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Metal-Free TEMPO-Promoted C(sp^3)–H Amination To Afford Multisubstituted Benzimidazoles

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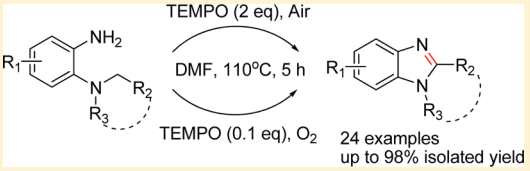
Supporting Information

ABSTRACT: An efficient TEMPO–air/cat. TEMPO–O_2 oxidative protocol was developed to synthesize multisubstituted or fused tetracyclic benzimidazoles via a metal-free oxidative C–N coupling between the sp^3 C–H and free N–H of readily available N^1-benzyl/alkyl-1,2-phenylenediamines.



The construction of the C–N bond is of fundamental and immense importance in organic synthesis because of its high prevalence in natural products, pharmaceuticals, and materials.[1−4] Of all C–N bond-forming reactions, direct oxidative C–N bond formation through functionalization of nonreactive C–H bonds represents an attractive and robust approach to the synthesis of nitrogen-containing compounds, affording a step-economical and environmentally benign alternative to traditional C–N bond-forming methods.[5] In particular, the amination of alkane C–H bonds is a long-standing challenge for the chemistry community because ubiquitous sp^3 C–H bonds are the most inactivated. To date, limited examples of oxidative C(sp^3)–N coupling reactions have been reported,[5−9] generally requiring metal catalysts and/or high temperature. The metal-free versions typically occur at benzylic or allylic C–H bonds with electron-poor nitrogen sources such as sulphonamides, carboxamides, or phthalimide[10−12] and with hypervalent iodine/iodine as the oxidant,[13,14] thus conferring a restricted substrate scope and applicability. Herein, we present a novel metal-free 2,2,6,6-tetramethylpiperidine-*N*-oxyl[15] (TEMPO)-promoted C(sp^3)–H amination by a "naked" amino group in air, leading to an efficient green synthesis of benzimidazoles from readily available *N*-benzyl/alkyl-1,2-phenylenediamines. Furthermore, this method can be extended to the synthesis of benzoxazoles from 2-(benzylamino)phenols.

The benzimidazole scaffold is observed in a large number of compounds of pharmaceutical interest.[16] Besides their use as marketed drugs like Telmisartan and Dexlansoprazole, benzimidazole derivatives have been reported to exhibit a wide spectrum of biological activities, such as anti-cancer,[17] anti-fungal,[18] anti-bacterial,[19] anti-leishimanial,[20] and anti-viral[21,22] activities. Classical methods to synthesize benzimidazoles include the condensation of 1,2-phenylenediamines with either aldehydes[23−26] or carboxylic acids under relatively harsh conditions[27,28] and the transition metal-catalyzed C–N coupling of *N*-(*ortho*-haloaryl)amidines[29] or *N*-(*ortho*-haloaryl)-amides[30,31] (Scheme 1). Recently, a more efficient strategy to build the benzimidazole was developed through direct C(sp^2)–H activation/C–N bond formation from *N*-arylamidines, taking place either in the presence of Pd or Cu catalyst[32,33] or stoichiometric hypervalent iodine oxidant.[34] Because these oxidative C–N coupling methods are limited to the arylamidine substrate via C(sp^2)–H imidation, development of a new C–N bond-forming procedure is still desirable to render a wider substrate scope for benzimidazole derivatization. Inspired by a recently reported functionalization of the α-C–H of amines by a broad range of nucleophiles such as active methylene species, aromatic nucleus, and alkynes,[35−37] we sought to introduce amino groups as nucleophiles to develop a general intramolecular oxidative C(sp^3)–N coupling reaction for the diversified synthesis of benzimidazole and related heterocycles (Scheme 1).

We started our study by designing N^1-benzylbenzene-1,2-diamine **1a** as the model substrate to generate desired benzimidazole product **2a**. Synthesis of the starting material was easily accessible by either reductive amination or alkylation/arylation of substituted 1,2-phenylenediamine, enabling structurally diverse substrate availability. Reaction conditions were screened for direct C(sp^3)–H amination (Table 1). PhI($OAc)_2$ (2 equiv) was chosen as the oxidant initially, and the reaction was performed at 120 °C for 10 h in toluene. Disappointingly, **1a** was rapidly oxidized to a complex mixture, with a fast change of the color of the reaction system. Because aniline is vulnerable to being oxidized, other oxidants were examined (entries 2–7). Gratifyingly, when TEMPO was used, desired product **1b** was obtained in 64% yield, whereas other oxidants initiated this transformation in low yields. Then, the solvent was surveyed (entries 2, 3, and 10–12), and the best result was achieved when DMF was used, affording **1b** in 95% yield with the reaction time shortened to 5 h (entry 3). Notably, the oxidative coupling still proceeded in good yield with a catalytic amount of TEMPO, but a higher temperature and much longer reaction time (40 h) were needed to complete the transformation (entry 9). Taking into account the

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Scheme 1. Different Approaches to Benzimidazole Derivatives

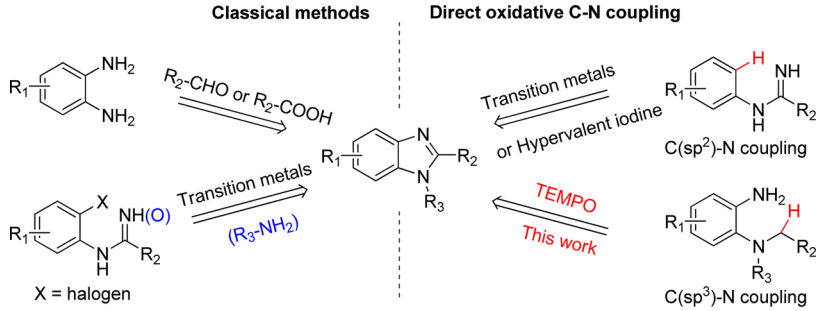
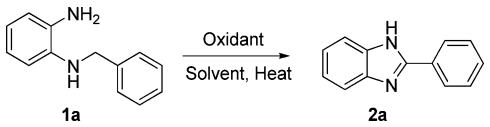


Table 1. Reaction Conditions Screening for the Oxidative C(sp^3)−N Coupling of *N*-Benzyl-1,2-phenylenediamine[a]



1a **2a**

entry	oxidant	solvent	*T* (°C)	yield (%)[b]
1	$PhI(OAc)_2$	toluene	120	NP
2	TEMPO	toluene	120	64
3	TEMPO	DMF	120	95
4[d]	TBHP	DMF	120	8
5[d]	*m*-CPBA	DMF	120	23
6[d]	$K_2S_2O_8$	DMF	120	trace
7[d]	$Cu(OAc)_2$	DMF	120	trace
8[d]		DMF	120	trace
9	TEMPO[e]	DMF	140	92
10	TEMPO	DCE	120[c]	31
11	TEMPO	1,4-dioxane	120[c]	28
12	TEMPO	acetonitrile	120[c]	33
13	TEMPO	DMF	140	97
14	**TEMPO**	**DMF**	**110**	**96**
15[f]	TEMPO	DMF	80	83

[a]Reaction conditions: **1a** (0.4 mmol), oxidant (0.8 mmol), solvent (4 mL), 5 h. [b]Isolated yield. [c]Sealed tube. [d]10 h. [e]TEMPO (0.1 equiv) was used, 40 h. [f]24 h.

applicability of the substrate scope and synthetic efficiency, the mild stoichiometric procedure was chosen for further investigation. Screening the reaction temperature proved 110 °C to be optimal (entries 3 and 13−15). Altogether, entry 14 stood out as an optimized set of conditions for this oxidative C(sp^3)−N cyclization reaction.[38]

Using the optimized conditions, we explored the scope and generality of this oxidative coupling protocol. First, the effect of substitution on the N^{α}-methylene moiety of the 1,2-phenylenediamine was investigated with respect to the yield of the oxidative C(sp^3)−H amination reaction (Table 2, **2a**−**2l**). Variously substituted phenyl groups were well-tolerated in this transformation to give corresponding benzimidazoles in moderate to excellent yields (**2a**−**2h**). The electronic effect of the substituent on the benzyl ring was further examined by reducing the reaction time to 2 h with representative substrates (**1a**, **1c**, **1d**, and **1e**). It is obvious that the electron-donating group is superior to the electron-withdrawing group (conversion rate: **1d** > **1a** > **1c** > **1e**), implying that a cationic intermediate might be involved and thus that the para-electron donating group on the benzyl ring is conferring a stabilization effect. Accordingly, the electron-withdrawing and reactive cyano substituent caused a significant drop in the yield (**2h**). However, the steric hindrance of the 2,6-dimethyl groups had little impact on the conversion (**2g**). Furthermore, picolyl and styryl groups were also well-tolerated for generating the desired products in good yields (**2i** and **2j**). Interestingly, alkyl-substituted substrates with either bulky cyclohexyl or small ethyl substituents were competent to provide the corresponding 2-alkyl benzimidazoles in moderate yields (**2k**−**2l**). The low yields relative to the aryl substitution might result from a smaller stabilization effect on the putative cationic intermediate.

Then, the scope of the 1,2-diamino-substituted aryl core was surveyed (Table 2, **2m**−**2v**). A range of N^1-benzyl(substituted benzene)-1,2-diamines were subjected to the optimized conditions. Alkyl, alkoxy, and halogen substituents on the 1,2-diaminophenyl ring were well-tolerated to give the corresponding benzimidazoles in excellent yields (**2m**−**2r**). Even with electron-withdrawing groups attached on the phenyl ring, the yields were still satisfying, although a prolonged reaction time was required (**2s** and **2t**). When N^1-benzylnaphthalene-1,2-diamine was applied, the reaction could produce 2-phenyl-1*H*-naphtho[2,3-*d*]imidazole in good yield (**2u**). However, the replacement of the phenyl group by pyridine resulted in no production of the desired imidazole (**2v**), but the corresponding imine (Table 2, compound **3**) was obtained instead. We assumed that the electron-deficient pyridine ring remarkably reduced the nucleophilicity of the amino group and thus retarded the nucleophilic annulation with the imine intermediate left.

More significantly, this method can be applied to the synthesis of fused polycyclic benzimidazoles, demonstrating the generality of this C(sp^3)−N coupling protocol. When the substrate bearing a tertiary amino structure participated in this reaction, N-methylated 2-phenylbenzimidazole or fused tetracyclic benzimidazoles could be harvested (Scheme 2), providing a novel and facile approach to sophisticated polycyclic benzimidazoles.

Furthermore, this methodology could be extended to the preparation of benzoxazole derivatives by using a hydroxyl group as the nucleophile (Scheme 3). When 2-benzylaminophenol was exposed to this TEMPO−air oxidation system, the desired product, 2-phenylbenzo[*d*]oxazole, was obtained in good yield, offering further synthetic utility of the metal-free oxidative C(sp^3)-heteroatom bond-forming reaction protocol.

Because the TEMPO-promoted oxidative coupling was performed in air, the role of O_2 in this reaction was explored by conducting several control experiments. When 2 equiv of TEMPO was used, the oxidative C(sp^3)−N cyclization proceeded smoothly regardless of the gas species (Table 3, entries 1−3), although a prolonged reaction time was required

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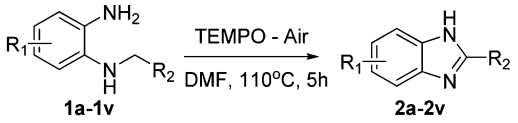
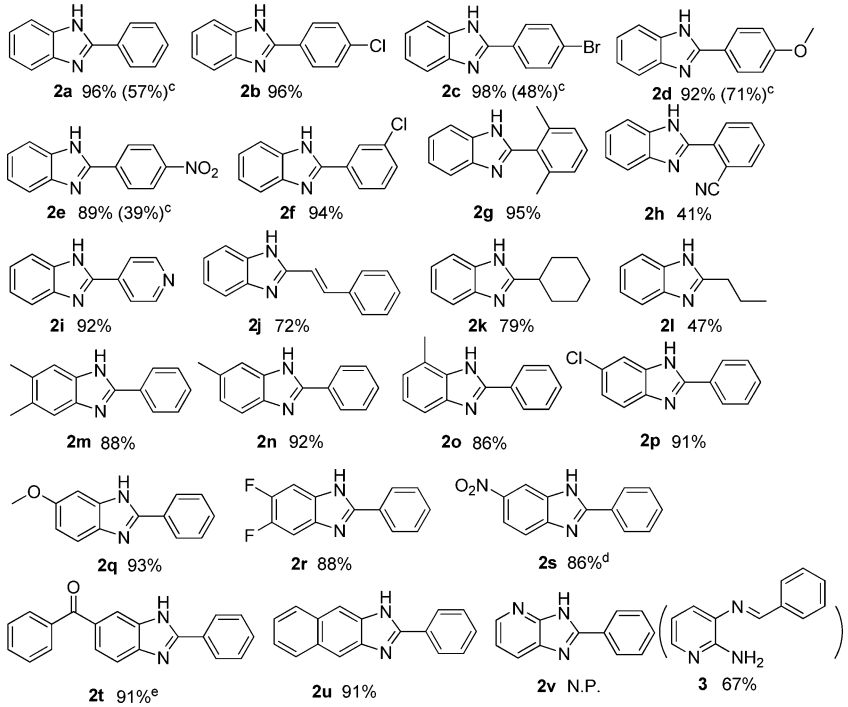
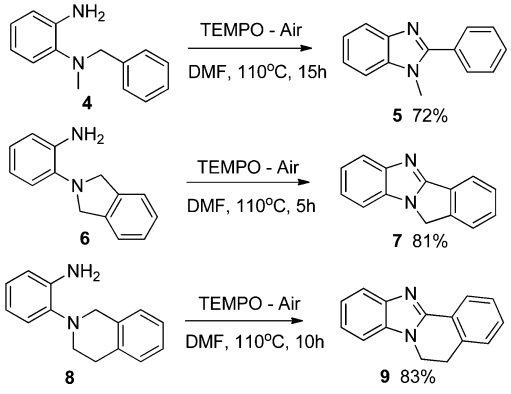
Table 2. Scope of the TEMPO-Promoted C−N Coupling of Substituted *N*-Benzyl/alkyl-1,2-phenylenediamines in Air[a,b]





[a]Reaction conditions: **1** (0.4 mmol), TEMPO (0.8 mmol, 2 equiv), DMF, 110 °C, 5 h. [b]Yield of isolated product. [c]2 h. [d]30 h. [e]15 h.

Scheme 2. Oxidative C−N Bond Formation with Tertiary Amines



Scheme 3. Application in the Synthesis of Benzoxazole Derivatives

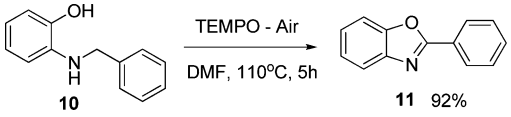
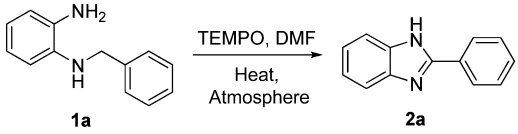


Table 3. Reaction Conditions Optimization for the TEMPO−O_2 Oxidation Protocol[a]



entry	equiv	atmosphere	T (°C)	reaction time (h)	yield (%)[b]
1	2	air	110	5	96
2	2	Ar	110	16	92
3	2	O_2	110	5	94
4	0.1	air	140	40	92
5	0.1	Ar	140	40	trace
6	0.1	O_2	140	5	90
7	**0.1**	**O_2**	**120**	**5**	**88**
8	0.1	O_2	110	9	83
9	0.1	O_2	80	40	53

[a]Reaction conditions: **1a** (0.4 mmol), TEMPO (2−0.1 equiv), 80−140 °C, DMF, under different atmospheres. [b]Yield of isolated product.

under an Ar atmosphere (entry 2). Under an O_2 atmosphere (entry 3), the overall reaction time was not shortened, but a more rapid conversion of the starting material to the reaction intermediate was observed by TLC detection compared to that performed under air conditions. However, when TEMPO was used in a catalytic amount (entries 4−9), the reaction temperature had to be elevated and the reaction time was remarkably extended in order to complete the conversion in air (entry 4), whereas only trace amount of the product was obtained under an Ar atmosphere, even with high temperature and a long reaction time (entry 5). However, the O_2 atmosphere dramatically promoted the TEMPO-catalyzed C(sp^3)−H functionalization in excellent yields with a shortened reaction time and lowered temperature (entries 6−9),

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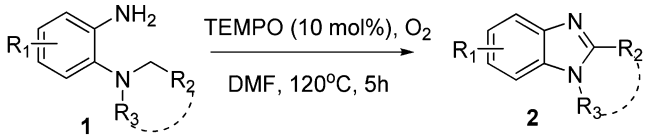
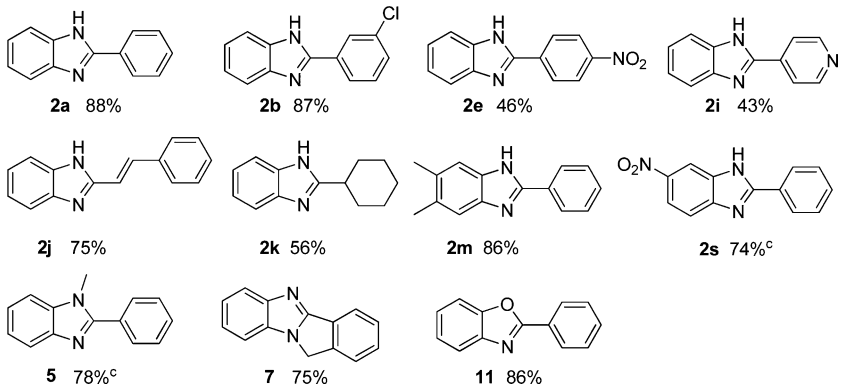
Table 4. Representative Reactions Utilizing the Catalytic TEMPO−O_2 Oxidative System[a,b]





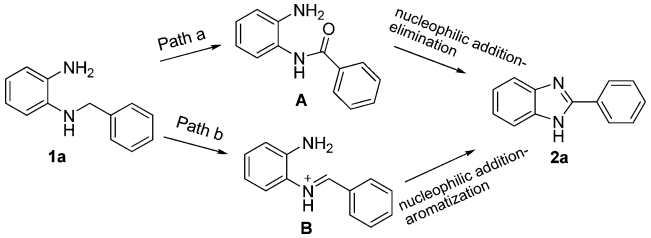
[a]Reaction conditions: **1** (0.4 mmol), TEMPO (0.04 mmol, 0.1 equiv), DMF, 120 °C, under an O_2 atmosphere (balloon), 5 h. [b]Yield of isolated product. [c]24 h.

indicating that O_2 is essential for the regeneration of catalytic TEMPO.

Because the TEMPO-catalyzed aerobic oxidative C(sp^3)−N coupling reaction provided an alternative to the synthesis of benzimidazoles with lower oxidant loading, albeit with slightly reduced yield (**2a**, 88 vs 96%), select substrates were tested under the new conditions (Table 4). Most of the reactions displayed relatively low synthetic efficiency compared to that of the TEMPO−air system. The 2-alkyl-substituted benzimidazole was formed in a moderate yield of 56% (**2k**). The electron-withdrawing substituent on the N^{α}-methylene attenuated the yield (**2e** and **2i**). Other structure types of benzimidazoles could be obtained in comparable yields.

To shed light on the mechanism of the metal-free oxidative C(sp^3)−H amination, additional control experiments were carried out. Initially, we postulated two possible intermediates involved in this reaction: amide **A** (Scheme 4, path a) or

Scheme 4. Possible Pathways for Intramolecular Oxidative C(sp^3)−N Coupling



iminium **B** (Scheme 4, path b). The latter has been commonly reported in cross-dehydrogenative coupling reactions.[36,39] Actually, the generation of an intermediate was observed during the reaction process by TLC detection, and it gradually diminished as the benzimidazole product was formed. We failed to isolate the intermediate by silica gel chromatography because of its instability, but ^{1}H NMR was successfully applied in monitoring the intermediate. The characteristic peaks at chemical shifts at 8.66 (CH from the imine carbon) and 5.20 ppm (NH_2 from the free amino group, distinct from the NH and NH_2 residue of the starting material) of the intermediate strongly suggest an imine-type intermediate in this reaction (see the Supporting Information). In addition, as mentioned above, the conversion stopped at the imine stage (Table 2, compound **3**) with electron-deficient substrate N^2-benzylpyridine-2,3-diamine (**1v**), providing further proof of path b. On the contrary, amide intermediate **A** was synthesized and exposed to the TEMPO−air conditions, but no reaction occurred.

Notably, a kinetic isotope effect (KIE) (k_H/k_D = 1.8), determined by an intermolecular competition reaction between **1a** and [D_7]**1a** (Supporting Information), indicated that the cleavage of the benzylic C−H bond was involved in the product-determining step. However, the relatively low KIE value[40,41] suggested a two-step mechanism involving a single-electron transfer (SET) from the aniline to TEMPO, leading to an anilinium radical cation,[42] followed by a hydrogen-transfer step to ultimately form the iminium intermediate rather than a direct hydrogen-abstraction process.[40]

Taken together, a plausible mechanism for this reaction is proposed in Scheme 5. First, aminium cation radical **A** was generated from an SET process by TEMPO.[40] This kind of radical cation species could facilitate a hydrogen transfer from the adjacent carbon to yield iminium-type intermediate **B**,[39,42] which was equilibrating with its amino carbenium form **C**.[43] Meanwhile, TEMPO was transformed to its hydroxylamine form, which can be reoxidized by air or O_2.[44,45] Subsequently, the nucleophilic attack on the iminium ion by the amino or hydroxyl group gave rise to intermediate **D**, which was further oxidized to the desired benzimidazole.

In summary, we have developed an efficient, clean, and mild TEMPO−air/cat. TEMPO−O_2 oxidative protocol to form C(sp^3)−N bonds without metal, base, and other additives. The novel oxidative direct C(sp^3)−H amination reaction affords a direct, simple, and environmentally friendly approach to access polysubstituted benzimidazoles from readily available N^1-benzyl/alkyl-1,2-phenylenediamines. Besides broadening the substrate scope for benzimidazole synthesis, our method offers

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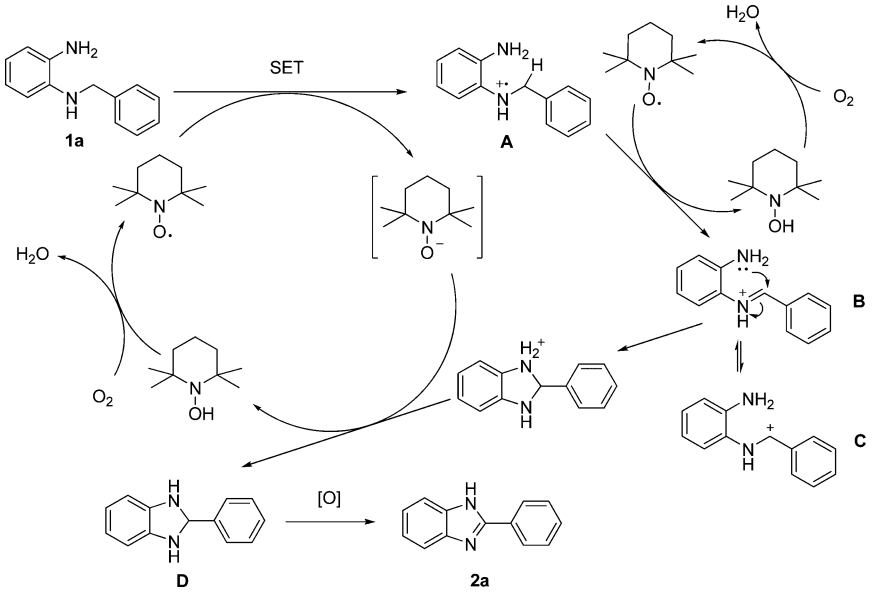
Scheme 5. Proposed Reaction Mechanism



a new strategy to construct fused polycyclic benzimidazoles as well as benzoxazole scaffolds.

EXPERIMENTAL SECTION

General Methods. Unless otherwise specified, all reactions were carried out in open glassware with magnetic stirring. Solvents were dried and distilled by standard procedures.[46] All reagents were weighed and handled in air at room temperature. Column chromatography was performed on silica gel (200−300 mesh). NMR spectra were recorded on a 300, 400, or 500 MHz NMR spectrometer. Chemical shifts for proton magnetic resonance spectra (^{1}H NMR) are quoted in parts per million (ppm) referenced to the appropriate solvent peak or 0.0 ppm for tetramethylsilane (TMS). The following abbreviations are used to describe the peak-splitting patterns when appropriate: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and dd, doublet of doublets. Coupling constants, J, are reported in hertz (Hz). Chemical shifts for ^{13}C NMR are reported in ppm referenced to the center line at 77.16 ppm of $CDCl_3$, 39.52 ppm of DMSO-d_6, or 49.00 ppm of CD_3OD. Notably, as previously reported by others,[33,47] because of the presence of tautomers, some of the ^{13}C NMR signals are hardly detectable for most of the NH-benzimidazoles; therefore, only distinct signals are reported here. HRMS samples were analyzed using a magnetic sector analyzer and an electron impact ionization method. All melting points are reported as ranges. The spectroscopic and physical data of known products were compared with that reported in the literatures.[29,34,48−52] Because of the solvent and temperature difference, the ^{13}C NMR spectrum was not exactly the same for every benzimidazole reported, but the majority of them were consistent (e.g., **2a**, **2c−2f**, **2l**, **2n**, **2q**, **5**, **7**, **9**, and **11**).[29,34,48,49,51]

General Procedure for the Synthesis of N-Substituted 1,2-Phenylenediamines 1a−1v.[53] To a solution of *O*-phenylenediamine (15 mmol, 1.5 equiv) in DMF (50 mL) were added K_2CO_3 (30.0 mmol, 3 equiv) and benzyl/alkyl bromide (10.0 mmol, 1 equiv). The mixture was stirred at room temperature for 4 h and then diluted with AcOEt (50 mL). The reaction solution was washed with saturated $NaHCO_3$ and saturated NaCl, dried over anhydrous Na_2SO_4, and filtered, and the filtrate was concentrated in vacuo. The residual oil was purified by silica gel column chromatography.

General Procedure for Synthesis of 1,2-Phenylenediamines with Tertiary Amines 4, 6, and 8.[54] To a solution of 2-fluoronitrobenzene (5.0 mmol, 1 equiv) in DMF (25 mL) were added K_2CO_3 (15.0 mmol, 3 equiv) and amine (5.5 mmol, 1.1 equiv). The reaction mixture was stirred at 60 °C for 5 h and then diluted with AcOEt (30 mL). Standard workup and purification by silica gel column chromatography gave the intermediate N-substituted 2-nitroaniline.

The resulting N-substituted 2-nitroaniline (300 mg) was dissolved in MeOH, and 10% palladium on activated carbon (60 mg) was added. The mixture was stirred under a hydrogen atmosphere for 2 h. The mixture was filtered through a pad of Celite and concentrated. The residue was purified by silica gel column chromatography.

General Procedure for the Synthesis of 2-(Benzylamino)-phenol 10.[55] To a solution of 2-aminophenol (12.0 mmol, 1.2 equiv) in MeOH (40 mL) was added benzaldehyde (10.0 mmol, 1 equiv) and AcOH (0.5 mL). After the mixture was stirred at room temperature for 30 min, $NaBH(OAc)_3$ (20.0 mmol, 2 equiv) was added, and the mixture was stirred for another 3 h at room temperature followed by the addition of water to quench the reaction. The mixture was diluted with MeOH, washed with water, saturated $NaHCO_3$, and saturated NaCl, dried over anhydrous Na_2SO_4, and filtered, and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography.

***N*^{1}-(2,6-Dimethylbenzyl)benzene-1,2-diamine (1g).** Eluent: petroleum ether/ethyl acetate = 3:1. Yield 73% (1650 mg). Light gray solid, mp 77−79 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20−7.06 (m, 3H), 6.83−6.97 (m, 2H), 6.78−6.70 (m, 2H), 4.25 (s, 2H), 3.25 (s, 3H), 2.42 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.1, 137.8, 135.5, 134.3, 128.4, 127.7, 120.8, 118.7, 116.3, 111.5, 42.9, 19.6. HRMS (EI) calcd for $C_{15}H_{18}N_2$ $[M]^+$, 226.1470; found, 226.1467.

2-(((2-Aminophenyl)amino)methyl)benzonitrile (1h). Eluent: petroleum ether/ethyl acetate = 2:1. Yield 77% (1723 mg). Brown solid, mp 93−95 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, J = 7.8 Hz, 1H), 7.54 (d, J = 3.6 Hz, 2H), 7.41−7.31 (m, 1H), 6.80−6.66 (m, 3H), 6.56 (d, J = 7.7 Hz, 1H), 4.57 (s, 2H), 3.96 (s, 1H), 3.41 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.5, 136.8, 134.7, 133.3, 133.1, 128.6, 127.8, 120.9, 119.6, 117.8, 117.1, 112.5, 111.6, 46.7. HRMS (EI) calcd for $C_{14}H_{13}N_3$ $[M]^+$, 223.1109; found, 223.1106.

***N*^{1}-Cinnamylbenzene-1,2-diamine (1j).** Eluent: petroleum ether/ethyl acetate = 2:1. Yield 72% (1617 mg). Light brown solid, mp 63−64 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42−7.18 (m, 5H), 6.87−6.78 (m, 1H), 6.77−6.60 (m, 4H), 6.38 (dt, J = 15.9, 5.9 Hz, 1H), 3.93 (dd, J = 5.9, 1.5 Hz, 2H), 3.41 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.6, 137.0, 134.4, 131.7, 128.7, 127.6, 127.3, 126.4, 120.9, 119.0, 116.7, 112.3, 46.6. HRMS (EI) calcd for $C_{15}H_{16}N_2$ $[M]^+$, 224.1313; found, 224.1305.

***N*^{1}-Benzyl-4,5-difluorobenzene-1,2-diamine (1r).** Eluent: petroleum ether/ethyl acetate = 3:1. Yield 67% (1562 mg). Light brown solid, mp 74−76 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42−7.26 (m,

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5H), 6.54 (dd, J = 11.2, 7.7 Hz, 1H), 6.44 (dd, J = 12.3, 7.7 Hz, 1H), 4.23 (s, 2H), 3.36 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.7 (dd, J = 236.7, 12.6 Hz), 143.0 (dd, J = 236.7, 12.6 Hz), 138.7, 134.11 (d, J = 5.9 Hz), 130.08 (d, J = 5.1 Hz), 128.9, 127.9, 127.7, 105.54 (d, J = 20.6 Hz), 101.43 (d, J = 21.9 Hz), 49.0. HRMS (EI) calcd for $C_{13}H_{12}F_2N_2$ $[M]^+$, 234.0969; found, 234.0970.

(4-Amino-3-(benzylamino)phenyl)(phenyl)methanone (1t). Eluent: petroleum ether/ethyl acetate = 3:1. Yield 77% (2328 mg). Light yellow solid, mp 92−93 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 7.1 Hz, 2H), 7.52 (t, J = 7.4 Hz, 1H), 7.45−7.27 (m, 8H), 7.24 (dd, J = 8.1, 1.6 Hz, 1H), 6.71 (d, J = 8.0 Hz, 1H), 4.31 (s, 2H), 3.80 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.0, 140.6, 139.0, 138.9, 136.0, 131.4, 129.7, 129.1, 128.8, 128.1, 128.0, 127.5, 124.5, 114.4, 114.2, 48.8. HRMS (EI) calcd for $C_{20}H_{18}N_2O$ $[M]^+$, 302.1419; found, 302.1415.

N^2-Benzylnaphthalene-2,3-diamine (1u). Eluent: petroleum ether/ethyl acetate = 3:1. Yield 74% (1843 mg). Light gray solid, mp 125−126 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62−7.51 (m, 2H), 7.47−7.28 (m, 5H), 7.25−7.16 (m, 2H), 7.06 (s, 1H), 6.93 (s, 1H), 4.42 (s, 2H), 4.00 (s, 1H), 3.57 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.0, 138.8, 135.6, 130.2, 128.7, 128.6, 128.0, 127.5, 125.9, 125.5, 123.4, 122.9, 111.4, 106.2, 48.7. HRMS (EI) calcd for $C_{17}H_{16}N_2$ $[M]^+$, 248.1313; found, 248.1319.

General Procedure for the Synthesis of Benzimidazoles and Benzoxazoles. *Method A.* To a solution of N-substituted 1,2-phenylenediamines/2-(benzylamino)phenol (0.4 mmol, 1 equiv) in DMF (4 mL) was added TEMPO (0.8 mmol, 2 equiv), and the mixture was stirred at 110 °C for 5 h. The mixture was then diluted with AcOEt, washed with water and a saturated NaCl(aq) solution, and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography and subsequently washed with *n*-hexane.

Method B. To a solution of N-substituted 1,2-phenylenediamine/2-(benzylamino)phenol (0.4 mmol, 1 equiv) in DMF (4 mL) was added TEMPO (0.04 mmol, 0.1 equiv), and the reaction tube was sealed and flushed with O_2. Then, the mixture was stirred at 120 °C for 5 h. The mixture was then diluted with AcOEt, washed with water and a saturated NaCl(aq) solution, and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography and subsequently washed with *n*-hexane.

2-Phenyl-1*H*-benzo[*d*]imidazole (2a). Eluent: petroleum ether/ethyl acetate = 3:1. Yield 96% (75 mg). White solid, mp 296−298 °C. ^{1}H NMR (400 MHz, CD_3OD) δ 8.12−8.06 (m, 2H), 7.61 (dd, J = 6.0, 3.2 Hz, 2H), 7.56−7.45 (m, 3H), 7.26 (dd, J = 6.1, 3.1 Hz, 2H). ^{13}C NMR (151 MHz, CD_3OD) δ 153.3, 131.4, 131.0, 130.1, 127.8, 123.9. HRMS (EI) calcd for $C_{13}H_{10}N_2$ $[M]^+$, 194.0844; found, 194.0840.

2-(4-Chlorophenyl)-1*H*-benzo[*d*]imidazole (2b). Eluent: petroleum ether/ethyl acetate = 3:1. Yield 96% (88 mg). White solid, mp 288−290 °C. ^{1}H NMR (300 MHz, CD_3OD) δ 8.07 (d, J = 8.8 Hz, 2H), 7.57 (t, J = 9.6 Hz, 4H), 7.27 (dd, J = 6.1, 3.2 Hz, 2H). ^{13}C NMR (151 MHz, DMSO) δ 150.2, 143.7, 135.0, 134.5, 129.1, 128.2, 122.8, 121.9, 119.0, 111.5. HRMS (EI) calcd for $C_{13}H_9ClN_2$ $[M]^+$, 228.0454; found, 228.0461.

2-(4-Bromophenyl)-1*H*-benzo[*d*]imidazole (2c). Eluent: petroleum ether/ethyl acetate = 2:1. Yield 98% (107 mg). White solid, mp 293−294 °C. ^{1}H NMR (300 MHz, CD_3OD) δ 8.00 (d, J = 8.5 Hz, 2H), 7.71 (d, J = 8.5 Hz, 2H), 7.61 (s, 2H), 7.31−7.23 (m, 2H). ^{13}C NMR (101 MHz, DMSO) δ 150.2, 143.7, 135.0, 132.0, 129.4, 128.4, 123.3, 122.8, 122.0, 119.0, 111.5. HRMS (EI) calcd for $C_{13}H_9BrN_2$ $[M]^+$, 271.9949; found, 271.9950.

2-(4-Methoxyphenyl)-1*H*-benzo[*d*]imidazole (2d). Eluent: petroleum ether/ethyl acetate = 2:1. Yield 92% (83 mg). White solid, mp 231−233 °C. ^{1}H NMR (400 MHz, CD_3OD) δ 8.05 (d, J = 8.9 Hz, 2H), 7.59 (dd, J = 6.0, 3.2 Hz, 2H), 7.25 (dd, J = 6.0, 3.1 Hz, 2H), 7.11 (d, J = 8.9 Hz, 2H), 3.90 (s, 3H). ^{13}C NMR (101 MHz, CD_3OD) δ 162.9, 153.5, 129.4, 123.6, 123.4, 115.5, 55.9. HRMS (EI) calcd for $C_{14}H_{12}N_2O$ $[M]^+$, 224.0950; found, 224.0951.

2-(4-Nitrophenyl)-1*H*-benzo[*d*]imidazole (2e). Eluent: petroleum ether/ethyl acetate = 6:1. Yield 89% (85 mg). Light yellow solid, mp 303−304 °C. ^{1}H NMR (300 MHz, CD_3OD) δ 8.39 (d, J = 8.9 Hz, 2H), 8.29 (d, J = 8.9 Hz, 2H), 7.64 (s, 2H), 7.31 (dd, J = 6.1, 3.1 Hz, 2H). ^{13}C NMR (151 MHz, DMSO) δ 149.0, 147.8, 136.0, 127.4, 124.3, 123.3, 122.5, 119.5, 111.9. HRMS (EI) calcd for $C_{13}H_9N_3O_2$ $[M]^+$, 239.0695; found, 239.0687.

2-(3-Chlorophenyl)-1*H*-benzo[*d*]imidazole (2f). Eluent: petroleum ether/ethyl acetate = 3:1. Yield 94% (86 mg). White solid, mp 233−235 °C. ^{1}H NMR (300 MHz, CD_3OD) δ 8.13 (tt, J = 2.1, 0.9 Hz, 1H), 8.01 (dddd, J = 7.0, 2.7, 1.9, 0.9 Hz, 1H), 7.69−7.47 (m, 4H), 7.28 (dt, J = 5.5, 3.7 Hz, 2H). ^{13}C NMR (101 MHz, CD_3OD) δ 151.7, 136.2, 132.9, 131.8, 131.1, 127.7, 126.0, 124.3. HRMS (EI) calcd for $C_{13}H_9ClN_2$ $[M]^+$, 228.0454; found, 228.0455.

2-(2,6-Dimethylphenyl)-1*H*-benzo[*d*]imidazole (2g). Eluent: petroleum ether/ethyl acetate = 3:1. Yield 95% (84 mg). White solid, mp 294−296 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (s, 2H), 7.32−7.24 (m, 3H), 7.11 (d, J = 7.6 Hz, 2H), 2.10 (s, 6H). ^{13}C NMR (151 MHz, CD_3OD) δ 153.2, 139.1, 132.3, 130.7, 128.5, 123.6, 20.00. HRMS (EI) calcd for $C_{15}H_{14}N_2$ $[M]^+$, 222.1157; found, 222.1154.

2-(1*H*-Benzo[*d*]imidazol-2-yl)benzonitrile (2h). Eluent: petroleum ether/ethyl acetate = 1:1. Yield 41% (36 mg). White solid, mp 252−254 °C. ^{1}H NMR (300 MHz, CD_3OD) δ 8.01−7.91 (m, 2H), 7.84 (td, J = 7.7, 1.4 Hz, 1H), 7.69 (td, J = 7.7, 1.3 Hz, 3H), 7.32 (dd, J = 6.1, 3.2 Hz, 2H). ^{13}C NMR (151 MHz, CD_3OD) δ 150.2, 135.7, 134.5, 134.4, 131.5, 131.1, 124.5, 118.8, 112.5. HRMS (EI) calcd for $C_{14}H_9N_3$ $[M]^+$, 219.0796; found, 219.0791.

2-(Pyridin-4-yl)-1*H*-benzo[*d*]imidazole (2i). Eluent: petroleum ether/ethyl acetate = 1:1. Yield 92% (72 mg). White solid, mp 219−221 °C. ^{1}H NMR (300 MHz, CD_3OD) δ 8.72 (d, J = 6.4 Hz, 2H), 8.08 (d, J = 6.4 Hz, 2H), 7.77−7.55 (m, 2H), 7.33 (dd, J = 6.3, 3.1 Hz, 2H). ^{13}C NMR (151 MHz, CD_3OD) δ 151.1, 150.0, 139.2, 125.0, 122.1. HRMS (EI) calcd for $C_{12}H_9N_3$ $[M]^+$, 195.0796; found, 195.0795.

(*E*)-2-Styryl-1*H*-benzo[*d*]imidazole (2j). Eluent: petroleum ether/ethyl acetate = 1:1. Yield 72% (63 mg). Light yellow solid, mp 201−203 °C. ^{1}H NMR (300 MHz, CD_3OD) δ 7.67−7.49 (m, 5H), 7.45−7.30 (m, 3H), 7.27−7.20 (m, 2H), 7.15 (d, J = 16.6 Hz, 1H). ^{13}C NMR (101 MHz, CD_3OD) δ 152.5, 137.1, 136.9, 130.2, 130.0, 128.2, 124.0, 117.3, 115.7. HRMS (EI) calcd for $C_{15}H_{12}N_2$ $[M]^+$, 220.1000; found, 220.0969.

2-Cyclohexyl-1*H*-benzo[*d*]imidazole (2k). Eluent: petroleum ether/ethyl acetate = 1:1. Yield 79% (63 mg). White solid, mp 284−286 °C. ^{1}H NMR (300 MHz, CD_3OD) δ 7.48 (d, J = 7.3 Hz, 2H), 7.21−7.12 (m, 2H), 2.90 (tt, J = 11.9, 3.5 Hz, 1H), 2.08 (ddd, J = 13.3, 3.6, 1.6 Hz, 2H), 1.89 (dt, J = 12.6, 3.3 Hz, 2H), 1.83−1.59 (m, 3H), 1.41 (tddd, J = 24.7, 15.6, 12.3, 3.3 Hz, 3H). ^{13}C NMR (101 MHz, CD_3OD) δ 160.8, 123.1, 115.2, 39.8, 32.8, 27.2, 27.0. HRMS (EI) calcd for $C_{13}H_{16}N_2$ $[M]^+$, 200.1313; found, 200.1308.

2-Propyl-1*H*-benzo[*d*]imidazole (2l). Eluent: dichlormethane/methanol = 20:1. Yield 47% (30 mg). White solid, mp 153−155 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (ddd, J = 6.0, 3.0, 1.3 Hz, 2H), 7.20 (ddd, J = 6.0, 3.0, 1.4 Hz, 2H), 2.92 (t, J = 7.6 Hz, 2H), 1.98−1.79 (m, 2H), 0.98 (t, J = 7.4 Hz, 3H). ^{13}C NMR (151 MHz, CD_3OD) δ 156.7, 139.5, 123.1, 115.3, 31.7, 22.7, 14.0. HRMS (EI) calcd for $C_{17}H_{12}N_2$ $[M]^+$, 160.1000; found, 160.0993.

5,6-Dimethyl-2-phenyl-1*H*-benzo[*d*]imidazole (2m). Eluent: petroleum ether/ethyl acetate = 2:1. Yield 88% (78 mg). White solid, mp 249−251 °C. ^{1}H NMR (300 MHz, CD_3OD) δ 8.04 (dq, J = 7.0, 1.4 Hz, 2H), 7.55−7.45 (m, 3H), 7.36 (s, 2H), 2.37 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 150.3, 130.5, 129.5, 128.9, 126.2, 20.1. HRMS (EI) calcd for $C_{15}H_{14}N_2$ $[M]^+$, 222.1157; found, 222.1152.

6-Methyl-2-phenyl-1*H*-benzo[*d*]imidazole (2n). Eluent: petroleum ether/ethyl acetate = 2:1. Yield 92% (77 mg). White solid, mp 240−242 °C. ^{1}H NMR (400 MHz, CD_3OD) δ 8.09−8.03 (m, 2H), 7.56−7.44 (m, 4H), 7.39 (s, 1H), 7.12−7.06 (m, 1H), 2.47 (s, 3H). ^{13}C NMR (101 MHz, CD_3OD) δ 153.0, 133.9, 131.2, 131.1, 130.1, 127.7, 125.4, 115.8, 21.7. HRMS (EI) calcd for $C_{14}H_{12}N_2$ $[M]^+$, 208.1000; found, 208.0996.

7-Methyl-2-phenyl-1*H*-benzo[*d*]imidazole (2o). Eluent: petroleum ether/ethyl acetate = 3:1. Yield 86% (72 mg). White solid, mp 248−250 °C. ^{1}H NMR (300 MHz, CD_3OD) δ 8.13 (d, J = 7.9 Hz,

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2H), 7.59−7.48 (m, 3H), 7.45 (d, J = 10.9 Hz, 1H), 7.14 (t, J = 7.7 Hz, 1H), 7.04 (d, J = 6.8 Hz, 1H), 2.62 (s, 3H). ^{13}C NMR (151 MHz, CD_3OD) δ 153.1, 131.3, 131.2, 130.0, 128.0, 124.5, 123.9. HRMS (EI) calcd for $C_{14}H_{12}N_2$ $[M]^+$, 208.1000; found, 208.0994.

6-Chloro-2-phenyl-1*H*-benzo[*d*]imidazole (2p). Eluent: petroleum ether/ethyl acetate = 3:1. Yield 91% (83 mg). White solid, mp 213−215 °C. ^{1}H NMR (300 MHz, CD_3OD) δ 8.10−8.01 (m, 2H), 7.62−7.49 (m, 5H), 7.23 (dd, J = 8.6, 2.0 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 152.7, 130.3, 129.7, 129.1, 126.6, 126.4, 122.4. HRMS (EI) calcd for $C_{13}H_9ClN_2$ $[M]^+$, 228.0454; found, 228.0462.

6-Methoxy-2-phenyl-1*H*-benzo[*d*]imidazole (2q). Eluent: petroleum ether/ethyl acetate = 3:1. Yield 93% (83 mg). White solid, mp 146−147 °C. ^{1}H NMR (300 MHz, CD_3OD) δ 8.04 (d, J = 7.1 Hz, 2H), 7.50 (ddq, J = 11.0, 9.1, 2.5 Hz, 4H), 7.09 (d, J = 2.4 Hz, 1H), 6.90 (dd, J = 8.8, 2.4 Hz, 1H), 3.85 (s, 3H). ^{13}C NMR (151 MHz, CD_3OD) δ 158.3, 152.9, 140.2, 135.5, 131.1, 131.1, 130.1, 127.5, 116.9, 113.7, 97.9, 56.1. HRMS (EI) calcd for $C_{14}H_{12}N_2O$ $[M]^+$, 224.0950; found, 224.0943.

5,6-Difluoro-2-phenyl-1*H*-benzo[*d*]imidazole (2r). Eluent: petroleum ether/ethyl acetate = 5:1. Yield 88% (81 mg). White solid, mp 213−215 °C. ^{1}H NMR (300 MHz, CD_3OD) δ 8.09−7.99 (m, 2H), 7.53 (dt, J = 7.1, 2.2 Hz, 3H), 7.44 (s, 2H). ^{13}C NMR (151 MHz, CD_3OD) δ 155.3, 150.2, 148.6, 131.7, 130.5, 130.2, 127.7, 106.5, 100.3. HRMS (EI) calcd for $C_{13}H_8F_2N_2$ $[M]^+$, 230.0656; found, 230.0653.

6-Nitro-2-phenyl-1*H*-benzo[*d*]imidazole (2s). Eluent: petroleum ether/ethyl acetate = 1:1. Yield 86% (82 mg). Light yellow solid, mp 204−206 °C. ^{1}H NMR (300 MHz, CD_3OD) δ 8.49 (d, J = 2.2 Hz, 1H), 8.19 (dd, J = 8.9, 2.2 Hz, 1H), 8.11 (dd, J = 6.7, 3.0 Hz, 2H), 7.70 (d, J = 8.9 Hz, 1H), 7.61−7.52 (m, 3H). ^{13}C NMR (151 MHz, CD_3OD) δ 157.7, 145.0, 132.4, 130.3, 130.0, 128.2, 119.5. HRMS (EI) calcd for $C_{13}H_9N_3O_2$ $[M]^+$, 239.0695; found, 239.0693.

Phenyl(2-phenyl-1*H*-benzo[*d*]imidazol-6-yl)methanone (2t). Eluent: petroleum ether/ethyl acetate = 1:1. Yield 91% (109 mg). Light yellow solid, mp 220−222 °C. ^{1}H NMR (300 MHz, CD_3OD) δ 8.15−8.08 (m, 2H), 8.05 (s, 1H), 7.79 (d, J = 6.9 Hz, 3H), 7.72 (s, 1H), 7.65 (t, J = 7.3 Hz, 1H), 7.61−7.50 (m, 5H). ^{13}C NMR (151 MHz, CD_3OD) δ 198.5, 139.6, 133.4, 132.0, 130.9, 130.4, 130.3, 129.4, 128.1, 126.3. HRMS (EI) calcd for $C_{10}H_{14}N_2O$ $[M]^+$, 298.1106; found, 298.1106.

2-Phenyl-1*H*-naphtho[2,3-*d*]imidazole (2u). Eluent: petroleum ether/ethyl acetate = 3:1. Yield 91% (89 mg). Light brown solid, mp 214−216 °C. ^{1}H NMR (300 MHz, CD_3OD) δ 8.22−8.14 (m, 2H), 8.13−7.89 (m, 4H), 7.64−7.53 (m, 3H), 7.38 (dd, J = 6.5, 3.2 Hz, 2H). ^{13}C NMR (101 MHz, CD_3OD) δ 157.4, 132.2, 132.1, 130.7, 130.2, 128.9, 128.3, 124.9. HRMS (EI) calcd for $C_{17}H_{12}N_2$ $[M]^+$, 244.1000; found, 244.0993.

(*E*)-N^3-Benzylidenepyridine-2,3-diamine (3). Eluent: dichloromethane/methanol = 20:1. Yield 67% (53 mg). Light yellow solid, mp 120−122 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (d, J = 1.1 Hz, 1H), 7.97 (d, J = 5.1 Hz, 1H), 7.94−7.85 (m, 2H), 7.51−7.42 (m, 3H), 7.22 (d, J = 1.4 Hz, 1H), 6.70−6.63 (m, 1H), 4.97 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.5, 154.8, 146.4, 136.1, 132.3, 131.8, 129.0, 123.5, 114.2. HRMS (EI) calcd for $C_{12}H_{11}N_3$ $[M]^+$, 197.0953; found, 197.0948.

1-Methyl-2-phenyl-1*H*-benzo[*d*]imidazole (5). Eluent: petroleum ether/ethyl acetate = 1:1. Yield 72% (60 mg). White solid, mp 91−93 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84−7.78 (m, 1H), 7.77−7.69 (m, 2H), 7.49 (dd, J = 5.1, 2.1 Hz, 3H), 7.41−7.25 (m, 3H), 3.82 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 153.8, 143.0, 136.6, 130.2, 129.8, 129.5, 128.7, 122.8, 122.5, 119.9, 109.7, 31.7. HRMS (EI) calcd for $C_{14}H_{12}N_2$ $[M]^+$, 208.1000; found, 208.0999.

11*H*-Benzo[4,5]imidazo[2,1-*a*]isoindole (7). Eluent: dichloromethane/methanol = 50:1. Yield 81% (67 mg). White solid, mp 211−213 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, J = 6.5 Hz, 1H), 7.84 (dd, J = 5.9, 3.3 Hz, 1H), 7.61−7.40 (m, 4H), 7.33−7.23 (m, 2H), 5.06 (s, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.6, 148.5, 143.6, 132.8, 129.6, 129.5, 128.9, 124.0, 122.8, 122.3, 122.2, 120.6, 109.5, 47.3. HRMS (EI) calcd for $C_{14}H_{10}N_2$ $[M]^+$, 206.0844; found, 206.0841.

5,6-Dihydrobenzo[4,5]imidazo[2,1-*a*]isoquinoline (9). Eluent: petroleum ether/ethyl acetate = 5:1. Yield 83% (73 mg). White solid, mp 147−149 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (dd, J = 6.9, 2.3 Hz, 1H), 7.86−7.76 (m, 1H), 7.44−7.21 (m, 6H), 4.27 (t, J = 6.8 Hz, 2H), 3.24 (t, J = 6.9 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 149.1, 143.9, 134.7, 134.3, 130.2, 128.1, 127.7, 126.6, 125.6, 122.7, 122.5, 119.7, 109.1, 40.4, 28.2. HRMS (EI) calcd for $C_{15}H_{12}N_2$ $[M]^+$, 220.1000; found, 220.0999.

2-Phenylbenzo[*d*]oxazole (11). Eluent: petroleum ether/ethyl acetate = 15:1. Yield 92% (72 mg). White solid, mp 102−103 °C. ^{1}H NMR (300 MHz, CD_3OD) δ 8.27−8.18 (m, 2H), 7.76−7.63 (m, 2H), 7.63−7.52 (m, 3H), 7.46−7.36 (m, 2H). ^{13}C NMR (101 MHz, DMSO) δ 162.3, 150.2, 141.5, 132.0, 129.4, 127.3, 126.4, 125.6, 124.9, 119.9, 111.0. HRMS (EI) calcd for $C_{13}H_9NO$ $[M]^+$, 195.0684; found, 195.0684.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra of starting compounds **1g**, **1h**, **1j**, **1r**, **1t**, and **1u** and final products **2a**−**2u**, **3**, **5**, **7**, **9**, and **11** and details of the reaction process monitoring experiment and deuterium KIE measurement. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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