Mn(III)-Based Oxidative Free Radical Cyclization of Unsaturated Ketones

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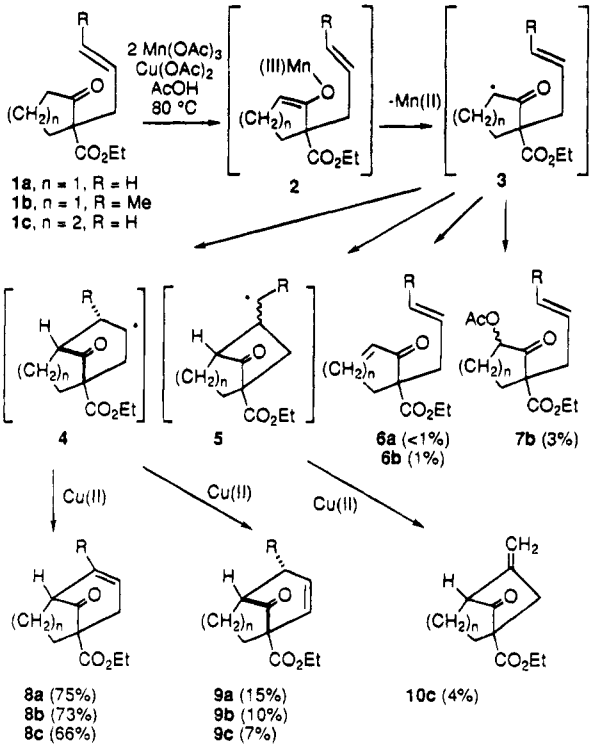
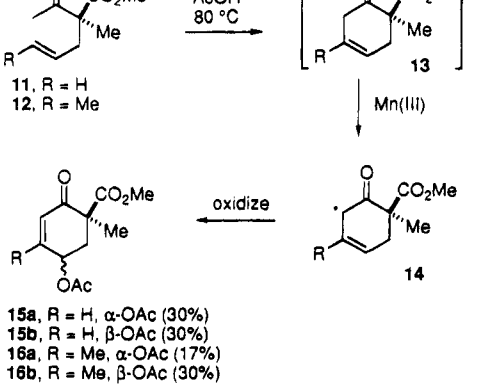
During the past decade Mn(III)-based oxidative free-radical cyclizations have been developed into a general procedure for producing highly functionalized products from simple precursors.[1,2] These cyclizations have been initiated by reaction of relatively acidic compounds, such as 1,3-diketones, acetoacetates, malonates, and α-sulfinyl or α-nitro ketones, with $Mn(OAc)_3$ to form a Mn(III) enolate, which undergoes electron transfer to give Mn(II) and a radical. The Mn(III)-based oxidative free-radical addition of simple symmetrical ketones, which can be used in large excess, to simple alkenes is well-known.[1a-c] However, oxidative free-radical cyclizations of unsaturated ketones have not been examined, presumably because of anticipated problems with both the regioselectivity of radical formation and further oxidation of the product ketones under the reaction conditions.

We report here that Mn(III)-based oxidative free-radical cyclization of unsaturated ketones is in fact a versatile synthetic procedure with broad applicability. Reaction of cyclopentanone **1** as a 0.1 M solution in HOAc with 2.5 equiv of $Mn(OAc)_3{\cdot}2H_2O$ and 1 equiv of $Cu(OAc)_2{\cdot}H_2O$ for 1.5 h at 80 °C affords 75% of bicyclo[3.2.1]-oct-3-en-8-one **8a**, 15% of bicyclo[3.2.1]oct-2-en-8-one **9a**, and <1% of **6a**. The slow step appears to be formation of Mn(III)-enolate **2a**, which undergoes electron transfer with loss of Mn(II) to give α-keto radical **3a**. 6-*endo*-Cyclization affords radical **4a**, which is oxidized by Cu(II) to give 90% of a 5:1 mixture of **8a** and **9a**. We have previously observed that Cu(II) oxidizes alkyl radicals selectively to afford the least hindered alkene.[3] Similar results are obtained with cyclopentanone **1b**, which gives 73% of **8b** and 10% of **9b**. Trace amounts of α,β-unsaturated enones **6a** and **6b** and α-acetoxycyclopentanone **7b** are obtained from oxidation of α-keto radical **3**. Cyclohexanone **1c** reacts more slowly (16 h, 80 °C) giving a similar mixture of 66% of bicyclo[3.3.1]non-3-en-9-one **8c**, 7% of bicyclo[3.3.1]non-2-en-9-one **9c** and 4% of **10c**, which is formed by a 5-*exo*-cyclization. These reactions proceed in excellent yield since ketone **1** can enolize in only one direction and bicyclic ketones **8** and **9** are not susceptible to further oxidation, because they cannot enolize.

If the product ketone enolizes, further oxidation will occur, efficiently providing γ-acetoxy-α,β-unsaturated ketones. Reaction of acetoacetate **11** with 6 equiv of $Mn(OAc)_3{\cdot}2H_2O$ and 1 equiv of $Cu(OAc)_2{\cdot}H_2O$ in AcOH for 48 h at 80 °C affords 60% of a 1:1 mixture of **15a** and **15b** in a net four-electron oxidation. Oxidative cyclization of **11** should give 3-cyclohexenone **13**, if cyclization proceeds analogously to the conversion of **1** to **8**. β,γ-Unsaturated ketone **13** is more acidic than **11** and is therefore rapidly oxidized to radical **14**, which is oxidized to **15**. Similar results are obtained with acetoacetate **12**.





The radical derived from oxidation of cyclopentanone **17a** undergoes 7-*endo*-cyclization to give **18a** (25%) and **19a** (10%) and 6-*exo*-cyclization to afford 25% of **20a**. Further Baeyer–Villiger-type oxidation of **20a** affords **21a** (12%).[4] Similar results are obtained with cyclohexanone **17b**.

(1) For reviews see: (a) de Klein, W. J. In *Organic Synthesis by Oxidation with Metal Compounds*; Mijs, W. J., de Jonge, C. R. H., Eds.; Plenum Press: New York, 1986; pp 261–314. (b) Badanyan, Sh. O.; Melikyan, G. G.; Mkrtchyan, D. A. *Russ. Chem. Rev.* **1989**, *58*, 286; *Uspekhi Khimii* **1989**, *58*, 475. (c) Melikyan, G. G. *Synthesis* **1993**, 833. (d) Iqbal, J.; Bhatia, B.; Nayyar, N. K. *Chem. Rev.* **1994**, *94*, 519.

(2) (a) Snider, B. B.; Mohan, R. M.; Kates, S. A. *J. Org. Chem.* **1985**, *50*, 3659. (b) Snider, B. B.; Patricia, J. J.; Kates, S. A. *J. Org. Chem.* **1988**, *53*, 2137. (c) Kates, S. A.; Dombroski, M. A.; Snider, B. B. *J. Org. Chem.* **1990**, *55*, 2427. (d) Zhang, Q.; Mohan, R.; Cook, L.; Kazanis, S.; Peisach, D.; Foxman, B. M.; Snider, B. B. *J. Org. Chem.* **1993**, *58*, 7640. (e) Snider, B. B. *Chemtracts—Org. Chem.* **1991**, *4*, 403.

(3) Snider, B. B.; Kwon, T. *J. Org. Chem.* **1990**, *55*, 1965.

(4) Pure keto ester **20a** gives a 1:1 mixture of **20a** and lactone **21a** under the reactions conditions, establishing that the lactone is formed by a Baeyer–Villiger-type reaction of **20a**. Examination of models suggests that Baeyer–Villiger reaction of **20a** occurs readily because the torsion angle $H_2C{=}CCHC$ in the stable conformer with a chair cyclohexanone is 118°, which is close to the optimal 90° for migration of an allylic group. Baeyer–Villiger reaction of endocyclic analogs **8** and **18a** should be slower since the torsion angle CH=CCHC is 29° and 6°, respectively, which is far from the optimal 90° for migration of an allylic group. Baeyer–Villiger reaction of exocyclic homologue **20b** is slow since the cyclohexanone is calculated to be more stable in the boat conformer with a $H_2C{=}CCHC$ torsion angle of 21°. We also observed a Baeyer–Villiger reaction of **23a**,[5a] which has a tertiary allylic group that should migrate more readily than the secondary allylic group of **8**.

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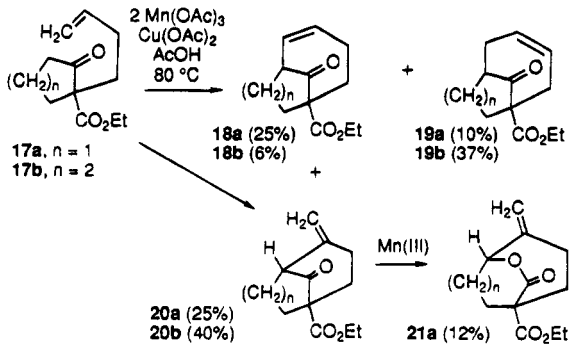
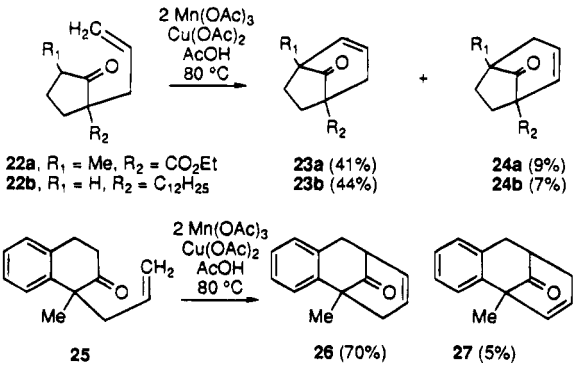


Oxidative cyclization of **22a** affords 41% of **23a** and 9% of **24a**, establishing that tertiary α-keto radicals can be formed by this process and undergo 6-*endo*-cyclization in good yield.[5a] Oxidative cyclization of 2-allyl-2-dodecylcyclopentanone (**22b**)[5b] and 1-methyl-1-allyl-2-tetralone (**25**) proceed in good yield indicating that the ester group present in **1** and **17** is not needed for the success of this sequence.



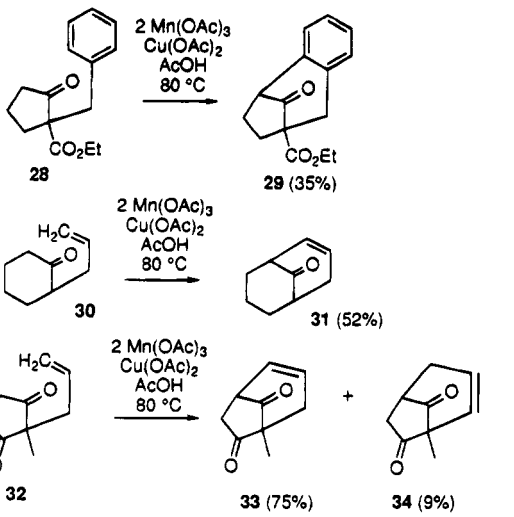
Oxidative cyclization of cyclopentanone **28** affords 35% of **29**, indicating that α-keto radicals generated by this procedure cyclize onto aromatic rings. Oxidation of the α-keto radical formed from **28** gives 10% of the enone analogous to **6** and 39% of the α-acetoxycyclopentanone analogous to **7** indicating that, as expected,[6] cyclization of the phenylbutyl radical obtained from **28** is much slower than cyclization of 5-hexenyl radical **3**.

Oxidation of 2-allylcyclohexanone (**30**) affords 52% of bicyclo[3.3.1]non-2-en-9-one (**31**).[5c] Enolization of the ketone should be the rate-determining step.[2b,7] Since the methylene protons are kinetically more acidic than the methine proton, enolization and oxidation give the secondary α-keto radical selectively. This suggests that it will be possible to selectively generate α-keto radicals from ketones that show a kinetic preference for deprotonation on one side, even if, as with **30**, there are α-hydrogens on both sides of the ketone.

(5) (a) Two percent of α-acetoxy ketone analogous to **7** and 24% of Baeyer–Villiger products are also obtained.[4] (b) Ten percent of α-acetoxy ketone analogous to **7** and 7% of an α-hydroxy ketone analogous to **7** are also obtained. (c) 6-Allyl-2-cyclohexenone (1%), 2-allyl-2-cyclohexenone (1%), 2-acetoxy-2-allylcyclohexanone (3%), 2-acetoxy-6-allylcyclohexanone (3%), and 5-acetoxybicyclo[3.3.1]non-2-en-9-one (4%) are also obtained. (d) Two percent of 2-allyl-2-methyl-4-cyclopentene-1,3-dione is also obtained.

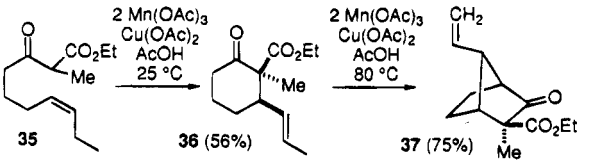
(6) (a) Kochi, J. K.; Gilliom, R. D. *J. Am. Chem. Soc.* **1964**, *86*, 5251. (b) Jenkins, C. L.; Kochi, J. K. *J. Am. Chem. Soc.* **1972**, *94*, 843.

(7) Heiba, E. I.; Dessau, R. M. *J. Am. Chem. Soc.* **1971**, *93*, 524.



Oxidation of 2-allyl-2-methylcyclopentane-1,3-dione (**32**) provides 75% of **33** and 9% of **34**.[5d] Bicyclo[3.2.1]-octenediones **33** and **34** could enolize and be oxidized further, but apparently are less acidic than the starting dione **32** and do not react further. Thus, while **11** and **12** give only acetoxy enones **15** and **16** resulting from further oxidation of **13**, in some cases it is possible to isolate products that can enolize.

The conversion of acetoacetate **35** to either propenylcyclohexanone **36** or vinylnorbornanone **37** at different temperatures clearly illustrates the difference in reactivity between 1,3-dicarbonyl compounds and ketones. We have previously reported the oxidative cyclization of **35** at 25 °C to give **36** (56%) as the major product; no **37** is obtained at room temperature.[2c] On the other hand, oxidation of **35** with 4 equiv of Mn(III) and Cu(II) for 56 h at 60 °C or 16 h at 80 °C provides 40% of **37** and only 10% of **36**. Oxidation of pure **36** under these conditions provides 75% of **37** and 8% of the enone analogous to **6**. At elevated temperatures cyclohexanone **36** is oxidized to the α-keto radical, which undergoes a 5-*exo*-cyclization stereospecifically to give a secondary radical, which is oxidized by Cu(II) to afford the less substituted double bond.[3]



These results vastly extend the scope of Mn(III)-based oxidative cyclizations beyond 1,3-dicarbonyl compounds. A wide variety of unsaturated ketones can now be used as substrates. The formation of **31** suggests that kinetically controlled enolization is the rate-determining step in α-keto radical formation. Bicyclic ketones that cannot enolize further are isolated in good yield. Monocyclic ketones that can enolize are oxidized to γ-acetoxy enones.

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Supporting Information Available: Experimental procedures and compound characterization data (10 pages).

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