$C(sp^3)$–H Peroxidation of 3-Substituted Indolin-2-ones under Metal-Free Conditions

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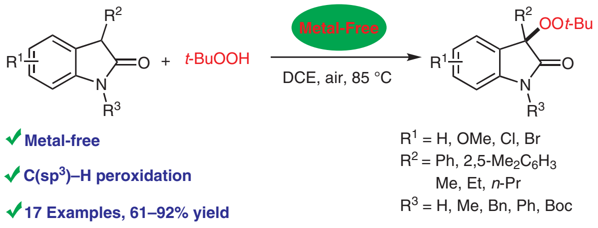

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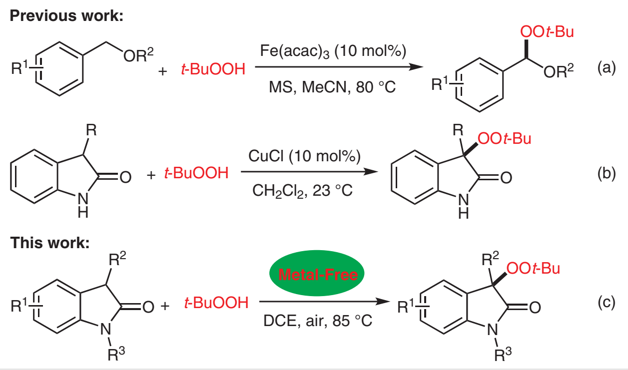
Abstract A $C(sp^3)$–H peroxidation of 3-substituted indolin-2-ones through radical coupling reaction has been developed under metal-free conditions. Using *tert*-butyl hydroperoxide both as an oxidant and as a peroxidation reagent to couple with the $C(sp^3)$–H bonds of 3-substituted indolin-2-ones can form a new C–O bond without using any additives. This simple strategy provides a green and efficient approach to 3-peroxyindolin-2-ones in moderate to excellent yields. The resulting 3-peroxyindolin-2-ones could be further transformed into 3-hydroxyindolin-2-ones.

Key words $C(sp^3)$–H peroxidation, metal-free, 3-substituted indolin-2-ones, *tert*-butyl hydroperoxide

The direct and selective functionalization of $C(sp^3)$–H bond is a 'young' and rapid-developing area in synthetic chemistry.[1] Transition-metal-catalyzed methods have recently become the mainstream of $C(sp^3)$–H functionalization.[2] However, from green chemistry and environmental points of view, establishing a metal-free approach to $C(sp^3)$–H functionalization would be a more elegant strategy.[3] Thus, the metal-free methods have emerged as a powerful 'chemical weapon' because it can overcome the drawbacks of the expensive and poisonous properties of metals or organometallics.[4]

Organic peroxides are ubiquitous and indispensable and are present in biologically active compounds with antimalarial,[5] anthelmintic,[6] and antitumor [7] activity. *tert*-Butyl hydroperoxide (*t*-BuOOH) plays a dual role as an oxidant and as a peroxidation reagent in the synthesis of organic peroxides. While significant results have been accomplished in the field of difunctionalization of alkenes by the use of *t*-BuOOH,[8] reactions involving direct peroxidation of $C(sp^3)$–H bonds remain rare. One efficient example was reported by Urabe and co-workers, who reported a Fe-promoted $C(sp^3)$–H bond functionalization of benzyl ethers with *t*-BuOOH. Various *tert*-butyl peroxyacetals were readily prepared from benzyl ethers, *t*-BuOOH, and a catalytic amount of $Fe(acac)_3$ at 80 °C (Scheme 1, a).[9] Very recently, M. Stoltz and co-workers developed a Cu-catalyzed $C(sp^3)$–H peroxidation of oxindole derivatives with *t*-BuOOH by using CuCl as a catalyst and dichloromethane (CH_2Cl_2) as solvent (Scheme 1, b).[10]



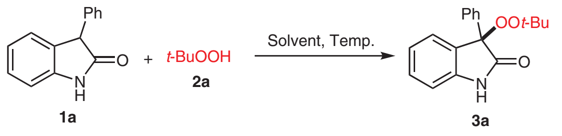
Scheme 1 $C(sp^3)$–H peroxidation using *t*-BuOOH

However, to the best of our knowledge, no example of metal-free direct $C(sp^3)$–H peroxidation has been described. In this regard, it is important to seek for a simple and efficient method to broaden this area. As part of our continuing efforts in modification indolin-2-ones and recent interests in the $C(sp^3)$–H peroxidation,[11] herein we present a $C(sp^3)$–H peroxidation of 3-substituted indolin-2-ones using *t*-BuOOH under metal-free conditions (Scheme 1, c). It is worth noting that this simple metal-free approach successfully provides a versatile method for obtaining a wide range of 3-peroxyindolin-2-ones.

Initially, the reaction of 3-phenylindolin-2-one (**1a**) with *t*-BuOOH (70% in water, **2a**) was chosen as a model reaction for optimizing the reaction conditions including solvent and temperature (Table 1). The reaction proceeded under the commonly used solvent dichloroethane (DCE) under air at 85 °C, and an unknown product was obtained in 91% yield that after identification turned out to be 3-(*tert*-butylperoxy)-3-phenylindolin-2-one (**3a**, Table 1, entry 1). In the light of this result, we turned our attention to examine the reaction temperature. While a lower reaction temperature only gave the desired product **3a** in 30% yield (Table 1, entry 2), a higher reaction temperature gave the same result as that at 85 °C (Table 1, entry 3). Notably, the amount of *t*-BuOOH affected the reaction: A decrease to 2.0 equiv was not beneficial to the formation of product **3a** (Table 1, entry 4), whereas an increase to 3.0 equiv only resulted in an identical result to that of 2.4 equiv *t*-BuOOH (Table 1, entry 5). Finally, the effect of solvent on the reaction performance was evaluated. When the reaction was carried out in MeCN, THF, and EtOH, the efficiency was lower than in DCE (Table 1, entry 1 vs entries 6–8). On the basis of these results, entry 1 represents the best conditions.

Having optimized the reaction conditions, the scope of the C(sp^3)–H peroxidation reaction by different 3-substituted indolin-2-ones with *t*-BuOOH was investigated (Table 2).[12] It is satisfactory that under the optimum reaction conditions, the 3-phenylindolin-2-one gave the desired product **3a** in 91% yield. In addition, introduction of an aryl- or alkyl-substituent at the C3-position of indolin-2-ones did not significantly affect the yield (products **3b–e**), giving the corresponding products in 70–81% yields (Table 2, entries 2–5). Next, we studied the effect of the aryl rings on this reaction. A range of the 3-substituted indolin-2-ones bearing an electron-donating group (R = OMe) or an electron-withdrawing groups (R = Cl, Br) in the 5-position of the aryl rings underwent the peroxidation and afforded the desired products with up to 92% yield (**3f–h**, Table 2, entries 6–8). Particularly noteworthy was the smooth transformation of the aryl halide substrates, thus allowing further modifications *via* cross-coupling reactions. To our delight, a large variety of functional groups (*N*-Me, *N*-Bn, and *N*-Ph substituents) as *N*-substituents of the 3-substituted indolin-2-ones were tolerated and gave the corresponding products in 87%, 86%, and 82% yields, respectively (**3i–k**, Table 2, entries 9–11). Moreover, the *N*-Boc-substituted substrate also reacted effectively with **2a** to give the corresponding product **3l** in 66% yield after prolonging the reaction time (Table 2, entry 12). It is interesting to note that this method was also effective for the synthesis of 3-peroxyindolin-2-ones **3m–p** and gave the peroxidation products in moderate yields (Table 2, entries 13–16). Unfortunately, indolin-2-one has poor selectivity for this peroxidation reaction and was converted into indoline-2,3-dione in 81% yield under the standard reaction conditions (Table 2, entry 17). In general, this method was successfully applied to a variety of 3-substituted indolin-2-ones, and these substrates were smoothly converted into the corresponding 3-peroxyindolin-2-ones in moderate to excellent yields.

Table 1 Optimization of the Reaction Conditions[a]



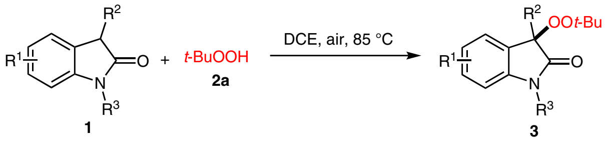
Entry	Solvent	Temp. (°C)	Yield (%)[b]
1	DCE	85	91
2	DCE	50	30
3	DCE	100	91
4[c]	DCE	85	78
5[d]	DCE	85	92
6	MeCN	85	77
7	THF	85	20
8	EtOH	85	5

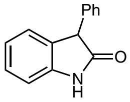
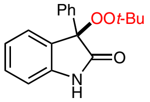
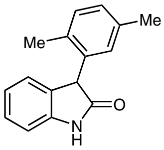
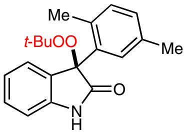
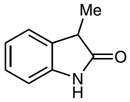
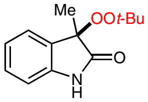
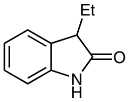
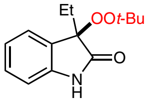
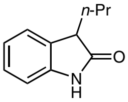
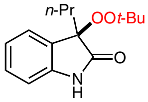
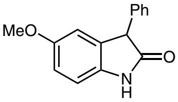
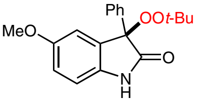
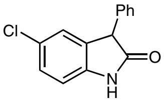
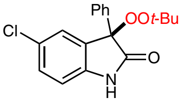
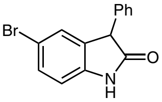
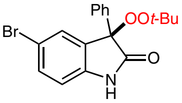
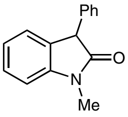
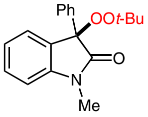
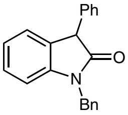
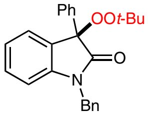
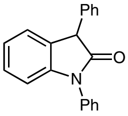
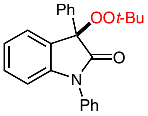
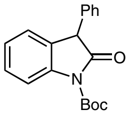
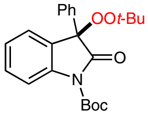
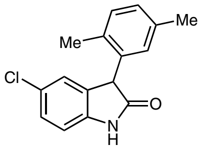
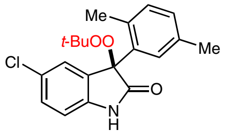
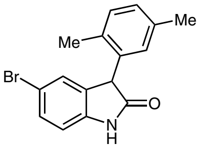
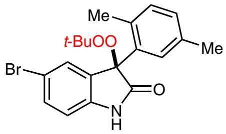
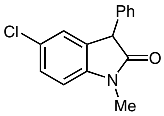
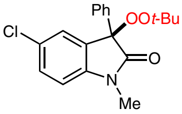
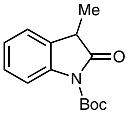
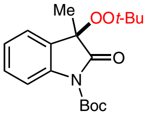
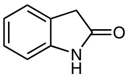
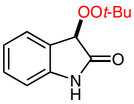
[a] Reaction conditions: **1a** (0.3 mmol), **2a** (70% in water, 0.72 mmol, 2.4 equiv), and solvent (2 mL) under air for 12 h.
[b] Isolated yields.
[c] **2a** (0.6 mmol, 2.0 equiv).
[d] **2a** (0.9 mmol, 3.0 equiv).

The study findings of transformations on the 3-peroxyindolin-2-ones are shown in Scheme 2. 3-Hydroxyindolin-2-ones were obtained in 72–76% yields when 3-peroxyindolin-2-ones were subjected to reduction conditions.[13]

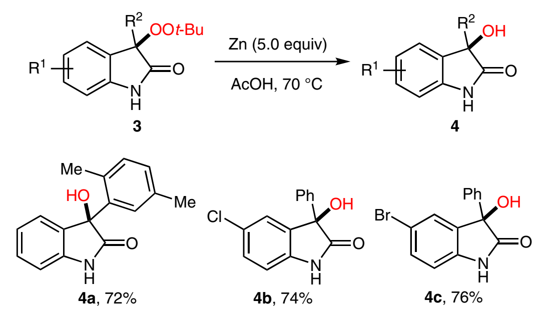
To obtain information about the reaction mechanism, several control experiments were carried out as shown in Scheme 3. When 3-phenylindolin-2-one (**1a**) and 2-(*tert*-butylperoxy)-2-methylpropane (*t*-BuOO*t*-Bu, **2b**) reacted under the standard reaction conditions, the desired product **3r** was not detected at all, and 95% of **1a** was recovered (Scheme 3, a). Subsequently, two radical inhibitors, 2,2,6,6-tetramethylpiperidinyloxyl (TEMPO) and 2,6-di-*tert*-butyl-4-methyl phenol (BHT), were added to the C(sp^3)–H peroxidation reaction: Adding 3.0 equiv of TEMPO or BHT completely inhibited the conversion of **1a**, which indicated that a radical process might be involved in this reaction (Scheme 3, b and c). However, a hydroxylation product **4d** was obtained in 32% yield when 3.0 equiv of TEMPO were added (Scheme 3, b). In addition, *t*-BuOOH was transformed by BHT into 3,5-di-*tert*-butyl-4-(tert-butylperoxy)-4-methylcyclohexa-2,5-dien-1-one (**5a**) in 71% yield, which suggest that a *t*-BuOO radical is involved (Scheme 3, c).[14]

Table 2 Reaction Scope of C(sp^3)–H Peroxidation[a]

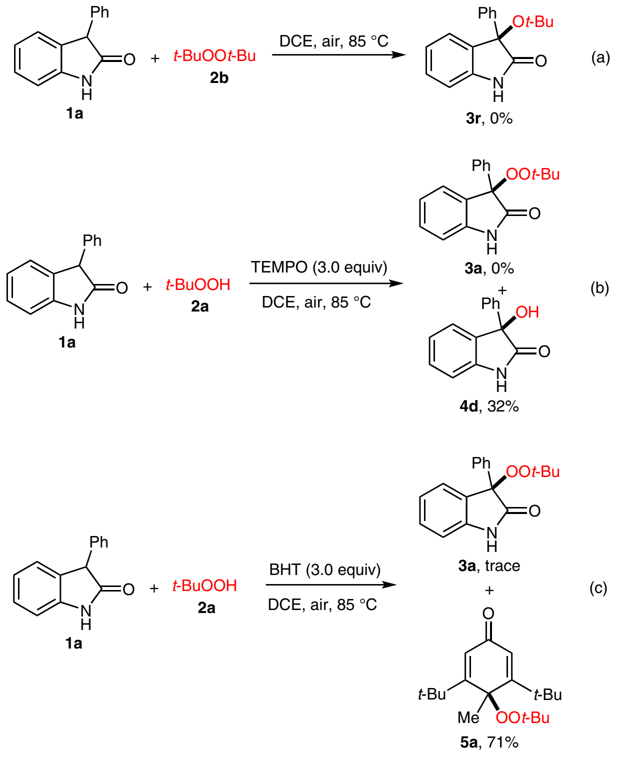


Entry	Substrate	Product	Yield (%)
1	 **1a**	 **3a**	91
2	 **1b**	 **3b**	81
3	 **1c**	 **3c**	76
4	 **1d**	 **3d**	73
5	 **1e**	 **3e**	70
6	 **1f**	 **3f**	92
7	 **1g**	 **3g**	83
8	 **1h**	 **3h**	73
9	 **1i**	 **3i**	87
10	 **1j**	 **3j**	86
11	 **1k**	 **3k**	82
12	 **1l**	 **3l**	66[b]
13	 **1m**	 **3m**	73
14	 **1n**	 **3n**	71
15	 **1o**	 **3o**	82
16	 **1p**	 **3p**	61[b]
17	 **1q**	 **3q**	trace[c]

[a] Reaction conditions: **1** (0.3 mmol), *t*-BuOOH (70% in water, 0.72 mmol), and DCE (2 mL) under air at 85 °C for 12 h.
[b] For 24 h.
[c] Indoline-2,3-dione was obtained in 81% yield.

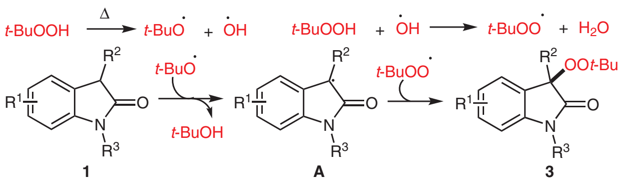


Scheme 2 Synthesis application of 3-peroxyindolin-2-ones



Scheme 3 Control experiments

The mechanism for the metal-free C(sp^3)–H peroxidation was proposed on the basis of present results and related works (Scheme 4).[15–17] Initially, the *t*-BuO and *t*-BuOO radicals were generated from the present system.[15] Subsequently, the *t*-BuO radical abstracts a hydrogen atom from substrate **1** to generate a key intermediate radical **A**.[16] Finally, radical **A** couples with a *t*-BuOO radical to afford the peroxidation product **3**.[17]



Scheme 4 Plausible mechanism

In summary, we have demonstrated a simple, efficient, and green sequence for C(sp^3)–H peroxidation. In this process, *t*-BuOOH was used as a peroxidation reagent which coupled with the C(sp^3)–H bonds of 3-substituted indolin-2-ones without using any metal catalysts. This method provides a practical route to 3-peroxyindolin-2-ones and exhibits a broad substrate scope with good functional group tolerance. Applications of this method toward asymmetric synthesis of 3-peroxyindolin-2-ones are the subject of ongoing investigations in our laboratory.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591520.

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(12) **General Procedure**

To a Schlenk tube were added 3-substituted indolin-2-ones **1** (0.3 mmol), *t*-BuOOH (**2a**, 70% in water, 0.72 mmol), and DCE (2 mL). Then the tube was stirred at 85 °C under air for the indicated time until complete consumption of starting material as monitored by TLC analysis. After the reaction was complete, the solution was concentrated under reduced pressure, and the mixture was purified by flash column chromatography over silica gel (hexane/ethyl acetate) to afford the desired products **3**. The products were analyzed by ^{1}H NMR and ^{13}C NMR spectroscopy, and mass spectrometry (see Supporting Information).

Typical Data for Representative Compound: 3-(*tert*-Butylperoxy)-3-phenylindolin-2-one (3a)

White solid (0.0811 g, 91% yield). ^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.62 (s, 1 H), 7.45–7.43 (m, 2 H), 7.34–7.25 (m, 5 H), 7.08 (t, *J* = 8.0 Hz, 1 H), 6.90 (d, *J* = 7.6 Hz, 1 H), 1.19 (s, 9 H). ^{13}C NMR (100 MHz, CDCl$_3$): δ= 176.3, 141.7, 136.0, 129.8, 129.0, 128.9, 128.5, 127.0, 126.5, 122.6, 110.2, 86.5, 80.9, 26.6. IR (KBr): 1678, 1113, 864 cm^{-1}. ESI-HRMS: *m*/*z* calcd for $C_{18}H_{20}NO_3$ [M + H]$^+$: 298.1438; found: 298.1434.

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