Manganese(III)-Based Oxidative Free-Radical Cyclizations

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Received June 26, 1995 (Revised Manuscript Received September 27, 1995)

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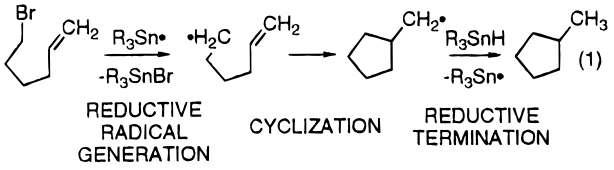
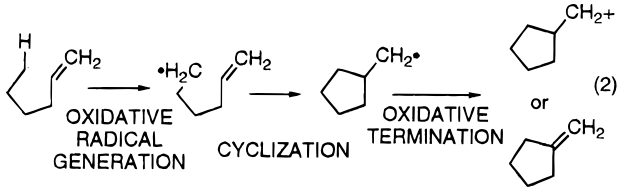
I. Introduction

A. Oxidative Free-Radical Cyclizations

Radical cyclization of alkenes has become a valuable method for the synthesis of cyclic compounds during the past 30 years.[1–3] A typical, widely used procedure involves the reduction of a halide or other functional group to a radical with R_3SnH, followed by cyclization and reduction of the resulting radical to a hydrocarbon in the chain propagation steps (eq 1). While this sequence often gives high yields of



products, this approach is limited, leading to relatively unfunctionalized products resulting from a net two-electron reduction. Oxidative free-radical cyclization in which the initial radical is generated oxidatively and/or the cyclic radical is terminated oxidatively, has considerable synthetic potential, since more highly functionalized products can be prepared from simple precursors (eq 2).



Oxidative formation of an acyclic radical involves the formal loss of a hydrogen atom. In practical

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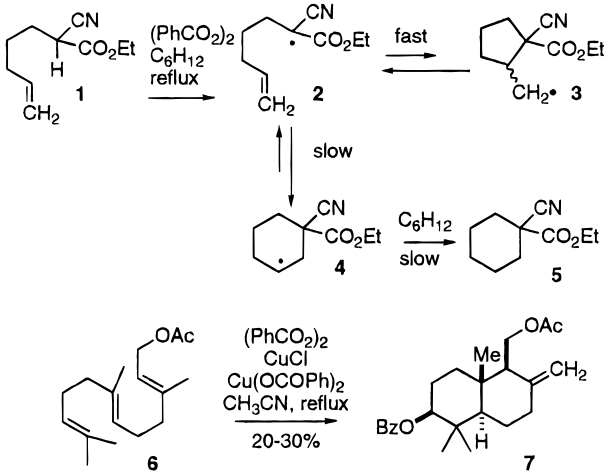
terms this is often accomplished by loss of a proton and oxidation of the resulting anion with a one-electron oxidant to generate a radical. The advantage of this method of radical formation is that the precursor is simple and usually readily available. A potential disadvantage is that the cyclization product may also be susceptible to further deprotonation and oxidation.

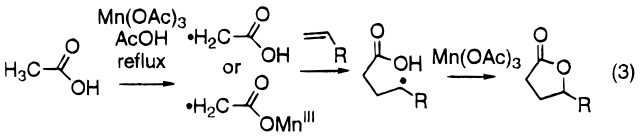
Oxidative termination of radical cyclizations is advantageous since more highly functionalized, versatile products are produced than from reductive terminations that deliver a hydrogen atom. Oxidation of the radical to a cation by one-electron oxidants, oxidation of the radical to an alkene with Cu(II) carboxylates, and reaction with heteroatom donors to give halides or sulfides are all oxidative terminations. The atom-transfer reactions developed by Curran that afford halides, and the thio transfer reactions developed by Barton are broadly useful procedures for oxidative termination of radical reactions.[1−3]

Some early synthetically useful radical cyclizations were carried out under oxidative conditions. Julia extensively explored the radical cyclization of unsaturated cyanoacetates.[4] Oxidation of **1** with benzoyl peroxide in cyclohexane at reflux generates radical **2** by hydrogen abstraction. Radical **2** cyclizes to give cyclopentylmethyl radical **3**. Since the only termination possibility is the slow abstraction of a hydrogen from cyclohexane, and the cyclization of **2** is reversible, the more stable cyclohexyl radical **4** is formed and abstracts a hydrogen from cyclohexane to give **5**. These reactions proceed by oxidative initiation, but are terminated reductively. Breslow reported the oxidative cyclization of farnesyl acetate (**6**) with benzoyl peroxide, cuprous chloride, and cupric benzoate in acetonitrile at reflux to generate 20−30% of **7**.[5] Both the initiation and termination of this tandem radical cyclization are oxidative. Unfortunately, initiation of a radical cyclization by addition of the benzoyloxy radical to an alkene does not appear to be generally applicable.



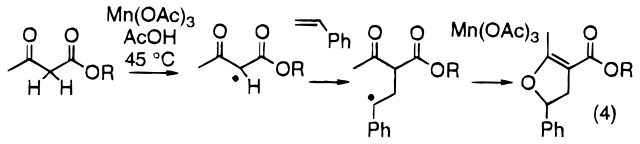
B. Mn(OAc)$_3$

The oxidative addition of acetic acid to alkenes reported by Heiba and Dessau[6] and Bush and Finkbeiner[7] in 1968 provides the basis for a general approach to oxidative free-radical cyclization. Heating the one-electron oxidant Mn(OAc)$_3$ in acetic acid at reflux (115 °C) generates the carboxymethyl radical. This adds to alkenes to give a radical, which is oxidized by a second equivalent of Mn(OAc)$_3$ to give a γ-lactone (eq 3). This sequence of steps generates



a radical oxidatively from acetic acid, efficiently forms a carbon−carbon bond, and produces a synthetically useful γ-lactone by oxidation of the carbon-centered radical. These oxidative additions have been extensively explored over the past 25 years and have been reviewed recently.[8−11] Unfortunately, Mn(III)-based oxidative cyclization of unsaturated acids is not possible, since the optimal solvent for this reaction, acetic acid, will be oxidized preferentially.

Heiba and Dessau reported in 1974 that β-keto esters and related dicarbonyl compounds are oxidized to radicals at 25−70 °C in acetic acid. For instance, oxidation of ethyl acetoacetate in the presence of styrene affords a dihydrofuran (eq 4).[12] The applica-

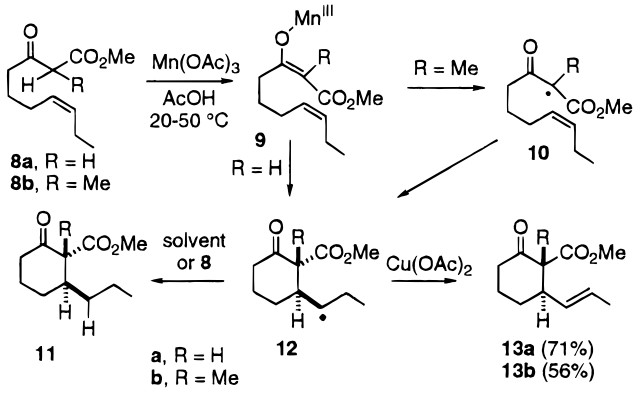


tion of Mn(III) to oxidative free-radical cyclizations was investigated initially by Corey, Fristad, and Snider. Corey and Kang reported the oxidative cyclization of unsaturated β-keto acids in 1984.[13] In 1985, we described the oxidative cyclization of unsaturated β-keto esters,[14] and Fristad surveyed the cyclization of unsaturated malonic and cyanoacetic acids.[15] In the past decade, Mn(III)-based oxidative free-radical cyclizations and annulations have been extensively investigated in my laboratory[14,16−46] and by Bertrand,[47−52] Chuang,[53−57] Citterio,[58−70] Cossy,[71−76] Narasaka,[77−81] Zoretic,[82−88] and others.[89−112]

This review is restricted to oxidative free-radical cyclizations and annulations; intermolecular additions have been reviewed recently and are not covered.[8−11] While the vast majority of the work has used Mn(III) or Mn(III)/Cu(II), other one-electron oxidants, most notably Ce(IV), Fe(III), and Cu(II), have also been employed.

The Mn(III)-based oxidative free-radical cyclization of **8a** and **8b** serves to introduce the factors that need to be understood to use these reactions in synthesis. Oxidative cyclization of β-keto ester **8a** with Mn(OAc)$_3$ affords a complex mixture of products. Primary and secondary radicals, such as **12**, are not oxidized by Mn(III). Heiba and Dessau found that Cu(OAc)$_2$ oxidizes secondary radicals 350 times faster than Mn(OAc)$_3$ does and that the two reagents can be used together.[113] Oxidative cyclization of **8a** with 2 equiv of Mn(OAc)$_3$ and 0.1−1 equiv of Cu(OAc)$_2$ in acetic acid affords 71% of **13a**. Cu(OAc)$_2$ reacts with radical **12a** to give a Cu(III) intermediate that undergoes oxidative elimination to give **13a**.[14,24] A similar

oxidative cyclization of **8b** affords 56% of **13b** as the major product.

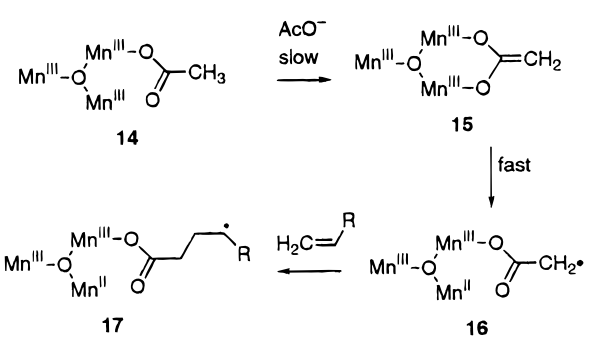


The first step in the reaction is the loss of a proton to give the Mn(III) enolate **9**. The next step of the reaction could involve cyclization of the unsaturated Mn(III) enolate **9** to give cyclic radical **12**. This is the operative pathway for R = H. Alternatively, loss of Mn(II) could give the Mn-free free radical **10**. This is the operative pathway for R = Me. These mechanistic considerations are discussed below in the section on initiation. Cyclization of **10b** from the conformation shown gives radical **12b** stereo- and regiospecifically as discussed in the section on cyclization. Finally, Cu(II) oxidation of **12** gives **13** regio- and stereospecifically as discussed below in the section on termination.

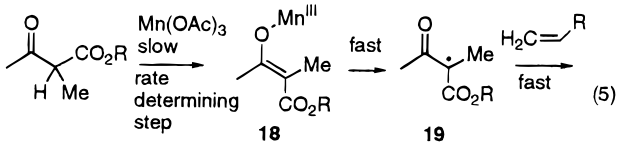
II. Initiation

A. Mechanistic Considerations

The mechanism of oxidation of monocarbonyl substrates with $Mn(OAc)_3 \cdot 2H_2O$ has been extensively studied. Fristad and Peterson showed that the rate-determining step in the oxidation of acetic acid by $Mn(OAc)_3 \cdot 2H_2O$, which is actually an oxo-centered triangle of Mn(III) with bridging acetates,[123] is the loss of a proton from a complexed acetate such as **14** to give **15**.[114−118] Rapid electron transfer to the oxo-centered metal system gives radical **16**, which adds to the alkene to give **17**. The rate of reaction is independent of alkene concentration, since the alkene is not involved in the rate-determining step. Fristad found that the log of the rate of oxidation relative to that of acetic acid equals $0.344(\Delta pK_a)$ for five mono-substituted acetic acids covering an acidity range for the α-proton of 16 pK_a units.[114−118]

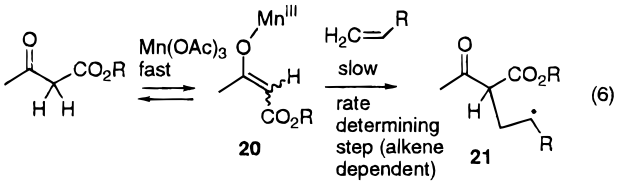


We found that a similar mechanism is operative in the oxidation of α-alkyl β-keto esters (see eq 5).[19]



Enolization to give **18** is slow; electron transfer with loss of Mn(II) to give **19** is rapid. The rate of reaction is therefore independent of alkene concentration or the nature of the tether in cyclizations. Radical **19** reacts from the geometry shown as determined by analysis of the stereochemistry of the products as discussed below. Comparable regio- and stereochemical results are obtained from a series of Mn(III)-based oxidative cyclizations and iodine or bromine atom-transfer cyclization.[29] This indicates that free radical **19** is involved in the Mn(III)-mediated oxidative cyclizations. Some differences in regiochemistry or stereochemistry between oxidative cyclizations and atom-transfer cyclizations would be expected if a Mn(III)-complexed radical were involved. Baciocchi and Giese showed by competitive rate measurements that free radicals are generated in the oxidation of malonate esters with cerium(IV) ammonium nitrate.[119] ESR studies have demonstrated that free radicals are formed from acid treatment of $Co(AcAc)_3$.[120]

On the other hand, we found that the enolization of α-unsubstituted β-keto esters is fast and reversible, and electron transfer to give the radical is very slow (see eq 6).[19] The rate-determining step depends on



alkene concentration and is presumably the reaction of the Mn(III) enolate **20** with the alkene to give radical **21** with loss of Mn(II). β-Keto ester radicals analogous to **19** do not appear to be intermediates in these reactions. 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 β-keto esters. 6-*exo*-cyclization is more rapid than 5-*exo*-cyclization.[19] The nature of the tether also affects the rate of oxidative cyclization of unsaturated β-keto acids.[13]

Why does the presence of the α-alkyl group change the mechanism of the reaction? A methyl group should slow down the formation of Mn(III) enolate **18**, since it is electron donating and decreases the acidity of the α-proton. On the other hand, the methyl group should facilitate the oxidation of **18** to **19** since it will stabilize the radical. Electrochemical data for the oxidation of enolates of β-dicarbonyl compounds to the radical in DMSO support this hypothesis. The presence of an α-methyl group facilitates the oxidation by 0.25−0.4 V.[121,122] The nature of the reaction depends on two variables: the rate of formation of the Mn(III) enolate, which

corresponds to the pK_a, and the ease of oxidation of the enolate to give a free radical. For most compounds enolization is the rate-determining step. For very acidic compounds such as α-unsubstituted β-keto esters and β-diketones, enolization occurs readily and oxidation is slow.

B. Substrates

β-Keto esters have been used extensively for Mn(III)-based oxidative cyclizations and react with $Mn(OAc)_3$ at room temperature or slightly above.[24] They may be cyclic or acyclic and may be α-unsubstituted or may contain an α-alkyl or chloro substituent. Cycloalkanones are formed if the unsaturated chain is attached to the ketone. γ-Lactones are formed from allylic acetoacetates.[48,49,51] Less acidic β-keto amides have seen limited use for the formation of lactams[71] or cycloalkanones.[40] Malonic esters have also been widely used and form radicals at 60−80 °C. Cycloalkanes are formed if an unsaturated chain is attached to the α-position. γ-Lactones are formed from allylic malonates.[41,48,49,51] β-Diketones have been used with some success for cyclizations to both alkenes and aromatic rings.[24,98,101,102] Other acidic carbonyl compounds such as β-keto acids,[13] β-keto sulfoxides,[27] β-keto sulfones,[27] and β-nitro ketones[105] have seen limited use.

Although Mn(III)-based oxidative additions of acetic acid have been widely used,[8−11] oxidative cyclizations of unsaturated acids have not been successfully carried out, because the solvent acetic acid is oxidized as readily as the substrate. We have recently found that oxidative cyclizations of unsaturated ketones can be carried out in high yield in acetic acid at 80 °C if the ketone selectively enolizes to one side and the product cannot enolize. These reactions are discussed in detail in section IX.

C. Oxidants

1. Mn(III)

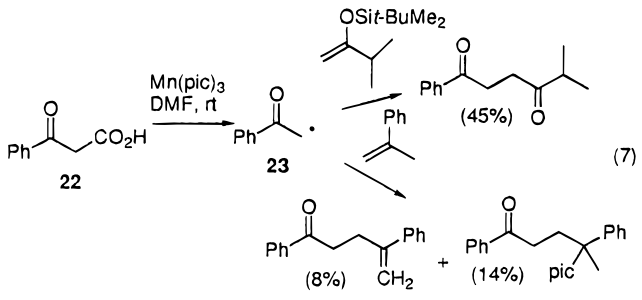
Commercially available $Mn(OAc)_3 \cdot 2H_2O$ has been used for the majority of oxidative cyclizations. This reagent can also be prepared easily from potassium permanganate and manganous acetate in acetic acid.[8] Anhydrous $Mn(OAc)_3$ is slightly more reactive than the dihydrate. Reaction times with the anhydrous reagent are usually somewhat shorter but the yield of products are usually comparable. Both trifluoroacetic acid and potassium or sodium acetate have been used with $Mn(OAc)_3$. Use of trifluoroacetic acid as a cosolvent usually increases the rate of the reaction, but often decreases the yield of products. Acetate anion may accelerate enolization and act as a buffer.

Acetic acid is the usual solvent for $Mn(OAc)_3 \cdot 2H_2O$ reactions. DMSO, ethanol, methanol, dioxane, and acetonitrile can also be used, although higher reaction temperatures are required and lower yields of products are sometimes obtained.[38] The use of ethanol can be advantageous in cyclizations to alkynes. Vinyl radicals formed by cyclization to alkynes are not readily oxidized by Mn(III) and will undergo undesired side reactions unless there is a good hydrogen donor available. Ethanol acts as a hydrogen donor, reducing the vinyl radical to an alkene and giving the α-hydroxyethyl radical, which is oxidized to acetaldehyde by Mn(III). Much higher yields of alkenes are obtained from cyclizations to alkynes in ethanol than in acetic acid.[28]

$Mn(OAc)_3 \cdot 2H_2O$ is not particularly expensive on a laboratory scale, but its use on an industrial scale may be problematic. Several groups have demonstrated that Mn(III) can be used in catalytic quantities and regenerated electrochemically *in situ*.[43,70,105,107−112] In some cases, good yields of products are obtained with only 0.2 equiv (10%) of Mn(III) or Mn(II). In other cases the electrochemically mediated reactions proceed in substantially lower yield or give different products. D'Annibale and Trogolo have recently reported that improved yields are obtained in some Mn(III) and Ce(IV) based oxidative cyclizations and additions if they are carried out with ultrasound irradiation.[89−91]

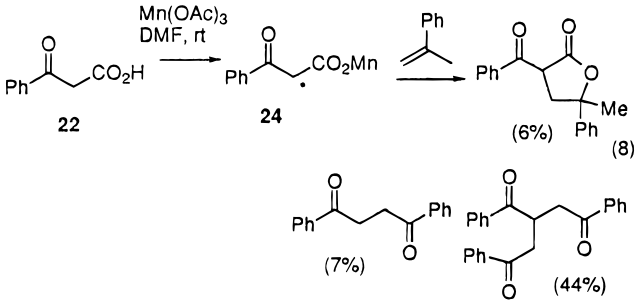
$Mn(OAc)_3$ is also involved in the termination step. It rapidly oxidizes tertiary radicals to cations that lose a proton to give an alkene or react with acetic acid to give acetate esters. $Mn(OAc)_3$ oxidizes allylic radicals to allylic acetates and oxidizes cyclohexadienyl radicals generated by additions to benzene rings to cations that lose a proton to regenerate the aromatic system. On the other hand, $Mn(OAc)_3$ oxidizes primary and secondary radicals slowly, so that hydrogen atom abstraction from solvent or starting material becomes the predominant process. Alkenes are formed efficiently from primary and secondary radicals by use of $Cu(OAc)_2$ as a cooxidant, as discussed in section III.

Narasaka introduced manganese(III) picolinate [$Mn(pic)_3$] in DMF as a useful reagent for oxidation of β-keto acids to radicals, the oxidative cleavage of cyclopropanols to give β-keto radicals, and the oxidation of nitroalkanes to cation radicals.[77−81] Very different results are obtained from oxidation of β-keto acid **22** with $Mn(OAc)_3 \cdot 2H_2O$ and $Mn(pic)_3$. Oxidation with $Mn(pic)_3$ in DMF results in decarboxylation to give the α-keto radical **23** as shown in eq 7.



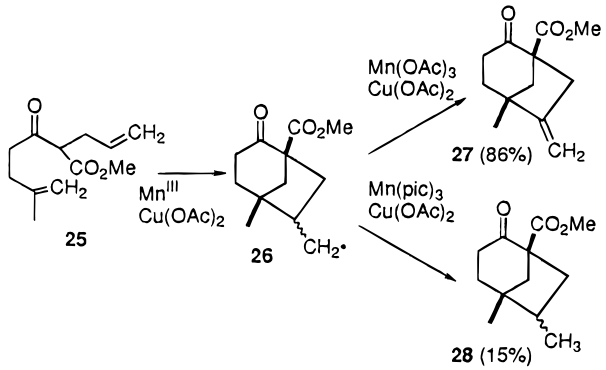
Radical **23** adds to enol silyl ethers to give good yields of 1,4-diketones and to α-methylstyrene to give a low yield of addition products. Oxidation of **22** with $Mn(OAc)_3$ in DMF leads to dimers and trimers and

β-keto acid radical **24** that adds to α-methylstyrene to give 6% of the lactone shown in eq 8. There are



several structural differences that may be responsible for the distinct reactions observed with these two reagents. The nitrogen of the picolinate coordinates to manganese, perturbing the oxidation potential.[124] $Mn(pic)_3$ has an octahedral manganese, with three picolinates bound to a single Mn(III),[125] while $Mn(OAc)_3$ is an oxo-centered trimer.[123]

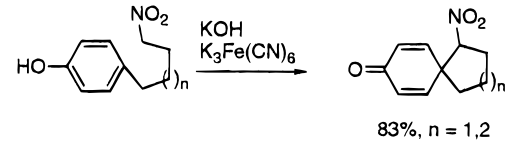
We examined the tandem oxidative cyclization of **25** with various Mn(III) reagents and $Cu(OAc)_2$.[38] Oxidative cyclization with $Mn(OAc)_3$ and $Cu(OAc)_2$ affords 86% of **27** and 0% of **28**, while use of $Mn(pic)_3$ and $Cu(OAc)_2$ leads to 0% of **27** and 15% of **28**. A series of control experiments established that the most likely explanation for this observation is that $Mn(pic)_2$, but not $Mn(OAc)_2$, reacts with the bicyclic radical **26** more rapidly than $Cu(OAc)_2$ does. This illustrates a general feature of oxidative radical cyclizations. A one-electron oxidant, e.g., Mn(III), Cu(II), Ce(IV), etc., is needed for both the generation of the acyclic radical and oxidation of the cyclic radical. Furthermore, the lower valent metal salt produced in these oxidations must not react rapidly with any of the radical intermediates. $Mn(pic)_3$ does not meet these requirements, since $Mn(pic)_2$ reacts with the cyclic radical more rapidly than $Cu(OAc)_2$ does; the alkyl$Mn(pic)_2$ intermediate produced in this reaction apparently abstracts a hydrogen giving reduced products such as **28**.



$Mn(AcAc)_3$ and MnF_3 are other readily available Mn(III) reagents. $Mn(AcAc)_3$ has been extensively used for oxidative coupling of phenols.[126] While both are suitable for oxidative radical cyclizations, they appear to offer no advantages over $Mn(OAc)_3 \cdot 2H_2O$.[38] Watt and Demir[127−133] have comprehensively developed the α′-oxidation of enones to α′-acyloxyenones discovered by Hunter.[134] During the course of this work they found that a wide variety of manganese(III) carboxylates could be prepared from $Mn(OAc)_3$ and the carboxylic acid *in situ* and used for α′-acyloxylation of enones and aryl alkyl ketones.[128−133] The utility of these manganese(III) carboxylates in oxidative free-radical cyclizations has not been examined.

2. Ce(IV), Fe(III), V(V), etc.

A wide variety of other one-electron oxidants have been used for generating free radicals, especially for the oxidative coupling of phenols.[11] Hirao et al. have used $VO(OEt)Cl_2$ to generate radicals from diketene in ethanol.[135] Kende has shown that alkaline potassium ferricyanide induces oxidative cyclization of phenols with a side chain bearing a nitro group or a readily enolizable carbonyl group (eqs 9 and 10).[136−139]



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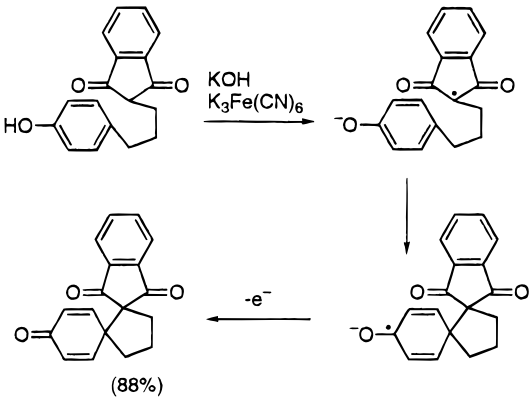


(10)

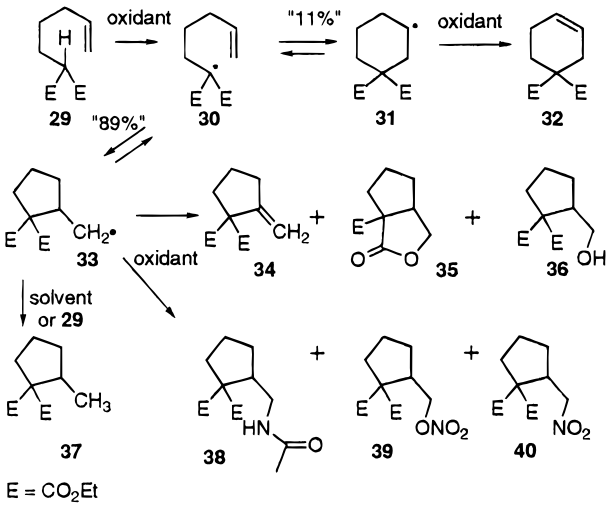
These reactions probably proceed by oxidation to the radical, cyclization to the radical anion, and further oxidation as shown in eq 10. Analogous reactions have also been carried out with $Mn(OAc)_3$ in a model study for fredericamycin A.[98]

Citterio and co-workers have comprehensively explored the use of ferric perchlorate in acetonitrile for oxidative intermolecular additions of malonate esters to styrenes and oxidative cyclizations of unsaturated malonate esters and compared this reagent to $Mn(OAc)_3$ and ceric ammonium nitrate.[58,61,63,64,67−69] $Co(OAc)_2$ and molecular oxygen in acetic acid have been used for the oxidative addition of β-diketones and β-keto esters to alkenes. The oxidant is probably Co(III), and the addition product is trapped with oxygen, leading to a dihydrofuran analogous to that formed in eq 4.[140−142] Baciocchi and co-workers have used ceric ammonium nitrate to oxidize malonate esters to radicals in alcohol solvents.[119,143] The utility of ceric ammonium nitrate for oxidative cyclization of malonate esters and β-keto esters to aromatic systems has been examined by Citterio and co-workers.[62−64,67,95]

All of these oxidants are capable of forming radicals from 1,3-dicarbonyl compounds. However, the oxidant is also necessary for termination of the radical reaction. The nature of the metal, the ligands

necessary to obtain the desired oxidation potential, and the solvent needed to achieve solubility of the metal salt all play a crucial role in determining the products formed from oxidation of the cyclic radical. The choice of oxidant is less important in reactions that are terminated by addition to an aromatic ring. The aromatic system will inevitably be regenerated in high yield by oxidation of the cyclohexadienyl radical to the cation and loss of a proton.

The differences in termination are clearly seen in the oxidative cyclization of diethyl 4-pentenylmalonate (**29**), which has been investigated with Ce(IV), Fe(III), and Mn(III). Oxidative cyclization of **29** with 2 equiv of $Mn(OAc)_3 \cdot 2H_2O$ and 1 equiv of $Cu(OAc)_2 \cdot H_2O$ in acetic acid at 55 °C gives 48% of lactone **35**, 20% of methylenecyclopentane **34**, and 7% of cyclohexene **32**.[28,29,38] Oxidation of **29** gives radical **30**, which cyclizes to a 9:1 mixture of cyclopentylmethyl radical **33** and cyclohexyl radical **31**, as has been observed in atom transfer cyclizations.[144] Oxidation of **31** with Mn(III) or Cu(II) gives **32**; oxidation of **33** with Cu(II) gives **34** and **35**. The ratio of **35** and **34** is solvent dependent, ranging from as high as 3.75:1 in acetonitrile to as low as 0.04:1 in DMSO, with intermediate values in AcOH (2.4:1), EtOH (0.64:1), DMF (0.55:1), and MeOH (0.48:1).



Oxidation of **29** with $Fe(ClO_4)_3 \cdot 9H_2O$ in acetonitrile at 20 °C affords 7% of **32**, 4% of **34**, 44% of **35**, 7% of the reduction product **37**, 10% of alcohol **36**, and 6% of amide **38**, which results from reaction with acetonitrile. The last three products were not observed with $Mn(OAc)_3$ and $Cu(OAc)_2$.

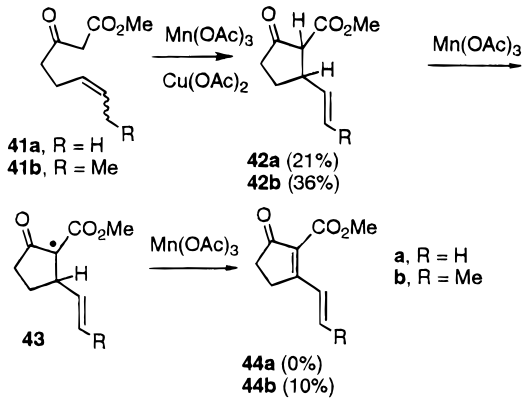
Oxidation of **29** with 2 equiv of ceric ammonium nitrate in methanol affords 20% of lactone **35**, 23% of nitrate **39**, 10% of methylenecyclopentane **34**, 12% of reduction product **37**, and 6% of cyclohexene **32**.[143] The formation of nitrate is suppressed using 2 equiv of both ceric ammonium nitrate and $Cu(OAc)_2$ in methanol, which affords 58% of **35**, 25% of **34**, and 4% of **32**. This product ratio is very similar to that obtained with $Mn(OAc)_3$ and $Cu(OAc)_2$ in acetic acid. However, oxidation of **29** with ceric ammonium nitrate in acetic acid affords 38% of nitro compound **40**, 35% of **35**, 6% of nitrate **39**, 2% of **34**, and 4% of **32**. Addition of 0.33 M Ac_2O to the reaction mixture favors the formation of nitrate **39** (46%) at the expense of lactone **35** (13%). Oxidative cyclization of **29** with 2 equiv of both ceric ammonium nitrate and $Cu(BF_4)_2$ affords 86% of lactone **35** in acetic acid and 81% of nitrate **39** in acetic acid containing acetic anhydride.

The oxidation of **29** with different oxidants demonstrates that the major differences are in the termination step. All oxidants give radical **30**, which cyclizes to a ~9:1 mixture of **33** and **31**. The oxidative termination step is oxidant, ligand, and solvent dependent.

D. Further Oxidation of the Product

Oxidative cyclization of unsaturated β-dicarbonyl compounds that have two α-hydrogens will give products that still have one α-hydrogen and can be oxidized further. These reactions can be divided into three categories, depending on whether the product is oxidized more slowly, at about the same rate, or much faster than the starting material. In the first category, the product is oxidized more slowly than the starting material, so that the cyclization proceeds in good yield. The formation of 71% of **13a** from **8a** is an example of this type of reaction.[14,24]

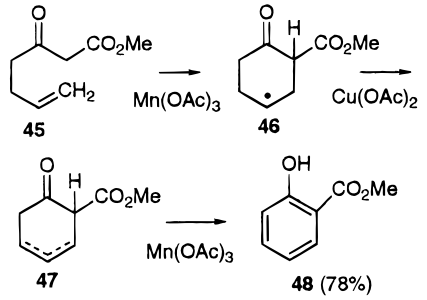
In the second category, the product is oxidized at a rate competitive with that of the starting material so that mixtures of products are obtained. For instance, oxidative cyclization of **41a** gives the expected product **42a** in only 21% yield, while **41b** affords 36% of **42b** and 10% of dienone **44b** formed by further oxidation of **42b**. 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.



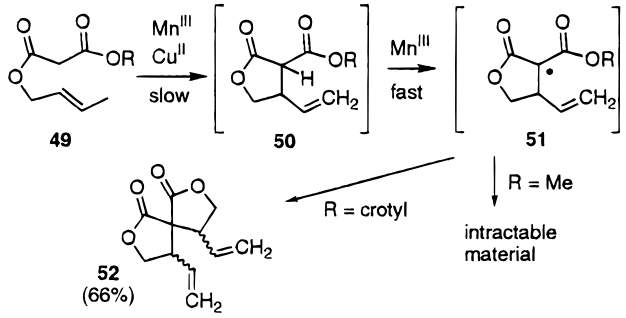
The rate-determining step in the cyclization of α-unsubstituted β-keto esters is addition of the double bond to the manganese enolate. Oxidative cyclization of **8a** is faster than oxidative cyclization of **41** since the double bond is better able to participate in the rate-determining step with a longer tether. Furthermore, oxidation of **42b** to **44b** (50%, 1 day) is much faster than the oxidation of **13b** (0%, 6 days). We cannot explain this difference, but note that **42** is ketonic while **13b** is enolic. In other cases we have also observed that enolic 1,3-dicarbonyl

compounds are oxidized slowly by Mn(III) (see **232a** below).

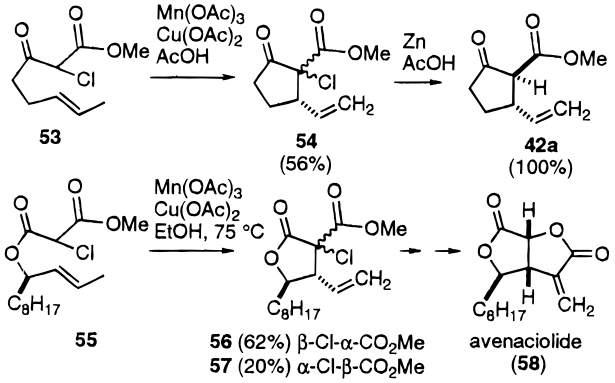
In the third category, the product is oxidized much more readily than the starting material so that none of the initial product is isolated. These reactions may still be synthetically useful if the products of further oxidation are monomeric. For instance, oxidative cyclization of **45** provides 78% of methyl salicylate (**48**).[17,21,100] Oxidative cyclization gives radical **46**; oxidation of **46** gives **47**, probably as a mixture of double-bond positional isomers. The unsaturated cyclic β-keto ester **47** is more acidic than **45** and is rapidly oxidized further by 2 equiv of Mn(III) to give a cyclohexadienone that tautomerizes to phenol **48**. The overall reaction consumes 4 equiv of $Mn(OAc)_3$.



The oxidative cyclization of crotyl malonate esters also falls into the third category. Oxidative cyclization of **49** affords **50**, which is rapidly oxidized to **51**. Radical **51** gives intractable material if R = Me, but affords 66% of **52** if R = crotyl.[49] The lactone group makes the α-hydrogen of **50** much more acidic[170] than those of **49** so that product lactone **50** is oxidized more rapidly than diester **49**.



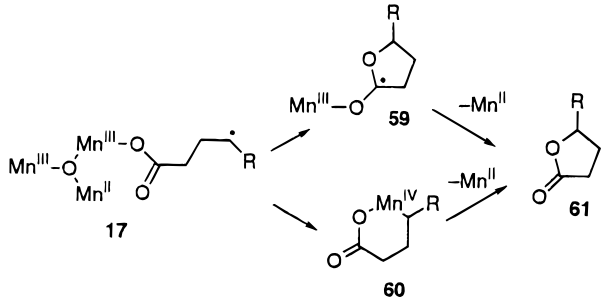
Further oxidation cannot occur if there are no acidic α-hydrogens in the product. α-Alkyl groups prevent further oxidation, but cannot then be removed. α-Chloro substituents serve as protecting groups preventing further oxidation of the product.[19,41,145,146] For instance, cyclopentanonecarboxylate ester **42a** can be prepared easily by oxidation of α-chloro β-keto ester **53**, giving **54**, which cannot be oxidized further. Reduction of **54**, which can be carried out most simply by addition of zinc dust to the reaction mixture, affords **42a** quantitatively. This one-pot procedure converts **53** to **42a** in 56% overall yield.[19] We found that α-chlorine substituents also prevent further oxidation of lactones. Oxidative cyclization of **55** affords 82% of a 3.1:1 mixture of **56** and **57**.[41] The other two stereoisomers with the octyl and vinyl groups *cis* are not formed. The mixture of **56** and **57** was elaborated to avenaciolide (**58**) by a sequence that used an SN2 reaction on the α-chloro lactone to form the second lactone ring.[41]



III. Termination

A. Oxidation by Mn(III)

Mn(III) will oxidize γ-carboxy radicals, e.g. **17**, to γ-lactones **61** regardless of whether the radical is secondary or tertiary.[8−11] Thus, the addition of acetic acid and substituted acetic acids to alkenes to give γ-lactones is a general reaction for all classes of alkenes. Mn(III) does not oxidize isolated primary or secondary radicals, so the oxidation of **17** may involve addition of the radical to the carboxylate to give **59**, which is readily oxidized to **61**, or the formation of **60** followed by reductive elimination of Mn(II) to yield **61**.



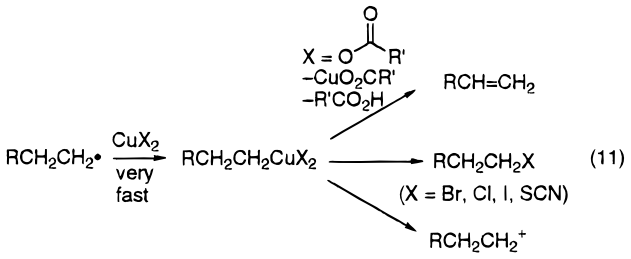
Addition of 1,3-dicarbonyl compounds to alkenes affords isolated radicals that do not contain a proximal manganese carboxylate, e.g., **12** and **26**. Mn(III) will oxidize tertiary radicals to cations that can lose a proton to give an alkene or react with solvent to give a tertiary acetate. Mn(III) will also oxidize allylic radicals to allylic acetates and cyclohexadienyl radicals, resulting from addition to aromatic rings, to the cation, which loses a proton to regenerate the aromatic system.

Mn(III) does not oxidize primary radicals such as **26** or secondary radicals such as **12**. If no cooxidant is used hydrogen abstraction is the major pathway.

B. Oxidation by $Cu(OAc)_2$

In the 1960s, Kochi and co-workers demonstrated that Cu(II) reacts rapidly with radicals ($\sim 10^6$ s^1 M^{-1})

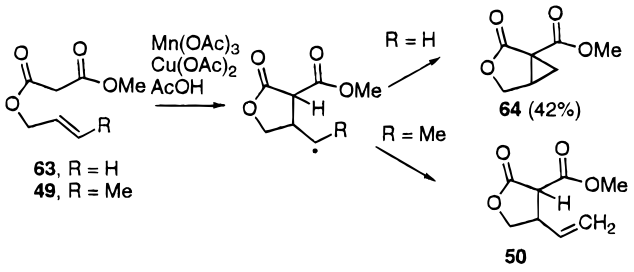
to give alkylcopper(III) intermediates (see eq 11).



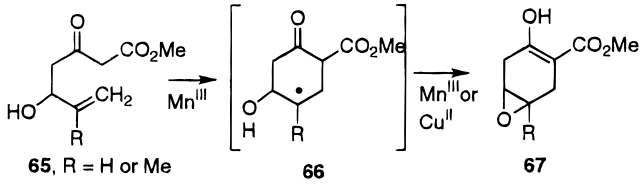
These can react further with loss of Cu(I) to either form an alkene by oxidative elimination, transfer a ligand to give RCH_2CH_2X, or form a carbocation.[147,148] Oxidative elimination to form alkenes is the preferred pathway from the reaction of copper(II) carboxylates with primary and secondary radicals. 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 the use of $Cu(OAc)_2$ is compatible with $Mn(OAc)_3$ and that Cu(II) oxidized secondary radicals to alkenes 350 times faster than Mn(III) does.[113] The Cu(I) that is produced in this oxidation is rapidly oxidized 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,[149] $Cu(OAc)_2$ oxidizes secondary radicals to give primarily (*E*)-alkenes and the less substituted double bond (Hofmann elimination product).[23] 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.

Oxidation of primary radicals to alkenes is usually quite efficient as in the conversion of **26** to **27**. However, the organocopper(III) intermediate formed from primary radicals can interact with adjacent functionality to give lactones as in the conversion of **33** to **35** discussed above and to give cyclopropanes as in the conversion of **63** to cyclopropane **64**. Secondary radicals do not usually undergo these side reactions. For instance, no cyclopropane is formed from **49**, which gives **50**, which reacts further as discussed above.

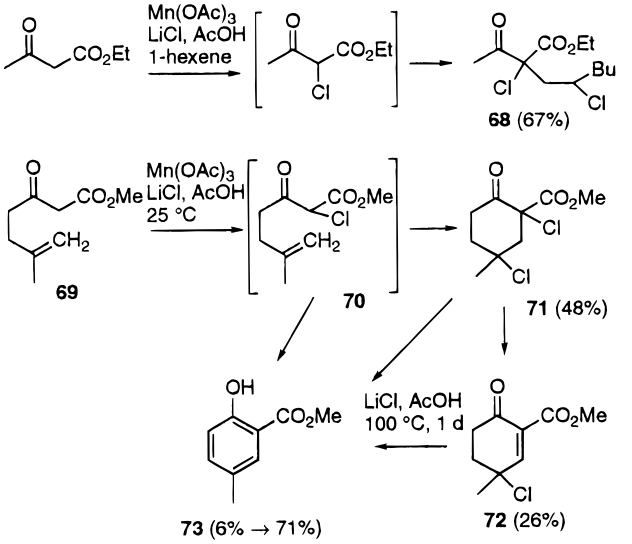


Oxidative cyclization of δ-hydroxy β-keto ester **65** was investigated as a potential route to resorcinols. To our surprise, the major product isolated in 50–60% yield is the epoxide **67**.[21] β-Hydroxy radical **66** is oxidized to the epoxide by Mn(III) or Cu(II). β-Hydroxy radicals generated by $Pb(OAc)_4$ oxidative decarboxylation of β-hydroxy acids are also oxidized to epoxides by either Pb(IV) or Cu(II) indicating that this is a general method for epoxide formation.[23]



C. Chlorination

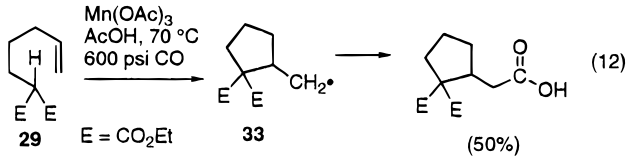
Vinogradov and Nikishin reported that oxidation of ethyl acetoacetate with 4 equiv of $Mn(OAc)_3$ and excess LiCl in the presence of 1-hexene results in the formation of dichloride **68**.[150,151] Chlorination of the α-position prevents further oxidation of the product. Unfortunately, the use of chloride is not compatible with Cu(II); only α,α-dichlorination is observed. The combination of $Mn(OAc)_3$ and LiCl has seen very limited use in intramolecular reactions.[19,21,24,25] Oxidative cyclization of **69** with $Mn(OAc)_3$ gives only 17% of salicylate **73**. However, oxidative cyclization of **69** with 4 equiv of $Mn(OAc)_3$ and 10 equiv of LiCl in acetic acid at room temperature for 16 h affords a mixture containing 48% of **71**, 26% of **72**, and 6% of salicylate **73**. Heating this mixture with 6 equiv of LiCl in acetic acid at 100 °C for 1 day converts the mixture to salicylate **73** in 71% overall yield.[21]



D. Addition to Nitriles and Carbon Monoxide

We have found that oxidative cyclizations can be terminated by addition to nitriles to give iminyl radicals that are reduced to imines, which are hydrolyzed to ketones on workup (see **323** → **325**).[31] Ryu and Alper reported that the radicals formed in oxidative cyclizations add to carbon monoxide to give acyl radicals, which are oxidized by Mn(III) to acyl

cations leading to carboxylic acids on workup (see eq 12).[97]

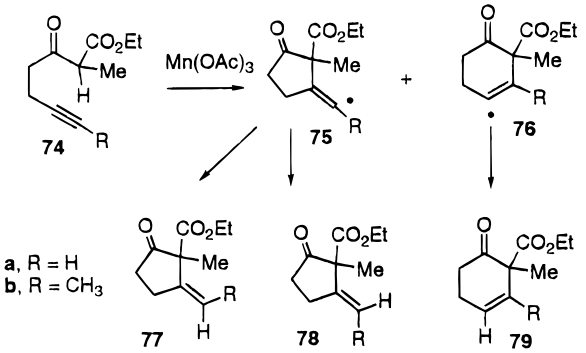


E. Hydrogen Abstraction

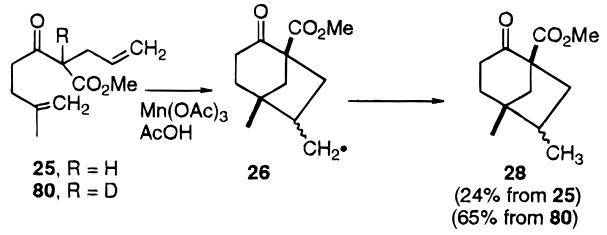
Reductive termination of the reaction sequence by hydrogen abstraction is occasionally the desired reaction. This is particularly important in converting vinyl radicals (obtained from addition to alkynes) to alkenes, since vinyl radicals are not oxidized to vinyl cations. The hydrogen can come from the solvent or from the α-hydrogen of another molecule of the β-dicarbonyl compound. Ethanol is the preferred solvent for these reactions, since it is a better hydrogen donor than acetic acid. Hydrogen transfer from ethanol gives the α-hydroxyethyl radical that is oxidized to acetaldehyde by Mn(III) so that these reactions still require 2 equiv of $Mn(OAc)_3$.[28]

Oxidative cyclization of **74a** with $Mn(OAc)_3$ in acetic acid proceeds in very low yield, giving 9% of a 1:6.3 mixture of **78a** and **79a**.[28] A similar reaction with anhydrous $Mn(OAc)_3$ in ethanol affords 32% of a 1.6:1 mixture of **78a** and **79a**. The low yield is probably due to the instability of methylenecyclopentane **78a**. Oxidative cyclization of **74b** under the same conditions provides 66% of a 1:2.6 mixture of **77b** and **78b**.

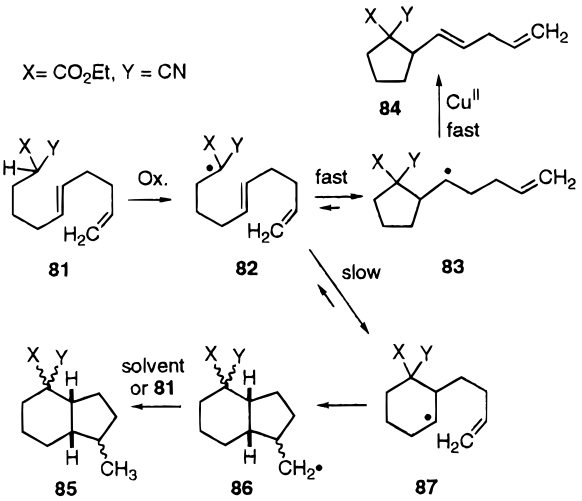
Reduction of vinyl radicals to alkenes and primary and secondary radicals to alkanes is also favored by the use of $Mn(pic)_3$, rather than $Mn(OAc)_3$, as the oxidant.[38,39,42] This was discussed in detail in section II.C.1.



Oxidative cyclization of **25** with $Mn(OAc)_3$ in acetic acid affords radical **26**, which abstracts a hydrogen atom from another molecule of **25** or from solvent to give 24% of **28**.[38] We were surprised to find that oxidation of **80** with an α-deuterium under the same conditions affords 65% of **28**.[38] Large kinetic isotope effects change the nature of the termination step so that **26** now abstracts a hydrogen only from the solvent and the radical is generated from **80** only by reaction with $Mn(OAc)_3$, not by intermolecular hydrogen transfer.



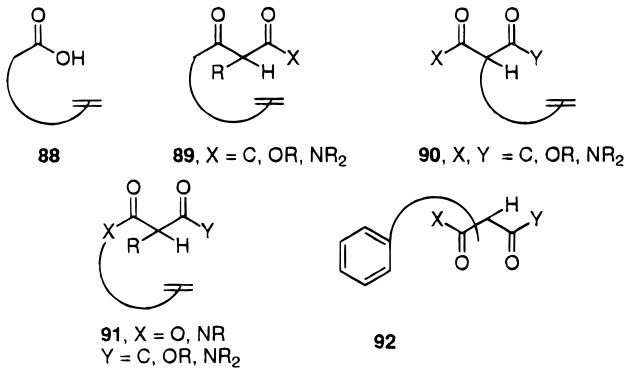
Oxidation of radicals by $Cu(OAc)_2$ is sufficiently rapid so that all oxidative cyclizations run in the presence of $Cu(OAc)_2$ are kinetically controlled. Since hydrogen-transfer reactions are much slower, rearrangement or isomerization of primary or secondary radicals can occur in the absence of $Cu(OAc)_2$. Oxidative cyclization of **81** with 2 equiv of $Mn(OAc)_3$ and 1 equiv of $Cu(OAc)_2$ in acetic acid for 2 days at 55 °C affords 35% of **84**.[36] A similar reaction with 2 equiv of $Mn(OAc)_3$ and no $Cu(OAc)_2$ in ethanol affords 35% of **85** as a mixture of stereoisomers. Under these conditions the cyclization of the stabilized radical **82** to give **83** is reversible and the more stable cyclohexyl radical **87** is formed. The unstabilized cyclohexyl radical **87** cyclizes irreversibly to **86**, which abstracts a hydrogen atom to give **85**. Cyclization of **81** with benzoyl peroxide in cyclohexane at reflux under Julia's conditions also affords **85**, contrary to earlier reports.[4]



IV. Monocyclization

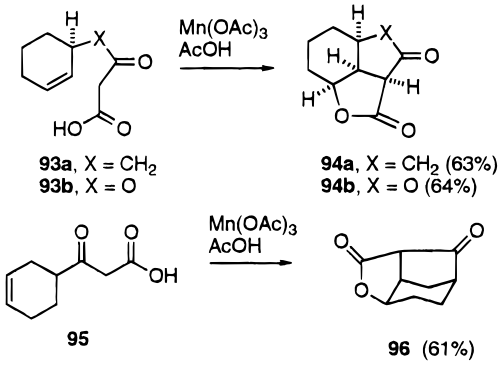
Cyclizations that form a single carbon−carbon bond are systematically surveyed in this section. The data are organized according the nature of the ring being formed and within that category by the type of dicarbonyl compound. Unsaturated acids **88** are discussed in section IV.A. The cyclizations of unsaturated ketones **89** that lead to cycloalkanones are discussed in section IV.B. The cyclizations of β-keto esters, β-diketones, and malonate esters **90** that lead to cycloalkanes are described in section IV.C. All cyclizations of **91** that lead to lactams or lactones are covered in section IV.D, while all oxidations of **92**

involving additions to aromatic rings are presented in section IV.E.

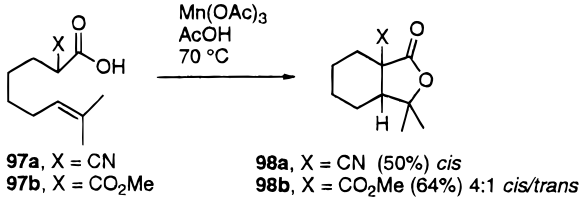


A. Radicals Derived from Acids

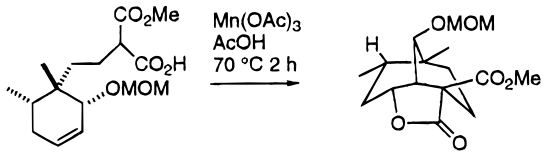
Some of the earliest examples of Mn(III)-based oxidative cyclizations involve β-keto acids, cyanoacetic acids, and half malonic esters. Since the cyclized radical is being oxidized to the lactone, Cu(II) is not needed as a cooxidant in these reactions. Corey reported that the oxidative cyclization of β-keto acid **93a** affords 63% of **94a**, while half malonate ester **93b** provides 64% of bis lactone **94b**.[13] The oxidative cyclization of β-keto acid **95** to **96** is much slower (23 °C, 24 h) than the cyclization of **93a** (23 °C, 20 min), indicating that addition of the double bond to the manganese enolate is the rate-determining step in these reactions as discussed above in section II.A.



Fristad reported that oxidative cyclization of cyanoacetic acid **97a** and half malonate ester **97b** in acetic acid at 70 °C provides ~50% of cyclohexane lactone **98**.[15] This procedure gives more complex mixtures of cyclopentane lactones with a one-carbon-shorter tether and cannot be used to make cycloheptane lactones.



Paquette reported the oxidative cyclization of **99** to afford 68% of **100**, which he elaborated to *epi*-upial.[99] Upial could not be prepared by an analogous route because the oxidative cyclization fails with the epimer with a β-OMOM group and proceeds in only 9% yield with the epimer with a β-methyl group. The two methyl groups and the MOM ether are equatorial on the cyclohexene ring of **99** forcing the malonate side chain to be axial, as required for cyclization. If either substituent is epimerized the cyclohexene will flip to the conformation with an equatorial malonate side chain. In this conformation the radical formed by oxidation of the half malonate ester probably undergoes intermolecular reactions before it can achieve the desired conformation for cyclization.

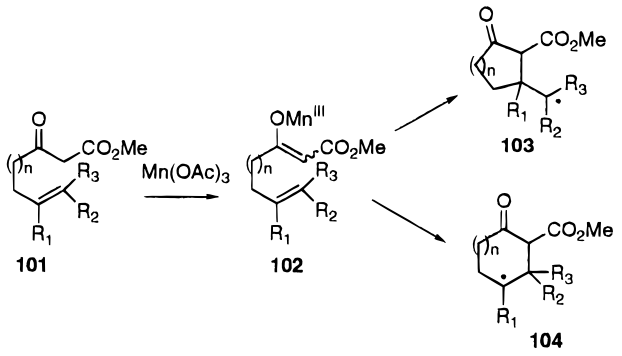


B. Radicals Derived from β-Keto Esters and β-Diketones That Lead to Cycloalkanones

Oxidative cyclizations of β-keto esters that form cycloalkanones have been extensively explored. The regiochemistry of the cyclizations is discussed in order of the length of the tether, which ranges from 5-hexenyl to 7-octenyl.

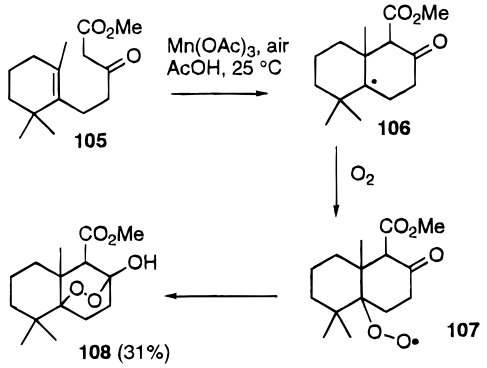
1. α-Unsubstituted β-Keto Esters

The oxidative cyclization of α-unsubstituted β-keto esters such as **101** proceeds through the cyclization of the alkene onto the manganese enolate of **102** to give either **103** or **104** as discussed in section II.A (see eq 6). 6-*endo*-Cyclization ($n = 1$) to give **104** is the exclusive reaction if the proximal carbon is more highly substituted than the distal carbon. Monosubstituted alkenes give cyclohexyl radical **104**, which is oxidized further providing a general synthesis of salicylate esters (see **45** → **48**).[17,21,100] Oxidative cyclization of **101**, $n = 1$, R_1 = alkyl, R_2 = alkyl or H, also proceeds exclusively 6-*endo* although complex mixtures are obtained from oxidation of the radical.[21]

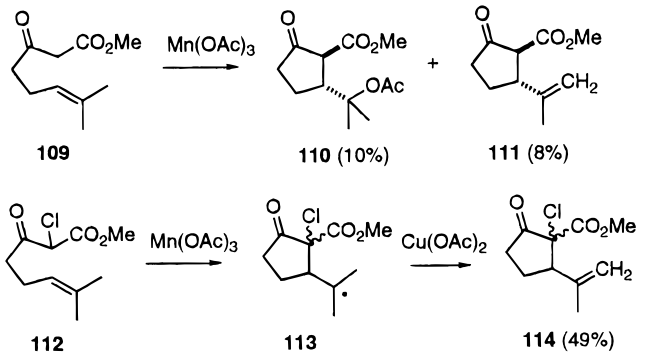


Oxidative cyclization of **105** with $Mn(OAc)_3$ in acetic acid in air affords 31% of 1,2-dioxin-3-ol **108**.[103] 6-*endo*-Cyclization gives cyclohexyl radical **106**, which reacts with oxygen to give alkylperoxy radical **107**, which abstracts a hydrogen atom to give **108**. The

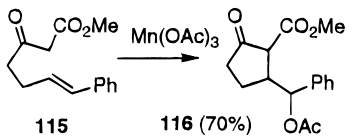
analogous formation of 1,2-dioxin-3-ols in intermolecular additions of β-dicarbonyl compounds to alkenes has been extensively studied.[152−158]



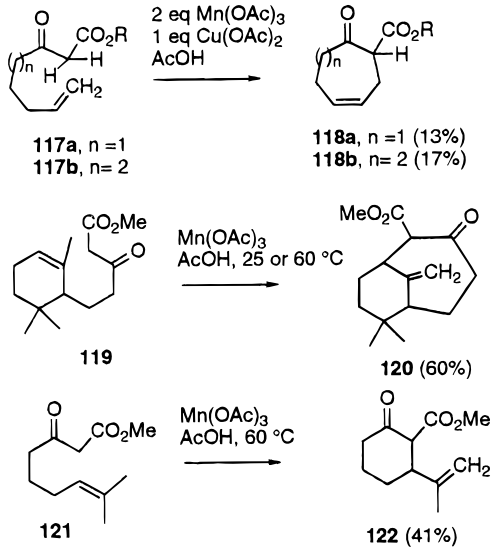
5-*exo*-Cyclization is the exclusive reaction with 1,2-disubstituted alkenes (see **41** → **42**) or if the distal carbon is more highly substituted. Oxidative cyclization of **109** with $Mn(OAc)_3 \cdot 2H_2O$ affords 10% of acetate **110** and 8% of alkene **111**. The low yield is due to the further oxidation of the products. The cyclized radical is oxidized to a cation, which loses a proton to give alkene **111** or reacts with solvent to give acetate **110**. Similar mixtures are obtained if $Cu(OAc)_2$ is used as a cooxidant, since Cu(II) also oxidizes tertiary radicals to alkenes. Oxidative cyclization of **112** with $Mn(OAc)_3 \cdot 2H_2O$ and $Cu(OAc)_2$ yields 49% of **114** as a 3:2 mixture of stereoisomers. Use of $Cu(OAc)_2$ as a cooxidant is necessary indicating that the electron-withdrawing chlorine group prevents oxidation of radical **113** to the cation by Mn(III) or Cu(II), allowing clean conversion to **114** by oxidative elimination with Cu(II).[19]



Oxidative cyclization of styrene **115** with $Mn(OAc)_3$ affords 70% of acetate **116**.[100] The secondary benzylic radical that is formed in the cyclization is oxidized by Mn(III) to the benzylic cation, which reacts with the solvent to give **116**. The improved yield of **116** as compared to **42** (21%) is probably due to conjugation of the double bond to the aromatic ring. The rate determining step, cyclization of **101**, $n = 1$, R_2 = Ph, should be much faster than cyclization of **101**, $n = 1$, R_2 = Me, while further oxidation of the products should occur at similar rates.

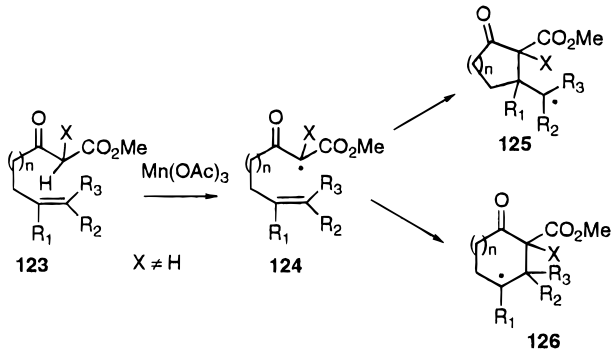


7-*endo*- and 8-*endo*-cyclization occurs exclusively for **101**, $n = 2,3$, if the proximal carbon is more highly substituted than the distal carbon. β-Keto esters **117a** and **117b** afford low yields of **118a** and **118b**, since further oxidation of the product is a competing side reaction.[20,30] Both White and Ruveda reported the oxidative cyclization of **119** to give **120** in 60% yield.[103,106] 6-*exo*-Cyclization occurs exclusively with 1,2-disubstituted alkenes (see **8a** → **13a**) and with alkenes in which the distal carbon is more highly substituted. For instance, **121** affords 41% of **122**.[14,24]



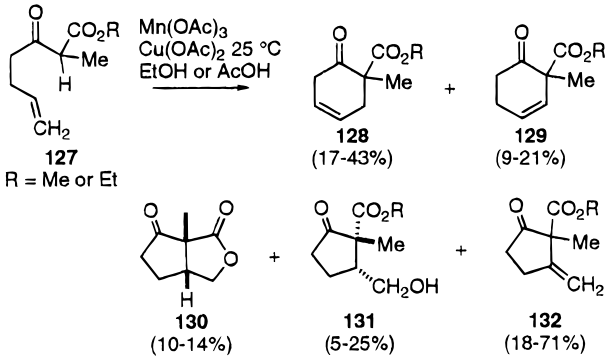
2. α-Substituted β-Keto Esters

The oxidative cyclization of α-substituted esters such as **123** proceeds through the formation of free radical **124**, which cyclizes to give either **125** or **126** as discussed in section II.A (see eq 5).

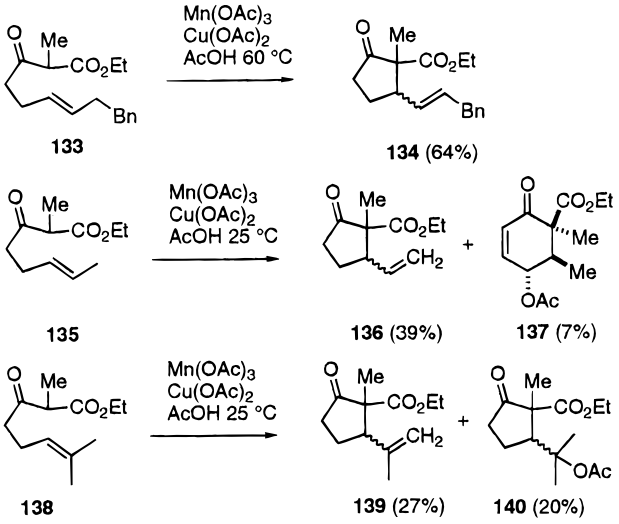


Oxidative cyclization of monosubstituted alkene **127** with 2 equiv of $Mn(OAc)_3$ and 1 equiv of $Cu(OAc)_2$ affords a mixture of **128**−**132**, which varies as a function of the solvent (acetic acid or ethanol) and the ester group (OMe or OEt).[28] A ∼1:1 mixture of 6-*endo*/5-*exo*-products is obtained in acetic acid, while a ∼1:2 mixture is formed in ethanol. This contrasts with the reaction of the analogous α-unsubstituted keto ester **45**, which gives only products resulting from 6-*endo*-cyclization of the manganese enolate.[21] Mixtures of 6-*endo*- and 5-*exo*-products are also obtained from terminal alkyne **74a**.[28] The pres-

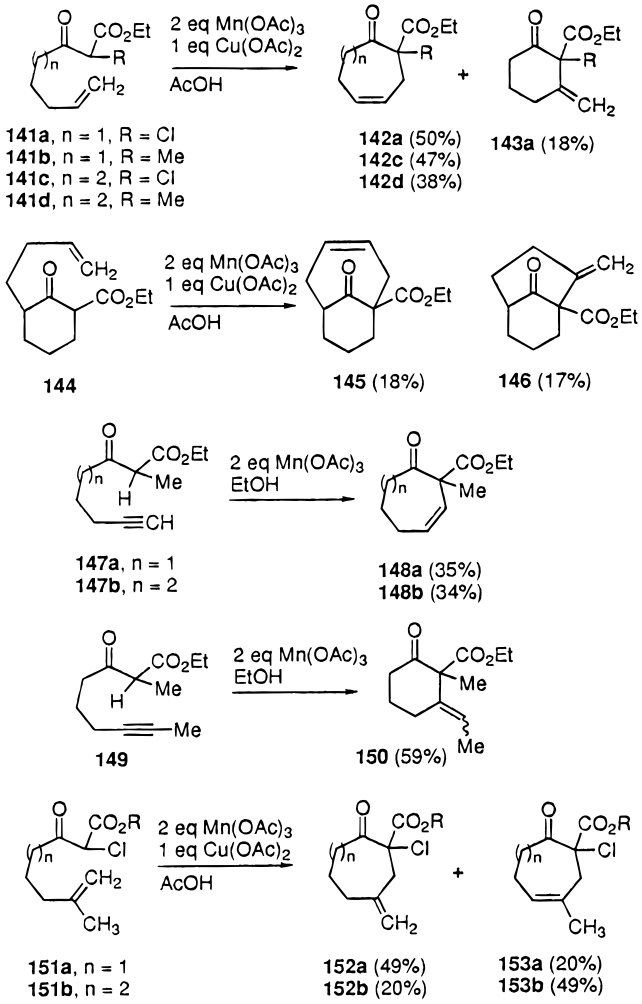
ence of the carbonyl group in the ring being formed favors the formation of the cyclohexyl radicals as compared to typical 5-hexenyl radicals, which give almost exclusively cyclopentylmethyl radicals.[1-3]



5-*exo*-Cyclization is the predominant or exclusive reaction with 1,2-disubstituted alkenes **133**, **135**, and alkyne **74b**.[17,24,28] Allylic acetate **137** is formed by further oxidation of the initially formed 3-cyclohexenone. Trisubstituted alkene **138** gives the expected mixture of alkene **139** and acetate **140**, both as mixtures of stereoisomers. 6-*endo*-Cyclization is the exclusive reaction with **123**, R_1 = alkyl, as discussed below in the tandem cyclizations section.



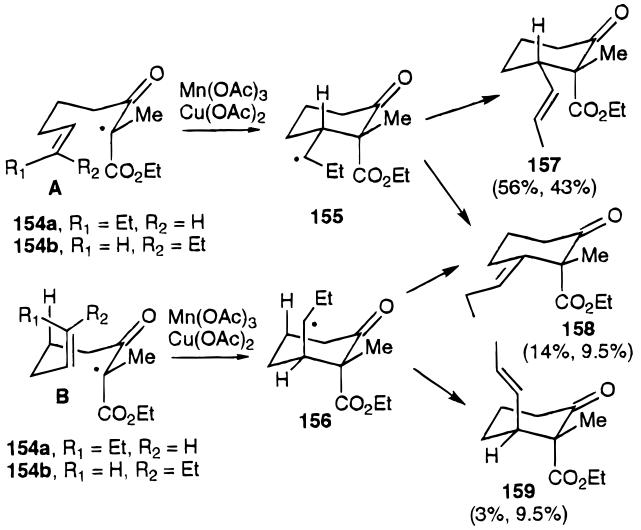
Cyclization of monosubstituted alkene **141a** affords 50% of 7-*endo*-cyclization product **142a** and 18% of 6-*exo*-cyclization product **143a**.[20,30] Analysis of the more complicated mixtures of products obtained from **141b** indicates that cyclization gives a ~2.5:1 mixture of cycloheptyl and cyclohexanemethyl radicals. Similar results are obtained with cyclic keto ester **144** which gives 35% of a 1:1 mixture of **145** and **146**.[24] The corresponding alkyne **147a** affords only 7-*endo*-product **148a** in 35% yield. Cyclization of 1,2-disubstituted alkenes results in exclusive 6-*exo*-cyclization (see **8b** → **13b** and **162** → **163** + **164**). Similarly, 6-*exo*-cyclization is observed with alkyne **149**. On the other hand, cyclization of 1,1-disubstituted alkene **151a** affords 69% of the 7-*endo*-cyclization products **152a** and **153a**.



Only 8-*endo*-cyclization has been observed with 7-octenyl radicals.[20,30] Alkene **141c** provides 47% of **142c**, while **141d** affords 38% of **142d**. The corresponding alkyne **147b** provides 34% of 8-*endo*-product **148b**. Finally, cyclization of 1,1-disubstituted alkene **151b** yields 69% of a mixture of 8-*exo*-cyclization products **152b** and **153b**.

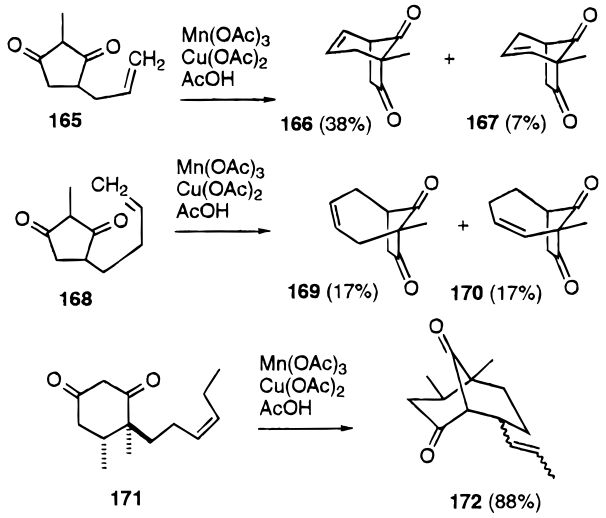
a. Stereochemistry of 6-endo- and 6-exo-Cyclizations. Radicals **154** and **160** cyclize through the conformations shown with the ester group oriented anti to the ketone. This is most clearly established by analysis of the products derived from 6-*endo*- and 6-*exo*-cyclizations. The cyclohexane ring is formed as a chair in both classes of cyclizations. 6-*exo*-Cyclization of *cis*-alkenyl radical **154a** gives a ~20:1 mixture of radicals **155** and **156**, while *trans*-alkenyl radical **154b** gives a 3:1 mixture of the same two radicals. Steric hindrance between the axial ring hydrogen shown and R_1 destabilizes transition state **B** leading to **156**. This interaction becomes more severe as R_1 increases in size resulting in much greater selectivity for **155** from the cis alkenyl radical **154a**. Radicals **155** and **156** are oxidized by Cu(II) to alkenes **157**–**159** in the yields shown (from **154a** and **154b**, respectively). The selective formation of the least substituted double bond as the *trans*-isomer is a general property of $Cu(OAc)_2$ oxidation of secondary radicals.[23] The cyclization of **160** has been shown to proceed through the chair transition state to give **161** in studies of tandem cyclizations discussed below. Oxidative cyclization of cyclic β-keto ester **162** also

proceeds through a chair transition state with an equatorial double bond affording 78% of **163** and only 4% of **164** with the more substituted double bond.



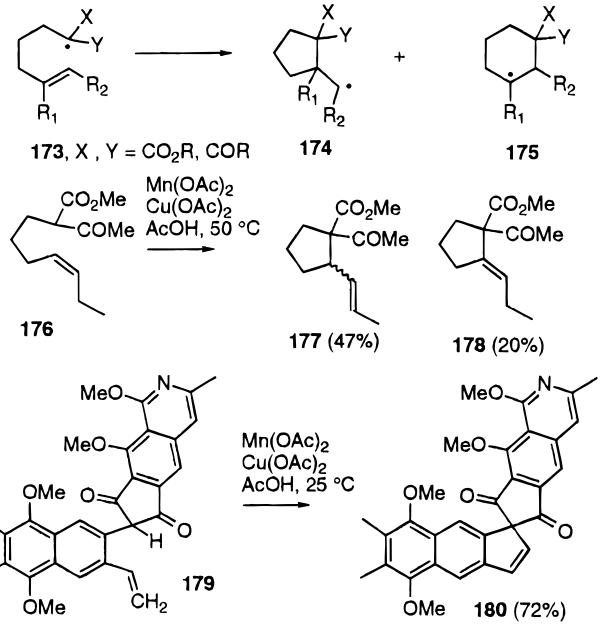
3. Diketones

Oxidative cyclization of a series of 4-alkenyl-2-methylcyclopentane-1,3-diones proceeds in moderate yield to give 6-*endo*- and 7-*endo*-cyclization products.[24] For instance, **165** affords 38% of **166** and 7% of **167**, while **168** gives 34% of a 1:1 mixture of **169** and **170**. Oxidative cyclization of cyclohexane-1,3-dione **171** affords 88% of a mixture of all four stereoisomers of **172**, all of which have been used for the total synthesis of upial.[46]



C. Radicals Derived from β-Keto Esters, β-Diketones, and Malonate Esters That Lead to Cycloalkanes

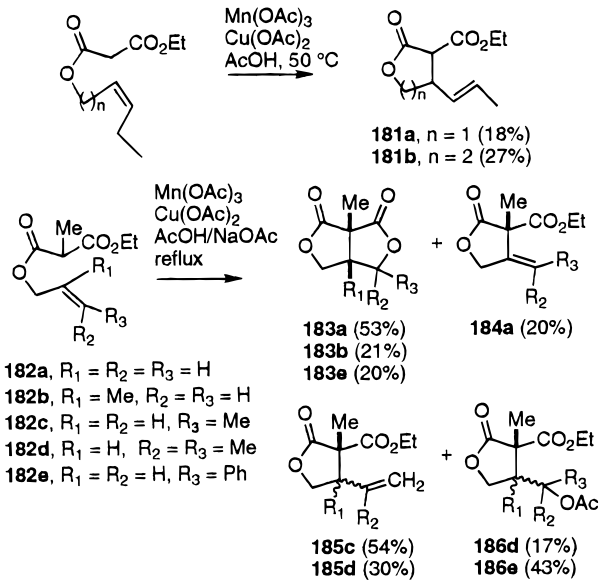
Radical **173**, which forms a cycloalkane rather than a cycloalkanone, shows the normal preference for 5-*exo*-cyclization to give **174** instead of 6-*endo*-cyclization to give **175**. With monosubstituted alkenyl radicals (**173**, R_1, R_2 = H) a 9:1 mixture of 5-*exo*-/6-*endo*-cyclization products are obtained (see **29**). 1,2-Disubstituted alkenyl radicals (**173**, R_1 = H, R_2 = alkyl) undergo exclusively 5-*exo*-cyclization (see **81**). Acetoacetate **176** affords 67% of a 7:3 mixture of **177** and **178**.[24] On the other hand, 6-*endo*-cyclization still occurs exclusively with trisubstituted alkenes (**173**, R_1, R_2 = alkyl).[16] Rama Rao reported a very unusual 5-*endo*-cyclization of indandione **179** that gives 72% of **180** in a model study for the synthesis of fredericamycin.[101,102]



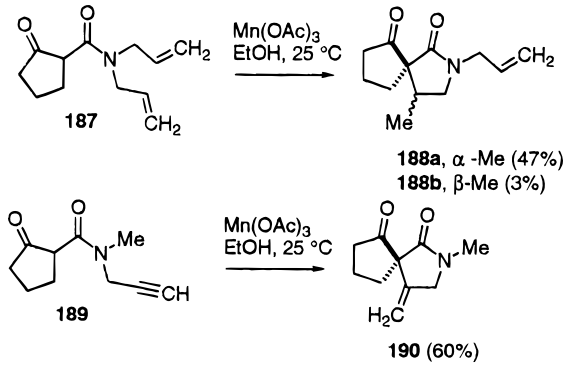
D. Radicals Derived from β-Keto Esters, β-Keto Amides, and Malonate Esters That Lead to Lactones and Lactams

Oxidative cyclization of allylic malonates and acetoacetates has been developed as a general route to γ-lactones by 5-*exo*-cyclizations.[24,41,47−49,51] There are no reports of 6-*endo*-cyclization even with a 1,1-disubstituted double bond (see **182b**). Except for a single example of 6-*exo*-cyclization there are no reports of the formation of δ- or larger lactones.[24] Bertrand found that oxidative cyclization of **63** provides 42% of cyclopropane **64**.[47−49] The analogous acetoacetate affords 57% of the cyclopropane.[48] We obtained modest yields of γ-lactone **181a** and δ-lactone **181b**.[24] The products are probably oxidized further as observed in the oxidative cyclization of crotyl malonate **49**.[49] Further oxidation is prevented by use of the α-chloromalonate (see **55** → **56** + **57**).[41]

Allylic α-methyl malonates **182** undergo 5-*exo*-cyclization to give the radical which undergoes the expected oxidative termination to give mixtures of alkenes, lactones, and acetates depending on the substitution pattern.[47−49]

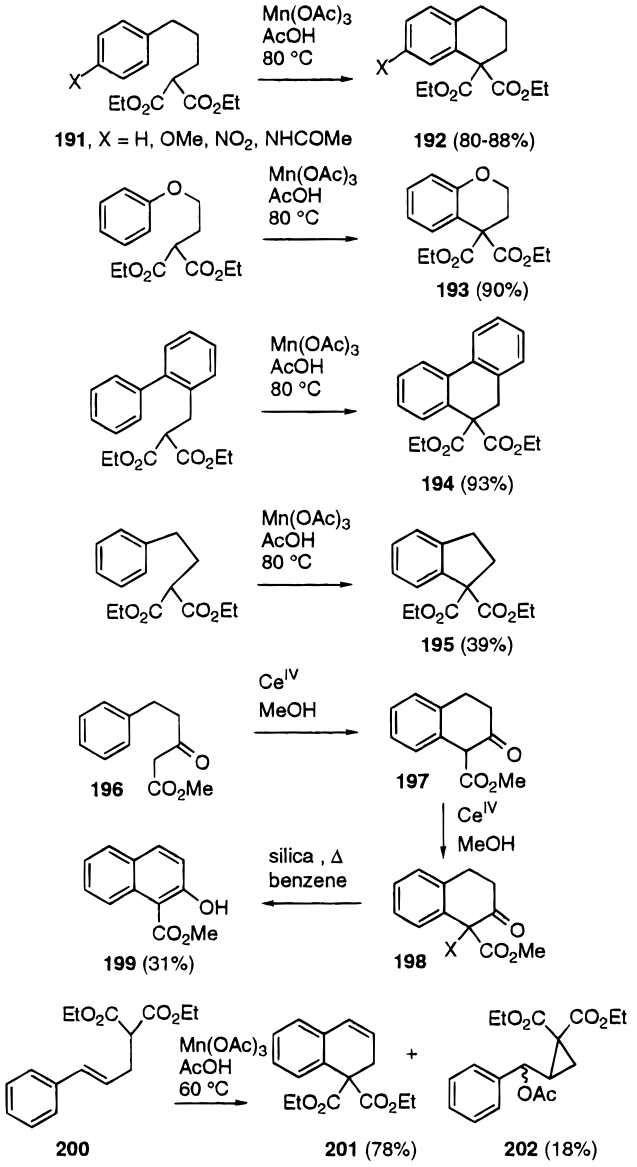


Cossy reported the oxidative cyclization of *N*,*N*-bis-(allyl) and *N*-propargyl β-keto amides **187** and **189** with $Mn(OAc)_3$ in EtOH for 1 h at room temperature to give good yields of γ-lactams **188** and **190**.[71,73] Under these conditions, in EtOH and in the absence of Cu(II), the cyclized radicals abstract a hydrogen from the solvent.[28]

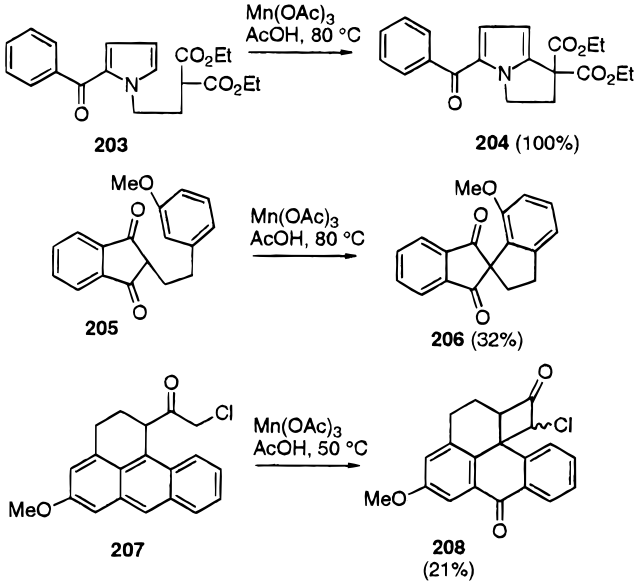


E. Additions to Aromatic Rings

Citterio comprehensively explored the $Mn(OAc)_3$-induced oxidative cyclization of α-arylalkylmalonate esters.[58,60,62,67,68] Oxidative cyclization of **191** in acetic acid at 80 °C affords 80−88% of **192**.[60] The reaction tolerates methoxy, acetamido, and nitro substituents on the aromatic ring. The reaction can be used for formation of chroman **193** and phenanthrene **194**.[60] Indan **195** is formed in modest yield.[60] These cyclizations can also be carried out with ceric ammonium nitrate and ferric perchlorate.[58,67,95] Oxidative cyclization of 5-aryl-3-oxopentanoates **196** with ceric ammonium nitrate in methanol leads to 2-hydroxy-1-naphthoate esters **199** in 30−60% yield.[62] $Mn(OAc)_3$ in acetic acid is usually less effective for these cyclizations. Dihydrotetralin **201** and cyclopropanes **202** are formed by oxidative cyclization of cinnamyl malonate **200** with $Mn(OAc)_3$ in acetic acid at 60 °C.[68] The double bond apparently isomerizes by reversible cyclization to the cyclopropylcarbinyl radical precursor of **202**.



Oxidative cyclization of acylpyrrole **203** with $Mn(OAc)_3$ in acetic acid at 80 °C affords a quantitative yield of ketorolac precursor **204**.[96] Oxidative cyclization of **205** with $Mn(OAc)_3$ in acetic acid at 100 °C gives 32% of **206**, a model for the synthesis of fredericamycin.[98] Oxidative cyclization of chloroacetamide **207** with $Mn(OAc)_3 \cdot 2H_2O$ in acetic acid at 50 °C yields 21% of β-lactam **208** which is formed by a 4-*exo*-cyclization.[92]

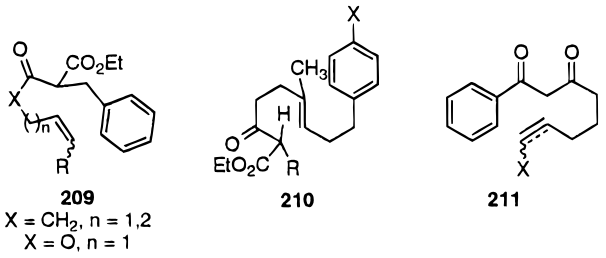


V. Tandem Cyclizations

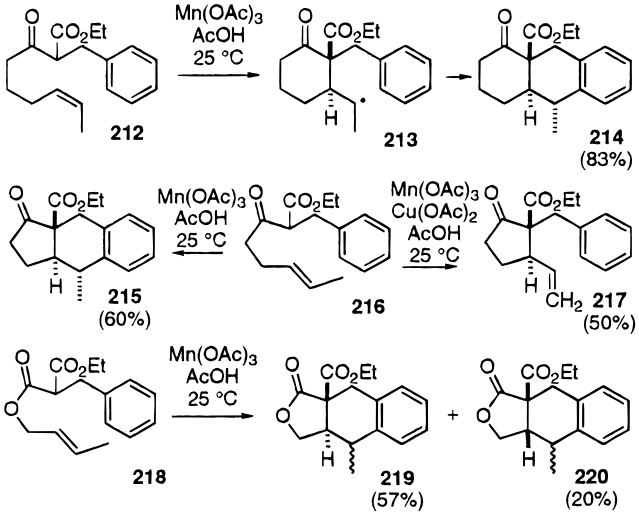
More complex targets can be made with excellent stereocontrol by tandem oxidative cyclizations. These reactions can be divided into two classes depending on whether the second cyclization is to an aromatic ring or to a second double bond.

A. Additions to a Double Bond and then an Arene

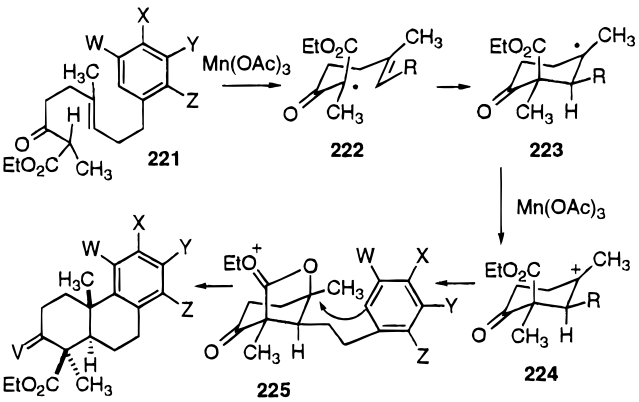
We have examined three classes of alkene/arene tandem cyclizations. The arene can be attached to the α-carbon as a benzyl group (**209**, X = CH_2, n = 1, 2),[17] to the same chain as the alkene as in **210**,[14,40] or to the carbonyl group as in **211**.[17,33,37] Bertrand has examined cyclizations of **209**, X = O, n = 1, that form tricyclic lactones.[51]



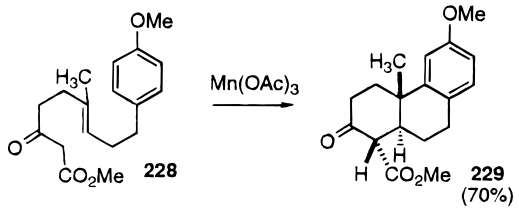
Oxidative cyclization of **212** with $Mn(OAc)_3$ in acetic acid at 25 °C provides 83% of **214** as a single stereoisomer.[17] The initial cyclization gives cyclohexanemethyl radical **213** stereospecifically as discussed above for the formation of **155**. The radical then adds to the aromatic ring to give **214** with an equatorial methyl group. Oxidative cyclization in the presence of $Cu(OAc)_2$ affords only **214**, indicating that the second cyclization is much faster than reaction of **213** with Cu(II). Cyclization of **216** is less stereoselective, providing 74% of a 12:2:1 mixture of **215** and two stereoisomers.[17] However, oxidative cyclization in the presence of $Cu(OAc)_2$ provides only 50% of **217**, indicating that reaction of the monocyclic radical with Cu(II) is much faster than the second cyclization, because a relatively strained *trans*-fused hydrindan is formed. Similarly, oxidative cyclization of **218** with $Mn(OAc)_3$ affords 57% of lactone **219** and 20% of lactone **220**.[51] If $Cu(OAc)_2$ is used as a cooxidant, 20% of **219** and 56% of the alkene analogous to **217** are formed.



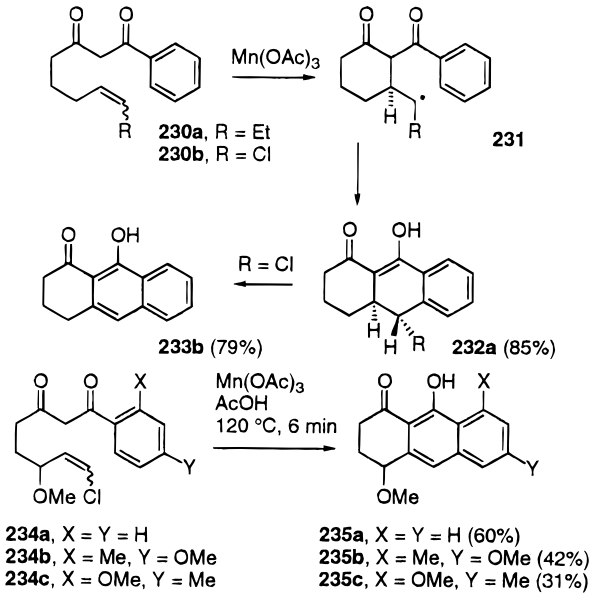
We found that oxidative cyclization of **221a** with 2 equiv of $Mn(OAc)_3$ in acetic acid at 15 °C or in MeOH at 0 °C provides 50−60% of **226a** as a single stereoisomer whose structure was established by Clemmensen reduction to give ethyl *O*-methylpodocarpate (**227a**).[14,17,40] Oxidation gives α-keto radical **222a** with the ester anti to the ketone. Cyclization occurs through a chairlike transition state to give tertiary radical **223a**. The evidence suggest that radical **223a** is oxidized to cation **224a**, which reacts with the axial ester group to give **225a**. A well-precedented Friedel−Crafts alkylation with inversion provides **226a**.[17] A similar cyclization of **221b** provides 90% of **226b**, suggesting that the oxidation of the electron-rich aromatic ring is responsible for the lower yield of **226a**. This reaction has since been used to prepare **226c**, which was converted to margolicin O-methyl ether,[164,165] and **226d**, which was converted to triptoquinones B and C.[166] Similarly, oxidative cycliza-



tion of α-unsubstituted β-keto ester **228** provides 70% of **229** with an equatorial ester group resulting from epimerization after cyclization.[14]

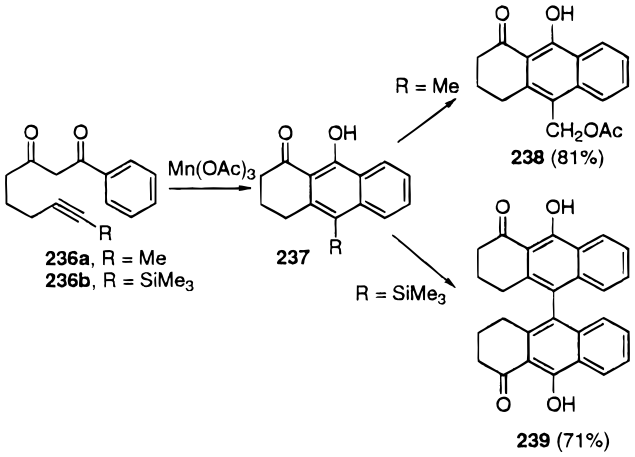


Tandem cyclizations can also be terminated by cyclization to an arene conjugated with a carbonyl group. Oxidative cyclization of either the *E*- or *Z*-isomer of **230a** with $Mn(OAc)_3$ in acetic acid affords radical **231a** which cyclizes to give **232a** with an equatorial ethyl group in 85% yield.[17,33] This reaction is useful for the synthesis of anthracycline and aureolic acid antibiotics, since it can be carried out without the ethyl group on the side chain. Cyclization of **230**, R = H, is unsuccessful, presumably because 7-*endo*-cyclization is faster. We were delighted to find that oxidative cyclization of **230b** with $Mn(OAc)_3$ in acetic acid for 15 h at 25 °C affords 79% of the desired naphthol **233b**. Cyclization proceeds as for **230a** to provide **232b**, which undergoes slow loss of hydrogen chloride to give **233b**. Similar cyclizations of methoxy chloroalkenes **234b** and **234c** provided **235b** and **235c**, which were demethylated with BBr_3 to complete the first syntheses of okicenone and aloesaponol III.[37]



Chlorine substituents on the alkene are generally useful for controlling the regioselectivity of the cyclization of 5-hexenyl or 6-heptenyl radicals generated by oxidation of an acetoacetate ester or 1,3-diketone with $Mn(OAc)_3 \cdot 2H_2O$.[33] *exo*-Cyclization is the exclusive process with radicals containing a chlorine on the distal double bond carbon, while *endo*-cyclization is the exclusive process with radicals containing a chlorine on the proximal double-bond carbon. Intra- and intermolecular competition experiments indicate that these effects are primarily steric. The chlorine substituent controls the regioselectivity of the cyclization by sterically hindering attack of the radical on the chlorine-bearing double-bond carbon thereby retarding formation of the β-chloroalkyl radical. The chlorine substituent does not electronically accelerate attack on the other end of the double bond to give the α-chloroalkyl radical, e.g. **231b**.[33]

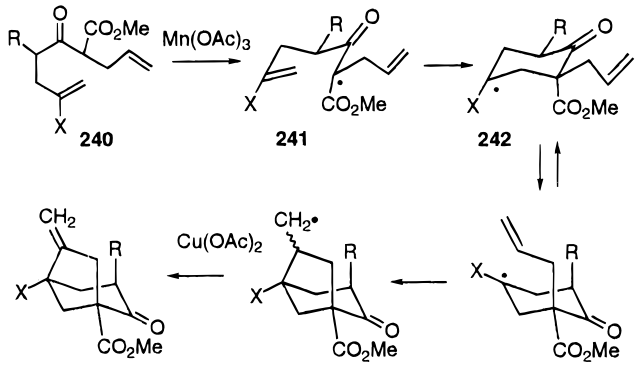
Alkynes can also be used in these tandem cyclizations, although the products initially formed are oxidized further.[33] Oxidative cyclization of **236a** with 4 equiv of $Mn(OAc)_3$ in acetic acid gives 81% of **238**. The initial product **237a** is oxidized to the quinone methide which reacts with acetic acid to give **238**. Oxidative cyclization of silylalkyne **236b** with 3 equiv of $Mn(OAc)_3$ in acetic acid gives 71% of **239**. The initial product **237b** undergoes rapid protodesilylation to give **237**, R = H, which is oxidatively dimerized to give **239**.



B. Additions to Two Double Bonds

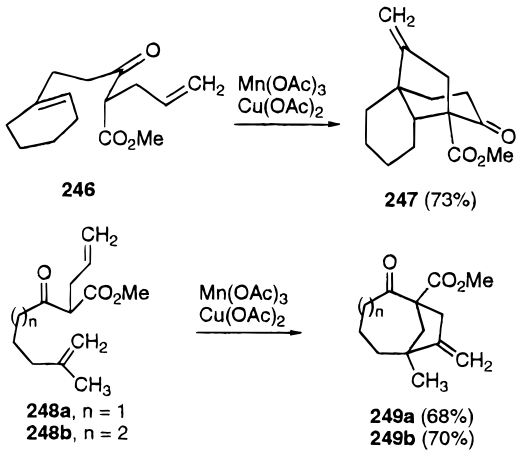
The utility of tandem oxidative cyclizations is clearly demonstrated in substrates in which both additions are to double bonds.[18,25,28,30,33,35] Oxidative cyclization of **240a** with 2 equiv of $Mn(OAc)_3$ and $Cu(OAc)_2$ in acetic acid at 25 °C affords 86% of bicyclo[3.2.1]octane **245a**. Oxidation affords α-keto radical **241**, which cyclizes exclusively 6-*endo* in the conformation shown to afford tertiary radical **242** with an equatorial allyl group. Chair−chair interconversion provides **243** with an axial allyl group. 5-*exo*-Cyclization of the 5-hexenyl radical of **243** gives **244** as a 2:1 mixture of *exo*- and *endo*-stereoisomers. Oxidation of both stereoisomers of **244** with Cu(II) provides **245a**.

The oxidative cyclization **240c** was examined as a model study for gibberellic acid. This reaction fails in acetic acid due to the instability of the enol ether, but is successful in ethanol, giving 52% of **245c** containing the complete gibberellic acid CD ring system.[28] This tandem cyclization sequence tolerates a wide variety of X substituents.[25,28] The yield is lower with $X = CH_2SiMe_3$ due to competing protodesilylation and with X = H due to competing 5-*exo*-cyclization of radical **241f**.

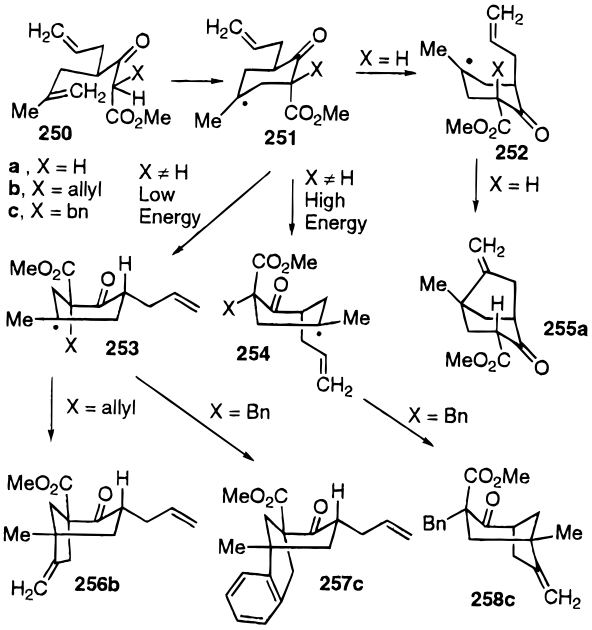


245a, R = H, X = Me (86%)
245b, R = H, X = Cl (72%)
245c, R = H, X = OMEM (52%)
245d, R = H, X = $OPO(OEt)_2$ (77%)
245e, R = H, X = CH_2SiMe_3 (30%)
245f, R = H, X = H (55%)
245g, R = Me, X = Me (48%)

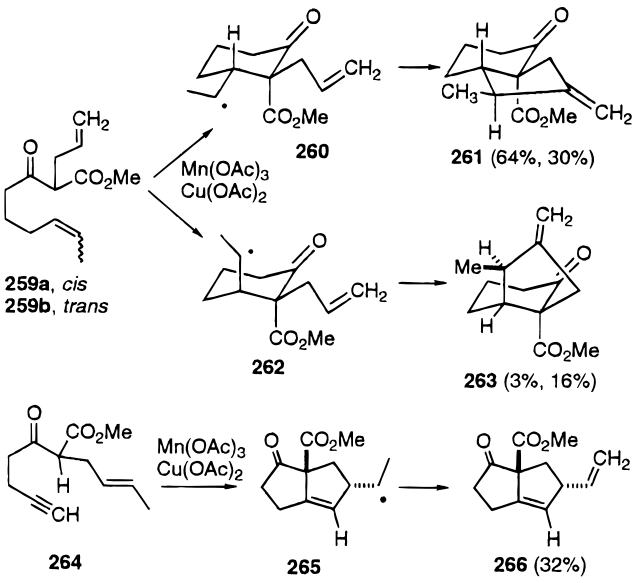
The reactive conformation of radical **241** was determined by placing substituents on the tether. Bicyclo[3.2.1]octanes containing axial substituents on the six-membered ring are the major products.[25] Oxidation of β-keto ester **240g** gives 48% of **245g** and only 9% of the diastereomer with an equatorial methyl group. The selective formation of the less stable product **245g** requires that the cyclohexyl radical undergo chair−chair interconversion prior to the second cyclization. Similarly, oxidative cyclization of **246** affords 73% of **247** with the substituent axial on the six-membered ring.[25] Tandem oxidative cyclizations in which the first cyclization is 7-*endo* or 8-*endo* can be used for the preparation of bicyclo[4.2.1]nonane **249a** (68%) and bicyclo[5.2.1]decane **249b** (70%).[30]



We examined the oxidative cyclization of γ,γ-bis(allylic) acetoacetates **250**.[35] Oxidation and cyclization affords cyclohexyl radical **251**. If X = H this undergoes chair-chair interconversion to give radical **252**, which cyclizes to **255a** (40%). 1,3-Diaxial interactions destabilize **252** if X ≠ H so that the second cyclization can only proceed through boat conformers **253** or **254**. Boat conformer **253** is calculated to be 3 kcal/mol more stable than boat conformer **254**. Therefore, **250b** cyclizes only through **253b** to give **256b** even though there are two allyl groups. α-Benzyl β-keto ester **250c** cyclizes equally through **253c** to give **257c** and through **254c** to give **258c**. Addition to the double bond to give **258c** would be much faster than addition to the aromatic ring to give **257c** in conformationally unbiased molecules.

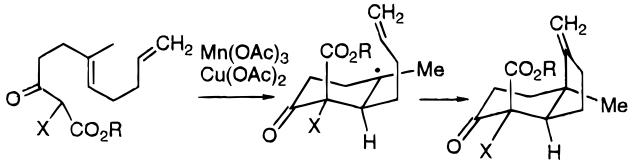


trans-Hydrindans can be prepared stereospecifically from *cis*-alkenes.[25,29] Oxidative cyclization of **259a** provides radical **260**, which reacts further to give 64% of *trans*-fused hydrindan **261**. Only 3% of the *cis*-fused isomer **263** is formed. The double-bond geometry plays an important role in the selectivity as discussed above in the cyclization of radical **154**. The *trans*-isomer of **259b** gives 30% of **261** and 16% of **263**. Oxidative cyclization of enyne **264** affords bicyclic radical **265**, which is oxidized by Cu(II) selectively to the least substituted alkene **266** in 32% yield.



Tandem cyclization can also be carried out with both double bonds in the same chain. Oxidative cyclization of α-unsubstituted β-keto ester **267a** affords 44% of **269a**, which is isolated as the enol tautomer. α-Substituted β-keto esters **267b**−**d** afford 33−50% of **269b**−**d**.[24,84] The initial cyclization

affords **268** with an axial ester group; the second 5-*exo*-cyclization provides exclusively the *cis*-fused hydrindan **269**.

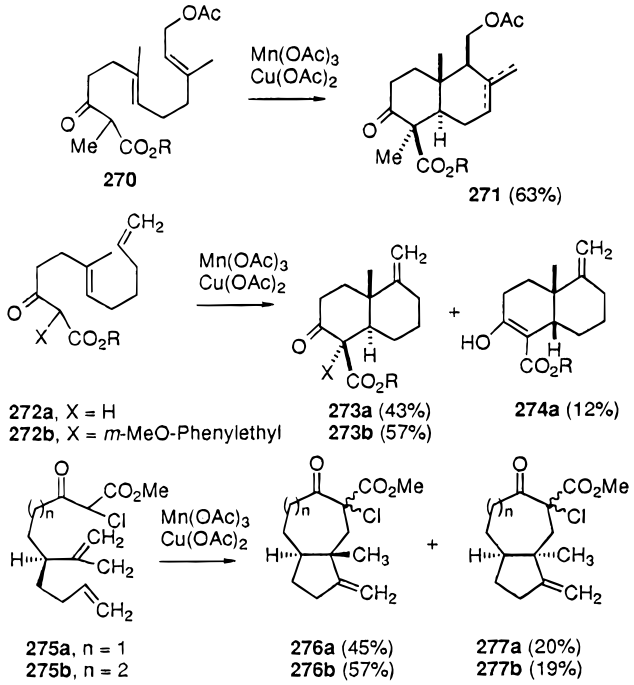


267a, X = H
267b, X = Me
267c, X = Cl
267d, X = *m*-MeO-Phenylethyl

268

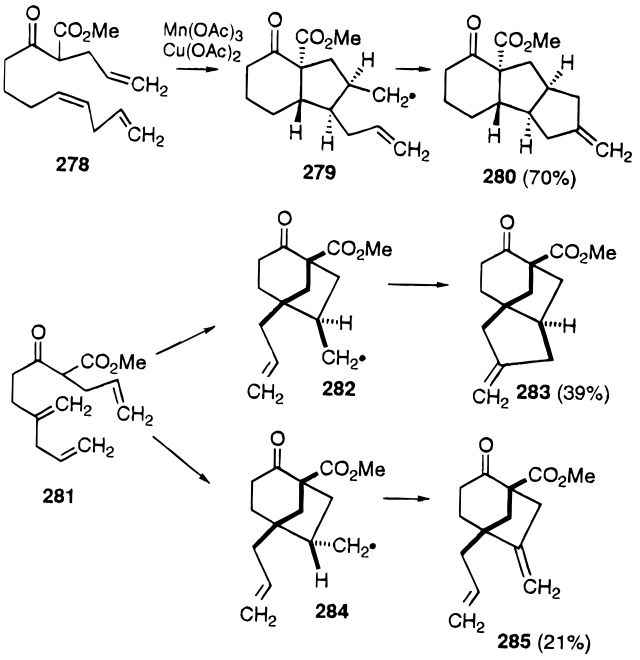
269a (44%)
269b (33%)
269c (48%)
269d (50%)

Tandem cyclizations leading to decalins give exclusively or predominantly the *trans*-fused ring system.[16,83] Oxidative cyclization of **270** affords 63% of **271** as a 10:3 mixture of *endo*- and *exo*-alkenes.[16] The second, 6-*endo*-cyclization gives the trans ring fusion.[16] Oxidative cyclization of α-unsubstituted β-keto ester **272a** affords 43% of *trans*-decalin **273a** along with 12% of *cis*-decalin **274a**.[83] α-Substituted β-keto ester **272b** affords 57% of *trans*-decalin **273b** as the only product. The second, 6-*exo*-cyclization gives the trans ring fusion. Bicyclo[5.3.0]decanes **276a** and **277a** and bicyclo[6.3.0]undecanes **276b** and **277b** are formed by tandem oxidative cyclization of **275**.[30] The second, 5-*exo*-cyclization affords predominantly the *trans*-ring fusion because the initial ring is either a cycloheptane or cyclooctane. This contrasts with the cyclization of **267** which yields exclusively the *cis*-hydrindan **269** because the initial ring is a cyclohexane.

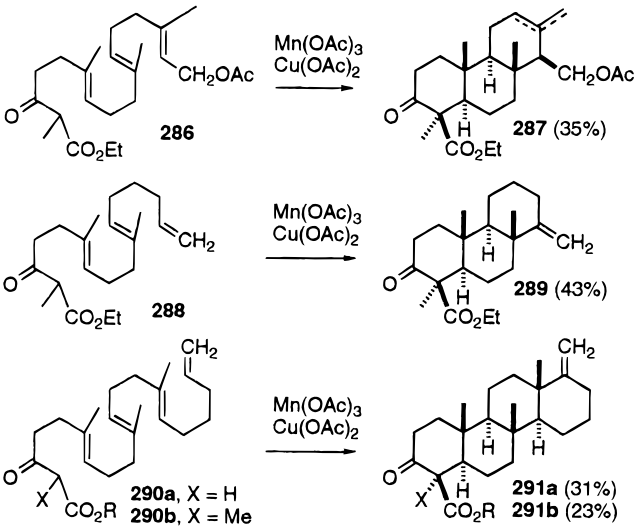


VI. Triple and Higher Cyclizations

We found that triple cyclizations can be carried out in high yield in properly designed systems.[25] Oxidative cyclization of **278** gives 70% of **280** as one of eight possible stereoisomers. Oxidative cyclization of **278** gives bicyclic radical **279**, as in the formation of **261**, with the allyl and methylene groups cis to each other and trans to the axial ester group. A third cyclization and oxidation gives **280**. Oxidative cyclization of **281** provides 39% of **283** and 21% of **285**. Oxidative cyclization of **281** affords a ~2:1 mixture of *exo*- and *endo*-bicyclic radicals **282** and **284** as in the formation of **244**. A third cyclization of **282** followed by Cu(II) oxidation provides **283**. A third cyclization of **284** is precluded by ring strain so oxidation by Cu(II) yields **285**.



Zoretic has developed a very efficient series of triple and tetra cyclizations leading to *trans*-decalin ring systems. Oxidative cyclization of **286** affords 35% of **287** as a 2:1 *endo*- and *exo*-alkene mixture.[88] Similarly, **288** affords 43% of **289**.[87] The products are useful for the synthesis of furanoditerpenes. The tetracyclization of **290a** affords 31% of **291a**, while **290b** provides 23% of **291b**.[85] These remarkable tetracyclizations construct four rings affording only one of 64 possible isomers!

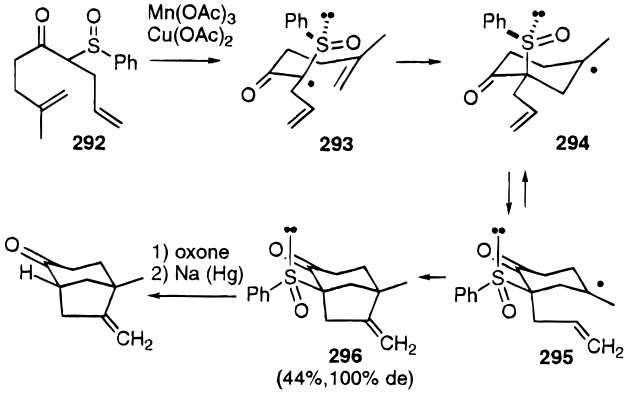


VII. Asymmetric Induction

The results described above amply demonstrate that oxidative free-radical cyclizations often proceed

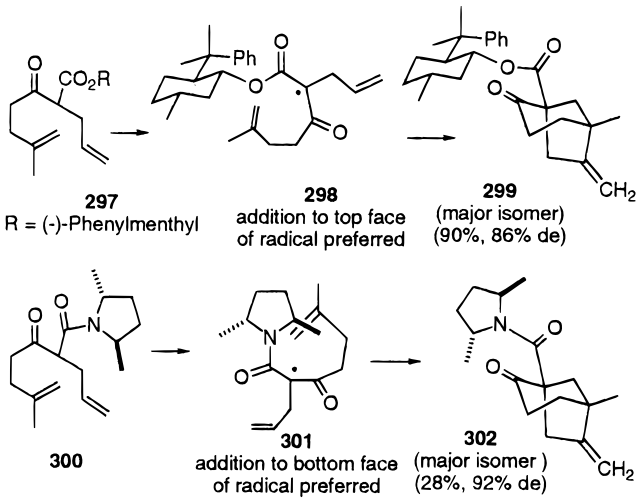
with excellent control of relative stereochemistry. We then turned our attention to using chiral auxiliaries to control the absolute stereochemistry, a topic of great current interest in free-radical chemistry.[159]

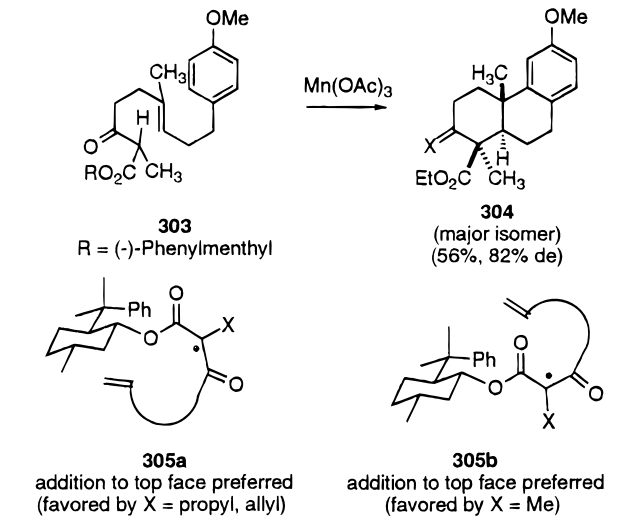
The use of β-keto sulfoxides was very appealing, since the chiral center is adjacent to the radical center. We were delighted to find that oxidative cyclization of **292** affords **296** with almost complete asymmetric induction.[27] This is consistent with α-keto radical **293**, with the carbonyl oxygen anti to the sulfoxide in an extended conformation, cyclizing through a chairlike transition state to give cyclohexyl radical **294**. Cyclization should take place with high selectivity, as shown, from the face of the α-keto radical with the small lone pair rather than the other face which is blocked by the phenyl group. Chair−chair interconversion of **294** to give **295**, followed by cyclization of the 5-hexenyl radical and oxidation by Cu(II) gives **296**. While the ~100% de in this cyclization is more than satisfactory, the yield is only 44% as compared to 86% for cyclization of the analogous β-keto ester **245a**.



We therefore turned our attention to ester or amide chiral auxiliaries that would proceed with acceptable de and in better chemical yield. We examined the cyclization of **297** with the methyl ester of **245a** replaced with chiral auxiliaries. The reactions proceed in high yield but modest de (23−60%), with the exception of the (−)-phenylmenthyl ester **297** which cyclizes to **299** in 90% yield with 86% de.[34,40] The direction of asymmetric induction is consistent with the cyclization of radical **298** from the top face in the conformation shown. 2,5-Dimethylpyrrolidine amide **300** cyclizes to **302** in even higher de (92%) but in only 28% yield, a result typical of oxidative cyclizations of β-keto amides.[34,40] The direction of asymmetric induction is consistent with the cyclization of radical **301** from the bottom face in the conformation shown. Zoretic reported that the oxidative cyclization of the camphor sultam β-keto imide analogous to **267a** proceeds in 49% yield with 50% de.[86]

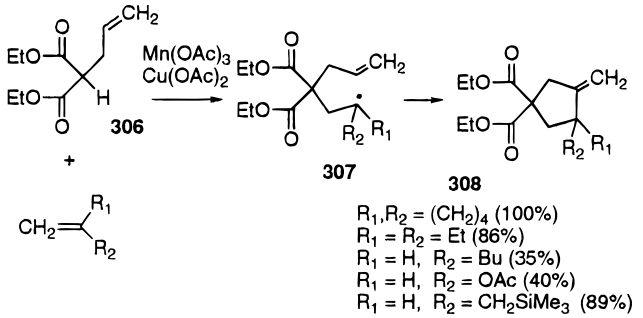
We next applied this reaction to the synthesis of (+)-podocarpic acid.[40] To our surprise, oxidative cyclization of **303** affords a 10:1 mixture (82% de) favoring the natural diastereomer **304**. This indicates that the reactive conformation of the radical obtained from **303** is not the same as that of radical **298**. After further experiments we concluded that the radical cyclizes through conformation **305a** if the α-substituent is propyl, allyl, and presumably anything larger than a methyl group, while the radical cyclizes through conformation **305b** if the α-substituent is methyl. Note that the ester group is anti to the carbonyl group in both radicals **305a** and **305b** as expected from studies discussed above in section IV.B.2.a.



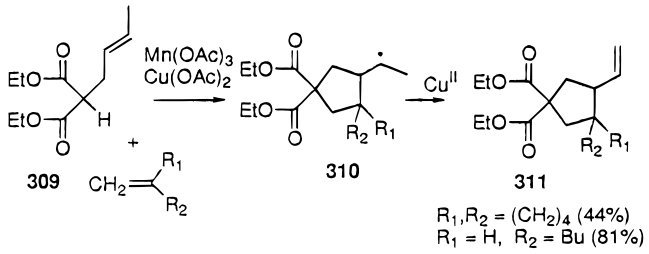


VIII. Annulations

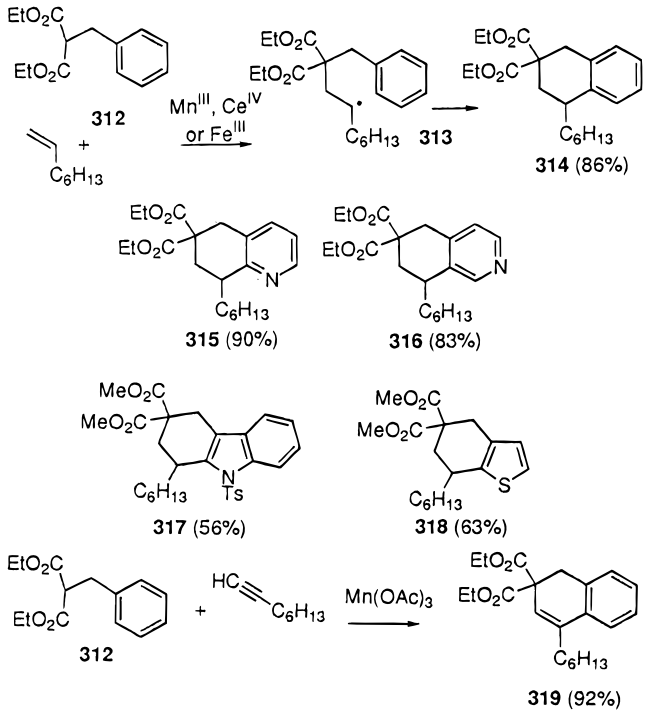
Oxidative free-radical cyclizations can also be used for annulations—tandem free-radical reactions in which the first carbon—carbon bond is formed by intermolecular addition and the second is formed by cyclization. We found that oxidation of diethyl allylmalonate (**306**) in the presence of an alkene leads to radical **307**, which undergoes a 5-*exo*-cyclization to give a cyclopentylmethyl radical that is oxidized by Cu(II) to **308** in the yields indicated.[22,53] The



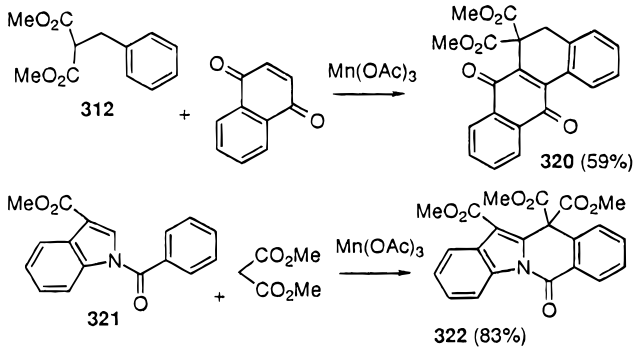
reaction is synthetically useful with 1,1-di- and monosubstituted alkenes and works better if the alkene is used in large excess. Oxidative addition of diethyl crotyl malonate (**309**) proceeds similarly to give cyclic radical **310**, which is oxidized by Cu(II) selectively to the least substituted alkene **311**.[22,53]



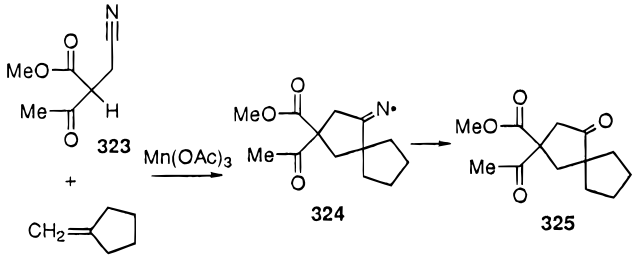
Citterio reported the oxidative annulations of diethyl benzylmalonate (**312**) with alkenes to give tetrahydronaphthalenes **314** as shown for 1-octene.[63,70] The reaction tolerates a wide variety of substituents on both the alkene and aromatic ring. Tetrahydroquinolines **315** are obtained from 2-pyridylmalonates and tetrahydroisoquinolines **316** are obtained from 4-pyridylmalonates; mixtures of products are obtained from 3-pyridylmalonates.[64] Mn(III), Ce(IV), or Fe(III) can be used as the oxidant in all of these reactions, which are terminated by oxidation to regenerate the aromatic ring. Chuang reported analogous annulations leading to indoles **317** and thiophenes **318**.[56] Citterio has shown that alkynes can be used. Oxidative annulation of diethyl benzylmalonate (**312**) with 1-octyne and $Mn(OAc)_3$ affords 92% of dihydronaphthalene **319**.[65,70]



Chuang found that dimethyl benzylmalonate undergoes annulation reactions with naphthoquinone to give **320**.[57] The addition of dimethyl malonate to *N*-aroylindole **321** is an example of a different class of oxidative annulations resulting from two successive radical reactions rather than a tandem addition−cyclization. The malonyl radical adds to the indole ring; the resulting product is oxidized a second time and adds to the aroyl group to give **322**.[55]



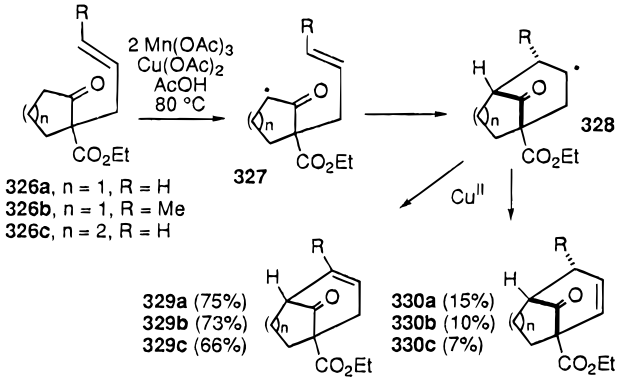
We have examined the termination of both tandem cyclizations and annulations by addition to nitrile groups.[31] In a typical example, (cyanomethyl)acetoacetate **323** adds to methylenecyclopentane to give a radical that undergoes 5-*exo*-cyclization to the nitrile group to give imino radical **324**. Hydrogen abstraction and hydrolysis of the imine provides cyclopentanone **325**.



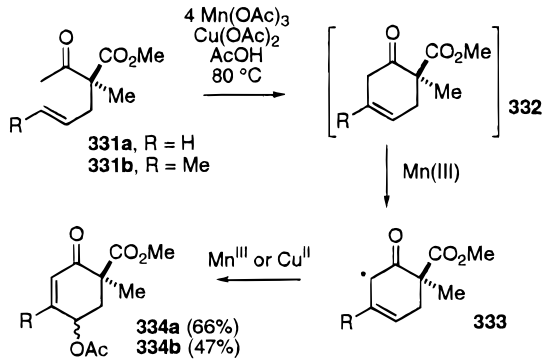
IX. Oxidation of Ketones

All of the oxidative cyclizations and annulations described above have been initiated by oxidation of relatively acidic compounds, such as 1,3-diketones, acetoacetates, malonates, and α-sulfinyl or α-nitro ketones. We have recently found that Mn(III)-based oxidative free-radical cyclization of unsaturated ketones is in fact a versatile synthetic procedure with broad applicability.[45] Reaction of cyclopentanone **326a** in HOAc with 2.5 equiv of $Mn(OAc)_3$ 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-2-en-8-one **329a** and 15% of bicyclo[3.2.1]oct-3-en-8-one **330a**. At 80 °C, oxidation gives α-keto radical **327a**. 6-*endo*-Cyclization affords radical **328a**, which is oxidized by Cu(II) to give 90% of a 5:1 mixture of **329a** and **330a**. Similar results are obtained with **326b**. Cyclohexanone **326c** reacts more slowly (18 h, 80 °C) giving a similar mixture of 66% of bicyclo[3.3.1]non-2-en-9-one **329c** and 7% of bicyclo[3.3.1]non-3-en-9-one **330c**. These reactions proceed in excellent yield since ketone **326** can enolize in only one direction and bicyclic ketones **329** and **330** are not susceptible to further oxidation, because they cannot enolize.

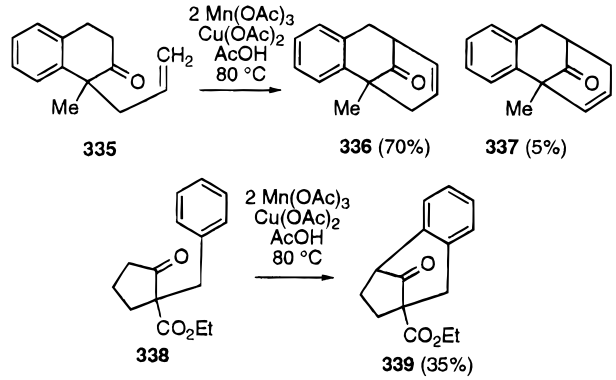
If the product ketone enolizes, further oxidation will occur, efficiently providing 4-acetoxy-2-cyclohexenones.[45] Reaction of acetoacetate **331a** with 6 equiv



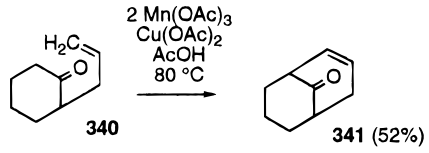
of $Mn(OAc)_3 \cdot 2H_2O$ and 1 equiv of $Cu(OAc)_2 \cdot H_2O$ in AcOH for 48 h at 80 °C affords 66% of **334a** as a 1:1 mixture of stereoisomers in a net four-electron oxidation. Oxidative cyclization of **331** should give 3-cyclohexenone **332**, if cyclization proceeds analogously to the conversion of **326** to **329**. β,γ-Unsaturated ketone **332** is more acidic than **331** and is rapidly oxidized to radical **333**, which is oxidized to **334a**.[171] Similar results are obtained with acetoacetate **331b**.



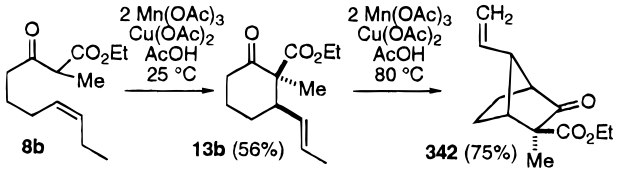
Oxidative cyclization of 1-methyl-1-allyl-2-tetralone (**335**) proceeds in good yield, indicating that the ester group present in **326** and **331** is not needed for the success of this sequence. Oxidative cyclization of cyclopentanone **338** affords 35% of **339**, indicating that α-keto radicals generated by this procedure cyclize onto aromatic rings.



Oxidation of 2-allylcyclohexanone (**340**) affords 52% of bicyclo[3.3.1]non-2-en-9-one (**341**). Enolization of the ketone should be the rate-determining step.[19] Since the methylene protons are kinetically more acidic than the methine proton, enolization and oxidation gives 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 **340**, there are α-hydrogens on both sides of the ketone.



The conversion of acetoacetate **8b** to either propenylcyclohexanone **13b (157)** or vinylnorbornanone **342** at different temperatures clearly illustrates the difference in reactivity between 1,3-dicarbonyl compounds and ketones. The oxidative cyclization of **8b** at 25 °C to give **13b** (56%) as the major product has been discussed above; no **342** is obtained at room temperature.[24] On the other hand, oxidation of **8b** with 4 equiv of Mn(III) and 1 equiv of Cu(II) for 56 h at 60 °C or 16 h at 80 °C provides 40% of **342** and only 10% of **13b**. Oxidation of pure **13b** under these conditions provides 75% of **342**. At elevated temperatures cyclohexanone **13b** 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.

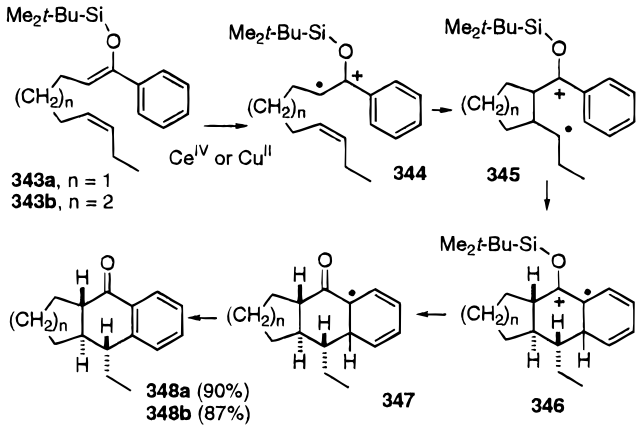


These results vastly extend the scope of Mn(III)-based oxidative cyclizations beyond 1,3-dicarbonyl compounds. A wide variety of unsaturated ketones can now be used as substrates. The formation of **341** suggests that kinetically controlled enolization is the rate-determining step in α-keto radical formation. Bicyclic ketones that cannot enolize further are isolated in good yield. Monocyclic ketones that can enolize are oxidized to γ-acetoxyenones.

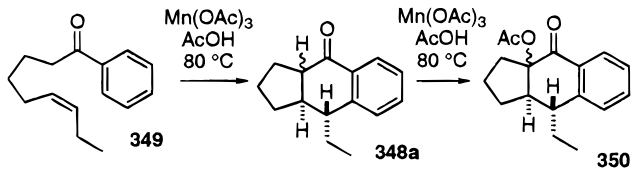
X. Oxidation of Enol Ethers and Enamines

Oxidative cyclization of δ,ϵ- and ϵ,ζ-unsaturated enol silyl ethers **343a** and **343b** with cupric triflate and cuprous oxide or ceric ammonium nitrate and sodium bicarbonate in acetonitrile provides the tricyclic ketones **348a** and **348b** stereoselectively.[26,32] These cyclizations proceed by oxidation of **343** to the cation radical **344**, followed by cyclization of **344** to cation radical **345**. This cation radical undergoes a second cyclization to give cation radical **346**, which loses the silyl group to give radical **347**, which undergoes a second oxidation and loses a proton to give **348**.

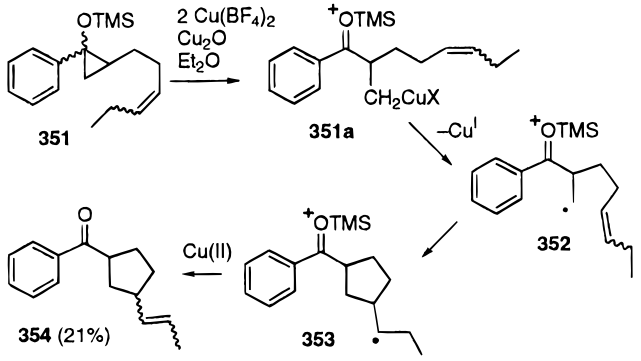
The advantage of oxidative cyclization of silyl enol ethers rather than ketones is that silyl enol ether **343** is oxidized under conditions that do not oxidize the



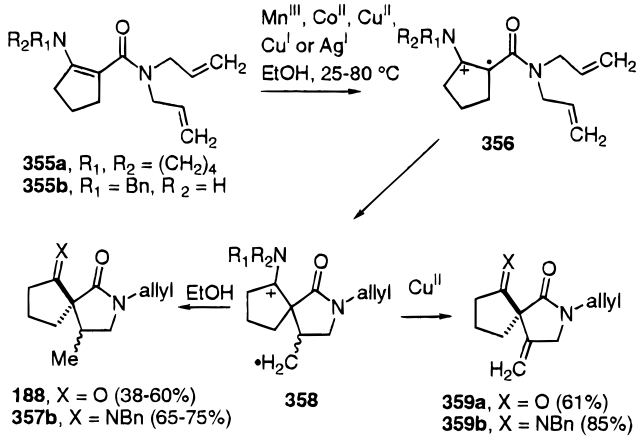
product ketone **348**. Oxidation of **349**, the ketone precursor to **343a**, with $Mn(OAc)_3$ in acetic acid at 80 °C also affords **348a**. However, **348a** is not stable to these conditions and is oxidized to a complex mixture containing both stereoisomers of **350**. The oxidative cyclization of silyl enol ethers proceeds through cation radicals, not radicals, with very different regioselectivity than is observed in radical cyclizations.[32]



Oxidation of siloxycyclopropane **351** with $Cu(BF_4)_2$ generates cation radical **352**, which cyclizes to **353**, which is oxidized to give 21% of cyclopentane **354**. This suggests that cation radicals are intermediates in the oxidative dimerization of siloxycyclopropanes with $Cu(BF_4)_2$.[160] Ryu has found that the intermediates prepared by treatment of silyloxycyclopropanes with $Cu(BF_4)_2$ add to dimethyl acetylenedicarboxylate and suggests that organocopper(II) intermediates such as **351a** are formed and add to the triple bond.[161] Cation radical **352** is probably formed by electrophilic ring opening of the cyclopropane with Cu(II) to give organocopper(II) intermediate **351a**, which loses Cu(I) to give **352**. Iwata has generated cation radicals that cyclize onto enol ethers by oxidation of cyclopropyl sulfides with ceric ammonium nitrate.[169]

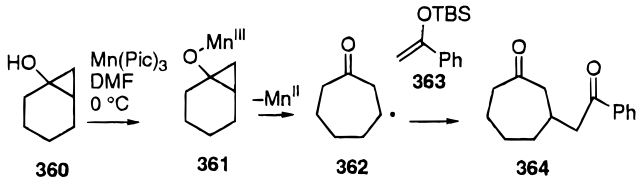


Cossy has examined oxidative cyclizations of the enamines prepared from β-keto amides **187** and **189**.[74,75] Oxidation of enamine **355** prepared from **187** and either pyrrolidine or benzylamine in ethanol with any of a variety of one-electron oxidants affords cation radical **356** that cyclizes to give cation radical **358**, which abstracts a hydrogen from ethanol to give **188** from the pyrrolidine enamine **355a** and benzyl imine **357b** from benzyl enamine **355b**. Modest (30%) asymmetric induction is obtained using enamines prepared from α-methylbenzylamine.[74] If Cu(II) is used as the oxidant, cation radical **358** is oxidized to **359**.[75]

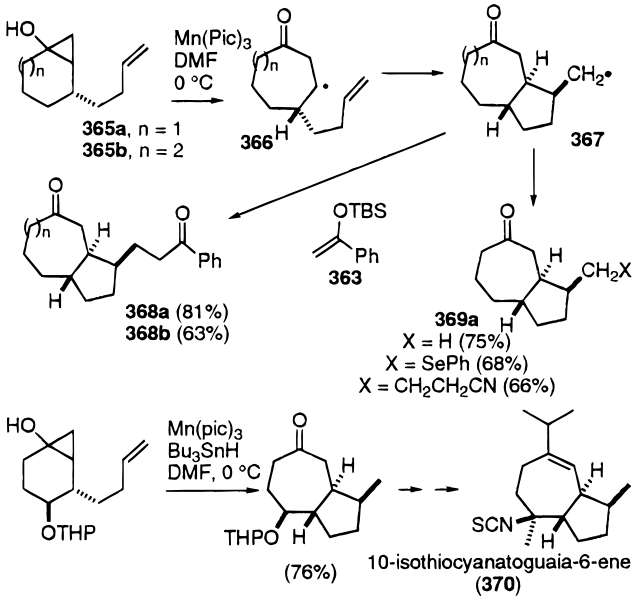


XI. Fragmentation–Cyclizations

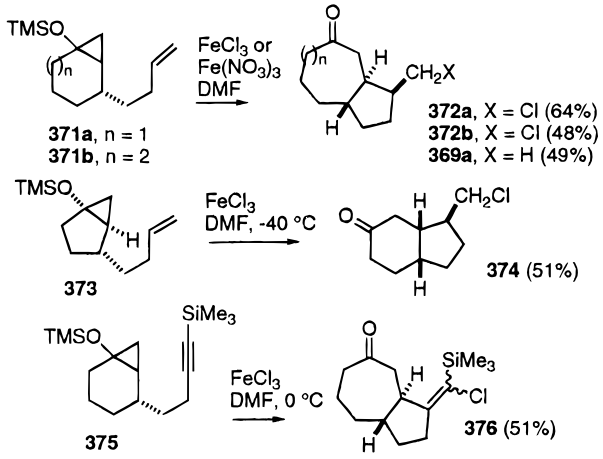
Narasaka generated β-keto radicals by oxidative fragmentation of cyclopropanols **360** with $Mn(pic)_3$ in DMF.[79,81] The manganese(III) alkoxide **361** fragments to give the most substituted radical **362**, which adds to silyl enol ether **363** to give diketone **364** after oxidation. The reaction has been extended to cyclizations by using unsaturated cyclopropanol **365**.[80] Reaction of **365** with 2.4 equiv of $Mn(pic)_3$ in DMF and 2.5 equiv of **363** affords radical **366**, which cyclizes to give **367**, which then reacts with **363** to afford diketone **368** stereoselectively. Alternatively, radical **367a** can be trapped with Bu_3SnH to give **369a**, X = H (75%), with diphenyl diselenide to provide **369a**, X = PhSe (68%), or with acrylonitrile and Bu_3SnH to give **369a**, X = CH_2CH_2CN (66%).[80] Narasaka synthesized 10-isothiocyanotoguaia-6-ene (**370**) using this fragmentation–cyclization as the key step.[168]



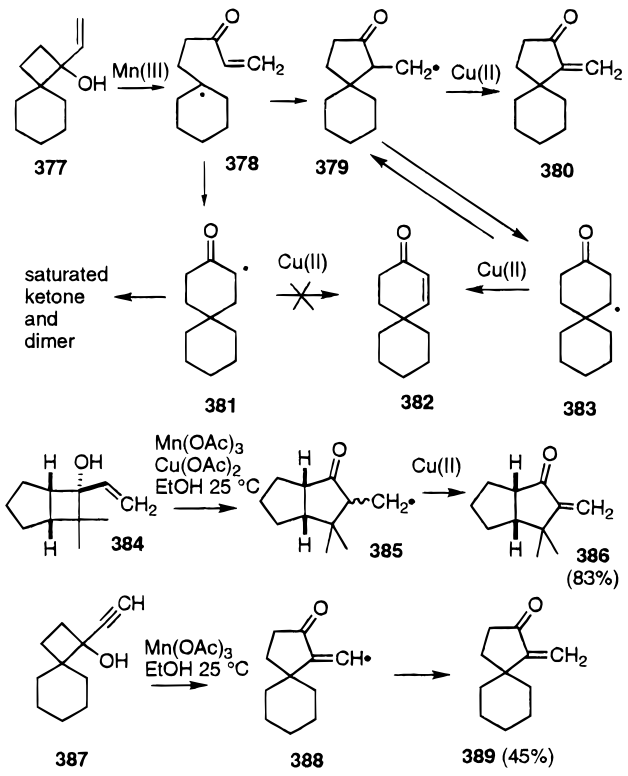
Booker-Milburn reported analogous cyclizations with $FeCl_3$ leading to chloroketones.[162,163] Reaction of **371a** or **371b** with $FeCl_3$ in DMF affords radical **367**, which reacts with $FeCl_3$ to provide **372a** (64%) or **372b** (48%) with a trans ring fusion. The bicyclic radical **367a** abstracts a hydrogen from the solvent to give 47% of **369a** if $Fe(NO_3)_3 \cdot 9H_2O$ is used as the



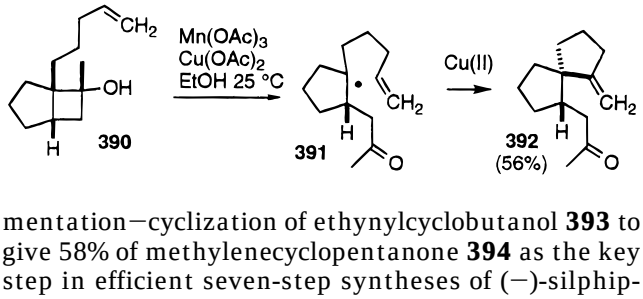
oxidant. Reaction of bicyclo[3.1.0]hexane **373** affords 51% of perhydroindan **374** with a cis ring fusion. Fragmentation−cyclization of silylalkyne **375** yields 51% of chloroalkene **376**.

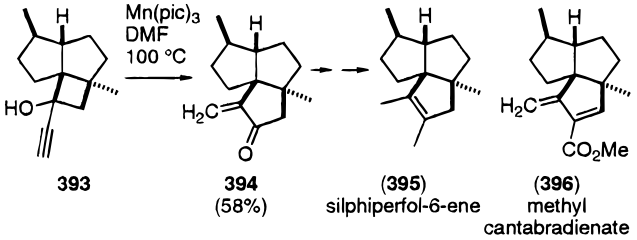


We developed a Mn(III)-based oxidative fragmentation−cyclization sequence that converts vinyl- and ethynylcyclobutanols to 2-methylenecyclopentanones and 2-cyclohexenones.[39] Oxidation of a vinyl cyclobutanol such as **377** with Mn(III) gives tertiary radical **378** that undergoes 5-*exo*-cyclization to yield **379**, which is oxidized by Cu(II) to give 2-methylenecyclopentanone **380**. Rearrangement of β-keto radical **379** via the cyclopropyloxy radical affords β-keto radical **383**, which is oxidized by Cu(II) to give cyclohexenone **382**. 6-*endo*-Cyclization of **378** provides α-keto radical **381**, which is not oxidized and instead dimerizes or abstracts a hydrogen atom to give the saturated ketone. 2-Methylenecyclopentanones are produced selectively from some vinyl cyclobutanols, such as **384**, which yields 83% of **386**. Other cyclobutanols, including **377**, form complex mixtures of products. We therefore developed an alternate route to 2-methylenecyclopentanones from ethynylcyclobutanols. Oxidative fragmentation and cyclization of **387** with Mn(III) affords β-keto vinyl radical **388**, which abstracts a hydrogen to give 45% of **389**.



Oxidative fragmentation sequences are also successful when the double bond is not conjugated to the ketone produced in the fragmentation. Oxidation of **390** with $Mn(OAc)_3$ and $Cu(OAc)_2$ in ethanol at 25 °C affords 56% of unsaturated spirocyclic ketone **392** as the major product.[39] We used the oxidative fragmentation−cyclization of ethynylcyclobutanol **393** to give 58% of methylenecyclopentanone **394** as the key step in efficient seven-step syntheses of (−)-silphiperfol-6-ene (**395**) and (−)-methyl cantabradienate (**396**).[42]





XII. Synthetic Applications

The reactions discussed above demonstrate the synthetic potential of Mn(III)-based oxidative cyclizations and annulations. The starting materials are readily available by alkylation of the mono- and dianions of β-dicarbonyl compounds. Mono, tandem,

triple, and tetra cyclizations proceed in high yield with excellent and predictable control of the regio- and stereochemistry. Oxidative termination with $Cu(OAc)_2$ inserts a double bond into the product regiospecifically producing highly functionalized, polycyclic products from simple, acyclic β-dicarbonyl substrates. Our recent work showing that oxidative cyclizations of simple ketones are synthetically useful under a wide variety of circumstances should significantly increase the scope of oxidative cyclization.[45]

Although the first oxidative free-radical cyclizations were reported only a decade ago, the reaction has already been used extensively in total synthesis. Specific examples of natural product syntheses using oxidative cyclization as a key step include the preparation of aloesaponol III (from **235c**),[37] avenaciolide (**58**),[38] a dihydro derivative of pallascensin D (from **120**),[106] *epi*-upial (from **100**),[99] fredericamycin models **180**[101] and **206**,[103] furanoditerpenes (from **287** and **289**),[87,88] the gibberellic acid CD ring system **245c**,[28] 10-isothiocyanotoguaia-6-ene (**370a**),[168] *N*-methyl-Δ^{18}-isokuomidine,[167] okicenone (from **235b**),[37] (+)- and (−)-podocarpic acid (**227**),[40] margolicin *O*-methyl ether (from **226c**),[164,165] triptoquinones B and C (from **226d**),[166] silphiperfol-6-ene (**395**),[42] methyl cantabradienate (**396**),[42] upial (from **172**),[46] and aryl tetralin lignans.[118] Over the past decade, oxidative free-radical cyclization has been developed into a broadly applicable synthetic method. Although further development is needed, the scope, limitations, and mechanism of these reactions are sufficiently well understood that they can be used predictably and reliably in organic synthesis.

XIII. Acknowledgments

I thank my collaborators, whose names occur in the references below, for their essential contributions to the work described. The generous support of the National Institutes of Health and the National Science Foundation is gratefully acknowledged.

XIV. References and Notes

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CR950026M