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Copper(I)-Catalyzed Regioselective Amination of *N*-Aryl Imines Using $TMSN_3$ and TBHP: A Route to Substituted Benzimidazoles

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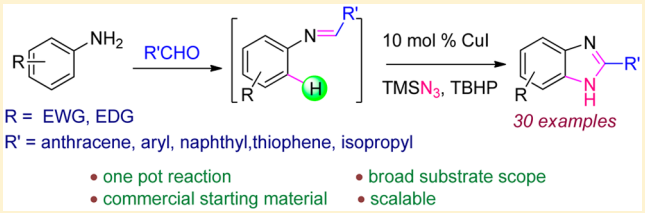
Supporting Information

ABSTRACT: A novel and efficient copper-catalyzed amination of *N*-aryl imines is described. This one-pot, multicomponent reaction, in which imine acts as a directing group by chelating to the metal center, affords a potential route for the transformation of the commercial aryl amines, aldehydes, and azides into valuable benzimidazole structural units with wide substrate scope and diversity. The synthetic and mechanistic aspects are presented.

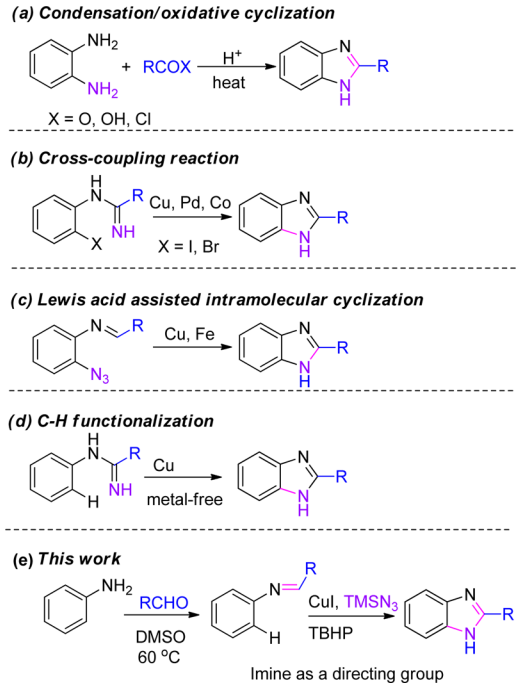


INTRODUCTION

Transition-metal-catalyzed C−H functionalization directed by functional groups affords a powerful tool for the atom economical regioselective construction of carbon−carbon and carbon−heteroatom bonds.[1] For the most part, the second row transition-metals such as Ru,[2] Rh,[3] Pt,[4] and Pd[5] have been studied. Few studies are focused on the copper-catalyzed systems,[6] which are particularly attractive because of their high abundance and low toxicity. Herein we report a novel one-pot multicomponent copper-catalyzed imine-chelated regioselective amination of *N*-aryl imines using trimethylsilyl azide ($TMSN_3$) in the presence of *tert*-butyl hydroperoxide (TBHP) at moderate temperature (Scheme 1e). This newly discovered reaction is simple, uses inexpensive copper catalyst, and converts readily available substrates into important benzimidazole core structures that tolerate an array of functional groups and substantial steric hindrance, via a sequential tandem condensation, C−H azidation, and C−N bond formation.

Benzimidazoles are an important class of compounds for the pharmaceutical industry.[7,8] The benzimidazole scaffold can be found in several commercial drugs such as Nexium, Attacand, Protonix, Prilosec, and Famvir as well as numerous experimental drug candidates (Figure 1). These structural frameworks are commonly made by condensation of 1,2-diaminoarenes with carboxylic acids or aldehydes followed by oxidative cyclization (Scheme 1a).[9] However, these approaches often suffer from limited substrate scope and sometimes the requirement for strong acidic conditions and high reaction temperature. Thus, an effort has been recently made on the development of new strategies to construct the benzimidazole structural motifs using the C−N cross-coupling reaction of 2-haloarylamidines (Scheme 1b),[10] intramolecular cyclization of 2-azido *N*-aryl imines (Scheme 1c),[11] and the C−H functionalization of *N*-arylamidines (Scheme 1d).[12] Hence, developing new ways to obtain benzimidazoles with structural diversity involving the direct C−H functionalization from readily available simple substrates would be fascinating while challenging at the same time.

Scheme 1. Main Strategies for Benzimidazole Syntheses



RESULTS AND DISCUSSION

We commenced the optimization studies with *p*-toluidine **1a** and benzaldehyde **2a** as model substrates using a series of copper sources with different solvents, azides, and oxidants (Table 1).

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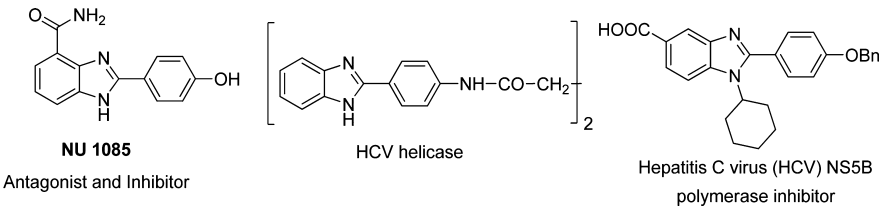
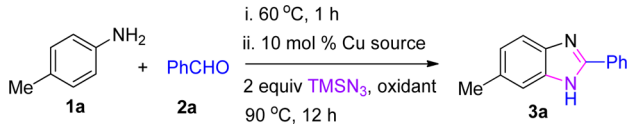


Figure 1. Examples of biologically important substituted 2-arylbenzimidazoles.

Table 1. Optimization of the Reaction Conditions[a]



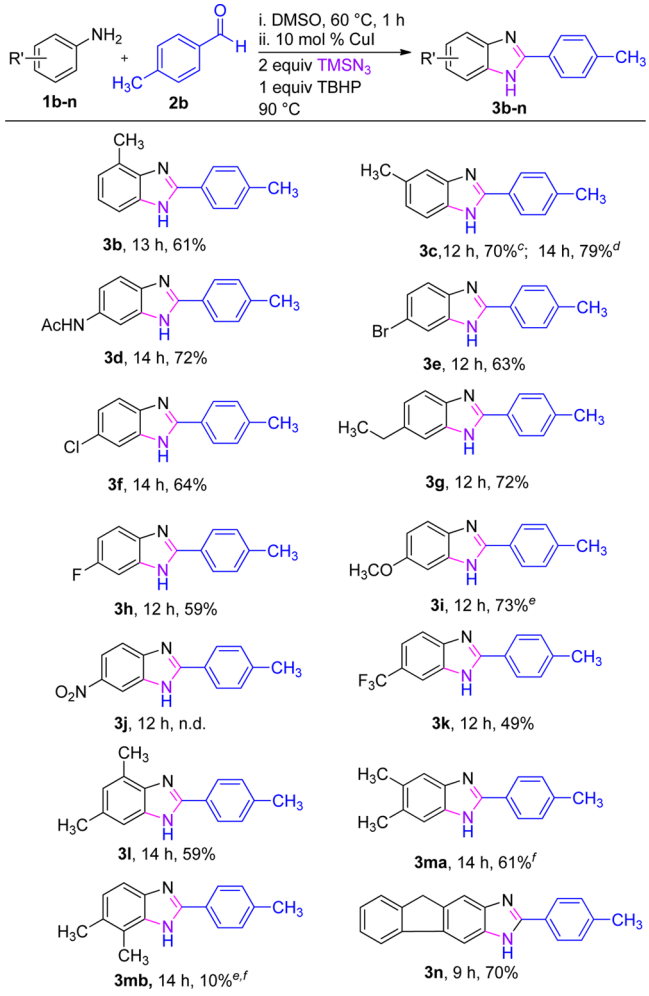
entry	[Cu] source	[N_3]	oxidant	solvent	yield (%)[b]
1	CuBr	$TMSN_3$	TBHP	CH_3CN	60
2	CuBr	$TMSN_3$	TBHP	toluene	5
3	CuBr	$TMSN_3$	TBHP	CH_2Cl_2	3
4	CuBr	$TMSN_3$	TBHP	THF	3
5	CuBr	$TMSN_3$	TBHP	DMF	16
6	CuBr	$TMSN_3$	TBHP	DMSO	72
7	CuBr	TsN_3	TBHP	DMSO	n.d.
8	CuBr	NaN_3	TBHP	DMSO	n.d.
9	CuBr	$TMSN_3$	30% H_2O_2	DMSO	n.d.
10	CuCl	$TMSN_3$	TBHP	DMSO	40
11	CuI	$TMSN_3$	TBHP	DMSO	77
12	$Cu(OAc)_2·H_2O$	$TMSN_3$	TBHP	DMSO	66
13	$CuCl_2$	$TMSN_3$	TBHP	DMSO	63
14	$CuBr_2$	$TMSN_3$	TBHP	DMSO	64
15	Cu_2O	$TMSN_3$	TBHP	DMSO	10
16	$Cu(OAc)_2$	$TMSN_3$	TBHP	DMSO	68
17	CuI	$TMSN_3$	TBHP	DMSO	56[c]
18	CuI	$TMSN_3$	TBHP	DMSO	59[d]
19	CuI	$TMSN_3$	TBHP	DMSO	61[e]
20	-	$TMSN_3$	TBHP	DMSO	n.d.
21	CuI	$TMSN_3$	-	DMSO	n.d.

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), solvent (0.5 mL), 60 °C, 1 h; copper source (10 mol %), azide (1 mmol), TBHP (0.5 mmol), 90 °C, 12 h. n.d. = not detected. [b]Isolated yield. [c]5 mol % CuI was used. [d]0.75 mmol of $TMSN_3$ was used. [e]0.25 mmol of TBHP was used.

Gratifyingly, the reaction took place to give 2-phenylbenzimidazole **3a** in 60% yield when the substrates **1a** (1 equiv) and **2a** (1.2 equiv) were stirred at 60 °C for 1 h to give an imine intermediate that was reacted with CuBr (10 mol %), $TMSN_3$ (2 equiv), and TBHP (1 equiv) at 90 °C for 12 h in CH_3CN (entry 1). The use of DMSO as a solvent led to an increase in the product yield to 72%, whereas solvents such as DMF, CH_2Cl_2, THF, and toluene gave inferior results (entries 2−6). Azides such as NaN_3 and TsN_3, and oxidant, 30% H_2O_2, failed to react (entries 7−9). Subsequent screening of the copper sources revealed that CuI exhibited superior results, leading to **3a** in 77% yield, while CuCl, $CuBr_2$, $CuCl_2$, $Cu(OAc)_2·H_2O$, $Cu(OAc)_2$, and Cu_2O afforded the target molecule in <68% yield (entries 10−16). Lowering the amount of the Cu-source (5 mol %), TBHP (0.5 equiv), or $TMSN_3$ (1.5 equiv) led to the formation of **3a** in <61% yield (entry 17−19). Control experiments confirmed that, in the absence of either the Cu-source or TBHP, the formation of **3a** was not observed (entries 20 and 21).

Having the optimal condition in hand, we investigated the scope of the protocol for the reaction of a series of substituted anilines and 2-aminofluorene with tolualdehyde **2b** as a representative example (Table 2). Aniline bearing electron-donating and electron-withdrawing substituents readily reacted, and a substituent at the 2-position had little effect on the yield. Reaction of 2-methylaniline gave benzimidazole **3b** in 61% yield, while 3-methylaniline underwent reaction to afford the desired **3c** in 70% yield. The reactions of anilines having 4-acetamide, 4-bromo, 4-chloro, 4-ethyl, 4-fluoro, 4-methyl, 4-methoxy, and 4-trifluoromethyl groups produced the corre-

Table 2. Reaction of Aryl Amines with Tolualdehyde[a,b]



[a]Reaction conditions: amine **1b−n** (1 mmol), aldehyde **2b** (1.2 mmol), DMSO (1 mL), 60 °C, 1 h; CuI (10 mol %), $TMSN_3$ (2 mmol), TBHP (1 mmol), and 90 °C. [b]Isolated yield. [c]3-Methylaniline was used. [d]4-Methylaniline was used. [e]Two tautomers were observed in nearly 1:1 ratios by ^1H NMR. [f]Obtained as a 1:6 mixture.

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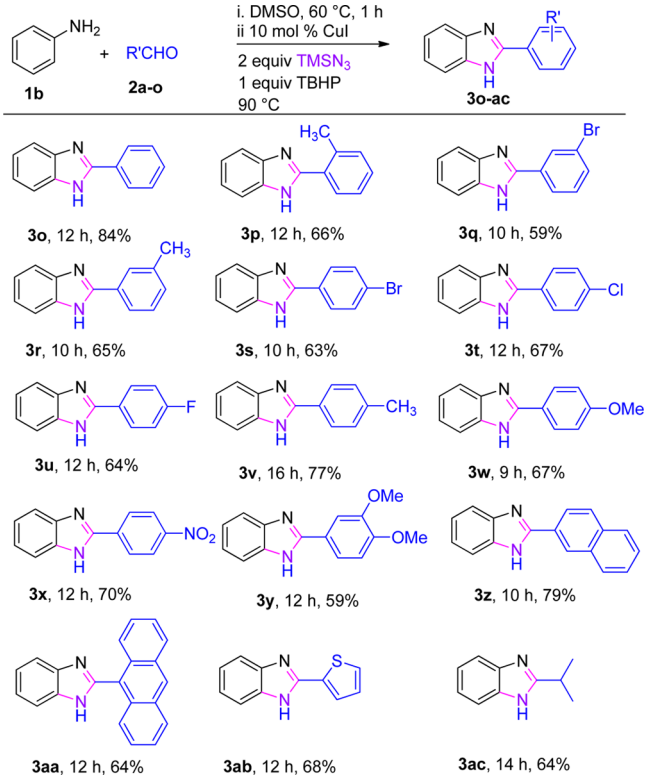
sponding benzimidazoles **3c–i** and **3k** in 49–73% yields. In contrast, aniline with a strong electron-withdrawing group, 4-nitro, failed to react, which suggests that the electronic nature of the aryl ring is crucial for the reaction. The reaction conditions are also effective for disubstituted substrates. 2,4-Dimethylaniline underwent reaction to furnish benzimidazole **3l** in 59% yield, while the reaction of 3,4-dimethylaniline led to the formation of a 1:6 mixture of **3ma** and **3mb** in 71% yield, which can be easily separated by column chromatography. In addition, 2-aminofluorene readily underwent reaction to afford the target product **3n** in 70% yield. Recrystallization of **3e** yielded single crystals whose structure was confirmed by X-ray analysis (see Supporting Information). Benzimidazoles **3i** and **3mb** produced nearly a 1:1 mixture of tautomers.[11a,18]

Next we applied the protocol for the reactions of aldehydes with aniline **1b** as a standard substrate (Table 3). The reaction

Table 3. Reaction of Aniline with Various Aldehydes[a,b]

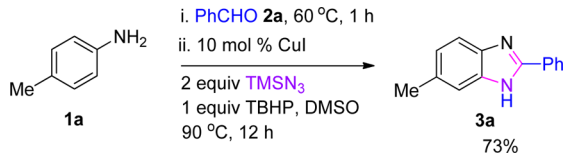


[a]Reaction conditions: aniline **1b** (1 mmol), aldehyde **2a–o** (1.2 mmol), DMSO (1 mL), 60 °C, 1 h; CuI (10 mol %), $TMSN_3$ (2 mmol), TBHP (1 mmol), and 90 °C. [b]Isolated yield.

of benzaldehyde **1a** produced benzimidazole **3o** in 84% yield. Substituted aromatic aldehydes with electron-donating and electron-withdrawing groups, 2-methyl, 3-bromo, 3-methyl, 4-bromo, 4-chloro, 4-fluoro, 4-methoxy, 4-methyl, and 4-nitro substituents, underwent reaction to give the corresponding benzimidazoles **3p–x** in 59–77% yields. The reaction of 3,4-dimethoxybenzaldehyde afforded **3y** in 59% yield, while 2-naphthaldehyde underwent reaction to furnish **3z** in 79% yield. Anthracene-9-carbaldehyde underwent reaction to provide the substituted benzimidazole **3aa** in 64% yield. The reaction of the heterocyclic aldehyde, thiophene-2-aldehyde, occurred to afford the target product **3ab** in 68% yield. In addition, an aliphatic aldehyde, isobutyraldehyde, underwent reaction to give 2-isopropylbenzimidazole **3ac** in 64% yield.

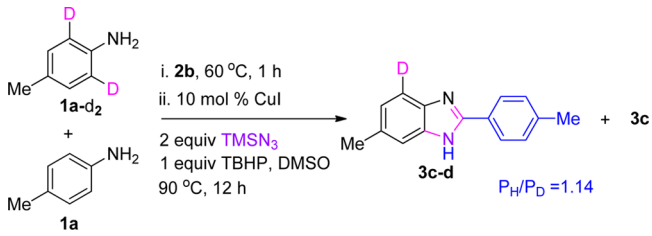
Finally, the scale up of the procedure was investigated using **1a** and **2a** as representative examples (Scheme 2). The reaction

Scheme 2. Gram-Scale Synthesis



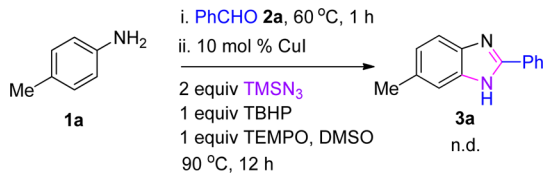
was efficient, and the target product was obtained in 73% yield. To obtain insight into the reaction pathway, an intermolecular kinetic isotope experiment between equimolar amounts of **1a**-d_2 and **2b** was performed (Scheme 3). At 1 h with 23%

Scheme 3. Kinetic Isotope Experiment



conversion, the reaction afforded P_H/P_D = 1.14, which suggests that the C–H bond cleavage is not involved in the product-determining step.[13] In addition, the radical scavenger experiment using TEMPO exhibited no reaction, which suggests that the reaction involves a radical intermediate (Scheme 4).[14]

Scheme 4. Radical Scavenger Experiment



Furthermore, the ESI-MS analyses of the reaction mixture of **1a**, **2b**, and $TMSN_3$ after 3 h revealed the presence of four major species **A**, **B**, **C**, and **3a** (Figure 2).[6i,k] Thus, the

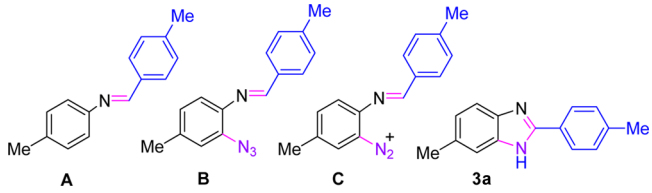


Figure 2. Major species identified using ESI-MS of the reaction mixture of **1a**, **2b**, and $TMSN_3$ after 3 h (see Supporting Information).[6k]

condensation of aldehyde with amine can give *N*-aryl imine ***a*** that may undergo chelation with CuI to afford ***b*** (Scheme 5). Oxidative addition of ***b*** with $TMSN_3$ can produce ***c*** that can react with TBHP to afford ***d***. The latter can convert into copper(II) species ***e*** by a single electron transfer (SET).[6a,f,h] Intramolecular N_3 transfer to aryl cation radical can give ***f*** that may lead to the formation of ***h*** via aryl cation ***g*** by SET.

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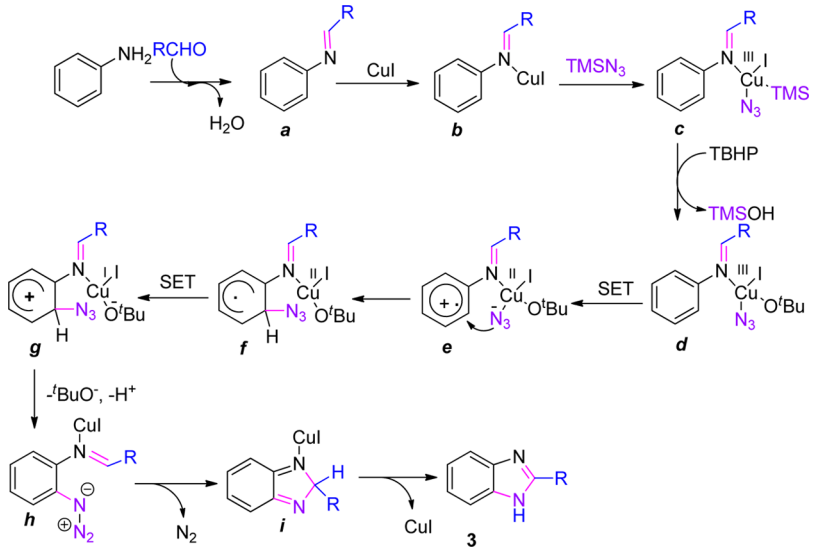
Scheme 5. Proposed Reaction Pathway



Cyclization of ***h*** may give ***i*** that can furnish the target product **3** by tautomerization to complete the catalytic cycle.

CONCLUSIONS

In summary, we have found that copper(I)-catalyzed imine-directed amination of *N*-aryl imines proceeds smoothly to afford substituted benzimidazoles. The use of inexpensive copper catalysts, the commercially available starting material, and the broad substrate scope are significant practical advantages. The tolerance of the functional groups is a synthetically useful feature.

EXPERIMENTAL SECTION

General Information. $Cu(OAc)_2$ (99%), $CuCl_2$ (99%), CuI (98%), CuBr (97%), CuCl (90%), Cu_2O (97%), $TMSN_3$ (95%), TBHP (98%, 5.5 M in decane), and $Cu(OAc)_2{\cdot}H_2O$ (98%) were purchased from commercial sources. The solvents were purchased and dried according to standard procedure prior to use.[15] Purification of the reaction products was carried out by column chromatography using silica gel (60−120 mesh). Analytical TLC was performed on silica gel G/GF 254 plate. NMR spectra were recorded on DRX-400 and 600 MHz using $CDCl_3$ and DMSO-d_6 as solvents and Me_4Si as internal standard. Chemical shifts (δ) were reported in ppm and spin−spin coupling constants (J) were given in hertz. Melting points were determined using melting point apparatus and are uncorrected. FT-IR spectra were recorded using an IR spectrometer. Mass spectra were recorded on a Q-Tof ESI-MS instrument. X-ray data were collected with a CCD area detector using Mo Kα radiation. The structures were solved by direct method using *SHELLX-97* (Göttingen, Germany).

General Procedure for Amination of *N*-Aryl Imines. Aniline **1** (1.0 mmol) and benzaldehyde **2** (1.2 mmol) were stirred at 60 °C for 1 h in DMSO (1 mL) under air. The mixture was then cooled to room temperature and treated with CuI (10 mol %, 0.1 mmol, 19 mg), $TMSN_3$ (2 equiv, 2.0 mmol, 230 mg), and TBHP (1 equiv, 1 mmol, 181 μL). The resultant mixture was stirred at 90 °C for the appropriate time (Table 1 and 2). The progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluent. The reaction mixture was then cooled to room temperature and was extracted with ethyl acetate (3 × 10 mL) and washed with brine (2 × 5 mL) and water (2 × 5 mL). The solution was dried over Na_2SO_4, passed through a short pad of Celite, and evaporated on a rotary evaporator to give a residue that was purified on silica gel column chromatography using *n*-hexane and ethyl acetate as eluent.

6-Methyl-2-phenyl-1H-benzo[d]imidazole ***3a***.[11a] Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.41; pale yellow solid; 160 mg, yield 77%; mp 243−244 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.77 (br s, 1H), 8.17 (d, J = 7.2 Hz, 2H), 7.55−7.32 (m, 5H), 7.05−7.00 (m, 1H), 2.43 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 150.9, 144.2, 142.0, 135.3, 133.1, 131.9, 130.7, 126.1, 123.3, 118.5, 111.1, 21.4; FT-IR (KBr) 3447, 3047, 2920, 2110, 1632, 1595, 1460, 1403, 1313, 1272, 1108, 969, 801, 699 cm^{-1}. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{14}H_{12}N_2H$ 209.1079, found 209.1073.

4-Methyl-2-(p-tolyl)-1H-benzo[d]imidazole ***3b***. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.41; liquid; 135 mg, yield 61%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.74 (br s, 1H), 8.10 (s, 2H), 7.36 (d, J = 7.8 Hz, 3H), 7.08 (d, J = 7.2 Hz, 1H), 6.98 (d, J = 6.6 Hz, 1H), 2.56 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 151.5, 140.5, 129.9, 127.4, 126.7, 123.6, 123.0, 21.6, 17.2; FT-IR (neat) 3402, 3029, 2917, 2115, 1620, 1504, 1485, 1439, 1373, 1285, 1117, 958, 827, 748 cm^{-1}. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{15}H_{14}N_2H$ 223.1235, found 223.1234.

5-Methyl-2-(p-tolyl)-1H-benzo[d]imidazole ***3c***. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.41; white solid; 155 mg, yield 70% (using 3-methylaniline) and 175 mg, yield 79% (using 4-methyl aniline); mp 163−164 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.62 (br s, 1H), 8.02 (s, 2H), 7.48−7.32 (m, 4H), 7.05−6.98 (m, 1H), 2.40 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 152.5, 140.3, 139.2, 138.0, 132.7, 129.9, 127.5, 126.9, 124.4, 115.2, 114.6, 21.8, 21.5; FT-IR (KBr) 3440, 2922, 2852, 1627, 1449, 1385, 1284, 1225, 1109, 1026, 922, 804, 741 cm^{-1}. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{15}H_{14}N_2H$ 223.1235, found 223.1230.

N-(2-(p-tolyl)-1H-benzo[d]imidazol-6-yl)acetamide ***3d***. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.41; pale yellow solid; 191 mg, yield 72%; mp 273−274 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.69 (br s, 1H), 9.97 (br s, 1H), 8.09 (d, J = 7.2 Hz, 1H), 8.03 (d, J = 8.0 Hz, 2H), 7.51 (s, 1H), 7.35 (d, J = 8.0 Hz, 2H), 7.20 (s, 1H), 2.36 (s, 3H), 2.07 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 167.9, 139.3, 134.6, 129.5, 127.5, 126.1, 118.4, 114.3, 101.5, 24.0, 20.9; FT-IR (KBr) 3439, 3200, 2920, 2854, 1671, 1609, 1563, 1456, 1391, 1272, 1156, 1033, 824, 715 cm^{-1}. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{16}H_{15}N_3OH$ 266.1293, found 266.1297.

6-Bromo-2-(p-tolyl)-1H-benzo[d]imidazole ***3e***.[16] Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.41; white solid; 180 mg, yield 63%; mp 232−233 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.03 (br s, 1H), 8.06 (d, J = 7.6 Hz, 2H), 7.77 (s, 1H), 7.52 (s, 1H), 7.37 (d, J = 6.8 Hz, 2H), 7.33 (d, J = 8.0 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6 + $CDCl_3$) δ 152.0, 139.1, 128.4, 126.1, 125.7, 125.6, 123.8, 20.3; FT-IR (KBr) 3449, 3015, 2917, 2110, 1620, 1448,

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1378, 1303, 1275, 1112, 1015, 911, 823, 729 cm^{-1}. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{14}H_{11}BrN_2H$ 287.0184, found 287.0191.

6-Chloro-2-(p-tolyl)-1H-benzo[d]imidazole **3f**. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.41; white solid; 155 mg, yield 64%; mp 234−235 °C; ^1H NMR (600 MHz, DMSO-d_6) δ 13.01 (br s, 1H), 8.06 (d, J = 7.8 Hz, 2H), 7.69−7.65 (m, 1H), 7.53 (d, J = 9.0 Hz, 1H), 7.37 (d, J = 8.4 Hz, 2H), 7.21 (s, 1H), 2.38 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6 + $CDCl_3$) δ 152.1, 139.0, 128.3, 126.1, 125.9, 125.6, 121.2, 20.2; FT-IR (KBr) 3435, 2922, 2857, 2110, 1620, 1583, 1439, 1378, 1308, 1275, 1219, 1061, 963, 809, 725 cm^{-1}. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{14}H_{11}ClN_2H$ 243.0689, found 243.0691.

6-Ethyl-2-(p-tolyl)-1H-benzo[d]imidazole **3g**. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.41; liquid; 170 mg, yield 72%; ^1H NMR (600 MHz, DMSO-d_6) δ 12.66 (br s, 1H), 8.04 (d, J = 8.4 Hz, 2H), 7.53 (d, J = 7.2 Hz, 1H), 7.45 (s, 1H), 7.35 (d, J = 8.4 Hz, 2H), 7.06−7.04 (m, 1H), 2.71 (s, 2H), 2.37 (s, 3H), 1.26−1.22 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.8, 140.2, 139.3, 129.8, 127.5, 123.3, 115.2, 113.5, 29.2, 21.4, 16.4; FT-IR (neat) 3417, 2962, 2925, 2859, 2103, 165, 1559, 1493, 1449, 1389, 1324, 1378, 1186, 1120, 1019, 965, 821, 728 cm^{-1}. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{16}H_{16}N_2H$ 237.1392, found 237.1399.

6-Fluoro-2-(p-tolyl)-1H-benzo[d]imidazole **3h**. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.41; white solid; 134 mg, yield 59%; mp 231−232 °C; ^1H NMR (600 MHz, DMSO-d_6) δ 12.94 (br s, 1H), 8.05 (d, J = 7.8 Hz, 2H), 7.63 (s, 1H), 7.50 (s, 1H), 7.37 (d, J = 7.8 Hz, 2H), 7.04 (s, 1H), 2.38 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 140.4, 130.1, 127.6, 126.9, 112.3, 110.7, 110.3, 21.8; FT-IR (KBr) 3058, 2855, 2752, 2113, 1901, 1734, 1653, 1630, 1595, 1577, 1497, 1443, 1422, 1365, 1309, 1220, 1141, 1022, 824, 727 cm^{-1}. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{14}H_{11}FN_2H$ 227.0985, found 227.0990.

6-Methoxy-2-(p-tolyl)-1H-benzo[d]imidazole **3i**. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.41; liquid; 174 mg, yield 73%; mixture of tautomers (1:1): ^1H NMR (600 MHz, DMSO-d_6) δ 12.65 (br s, 2H), 8.02 (s, 4H), 7.52 (s, 1H), 7.38 (s, 1H), 7.33 (s, 4H), 7.18 (s, 1H), 6.97 (s, 1H), 6.81 (s, 2H), 3.87 (s, 6H), 2.37 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8, 152.2, 140.3, 129.9, 127.4, 126.6, 116.2, 112.5, 97.8, 56.0, 21.6; FT-IR (neat) 3430, 2927, 2857, 2110, 1630, 1597, 1453, 1425, 1392, 1266, 1201, 1159, 1107, 1033, 949, 823, 729 cm^{-1}. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{15}H_{14}N_2OH$ 239.1184, found 239.1189.

2-(p-Tolyl)-6-(trifluoromethyl)-1H-benzo[d]imidazole **3k**.[17] Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.31; white solid; 135 mg, yield 49%; mp 192−193 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 13.28 (br s, 2H), 8.10 (d, J = 7.6 Hz, 2H), 7.84−7.81 (m, 1H), 7.72 (d, J = 8.8 Hz, 1H), 7.54 (d, J = 8.8 Hz, 1H), 7.41 (d, J = 7.2 Hz, 1H), 2.39 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 153.9, 140.2, 129.6, 126.7, 119.0; FT-IR (KBr) 3464, 3124, 2924, 1889, 1615, 1562, 1509, 1427, 1329, 1239, 1218, 1055, 1022, 936, 826, 728 cm^{-1}. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{15}H_{11}N_2F_3H$ 277.0953, found 277.0961.

4,6-Dimethyl-2-(p-tolyl)-1H-benzo[d]imidazole **3l**. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.41; liquid; 140 mg, yield 59%; ^1H NMR (600 MHz, DMSO-d_6) δ 12.57 (br s, 1H), 8.07 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H), 7.15 (s, 1H), 6.81 (s, 1H), 2.52 (s, 3H), 2.38 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 151.4, 140.2, 132.8, 129.9, 127.6, 126.7, 125.2, 21.8, 21.6, 17.2; FT-IR (neat) 3444, 2917, 2857, 1901, 1630, 1593, 1429, 1387, 1257, 1182, 1033, 958, 827, 725 cm^{-1}. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{16}H_{16}N_2H$ 237.1392, found 237.1392.

5,6-Dimethyl-2-(p-tolyl)-1H-benzo[d]imidazole **3ma**. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.41; white solid; 144 mg, yield 61%; mp 233−224 °C; ^1H NMR (600 MHz, DMSO-d_6) δ 12.52 (br s, 1H), 8.03 (d, J = 7.8 Hz, 2H), 7.40 (s, 1H), 7.33 (d, J = 7.8 Hz, 2H), 7.26 (s, 1H), 2.37 (s, 3H), 2.32 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 150.5, 142.5, 139.1, 133.4, 130.8, 129.4, 129.1, 127.7, 126.1, 118.8, 111.2, 20.9, 20.0 ; FT-IR (KBr) 3435, 3015, 2917, 2087, 1900, 1625, 1588, 1499, 1448, 1387, 1308, 1289, 1121, 1308, 1121, 1005, 827, 720 cm^{-1}. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{16}H_{16}N_2H$ 237.1392, found 237.1390.

6,7-Dimethyl-2-(p-tolyl)-1H-benzo[d]imidazole **3mb**. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.31; yellow solid; 24 mg, yield 10%; mp 190−191 °C; mixture of tautomers (1:1): ^1H NMR (400 MHz, DMSO-d_6) δ 12.64 (br s, 1H), 12.30 (br s, 1H), 8.16 (d, J = 8.0 Hz, 2H), 8.09 (d, J = 7.6 Hz, 2H), 7.38−7.36 (m, 5H), 7.24 (d, J = 8.0 Hz, 1H), 7.03−7.00 (m, 2H), 2.53 (s, 6H), 2.40 (s, 6H), 2.36 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 151.3, 140.2, 132.0, 129.9, 127.5, 126.7, 126.5, 21.6, 20.6; FT-IR (KBr) 3596, 2919, 2102, 1625, 1503, 1437, 1384, 1310, 1260, 1122, 1019, 958, 827, 727 cm^{-1}. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{16}H_{16}N_2H$ 237.1392, found 237.1399.

2-(p-Tolyl)-3,9-dihydrofluoreno[2,3-d]imidazole **3n**. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.41; thick brown gummy liquid; 207 mg, yield 70%; ^1H NMR (400 MHz, $CDCl_3$) δ 12.91 (br s, 1H), 8.11 (s, 1H), 8.07 (d, J = 7.2 Hz, 2H), 7.94 (s, 1H), 7.79−7.68 (m, 1H), 7.55 (s, 1H), 7.37 (d, J = 7.2 Hz, 3H), 7.27 (s, 1H), 3.98 (s, 2H), 2.38 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 151.6, 142.4, 139.5, 139.4, 129.5, 127.5, 126.7, 126.4, 126.3, 125.1, 125.0, 57.9, 20.9; FT-IR (neat) 3435, 2924, 2257, 1644, 1431, 1382, 1272, 1047, 1030, 998, 826, 764 cm^{-1}. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{21}H_{16}N_2H$ 297.1392, found 297.1393.

2-Phenyl-1H-benzo[d]imidazole **3o**.[18] Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.41; pale yellow solid; 163 mg, yield 84%; mp 292−293 °C; ^1H NMR (600 MHz, DMSO-d_6) δ 12.92 (br s, 1H), 8.18 (d, J = 9.0 Hz, 2H), 7.67 (d, J = 7.2 Hz, 1H), 7.56−7.49 (m, 4H), 7.22−7.19 (m, 2H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 151.3, 143.8, 135.0, 130.2, 129.9, 129.0, 126.5, 122.6, 121.8, 118.2, 111.4; FT-IR (KBr) 3442, 2961, 2919, 2112, 1565, 1440, 1360, 1283, 1120, 1088, 995, 893, 743 cm^{-1}. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{13}H_{10}N_2H$ 195.0922, found 195.0922.

2-(o-Tolyl)-1H-benzo[d]imidazole **3p**.[18] Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.41; white solid; 137 mg, yield 66%; mp 223−224 °C; ^1H NMR (600 MHz, DMSO-d_6) δ 12.62 (br s, 1H), 7.73 (d, J = 7.2 Hz, 1H), 7.67 (s, 1H), 7.53 (s, 1H), 7.41−7.35 (m, 3H), 7.21 (s, 2H), 2.59 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 152.0, 143.7, 137.0, 131.3, 130.1, 129.5, 129.4, 126.0, 122.4, 121.5, 119.0, 111.3, 21.0; FT-IR (KBr) 3440, 3048, 2973, 2721, 1938, 1619, 1597, 1448, 1406, 1369, 1275, 1229, 1047, 972, 879 cm^{-1}. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{14}H_{12}N_2H$ 209.1079, found 209.1077.

2-(3-Bromophenyl)-1H-benzo[d]imidazole **3q**.[18] Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.41; pale yellow solid; 161 mg, yield 59%; mp 223−224 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 13.05 (br s, 1H), 8.37 (s, 1H), 8.19 (d, J = 8.0 Hz, 1H), 7.70 (d, J = 6.4 Hz, 2H), 7.56−7.50 (m, 2H), 7.25−7.21 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 149.6, 143.7, 135.0, 132.5, 132.4, 131.1, 128.9, 125.4, 122.9, 122.3, 121.9, 119.1, 111.5; FT-IR (KBr) 3326, 3048, 2529, 2112, 1698, 1649, 1595, 1544, 1445, 1315, 1226, 1156, 970, 743 cm^{-1}. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{13}H_9BrN_2H$ 273.0027, found 273.0030.

2-(m-Tolyl)-1H-benzo[d]imidazole **3r**.[19] Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.41; white solid; 135 mg, yield 65%; mp 231−232 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 12.88 (br s, 1H), 8.02 (s, 1H), 7.97 (d, J = 7.6 Hz, 1H), 7.64 (s, 1H), 7.53 (d, J = 4.4 Hz, 1H), 7.45 (t, J = 7.6 Hz, 1H), 7.31 (d, J = 7.2 Hz, 1H), 7.20 (d, J = 3.6 Hz, 2H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 151.8, 144.2, 138.6, 135.4, 130.9, 130.5, 129.3, 127.4, 124.0, 122.9, 122.0, 119.2, 111.7, 21.5; FT-IR (KBr) 3439, 2920, 2859, 2114, 1685, 1554, 1443, 1308, 1239, 1122, 1039, 957, 822, 728 cm^{-1}. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{14}H_{12}N_2$ H 209.1079, found 209.1088.

2-(4-Bromophenyl)-1H-benzo[d]imidazole **3s**.[18] Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.41; pale yellow solid; 172 mg, yield 63%; mp 255−256 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 13.00 (br s, 1H), 8.13 (m, 2H), 7.78 (d, J = 7.6 Hz, 2H), 7.66 (s, 1H), 7.55 (s, 1H), 7.22 (s, 2H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 150.2, 143.7, 135.1, 129.4, 129.0, 128.3, 123.4, 123.2, 122.3, 118.9, 111.7; FT-IR (KBr) 3449, 3052, 2112, 1622, 1590, 1490, 1427, 1300, 1273, 1224, 1114, 1069, 1009, 963, 828, 745 cm^{-1}. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{13}H_9BrN_2H$ 273.0027, found 273.0036.

2-(4-Chlorophenyl)-1H-benzo[d]imidazole **3t**.[18] Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.41; pale yellow solid; 153

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mg, yield 67%; mp 265−266 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.97 (br s, 1H), 8.19 (d, J = 8.4 Hz, 2H), 7.68 (d, J = 7.8 Hz, 1H), 7.63 (d, J = 8.4 Hz, 2H), 7.54 (d, J = 7.8 Hz, 1H), 7.23−7.20 (m, 2H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 150.1, 143.7, 135.0, 134.4, 129.0, 128.7, 128.1, 122.7, 121.8, 118.9, 111.4; FT-IR (KBr) 3442, 2997, 2951, 2112, 1630, 1587, 1486, 1429, 1300, 1273, 1225, 1089, 1015, 965, 831, 746 cm^{-1}. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{13}H_9ClN_2H$ 229.0533, found 229.0533.

2-(4-Fluorophenyl)-1H-benzo[d]imidazole **3u**.[20] Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.41; pale yellow solid; 136 mg, yield 64%; mp 240−241 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.93 (br s, 1H), 8.23 (m, 2H), 7.66 (d, J = 6.4 Hz, 1H), 7.53 (d, J = 6.4 Hz, 1H), 7.42−7.38 (m, 2H), 7.20 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.7, 162.3, 150.8, 144.2, 135.4, 129.2, 127.2, 123, 122.1, 119.2, 111.6, 111.7; FT-IR (KBr) 3443, 2917, 2854, 2113, 1603, 1497, 1475, 1433, 1276, 1229, 1157, 1111, 967, 838, 747 cm^{-1}. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{13}H_9FN_2H$ 213.0828, found 213.0820.

2-(p-Tolyl)-1H-benzo[d]imidazole **3v**.[18] Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.41; white solid; 160 mg, yield 77%; mp 275−276 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.85 (br s, 1H), 8.07 (d, J = 7.2 Hz, 2H), 7.63 (s, 1H), 7.52 (s, 1H), 7.36 (d, J = 6.8 Hz, 2H), 7.19 (s, 2H), 2.37 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 151.4, 143.8, 139.6, 135.0, 129.5, 127.5, 126.4, 122.4, 121.6, 118.7, 111.2, 21.0; FT-IR (KBr) 3440, 2927, 2852, 2106, 1630, 1457, 1261, 1196, 1038, 823, 715 cm^{-1}. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{14}H_{12}N_2H$ 209.1079, found 209.1087.

2-(4-Methoxyphenyl)-1H-benzo[d]imidazole **3w**.[18] Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.41; pale yellow solid ; 151 mg, yield 67%; mp 218−219 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.76 (br s, 1H), 8.13 (d, J = 7.2 Hz, 2H), 7.56 (s, 2H), 7.17−7.10 (m, 4H), 3.83 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 160.6, 151.4, 128.0, 122.7, 121.7, 114.4, 114.3, 111.2, 55.3; FT-IR (KBr) 3472, 2921, 2836, 2113, 1611, 1501, 1476, 1453, 1295, 1254, 1179, 1124, 1034, 965, 845, 745 cm^{-1}. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{14}H_{12}N_2OH$ 225.1028, found 225.1033.

2-(4-Nitrophenyl)-1H-benzo[d]imidazole **3x**.[11b] Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.41; Brown solid; 167 mg, yield 70%; mp 260−261 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.30 (br s, 1H), 8.40−8.37 (m, 4H), 7.67 (s, 2H), 7.27 (s, 2H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 150.0, 149.0, 147.7, 136.0, 134.5, 127.32, 127.3, 124.14, 124.1, 122.9, 114.9; FT-IR (KBr) 3451, 2661, 2110, 1667, 1603, 1516, 1433, 1340, 1290, 1101, 1008, 967, 854, 742 cm^{-1}. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{13}H_9N_3O_2H$ 240.0773, found 240.0770.

2-(3,4-Dimethoxyphenyl)-1H-benzo[d]imidazole **3y**.[21] Analytical TLC on silica gel, 1:3 ethyl acetate/hexane; R_f = 0.41; Pale Yellow solid; 150 mg, yield 59%; mp 181−182 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.77 (br s, 1H), 7.75 (s, 2H), 7.63 (s, 1H), 7.51 (s, 1H), 7.17 (s, 3H), 3.88 (s, 3H), 3.84 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 151.6, 150.5, 150.3, 149.0, 122.8, 122.4, 121.8, 119.5, 119.4, 111.8, 109.8, 55.6; FT-IR (KBr) 3195, 2987, 2842, 1620, 1508, 1481, 1432, 1264, 1198, 1115, 1039, 945, 847, 743 cm^{-1}. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{15}H_{14}N_2O_2H$ 255.1134, found 255.1140.

2-(Naphthalen-2-yl)-1H-benzo[d]imidazole **3z**.[21] Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.41; pale yellow solid; 194 mg, yield 79%; mp 192−193 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.07 (br s, 1H), 8.74 (s, 1H), 8.33−8.29 (m, 1H), 8.09 (d, J = 8.4 Hz, 1H), 8.05 (d, J = 6.6 Hz, 1H), 7.99 (d, J = 6.6 Hz, 1H), 7.71 (d, J = 5.4 Hz, 1H), 7.61−7.58 (m, 3H), 7.23 (s, 2H); ^{13}C NMR (150 MHz, DMSO-d_6 + $CDCl_3$) δ 151.1, 133.1, 133.0, 132.4, 127.7, 127.6, 127.1, 126.9, 126.6, 126.1, 125.9, 125.6, 125.4, 123.3, 121.6, 114.4, 113.4; FT-IR (KBr) 3450, 3053, 2111, 1653, 1588, 1504, 1441, 1405, 1334, 1282, 1136, 1096, 982, 907, 18, 742 cm^{-1}. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{17}H_{12}N_2H$ 245.1079, found 245.1091.

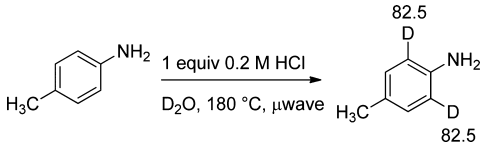
2-(Anthracen-9-yl)-1H-benzo[d]imidazole **3aa**.[22] Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.71; yellow solid; 188 mg, yield 64%; mp 261−262 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.0 (br, s, 1H), 8.85 (s, 1H), 8.22 (d, J = 8.4 Hz, 2H), 7.83 (d, J = 7.2 Hz, 1H), 7.69 (d, J = 9.0 Hz, 2H), 7.61−7.57 (m, 3H), 7.53−7.50 (m, 2H), 7.33−7.31 (m, 2H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 149.5, 130.6, 130.5, 128.8, 128.5, 126.8, 125.8, 125.64, 125.6, 122.5, 121.6, 119.1, 111.4; FT-IR (KBr) 3435, 3398, 2922, 2106, 1625, 1448, 1401, 1373, 1331, 1271, 1229, 1033, 921, 883, 790, 743 cm^{-1}. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{21}H_{14}N_2$ H 295.1235, found 295.1233.

2-(Thiophen-2-yl)-1H-benzo[d]imidazole **3ab**.[18] Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.41; pale yellow solid; 136 mg, yield 68%; mp 343−344 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.95 (br s, 1H), 7.82 (d, J = 3.6 Hz, 1H), 7.71 (d, J = 5.4 Hz, 1H), 7.60 (s, 1H), 7.50 (s, 1H), 7.23−7.19 (m, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 147.4, 143.9, 135.0, 134.0, 129.1, 128.7, 127.1, 123.0, 122.2, 118.9, 111.5; FT-IR (KBr) cm^{-1}. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{11}H_8N_2SH$ 201.0486, found 201.0491.

2-Isopropyl-1H-benzo[d]imidazole **3ac**.[18] Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.31; pale yellow solid; 102 mg, yield 64%; mp 232−233 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31−7.26 (m, 2H), 6.98−6.92 (m, 2H), 3.04−2.99 (m, 1H), 1.27−1.20 (m, 6H); ^{13}C NMR (150 MHz, DMSO-d_6) δ160.1, 121.2, 28.7, 21.3; FT-IR (KBr) 3441, 2973, 2887, 2114, 1622, 1535, 1455, 1415, 1323, 1273, 1092, 995, 750 cm^{-1}. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{10}H_{12}N_2H$ 161.1079, found 161.1087.

Kinetic Isotope Studies. *Preperation of p-Toluidine-d$_2$ (Scheme 6).* The titled compound was perpared according to the reported procedure.[2] Deuterium incorporation (82.5%) was determined by ^{1}H NMR analysis of the mixture. Characterization data for the deuterated product: analytical TLC on silica gel, 1/4 ethyl acetate/hexane R_f = 0.32; pale brown solid; 185 mg, yield 85%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (s, 2H), 3.47 (br s, 2H), 2.23 (s, 3H).

Scheme 6



Intermolecular Kinetic Isotope Study (Scheme 3).[23] *p*-Toluidine **1a** (64 mg), *p*-toluidine-d_2 **1a-d_2** (100 mg), and *p*-tolualdehyde **2b** (1.2 equiv, 1.82 mmol, 218 mg) were stirred at 60 °C for 1 h in DMSO (1 mL) under air. The reaction mixture was then cooled to room temperature and treated with CuI (10 mol %, 0.152 mmol, 29 mg), $TMSN_3$ (2 equiv, 3.0 mmol, 350 mg), and TBHP (1 equiv, 1.52 mmol, 275 μL). The resultant mixture was stirred at 90 °C for 1 h to give 24% conversion. The resulting mixture was extracted with ethyl acetate (3 × 10 mL) and washed with brine (2 × 5 mL) and water (2 × 5 mL). Drying (Na_2SO_4) and passing through Celite gave a clear solution, which was evaporated on a rotary evaporator to give a residue that was purified on silica gel column chromatography using *n*-hexane and ethyl acetate as eluent (40 mg, yield 18%). The ratio of deuterium to hydrogen was determined from the ^{1}H NMR relative integration values of H_a (7.47 ppm) based on H_b (7.05 ppm).

■ ASSOCIATED CONTENT

Supporting Information

Mass spectrum of the reaction mixture of **1a** and **2b** with $TMSN_3$, crystal data of **3e**, and NMR spectra (^{1}H and ^{13}C) of the products. 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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