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Mild Manganese(III) Acetate Catalyzed Allylic Oxidation: Application to Simple and Complex Alkenes

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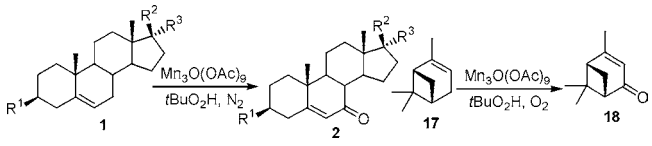
ABSTRACT



Manganese(III) acetate catalyzed allylic oxidation of alkenes to the corresponding enones was investigated, showing excellent regioselectivity and chemoselectivity (functional group compatibility). Δ^5-Steroids were transformed into bioactive Δ^5-en-7-ones under a nitrogen atmosphere, whereas simple alkenes were converted into the corresponding enones under an oxygen atmosphere in good yields.

Allylic oxidation is an important and useful reaction in many areas of organic synthesis.[1] Allylic oxidation of Δ^5-steroids to Δ^5-en-7-ones is of interest because Δ^5-en-7-ones show excellent results in the prevention and treatment of cancer and can inhibit the biosynthesis of sterol.[2] Allylic oxidation with metal complexes frequently encounters problems such as low functional group tolerance, low regioselectivity, high cost, and difficult catalyst preparation.[3] Herein, we report the use of inexpensive and commercially available manganese(III) acetate as the catalyst and of *tert*-butylhydroperoxide (TBHP) as the cooxidant for mild, efficient, regioselective, chemoselective (functional group compatible), allylic oxidation of simple and complex alkenes.

Manganese(III) acetate is commonly used as a radical cyclization[4] or α-keto-acetoxylation[5] reagent. Few reports[6] used Mn(III) in allylic oxidation, with epoxide and allyl acetate as the major products, and an enone was isolated in an exceptional case.[6a] Mn(III) is an unstable state which readily disproportionates to Mn(II) and Mn(IV) in aqueous media.[7] Fortunately, manganese(III) acetate has a trinuclear structure;[4,8] hence, the Mn(III) state can be stabilized, and the reactive acetate radical is a well-known source for acetoxylation.[4]

Initially, cholesteryl acetate (**1a**) was subjected to investigation using commercially available manganese(III) acetate dihydrate as the catalyst and TBHP as the cooxidant in various solvents at room temperature. 3 Å Molecular sieves were added to remove the trace amount of water to alleviate the disproportionation of manganese(III) acetate.[7] After 48 h, the best yield of Δ^5-en-7-one **2a** (87%) (Table 1) was recorded using 10 mol % of catalyst, 5 equiv of TBHP, and

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(3) Examples for metal-based allylic oxidation. Cr-based: (a) Muzart, J. *Chem. Rev.* **1992**, *92*, 113. Cu-based: (b) Salvador, J. A. R.; Sá e Melo, M. L.; Campos Neves, A. S. *Tetrahedron Lett.* **1997**, *38*, 119. Co-based: (c) Salvador, J. A. R.; Clark, J. H. *Chem. Commun.* **2001**, *6*, 33. (d) Jurado-Gonzalez, M.; Sullivan, A. C.; Wilson, J. R. H. *Tetrahedron Lett.* **2003**, *44*, 4283. Fe-based: (e) Barton, D. R. H.; Le Gloahec, V. N. *Tetrahedron* **1998**, *54*, 15457. Pd-based: (f) Yu, J. Q.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 3232. (g) Yu, J. Q.; Wu, H. C.; Corey, E. J. *Org. Lett.* **2005**, *7*, 1415. Rh-based: (h) Catino, A. J.; Forslund, R. E.; Doyle, M. P. *J. Am. Chem. Soc.* **2004**, *126*, 13622.

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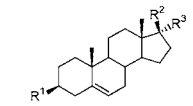
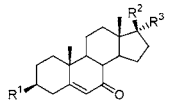
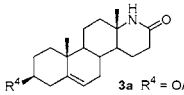
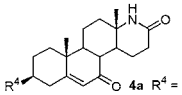
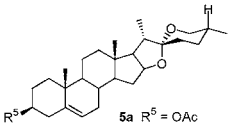
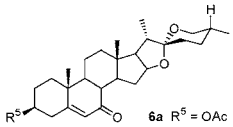
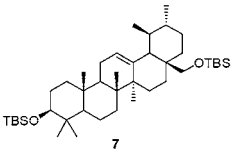
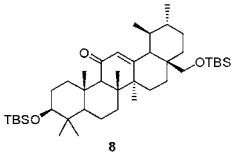
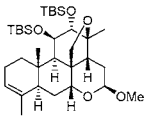
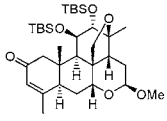
Table 1. Allylic Oxidation of Complex Alkenes

entry[a]	substrate	product	time (h), yield (%)
1	 **1a** R^1 = OAc, R^2 = C_8H_{17}, R^3 = H	 **2a** R^1 = OAc, R^2 = C_8H_{17}, R^3 = H	48, 87
2[b]	**1a** R^1 = OAc, R^2 = C_8H_{17}, R^3 = H	**2a** R^1 = OAc, R^2 = C_8H_{17}, R^3 = H	48, 85
3[c]	**1a** R^1 = OAc, R^2 = C_8H_{17}, R^3 = H	**2a** R^1 = OAc, R^2 = C_8H_{17}, R^3 = H	4, 70
4	**1b** R^1 = OAc, R^2 = R^3 = O	**2b** R^1 = OAc, R^2 = R^3 = O	30, 91
5	**1c** R^1 = OAc, R^2 = Ac, R^3 = H	**2c** R^1 = OAc, R^2 = Ac, R^3 = H	30, 83
6	**1d** R^1 = R^2 = OAc, R^3 = H	**2d** R^1 = R^2 = OAc, R^3 = H	27, 83
7	**1e** R^1 = OAc, R^2 =  , R^3 = H	**2e** R^1 = OAc, R^2 =  , R^3 = H	24, 96
8	**1f** R^1 = OTBS, R^2 = C_8H_{17}, R^3 = H	**2f** R^1 = OTBS, R^2 = C_8H_{17}, R^3 = H	48, 99
9	**1g** R^1 = OTBS, R^2 = R^3 = O	**2g** R^1 = OTBS, R^2 = R^3 = O	48, 90
10	**1h** R^1 = OTBS, R^2 = Ac, R^3 = H	**2h** R^1 = OTBS, R^2 = Ac, R^3 = H	28, 90
11	**1i** R^1 = OTBS, R^2 = OTBS, R^3 = H	**2i** R^1 = OTBS, R^2 = OTBS, R^3 = H	30, 89
12	**1j** R^1 = OAc, R^2 = OH, R^3 = H	**2j** R^1 = OAc, R^2 = OH, R^3 = H	42, 68
13	 **3a** R^4 = OAc	 **4a** R^4 = OAc	48, 82
14	**3b** R^4 = OTBS	**4b** R^4 = OTBS	48, 86
15	 **5a** R^5 = OAc	 **6a** R^5 = OAc	16, 72[d]
16	**5b** R^5 = OTBS	**6b** R^5 = OTBS	20, 72[d]
17	 **7**	 **8**	48, 78[d]
18	 **9**	 **10**	12, 72

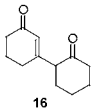
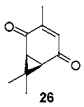
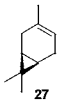
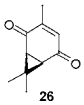
[a] For experimental details, see Supporting Information. [b] 1.0 g scale. [c] Reaction performed at 40 °C. [d] Starting material was recovered. See Supporting Information. [e] Dichloromethane was added due to solubility; EtOAc/CH_2Cl_2 = 1:1.

ethyl acetate as the solvent.[9] The workup procedure is simple, involving filtration and removal of solvent from the filtrate. In addition to cholesteryl acetate (**1a**), good yields were obtained for other steroids with different carbon skeletons and functionalities (**1b**−**j**, **3**, **5**, and **7**)[9] (Table 1, entries 1−17). Excellent regioselectivities were achieved in entries 1−16, in which the less-hindered C-7's were selectively oxidized to the corresponding Δ^5-en-7-ones.

Scaling up to a gram-scale reaction did not affect the chemical yield (entry 2). Increasing the temperature enhanced the reaction rate dramatically but with a reduction in yield (entry 3). The excellent chemoselectivity of the reaction is noteworthy because various functional and protecting groups (acetate, acetal, lactam, ketone, cyclic ether, and silyl ether) survived the mild oxidation conditions. The chemoselective allylic oxidation proceeded smoothly without oxidizing a free secondary hydroxyl group which is unprecedented (entry 12). Furthermore, the present protocol was successfully applied to complex alkene **9**, without isomerizing the trisubstituted alkene to the tetrasubstituted alkene, to give enone **10**, a key step in the first total synthesis of (−)-samaderine Y (entry 18).[10]

Allylic oxidation of simple alkenes was also investigated. They were oxidized to the corresponding enones smoothly under an oxygen atmosphere[7] (Table 2, entries 19−27).[9]

Table 2. Allylic Oxidation of Simple Alkenes

entry[a]	substrate	product	time (h), yield (%)
19	 **11**	 **12**	48, 52[c]
20	 **13**	 **14**	48, 70
21	 **15**	 **16**	48, 71
22	 **17**	 **18**	48, 63
23	 **19**	 **20**	48, 52[c]
24	 **21**	 **22**	48, 74[b]
25	 **23**	 **24**	48, 71
26	 **25**	 **26**	48, 65
27	 **27**	 **26**	48, 60

[a] For experimental details, see Supporting Information. [b] Starting material was recovered; see Supporting Information. [c] High volatility of the substrate and/or product resulted in material loss and, hence, low reaction yield.

Similar to allylic oxidation of complex alkenes, excellent regioselectivities in the abstraction of the hydrogen atom on secondary over primary carbon were observed. Interestingly, (+)-2-carene (**25**) (after isomerization) and (+)-3-carene (**27**)

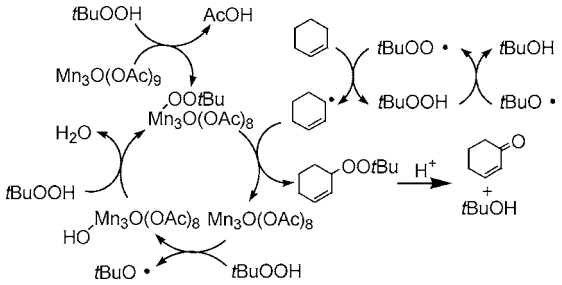
(9) For details, please refer to the Supporting Information.

(10) Shing, T. K. M.; Yeung, Y.-Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 7981.

were transformed into the same enedione **26**. Moreover, functional group (phenyl, ketone, acetal) compatibility was further demonstrated here. Rigid cyclopropane and cyclobutane rings survived the conditions without ring opening.

For mechanistic studies, the pH value dropped gradually during the reaction. After 6 h, a reddish-brown suspension was observed and the pH was about 5. The acidity increased to pH 4 after 36 h. A plausible explanation is that an acetate unit in $Mn_3O(OAc)_9$ was displaced by a TBHP molecule to give in situ acetic acid which is responsible for the mild acidity of the reaction (Scheme 1). Fortunately, acid-sensitive

Scheme 1. Proposed Catalytic Cycle of Manganese(III) Acetate Catalyzed Allylic Oxidation

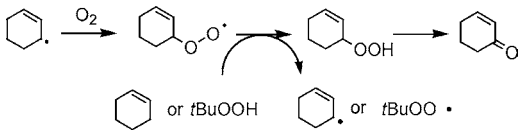


acetal moieties survived the conditions (entries 7, 15, 16, 18, and 23).

^{1}H NMR studies supported our proposal that a new *t*-Bu signal was observed at 1.18 ppm after the addition of manganese(III) acetate to a solution of TBHP.[9] We believe that *t*-BuOOMn$_3$O(OAc)$_8$ is the active species. For the reaction of 1-phenylcyclohexene (**13**), the corresponding *tert*-butyl peroxy ether was isolated.[9] Resubmitting the *tert*-butyl peroxy ether to allylic oxidation gave the corresponding enone **14**, a mechanism in accordance with that reported in the literature.[3f,g] The formation of acetone and molecular oxygen during the reaction indicated the existence of *tert*-butoxy and *tert*-butyl peroxy radicals, respectively, which is consistent with the radical nature of the reaction.[9] Facile oxidation of benzylic carbons to the corresponding ketones also demonstrated the case.[9] The *tert*-butyl peroxy radical was successfully traced[9] using electron paramagnetic resonance (EPR) spectroscopy, and the results matched those reported in the literature.[11] Termination of the reaction upon addition of 2,6-di-*tert*-butyl-4-methylphenol corroborated this phenomenon. On the basis of the above findings, a proposed catalytic cycle of the allylic oxidation is illustrated in Scheme 1, which involves selective allylic hydrogen abstraction to generate the allyl radical, transfer of the *tert*-butyl peroxy ligand from the metal center to the allyl radical, and acid-promoted degradation of the *tert*-butyl peroxy ether to the corresponding enone. The oxidation preference of the allylic methylene group to the methyl group (entries 18, 19, 22, and 24−27) should attribute to the greater radical stability of the secondary carbon than that of the primary carbon.[12]

For allylic oxidation of simple alkenes in an oxygen atmosphere (entries 19−27), oxygen would react with a cyclohexene radical to give a peroxy radical which should be useful in the hydrogen abstraction of cyclohexene or *t*-BuOOH to give more radical species (Scheme 2).[3f,9] The resulting peroxide could be oxidized to enone.

Scheme 2. Proposed Reaction between Cyclohexene and Oxygen



In summary, a mild, efficient, regioselective, and highly functional group compatible allylic oxidation protocol using manganese(III) acetate dihydrate as the catalyst has been developed.

Acknowledgment. This work was supported by a CUHK direct grant. Special thanks go to Prof. H. K. Lee, Department of Chemistry, The Chinese University of Hong Kong, for valuable advice on mechanistic studies.

Supporting Information Available: Experimental procedures and additional information. This material is available free of charge via the Internet at http://pubs.acs.org.

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