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Metal-free, highly efficient organocatalytic amination of benzylic C–H bonds†

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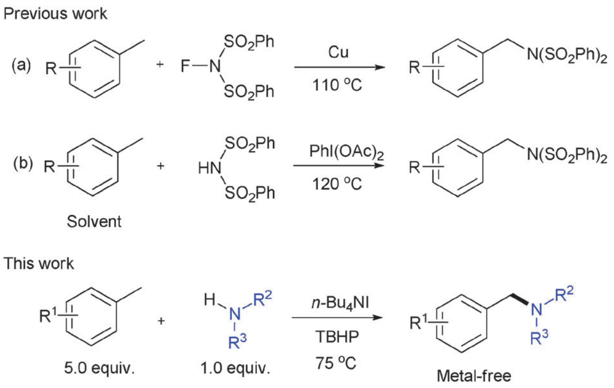
A new synthetic approach toward direct C–N bond formation through sp^3 C–H activation has been developed under metal-free conditions. Both primary and secondary benzylic C–H substrates could react smoothly with various amines to give only mono-amination products with good to excellent yields.

The C–N bonds are ubiquitous in natural and synthetic bioactive compounds.[1] Direct amination of C–H bonds is one of the most exciting strategies to synthesize nitrogen-containing molecules. In recent years, transition-metal-catalyzed C–H amination has made considerable achievements.[2] However, the presence of heavy metal residues is a problem in the pharmaceutical industry, and the effects on health have caused public concern. In this context, the metal-free system "n-Bu$_4$NI–TBHP" has been the focus of recent interest.[3,4] Although some excellent methodologies for C–O bond formation have been reported,[5a–f] n-Bu$_4$NI catalyzed C–N bond formation through sp^3 C–H activation has not been placed a high value.[4a,b] As part of our ongoing interest in sp^3 C–H activation,[4e] we are interested in developing a novel organocatalyzed sp^3 C–H bond amination protocol.

Toluene and xylenes are important chemical raw materials. The selective amination of C–H bonds is particularly important since it can yield industrially important chemicals. To date, methodologies for direct conversion of benzylic C–H bonds into C–N bonds through sp^3 C–H activation are relatively scarce.[6,7] Primary benzylic hydrocarbons such as toluene typically afford low yields, and a large excess of toluene is usually necessary.[6d,e] Herein, we report an n-Bu$_4$NI-catalyzed highly selective benzylic C–H bond amination protocol using TBHP as an oxidant (Scheme 1).



Scheme 1 Amination of benzylic C–H bonds.

Initially, p-xylene **1a** and 1H-benzotriazole **2a** were selected as the model substrates to optimize the reaction conditions (Table 1). The oxidative coupling product **3a** could be formed using n-Bu$_4$NI as a catalyst. Encouraged by this result, we investigated different organocatalysts. As shown in Table 1, n-Bu$_4$NI showed the best catalytic activity (Table 1, entry 1). Other catalysts such as n-Bu$_4$NBr, n-Bu$_4$NCl and n-Bu$_4$NOH gave unsatisfactory results (Table 1, entries 2–4). TBHP was found to play an important role in the process. The use of other peroxides, O$_2$ or K$_2$S$_2$O$_8$ instead of TBHP decreased the yields dramatically (Table 1, entries 5–8). To our delight, the coupling reaction proceeded smoothly, giving the desired product **3a** with 90% yield, with the use of 10 mol% n-Bu$_4$NI (Table 1, entry 9). In addition, no **3a** was observed when either n-Bu$_4$NI or TBHP was absent (Table 1, entries 10 and 11). Among the reaction temperatures examined, it turned out that 75 °C was the most suitable (Table 1, entry 9).

With the optimized conditions in hand (Table 1, entry 9), different substrates with benzylic C–H bonds were tested (Table 2). Both xylenes and mesitylene could be successfully converted to the corresponding products in good to excellent yields (Table 2, **3a–d**). Intriguingly, the benzylic amination was also highly selective, affording only mono-amination products, and no multi-amination or aromatic C–H amination products

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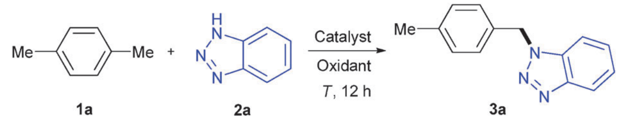
Table 1 Optimization of reaction conditions[a]



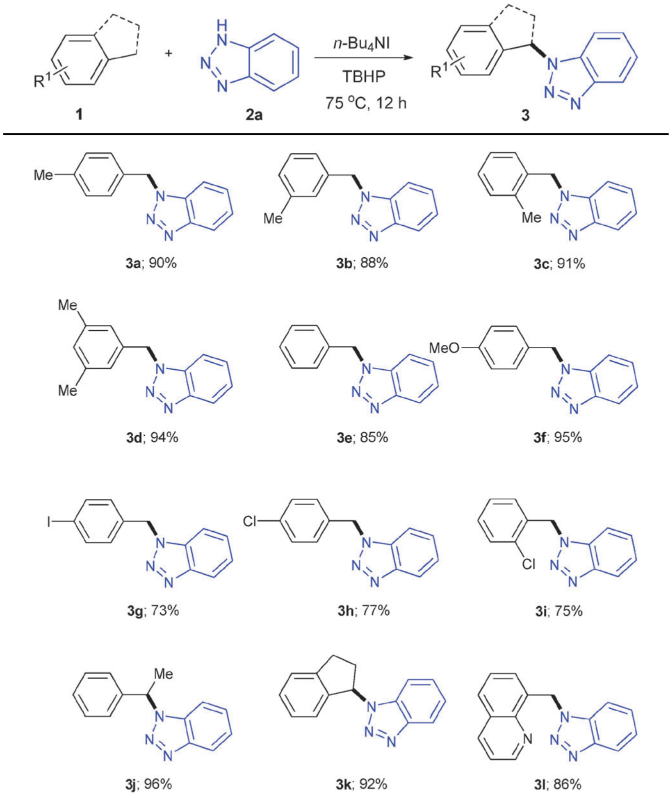
Entry	Catalyst (mol%)	Oxidant[b]	*T* (°C)	Yield[c] (%)
1	*n*-Bu_4NI (20)	TBHP	75	91
2	*n*-Bu_4NBr (20)	TBHP	75	Trace
3	*n*-Bu_4NCl (20)	TBHP	75	N.D.[d]
4	*n*-Bu_4NOH (20)	TBHP	75	N.D.
5	*n*-Bu_4NI (20)	H_2O_2	75	N.D.
6	*n*-Bu_4NI (20)	DTBP	75	Trace
7	*n*-Bu_4NI (20)	O_2[e]	75	N.D.
8	*n*-Bu_4NI (20)	$K_2S_2O_8$	75	N.D.
9	*n*-Bu_4NI (10)	TBHP	75	90
10	—	TBHP	75	N.D.
11	*n*-Bu_4NI (10)	—	75	N.D.
12	*n*-Bu_4NI (10)	TBHP	60	57
13	*n*-Bu_4NI (10)	TBHP	90	87
14[d]	*n*-Bu_4NI (10)	TBHP	120	79

[a] Reaction conditions: **1a** (1.5 mmol), **2a** (0.3 mmol), oxidant (0.9 mmol), 75 °C, 12 h, air. [b] TBHP: *tert*-butyl hydroperoxide 70% in water, H_2O_2 30% in water, DTBP: di-*tert*-butyl peroxide 98%. [c] Isolated yield. [d] Not detected. [e] Under an oxygen atmosphere (1.0 atm).

were detected. To our delight, it was found that toluene was still very effective in our catalytic system and can give a good result (Table 2, **3e**). Subsequently, substrates with various functional groups were examined. Toluene substrates bearing electron-donating substituents were converted into the corresponding products with higher yields than electron-withdrawing substituents (Table 2, **3f–h**). 2- or 3-substituted toluenes were also tolerated in this protocol (Table 2, **3b**, **3c**, **3i**). When ethylbenzene or indane was employed, the reaction could proceed smoothly to furnish the C–N coupling products with excellent yields (Table 2, **3j–k**). Moreover, 8-methylquinoline could also undergo the coupling reaction to provide the desired products in good yield (Table 2, **3l**).

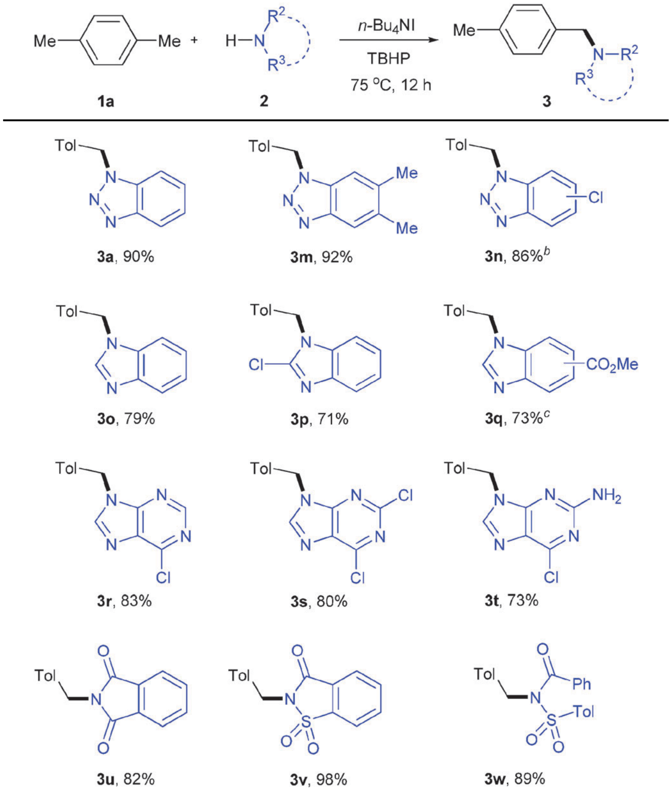
To further explore the potential of our methodology, a variety of amines were investigated, and the results are summarized in Table 3. To our delight, benzotriazoles with different substituents could be converted to the desired products (Table 3, **3m–n**) in good to excellent yields. Subsequently, three benzimidazoles were examined (Table 3, **3o–q**). They could also react with primary benzylic C–H bonds. Benzimidazole bearing electron-withdrawing groups showed lower activity. Notably, various purine derivatives could react with *p*-xylene smoothly in good to high yields (Table 3, **3r–t**). 2-Amino-6-chloropurine could also be tolerated in this protocol, and only an N-9 substituted product was detected. The phthalimide was also highly selective, affording only the benzylic amination product as demonstrated in this protocol (Table 3, **3u**), its coupled with aryl sp^2 C–H bond when using $PhI(OAc)_2$ as an oxidant.[6d] Moreover, saccharin and sulfonamide

Table 2 Scope of benzyl C–H substrates[a]



[a] Standard reaction conditions: **1** (1.5 mmol), **2a** (0.3 mmol), *n*-Bu_4NI (10 mol%), TBHP (0.9 mmol, 70% in water), 75 °C, 12 h, air. Yields are for the isolated products.

Table 3 Scope of amines[a]



[a] Standard reaction conditions: **1a** (1.5 mmol), **2** (0.3 mmol), *n*-Bu_4NI (10 mol%), TBHP (0.9 mmol, 70% in water), 75 °C, 12 h, air. Yields are for the isolated products. [b] **3n** = 5-Chlorobenzotriazole (see ESI). [c] **3q** = Methyl benzimidazole-5-carboxylate (see ESI).

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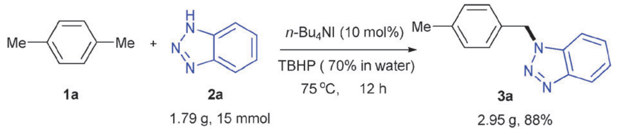
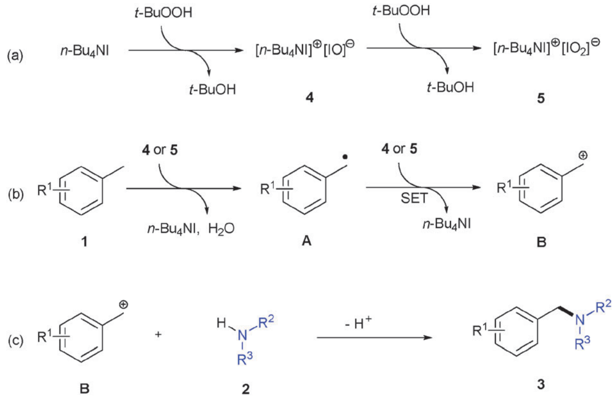


Scheme 2 A gram scale amination of *p*-xylene. Reaction conditions: **1a** (75 mmol), **2a** (15 mmol), n-Bu$_4$NI (1.5 mmol), TBHP (45 mmol, 70% in water), 75 °C, 12 h, air.



Scheme 3 Plausible mechanism.

could also undergo the oxidation reaction to provide the desired products with high efficiency (Table 3, **3v–w**).

To demonstrate the practicability of this protocol, the n-Bu$_4$NI-catalyzed reaction was scaled-up to the gram scale. A gram scale amination of *p*-xylene was easily performed under standard reaction conditions to furnish the desired product in 88% isolated yield (Scheme 2).

To probe the reaction mechanism, several control experiments were conducted (see ESI†). When a radical inhibitor, BHT (2,6-di-*tert*-butyl-4-methylphenol), was introduced into the reaction mixture, the formation of the desired product **3e** was completely suppressed. Furthermore, replacing n-Bu$_4$NI with I$_2$ led to no product. Interestingly, the reaction proceeded smoothly by the combined use of n-Bu$_4$NOH and I$_2$, affording the desired product **3e** in 76% yield. Based on the similar results reported by Yu *et al.*[5e] and Ishihara *et al.*,[5a] we suppose that the active hypoiodite $[n\text{-Bu}_4\text{N}]^+[\text{IO}]^-$ or iodite $[n\text{-Bu}_4\text{N}]^+[\text{IO}_2]^-$ plays an important role in the sp^3 C–H amine reactions. Additionally, the benzyl radical intermediate was trapped by a radical scavenger, TEMPO (2,2,6,6-*tetra*-methylpiperidine-*N*-oxyl), and the oxyamination product was isolated in 62% yield.

Based on the above results, a plausible mechanism is proposed in Scheme 3. Initially, n-Bu$_4$NI is oxidized by TBHP to generate the active iodine species ammonium hypoiodite **4** or iodite **5** (Scheme 3a). Subsequently **4** or **5** induces the homolysis of a benzyl C–H bond to give the benzyl radical **A**,[5e] which is then oxidized by active iodine species to form the benzyl cation **B** (Scheme 3b).[6e,8] Finally, the nucleophilic reaction of amine **2** with the benzyl cation **B** forms the desired product **3** (Scheme 3c).

In conclusion, we have reported a novel n-Bu$_4$NI catalyzed operationally simple method for the oxidative coupling of benzylic C–H substrates with unmodified amines. Various amination products were obtained with good to excellent yields using TBHP (70% in water) as an environmentally benign oxidant. This method affords a facile metal-free approach for synthesis of imidazole and purine nucleoside derivatives. The possible mechanistic pathway is also proposed on the basis of control experiments.

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