

# Catalytic $\alpha$ -hydroxy carbon radical generation and addition. Synthesis of $\alpha$ -hydroxy- $\gamma$ -lactones from alcohols, $\alpha,\beta$ -unsaturated esters and dioxygen

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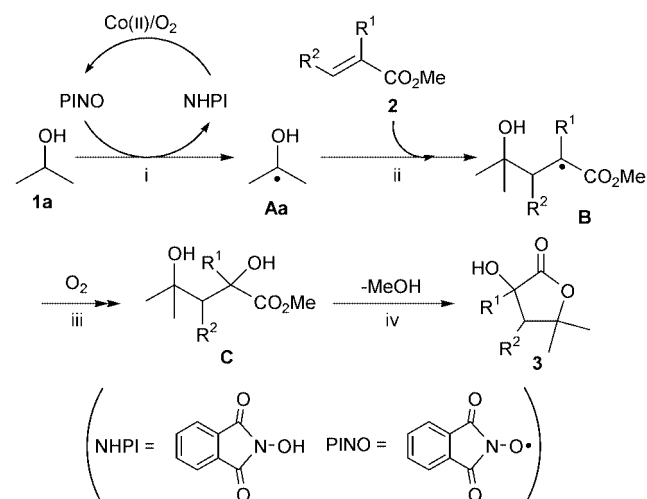
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**A catalytic method for  $\alpha$ -hydroxy carbon radical generation from alcohols has been developed and a convenient and synthetically useful approach to  $\alpha$ -hydroxy- $\gamma$ -lactones constructed.**

Free radical reactions have attracted much attention in the synthesis of organic compounds because of their many advantages over ionic reactions, and therefore a variety of methodologies have been developed for the generation of carbon radicals.<sup>1</sup> To our knowledge, however, a limited number of methods, *e.g.* peroxide-<sup>1,2</sup> and photo-<sup>1,3</sup> initiated techniques and redox systems using metal ions,<sup>1,4</sup> have been used for the generation of carbon radicals from alcohols. Therefore, we believe that the catalytic carbon radical formation from alcohols and its use in organic synthesis are of interest and very useful as a synthetic tool. However, such a method has, as yet, not been realized.

Recently, we have shown that phthalimide *N*-oxyl (PINO), generated from *N*-hydroxyphthalimide (NHPI) and dioxygen, can abstract the hydrogen atom from alkanes to form alkyl radicals which are readily captured by O<sub>2</sub> to give oxygenated compounds such as alcohols, ketones and carboxylic acids.<sup>5</sup> As an application of this procedure, we report here, the first successful catalytic  $\alpha$ -hydroxy carbon radical generation from alcohols using NHPI combined with cobalt species as the catalyst under O<sub>2</sub> (1 atm) and trapping the resulting  $\alpha$ -hydroxy radicals by  $\alpha,\beta$ -unsaturated esters leading to  $\alpha$ -hydroxy- $\gamma$ -lactones which are very difficult to obtain by conventional methods. Such lactones are very attractive as valuable synthetic precursors for species such as  $\alpha,\beta$ -butenolides which have potent biological activity<sup>6</sup> as well as fine chemicals which are expected to be widely used in chemical industry.<sup>7</sup>

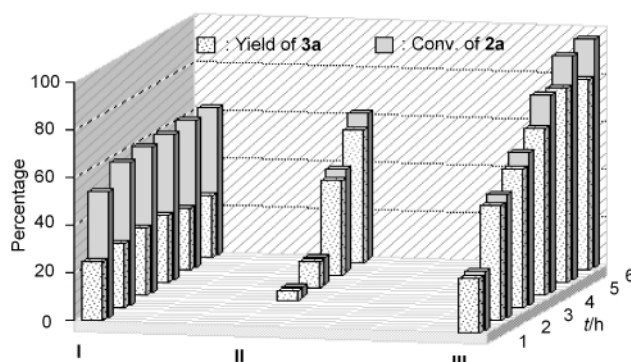
An outline of our approach is shown in Scheme 1: (i) *in situ* generation of an  $\alpha$ -hydroxy carbon radical **Aa** from an alcohol assisted by NHPI/Co(II) under O<sub>2</sub>; (ii) the addition of the radical **Aa** to an  $\alpha,\beta$ -unsaturated ester; (iii) trapping of the radical **B** by



Scheme 1

O<sub>2</sub>; (iv) the intramolecular cyclization of the resulting 1,3-diol **C** to yield  $\alpha$ -hydroxy- $\gamma$ -lactone **3**.

Initially, the generation of an  $\alpha$ -hydroxy carbon radical from isopropyl alcohol **1a** and the trapping of this radical by methyl acrylate **2a** were examined by the use of three different combined catalytic systems: NHPI/Co(OAc)<sub>2</sub> **I**, NHPI/Co(acac)<sub>3</sub> **II** and NHPI/Co(OAc)<sub>2</sub>/Co(acac)<sub>3</sub> **III** under O<sub>2</sub> (1 atm) at 60 °C, leading to  $\alpha$ -hydroxy- $\gamma,\gamma$ -dimethyl- $\gamma$ -butyrolactone **3a** in 27–78% yields (Fig. 1).<sup>†</sup> Inspection of Fig. 1 indicates that the reaction *via* catalyst **I** is terminated at an early stage and that catalyst **II** gives a higher yield of **3a**, although an induction period of 3 h was observed. The Co(III) ion is well known to be gradually reduced to Co(II) by organic substrates *via* a one-electron transfer process.<sup>8</sup> Therefore, it is thought that the induction period observed in the catalytic system **II** would correspond to the time required for the generation of Co(II) during the reaction. In order to shorten the induction period, we carried out the above reaction by adding a small amount of Co(II) ion [as Co(OAc)<sub>2</sub>] to the NHPI/Co(III) system. As expected, a reduction of the induction period of the reaction was observed, and the best yield of **3a** (78%) was obtained by the use of the catalytic system **III**. On the basis of these results, a variety of alkenes were treated with **1a** under O<sub>2</sub> using the NHPI/Co(OAc)<sub>2</sub>/Co(acac)<sub>3</sub> system (Table 1).



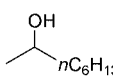
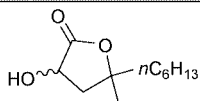
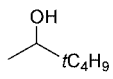
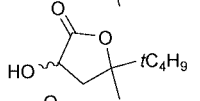
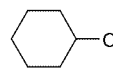
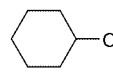
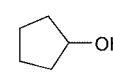
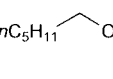
**Fig. 1** Time dependence for the reaction of isopropyl alcohol **1a** with methyl acrylate **2a** to give **3a** under O<sub>2</sub> (1 atm) using NHPI/Co(OAc)<sub>2</sub> **I**, NHPI/Co(acac)<sub>3</sub> **II** and NHPI/Co(OAc)<sub>2</sub>/Co(acac)<sub>3</sub> **III**. **2a** (3 mmol) was reacted with **1a** (10 equiv.) in the presence of NHPI (10 mol%) under O<sub>2</sub> (1 atm), 60 °C in MeCN (0.5 mL). **I**: Co(OAc)<sub>2</sub> (1 mol%), **II**: Co(acac)<sub>3</sub> (1 mol%), **III**: Co(OAc)<sub>2</sub> (0.1 mol%) and Co(acac)<sub>3</sub> (1 mol%).

**Table 1** Reaction of various alkenes CHR<sup>2</sup>=CR<sup>1</sup>CO<sub>2</sub>Me with **1a**<sup>a</sup>

Run	R <sup>1</sup>	R <sup>2</sup>	Alkene	T/°C	Yield of <b>3b-d</b> (%) <sup>b</sup>
1	Me	H	<b>2b</b>	70	71 ( <b>3b</b> )
2	H	Me	<b>2c</b>	70	14 (74/26) <sup>c</sup> ( <b>3c</b> )
3 <sup>d,e</sup>	H	CO <sub>2</sub> Me	<b>2d</b>	25	90 (76/24) <sup>c</sup> ( <b>3d</b> )
4 <sup>d</sup>	H	CO <sub>2</sub> Me	<b>2e</b>	25	86 (75/25) <sup>c</sup> ( <b>3d</b> )

<sup>a</sup> **2** (3 mmol) was reacted with **1a** (10 equiv.) under O<sub>2</sub> (1 atm) in the presence of NHPI (10 mol%), Co(OAc)<sub>2</sub> (0.1 mol%) and Co(acac)<sub>3</sub> (1 mol%) in MeCN (0.5 mL) for 8 h. <sup>b</sup> Isolated yield. <sup>c</sup> *trans/cis* ratio. <sup>d</sup> Reaction was carried out in the presence of Co(OAc)<sub>2</sub> (1 mol%) without Co(acac)<sub>3</sub>. <sup>e</sup> 24 h. Air used. <sup>f</sup> Maleate.

**Table 2** Reaction of **2a** with various alcohols

Run <sup>a</sup>	Alcohol	t/h	Product <sup>b</sup> (%)
1		5	 <b>3f</b> (74)[52/48] <sup>c</sup>
2		8	 <b>3g</b> (71)[60/40] <sup>c</sup>
3		3	<b>3h</b> (83)
4 <sup>d</sup>		5	<b>3h</b> (76)
5		8	<b>3i</b> (80)
6		5	<b>3j</b> (41)[56/44] <sup>c</sup>

<sup>a</sup> **2a** (3 mmol) was reacted with **1** (5 equiv.) in the presence of NHPI (10 mol%), Co(OAc)<sub>2</sub> (0.1 mol%) and Co(acac)<sub>3</sub> (1 mol%) under O<sub>2</sub> (1 atm) in MeCN (0.5 mL). <sup>b</sup> Isolated yield. <sup>c</sup> *trans/cis* ratio by GLC. <sup>d</sup> **1d** (3 equiv.) used.

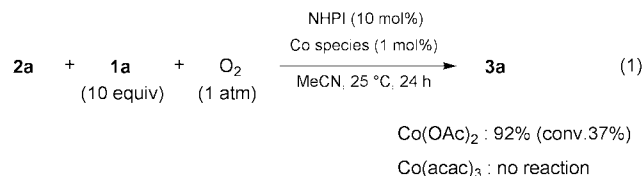
From  $\alpha$ - and  $\beta$ -methyl substituted acrylates, methacrylate **2b** and crotonate **2c**, the corresponding  $\alpha$ -hydroxy- $\gamma$ -lactones, **3b** and **3c**, were obtained in 71 and 14% yields, respectively. The lower reactivity of **2c** may be due to the  $\beta$ -CH<sub>3</sub> group which exerts steric hindrance towards the attacking radical **Aa**.<sup>9</sup> Reactions with methyl maleate **2d** and methyl fumarate **2e** proceeded smoothly even at 25 °C to afford  $\alpha$ -hydroxy- $\beta$ -carbomethoxy- $\gamma$ -lactone **3d** in excellent yields, respectively. It is known that the incorporation of an electron-withdrawing substituent into the alkene decreases the SOMO–LUMO energy difference, and thus increases the rate of addition of alkyl radicals which possess nucleophilic reactivity.<sup>9</sup>

This new method for the construction of  $\alpha$ -hydroxy- $\gamma$ -lactones was quite general for a variety of alcohols (Table 2).<sup>‡</sup> From cyclic alcohols,  $\alpha$ -hydroxy- $\gamma$ -spirolactones, which so far have been very difficult to synthesize, were obtained in high yields. Like secondary alcohols, the primary alcohol, hexa-1-nol **1j**, was found to generate the 1-hydroxyhexyl radical which then adds to **2a**, giving the corresponding  $\gamma$ -lactone **3j** (41%).

From viewpoints of low cost material, reaction efficiency and reaction simplicity, the present reaction is an innovative approach for the synthesis of  $\alpha$ -hydroxy- $\gamma$ -lactones which have considerable industrial potential.<sup>10</sup>

To gain further insight into the role of the cobalt species in the present reaction, the reaction of **1a** with **2a** by the NHPI/Co(II) system at room temperature was compared with that by the NHPI/Co(III) system [eqn. (1)]. The reaction *via* the NHPI/Co(II) system occurred at room temperature to give **3a** in excellent selectivity (92%) at 37% conversion, while the same reaction with the NHPI/Co(III) system was not observed even after 24 h. These results indicate that the presence of Co(II) is

important to initiate the reaction. In a previous paper, we reported that a Co(III)–dioxygen complex derived from Co(II) species and O<sub>2</sub> accelerates the generation of PINO from NHPI.<sup>5</sup> Efforts to expand this method and to elucidate the reaction mechanisms are currently in progress.



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## Notes and references

<sup>†</sup> *Typical procedure* for the synthesis of  $\alpha$ -hydroxy- $\gamma$ -lactones **3a**: to a solution of alcohol **1a** (30 mmol), NHPI (0.3 mmol), Co(OAc)<sub>2</sub> (0.003 mmol) and Co(acac)<sub>3</sub> (0.03 mmol) in acetonitrile (0.5 mL) in a two-necked flask equipped with a balloon filled with O<sub>2</sub> (1 atm) was added **2a** (3 mmol). After the mixture was vigorously stirred at 60 °C for 5 h, rotary evaporation of the solvent and unreacted alcohol followed by flash chromatography on silica gel afforded dihydro-3-hydroxy-5,5-dimethyl-2(3H)-furanone **3a** (78% yield).

<sup>‡</sup> The present reaction resulted in concomitant formation of oxidation products, ketones or aldehydes, of the alcohols in the range of 0.6 to 1.2-fold of the resulting lactones.

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