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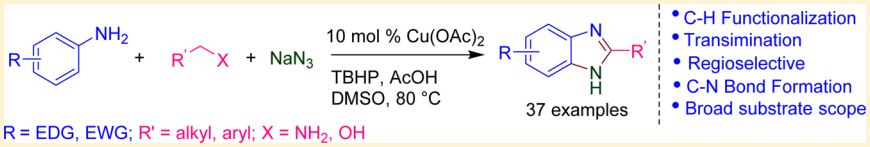
Copper(II)-Catalyzed Oxidative Cross-Coupling of Anilines, Primary Alkyl Amines, and Sodium Azide Using TBHP: A Route to 2-Substituted Benzimidazoles

Devulapally Mahesh, Pradeep Sadhu, and Tharmalingam Punniyamurthy*

Department of Chemistry, Indian Institute of Technology Guwahati, Guwahati 781039, India

Supporting Information



ABSTRACT: Copper(II)-catalyzed oxidative cross-coupling of anilines, primary alkyl amines, and sodium azide is described in the presence of TBHP at moderate temperature. This one-pot multicomponent protocol involves a domino C−H functionalization, transimination, *ortho*-selective amination, and a cyclization sequence. The broad substrate scope and functional group compatibility are the significant practical features. The protocol can be extended to the coupling of benzyl alcohols with moderate yields.

INTRODUCTION

Recent advances in transition-metal-catalyzed C−H functionalization reactions using directing groups have led to the development of effective methods for the regioselective carbon−carbon and carbon−heteroatom bond formations.[1] Among them, C−N bond formation has attracted considerable attention due to the presence of this moiety in numerous compounds that are of biological, medicinal, and material interests.[2−5] More recently, *ortho*-selective C−H azidation of arene has been accomplished using $-NH_2$[2c] and imine[2d] as the directing groups. Herein, we report an efficient copper-catalyzed oxidative cross-coupling of anilines, primary alkyl amines, and sodium azide to afford functionalized benzimidazoles via a domino transimination, *ortho*-selective amination, and cyclization sequence. The utilization of the readily accessible simple substrates and the broad substrate scope are the significant practical advantages. These reaction conditions can be utilized for the coupling of benzyl alcohols in moderate yields.

Benzimidazoles are privileged structural scaffolds due to their interesting medicinal and biological properties.[6] For example, compounds bearing benzimidazole motifs exhibit a broad spectrum of biological properties such as antiviral,[6a] anticancer,[6b] antibacterial,[6c] antifungal,[6d] and anti-HIV activities (Figure 1). In addition, benzimidazole structural frameworks are found to be useful for the fabrication of organic light-emitting diodes (OLEDs).[7] Traditionally, the preparation of benzimidazoles is performed via condensation of 1,2-diaminoarene with aldehydes or carboxylic acids followed by oxidative cyclization. However, these methods often suffer due to the limited substrate scope and harsh reaction conditions.[8] To overcome these drawbacks, transition-metal-catalyzed cross-coupling of aryl halides and their analogues with N−H nucleophiles has been explored.[9] More recently, a few studies are focused on the C−H functionalization and C−N bond formation of amidines[10] and benzylamine with 2-aminoanilines[11] to afford functionalized benzimidazoles (Scheme 1a). These reactions are attractive as they are effective under relatively mild conditions with a broad substrate scope. Development of the oxidative coupling of the readily accessible substituted anilines, primary alkyl amines, and sodium azide via a domino sp^3 and sp^2 C−H functionalization strategy would thus be valuable (Scheme 1b).

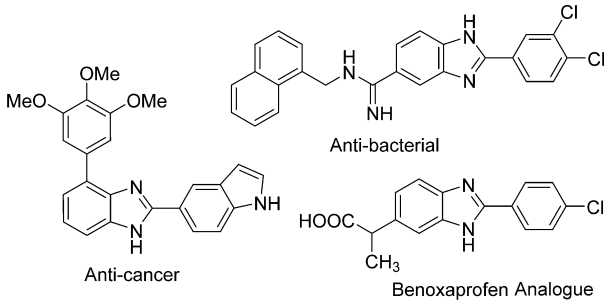


Figure 1. Examples of some biologically important benzimidazoles.

RESULTS AND DISCUSSION

First, we commenced the optimization studies using aniline **1a** and benzylamine **2a** as model substrates with NaN_3, employing different Cu sources, oxidants, and solvents (Table 1). Gratifyingly, the oxidative cross-coupling readily occurred to afford 2-phenylbenzimidazole **3a** in a trace amount when

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Scheme 1. Methods for Benzimidazoles Using Primary Alkyl Amines via Transimination

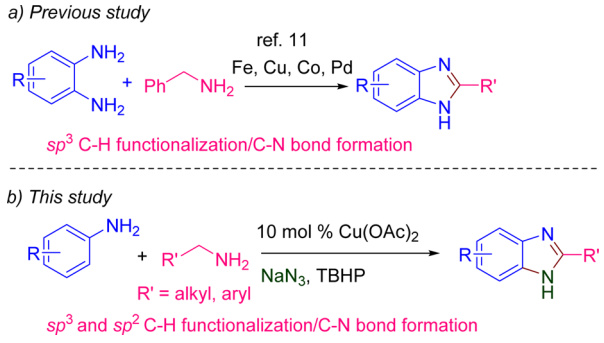
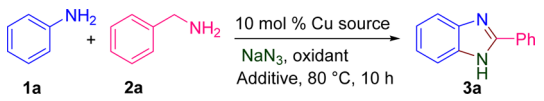


Table 1. Optimization of the Reaction Conditions[a]



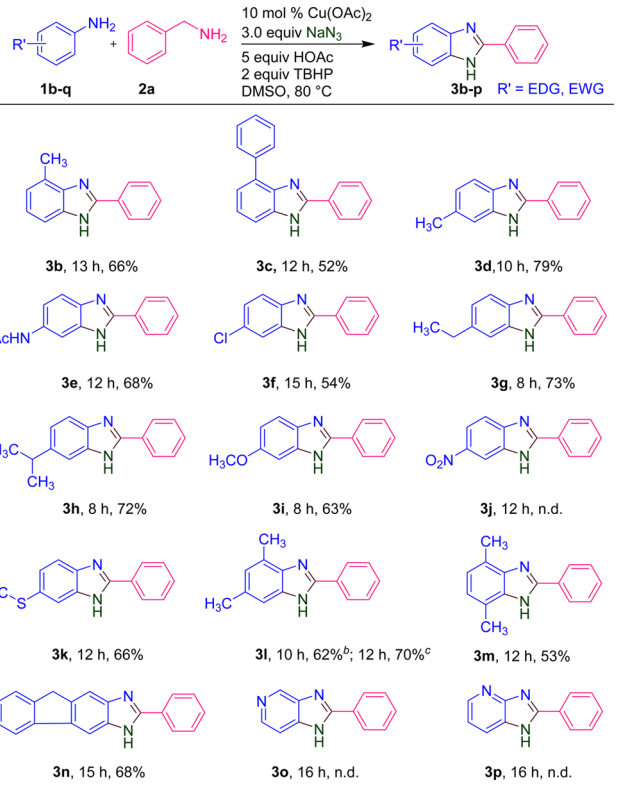
entry	Cu source	additive	solvent	3a (%)[b]
1	CuI		DMSO	trace
2	CuI	CH_3COOH	DMSO	44
3	CuI	$(CH_3)_3CCOOH$	DMSO	trace
4	CuI	CF_3COOH	DMSO	trace
5	CuBr	CH_3COOH	DMSO	31
6	CuCl	CH_3COOH	DMSO	50
7	$CuCl_2$	CH_3COOH	DMSO	60
8	$Cu(OAc)_2$	CH_3COOH	DMSO	82
9	$Cu(SO_4)_2{\cdot}5H_2O$	CH_3COOH	DMSO	trace
10[c]	$Cu(OAc)_2$	CH_3COOH	DMSO	trace
11	$Cu(OAc)_2$	CH_3COOH	DMF	56
12	$Cu(OAc)_2$	CH_3COOH	toluene	24
13	$Cu(OAc)_2$	CH_3COOH	1,4-dioxane	43
14	$Cu(OAc)_2$	CH_3COOH	CH_3CN	46
15[d]	$Cu(OAc)_2$	CH_3COOH	DMSO	38
16[e]	$Cu(OAc)_2$	CH_3COOH	DMSO	35
17		CH_3COOH	DMSO	nd
18[f]	$Cu(OAc)_2$	CH_3COOH	DMSO	nd

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), [Cu] (10 mol %), NaN_3 (1.5 mmol), TBHP (1 mmol), AcOH (2.5 mmol), solvent (0.5 mL), 80 °C, 10 h. [b]Determined by 600 MHz ^1H NMR. [c]Using air, 30% H_2O_2, or DTBP. [d]$Cu(OAc)_2$ (5 mol %). [e]AcOH (5 mmol). [f]No TBHP; nd = not detected.

substrates **1a** and **2a** were stirred at 80 °C for 10 h with 10 mol % of CuI, 3 equiv of NaN_3, and 2 equiv of TBHP in DMSO (entry 1). The use of CH_3COOH as an additive led an increase in the yield to 44%, whereas CF_3COOH and $(CH_3)_3CCOOH$ produced inferior results (entries 2−4). Subsequent screening of the copper sources led to a further increase in the yield to 82% using $Cu(OAc)_2$, whereas CuBr, CuCl, and $CuCl_2$ showed moderate catalytic activity (entries 5−8). In contrast, $Cu(SO_4)_2{\cdot}5H_2O$ afforded **3a** in a trace amount (entry 9). Similar results were observed using air, 30% H_2O_2, and DTBP as the oxidants (entry 10). DMSO was found to be the solvent of choice, whereas DMF, toluene, 1,4-dioxane, and CH_3CN furnished **3a** in moderate yields (entries 11−14); varying the amount of the catalyst (5 mol %) or additive (10 equiv) led to a decrease in the yield to <38% (entries 15 and 16). Control experiments confirmed that, without the copper catalyst or TBHP, the formation of **3a** was not observed (entries 17 and 18).

Having the optimal conditions, the reaction of substituted anilines **1b−q** was next explored using benzylamine **2a** as a standard substrate (Scheme 2). Anilines **1b** and **1c** with methyl

Scheme 2. Reaction of Substituted Anilines with Benzylamine[a]



[a]Reaction conditions: amines **1b−q** (1 mmol), benzylamine **2a** (1.2 mmol), $Cu(OAc)_2$ (10 mol %), NaN_3 (3 mmol), TBHP (2 mmol), AcOH (5 mmol), DMSO (1 mL), 80 °C. [b]3,5-Dimethylaniline used. [c]2,4-Dimethylaniline used.

and phenyl groups at the 2-position underwent the reaction to give benzimidazoles **3b** and **3c** in 66 and 52% yields, respectively. Similarly, anilines **1d−i** bearing acetamide, chloro, ethyl, isopropyl, methoxy, and methyl functionalities at the 4-position furnished the corresponding benzimidazoles **3d−i** in 54−79% yields, whereas aniline **1j** with a strong electron-withdrawing nitro group failed to react and the formation of benzimidazole **3j** was not observed. However, the reaction of aniline **1k** with a 4-thiomethyl group produced benzimidazole **3k** in 66% yield, while anilines **1l−n** with methyl groups at the 2,4-, 3,5-, and 2,5-positions provided benzimidazoles **3l,m** in 53−70% yields. A similar result was observed with 2-aminofluorene **1o**, affording benzimidazole **3n** in 68% yield. In contrast, the reaction of heterocyclic amines such as 2-aminopyridine **1p** and 3-aminopyridine **1q** failed to produce benzimidazoles **3o,p**, and the starting materials remained intact.

Next, the reaction of primary alkyl amines was explored with aniline as the standard substrate (Scheme 3). Benzylamines **2b,c** bearing substitution at the 2-position with methyl and methoxy groups underwent the reaction to furnish benzimidazoles **3q** and **3r** in 74 and 75% yields, respectively. A similar result was observed with benzylamine **2d** bearing a 3-chloro group, affording **3s** in 71% yield. The reaction of benzylamines **2e−h** bearing substitution at the 4-position with chloro, fluoro,

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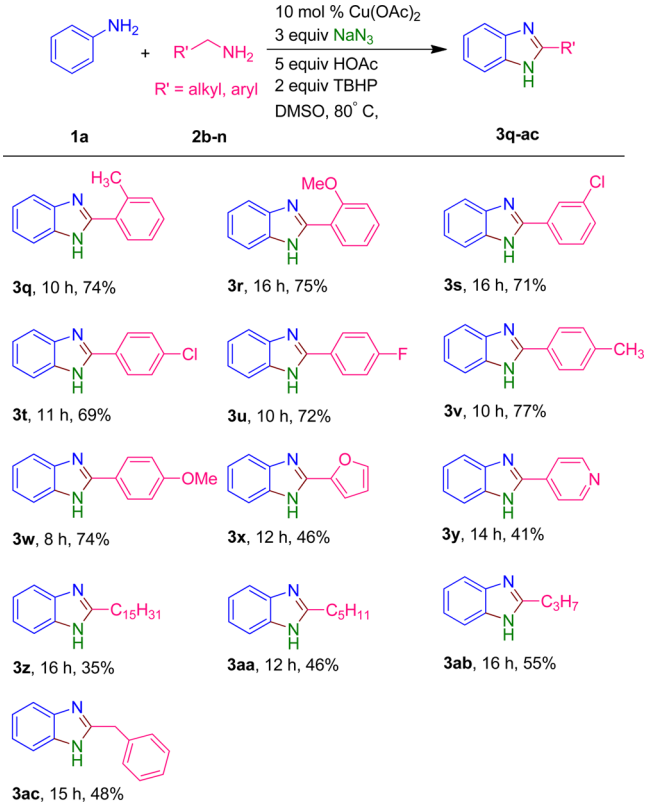
Scheme 3. Reaction of Alkyl Amines with Aniline[a]

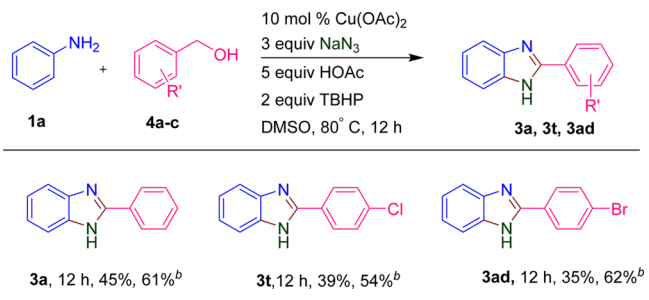


[a]Reaction conditions: aniline **1a** (1 mmol), alkyl amines **2b−n** (1.2 mmol), $Cu(OAc)_2$ (10 mol %), NaN_3 (3 mmol), TBHP (2 mmol), AcOH (5 mmol), DMSO (1 mL), 80 °C.

methoxy, and methyl groups produced the corresponding benzimidazoles **3t−w** in 69−77% yields. In addition, heterocyclic substrates such as furfurylamine **2i** and 4-picolylamine **2j** underwent the reaction to give benzimidazoles **3x** and **3y** in 46 and 41% yields, respectively. Furthermore, aliphatic amines such as butylamine **2k**, hexylamine **2l**, hexadecane-1-amine **2m**, and 2-phenyl ethanamine **2n** could be cross-coupled to afford 2-alkyl benzimidazoles **3z−ac** in 35−55% yields.

The reaction conditions are also compatible for the reaction of benzyl alcohol analogues (Scheme 4). For example, benzyl alcohol **4a** underwent the reaction to furnish benzimidazole **3a**

Scheme 4. Reaction of Aniline with Benzyl Alcohols[a]

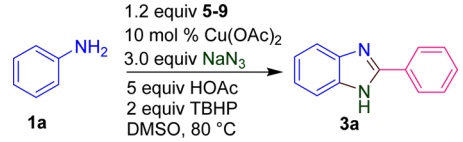


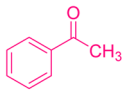
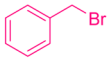
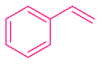
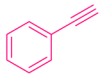
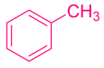
[a]Reaction conditions: aniline **1a** (1 mmol), benzyl alcohols **4a−c** (1.2 mmol), $Cu(OAc)_2$ (10 mol %), NaN_3 (3 mmol), TBHP (2 mmol), AcOH (5 mmol), DMSO (1 mL), 80 °C. [b]Alcohols **4a−c** (3 mmol) used.

in 45% yield. Increasing the quantity of benzyl alcohol **4a** from 1.2 to 3 equiv led to an improvement in the yield to 61%. Similar results were observed with benzyl alcohols bearing bromo and chloro functionalities at the 4-position, affording benzimidazoles **3t** and **3ad** in moderate yields.

Finally, the utility of the protocol was investigated for the reaction of aldehyde precursors **5−9** (Table 2). The reaction of

Table 2. Reaction of Aldehyde Precursors with Aniline[a]



entry	aldehyde precursor	**3a** (%)
1	 **5**	n.d.
2	 **6**	9
3	 **7**	n.d.
4	 **8**	30
5	 **9**	5

[a]Reaction conditions: aniline **1a** (1 mmol), aldehyde precursors **5−10** (1.2 mmol), $Cu(OAc)_2$ (10 mol %), NaN_3 (3 mmol), TBHP (2 mmol), AcOH (5 mmol), DMSO (1 mL), 80 °C.

acetophenone **5** and styrene **7** exhibited no benzimidazole formation, whereas benzyl bromide **6** and phenylacetylene **8** and toluene **9** underwent the reaction to produce the corresponding benzimidazoles in 5−30% yields. These results suggest that a broad range of substrates can be cross-coupled in moderate to good yields.

Some of these benzimidazoles **3b**, **3d,e**, **3i**, **3l**, and **3n** are formed as a mixture of tautomers. To reveal the exact structure, variable-temperature ^1H NMR experiments of **3d** were pursued as a representative example (see Supporting Information). As anticipated, the formation of a single tautomer was observed when heated to 50 °C; however, the corresponding NOE experiment failed to suggest the exact structure of the tautomer due to the lack of N−H interaction with an aromatic H atom.

To understand the reaction pathway, the intermolecular kinetic isotope experiment was performed between **1d** and **1d-d_2**, and P_H/P_D was found to be 1.0 (23% conv, 2.5 h), which suggests that the C−H bond cleavage may not be involved in the product-determining step (Scheme 5).[12] Further, the radical scavenger experiment using TEMPO exhibited no benzimidazole formation, which suggests that a radical intermediate may be involved (Scheme 6).[13] In addition, the ESI-MS analysis of the reaction mixture of **1a** and **2a** revealed the presence of three major species, **A**, **B**, and benzimidazole **3a**

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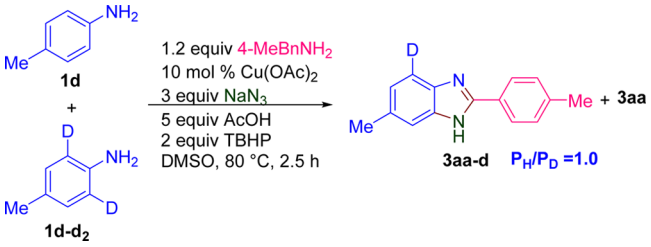
Scheme 5. Kinetic Isotope Experiment

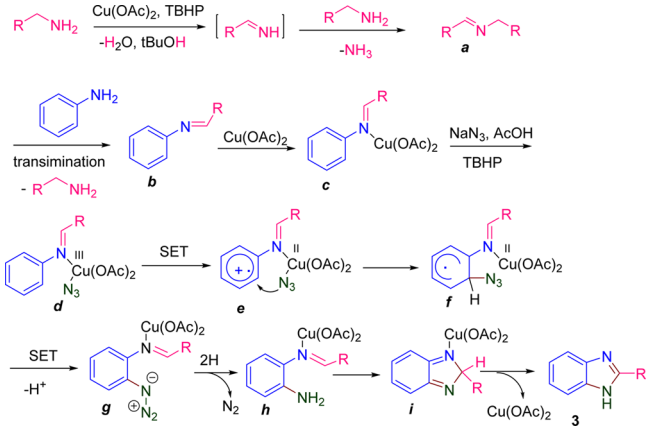


Scheme 6. Radical Scavenger Experiment

(Figure 2). Formation of **A** suggests that the oxidative coupling of benzylamine may be involved via sp^3 C−H functionalization,[14] while intermediate **B** reveals the involvement of transimination[15] of **A** with aniline followed by imine-directed[2d] *ortho*-selective sp^2 C−H azidation. The subsequent $Cu(OAc)_2$-catalyzed reduction of $-N_3$ may produce $-NH_2$ under heating.[9g] The absence of the peaks corresponding to 2-azidoaniline or 2-aminoaniline suggests that the reaction may not involve $-NH_2$ as the directing group for the azidation.[2c] Thus, the copper(II)-catalyzed oxidative coupling of alkyl amine can give imine ***a***,[14] which can undergo transimination[15] with aniline to form ***b***. Coordination[16] of ***b*** with $Cu(OAc)_2$ can furnish ***c***, which may subsequently combine with the in situ generated N_3 radical from HN_3 and TBHP to form intermediate ***d***.[2c] A single electron transfer[17] (SET) from the aryl ring to the metal center may lead to the formation of ***e***, which can convert into ***f*** by azido transfer into the aryl ring.[17] The latter may convert into ***g*** via the SET process, which could be reduced to ***h*** under heating in the presence of $Cu(OAc)_2$.[9g] Intramolecular oxidative cyclization of ***h*** can produce ***i*** that can aromatize to afford **3** and copper(II) to complete the catalytic cycle (Scheme 7). The role of AcOH is to generate HN_3 from NaN_3. Furthermore, intermediate ***b***, prepared from aniline and benzaldehyde, underwent the reaction to produce benzimidazole **3a** in 77% yield (eq 1). These results clearly suggest that the reaction may proceed via intermediate ***b*** using imine as the directing group.

Figure 2. Major species identified using ESI-MS of the reaction mixture of **1a** and **2a** after 5 h (see Supporting Information).

Scheme 7. Proposed Reaction Pathway



CONCLUSIONS

In summary, copper-catalyzed oxidative cross-coupling of anilines, alkyl primary amines, and sodium azide has been demonstrated using domino sp^3 and sp^2 C−H functionalization, transimination, *ortho*-selective azidation, and a cyclization process. The broad substrates scope, functional group compatibility, and one-pot domino process are the significant practical features. This study may open an avenue for further development of a C−H functionalization strategy for the regioselective construction of diverse nitrogen-containing heterocycles from the readily available simple substrates at relatively mild reaction conditions.

EXPERIMENTAL SECTION

General Information. $Cu(OAc)_2$ (99%), CuI (98%), CuCl (90%), $CuCl_2$ (97%), TBHP (~5.5 M in decane, over 4 Å molecular sieves), NaN_3 (99%), CuBr (97%), and $CuSO_4{\cdot}5H_2O$ (99%) were purchased from commercial sources and used as received. Purification of the reaction products was carried out by column chromatography using silica gel (60−120 mesh). Analytical TLC was performed on a silica gel G/GF 254 plate. NMR spectra were recorded on 600 and 400 MHz NMR spectrometers using DMSO-d_6 and $CDCl_3$ as solvents and Me_4Si as an internal standard. Chemical shifts (δ) are reported in parts per million, and spin−spin coupling constants (J) are given in hertz. Melting points were determined using a melting point apparatus and were uncorrected. FT-IR spectra were recorded using an IR spectrometer. Mass spectra were recorded on a Q-Tof ESI-MS instrument.

General Procedure for the Synthesis of Benzimidazoles. To a stirred solution of aniline **1** (1.0 mmol), $Cu(OAc)_2$ (10 mol %, 0.1 mmol, 18 mg), NaN_3 (3 equiv, 3.0 mmol, 195 mg), AcOH (5 equiv, 5.0 mmol, 300 mg), and TBHP (2 equiv, 2 mmol, 360 μL) in DMSO (1 mL) was added alkyl amine **2** or alcohol **4** (1.2 mmol), and the resultant mixture was stirred at 80 °C for the appropriate time. The progress of the reaction was monitored by TLC using ethyl acetate and hexane as an eluent. After completion, the reaction mixture was cooled to room temperature and treated with saturated $NaHCO_3$ (5 mL). The solution was then extracted with ethyl acetate (3 × 10 mL) and washed with brine (2 × 5 mL) and water (1 × 5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified by silica gel column chromatography using *n*-hexane and ethyl acetate as an eluent to afford analytically pure products.

2-Phenyl-1H-benzo[d]imidazole ***3a***.[2d] Analytical TLC on silica gel, 1:3 ethyl acetate/hexane, R_f = 0.41; white solid; 137 mg, yield 70%; mp 290−291 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.92 (br s, 1H), 8.19 (d, J = 7.8 Hz, 2H), 7.67 (s, 1H), 7.56−7.48 (m, 4H), 7.20 (s, 2H); $^{13}C\{^1H\}$ NMR (150 MHz, DMSO-d_6) δ 151.2, 143.8, 135.0, 130.1, 129.8, 128.9, 126.4, 122.5, 121.6, 118.9, 111.3; FT-IR (KBr) 3436, 3048, 2962, 2922, 2114, 1623, 1591, 1462, 1411, 1374, 1276,

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1120, 1029, 971, 744, 703 cm^{-1}; HRMS (ESI) m/z [M + H] calcd for $C_{13}H_{10}N_2H$ 195.0922, found 195.0913.

4-Methyl-2-phenyl-1H-benzo[d]imidazole **3b**.[18a] Analytical TLC on silica gel, 1:3 ethyl acetate/hexane, R_f = 0.42; white solid; 137 mg, yield 66%; mp 247−248 °C; mixture of tautomers (1.2:1); ^1H NMR (600 MHz, DMSO-d_6) δ 12.83 (br s, 1H), 12.57 (br s, 1H), 8.26−8.18 (m, 4H), 7.55−7.49 (m, 7H), 7.35 (d, J = 7.2 Hz, 1H), 7.11−7.07 (m, 2H), 6.99 (s, 2H) 2.59 (s, 3H), 2.57 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 151.2, 150.4, 143.5, 143.2, 134.7, 134.5, 130.3, 129.74, 129.7, 128.9, 128.8, 128.4, 126.7, 126.5, 126.4, 123.1, 122.5, 121.9, 121.8, 121.3, 116.3, 108.8, 17.2, 16.7; FT-IR (neat) 3435, 3051, 2921, 2854, 2717, 2115, 1619, 1537, 1481, 1458, 1371, 1287, 785, 746, 703 cm^{-1}; HRMS (ESI) m/z [M + H] calcd for $C_{14}H_{12}N_2H$ 209.1078, found 209.1057.

2,4-Diphenyl-1H-benzo[d]imidazole **3c**. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane, R_f = 0.42; white solid; 141 mg, yield 52%; mp 256−257 °C;^1H NMR (400 MHz, DMSO-d_6) δ 13.06 (br s, 1H), 8.21−8.16 (m, 4H), 7.59−7.50 (m, 6H), 7.44 (d, J = 7.6 Hz, 1H), 7.40 (t, J = 7.2 Hz, 1H), 7.33 (t, J = 8.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 151.2, 141.3, 138.3, 135.8, 130.6, 130.1, 129.8, 128.9, 128.8, 128.5, 128.2, 127.0, 126.5, 122.9, 120.5, 110.6; FT-IR (neat) 3435, 3057, 2921, 2851, 2114, 1617, 1457, 1415, 1390, 1316, 1244, 1112, 1027, 750, 697 cm^{-1}; HRMS (ESI) m/z [M + H] calcd for $C_{19}H_{14}N_2H$ 271.1235, found 271.1229.

6-Methyl-2-phenyl-1H-benzo[d]imidazole **3d**.[2d] Analytical TLC on silica gel, 1:3 ethyl acetate/hexane, R_f = 0.42; white solid; 164 mg, yield 79%; mp 246−247 °C; mixture of tautomers (1:1.3); ^1H NMR (600 MHz, DMSO-d_6) δ 12.77 (br s, 1H), 12.74 (br s, 1H), 8.16 (d, J = 7.8 Hz, 4H), 7.55−7.52 (m, 5H), 7.48−7.45 (m, 3H), 7.41 (d, J = 8.4 Hz, 1H), 7.31 (s, 1H), 7.04 (d, J = 8.4 Hz, 1H), 7.01 (d, J = 8.4 Hz, 1H), 2.43 (s, 3H), 2.41 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, DMSO-d_6) δ 150.8, 142.0, 131.8, 130.3, 129.6, 128.9, 126.3, 123.9, 123.3, 118.5, 111.0, 21.3; FT-IR (KBr) 3435, 3047, 2921, 2856, 2110, 1631, 1595, 1463, 1401, 1308, 1276, 1112, 972, 804, 702, 689 cm^{-1}; HRMS (ESI) m/z [M + H] calcd for $C_{14}H_{12}N_2H$ 209.1078, found 209.1071.

N-(2-Phenyl-1H-benzo[d]imidazol-6-yl)acetamide **3e**. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane, R_f = 0.41; pale yellow solid; 171 mg, yield 68%; mp 262−263 °C; mixture of tautomers (1:2.1); ^1H NMR (600 MHz, DMSO-d_6) δ 12.85 (br s, 1H), 12.79 (br s, 1H), 10.03 (br s, 1H), 9.93 (br s, 1H), 8.16−8.13 (m, 4H), 8.02 (s, 1H), 7.58−7.52 (m, 5H), 7.47−7.45 (m, 2H), 7.39−7.37 (m, 2H), 7.21−7.19 (m, 2H), 2.09 (s, 3H), 2.07 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, DMSO-d_6) δ 168.1, 168.0, 151.7, 151.0, 143.9, 140.0, 135.1, 134.9, 131.3, 130.2, 129.6, 129.0, 126.4, 126.2, 118.7, 115.8, 114.5, 110.9, 109.3, 101.5, 24.1; FT-IR (KBr) 3436, 2957, 2922, 2851, 2130, 1643, 1497, 1463, 1313, 1259, 1178, 1025, 994, 822, 694 cm^{-1}; HRMS (ESI) m/z [M + H] calcd for $C_{15}H_{13}N_3OH$ 252.1137, found 252.1146.

6-Chloro-2-phenyl-1H-benzo[d]imidazole **3f**.[9c] Analytical TLC on silica gel, 1:3 ethyl acetate/hexane, R_f = 0.48; white solid; 123 mg yield 54%; mp 200−201 °C; ^1H NMR (600 MHz, DMSO-d_6) δ 13.12 (br s, 1H), 8.17 (d, J = 7.8 Hz, 2H), 7.69−7.50 (m, 5H), 7.23 (d, J = 7.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (150 MHz, DMSO-d_6) δ 152.7, 130.2, 129.7, 129.0, 126.6, 126.5, 122.4; FT-IR (KBr) 3444, 2920, 2119, 1624, 1584, 1462, 1450, 1438, 1384, 1275, 1107, 1062, 808, 692 cm^{-1}; HRMS (ESI) m/z [M + H] calcd for $C_{13}H_9ClN_2H$229.0532, found 229.0512.

6-Ethyl-2-phenyl-1H-benzo[d]imidazole **3g**. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane, R_f = 0.43; brown liquid; 162 mg, yield 73%;^1H NMR (400 MHz, DMSO-d_6) δ 12.82 (br s, 1H), 8.20 (d, J = 8.4 Hz, 2H), 7.57−7.47 (m, 3H), 7.46−7.41 (m, 2H), 7.07 (d, J = 8.4 Hz, 1H), 2.74 (q, J = 7.6 Hz, 2H), 1.25 (t, J = 7.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 130.4, 129.7, 128.9, 126.3, 28.5, 16.4; FT-IR (neat) 3390, 3064, 2963, 2928, 2106, 1628, 1595, 1453, 1431, 1405, 1374, 1280, 1055, 814, 776, 692 cm^{-1}; HRMS (ESI) m/z [M + H] calcd for $C_{15}H_{14}N_2H$ 223.1235, found 223.1235.

6-Isopropyl-2-phenyl-1H-benzo[d]imidazole **3h**. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane, R_f = 0.45; liquid; 170 mg, yield 72%; ^1H NMR (600 MHz, DMSO-d_6) δ 12.82 (br s, 1H), 8.20 (s, 2H), 7.59−7.52 (m, 3H), 7.47−7.36 (m, 2H), 7.09 (s, 1H), 2.99 (s, 1H), 1.26 (d, J = 7.2 Hz, 6H); tautomers (1:1); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 151.0, 143.2, 142.3, 135.2, 130.4, 129.6, 128.9, 126.3, 121.6, 120.7, 118.6, 115.8, 110.9, 108.3, 33.7, 24.4; FT-IR (neat) 3400, 3067, 2959, 2927, 2256, 2104, 1628, 1541, 1463, 1431, 1364, 1288, 1047, 815, 776 cm^{-1}; HRMS (ESI) m/z [M + H] calcd for $C_{16}H_{16}N_2H$ 237.1392, found 237.1393.

6-Methoxy-2-phenyl-1H-benzo[d]imidazole **3i**.[9c] Analytical TLC on silica gel, 1:3 ethyl acetate/hexane, R_f = 0.35; liquid; 141 mg, yield 63%; tautomers (1:1); ^1H NMR (600 MHz, DMSO-d_6) δ 12.82 (br s, 2H), 8.18−8.17 (m, 4H), 7.57−7.52 (m, 6H), 7.46−7.44 (m, 2H), 7.31−7.20 (m, 1H), 7.04 (s, 1H), 6.86 (s, 2H), 3.81 (s, 6H); tautomers (1:1); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 156.1, 150.5, 138.4, 130.4, 129.5, 128.9, 128.3, 127.3, 126.7, 126.2, 119.4, 112.3, 111.6, 111.2, 101.4, 94.5, 55.5; FT-IR (neat) 3414, 2924, 2854, 2255, 1631, 1594, 1539, 1490, 1455, 1434, 1159, 1117, 1026, 823, 778 cm^{-1}; HRMS (ESI) m/z [M + H] calcd for $C_{14}H_{12}N_2OH$ 225.1028, found 225.1031.

6-(Methylthio)-2-phenyl-1H-benzo[d]imidazole **3k**.[18b] Analytical TLC on silica gel, 1:3 ethyl acetate/hexane, R_f = 0.31; liquid; 158 mg, yield 66%; ^1H NMR (600 MHz, DMSO-d_6) δ 12.97 (br s, 1H), 8.19 (d, J = 7.8 Hz, 2H), 7.55−7.53 (m, 3H), 7.49−7.46 (m, 2H), 7.17 (d, J = 4.8 Hz, 1H), 2.52 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, DMSO-d_6) δ 151.4, 130.0, 129.9, 129.0, 126.5, 122.9, 121.9, 119.2, 117.2, 111.9, 109.4, 16.5; FT-IR (KBr) 3400, 2920, 2856, 2255, 2126, 1624, 1582, 1537, 1463, 1441, 1422, 1278, 1025, 1004, 806, 777 cm^{-1}; HRMS (ESI) m/z [M + H] calcd for $C_{14}H_{12}N_2SH$ 241.0799, found 241.0796.

4,6-Dimethyl-2-phenyl-1H-benzo[d]imidazole **3l**.[9c] Analytical TLC on silica gel, 1:3 ethyl acetate/hexane, R_f = 0.41; white solid; 138 mg, yield 62% (3,5-diMe aniline) and 155 mg, 70% (2,4-diMe aniline); mp 190−191 °C; tautomers (1:0.6); ^1H NMR (600 MHz, DMSO-d_6) δ 12.67 (br s, 1H), 12.46 (br s, 1H), 8.23 (d, J = 7.8 Hz, 2H), 8.16 (d, J = 7.2 Hz, 2H), 7.54−7.45 (m, 6H), 7.26 (s, 1H), 7.12 (s, 1H), 6.83−6.82 (m, 2H) 2.54−2.50 (m, 6H), 2.50−2.37 (m, 6H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 151.0, 149.9, 143.9, 141.4, 134.8, 132.7, 131.7, 130.6, 130.5, 129.6, 129.4, 128.9, 128.8, 127.8, 126.6, 126.2, 124.7, 123.6, 120.7, 116.0, 108.5, 21.4, 21.2, 17.1, 16.6; FT-IR (neat) 3456, 3146, 2922, 2853, 2108, 1683, 1627, 1456, 1406, 1332, 1254, 1031, 838, 701, 682 cm^{-1}; HRMS (ESI) m/z [M + H] calcd for $C_{15}H_{14}N_2H$ 223.1235, found 223.1231.

4,7-Dimethyl-2-phenyl-1H-benzo[d]imidazole **3m**. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane, R_f = 0.41; white solid; 118 mg, yield 53%; mp 231−232 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 12.63 (br s, 1H), 8.37−8.35 (m, 2H), 7.68−7.60 (m, 3H), 7.02−7.00 (m, 2H), 2.68−2.62 (m, 6H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 150.4, 134.2, 130.5, 129.6, 128.8, 126.7, 125.5, 123.0, 121.9, 118.5,112.8, 17.0, 16.5; FT-IR (neat) 3435, 2922, 2852, 2108, 1625, 1457, 1410, 1313, 1264, 1029, 963, 705 cm^{-1}; HRMS (ESI) m/z [M + H] calcd for $C_{15}H_{14}N_2H$ 223.1235, found 223.1241.

2-Phenyl-3,9-dihydrofluoreno[2,3-d]imidazole **3n**. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane, R_f = 0.45; white solid; 192 mg, yield 68%; mixture of tautomers (1:1); ^1H NMR (600 MHz, $CDCl_3$) δ 13.05 (br s, 1H), 12.97 (br s, 1H), 8.24−8.20 (m, 4H), 7.96−7.87 (m, 2H), 7.77−7.69 (m, 2H), 7.64−7.48 (m, 10H), 7.39−7.36 (m, 2H), 7.28−7.26 (m, 2H), 4.15- 4.11 (m, 1H), 3.99 (s, 1H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 151.5, 130.2 129.7, 128.9, 126.7, 126.5, 126.3, 125.0, 115.1; FT-IR (neat) 3433, 2922, 1629, 1457, 1433, 1403, 1311, 1107, 962, 854, 768, 725, 751, 698 cm^{-1}; HRMS (ESI) m/z [M + H] calcd for $C_{20}H_{14}N_2H$ 283.1235, found 283.1235.

2-(o-Tolyl)-1H-benzo[d]imidazole **3q**.[2d] Analytical TLC on silica gel, 1:3 ethyl acetate/hexane, R_f = 0.41; white solid; 154 mg, yield 74%; mp 223−224 °C; ^1H NMR (600 MHz, DMSO-d_6) δ 12.63 (br s, 1H), 7.75 (d, J = 7.2 Hz, 1H), 7.67 (s, 1H), 7.54 (s, 1H), 7.41−7.35 (m, 3H), 7.21 (s, 2H), 2.61 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, DMSO-d_6) δ 151.9, 143.6, 137.0, 134.3, 131.3, 130.1, 129.4, 129.3, 126.0, 122.3, 121.4, 118.9, 111.3, 21.0; FT-IR (KBr) 3435, 3052, 2959, 2786, 2111, 1620, 1542, 1454, 1409, 1367, 1216, 1092, 900, 765, 746, 733 cm^{-1}; HRMS (ESI) m/z [M + H] calcd for $C_{14}H_{12}N_2H$ 209.1079, found 209.1085.

2-(2-Methoxyphenyl)-1H-benzo[d]imidazole **3r**. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane, R_f = 0.41; white solid; 168 mg, yield 75%; mp 236−237 °C; ^1H NMR (600 MHz, DMSO-d_6) δ 12.13 (br s, 1H), 8.33 (d, J = 7.2 Hz, 1H), 7.65−7.60 (m, 2H), 7.49 (t, J =

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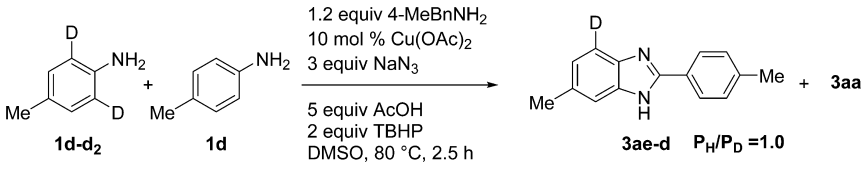
Scheme 8



7.8 Hz, 1H), 7.25 (d, J = 8.4 Hz, 1H), 7.20 (t, J = 7.8 Hz, 2H) 7.13 (t, J = 7.2 Hz, 1H), 4.02 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, DMSO-d_6) δ 156.8, 149.0, 142.8, 134.8, 131.2, 129.8, 122.1, 121.6, 120.9, 118.5, 118.1, 112.1, 55.7; FT-IR (KBr) 3436, 3007, 2964, 2111, 1604, 1584, 1474, 1435, 1373, 1281, 1244, 1089, 1022, 966, 746 cm^{-1}; HRMS (ESI) m/z [M + H] calcd for $C_{14}H_{12}N_2OH$ 225.1027, found 225.1027.

2-(3-Chlorophenyl)-1H-benzo[d]imidazole **3s**.[9c] Analytical TLC on silica gel, 1:3 ethyl acetate/hexane, R_f = 0.41; white solid; 162 mg, yield 71%; mp 239−240 °C;^{1}H NMR (600 MHz, DMSO-d_6) δ 13.06 (br s, 1H), 8.23−8.22 (m, 1H), 8.15 (d, J = 7.8 Hz, 1H), 7.69 (d, J = 7.8 Hz, 1H), 7.60−7.54 (m, 3H), 7.26−7.20 (m, 2H); $^{13}C\{^1H\}$ NMR (150 MHz, DMSO-d_6) δ 149.8, 143.7, 135.0, 133.8, 132.2, 130.9, 129.5, 126.1, 125.0, 122.9, 122.0, 119.1, 111.6; FT-IR (KBr) 3434, 3045, 2964, 2877, 2788, 2113, 1602, 1591, 1541, 1442, 1403, 1285, 1229, 1079, 998, 925, 743 cm^{-1}; HRMS (ESI) m/z [M + H] calcd for $C_{13}H_9ClN_2$ H 229.0533, found 229.0518.

2-(4-Chlorophenyl)-1H-benzo[d]imidazole **3t**.[2d] Analytical TLC on silica gel, 1:3 ethyl acetate/hexane, R_f = 0.41; pale yellow solid; 157 mg, yield 69%; mp 266−267 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.0 (br s, 1H), 8.19 (d, J = 7.2 Hz, 2H), 7.63−7.56 (m, 4H), 7.21 (s, 2H); $^{13}C\{^1H\}$ NMR (150 MHz, DMSO-d_6) δ 150.2, 134.5, 129.0, 128.1, 122.3, 118.9, 111.5; FT-IR (KBr) 3445, 2996, 2957, 2116, 1635, 1583, 1482, 1421, 1323, 1256, 1234, 1095, 1025, 966, 835, 757 cm^{-1}; HRMS (ESI) m/z [M + H] calcd for $C_{13}H_9ClN_2H$ 229.0532, found 229.0529.

2-(4-Fluorophenyl)-1H-benzo[d]imidazole **3u**.[2d] Analytical TLC on silica gel, 1:3 ethyl acetate/hexane, R_f = 0.41; yellow solid; 153 mg, yield 72%; mp 239−240 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.92 (br s, 1H), 8.22 (s, 2H), 7.65 (s, 1H), 7.53 (s, 1H), 7.40 (s, 2H), 7.20 (s, 2H); $^{13}C\{^1H\}$ NMR (150 MHz, DMSO-d_6) δ 164.0 (d, J = 247.0 Hz,), 150.5, 143.8, 135.1, 128.8 (d, J = 7.5 Hz), 126.9, 122.6, 121.8, 118.9, 116.2 (d, 22.5 Hz), 111.4; FT-IR (KBr) 3435, 3052, 2960, 2854, 2116, 1603, 1497, 1475, 1433, 1276, 1228, 1156, 1110, 837, 747 cm^{-1}; HRMS (ESI) m/z [M + H] calcd for $C_{13}H_9FN_2H$ 213.0828, found 213.0821.

2-(p-Tolyl)-1H-benzo[d]imidazole **3v**.[2d] 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 (600 MHz, DMSO-d_6) δ 12.85 (br s, 1H), 8.08 (d, J = 9 Hz, 2H), 7.65−7.63 (m, 1H), 7.52 (s, 1H), 7.36 (d, J = 9 Hz, 2H), 7.20−7.17 (m, 2H), 2.38 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, DMSO-d_6) δ 151.4, 143.9, 139.6, 135.0, 129.5, 127.5, 126.4, 122.4, 121.6, 118.7, 111.2, 21.0; FT-IR (KBr) 3435, 3053, 2961, 2919, 2855, 2115, 1621, 1588, 1448, 1430, 1226, 1122, 1042, 821, 747 cm^{-1}; HRMS (ESI) m/z [M + H] calcd for $C_{14}H_{12}N_2H$ 209.1079, found 209.1065.

2-(4-Methoxyphenyl)-1H-benzo[d]imidazole **3w**.[2d] Analytical TLC on silica gel, 1:3 ethyl acetate/hexane, R_f = 0.41; white solid ; 166 mg, yield 74%; mp 217−218 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.75 (br s, 1H), 8.12 (s, 2H), 7.62 (s, 1H), 7.49 (s, 1H), 7.17−7.11 (m, 4H), 3.84 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, DMSO-d_6) δ 160.6, 151.4, 143.9, 135.0, 128.1, 122.7, 122.1, 121.5, 118.5, 114.4, 111.0, 55.3; FT-IR (KBr) 3472, 3054, 2923, 2855, 2113, 1611, 1500, 1476, 1453, 1295, 1254, 1179, 1124, 1033, 965, 845, 745 cm^{-1}; HRMS (ESI) m/z [M + H] calcd for $C_{14}H_{12}N_2OH$ 225.1027, found 225.1026.

2-(Furan-2-yl)-1H-benzo[d]imidazole **3x**.[9f] Analytical TLC on silica gel, 1:3 ethyl acetate/hexane, R_f = 0.35; white solid ; 85 mg, yield 46%; mp 284−285 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.94 (br s, 1H), 7.95 (s, 1H), 7.63 (d, J = 7.6 Hz, 1H), 7.50 (d, J = 7.2 Hz, 1H), 7.20−7.19 (m, 3H), 6.73 (s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 145.6, 144.7, 143.7, 134.2, 122.7, 121.8, 118.8, 112.4, 111.4, 110.5; FT-IR (KBr) 3434, 3059, 2924, 2853, 2663, 1630, 1525, 1443, 1416, 1364, 1278, 1234, 1014, 979, 906, 883, 738, 589 cm^{-1}; HRMS (ESI) m/z [M + H] calcd for $C_{11}H_8N_2OH$ 185.0715, found 185.0715

2-(Pyridin-4-yl)-1H-benzo[d]imidazole **3y**.[9h] Analytical TLC on silica gel, 1:3 ethyl acetate/hexane, R_f = 0.20; pale yellow solid; 80 mg, yield 41%; mp 220−221 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.27 (br s, 1H), 8.76 (s, 2H), 8.10 (s, 2H), 7.74 (d, J = 7.2 Hz, 1H), 7.60 (d, J = 7.2 Hz, 1H), 7.30−7.25 (m, 2H); $^{13}C\{^1H\}$ NMR (150 MHz, DMSO-d_6) δ 150.5, 149.8, 148.8, 143.6, 137.1, 135.0, 123.6, 122.3, 120.3, 119.5, 111.8; FT-IR (KBr) 3418, 2925, 2255, 2128, 1646, 1609, 1433, 1384, 1317, 1234, 1048, 1025, 1001, 765 cm^{-1}; HRMS (ESI) m/z [M + H] calcd for $C_{12}H_9N_3H$ 196.0875, found 196.0875.

2-Pentadecyl-1H-benzo[d]imidazole **3z**. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane, R_f = 0.35; white solid; 115 mg, yield 35%; mp 91−92 °C;^{1}H NMR (600 MHz, DMSO-d_6) δ 12.14 (br s, 1H), 7.44 (s, 2H), 7.09 (s, 2H), 2.77 (s, 2H), 1.74 (s, 2H), 1.22 (s, 24H) 0.84 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, DMSO-d_6) δ 31.3, 29.0, 28.9, 28.73, 28.7, 28.5, 27.6, 22.1, 14.0; FT-IR (KBr) 3435, 3089, 2954, 2920, 2849, 2101, 1625, 1541, 1470, 1458, 1206, 1155, 753, 744 cm^{-1}; HRMS (ESI) m/z [M + H] calcd for $C_{22}H_{36}N_2H$ 329.2956, found 329.2936.

2-Pentyl-1H-benzo[d]imidazole **3aa**.[18] Analytical TLC on silica gel, 1:3 ethyl acetate/hexane, R_f = 0.35; brown solid; 86 mg, yield 46%; mp 140−141 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.16 (br s, 1H), 7.44 (s, 2H), 7.10−7.09 (m, 2H), 2.79 (t, J = 7.2 Hz, 2H), 1.77−1.74 (m, 2H), 1.32−1.30 (m, 4H), 0.87−0.84 (m, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, DMSO-d_6) δ 155.3, 121.1, 30.9, 28.5, 27.3, 21.9, 13.9; FT-IR (KBr) 3390, 3050, 2951, 2924, 2852, 2773, 2257, 2128, 1647, 1537, 1447, 1418, 1233, 1024, 998, 766 cm^{-1}; HRMS (ESI) m/z [M + H] calcd for $C_{12}H_{16}N_2H$ 189.1392, found 189.1394.

2-Propyl-1H-benzo[d]imidazole **3ab**.[18a] Analytical TLC on silica gel, 1:3 ethyl acetate/hexane, R_f = 0.35; brown solid; 88 mg, yield 55%; mp 230−231 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.15 (br s, 1H), 7.45 (s, 2H), 7.10 (s, 2H), 2.78 (t, J = 7.2 Hz, 2H), 1.80−1.76 (m, 2H), 0.95 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, DMSO-d_6) δ 155.0, 121.1, 30.5, 21.0, 13.7; FT-IR (KBr) 3434, 2257, 2129, 1646, 1047, 1025, 996, 827, 766, 688 cm^{-1}; HRMS (ESI) m/z [M + H] calcd for $C_{10}H_{12}N_2H$ 161.1079, found 161.1078.

2-Benzyl-1H-benzo[d]imidazole **3ac**.[9c] Analytical TLC on silica gel, 1:3 ethyl acetate/hexane, R_f = 0.41; white solid; 100 mg, yield 48%; mp 221−222 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.29 (br s, 1H), 7.46 (s, 2H), 7.34−7.30 (m, 4H), 7.24−7.21 (m, 1H), 7.13−7.10 (m, 2H), 4.16 (s, 2H); $^{13}C\{^1H\}$ NMR (150 MHz, DMSO-d_6) δ 153.3, 137.4, 128.5, 128.2, 126.3, 121.1, 34.7; FT-IR (KBr) 3436, 3049, 2923, 2683, 1623, 1536, 1493, 1456, 1426, 1270, 1222, 1147, 1024, 748, 722 cm^{-1}; HRMS (ESI) m/z [M + H] calcd for $C_{14}H_{12}N_2H$ 209.1078, found 209.1071.

2-(4-Bromophenyl)-1H-benzo[d]imidazole **3ad**.[2d] Analytical TLC on silica gel, 1:3 ethyl acetate/hexane, R_f = 0.41; pale yellow solid; 95 mg, yield 35%; mp 260−261 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.00 (br s, 1H), 8.13−8.08 (m, 2H), 7.78 (d, J = 7.2 Hz, 2H), 7.68 (d, J = 8.0 Hz, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.23−7.19 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 150.0, 143.5, 134.8, 131.8, 129.2, 128.1, 123.0, 122.6, 121.6, 118.7, 111.2; FT-IR (KBr) 3435, 3056, 2120, 1619, 1584, 1485, 1423, 1297, 1270, 1221, 1197, 1064, 1005, 960, 820, 742 cm^{-1}; HRMS (ESI) m/z [M + H] calcd for $C_{13}H_9BrN_2H$ 273.0027, found 273.0028.

Kinetic Isotope Study. To a stirred solution of *p*-toluidine **1d** (0.18 mmol, 20 mg), *p*-toluidine **1d**-d_2[12b] (0.32 mmol, 35 mg), $Cu(OAc)_2$ (10 mol %, 0.05 mmol, 9 mg), NaN_3 (3 equiv, 1.5 mmol, 97 mg), AcOH (5 equiv, 2.5 mmol, 150 mg), and TBHP (2 equiv, 1

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J. Org. Chem. 2016, 81, 3227−3234

mmol, 90 μL) in DMSO (0.5 mL) was added 4-MeBnNH$_2$ **2g** (1.2 equiv, 0.6 mmol, 73 mg), and the resultant mixture was stirred at 80 °C (Scheme 8). After 2.5 h, the reaction mixture was cooled to room temperature and treated with saturated $NaHCO_3$ (3 mL). The mixture was then extracted with ethyl acetate (3 × 5 mL) and washed with brine (2 × 3 mL) and water (1 × 5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using hexane and ethyl acetate as an eluent to afford a mixture of **3ae−d** and **3ae** as a white solid in 19% (21 mg) yield. The ratio of deuterium to hydrogen was determined by the ^{1}H NMR relative integration values of H_a (7.95 ppm) based on H_b (7.51 ppm).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00186.

ESI-MS spectrum of the reaction mixture of **1a** and **2a**, variable-temperature NMR spectra of **3d**, and ^{1}H and ^{13}C NMR spectra of the products (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: tpunni@iitg.ernet.in.

Notes

The authors declare no competing financial interest.

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