JOC The Journal of Organic Chemistry

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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.0c00316 • Publication Date (Web): 13 Apr 2020

Just Accepted

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Electrochemical HI-Mediated Intermolecular C-N Bond Formation to Synthesize Imidazoles from Aryl Ketones and Benzylamines

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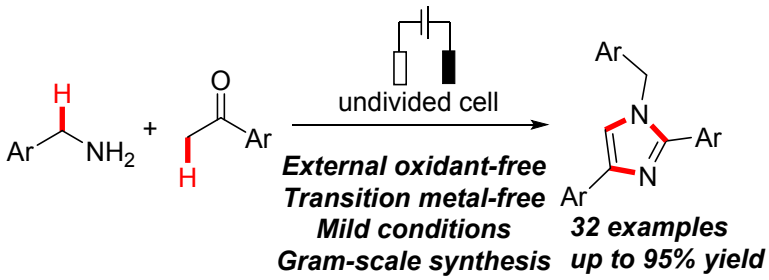


ABSTRACT

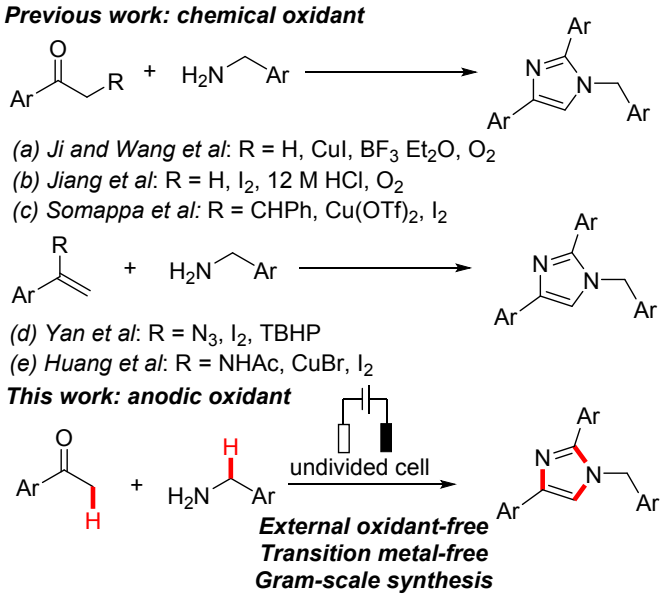
An efficient and novel electrochemical oxidative tandem cyclization of aryl ketones and benzylamines for the synthesis of 1,2,4-trisubstituted-(1*H*)-imidazoles has been developed under metal- and oxidant-free conditions. This direct C-N bond formation strategy, with a broad functional group tolerance, afford the desired imidazoles in moderate to excellent yields.

INTRODUCTION

Recently, the C-N bond formation has drawn attention for the construction of nitrogen-containing molecules *via* direct C-H amination.[1] Compared with the Ullmann, Buchwald and Hartwig reaction,[2] the direct C-H amination, especially the C-H/N-H coupling reaction, provided a green and atom-economical approach for the synthesis of various functional nitrogen-containing skeleton.[3]

Imidazoles are an important class of nitrogen heterocycles owing to their biological and pharmacological activities, such as antitumor, antiplasmodium, antifungal and PPARδ modulator.[4] In addition, the imidazoles has also been used in materials and organic chemistry.[5] Accordingly, various of method have been developed for the synthesis of 1,2,4-trisubstituted-(1*H*)-imidazoles. Ji reported a CuI/BF_3•Et_2O-co-catalyzed tandem C-N cyclization reaction of ketones with benzylamines for the construction of 1,2,4-trisubstituted-(1*H*)-imidazoles under neat conditions and in the presence of O_2 (scheme 1a).[6] Jiang described a metal-free method for the synthesis of imidazoles from ketones and benzylamines using I_2 and 12 M HCl (scheme 1b).[7] The $Cu(OTf)_2/I_2$-catalyzed C=C bond cleavage for the synthesis of imidazoles from chalcones and benzylamines have also been developed (scheme 1c).[8] Moreover, the imidazoles have been synthesized form benzylamines with vinyl azides or

enamides have also been prepared by Yan and Huang, respectively (scheme 1d and 1e).[9] However, these strategies suffer from stoichiometric chemical oxidants, heavy metal residues and functionalized starting materials. Thus, the development of green and efficient multiple-component strategy for the synthesis of imidazoles under metal-free and oxidant-free conditions is highly desirable.



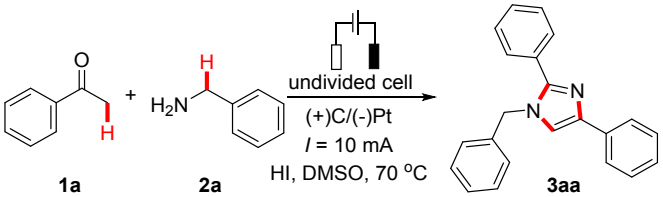
Scheme 1. Method for the synthesis of 1,2,4-trisubstituted imidazoles

Electrosynthesis has enabled as a useful synthetic tool for the assembly of valuable chemical transformations *via* anodic oxidant process.[10] Recently, various anodic oxidation cyclization reaction has been developed for the synthesis of nitrogen containing heterocycles via C-N bond formation.[11] On the other hand, the electrochemical promoted formation C-N bond for the synthesis of heterocyclic compounds such as imidazoles, are extremely limited. Yu developed an electrochemically mediated synthesis of imidazo[1,2-a]pyridines from acetophenones, unsatruated and alkyl ketones with 2-aminopyridines through the intermolecular C-N bond formation.[12] Wang reported an electrochemical tandem cyclization for the construction of imidazo[1,5-a]quinolines in the presence of iodine.[13] Inspired by these studies and our previous works[14], herein, we disclosed the electrochemical oxidative transformation of aryl ketones with benzylamines into 1,2,4-trisubstituted-(1*H*)-imidazoles under transition metal and oxidant free conditions.

RESULTS AND DISCUSSION

Initially, the reaction of acetophenone (**1a**) with benzylamine (**2a**) as model substrates in an undivided cell under 10 mA constant current using HI as the catalyst, *n*-$BuNBF_4$ as the electrolyte, C(+)/Pt(-) as the electrodes in DMSO at 70 °C for 6 h was studied, the desired product **3aa** was obtained in 83% yield (table 1, entry 1). When PTSA (*p*-toluenesulfonic acid) instead of HI as the catalyst, no target product was found (table 1, entry 2). Further, a series of iodine slats were screened, such as, KI, TBAI (tetrabutylammonium iodide) and TBAI/HOAc, no significant increase of product **3aa** was observed (table 1, entries 3-5). The effect of electrolytes was also investigated, and *n*-$BuNBF_4$ showed better result for this transformation (table 1, entries 6-7). Either increasing or decreasing the electric current resulted in a lower yield of **3aa** (table 1, entries 8-9). No desired imidazole was detected when the reaction was carried without HI (table 1, entry 10). The lower yield was afforded by increasing or decreasing the amount of HI (table 1, entries 11-12). When the reaction carried at 60 °C, the product of **3aa** was obtained in 56% yield (table 1, entry 13). No significant improvement of the yield of **3aa** with higher temperature (table 1, entry 14). Furthermore, EtOH and MeCN as solvent were examined, and DMSO gave the best result (table 1, entries 15-16). Used Pt or Ni plate instead of carbon rod as an anode, the yield of corresponding product was decreased (table 1, entries 17-18). Notably, no desired product was afforded in the absence of electric current , and the oxazole obtained in 7% yield. (table 1, entry 19). Additionally, a 5 mmol scale reaction of **1a** with **2a** was carried out, affording the desired product in 71% yield (table 1, entry 20).

Table 1. Screening of Optimal Conditions[a]



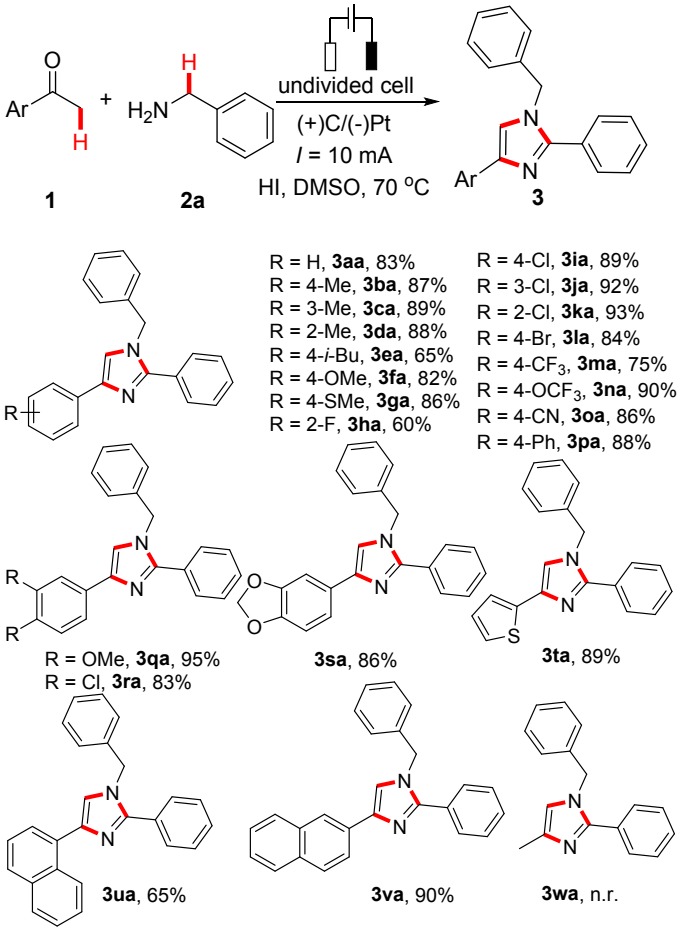
Entry	Variation from the standard conditions	Yield [%]
1	none	83
2	PTSA instead of HI	N. R.

3	KI instead of HI	47
4	TBAI instead of HI	13
5	TBAI, HOAc (20 mol%) instead of HI	55
6	KI instead of *n*-$BuNBF_4$	75
7	$LiClO_4$ instead of *n*-$BuNBF_4$	51
8	I = 15 mA instead of I = 10 mA, 4 h	63
9	I = 5 mA instead of I = 10 mA, 10 h	60
10	no HI	N. R.
11	HI (50 mol%)	72
12	HI (10 mol%)	45
13	At 60 °C	56
14	At 80 °C	74
15	EtOH instead of DMSO	77
16	MeCN instead of DMSO	trace
17	(+)Pt/(−)Pt instead of (+)C/(−)Pt, 10 mA/cm^2	72
18[b]	(+)Ni/(−)Pt instead of (+)C/(−)Pt, 10 mA/cm^2	75
19	no electric current, 24 h	N. R.
20[c]	none	71

[a]Reaction conditions: carbon rod anode, Pt plate cathode (1cm×1cm), undivided cell, I = 10 mA (10 mA/cm^2), **1a** (0.3 mmol), **2a** (1.2 mmol), HI (20 mol%, 50% aq), *n*-$BuNBF_4$ (0.1 mmol), DMSO (10 mL), under air atmosphere at 70 °C for 6 h, 7.5 F/mol. [b]Ni plate anode (1cm×1cm). [c]**1a** (5 mmol).

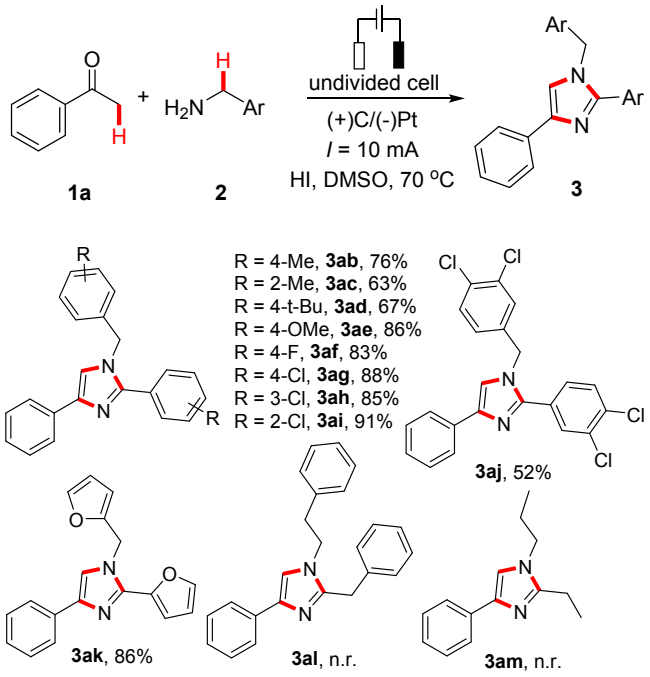
With the optimized protocol in hand, various kinds of aryl ketones with benzylamine were examined in **scheme 2**. Various substituted aryl ketones bearing electron-donating or electron-withdrawing groups were tested, furnishing the imidazoles **3aa-3sa** in moderate to excellent yields. Surprisingly, the aryl ketone brings thio- group reacted with **2a** smoothly to afford **3ga** in 86% yield, which indicated that the oxidation pecks of starting materials is lower than the thio- group. It is worth mentioning that halogen-substituted ketones **3ha-3la** (F, Cl, Br) were also tolerated in this electrochemical transformation, but 2-F substituted ketone gave slightly lower yield. The electron deficient 4-acetylbenzonitrile was used with **2a**, the product **3oa** was prepared in 86% yied. In addition, heterocyclic,1-naphthyl and 2-naphthyl derived ketone gave the corresponding product **3ta-3va** in 89%, 65% and 90% yield, respectively. However, when aliphatic ketone was employed, no desired product **3wa** was obtained, likely due to the low activity of aliphatic ketone under the present conditions.

Scheme 2. Substrate scope of aryl ketones[a]

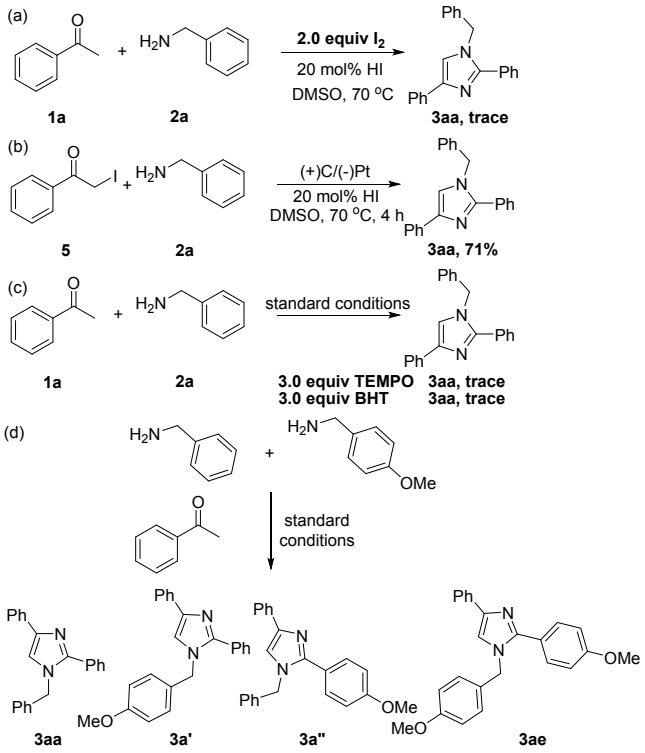


Furthermore, acetophenone with a variety of benzylamines were tested under electrolytic conditions. As shown in **scheme 3**, benzylamine derivatives with various functional groups such as -Me, -*t*-Bu, -OMe, -F, -Cl were subjected to the reaction, a moderate to good yield of corresponding products **3ab-3ai** were provided. When (3,4-dichlorophenyl)-methanamine **2j** reacted with acetophenone **1a** under optimized protocol, the 1,2,4-trisubstitued imidazole **3aj** was achieved in 52% yield. Moreover, heterocyclic methanamine performed smoothly with **1a**, furnishing the corresponding product **3ak** in good yield. However, phenylethylamine and *n*-propylamine are not afford the desired product after the reaction.

Scheme 3. Substrate scope of benzylamines[a]

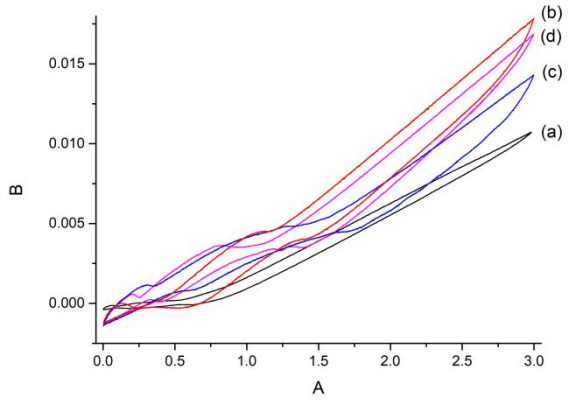


To get insight into the electrochemical oxidative C-N bond formation reaction, several control experiments were carried out (**scheme 4**). Firstly, **1a** and **2a** reacted with stoichiometric iodine as oxidant, 20 mol% HI as catalyst, no desired product **3aa** was detected, and afford the oxazole in 45% yield[3f] (**scheme 4a**). Moreover, 2-iodo-acetopheneone **5** instead of **1a** was investigated under electrochemical conditions, the 1*H*-imidazole was obtained in 71% yield (**scheme 4b**). In addition, 3.0 equiv of TEMPO (2,2,6,6-tetramethylpiperidin-1-oxyl) and BHT (2,6-di-tert-butyl-4-methylphenol) was added to the electrochemical reaction and only trace of **3aa** was isolated (**scheme 4c**). The competition experiment of acetophenone, benzylamine with 4-methoxybenzylamine were examined, only 43% yield of **3aa** was observed (**scheme 4d**).



Scheme 4. Control experiments

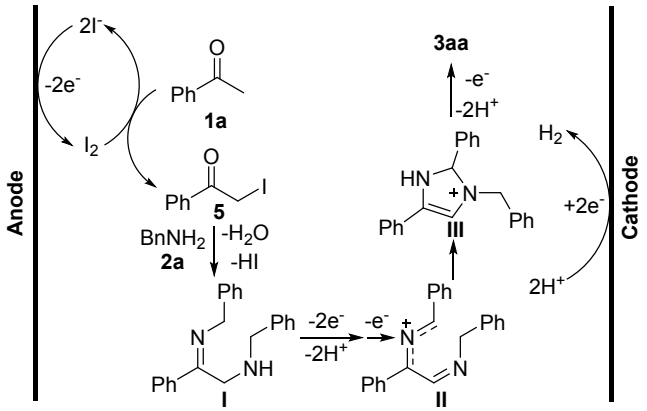
To further understand the electrochemical oxidative C-N bond formation process, cyclic voltammograms were performed in scheme 5. The CV of HI (curve b) exhibited two oxidation peaks at 0.12 v and 1.1 v *vs* Ag/AgCl. The mixture of HI with **1a** presented two oxidation peaks at 0.31 v and 1.29 v *vs* Ag/AgCl (curve c), the pecks of 1.29 v may result from 2-iodo-acetopheneone. In addition, the oxidation peck of the mixture of HI, **1a** and **2a** was observed at 0.81 v *vs* Ag/AgCl (curve d), due to the reaction of the mixture is in progress.



Scheme 5. Cyclic voltammogram recorded on (+)C/(-)Pt in *n*-BuNBF$_4$ (0.1 mmol)/DMSO (10 mL) at 70 °C;

Ag/AgCl as reference electrode, at 25 mV/s scan rate: (a) background; (b) HI (0.06 mmol) ; (c) HI (0.06 mmol) + 1a (0.3 mmol); (d) HI (0.06 mmol) + 1a (0.3 mmol) + 2a (1.2 mmol).

Based on our experimental results and previous works[15], a plausible reaction mechanism for electrochemical oxidative tandem cyclization of aryl ketones and benzylamines was proposed in **scheme 6**. Firstly, the molecular iodine is generated *via* the anodic oxidation of I^-.[14] Then, molecular iodine reacted with **1a** to formed the 2-iodo-acetopheneone **5**,[11] which undergoes nucleophilic substitution/condensation with **2a** to afford the intermediate **I**. Subsequently, intramolecular oxidative cyclization of the intermediate **I** to give the intermediate **III**. Finally, the proton elimination/oxidation of the intermediate **III** generated the final product **3aa**.



Scheme 6. Proposed reaction mechanism

In summary, we have discovered a novel and efficient protocol for the synthesis of 1,2,4-trisubstituted-(1*H*)-imidazoles *via* electrochemical oxidative C-N bond formation reaction under metal- and oxidant-free conditions by using readily available starting materials. This approach exhibited a wide of functional groups tolerance and provided access to various imidazoles in moderate to excellent yields.

EXPERIMENTAL SECTION

General methods: ^{1}H, ^{13}C and ^{19}F spectra were recorded a Bruker AVANCE II 400 MHz spectrometer using $CDCl_3$ as the solvent and TMS as an internal standard. HRMS were obtained from the Bruker micrOTOF-Q II. All reagents and solvents are commercially available compounds and without further purification. Melting points were recorded a X-4 instrument and were uncorrected.

General procedure: A 25 mL two-necked flask, equipped with Pt plate cathode (1cm×1cm), carbon rod anode (ϕ 6 mm), and a magnetic stir bar. The mixture of acetophenone (0.3 mmol, 36 mg), benzylamine (1.2 mmol, 129 mg), HI (0.06 mmol, 7.7 mg), *n*-$BuNBF_4$ (0.1 mmol, 33.0 mg) and DMSO (10 mL) was stirred at a constant current of 10 mA under air at 70 °C (metal bath) for 6 h. Upon completion, the mixture was cooled to room temperature, washed with water, extracted with EtOAc (15 mL×3), dried with anhydrous Na_2SO_4, and concentrated. The desired product **3** was obtained by column chromatography (PE/EtOAc=15:1).

Gram-Scale synthesis of 3aa. In 250 mL three-necked flask, equipped with (+)C/(-)Pt electrode, with **1a** (5.0 mmol, 601 mg), **2a** (20 mmol, 2.14 g), HI (1.0 mmol, 128 mg), *n*-$BuNBF_4$ (1.5 mmol, 494 mg) and DMSO (100 mL). The mixture was stirred at a constant current of 10 mA under air at 70 °C (metal bath). Upon completion (monitored by TLC), the mixture was cooled to room temperature, washed with water, extracted with EtOAc (40 mL×3), dried with anhydrous Na_2SO_4, concentrated, and purified. The desired product **3aa** was obtained in 71% (1.10 g) yield.

1-benzyl-2,4-diphenyl-1*H*-imidazole (**3aa**).[6] Yellow solid, yield 83% (77 mg, PE/EtOAc=15:1 as eluent), mp 116 - 117 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.6 Hz, 2H), 7.59 (dd, *J* = 6.3, 2.7 Hz, 2H), 7.43 - 7.21 (m, 10H), 7.11 (d, *J* = 7.1 Hz, 2H), 5.18 (s, 2H).^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 148.7, 141.5, 136.9, 134.0, 130.4, 129.1, 129.1, 128.7, 128.6, 128.0, 126.9, 126.7, 125.0, 116.9, 50.5.

1-benzyl-2-phenyl-4-(p-tolyl)-1*H*-imidazole (**3ba**).[6] Yellow solid, yield 87% (85 mg, PE/EtOAc=15:1 as eluent), mp 126 - 127 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.1 Hz, 2H), 7.57 (m, 2H), 7.34 (dm, 3H), 7.32 - 7.25 (m, 3H), 7.16 - 7.12 (m, 3H), 7.05 (m, 2H), 5.09 (s, 2H), 2.30 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 148.5, 141.7, 137.1, 136.5, 130.6, 129.1, 129.1, 129.0,

128.7, 128.5, 128.3, 128.04, 126.8, 125.0, 116.6, 50.5, 21.41.

1-benzyl-2-phenyl-4-(m-tolyl)-1*H*-imidazole (**3ca**).[9b] Yellow solid, yield 89% (87 mg, PE/EtOAc=15:1 as eluent), mp 125 - 126 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.57 (m, 3H), 7.36 (m, 3H), 7.32 - 7.25 (m, 3H), 7.20 - 7.16 (m, 2H), 7.10 - 7.00 (m, 3H), 5.12 (s, 2H), 2.34 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 148.5, 141.6, 138.1, 136.9, 133.9, 130.4, 129.0, 129.0, 128.6, 128.4, 128.3, 127.9, 127.62, 126.6, 125.7, 122.1, 116.9, 50.4, 21.5.

1-benzyl-2-phenyl-4-(o-tolyl)-1*H*-imidazole (**3da**).[7] Yellow solid, yield 88% (86 mg, PE/EtOAc=15:1 as eluent), mp 112 - 114 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 6.8 Hz, 1H), 7.65 - 7.58 (m, 2H), 7.40 - 7.37 (m, 3H), 7.34 - 7.28 (m, 3H), 7.23 - 7.15 (m, 3H), 7.13 - 7.07 (m, 3H), 5.21 (s, 2H), 2.48 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 147.8, 140.9, 137.1, 134.9, 133.5, 130.8, 130.5, 129.1, 129.0, 129.0, 128.7, 128.6, 128.0, 126.9, 126.6, 126.0, 119.7, 50.5, 22.0.

1-benzyl-4-(4-isobutylphenyl)-2-phenyl-1*H*-imidazole (**3ea,** PE/EtOAc=15:1 as eluent).[7] Yellow solid, yield 65% (71 mg), mp 111 - 113 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.1 Hz, 2H), 7.59 (dd, *J* = 6.5, 3.2 Hz, 2H), 7.41 (m, 3H), 7.39 - 7.30 (m, 4H), 7.22 (s, 1H), 7.18 - 7.13 (m, 3H), 5.22 (s, 2H), 2.47 (d, *J* = 7.2 Hz, 2H), 1.87 (m, 1H), 0.91 (s, 3H), 0.89 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 148.5, 141.7, 140.4, 136.9, 131.4, 130.4, 129.4, 129.0, 129.0, 129.0, 128.6, 128.0, 126.7, 124.7, 116.5, 50.5, 45.2, 30.3, 22.4.

1-benzyl-4-(4-methoxyphenyl)-2-phenyl-1*H*-imidazole (**3fa**).[6] Yellow solid, yield 82% (84 mg, PE/EtOAc=10:1 as eluent), mp 146 - 148 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 - 7.72 (m, 2H), 7.63 - 7.55 (m, 2H), 7.40 (dd, *J* = 5.1, 1.9 Hz, 3H), 7.33 (dd, *J* = 5.3, 2.2 Hz, 3H), 7.17 - 7.10 (m, 3H), 6.94 - 6.87 (m, 2H), 5.18 (s, 2H), 3.80 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 158.7, 148.5, 141.4, 137.0, 130.5, 129.0, 129.0, 129.0, 128.7, 128.0, 127.0, 126.7, 126.2, 115.9, 114.0, 55.3, 50.5.

1-benzyl-4-(4-(methylthio)phenyl)-2-phenyl-1*H*-imidazole (**3ga**). Yellow solid, yield 86% (92 mg, PE/EtOAc=10:1 as eluent), mp 158 - 159 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 - 7.71 (m, 2H), 7.62 - 7.55 (m, 2H), 7.40 (dt, *J* = 4.6, 2.8 Hz, 3H), 7.32 (pd, *J* = 5.9, 5.1, 2.4 Hz, 3H), 7.26 - 7.23 (m, 2H), 7.19 (s, 1H), 7.14 - 7.07 (m, 2H), 5.17 (s, 2H), 2.46 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 148.7, 141.1, 136.8, 136.5, 131.2, 130.4, 129.1, 129.1, 129.0, 128.7, 128.0, 127.0, 126.7, 125.4, 116.7, 50.5, 16.1. HRMS (ESI-TOF) m/z calcd for $C_{23}H_{21}N_2S$ $[M+H]^+$ 357.1420, found 357.1415.

1-benzyl-4-(2-fluorophenyl)-2-phenyl-1*H*-imidazole (**3ha**).[9a] Yellow solid, yield 60% (59 mg, PE/EtOAc=15:1 as eluent), mp 68 - 69 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 - 8.23 (m, 1H), 7.60 (m, 2H), 7.48 (d, *J* = 4.0 Hz, 1H), 7.42 (m, 3H), 7.34 (m, 3H), 7.23 - 7.18 (m, 2H), 7.16 - 7.04 (m, 3H), 5.24 (s, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 159.7 (d, *J* = 245.8 Hz) 148.1, 136.8, 135.0 (d, *J* = 1.9 Hz), 130.3, 129.1, 129.0 (d, *J* = 2.8 Hz), 128.7, 128.0, 127.7 (d, *J* = 4.3 Hz), 127.6 (d, *J* = 8.5 Hz), 126.6, 124.3 (d, *J* = 3.1 Hz), 121.2 (d, *J* = 14.3 Hz), 115.4 (d, *J* = 22.0 Hz), 50.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ -114.55.

1-benzyl-4-(4-chlorophenyl)-2-phenyl-1*H*-imidazole (**3ia**).[6] Yellow solid, yield 89% (92 mg, PE/EtOAc=15:1 as eluent), mp 125 - 127 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 - 7.68 (m, 2H), 7.65 - 7.55 (m, 2H), 7.45 - 7.39 (m, 3H), 7.32 (m, 5H), 7.20 (s, 1H), 7.11 (m, 2H), 5.18 (s, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 148.8, 140.5, 136.7, 132.7, 132.3, 130.3, 129.2, 129.1, 129.0, 128.7, 128.7, 128.1, 126.7, 126.2, 117.02, 50.6.

1-benzyl-4-(3-chlorophenyl)-2-phenyl-1*H*-imidazole (**3ja**).[9a] Yellow solid, yield 92% (95 mg, PE/EtOAc=15:1 as eluent), mp 97 - 98 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.62 - 7.60 (d, *J* = 7.6 Hz, 1H), 7.49 - 7.47 (m, 2H), 7.33 - 7.32 (m, 3H), 7.28 - 7.26 (m, 3H), 7.25 (s, 2H), 7.21 - 7.13 (m, 1H), 7.07 - 7.04 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 148.7, 139.8, 136.3, 135.5, 134.3, 130.2, 129.7, 129.0, 128.9, 128.9, 128.5, 128.2, 128.0, 126.5, 124.9, 123.0, 117.4, 60.3.

1-benzyl-4-(2-chlorophenyl)-2-phenyl-1*H*-imidazole (**3ka**).[9a] Yellow solid, yield 93% (96 mg, PE/EtOAc=15:1 as eluent), mp 60 - 62 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.73 (s, 1H), 7.58 (dd, *J* = 6.6, 3.0 Hz, 2H), 7.38 (dd, *J* = 5.2, 1.7 Hz, 4H), 7.33 - 7.24 (m, 4H), 7.15 - 7.07 (m, 3H), 5.19 (s, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 147.8, 137.5, 136.9, 132.5, 130.8, 130.3, 130.2, 129.8, 129.1, 129.1, 129.1, 128.7, 128.0, 127.6, 127.0, 126.6, 121.74, 50.6.

1-benzyl-4-(4-bromophenyl)-2-phenyl-1*H*-imidazole

(**3la**).[7] Yellow solid, yield 84% (98 mg, PE/EtOAc=15:1 as eluent), mp 164 - 166 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (dd, *J* = 8.8, 2.1 Hz, 2H), 7.58 (dd, *J* = 6.6, 3.0 Hz, 2H), 7.46 (d, *J* = 8.6 Hz, 2H), 7.43 - 7.38 (m, 3H), 7.32 (dd, *J* = 9.7, 7.3 Hz, 3H), 7.21 (s, 1H), 7.11 (d, *J* = 6.6 Hz, 2H), 5.18 (s, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 148.9, 140.5, 136.7, 133.1, 131.6, 130.2, 129.2, 129.1, 129.1, 129.0, 128.7, 128.1, 126.74, 126.7, 126.5, 120.5, 117.1, 50.6.

1-benzyl-2-phenyl-4-(4-(trifluoromethyl)phenyl)-1H-imidazole (**3ma**).[6] Yellow solid, yield 75% (85 mg, PE/EtOAc=12:1 as eluent), mp 133 - 135 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.1 Hz, 2H), 7.64 - 7.57 (m, 4H), 7.48 - 7.41 (m, 3H), 7.34 - 7.28 (m, 4H), 7.13 (d, *J* = 6.7 Hz, 2H), 5.22 (s, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 149.2, 140.3, 137.6, 136.6, 130.2, 129.4, 129.2, 129.1, 128.9, 128.7, 128.5, 128.3, 126.8, 125.6 (q, *J* = 3.8 Hz), 125.0, 118.1, 50.7. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.24.

1-benzyl-2-phenyl-4-(4-(trifluoromethoxy)phenyl)-1*H*-imidazole (**3na**). Yellow solid, yield 90% (106 mg, PE/EtOAc=10:1 as eluent), mp 165 - 167 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.7 Hz, 2H), 7.59 (dd, *J* = 6.5, 2.8 Hz, 2H), 7.42 (dt, *J* = 5.9, 3.5 Hz, 3H), 7.33 (dq, *J* = 10.6, 5.0, 3.6 Hz, 3H), 7.25 - 7.18 (m, 3H), 7.11 (d, *J* = 6.9 Hz, 2H), 5.20 (s, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 148.9, 148.0, 148.0, 140.3, 136.7, 133.0, 130.2, 129.2, 129.1, 129.0, 128.7, 128.1, 126.7, 126.2, 121.2, 117.1, 50.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ -57.78. HRMS (ESI-TOF) m/z calcd for $C_{23}H_{18}N_2F_3O$ $[M+H]^+$ 395.1366, found 395.1371.

4-(1-benzyl-2-phenyl-1*H*-imidazol-4-yl)benzonitrile (**3oa**). Yellow solid, yield 86% (86 mg, PE/EtOAc=12:1 as eluent), mp 152 - 154 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 - 7.87 (m, 2H), 7.67 - 7.57 (m, 4H), 7.47 - 7.41 (m, 3H), 7.40 - 7.32 (m, 4H), 7.17 - 7.10 (m, 2H), 5.23 (s, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 149.4, 139.6, 138.5, 136.4, 132.5, 129.9, 129.5, 129.2, 129.0, 128.8, 128.3, 126.8, 125.2, 119.4, 118.73, 109.7, 50.7. HRMS (ESI-TOF) m/z calcd for $C_{23}H_{18}N_3$ $[M+H]^+$ 336.1495, found 336.1489.

4-([1,1'-biphenyl]-4-yl)-1-benzyl-2-phenyl-1*H*-imidazole (**3pa**).[9b] Yellow solid, yield 88% (100 mg, PE/EtOAc=15:1 as eluent), mp 128 - 130 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.3 Hz, 2H), 7.61 (dd, *J* = 8.0, 4.2 Hz, 6H), 7.46 - 7.39 (m, 5H), 7.37 - 7.29 (m, 4H), 7.26 (s, 1H), 7.12 (d, *J* = 6.8 Hz, 2H), 5.20 (s, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 148.8, 141.2, 141.0, 139.5, 136.9, 133.1, 130.4, 129.1, 129.1, 128.8, 128.7, 128.1, 127.3, 127.1, 126.9, 126.7, 125.34, 117.1, 50.6.

1-benzyl-4-(3,4-dimethoxyphenyl)-2-phenyl-1*H*-imidazole (**3qa**).[8] Yellow solid, yield 95% (105 mg, PE/EtOAc=8:1 as eluent), mp 105 - 107 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 - 7.45 (m, 2H), 7.36 (d, *J* = 1.8 Hz, 1H), 7.28 (dd, *J* = 5.1, 1.8 Hz, 3H), 7.25 - 7.15 (m, 4H), 7.05 (s, 1H), 6.99 (d, *J* = 6.8 Hz, 2H), 6.74 (d, *J* = 8.4 Hz, 1H), 5.05 (s, 2H), 3.82 (s, 3H), 3.75 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 149.1, 148.4, 148.1, 141.4, 137.0, 130.5, 129.0, 128.7, 128.0, 127.4, 126.6, 117.3, 116.2, 111.3, 108.4, 56.0, 55.9, 50.4.

1-benzyl-4-(3,4-dichlorophenyl)-2-phenyl-1*H*-imidazole (**3ra**).[9b] Yellow solid, yield 83% (94 mg, PE/EtOAc=12:1 as eluent), mp 132 - 134 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 1.7 Hz, 1H), 7.64 - 7.54 (m, 3H), 7.45 - 7.29 (m, 7H), 7.21 (s, 1H), 7.11 (d, *J* = 7.0 Hz, 2H), 5.18 (s, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 149.06, 139.36, 136.5, 134.3, 132.7, 130.5, 130.2, 130.1, 129.3, 129.2, 129.0, 128.8, 128.2, 126.8, 126.7, 124.2, 117.6, 50.7.

4-(benzo[d][1,3]dioxol-5-yl)-1-benzyl-2-phenyl-1*H*-imidazole (**3sa**). Yellow solid, yield 86% (91 mg, PE/EtOAc=10:1 as eluent), mp 161 - 162 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 - 7.57 (m, 2H), 7.39 (dd, *J* = 4.8, 1.6 Hz, 3H), 7.33 - 7.31 (m, 5H), 7.11 (d, *J* = 6 Hz, 3H), 6.80 (d, *J* = 8.4 Hz, 1H), 5.91 (s, 2H), 5.17 (s, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 148.4, 147.9, 141.4, 140.3, 136.9, 130.4, 129.1, 129.0, 128.7, 128.6, 128.4, 127.0, 126.7, 118.4, 116.1, 108.5, 105.8, 100.9, 53.2. HRMS (ESI-TOF) m/z calcd for $C_{23}H_{18}N_2O_2$ $[M+H]^+$ 354.1363, found 354.1365.

1-benzyl-2-phenyl-4-(thiophen-2-yl)-1*H*-imidazole (**3ta**).[8] Yellow solid, yield 89% (84 mg, PE/EtOAc=15:1 as eluent), mp 98 - 100 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 - 7.52 (m, 2H), 7.43 - 7.36 (m, 3H), 7.33 - 7.28 (m, 4H), 7.15 (dd, *J* = 5.1, 1.0 Hz, 1H), 7.13 - 7.06 (m, 3H), 7.00 (dd, *J* = 5.0, 3.6 Hz, 1H), 5.15 (s, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 148.5, 137.9, 136.8, 136.7, 130.1, 129.2, 129.1, 129.1, 128.7, 128.1, 127.6, 126.7, 123.4, 122.1, 116.3, 50.5.

1-benzyl-4-(naphthalen-1-yl)-2-phenyl-1*H*-imidazole (**3ua**).[9b] Yellow solid, yield 65% (70 mg, PE/EtOAc=15:1 as eluent), mp 126 - 127 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 - 8.56 (m, 1H), 7.88 - 7.85 (m, 1H), 7.83 - 7.79 (m, 2H), 7.72 - 7.65 (m, 2H), 7.52 - 7.46 (m, 3H), 7.45 - 7.42 (m, 2H), 7.38 - 7.37 (m, 2H), 7.35 - 7.32 (m, 2H), 7.26 (d, *J* = 7.1 Hz, 2H), 7.20 (d, *J* = 7.1 Hz, 2H), 5.32 (s, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 148.3, 140.8, 137.0, 134.0, 131.9, 131.3, 130.5, 129.1, 129.1, 129.0, 128.7, 128.3, 128.0, 127.7, 126.7, 126.7, 126.1, 126.0, 125.6, 125.5, 120.0, 50.6.

1-benzyl-4-(naphthalen-2-yl)-2-phenyl-1*H*-imidazole (**3va**).[9b] Yellow solid, yield 90% (97 mg, PE/EtOAc=15:1 as eluent), mp 136 - 138 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.89 - 7.82 (m, 2H), 7.82 - 7.75 (m, 2H), 7.64 - 7.56 (m, 2H), 7.39 (td, *J* = 6.3, 4.3 Hz, 5H), 7.34 - 7.24 (m, 4H), 7.08 (d, *J* = 6.6 Hz, 2H), 5.13 (s, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 148.9, 141.5, 136.9, 133.9, 132.7, 131.5, 130.4, 129.2, 129.1, 129.1, 128.8, 128.2, 128.2, 128.1, 127.7, 126.8, 126.2, 125.4, 123.8, 123.1, 117.5, 50.6.

1-(4-methylbenzyl)-4-phenyl-2-(p-tolyl)-1*H*-imidazole (**3ab**).[9b] Yellow solid, yield 76% (77 mg, PE/EtOAc=15:1 as eluent), mp 94 - 95 °C.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 - 7.78 (m, 2H), 7.50 (dd, *J* = 8.3, 1.8 Hz, 2H), 7.38 - 7.33 (m, 2H), 7.24 - 7.21 (m, 4H), 7.16 (d, *J* = 7.9 Hz, 2H), 7.03 (d, *J* = 8.0 Hz, 2H), 5.16 (s, 2H), 2.38 (s, 3H), 2.34 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 148.7, 141.3, 139.0, 137.8, 134.1, 133.9, 129.7, 129.3, 129.0, 128.5, 127.6, 126.7, 126.7, 124.9, 116.6, 50.3, 21.4, 21.2.

1-(2-methylbenzyl)-4-phenyl-2-(o-tolyl)-1*H*-imidazole (**3ac**).[8] Yellow solid, yield 63% (64 mg, PE/EtOAc=15:1 as eluent), mp 104 - 106 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 - 7.97 (m, 2H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.38 - 7.22 (m, 4H), 7.22 - 7.04 (m, 5H), 6.59 (d, *J* = 7.1 Hz, 1H), 5.03 (s, 2H), 2.20 (s, 3H), 2.14 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 151.0, 143.6, 138.5, 134.4, 134.3, 133.6, 130.6, 130.2, 130.0, 129.9, 129.8, 128.2, 127.6, 127.5, 127.4, 126.5, 125.7, 125.59, 115.4, 48.6, 19.8, 19.1.

1-(4-(tert-butyl)benzyl)-2-(4-(tert-butyl)phenyl)-4-phenyl-1*H*-imidazole (**3ad**). Yellow solid, yield 67% (85 mg, PE/EtOAc=15:1 as eluent), mp 127 - 128 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.4 Hz, 2H), 7.48 (m, 3H), 7.45 - 7.33 (m, 7H), 6.98 (d, *J* = 8.2 Hz, 2H), 5.32 (s, 2H), 1.32 (s, 9H), 1.31 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 152.7, 151.9, 150.7, 144.4, 134.0, 133.6, 132.1, 128.7, 128.3, 127.7, 127.6, 126.3, 126.0, 125.9, 125.8, 51.2, 34.9, 34.7, 31.5, 31.4. HRMS (ESI-TOF) m/z calcd for $C_{30}H_{35}N_2$ $[M+H]^+$ 423.2795, found 423.2798.

1-(4-methoxybenzyl)-2-(4-methoxyphenyl)-4-phenyl-1*H*-imidazole (**3ae**).[9b] Yellow solid, yield 86% (96 mg, PE/EtOAc=10:1 as eluent), mp 117 - 119 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.2 Hz, 2H), 7.58 - 7.50 (m, 2H), 7.34 (t, *J* = 7.7 Hz, 2H), 7.24 - 7.18 (m, 2H), 7.04 (d, *J* = 8.6 Hz, 2H), 6.97 - 6.91 (m, 2H), 6.90 - 6.84 (m, 2H), 5.09 (s, 2H), 3.81 (s, 3H), 3.78 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 160.2, 159.3, 134.2, 130.5, 128.9, 128.5, 128.1, 126.7, 124.9, 123.0, 116.5, 114.4, 114.1, 55.4, 55.3, 50.0.

1-(4-fluorobenzyl)-2-(4-fluorophenyl)-4-phenyl-1*H*-imidazole (**3af,**).[9b] Yellow solid, yield 83% (86 mg, PE/EtOAc=15:1 as eluent), mp 82-83 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.4 Hz, 2H), 7.54 (dd, *J* = 8.6, 5.4 Hz, 2H), 7.37 (t, *J* = 7.5 Hz, 2H), 7.25 (t, *J* = 5.9 Hz, 2H), 7.14 - 6.99 (m, 6H), 5.15 (s, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 163.2 (d, *J* = 250.5 Hz), 162.4 (d, *J* = 248.3 Hz), 147.6, 141.6, 133.8, 132.4 (d, *J* = 3.3 Hz), 131.0 (d, *J* = 8.5 Hz), 128.6, 128.4 (d, *J* = 8.1 Hz), 127.0, 126.5 (d, *J* = 3.4 Hz), 124.9, 116.7, 116.1 (d, *J* = 21.7 Hz), 115.8 (d, *J* = 21.8 Hz), 49.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.51, -113.71.

1-(4-chlorobenzyl)-2-(4-chlorophenyl)-4-phenyl-1*H*-imidazole (**3ag**).[9b] Yellow solid, yield 88% (100 mg, PE/EtOAc=15:1 as eluent), mp 100 - 102 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.5 Hz, 2H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.41 - 7.32 (m, 4H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.26 - 7.19 (m, 2H), 6.99 (d, *J* = 8.3 Hz, 2H), 5.11 (s, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 147.4, 141.9, 135.3, 135.1, 134.0, 133.7, 130.2, 129.3, 129.0, 128.7, 128.7, 127.9, 127.1, 125.0, 117.1, 49.9.

1-(3-chlorobenzyl)-2-(3-chlorophenyl)-4-phenyl-1*H*-imidazole (**3ah**).[7] Yellow solid, yield 85% (96 mg, PE/EtOAc=15:1 as eluent), mp 125 - 127 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 - 7.96 (m, 2H), 7.56 - 7.52 (m, 1H), 7.48 - 7.26 (m, 9H), 7.06 (s, 1H), 6.93 - 6.84 (m, 1H), 5.28 (s, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 150.3, 145.1, 138.2, 135.1, 134.8, 133.4, 131.8, 130.4, 130.0, 129.7, 129.1, 128.3, 128.2, 127.8, 127.7, 126.6, 126.3,

124.2, 117.6, 50.8.

1-(2-chlorobenzyl)-2-(2-chlorophenyl)-4-phenyl-1*H*-imidazole (**3ai**).[8] Yellow solid, yield 91% (103 mg, PE/EtOAc=15:1 as eluent), mp 135 - 136 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.5 Hz, 2H), 7.46 (d, *J* = 7.7 Hz, 2H), 7.33 (td, *J* = 14.7, 12.6, 7.0 Hz, 5H), 7.26 - 7.12 (m, 4H), 6.91 (d, *J* = 7.2 Hz, 1H), 5.08 (s, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 146.0, 141.6, 134.7, 134.0, 133.9, 133.1, 132.8, 131.1, 130.0, 129.8, 129.6, 129.3, 128.6, 127.3, 127.1, 126.9, 124.9, 115.9, 48.2.

1-(3,4-dichlorobenzyl)-2-(3,4-dichlorophenyl)-4-phenyl-1*H*-imidazole (**3aj**).[8] Yellow solid, yield 52% (70 mg, PE/EtOAc=12:1 as eluent), mp 186 - 187 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 - 7.95 (m, 2H), 7.64 (d, *J* = 1.9 Hz, 1H), 7.49 - 7.41 (m, 4H), 7.39 - 7.33 (m, 2H), 7.26 (s, 1H), 7.17 (d, *J* = 1.8 Hz, 1H), 6.84 (dd, *J* = 8.3, 1.9 Hz, 1H), 5.27 (s, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 149.3, 145.4, 136.1, 134.2, 133.6, 133.3, 133.1, 132.4, 131.3, 130.8, 129.8, 129.5, 128.4, 128.4, 128.1, 128.0, 127.6, 127.5, 125.2, 117.4, 50.4.

2-(furan-2-yl)-1-(furan-2-ylmethyl)-4-phenyl-1*H*-imidazole (**3ak**).[9a] Yellow solid, yield 86% (75 mg, PE/EtOAc=15:1 as eluent), mp 103 - 104 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 - 7.76 (m, 2H), 7.56 - 7.52 (m, 1H), 7.39 - 7.33 (m, 3H), 7.26 - 7.20 (m, 2H), 6.94 (d, *J* = 3.4 Hz, 1H), 6.53 (dd, *J* = 3.4, 1.8 Hz, 1H), 6.33 (dd, *J* = 3.1, 1.9 Hz, 1H), 6.29 (d, *J* = 3.2 Hz, 1H), 5.36 (s, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 149.3, 145.4, 143.1, 142.8, 141.7, 139.1, 133.7, 128.5, 127.0, 125.0, 116.7, 111.6, 110.7, 110.3, 109.0, 43.9.

ACKNOWLEDGMENT

This work was supported by Natural Science Foundation of China (No. 51974122), National Natural Science Foundation of Hunan Province (No. 2019JJ50214).

Supporting Information Available: The copies of ^{1}H, ^{13}C and ^{19}F NMR spectra (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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