Bull. Chem. Soc. Jpn., 78, 1673–1676 (2005)

A Remarkable Effect of Bases on the Catalytic Radical Addition of Cyanoacetates to Alkenes Using a Mn(II)/Co(II)/O_2 Redox System

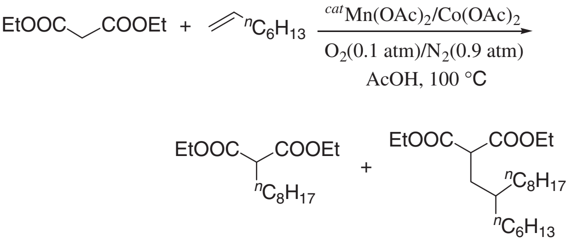
Takashi Kagayama, Takahiro Fuke, Satoshi Sakaguchi, and Yasutaka Ishii*

Department of Applied Chemistry and High Technology Research Center, Faculty of Engineering,
Kansai University, Suita, Osaka 564-8680

Received March 16, 2005; E-mail: ishii@ipcku.kansai-u.ac.jp

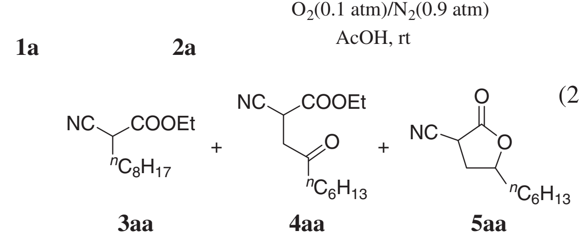
A remarkable addition effect of bases, like AcOK, was observed in the radical addition of cyanoacetates to alkenes catalyzed by a Mn(II)/Co(II)/O_2 redox system. Thus, a carbon radical from ethyl cyanoacetate could be catalytically generated by adding AcOK to the Mn(II)/Co(II)/O_2 redox system, even at room temperature, and the resulting carbon radical readily added to 1-octene to give an adduct, ethyl 2-cyanodecanoate, in good yield, while no reaction took place at all in the absence of AcOK. Ethyl cyanoacetate added smoothly to a variety of alkenes under mild conditions in the presence of a base to lead to the corresponding adducts in fair-to-good yields. It is reasonable to assume that the base added accelerated the deprotonation from a transient carbocation intermediate generated by the one-electron oxidation of ethyl cyanoacetate by the Mn(III) ion. This method provides an alternative route to alkylation of cyanoacetates under mild conditions.

The addition of activated methylene compounds like malonates and cyanoacetates to alkenes has been reported to be promoted by the action of higher-valence transition metal ions, like Mn(III), Fe(III), and Ce(IV).[1] Among metal oxidants employed, Mn(III) is often used as a one-electron oxidant of activated methylene compounds in a variety of synthetic reactions.[2–5] For example, Fristad[2a,2b] and Lamarque[2c] reported on the synthesis of bicyclic γ-lactones from cycloalkenes and potassium monomethyl malonate by the use of excess $Mn(OAc)_3$. Kurosawa et al. have reported several Mn(III)-mediated reactions of 1,1′-diarylalkenes with β-keto esters and β-diketones under O_2, leading to cyclic peroxides.[3] It has been reported that electrophilic radicals generated by the oxidation of β-keto esters with Mn(III) can be trapped by O_2 to form δ-hydroxy-α-keto esters.[4] The hydroxylation of α-methoxycarbonyl γ-lactones with O_2 is promoted by $Mn(OAc)_3$.[5] Although these Mn(III)-mediated radical reactions are very attractive as synthetic tools, a serious drawback of this method is that a large excess of Mn(III) ions is required to complete the reactions. In addition, the reaction calls for performance at relatively higher temperature to result in undesired side reactions. Therefore, if the Mn(III)-promoted free-radical reactions can be carried out via a catalytic process of the metal ions under mild conditions, the importance of the reactions would be vastly increased from both synthetic and environmental viewpoints. Recently, we succeeded in a catalytic free-radical addition of ketones and acid anhydrides to alkenes by using a Mn(II)/Co(II)/O_2 redox system. For instance, α-keto radicals derived from aliphatic and cyclic ketones added to alkenes, like 1-octene in the presence of very small amounts of $Mn(OAc)_2$ (0.5 mol %) and $Co(OAc)_2$ (0.1 mol %) under atmospheric dioxygen (1 atm) in acetic acid at 80 °C gave the corresponding α-alkylated ketones in fair-to-good yields.[6] The application of this system to the reaction of enolizable carbonyl compounds, like dimethyl malonate, with alkenes, like 1-octene, led to a monoadduct together with an undesired diadduct formed by the further addition of the monoadduct radical to 1-octene, since the reaction must be carried out at a relatively higher temperature of around 100 °C (Eq. 1).[7] If the reaction can be carried out at low temperature, the selectivity of the radical addition is expected to be improved.



(1)

We have now found a remarkable addition effect of bases to a Mn(II)/Co(II)/O_2 redox couple in the radical addition of activated methylene compounds to various alkenes. Thus, the addition of ethyl cyanoacetate (**1a**) to 1-octene (**2a**) was efficiently achieved at room temperature through a catalytic process by adding a weak base, like AcOK, to a Mn(II)/Co(II)/O_2 redox couple to give selectively ethyl 2-cyanodecanoate (**3aa**) in good yield together with small amounts of additional reaction products, ethyl 2-cyano-4-oxadecanoate (**4aa**) and 2-cyano-4-hexyl-γ-butyrolactone (**5aa**) (Eq. 2).



(2)

DOI 10.1246/bcsj.78.1673

Table 1. Radical Addition of **1a** to **2a** Catalyzed by $Mn(OAc)_2/Co(OAc)_2$ under Various Conditions[a)]

Run	Base /mmol	Conv.[b)] /%	Yield/%[b)]		
			3aa	**4aa**	**5aa**
1	—	<1	—	—	—
2	AcOK (2)	99	81	3	1
3[c)]	AcOK (2)	9	—	—	—
4[d)]	AcOK (2)	10	—	—	—
5	KOH (2)	99	76	1	3
6	AcONa (2)	99	51	1	2
7	AcOK (1)	85	66	1	4
8	Et_3N (2)	99	80	0	4
9[e)]	AcOK (2)	8	—	—	—
10[f)]	AcOK (2)	12	0	1	1

a) **1a** (3 mmol) was reacted with **2a** (60 mmol), $Mn(OAc)_2 \cdot 4H_2O$ (0.06 mmol), and $Co(OAc)_2 \cdot 4H_2O$ (0.03 mmol) in AcOH (2 mL) under O_2 (0.1 atm) and N_2 (0.9 atm) at room temperature (ca. 25 °C) for 15 h. b) Based on **1a** used. c) In the absence of $Co(OAc)_2$. d) In the absence of $Mn(OAc)_2$. e) Pure oxygen was used. f) Air was used.

In order to reveal the effect of bases, the reaction of ethyl cyanoacetate (**1a**) with 1-octene (**2a**) was chosen as a model reaction, and was carried out under various conditions (Table 1).

The reaction of **1a** with **2a** in the presence of $Mn(OAc)_2$ (2 mol %), $Co(OAc)_2$ (1 mol %), and AcOK (67 mol %) under a mixed gas of O_2 (0.1 atm) and N_2 (0.9 atm) in acetic acid at room temperature (ca. 25 °C) for 15 h gave **3aa** in 81% yield and **4aa** (3%) as well as **5aa** (1%) (Run 2). However, no reaction took place at all in the absence of AcOK under these conditions (Run 1). Since this type of compound is usually prepared by the reaction of enolates with alkyl halides, it is interesting to note that the present method can be catalytically performed by the reaction between **1a** and **2a** instead of alkyl halides without the formation of salt. In addition, further alkylation of **3aa** was not observed.

Usually, the radical addition to alkenes using a radical initiator calls for a higher temperature than 100 °C to generate a radical species from **1a**. For instance, the radical addition of **1a** to β-pinene by using di-*t*-butyl peroxide as the radical initiator is carried out at a higher temperature (140–150 °C) to thermally decompose the peroxide.[8] Therefore, it is noteworthy that the present reaction proceeded smoothly even at room temperature. When either $Co(OAc)_2$ or $Mn(OAc)_2$ was removed from the catalytic system, no reactions were observed (Runs 3 and 4). This fact shows that both $Co(OAc)_2$ and $Mn(OAc)_2$ are needed to promote the addition of **1a** to **2a**. The addition of KOH to the reaction system had the same effect as that of AcOK, probably because of the in situ generation of AcOK under the present conditions in which acetic acid is present in excess. Thus, **2a** was obtained in almost the same yield using KOH (Run 5). AcONa also enhanced the present reaction, but the selectivity of the reaction was slightly lowered compared with the addition of AcOK (Run 6). An organic base, like triethylamine, served as an effective base (Run 8).

We next examined the influence of the oxygen concentration on the present catalytic radical addition promoted by the $Mn(OAc)_2/Co(OAc)_2/AcOK$ system. The reaction under air (1 atm) or pure oxygen (1 atm) resulted in a considerable decrease of the conversion of **1a** (Runs 9 and 10). For instance, the reaction under O_2 (1 atm) was markedly retarded, and unreacted **1a** was mostly recovered, even after 15 h (Run 9). This observation suggests that the oxygen concentration affects strongly the redox circuits in the $Mn(OAc)_2/Co(OAc)_2/O_2$ couple.

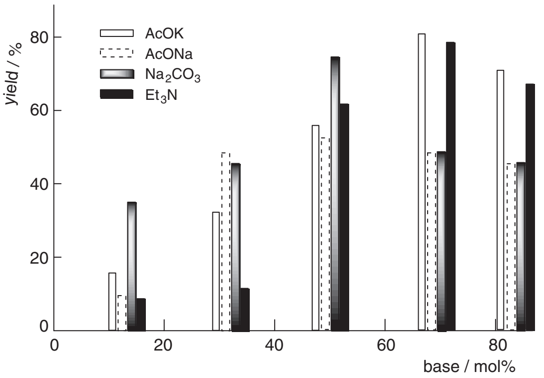


Fig. 1. Effect of base on the reaction of **1a** with **2a**.

In order to obtain further insight into the bases, the effect of several bases for the reaction of **1a** with **2a** by the $Mn(OAc)_2/Co(OAc)_2/O_2$ system was examined (Fig. 1).

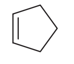
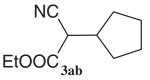
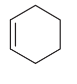
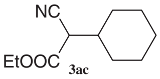
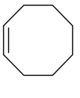
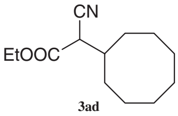
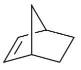
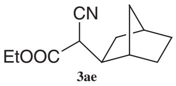
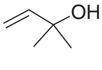
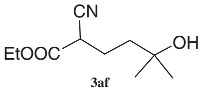
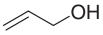
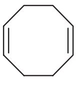
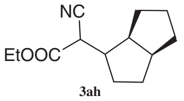
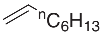
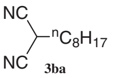
The amount of each base needed to obtain the best yield of **3a** from **1a** and **2a** was found to be different from each other. Owing to the complexity of the present reaction system, it seems rather difficult to clearly explain the effect of bases for the radical addition of **1a** to **2a**. The redox potentials of the $Mn(OAc)_2/Co(OAc)_2/O_2$ couple, and the deprotonation ability of the bases from **1a** may be changed by the quantity of base added.

On the basis of these results, the effects of AcOK on the reaction of **1a** with various alkenes and dienes by $Mn(OAc)_2/Co(OAc)_2/O_2$ at 25–55 °C are given in Table 2.

The reaction of **1a** with cyclopentene (**2b**) at room temperature afforded ethyl 2-cyano-2-cyclopentyl acetate (**3ab**) in high yield (93%) (Run 1). The same reaction in the absence of AcOK gave **3ab** in low yield (12%) (Run 2). A similar result was obtained in the reaction of **1a** with cyclohexene (**2c**) to give the corresponding adduct **3ac** (94%) (Run 3). However, cyclooctene (**2d**) was found to be less reactive than **2b** and **2c**. Thus, the reaction of **1a** with **2d** at 55 °C afforded adduct **3ad** in 42% yield at 65% conversion (Run 4). On the other hand, the addition of **1a** to norbornene (**2e**) afforded ethyl 2-cyano-2-norbornyl acetate (**3ae**) in quantitative yield (99%) (Run 5). It is interesting to note that **1a** was added to 2-methyl-3-buten-2-ol (**2f**) to form adduct **3af** in good yield (92%) (Run 6), while the reaction with allyl alcohol (**2g**) resulted in a complex mixture because of the polymerization of **2g** in preference to the addition of **1a** to **2g** (Run 7). The reaction of **1a** with 1,5-cyclooctadiene (**2h**) afforded a fused adduct (**3ah**) in 86% yield (Run 9). This type of intramolecular cyclization has been reported by Linker.[1f] Like **1a**, malononitrile (**1b**) was added smoothly to **2a** at room temperature to give 2-octyl malononitrile (**3ba**) (76%) (Run 10).

We next compared the effect of AcOK in the radical addition of **1a** to alkenes by the $Mn(OAc)_2/Co(OAc)_2$ system; the addition of **1a** to **2a** was compared with that of malononi-

Table 2. Addition of **1a** to Served Alkenes Catalyzed by $Mn(OAc)_2/Co(OAc)_2/AcOK$ under O_2 (0.1 atm)/N_2 (0.9 atm)[a)]

Run	Alkenes	Product	Yield/%[b)]
1[e)]	 **2b**	 3ab	93(85)
2[c)]		**3ab**	12
3	 **2c**	 3ac	94(81)
4[d)]	 **2d**	 3ad	42(39)
5[e)]	 **2e**	 3ae	99(93)
6[f)]	 **2f**	 3af	92(85)
7	 **2g**	complex mixture	
8	 **2h**	 3ah	20
9[d)]		**3ah**	86(82)
10[g)]	 **2a**	 3ba	76(65)

a) Alkene (3 mmol) was reacted with **1a** (60 mmol) in the presence of $Mn(OAc)_2 \cdot 4H_2O$ (0.06 mmol), $Co(OAc)_2 \cdot 4H_2O$ (0.03 mmol), and AcOK (2 mmol) at room temperature for 15 h. b) Based on alkenes used. Parenthesis shows isolated yields. c) In the absence of AcOK. d) At 55 °C. e) **2e** (4 mmol) was used. f) **2f** (4 mmol) was used. g) Malononitrile (**1b**) (30 mmol) was used.

trile (**1b**) and dimethyl malonate (**1c**), differing in pK_a values from **1a** and **2a** (Fig. 2).

It was found that the addition of **1b** to **2a** took place more smoothly than **1a**, and that the yield of the adducts increased with increasing the amount of AcOK added to the reaction system. However, **1c**, having less acidic methylene protons than those of **1a** and **1b**, was not added to **2a** at all at room temperature.

On the basis of these results, a plausible reaction path in the present radical addition is shown in Scheme 1.

It is reasonable to assume that the reaction is initiated by the one-electron oxidation of **1a** by Mn(III) to form a transient carbocation intermediate [**A**], followed by deprotonation to form Mn(III) enolate (**B**). The liberation of Mn(II) from the enolate **B** afforded a cyano(ethoxycarbonyl)methyl radical (**C**), which readily added to alkene **2a**, leading to an adduct radical (**D**). The hydrogen abstraction of the **D** from an H-donor led to adduct **3a**. The fact that the reaction took place smoothly in more easily enolizable **2b** having a low pK_a suggests that a base, like AcO^-, promotes the abstraction of a proton from **A**. Since both inorganic and organic bases served as good additives in the present reaction, and the reaction depended on the amount of bases, this step is thought to be the slowest in the sequential reactions. It is believed that the Mn(III) is formed by the oxidation of Mn(II) with Co(III)–oxygen complexes derived from Co(II) and oxygen. It is well-known that a Co(II) species reacts with molecular oxygen to give a peroxocobalt(III) and/or superoxocobalt(III) species.[9] Therefore, the present radical addition calls for the coexistence of Co(II) and Mn(II) as essential catalyst components. In fact, no reaction occurred when either $Co(OAc)_2$ or $Mn(OAc)_2$ was removed from the catalytic system, even in the presence of oxygen, as shown in Runs 3 and 4 (Table 1). The reaction of **1a** with **2a** using anhydrous $Mn(OAc)_2$ and $Co(OAc)_2$ in anhydrous acetic acid afforded **3a** in low yield, probably because of a difficulty concerning the dissociation of AcOK, while a small amount of water added to this reaction system resulted in **3a** in good yield. A similar acceleration effect of AcOK was reported in the stoichiometric Mn(III)-mediated γ-lactone annulation of acetic acid and alkenes.[3a,b]

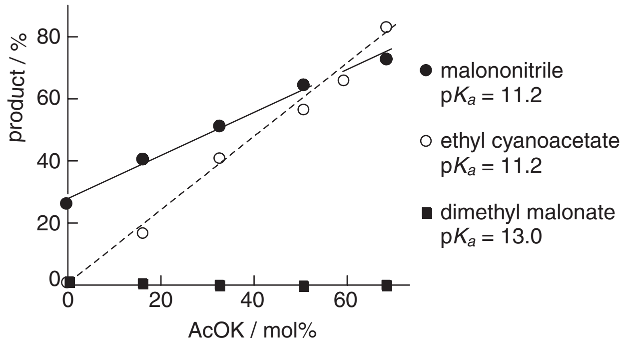
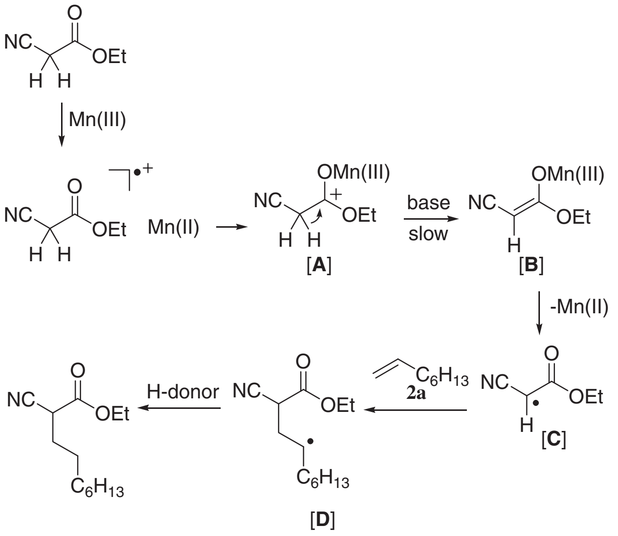


Fig. 2. Reaction of **2a** with activated methylene compounds under the influence of AcOK. **2a** (3 mmol), activated methylene compounds (60 mmol), $Mn(OAc)_2$ (0.06 mmol), $Co(OAc)_2$ (0.03 mmol), and AcOK at room temperature (ca. 25 °C) for 15 h.



Scheme 1. A possible reaction path for reaction of **1a** with **2a** by the $Mn(OAc)_2/Co(OAc)_2/AcOK/O_2$ system.

In conclusion, we have observed a remarkable effect of bases, like AcOK and amines, on the radical addition of **1a** to alkenes and dienes by using a Mn(II)/Co(II)/O_2 redox couple. This method provides an alternative route to the reaction between enolates and electrophiles, like alkyl halides, under mild conditions.

Experimental

All starting materials were commercially available and used without any purification. GLC analysis was performed with a flame ionization detector using a 0.2 mm × 25 m capillary column (OV-1). ^{1}H and ^{13}C NMR were measured at 270 MHz and 67.5 MHz, respectively, in $CDCl_3$ with Me_4Si as the internal standard.

A typical reaction procedure: To a solution of **1** (60 mmol), $Mn(OAc)_2 \cdot 4H_2O$ (0.06 mmol, 2.0 mol %), and $Co(OAc)_2 \cdot 4H_2O$ (0.03 mmol, 1.0 mol %) in a two-necked flask equipped with a balloon filled with an appropriate concentration of O_2 was added **2** (1 mmol); the mixture was stirred at room temperature for 5 h. The product was isolated by column chromatography (230–400 mesh silica gel, hexane:ethyl acetate = 1:1). The conversions and yields of products were estimated from the peak areas based on the internal standard technique using GLC.

Compounds **3aa**,[10] **3ab**,[11] **3ac**,[12] **3ad**,[12] **3af**,[13] **3ah**,[14] and **3ba**[7] were reported previously.

This work was partially supported by a Grant-in-Aid for Scientific Research (S) from the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan.

References

1 a) "Basic Principles and Applications," in "Radicals in Organic Synthesis," ed by M. P. Renaud, Wiley-VCH, New York (2001), Vols. 1 and 2. b) "Free Radical Chain Reactions in Organic Synthesis," ed by W. B. Motherwell and D. Chich, Academic, London (1992). c) D. P. Curran, "Comprehensive Organic Synthesis," ed by B. Trost and M. I. Fleming, Pergamon, Oxford (1991), Vol. 4, Chaps. 4.1 and 4.2. d) D. P. Curran, *Synthesis*, **1988**, 417; D. P. Curran, *Synthesis*, **1988**, 489. e) "Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds," ed by B. Giese, Pergamon Press, Oxford (1986). f) T. Linker, B. Kersten, U. Linker, K. Peter, E. Peter, and. G. von Schnering, *Synlett*, **1996**, 468. g) "Organic Synthesis by Oxidation with Metal Compounds," ed by W. J. Migs and C. R. H. I. de Jonge, Plenam Press, New York (1986). h) M. Hajek and J. Malek, *Synthesis*, **1976**, 315. i) M. Hajec, P. Silhavy, and J. Malek, *Tetrahedron Lett.*, **36**, 3193 (1974). j) G. I. Nikishin, M. G. Viogradov, and T. M. Fedorova, *J. Chem. Soc., Chem. Commun.*, **1973**, 693.

2 a) W. E. Fristad and J. R. Peterson, *J. Org. Chem.*, **50**, 10 (1985). b) W. E. Fristad, J. R. Peterson, and A. B. Arnst, *J. Org. Chem.*, **50**, 3143 (1985). c) L. Lamarque, A. Meou, and P. Brun, *Tetrahedron*, **54**, 6497 (1998).

3 a) A. Yamada, Y. Iwahara, H. Nishino, and K. Kurosawa, *J. Chem. Soc., Perkin Trans. 1*, **1993**, 609. b) C.-Y. Qian, T. Yamada, H. Nishino, and K. Kurosawa, *Bull. Chem. Soc. Jpn.*, **65**, 1371 (1992). c) V.-H. Nguyen, H. Nishino, and K. Kurosawa, *Tetrahedron Lett.*, **37**, 4949 (1996). d) V.-H. Nguyen, H. Nishino, and K. Kurosawa, *Tetrahedron Lett.*, **38**, 1773 (1997).

4 T. Ohshima, M. Sodeoka, and M. Shibasaki, *Tetrahedron Lett.*, **34**, 8509 (1993).

5 L. Lamarque, A. Meou, and P. Brun, *Can. J. Chem.*, **78**, 128 (2000).

6 T. Iwahama, S. Sakaguchi, and Y. Ishii, *Chem. Commun.*, **2000**, 2317.

7 K. Hirase, T. Iwahama, S. Sakaguchi, and Y. Ishii, *J. Org. Chem.*, **67**, 970 (2002).

8 M. Cazaux and R. Lalande, *Bull. Soc. Chim. Fr.*, **1966**, 3381.

9 a) F. Basolo, R. D. Jones, and D. A. Summerville, *Chem. Rev.*, **79**, 139 (1979). b) C. L. Wong, J. A. Switer, K. P. Balakrishnan, and J. F. Endicott, *J. Am. Chem. Soc.*, **102**, 5511 (1980). c) R. S. Drago, J. P. Cannady, and A. Leslie, *J. Am. Chem. Soc.*, **102**, 6014 (1980).

10 R. Shundo, I. Nisiguchi, Y. Matsubara, and T. Hirashima, *Chem. Lett.*, **1990**, 2285.

11 R. Shundo, I. Nishiguchi, Y. Matsubara, and T. Hirashima, *Tetrahedron*, **47**, 831 (1991).

12 B. C. Ranu and S. Samanta, *Tetrahedron*, **59**, 7901 (2003).

13 J. M. Surzur and P. Teissier, *Bull. Soc. Chim. Fr.*, **1970**, 653.

14 R. Shundo, Y. Matsubara, I. Nisiguchi, and T. Hirashima, *Chem. Express*, **6**, 547 (1991).