Generation of β-Keto Radicals from Cyclopropanols Catalyzed by $AgNO_3$

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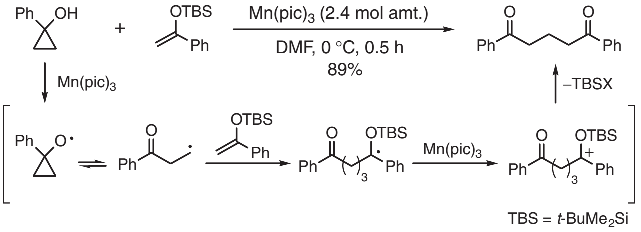
Various β-keto radicals are generated from cyclopropanols by treatment with a catalytic amount of $AgNO_3$ and $(NH_4)_2S_2O_8$ as a reoxidant in the presence of pyridine. Thus, generated β-keto radicals react with alkenes to yield addition products.

In the previous papers, our laboratory reported that the treatment of cyclopropanols with manganese(III) tris(2-pyridinecarboxylate) $[Mn(pic)_3]$ generates β-keto radicals,[1] which add to either electron-rich or deficient alkenes to give the corresponding addition products (Scheme 1).[2]

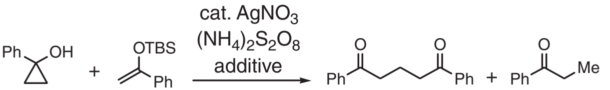


Scheme 1.

Though this oxidative radical generation exhibits wide generality, the use of a stoichiometric amount of $Mn(pic)_3$ prevents the application to a large-scale synthesis. In fact, in our total synthesis of a natural product, sordaricin,[3] it was desired to improve this stoichiometric reaction to a catalytic process. Herein, we would like to report a catalytic β-keto radical formation from cyclopropanol derivatives by the use of $AgNO_3$–$(NH_4)_2S_2O_8$–pyridine system.

Peroxodisulfate salts, $[M^{2+}S_2O_8{}^{2-}]$ are widely used as an oxidant of metal salts.[4] For example, Citterio et al. reported the generation of α-keto radicals from ketones by the use of a catalytic amount of $AgNO_3$ and $Na_2S_2O_8$ as a reoxidant in aqueous media, in which Ag^{II} species were supposed to participate in the oxidation.[5]

We considered that cyclopropanols might be oxidized even with Ag^{I} species under mild reaction conditions and examined the reaction of 1-phenylcyclopropanol (**1a**)[6] and α-(t-butyldimethylsiloxy)styrene (**2a**) with the combination of cat. $AgNO_3$ and $(NH_4)_2S_2O_8$ (Eq 1).[7] When a 0.1 molar amount of $AgNO_3$ and 2.4 molar amounts of $(NH_4)_2S_2O_8$ were added to a mixture of **1a** and **2a** in DMF, the reaction proceeded at room temperature to afford the addition product **3aa** and propiophenone (**4**) in 20 and 53% yield, respectively. Then, the reaction was examined in the presence of various amines, which would act as a trapping reagent of the acid generating during this oxidation and also as a ligand coordinating to Ag^{I} species.[8] When 2 molar amounts of pyridine was added, the yield of **3aa** was improved to 86%,[9] while 2,6-lutidine, 2,2-bipyridine, pyrazine, and DBU were not so effective for this reaction.[10] Contrary to the formation of highly reactive Ag^{II} species by the oxidation with peroxodisulfate salts under harsh conditions (for example, refluxing in water),[5] this catalytic reaction under milder conditions presumably proceeds via Ag^{I}–Ag^{0} cycle.[11]



1a **2a** **3aa** **4** (1)

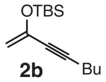
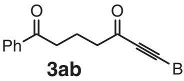
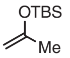
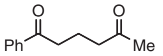
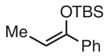
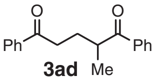
	3aa	4
in the absence of additive	20%	53%
in the presence of pyridine	86%	10%

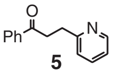
Next, the reactions of **1a** and various silyl enol ethers were examined as shown in Table 1. Silyl enol ethers having a terminal methylene moiety **2b** and **2c** gave the corresponding products **3ab** and **3ac** in good yield (Runs 1 and 2). In the case of trisubstituted silyl enol ether **2d**, the reaction proceeded slowly to give the desired product **3ad** in only 19% yield with the adduct of β-keto radical and pyridine **5**[12] in 27% yield and with a 25% recovery of **1a** (Run 3).

A wide range of cyclopropanols[13] reacted with silyl enol ethers **2a** and **2b** as summarized in Table 2. 1-Phenethylcyclopropanol (**1b**) reacted with **2a** and **2b** to afford the corresponding adducts in good yield (Run 1 and 2). As shown in Run 3–5, 1-trimethylsilylcyclopropanol (**1c**) and cyclopropanone hemiacetal **1d** could be employed as β-trimethylsilylcarbonyl and β-ethoxycarbonyl radical sources, respectively. The reaction of bicyclo[4.1.0]heptan-1-ol (**1e**) gave the ring-expanded seven-membered adduct **3ea** as a major product (Run 6). 1-(2-Oxoalkyl)-cyclopropanol derivative **1f** was found to act as a β-diketone unit to give tricarbonyl compound **3fa** by the reaction with **2a** in moderate yield (Run 7), while the protection of the carbonyl group of **1f** as an acetal improved the yield to 79% (Run 8).

Three component coupling[14] was carried out with the combination of cyclopropanols and electoron-deficient and rich al-

Table 1. The reactions of 1-phenylcyclopropanol (**1a**) with various silyl enol ethers **2**[a]

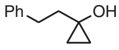
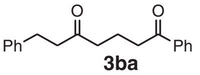
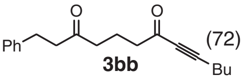
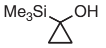
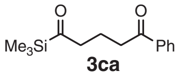
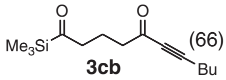
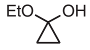
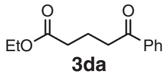
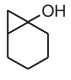
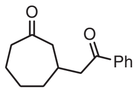
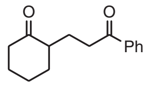
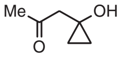
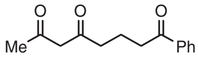
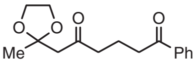
Run	Silyl enol ether	Time/h	Product (yield/%)[b]
1	 **2b**	3	 **3ab** (78)
2	 **2c**	2	 **3ac** (75)
3[c]	 **2d**	6	 **3ad** (19)



5

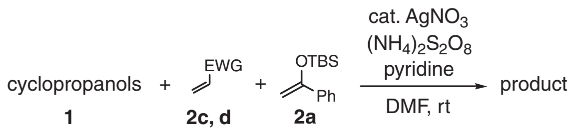
[a]Reaction conditions; DMF, rt. **1a**:**2**:$AgNO_3$:$(NH_4)_2S_2O_8$:pyridine = 1:2:0.1:2.4:2. [b]Isolated yield based on cyclopropanol **1a**. [c]**5** was obtained in 27% yield, and **1a** was recovered in 25% yield.

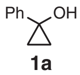
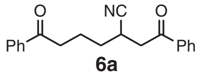
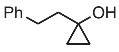
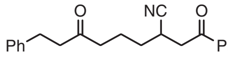
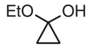
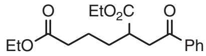
Table 2. The oxidative radical reaction of various cyclopropanols **1** with silyl enol ethers **2a** and **2b**[a]

Run	Cyclopropanol	**2a** or **2b**	Product (yield/%)[b]
1	 **1b**	**2a**	 **3ba** (81)
2	**1b**	**2b**	 **3bb** (72)
3	 **1c**	**2a**	 **3ca** (56)
4	**1c**	**2b**	 **3cb** (66)
5	 **1d**	**2a**	 **3da** (76)
6	 **1e**	**2a**	 **3ea** (59)  **3ea′** (13)
7	 **1f**	**2a**	 **3fa** (51)
8	 **1g**	**2a**	 **3ga** (79)

[a]Reaction conditions; DMF, rt, 2.5–5.5 h. **1**:**2**:$AgNO_3$:$(NH_4)_2S_2O_8$:pyridine = 1:2:0.1:2.4:2. [b]Isolated yield based on cyclopropanol **1**.

Table 3. Three component coupling reactions[a]

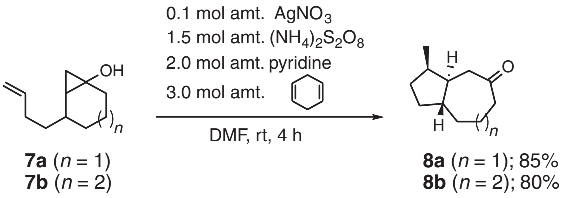


Run	Cyclopropanol	EWG	Product (yield/%)[b,c]
1	 **1a**	CN **2c**	 **6a** (62)
2	 **1b**	CN **2c**	 **6b** (65)
3	 **1d**	CO_2Et **2d**	 **6d** (59)

[a]Reaction conditions; DMF, rt, 3.5–4 h. **1a**:**2**:$AgNO_3$:$(NH_4)_2S_2O_8$:pyridine = 1:2:0.1:2.4:2. [b]Isolated yield based on cyclopropanol **1a**. [c]The undesirable cross-addition products **3** were obtained in 6% (**3aa**), 5% (**3ba**), and 14% (**3da**) yield, respectively.

kenes. Electron-deficient alkenes were expected to react firstly with nucleophilic β-keto radicals to generate electron-deficient radicals, which would be trapped finally with electron-rich alkenes. As expected, cyclopropanols (**1a**, **1b**, and **1d**) reacted with electoron-deficient alkenes (**2c** or **2d**), and electron-rich alkene **2a** in this order, and the three components coupling products (**6a**, **6b**, and **6d**) were obtained in good to moderate yield with a small amount of cyclopropanol-electron-rich alkene addition products **3** (Table 3).

This catalytic system could be applied to the intramolecular radical addition of bicyclo[n.1.0] compounds bearing an alkene moiety at the suitable position (Eq 2). 5-(3-Butenyl)bicyclo[4.1.0]heptan-1-ol (**7a**) and 6-(3-butenyl)bicyclo[5.1.0]octan-1-ol (**7b**) were successfully transformed to bicyclo[5.3.0]decan-3-one derivative **8a** having a guaiane skeleton, and bicyclo[6.3.0]dodecan-3-one derivative **8b** with high stereoselectivity[2e] under this catalytic system in the presence of 1,4-cyclohexadiene as a radical-trapping reagent.



(2)

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References and Notes

1 There are some reports on the generation of β-keto radicals from cyclopropanols and their addition reactions by the stoichiometric use of metallic oxidants. For example, see: a) Fe^{III}, Cu^{II}: S. E. Schaafsma, R. Jorritsma, H. Steinberg, T. J. de Boer, *Tetrahedron Lett.* **1973**, *14*, 827. b) Cu^{II}: B. B. Snider, T. Kwon, *J. Org. Chem.* **1992**, *57*, 2399. c) Fe^{III}: K. I. Booker-Milburn, A. Barker, W. Brailsford, B. Cox, T. E. Mansley, *Tetrahedron* **1998**, *54*, 15321.
2 a) N. Iwasawa, S. Hayakawa, K. Isobe, K. Narasaka, *Chem. Lett.* **1991**, 1193. b) N. Iwasawa, S. Hayakawa, M. Funahashi, K. Isobe, K. Narasaka, *Bull. Chem. Soc. Jpn.* **1993**, *66*, 819. c) N. Iwasawa, M. Funahashi, S. Hatakawa, K. Narasaka, *Chem. Lett.* **1993**, 545. d) K. Narasaka, *Pure Appl. Chem.* **1997**, *69*, 601. e) N. Iwasawa, M. Funahashi, S. Hatakawa, T. Ikeno, K. Narasaka, *Bull. Chem. Soc. Jpn.* **1999**, *72*, 85.
3 M. Kitamura, S. Chiba, K. Narasaka, *Chem. Lett.* **2004**, *33*, 942.
4 F. Minisci, A. Citterio, *Acc. Chem. Res.* **1983**, *16*, 27.
5 A. Citterio, F. Ferrario, S. de Bernardinis, *J. Chem. Res., Synop.* **1983**, 310.
6 **1a** was decomposed at 0.05–0.1 V by cyclic voltammetry. [1 mA in DMF; supporting electrocycle: 0.1 M n-Bu_4NClO_4; working electrode: glassy carbon; counter electrode: platinum wire; reference electrode: Ag/AgCl [$E_{1/2}$ (ferrocene/ferricinium) = +0.65 V] at 25 °C; scan rate: 100 mV s^{-1}.
7 In the case of the combined use of a 0.1 molar amount of $Mn(pic)_3$ and $(NH_4)_2S_2O_8$ in DMF, the reaction proceeded at 50 °C to afford **3a** and **4** in 10 and 22% yield, respectively.
8 K. Nilsson, Å. Oskarsson, *Acta Chem. Scand., Ser. A* **1982**, *36*, 605.
9 When **1a** was treated in the absence of **2a**, propiophenone **4**, the self-coupling product of the β-keto radical, and the adduct of β-keto radical and pyridine **5** were obtained in 12, 31, and 6% yield, respectively. When **2a** was treated in the absence of the cyclopropanol, **2a** was recovered without the formation of the self-coupling product of **2a**.
10 When 2,6-lutidine was added, the reaction did not proceed at all. In the cases of pyrazine, 2,2-bipyridine, and DBU, **3aa** was obtained in 41, 55, and 66% yield, respectively.
11 The oxidation potential of Ag(II) species is enough to oxidize silyl enol ethers. Under the present catalytic system, silyl enol ethers were not oxidized as mentioned in Ref. 10. The one electron oxidation potential of various silyl enol ethers, see: S. Fukuzumi, M. Fujita, J. Otera, Y. Fujita, *J. Am. Chem. Soc.* **1992**, *114*, 10271.
12 F. Minisci, C. Giordano, E. Vismara, S. Levi, V. Tortelli, *J. Am. Chem. Soc.* **1984**, *106*, 7146.
13 For synthetic methods of cyclopropanols **1**, see: O. G. Kulinkovich, *Chem. Rev.* **2003**, *103*, 2597, and references therein.
14 K. Mizuno, M. Ikeda, S. Toda, Y. Otsuji, *J. Am. Chem. Soc.* **1988**, *110*, 1288.

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