Radical C–H Oxidation

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Site-Selective Oxidation of Unactivated C_{sp^3}–H Bonds with Hypervalent Iodine(III) Reagents

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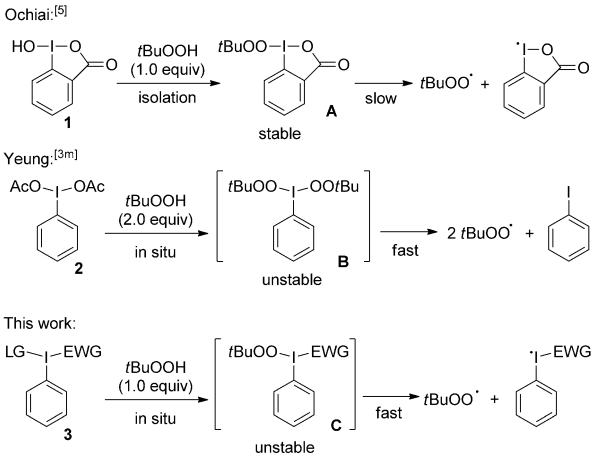
Functionalization of unactivated C_{sp^3}–H bonds is one of the most sought-after chemical transformations and has high potential to simplify synthetic sequences as well as to expedite the functionalization of various organic molecules.[1] Unfortunately, such a transformation remains challenging owing to the high bond energy of C–H, thereby making it inert toward various reagents and catalysts. Initial attempts to transform these bonds through either metal-mediated or metal-free reactions has often resulted in poor yields and/or low selectivity, thus making those methods less practical for synthesis.[2] In recent years, several methods have emerged that efficiently transform saturated C–H bonds in a site-specific manner.[3] Du Bois and co-workers reported a metal-free approach, in which they used a catalytic amount of pentafluorophenyl-substituted benzoxathiazine for the hydroxylation of aliphatic tertiary C–H bonds in the presence of H_2O_2 in acetic acid.[3j] Curci and co-workers used a stoichiometric amount of methyl(trifluoromethyl)dioxirane (TFDO) to oxidize tertiary C–H bonds, although the instability of the reagent makes it difficult to handle.[2c,3b] White and co-workers have shown that a bulky Fe-based catalyst can efficiently oxidize unactivated secondary C–H bonds in a highly predictable fashion.[2c,3e,h,i] In marked contrast, however, there is no report of the use of a metal-free system for the site-selective oxidation of unactivated secondary C–H bonds in the absence of directing groups. Herein, we report our initial results on the oxidation of unactivated secondary C–H bonds in the absence of directing groups with a hypervalent iodine(III) reagent with predictable site-selectivity.[4]

Our proposed method to generate radical reagents from hypervalent iodine(III) compounds for the site-selective oxidation of unactivated C–H bond is depicted in Scheme 1. Ochiai et al. prepared stable *tert*-butylperoxy iodane **A** from hypervalent iodane **1** through a ligand exchange reaction in the presence of a Lewis acid.[5] The stability of the reagent stems from fixation of an axial peroxy ligand and an equatorial aromatic ligand on the iodine(III) center. In solution, slow homolytic cleavage of the peroxy–iodine bond results in formation of a peroxy radical and an iodane



Scheme 1. Methods for the generation of radicals from hypervalent iodine(III) reagents. EWG = electron-withdrawing group, LG = leaving group.

radical. When **1** was used in the oxidation *tert*-butyl-substituted cyclohexane, very small amounts of products were obtained after 24 h (Table 1, entry 1). Yeung and co-workers generated *tert*-butylperoxy radicals under mild reaction conditions from diacetoxyiodobenzene (DIB; **2**).[3m] Both acetyl groups on the iodine are replaced by *tert*-butylperoxy groups, thus resulting in the formation of highly the unstable bis(*tert*-butylperoxy) iodane intermediate **B**. As a result, intermediate **B** quickly decomposes to generate *tert*-butylperoxy radicals, which oxidized *tert*-butylcyclohexane in a nonselective fashion (Table 1, entry 2). We are interested in generating an iodanyl radical with enhanced reactivity/selectivity under mild reaction conditions. To this end, we decided to employ acyclic iodane reagent **3** with two different ligands, where one ligand acts as a steric/electronic modifier on the iodine center and the other as a leaving group, which is replaced by a peroxy substituent. With this approach, unstable iodane intermediate **C** would be generated, thus leading to the formation of both an iodanyl radical and a *tert*-butylperoxy radical. We intend to accelerate the formation of **C** by choosing an appropriate leaving group (LG), and create a more-reactive iodanyl radical by tuning the electron-withdrawing group (EWG) on the iodine center. Competition between the *tert*-butylperoxy radical and iodanyl radical for the deprotonation step is inevitable, and thus increasing the reactivity of the more-site-selective iodanyl radical should improve the selectivity. An investigation of different ligands revealed that a more electron-withdrawing group provides the better selectivity (Table 1, entries 3 and 4). For the leaving group (LG), both

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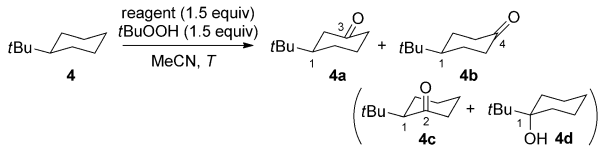
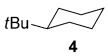
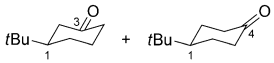
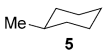
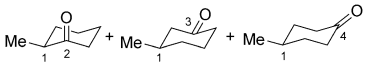
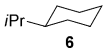
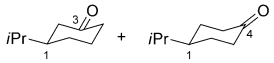
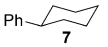
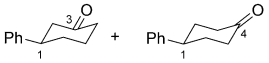
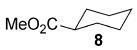
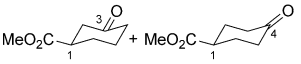
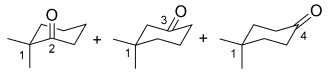
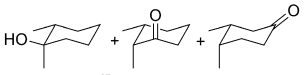
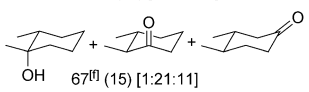
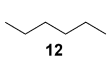
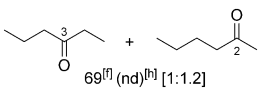
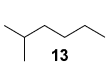
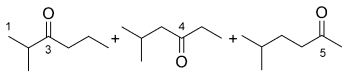
Table 1: Site-selective oxidation of *tert*-butylcyclohexane by hypervalent iodine(III) reagents **1**–**3e**.[a]



Entry	Reagent	LG	EWG	*T* [°C]	*t* [h]	Yield [%][b,c]	**4a**/**4b**[d]
1	**1**	–	–	RT	24	8 (89)	2.6:1
2	**2**	–	–	0	0.5	36 (58)	2.2:1
3	**3a**	OTMS	TFA	0	0.5	29 (61)	2.8:1
4	**3b**	OTMS	OTf	0	0.5	11 (84)	3.9:1
5	**3c**	OAc	OTf	0	0.5	40 (57)	3.8:1
6	**3d**	$OP(O)Ph_2$	OTf	0	0.5	51 (42)	3.9:1
7	**3e**	OTf	OTf	0	0.5	18 (71)	3.9:1
8[e]	**3d**	$OP(O)Ph_2$	OTf	−20	4	59 (27)	4.4:1
9[e,f]	**3d**	$OP(O)Ph_2$	OTf	−20	4	91 (<5)	4.6:1
10[e,f,g]	**3d**	$OP(O)Ph_2$	OTf	−20	4	42 (46)	4.5:1

[a] Unless otherwise specified, reactions were conducted in the presence of hypervalent iodine(III) reagent (1.5 equiv) and *tert*-butyl hydroperoxide (TBHP) (1.5 equiv) in acetonitrile under the given reaction conditions. [b] Yield of the isolated products. [c] The number in brackets is the percentage of remaining starting material in the reaction mixture, as determined by ^{1}H NMR spectroscopy with nitromethane as internal standard. [d] Regioisomers **4c** and **4d** were not observed. [e] Molecular sieves (4 Å) were used. [f] Potassium carbonate (2.0 equiv) was used. [g] Cumene hydroperoxide (1.5 equiv) was used. [h] These reagents were prepared in situ according to the published protocols.[6] Tf = triflate, TFA = trifluoroacetic acid, TMS = trimethylsilyl.

Table 2: Site-selective oxidation of secondary C–H bonds by hypervalent iodine(III) reagent **3d**.[a]

Entry	Substrate	Oxidation Products Yield [%][b,c] [ratio of regioisomers]
1		 89[d,e] (<5) [4.5:1]
2		 80[f] (9) [1:3.8:1]
3		 83[d] (<5) [4.0:1]
4		 86[d] (<5) [4.3:1]
5		 68[d,g] (23) [1.9:1]
6		 79[f] (12) [1.4:1.6:1]
7		 73[f] (10) [1:4.7:2.8]
8		 67[f] (15) [1:21:11]
9		 69[f] (nd)[h] [1:1.2]
10		 71[f] (nd)[h] [1.4:1:4.8]

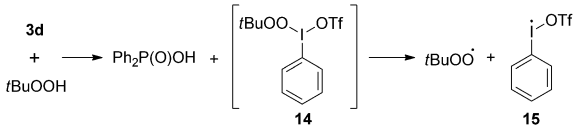
[a] Unless otherwise specified, reactions were conducted in the presence of **3d** (1.5 equiv), TBHP (1.5 equiv), molecular sieves (4 Å), and K_2CO_3 (1.5 equiv) in acetonitrile at −20 °C for 4 h. [b] Yields were calculated as a sum of all regioisomers. [c] The number in brackets is the percentage of remaining starting material in the reaction mixture, as determined by ^{1}H NMR spectroscopy with nitromethane as internal standard. [d] Yield of the isolated products. [e] 1.0 mmol scale. [f] Yield and regioselectivity were determined by GC analysis. Nitromethane was used as internal standard for calculating the yield. [g] Use of 2.0 equiv of **3d** and TBHP. [h] nd = not determined.

acidity and lability of the ligand influence the selectivity as well as the reactivity; in the presence of the (diphenylphosphinoyl)oxy group the best yield and selectivity were obtained (Table 1, entries 5–7). Better selectivity and higher yield were achieved by lowering the reaction temperature (Table 1, entry 8) and by using molecular sieves (4 Å) and potassium carbonate (Table 1, entry 9). The use of cumene hydroperoxide as a peroxide source did not alter the selectivity; however, a lower yield was obtained (Table 1, entry 10).

With the optimal reagent and conditions established, we investigated other substrates with different steric, and electronic influences as shown in Table 2. The bulkiness of the substituents on the cyclohexane substrates affects the site selectivity of the reagent; an increase in the size of substituents shifted the site of oxidation toward the C3 position (Table 2, entries 1–6). Whereas the oxidation by TFDO was specific to tertiary C–H bonds in similar substrates,[3b,7] oxidation at such hindered sites was disfavored with **3d**.[8] No C–H hydroxylation occurred at the electronically favored benzylic position in phenylcyclohexane (Table 2, entry 4).[9] Use of an electronically deactivating group, such as an ester, inhibits oxidation at proximal methylene sites, thereby increasing the relative amount of oxidation at C4 (Table 2, entry 5). Previous reports on the oxidation of *cis*-1,2-dimethylcyclohexane (**10**) with a bulky iron catalyst showed preferred oxidation at the relatively accessible equatorial tertiary site (*tert*/*sec* = 4:1), whereas preferential oxidation of the secondary C–H bond (*tert*:*sec* = 1:2) was observed with the corresponding *trans*-isomer **11**, having only the axial tertiary C–H bonds.[3i] In marked contrast, however, when reagent **3d** was used only small and trace amounts of C1 oxidation products were produced from *cis*- and *trans*-1,2-dimethylcyclohexane, **10** and **11**, respectively (Table 2, entries 7 and 8). These results clearly indicate that **3d** is able to discriminate the steric environment of substituted cyclohexanes. Acyclic hydrocarbons without steric and electronic biasing substituents were also investigated (Table 2, entries 9 and 10). As expected, in the absence of steric and electronic biasing groups, no significant site selectivity was observed in hexane (Table 2, entry 9). Oxidation at the C5 site was mainly

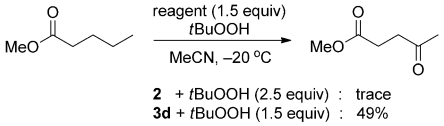
observed in the case of 2-methylhexane **13** owing to the steric influence of the terminal dimethyl moieties (Table 2, entry 10).

Next, we attempted to identify the radical source responsible for the observed specificity. A possible pathway for the generation of radicals has been proposed (Scheme 2). Previous evidence, independently found by the groups of



Scheme 2. Proposed pathway for the formation of iodanyl radical.

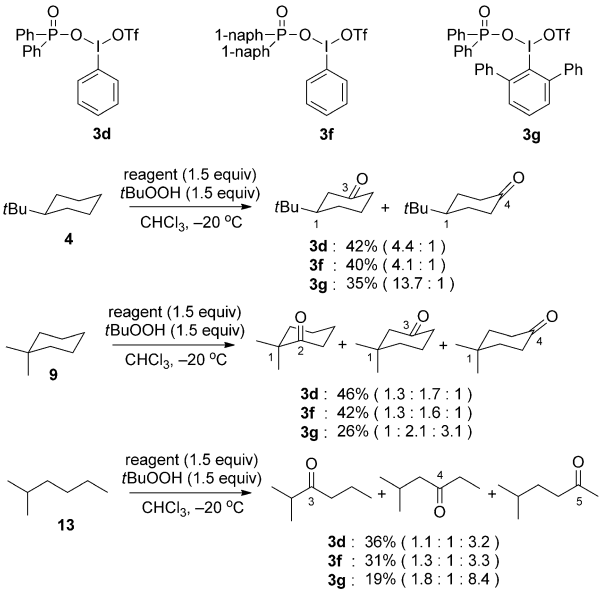
Ochiai[5] and Plesnicar,[10] led to their proposal on the formation of intermediate **14**, and then *tert*-butylperoxy radical, and iodanyl radical **15** upon homolytic bond cleavage of the weaker hypervalent iodine(III)–peroxy bond. Therefore, both the *tert*-butylperoxy and iodanyl radical **15** are potentially involved in the hydrogen abstraction of substrates. Plesnicar and co-workers proposed the formation of bis(*tert*-butylperoxy)iodosobenzene intermediate when DIB was mixed with 2 equivalents of TBHP; this intermediate quickly decomposed to peroxy radicals and iodobenzene at −80 °C.[10] In our case, however, the reaction was conducted at a much higher temperature (−20 °C), and moreover, the use of an excess amount of TBHP did not affect the yield or selectivity. When the hydroperoxide source was switched from TBHP to cumene hydroperoixde, there were no apparent change in selectivity (Table 1, entry 10). This finding suggests that the peroxy radical may not participate in the outcome of the site selectivity. In addition, when methyl valerate was subjected to the oxidation, the use of reagent **3d** gave methyl levulinate in 49 % yield (Scheme 3). However, under the same conditions,



Scheme 3. Oxidation of methyl valerate with **2** and **3d**.

only a trace amount of methyl levulinate was obtained with the *tert*-butylperoxy radicals generated in situ from **2** and TBHP.[11] These results suggest that a more-reactive radical, which is generated in situ, is responsible for the site specific oxidation of unactivated C–H bonds.

To gain further insight into the mechanism, we prepared hypervalent iodine(III) reagents **3f** and **3g** (Scheme 4). As expected, a change in steric bulkiness on the diarylphosphinic group lead to no major change in the site- selectivity or the rate of the oxidation of *tert*-butylcyclohexane (**4**) with **3f**. In contrast, when the steric bulkiness around the iodine center was increased as shown in **3g**, the selectivity toward the C3 site was markedly increased to approximately 14:1. Similarly,



Scheme 4. Hypervalent iodine(III) reagents **3**.[12] naph = naphthalene.

for 1,1-dimethylcyclohexane (**9**), the relative amount of oxidized product at the sterically less-hindered C4 site was increased drastically with **3g**. A similar site-selectivity was also observed in acyclic substrates. For 2-methylhexane (**13**), use of the bulkier reagent **3g** gave increased selectivity, with oxidation occurring mostly at the C5 position with only a small amount of oxidation at the C4 position. The yield was lower when reagent **3g** was used, presumably because of the increased steric hindrance around the iodanyl radical center. These results imply that the iodanyl radical **15** plays a key role in the regiodetermining step of the oxidation.

Although it is premature to draw a conclusive mechanism at this stage, the results disclosed above suggest the reaction follows a similar pathway to that suggested by the groups of Ochiai[5] and Plesnicar.[10] The reaction is initiated by cleavage of the hypervalent iodine(III)–peroxy bond of **3d** to generate a *tert*-butylperoxy radical and iodanyl radical. The iodanyl radical abstracts an hydrogen atom in a site-selective fashion from the substrate, and the resulting carbon-centered radical is trapped by the *tert*-butylperoxy radical.[13] The alkyl peroxide, thus formed, is further transformed to the corresponding ketone.

In summary, we have succeeded in the site-selective oxidation of unactivated C_{sp^3}–H bonds by (diphenylphosphinoyl)oxy hypervalent iodine(III) reagent. The preparation and derivatization of the reagent are simple and inexpensive, thus allowing us to rationally design various reagents to optimize the site selectivity as necessary. Further investigations into the mechanism and into applications toward other systems are currently underway in our laboratory.

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Keywords: C–H activation · hypervalent iodine · oxidation · radicals · synthetic methods

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[12] All reactions were conducted using chloroform because of the poor solubility of reagent **3f** in acetonitrile.

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