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Mechanisms of $Mn(OAc)_3$-based oxidative free-radical additions and cyclizations

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ABSTRACT

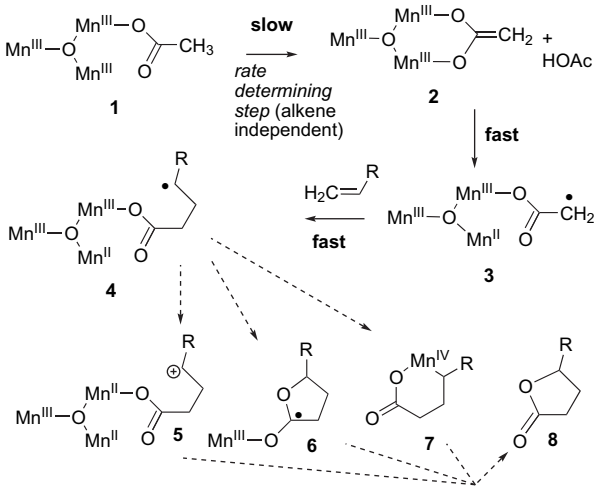
The mechanistic details of $Mn(OAc)_3$-based oxidative free-radical additions and cyclizations are reviewed. The mechanisms of electron transfer to generate radicals, electron transfer to convert the radicals to oxidized products, and further oxidation of the products are covered.

1. Introduction

The oxidative addition of acetic acid to alkenes by two equivalents of $Mn(OAc)_3$ in AcOH at reflux to give γ-lactones was first reported in 1968 by Heiba and Dessau,[1a] and Bush and Finkbeiner.[1b] Over the past 40 years the use of $Mn(OAc)_3$ to oxidatively initiate free-radical reactions of mono and 1,3-dicarbonyl compounds has been extensively developed and widely reviewed with an emphasis on synthetic applications.[2] These reactions are mechanistically complex with several competing pathways. Slight changes in the substrate or reaction conditions can produce major changes in the reaction pathway that can have a major impact on the products formed. The mechanistic details needed to predictably use these reactions are widely scattered. In this brief review, the various mechanisms of these reactions are presented with a focus on the one-electron oxidation initiation step that generates a free radical and the oxidation step that converts a free radical to the final product.

2. Oxidative addition of acetic acid to alkenes with $Mn(OAc)_3$

Fristad and Peterson extensively studied the mechanism of the oxidative addition of acetic acid to alkenes to form lactones.[3] The hydrated form of $Mn(OAc)_3$, that is usually used, $Mn(OAc)_3 \cdot 2H_2O$, is an oxo-centered trimer of Mn^{III} with bridging acetates.[3] The rate determining step is the loss of a proton from a complexed acetate such as **1** to give a bis Mn^{III} enolate such as **2** (see Scheme 1). This is followed by a rapid electron transfer with loss of Mn^{II} to form the complexed free-radical **3**. The carbon–carbon bond forming step involves the addition of radical **3** to an alkene to give radical **4**. The alkene is not involved in the rate determining step, which requires that a slow step occurs before formation of the carbon–carbon bond. Enolization is likely to be the rate determining step because the log of the rate of oxidation relative to that of acetic acid equals $0.344(\Delta pK_a)$ for five monosubstituted acetic acids covering a broad acidity range. Enolization appears to be irreversible since deuterium is not incorporated into **1** when the reaction is run in deuterated acetic acid.



Scheme 1. Mechanism of lactone formation from acetic acid, $Mn(OAc)_3$ and alkenes.

The conversion of radical **4** to the final product lactone **8** also involves an oxidative electron transfer. The detailed mechanism of this oxidation is not known, but it is well known that Mn^{III} will not oxidize isolated secondary radicals to cations. Therefore the carboxylate group must be intimately involved in the oxidation step. One possibility is the oxidation of the radical by Mn^{III} bound to the carboxylate to give cation **5** that cyclizes to **8**. A second possibility involves addition of the radical to the oxygen of the carbonyl group

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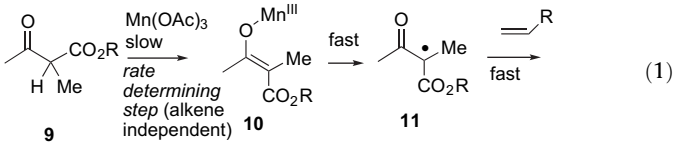
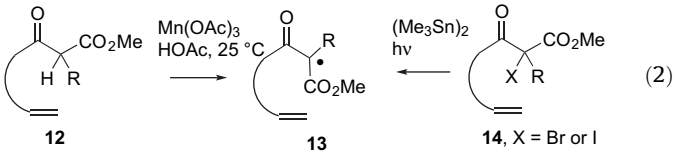
to give radical **6**, which should undergo electron transfer with loss of Mn^{II} to give lactone **8**. A final possibility involves bonding of the Mn^{III} to the radical to give metallocycle **7**, which undergoes reductive elimination with loss of Mn^{II} to give lactone **8**. Numerous variations of these mechanisms can also be considered.

3. Electron transfer to generate radicals

Our studies of the oxidation of α-alkyl β-keto esters such as **9** with $Mn(OAc)_3$ indicated that enolization is also the rate determining step (see Eq.(1)).[4] Formation of **10** by enolization is slow and electron transfer with loss of Mn^{II} to give radical **11** is rapid. The rate of reaction is therefore independent of alkene concentration or the nature of the tether in cyclizations. The geometry of radical **11** with the carbonyl group anti to the ester is inferred by analysis of the stereochemistry of the cyclic products formed. In collaboration with Dennis Curran, we carried out a comparison series of reactions in which radical **13** was obtained by oxidation of a series of β-keto esters **12** with $Mn(OAc)_3$ or by atom transfer reaction from α-halo-β-keto esters with hexamethylditin (see Eq. (2)).[5] Comparable regio- and stereochemical results were obtained in all cases strongly suggesting that free radical **13**, which is no longer complexed to manganese, is involved in the $Mn(OAc)_3$-mediated oxidative cyclizations. Some differences in regiochemistry or stereochemistry between oxidative cyclizations and atom-transfer cyclizations would be expected if a metal-complexed radical were involved.

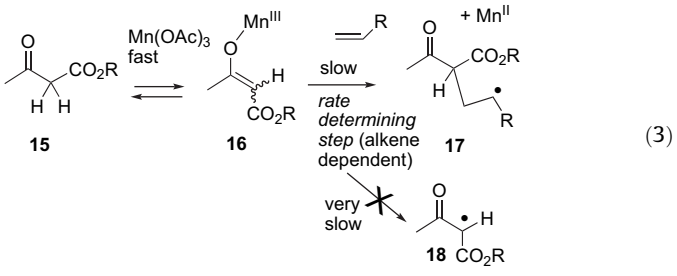


(1)



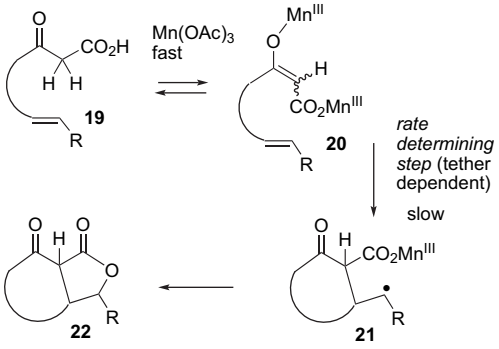
(2)

To our initial surprise, replacement of the methyl group of **9** with the second α-hydrogen atom of **15** changes the rate determining step in the mechanism. Enolization of **15** to give **16** is fast and reversible, and electron transfer to give the radical **18** is very slow and probably not relevant to product formation (see Eq. (3)).[4] The rate depends on alkene concentration and the rate determining step is presumably the reaction of Mn^{III} enolate **16** with the alkene to give radical **17** with loss of Mn^{II}. If addition of the alkene to the Mn^{III} enolate is the rate determining step, the length of the tether should, and does, affect the rate of oxidative cyclization of unsaturated α-unsubstituted β-keto esters.



(3)

Corey studied the oxidative free-radical cyclization of a series of unsaturated β-keto acids **19** with $Mn(OAc)_3$.[6] The nature of the tether also affects the rate of oxidative cyclization of unsaturated β-keto acids. The time required for complete reaction ranges from 20 min to 24 h as a function of the nature of the tether. Therefore, the mechanism for these reactions also involves a fast and reversible formation of enolate **20**, followed by a slow, rate determining addition of the alkene to the manganese enolate to give radical **21** with loss of Mn^{II}. The oxidation of radical **21** to give lactone **22** is analogous to the oxidation of radical **4** to give lactone **8**.

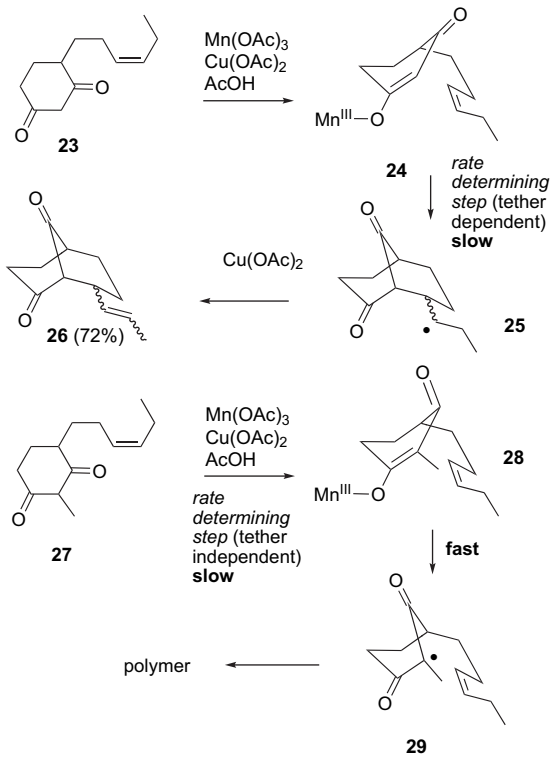


(4)

Why does the presence of the α-alkyl group have such a profound effect on the mechanism of the reaction? The rate of enolization will depend on the both the thermodynamic and kinetic acidity of the α-proton(s). Introduction of an electron-donating alkyl group decreases the thermodynamic acidity of the α-proton by 1–2 orders of magnitude. All α-substituents, regardless of their electronic character, will sterically retard the enolization. On the other hand, the α-alkyl group should facilitate the oxidation of **18**–**19**. Electrochemical data for the oxidation of enolates of β-dicarbonyl compounds to the radical in DMSO indicates that an α-methyl group facilitates the oxidation by 0.25−0.4 V.[7]

The introduction of an α-alkyl substituent increases the p*K*a, which decrease the rate of enolate formation and accelerates the oxidation by making the enolate easier to oxidize. This mechanism with rate determining enolate formation holds for monocarbonyl and less acidic 1,3-dicarbonyl compounds. For more acidic compounds such as α-unsubstituted β-keto esters and acids and β-diketones, enolization occurs readily and oxidation is slow. $Mn(AcAc)_3$ is a stable commercially available Mn^{III} enolate. For these compounds, the rate determining step appears to be the interaction of the Mn^{III} enolate with an alkene to form a radical such as **17** or **20** with loss of Mn^{II}. Unfortunately, the addition of a Mn^{III} enolate to an alkene to give a radical and Mn^{II} does not fit well with our arrow pushing model of organic chemistry making it hard to conceptualize this mechanism, which is required by the observation of rate dependence on alkene concentration or tether length. Mechanisms are still routinely drawn with intermediates such as **18** that are not consistent with experimental data.

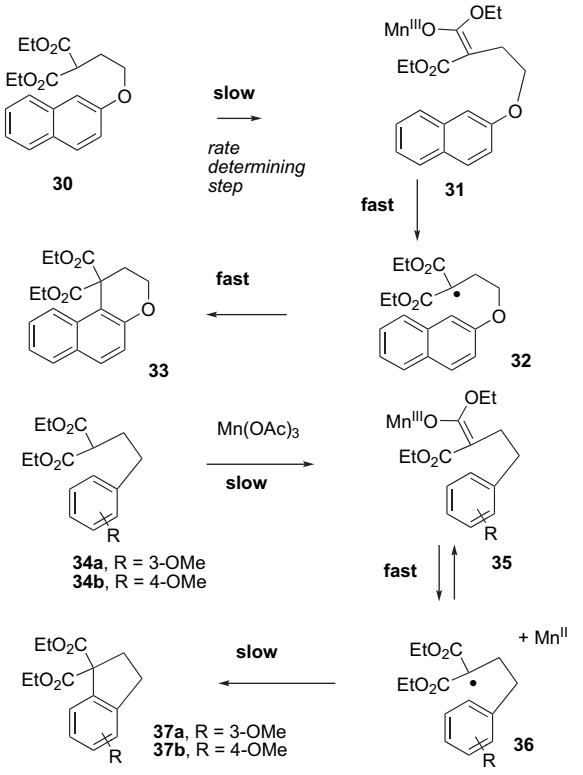
The different mechanisms of these reactions can have profound effects on the yields of these reactions. For instance, treatment of **23** with $Mn(OAc)_3$ and $Cu(OAc)_2$ in AcOH at 25 °C for 2 h affords **26** in 72% yield as a mixture of stereoisomers (see Scheme 2).[8] A similar reaction with **27** affords a complex polymeric mixture. Reaction of **23** with Mn^{III} should give enolate **24** rapidly. Loss of Mn^{II} from **24** to give the radical will be very slow because there is a hydrogen atom at the α-position of the enolate. The slow rate determining step is cyclization of the alkene onto the Mn^{III} enolate with loss of Mn^{II} to give radical **25**, which is oxidized by $Cu(OAc)_2$ to give **26** as discussed below. On the other hand, **27** reacts with Mn^{III} in a slower rate determining step to give α-methyl enolate **28**. Rapid loss of



Scheme 2. Comparison of the reaction of diketone **23** and α-methyl diketone **27**.

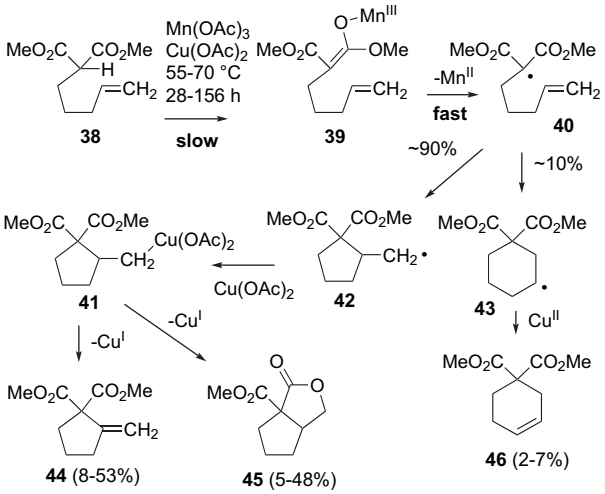
Mn^{II} affords radical **29**, which polymerizes rather than cyclizing through the higher energy conformation shown with the alkene in close proximity to the free radical.

In a study of $Mn(OAc)_3$-based oxidative cyclization of α-arylalkylmalonates, Citterio suggested a variation of this mechanism.[9] The reaction of malonate **30** to give **33** was shown to be first order in both **30** and Mn^{III} as expected for the rate determining formation of enolate **31** from an α-substituted substrate (see Scheme 3). Loss of Mn^{II} from **31** to give radical **32** and cyclization of radical **32** to give **33** are rapid. However, the oxidative cyclization of **34a** afforded **37a** in 44% yield after 3 h with 93% conversion of **34a** whereas the oxidative cyclization of **34b** afforded **37b** in only 30% yield after 24 h with only 60% conversion of **34b**. This was explained by suggesting that the loss of Mn^{II} from enolate **35** to give radical **36** is reversible. Cyclization of **36** to form an indane is slow and the 4-methoxy group further retards this cyclization so that substrate dependence is observed.

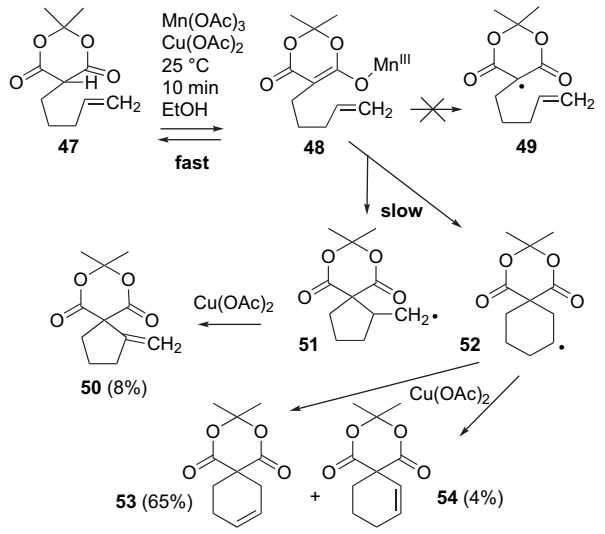


Scheme 3. Mechanisms of the oxidative cyclizations of **30** and **34**.

The different mechanisms and their effect on the products formed show up very clearly in a comparison of the reactions of dimethyl 4-pentenylmalonate (**38**) and 4-pentenyl Meldrum's acid (**47**) (see Schemes 4 and 5). Enolization of dimethyl 4-pentenylmalonate (**38**) to give manganese enolate **39** is the slow, rate determining step.[10] Rapid loss of Mn^{II} from **39** generates radical **40**, which cyclizes to give a ~9:1 mixture of cyclopentanemethyl radical **42** and cyclohexyl radical **43**. Reaction of **42** with $Cu(OAc)_2$ gives Cu^{III} intermediate **41**, which undergoes oxidative elimination to give methylenecyclopentane **44** and ligand transfer to give lactone **45**. A similar oxidation converts **43** to cyclohexene **46**. Reaction in AcOH (55 °C, 28 h) affords a 2.5:1 mixture of **45** and **44**. Reaction in EtOH (60 °C, 156 h) is much slower, but yields a 2:3



Scheme 4. Oxidative cyclization of malonate **38**.

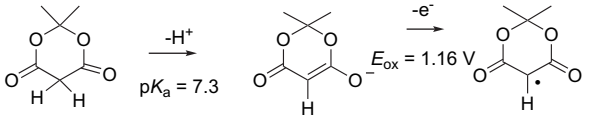


Scheme 5. Oxidative cyclization of Meldrum's acid **47**.

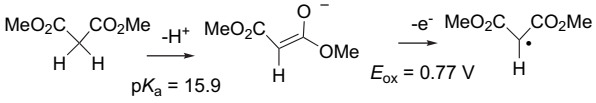
mixture of **45** and **44**, whereas reaction in DMSO (75 °C, 68 h) forms a 1:10 mixture of **45** and **44**.[10]

Oxidative cyclization of **47** in EtOH with $Mn(OAc)_3$ and 1 equiv of $Cu(OAc)_2$ for 10 min at 25 °C provides 8% of methylenecyclopentane **50**, 65% of cyclohexene **53** and 4% of cyclohexene **54**.[11] Oxidation of cyclohexyl radical **52** with Cu^{II} selectively removes the least hindered proton to form mainly cyclohexene **53**. As expected, oxidative cyclization of **47**, with a half life in EtOH of <5 min at 25 °C and 2 h at −30 °C, is much faster than that of the less acidic dimethyl ester **38**, which requires 156 h at 60 °C for complete reaction. More surprisingly, **47** provides predominantly products derived from cyclohexyl radical **52**, whereas **38** yields mainly products derived from cyclopentanemethyl radical **42** suggesting that these two reactions are mechanistically distinct. Furthermore, oxidative cyclization of the analogue of **47** with a hexyl group on the distal end of the double bond proceeds with a half life of 2 h at 25 °C. The change in half life from <5 min with **47** to 2 h with the addition of an alkyl substituent establishes that the double bond participates in the rate determining step, which is cyclization of **48** to give **51** and **52**. Loss of a proton from **47** to give Mn^{III} enolate **48** should be rapid and reversible. Loss of Mn^{II} from enolate **48** to form radical **49** cannot be occurring because this reaction would proceed at the same rate regardless of substituents on the double bond.

Bausch's studies of the oxidation potential of the enolates of dimethyl malonate and Meldrum's acid in DMSO provide data that helps explain the differing behavior of malonate **38** and Meldrum's acid **47**.[12] The pK_as of Meldrum's acid and dimethyl malonate in DMSO are 7.3 and 15.9, respectively, indicating that enolization of Meldrum's acid is favored by 11.8 kcal/mol (Eqs. (5) and (6)). On the other hand the oxidation potentials of the enolates are 1.16 and 0.77 V, respectively, indicating that it is 9 kcal/mol easier to oxidize the enolate of dimethyl malonate. Loss of a proton from **38** to give enolate **39** should be slow, and of Mn^{II} from **39** to give acyclic radical **40** should be fast. On the other hand, loss of a proton from **47** to give enolate **48** should be fast. However, loss of Mn^{II} to give acyclic radical **49** will be slow because the oxidation potential of **48** is large, so that cyclization of **48** to **51** and **52** is the rate determining step. Since these two cyclizations are mechanistically distinct, there is no contradiction in the preferential formation of cyclopentanemethyl radical **42** from **38** and cyclohexyl radical **52** from **47**.

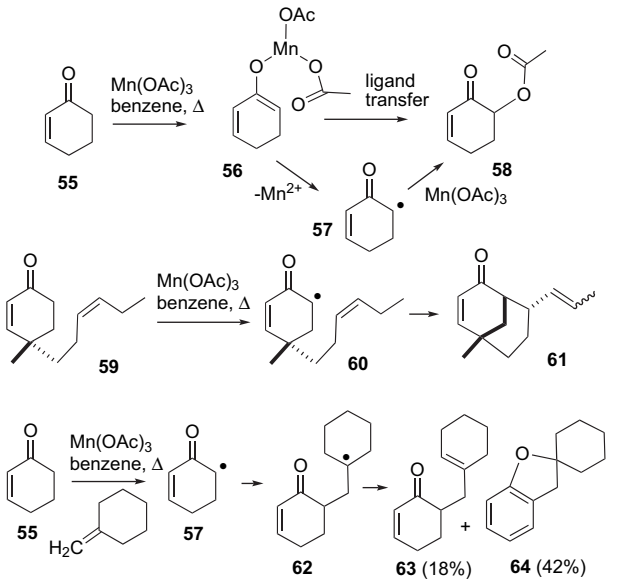


(5)



(6)

Demir and Watt have developed a widely used and versatile α′-acetoxylation of α,β-unsaturated ketones with anhydrous $Mn(OAc)_3$ in benzene (see Scheme 6).[2i,13] Initially this reaction was proposed to proceed by conversion of the enone **55** to the manganese enolate **56** followed by ligand transfer to give the observed product **58**. However, α-keto radical **57** can be formed by oxidation of 2-cyclohexenone (**55**) and is probably also an intermediate in the formation of **58**. For instance, oxidative cyclization of **59** afforded **61** in 61% yield via the intermediacy of radical **60**[14] and oxidation of cyclohexenone (**55**) in the presence of methylenecyclohexane afforded dihydro-benzofuran **64** (42%) and enone **63** (18%) resulting from formation of α-keto radical **57**, which adds to the alkene to



Scheme 6. Oxidative acetoxylation or alkene addition reactions of α,β-unsaturated ketones.

give **62**, which then reacts further to give **63** and **64**.[15] Saturated ketones are also converted to α-keto radicals.[16]

Narasaka introduced manganese picolinate [$Mn(pic)_3$].[17] $Mn(pic)_3$ has an octahedral manganese, with three picolinates bound to a single Mn^{III}, while $Mn(OAc)_3$ is an oxo-centered trimer. Not surprisingly, there are important differences in the reactivity of $Mn(OAc)_3$ and $Mn(pic)_3$, which have been fully addressed.[10b,17] For instance, $Mn(pic)_3$, or $Mn(pic)_2$, which is produced as a byproduct of oxidative radical formation, can suppress the oxidation of some radicals by $Cu(OAc)_2$.[10b]

Ceric ammonium nitrate (CAN) and the non-polar variant ceric tetrabutylammonium nitrate (CTAN) have been widely used to generate radicals oxidatively.[18] These reactions were initially studied mechanistically by Baciocchi and Ruzziconi[19] and more recently by Flowers.[20] CAN oxidations are quite different from $Mn(OAc)_3$ oxidations in that oxidation can occur without initial deprotonation of the dicarbonyl compound. The enol tautomer is oxidized to the radical cation, which may lose a proton to give a radical.

A more significant difference involves the conversion of the radical intermediates to products. $Mn(OAc)_3$ is often used with $Cu(OAc)_2$, which oxidizes radicals to alkenes selectively as discussed below. CAN is much cheaper than $Mn(OAc)_3$ and can be used in a wide variety of solvents, whereas AcOH is usually the best solvent for $Mn(OAc)_3$ reactions. However, $Cu(OAc)_2$ cannot be used with CAN so products such as **26** and **61** cannot be obtained from CAN oxidations and α-acetoxy enones such **58** cannot be obtained with CAN. Furthermore, nitrate esters are often formed with CAN.[21] Both CAN and $Mn(OAc)_3$ can be used to generate radicals, but the nature of the oxidation steps that lead to products are quite different as is seen in the detailed study of the oxidation of 4-pentenylmalonate esters with $Mn(OAc)_3$[10] and CAN[21] so that $Mn(OAc)_3$ is the preferred reagent for many applications.

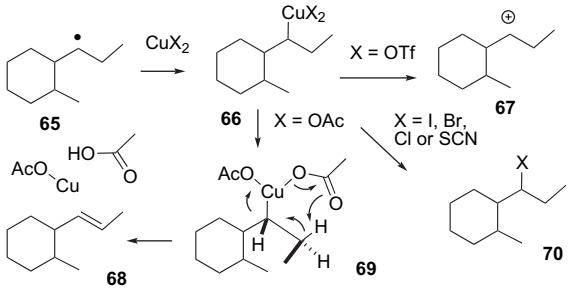
4. Electron transfer to convert radicals to products

Mn^{III} will oxidize γ-carboxy radicals such as **4** that are formed by oxidation addition of acetate to alkenes to γ-lactone **8** regardless of whether the radical is secondary or tertiary. The addition of acetic acid and substituted acetic acids to alkenes to give γ-lactones is general for alkenes. However, isolated primary or secondary radicals abstract a hydrogen atom from the solvent more rapidly than

they are oxidized by Mn^{III}, so the oxidation of **4** must involve participation by the carboxylate. This might involve intramolecular transfer by a bound Mn^{III} to give **5**, addition of the radical to the carboxylate to give **6**, which would be readily oxidized to **8**, or by the formation of **7** followed by reductive elimination of Mn^{II} to yield **8**. Mn^{III} will oxidize tertiary radicals to give tertiary cations that undergo normal E1 and S_N1 reactions.

Addition of 1,3-dicarbonyl compounds to alkenes affords isolated radicals such as **17** and **25** that do not contain a proximal manganese carboxylate. If these radicals are tertiary, they will be oxidized by Mn^{III} to cations that can lose a proton to give an alkene or react with solvent to give a tertiary acetate. Mn^{III} will also oxidize allylic radicals to allylic acetates and cyclohexadienyl radicals, which are formed by the addition of radicals to aromatic rings, to cyclohexadienyl cations, which lose a proton to give substituted aromatic rings as in the formation of **33** and **37**. Hydrogen atom abstraction from solvent is the major pathway if these radicals are primary or secondary, e.g. **17** and **25**, unless $Cu(OAc)_3$ or another co-oxidant is used.

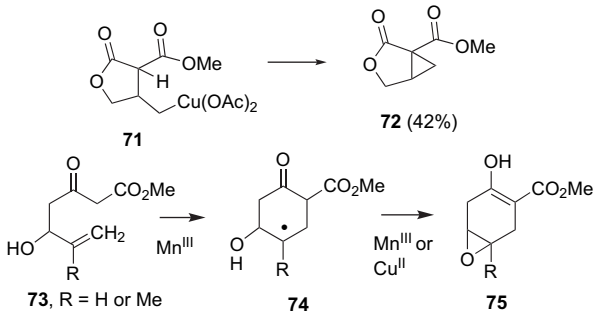
Kochi and co-workers demonstrated that Cu^{II} reacts rapidly ($\sim 10^6\ s^1\ M^{-1}$) with radicals such as **65** to give alkylcopper^{III} intermediates such as **66** (see Scheme 7).[22] These can react further with loss of Cu^{I} to form either an alkene **68** by oxidative elimination, to transfer a ligand to give **70**, or to form carbocation **67**. Formation of alkene **68** by oxidative elimination is the major pathway from the reaction of $Cu(OAc)_2$ with primary and secondary radicals. Tertiary, allylic, and other easily oxidized radicals give cations with copper^{II} carboxylates. Other Cu^{II} salts give cations and ligand transfer products with all types of radicals. Heiba and Dessau found that $Cu(OAc)_2$ is compatible with $Mn(OAc)_3$ and that Cu^{II} oxidizes secondary radicals to alkenes 350 times faster than Mn^{III} does.[23] The Cu^{I} that is produced is rapidly reoxidized to Cu^{II} by Mn^{III} so that only a catalytic amount of $Cu(OAc)_2$ is needed and 2 equiv of $Mn(OAc)_3$ are still required. During the course of our studies we observed that, contrary to earlier indications,[24] $Cu(OAc)_2$ oxidizes secondary radicals to give primarily (*E*)-alkenes and the less substituted double bond (Hofmann elimination product).[25] This selectivity is synthetically valuable since Cu^{II} oxidation of primary and secondary radicals formed in oxidative cyclizations often gives primarily or exclusively a single regio- and stereoisomer as detailed below.



Scheme 7. Oxidation of radicals by Cu^{II} salts.

The elimination probably occurs by formation of an alkyl Cu^{III} intermediate with two bound acetates. The acetate abstracts a proton with formation of an alkene, acetic acid and Cu(OAc) in a syn elimination (see **69**). Preference for the formation of the less substituted double bond (Hofmann product) and (*E*)-alkene is usually observed in syn eliminations. This mechanism also explains the observation that elimination occurs selectively only with copper carboxylates. Ligand transfer or oxidation to the cation occurs with copper halides, triflate, or sulfate.

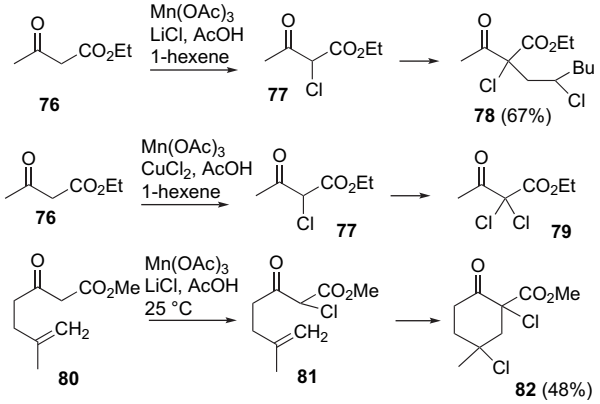
Secondary radicals are almost always oxidized to alkenes by Cu(OAc). The organocopper^{III} intermediate formed from primary radicals can interact with adjacent functionality to give lactones as in the conversion of radical **42** to lactone **45** and to give cyclopropanes as in the conversion of **71** to cyclopropane **72** (see Scheme 8).



Scheme 8. Oxidation of radicals to form cyclopropanes or epoxides.

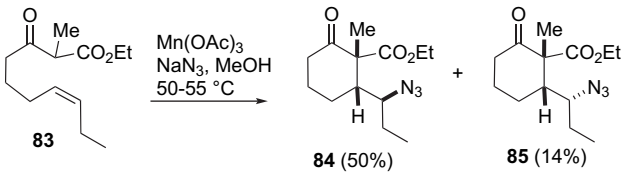
Oxidative cyclization of δ-hydroxy β-keto ester **73** affords epoxide **75** as the major product in 50–60% yield.[26] β-Hydroxy radical **74** is oxidized to the epoxide by either Mn^{III} or Cu^{II} in a process, that is analogous to the oxidation of radical **4** to lactone **8**. Epoxides are also formed from β-hydroxy radicals generated by $Pb(OAc)_4$ oxidative decarboxylation of β-hydroxy acids by either Pb^{IV} or Cu^{II}, which suggest that oxidation of β-hydroxy radicals to epoxides is general.[25]

Addition of other anions to the reaction mixture affects the nature of the electron transfer process. For instance, Vinogradov and Nikishin reported that oxidation of ethyl acetoacetate (**76**) with 4 equiv of $Mn(OAc)_3$ and excess LiCl in the presence of 1-hexene results in the formation of dichloride **78** (see Scheme 9).[27,28] Monochloride **77** is formed initially. The use of chloride ion is not compatible with Cu^{II}; only α,α-dichlorination to give **79** is observed. The combination of $Mn(OAc)_3$ and LiCl has seen very limited synthetic applications because the chlorides that are formed are of little utility. However, oxidation of **80** with $Mn(OAc)_3$ and excess LiCl forms **81**, which reacts further to give **82** as the major product.[4,26]



Scheme 9. Oxidative reaction of radicals with chloride.

The radicals formed in the Mn^{III}-based oxidative free-radical cyclizations of β-keto esters and malonate esters can be trapped oxidatively with $Mn(OAc)_3$ and sodium azide to provide cyclic and



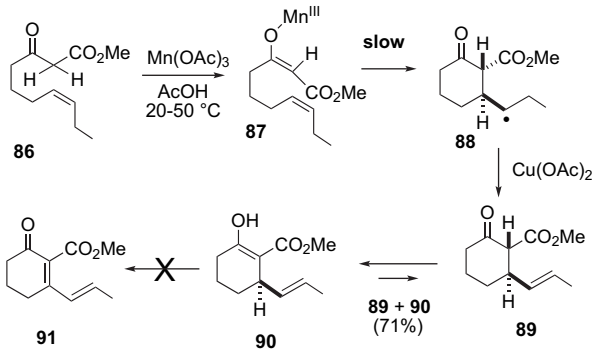
Scheme 10. Oxidative reaction of radicals with azide.

bicyclic azides such as **84** and **85** in 30–80% yield (see Scheme 10). Reduction of the azides affords bicyclic and tricyclic lactams.[29]

These reactions can also be terminated by the addition of the radical to a nitrile or carbon monoxide, or by hydrogen atom abstraction from the solvent. This is particularly useful in converting vinyl radicals (obtained from addition to alkynes) to alkenes, since vinyl radicals are not oxidized to vinyl cations. The hydrogen atom can come from the solvent or from the α-hydrogen atom of another molecule of the β-dicarbonyl compound. Ethanol is the preferred solvent for these reactions, since it is a better hydrogen atom donor than acetic acid.[10a,30] These reactions have been reviewed previously[2] and are not discussed in detail here because they don't involve electron transfer.

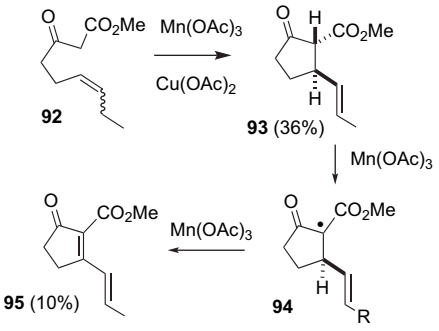
5. Further oxidation of products

Oxidative cyclization of unsaturated β-dicarbonyl compounds that have two α-hydrogen atoms will give products that still have one α-hydrogen atom and can be oxidized further. If the product is oxidized more slowly than the starting material, the cyclization product can be isolated in good yield. Reaction of **86** with $Mn(OAc)_3$ affords enolate **87**, which cyclizes to **88** in the slow rate determining step (see Scheme 11). Oxidation by $Cu(OAc)_2$ provides ketone **89**, which tautomerizes to give a 1.3:1 equilibrium mixture of enol **90** and ketone **89** in 71% yield.[31,32] Further oxidation of **89** or **90** to give **91** does not occur.



Scheme 11. Oxidative cyclization of **86**.

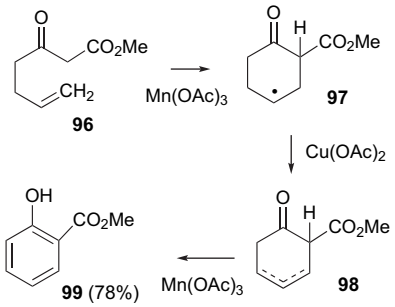
In other cases, the product is oxidized at a rate competitive with that of the starting material so that mixtures of products are obtained. For instance, oxidative cyclization of **92** affords 36% of **93** and 10% of dienone **95** formed by further oxidation of **93** to give radical **94**, which is further oxidized to give **95** (see Scheme 12). Competitive oxidation of the product is usually not a problem in intermolecular addition reactions because a vast excess of the oxidizable substrate, such as acetone or acetic acid, is usually used as solvent. Use of excess substrate is not possible in oxidative cyclizations.



Scheme 12. Oxidative cyclization of **92** and further oxidation to **95**.

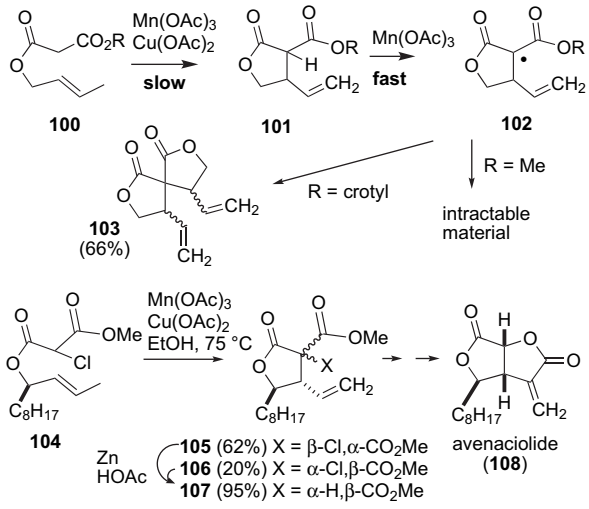
The rate determining step in the cyclization of α-unsubstituted β-keto esters is the addition of the double bond to the manganese enolate. Oxidative cyclization of **86** is faster than oxidative cyclization of **92** since the double bond is better able to participate in the rate determining step with a longer tether. Furthermore, oxidation of **93**–**95** (50%, 1 day) is much faster than the oxidation of **89** and **90** (0%, 6 days). We cannot explain this difference, but note that **93** is ketonic, whereas **90** is enolic. In other cases we have also observed that enolic 1,3-dicarbonyl compounds are oxidized slowly by $Mn(OAc)_3$.

In the third category, the product is oxidized much more readily than the starting material so that none of the initial product is isolated. These reactions may still be synthetically useful if the products of further oxidation are monomeric. For instance, oxidative cyclization of **96** provides 78% of methyl salicylate (**99**) (see Scheme 13).[26] Oxidative cyclization gives radical **97**; oxidation of **97** by Cu^{II} gives **98**, probably as a mixture of double bond positional isomers. The unsaturated cyclic β-keto ester **98** is more acidic than **96** and is rapidly oxidized further by 2 equiv of Mn^{III} to give a cyclohexadienone that tautomerizes to phenol **99**. The overall reaction consumes 4 equiv of $Mn(OAc)_3$. Oxidation of simple ketones will often give products that can be oxidized further. The oxidative cyclization of alkenyl substituted cyclic ketones works well because enolization (and further oxidation) of the bicyclic ketone product is prevented by Bredt's rule.[16]



Scheme 13. Oxidative cyclization to form salicylate esters.

The oxidative cyclization of crotyl malonate esters also falls into the third category. Oxidative cyclization of **100** affords **101**, which is rapidly oxidized to radical **102** (see Scheme 14). Radical **102** gives intractable material if R=Me, but affords 66% of **103** if R=crotyl.[33]



Scheme 14. Oxidative cyclization of allylic malonates and α-chloromalonates.

The lactone group makes the α-hydrogen of **101** much more acidic[34] than those of **100** so that product lactone **101** is oxidized more rapidly than diester **100**.

Further oxidation cannot occur if there are no acidic α-hydrogens in the product. α-Alkyl groups prevent further oxidation, but cannot then be removed. α-Chloro substituents serve as protecting groups preventing further oxidation of the product.[4,35–37] Oxidative cyclization of **104** affords 82% of a 3.1:1 mixture of **105** and **106**, which was elaborated to avenaciolide (**108**). Alternatively, reduction of the mixture with Zn afforded 95% of lactone **107**, which is not accessible by oxidative cyclization of the unchlorinated malonate because **107** is oxidized further analogously to **101**.[35]

6. Conclusion

$Mn(OAc)_3$-based oxidative free-radical additions and cyclizations proceed by at least two different mechanisms. For compounds that are not acidic and form easily oxidized enolates, the slow rate determining step involves formation of the Mn^{III} enolate followed by rapid Mn^{II} loss to generate a manganese-free free-radical. For more acidic compounds that form harder to oxidize enolates, the slow rate determining step involves addition of the alkene to the manganese enolate with loss of Mn^{II} and formation of a carbon–carbon bond in the same steps. The product radical can be oxidized to alkenes by $Cu(OAc)_2$ through Cu^{III} intermediate **69** by a Hofmann type elimination to give selectively the less substituted (*E*)-alkene.

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