



Iron-catalyzed alkoxyacylation–peroxidation of alkenes with carbazates and T-Hydro



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ABSTRACT

Iron-catalyzed alkoxyacylation–peroxidation of alkenes with carbazates and T-Hydro was developed. A variety of β -ester peroxides were synthesized efficiently and selectively in a single step starting from readily available starting materials.

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Peroxidation is a fundamental methodology to introduce a peroxy (–OO–) group into organic molecules, which are receiving considerable attention in pharmaceutical industries, biochemistry, and synthetic chemistry. A number of peroxidation reactions have been developed.¹ Autoxidation is widely used to prepare various cyclic peroxides and hydroperoxides under O₂ or air.² Kharasch oxidation also presents an efficient method to synthesize the mixed peroxides using transition metal and hydroperoxides.³ Besides, the addition of peroxy radicals to alkenes and the nucleophilic substitution of hydroperoxides with electrophiles are complementary strategies to synthesize the peroxides.⁴ Nevertheless, the selectivity and efficiency of the peroxidation are still great challenges. Therefore, new peroxidation methods are highly desirable and valuable.

Difunctionalization of alkenes has attracted much attention because of its rapid introduction of two functional groups across a C–C double bond in a single operation.⁵ Recently, difunctionalization of alkenes with a peroxy and another functional group is becoming an attractive strategy for the preparation of organic peroxides (Scheme 1). In 2010, Taniguchi group disclosed an alkoxyacylation–hydroperoxidation of alkenes by aerobic oxidation of hydrazines, in which the OOH group was easily decomposed to a OH group (Eq. 1).⁶ Later, Taniguchi,⁷ Heinrich,⁸ and Leow⁹ groups revealed the method could be also applied to introduce aryl and hydroperoxy group to alkenes selectively (Eq. 1). In 2011, we demonstrated an acylation–peroxidation reaction, where a stable

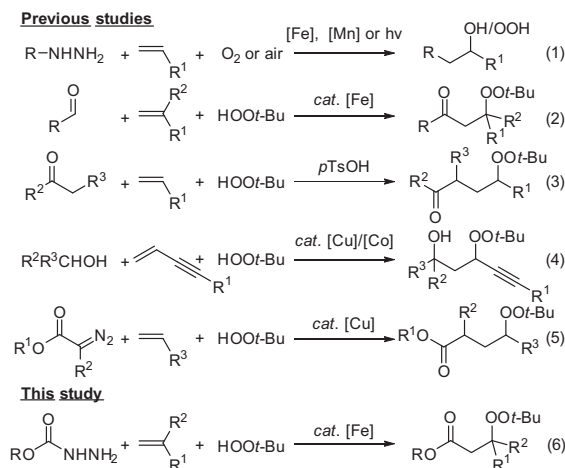
tert-butyl peroxy group could be selectively introduced instead of a frangible hydroperoxy group (Eq. 2).¹⁰ In 2014, Klusmann group reported a carbo-peroxidation of alkenes using ketones and TBHP (*tert*-butyl hydroperoxide; Eq. 3).¹¹ In 2015, Loh¹² and Wan¹³ groups successfully applied alcohols and diazo compounds as alkyl groups to realize the alkylation–peroxidation of alkenes¹⁴ (Eqs. 4 and 5). Herein, we would like to report an iron-catalyzed¹⁵ alkoxyacylation–peroxidation reaction of alkenes with carbazates and T-Hydro (70% TBHP in water; Eq. 6).

To determine the best reaction conditions, methyl carbazate **1a** and benzyl methacrylate **2a** were chosen as model substrates (Table 1). A 78% yield of the desired peroxide **3a** was obtained by the reaction of **1a**, **2a**, and T-Hydro with iron phthalocyanine ([Fe(Pc)]) as catalyst in CH₂Cl₂ (entry 1). However, other tested iron salts showed no catalytic activity (entries 2–4). Interestingly, the desired product **3a** was obtained in 33% yield at 50 °C in the presence of FeCl₂·4H₂O (entry 5). These results indicated that the Pc ligand of [Fe(Pc)] might enhance the reducibility of iron catalyst and the methoxycarbonyl radical could be generated from methyl carbazate **1a** at 0 °C accordingly.^{6–9} CuCl₂ led to **3a** in 24% yield (entry 6), while **3a** was not detected using CoCl₂ and MnCl₂ (entries 7 and 8). Screening reaction conditions identified CH₂Cl₂ as a better solvent (entries 9–12). The yields of **3a** were substantially reduced by decreasing the amount of **1a** and T-Hydro (entries 13 and 14). It should be noted that **3a** was not obtained in the absence of catalyst (entry 15).

Subsequently, the scope of the substrates was investigated under the optimized reaction conditions (Table 2). To our delight,

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Scheme 1. Peroxidation via difunctionalization of alkenes.

Table 1
Optimization of the reaction conditions^a

Entry	Cat.	Solvent	3a ^b (%)
1	[Fe(Pc)]	CH ₂ Cl ₂	78
2	FeCl ₂ ·4H ₂ O	CH ₂ Cl ₂	N.D. ^c
3	FeCl ₃ ·6H ₂ O	CH ₂ Cl ₂	N.D. ^c
4	Fe(OAc) ₂	CH ₂ Cl ₂	N.D. ^c
5	FeCl ₂ ·4H ₂ O	CH ₂ Cl ₂	33 ^d
6	CuCl ₂	CH ₂ Cl ₂	24
7	CoCl ₂	CH ₂ Cl ₂	N.D. ^c
8	MnCl ₂	CH ₂ Cl ₂	N.D. ^c
9	[Fe(Pc)]	DCE	65
10	[Fe(Pc)]	MeCN	12
11	[Fe(Pc)]	PhMe	68
12	[Fe(Pc)]	DMF	N.D. ^c
13	[Fe(Pc)]	CH ₂ Cl ₂	21 ^e
14	[Fe(Pc)]	CH ₂ Cl ₂	40 ^f
15	—	CH ₂ Cl ₂	N.D. ^c

^a Conditions: **1a** (1.5 mmol), **2a** (0.5 mmol), T-Hydro (4.0 mmol), cat. (5.0 mol %), solvent (2.0 mL), 0 °C, 30 min, under N₂.

^b Reported yields were based on **2a** and determined by ¹H NMR using an internal standard.

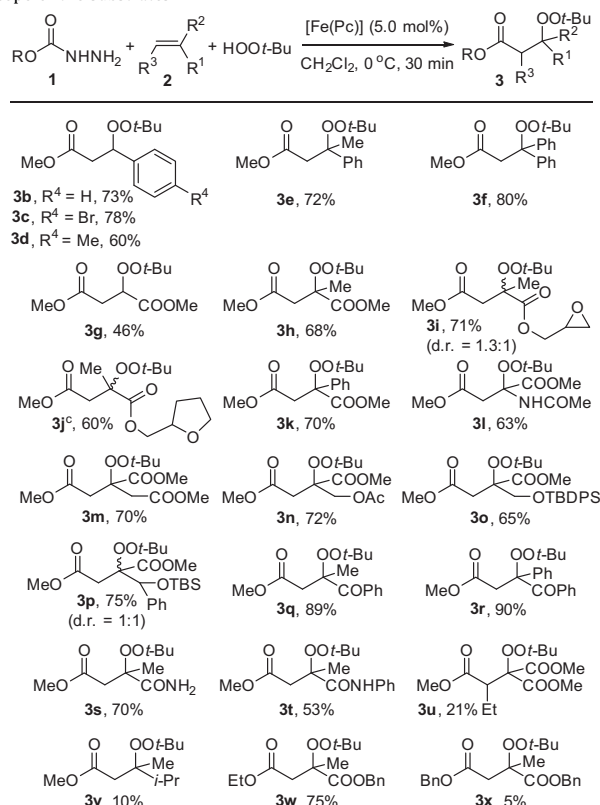
^c Not detected by ¹H NMR.

^d TBHP (4.0 mmol), 50 °C.

^e **1a** (0.5 mmol).

^f T-Hydro (2.0 mmol).

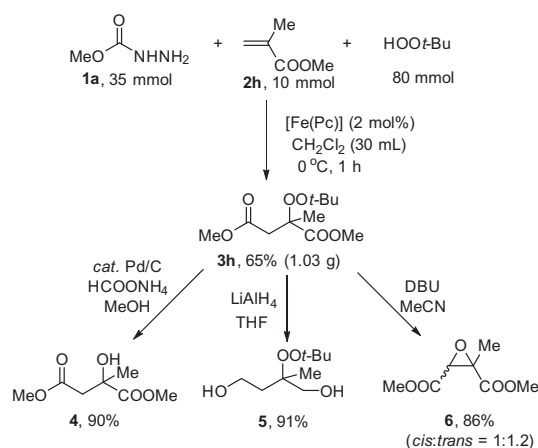
both styrenes and acrylates as alkene **2** reacted with methyl carbazate **1a** and T-Hydro smoothly to give the corresponding alkoxy-carbonylation–peroxidation products **3b–3p** in good isolated yields. Importantly, a variety of functional groups were quite compatible with this transformation. It is unfortunate that a 1:1 ratio of two diastereoisomers **3p** and 1.3:1 ratio of two diastereoisomers **3i** were obtained, indicating that the diastereoselectivity of the peroxidation step could not be controlled. Gratifyingly, α-methylene ketones provided the desired products **3q** and **3r** in excellent yields. Furthermore, methacrylamide and N-phenylmethacrylamide were compatible with the reaction conditions to be converted into the desired products **3s** and **3t** in good yields. However, tri-substituted acrylates and aliphatic alkenes led to the desired product **3u** and **3v** in much low yields. Although ethyl carbazate gave **3w** in 75% yield, benzyl carbazate was converted into product **3x** in only 5% yield owing to the decomposition of

Table 2
Scope of the substrates^{a,b}

^a Conditions: **1** (1.5 mmol), **2** (0.5 mmol), T-Hydro (4.0 mmol), [Fe(Pc)] (5.0 mol %), CH₂Cl₂ (2.0 mL), 0 °C, 30 min, under N₂.

^b Isolated yields.

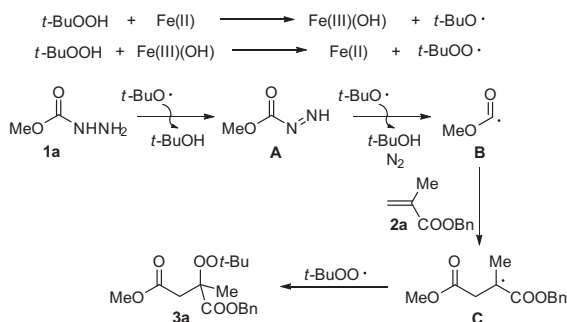
^c The NMR spectra of isomers **3j** were overlapped and the diastereoselectivity ratio of **3j** could not be determined.



Scheme 2. A large-scale synthesis and applications.

these carbazates.^{6,16} It should be noted that the synthesized β-ester peroxides are generally stable up to 100 °C (see Supporting information).

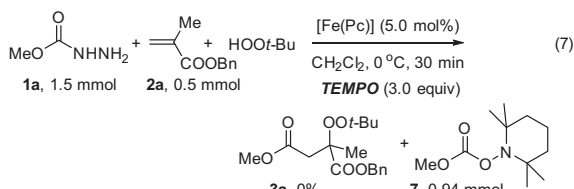
To demonstrate the protocol is practical and useful in organic synthesis, Gram-scale synthesis and applications were investigated (Scheme 2). A 10 mmol-scale of **2h** reacted with **1a** and T-Hydro in the presence of 2.0 mol % [Fe(Pc)] providing **3h** in 1.03 g (65% yield). The peroxy band of **3h** could be easily cleaved to



Scheme 3. A proposed mechanism.

generate the corresponding tertiary alcohol **4** by using ammonium formate as a hydrogen donor and palladium on carbon as catalyst. The reduction of **3h** gave dihydroxyl peroxide **5** efficiently by LiAlH_4 in THF. The epoxide product **6** was obtained smoothly in the presence of a catalytic amount of DBU.^{10b,17}

To probe the possible pathways of the present transformation, a radical trapping experiment was conducted. The desired product **3a** was not obtained by the reaction of **1a**, **2a**, and T-Hydro in the presence of TEMPO. Instead, the TEMPO-adduct product **7** from methyl carbazate **1a** was isolated (Eq. 7). This result provided an evidence for the formation of alkoxy-carbonyl radical in the present transformation.



A plausible mechanism for the alkoxy-carbonylation–peroxidation reaction of alkene is proposed (Scheme 3). Initially, the *tert*-butoxyl and *tert*-butylperoxyl radicals are generated via iron-catalyzed decomposition of T-Hydro. The oxidation of methyl carbazate **1a** by *tert*-butoxyl radical gives the diazene intermediate **A**, which is further decomposed to generate the methoxycarbonyl radical **B** with the release of N_2 .^{6,18} Subsequently, the addition of **B** to alkene **2a** leads to the radical intermediate **C**, which is coupled with *tert*-butylperoxyl radical to give the final product **3a**.

In conclusion, we have developed a novel and high yielding alkoxy-carbonylation–peroxidation of alkenes through iron catalysis. The reaction provides practical and selective access to β -ester peroxides in a single step starting from readily available starting materials. Further applications of β -ester peroxides for synthetic chemistry are in progress.

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Supplementary data

Supplementary data (experimental procedures, spectrum data, and NMR spectra of the compounds) associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.tetlet.2015.10.052>.

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