

Catalytic radical addition of ketones to alkenes by a metal–dioxygen redox system

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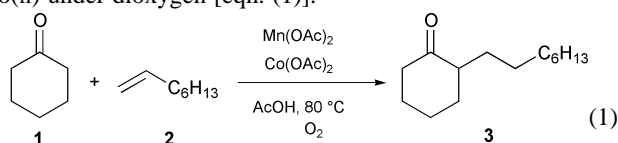
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Radical addition of ketones to alkenes catalyzed by $\text{Mn}(\text{OAc})_2$ combined with $\text{Co}(\text{OAc})_2$ using dioxygen as oxidant was developed; for instance, the reaction of cyclohexanone with oct-1-ene in the presence of very small amounts of $\text{Mn}(\text{OAc})_2$ and $\text{Co}(\text{OAc})_2$ under air (1 atm) gave 2-octylcyclohexanone in good selectivity; from styrene, a six-membered cyclic peroxide was isolated in good yield.

Free radical reactions in organic synthesis have been recognized as a powerful tool for the construction of C–C and C–X (X = H or heteroatoms) bonds.¹ However, a limited number of methods have appeared for the generation of α -keto carbon radicals in spite of their synthetic importance.^{1,2} Among the methods developed for this purpose, peroxide- and metal-initiated reactions of ketones are often used.^{2a–d} Thus, the addition of α -keto radicals to alkenes which leads to α -alkylated ketones is practiced by the use of high oxidation state metal ions such as $\text{Mn}(\text{III})$, $\text{Ce}(\text{IV})$, $\text{Ag}(\text{II})$ and $\text{Pb}(\text{IV})$.^{2c,d} Unfortunately, most reported procedures call for a large quantity of the metal reagent. To the best of our knowledge, there is only one report on the catalytic addition of α -keto radicals to alkenes via a catalytic process using AgNO_3 and $\text{Na}_2\text{S}_2\text{O}_3$ as the reoxidant.³ If the addition of ketones to alkenes can be achieved by using a catalytic amount of metal ions in combination with an appropriate oxidizing agent, the reaction would become an effective tool for the synthesis of α -alkylated ketones. From environmental and economic aspects, molecular oxygen is the best candidate as the oxidant to regenerate the reduced metal ions to a high oxidation state, but such a catalytic system has not yet been developed. Here we wish to report a novel catalytic radical addition of ketones to alkenes by $\text{Mn}(\text{II})$ combined with $\text{Co}(\text{II})$ under dioxygen [eqn. (1)].



To highlight the possibility of using dioxygen as reoxidant, the addition of cyclohexanone (**1**) to oct-1-ene (**2**) was carried out in the presence of a catalytic amount of $\text{Mn}(\text{OAc})_3$ (0.5 mol%) having one-electron oxidizing ability under either an inert gas (N_2) or air (1 atm) in AcOH at 80°C for 5 h (Table 1, runs 1 and 2).[†] The reaction under N_2 led to an adduct, 2-octylcyclohexanone (**3**), in low yield (4%), while the reaction under air afforded **3** in better yield (26%). This fact indicates that the reduced $\text{Mn}(\text{II})$ species can be continually reoxidized to $\text{Mn}(\text{III})$ by O_2 making use of $\text{Mn}(\text{OAc})_2$, which is cheaper than $\text{Mn}(\text{OAc})_3$, more viable for reactions under O_2 instead of $\text{Mn}(\text{OAc})_3$. In fact, $\text{Mn}(\text{OAc})_2$ in the presence of O_2 promoted the reaction to a similar extent as $\text{Mn}(\text{OAc})_3$ did (run 3). Needless to say, the reaction did not take place at all by $\text{Mn}(\text{OAc})_2$ under N_2 (run 4).

The present reaction was found to be facilitated by adding a small amount of $\text{Co}(\text{OAc})_2$ (0.1 mol%) to $\text{Mn}(\text{OAc})_2$ (0.5 mol%) to give **3** in 88% selectivity at 41% conversion (run 6), while the reaction was not induced by $\text{Co}(\text{II})$ alone (run 7).[‡] The addition proceeded smoothly even with a very small amount of

Table 1 Reaction of cyclohexanone (**1**) to oct-1-ene (**2**) by $\text{Mn}(\text{OAc})_2$ combined with $\text{Co}(\text{OAc})_2$ under various conditions^a

Run	mol%		Oxygen source (N_2 – O_2 atm)	Time/h	Conv. (%) ^b	Select. (%) ^c
	Mn	Co				
1 ^d	0.5	—	N_2	5	< 10	4 ^e
2 ^d	0.5	—	Air	5	35	26 ^e
3	0.5	—	Air	5	32	69
4	0.5	—	N_2	5	No reaction	
5 ^d	0.5	0.1	N_2	5	< 8	5 ^e
6	0.5	0.1	Air	5	41	88
7	—	0.5	Air	5	< 2	Trace
8	0.5	0.1	Air	10	57	83
9 ^f	0.5	0.1	Air	10	57	85
10 ^g	0.01	0.005	Air	10	30	72
11	0.5	0.1	0.9:0.1	10	11	80
12	0.5	0.1	0.5:0.5	10	72	83
13	0.5	—	0.5:0.5	10	49	72
14	0.5	0.1	0.3:0.7	10	69	81
15	0.5	0.1	O_2	10	87	62
16	0.1	0.05	0.5:0.5	10	70	85

^a **2** (2 mmol) was allowed to react with **1** (20 mmol) under dioxygen in the presence of $\text{Mn}(\text{OAc})_2$ and $\text{Co}(\text{OAc})_2$ in AcOH (2 mL) at 80°C .

^b Conversion of **2**. ^c Based on **2** reacted. ^d $\text{Mn}(\text{OAc})_3$ was used instead of $\text{Mn}(\text{OAc})_2$. ^e Yield based on **2** used. ^f AcOH (0.5 mL) was used. ^g **1** (5 eq.) was used.

$\text{Mn}(\text{OAc})_2$ and $\text{Co}(\text{OAc})_2$ (run 10). Since $\text{Co}(\text{II})$ ions are well-known to react easily with O_2 to form a $\text{Co}(\text{III})$ –dioxygen complex such as a superoxocobalt(III) or peroxocobalt(III) complex,⁴ it is thought that such a $\text{Co}(\text{III})$ species catalyzes the reoxidation of the reduced $\text{Mn}(\text{II})$ to $\text{Mn}(\text{III})$ under O_2 .

The remarkable effect of oxygen concentration on the reaction of **1** with **2** was observed (runs 11–16). When a mixed gas of 0.5:0.5 atm of N_2 – O_2 was employed, **3** was obtained in 83% selectivity at 72% conversion (run 12).

On the basis of these results, the addition of various ketones to alkenes was examined under the optimized reaction conditions (Table 2).

Both cyclic and aliphatic ketones were added to **2** to give the corresponding adducts in fair to good yields (runs 1–4). The reaction of an unsymmetrical ketone such as pentan-2-one (**4**) with **2** led to two structural isomers, 3-ethylundecan-2-one (**5**) and tridecan-4-one (**6**), in a ratio of ca. 6:1. The preferential formation of **5** is believed to be due to the fact that the secondary carbon radical is more easily generated than the primary one.

From isopropenyl acetate, γ -acetoxy ketone was obtained in relatively good selectivity (run 5). The reaction of **1** with styrene (**7**) did not form the expected adduct but gave a cyclic peroxide (**8**) in 41% yield (run 6). Such six-membered cyclic peroxides are known to exhibit significant biological activities.⁵ The peroxide **8** may be formed through the reaction path shown in Scheme 1. A benzyl radical (**B**) derived from the addition of an α -keto radical (**A**) to **7** reacts with O_2 rather than **1**, giving an alkylperoxy radical (**C**) which then undergoes intramolecular cyclization leading to **8**.⁶ It is believed that the benzyl radical **B** which is stabilized by conjugation with the phenyl group is

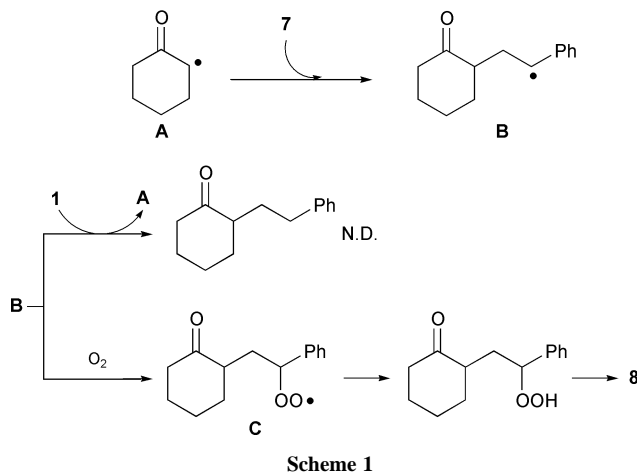
Table 2 Reaction of various ketones with alkenes^a

Run	Ketone	Alkene	Conv. (%) ^b	Products	Select. (%) ^c
1		2	78		85
2 ^d		2	68		82
3		2	73		62
4		2	78		71
				5 + 6	(6 : 1) ^e
5	1		86		61
6 ^{d,f}	1	7	92		41 ^g
7 ^{d,h}	1	7	96	8	70 ⁱ

^a Alkenes (2 mmol) were allowed to react with ketones (20 mmol) under 0.5:0.5 atm of N₂-O₂ in the presence of Mn(OAc)₂ (0.5 mol%) and Co(OAc)₂ (0.1 mol%) in AcOH (2 mL) at 80 °C for 10 h. ^b Conversion of alkenes. ^c Based on alkenes reacted. ^d Ketone (10 mmol) was used. ^e Ratio of **5**:**6**. ^f Reaction was carried out at 70 °C for 3 h. ^g ¹H-NMR yield based on **7** used. ^h Reaction was carried out in the absence of Co(OAc)₂ under O₂ (1 atm). ⁱ Isolated yield based on **7** used.

unable to abstract a hydrogen atom from **1**. Since Co ions are known to promote the redox decomposition of the peroxides,⁷ the reaction was conducted without Co(II) to give **8** in 70% yield (run 7).

In conclusion, we have developed a novel catalytic method for the addition of ketones to alkenes by the combined use of Mn(II) and Co(II) salts using dioxygen as the reoxidant. This method provides an alternative route to α -alkylated cycloalkanes which are attractive compounds as fine chemicals such as fragrances. Further investigation to extend the present method and to elucidate the role of the Co(II) species is currently in progress.



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Notes and references

† A typical procedure for reaction of cyclohexanone **1** with oct-1-ene **2**: To a solution of **1** (20 mmol), Mn(OAc)₂ (0.1–0.5 mol%) and Co(OAc)₂ (0.05–0.1 mol%) in AcOH (2 mL) in a two-necked flask equipped with a balloon filled with an appropriate concentration of O₂ was added **2** (2 mmol), and the mixture was stirred at 80 °C for 5 h. After evaporation of AcOH and unreacted **1**, 2-octylcyclohexanone (**3**) was isolated by flash chromatography on silica gel (*n*-hexane–AcOEt = 5:1).

‡ By the reaction using the combined catalytic systems of Mn(OAc)₂ with other metals such as Cu(OAc)₂, VO(acac)₂, Ni(acac)₂ and Fe(acac)₃, the yield of **3** was not improved.

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