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C–H Oxygenation at Tertiary Carbon Centers Using Iodine Oxidant

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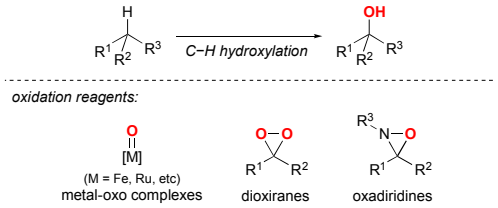
An oxidation system in which iodic acid (HIO_3) is used as an oxidant in the presence of *N*-hydroxyphthalimide (NHPI) permitted the selective hydroxylation of tertiary C–H bonds and the lactonization of carboxylic acids containing a tertiary carbon center. These reactions are operationally simple and proceed under metal-free conditions using commercially available reagents, thus offering an ideal tool for the efficient oxidation of C–H bonds at tertiary carbon centers.

The selective oxygenation of C(sp^3)–H bonds is one of the most fundamental transformations in organic synthesis because it permits the straightforward synthesis of valuable oxygen-containing compounds from simple starting materials.[1] Over the past decades, extensive efforts have been devoted to the development of new approaches for the direct conversion of a C(sp^3)–H bond to a C(sp^3)–O bond (Scheme 1). The most general method for C(sp^3)–H oxygenation in a site-selective manner has relied on the application of defined transition-metal-oxo complexes, and significant progress has been made in C–H hydroxylation at a tertiary carbon center, thus enabling the functionalization of complex molecules.[2,3] Methods that do not involve the use of transition-metal catalysts, oxidants such as dioxiranes[4,5] and perfluorinated oxaziridines[6] have been widely used, although the preparation of these reagents is laborious and potentially hazardous. Catalytic methods, in which organocatalysts are employed with terminal oxidants to generate active dioxiranes and oxaziridines in situ, have recently emerged as a promising synthetic tool,[7,8] even though there are still some drawbacks, such as the use of elaborate catalysts and the relatively low efficiency of such reations. Most recently, the use of commercially available and inexpensive persulfate salts for oxidizing such bonds has been reported but these reagents have only been applied to substrates bearing a nitrogen-containing functionality.[9] In this context, a novel synthetic strategy for the efficient and operationally simple hydroxylation of C(sp^3)–H bonds with readily available reagents would be highly desirable.[10,11]



Scheme 1 Representative examples of C(sp^3)–H bond hydroxylation.

N-hydroxyphthalimide (NHPI), which is a cheap and commercially available reagent, is widely used as a hydrogen-atom tranfer (HAT) mediator in C(sp^3)–H oxidation.[12] However, despite the great advances, except for adamantane derivatives, NHPI has rarely been used in the oxidative functionalization of C–H bonds at tertiary carbon centers. Our group recently reported on the development of the NHPI-mediated Ritter-type C–H amination at tertiary carbon centers using iodic acid (HIO_3) as an oxidant (Scheme 2a).[13] As part of our continuing interest in the oxidative functionalization of C(sp^3)–H bonds, we herein report on a new approach to the site-selective C–H oxygenation at tertiary carbon centers by employing a NHPI/HIO_3 oxidation system.

Based on our previous work on the Ritter-type C–H amination,[13] a possible pathway for C–H hydroxylation using HIO_3 in the presence of NHPI as a catalyst is described (Scheme 2b). In this system, NHPI is initially oxidized to phthalimide *N*-oxyl (PINO) by HIO_3, which leads to the generation of I_2 and H_2O. The site-selective C–H bond cleavage by PINO then generates a tertiary alkyl radical species, which is rapidly trapped by I_2. The resulting alkyl iodide is oxidized by the remaining HIO_3 to provide an alkyl-λ^3-iodane species that undergoes substitution by the in situ-generated H_2O to afford tertiary alcohols.

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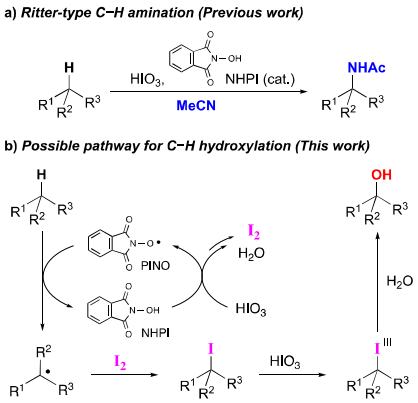
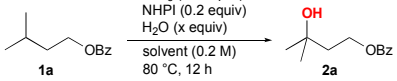


Scheme 2 C(sp^3)–H bond functionalization using HIO_3 with NHPI.

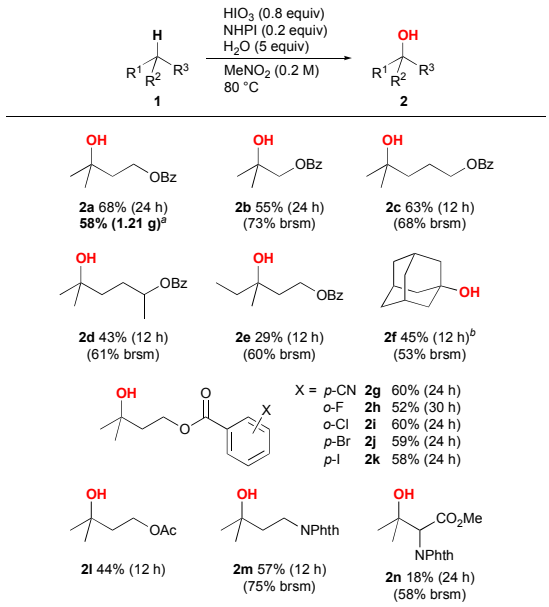
Table 1 Optimization of reaction conditions[a]



Entry	Solvent	H_2O [equiv]	Yield[b] [%]	RSM[b] [%]
1	H_2O	–	0	>95
2	$MeNO_2$	–	32	40
3	$MeNO_2$	20	38	52
4	$MeNO_2$	15	42	47
5	$MeNO_2$	10	50	48
6	$MeNO_2$	5	62	20
7[c]	$MeNO_2$	5	72	<5
8[c,d]	$MeNO_2$	5	67	6
9[e]	$MeNO_2$	5	49	32
10[f]	$MeNO_2$	5	61	19
11	MeOH	–	0	>95
12	AcOH	–	15 (47)[g]	<5

[a] Reactions were performed on a 0.4 mmol scale under a nitrogen atmosphere unless othewise noted. [b] Yields are based on the amount of **1a** used. Determined by ^1H NMR analysis of the crude product using bromoform as an internal standard. [c] Reaction was conducted for 24 h. [d] I_2O_5 (0.4 equiv) was used instead of HIO_3. [e] Reaction was conducted under O_2 (1 atm). [f] Reaction was conducted in the dark. [g] Yield of the C–H acetoxylated product. RSM = recovered starting material.

With this design in mind, we started our investigation by screening solvents for the C(sp^3)–H hydroxylation of isoamyl benzoate (**1a**) using HIO_3 and NHPI under a nitrogen atmosphere (Table 1). No reaction occurred when the reaction was conducted in water, due to the low solubility of **1a** as well as NHPI in water (entry 1). Several organic solvents were then screened, and the hydroxylation was found to proceed, producing **2a** in 32% yield when nitromethane was used as a solvent (entry 2). The efficiency of the hydroxylation reaction was improved by the addition of water, and 5 equiv of water proved to be the most effective, with **2a** being formed in 62% yield, with 20% of **1a** being recovered (entries 3–6). Further investigations revealed that, when the reaction reached completion after 24 h, the yield of **2a** was increased up to 72% (entry 7). The reactivity of iodine pentoxide (I_2O_5) was similar to that of HIO_3 (entry 8), while no **2a** was detected when other pentavalent ioidne reagents such as $NaIO_3$, NH_4IO_3, and 2-iodoxybenzoic acid (IBX), were used.[14] Unexpectedly, the presence of oxygen, which is usually needed to promote NHPI-catalyzed C(sp^3)–H oxidations, had a negative effect on this hydroxylation (entry 9). The reaction appears to proceed via a radical process but does not involve a light-induced process, since the reaction worked equally well, even in the dark (entry 6 vs. 10). Encouraged by the success of the C(sp^3)–H hydroxylation, we next examined use of other oxygen nucleophiles in the C(sp^3)–H oxygenation reaction. When the reaction was run in methanol, neither the desired methyl ether product nor **2a** (entry 11) were produced. Meanwhile, when acetic acid was used as a solvent, the predominant reaction was C(sp^3)–H acetoxylation, leading to the production of the corresponding acetate with the concomitant formation of the alcohol **2a** (entry 12).[15]



Scheme 3 Substrate scope for C–H bond hydroxylation. Reactions were conducted on a 0.4 mmol scale. Yields are isolated yields based on the amount of **1** used. [a] Reaction was conducted on a 10 mmol scale. [b] A mixed solvent of $MeNO_2$/1,2-dichloroethane (1:1, v/v) was used. brsm = based on recovered starting material.

We next investigated the utility and scope of the C(sp^3)–H hydroxylation (Scheme 3). To demonstarate the synthetic utility, the reaction using **1a** on a gram-scale (10 mmol) was carried out, affording **2a** in an acceptable yield (58%, 1.21 g). The effect of an electron-withdrawing benzoate group was evaluated by the reaction using substrates **1a–c**. Isobutyl benzoate (**1b**), in which a tertiary C–H bond is located at the β-position to the oxygen atom of the benzoate group, showed a lower reactivity than that of **1a**, which is explained by the electron deficient character of the C–H bond, providing the product **2b** in 55% yield, with 25% (^1H NMR) of the starting material being recovered. In contrast, a tertiary C–H bond remote from the benzoate group showed a high reactivity, and the reaction reached completion within 12 h (**2c**). A secondary alcohol derivative was also suitable for use in this reaction

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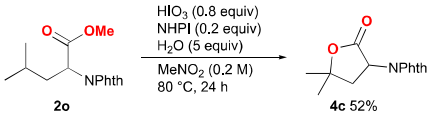
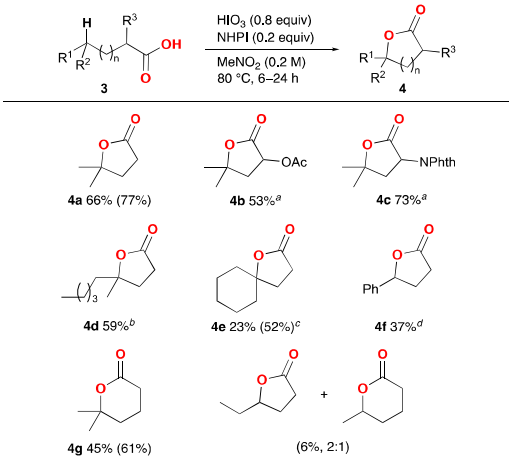
system (**2d**). The replacement of a methyl group with an ethyl group at the reaction site resulted in a low yield of **2e**, probably because of a steric hindrance. Adamantane was also successfully converted into the 1-adamantanol (**2f**) using a nitromethane/1,2-dichloroethane mixed solvent.[16,17] We next surveyed the functional group tolerance for this reaction. Isoamyl benzoate derivatives, which contain cyano (**2g**), fluoro (**2h**), chloro (**2i**), bromo (**2j**), and iodo (**2k**) groups on the phenyl ring, all provided the corresponding alcohols without the loss of their functionalities. In addition, an acetyl protected alcohol (**2l**), a phthaloyl protected amine (**2m**), and a valine derivative (**2n**) were also compatible with this hydroxylation. The use of a valine derivative resulted in a low yield because of the strong electron deficient character of the C–H bond in this molecule.



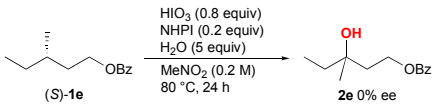
Scheme 4 Lactonization of *N*-phthaloyl leucine methyl ester **2o**.



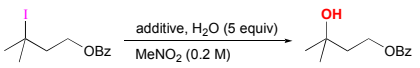
Scheme 5 Substrate scope for the lactonization of carboxylic acids. Reactions were conducted on a 0.4 mmol scale. Yields are isolated yields based on the amount of **3** used. Values in parentheses are yields determined by ^{1}H NMR analysis of the crude product. [a] HIO_3 (1.2 equiv) was used. [b] I_2O_5 (0.8 equiv) was used instead of HIO_3. [c] I_2O_5 (0.4 equiv) was used instead of HIO_3. [d] Reaction was conducted at 60 °C.

When the *N*-phthaloyl leucine methyl ester **2o** was selected as a substrate under hydroxylation reaction conditions, cyclization proceeded to afford the γ-lactone **4c** instead of the corresponding tertiary alcohol (Scheme 4). This unexpected result and the success in C(sp^3)–H acetoxylation (Table 1, entry 12) encouraged us to investigate the lactonization of carboxylic acids containing a tertiary carbon center. To our delight, the NHPI/HIO_3 oxidation system was found to be quite effective for preparing lactones directly from readily available carboxylic acids (Scheme 5). 4-Methylvaleric acid underwent smooth lactonization, with the formation of the corresponding γ-lactone **4a**. Lactones containing acetoxy (**4b**) and phthalimido (**4c**) groups were also readily accessed with this method in good yields. The lactonization of 4-methylnonanoic acid also proceeded smoothly to form **4d**. Furthermore, the present reaction could be applied to spirolactonization (**4e**).[18] A benzylic C–H bond showed a high reactivity, and the reaction was therefore conducted at 60 °C to suppress the competitive formation of a ketone, providing **4f** in moderate yield. In addition to the synthesis of γ-lactones, this reaction system was also successfully applied to the synthesis of the δ-lactone **4g**. However, disappointingly, a mixture of γ- and δ-lactones was obtained in very low yield when hexanoic acid, which does not contain a tertiary carbon center, was used as a substrate. The formal dehydrogenative lactonization of carboxylic acids is rare and remains a challenging issue.[19] The present reaction offers a simple and powerful tool for the synthesis of lactones from readily available carboxylic acids.

a) Stereochemical course of the hydroxylation



b) Reaction starting from alkyl iodide



Entry	Additive [x equiv]	Conditions	Yield [%]
1	none	80 °C, 10 min	<5
2	HIO_3 (0.8)	80 °C, 10 min	13
3	HIO_3 (0.8)	80 °C, 1 h, slow addition	34
4	none	rt, 10 min	0
5	HIO_3 (0.8)	rt, 10 min	95

Scheme 6 Mechanistic investigations.

Some additional experiments were performed in attempts to further investigate the reaction pathway for this hydroxylation depicted in Scheme 2b. To evaluate the stereochemical course of the reaction, enantiopure (*S*)-**1e** was subjected to the standard reaction conditions, resulting in the formation of racemic **2e** (Scheme 6a). This result is consistent with a pathway that proceeds via an alkyl radical intermediate, which would result in the loss of stereochemical information.[14,20] Based on our previous work,[13] we considered it likely that an alkyl iodide and the corresponding alkyl-λ^3-iodane would be generated in-situ as reaction intermediates in this hydroxylation. To confirm the reaction pathway, several reactions were examined employing the separately prepared alkyl iodide **5** to determine whether it is converted into **2a** (Scheme 6b). In the absence of HIO_3, only a trace amount of **2a** was formed[21] while the hydroxylation proceeded in the presence of HIO_3 under the otherwise same conditions to provide **2a** even in low yield (entries 1 and 2). The slow addition of **5** to a suspension of HIO_3 in $MeNO_2$ at 80 °C resulted in a slight increase in the yield of **2a** to 34% (entry 3). The necessity of HIO_3 for this transformation was more clearly demonstrated by running the reaction at room temperature. Although, running the reaction in the absence of HIO_3 led to the full recovery of the starting material, in the presence of HIO_3, **2a** was formed quantitatively (entries 4 and 5).[22] These

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results strongly support the reaction pathway shown in Scheme 2b, in which an alkyl iodide is generated and oxidized by HIO_3 to the corresponding hypervalent iodine species, which then undergoes hydroxylation.[23]

In conclusion, we report on the development of a new class of metal-free C–H oxygenation reactions at tertiary carbon centers using commercially available and easily handled HIO_3 and NHPI. Various tertiary alcohols as well as lactones can be prepared by this operationally simple and environmentally benign method. Further investigations of applications of this method to the synthesis of more complex molecules are currently in progress.

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21 The iodide **5** was hydrolyzed *in situ*, and benzoic acid was produced.
22 An acid-promoted mechanism can be ruled out, since **2a** was not produced in the presence of CF_3CO_2H instead of HIO_3.
23 The lactonization appears to proceed through a similar reaction pathway, but the details of the mechanism remain unclear.

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An oxidation system which employs iodic acid and *N*-hydroxyphthalimide permitted effective oxygenation of tertiary C–H bonds.