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ISSN 1359-7345



**COMMUNICATION**

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**175** YEARS



Cite this: *Chem. Commun.*, 2016, 52, 13082

Received 1st September 2016,  
Accepted 21st September 2016

DOI: 10.1039/c6cc07164c

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# Ritter-type amination of C–H bonds at tertiary carbon centers using iodic acid as an oxidant†

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**The Ritter-type amination of a tertiary C–H bond using iodic acid (HIO<sub>3</sub>) as an oxidant, in the presence of *N*-hydroxyphthalimide (NHPI) is reported. This operationally simple method is conducted under metal-free conditions, is scalable, and efficiently provides valuable  $\alpha$ -tertiary amine derivatives.**

Incorporation of an amino functional group into an organic molecule *via* the direct conversion of a C(sp<sup>3</sup>)–H bond to a C(sp<sup>3</sup>)–N bond is one of the most powerful and straightforward strategies for preparing nitrogen-containing organic compounds.<sup>1</sup> The intermolecular, direct amination of C–H bonds at tertiary carbon centers is a particularly attractive transformation that produces  $\alpha$ -tertiary amine derivatives, which are potentially useful building blocks for new types of drugs and in medicinal chemistry.<sup>2</sup> In the past decades, the insertion of a nitrene has evolved to be one of the most reliable methods for the direct amination of C(sp<sup>3</sup>)–H bonds. However, in the case of reactions that involve unactivated tertiary C–H bonds, a superstoichiometric amount of substrate is required. As a result, its use in functionalizing valuable complex molecules has remained undeveloped.<sup>3,4</sup> To overcome these problems, Du Bois *et al.* recently reported on an elegant method for selective tertiary C–H amination using the originally developed rhodium catalyst.<sup>5</sup> In this reaction, the substrate can be used as the limiting reagent. In addition, most recently, tertiary C–H azidation has also emerged as a promising approach,<sup>6</sup> and these methods were reported to be applicable to the late stage functionalization of complex molecules. However, despite these advances, the direct and site-selective conversion of an unactivated tertiary C–H bond to a C–N bond, particularly under metal-free conditions, continues to be a challenging and highly demanding task.<sup>7,8</sup>

Ritter-type C–H aminations, where nitriles function as the nitrogen source, are a potentially efficient strategy for intermolecular

tertiary C–H amination reactions. However, only a few oxidation systems have been reported that are suitable for the reaction, and thus its applications have been quite limited to date. Early reports were limited to the reaction of adamantane derivatives.<sup>9</sup> Although the amination of benzylic C–H bonds using *N*-hydroxyphthalimide (NHPI) combined with ceric ammonium nitrate (CAN) as an oxidant was developed by Ishii *et al.*, the reaction with respect to tertiary C–H bonds, with the exception of adamantane derivatives, has not been extensively explored.<sup>10</sup> Baran *et al.* recently developed a practical Ritter-type tertiary C–H amination involving a guided C–H oxidation approach using substoichiometric amounts of copper and zinc salts.<sup>11</sup> The proposed reaction pathway involves the metal-oxidant-mediated single-electron oxidation of an *in situ* generated alkyl radical species to produce a carbocation intermediate. To develop a more efficient Ritter-type tertiary C–H amination that does not involve the use of metal oxidants, we conceived a new approach using iodine-based oxidants, in which C–H iodination would be induced to provide tertiary alkyl iodides and the corresponding iodine(III) species with a higher oxidation state that could undergo a subsequent substitution by nitriles (Scheme 1).<sup>12</sup> Herein, we report on the Ritter-type amination of unactivated tertiary C–H bonds using iodic acid (HIO<sub>3</sub>) as an oxidant in the presence of NHPI.

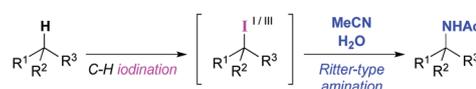
We began our investigation by screening oxidants for the amination of isoamyl benzoate (**1a**), which is used as a limiting reagent (Table 1).<sup>13</sup> On the basis of the reaction conditions reported by Ishii,<sup>10</sup> we first surveyed the effect of several common oxidants for the reaction in the presence of NHPI in MeCN at 80 °C for 12 h. When CAN was used, tertiary C–H amination proceeded to give **2a** in low yield (entry 1).

Neither Oxone nor *m*-chloroperbenzoic acid (*m*CPBA) showed any reactivity for this reaction (entries 2 and 3), and PhI(OAc)<sub>2</sub>

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† Electronic supplementary information (ESI) available: Experimental details, characterization data, and spectra. See DOI: 10.1039/c6cc07164c



Scheme 1 Strategy for a Ritter-type C–H amination at a tertiary carbon center.



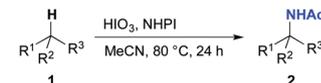
Table 1 Survey of oxidants<sup>a</sup>

Entry	Oxidant	Yield <sup>b</sup> [%]
1	CAN	19
2	Oxone	0
3	mCPBA	0
4	PhI(OAc) <sub>2</sub>	< 5
5 <sup>c</sup>	CAN	53
6 <sup>c</sup>	Oxone	69
7 <sup>c</sup>	mCPBA	65
8 <sup>c</sup>	PhI(OAc) <sub>2</sub>	< 5
9 <sup>d</sup>	HIO <sub>3</sub>	72
10 <sup>d,e</sup>	HIO <sub>3</sub>	74 (71)
11 <sup>d,e</sup>	none	0
12 <sup>d,e,f</sup>	HIO <sub>3</sub>	0
13 <sup>d,e,g</sup>	HIO <sub>3</sub>	72

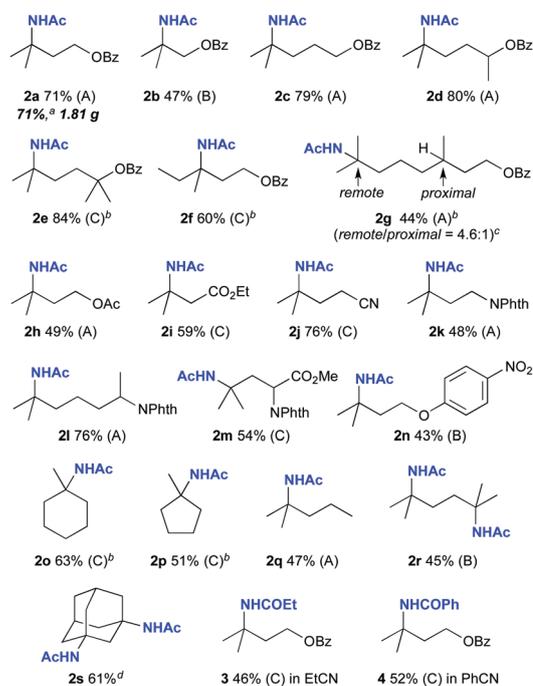
<sup>a</sup> Reaction conditions: **1a** (0.2 mmol), oxidant (0.4 mmol), NHPI (0.08 mmol), MeCN (1 mL), 80 °C. <sup>b</sup> Determined by <sup>1</sup>H NMR analysis of the crude product using 1,1,2,2-tetrachloroethane as an internal standard. Yield in parenthesis is the isolated yield based on the amount of **1a** used. <sup>c</sup> I<sub>2</sub> (0.5 equiv.) was added. <sup>d</sup> Reactions were conducted on a 0.4 mmol scale. <sup>e</sup> Reactions were conducted using HIO<sub>3</sub> (0.8 equiv.), NHPI (0.2 equiv.), and MeCN (2 mL) for 24 h. <sup>f</sup> Reaction was conducted without NHPI. <sup>g</sup> Reaction was conducted under dark.

gave only a trace amount of **2a** (entry 4). Next, to trap the *in situ* generated alkyl radical species, we examined the reaction using CAN with the addition of 0.5 equiv. of I<sub>2</sub>, as an iodine source, and were pleased to find that the amination proceeded efficiently, affording **2a** in 53% yield (entry 5). Interestingly, when I<sub>2</sub> was present in the reaction system, both Oxone and mCPBA also effectively promoted the amination (entries 6 and 7) although they were completely inactive when used as the sole oxidant. Meanwhile, **2a** was not produced when PhI(OAc)<sub>2</sub> was used in the reaction (entry 8). These results prompted us to explore a more effective oxidant for this reaction. We hypothesized that iodic acid (HIO<sub>3</sub>) and iodine pentoxide (I<sub>2</sub>O<sub>5</sub>) might be promising oxidants<sup>14</sup> since they are commercially available, low cost, and stable even at high temperatures and can be reduced *in situ* to generate I<sub>2</sub> and H<sub>2</sub>O,<sup>14k,l</sup> both of which are requisite components in this Ritter-type amination. When we examined the use of HIO<sub>3</sub>, the amination proceeded efficiently without the need for added I<sub>2</sub>, affording **2a** in 72% yield (entry 9).<sup>15</sup> Furthermore, attempts to reduce the amount of reagents employed revealed that the use of HIO<sub>3</sub> (0.8 equiv.) and NHPI (0.2 equiv.) in conjunction with a longer reaction time of 24 h provided **2a** in 74% yield (entry 10).<sup>13</sup> Control experiments in the absence of either HIO<sub>3</sub> or NHPI revealed that both reagents were required for this transformation (entries 11 and 12). In addition, the reaction does not require a light-induced process since the reaction proceeded equally well, even in the dark (entry 13).

We next investigated the ability and scope of this Ritter-type C–H amination (Scheme 2). To establish the synthetic utility of this amination, we carried out the reaction using **1a** on a gram-scale (10 mmol), which resulted in the formation of **2a** in 71% yield (1.81 g).<sup>13</sup> Electronic effects on the reaction were evaluated by using a series of substrates bearing a benzoate group as an electron-withdrawing group (EWG). Isobutyl benzoate, which



conditions A: HIO<sub>3</sub> (0.8 equiv.), NHPI (0.2 equiv.).  
B: HIO<sub>3</sub> (2.0 equiv.), NHPI (0.8 equiv.).  
C: HIO<sub>3</sub> (2.0 equiv.), NHPI (0.4 equiv.).



**Scheme 2** Substrate scope. Reactions were conducted on a 0.4 mmol scale. Yields are isolated yields based on the amount of **1** used. Reaction conditions are shown in parentheses. <sup>a</sup> Reaction was conducted on a 10 mmol scale. <sup>b</sup> Reaction was conducted for 12 h. <sup>c</sup> The ratio was determined by GC analysis of the crude product. <sup>d</sup> HIO<sub>3</sub> (1.2 equiv.) and NHPI (0.2 equiv.) were used. Monoaminated product was obtained in 13% yield.

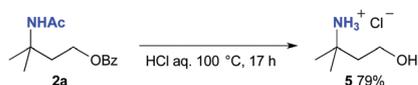
contains a tertiary C–H moiety β to the oxygen atom of the benzoate group, showed a low reactivity because of the electron deficient character of the C–H bond, and the product **2b** was obtained in a relatively lower yield than that for **2a**. In contrast, a tertiary C–H bond remote from the benzoate group showed a high reactivity (**2c**). Similarly, secondary and tertiary alcohol derivatives as well as primary alcohols were also suitable for use in this reaction system, providing **2d** and **2e** in high yields, respectively. The replacement of a methyl group with an ethyl group at the reaction site had a slight effect on the reaction (**2f**). When a benzoate derived from 3,7-dimethyl-1-octanol, which has two tertiary carbon centers, was examined, the tertiary C–H bond remote from the benzoate group selectively underwent amination over the proximal site, selectively furnishing **2g** (remote/proximal = 4.6 : 1).<sup>13</sup> This selectivity can be attributed to the electronic effect by an EWG, and this trend is consistent with previously reported findings on selectivity for the oxidation of C–H bonds.<sup>6b,16</sup> Substrates bearing functional groups, including an acetoxy protected alcohol (**2h**), an ester (**2i**), a nitrile (**2j**), phthaloyl protected amines (**2k** and **2l**), and a leucine derivative (**2m**), were also compatible with the reaction. The amination of a substrate containing a phenoxy moiety, leading to a medically important phenoxypropylamine framework, was sluggish because of the



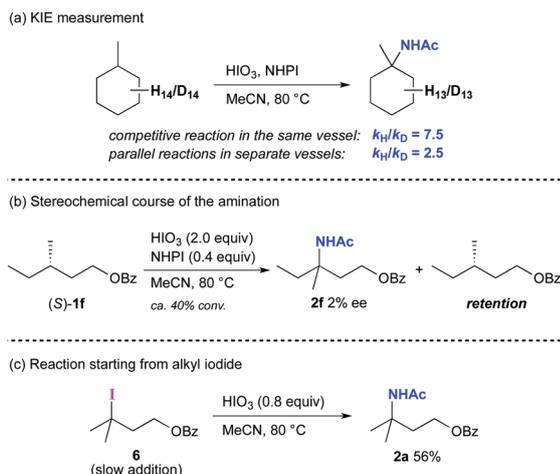
competitive electrophilic iodination of the aromatic ring. Therefore, to prevent this side reaction, the effect of the incorporation of a nitro group at the *para* position in the phenyl ring was examined, which resulted in the formation of the desired **2n**. Furthermore, in this system, cyclic and noncyclic hydrocarbons also underwent selective C–H amination at tertiary carbon centers (**2o–2s**). It is noteworthy that a double C–H amination was successfully achieved in the reactions of 2,5-dimethylhexane as well as adamantane (**2r** and **2s**).<sup>13</sup> Finally, the use of propionitrile and benzonitrile as a solvent instead of acetonitrile provided the corresponding products **3** and **4**, respectively.

Acid hydrolysis of **2a** effectively removed the acetamide moiety as well as the benzoate moiety to give 1,3-aminoalcohol **5** as the HCl salt (Scheme 3).

We performed several experiments in attempts to gain insights into the reaction mechanism (Scheme 4). Initially, kinetic isotope effects (KIEs) were measured with methylcyclohexane and methylcyclohexane-*d*<sub>14</sub> for both competitive reactions in the same vessel and parallel reactions in separate vessels (Scheme 4a). A significant primary KIE (7.5) was observed for the competitive reaction in the same vessel, and a relatively smaller KIE (2.5) was detected when parallel reactions were carried out in separate vessels. The KIE (2.5) value in the parallel reactions indicates that C–H bond cleavage is likely the rate-determining step. In addition, C–H bond cleavage *via* hydrogen abstraction by a phthalimide-*N*-oxyl (PINO) radical was indicated by the quite large KIE (7.5) for the reaction in the same vessel.<sup>17</sup> The difference in the KIE values between these two methods suggests that the rate of oxidation of NHPI to PINO, prior to the rate-determining C–H bond cleavage step, could affect the overall reaction rate. Next, to evaluate the stereochemical course for the reaction, the reaction using an enantiopure (*S*)-**1f** was carried out under the standard conditions (*ca.* 40% conversion after 6 h),



Scheme 3 Hydrolysis of the acetamide product **2a**.



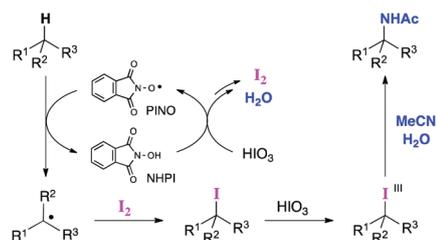
Scheme 4 Mechanistic investigations.

resulting in the formation of nearly racemic **2f** (Scheme 4b). Furthermore, the starting material was recovered with complete retention of its stereochemistry, indicating that the C–H bond cleavage is irreversible.<sup>18</sup> These results are consistent with a reaction pathway that involves an alkyl free-radical intermediate that causes the loss of stereochemical information.<sup>7b</sup> Although we considered the possibility that an alkyl iodide could be generated *in situ* as a reaction intermediate, the corresponding iodine(I/III) species was not observed in the reaction system. Therefore, to get insights into the nature of the reaction intermediate, several reactions were performed employing the separately prepared alkyl iodide **6** to determine whether it is converted into **2a**. Stirring a solution of **6** in MeCN at 80 °C failed to give **2a**,<sup>19</sup> while the amination proceeded in the presence of HIO<sub>3</sub> under otherwise the same conditions to provide **2a** even in low yield (9%).<sup>13</sup> In the C–H amination under the standard conditions, an alkyl iodide could be generated *in situ* catalytically. With this consideration in mind, the slow addition of **6** to a suspension of HIO<sub>3</sub> in MeCN at 80 °C was examined, and the yield of **2a** was increased to 56% (Scheme 4c). These results strongly support a reaction pathway in which an alkyl iodide is generated and oxidized by HIO<sub>3</sub> to the corresponding hypervalent iodine species, which then undergoes a Ritter-type amination.<sup>20,21</sup>

Based on the experimental results presented herein and previous reports,<sup>17</sup> a proposed reaction pathway is depicted in Scheme 5. First, NHPI is oxidized to PINO by HIO<sub>3</sub>, which leads to the generation of I<sub>2</sub> and H<sub>2</sub>O. Then, the rate determining C–H bond cleavage by PINO provides an alkyl radical species, which is rapidly trapped by I<sub>2</sub>. The resulting alkyl iodide is then oxidized by HIO<sub>3</sub> to generate an iodine(III) species that undergoes a Ritter-type amination, thus affording the amide product.

In conclusion, we report on the development of a new class of metal-free Ritter-type C–H amination reactions at tertiary carbon centers using commercially available and easily handled HIO<sub>3</sub> and NHPI. Various  $\alpha$ -tertiary amine derivatives can be prepared by this operationally simple and environmentally benign method. Preliminary mechanistic investigations suggest that the reaction proceeds *via* a unique reaction pathway that involves the formation of alkyl iodides(I/III) as reaction intermediates. The present study is an important example of expanding the utility of HIO<sub>3</sub> in organic synthesis. Further investigations of the mechanism and applications of this method to the synthesis of more complex molecules are currently underway.

This work was supported by JSPS KAKENHI Grant Number JP16K17868.



Scheme 5 Proposed reaction pathway.



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