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Copper-Catalyzed Simultaneous Activation of C–H and N–H Bonds: Three-Component One-Pot Cascade Synthesis of Multi-substituted Imidazoles

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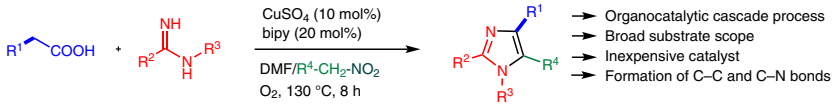

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Abstract A copper-catalyzed expedient, practical, and straightforward approach for the one-pot three-component modular synthesis of multi-substituted imidazoles has been described by using arylacetic acids, *N*-arylbenzamidines, and nitroalkanes. The reaction involves simultaneous activation of C–H and N–H bonds of arylacetic acids and *N*-arylbenzamidines, respectively. The use of inexpensive copper sulfate as a catalyst, readily available starting materials, and Celite-free workup makes this protocol economically viable. Multisubstituted imidazoles were obtained in moderate to good yields with significant functional group tolerance and high regioselectivity.

Key words arylacetic acid, *N*-arylbenzamidine, C–H bond activation, N–H bond activation, $CuSO_4$, imidazole

In recent years, C–H functionalization has become a widely admired, elegant tool in organic synthesis due to selective construction of new bonds and rapid assembly of complex molecular framework from easily available simple starting materials. The mechanistic understanding of C–H functionalization has enabled extensive efforts for carbon–carbon and carbon–heteroatom bonds formation which has prompted the development of innovative synthetic strategies.[1,2] Obviously, identifying a specific method is always a crucial starting point. Among various transition elements, copper has extensively been employed for C–H functionalization due to its variable oxidation states. Indeed, multi-component-based target-oriented cascade strategies provided an efficient entry to nitrogen heterocycles owing to their multiple bond breaking and bond forming ability within a single step. A steady growth in their development bears witness to their usability.

Imidazole is a widely explored nitrogen heterocycle owing to its existence in many natural products[3] and pharmaceutical compounds.[4] Imidazole derivatives are known to exhibit a wide range of medicinal properties,[5] such as antifungal,[6] antitumor,[7] antibacterial,[8] antiplasmodium,[9] and anti-inflammatory.[10] Furthermore, they are also key constituents of numerous functional materials,[11] such as organic semiconductors,[12] dyes,[13] optoelectronic materials,[14] etc. In addition to this, imidazole salts are considered as elegant materials due to their liquid nature at room temperature and have been extensively used as catalysts and/or green reaction media as well as electrolytes for solar cells and batteries. These significant potential applications have led to the development of various methods for the synthesis of imidazole scaffolds with wide substitution patterns. Beside the classical and simple one-pot synthesis of imidazoles by using 1,2-diketones/α-hydroxy ketones/α-halo ketones/α-amino ketones, primary amine, an aldehyde, and ammonium acetate, several novel protocols, such as aldimine cross-coupling,[15] catalyst-free domino reaction of 2-azido acrylates and nitrones,[16] cycloaddition of amidines and nitroolefins,[17] the three-component reaction,[18] Ni-catalyzed dehydrogenation of benzylic-type imines,[19] and Zn-catalyzed cyclization of 2-(tetrazol-5-yl)-2*H*-azirines and imines,[20] have been reported. Moreover, Chiba and Chen synthesized imidazole from oximes by using copper(I) iodide and K_3PO_4.[21] Mirzaei and co-workers also reported the synthesis of *N*-substituted 2,4-diarylimidazoles via a multi-

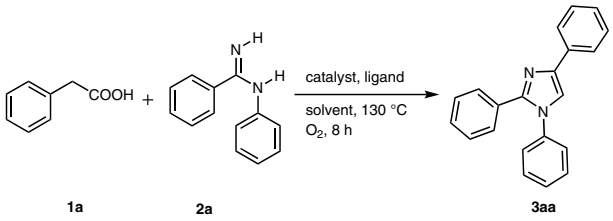
component reaction,[22] while Meille and co-workers synthesized imidazoles through $FeCl_3$-mediated ring opening of 2*H*-azirines.[23]

Amidines have been widely employed synthetic precursors due to their easy availability and ability to furnish multisubstituted imidazoles via [3+2] cycloaddition reaction or radical pathway. In this context, Chen and co-workers reported the synthesis of trisubstituted imidazoles from acetophenones[24] by using a combination of I_2 with zinc iodide as catalysts, whereas Mandal and co-workers[25] synthesized imidazoles from phenacyl bromide by using $KHCO_3$ as a base. An iron-catalyzed protocol was established for aldehydes[18c] while [3+2] cycloaddition of nitrovinylbenzene was accomplished by using copper(I) iodide.[17a] Moreover, Neuville and Li have described the synthesis of trisubstituted imidazoles from phenylacetylene by using copper chloride as a catalyst over a period of 24 hours[26] while Mahajan and co-workers used nitrosovinylbenzene in dichloromethane to form imidazoles.[27] 1,3-Dicarbonyl compounds, ketones, and chalcones are successfully used along with amidines for the synthesis of imidazoles.[28]

Despite the proven useful track record of previously reported methods, the requirements for functionalized substrates, high catalyst loading, long reaction times, and low yields of products limit their wider applicability. Indeed, our interest in metal-catalyzed C–H functionalization mediated tandem synthesis of N-heterocycles[29] has led us to the one-pot, three-component synthesis of multisubstituted imidazoles using arylacetic acids, *N*-arylbenzamidines, and nitroalkanes under aerobic oxidative conditions through simultaneous C–H and N–H bond activation. An easy sp^3 C–H bond activation followed by decarboxylation under mild reaction conditions is the key factor behind the selection of arylacetic acids.

We anticipated phenylacetic acid (**1a**) as the most suitable starting arylacetic acid for fine-tuning the reaction parameters to accomplish highest yield of imidazole scaffold. When the reaction of phenylacetic acid (**1a**, 1.5 equiv) with *N*-phenylbenzamidine (**2a**, 1.0 equiv) was performed in the presence of 5 mol% of $CuSO_4$ as a catalyst in DMF/CH_3NO_2 solvent system under an oxygen atmosphere at 130 °C, the desired 1,2,4-triphenyl-1*H*-imidazole (**3aa**) was isolated in only 10% yield, but the yield was enhanced to 20% when catalyst loading was increased to 10 mol% (Table 1, entry 1). Nitromethane acted as a single carbon synthon. We were delighted to find a great increase in the yield when 2,2′-bipyridyl (bipy) was used as a ligand along with 10 mol% of $CuSO_4$ (entry 2), this could be attributed to the stabilization of Cu^{2+} species by the 2,2′-bipyridyl ligand. This encouraging result prompted us to focus our attention on screening different parameters encompassing temperature, catalyst and ligand loading, substrate concentration, and solvent system in order to explore the optimal reaction conditions. The detrimental role of temperature and concentration of phenylacetic acid was noticed as the yield of imidazole diminished with lower temperature (entry 3) as well as concentration of phenylacetic acid (entry 4). Notably, no reaction occurred under nitrogen or argon atmosphere (entry 5). Various copper catalysts were tested, but they failed to provide an improved outcome (entries 6–11). Various ligands were also screened under standard conditions, however, they gave lower yields of **3aa** when compared to

Table 1 Optimization of the Reaction Conditions[a]



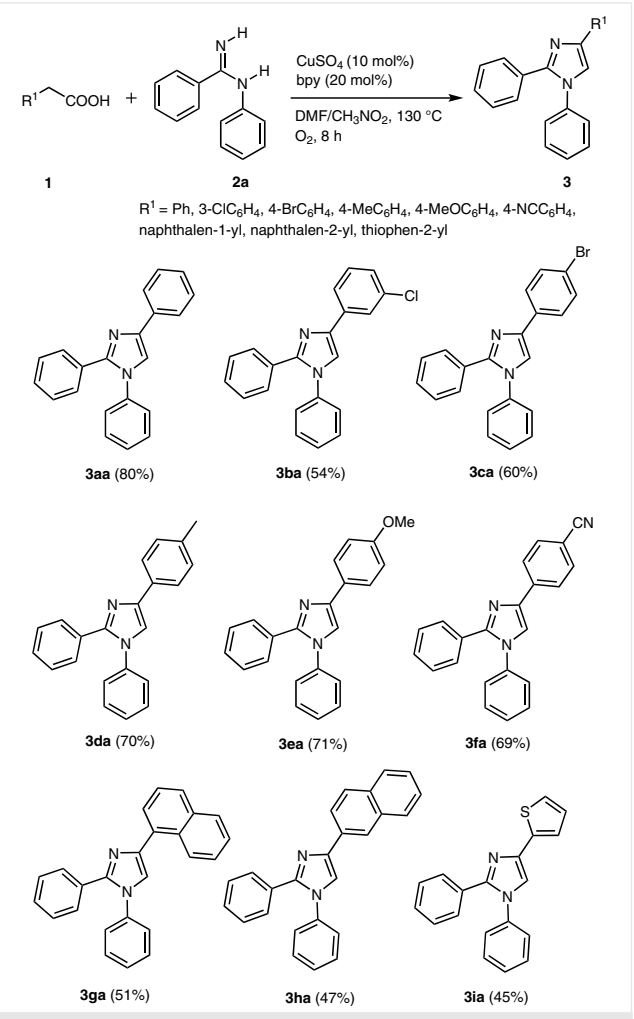
1a 2a 3aa

Entry	Catalyst (mol%)	Ligand (mol%)	Solvent	Yield (%)[b]
1	$CuSO_4$ (10) $CuSO_4$ (5)	–	DMF/CH_3NO_2	20 10
2	$CuSO_4$ (10)	bipy (20) bipy (10)	DMF/CH_3NO_2	80 60
3	$CuSO_4$ (10)	bipy (20)	DMF/CH_3NO_2	80 50[c] 44[d] 20[e]
4	$CuSO_4$ (10)	bipy (20)	DMF/CH_3NO_2	60[f] 20[g]
5[h]	$CuSO_4$ (10)	bipy (20)	DMF/CH_3NO_2	n.r.
6	CuI (10)	bipy (20)	DMF/CH_3NO_2	25
7	CuCl (10)	bipy (20)	DMF/CH_3NO_2	32
8	$CuCl_2$ (10)	bipy (20)	DMF/CH_3NO_2	40
9	CuBr (10)	bipy (20)	DMF/CH_3NO_2	28
10	$CuBr_2$ (10)	bipy (20)	DMF/CH_3NO_2	43
11	$Cu(OAc)_2$ (10)	bipy (20)	DMF/CH_3NO_2	54
12	$CuSO_4$ (10)	*o*-Phen (20)	DMF/CH_3NO_2	37
13	$CuSO_4$ (10)	Ph_3P (20)	DMF/CH_3NO_2	23
14	$CuSO_4$ (10)	8-hydroxyquinoline (20)	DMF/CH_3NO_2	31
15	$CuSO_4$ (10)	bipy (20)	DMF/CH_3NO_2	49
16	$CuSO_4$ (10)	bipy (20)	1,2-DCE/CH_3NO_2	41
17	$CuSO_4$ (10)	bipy (20)	1,4-dioxane/CH_3NO_2	55
18	$CuSO_4$ (10)	bipy (20)	DMI/CH_3NO_2	52

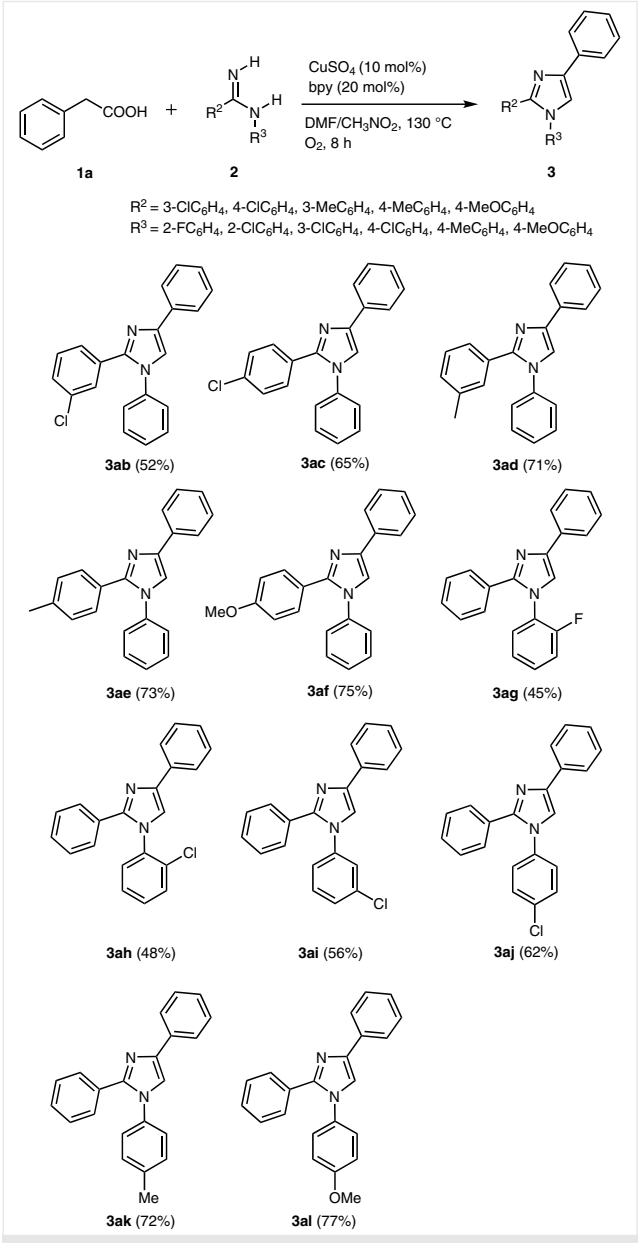
[a] Reaction conditions: phenylacetic acid (**1a**, 1.5 mmol), *N*-phenylbenzamidine (**1b**, 1.0 mmol), catalyst (10 mol%), ligand (20 mol%), solvent (2.0 mL), 130 °C, 8 h, under O_2 atmosphere.
[b] Yield of isolated product after column chromatography.
[c] Reaction performed at 120 °C.
[d] Reaction performed at 110 °C.
[e] Reaction performed at 90 °C.
[f] Phenylacetic acid (1.0 mmol).
[g] Phenylacetic acid (0.5 mmol).
[h] Reaction performed under N_2 atmosphere or argon atmosphere.

2,2′-bipyridyl (entries 12–14). Moreover, different solvent systems, DMSO/CH_3NO_2, 1,2-DCE/CH_3NO_2, 1,4-dioxane/CH_3NO_2, 1,3-dimethylimidazolidin-2-one (DMI)/CH_3NO_2, were also screened, but unfortunately lower yields of the product were observed (entries 15–18). All these observations implied that the best conditions are: phenylacetic acid (**1a**, 1.5 equiv), *N*-phenylbenzamidine (**2a**, 1.0 equiv), $CuSO_4$ (10 mol%), 2,2′-bipyridyl (bipy, 20 mol%), DMF/CH_3NO_2, 130 °C, under oxygen. A Celite-free workup, unlike $FeCl_3$-catalyzed reactions, leads to enhancement of the yield which apparently demonstrates the potential applicability of this protocol for large-scale synthesis.

With these optimized conditions in hand, we evaluated the substrate scope of this method by using various arylacetic acids, *N*-arylbenzamidines, and nitroalkanes as generalization with respect to different substituents and substitution pattern is mandatory for the wider acceptability of process. At the outset, diverse arylacetic acids **1a–i** were screened under the optimized conditions and it was found that nature of the substituents govern the yield of the product (Scheme 1). *N*-Phenylbenzamidine (**2a**) on reaction with phenylacetic acid (**1a**) afforded 1,2,4-triphenyl-1*H*-imidazole (**3aa**) in 80% yield. 3-Chloro- **1b** and 4-bromo-substituted phenylacetic acid **1c** gave imidazoles **3ba** and **3ca** in moderate yields. Notably, 4-methyl- **1d** and 4-meth-



Scheme 1 Scope of various arylacetic acids in the copper-catalyzed synthesis of imidazoles. *Reagents and conditions*: arylacetic acid **1** (1.5 mmol), *N*-phenylbenzamidine (**2a**, 1.0 mmol), $CuSO_4$ (10 mol%), 2,2′-bipyridyl (20 mol%), DMF/CH_3NO_2 (1.5:0.5 mL), 130 °C, 8 h, under O_2 atmosphere; isolated yields are given.



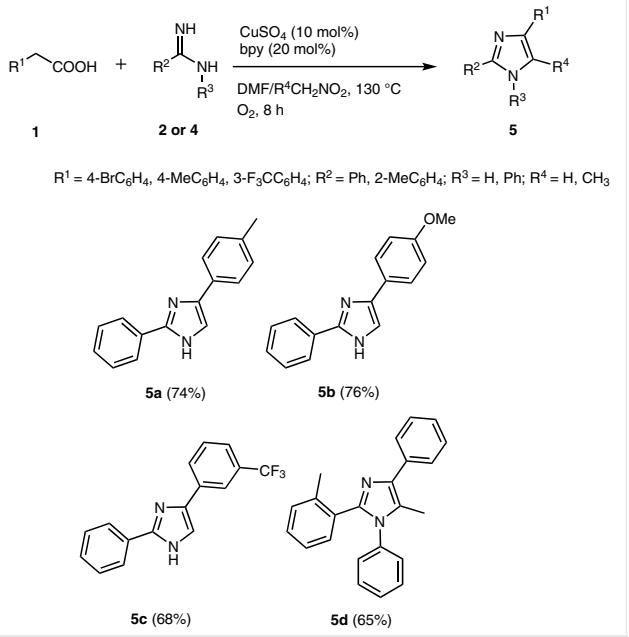
Scheme 2 Scope of various N-substituted amidines in the copper-catalyzed synthesis of imidazoles. *Reagents and conditions*: phenylacetic acid (**1a**, 1.5 mmol), *N*-arylbenzamidine **2** (1.0 mmol), $CuSO_4$ (10 mol%), 2,2′-bipyridyl (20 mol%), DMF/CH_3NO_2 (1.5:0.5 mL), 130 °C, 8 h, O_2 atmosphere; isolated yields are given.

oxy-substituted arylacetic acid **1e** gave the corresponding imidazoles **3da** and **3ea** in 70% and 71% yields, respectively. Arylacetic acid **1f** bearing an electron-withdrawing 4-CN group gave desired imidazole **3fa** in 69% yield. Along with this we further screened naphthalene-1-acetic acid (**1g**) and naphthalene-2-acetic acid (**1h**) which furnished product **3ga** and **3ha** with moderate yields 51% and 47%, respectively. Moreover, we carried out the reaction of heterocyclic acetic acid, thiophene-2-acetic acid (**1i**) with *N*-phenylbenzamidine (**2a**) resulting in product **3ia** in 45% yield.

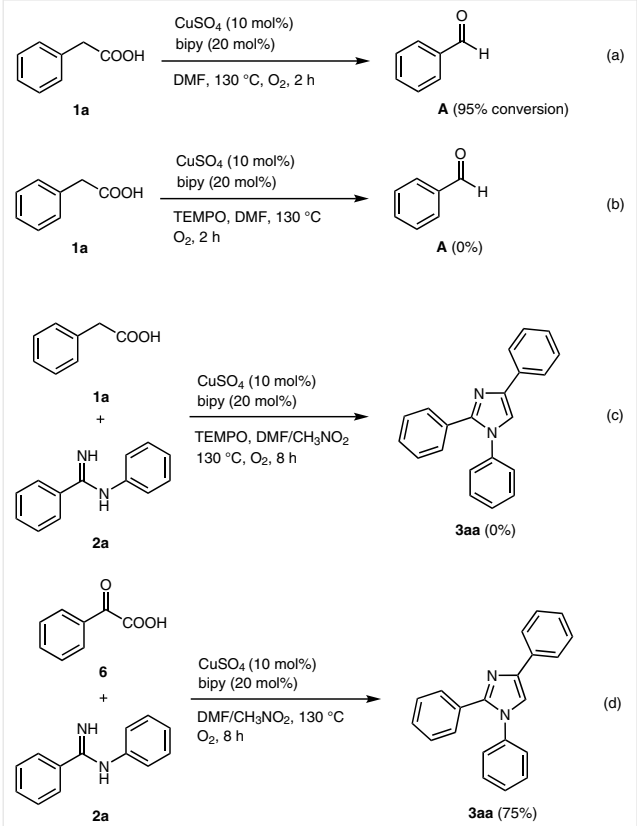
Furthermore, we assessed the use of various *N*-arylbenzamidines **2a–l** bearing substituents of varying electronic character and steric effect on both the phenyl rings with phenylacetic acid (**1a**) (Scheme 2). Indeed, *N*-phenylbenzamidines bearing halogen substituents (3-Cl **2b** and 4-Cl **2c**) as well as electron-donating substituents (3-Me **2d**, 4-Me **2e**, and 4-OMe **2f**) gave imidazoles **3ab–af** in moderate to good yields (52–75%). However, an *N*-phenylbenzamidine bearing NO_2 group (not shown) did not react with phenylacetic acid under the same reaction conditions. Similarly, the effects of the substituents on the *N*-phenyl ring of the *N*-arylbenzamidine were also investigated. A moderate yields (45–62%) of imidazoles **3ag–aj** were observed for *N*-arylbenzamidines bearing halogen substituents (2-F **2g**, 2-Cl **2h**, 3-Cl **2i**, and 4-Cl **2j**). *N*-Arylbenzamidines bearing electron-donating substituents (4-Me **2k** and 4-OMe **2l**) gave the corresponding imidazoles **3ak** and **3al** in 72% and 77% yields. No product formation was observed for *N*-arylbenzamidines bearing a NO_2 substituent.

Encouraged by these results, we next turned our attention to the synthesis of disubstituted and tetrasubstituted imidazoles by exploring the use of benzamidine and nitroethane, respectively (Scheme 3). The use of arylacetic acids bearing electron-donating (4-Me **1d** and 4-OMe **1e**) substituents with benzamidine (**4**) afforded respective disubstituted imidazoles **5a** and **5b** in 74% and 76% yields, respectively. An arylacetic acid **1j** with an electron-withdrawing (3-CF_3) substituent with benzamidine (**4**) produced corresponding disubstituted imidazoles **5c** in 68% yield. *N*-Phenylbenzamidine (**2a)** bearing an electron donating (2-Me) group on reaction with phenylacetic acid (**1a**) in the presence of DMF/nitroethane solvent system afforded tetrasubstituted imidazole **5d** in 65% yield.

To gain insight on the role of Cu^{II}(Ln) and endorse our hypothesis, a few controlled experiments were conducted. Initially, when a mixture of phenylacetic acid (**1a**), $CuSO_4$, and 2,2′-bipyridyl was heated in DMF at 130 °C for 2 hours under an O_2 atmosphere, 95% conversion into benzaldehyde (**A**) was observed [Scheme 4 (a)]. The same reaction failed to give benzaldehyde (**A**) in the presence of radical inhibitor TEMPO [Scheme 4 (b)]. This clearly indicated that reaction



Scheme 3 Scope of benzamidines and nitroethane in the copper-catalyzed synthesis of imidazoles. *Reagents and conditions*: arylacetic acid **1** (1.5 mmol), *N*-arylbenzamidine **2** or benzamidine **4** (1.0 mmol), $CuSO_4$ (10 mol%), 2,2′-bipyridyl (20 mol%), DMF/CH_3NO_2 or DMF/$EtNO_2$ (2 mL), 130 °C, 8 h, O_2 atmosphere; isolated yields are given.



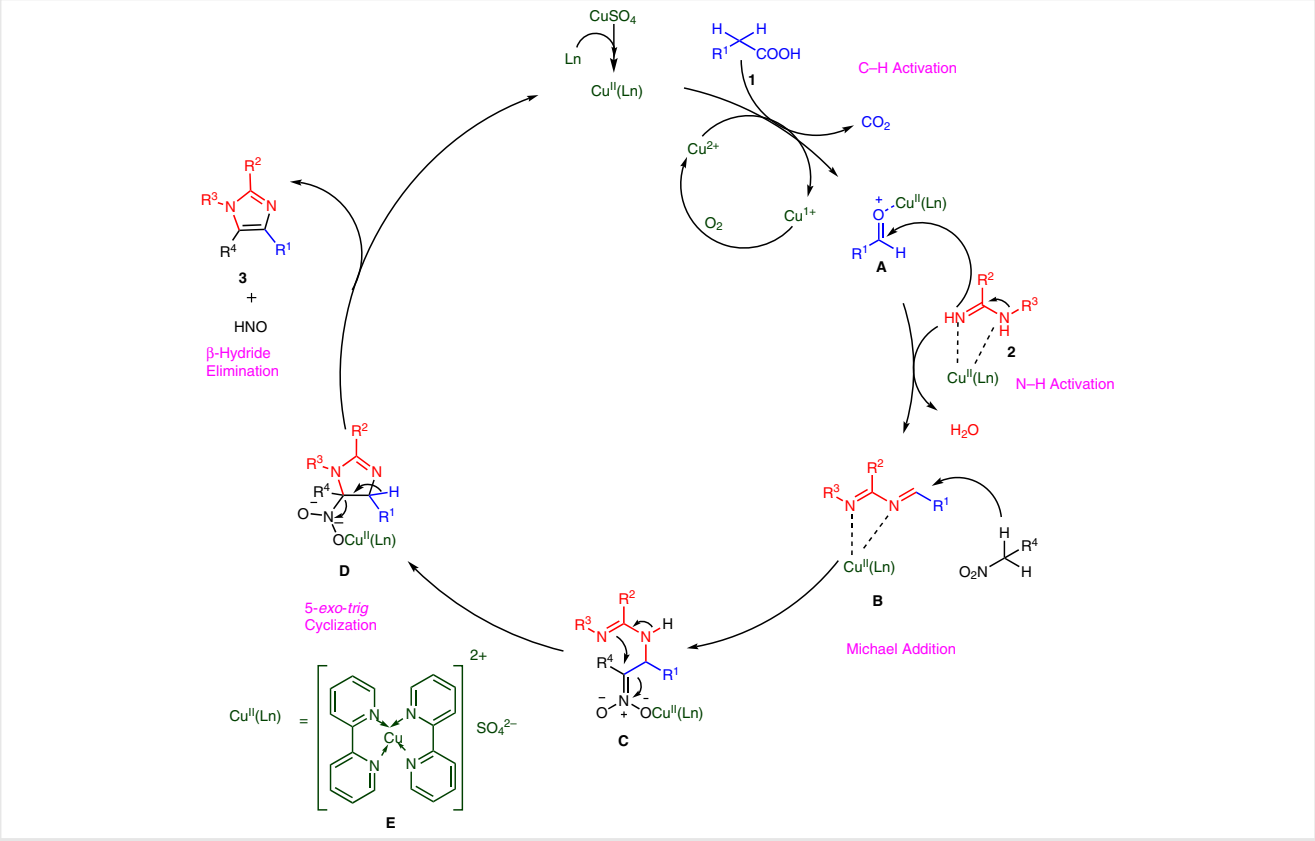
Scheme 4 Control experiments

has proceeded by following single electron transfer (SET) pathway owing to Cu^{II}(Ln). Similarly no product was observed when Cu^{II}(Ln)-catalyzed reaction of phenylacetic acid (**1a**) and *N*-phenylbenzamidine (**2a**) was carried out in the presence of TEMPO [Scheme 4 (c)]. In order to confirm that the reaction proceeds through the formation of an α-keto acid, we carried out the reaction of α-keto acid **6** with *N*-phenylbenzamidine (**2a**) under the optimized reaction conditions [Scheme 4 (d)] and found that the reaction produced imidazole **3aa** in 75% yield, thereby indicating the formation of an α-keto acid as an intermediate in this reaction.

A plausible mechanism, developed from these results and the literature reports, is depicted in Scheme 5. Initially, Cu^{II}(Ln) **E** catalyzed C–H activation of arylacetic acid **1** occurs in the presence of oxygen via peroxide linkage formation to afford α-keto acid,[30,31] which on oxidative decarboxylation gives aromatic aldehyde **A**. Further, *N*-arylbenzamidine **2** in the presence of Cu^{II}(Ln) **E** undergoes autooxidation to generate a stable biradical via N–H activation.[17a,32] This, on nucleophilic substitution reaction with aromatic aldehyde, yields intermediate **B**. Then nitroalkane (Michael donor) undergoes regioselective Michael addition[33,34] with intermediate **B** to form basic skeleton **C** which forms thermodynamically stable intermediate having a five-membered ring **D**. The stereoelectronic effect of **C** drives radical 5-*exo*-*trig* cyclization[35] due to better orbital overlapping to give intermediate **D**, which in the presence of Cu^{II}(Ln) **E** complex undergoes β-hydride elimination to give substituted imidazole **3** as the desired product with the liberation of nitroxyl gas.

We have developed a copper-catalyzed efficient protocol for the synthesis of multisubstituted imidazoles via simultaneously C–H and N–H activation of easily available arylacetic acids and *N*-arylbenzamidines. Also we report phenylacetic acid as an alternative to benzaldehyde since it offer advantages like wide substrate scope, stable and robust nature, etc. We strongly believe that this method will open a new avenue for the synthesis of biologically important multisubstituted imidazoles and should find broad application in modern synthetic chemistry as well as medicinal chemistry.

N-Arylbenzamidines were synthesized according to a literature procedure.[36] Chemical reagents were purchased from commercial suppliers. All the solvents were purchased from Spectrochem and were used as received. DMF was dried by using vacuum distillation and was stored over 4–Å molecular sieves before use. All reactions were performed in a round-bottom flask and monitored by TLC performed on aluminum plates (0.25 mm, E. Merck) precoated with silica gel (Merck



Scheme 5 Proposed reaction mechanism

60 F-254). Developed TLC plates were visualized under a short-wavelength UV lamp. Reactions were conducted under open air and O_2 atmosphere. Yields refer to spectroscopically (^{1}H, ^{13}C NMR) homogeneous material obtained after column chromatography performed on silica gel (230–400 mesh) supplied by Avra laboratories, India. Petroleum ether = PE. ^{1}H and ^{13}C NMR were recorded in $CDCl_3$ on a Bruker 400 and 300 MHz spectrometer relative to TMS (δ = 0.0) as an internal standard. High-resolution mass spectra (HRMS) were obtained by using positive electrospray ionization (ESI) and the time-of-flight (TOF) method. Melting points were recorded on a standard melting point apparatus from Sunder Industrial Product, Mumbai and are uncorrected.

Multisubstituted Imidazoles 3 and 5; General Procedure

A round-bottom flask was charged with arylacetic acid **1** (1.5 mmol), *N*-arylbenzamidine **2** or **4** (1.0 mmol), $CuSO_4$ (10 mol%), and 2,2′-bipyridyl (20 mol%). A pre-oxygen degassed solvent system of DMF/nitroalkane (1.5:0.5 mL) was added to above mixture. The resulting mixture was heated at 130 °C for 8 h. The reaction progress was monitored by using TLC. After completion of the reaction, water was added to the mixture and the aqueous layer was extracted with EtOAc. The combined organic layers were dried (anhyd Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash column chromatography (230–400 mesh silica gel, EtOAc/*n*-hexane) to afford imidazoles **3** or **5**.

1,2,4-Triphenyl-1*H*-imidazole (3aa)[18c]

Purified by column chromatography (EtOAc/PE 1:9) as a yellow oil; yield: 120 mg (80%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 8 Hz, 2 H), 7.47–7.45 (m, 3 H), 7.43–7.39 (m, 5 H), 7.33 (s, 1 H), 7.28–7.24 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.4, 142.1, 138.8, 134.2, 130.6, 129.9, 129.2, 129.0, 128.9, 128.6, 127.4, 126.4, 126.2, 125.5, 118.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{17}N_2$: 297.1392; found: 297.1390.

4-(3-Chlorophenyl)-1,2-diphenyl-1*H*-imidazole (3ba)

Purified by column chromatography (EtOAc/PE 1:9) as a yellow oil; yield: 83 mg (54%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90–7.87 (m, 1 H), 7.75–7.73 (m, 1 H), 7.47–7.38 (m, 6 H), 7.31–7.21 (m, 7 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.5, 138.3, 135.7, 134.7, 130.0, 129.6, 128.9, 128.7, 128.4, 128.4, 128.4, 128.3, 127.0, 125.9, 125.2, 123.1, 119.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{16}ClN_2$: 331.1002; found: 331.1005.

4-(4-Bromophenyl)-1,2-diphenyl-1*H*-imidazole (3ca)[23]

Purified by column chromatography (EtOAc/PE 1:9) as a yellow oil; yield: 95 mg (60%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.79–7.74 (tt, *J* = 3 Hz, 2 H), 7.54–7.49 (tt, *J* = 3 Hz, 2 H), 7.46–7.39 (m, 6 H), 7.28–7.24 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.7, 141.8, 136.4, 133.8, 131.8, 130.7, 130.2, 129.4, 128.6, 128.3, 128.1, 127.8, 127.0, 125.1, 118.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{16}BrN_2$: 375.0497; found: 375.0495.

1,2-Diphenyl-4-(*p*-tolyl)-1*H*-imidazole (3da)[24]

Purified by column chromatography (EtOAc/PE 1:9) as a yellow oil; yield: 107 mg (70%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.91–7.88 (m, 2 H), 7.49–7.46 (m, 2 H), 7.42–7.37 (m, 3 H), 7.29–7.24 (m, 4 H), 7.21 (s, 1 H), 7.18 (s, 1 H), 7.16–7.12 (m, 2 H), 2.39 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.9, 141.8, 138.6, 136.7, 131.1, 130.4, 129.5, 129.3, 128.8, 128.4, 128.2, 128.1, 125.9, 125.0, 118.1, 21.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{19}N_2$: 311.1548; found: 311.1545.

4-(4-Methoxyphenyl)-1,2-diphenyl-1*H*-imidazole (3ea)[18c]

Purified by column chromatography (EtOAc/PE 1:9) as a light yellow oil; yield: 109 mg (71%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84–7.81 (distorted t, *J* = 3.2, 2.0 Hz, 2 H), 7.46–7.44 (m, 2 H), 7.39–7.35 (m, 4 H), 7.28–7.23 (m, 5 H), 6.97–6.93 (tt, *J* = 3.2, 2.0 Hz, 2 H), 3.82 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.9, 146.9, 141.6, 138.6, 134.3, 131.8, 129.6, 128.5, 128.3, 126.4, 125.9, 124.6, 120.5, 117.7, 114.1, 55.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{19}N_2O$: 327.1497; found: 327.1499.

4-(1,2-Diphenyl-1*H*-imidazol-4-yl)benzonitrile (3fa)[18c]

Purified by column chromatography (EtOAc/PE 1:9) as a pale yellow solid; yield: 106 mg (69%); mp 198–200 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89–7.88 (m, 1 H), 7.86 (d, *J* = 4.0 Hz, 1 H), 7.66 (d, *J* = 1.2 Hz, 1 H), 7.64 (s, 1 H), 7.56 (t, *J* = 4 Hz, 1 H), 7.54 (t, *J* = 1.6 Hz, 1 H), 7.52–7.47 (m, 4 H), 7.40 (t, *J* = 1.6 Hz, 1 H), 7.38 (s, 1 H), 7.36 (t, *J* = 1.6 Hz, 1 H), 7.18–7.14 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.9, 142.0, 138.3, 133.7, 131.5, 130.3, 129.8, 129.3, 128.7, 128.6, 127.2, 125.9, 125.1, 122.9, 120.0, 118.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{16}N_3$: 322.1344; found: 322.1347.

4-(Naphthalen-1-yl)-1,2-diphenyl-1*H*-imidazole (3ga)

Purified by column chromatography (EtOAc/PE 3:7) as a yellow oil; yield: 79 mg (51%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.93 (s, 1 H), 7.74–7.71 (m, 3 H), 7.51 (d, *J* = 7.5 Hz, 3 H), 7.46–7.37 (m, 4 H), 7.32 (t, *J* = 7.5 Hz, 3 H), 7.22 (d, *J* = 8.1 Hz, 2 H), 7.15 (s, 1 H), 7.04 (t, *J* = 7.5 Hz, 1 H).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{19}N_2$: 347.1548; found: 347.1550.

4-(Naphthalen-2-yl)-1,2-diphenyl-1*H*-imidazole (3ha)

Purified by column chromatography (EtOAc/PE 3:7) as a yellow oil; yield: 73 mg (47%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.03 (s, 1 H), 7.80–7.82 (m, 4 H), 7.63 (d, *J* = 7.8 Hz, 3 H), 7.51 (t, *J* = 2.7 Hz, 1 H), 7.48 (t, *J* = 1.2 Hz, 1 H), 7.45–7.40 (m, 3 H), 7.34 (t, *J* = 8.1 Hz, 3 H), 7.13 (t, *J* = 7.5 Hz, 2 H).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{19}N_2$: 347.1548; found: 347.1546.

1,2-Diphenyl-4-(thiophen-2-yl)-1*H*-imidazole (3ia)

Purified by column chromatography (EtOAc/PE 4:6) as a yellow oil; yield: 70 mg (45%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.99 (s, 1 H), 7.86 (d, *J* = 6.9 Hz, 2 H), 7.64 (t, *J* = 7.8 Hz, 3 H), 7.53–7.43 (m, 4 H), 7.35 (t, *J* = 8.1 Hz, 3 H), 7.14 (t, *J* = 7.5 Hz, 1 H).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{15}N_2S$: 303.0950; found: 303.0958.

2-(3-Chlorophenyl)-1,4-diphenyl-1*H*-imidazole (3ab)[23]

Purified by column chromatography (EtOAc/PE 1:9) as a yellow oil; yield: 80 mg (52%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87–7.84 (m, 2 H), 7.55 (t, *J* = 2.0 Hz, 1 H), 7.43–7.41 (m, 4 H), 7.39–7.36 (m, 2 H), 7.27–7.24 (m, 3 H), 7.18 (t, *J* = 1.6 Hz, 1 H), 7.15 (s, 1 H), 7.13 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.5, 142.0, 138.2, 134.4, 133.7, 132.0, 129.7, 129.4, 128.9, 128.8, 128.6, 128.6, 127.3, 126.8, 125.9, 125.1, 119.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{16}ClN_2$: 331.1002; found: 331.0998.

2-(4-Chlorophenyl)-1,4-diphenyl-1*H*-imidazole (3ac)[37]

Purified by column chromatography (EtOAc/PE 1:9) as a yellow oil; yield: 100 mg (65%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88–7.85 (m, 2 H), 7.45–7.38 (m, 8 H), 7.33 (t, *J* = 2.0 Hz, 1 H), 7.31–7.29 (m, 1 H), 7.27–7.25 (m, 2 H), 7.24 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.9, 142.0, 138.3, 133.7, 131.5, 130.3, 129.8, 129.3, 128.7, 128.6, 127.2, 125.9, 125.1, 122.9, 118.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{16}ClN_2$: 331.1002; found: 331.0999.

1,4-Diphenyl-2-(*m*-tolyl)-1*H*-imidazole (3ad)[37]

Purified by column chromatography (EtOAc/PE 1:9) as a yellow oil; yield: 108 mg (71%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.89–7.86 (m, 2 H), 7.43–7.37 (m, 6 H), 7.33 (d, *J* = 6.0 Hz, 2 H), 7.28–7.26 (m, 2 H), 7.24 (s, 1 H), 7.06 (d, *J* = 6.0 Hz, 2 H), 2.31 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.2, 141.6, 138.7, 138.5, 134.0, 129.6, 129.5, 129.3, 129.0, 128.8, 128.7, 128.2, 127.5, 127.0, 125.9, 125.1, 118.4, 21.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{19}N_2$: 311.1548; found: 311.1545.

1,4-Diphenyl-2-(*p*-tolyl)-1*H*-imidazole (3ae)[17b]

Purified by column chromatography (EtOAc/PE 1:9) as a yellow oil; yield: 110 mg (73%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89–7.87 (m, 2 H), 7.43–7.35 (m, 7 H), 7.34 (t, *J* = 2.0 Hz, 1 H), 7.32 (t, *J* = 2.0 Hz, 1 H), 7.28–7.25 (m, 3 H), 7.24 (s, 1 H), 2.31 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.3, 141.6, 138.7, 138.5, 134.0, 129.5, 129.0, 128.8, 128.7, 128.2, 127.5, 127.0, 125.9, 125.1, 118.4, 21.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{19}N_2$: 311.1548; found: 311.1549.

2-(4-Methoxyphenyl)-1,4-diphenyl-1*H*-imidazole (3af)[37]

Purified by column chromatography (EtOAc/PE 1:9) as a yellow oil; yield: 116 mg (75%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.84–7.80 (distorted t, *J* = 2.1, 1.5 Hz, 3 H), 7.64 (d, *J* = 5.7 Hz, 1 H), 7.44–7.36 (m, 5 H), 7.26–7.22 (m, 4 H), 6.96–6.92 (distorted tt, *J* = 2.1, 1.5 Hz, 2 H), 3.81 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.9, 146.9, 141.6, 138.6, 131.8, 129.6, 128.9, 128.3, 128.2, 127.2, 126.4, 125.9, 124.6, 117.7, 114.1, 55.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{19}N_2O$: 327.1497; found: 327.1494.

1-(2-Fluorophenyl)-2,4-diphenyl-1*H*-imidazole (3ag)

Purified by column chromatography (EtOAc/PE 1:9) as a yellow oil; yield: 69 mg (45%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91–7.89 (m, 1 H), 7.76–7.74 (tt, *J* = 1.2 Hz, 1 H), 7.45–7.37 (m, 7 H), 7.29–7.24 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.4, 142.0, 138.8, 134.2, 134.1, 130.6, 129.9, 129.2, 129.0, 128.9, 128.7, 128.6, 127.4, 126.4, 126.2, 125.5, 118.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{16}FN_2$: 315.1298; found: 315.1301.

1-(2-Chlorophenyl)-2,4-diphenyl-1*H*-imidazole (3ah)

Purified by column chromatography (EtOAc/PE 1:9) as a yellow oil; yield: 74 mg (48%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89–7.86 (m, 2 H), 7.44 (s, 2 H), 7.39 (d, *J* = 7.6 Hz, 2 H), 7.36 (distorted t, *J* = 2.0, 1.2 Hz, 1 H), 7.34–7.28 (m, 6 H), 7.25 (s, 1 H), 7.11–7.09 (distorted tt, *J* = 1.6, 1.2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.9, 141.9, 139.4, 135.0, 133.4, 131.4, 130.4, 129.8, 128.8, 128.7, 128.6, 128.3, 127.1, 125.8, 125.0, 124.1, 118.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{16}ClN_2$: 331.1002; found: 331.1005.

1-(3-Chlorophenyl)-2,4-diphenyl-1*H*-imidazole (3ai)[37]

Purified by column chromatography (EtOAc/PE 1:9) as a yellow oil; yield: 86 mg (56%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89–7.86 (m, 2 H), 7.46–7.35 (m, 6 H), 7.33–7.25 (m, 6 H), 7.11–7.08 (distorted tt, *J* = 1.6, 1.2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.3, 142.0, 138.8, 134.4, 133.6, 130.6, 129.9, 129.2, 129.0, 128.9, 128.7, 128.6, 127.4, 126.4, 126.2, 125.5, 118.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{16}ClN_2$: 331.1002; found: 331.0997.

1-(4-Chlorophenyl)-2,4-diphenyl-1*H*-imidazole (3aj)[24]

Purified by column chromatography (EtOAc/PE 1:9) as a yellow oil; yield: 95 mg (62%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.93–7.89 (m, 2 H), 7.54–7.51 (tt, *J* = 0.9 Hz, 1 H), 7.47–7.43 (m, 2 H), 7.41–7.36 (m, 5 H), 7.34–7.32 (m, 2 H), 7.27–7.24 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.7, 141.8, 136.4, 133.8, 131.8, 130.7, 130.2, 129.4, 128.6, 128.3, 128.1, 127.8, 127.0, 125.1, 118.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{16}ClN_2$: 331.1002; found: 331.1004.

2,4-Diphenyl-1-(*p*-tolyl)-1*H*-imidazole (3ak)[18c]

Purified by column chromatography (EtOAc/PE 1:9) as a light yellow oil; yield: 110 mg (72%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.91–7.88 (m, 2 H), 7.49–7.46 (m, 2 H), 7.42–7.37 (m, 3 H), 7.29–7.25 (m, 4 H), 7.21 (s, 1 H), 7.18 (s, 1 H), 7.16–7.12 (m, 2 H), 2.39 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.0, 141.5, 138.2, 136.0, 133.8, 130.3, 130.1, 128.8, 128.6, 128.4, 128.2, 127.0, 125.6, 125.1, 118.7, 21.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{19}N_2$: 311.1548; found: 311.1552.

1-(4-Methoxyphenyl)-2,4-diphenyl-1*H*-imidazole (3al)[17b]

Purified by column chromatography (EtOAc/PE 1:9) as a light yellow oil; yield: 118 mg (77%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90–7.87 (m, 2 H), 7.49–7.45 (m, 2 H), 7.42–7.37 (m, 3 H), 7.27–7.23 (m, 4 H), 7.20–7.15 (distorted tt, *J* = 4.4, 2.8 Hz, 2 H), 6.92–6.87 (distorted tt, *J* = 4.4, 2.8 Hz, 2 H), 3.82 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.3, 147.1, 141.9, 134.0, 131.5, 130.4, 128.7, 128.6, 128.3, 128.2, 127.1, 126.9, 125.0, 118.9, 114.6, 55.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{19}N_2O$: 327.1497; found: 327.1500.

2-Phenyl-4-(*p*-tolyl)-1*H*-imidazole (5a)[38]

Purified by column chromatography (EtOAc/PE 3:7) as a white solid; yield: 105 mg (74%); mp 156–158 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.17 (br s, 1 H), 7.83–7.81 (dd, *J* = 7.3, 3.6 Hz, 2 H), 7.52–7.50 (d, *J* = 8.0 Hz, 2 H), 7.18–7.12 (m, 3 H), 7.09 (s, 1 H), 7.03 (d, *J* = 7.9 Hz, 1 H), 2.22 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.3, 137.6, 129.5, 128.8, 128.3, 128.1, 127.9, 126.1, 125.3, 116.9, 21.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{15}N_2$: 235.1230; found: 235.1231.

4-(4-Methoxyphenyl)-2-phenyl-1*H*-imidazole (5b)[39]

Purified by column chromatography (EtOAc/PE 3:7) as a white solid; yield: 108 mg (76%); mp 260–262 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.58 (br s, 1 H), 7.80–7.73 (m, 2 H), 7.50 (d, *J* = 8.7 Hz, 1 H), 7.29–7.09 (m, 5 H), 6.97 (s, 1 H), 6.72 (d, *J* = 8.7 Hz, 1 H), 3.65 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.1, 146.4, 137.6, 130.5, 129.1, 128.7, 126.6, 125.9, 125.6, 114.1, 113.2, 55.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{15}N_2O$: 251.1179; found: 251.1180.

2-Phenyl-4-[3-(trifluoromethyl)phenyl]-1*H*-imidazole (5c)[39]

Purified by column chromatography (EtOAc/PE 3:7) as a yellow solid; yield: 101 mg (68%); mp 264–266 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.94 (br s, 1 H), 7.94 (s, 1 H), 7.83 (distorted t, *J* = 8.8, 7.3 Hz, 3 H), 7.46 (d, *J* = 7.6 Hz, 1 H), 7.39 (t, *J* = 7.7 Hz, 1 H), 7.28–7.25 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.9, 138.5, 133.4, 131.4–130.5 [q, *J* = 32.2 Hz, 1 C (-CF_3)], 129.2, 129.1, 128.8, 128.3, 125.8, 125.5, 123.6, 122.8, 120.1, 117.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{12}F_3N_2$: 289.0947; found: 289.0948.

5-Methyl-1,4-diphenyl-2-(*o*-tolyl)-1*H*-imidazole (5d)

Purified by column chromatography (EtOAc/PE 1:9) as a colorless oil; yield: 103mg (65%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 7.6 Hz, 2 H), 7.47 (distorted t, *J* = 8.1, 7.3 Hz, 5 H), 7.33 (distorted t, *J* = 8.0, 5.6 Hz, 3 H), 7.24–7.22 (m, 2 H), 7.03 (d, *J* = 8.0 Hz, 2 H), 2.29 (s, 3 H), 2.28 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.4, 138.0, 137.4, 135.0, 132.2, 129.7, 129.5, 129.2, 129.0, 128.9, 128.8, 128.7, 128.5, 128.4, 126.5, 126.1.

HRMS (ESI): *m*/*z* [M + H]$^+$calcd for $C_{23}H_{21}N_2$: 325.1699; found: 325.1701.

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Supporting Information

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