Synthesis W. Sun et al. Paper

One-Pot Synthesis of Polysubstituted Imidazoles Based on $Pd(OAc)_2/Ce(SO_4)_2/Bi(NO_3)_3$ Trimetallic Cascade of Decarboxylation/Wacker-Type Oxidation/Debus–Radziszewski Reaction

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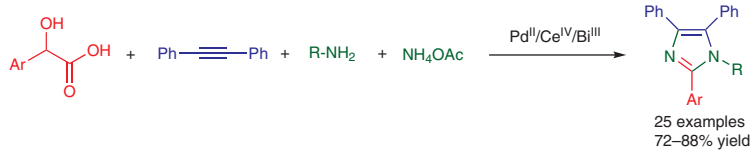

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Abstract A novel and highly efficient one-pot synthesis of polysubstituted imidazoles from α-hydroxyphenylacetic acids, diphenylacetylene, and amines has been achieved by $Pd(OAc)_2/Ce(SO_4)_2/Bi(NO_3)_3$ trimetallic catalytic system. A series of control experiments showed that this overall reaction occurs through a one-pot cascade process combining the steps of decarboxylation of α-hydroxyphenylacetic acids, Wacker-type oxidation of diphenylacetylene, and Debus–Radziszewski annulation of aryl aldehydes and benzil generated in situ, as well as amines. This reaction represents a novel multicomponent reaction using α-hydroxyphenylacetic acids and diphenylacetylene as sources of aryl aldehydes and a β-diketone. This process exhibits a broad substrate scope and a good functional group tolerance to assemble the corresponding polysubstituted imidazoles in excellent yields (72–88%) under mild conditions.

Key words $Pd^{II}/Ce^{IV}/Bi^{III}$ trimetallic system, imidazole, decarboxylation, Wacker-type oxidation, Debus–Radziszewski reaction

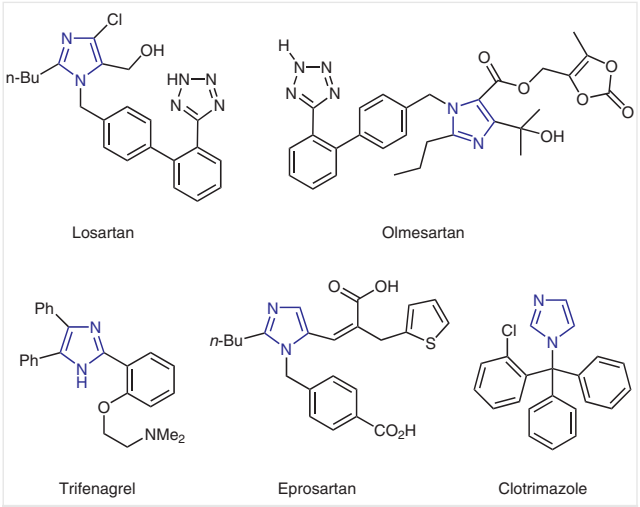


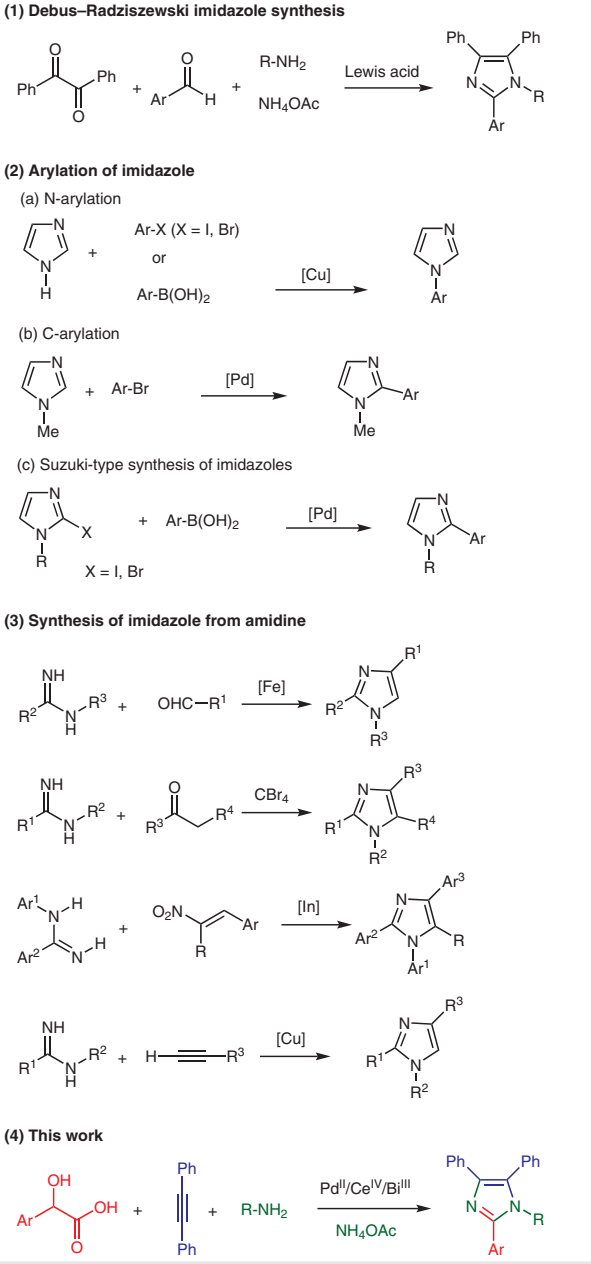
Figure 1 Representative imidazole skeleton in some commercial pharmaceuticals

Nitrogen-rich heterocycles bearing an imidazole structural scaffold are widely found in wide range of naturally occurring compounds, pharmaceuticals, agrochemicals, and essential intermediates.[1] Many of imidazole derivatives act as p38 MAP kinase inhibitors,[2] B-Raf kinase inhibitors,[3] glucagon receptor antagonists,[4] anti-inflammatories,[5] and antitumor agents.[6] Imidazole moiety also is an integral part of many commercial drugs[7] such as Losartan, Olmesartan, Trifenagrel, Eprosartan, and Clotrimazole (Figure 1).

Due to their pharmacological and biological importance, recently many efforts have been focused on the synthesis of the privileged imidazole derivatives with diverse functional groups. Typically, there are three main methods to construct imidazole derivatives: (1) Debus–Radziszewski imidazole synthesis, that is, one-pot multicomponent reaction (MCR) of 1,2-dicarbonyl compound/α-hydroxyketone, aldehyde, primary amine and/or ammonia source (Scheme 1, Path 1);[7d,8] (2) transition-metal-catalyzed arylation of imidazoles/haloimidazoles (Scheme 1, Path 2);[9] (3) MCRs of amidine with aldehydes, ketones, nitroolefins, and alkynes, respectively (Scheme 1, Path 3).[10]

These documented protocols have their own merits and disadvantages, however, most employed substrates are confined to 1,2-diketones, aldehydes, primary amines, amidines, and nitroalkenes, thus leading to imidazoles with poor functional group diversity.

Therefore, the development of a simple, effective, high-yielding method to access this heterocyclic architecture from readily available and easily extensible starting materials is still of great demand. The commercially available α-hydroxyphenylacetic acids and alkynes can be viewed as potential surrogates of aryl aldehydes and 1,2-dicarbonyl



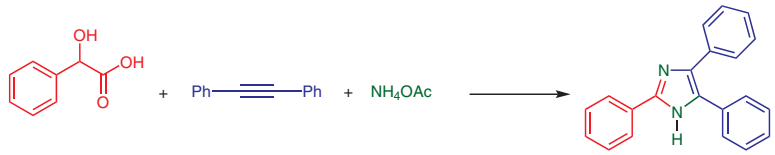
Scheme 1 Synthetic strategies for the construction of substituted imidazoles

compounds. We assume that it may be a new protocol for the synthesis of polysubstituted imidazoles from α-hydroxyphenylacetic acids with alkynes in the presence of a suitable catalytic system. In light of this hypothesis, we present here the first successful attempt on a $Pd(OAc)_2/Bi(NO_3)_3/Ce(SO_4)_2$ trimetallic system catalyzed MCRs of α-hydroxyphenylacetic acids, diphenylacetylene, primary amines and/or ammonium acetate for construction of polysubstituted imidazoles under mild conditions.

To explore the feasibility of our strategy, we began our study by exerting α-hydroxyphenylacetic acid, diphenylacetylene, and ammonium acetate as a model reaction, which was conducted in the presence of various catalytic system. The results are summarized in Table 1. Initially, when the common catalyst such as $Pd(OAc)_2$, $Ce(SO_4)_2{\cdot}4H_2O$, and $Bi(NO_3)_3{\cdot}5H_2O$ were employed, no product was observed (Table 1, entries 1–3). Then we combined $Pd(OAc)_2$ with $Bi(NO_3)_3{\cdot}5H_2O$, and $Ce(SO_4)_2{\cdot}4H_2O$ with $Bi(NO_3)_3{\cdot}5H_2O$, as well as $Pd(OAc)_2$ with $Ce(SO_4)_2{\cdot}4H_2O$ as a binary catalyst; here also no product or trace amount of product was detected (entries 4–7). To our delight, we found that the desired product was obtained in 40% yield when $Bi(NO_3)_3{\cdot}5H_2O$ was added, suggesting that all three $Pd^{2+}/Ce^{4+}/Bi^{3+}$ metals are required (entry 8). These results encouraged us to investigate the effect of $Bi(NO_3)_3$ on the reaction in order to further increase the yield. Obvious impact of molar ratio of $Ce(SO_4)_2{\cdot}4H_2O$ and $Bi(NO_3)_3{\cdot}5H_2O$ on the reaction was observed on the model (entries 8–13). It was found that the Ce/Bi molar ratio of 1/2 is the best (entry 10). In addition, $PdCl_2$ is slightly inefficient in place of $Pd(OAc)_2$ (entry 11). It should be noted that pivalic acid (PivOH) plays a pivotal role in this transformation, as demonstrated by the fact that the yields decreased when PivOH was absent (entry 14). Other additives such as acetic acid (AcOH), trifluoroacetic acid (TFA), and $BF_3{\cdot}OEt_2$, tetrabutylammonium bromide (TBAB), and sodium dodecylbenzene sulfonate (SDBS) are less efficient instead of PivOH in this model (entries 15–19). Further screening of solvents demonstrated that DMSO/H_2O (4:1 v/v) was the most suitable solvent (entry 10) among neat DMSO, DMF, H_2O, 1,4-dioxane, toluene, and dichloromethane (entries 21–27). Lower yield was obtained when the reaction was performed in DMF under nitrogen atmosphere compared with the reaction done in the air (entry 23). Moreover, the model reaction run successfully in DMSO/H_2O (4:1 v/v) under inert atmosphere, which illustrated DMSO serves an oxidant in this reaction (entry 20). For practical application, good stability and reusability of the catalytic system are highly preferable. Along this line we have investigated the recyclability of trimetallic catalysts for the model reaction. After the post-treatment process of the reaction, the mixture was extracted with ethyl acetate to leave the catalysts in the bottom of Schlenk tube. Then they were reused directly for the next run without any further treatment. The experiment result showed that the reused co-catalysts lose their catalytic performance and afford no desire products (entry 10).

With the optimized conditions in hand, the scope and generality of this reaction were explored. Various α-hydroxyphenylacetic acids with electron-withdrawing and electron-donating group on the phenyl ring were first examined and the results are shown in Scheme 2. It was found that the electronic effect of the substrates has no apparent impact on the product yields (products **5a–i**). The substitu-

Table 1 Optimization of Conditions for the Formation of **5a**[a]



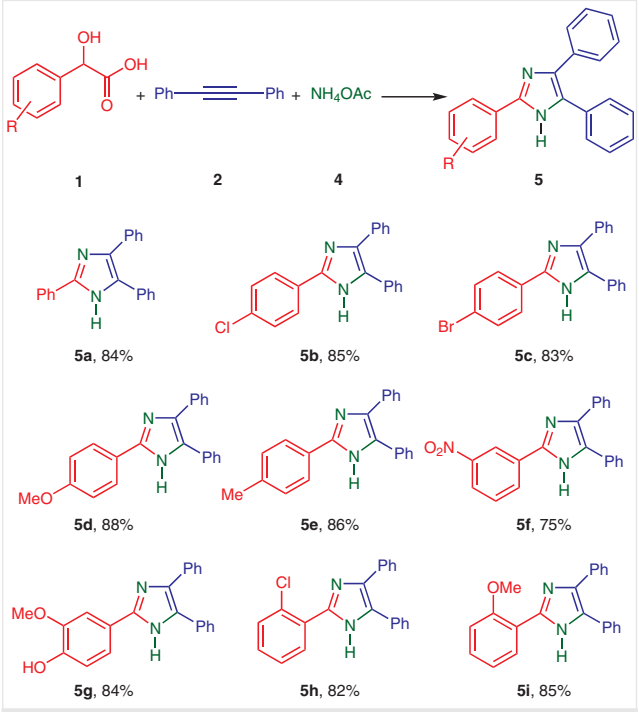
1 2 4 5a

Entry	Catalyst (mol%)	Solvent (v/v)	Additive (equiv)	Yield (%)[b]
1	$Pd(OAc)_2$ (5)	DMSO/H_2O (4:1)	–	n.d.
2	$Ce(SO_4)_2$ (10)	DMSO/H_2O (4:1)	–	n.d.
3	$Bi(NO_3)_3$ (10)	DMSO/H_2O (4:1)	–	n.d.
4	$Pd(OAc)_2$ (5)/$Bi(NO_3)_3$ (20)	DMSO/H_2O (4:1)	–	n.d.
5	$Ce(SO_4)_2$ (10)/$Bi(NO_3)_3$ (20)	DMSO/H_2O (4:1)	–	n.d.
6	$Pd(OAc)_2$ (5)/$Ce(SO_4)_2$ (10)	DMSO/H_2O (4:1)	–	trace
7	$Pd(OAc)_2$ (5)/$Ce(SO_4)_2$ (10)	DMSO/H_2O (4:1)	PivOH (2)	trace
8	$Pd(OAc)_2$ (5)/$Ce(SO_4)_2$ (10)/$Bi(NO_3)_3$ (10)	DMSO/H_2O (4:1)	PivOH (2)	40
9	$Pd(OAc)_2$ (5)/$Ce(SO_4)_2$ (20)/$Bi(NO_3)_3$ (20)	DMSO/H_2O (4:1)	PivOH (2)	58
10	$Pd(OAc)_2$ (5)/$Ce(SO_4)_2$ (20)/$Bi(NO_3)_3$ (40)	DMSO/H_2O (4:1)	PivOH (2)	84 (trace)[c]
11	$PdCl_2$ (5)/$Ce(SO_4)_2$ (20)/$Bi(NO_3)_3$ (40)	DMSO/H_2O (4:1)	PivOH (2)	80
12	$Pd(OAc)_2$ (5)/$Ce(SO_4)_2$ (10)/$Bi(NO_3)_3$ (40)	DMSO/H_2O (4:1)	PivOH (2)	72
13	$Pd(OAc)_2$ (5)/$Ce(SO_4)_2$ (30)/$Bi(NO_3)_3$ (20)	DMSO/H_2O (4:1)	PivOH (2)	36
14	$Pd(OAc)_2$ (5)/$Ce(SO_4)_2$ (20)/$Bi(NO_3)_3$ (40)	DMSO/H_2O (4:1)	–	70
15	$Pd(OAc)_2$ (5)/$Ce(SO_4)_2$ (20)/$Bi(NO_3)_3$ (40)	DMSO/H_2O (4:1)	AcOH (2)	40
16	$Pd(OAc)_2$ (5)/$Ce(SO_4)_2$ (20)/$Bi(NO_3)_3$ (40)	DMSO/H_2O (4:1)	TFA (2)	n.d.
17	$Pd(OAc)_2$ (5)/$Ce(SO_4)_2$ (20)/$Bi(NO_3)_3$ (40)	DMSO/H_2O (4:1)	$BF_3{\cdot}OEt_2$ (0.5)	n.d.
18	$Pd(OAc)_2$ (5)/$Ce(SO_4)_2$ (20)/$Bi(NO_3)_3$ (40)	DMSO/H_2O (4:1)	TBAB (2)	34
19	$Pd(OAc)_2$ (5)/$Ce(SO_4)_2$ (20)/$Bi(NO_3)_3$ (40)	DMSO/H_2O (4:1)	SDBS (2)	trace
20	$Pd(OAc)_2$ (5)/$Ce(SO_4)_2$ (20)/$Bi(NO_3)_3$ (40)	DMSO/H_2O (4:1)	PivOH (2)	86[d]
21	$Pd(OAc)_2$ (5)/$Ce(SO_4)_2$ (20)/$Bi(NO_3)_3$ (40)	DMSO	PivOH (2)	65
22	$Pd(OAc)_2$ (5)/$Ce(SO_4)_2$ (20)/$Bi(NO_3)_3$ (40)	H_2O	PivOH (2)	n.d.
23	$Pd(OAc)_2$ (5)/$Ce(SO_4)_2$ (20)/$Bi(NO_3)_3$ (40)	DMF	PivOH (2)	15[d] (68)[e]
24	$Pd(OAc)_2$ (5)/$Ce(SO_4)_2$ (20)/$Bi(NO_3)_3$ (40)	1,4-dioxane	PivOH (2)	trace
25	$Pd(OAc)_2$ (5)/$Ce(SO_4)_2$ (20)/$Bi(NO_3)_3$ (40)	EtOH	PivOH (2)	trace
26	$Pd(OAc)_2$ (5)/$Ce(SO_4)_2$ (20)/$Bi(NO_3)_3$ (40)	toluene	PivOH (2)	n.d.
27	$Pd(OAc)_2$ (5)/$Ce(SO_4)_2$ (20)/$Bi(NO_3)_3$ (40)	CH_2Cl_2	PivOH (2)	n.d.

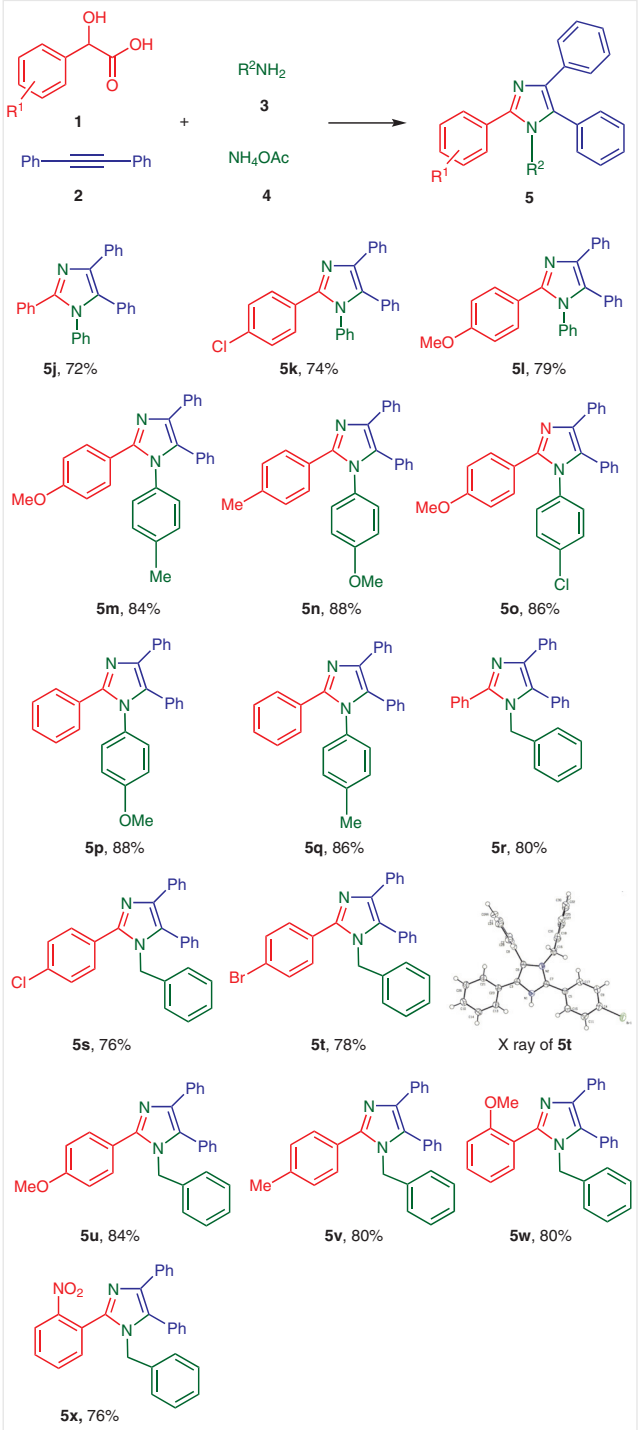
[a] All reactions were carried out with **1a** (1.5 mmol), **2** (1.0 mmol), **4** (3.0 mmol), and a catalytic amount of the catalyst in solvent (2 mL) at 120 °C for 10 h.
[b] Isolated yields. n.d.: Not detected.
[c] The yield was based on the next run.
[d] Under N_2 atmosphere.
[e] Prolonged to 48 h in the air.

ents (Cl, Br, NO_2) on the substrate remain intact under the present reaction conditions and afforded good product yields.

Having successfully evidenced the domain of α-hydroxyphenylacetic acids by this novel approach, we were encouraged to conduct further exploration on the scope of amines, and the results are shown in Scheme 3. As can be seen from the results, the electronic effect of substituents on the aromatic ring of anilines exerted no significant effect on the reaction and produced the desired imidazoles in excellent yields (products **5j–q**). These results indicated that



Scheme 2 Scope of α-hydroxyphenylacetic acids for the synthesis of polysubstituted imidazoles under optimal conditions. Isolated yield of each product is shown.



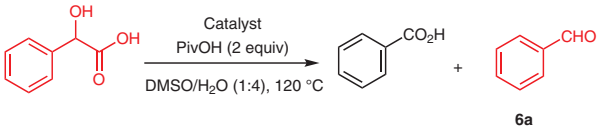
Scheme 3 Scope of amines for the synthesis of polysubstituted imidazoles under optimal conditions. Isolated yield of each product is shown.

the reaction may be extensible. Then we turned our attention toward benzylamines and found the benzylamines reacted well under the optimal condition to give the corresponding imidazoles in excellent yields (products **5r–x**) (Scheme 3).

To gain further insights into the reaction mechanism, some control experiments were carried out (Table 2). First, the decarboxylative reaction of α-hydroxyphenylacetic acids was conducted in various of catalytic system to clarify the role of catalyst. We found that the decarboxylation procedure still proceeded without the presence of $Bi(NO_3)_3$ (Table 2, a). This result indicated that $Pd(OAc)_2$ and $Ce(SO_4)_2$ play a crucial impact on the decarboxylation. Subsequently, diphenylacetylene was employed under aforementioned optimized conditions to afford the desired benzil via Wacker-type oxidation[11] in 97% yield (Table 2, b). Unlike the decarboxylative procedure (Table 2, a), $Pd(OAc)_2$, $Ce(SO_4)_2$, and $Bi(NO_3)_3$ are all indispensable for the reaction; the desired product could not be obtained in the absence of any one of them. Meanwhile, in case the catalytic activity is not high enough, pivalic acid is applied to enhance reactivity (Table 2, b). The improvement of catalytic efficiency may be attributed to the formation of highly electrophilic $Pd^{+}(PivO)$[12] and to the formation of a $Pd^{+}(PivO)/Ce^{4+}/Bi^{3+}$-π-complex intermediate through the coordination of the C≡C bond with $Pd^{+}(PivO)$, Ce^{4+}, and Bi^{3+} species.[13b]

Table 2 Control Experiments

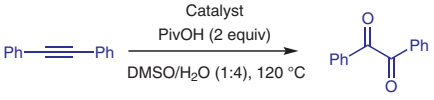
a) Decarboxylation of mandelic acid



6a

Catalyst (mol%)	Yield (%)[a] of **6a**
$Pd(OAc)_2$ (5)	n.d.
$Ce(SO_4)_2$ (20)	42
$Bi(NO_3)_3$ (40)	n.d.
$Pd(OAc)_2$ (5)/$Ce(SO_4)_2$ (20)	95

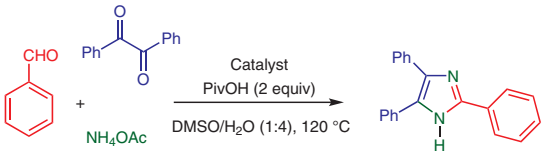
b) Wacker-type oxidation



7a

Catalyst (mol%)	Yield (%)[a] of **7a**
$Pd(OAc)_2$ (5)	n.d.
$Ce(SO_4)_2$ (20)	n.d.
$Bi(NO_3)_3$ (40)	n.d.
$Pd(OAc)_2$ (5)/$Ce(SO_4)_2$ (20)	12
$Pd(OAc)_2$ (5)/$Bi(NO_3)_3$ (40)	n.d.
$Ce(SO_4)_2$ (20)/$Bi(NO_3)_3$ (40)	n.d.
$Pd(OAc)_2$ (5)/$Ce(SO_4)_2$ (20)/$Bi(NO_3)_3$ (40)	97

c) Debus–Radziszewski imidazole synthesis



5a

Catalyst (mol%)	Yield (%) of **5a**
$Pd(OAc)_2$ (5)/$Ce(SO_4)_2$ (20)/$Bi(NO_3)_3$ (40)	84

[a] n.d. = not detected.

Remarkably, the recent reports for conversion of 1,2-diphenylacetylene into benzil were performed in the presence of an abnormal NHC-Ru^{II} complex catalyst, [bis(trifluoroacetoxy)iodo]benzene (PIFA), or need a long-term process (over 24 h) under hash condition.[14] These results showed that our $Pd(OAc)_2$/$Ce(SO_4)_2$/$Bi(NO_3)_3$ trimetallic system exhibited much more catalytic activity than the documented protocols. These control experiments of decarboxylation and Wacker-type oxidation suggest that aryl aldehyde and benzil should be the true intermediates. To confirm that the process commences with the formation of these two key intermediates, the rates of substrate conversion and product outcome were measured by GC/MS analysis (Figure 2). As can be seen, imidazole yields increased rapidly with the conversion of hydroxyphenylacetic acid and 1,2-diphenylacetylene. These results suggest that aryl aldehyde and benzil should be the true intermediates in this transformation. Finally, when benzaldehyde, benzil, and ammonium acetate were subjected to standard conditions, the desired product was successfully isolated in 88% yield (Table 2, c).

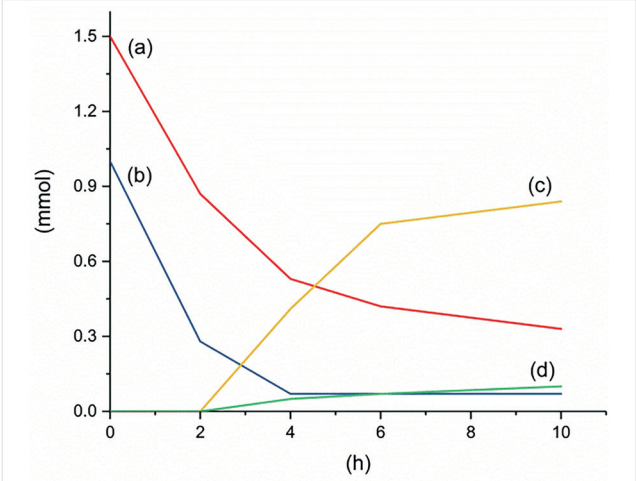
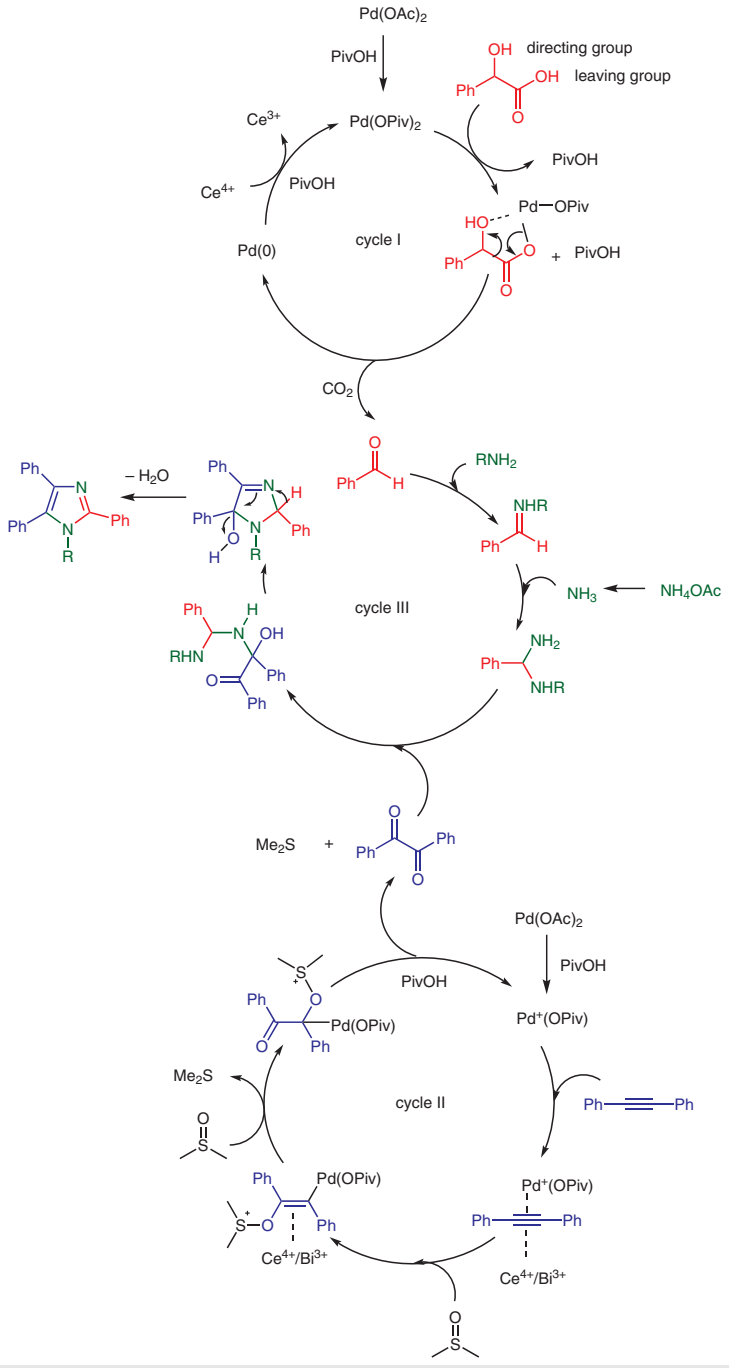


Figure 2 (a) α-Hydroxyphenylacetic acid, (b) diphenylacetylene, (c) 2,4,5-triphenyl-1*H*-imidazole, (d) 2,4,5-triphenyloxazole.

On the basis of above experimental results and previous reports,[13] a plausible mechanism for the formation of substituted imidazole from hydroxyphenylacetic acids, diphenylacetylene, and amines described herein is proposed in Scheme 4. In cycle I, the first process involves an anion exchange of pivalate with $Pd(OAc)_2$ to generate $Pd(OPiv)_2$. Further anion exchange of $Pd(OPiv)_2$ with hydroxyphenylacetic acid affords the palladium carboxylate intermediate, which undergoes a direct oxidative decarboxylation to the corresponding aryl aldehydes. In cycle II, the highly electrophilic cationic species $Pd^{+}(OPiv)$ is generated in situ through bonding pivalate by using PivOH as an additive.[12] The cationic $Pd^{+}(OPiv)$ species combines with Ce^{4+} and Bi^{3+} to form a $Pd(OPiv)_2/Ce^{4+}/Bi^{3+}$-π-complex intermediate,[13b] which should greatly activate the C≡C bond of the alkyne through the coordination to generate the acceptors of DMSO. The nucleophilic addition of DMSO to the thus generated π-complex intermediate followed by the release of Me_2S and the addition of another DMSO produces a keto alcohol-like intermediate, which proceeds to afford the corresponding diphenyl diketone derivatives along with the $Pd^{+}(OPiv)/Ce^{4+}/Bi^{3+}$ trimetallic species and Me_2S. Noticeably, the π-complex leads to a more efficient nucleophilic attack of DMSO onto the activated C≡C bond of the alkyne than $Pd(OAc)_2$ alone, thus affording more efficient alkyne oxidation. In cycle III, the reaction starts with formation of benz-

aldehyde and benzil from hydroxyphenylacetic acids (cycle I) and diphenylacetylene (cycle II), respectively. Then, the condensation of the benzaldehyde with primary amine and/or ammonia generates the diamine intermediate. Finally, the condensation of diamine intermediate with benzil generated in situ leads to cyclization, dehydration, and [1,5] hydrogen shift and eventually to the formation of substituted imidazoles.

In summary, a novel and facile $Pd(OAc)_2/Ce(SO_4)_2/Bi(NO_3)_3$ trimetallic catalytic system has been developed and applied to the construction of a diverse range of multisubstituted imidazoles starting from readily available α-hydroxyphenyl-



Scheme 4 Plausible mechanism

acetic acids, diphenylacetylene, primary amine, and ammonium acetate. Various substituents in α-hydroxyphenylacetic acids, anilines, and benzylamines are tolerated well in this approach. This operationally practical protocol might be a useful and widely applicable pathway to construct valuable scaffolds of complex molecules in medicinal, organic, and material chemistry.

All chemicals were purchased from Aladdin, Alfa Aesar, Inochem, and Acros and used without further purification. Reactions were carried out in a Schlenk tube equipped with a stirring bar. The reaction temperatures were maintained by thermostat-controlled oil baths. Reaction procedures were monitored by TLC and Shimadzu QP2010 plus gas chromatography–mass chromatography (GC-MS). Melting pointing was measured by an Electrothermal X6 microscopic digital melting pointing apparatus. ^{1}H NMR spectra were recorded on a Bruker 300 Advance spectrometer (300 MHz) at 25 °C with $CDCl_3$ or DMSO-d_6 as solvent and TMS as internal standard; their residual protons were designated to 7.26 and 2.52 ppm, respectively. ^{13}C NMR spectra were recorded on a Bruker 300 Advance spectrometer (100 MHz) at 25 °C with $CDCl_3$ or DMSO-d_6 as solvent; the chemical shifts were attributed to 77.16 ppm ($CDCl_3$) and 39.5 ppm (DMSO-d_6). Fourier transform infrared (FT-IR) spectra were recorded from KBr pellets on a Bruker Equinox-55 spectrophotometer.

2,4,5-Trisubstituted 1*H*-Imidazoles; General Procedure

1,2-Diphenlyacetylene (1.0 mmol), the respective α-hydroxyphenylacetic acid (1.5 mmol), pivalic acid (2.0 mmol), $Pd(OAc)_2$ (5 mol%), $Ce(SO_4)_2{\cdot}4H_2O$ (20 mol%), and $Bi(NO_3)_3$ (40 mol%) were dissolved in the reaction solvent [DMSO/H_2O (4:1 v/v), 2 mL] in a 25 mL Schlenk tube and the contents were stirred at 120 °C for 2 h. After that NH_4OAc (3.0 mmol), and for the preparation of 1-substituted product, the respective primary amine (1.0 mmol) were added and further stirred at 120 °C for 10 h. The process was tracked by TLC or GC-MS. Upon completion of the reaction, the mixture was cooled to r.t. and extracted with CH_2Cl_2. The combined organic phases were successively washed by brine and H_2O, and dried (Na_2SO_4). The solvent was removed on a rotary evaporator and the crude product was purified by PTLC or column chromatography using EtOAc/*n*-hexane (1:6, v/v) to afforded the desire pure product.

2,4,5-Triphenyl-1*H*-imidazole (5a)

White solid; yield: 248.8 mg (84%); mp 270–272 °C (Lit.[15] mp 270–273 °C).

IR (KBr): 3036, 2850, 1600, 1488, 1460 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.71 (s, 1 H), 8.10 (d, *J* = 8.0 Hz, 2 H), 7.60–7.26 (m, 13 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 145.94, 137.54, 135.62, 131.53, 130.79, 129.14, 128.92, 128.71, 128.66, 128.24, 127.52, 126.97, 125.63.

MS (ESI): *m*/*z* (%) = 297.2 [M + H]$^+$.

2-(4-Chlorophenyl)-4,5-diphenyl-1*H*-imidazole (5b)

Off-white solid; yield: 280.5 mg (85%); mp 264–265 °C (Lit.[15] mp 260–262 °C).

IR (KBr): 3025, 2837, 1600, 1487, 1449, 1085 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.98 (s, 1 H), 8.17 (d, *J* = 8.6 Hz, 2 H), 7.55 (d, *J* = 8.5 Hz, 6 H), 7.35 (dt, *J* = 14.5, 6.7 Hz, 6 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 144.91, 136.03, 133.18, 132.66, 130.06, 129.98, 129.63, 129.19, 128.87, 128.23, 127.69, 127.42.

MS (ESI): *m*/*z* (%) = 331.1 [M + H]$^+$.

2-(4-Bromophenyl)-4,5-diphenyl-1*H*-imidazole (5c)

Off-white solid; yield: 310.5 mg (83%); mp 261–262 °C (Lit.[16] mp 260–262 °C).

IR (KBr): 3025, 2837, 1604, 1485, 1448, 1088 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.81 (s, 1 H), 8.05 (d, *J* = 8.6 Hz, 2 H), 7.69 (d, *J* = 8.6 Hz, 2 H), 7.59–7.20 (m, 10 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 144.93, 137.79, 135.44, 132.14, 131.37, 129.99, 129.14, 129.07, 128.89, 128.67, 128.34, 127.57, 127.54, 127.08, 121.86.

MS (ESI): *m*/*z* (%) = 375.1 [M + H]$^+$.

2-(4-Methoxyphenyl)-4,5-diphenyl-1*H*-imidazole (5d)

Off-white solid; yield: 287.0 mg (88%); mp 232–234 °C (Lit.[15] mp 231–233 °C).

IR (KBr): 3025, 2961, 1612, 1496, 1449, 1255 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.54 (s, 1 H), 8.05 (d, *J* = 8.8 Hz, 2 H), 7.59–7.21 (m, 10 H), 7.06 (d, *J* = 8.8 Hz, 2 H), 3.82 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.87, 146.10, 137.23, 135.79, 131.71, 130.08, 129.98, 129.09, 128.82, 128.62, 128.12, 128.07, 127.52, 127.17, 126.87, 123.60, 114.55, 55.66.

MS (ESI): *m*/*z* (%) = 327.1 [M + H]$^+$.

4,5-Diphenyl-2-(*p*-tolyl)-1*H*-imidazole (5e)

Off-white solid; yield: 266.8 mg (86%); mp 227–229 °C (Lit.[15] mp 228–230 °C).

IR (KBr): 3035, 2857, 1602, 1500, 1487, 1449 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.62 (s, 1 H), 7.99 (d, *J* = 8.2 Hz, 2 H), 7.61–7.46 (m, 4 H), 7.47–7.20 (m, 8 H), 2.35 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 146.14, 138.13, 137.39, 135.72, 131.62, 129.71, 129.10, 128.87, 128.63, 128.40, 128.16, 127.53, 126.92, 125.63, 21.37.

MS (ESI): *m*/*z* (%) = 311.2 [M + H]$^+$.

2-(3-Nitrophenyl)-4,5-diphenyl-1*H*-imidazole (5f)

Orange solid; yield: 255.8 mg (75%); mp 312–314 °C (Lit.[16] mp 311–313 °C).

IR (KBr): 3441, 3055, 1599, 1485, 1448, 1365 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 13.11 (s, 1 H), 8.96 (s, 1 H), 8.52 (d, *J* = 7.9 Hz, 1 H), 8.22 (d, *J* = 8.3 Hz, 1 H), 7.79 (t, *J* = 8.0 Hz, 1 H), 7.60–7.24 (m, 10 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 148.80, 143.37, 136.00, 131.61, 130.85, 130.05, 129.95, 129.67, 129.16, 128.87, 128.72, 128.51, 127.59, 127.25.

MS (ESI): *m*/*z* (%) = 342.1 [M + H]$^+$.

2-(3-Methoxy-4-hydroxyphenyl)-4,5-diphenyl-1*H*-imidazole (5g)

White solid; yield: 287.4 mg (84%); mp 250–252 °C (Lit.[16] mp 254–256 °C).

IR (KBr): 3511, 3030, 2965, 1605, 1495, 1228 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.49 (s, 1 H), 7.68 (d, *J* = 2.0 Hz, 1 H), 7.62–7.50 (m, 5 H), 7.34 (t, *J* = 12.8 Hz, 5 H), 6.90 (d, *J* = 8.2 Hz, 1 H), 3.87 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 148.15, 147.56, 146.58, 128.85, 122.38, 118.85, 116.09, 109.80, 56.13.

MS (ESI): *m*/*z* (%) = 343.1 [M + H]$^+$.

2-(2-Chlorophenyl)-4,5-diphenyl-1*H*-imidazole (5h)

Pale yellow solid; yield: 271.3 mg (82%); mp 189–191 °C (Lit.[15] mp 190–192 °C).

IR (KBr): 3025, 2837, 1597, 1482, 1445, 1082 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.41 (dd, *J* = 7.9, 1.7 Hz, 1 H), 8.01–7.94 (m, 2 H), 7.68–7.61 (m, 1 H), 7.50 (t, *J* = 7.8 Hz, 2 H), 7.46–7.36 (m, 1 H), 7.38–7.32 (m, 5 H), 7.31–7.26 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.20, 134.94, 132.97, 130.90, 130.47, 129.93, 129.69, 129.63, 129.05, 128.69, 127.81, 127.60, 127.50.

MS (ESI): *m*/*z* (%) = 331.1 [M + H]$^+$.

2-(2-Methoxyphenyl)-4,5-diphenyl-1*H*-imidazole (5i)

White solid; yield: 277.2 mg (85%); mp 200–201 °C (Lit.[15] mp 200–202 °C).

IR (KBr): 3008, 2951, 1600, 1486, 1459, 1205 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.49 (dd, *J* = 7.8, 1.8 Hz, 1 H), 7.58 (s, 4 H), 7.41–7.22 (m, 8 H), 7.11 (td, *J* = 7.5, 1.0 Hz, 1 H), 7.02–6.99 (m, 1 H), 4.01 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.72, 144.05, 129.56, 128.65, 128.61, 127.81, 127.25, 126.82, 121.68, 118.11, 111.20, 55.91.

MS (ESI): *m*/*z* (%) = 327.1 [M + H]$^+$.

1,2,4,5-Tetraphenyl-1*H*-imidazole (5j)

Pale white solid; yield: 268.0 mg (72%); mp 216–217 °C (Lit.[17] mp 211–216 °C).

IR (KBr): 3055, 1600, 1500, 1350 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.65–7.54 (m, 2 H), 7.46–7.40 (m, 2 H), 7.28–7.17 (m, 12 H), 7.12 (dd, *J* = 7.5, 2.2 Hz, 2 H), 7.03 (dd, *J* = 7.6, 2.1 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.93, 138.25, 137.09, 134.40, 131.14, 130.87, 130.63, 130.48, 129.09, 128.99, 128.45, 128.37, 128.30, 128.28, 128.19, 128.13, 127.99, 127.44, 126.65.

MS (ESI): *m*/*z* (%) = 373.2 [M + H]$^+$.

2-(4-Chlorophenyl)-1,4,5-triphenyl-1*H*-imidazole (5k)

Yellow solid; yield: 301.1 mg (74%); mp 160–162 °C (Lit.[17] mp 160–165 °C).

IR (KBr): 3058, 3030, 2940, 1605, 1477, 1350, 1088 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.58 (d, *J* = 7.9 Hz, 2 H), 7.35 (d, *J* = 8.6 Hz, 2 H), 7.30–7.17 (m, 11 H), 7.11 (dd, *J* = 7.6, 2.1 Hz, 2 H), 7.03 (dd, *J* = 7.7, 2.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.76, 138.42, 136.87, 134.36, 134.20, 131.17, 131.09, 130.39, 130.12, 129.27, 128.94, 128.53, 128.40, 128.37, 128.23, 128.11, 127.39, 126.77.

MS (ESI): *m*/*z* (%) = 407.9 [M + H]$^+$.

2-(4-Methoxyphenyl)-1,4,5-triphenyl-1*H*-imidazole (5l)

White solid; yield: 307.7 mg (79%); mp 182–184 °C (Lit.[18] mp 183–185 °C).

IR (KBr): 3030, 1604, 1530, 1493, 1350 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.59 (d, *J* = 6.8 Hz, 2 H), 7.35 (d, *J* = 8.8 Hz, 2 H), 7.29–7.00 (m, 14 H), 6.76 (d, *J* = 8.8 Hz, 2 H), 3.76 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.61, 146.90, 137.97, 137.21, 134.46, 131.14, 130.73, 130.48, 130.35, 129.08, 128.49, 128.33, 128.20, 128.16, 127.90, 127.44, 126.57, 123.04, 113.56, 55.23.

MS (ESI): *m*/*z* (%) = 403.2 [M + H]$^+$.

2-(4-Methoxyphenyl)-4,5-diphenyl-1-(*p*-tolyl)-1*H*-imidazole (5m)

Pale white solid; yield: 349.6 mg (84%); mp 180–182 °C (Lit.[19] mp 176–178 °C).

IR (KBr): 3028, 1604, 1550, 1483, 1340 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.63–7.53 (m, 2 H), 7.36 (d, *J* = 8.9 Hz, 2 H), 7.21 (pd, *J* = 7.7, 7.0, 3.4 Hz, 6 H), 7.15–7.07 (m, 2 H), 7.03 (d, *J* = 8.1 Hz, 2 H), 6.90 (d, *J* = 8.2 Hz, 2 H), 6.76 (d, *J* = 8.9 Hz, 2 H), 3.76 (s, 3 H), 2.30 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.53, 146.93, 138.08, 137.88, 134.56, 131.15, 130.84, 130.54, 130.32, 129.70, 128.43, 128.30, 128.16, 128.13, 127.82, 127.42, 126.49, 123.19, 113.53, 55.22, 21.21.

MS (ESI): *m*/*z* (%) = 417.2 [M + H]$^+$.

1-(4-Methoxyphenyl)-4,5-diphenyl-2-(*p*-tolyl)-1*H*-imidazole (5n)

White solid; yield: 366.3 mg (88%); mp 170–172 °C (Lit.[20] mp 176–177 °C).

IR (KBr): 3030, 1604, 1547, 1473, 1342 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.59 (dd, *J* = 8.2, 1.4 Hz, 2 H), 7.38–7.01 (m, 12 H), 7.01–6.90 (m, 2 H), 6.81–6.69 (m, 2 H), 3.76 (s, 3 H), 2.30 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.04, 147.18, 138.07, 137.93, 134.56, 131.15, 130.88, 130.82, 129.98, 129.46, 128.84, 128.79, 128.33, 128.13, 127.83, 127.73, 127.40, 126.50, 114.17, 55.37, 21.31.

MS (ESI): *m*/*z* (%) = 417.2 [M + H]$^+$.

1-(4-Chlorophenyl)-2-(4-methoxyphenyl)-4,5-diphenyl-1*H*-imidazole (5o)

Yellow solid; yield: 375.0 mg (86%); mp 175–177 °C (Lit.[21] mp 176–177 °C).

IR (KBr): 3060, 2950, 1479, 1458, 1072 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.57 (dd, *J* = 8.2, 1.4 Hz, 2 H), 7.44–7.33 (m, 2 H), 7.30–7.17 (m, 8 H), 7.17–7.07 (m, 2 H), 7.01–6.89 (m, 2 H), 6.83–6.71 (m, 2 H), 3.77 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.26, 149.97, 145.86, 138.22, 134.25, 131.37, 131.10, 130.50, 130.06, 129.57, 129.37, 129.04, 128.40, 128.38, 128.20, 128.03, 127.35, 126.69, 114.36, 55.40.

MS (ESI): *m*/*z* (%) = 437.1 [M + H]$^+$.

1-(4-Methoxyphenyl)-2,4,5-triphenyl-1*H*-imidazole (5p)

Yellow solid; yield: 353.9 mg (88%); mp 175–176 °C (Lit.[21] mp 175–177 °C).

IR (KBr): 3030, 1600, 1525, 1495, 1348 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.59 (d, *J* = 7.7 Hz, 2 H), 7.45 (dd, *J* = 6.7, 3.0 Hz, 2 H), 7.32–7.08 (m, 6 H), 6.95 (d, *J* = 8.4 Hz, 2 H), 6.75 (d, *J* = 8.4 Hz, 2 H), 3.76 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.10, 147.05, 138.09, 134.49, 131.15, 131.09, 130.74, 130.58, 129.85, 129.43, 128.93, 128.36, 128.20, 128.16, 128.12, 127.91, 127.41, 126.57, 114.21, 55.38.

MS (ESI): *m*/*z* (%) = 403.2 $[M + H]^+$.

2,4,5-Triphenyl-1-(*p*-tolyl)-1*H*-imidazole (5q)

Light yellow solid; yield: 316.7 mg (86%); mp 177–179 °C (Lit.[15] mp 176–177 °C).

IR (KBr): 3038, 2850, 1599, 1498, 1485, 1448 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.59 (d, *J* = 7.7 Hz, 2 H), 7.44 (dd, *J* = 6.9, 2.9 Hz, 2 H), 7.28–7.10 (m, 11 H), 7.03 (d, *J* = 8.0 Hz, 2 H), 6.91 (d, *J* = 8.2 Hz, 2 H), 2.30 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.96, 138.18, 138.14, 134.46, 134.44, 131.15, 130.94, 130.73, 130.57, 129.71, 128.97, 128.34, 128.23, 128.16, 128.12, 128.09, 127.92, 127.44, 126.59, 21.21.

MS (ESI): *m*/*z* (%) = 387.2 $[M + H]^+$.

1-Benzyl-2,4,5-triphenyl-1*H*-imidazole (5r)

Yellow solid; yield: 309.0 mg (80%); mp 166–167 °C (Lit.[16] mp 161–163 °C).

IR (KBr): 3057, 1601, 1497, 1500, 1350 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.63 (dd, *J* = 6.7, 3.0 Hz, 2 H), 7.56 (d, *J* = 7.1 Hz, 2 H), 7.42–7.27 (m, 5 H), 7.25–7.05 (m, 9 H), 6.82–6.71 (m, 2 H), 5.08 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.10, 138.09, 137.57, 134.49, 131.10, 131.05, 130.96, 130.09, 129.10, 128.94, 128.83, 128.66, 128.63, 128.61, 128.12, 127.38, 126.82, 126.40, 126.04, 48.31.

MS (ESI): *m*/*z* (%) = 387.2 $[M + H]^+$.

1-Benzyl-2-(4-chlorophenyl)-4,5-diphenyl-1*H*-imidazole (5s)

White solid; yield: 319.2 mg (76%); mp 164–165 °C (Lit.[16] mp 160–162 °C).

IR (KBr): 3060, 3029, 2939, 1600, 1477, 1356, 1087 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.57 (dd, *J* = 7.8, 4.4 Hz, 4 H), 7.33 (t, *J* = 8.0 Hz, 5 H), 7.25–7.08 (m, 8 H), 6.85–6.75 (m, 2 H), 5.07 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.86, 138.29, 137.34, 135.01, 134.29, 131.04, 130.78, 130.47, 130.27, 129.40, 128.91, 128.87, 128.81, 128.75, 128.18, 127.55, 126.82, 126.55, 125.89, 48.32.

MS (ESI): *m*/*z* (%) = 421.1 $[M + H]^+$.

1-Benzyl-2-(4-bromophenyl)-4,5-diphenyl-1*H*-imidazole (5t)

Light yellow solid; yield: 362.0 mg (78%); mp 170–172 °C (Lit.[16] mp 171–174 °C).

IR (KBr): 3059, 3029, 2940, 1598, 1476, 1356, 1069 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.52 (d, *J* = 13.1 Hz, 6 H), 7.35–7.11 (m, 11 H), 6.79 (d, *J* = 6.5 Hz, 2 H), 5.07 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.88, 138.36, 137.33, 134.31, 131.82, 131.04, 130.77, 130.52, 130.50, 129.86, 128.91, 128.82, 128.76, 128.70, 128.18, 127.56, 126.82, 126.56, 125.87, 123.29, 48.32.

MS (ESI): *m*/*z* (%) = 465.1 $[M + H]^+$.

1-Benzyl-2-(4-methoxyphenyl)-4,5-diphenyl-1*H*-imidazole (5u)

White solid; yield: 349.4 mg (84%); mp 158–160 °C (Lit.[16] mp 159–161 °C).

IR (KBr): 3026, 1605, 1531, 1493, 1350 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.62–7.51 (m, 4 H), 7.34–7.27 (m, 3 H), 7.23–7.12 (m, 8 H), 6.93–6.86 (m, 2 H), 6.85–6.75 (m, 2 H), 5.06 (s, 2 H), 3.78 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.12, 148.04, 137.84, 137.69, 134.57, 131.14, 131.09, 130.45, 129.80, 128.80, 128.62, 128.59, 128.10, 127.35, 126.82, 126.33, 126.01, 123.38, 114.04, 55.34, 48.24.

MS (ESI): *m*/*z* (%) = 417.2 $[M + H]^+$.

1-Benzyl-4,5-diphenyl-2-(*p*-tolyl)-1*H*-imidazole (5v)

Brown solid; yield: 349.4 mg (80%); mp 162–165 °C (Lit.[16] mp 165–168 °C).

IR (KBr): 3026, 2925, 1598, 1482, 1330 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.62–7.49 (m, 4 H), 7.35–7.08 (m, 13 H), 6.84–6.75 (m, 2 H), 5.09 (s, 2 H), 2.36 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.98, 148.21, 138.86, 137.92, 137.66, 134.51, 131.09, 129.90, 129.30, 128.96, 128.78, 128.57, 128.08, 127.99, 127.32, 126.81, 126.33, 126.01, 48.28, 21.39.

MS (ESI): *m*/*z* (%) = 401.2 $[M + H]^+$.

1-Benzyl-2-(2-methoxyphenyl)-4,5-diphenyl-1*H*-imidazole (5w)

Yellow solid; yield: 330.0 mg (80%); mp 176–178 °C (Lit.[22] mp 175–178 °C).

IR (KBr): 3028, 1600, 1534, 1490, 1352 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.57 (d, *J* = 5.0 Hz, 3 H), 7.48 (d, *J* = 5.1 Hz, 1 H), 7.28–7.01 (m, 11 H), 6.98 (t, *J* = 5.0 Hz, 1 H), 6.92 (d, *J* = 5.7 Hz, 1 H), 6.67–6.62 (m, 2 H), 4.92 (s, 2 H), 3.76 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.47, 145.61, 137.81, 137.39, 134.67, 132.83, 131.41, 131.15, 130.94, 129.07, 128.75, 128.60, 128.44, 128.12, 127.99, 127.04, 126.76, 126.62, 126.14, 120.97, 110.94, 55.51, 48.24.

MS (ESI): *m*/*z* (%) = 417.2 $[M + H]^+$.

1-Benzyl-2-(2-nitrophenyl)-4,5-diphenyl-1*H*-imidazole (5x)

Brown solid; yield: 327.7 mg (76%); mp 150–153 °C (Lit.[23] mp 152–155 °C).

IR (KBr): 3025 1608, 1530, 1490, 1353 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.12–8.06 (m, 1 H), 7.57–7.48 (m, 3 H), 7.45–7.30 (m, 6 H), 7.22–7.07 (m, 5 H), 6.72 (dd, *J* = 7.5, 2.0 Hz, 2 H), 4.87 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.98, 143.07, 138.09, 136.62, 134.17, 133.28, 133.08, 131.16, 130.66, 130.42, 130.13, 129.00, 128.87, 128.45, 128.12, 127.55, 126.71, 126.55, 126.49, 124.72, 48.36.

MS (ESI): *m*/*z* (%) = 432.2 $[M + H]^+$.

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Supporting Information

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