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N-Hydroxyphthalimide-catalyzed radical addition of 1,3-dioxolanes and molecular oxygen to alkenes under ambient conditions: a new route to β-oxycarbonyl compounds

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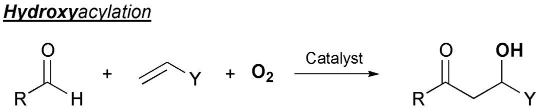
A novel catalytic hydroxyacylation of alkenes using 1,3-dioxolanes and molecular oxygen has been developed, and the reaction of 2-methyl-1,3-dioxolane with methyl acrylate under dioxygen atmosphere in the presence of catalytic amounts of NHPI and Co(OAc)$_2$ produced the corresponding adduct in 81% yield.

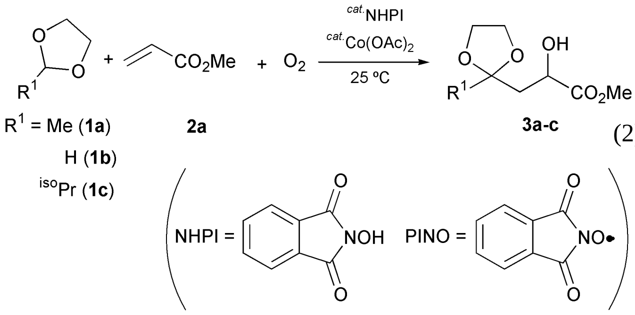
Addition of aldehydes to terminal alkenes has received attention as a method for the synthesis of ketones from aldehydes.[1] The frequently used methodologies are the direct hydroacylation of alkenes with aldehydes by transition-metal catalysts[1] and the addition of acyl radicals to alkenes bearing electron-withdrawing substituents such as fumarate by radical initiators.[2] If the concomitant introduction of acyl and hydroxy moieties to alkenes can be carried out by a cascade reaction, this type of reaction is referred to as *hydroxyacylation* and would provide a novel route to β-oxycarbonyl compounds which constitute important structural subunits in key intermediates leading to pharmaceuticals [eqn. (1)].[3] Although there is one report on the hydroxyacylation of alkenes like acrylates with acyl radicals from aldehydes using dioxygen as a hydroxy source assisted by a cobalt(II) Schiff-base complex,[4] the attempt was not fully successful due to the decarbonylation from acyl radicals as well as the reaction of acyl radicals with O$_2$ leading to carboxylic acids which cause undesired side reactions.



(1)

To overcome these drawbacks arising from acyl radicals, we employed 1,3-dioxolanes, masked aldehydes, as an acyl source in place of an aldehyde.[5] This paper describes the development of a novel catalytic method leading to β-hydroxy carbonyl compounds after deprotection under acidic conditions.

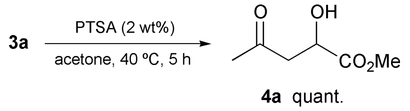
Recently, we have shown that *N*-hydroxyphthalimide (NHPI) combined with a Co(II) species serves as a catalyst for the generation of alkyl radicals from alkanes even under ambient conditions, and that the resulting alkyl radicals are readily captured by O$_2$ to give oxygenated products.[6] In this catalytic system, phthalimide *N*-oxyl (PINO) is the active species abstracting hydrogen atoms from the alkanes.[6a] This finding prompted us to study the generation of α,α-dioxaalkyl radicals from 1,3-dioxolanes and their addition to alkenes using the NHPI/Co(II)–O$_2$ catalytic system [eqn. (2)].



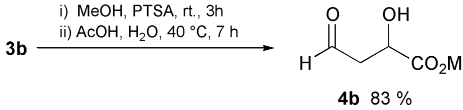
(2)

At the beginning, a mixture of 2-methyl-1,3-dioxolane (**1a**) (15 mmol) and methyl acrylate (**2a**) (3 mmol) was allowed to react under O$_2$ (1 atm) in the presence of NHPI (5 mol%) and a small amount of Co(OAc)$_2$ (0.05 mol%) at rt for 3 h (Table 1, Run 1).† The apparent hydroxyacylation based on the concomitant introduction of a dioxaalkyl radical and a hydroxy group to **2a** was achieved to form β-hydroxy ketal (**3a**) in 81% yield. In a previous paper, we showed that a Co(III)–dioxygen complex derived from the Co(II) species and O$_2$ assists the formation of a PINO radical from the NHPI.[6a] Accordingly, the Co(III) which fails to react with O$_2$ could not promote the reaction under O$_2$ at rt (Run 2).[6a,7]

From 1,3-dioxolane (**1b**), the corresponding adduct **3b** was obtained in high yield (82%) (Run 4). The introduction of the masked formyl group to **2a** is promising, since the direct use of formaldehyde is restricted due to its intractability. These dioxolane moieties could be easily deprotected upon treatment under acidic conditions to form the corresponding carbonyl compounds [eqns. (3) and (4)].



(3)



(4)

The reaction of **1a** or **1b** with various alkenes was run under selected reaction conditions (Table 2). Acrylonitrile (**2e**) was found to serve as a good acceptor of **1a** and **1b** in a similar manner as **2a**, giving cyanohydrin derivatives in good yields. However, methyl crotonate (**2c**) bearing a β-methyl group retarded the hydroxyacylation, probably owing to the steric hindrance towards attack by an α,α-dioxaalkyl radical on **2c**.[8] To our surprise, methyl vinyl ketone (**5a**) reacted with **1a** to afford a cleaved product, 3-(1,3-dioxolan-2-yl)butanoic acid (**6**) in 83% yield along with 3-(1,3-dioxolan-2-yl)butylaldehyde (**7**)

Table 1 Reaction of **1a–c** with methyl acrylate (**2a**)[a]

Run	1a–c	NHPI/ mol%	Co(II)/ mol%	*t*/h	Yield (%)[b]
1	**1a**	5	0.05	3	81
2[c]	**1a**	5	0.05	3	n.d.
3	**1a**	—	0.05	3	1
4[d]	**1b**	10	0.1	2	82
5	**1c**	5	0.1	14	76

[a] **2a** (3 mmol) was allowed to react with **1a–c** (15 mmol) in the presence of NHPI and Co(OAc)$_2$ under atmospheric oxygen at rt. [b] GC yield. [c] Co(acac)$_3$ was used. [d] **1b** (30 mmol) was used.

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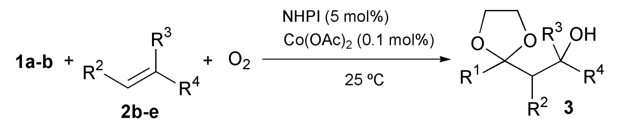
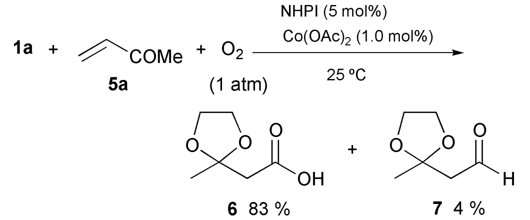
Table 2 Reaction of **1a**–**b** with various alkenes under ambient conditions[a]



		2b–**e**					
Run	**1a**–**b**	R^2	R^3	R^4		*t*/h	**3** (%)[b]
1	**1a**	H	Me	CO_2Me	**2b**	15	84
2[c]	**1a**	Me	H	CO_2Me	**2c**	15	16
3[d]	**1a**	CO_2Et	H	CO_2Et	**2d**	2	77
4	**1a**	H	H	CN	**2e**	16	77[e]
5	**1b**	H	Me	CO_2Me	**2d**	15	60
6	**1b**	H	H	CN	**2e**	16	60[e]

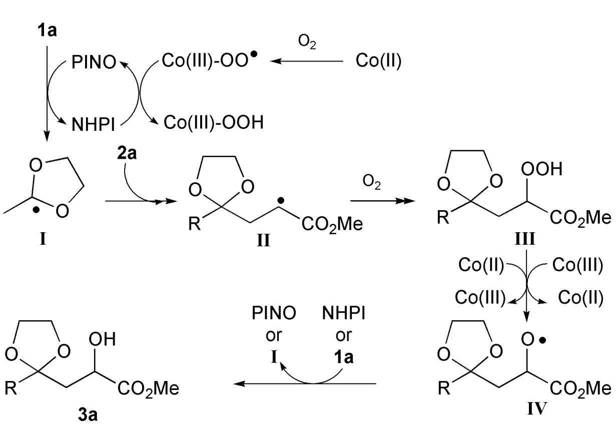
[a] **2b**–**e** (3 mmol) were allowed to react with **1a**–**b** (15 mmol) in the presence of NHPI (5 mol%) and $Co(OAc)_2$ (0.1 mol%) under atmospheric oxygen at rt. [b] GC yield. [c] NHPI (10 mol%) was used. [d] $Co(OAc)_2$ (0.05 mol%) was used. [e] Isolated yield.

(4%) [eqn. (5)]. The carboxylic acid **6** is considered to be formed *via* the further oxidation of aldehyde **7**.[9]

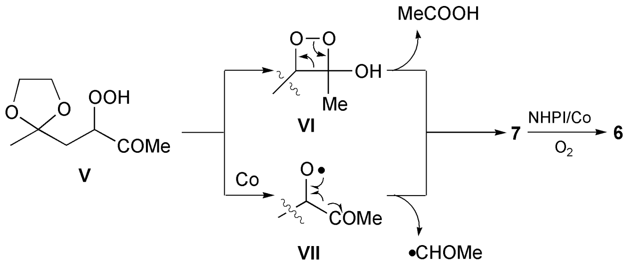


(5)

A plausible reaction path for the apparent hydroxyacylation of **2a** with **1a** under dioxygen is shown in Scheme 1. The reaction may be initiated by the hydrogen atom abstraction from NHPI by the action of the Co(III)–dioxygen complex, giving PINO which then abstracts the dioxolane hydrogen of the **1a** to form an dioxolane radical **I**. The **I** radical having a highly nucleophilic character seems to readily add to **2a**, yielding a radical species **II**. Under the conditions in which O_2 is present in the reaction system, the resulting radical **II** is rapidly trapped by O_2 to give a hydroperoxide **III**. It is well-known that hydroperoxides like **III** are subjected to redox decomposition by Co ions to form an alkoxyl radical **IV** which is eventually converted into **3a** through the hydrogen abstraction from either NHPI or **1a**.[10]



Scheme 1 Proposed reaction path for the radical addition of **1a** to **2a** under dioxygen in the presence of NHPI and $Co(OAc)_2$.



Scheme 2

Although it seems rather hazardous to make an accurate assessment about the reaction path for the formation of **6** from **1a** and methyl vinyl ketone **5a**, we can make two proposals which seem to agree with the experimental results. It is probable that an α-hydroperoxyketone **V** derived from **1a** and **5a** might decompose into aldehyde **7** *via* formation of a hydroxydioxetane **VI** (Scheme 2). This type of reaction through the hydroxydioxetane is shown in the autoxidation of ketones like diisopropyl ketone.[11] However, an alternative proposal is also possible, *viz.* the hydroperoxide **V** is subject to the redox decomposition to generate an alkoxy radical intermediate **VII** which then is converted into **7** *via* β-scission.

In conclusion, we have developed a novel method for the introduction of both a masked acyl or formyl group and a hydroxy or keto function to a double bond of alkenes. Further work on the extension of this method is actively underway.

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Notes and references

† *A typical procedure for reaction of 2-methyl-1,3-dioxolane **1a** with methyl acrylate **2a***: To a solution of **1a** (15 mmol), NHPI (0.15 mmol) and $Co(OAc)_2$ (0.0015 mmol) in a two-necked flask, equipped with a balloon filled with O_2 (1 atm), was added **2a** (3 mmol). The mixture was vigorously stirred at rt for 3 h. The recovery of unreacted **1a** under a reduced pressure followed by flash chromatography on silica gel (*n*-hexane–AcOEt = 1 : 2) afforded methyl 2-hydroxy-4-(1,3-dioxolan-2-yl)valerate (**3a**) (462 mg, 81% yield) as a colorless liquid.

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