pd(TFA)_2$	L9		40
12[c]	$Pd(TFA)_2$	L2	TFA (2.0 equiv)	56
13[c]	$Pd(TFA)_2$	L2	$CF_3CO_2NH_4$ (1.0 equiv)	73
14[d]	$Pd(TFA)_2$	L2	$CF_3CO_2NH_4$ (1.0 equiv)	52

[a] Standard reaction conditions: **1a** (0.5 mmol), **2a** (0.75 mmol, 1.5 equiv), palladium(II) (0.05 mmol, 10 mol%), ligand (0.05 mmol, 10 mol%), toluene (2.0 mL). microwave irradiation at 130 ˚C for 2.5 h. [b] Isolated yield based on **1a**. [c] Entries 12-13 refluxed for 4 h. [d] $Pd(TFA)_2$(II) (0.025 mmol, 5 mol%), **L2** (0.025 mmol, 5 mol%), refluxed for 4 h.

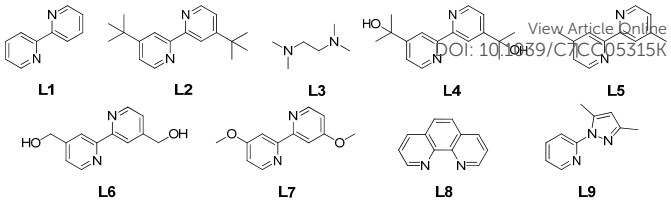
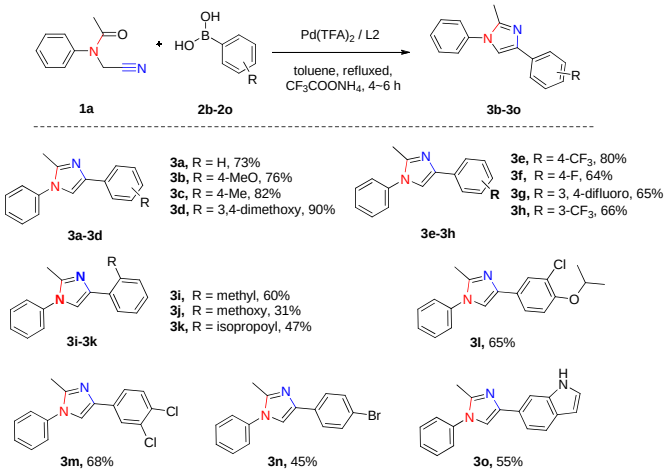


Fig. 1 Structures of bipyridyl ligands.

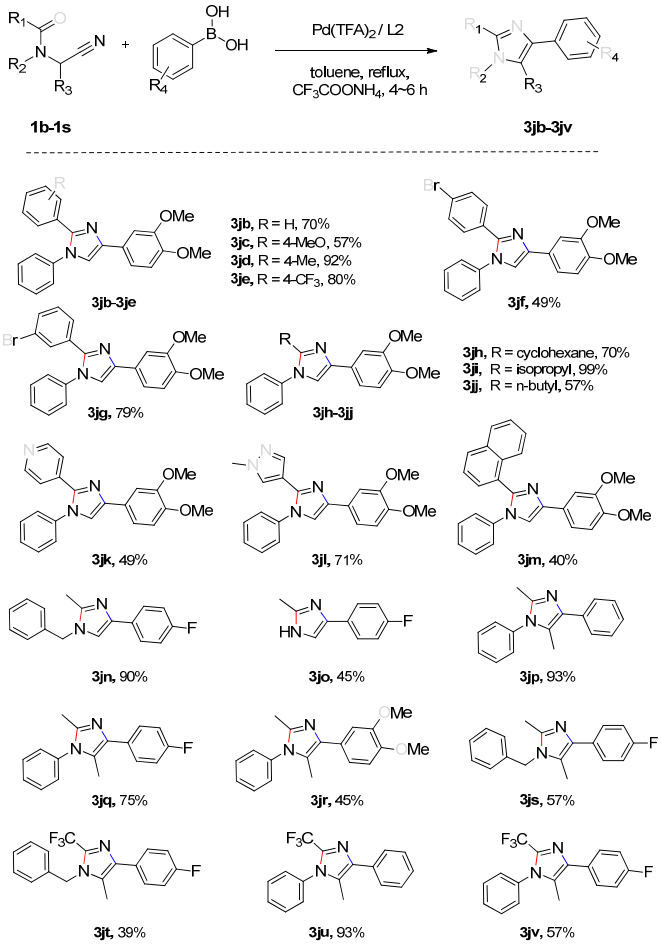
the product (**3o**) in 55% yield was obtained.

After investigation of boronic acids, our focus was directed to construction of *di-*, *tri-*, and *tetra-* substituted imidazoles. Aminoacetonitrile was initially investigated to prepare tri-substituted imidazoles (Scheme 3, **3jb**-**3jo**). When R_1 groups are aryl rings with electron-donating or electron-withdrawing groups, the protocol was able to afford the products with moderate to good yields (**3jb**-**3je**, 57-80%). R_1 with halogenated aryl rings gave similar results (**3jf**, 45%**; 3jg**, 79%). The method was robust when R_1 were aliphatic substituents, such as cyclohexyl (**3ji**, 70%), isopropyl (**3jj**, 89%), and n-butyl (**3jk**, 57%). Fused ring and hetero-aromatic substrates were challenging, while naphthyl (**3jl**, 40%), pyridyl (**3jm**, 49%) and pyrazolyl (**3jn**, 71%) showed decreased reactivity. *N*-substituted alkyl group such as benzyl at R_2 position (**3jn**, 90%) proceeded smoothly with excellent yield. Besides, **3jn** could easily be further transformed into di-substituted imidazole **3jo** through a simple benzyl group deprotection. Furthermore, in order to prove that the protocol could construct disubstituted imidazole, preparation of **3jo** with R_1 and R_2 as hydrogens was demonstrated (45%).

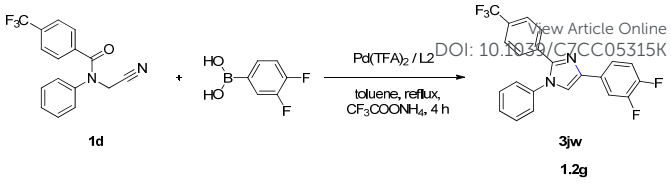
Direct synthesis of 1, 2, 4, 5-tetrasubstituted imidazoles with different functional groups remained a challenge. Remarkably, our method demonstrated that the reactions could proceed smoothly to generate the tetra-substituted imidazoles when R_1 and R_3 are both methyl groups (**3jp**-**3js**), or trifluoromethyl and methyl groups, respectively (**3jt**-**3jv**). Worth mentioning, the aminoacetonitrile with R_1 position being strong withdrawing trifluoromethyl group gave a



Scheme 2 Scope of boronic acid. Standard reaction conditions: **1a** (0.5 mmol), boronic acid (0.75 mmol, 1.5 equiv), $Pd(TFA)_2$ (0.05 mmol, 10 mol%), ligand (0.05 mmol, 10 mol%), $CF_3CO_2NH_4$ (0.5 mmol, 1.0 equiv), toluene (2.0 mL), refluxed for 4~6 h; Isolated yield based on **1a**.



Scheme 3 Scope of aminoacetonitrile. Standard Reaction conditions: **1b**-**1s** (0.5 mmol), boronic acid (0.75 mmol, 1.5 equiv), $Pd(TFA)_2$ (0.05 mmol, 10 mol%), ligand (0.05 mmol, 10 mol%), $CF_3CO_2NH_4$ (0.5 mmol, 1.0 equiv), toluene (2.0 mL), refluxed for 4~6 h; Isolated yield based on **1b**-**1s**.



Scheme 4 Gram-scale Synthesis.

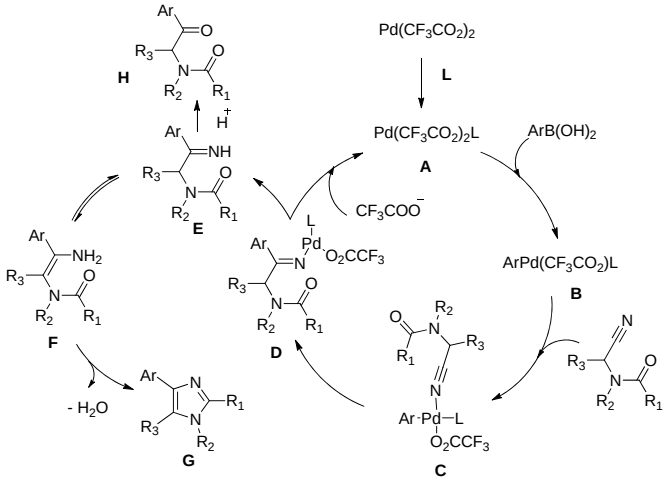


Fig. 2 A plausible mechanism was proposed.

lower yield than with methyl group.

To substantiate the feasibility of this method, a gram scale synthesis (Scheme 4) was performed using aminoacetonitrile **1d** (1.53 g, 5 mmol), (3,4-difluorophenyl)boronic acid (1.2 g, 7.5 mmol), $Pd(TFA)_2$ (0.5 mmol), **L2** (0.5 mmol) and $CF_3CO_2NH_4$ (5 mmol) in anhydrous toluene. The product (**3jw**) could be obtained in 60% yield.

A plausible mechanism was shown in Fig. 2.[9, 12] First, the metal Pd(II) catalyst **A** undergoes transmetalation with the aryl boronic acid to generate **B**. Coordination of nitrile provides the intermediate **C**. The key step is an intramolecular insertion of the aryl group to the nitrile to form the corresponding ketimine Pd(II) complex **D**. Exchange of ketimine with CF_3COO^- on Pd(II) complex **D** affords the ketimine **E** and regenerates the Pd(II) catalyst **A**. Tautomerization between **E** and **F** followed by a cyclization eventually afford the corresponding multi-substituted imidazole **G**.

In summary, a novel and efficient strategy has been developed for the controllable construction of *di*-, *tri*- and *tetra*- substituted imidazoles at will via palladium catalyzed C-C bond formation and a cascade intra-molecular C-N bond cyclization. The protocol was the first report to prepare multi-substituted imidazoles from readily accessible aminoacetonitrile and boronic acid. Further studies to explore the possibility for synthesis of various heterocycles are currently underway.

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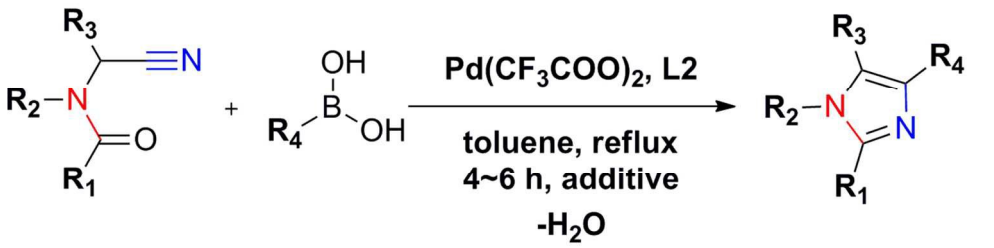

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