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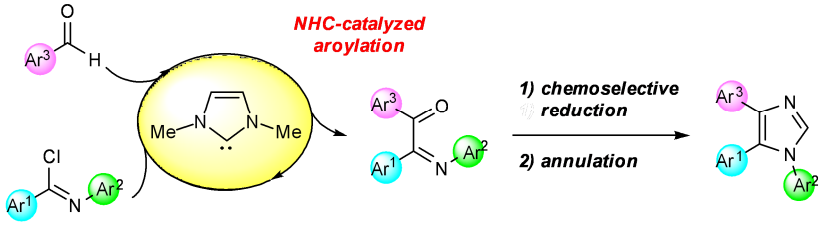

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ABSTRACT

An alternative synthetic route to 1,4,5-trisubstituted imidazoles from α-imino ketone, which can be prepared from imidoyl chlorides and aromatic aldehydes via *N*-heterocyclec carbene-catalyzed aroylation was developed. This methodology consists of simple transformations, allowing a rapid access to imidazole derivatives with various aryl substituents at the desired positions.

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1. Introduction

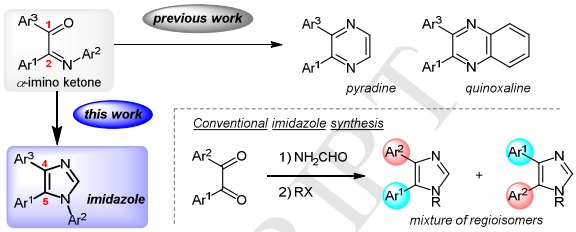
N-Heterocyclic compounds are of great interest for drug discovery and are widely used as active components of pharmaceuticals. The high electronegativity of the nitrogen atom results in polarization of the C–N bond, which allows interactions between the heterocycle and biomolecules such as enzymes and receptors, through hydrogen bond formation with hydrophilic groups. Aromatic heterocycles can also interact through van der Waals interactions.[1]

Among nitrogen-containing heterocycles, imidazoles are of particular interest because of their abundance in biomolecules, including histidine, histamine,[2a] cyano cobalamin,[2b] and bioactive natural products such as sceptrin[2c] and nagelamides S[2d]. Furthermore, they typically appear in biologically active compounds such as anticancer,[3] antibacterial,[4] and antitubercular agents.[5] For example, dacarbazine is a chemotherapeutic agent for the treatment of various cancers; the methyldiazonium ions derived from its metabolism cause DNA methylation and inhibition of cell proliferation.[6] Another example is SK&F 86002, a pyridinyl imidazole-based p38 mitogen-activated protein kinase inhibitor with anti-inflammatory activity owing to the downregulation of inflammatory cytokine production in the monocyte/macrophage cell line THP-1.[7] Moreover, SK&F 86002 and its analogues have been used to treat Ebola virus infections.[8]

Imidazoles and their salts also have many other applications, e.g., in materials science[9] and synthetic organic chemistry.[10, 11] In particular, 2-substituted imidazole derivatives, such as 2-ethylimidazole, are widely used as hardeners for epoxy resins in the materials industry.[12] Moreover, *N*-heterocyclic carbenes (NHCs) generated from imidazolium salts can act as ligands for transition metal catalysts and as organocatalysts for reactions such as umpolung and homoenolate reactions.[11] In addition, *N*,*N*-dialkylimidazolium salts are among the most widely used ionic liquids, which find application as electrolytes and reaction solvents.[13] Because of their numerous advantages, the development of new and efficient synthetic methods to access imidazole derivatives is a subject of interest in various fields.

The classical methods for the construction of imidazole rings include condensation of benzils with two equivalents of formamide,[14] and amination of α-bromo ketones followed by annulation of the resulting amino ketones with formamide.[15] In addition, to date, various synthetic strategies have been developed to prepare imidazoles, such as pivalic acid –promoted multicomponent reaction involving the oxidation of internal alkynes to form benzil intermediates followed by cyclocondensation of amidines,[16] and metal-catalyzed domino reaction of propargylamines with tert-butylisonitrile.[17] In particular, a number of transition metal-catalyzed approaches have been reported.[18] However, to the best of our knowledge, the selective synthesis of arbitrarily substituted triarylimidazoles from commercially available and inexpensive starting materials remains a challenge. Recently, Ila et al. reported a one-pot synthesis of 2,4,5-trisubstituted imidazoles from 1,3-bisaryl-monothio-1,3-diketones.[19] However, efficient and general methods for the regioselective synthesis of multisubstituted imidazoles have not yet been developed.

With this motivation, we investigated a straightforward selective route to trisubstituted imidazoles, which includes an NHC-catalyzed aroylation reaction, chemoselective reduction of the imino group, and annulation between the resulting secondary amine and formamide. Our recently reported protocol for the synthesis of pyradines and quinoxalines from α-imino ketones as versatile intermediates also urged us to develop a new synthetic route to imidazoles. In our synthesis, the 1-, 4-, and 5-substituents of imidazoles originate from the *N*-, 1-, and 2-substituents of iminoethanones, respectively, allowing us to access single isomers exclusively in contrast to the conventional synthetic method for 1,4,5-substituted imidazoles (Scheme 1). In other words, with an appropriate choice of starting materials, it is possible to synthesize 1,4,5-trisubstituted triazoles bearing the desired substituents at the expected positions.

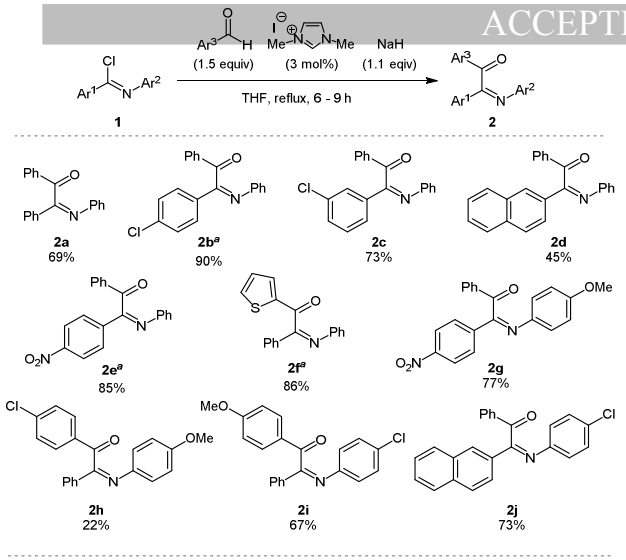


Scheme 1. Synthesis of heterocycles from α-imino ketones

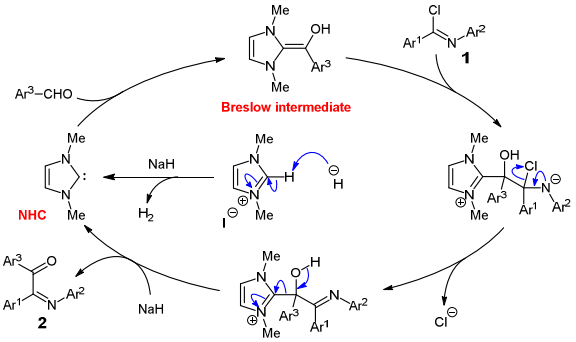
2. Results and discussion

First, the NHC-catalyzed aroylation was examined based on our previously reported procedure (Scheme 2).[20] Starting *N*-arylbenzimidoyl chlorides **1** were easily prepared by chlorination of the corresponding *N*-arylbenzamides. The reaction of **1** with aromatic aldehydes (1.5 equiv) in THF for 6–9 h in the presence of the NHC derived from the 1,3-dimethylimidazolium iodide precursor (3 mol%) and sodium hydride (1.1 equiv) afforded the desired α-imino ketones (for reaction mechanism, see the Supplementary data). As shown in the mechanism in Scheme 3, the NHC-catalyzed aroylation of **1** proceeded through the Breslow intermediate, which was formed from the aldehyde and the carbene generated by abstraction of the proton at the 2-position of the imidazolium salt and served as an acyl anion equivalent. The substrate scope of the reaction was investigated, and the results are summarized in Scheme 2. Electron-deficient benzimidoyl chlorides and sterically hindered naphthyl derivatives were well tolerated to give the corresponding adducts in moderate to high yields (**2b**–**2e**, **2j**). The reaction of *N*-(4-methoxyphenyl)benzimidoyl chloride provided aroylated compound **2h** in low yield, presumably because of the low electrophilicity of the imino carbon atom owing to the electron-donating effect of the *N*-4-methoxyphenyl group. This effect was confirmed by the aroylation of benzimidoyl chlorides bearing an aliphatic substituent on the imine nitrogen atom, which did not afford the corresponding α-imino ketones. However, this finding is contrary to the report by Huang et al., which indicates that *N*-(*n*-octyl)trifluoroacetimidoyl chloride gives the corresponding aroylated compound under similar conditions.[21]

The subsequent selective reduction of a functional group can be challenging in the presence of other functional groups with similar chemical reactivity, such as carbonyl and imino groups. Our preliminary studies showed that the reducing agents commonly used in reductive amination reactions, namely, sodium triacetoxyborohydride, sodium cyanoborohydride, and Hantzsch ester, were not suitable for the chemoselective reduction of α-imino ketones (see Supplementary data). To overcome this problem, we used 2-picoline borane, which was previously reported as an alternative reagent for reductive amination.[22] An evaluation of reduction conditions revealed that high yields were achieved by using an equimolar amount of 2-picoline borane at room temperature in the presence of a catalytic amount of phenylphosphinic acid (Table 1).

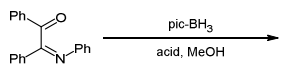


Scheme 2. Substrate scope of the aroylation reaction.
[a] Previous data reported by our group. 1.3 equiv of NaH was used.[20]



Scheme 3. Mechanism of the aroylation reaction

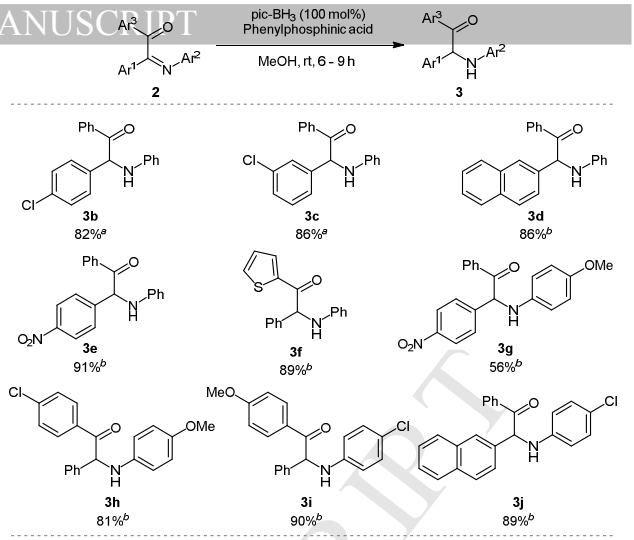
Table 1. Optimization of the chemoselective reduction conditions



Entry	Pic-BH3 (mol%)	Condition	Yield (%)
1	33	6 h, 0 °C, AcOH (excess)	22
2	33	6 h, 0 °C, $C_6H_5P(O)(OH)H$[a]	21
3	50	8 h, rt, $C_6H_5P(O)(OH)H$[a]	53
4	66	6 h, rt, $C_6H_5P(O)(OH)H$[a]	74
5	100	6 h, rt, $C_6H_5P(O)(OH)H$[a]	84
6	100	6 h, rt, $C_6H_5P(O)(OH)H$[b]	84
7	100	6 h, rt, AcOH (excess)	78

[a] 100 mol% of phenylphosphinic acid was used. [b] 20 mol% of phenylphosphinic acid was used.

With the optimized conditions in hand, the substrate scope of the chemoselective reduction was investigated (Scheme 4). Imine moieties bearing an electron-withdrawing or electron-donating group were selectively reduced to afford the desired secondary amines (**3b**, **3c**, **3e**, **3h**, **3i**, **3j**). Substrates with a naphthyl or heteroaryl substituent were also applicable to the reaction to give **3d**, **3j** or **3f**, respectively. On the other hand, the reaction of **2g** was sluggish, probably because of the low reactivity of the imino carbon owing to the push-pull structure.



Scheme 4. Substrate scope of the chemoselective reduction.

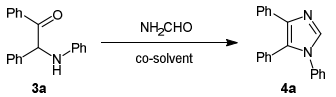
[a] 20 mol% of phenylphosphinic acid was used. [b] 50 mol% of phenylphosphinic acid was used, and the reaction was conducted in MeOH/CH_2Cl_2 (5/1).

Next, the annulation between α-amino ketones and formamide to form the corresponding imidazoles was examined (Table 2). The reaction conditions were optimized using compound **3a** as a model substrate. First, formamide solutions containing high (M = 0.4) or low (M = 0.03) concentrations of **3a** were heated in an open system (Table 2, entries 1, 2). However, the desired compound was not obtained owing to rapid self-condensation of **3a**. Thus, to prevent self-condensation, an ethyl acetate solution of **3a** was added over 1 h to a large excess of formamide at 180 °C, and the reaction was continued at the same temperature for 7 h to afford desired imidazole **4a** in low yield (Table 2, entries 3, 4).

When THF was used instead of ethyl acetate, the yield of **4a** increased up to 72% (Table 2, entry 6). Other attempts were made to further improve the efficiency of the annulation. A slower addition rate of the THF solution of **3a** by using a syringe pump under an argon atmosphere combined with the use of diethyl ether as the extraction solvent instead of ethyl acetate led to an improved yield (Table 2, entry 7). With the aim of accelerating the reaction, a Brønsted acid was tested as a catalyst, but a lower yield was observed (Table 2, entries 8, 9). Moreover, addition of a Lewis acid or a hypervalent iodine reagent[22] was not beneficial for the annulation, instead promoting the three-component condensation of formamide (Table 2, entries 10, 11). These results indicate that the transformation should be carried out under an argon atmosphere, and that an acidic environment was detrimental to the reaction rate and yield. Moreover, the slow addition of the α-amino ketone in THF via a syringe pump over 2 h was found to be crucial.

We next investigated the scope of the annulation reaction using a variety of α-amino ketones (Scheme 5). Under the optimized conditions, both electron-rich and electron-deficient aromatic substrates afforded the corresponding imidazoles in good yields. Notably, the reaction of nitro substituted α-amino ketones **3e** and **3g** did not proceed at all, probably because of their instability and the low nucleophilicity of the amino group, and the corresponding oxidation products, i.e., α-imino ketones **2e** and **2g**, were obtained.

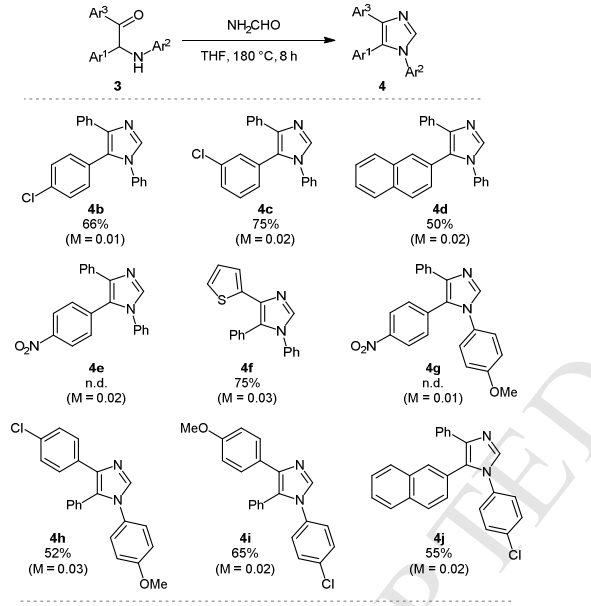
Table 2. Optimization of the annulation conditions



3a 4a

Entry	NH_2CHO (mL)	Co-solvent	Condition	Yield (%)
1	5 (M = 0.4)	-	140 °C	n.d.
2	35 (M = 0.03)	-	200 °C	n.d.
3[a]	30 (M = 0.04)	AcOEt	180 °C	10
4[a]	50 (M = 0.02)	AcOEt	180 °C	55
5[a]	30 (M = 0.05)	THF	180 °C	51
6[a]	50 (M = 0.03)	THF	180 °C	72
7[b]	50 (M = 0.02)	THF	180 °C	83
8[b]	50 (M = 0.02)	THF	180 °C, AcOH	77
9[b]	50 (M = 0.02)	THF	180 °C, HCl	59
10[b]	50 (M = 0.03)	THF	120 °C, $BF_3 \cdot Et_2O$	21
11[b]	50 (M = 0.02)	THF	rt, PIFA[c]	trace

[a] Addition over 1 h using a dropping funnel, and a reaction time of 7 h. [b] Addition over 2 h using a syringe pump under an argon atmosphere, and a reaction time of 8 h. [c] PIFA: [bis(trifluoroacetoxy)iodo]benzene.[23]



Scheme 5. Substrate scope of the annulation reaction.

In summary, we have developed a regioselective synthesis of 1,4,5-triaryl imidazoles from easily accessible starting materials. The key reactions are NHC-catalyzed aroylation of imidoyl chlorides with aromatic aldehydes, chemoselective reduction of the aroylated compounds, and annulation of the resulting α-amino ketones with formamide. This methodology allows rapid access to imidazole derivatives, paving the way for the construction of chemical libraries that will be of great value in the pharmaceutical and agrochemical industries. Further derivatization of the resulting imidazoles, such as regioselective functionalization, is in progress and will be reported in due course.

3. Experimental

3.1. Materials & methods

Reagents and solvents were purchased from commercial sources and used without further purification. All reactions were performed under argon and stirring unless otherwise noted. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a JEOL JNM-ECX (300 and 500 MHz) spectrometer. Chemical shifts were recorded in parts per million (ppm, δ) relative to tetramethylsilane (δ 0.00). ^{1}H NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), dd (doublet of doublets), dt (doublet of triplets), m (multiplets), etc. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a JEOL JNM-ECX (75 and 125 MHz) spectrometer. Mass spectra were recorded using a TOF (ESI) analyzer or a magnetic sector (FAB) analyzer, and IR spectra were recorded on a JASCO FT-IR 4100 spectrometer. Melting points were measured using an ATM-02, AS ONE melting point apparatus. Medium-pressure liquid chromatography was performed using a Yamazen YFLC W-Prep 2XY system. For slow addition of solutions, a SIMDOS® 02 diaphragm dosing pump (KNF Japan) was used. Column chromatography was performed using acidic Wako-gel 300 (45–75 μm) by Wako Chemicals. For thin-layer chromatography (TLC) analysis, Merck TLC plates (silica gel 60G F254 0.25 mm) were used. The TLC plates were visualized by fluorescence under a UV lamp (254 or 365 nm).

3.1.1. General procedure for synthesis of α-imino ketones

To *N*-arylimidoyl chlorides (10.4 mmol) in two-necked flask equipped with a magnetic stir bar, 1.5 equiv. of aromatic aldehyde (16.1 mmol), 3 mol % of 1.3-dimethyimidazolium iodide (0.0701 g, 0.313 mmol) and THF (60 mL) was addded, then 1.1 equiv. of sodium hydride (0.458g, 11.4 mmol) was added at 0 °C, and the resulting solution was stirred at reflux temperature for 6 - 9 hours. After completion of the reaction, the solution was poured into ice water (50 mL), extracted three times with AcOEt. The organic layer was washed with brine, and dried over Na_2SO_4. After filtration and concentration under reduced pressure, the residue was purified by silica gel column chromatography (*n*-hexane: AcOEt = 24: 1) to afford α-imino ketones **2a** – **2j**.

*3.1.1.1. 1,2-Diphenyl-2-(phenylimino)ethanone (**2a**[24]).* Yellow solid (recrystallized from AcOEt/*n*-hexane); 70% yield (1.50 g), R_f = 0.51 (9:1 *n*-hexane/AcOEt), ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.89 (dt, J = 6.4, 1.7 Hz, 2H), 7.76 (dt, J = 7.7, 1.2 Hz, 2H), 7.51-7.42 (m, 4H), 7.34 (t, J = 7.6 Hz, 2H), 7.13 (t, J = 7.7 Hz, 2H), 6.95-6.87 (m, 3H), ^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.6, 177.5, 166.2, 149.2, 135.1, 134.6, 134.3, 131.6, 128.8, 128.6, 128.1, 124.6, 120.4.

*3.1.1.2. 2-(3-Chlorophenyl)-1-phenyl-2-(phenylimino)ethanone (**2c**[25]).* Yellow solid (recrystallized from AcOEt/*n*-hexane); 73% yield (1.51 g); R_f = 0.49 (9:1 *n*-hexane/AcOEt); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.98 (t, J = 1.6 Hz, 1H), 7.74 (dt, J = 8.4, 1.6 Hz, 2H), 7.68 (dt, J = 7.8, 1.6 Hz, 1H), 7.52-7.45 (m, 2H), 7.39-7.32 (m, 3H), 7.14 (t, J = 8.4 Hz, 2H), 6.97-6.86 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.9, 164.7, 148.7, 136.7, 135.01, 134.47, 134.2, 131.6, 130.0, 129.2, 128.8, 128.6, 127.7, 126.4, 125.0, 120.3.

*3.1.1.3. 2-(Naphthalene-2-yl)-1-phenyl-2-(phenylimino)ethanone (**2d**).* Yellow solid (recrystallized from AcOEt/*n*-hexane); 45% yield (0.949 g); mp 151 – 153 °C; R_f = 0.44 (9:1 *n*-hexane/AcOEt); IR (FT): cm^{-1} = 1666 (C=O), ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.25 (dd, J = 8.6, 1.7 Hz, 1H), 8.11 (s, 1H), 7.94 (d, J = 8.6 Hz, 1H), 7.88-7.78 (m, 4H), 7.58-7.45 (m, 3H), 7.34 (t, J = 7.8 Hz, 2H), 7.15 (t, J = 7.8 Hz, 2H), 6.94 (t, J = 8.4 Hz, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 197.6, 166.3, 134.9, 134.8, 134.3, 132.8, 132.5, 130.0, 129.3, 129.1, 128.8, 128.6, 127.9, 127.8, 126.7, 124.7, 123.7, 120.5; HRMS (FAB): *m/z*

[335.1310] calcd. for $C_{24}H_{18}NO$ (M+H): 336.1388; found: 336.1389.

*3.1.1.4. 2-(4-Methoxyphenylimino)-2-(4-nitrophenyl)-1-phenylethanone (**2g**).* Orange solid (recrystallized from AcOEt/*n*-hexane); 77% yield (1.31 g); mp 128 – 129 °C; R_f = 0.22 (9:1 *n*-hexane/AcOEt); IR (FT): cm^{-1} = 1662 (C=O), 1521, 1504, 1362, 1343 (NO_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.27 (dt, *J* = 9.2, 2.2 Hz, 2H), 8.05 (dt, *J* = 9.2, 2.2 Hz, 2H), 7.75 (d, *J* = 7.4 Hz, 2H), 7.52 (tt, *J* = 7.4, 1.4 Hz, 1H), 7.37 (t, *J* = 7.4 Hz, 2H), 6.96 (dt, *J* = 9.6, 2.8 Hz, 2H), 6.71 (dt, *J* = 9.6, 2.8 Hz, 2H), 3.70 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 198.0, 162.3, 157.9, 149.2, 141.4, 140.8, 134.8, 133.9, 129.2, 129.1, 128.8, 123.9, 122.7, 114.1, 55.3; HRMS (FAB): *m/z* [360.1110] calcd. for $C_{21}H_{17}N_2O_4$ (M+H): 361.1188; found: 361.1199.

*3.1.1.5. 1-(4-Chlorophenyl)-2-(4-methoxyphenylimino)-2-phenylethanone (**2h**).* Orange solid (recrystallized from CH_2Cl_2/*n*-hexane); 22% yield (0.154 g); mp 146 – 147 °C; R_f = 0.39 (9:1 *n*-hexane/AcOEt); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 6.9 Hz, 2H) , 7.70 (dt, *J* = 8.8, 2.1 Hz, 2H), 7.49-7.41 (m, 3H), 7.31 (d, *J* = 8.6 Hz, 2H), 6.88 (dt, *J* = 9.7, 2.7 Hz, 2H), 6.69 (dt, *J* = 9.7, 2.7 Hz, 2H), 3.70 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.5, 164.8, 157.1, 142.1, 141.0, 135.1, 132.8, 131.5, 130.5, 129.3, 128.8, 127.9, 122.2, 114.0, 55.3; HRMS (FAB): *m/z* [349.0870] calcd. for $C_{21}H_{17}ClNO_2$ (M+H): 350.0948; found: 350.0953.

*3.1.1.6. 2-(4-Chlorophenylimino)-1-(4-methoxyphenyl)-2-phenylethanone (**2i**).* Yellow solid (recrystallized from AcOEt/*n*-hexane); 67% yield (1.48 g); mp 120 – 122 °C; R_f = 0.29 (9:1 *n*-hexane/AcOEt); IR (FT): cm^{-1} = 1663 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.87 (dt, *J* = 7.3, 2.2 Hz, 2H) , 7.73 (dt, *J* = 9.4, 2.4 Hz, 2H), 7.50-7.41 (m, 3H), 7.11 (dt, *J* = 9.4, 2.4 Hz, 2H), 6.86-6.81 (m, 4H), 3.82 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 195.3, 190.8, 167.1, 164.6, 147.9, 135.0, 131.8, 129.9, 128.8, 128.7, 128.1, 127.6, 121.8, 114.3, 55.5; HRMS (FAB): *m/z* [349.0870] calcd. for $C_{21}H_{17}ClNO_2$ (M+H): 350.0948; found: 350.0959.

*3.1.1.7. 2-(4-Chlorophenylimino)-2-(naphthalene-2-yl)-1-phenylethanone (**2j**).* Yellow solid (recrystallized from AcOEt/*n*-hexane); 73% yield (1.36 g), mp 140 - 141 °C; R_f = 0.45 (9:1 *n*-hexane/AcOEt); IR (FT): cm^{-1} = 1661 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.22 (dd, *J* = 8.6, 1.7 Hz, 1H), 8.09 (s, 1H), 7.94 (d, *J* = 8.6 Hz, 1H), 7.87 (d, *J* = 8.6 Hz, 1H), 7.83-7.78 (m, 3H), 7.58-7.46 (m, 3H), 7.36 (t, *J* = 7.7 Hz, 2H), 7.12 (dt, *J* = 9.2, 2.5 Hz, 2H), 6.87 (dt, *J* = 9.2, 2.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 197.2, 167.0, 147.8, 135.0, 134.6, 134.5, 132.7, 132.2, 130.2, 130.0, 129.3, 129.2, 129.0, 128.8, 128.1, 127.8, 126.8, 123.5, 121.9; HRMS (FAB): *m/z* [369.0920] calcd. for $C_{24}H_{17}ClNO$ (M+H): 370.0999; found: 370.1020.

3.1.2. General procedure for synthesis of α-amino ketones

For most of α-iminoketones (**2d** – **2j**): A mixture of α-iminoketones (3.02 mmol), 2-picolineborane (0.333 g, 3.02 mmol), and phenylphosphinic acid (0.0876 g, 0.61 mmol) in MeOH and CH_2Cl_2 (24 mL, 5/1) was stirred at room temperature for 6 - 9 hours. For other α-imino ketones (**2a** – **2c**): The reaction was carried out in MeOH. Then, 20 mL of water was added and the mixture was evaporated to remove organic solvent. Subsequently, the product was extracted three times with AcOEt and the organic layer was washed with brine, and dried over Na_2SO_4. After concentration under reduced pressure, the residue was purified by silica gel column chromatography (*n*-hexane: AcOEt = 9: 1) to afford α-aminoketones **3a** – **3j**.

*3.1.2.1. 1,2-Diphenyl-2-(phenylamino)ethanone (**3a**[26]).* Yellow solid (recrystallized from CH_2Cl_2/*n*-hexane); 84% yield (0.705 g); R_f = 0.35 (*n*-hexane: AcOEt = 8 : 1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.00 (dt, *J* = 6.8, 1.5 Hz, 2H), 7.54 (tt, *J* = 7.3, 1.6 Hz, 1H), 7.46-7.40 (m, 4H), 7.31-7.10 (m, 5H), 6.70-6.65 (m, 3H), 6.02 (d, *J* = 6.4 Hz, 1H), 5.40 (d, *J* = 6.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.0, 146.1, 137.7, 135.1, 133.5, 129.2, 129.0, 128.9, 128.7, 128.4, 128.1, 117.8, 113.5, 62.7.

*3.1.2.2. 2-(4-Chlorophenyl)-1-phenyl-2-(phenylamino)ethanone (**3b**).* Yellow solid (recrystallized from CH_2Cl_2/*n*-hexane); 82% yield (0.685 g); mp 112 – 114 °C; R_f = 0.34 (8:1 *n*-hexane/AcOEt); IR (FT): cm^{-1} = 3417 (N-H), 1669 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 7.4 Hz, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.4 Hz, 2H), 7.38 (dt, *J* = 9.0, 2.3 Hz, 2H), 7.23-7.25 (m, 2H) , 7.13 (t, *J* = 7.6 Hz, 2H), 6.70 (t, *J* = 7.6 Hz, 1H), 6.64 (d, *J* = 7.6 Hz, 2H), 6.00 (d, *J* = 5.5 Hz, 1H), 5.42 (d, *J* = 5.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 196.6, 145.8, 136.3, 134.8, 134.0, 133.7, 129.4, 129.29, 129.25, 128.8, 128.8, 118.1, 113.5, 61.9; HRMS (FAB): *m/z* [321.0920] calcd. for $C_{20}H_{17}ClNO$ (M+H): 322.0999; found: 322.0993.

*3.1.2.3. 2-(3-Chlorophenyl)-1-phenyl-2-(phenylamino)ethanone (**3c**).* Yellow oil; 86% yield (0.634 g); R_f = 0.33 (8:1 *n*-hexane/AcOEt); IR (FT): cm^{-1} = 3400 (N-H), 1683 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 7.4 Hz, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.44-7.48 (m, 3H), 7.34 (d, *J* = 7.4 Hz, 1H), 7.13-7.23 (m, 4H), 6.65-6.72 (m, 3H), 5.99 (d, *J* = 6.1 Hz, 1H), 5.43 (d, *J* = 6.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 196.4, 145.7, 139.9, 134.9, 134.7, 133.8, 130.2, 129.3, 128.82, 128.77, 128.3, 128.0, 126.3, 118.1, 113.4, 62.0; HRMS (FAB): *m/z* [321.0920] calcd. for $C_{20}H_{17}ClNO$ (M+H): 322.0999; found: 322.0991.

*3.1.2.4. 2-(Naphthalene-2-yl)-1-phenyl-2-(phenylamino)ethanone (**3d**).* Yellow solid (recrystallized from CH_2Cl_2/*n*-hexane); 87% yield (0.684 g); mp 133 – 135 °C; R_f = 0.34 (8:1 *n*-hexane/AcOEt); IR (FT): cm^{-1} = 3407 (N-H), 1677 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.03 (dt, *J* = 6.9, 1.6 Hz, 2H), 7.93 (d, *J* = 1.4 Hz, 1H), 7.80-7.73 (m, 3H), 7.56-7.39 (m, 6H), 7.12 (tt, *J* = 8.0, 1.9 Hz, 2H), 6.73-6.64 (m, 3H), 6.19 (d, *J* = 6.2 Hz, 1H), 5.51 (d, *J* = 6.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.0, 146.1, 135.2, 135.0, 133.5, 133.4, 133.0, 129.2, 129.0, 128.9, 128.7, 127.9, 127.6, 126.3, 125.4, 117.9, 113.5, 62.8; HRMS (FAB): *m/z* [337.1467] calcd. for $C_{24}H_{20}NO$ (M+H): 338.1545; found: 338.1551.

*3.1.2.5. 2-(4-Nitrophenyl)-1-phenyl-2-(phenylamino)ethanone (**3e**).* Yellow solid (recrystallized from CH_2Cl_2/*n*-hexane); 91% yield (0.485 g); mp 58 – 60 °C; R_f = 0.18 (8:1 *n*-hexane/AcOEt); IR (FT): cm^{-1} = 3378 (N-H), 1679 (C=O), 1521, 1342 (NO_2); ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.13 (d, *J* = 8.6 Hz, 2H), 7.98 (d, *J* = 8.0 Hz, 2H), 7.59-7.64 (m, 3H), 7.48 (t, *J* = 7.4 Hz, 2H), 7.15 (t, *J* = 8.0 Hz, 2H), 6.73 (t, *J* = 7.4 Hz, 1H), 6.64 (d, *J* = 7.4 Hz, 2H), 6.14 (d, *J* = 6.1 Hz, 1H), 5.53 (d, *J* = 6.1 Hz, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 195.7, 147.6, 145.4, 145.3, 134.5, 134.2, 129.4, 129.0, 128.9, 124.2, 118.5, 113.5, 77.3, 62.1; HRMS (FAB): *m/z* [332.1161] calcd. for $C_{20}H_{17}N_2O_3$ (M+H): 333.1239; found: 333.1216.

*3.1.2.6. 2-Phenyl-2-(phenylamino)-1-(thiophene-2-yl)ethanone (**3f**).* Light yellow solid (recrystallized from CH_2Cl_2/*n*-hexane); 89% yield (0.442 g); mp 138 – 140 °C; R_f = 0.32 (8:1 *n*-hexane/AcOEt); IR (FT): cm^{-1} = 3397 (N-H), 1645 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.89-7.88 (m, 1H), 7.65-7.64 (m, 1H), 7.51 (dt, *J* = 8.4, 1.7 Hz, 2H), 7.33 (t, *J* = 7.4 Hz, 2H), 7.26-7.27 (m, 1H), 7.15-7.11 (m, 3H), 6.69-6.65 (m, 3H), 5.79 (s, 1H), 5.25 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 189.7, 146.0,

141.2, 137.9, 134.6, 133.2, 129.2, 129.0, 128.3, 128.2, 128.0, 118.0, 113.5, 64.1; HRMS (FAB): *m/z* [293.0824] calcd. for $C_{18}H_{16}NOS$ (M+H): 294.0953; found: 294.0977.

*3.1.2.7. 2-(4-Methoxyphenylamino)-2-(4-nitrophenyl)-1-phenylethanone (**3g**).* Red solid (recrystallized from CH_2Cl_2/*n*-hexane); 70% yield (0.241 g); mp 119 – 121 °C; R_f = 0.12 (8:1 *n*-hexane/AcOEt); IR (FT): cm^{-1} = 3383 (N-H), 1685 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.12 (dt, J = 9.0, 2.0 Hz, 2H), 7.96 (d, *J* = 7.8 Hz, 2H), 7.62-7.57 (m, 3H), 7.47 (t, *J* = 7.8 Hz, 2H), 6.73 (dt, *J* = 9.7, 2.9 Hz, 2H), 6.60 (dt, *J* = 9.7, 2.9 Hz, 2H), 6.07 (d, *J* = 5.4 Hz, 1H), 5.21 (d, *J* = 5.4 Hz, 1H), 3.70 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 196.2, 152.8, 147.6, 145.6, 139.4, 134.6, 134.1, 129.0, 128.9, 128.8, 124.2, 115.01, 114.98, 63.1, 55.7; HRMS (FAB): *m/z* [362.1267] calcd. for $C_{21}H_{18}N_2O_4$ (M): 362.1267; found: 362.1267.

*3.1.2.8. 1-(4-Chlorophenyl)-2-(4-methoxyphenylamino)-2-phenylethanone (**3h**).* Yellow solid (recrystallized from CH_2Cl_2/*n*-hexane); 81% yield (0.143 g); mp 138 – 140 °C; R_f = 0.29 (8:1 *n*-hexane/AcOEt); IR (FT): cm^{-1} = 3399 (N-H), 1674 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.92 (d, *J* = 8.6 Hz, 2H), 7.41-7.21 (m, 7H), 6.72 (d, *J* = 9.4 Hz, 2H), 6.62 (dd, *J* = 9.4, 2.9 Hz, 2H), 5.90 (s, 1H), 5.03 (s, 1H), 3.71 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 196.3, 152.5, 140.2, 139.9, 137.6, 133.4, 130.2, 129.2, 129.0, 128.2, 128.1, 115.1, 114.9, 64.0, 55.7; HRMS (FAB): *m/z* [351.1026] calcd. for $C_{21}H_{19}ClNO_2$ (M+H): 352.1104; found: 352.1099.

*3.1.2.9. 2-(4-Chlorophenylamino)-1-(4-methoxyphenyl)-2-phenylethanone (**3i**).* Yellow solid (recrystallized from CH_2Cl_2/*n*-hexane); 90% yield (0.486 g); mp 131 – 133 °C; R_f = 0.23 (8:1 *n*-hexane/AcOEt); IR (FT): cm^{-1} = 3398 (N-H), 1673 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.03 (dt, *J* = 9.4, 2.3 Hz, 2H), 7.46 (d, *J* = 7.4 Hz, 2H), 7.32-7.27 (m, 2H), 7.23 (t, *J* = 7.4 Hz, 1H), 7.08 (dt, *J* = 9.6, 2.7 Hz, 2H), 6.92 (dt, *J* = 9.4, 2.3 Hz, 2H), 6.60 (dt, *J* = 9.6, 2.7 Hz, 2H), 5.96 (d, *J* = 6.9 Hz, 1H), 5.51 (d, *J* = 6.9 Hz, 1H), 3.84 (s, 3H), ^{13}C NMR (125 MHz, $CDCl_3$): δ = 194.9, 163.9, 144.7, 137.7, 131.2, 129.02, 128.97, 128.1, 127.9, 127.5, 122.2, 114.5, 113.9, 62.1, 55.4.; HRMS (FAB): *m/z* [351.1026] calcd. for $C_{21}H_{19}ClNO_2$ (M+H): 352.1104; found: 352.1070.

*3.1.2.10. 2-(4-Chlorophenylamino)-2-(naphthalene-2-yl)-1-phenylethanone (**3j**).* Light yellow solid (recrystallized from acetone/*n*-hexane); 89% yield (0.464 g); mp 156 – 158 °C; R_f = 0.37 (8:1 *n*-hexane/AcOEt); IR (FT): cm^{-1} = 3398 (N-H), 1673 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 8.0 Hz, 2H), 7.90 (s, 1H), 7.74-7.79 (m, 3H), 7.41-7.54 (m, 6H), 7.05 (d, *J* = 9.2 Hz, 2H), 6.63 (d, *J* = 9.2 Hz, 2H), 6.14 (d, *J* = 6.3 Hz, 1H), 5.55 (d, *J* = 6.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 196.5, 144.6, 134.8, 134.7, 133.7, 133.3, 133.0, 129.2, 129.1, 128.9, 128.7, 127.9, 127.70, 127.68, 126.4, 125.2, 114.6, 62.8; HRMS (FAB): *m/z* [371.1077] calcd. for $C_{24}H_{19}ClNO$ (M+H): 372.1155; found: 372.1174.

3.1.3. General procedure for synthesis of imidazoles

Two-necked flask attached with a condenser was charged with formamide (50 mL), which was heated to 180 °C with stirring. A solution of α-amino ketone in THF (15 mL) was then added dropwise over 2 h using a syringe pump and the resulting mixture was reacted for 6 h with stirring at 180 °C. After cooling, the dark brown reaction mixture was treated with an equal volume of water and 20 mL of 15 % aqueous NaOH. Then, the mixture was extracted three times with Et_2O, washed with brine, and dried over Na_2SO_4. After filtration and concentration under reduced pressure, the residue was purified by silica gel column chromatography (n-hexane: AcOEt = 2: 1) to afford imidazoles 4a – 4j.

*3.1.3.1. 1,4,5-Triphenyl-1H-imidazole (**4a**[27]).* 1,2-Diphenyl-2-(phenylamino)ethanone **3a** (0.542 g, 1.90 mmol) was reacted with formamide according to general procedure 3.1.3. White solid (recrystallized from CH_2Cl_2/*n*-hexane); 84% yield (0.280 g); R_f = 0.32 (2:1 *n*-hexane/AcOEt); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.78 (s, 1H), 7.54 (dd, *J* = 8.6, 1.1 Hz, 2H), 7.33-7.24 (m, 8H), 7.21-7.10 (m, 5H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 138.9, 137.4, 136.4, 134.4, 130.8, 130.1, 129.2, 128.65, 128.56, 128.2, 128.1, 127.9, 127.2, 126.7, 125.8.

*3.1.3.2. 5-(4-Chlorophenyl)-1,4-diphenyl-1H-imidazole (**4b**).* 2-(4-Chlorophenyl)-1-phenyl-2-(phenylamino)ethanone **3b** (0.228 g, 0.690 mmol) was reacted with formamide according to general procedure. White solid (recrystallized from CH_2Cl_2/*n*-hexane); 65% yield (0.411 g); mp 171 – 172 °C; R_f = 0.29 (2:1 *n*-hexane/AcOEt); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 1.1 Hz, 1H), 7.52 (d, *J* = 8.6 Hz, 2H), 7.37-7.35 (m, 3H), 7.29-7.21 (m, 5H), 7.12-7.06 (m, 4H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 139.4, 137.7, 136.2, 134.1, 132.0, 129.4, 128.9, 128.6, 128.3, 128.2, 127.3, 126.9, 125.8; HRMS (FAB): *m/z* [330.0924] calcd. for $C_{21}H_{16}ClN_2$ (M+H): 331.1002; found: 331.1009.

*3.1.3.3. 5-(3-Chlorophenyl)-1,4-diphenyl-1H-imidazole (**4c**).* 2-(3-Chlorophenyl)-1-phenyl-2-(phenylamino)ethanone **3c** (0.334 g, 1.01 mmol) was reacted with formamide according to general procedure. White solid (recrystallized from CH_2Cl_2/*n*-hexane); 75% yield (0.321 g); mp 139 – 141 °C; R_f = 0.33 (2:1 *n*-hexane/AcOEt); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.78 (s, 1H), 7.53 (dt, *J* = 6.3, 1.7 Hz, 2H), 7.37-7.35 (m, 3H), 7.31-7.10 (m, 8H), 7.03 (dt, *J* = 7.6, 1.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 139.6, 137.7, 136.1, 134.3, 134.0, 132.0, 130.6, 129.8, 129.4, 129.0, 128.3, 128.2, 127.3, 127.1, 127.0, 125.8; HRMS (FAB): *m/z* [330.0924] calcd. for $C_{21}H_{16}ClN_2$ (M+H): 331.1002, found: 331.0979.

*3.1.3.4. 5-(Naphthalen-2-yl)-1,4-diphenyl-1H-imidazole (**4d**).* 2-(Naphthalene-2-yl)-1-phenyl-2-(phenylamino)ethanone **3d** (0.378 g, 1.09 mmol) was reacted with formamide according to general procedure. White solid (recrystallized from CH_2Cl_2/*n*-hexane); 50% yield (0.184 g); mp 202 – 204 °C; R_f = 0.31 (2:1 *n*-hexane/AcOEt); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.83-7.80 (m, 2H), 7.73 (d, *J* = 8.6 Hz, 1H), 7.65 (d, *J* = 6.6 Hz, 2H), 7.56 (dd, *J* = 6.6, 1.4 Hz, 2H), 7.50-7.44 (m, 2H), 7.31-7.13 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 139.3, 137.6, 136.4, 134.4, 133.2, 132.7, 130.1, 129.3, 128.5, 128.21, 128.15, 128.1, 127.9, 127.7, 127.6, 127.3, 126.7, 126.5, 126.3, 125.8; HRMS (FAB): *m/z* [346.1470] calcd. for $C_{25}H_{19}N_2$ (M+H): 347.1548, found: 347.1538.

*3.1.3.5. 1,5-Diphenyl-4-(thiophen-2-yl)-1H-imidazole (**4f**).* 2-Phenyl-2-(phenylamino)-1-(thiophene-2-yl)ethanone ***3f*** (0.426 g, 1.41 mmol) was reacted with formamide according to general procedure. White solid (recrystallized from CH_2Cl_2/*n*-hexane); 75% yield (0.264 g); mp 127 – 129 °C; R_f = 0.38 (2:1 *n*-hexane/AcOEt); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.74 (s, 1H), 7.34-7.25 (m, 8H), 7.16-7.09 (m, 3H), 6.97 (dd, *J* = 3.9, 1.2 Hz, 1H), 6.89 (t, *J* = 3.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 137.9, 137.1, 136.2, 134.6, 131.0, 129.5, 129.3, 128.6, 128.0, 127.6, 127.2, 125.5, 123.8, 122.8; HRMS (FAB): *m/z* [302.0878] calcd. for $C_{19}H_{15}N_2S$ (M+H): 303.0956, found: 303.0972.

*3.1.3.6. 4-(4-Chlorophenyl)-1-(4-methoxyphenyl)-5-phenyl-1H-imidazole (**4h**).* 1-(4-Chlorophenyl)-2-(4-methoxyphenylamino)-2-phenylethanone **3h** (0.595 g, 1.70 mmol) was reacted with formamide according to general procedure. White solid (recrystallized from CH_2Cl_2/*n*-hexane); 52% yield (0.0319 g); mp 180 – 181 °C; R_f = 0.27 (2:1 *n*-hexane/AcOEt); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.72 (s, 1H), 7.46 (d, *J* = 8.6 Hz, 2H), 7.25-7.30 (m, 3H), 7.21 (d, *J* = 8.6 Hz, 2H), 7.13 (dd, *J* = 6.6, 1.4 Hz, 2H), 7.03 (d, *J* = 8.6 Hz, 2H), 6.82 (d, *J* = 8.6 Hz, 2H), 3.79 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.1, 137.6, 137.5, 133.1, 132.3, 130.7, 129.9, 129.2, 128.6, 128.3, 128.2, 127.1, 114.3, 55.4; HRMS (FAB): *m*/*z* [360.1029] calcd. for $C_{22}H_{18}ClN_2O$ (M+H): 361.1108, found: 361.1088.

*3.1.3.7. 1-(4-Chlorophenyl)-4-(4-methoxyphenyl)-5-phenyl-1H-imidazole (**4i**).* 2-(4-Chlorophenylamino)-1-(4-methoxyphenyl)-2-phenylethanone **3i** (0.440 g, 1.22 mmol) was reacted with formamide according to general procedure. White solid (recrystallized from CH_2Cl_2/*n*-hexane); 65% yield (0.144 g); mp 206 – 208 °C; R_f = 0.24 (2:1 *n*-hexane/AcOEt); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.73 (s, 1H), 7.45 (dt, *J* = 9.5, 2.6 Hz, 2H), 7.31-7.26 (m, 5H), 7.15-7.13 (m, 2H), 7.04 (dt, *J* = 9.5, 2.6 Hz, 2H), 6.80 (dt, *J* = 9.5, 2.6 Hz, 2H), 3.79 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.6, 139.1, 137.0, 135.1, 133.8, 130.8, 130.0, 129.4, 128.7, 128.4, 128.2, 127.6, 126.9, 113.7, 55.2; HRMS (FAB): *m*/*z* [360.1029] calcd. for $C_{22}H_{18}ClN_2O$ (M+H): 361.1108, found: 361.1105.

*3.1.3.8. 1-(4-Chlorophenyl)-5-(naphthalen-2-yl)-4-phenyl-1H-imidazole (**4j**).* 2-(4-Chlorophenylamino)-2-(naphthalene-2-yl)-1-phenylethanone **3j** (0.417 g, 1.20 mmol) was reacted with formamide according to general procedure. White solid (recrystallized from CH_2Cl_2/*n*-hexane); 53% yield (0.241 g); mp 249 – 251 °C; R_f = 0.37 (2:1 *n*-hexane/AcOEt); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.84-7.75 (m, 3H), 7.68-7.65 (m, 2H), 7.55-7.45 (m, 4H), 7.28-7.17 (m, 6H), 7.08 (dt, *J* = 9.4, 2.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 139.6, 137.4, 135.0, 134.2, 133.9, 133.2, 132.8, 130.2, 129.5, 128.5, 128.4, 128.3, 128.1, 128.0, 127.7, 127.2, 126.89, 126.86, 126.7, 126.4; HRMS (FAB): *m*/*z* [380.1080] calcd. for $C_{25}H_{18}ClN_2$ (M+H): 381.1159, found: 381.1178.

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Supplementary Material

Supplementary data related to this article can be found at.