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Iron-Catalyzed Oxidative Addition of Alkoxycarbonyl Radicals to Alkenes with Carbazates and Air**

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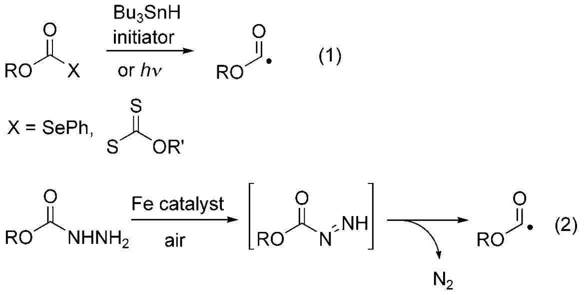
Carbonylation reactions are powerful tools for C−C bond formation in synthetic chemistry.[1] In this area, carbonyl radicals, such as acyl, alkoxycarbonyl, and carbamoyl radicals, are useful reactive intermediates because they enable the direct introduction of a carbonyl moiety, such as ketone, ester, or amide group, into organic compounds by addition to a multiple bond.[2] Many methods for the generation of acyl radicals and reactions of acyl radicals have been reported.[3] Reactions of carbamoyl radicals are relatively well-known,[4] but examples of reactions of alkoxycarbonyl radicals are limited.[5] In general, alkoxycarbonyl and carbamoyl radicals are generated from the corresponding selenides and xanthates by treatment with a combination of Bu_3SnH and an initiator and photoirradiation [Scheme 1, Eq. (1)].[4,5] However, these methods have the disadvantage that they require the use of toxic reagents and special equipment.

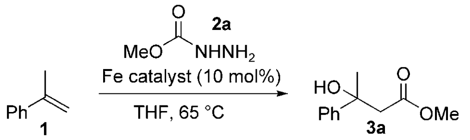


Scheme 1. Methods for the generation of alkoxycarbonyl radicals.

It is known that radical species are generated from hydrazine compounds through the formation of diazenes in the presence of oxidants, such as oxygen and transition metals.[6] A number of radical reactions based on the oxidation of hydrazines have been reported.[7] Herein, we report an iron-catalyzed intermolecular oxidative addition of alkoxycarbonyl radicals derived from carbazates to alkenes in air [Scheme 1, Eq. (2)]. Recently, iron has received attention as a low-toxic and inexpensive substitute for rare metals, such as palladium.[8] Many iron-catalyzed reactions, such as the oxidation of olefins or C−H bonds and carbon–carbon or carbon–heteroatom coupling reactions, have been developed.[9]

To determine the best reaction conditions, we chose α-methylstyrene (**1**) and methyl carbazate (**2a**) as model substrates. The treatment of a mixture of **1** and **2a** (2.2 equiv) with $FeCl_3$ (10 mol%) in THF at reflux in air gave β-hydroxyester **3a** in 36% yield (Table 1, entry 1).[10,11] A reaction with $Fe(NO_3)_3$ as the catalyst gave only a trace amount of **2a** (Table 1, entry 2). When iron phthalocyanine ([Fe(Pc)]; 10 mol%) was used in air, product **3a** was obtained in excellent yield (Table 1, entry 3). The use of a minimum amount of **2a** (1.2 equiv) led to significantly lower yield of **3a** (Table 1, entry 4), whereas no improvement in yield was observed with 3.0 equivalents of **2a** (Table 1, entry 5). The reaction time under a pure O_2 atmosphere instead of air was shorter, but the yield of **3a** was decreased (Table 1, entry 6). The use of half the amount of the catalyst slightly prolonged the reaction time, but the yield of **3a** was still good (Table 1, entry 7). In the absence of an iron catalyst, no reaction was observed (Table 1, entry 8).

Table 1: Optimization of the reaction conditions.



Entry	Catalyst	**2a** [equiv]	Atmosphere	*t* [h]	Yield [%][a]
1	$FeCl_3$	2.2	air	100	36
2	$Fe(NO_3)_3$	2.2	air	48	4
3	[Fe(Pc)]	2.2	air	44	82
4	[Fe(Pc)]	1.2	air	18.5	40
5	[Fe(Pc)]	3.0	air	43	84
6	[Fe(Pc)]	2.2	O_2	6	45
7[b]	[Fe(Pc)]	2.2	air	48	71
8	none	2.2	air	48	n.r.[c]

[a] Yield of the isolated product. [b] The reaction was carried out with 5 mol% of [Fe(Pc)]. [c] No reaction.

Next, we examined the reaction of α-methylstyrene (**1**) with various carbazates in the presence of the catalyst [Fe(Pc)] (Table 2). The reactions of various carbazates and **1** gave β-hydroxyesters **3a–e** in moderate and good yields (Table 2, entries 1–5). However, *tert*-butyl carbazate (**2f**) and benzyl carbazate (**2g**) were converted into products **3f** and **3g**

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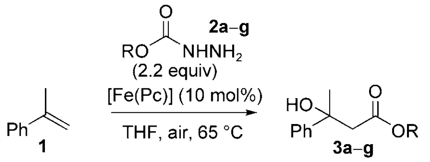
Table 2: Radical reactions of various carbazates.

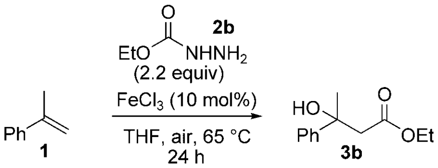


Entry	2	*t* [h]	Yield [%][a]
1	**a** (R = Me)	44	82
2	**b** (R = Et)	28	64
3	**c** (R = *i*Pr)	50	57
4	**d** (R = Ph)	100	47
5	**e** (R = CH_2CCl_3)	45	64
6	**f** (R = *t*Bu)	38	7
7	**g** (R = Bn)	33	3

[a] Yield of the isolated product.

in very low yields as a result of the decomposition of these carbazates (Table 2, entries 6 and 7).[12]

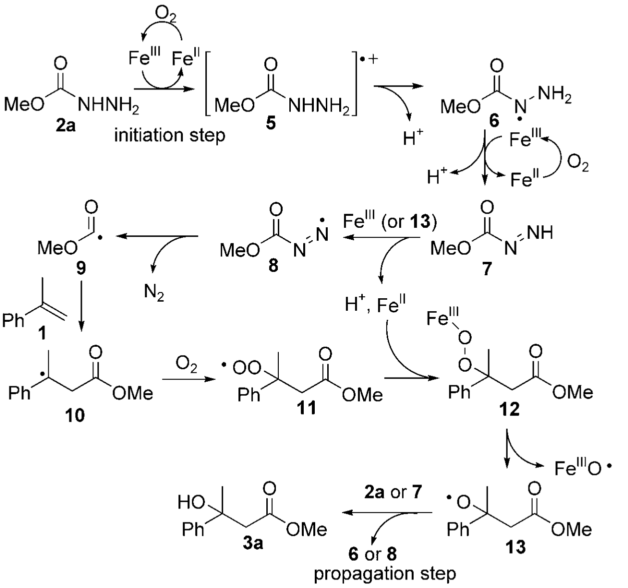
The $FeCl_3$-catalyzed reaction of ethyl carbazate (**2b**) proceeded readily to give β-hydroxyester **3b** in better yield than that observed for the equivalent reaction of methyl carbazate (**2a**; Scheme 2 and Table 1, entry 1). Recently, Buchwald and Bolm reported that a trace amount of copper as a contaminant of $FeCl_3$ plays the role of a catalyst in some iron-catalyzed reactions.[13] Therefore, we also examined the reaction with highly purified $FeCl_3$ (> 99.99 %). When **1** was treated with ethyl carbazate (**2b**) in the presence of $FeCl_3$ of greater than 99.99 % purity instead of the standard $FeCl_3$ reagent (> 97 %), no change in the yield of β-hydroxyester **3b** was observed (Scheme 2). This result clearly indicates that the present reaction is catalyzed by iron.



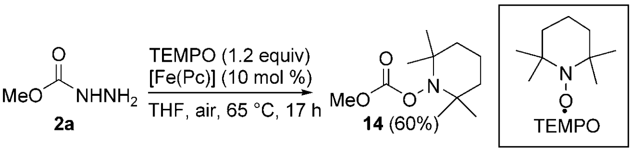
$FeCl_3$ purity	$FeCl_3$ commercial source	Yield of **3b**
>97%	Nacalai Tesque	59%
>99.99%	Aldrich	57%

Scheme 2. Reaction of ethyl carbazate (**2b**) and **1** in the presence of $FeCl_3$.

A plausible mechanism for the reaction is shown in Scheme 3. The reaction may be initiated by single-electron transfer between methyl carbazate (**2a**) and an Fe^{III} species generated in the presence of oxygen to give the cation radical **5**. Deprotonation of the cation radical **5** generates the radical intermediate **6**, and the subsequent process involving the single-electron oxidation of **6** by an Fe^{III} species and deprotonation gives diazene **7**. Diazene **7** undergoes oxidation by a similar pathway (or hydrogen abstraction by the alkoxy radical **13**) to give the radical intermediate **8**, from which the methoxycarbonyl radical **9** is formed with the release of molecular nitrogen.[6,14,15] The addition of radical **9** to alkene **1** and subsequent trapping of the resultant radical intermediate **10** by molecular oxygen then affords the peroxy radical **11**, which reacts with an Fe^{II} species to give the iron complex **12**. Finally, the O–O bond of **12** undergoes cleavage to generate the alkoxy radical **13**, followed by hydrogen abstraction from carbazate **2a** or diazene **7** to give β-hydroxyester **3a**;[16] intermediate **6** or **8** might be generated along with an Fe^{III} species in this step. When **2a** was treated with a stoichiometric amount of 2,2,6,6-tetramethyl-1-piperidine-1-oxyl (TEMPO) in the presence of [Fe(Pc)] and air, compound **14** was obtained in good yield (Scheme 4). This result supports the generation of methoxycarbonyl radical **9** in this reaction.[17]



Scheme 3. Plausible mechanism.



Scheme 4. Reaction of methyl carbazate (**2a**) and TEMPO.

Finally, we investigated the generality of this iron-catalyzed radical reaction of alkenes with methyl carbazate (**2a**; Table 3). 2-Aryl propenes **1a–d** bearing methoxy, nitro, and halogen substituents on the aromatic ring or a naphthyl group provided the corresponding β-hydroxyesters **4a–d** in good yields (Table 3, entries 1–4). The reaction of styrene (**1e**) gave β-hydroxyester **4e** together with an equal amount of the β-ketoester **4e′** produced by the oxidation of **4e** (Table 3, entry 5). Alkenes **1f–h**, with a similar electronic structure to that of styrene, were also converted into the corresponding β-hydroxyesters **4f–h** (Table 3, entries 6–8). The reaction of enyne **1i** proceeded smoothly to give β-

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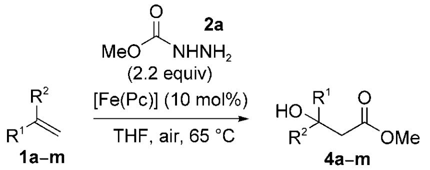
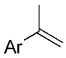
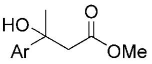
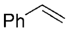
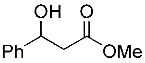
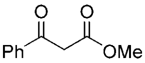
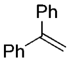
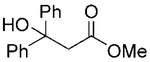
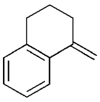
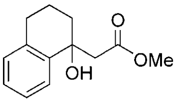
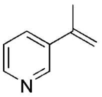
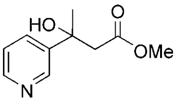
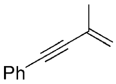
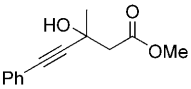
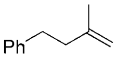
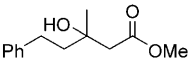
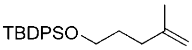
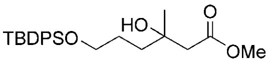
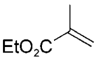
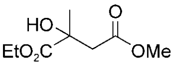
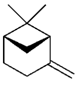
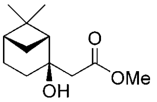
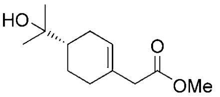
Table 3: Radical reactions of various alkenes.



Entry	1		t [h]	4	Yield [%][a]
					
1	Ar = 4-MeOC$_6$H$_4$	a	22		67
2	Ar = 4-NO$_2$C$_6$H$_4$	b	28		61
3	Ar = 4-BrC$_6$H$_4$	c	25		81
4	Ar = β-C$_{10}$H$_7$	d	24		72
5		e	35		42
					37
6		f	24		62
7		g	24		71
8		h	33		72
9		i	27		73
10[b]		j	47		57
11[b]		k	46		38
12		l	26		73
13[b]		m	47		21
					24

[a] Yield of the isolated product. [b] The reaction was carried out with 5 equivalents of **2a**. TBDPS = *tert*-butyldiphenylsilyl.

hydroxyester **4i** in good yield (Table 3, entry 9). Although lower reactivity was observed for the nonconjugated alkenes **1j** and **1k**, the use of an increased amount of **2a** led to the formation of the corresponding β-hydroxyesters **4j** and **4k** in moderate yields (Table 3, entries 10 and 11). Ethyl methacrylate (**1l**) readily underwent radical addition to give the succinate derivative **4l** (Table 3, entry 12). Notably, no Michael addition of methyl carbazate (**2a**) to alkene **1l** was observed. When β-pinene (**1m**) was used as a substrate, cleavage of the cyclobutane following the addition of the alkoxycarbonyl radical gave ester **4m′** along with β-hydroxyester **4m** (Table 1, entry 13).

In summary, we have developed a method for the formation of alkoxycarbonyl radicals from carbazates with iron catalysts and air. The present iron-catalyzed reaction of alkoxycarbonyl radicals has several advantages: 1) many carbazate precursors of alkoxycarbonyl radicals are stable solids and are readily available; 2) the reaction is environmentally friendly, since the iron catalyst has low toxicity and is inexpensive, molecular oxygen is used as an oxidant, and the group eliminated from the radical precursors is molecular nitrogen; and 3) the experimental procedure is very simple and safe. Further studies directed toward the application of iron-catalyzed radical reactions to various substrates are currently under way in our laboratory.

Experimental Section

General procedure: A mixture of the alkene (0.5 mmol), methyl carbazate (99.1 mg, 1.1 mmol), and [Fe(Pc)] (28.4 mg, 0.05 mmol) in THF (2.5 mL) was heated at 65 °C in air. After removal of the solvent under reduced pressure, the residue was purified by silica-gel chromatography (hexane/EtOAc). **Caution**: The corresponding peroxide is known to be generated from THF in the presence of oxygen. Although we have never detected peroxides in this reaction, appropriate caution should always be paid when the reaction is carried out a large scale.

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Keywords: carbazates · iron catalysis · oxygenation · radical reactions · synthetic methods

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