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## COMMUNICATION

## KI-catalyzed imidation of sp<sup>3</sup> C-H bond adjacent to amide nitrogen atom<sup>†</sup>

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We have developed a new KI-catalyzed method for the imidation of an sp<sup>3</sup> C–H bond adjacent to an amide nitrogen atom by using TBHP (*tert*-butyl hydroperoxide, 70% aqueous solution) as the oxidant. This novel procedure tolerated air and moisture and provided a series of novel products in moderate to excellent yields under mild conditions.

Direct C-H bond activation and subsequent coupling with other reagents to form new C-C and C-heteroatom bonds provide important alternative methods for the synthesis of novel compounds.<sup>1</sup> Recently, the transition-metal-catalyzed cross-dehydrogenative-coupling (CDC) reaction in C-H bond activation and subsequent formation of new C-C and C-heteroatom bonds has attracted much attention.<sup>2</sup> The applications of this novel methodology allow the functionalization of sp, sp<sup>2</sup> and sp<sup>3</sup> C-H bonds, and it was found that the presence of an adjacent heteroatom was essential for the functionalization of sp<sup>3</sup> C-H bonds.<sup>3,4</sup> Most of the past works focused on aryl substituted substrates, such as the functionalization of the sp<sup>3</sup> C-H bond adjacent to the nitrogen of N,N-dimethylaniline and 1,2,3,4-tetrahydroisoquinoline and the sp<sup>3</sup> C-H bond adjacent to the oxygen of isochroman.<sup>3,4</sup> Similar reactions of non-aryl substituted substrates have rarely been reported. Xu et al. reported an alkynylation reaction of the C-H in the methylamino group of an aliphatic amine mediated by copper-diethyl azodicarboxylate.5 Very recently, Li and coworkers developed a thiolation reaction of the sp<sup>3</sup> C-H bond adjacent to an amide nitrogen atom mediated by TBHP, without the use of metal catalyst.<sup>6</sup> However, examples of direct C-H bond oxidative activation adjacent to an amide nitrogen are still limited.

In addition, C–N bond formation has also attracted broad attention because of its prevalence in therapeutic drugs and natural products.<sup>7</sup> Traditional C–N bond formation that is based on functional group interconversion cannot satisfy the present-day need of atom economy and green chemistry.<sup>8</sup> In the past decade, much progress in intramolecular and intermolecular amidation of the C–H bond has been made.<sup>9</sup> In many of these

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reactions, nitrene derivatives were used as the primary nitrogen sources and transition-metal catalysts were used. Recently, Fu and co-workers reported copper-catalyzed amidation of the sp<sup>3</sup> C–H bond adjacent to a nitrogen atom in *N*,*N*-dimethylaniline *via* a CDC process.<sup>10</sup> However, there is still no published report on the amidation of the sp<sup>3</sup> C–H bond adjacent to an amide nitrogen atom. Herein, we developed a transition-metal-free method for the amidation of the sp<sup>3</sup> C–H bond in amides through a CDC process. This novel reaction is catalyzed by KI in the presence of TBHP under mild conditions and provides products containing potential bioactivity<sup>11</sup> in moderate to excellent yields without the need to exclude air and moisture.

Table 1 shows the optimization of reaction conditions. By using phthalimide as the nitrogen source and N,N-dimethylacetamide as the substrate in the presence of *tert*-butyl hydroperoxide (TBHP), no product was observed (entry 1). However, when NaI was added to the reaction, 81% yield of **3a** was obtained. Further

> catalyst TBHP (70% aqueous solution)

 Table 1
 Condition optimization studies<sup>a</sup>



<sup>*a*</sup> Reaction conditions: phthalimide (1 mmol), *N*,*N*-dimethylacetamide (1 mL, 9 mmol). <sup>*b*</sup> Isolated yield. <sup>*c*</sup> 2 equiv TBHP. <sup>*d*</sup> 3 h. <sup>*e*</sup> At 80 °C. <sup>*f*</sup> In dark. <sup>*g*</sup> N<sub>2</sub> protection.

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investigation of other iodides showed that KI provided the most efficient catalysis (entries 2-5).<sup>12</sup> Employing KBr and KCl as catalysts yielded no product in this reaction (entries 6 and 7). Considering the beneficial effects of transition-metals in C-H bond activation, several metal salts, such as FeCl<sub>3</sub>, FeSO<sub>4</sub> and SnCl<sub>2</sub>, were added to the reaction but no product was obtained (entries 8-12). When CuCl was added, a small amount of product was obtained; however, CuI catalyzed the reaction to furnish 3a in moderate yield (entries 10 and 11), further indicating that iodide was essential for this transformation. Subsequent exploration in reactant ratios showed that 0.2 equiv of KI and 4 equiv of TBHP to the imide provided the highest yield (entries 3, 14 and 15). Increasing reaction time to 3 h did not provide significant improvement in the product yield (entry 13). Reducing temperature to 80 °C decreased the yield slightly (entry 16). It is noteworthy that tolerance of air, moisture and light was also observed (entries 17 and 18), which greatly simplified the performance of the reactions compared with other catalytic methods. Finally, the optimal reaction conditions were determined as the following: 0.2 equiv KI and 4 equiv TBHP relative to imide at 90 °C for 1 h.

Under the optimized conditions, the scope of this reaction was then investigated. Table 2 shows that various imides and amides reacted to generate the desired products in moderate to excellent yields. The reactions of phthalimides substituted by electronwithdrawing groups proceeded slowly but gave excellent yields after 3 h (3b and 3c). A phthalimide derivative bearing an electron-donating group afforded the product in an excellent yield of 91% (3d). Moreover, although it was reported that benzylic C-H can be easily oxidized by the KI-TBHP system,<sup>13</sup> the benzylic C-H of 4-methylphthalimide was not affected by this procedure. 1,8-Naphthalimide and its chlorinated derivative reacted smoothly in 1 h and yielded the respective products in excellent yields (3e and 3f). Aliphatic imides also reacted smoothly under the optimized condition, albeit with moderate to good yields (3g-3i). However, sulfonamide was found to be a poor substrate and the product was isolated only in 44% yield even the reaction time was prolonged to 24 h (3j). In addition to N,N-dimethylacetamide, various types of amides were also tested. N,N-dimethylformamide (DMF) gave the desired product in 54% yield (3k), and we found that adding the oxidant in two portions increased the yield to 73%. Interestingly, when N-methylpyrrolidone (NMP) was subjected to this procedure, the methylene C-H was preferentially activated and the reaction proceeded in high regioselectivity (3m): no methyl-substituted product was observed. Subsequent exploration of other amides also afforded the target products in good to excellent yields (31, 3n and 30).

When *N*,*N*-dimethylaniline was subjected to our procedure, the desired products were obtained in excellent yields (Scheme 1, **3p** and **3q**). Compared with previous copper catalyzed reaction conditions,<sup>10</sup> this methodology is not sensitive to air and moisture and could be performed in an open flask.

To investigate a plausible reaction mechanism, a radicaltrapping reagent 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was added to the reaction mixture. As shown in Scheme 2a, condensation product 3x was obtained in 71% yield, indicating that the reaction likely proceeded through a free radical intermediate. Previous studies indicated that hypoiodite species could be produced in the presence of iodide and TBHP.<sup>12b,e,14</sup> However,





<sup>*a*</sup> Reaction conditions: amide (1 mL, 9 mmol), imide (except for **3j** which is an amide) (1 mmol), TBHP (4 mmol, 70% aqueous solution), KI (0.2 mmol). Isolated yields are shown. <sup>*b*</sup>12 h. <sup>*c*</sup>24 h. <sup>*d*</sup>2 mmol of TBHP (70% aqueous solution) was added first and 2 mmol after 0.5 h.



Scheme 1 Imidation of N,N-dimethylaniline.

when the reaction was conducted in the presence of  $I_2$  and KOH, which generated hypoiodite species *in situ*, no product was observed (Scheme 2b). Therefore, the hypoiodite intermediate could not be involved in this procedure.

Based on these results, a plausible reaction mechanism is proposed in Scheme 3. TBHP firstly reacts with iodide anion and



Scheme 2 Investigation of possible reaction mechanism.



Scheme 3 Plausible reaction mechanism.

generates three important species: *tert*-butyl oxide free radical, iodine and hydroxyl anion.<sup>3/</sup> The oxide free radical reacts with amide and produces intermediate **A**, which is subsequently oxidized by iodine to generate specie **B** and iodide anion, completing a catalytic cycle. The deprotonated imide reacts with intermediate **B** to furnish the target product **C**.

In conclusion, we have developed a novel method for the imidation of sp<sup>3</sup> C–H bonds adjacent to an amide nitrogen atom by employing iodide anion as catalyst. Considering the mild conditions and readily available reagents used in the reaction, this new methodology may represent an efficient method for the direct construction of C–N bonds by oxidative activation of sp<sup>3</sup> C–H bonds adjacent to an amide nitrogen atom.

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