DOI: 10.1002/adsc.201200582

Practical Synthesis of Polysubstituted Imidazoles *via* Iodine-Catalyzed Aerobic Oxidative Cyclization of Aryl Ketones and Benzylamines

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Received: July 4, 2012; Revised: August 12, 2012; Published online: ■■ ■■, 0000

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201200582.

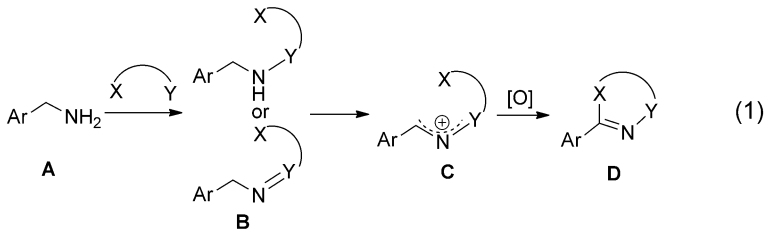
Abstract: A practical synthetic method for polysubstituted imidazoles *via* iodine-catalyzed aerobic oxidative cyclization of aryl ketones and benzylamines has been developed. It was found to tolerate a broad range of substrates to prepare polysubstituted imidazole derivatives in a one-pot manner, and thus importantly allowed product diversity for imidazole chemistry. Additionally, the resultant 1,2,4-trisubstituted imidazoles could be conveniently transformed to functionalized 1,2,4,5-tetrasubstituted imidazoles *via* electrophilic substitution or direct C–H functionalization, or 2,4-diaryl-1*H*-imidazoles by debenzylation reaction, which further indicates potential applications of this method in synthetic and pharmaceutical chemistry.

Keywords: aerobic oxidative cyclization; aryl ketones; benzylamines; iodine-catalyzed reaction; polysubstituted imidazoles

Introduction

Imidazole is one of ubiquitous structural units in numerous drug molecules and natural products.[1] Moreover, imidazole derivatives play important roles in synthetic chemistry: (a) as building blocks of naturally occurring products and complex meaningful molecules,[2] (b) as efficient organic catalysts to promote facile reaction processes,[3] (c) as ligands in metalloenzymes,[4] (d) as precursors of carbene ligands[5] and environmentally friendly ionic solvents.[6] In the past years, while the classic Debus–Radziszewski reaction and Bredereck synthesis opened the way to the preparation of imidazoles,[7] various synthetic methods for imidazole derivatives have been developed.[8] In terms of the starting materials, these are mainly focused on amides,[9] imines,[10] nitriles,[11] amino acids,[12] isocyanides,[13] and other precursors.[14] Despite primordial efficiency in synthetic chemistry, the synthesis of imidazole has yet to develop in terms of accessibility of starting materials and product diversity. As known in this case, 1,2,4-trisubstituted imidazoles,[15] which are prevalent in bioactive natural products including many inhibitors of kinase,[16] have been mainly accessed through condensation of α-halo ketones, aldehydes, and amines, however, the direct cyclization of acyclic precursors has been rarely reported. Hence, the development of a simple procedure for acquisition of imidazole derivatives from easily available starting materials remains as a continuing challenge.

Recently, increasing attention has been drawn to the preparation of nitrogen-containing heterocyclic compounds *via* oxidative cyclization using benzylamines as the starting materials.[17] Generally, the intermolecular cross-coupling or condensation reaction of benzylamine forms amine or imine species **B** [Eq. (1), **A**→**B**], and intermediate **C** can be accessed under oxidative conditions by sp^3 C–H functionalization.[18] Intramolecular attack of an O or N nucleophilic atom to an electrophilically activated carbon atom initiates oxidative cyclization to afford the final nitrogen-containing heterocyclic compounds **D**. Although oxidation in this system may not proceed as a distinct step, the overall reactivity patterns observed are reminiscent and thus allow benzylamine compounds to be perceived of as simpler and direct alternatives to a diverse range of nitrogen-containing heterocyclic products.



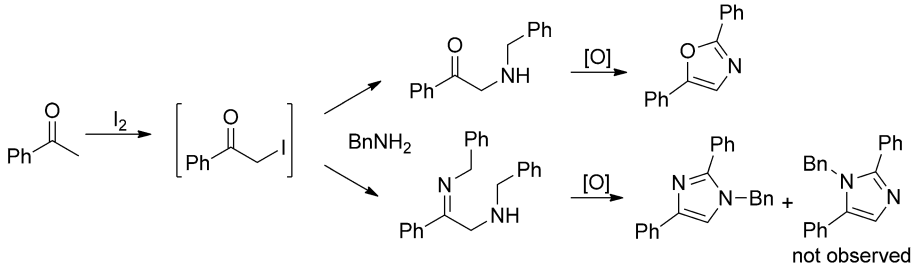
Results and Discussion

Very recently, our group has developed a new type of one-pot, transition metal-free domino process to synthesize polysubstituted oxazoles through a TBHP/I_2-mediated oxidative cyclization from easily available arylalkenes and benzylic amines.[19] In order to further extend the applicability of this reaction system, we were inspired to subject aryl ketones to this reaction conditions to construct heterocyclic compounds.[20] We initially presumed that 2,5-disubstituted oxazoles and 1,2,5-trisubstituted imidazoles could be selectively furnished in an analogous manner. Interestingly, further investigation suggested that the 1,2,4-trisubstituted rather than the 1,2,5-trisubstituted imidazole derivative was regioselectively formed under controlled reaction conditions when we employed acetophenone and benzylamine as the substrates (Scheme 1). As part of our continuing interest in the synthesis of nitrogen-containing heterocyclic compounds,[21] we herein disclose a new and convenient protocol to construct highly substituted imidazoles *via* iodine-mediated aerobic oxidative cyclization of readily available aryl ketones and benzylamines.

As shown in Table 1, we first performed the reaction with **1a** (0.5 mmol), **2a** (2.5 equiv.), I_2 (1.0 equiv.), CuO[20b,d] (1.0 equiv.) in DMSO (2 mL) at 90 °C for 5 h, and 2,5-diphenyloxazole **3aa** was isolated in 78% yield (entry 1). A variety of additives was then examined. While 0.2 equiv. of CuO and $CuCl_2$ afforded small amounts of imidazole product and $FeCl_3$ afforded poor selectivity (entries 2–4), $PdCl_2$ and TsOH gave significant rate enhancements (entries 5 and 6), suggesting the acid system could turn the selectivity over favouring imidazole products. Further investigation revealed that the addition of 10 μL (0.24 equiv.) of 12 M HCl proved to be optimal for the selective generation of **4aa** giving exclusively the product in 57% yield (entry 7), which revealed that the condensation of acetophenone and benzylamine would be significantly promoted under acidic conditions.

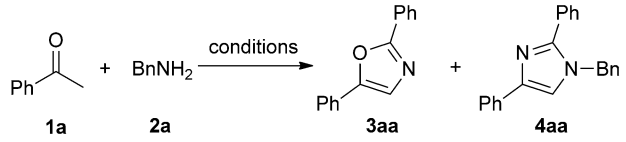
When 0.2 equiv. of iodine were used, the yield decreased to 43% with some benzyl(1-phenylethylidene)amine remaining, which indicated that more oxidant should be added for complete oxidative cyclization (Table 1, entry 8). Several oxidants were tested. While *t*-BuOOH (TBHP) and 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) just gave poor selectivity, 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) gave lower yield of the desired product (entries 9–11). Gratifyingly, the imidazole product was formed in good yield when the reaction was conducted under an oxygen atmosphere (entry 12). Other Brønsted acids such as HOTf were found to disfavour the reaction selectivity (entry 13). While KI (1 equiv.) instead of iodine led to **4aa** in a moderate yield (entry 14), neither oxazole nor imidazole was detected without iodine reagent (entry 15). Solvent testing showed that DMSO was an incomparable medium (entries 16–18). Subjecting $BnNH_2$·HCl to this reaction without additional HCl slightly improved the yield (entry 19). But we gave up using amine hydrochloride for the purpose of easy operation. Finally, this reaction was found to be optimal at 90 °C (entries 20 and 21).

To enhance understanding of the role of the Brønsted acid, we decided to investigate the effect of HCl on the generation of imidazole and the stoichiometry of the reaction (Figure 1). Generally, it was beneficial for the formation of **4aa** when using more benzylamine, but obviously no or excessive HCl de-



Scheme 1. Proposed synthetic procedure from aryl ketones.

Table 1. Optimization of reaction conditions.[a]



1a 2a 3aa 4aa

Entry	Catalyst (equiv.)	Additive (equiv.)	Solvent	Yield [%][b] 3aa	4aa
1	I_2 (1.0)	CuO (1.0)	DMSO	78	trace
2	I_2 (1.0)	CuO (0.2)	DMSO	62	10
3	I_2 (1.0)	$CuCl_2$ (0.2)	DMSO	70	12
4	I_2 (1.0)	$FeCl_3$ (0.2)	DMSO	37	42
5	I_2 (1.0)	$PdCl_2$ (0.2)	DMSO	8	61
6	I_2 (1.0)	TsOH (0.2)	DMSO	7	48
7	I_2 (1.0)	HCl[c]	DMSO	trace	57
8	I_2 (0.2)	HCl	DMSO	n.p.	43
9	I_2 (0.2)	HCl, TBHP (2.0)	DMSO	22	35
10	I_2 (0.2)	HCl, DDQ (2.0)	DMSO	n.p.	12
11	I_2 (0.2)	HCl, TEMPO (2.0)	DMSO	15	58
12[d]	I_2 (0.2)	HCl	DMSO	n.p.	85
13[d]	I_2 (0.2)	HOTf (0.2)	DMSO	10	70
14[d]	KI (1.0)	HCl	DMSO	n.p.	40
15[d]	–	HCl	DMSO	n.p.	n.p.
16[d]	I_2 (0.2)	HCl	toluene	n.p.	trace
17[d]	I_2 (0.2)	HCl	DMF	n.p.	27
18[d]	I_2 (0.2)	HCl	H_2O	n.p.	n.p.
19[d,e]	I_2 (0.2)	–	DMSO	n.p.	87
20[d,f]	I_2 (0.2)	HCl	DMSO	n.p.	80
21[d,g]	I_2 (0.2)	HCl	DMSO	n.p.	84

[a] Unless otherwise indicated, the reaction was carried out with **1a** (0.5 mmol), **2a** (2.5 equiv.) in solvent (2 mL) at 90 °C for 5 h; n.p. means no product was detected.
[b] Isolated yield.
[c] All HCl entries in this table refer to 10 μL (0.24 equiv.) of 12 M HCl.
[d] Using an O_2 balloon.
[e] $BnNH_2$·HCl instead of $BnNH_2$ was used as the substrate.
[f] At 80 °C.
[g] At 95 °C.

creased the yield. Meaningfully, the addition of HCl seemed to inhibit the oxidation of **2a** to phenyl aldehyde because a large excess of benzylamine was no longer necessary in this oxidative system. More concentrated hydrochloric acid (20 μL) disfavoured the generation of imidazole product, because condensation, one of the key steps, was sensitive to water, consistent with the control experiment, as could be seen in Figure 2. **1a** and $BnNH_2$·HCl were operated with 20 mol% of iodine under an oxygen atmosphere, and one to four equivalents of water as the additive was added to the reaction to screen the transformation. It was found that while the addition of one equivalent of water had a slightly adverse influence on the yield

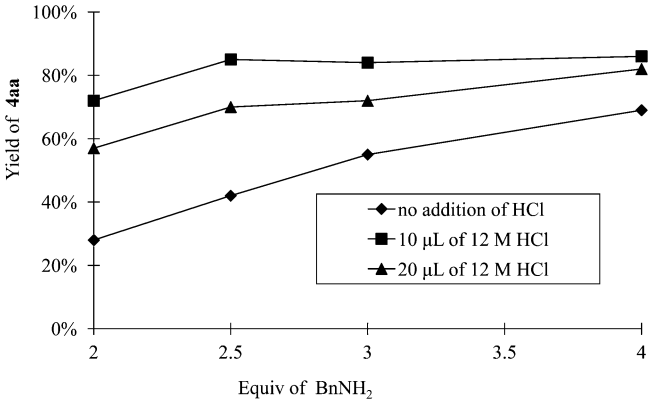


Figure 1. The effect of HCl on the generation of imidazole and the stoichiometry of the reaction.

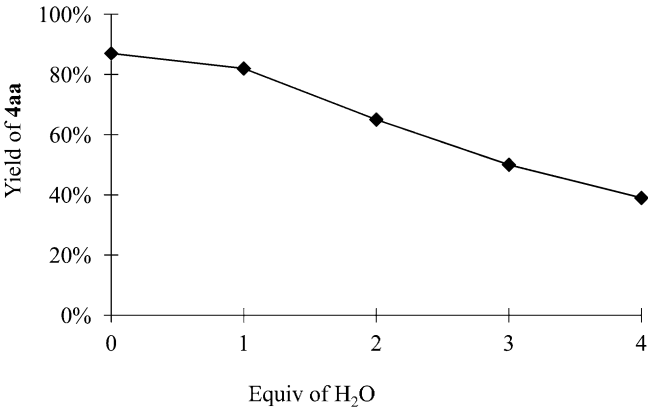
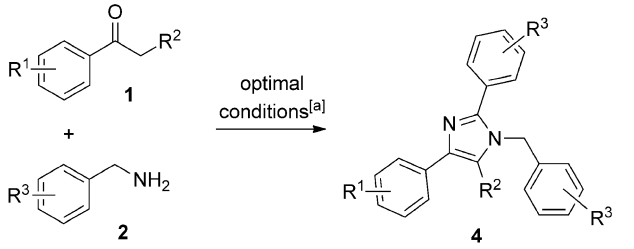


Figure 2. The effect of H_2O on the generation of imidazole.

of **4aa**, it decreased linearly with the increase of water.

Having identified the optimal reaction conditions, we next explored the generality and scope of the substrates of this reaction. Various aryl-substituted ketones were successfully applied to this system. Generally, higher yields were obtained with electron-donating substituents on the aromatic ring, such as alkyl and methoxy (Table 2, entries 2–7), and a certain influence on the yield could be seen when substituents are present on the *para*, *meta*, and *ortho* positions of the aryl ketones, such as **1e**, **1f**, and **1g**. Aryl ketones with halogen atoms on the aromatic ring were also tolerated (Table 2, entries 8–10). Both 1-(4-nitrophenyl)-ethanone (**1k**) and 1-naphthalen-2-yl-ethanone (**1l**) successfully provided the functionalized imidazoles **4ka** and **4la**, although in moderate yields (58 and 49%, respectively) (Table 2, entries 11 and 12). Besides, aryl ketones **1m** and **1n** showed considerably different reactivities for the target 1,2,4,5-tetrasubstituted imidazoles (91% and 35%, respectively, Table 2, entries 13 and 14).

Table 2. Generality of the aryl ketones and benzylamines.



Entry	**1** (R^1/R^2)	**2** (R^3)	**4**	Yield [%][b]
1	**1a**	**2a**	**4aa**	85
2	**1b** (4-Me/H)	**2a**	**4ba**	80
3	**1c** (2-Me/H)	**2a**	**4ca**	73
4	**1d** (4-isobutyl/H)	**2a**	**4da**	89
5	**1e** (4-OMe/H)	**2a**	**4ea**	88
6	**1f** (3-OMe/H)	**2a**	**4fa**	80
7	**1g** (2-OMe/H)	**2a**	**4ga**	65
8	**1h** (4-F/H)	**2a**	**4ha**	70
9	**1i** (4-Cl/H)	**2a**	**4ia**	70
10	**1j** (4-Br/H)	**2a**	**4ja**	59
11	**1k** (4-NO_2/H)	**2a**	**4ka**	58
12	**1l** (naphthyl/H)	**2a**	**4la**	49
13	**1m** (H/Ph)	**2a**	**4ma**	91
14	**1n** (H/Me)	**2a**	**4na**	35
15	**1a**	**2b** (4-Me)	**4ab**	90
16	**1a**	**2c** (4-F)	**4ac**	76
17	**1a**	**2d** (3-Cl)	**4ad**	78
18	**1a**	**2e** (4-OMe)	**4ae**	84
19	**1a**	**2f** (3-OMe)	**4af**	82
20	**1h**	**2c**	**4hc**	59
21	**1h**	**2e**	**4he**	81
22	**1e**	**2e**	**4ee**	90

[a] The reaction was carried out with **1** (0.5 mmol), **2** (2.5 equiv.), I_2 (20 mol%), and 10 μL (0.24 equiv.) of 12 M HCl in DMSO (2 mL) under O_2 (1 atm) at 90 °C for 5 h.
[b] Isolated yield.

Furthermore, various benzylamine derivatives were employed (Table 2, entries 15–19). In accordance with previous results, while the electron-donating group on the aromatic ring was favourable, electron-deficient substituents decreased the reaction yield. Finally, the electronic effect of the reaction was further confirmed by using the substrates with 4-F and 4-OMe on the aromatic ring (Table 2, entries 20–22). The structure of

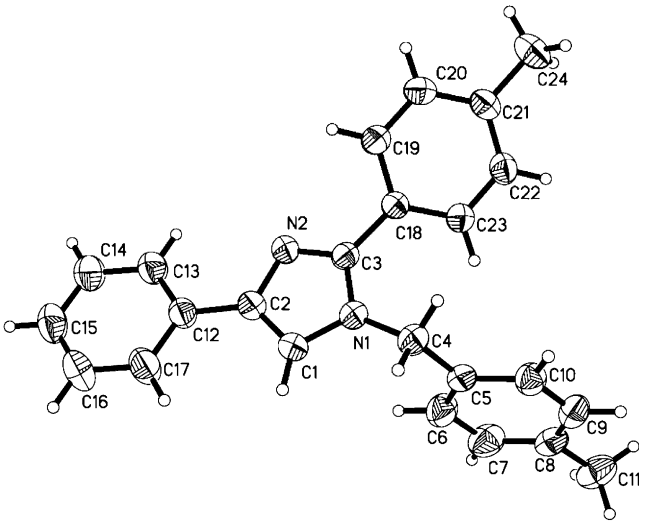
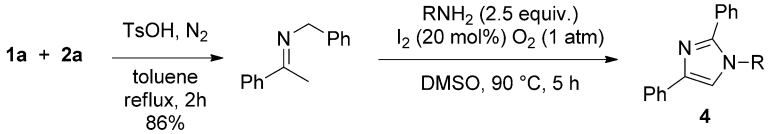


Figure 3. X-ray structure of compound **4ab**.

4ab was corroborated by the X-ray crystallographic analysis (Figure 3).[22]

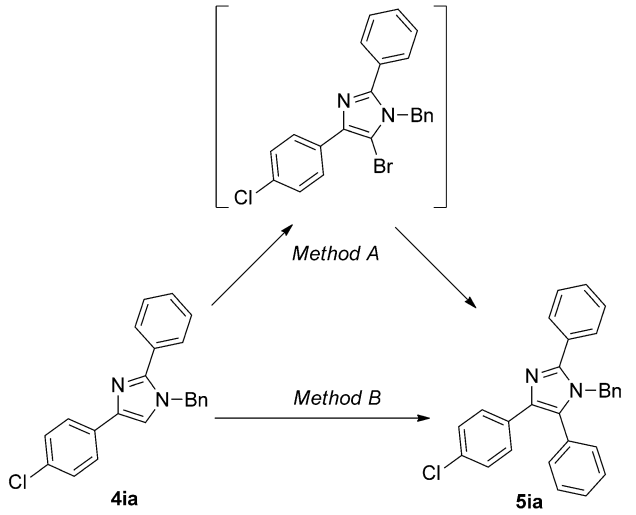
For further exploration of the synthetic utilities of this method, benzyl-(1-phenylethylidene)-imine was first prepared in 86% GC yield by TsOH-catalyzed condensation of **1a** and **2a** in toluene under nitrogen for 2 h (Scheme 2). We were delighted that the imine was successfully reacted with alkylamines to afford the expected 1,2,4-trisubstituted imidazoles *via* this iodine-catalyzed oxidative cyclization reaction. Although excess alkylamine was used in this process, this one-pot synthesis of functionalized imidazoles in competitive yields from readily available starting materials was attractive and more importantly allowed product diversity.

The resultant 1,2,4-trisubstituted imidazoles contain an unsubstituted 5-position on the imidazole ring as handle for further manipulations.[23] For example, palladium-catalyzed direct C-5 arylation of **4ia** with iodobenzene smoothly gave 1,2,4,5-tetrasubstituted imidazole **5ia** in 72% yield (Scheme 3). Bromination[24] of **4ia** with *N*-bromosuccinimide (NBS) followed by palladium-catalyzed Suzuki–Miyaura cross-coupling reaction with phenylboronic acid also proceeded well to give **5ia** in 85% overall yield.



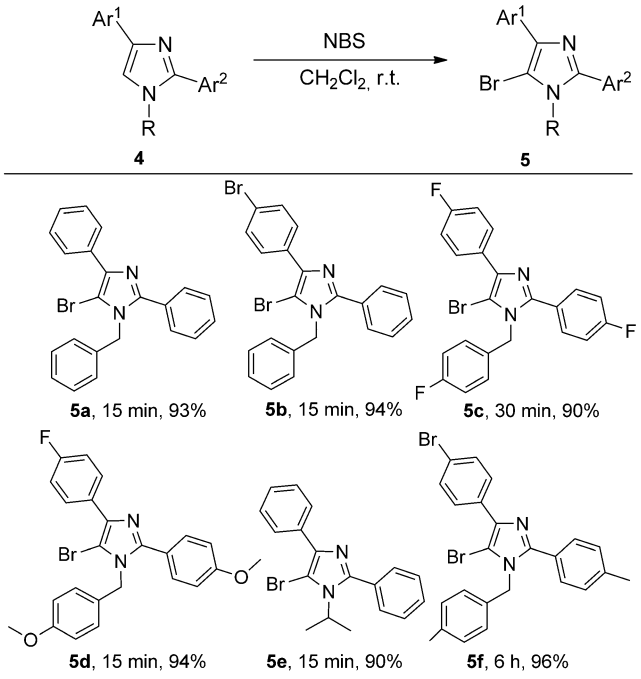
4aaa: R = Et, 42%
4aab: R = *n*-Pr, 50%
4aac: R = *n*-Bu, 46%
4aad: R = *i*-Pr, 55%
4aae: R = *sec*-Bu, 56%
4aaf: R = *t*-Bu, 66%
4aag: R = cyclohexyl, 35%

Scheme 2. One-pot synthesis of 1,2,4-trisubstituted imidazole derivatives.

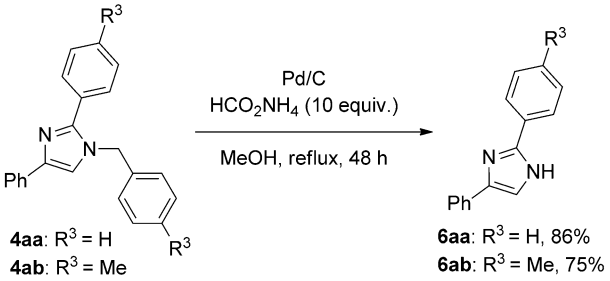


Scheme 3. C-5 arylation of **4ia**. *Method A:* 1) NBS (1.1 equiv.), CH_2Cl_2, room temperature, 20 min, 92%; 2) $PhB(OH)_2$ (2 equiv.), $PdCl_2(dppf)$ (5 mol%), Et_3BnNCl (5 mol%), CsF (3 equiv.), $PhMe/H_2O$, 100 °C, 24 h, 94%. *Method B:* PhI (2 equiv.), $Pd(OAc)_2$ (5 mol%), PPh_3 (10 mol%), K_2CO_3 (3 equiv.), DMF, 140 °C, 36 h, 72%.

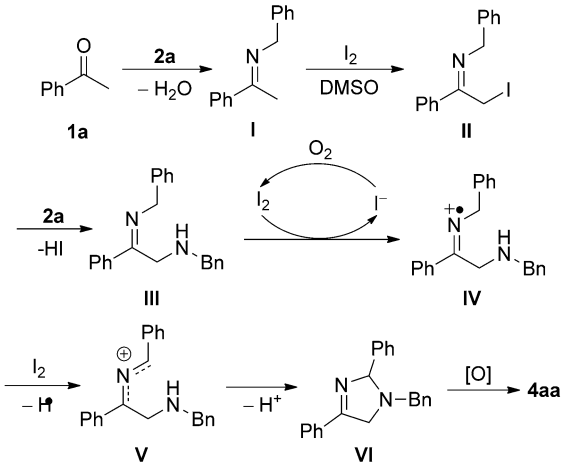
In terms of the higher efficiency of the latter fractional step method, we treated imidazoles **4** with NBS in CH_2Cl_2 at room temperature and prepared a series of 5-bromo-substituted imidazoles **5a–5f** in excellent yields (Scheme 4). Distinct reaction times were observed by TLC monitoring when subjecting imidazoles with different substituents on the aromatic ring. Interestingly, when 2.2 equivalents of NBS was employed, **4ab** was converted to **5f** in 96% yield after 6 h by electrophilic substitution on both the 5-position of the imidazole ring and the *para* position of the phenyl group.



Scheme 4. Bromination of 1,2,4-trisubstituted imidazoles. All reactions were performed at 0.2 M with 1.1 equiv. of NBS. **5f** was obtained from **4ab** by using 2.2 equiv. of NBS.



Scheme 5. *N*-Debenzylation of *N*-protected imidazoles.



Scheme 6. Plausible reaction mechanism.

Ultimately, the feasibility of the resultant *N*-benzyl-protected imidazoles was established by a literature procedure for the efficient debenzylation.[24] Imidazoles **4aa** and **4ab** were treated with an equal weight of 10% Pd/C in methanol and a large molar excess of anhydrous ammonium formate, and the mixture was refluxed for 48 h to give 2,4-diaryl-substituted imidazoles **6aa** and **6ab** in 86% and 75% yield, respectively (Scheme 5).

On the basis of the above results, a reasonable mechanism for this oxidative cyclization reaction of aryl ketones and benzylamines was proposed (Scheme 6). Imine **I**, *in situ*-formed by condensation of **1a** and **2a**, would undergo α-iodination to generate **II** in the media of DMSO.[20d] Actually, an α-iodination/condensation sequence could also furnish intermediate **II**. Coupling reaction of **II** with **2a** led to intermediate **III**. Subsequently, **III** was oxidized to intermediate **V** *via* sp^3 C–H functionalization under iodine-mediated reaction conditions. Intramolecular

nucleophilic cyclization of **V** and further oxidation gave the final imidazole **4aa**. The resulting iodine anion could be oxidized to iodine under oxygen atmosphere, which was confirmed by the fact observed previously that KI could also promote the reaction.

Conclusions

In summary, we have developed a new and efficient method to construct polysubstituted imidazoles *via* iodine-catalyzed aerobic oxidative cyclization of aryl ketones and benzylamines in a one-pot manner. It is noteworthy that three C–N bonds were formed in this transformation, and Brønsted acid has a dual function of promoting the condensation and inhibiting the oxidation of benzylamine. Moreover, the resultant 1,2,4-trisubstituted imidazoles could be efficiently converted to other functional imidazole products through substitution, coupling reaction or other transformation. Ongoing research involves further broadening the synthetic scope of the methodology and its potential applications in natural product synthesis is currently underway in our laboratory.

Experimental Section

General Methods

Melting points were measured with a melting point instrument and were uncorrected. ^{1}H and ^{13}C NMR spectra were recorded using a 400 MHz NMR spectrometer. The chemical shifts were referenced to signals at 7.26 and 77.0 ppm, respectively, and $CDCl_3$ was used as the solvent with TMS as the internal standard. IR spectra were obtained as potassium bromide pellets or as liquid films between two potassium bromide pellets. High-resolution mass spectra were obtained with a LCMS-IT-TOF mass spectrometer. TLC was performed by using commercially prepared 100–400 mesh silica gel plates (GF254) and visualization was effected at 254 nm.

The Effect of Brønsted Acid on the Generation of Imidazole and the Stoichiometry of the Reaction

The mixture of acetophenone (**1a**, 0.5 mmol, 1 equiv.), benzylamine (**2a**), I_2 (20 mol%) and concentrated hydrochloric acid (12 M) was stirred in DMSO (2 mL) at 90 °C under oxygen atmosphere for 5 h. And then the reaction was quenched by the addition of 10 mL water. The aqueous solution was extracted with diethyl ether (3×10 mL) and the combined extract was dried with anhydrous $MgSO_4$. The solvent was removed and the crude product was separated by flash column chromatography on silica gel to give the pure product **4aa**.

The Effect of H_2O on the Generation of Imidazole

The mixture of acetophenone (**1a**, 0.5 mmol, 1 equiv.), benzylamine hydrochloride ($BnNH_2$·HCl, 2.5 equiv.), I_2 (20 mol%) and deionized water was stirred in DMSO (2 mL) at 90 °C under oxygen atmosphere for 5 h. And then the 10 mL water was added to quench the reaction. The aqueous solution was extracted with diethyl ether (3× 10 mL) and the combined extract was dried over anhydrous $MgSO_4$. The solvent was removed and the crude product was separated by flash column chromatography on silica gel to give the product imidazole **4aa**.

General Procedure for the Synthesis of Polysubstituted Imidazoles 4aa-4ee

The mixture of aryl ketone (**1**, 0.5 mmol), benzylamine (**2**, 2.5 mmol), I_2 (20 mol%) and concentrated hydrochloric acid (10 μL, 20 mol%) was stirred in DMSO (2 mL) at 90 °C under oxygen atmosphere for 5 h. And then the 10 mL water was added to quench the reaction. The aqueous solution was extracted with diethyl ether (3×10 mL) and the combined extract was dried with anhydrous $MgSO_4$. The solvent was removed and the crude product was separated by flash column chromatography on silica gel to give the pure product.

1-Benzyl-2,4-diphenyl-1*H*-imidazole[25] **(4aa):** White solid, mp 122–124 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (d, J = 8.4 Hz, 2H), 7.59–7.57 (m, 2H), 7.39–7.18 (m, 10H), 7.07 (d, J = 6.7 Hz, 2H), 5.13 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.4, 141.3, 136.7, 133.9, 130.3, 128.9, 128.84, 128.83, 128.5, 128.4, 127.8, 126.7, 126.5, 124.8, 116.8, 50.3; HR-MS (ESI): m/z = 311.1522, calcd. for $C_{22}H_{18}N_2$ $[M+H]^+$: 311.1548.

1-Benzyl-2-phenyl-4-*p*-tolyl-1*H*-imidazole (4ba): White solid, mp 109–111 °C. IR (KBr): ν = 1670, 1451, 1178, 824, 764, 730, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 (d, J = 8.1 Hz, 2H), 7.63–7.61 (m, 2H), 7.44–7.31 (m, 6H), 7.22–7.13 (m, 5H), 5.22 (s, 2H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.4, 141.5, 136.8, 136.5, 131.0, 129.2, 129.0, 128.98, 128.97 128.6, 128.3, 127.9, 126.7, 124.9, 116.3, 50.5, 21.2: HR-MS (ESI): m/z = 325.1703, calcd. for $C_{23}H_{20}N_2$ $[M+H]^+$: 325.1705.

1-Benzyl-2-phenyl-4-*o*-tolyl-1*H*-imidazole (4ca): White solid, mp 104–106 °C. IR (KBr): ν = 1671, 1457, 1402, 1363, 1244, 1032, 761, 730, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95 (d, J = 7.7 Hz, 1H), 7.64–7.61 (m, 2H), 7.41–7.11 (m, 12H), 5.27 (s, 2H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.6, 140.7, 136.9, 134.9, 130.7, 130.3, 130.0, 129.99, 129.9, 129.0, 128.9, 128.6, 127.9, 126.8, 126.5, 125.9, 119.6, 50.4, 21.8; HR-MS (ESI): m/z = 325.1697, calcd. for $C_{23}H_{20}N_2$ $[M+H]^+$: 325.1705.

1-Benzyl-4-(4-isobutylphenyl)-2-phenyl-1*H*-imidazole (4da): White solid, mp 112–114 °C. IR (KBr): ν = 1606, 1457, 1361, 1176, 1022, 848, 763, 728, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, J = 7.8 Hz, 2H), 7.63–7.61 (m, 2H), 7.43–7.30 (m, 6H), 7.22 (s, 1H), 7.17–7.13 (m, 4H), 5.22 (s, 2H), 2.49 (d, J = 7.1 Hz, 2H), 1.93–1.83 (m, 1H), 0.92 (d, J = 6.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.4, 141.6, 140.4, 136.9, 131.4, 130.4, 129.3, 129.0, 128.94, 128.92, 128.6, 127.9, 126.6, 124.7, 116.4, 50.4, 45.2, 30.2, 22.3; HR-MS (ESI): m/z = 367.2172, calcd. for $C_{26}H_{26}N_2$ $[M+H]^+$: 367.2174.

1-Benzyl-4-(4-methoxyphenyl)-2-phenyl-1*H*-imidazole (4ea): White solid, mp 110–112 °C. IR (KBr): ν = 1612, 1496, 1454, 1245, 1174, 1028, 947, 836, 768, 728, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.78$ (d, $J = 8.7$ Hz, 2H), 7.63–7.61 (m, 2H), 7.44–7.31 (m, 6H), 7.16–7.13 (m, 3H), 6.92 (d, $J = 8.7$ Hz, 2H), 5.20 (s, 2H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 158.7$, 148.4, 141.4, 137.0, 130.6, 129.04, 129.01, 128.9, 128.6, 128.0, 127.0, 126.7, 126.2, 115.8, 114.0, 55.3, 50.5: HR-MS (ESI): $m/z = 341.1649$, calcd. for $C_{23}H_{20}N_2O$ $[M+H]^+$: 341.1654.

1-Benzyl-4-(3-methoxyphenyl)-2-phenyl-1*H*-imidazole (4fa): White solid, mp 98–100 °C. IR (KBr): ν = 1603, 1458, 1238, 1168, 1042, 844, 769, 729, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.62$–7.59 (m, 2H), 7.45–7.24 (m, 10H), 7.12 (d, $J = 7.3$ Hz, 2H), 6.79 (d, $J = 8.2$ Hz, 1H), 5.20 (s, 2H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 159.9, 148.5, 141.3, 136.7, 135.4, 130.3, 129.4, 129.0, 128.97, 128.95, 128.6, 127.9, 126.6, 117.4, 117.1, 113.0, 109.8, 55.3, 50.4; HR-MS (ESI): $m/z = 341.1648$, calcd. for $C_{23}H_{20}N_2O$ $[M+H]^+$: 341.1654.

1-Benzyl-4-(2-methoxyphenyl)-2-phenyl-1*H*-imidazole (4ga): White solid, mp 105–107 °C. IR (KBr): ν = 1611, 1452, 1258, 1167, 1073, 852, 771, 730, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.36$ (d, $J = 7.7$ Hz, 1H), 7.61–7.58 (m, 3H), 7.39–7.19 (m, 7H), 7.12 (d, $J = 7.4$ Hz, 2H), 7.05 (t, $J = 7.5$ Hz, 1H), 6.93 (d, $J = 8.2$ Hz, 1H), 5.23 (s, 2H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 155.9$, 147.3, 137.2, 136.8, 130.5, 128.94, 128.87, 128.8, 128.5, 127.7, 127.5, 127.3, 126.4, 122.6, 121.4, 120.8, 110.5, 55.2, 50.3; HR-MS (ESI): $m/z = 341.1640$, calcd. for $C_{23}H_{20}N_2O$ $[M+H]^+$: 341.1654.

1-Benzyl-4-(4-fluorophenyl)-2-phenyl-1*H*-imidazole (4ha): White solid, mp 92–94 °C. IR (KBr): ν = 1668, 1495, 1456, 1224, 841, 768, 731, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.80$ (dd, $J = 8.8$, 5.5 Hz, 2H), 7.63–7.60 (m, 2H), 7.45–7.32 (m, 6H), 7.19 (s, 1H), 7.14 (d, $J = 6.8$ Hz, 2H), 7.06 (t, $J = 8.8$ Hz, 2H), 5.22 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 162.0$, 148.6, 140.6, 136.7, 130.2, 129.1, 129.0, 128.99, 128.8, 128.6, 128.0, 126.7, 126.5, 116.4, 115.4, 50.5; HR-MS (ESI): $m/z = 329.1461$, calcd. for $C_{22}H_{17}FN_2$ $[M+H]^+$: 329.1454.

1-Benzyl-4-(4-chlorophenyl)-2-phenyl-1*H*-imidazole (4ia): White solid, mp 128–130 °C. IR (KBr): ν = 1601, 1450, 1261, 1072, 996, 834, 763, 728, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.77$ (d, $J = 8.4$ Hz, 2H), 7.62–7.60 (m, 2H), 7.44–7.32 (m, 8H), 7.22 (s, 1H), 7.14 (d, $J = 7.1$ Hz, 2H), 5.21 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 148.7$, 140.4, 136.6, 132.6, 132.3, 130.2, 129.1, 129.0, 128.97, 128.62, 128.61, 128.0, 126.7, 126.2, 116.9, 50.5; HR-MS (ESI): $m/z =$ 345.1149, calcd. for $C_{22}H_{17}ClN_2$ $[M+H]^+$: 345.1158.

1-Benzyl-4-(4-bromophenyl)-2-phenyl-1*H*-imidazole[26] **(4ja):** White solid, mp 152–154 °C. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.66$ (d, $J = 8.5$ Hz, 2H), 7.58–7.55 (m, 2H), 7.42 (d, $J = 8.5$ Hz, 2H), 7.38–7.25 (m, 6H), 7.15 (s, 1H), 7.06 (d, $J = 8.0$ Hz, 2H), 5.11 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 148.6$, 140.2, 136.5, 132.9, 131.4, 130.1, 128.9, 128.8, 128.7, 128.5, 127.9, 126.5, 126.3, 120.2, 116.9, 50.3; HR-MS (ESI): $m/z = 389.0637$, calcd. for $C_{22}H_{17}BrN_2$ $[M+H]^+$: 389.0653.

1-Benzyl-4-(4-nitrophenyl)-2-phenyl-1*H*-imidazole (4ka): White solid, mp 121–123 °C. IR (KBr): ν = 1598, 1509, 1332, 1182, 1106, 945, 732, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.21$ (d, $J = 9.0$ Hz, 2H), 7.96 (d, $J = 8.9$ Hz, 2H), 7.63–7.61 (m, 2H), 7.46–7.32 (m, 7H), 7.15 (d, $J = 6.6$ Hz, 2H), 5.25 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 149.6$, 146.3, 140.4, 139.3, 136.2, 129.8, 129.5, 129.1, 129.0, 128.8, 128.3, 126.8, 125.1, 124.1, 119.2, 50.8; HR-MS (ESI): $m/z =$ 356.1395, calcd. for $C_{22}H_{17}N_3O_2$ $[M+H]^+$: 356.1399.

1-Benzyl-4-naphthalen-2-yl-2-phenyl-1*H*-imidazole (4la): White solid, mp 127–129 °C. IR (KBr): ν = 1629, 1456, 1456, 1243, 1045, 854, 765, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.41$ (s, 1H), 7.91–7.80 (m, 4H), 7.66 (d, $J = 8.0$ Hz, 2H), 7.46–7.33 (m, 9H), 7.17 (d, $J = 7.4$ Hz, 2H), 5.24 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 148.8$, 141.4, 136.7, 133.8, 132.6, 131.2, 130.2, 129.12, 129.08, 129.0, 128.7, 128.10, 128.06, 128.0, 127.6, 126.7, 126.0, 125.3, 123.7, 123.1, 117.3, 50.5; HR-MS (ESI): $m/z = 361.1698$, calcd. for $C_{26}H_{20}N_2$ $[M+H]^+$: 361.1705.

1-Benzyl-2,4,5-triphenyl-1*H*-imidazole[27] **(4ma):** White solid, mp 159–161 °C. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.64$–7.57 (m, 4H), 7.32–7.07 (m, 14H), 6.75 (d, $J = 5.7$ Hz, 2H), 5.04 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 147.8$, 137.9, 137.3, 134.3, 130.8, 130.7, 129.9, 128.8, 128.6, 128.5, 128.4, 128.3, 128.3, 127.9, 127.8, 127.1, 126.6, 126.1, 125.7, 48.0; HR-MS (ESI): $m/z = 387.1858$, calcd. for $C_{28}H_{23}N_2$ $[M+H]^+$: 387.1861.

1-Benzyl-5-methyl-2,4-diphenyl-1*H*-imidazole[28] **(4na):** White solid, mp 139–141 °C. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.76$ (d, $J = 7.7$ Hz, 2H), 7.56–7.54 (m, 2H), 7.40–7.21 (m, 9H), 7.00 (d, $J = 7.3$ Hz, 2H), 5.14 (s, 2H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 147.3$, 137.6, 136.8, 135.1, 130.7, 128.8, 128.6, 128.5, 128.3, 128.1, 127.4, 127.1, 126.1, 125.4, 124.7, 47.8, 10.3; HR-MS (ESI): $m/z = 325.1718$, calcd. for $C_{23}H_{20}N_2$ $[M+H]^+$: 325.1705.

1-(4-Methylbenzyl)-4-phenyl-2-*p*-tolyl-1*H*-imidazole (4ab): White solid, mp 111–113 °C. IR (KBr): ν = 1608, 1450, 1243, 1181, 1025, 823, 738, 695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.81$ (d, $J = 7.7$ Hz, 2H), 7.49 (d, $J = 8.0$ Hz, 2H), 7.33 (t, $J = 7.7$ Hz, 2H), 7.21–7.18 (m, 4H), 7.12 (d, $J =$ 7.9 Hz, 2H), 7.00 (d, $J = 8.0$ Hz, 2H), 5.11 (s, 2H), 2.36 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 148.7$, 141.3, 138.9, 137.7, 134.3, 134.0, 129.7, 129.3, 129.0, 128.6, 127.7, 126.8, 126.7, 125.0, 116.7, 50.3, 21.4, 21.1; HR-MS (ESI): $m/z = 339.1859$, calcd. for $C_{24}H_{22}N_2$ $[M+H]^+$: 339.1861.

1-(4-Fluorobenzyl)-2-(4-fluorophenyl)-4-phenyl-1*H*-imidazole (4ac): White solid, mp 108–110 °C. IR (KBr): ν = 1613, 1455, 1285, 1053, 946, 737, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.81$ (d, $J = 8.4$ Hz, 2H), 7.54–7.50 (m, 2H), 7.35 (t, $J = 7.7$ Hz, 2H), 7.24–7.19 (m, 2H), 7.08–6.97 (m, 6H), 5.09 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 163.1$, 162.3, 147.4, 141.5, 133.7, 132.3, 130.8, 128.5, 128.3, 126.9, 126.4, 124.8, 116.6, 115.9, 115.6, 49.7; HR-MS (ESI): $m/z =$ 347.1356, calcd. for $C_{22}H_{16}F_2N_2$ $[M+H]^+$: 347.1360.

1-(3-Chlorobenzyl)-2-(3-chlorophenyl)-4-phenyl-1*H*-imidazole (4ad): White solid, mp 125–127 °C. IR (KBr): ν = 1599, 1473, 1203, 1083, 887, 784, 750, 691 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.83$ (d, $J = 8.4$ Hz, 2H), 7.63 (s, 1H), 7.40–7.24 (m, 9H), 7.12 (s, 1H), 7.99–6.97 (m, 1H), 5.18 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 147.0$, 142.0, 138.4, 135.1, 134.7, 133.6, 131.9, 130.4, 129.9, 129.21, 129.18, 128.6, 128.4, 127.1, 126.78, 126.77, 124.9, 124.7, 117.1, 50.0; HR-MS (ESI): $m/z = 379.0763$, calcd. for $C_{22}H_{16}Cl_2N_2$ $[M+H]^+$: 379.0769.

1-(4-Methoxybenzyl)-2-(4-methoxyphenyl)-4-phenyl-1*H*-imidazole (4ae): White solid, mp 117–119 °C. IR (KBr): ν =

1611, 1514, 1452, 1249, 1177, 1030, 834, 743, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.84$ (d, $J = 8.4$ Hz, 2H), 7.57–7.53 (m, 2H), 7.36 (t, $J = 7.7$ Hz, 2H), 7.26–7.20 (m, 2H), 7.06 (d, $J = 8.7$ Hz, 2H), 6.97–6.94 (m, 2H), 6.89–6.86 (m, 2H), 5.11 (s, 2H), 3.83 (s, 3H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 160.1$, 159.2, 148.3, 141.0, 134.1, 130.3, 128.8, 128.4, 128.0, 126.6, 124.8, 122.9, 116.3, 114.2, 113.9, 55.22, 55.19, 49.9; HR-MS (ESI): $m/z = 371.1755$, calcd. for $C_{24}H_{22}N_2O_2$ $[M+H]^+$: 371.1760.

1-(3-Methoxybenzyl)-2-(3-methoxyphenyl)-4-phenyl-1*H*-imidazole (4af): White solid, mp 113–115 °C. IR (KBr): $\nu =$ 1601, 1460, 1262, 1155, 1040, 863, 784, 734, 695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.83$ (d, $J = 7.4$ Hz, 2H), 7.37–7.17 (m, 8H), 6.94 (d, $J = 7.1$ Hz, 1H), 6.83 (d, $J =$ 8.3 Hz, 1H), 6.71 (d, $J = 7.6$ Hz, 1H), 6.65 (s, 1H), 5.17 (s, 2H), 3.74 (s, 3H), 3.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 160.1$, 159.6, 148.3, 141.4, 138.4, 133.9, 131.5, 130.0, 129.6, 128.5, 126.7, 124.9, 121.1, 118.8, 116.9, 115.3, 114.0, 113.1, 112.4, 55.18, 55.16, 50.4; HR-MS (ESI): $m/z =$ 371.1753, calcd. for $C_{24}H_{22}N_2O_2$ $[M+H]^+$: 371.1760.

1-(4-Fluorobenzyl)-2,4-bis(4-fluorophenyl)-1*H*-imidazole (4hc): White solid, mp 124–126 °C. IR (KBr): $\nu = 1604$, 1503, 1227, 1157, 1093, 840, 765 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.78$ (dd, $J = 8.6$, 5.5 Hz, 2H), 7.55 (dd, $J = 8.5$, 5.4 Hz, 2H), 7.17–7.02 (m, 9H), 5.15 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 162.7$, 162.4, 162.0, 147.6, 140.8, 132.3, 130.9, 130.1, 128.4, 126.5, 116.28, 116.26, 116.0, 115.8, 115.4, 49.9; HR-MS (ESI): $m/z = 365.1269$, calcd. for $C_{22}H_{15}F_3N_2$ $[M+H]^+$: 365.1266.

4-(4-Fluorophenyl)-1-(4-methoxybenzyl)-2-(4-methoxyphenyl)-1*H*-imidazole (4he): White solid, mp 121–123 °C. IR (KBr): $\nu = 1607$, 1505, 1249, 1178, 1030, 949, 836, 765 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.78$ (dd, $J = 8.6$, 5.5 Hz, 2H), 7.54 (d, $J = 8.6$ Hz, 2H), 7.14 (s, 1H), 7.08–7.02 (m, 4H), 6.96 (d, $J = 8.7$ Hz, 2H), 6.88 (d, $J = 8.6$ Hz, 2H), 5.11 (s, 2H), 3.84 (s, 3H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 161.9$, 160.2, 159.3, 148.4, 140.3, 130.4, 128.8, 128.1, 126.4, 122.9, 115.9, 115.3, 114.4, 114.0, 111.5, 55.30, 55.27, 50.0; HR-MS (ESI): $m/z = 389.1660$, calcd. for $C_{24}H_{21}FN_2O_2$ $[M+H]^+$: 389.1665.

1-(4-Methoxybenzyl)-2,4-bis(4-methoxyphenyl)-1*H*-imidazole (4ee): White solid, mp 118–120 °C. IR (KBr): $\nu = 1609$, 1455, 1278, 1150, 1042, 828, 739, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.74$ (d, $J = 8.8$ Hz, 2H), 7.54 (d, $J =$ 8.8 Hz, 2H), 7.10 (s, 1H), 7.06 (d, $J = 8.7$ Hz, 2H), 6.96–6.86 (m, 6H), 5.10 (s, 2H), 3.83 (s, 3H), 3.81 (s, 3H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 160.1$, 159.2, 158.6, 148.1, 141.0, 130.4, 128.9, 128.1, 127.0, 126.1, 123.0, 115.3, 114.3, 114.0, 113.9, 55.28, 55.26, 55.2, 49.9; HR-MS (ESI): $m/z = 401.1855$, calcd. for $C_{25}H_{24}N_2O_3$ $[M+H]^+$: 401.1865.

General Procedure for the Synthesis of Polysubstituted Imidazoles 4aaa–4aag in a One-Pot Manner

The mixture of acetophenone (**1a**, 0.5 mmol), benzylamine (**2a**, 0.5 mmol) and TsOH (10 mol%) was stirred in toluene (2 mL) at reflux conditions under nitrogen atmosphere for 2 h. And then the solution was evaporated to dryness under reduced pressure. Arylamine (2.5 equiv.), I_2 (20 mol%) and DMSO (2 mL) were added and the reaction was heated to 90 °C under oxygen atmosphere with stirring for 5 h. After completion of the reaction, 10 mL water were added to quench the reaction. The aqueous solution was extracted with diethyl ether (3×10 mL) and the combined extract was dried with anhydrous $MgSO_4$. The solvent was removed and the crude product was separated by flash column chromatography on silica gel to give the pure product.

1-Ethyl-2,4-diphenyl-1*H*-imidazole (4aaa): White solid, mp 90–92 °C. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.85$ (d, $J =$ 8.0 Hz, 2H), 7.64 (d, $J = 7.7$ Hz, 2H), 7.49–7.43 (m, 3H), 7.38 (t, $J = 7.6$ Hz, 2H), 7.33 (s, 1H), 7.24 (t, $J = 7.6$ Hz, 1H), 4.06 (q, $J = 7.3$ Hz, 2H), 1.44 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 147.8$, 141.3, 134.2, 130.8, 129.0, 128.8, 128.6, 128.5, 126.7, 124.9, 115.5, 41.7, 16.5; HR-MS (ESI): $m/z = 249.1405$, calcd. for $C_{17}H_{16}N_2$ $[M+H]^+$: 249.1392.

2,4-Diphenyl-1-propyl-1*H*-imidazole[26] **(4aab):** White solid, mp 87–89 °C. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.85$ (d, $J = 7.2$ Hz, 2H), 7.63 (d, $J = 7.7$ Hz, 2H), 7.49–7.36 (m, 5H), 7.31 (s, 1H), 7.24 (t, $J = 7.4$ Hz, 1H), 3.97 (t, $J = 7.6$ Hz, 2H), 1.86–1.76 (m, 2H), 0.91 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 148.1$, 141.1, 134.2, 131.0, 129.1, 128.8, 128.6, 128.5, 126.6, 124.9, 116.0, 48.5, 24.4, 11.1; HR-MS (ESI): $m/z = 263.1542$, calcd. for $C_{18}H_{18}N_2$ $[M+H]^+$: 263.1548.

1-Butyl-2,4-diphenyl-1*H*-imidazole (4aac): White solid, mp 81–83 °C. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.20$ (d, $J =$ 7.3 Hz, 2H), 7.97 (d, $J = 6.7$ Hz, 2H), 7.80 (d, $J = 7.4$ Hz, 2H), 7.74–7.68 (m, 3H), 7.65 (s, 1H), 7.58 (t, $J = 7.5$ Hz, 1H), 4.34 (t, $J = 7.4$ Hz, 2H), 2.14–2.06 (m, 2H), 1.70–1.60 (m, 2H), 1.23 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 148.1$, 141.1, 134.2, 130.9, 129.1, 128.7, 128.50, 128.46, 126.6, 124.8, 116.0, 46.6, 33.1, 19.7, 13.5. HR-MS (ESI): $m/z =$ 277.1712, calcd. for $C_{19}H_{20}N_2$ $[M+H]^+$: 277.1705.

1-Isopropyl-2,4-diphenyl-1*H*-imidazole[29] **(4aad):** White solid, mp 117–119 °C. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.85$ (d, $J = 7.2$ Hz, 2H), 7.58 (dd, $J = 8.0$, 1.5 Hz, 2H), 7.48–7.34 (m, 6H), 7.21 (t, $J = 7.4$ Hz, 1H), 4.57–4.47 (m, 1H), 1.44 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 147.4$, 141.3, 134.2, 131.0, 129.2, 128.7, 128.5, 128.4, 126.5, 124.7, 111.7, 47.9, 23.9; HR-MS (ESI): $m/z = 263.1534$, calcd. for $C_{18}H_{18}N_2$ $[M+H]^+$: 263.1548.

1-*sec*-Butyl-2,4-diphenyl-1*H*-imidazole (4aae): White solid, mp 94–96 °C. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.87$ (d, $J = 8.0$ Hz, 2H), 7.58 (d, $J = 7.8$ Hz, 2H), 7.48–7.35 (m, 6H), 7.24 (t, $J = 7.4$ Hz, 1H), 4.28–4.20 (m, 1H), 1.84–1.70 (m, 2H), 1.48 (d, $J = 6.7$ Hz, 3H), 0.76 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 148.3$, 141.5, 134.3, 131.2, 129.4, 128.8, 128.5, 128.4, 126.5, 124.8, 111.6, 53.8, 31.0, 22.1, 10.6; HR-MS (ESI): $m/z = 277.1709$, calcd. for $C_{19}H_{20}N_2$ $[M+H]^+$: 277.1705.

1-*tert*-Butyl-2,4-diphenyl-1*H*-imidazole (4aaf): White solid, mp 134–136 °C. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.82$ (d, $J = 7.1$ Hz, 2H), 7.51–7.48 (m, 2H), 7.44–7.33 (m, 6H), 7.21 (t, $J = 7.4$ Hz, 1H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 147.7$, 138.9, 134.9, 134.2, 130.8, 128.9, 128.4, 127.9, 126.5, 124.8, 113.7, 57.1, 31.6; HR-MS (ESI): $m/z =$ 277.1691, calcd. for $C_{19}H_{20}N_2$ $[M+H]^+$: 277.1705.

1-Cyclohexyl-2,4-diphenyl-1*H*-imidazole (4aag): White solid, mp 125–127 °C. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.85$ (d, $J = 7.3$ Hz, 2H), 7.60 (d, $J = 8.2$ Hz, 2H), 7.50–7.35 (m, 6H), 7.23 (t, $J = 7.4$ Hz, 1H), 4.13–4.05 (m, 1H), 2.06 (d, $J =$

13.7 Hz, 2H), 1.88 (d, $J=12.9$ Hz, 2H), 1.75–1.66 (m, 3H), 1.37–1.23 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=147.5$, 141.1, 134.3, 131.1, 129.2, 128.7, 128.6, 128.4, 126.5, 124.8, 112.7, 55.8, 34.7, 25.6, 25.2; HR-MS (ESI): $m/z=303.1859$, calcd. for $C_{21}H_{22}N_2$ $[M+H]^+$: 303.1861.

General Procedure for Bromination of the Resultant 1,2,4-Trisubstituted Imidazoles

A round-bottom flask equipped with a magnetic stirrer bar was charged with 0.2 mmol of imidazole dissolved in 1.0 mL CH_2Cl_2, and the solution of NBS (1.1 equiv. in 1.0 mL CH_2Cl_2) was dropwise added at room temperature. After completion of the reaction (as monitored by TLC), the mixture was directly subjected to flash column chromatography on silica gel to give the pure product.

1-Benzyl-5-bromo-2,4-diphenyl-1*H*-imidazole (5a): White solid, mp 106–108 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=8.09$ (d, $J=7.2$ Hz, 2H), 7.56–7.53 (m, 2H), 7.44–7.27 (m, 9H), 7.04 (d, $J=7.0$ Hz, 2H), 5.29 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=149.1$, 138.5, 136.3, 133.1, 130.3, 129.3, 128.9, 128.7, 128.6, 128.2, 127.6, 127.3, 126.8, 125.8, 101.6, 49.3; HR-MS (ESI): $m/z=389.0646$, calcd. for $C_{22}H_{17}BrN_2$ $[M+H]^+$: 389.0653.

1-Benzyl-5-bromo-4-(4-bromophenyl)-2-phenyl-1*H*-imidazole (5b): White solid, mp 149–151 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.99$ (d, $J=8.5$ Hz, 2H), 7.56–7.54 (m, 4H), 7.42–7.30 (m, 6H), 7.06 (d, $J=7.4$ Hz, 2H), 5.31 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=149.3$, 137.5, 136.1, 132.1, 131.3, 130.1, 129.5, 128.9, 128.71, 128.67, 128.3, 127.7, 125.8, 121.2, 101.8, 49.4; HR-MS (ESI): $m/z=466.9752$, calcd. for $C_{22}H_{16}Br_2N_2$ $[M+H]^+$: 466.9758.

5-Bromo-1-(4-fluorobenzyl)-2,4-bis(4-fluorophenyl)-1*H*-imidazole (5c): White solid, mp 150–152 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=8.03$ (dd, $J=8.3$, 5.7 Hz, 2H), 7.49 (dd, $J=8.2$, 5.5 Hz, 2H), 7.14–6.99 (m, 8H), 5.25 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=163.5$, 162.3, 162.3, 148.2, 138.0, 131.8, 130.8 129.1, 128.6, 127.7, 126.4, 116.1, 115.9, 115.3, 101.2, 48.8; HR-MS (ESI): $m/z=443.0364$, calcd. for $C_{22}H_{14}BrF_3N_2$ $[M+H]^+$: 443.0371.

5-Bromo-4-(4-fluorophenyl)-1-(4-methoxybenzyl)-2-(4-methoxyphenyl)-1*H*-imidazole (5d): White solid, mp 147–149 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=8.05$ (dd, $J=8.6$, 5.6 Hz, 2H), 7.47 (d, $J=8.6$ Hz, 2H), 7.10 (t, $J=8.7$ Hz, 2H), 6.97 (d, $J=8.6$ Hz, 2H), 6.91 (d, $J=8.7$ Hz, 2H), 6.86 (d, $J=8.6$ Hz, 2H), 5.21 (s, 2H), 3.80 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=162.2$, 160.5, 159.1, 149.1, 137.5, 130.2, 129.5, 128.6, 128.4, 127.3, 122.8, 115.2, 114.3, 114.1, 100.8, 55.3, 55.3, 48.9; HR-MS (ESI): $m/z=467.0756$, calcd. for $C_{24}H_{20}BrFN_2O_2$ $[M+H]^+$: 467.0770.

5-Bromo-1-isopropyl-2,4-diphenyl-1*H*-imidazole (5e): White solid, mp 108–110 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.99$ (d, $J=8.1$ Hz, 2H), 7.57–7.47 (m, 5H), 7.42 (t, $J=7.7$ Hz, 2H), 7.30 (t, $J=7.3$ Hz, 1H), 4.77–4.66 (m, 1H), 1.62 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=149.0$, 139.3, 133.2, 131.4, 129.6, 129.3, 128.5, 128.1, 127.4, 127.2, 98.2, 50.6, 21.7; HR-MS (ESI): $m/z=341.0639$, calcd. for $C_{18}H_{17}BrN_2$ $[M+H]^+$: 341.0653.

5-Bromo-4-(4-bromophenyl)-1-(4-methylbenzyl)-2-*p*-tolyl-1*H*-imidazole (5f): White solid, mp 130–132 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.98$ (d, $J=8.3$ Hz, 2H), 7.54 (d, $J=8.3$ Hz, 2H), 7.44 (d, $J=7.9$ Hz, 2H), 7.19 (d, $J=7.9$ Hz, 2H), 7.15 (d, $J=7.8$ Hz, 2H), 6.94 (d, $J=7.8$ Hz, 2H), 5.26 (s, 2H), 2.38 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=149.4$, 139.4, 137.3, 137.3, 133.2, 132.2, 131.3, 129.5, 129.3, 128.6, 128.3, 127.3, 125.7, 121.0, 101.5, 49.2, 21.3, 21.0; HR-MS (ESI): $m/z=495.0063$, calcd. for $C_{24}H_{20}Br_2N_2$ $[M+H]^+$: 495.0071.

1-Benzyl-4-(4-chlorophenyl)-2,5-diphenyl-1*H*-imidazole (5ia): White solid, mp 176–178 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.67$–7.65 (m, 2H), 7.54–7.52 (m, 2H), 7.41–7.30 (m, 6H), 7.21–7.16 (m, 7H), 6.82–6.79 (m, 2H), 5.11 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta=148.1$, 137.3, 137.0, 133.0, 131.9, 130.9, 130.7, 130.6, 130.2, 129.0, 128.9, 128.8, 128.7, 128.6, 128.5, 128.1, 127.9, 127.3, 125.9, 48.25; HR-MS (ESI): $m/z=421.1454$, calcd. for $C_{28}H_{21}ClN_2$ $[M+H]^+$: 421.1472.

Acknowledgements

We thank the National Natural Science Foundation of China (20932002 and 21172076), the National Basic Research Program of China (973 Program) (No. 2011CB808600), the Guangdong Natural Science Foundation (No. 10351064101000000), the China Postdoctoral Science Foundation (2011M501318) and the Fundamental Research Funds for the Central Universities (2010ZP0003, 2012ZP0011) for financial support.

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