Facile One-Pot Synthesis of *N*-Alkylated Benzimidazole and Benzotriazole from Carbonyl Compounds

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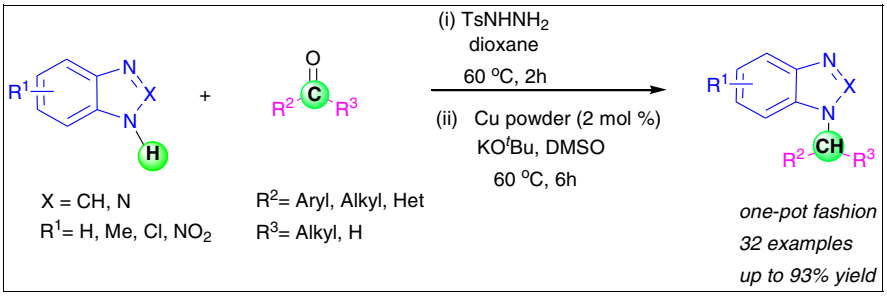

An efficient one-pot *N*-alkylation of benzimidazole and benzotriazole from carbonyl compounds and tosylhydrazide has been accomplished via copper powder-catalyzed N—H bond insertion affording *N*-alkylated products in good yields. The reaction can tolerate a wide range of carbonyl compounds, such as aryl, alkyl, heterocyclic and α,β-unsaturated ketones, and aldehydes.

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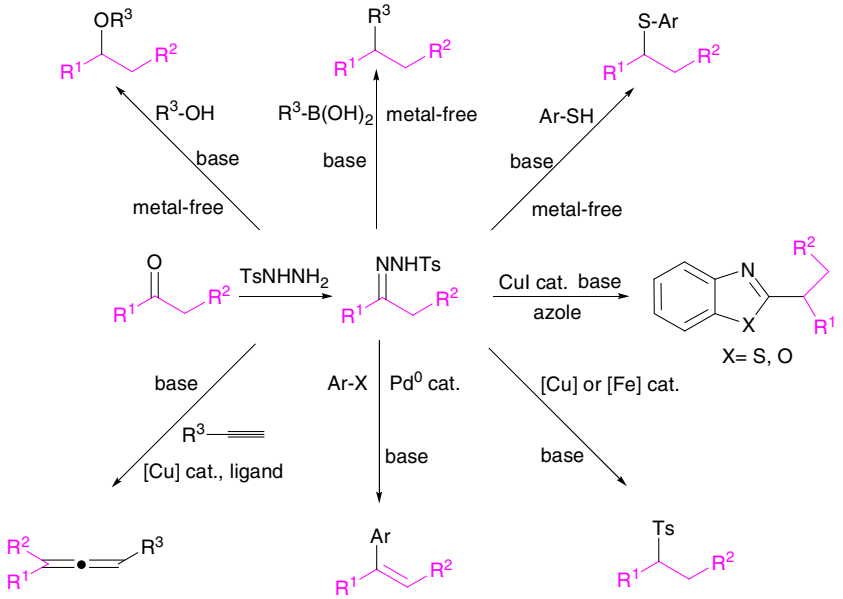
INTRODUCTION

Benzimidazoles and benzotriazoles are important reagents in organic synthesis [1] and can serve as ligands to transition metals for modeling biological systems [2]. More importantly, their derivatives are common structure motifs in natural products and have various pharmacological properties, such as antiulcers, antihypertensives, antivirals, antifungals, anticancers, and antihistamines [3]. Consequently, the development of highly efficient methods for the synthesis of functional benzimidazoles and benzotriazoles is very important. It is clear that *N*-alkylation of azoles plays a pivotal role in the synthesis of their derivatives. Traditionally, the *N*-alkylation of azoles requires deprotonation followed by a nucleophilic substitution with an electrophile (RX= aryl or alkyl halide, X = halide, OTs = tosylate, OTf = triflate, etc.) [4]. As a matter of fact, several drawbacks of these reactions exist, such as requiring strong bases, generating stoichiometric amount of wasteful (in)organic salts, and low secondary/tertiary amine product selectivity [4]. Therefore, it is necessary to develop improved synthetic methodologies for the *N*-alkylation of azoles by employing new alkylation reagents and catalysts.

In recent years, *N*-tosylhydrazones have been proven to be versatile synthetic intermediates and used as *in situ* source of diazo compounds in various reactions [5]. In this context, we focused on *N*-tosylhydrazones as readily available coupling reagents in carbon—carbon and carbon—heteroatom bond-forming reactions through transition-metal-catalyzed and metal-free processes (Scheme 1) [6–9]. In the few past years, Barluenga [6], Wang [7], Alami [8], Cuevas-Yañez, and others [9] had illustrated that the utility of *N*-tosylhydrazones represented a very convenient method for the unconventional modification of carbonyl compounds. Especially, Cuevas-Yañez reported $Cu(acac)_2$-catalyzed *N*-alkylation of imidazoles using *p*-toluenesulfonylhydrazones as alkylated reagents [9f]. However, drawbacks of this reaction include the following: (1) the reaction must be performed by two steps, which means requirement of long reaction time (37 h) and more experimental operations; (2) the use of additive (n-$Bn_4N^+Br^-$) and exclusion of air; (3) only *N*-alkylation of benzimidazole and poor functional-group tolerance; and (4) the requirement of relatively expensive and toxic transition metal catalyst. For these reasons, the development of the simple, general, and ecofriendly methods of *N*-alkylation of azoles is one of the valuable goals for the preparation of various nitrogen-containing compounds. Therefore, we want to investigate whether the N—H insertion of azoles could be performed in a simple one-pot fashion directly from the carbonyl compound without the isolation of the intermediate *N*-tosylhydrazone because *N*-tosylhydrazones can be easily prepared by mixing tosylhydrazide with the corresponding ketone or aldehyde [5]. Herein, we describe an efficient

Scheme 1. Recent applications of tosylhydrazones for the unconventional elaboration of carbonyl compounds.



and convenient one-pot protocol for the synthesis of *N*-alkylated benzimidazoles and benzotriazoles using carbonyl compounds and tosylhydrazide as the starting substrates and inexpensive element copper as the catalyst.

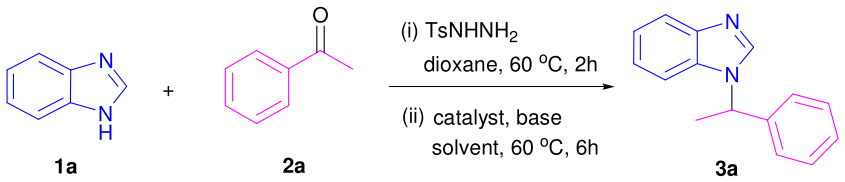
RESULTS AND DISCUSSION

In our initial experiments, 4-methylacetophenone (**2a**), $TsNHNH_2$, and benzimidazole (**1a**) were mixed in one pot with the catalyst of CuBr and the base of K_2CO_3 together in DMSO at 60°C for 6h, we only obtained trace amount of the desired product **3a**. After that, we decided to employ a one-pot, two-step sequence reaction to carry out our following experiments. In the latter experiments, the carbonyl compound **2a** and tosylhydrazide were added in dioxane, and the solution was stirred at 60°C for 2h firstly. After that, benzimidazole (**1a**), CuBr, K_2CO_3, and DMSO were added to the aforementioned solution, and this mixture was stirred at 60°C for another 6h. To our delight, the corresponding *N*-alkylated product was isolated although the yield was only 20% (Table 1, entry 1). Subsequently, we used this two-step sequence reaction to optimize the reaction conditions (Table 1). Not surprisingly, the reaction could not perform in the absence of either copper salt or base. After some initial experiments, we found that in the presence of KO^tBu, the reaction that was catalyzed by low amount of CuBr (2 mol%) could afford *N*-alkylated benzimidazole in 45% yield (Table 1, entries 1–4). Encouraged by these initial results, various copper catalysts were used to better the yield. Overall, some simple copper halide salts with different oxidation state (I or II) could make the reaction work and provide the product in moderate yields, but $Cu(OAc)_2$ was not efficient in the reaction (Table 1, entries 5–9). Fortunately, the cheap and low-toxic copper powder showed the best ability of catalysis and afforded the product **3a** in 88% yield (Table 1, entry 7). After that, it was observed that the solvent significantly affected the C—N bond formation. The tested solvents, such as dioxane, THF, benzene, CH_2Cl_2, and DMF, were all inefficient for the reaction, but DMSO could render C—N bond formation successful (Table 1, entries 10–15). After a screening of reaction conditions, the optimum conditions for *N*-alkylation were identified as follows: the carbonyl compound (1.0 equiv) and $TsNHNH_2$ (1.0 equiv) in dioxane at 60°C for 2h, then add benzimidazole (1.2 equiv), Cu powder (2 mol%) as the catalyst, KO^tBu (2.0 equiv) as the base and DMSO as the solvent to the aforementioned mixture at 60°C for another 6h (more optimized experiments, see the Supporting Information).

With the optimized reaction conditions established, the scope of the reaction was studied using various benzimidazoles (**1a–d**) and a range of carbonyl compounds **2a–p**. As presented in Table 2, the *N*-alkylation is general and functional-group tolerant. The reaction can be performed with various ketones and aldehydes affording the corresponding products **3a–3o** in good yields (Table 2, entries 1–15). Other substituted benzimidazoles could be employed as efficient substrates in the reaction to provide expected products in good yields (Table 2, entries 17–21). It is remarkable that electron-withdrawing groups Cl-substituted and NO_2-substituted benzimidazoles give rise to exclusive regioisomer in good yields (Table 2, entries 20, and 21). Overall, the reaction was not significantly affected by the substrates on the aromatic ring of carbonyl compounds

Table 1

Optimization of reaction conditions.[a]



1a **2a** **3a**

Entry	Catalyst	Base	Solvent	Yield[b] (%)
1	CuBr	K_2CO_3	DMSO	20
2	CuBr	KO^{t}Bu	DMSO	45
3	CuBr	K_3PO_4	DMSO	21
4	CuBr	Cs_2CO_3	DMSO	0
5	CuCl	KO^{t}Bu	DMSO	40
6	CuI	KO^{t}Bu	DMSO	35
7	**Cu powder**	**KO^{t}Bu**	**DMSO**	**88**
8	$CuCl_2$	KO^{t}Bu	DMSO	65
9	$Cu(OAc)_2$	KO^{t}Bu	DMSO	Trace
10	Cu powder	KO^{t}Bu	Dioxane	0
11	Cu powder	KO^{t}Bu	THF	0
12	Cu powder	KO^{t}Bu	Benzene	0
13	Cu powder	KO^{t}Bu	CH_2Cl_2	0
14	Cu powder	KO^{t}Bu	CH_3CN	0
15	Cu powder	KO^{t}Bu	DMF	0

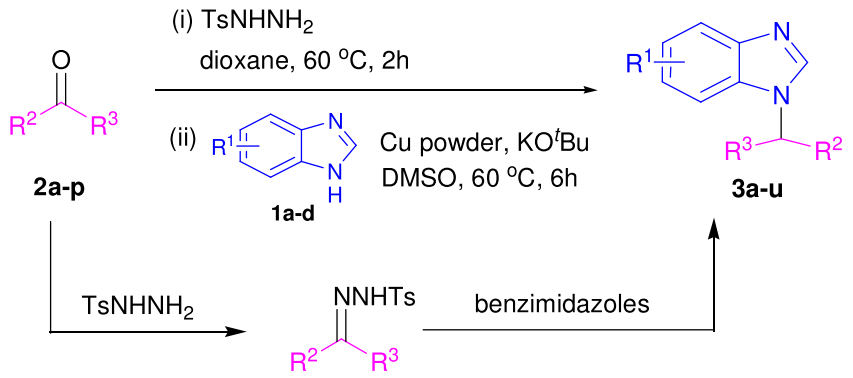
1a is benzimidazole, **2a** is acetophenone, **3a** is N-alkylated benzimidazole (1-(1-Phenylethyl)-1H-benzo[d]imidazole)
[a]Reaction conditions: **2a** (0.3 mmol), $TsNHNH_2$ (0.3 mmol), dioxane, 60°C, 2h; then **1a** (0.4 mmol), catalyst (2 mol%), base (2.0 equiv), solvent (1.0 mL), 60°C, 6h.
[b]Isolated yield based on **2a**.

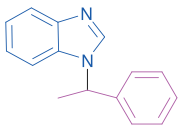
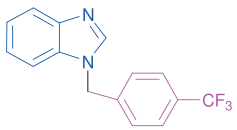
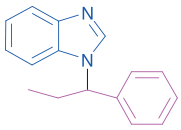
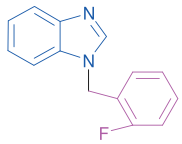
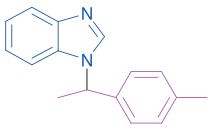
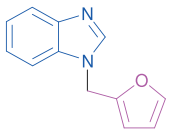
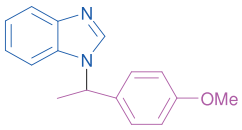
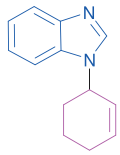
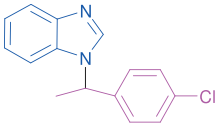
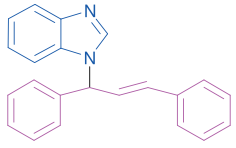
(Table 2, entries 1–13). Both electron-donating and electron-withdrawing groups were tolerated under the reaction conditions. Particularly, halogen substitutions in aromatic rings were tolerated (Table 2, entries 5–7, 13), enabling further derivatizations through metal-catalyzed cross-coupling techniques [11]. Moreover, the carbonyl compounds **2h** and **2i** were tolerated under the reaction conditions (Table 2, entries 8, and 9), which could carry out further direct functionalization of sp^3 C—H bond adjacent to heteroatoms (such as O or N) to provide other useful products.[12] In terms of steric hindrance, the reaction was also not noticeably affected, even though obtaining the corresponding products in slightly diminished yields by using sterically hindered ketones and aldehydes (Table 2, entries 7, 10–11, 13). To our delight, the C—N coupling could proceed smoothly in the case of heteroaromatic 2-furaldehyde, providing the expected product in 90% yield (Table 2, entry 14). We also tried to apply this reaction system to the direct allylation. Consequently, cyclohex-2-enone as the substrate gave rise to allylation product **3o** in 88% yield (Table 2, entry 15). Unfortunately, the coupling reaction with monosubstituted acyclic α,β-unsaturated ketone, such as chalcone, generated 3,5-diphenyl-1*H*-pyrazole instead of the expected product **3p**. This outcome is attributed to the decomposition of the hydrazone followed by electrocyclic ring closure [6d].

Encouraged by the results obtained with benzimidazoles, we proceeded to apply this catalytic system to other nitrogen nucleophiles. However, the results were disappointing (see the Supporting Information). To our delight, it was found that benzotriazole could be employed in the *N*-alkylation without changing the reaction conditions (Scheme 2). Obviously, the transformation seemed to be general and successful, as ketones or aldehydes were converted into corresponding products **5a–i** in good to excellent yields by using the aforementioned conditions (Scheme 2). Specifically, no significant difference in reactivity was observed for the examined reactants with varied electronic properties, although the reaction of the carbonyl compound **2m** with benzotriazole afforded a slightly diminished yield (Scheme 2, **5g**). Furthermore, the steric hindrance did not significantly affect the reaction as well, because the sterically hindered **2g**, **2j**, and **2m** generated the desired product **5e**, **5g**, and **5h** in good yields (Scheme 2). Finally, it was found that cyclohex-2-enone could also work and give rise to allylation product **5i** in 84% yield (Scheme 2, **5i**).

Table 2

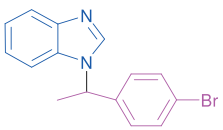
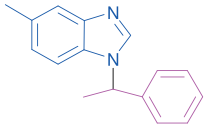
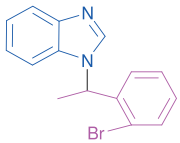
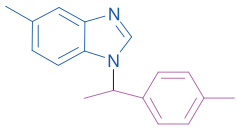
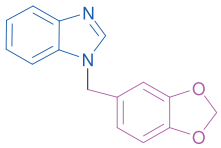
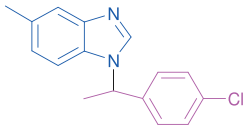
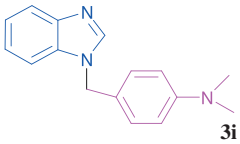
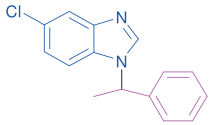
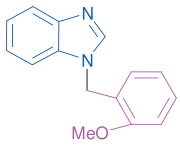
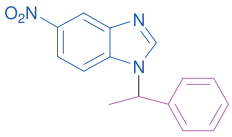
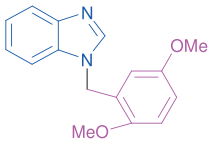
One-pot *N*-alkylation of benzimidazoles with a wide range of carbonyl compounds.[a]



Entry	Product	Yield[b] (%)	Entry	Product	Yield[b] (%)
1	 **3a**	88	12	 **3l**	80
2	 **3b**	86	13	 **3m**	78
3	 **3c**	85	14	 **3n**	90
4	 **3d**	86	15	 **3o**	88
5	 **3e**	86	16[c]	 **3p**	0

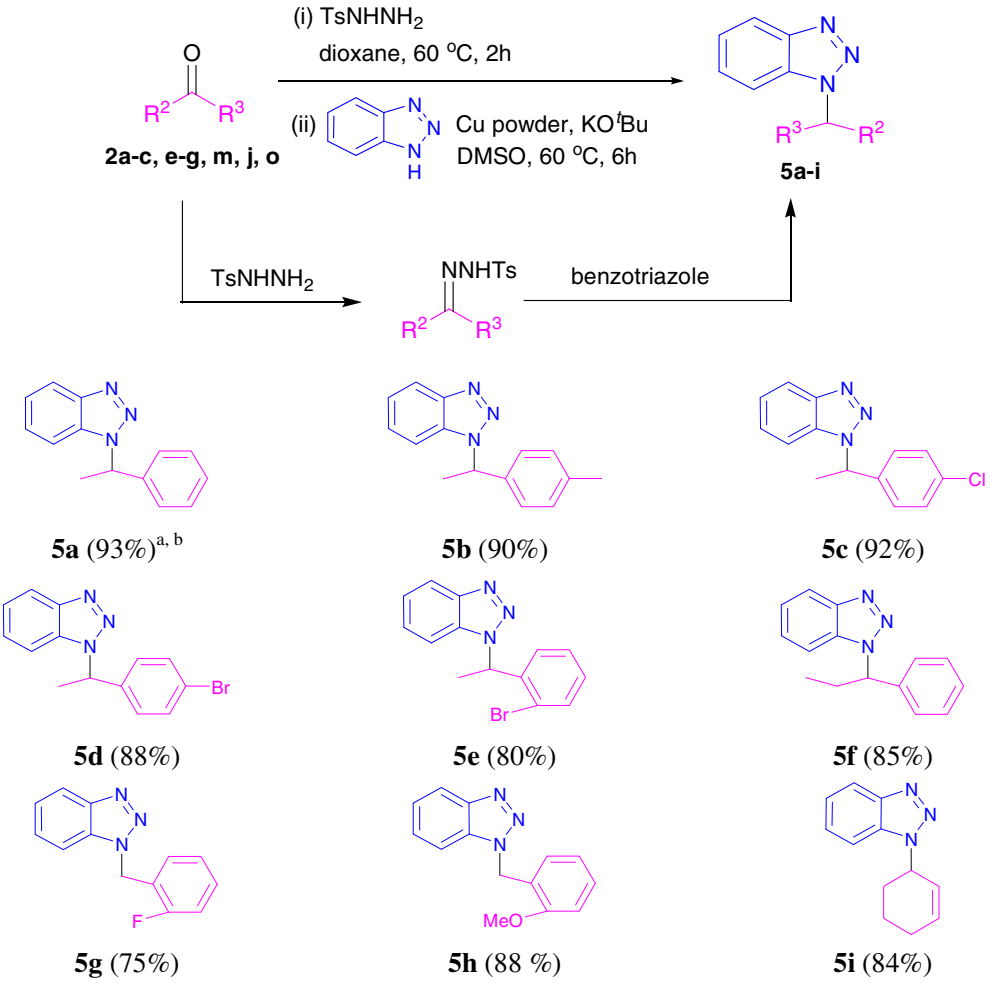
(*Continued*)

Table 2
(Continued)

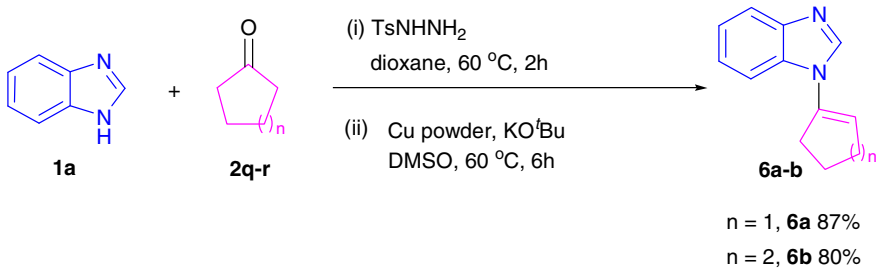
Entry	Product	Yield[b] (%)	Entry	Product	Yield[b] (%)
6	 **3f**	85	17[d]	 **3q**	80 (1:1)
7	 **3g**	81	18[d]	 **3r**	85 (1:1)
8	 **3h**	83	19[d]	 **3s**	82 (1:0.9)
9	 **3i**	78	20	 **3t**	82
10	 **3j**	81	21	 **3u**	83
11	 **3k**	83			

[a]Reaction conditions: **2** (0.3 mmol), $TsNHNH_2$ (0.3 mmol), dioxane, 60°C, 2h; then **1** (0.4 mmol), Cu powder (2 mol%), KO^{t}Bu (2.0 equiv), DMSO (1.0 mL), 60°C, 6h.
[b]Isolated yield.
[c]No expected product obtained.
[d]Two chromatographically inseparable regioisomers combined; the ratios of two isomers are determined on the basis of ^{1}H-NMR spectroscope and reported in the parentheses.

Scheme 2. One-pot *N*-alkylation of benzotriazole with a wide range of carbonyl compounds. [a]Reaction conditions: 2 (0.3 mmol), $TsNHNH_2$ (0.3 mmol), dioxane, 60°C, 2h; then benzotriazole (0.4 mmol), Cu powder (2 mol%), KO^{t}Bu (2.0 equiv), DMSO (1.0 mL), 60°C, 6h. [b]Isolated yields.



Scheme 3. One-pot *N*-alkylation of benzimidazole with cyclopentanone and cyclohexanone.



Surprisingly, when employing cyclopentanone and cyclohexanone as the substrates, the different products 1-cyclopentenyl-1*H*-benzo[*d*]imidazole (**6a**) and 1-cyclohexenyl-1*H*-benzo[*d*]imidazole (**6b**) were obtained (Scheme 3). In terms of mechanism, it might be derived from the process of 1,2 hydrogen shift of the Cu carbene intermediate [7,6].

On the basis of Barluenga [6], Wang [7], and Cuevas-Yañez's [9f] understanding of the metal-catalyzed cross-coupling reactions of *N*-tosylhydrazones, we proposed a plausible mechanism of this *N*-alkylation. First of all, the carbonyl compound transforms into the *N*-tosylhydrazone with $TsNHNH_2$ [5]. Then, the *N*-tosylhydrazone decomposes

under thermal condition in the presence of base through the formation of the diazo compound [6a]. Subsequently, the diazo compound releases the nitrogen and forms the Cu carbene complex in the presence of copper [8a,7a]. Finally, the insertion reaction of the copper carbene into N—H bond of benzimidazole happens [5,10,13,14,15], which gives rise to the corresponding *N*-alkylated product.

CONCLUSION

In conclusion, the one-pot, two-step sequence reaction of benzimidazole and benzotriazole with the carbonyl compounds represents a general, functional-group tolerate, operationally simple, and efficient access to *N*-alkylation. This transformation, catalyzed by low amount of copper powder (2 mol%), provides the corresponding *N*-alkylated products in good to excellent yields, which render the potential industrial application possible because of the cheap and low-toxic catalyst. It is believable that the reaction system could be a better alternative to existing methodologies [4,10] for the *N*-alkylation of benzimidazoles and benzotriazoles.

EXPERIMENTAL

General procedure for Cu powder-catalyzed one-pot fashion *N*-alkylation of benzimidazole with various carbonyl compounds. Firstly, a solution of corresponding carbonyl compound (1.0 mmol) and tosylhydrazide (1.0 mmol) in 3 mL dioxane was stirred at 60°C for 2h. After that, benzimidazole (1.3 mmol), Cu powder (2.0 mol%), KO^{t}Bu (2.0 equiv), and DMSO (3 mL) were added to the aforementioned solution. The mixture was stirred at 60°C for another 6h. When the reaction was completed, the crude reaction mixture was allowed to reach RT, and then the mixture was diluted with ethyl acetate and filtered. The filtrate was extracted twice with water. After that, the combined organic layer was washed with brine, then dried over Na_2SO_4, and filtered. Finally, the solvent was removed under reduced pressure to obtain the crude product, which was further purified by silica gel chromatography (petroleum/ethyl acetate = 1/1 as eluent) to yield corresponding product. The identity and purity of the products was confirmed by ^{1}H-NMR and ^{13}C-NMR spectroscopic analysis.

1-(1-Phenylethyl)-1H-benzo[d]imidazole (3a). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.10 (s, 1H), 7.83–7.81 (d, J = 8 Hz, 1H), 7.35–7.18 (m, 8H), 5.65–5.59 (q, J = 7.2 Hz, 1H), 2.01–1.99 (d, J = 7.2 Hz, 3H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): 140.6, 128.9, 128.0, 125.9, 122.8, 122.2, 120.3, 110.6, 55.2, 21.5 ppm. MS: *m/z* (%) = 223 (M^+, 100), 119 (3). IR 2932, 1611, 1513, 1248, 1030, 834, 746 cm^{-1}. ESI HRMS: Calcd for $C_{15}H_{14}N_2$ $[M+H]^+$: 223.1230, found: 223.1226.

1-(1-Phenylpropyl)-1H-benzo[d]imidazole (3b). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.15 (s, 1H), 7.83–7.80 (d, J = 7.5 Hz, 1H), 7.36–7.18 (m, 8H), 5.33–5.28 (t, J = 7.5 Hz, 1H), 2.48–2.35 (m, 2H), 1.02–0.97 (t, J = 7.2 Hz, 3H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): 139.4, 128.8, 128.0, 126.4, 122.8, 122.2, 120.2, 110.5, 61.7, 27.8, 11.2 ppm. ESI HRMS: Calcd for $C_{16}H_{16}N_2$ $[M+H]^+$: 237.1386, found: 237.1378.

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