

# Iron-Catalyzed Carbonylation-Peroxidation of Alkenes with Aldehydes and Hydroperoxides

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**S** Supporting Information

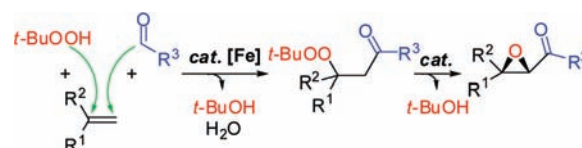
**ABSTRACT:** A three-component reaction of alkenes, aldehydes, and hydroperoxides catalyzed by FeCl<sub>2</sub> to β-peroxy ketones has been achieved. This three-component reaction can be also applied to the synthesis of α-carbonyl epoxides, through either a stepwise base-induced epoxidation of the separated β-peroxy ketone products or a one-pot process by simply adding base to the reaction mixture after the completion of the three-component reaction.

Difunctionalization of alkenes is a class of significant synthetic reactions that allow for the buildup of molecular complexity in a single procedure. Dihydroxylation<sup>1</sup> and Palladium-catalyzed oxidative difunctionalization of alkenes<sup>2</sup> demonstrated its high impacts on synthetic chemistry.<sup>3</sup> Carbonylation of alkenes<sup>4</sup> has been developed as one of powerful methods for synthesis of carbonyl compounds, including large-scale commodity products and versatile chemical intermediates. However, difunctionalization of alkenes to introduce a carbonyl group and another different functional group such as alcohol, amine, and peroxide is still a distinct challenge.<sup>4,5</sup> Herein, we wish to disclose a novel iron-catalyzed, three-component carbonylation–peroxidation reaction of alkene, aldehyde, and hydroperoxide to afford β-peroxy ketones (Scheme 1). This iron-catalyzed, three-component reaction can be also applied to the synthesis of α-carbonyl epoxide through either a stepwise base-induced epoxidation of the separated β-peroxy ketone products or a one-pot process by simply adding base to the reaction mixture after the completion of three-component reaction.

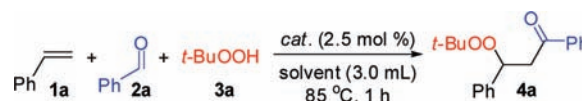
The application of readily available and nontoxic iron catalysts instead of expensive and sensitive catalysts is highly attractive for chemical synthesis.<sup>6</sup> Recently, great progress has been made in exploring iron-catalyzed C–H transformation.<sup>7</sup> Our group and others successfully employed a Fe(II or III)/peroxide catalytic system for C–C bond formation.<sup>8,9</sup> Inspired by these, we challenged ourselves to see whether difunctionalization of alkenes with a carbonyl group and another group, such as alkoxy and peroxy group, could be also reached.

The reaction of styrene **1a**, benzaldehyde **2a**, and *tert*-butyl hydroperoxide **3a** was chosen as a model to investigate our tentative idea (Table 1).<sup>10</sup> To our delight, a 91% yield of the desired carbonylation–peroxidation product **4a** was achieved in the presence of 5 equiv of **2a** and 3 equiv of **3a** using FeCl<sub>2</sub> as catalyst (entry 6). The efficiency of this transformation was dramatically affected by the choice of solvents and iron catalysts (entries 7–15). It should be noted that **4a** was indeed formed without a catalyst, albeit

**Scheme 1. Catalytic Carbonylation–Peroxidation–Epoxidation**



**Table 1. Optimization of the Reaction Conditions<sup>a</sup>**



entry	2a (equiv)	3a (equiv)	catalyst (2.5 mol %)	solvent (3.0 mL)	yield 4a (%) <sup>b</sup>
1	1	3	FeCl <sub>2</sub>	MeCN	13
2	3	3	FeCl <sub>2</sub>	MeCN	53
3	3	2	FeCl <sub>2</sub>	MeCN	37
4	3	1	FeCl <sub>2</sub>	MeCN	15
5	4	3	FeCl <sub>2</sub>	MeCN	71
6	5	3	FeCl <sub>2</sub>	MeCN	91
7	5	3	FeCl <sub>2</sub>	DCE <sup>c</sup>	67
8	5	3	FeCl <sub>2</sub>	PhMe <sup>c</sup>	55
9	5	3	FeCl <sub>2</sub>	DMSO <sup>c</sup>	15
10	5	3	FeCl <sub>2</sub>	H <sub>2</sub> O <sup>c</sup>	38
11	5	3	FeCl <sub>3</sub>	MeCN	66
12	5	3	FeCl <sub>3</sub> ·6H <sub>2</sub> O	MeCN	63
13	5	3	FeBr <sub>2</sub>	MeCN	79
14	5	3	Fe(OAc) <sub>2</sub>	MeCN	<5
15	5	3	Fe(acac) <sub>2</sub>	MeCN	<5
16	5	3	-	MeCN	41

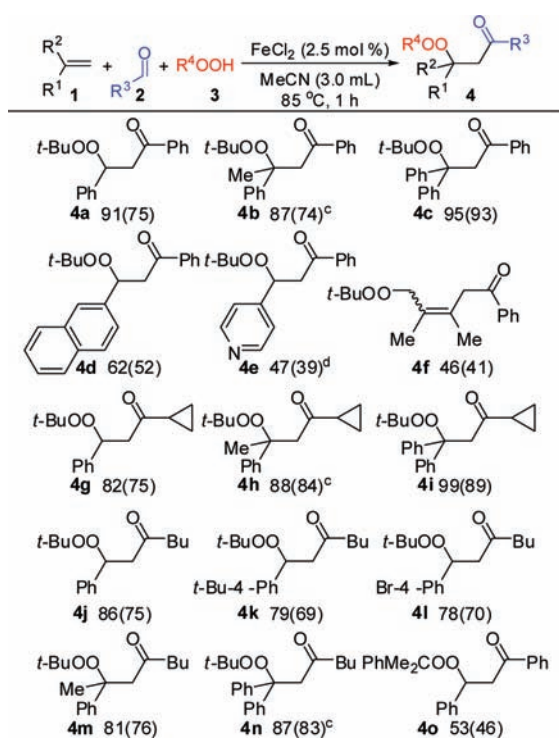
<sup>a</sup> Conditions: **1a** (0.5 mmol), 85 °C, 1 h, under N<sub>2</sub>. <sup>b</sup> Reported yields were based on **1a** and determined by <sup>1</sup>H NMR using an internal standard. <sup>c</sup> 100 °C.

in a low yield (entry 16). The regioselectivity of this transformation was confirmed by the condensation of **4a** with 2,4-dinitrophenyl hydrazine **5** (eq 1). X-ray diffraction analysis revealed that carbonyl

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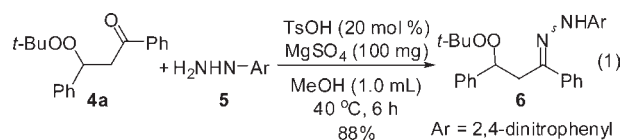
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**Table 2. The Representative Results for the Carbonylation–Peroxidation Reaction<sup>a, b</sup>**

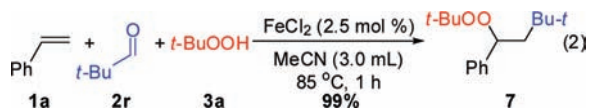


<sup>a</sup> Conditions: **1** (0.5 mmol), **2** (2.5 mmol), **3** (1.5 mmol), MeCN (3.0 mL), under N<sub>2</sub>. <sup>b</sup> Reported yields were based on **1** and determined by <sup>1</sup>H NMR using an internal standard; isolated yields were given in parentheses. <sup>c</sup> 2 h. <sup>d</sup>  $\beta$ -Hydroxy ketone **4e'** was also obtained in 25% yield.

group attached to the  $\beta$ -carbon of styrene (see Supporting Information).



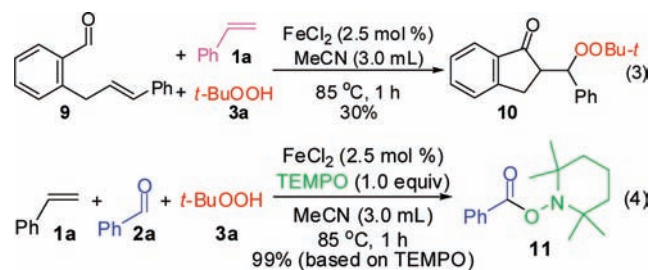
The scopes of the substrates were investigated under the optimized reaction conditions (Table 2).  $\alpha$ -Substituted styrenes afforded the desired products, **4b** and **4c**, in excellent yields. 2-Vinylnaphthalene, 4-vinylpyridine, and 1,3-butadiene led to the corresponding products in moderate yields. Gratifyingly, aliphatic aldehydes were successfully applied to this transform under the standard conditions. In most cases, the carbonylation–peroxidation products were obtained in synthetically useful yields. Interestingly, the decarbonylation product **7** instead of the desired carbonylation–peroxidation product was obtained quantitatively when pivaldehyde **2r** was applied under the standard conditions (eq 2). This result indicated that decarbonylation competes with carbonylation kinetically depended on the nature of substituent of aldehydes.<sup>11</sup>



Epoxidation of alkenes is an important chemical process in synthetic chemistry.  $\alpha$ -Carbonyl epoxides could be synthesized by

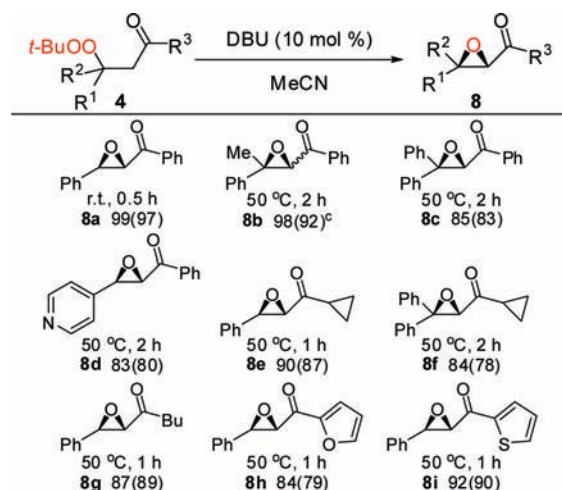
the reactions of  $\alpha,\beta$ -unsaturated ketones with hydroperoxides under base conditions.<sup>12</sup> Mechanistically,  $\beta$ -peroxy ketone is a key intermediate in these reactions. With our established three-component protocol, epoxidation of **4** was investigated subsequently. After brief screening of base, it was found that 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) efficiently catalyzed the epoxidation of **4** to furnish the corresponding epoxides **8** (Table 3).<sup>13</sup> Delightfully, we found that the  $\alpha$ -carbonyl epoxides could be prepared by a one-pot process based on the established carbonylation–peroxidation–epoxidation methodologies (Scheme 2). The desired epoxides were efficiently obtained from the three-component reactions of alkene, aldehyde, and hydroperoxide.

In an attempt to rationalize the possible pathways for this exclusively regioselective carbonylation–peroxidation transformation, alkenyl aldehyde **9** was synthesized and subjected to the standard reaction conditions (eq 3). Intramolecular carbonylation–peroxidation product **10** was obtained. Although this intramolecular transformation turned out to be less efficient compared with the intermolecular cases, importantly, the expected products derived from styrene **1a** were not detected by <sup>1</sup>H NMR analysis (eq 3). This result indicates that the reaction undergoes carbonylation followed by peroxidation. Furthermore, TEMPO-adduct aldehyde **11** was isolated quantitatively when TEMPO was introduced to the reaction, while the formation of **4a** was completely suppressed (eq 4). This result provided good evidence that (1) acyl radical was formed under the standard conditions; (2) cationic pathway is unlikely involved in this reaction.<sup>14</sup> In addition, the reactions of *tert*-butyl peroxybenzote with styrene did not provide the expected carbonylation–peroxidation product under the standard reaction conditions. Therefore, the possibility of *tert*-butyl peroxybenzote generated in situ as a possible intermediate could be excluded for this transformation.<sup>15</sup>



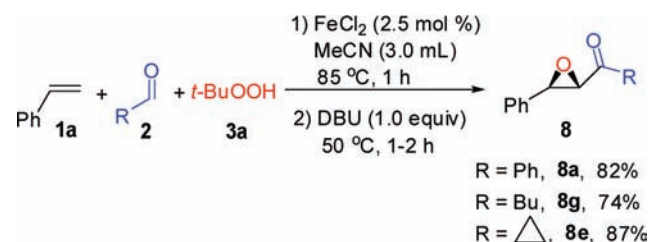
On the basis of the above results and literature reports,<sup>16</sup> a tentative reaction mechanism for iron-catalyzed carbonylation–peroxidation of alkenes is given in Scheme 3. Alkoxy and alkylperoxy radicals are generated from a series of steps, including steps (a) and (b), by iron catalyst. Subsequently, hydrogen abstraction by oxyl radicals, such as *tert*-butoxyl radical, gives acyl radical (step c). The radical addition followed by radical coupling<sup>17</sup> leads to the final product (steps d and e). However, further studies are needed to disclose the exact mechanistic details of this transformation.

In summary, we have demonstrated a novel and practical protocol of iron-catalyzed carbonylation–peroxidation of alkenes.  $\beta$ -Peroxy ketones were selectively and efficiently constructed by the three-component reaction of alkenes, aldehydes, and hydroperoxides. The three-component reaction was further applied to the synthesis of  $\alpha$ -carbonyl epoxides. Further studies on the

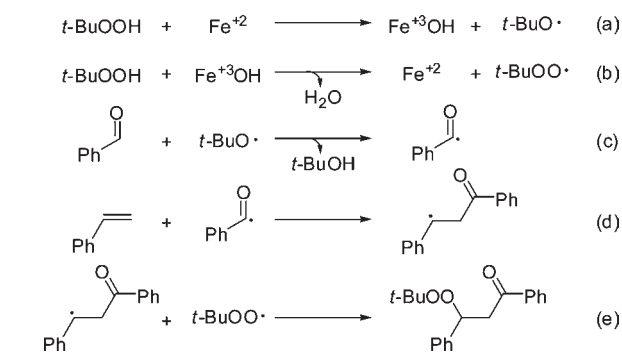
Table 3. DBU-Catalyzed Epoxidation Reactions<sup>a, b</sup>

<sup>a</sup> Conditions: **4** (0.2 mmol), DBU (0.02 mmol), MeCN (2.0 mL), under N<sub>2</sub>. <sup>b</sup> Reported yields were NMR yields using an internal standard; isolated yields were given in parentheses. <sup>c</sup> Two stereoisomers were obtained in a ratio of 2.2:1.

Scheme 2. One-Pot Procedure for Synthesis of Epoxides via Three-Component Reactions



Scheme 3. A Proposed Reaction Mechanism for Iron-Catalyzed Carbonylation–Peroxidation



mechanism, intramolecular reactions, and asymmetric synthesis of epoxides are in progress.

## ■ ASSOCIATED CONTENT

**S** Supporting Information. Experimental procedures, spectrum data, X-ray data for **6** (CIF), and NMR spectra of the

compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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