Transition Metal-Promoted Free-Radical Reactions in Organic Synthesis: The Formation of Carbon–Carbon Bonds

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Contents

I. Introduction 519
A. Oxidative Process 519
B. Reductive Process 520
II. Reactions of Radicals Generated by an Oxidative Process 520
A. Titanium 520
B. Vanadium 521
C. Manganese 522
D. Iron 535
E. Cobalt 539
F. Copper 540
III. Reactions of Radicals Generated by a Reductive Process 542
A. Titanium 542
a. Carbonyl Coupling Reactions 542
b. Epoxide–Olefin Coupling Reactions 545
c. δ-Enone Coupling Reactions 546
B. Vanadium 546
C. Chromium 547
D. Iron 548
E. Cobalt 548
a. Vitamin B_{12}-Catalyzed Radical Reactions 548
b. Organocobalt-Mediated Radical Reactions 550
F. Copper 555
G. Niobium 558
H. Ruthenium 558
IV. Conclusion 561
V. Acknowledgments 561
VI. References 561

I. Introduction

The formation of a carbon–carbon bond using free radicals has ushered a new era[1-8] in the domain of synthetic organic chemistry. This development, which took place during the last decade, has clearly changed the old notion of free-radical reactions being "notorously uncontrollable". Consequently, synthetic organic chemists are now more confident in dealing with these reactions after realizing that they can be carried out in more precise and controlled manner. The pioneering work from the groups of Julia,[1] Walling,[9] and Ingold and Beckwith[2,12-19] have coaxed many others to venture out in the area of synthesis using free radicals, and these efforts have culminated in adding a new dimension to the repertoire of synthetic methodology. The application of their fine work was first demonstrated by Hart[5] and Stork,[10] and later by Curran[8] and others. Giese's excellent physical organic work laid the foundation[6] for applications in intermolecular carbon–carbon bond-forming processes. Later advances in this area dealt with the aspect of stereochemistry largely due to the work of Houk and Rajan Babu[11] which provided a clear insight into the stereochemical control during the intramolecular free-radical cyclizations, and this development has encouraged hectic activity in the area of complex natural products synthesis. The carbon-centered radicals can be produced by cleaving a C–halogen, C–S, or C–OR bond with tributyltin radical generated in situ from tributyltin hydride or hexabutylditin. A disadvantage of the use of stannanes in radical reactions has been that product's radical centers are normally reduced by hydrogen-atom transfer and this results in the loss of functionality in proceeding from starting material to product.

The last decade has also seen the emergence of transition metal-promoted radical reactions[20-37] as a useful alternative to the stannane-based radical chemistry largely due to the pioneering efforts of Kharash,[20] Kochi,[21] and Minici,[31] who showed that the carbon-centered radicals may be generated using organometallic reagents. The advantage of the former method over the latter is that these reactions are usually terminated with the introduction of a functionality in the product. Transition metal-promoted radical reactions have found widespread use in organic synthesis, and one of the most well-known examples of this application is the conjugate addition reaction[38] of organocopper reagents to enones. The exciting development in this area is beginning to show its potential, as evidenced from the application of this methodology in strategy-level bond formation during the synthesis of complex molecules. The advantage associated with transition metal-promoted reactions have led to hectic research activity, and as a result, titanium-, manganese-, iron-, cobalt-, copper-, and ruthenium-mediated free-radical reactions have emerged as important synthetic methods for a new carbon–carbon bond formation. In view of their importance in organic synthesis, this review highlights the application of transition metal-promoted free-radical reaction in carbon–carbon bond formation and covers the literature up to May 1993.

Transition metal-promoted reaction of carbon-centered radicals may be divided into the following two categories. (a) reactions of radicals generated by an oxidative process and (b) reactions of radicals generated by a reductive process.

A. Oxidative Process

The metal acts as an oxidant in this process, and it involves the generation of radicals by an electron transfer[39-64] from radical precursor to the metal complex

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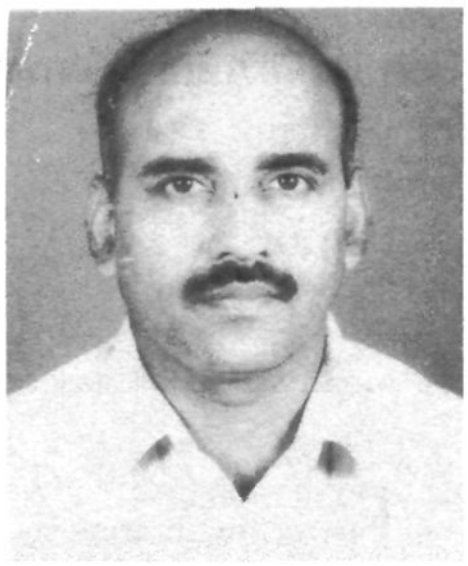

Javed Iqbal obtained a Ph.D. from Delhi University in 1977 and subsequently moved to Cambridge University as a SERC post-doctoral fellow with Dr. Ian Fleming from 1979 to 1982. He has also spent a year as a research fellow with Professor J. E. Baldwin, FRS, at Oxford University from 1982 to 1983. After spending a year (1983–1984) as Maitre assistant in Professor R. J. P. Corriu's laboratory at Universite de Montpellier, France, he joined Delhi University in 1985 and subsequently moved to I. I. T. Kanpur where he is now a Professor. His main research interests are in development of new synthetic methodology using cobalt-catalyzed reactions, transition metal-promoted free-radical reactions, and catalytic assymmetric synthesis using chiral cobalt complexes.

Beena Bhatia did her undergraduate studies at Delhi University and worked for her Ph.D. with Professor Javed Iqbal at Indian Institute of Technology, Kanpur. She is currently working as a post-doctorate fellow with Professor Javed Iqbal. Her research interest is in metal-catalyzed organic reactions and synthetic organic chemistry.

(Scheme 1). The reaction proceeds via an organometallic reagent which may lead to the carbon-centered radical on homolytic cleavage of carbon–metal bond.

B. Reductive Process

The metal acts as a reductant in this process and the carbon-centered radicals can be generated by an atom transfer or electron transfer from metal complex to the radical precursor. The reaction may proceed via an organometallic reagent which eventually leads to a free radical via homolytic cleavage of the metal–carbon bond (Scheme 2).

II. Reactions of Radicals Generated by an Oxidative Process

Transition metal-promoted generation of carbon-centered radical by an oxidative process can be achieved efficiently, and this process has found numerous

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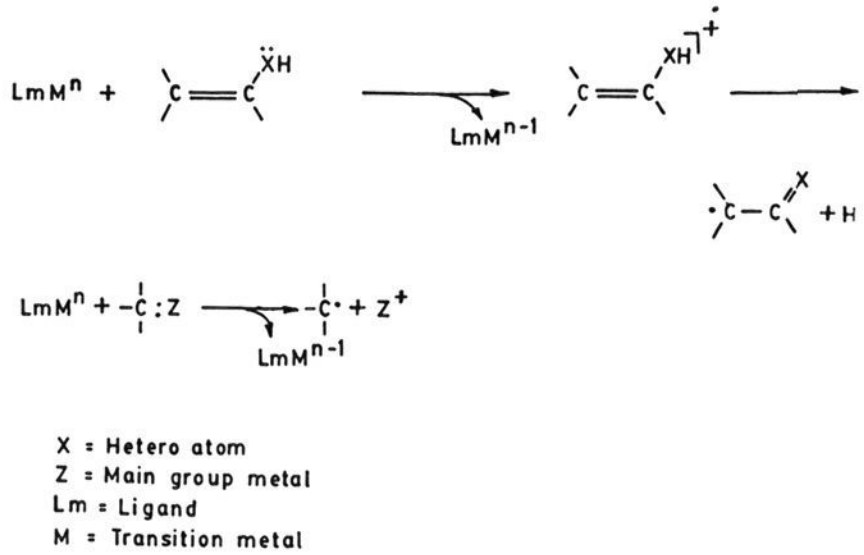
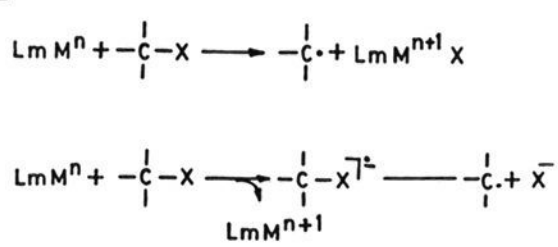
Scheme 1



Scheme 2

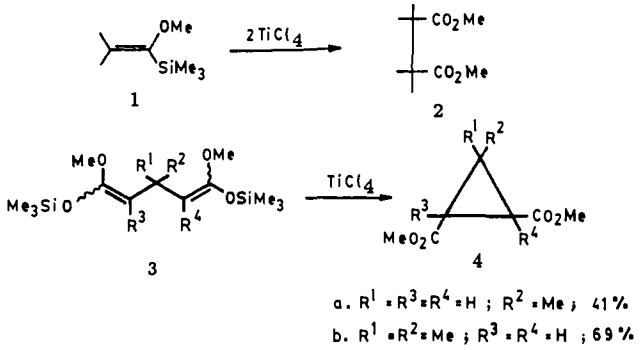


applications during the synthesis of a wide variety of organic molecules. The following section deals with the review of the radical reactions promoted by transition metals (Ti, V, Mn, Fe, Co, and Cu), and it is arranged according to the atomic number of these metals.

A. Titanium

Low-valent titanium complexes are good reducing agents, and they bring about efficient coupling reactions (section III.1) with a variety of carbonyl compounds via radical process. In contrast, the titanium-promoted

Scheme 3



radical formation by oxidative process using high-valent titanium complexes are rare and only few instances are known for such a transformation. Ojima and co-workers have shown[65] that ketene silyl acetal **1** undergoes dimerization in the presence of $TiCl_4$ to give diesters **2**. Similarly, it was demonstrated that 1,5-bis(trimethylsiloxy)-1,5-dimethoxy-1,4-pentadines (**3**) cyclize stereoselectively[66] to dimethyl *trans*-cyclopropane-1,2-dicarboxylates (**4**) on treatment with $TiCl_4$ (Scheme 3). $TiCl_4$ causes coupling only of ketene silyl acetals and not of enol silyl ethers derived from ketones. The mechanism of these reactions is similar to the $Cu(OTf)_2$-induced (see section III) cyclization of dienolates or the coupling of enol silyl ethers.

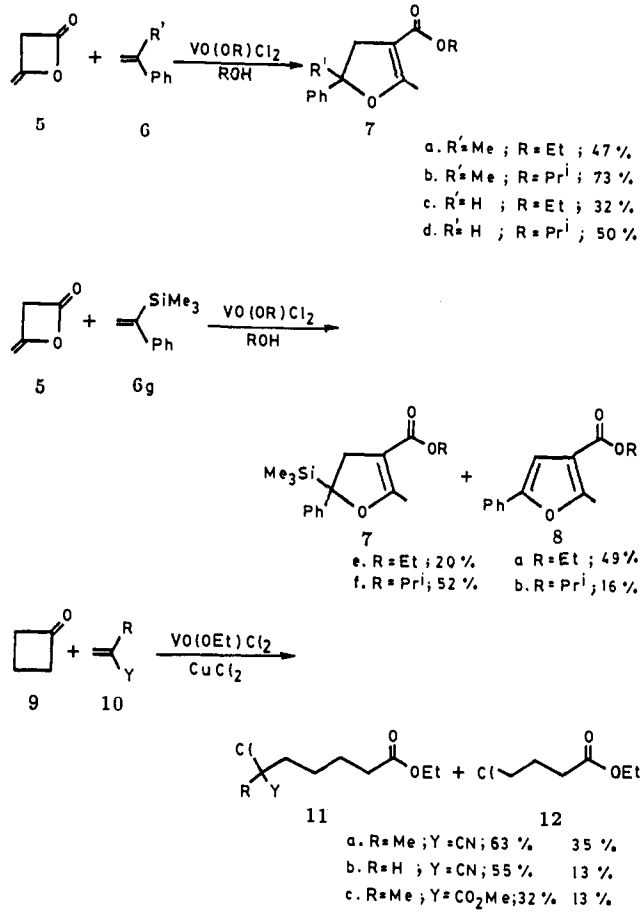
B. Vanadium

Pentavalent vanadium compounds are generally considered to be one electron oxidants,[67,68] and $VO(OR)Cl_2$ has been found to be a versatile Lewis acid in organic media; it can achieve oxidative transformation of carbonyl compounds such as catalytic ring opening[69] oxygenation, dehydrogenative aromatization,[70] and decarboxylative deamination.[71] Hirao et al. have shown that diketene **5** undergoes a $VO(OR)Cl_2$-induced cyclization[72] with styrenes **6** via ring opening to give 3-(alkoxycarbonyl)-2-methyl-5-phenyl-4,5-dihydrofurans (**7**). Desilylative aromatization to the furan **8** is observed in the reaction with α-(trimethylsilyl)styrene **6**. Treatment of cyclobutanone with $VO(OEt)Cl_2$ in the presence of olefin **10** bearing an electron-withdrawing substituent gives the adducts **11** and **12** via a novel oxidative[73] ring-opening reaction (Scheme 4). A homolytic process seems to be involved in the present ring-enlargement reaction as the authors have proposed the intermediacy of β-oxo and τ-oxo radical for the transformations in Scheme 4.

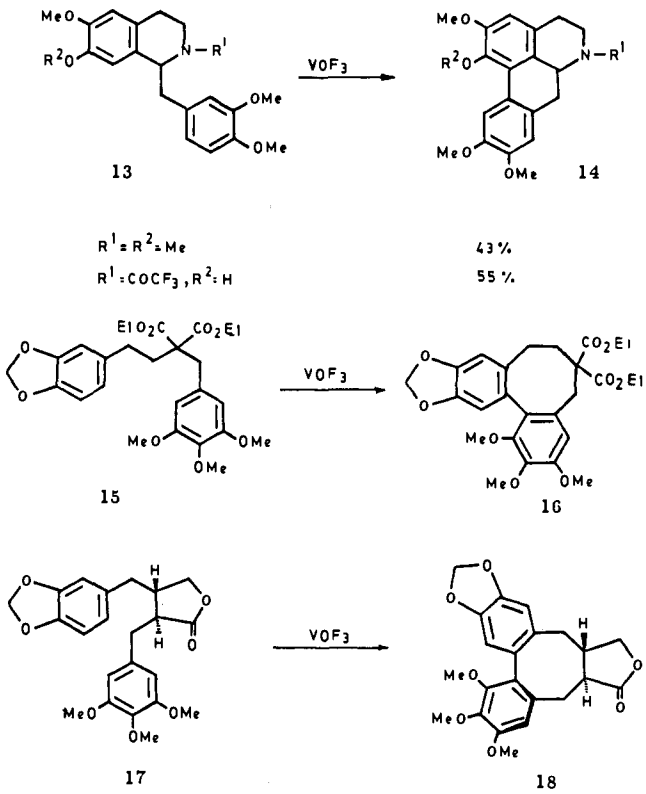
Vanadium oxytrichloride and oxytrifluoride have proven to be good reagents for the oxidative coupling of a variety of phenols and aromatic ethers. Vanadium oxytrichloride oxidizes phenol and 1-naphthol to the corresponding para-coupled products[74,75] in moderate to good yield. (±)-Laudauosine (**13a**) can be oxidized with vanadium oxytrifluoride in trifluoroacetic and fluorosulfonic acid to (±)-glaucine (**14a**). The same oxidant also affected phenol–phenol ether coupling in the alkaloid series, with *N*-(trifluoroacetyl)codamine (**13b**) yielding the aporphine (±)-*N*-(trifluoroacetyl)-wilsonirine (**14b**).

(±)-Steganacin (**16**) can be synthesized using intramolecular coupling of the malonate-derived bisaryl butane **15** using VOF_3 at 25 °C. Similarly (±)-isostegane

Scheme 4



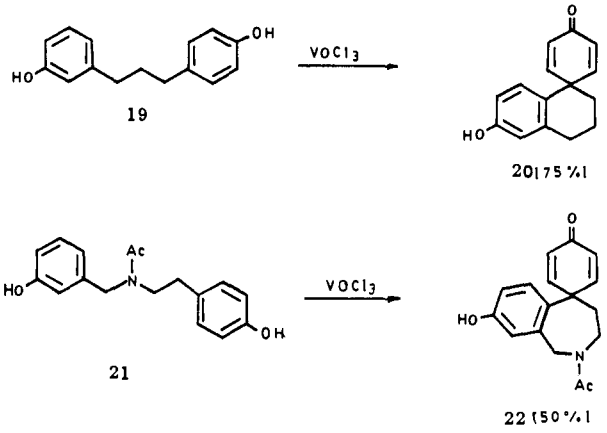
Scheme 5



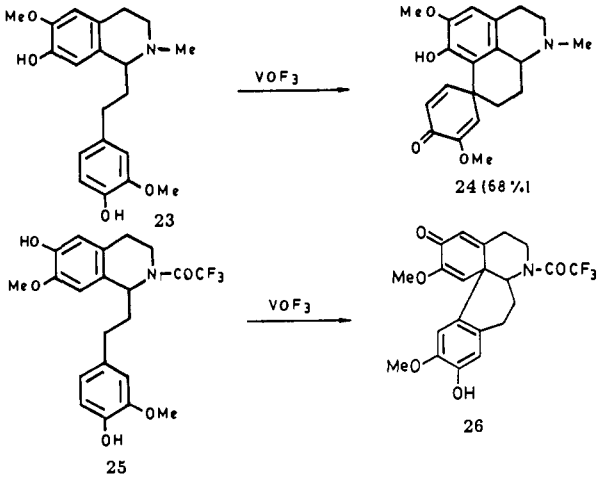
(**18**) was synthesized by oxidation[76–78] of (±)-dibenzylbutyrolactone **17** using VOF_3 at 45 °C (Scheme 5).

Spirodienones **20** can be synthesized from 3,4′-dihydroxy diaryl propanes **19** on treatment with $VOCl_3$

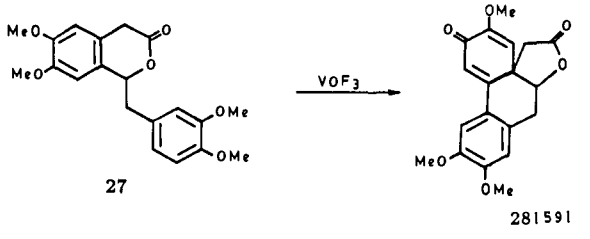
Scheme 6



Scheme 7



Scheme 8



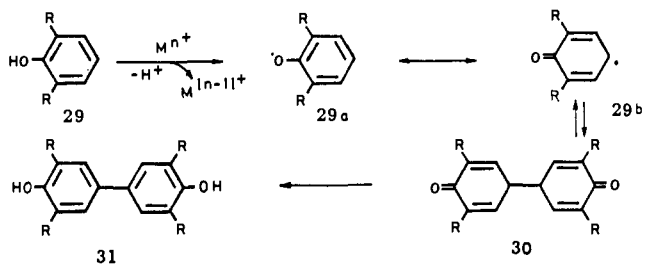
at −78 °C in ether. Similarly the amide **21** can be converted[79-61] to the spiro-linked benzapepine **22** on oxidation with $VOCl_3$ (Scheme 6).

Vanadium oxytrifluoride induces a selective ortho–para or para–para coupling on 4′,7-dihydroxy and 6,4′-dihydroxy tetrahydroisoquinoline derivative **23** and **25** to give[82] the spirotetracycles **24** and **26**, respectively (Scheme 7).

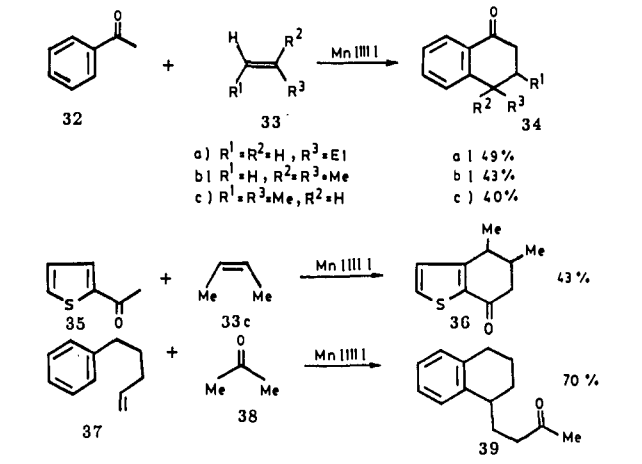
The benzyl lactone **27** afforded a rearranged[83] spirolactone **28** on treatment with VOF_3 (Scheme 8).

The generally accepted mechanism for these oxidations involves the metal-induced electron transfer. Both inner-sphere and outer-sphere electron-transfer processes have been implicated in these couplings. Oxidation to the radical may proceed from the phenol **29** or phenolate anion according to pH. The coupling of **29b** results in the intermediate **30** which upon enolization produces the biphenyl **31** (Scheme 9). Aryl ethers are believed to undergo[84] these couplings via a radical cation.

Scheme 9



Scheme 10



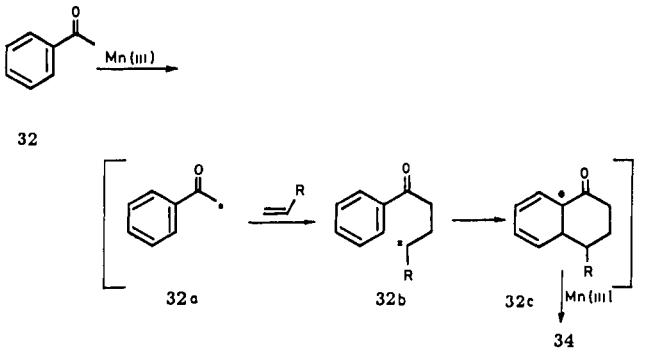
C. Manganese

Heiba and Dessau and Bush and Finkbeiner have demonstrated that acetic acid is oxidized by $Mn(OAc)_3 \cdot 2H_2O$ in acetic acid to the carboxymethyl radical which adds to alkene to give a radical which is oxidized by a second equivalent of $Mn(OAc)_3 \cdot 2H_2O$ to give a γ-lactone. The mechanism of this reaction has been extensively explored, and further synthetic applications have been developed by Heiba and Dassau,[85-90] Bush,[91] Kooyman,[92] Nikishin and Vinogradov,[93-105] McQuillin,[106,107] Fristad,[108-114] Corey,[115-117] and others.[56-65] In a similar manner, ketones, esters, and aldehydes are also oxidized by Mn(III) acetate to give α-oxoalkyl radicals that can add to olefins to form a variety of interesting products. Substituted α-tetralones **34** have been synthesized by Mn(III)-promoted addition of aromatic methyl ketone **32** to various olefins **33**. Similarly, the synthesis of **36** and **39** can be achieved using methyl ketone **35** derived from thiophene or by addition of acetone **38** to aromatic olefins **37** (Scheme 10).

These reactions are considered to proceed via a radical process where Mn(III) initiates the oxidation of methyl ketone to give **32a** which undergoes intermolecular addition to the olefins to produce a new radical **32b**. Intramolecular addition of radical **32b** to aromatic ring gives rise to a stabilized radical **32c** which is oxidized with Mn(III) to restore the aromaticity and yield the tetralone or tetralin **34**, **36**, or **39** respectively (Scheme 11).

The latter methodology has been used in the synthesis of fungicide pyrenophorin (**42**) by Uguen and Breuilles. Treatment of acetone with olefin **40** gave the coupled product **41** which was transformed to the natural product **42** by routine functional group manipulation (Scheme 12).

Scheme 11



Scheme 12

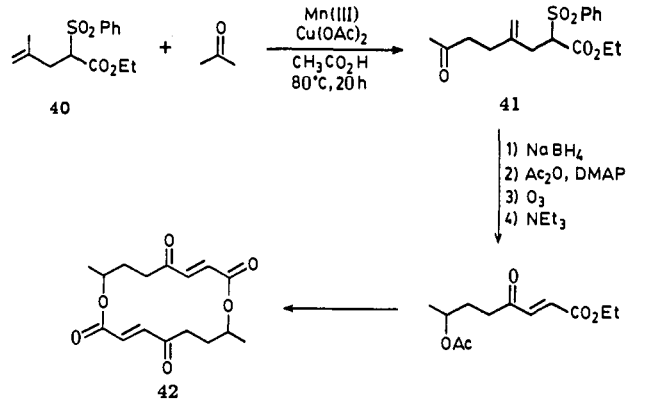
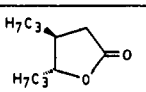
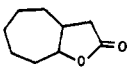
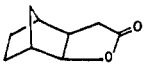
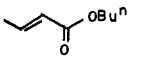
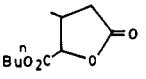
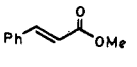
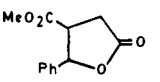


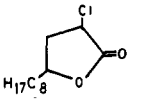
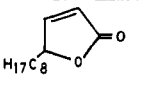
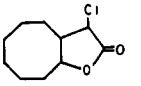
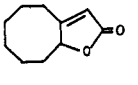
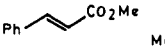
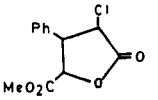
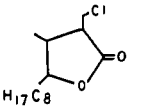
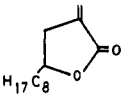
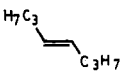
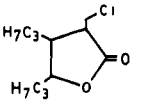
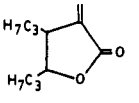
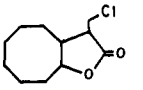
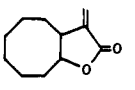
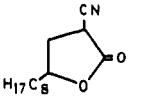
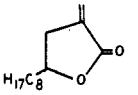
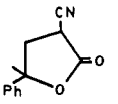
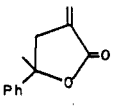
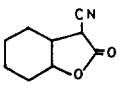
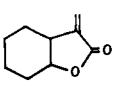
Table 1. Mn(III)-Promoted Synthesis of γ-Lactones from Acetic Acids and Olefins

Entry	Alkene	Product(s) Yield (%)[a]	Cis : Trans
1			1 : 33
2			1 : 24
3			—
4			1 : 38
5			1 : 26

a) Only major products are mentioned here.

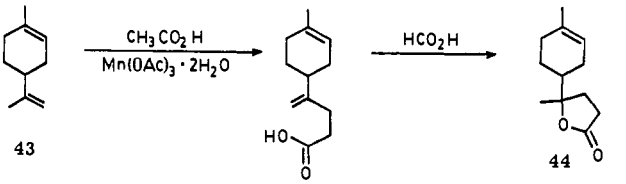
The pioneering work of Fristad and co-workers has been highlighted[108-114] by the synthesis of a variety of γ-lactones[108] from carboxylic acids and olefins (Table 1). These workers have also shown that chloroacetic acid, 3-chloropropionic acid, and cyanoacetic acids can be converted into the corresponding[110] lactones in high yields (Table 2). The utility of this procedure has been amply demonstrated by Gardrat for the synthesis[119] of terpene lactone norbisabolide (44) from limonene (43) and acetic acid in the presence of manganese(III)/copper(II) acetates (Scheme 13). Manganese(III) acetate-promoted oxidation of malonic acid (46) in the

Table 2. Mn(III)-Promoted Lactonization Using Chloroacetic, 3-Chloropropanoic and Cyanoacetic Acids and Olefins

entry	acid	alkene	lactone (yield, %)[a]	α,β-unsaturated, γ-lactone[b-d]
1	$ClCH_2CO_2H$			
2				
3				
4	$ClCH_2CH_2CO_2H$			
5				
6				
7	$NCCH_2CO_2H$			
8				
9				

[a] All the lactones were obtained as mixture of diastereomers. [b] Chloro lactones were converted into iodo lactone (NaI–acetone) followed by refluxing with Et_3N–THF. [c] α-Methylene, γ-lactones were obtained by treatment with 1,8-bis(dimethylamino)naphthalene in THF. [d] The α-cyano lactones were reductively methylated (H_2, Rα-Ni, CH_2O) and then treated sequentially with MeI and $NaHCO_3$ to yield α-methylene, γ-lactones.

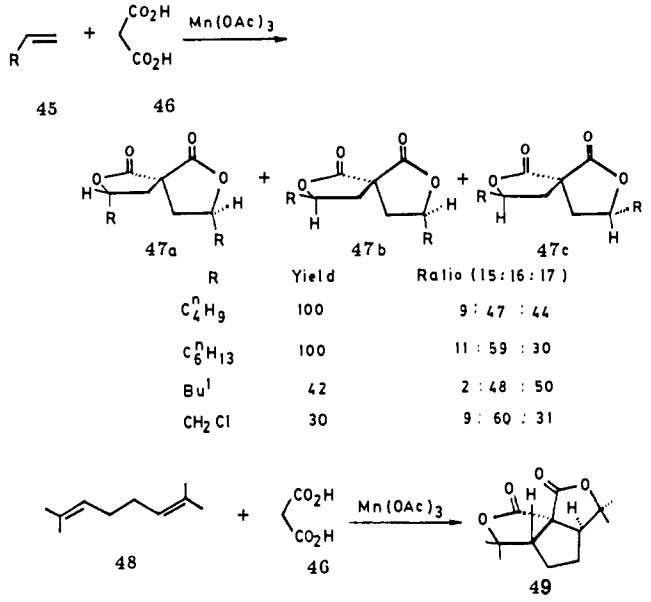
Scheme 13



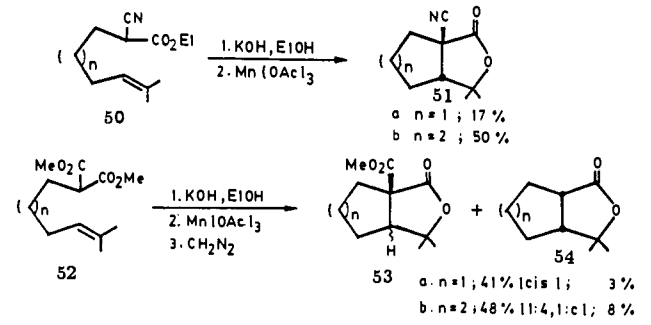
presence of alkenes 45 results in the formation of spiro-fused lactones, 2,7-dioxaspiro[4.4]nonane-1,6-diones (47a–c). They have also converted 1,5-diene 48 to the corresponding single tricyclic bridged spirodilactone 49 in moderate yields (Scheme 14).

Bicyclo[3.3.0]- and -[4.3.0] lactones 51, 53, and 54 can be prepared by an intramolecular lactone annulation[112] of potassium carboxylate salt of unsaturated cyanoacetates 50 and malonates 52 onto olefins in the presence of manganese(III) acetate (Scheme 15).

Scheme 14



Scheme 15



Bertrand et al. have shown that $Mn(OAc)_3$ oxidizes allyl acetoacetate or allylmalonate **55** to 3-oxabicyclo-[3.1.0]hexan-2-one derivatives **56**, whereas under similar conditions cinnamyl and crotyl esters **55d–e** lead to monocyclic γ-lactone derivatives **57** and **59** and dilactones **58**. One equivalent of $Cu(OAc)_2$ is used to oxidize the radicals to cations which leads to the formation of the observed products. It is also interesting to note that fast oxidation of the cyclic carbon radicals with Cu prevents[120] reversibility and leads exclusively to five-membered-ring products (Scheme 16).

With the methylmalonates **55f** the methyl group blocks[121] further reaction at the reactive center. Compound **55f** generates a primary radical **60**, which undergoes oxidative substitution to give dilactone **61** or oxidative elimination to give the methylene lactone **62** (Scheme 17). If **62** is not further oxidized under the reaction conditions, the ratio of **61**/**62** is an indication of the stereoselectivity of the radical cyclization since only the stereoisomer of radical **60** in which the ester is syn to the reactive center can produce the dilactone.

The dicrotyl malonate (**63**), via two successive[121] radical cyclizations, leads to a mixture of three spirodilactones **64** in the relative proportions of 38:54:8 (Scheme 18).

Intramolecular addition to triple bond can be promoted[121] by Mn(III)–Cu(II) combination as indicated by the oxidation of **65** to the corresponding methylene lactone **62** and the vinyl acetate **66** (Scheme 19). The unsubstituted ethyl propargyl malonate gave polymeric material under these conditions.

Corey and Kang have developed a novel Mn(III)-promoted general synthesis of polycyclic γ-lactones by a double annulation[115] reaction using a monoester derived from malonic acid. Thus 4-(2-cyclopentenyl)-3-oxobutanoic acid (**67a**) and the corresponding cyclohexyl derivative **67b** when stirred with $Mn_3O(OAc)_7$ in AcOH at 23 °C for 20 min gave keto lactone **68a** and **68b**, respectively, whereas the malonate monoester **69** yielded di-γ-lactone **70** in good yields. In similar experiments keto acid **71** was transformed into the tricyclic bridged lactone **72** (Scheme 20).

Bertrand et al. have demonstrated the influence of Cu(II) upon the chemoselectivity[122] during the Mn(III)-mediated tandem oxidative cyclizations of benzylmalonic acids. The reaction of **73** in the presence of Mn(III) and Cu(II) gives the dilactone **74** (10%), tricyclic lactone **75** (24%), and unsaturated monolactone **76** (56%), whereas the reaction in the absence of Cu(II) leads to mainly a mixture of tricyclic lactones **75** (57%) and **77** (20%). The traces of lactones **74** and **76** in the latter reaction indicates that the radical addition to the benzene ring is faster than its oxidation with Mn(III) (Scheme 21).

A regio- and stereocontrolled synthesis of substituted lactams **79** and spirolactams **81–83** can be achieved[123–124] by a Mn(III)-promoted intramolecular oxidative cyclization of N,N-unsaturated dialkyl-β-oxoamides **78**, **80**, and **83** respectively (Scheme 22).

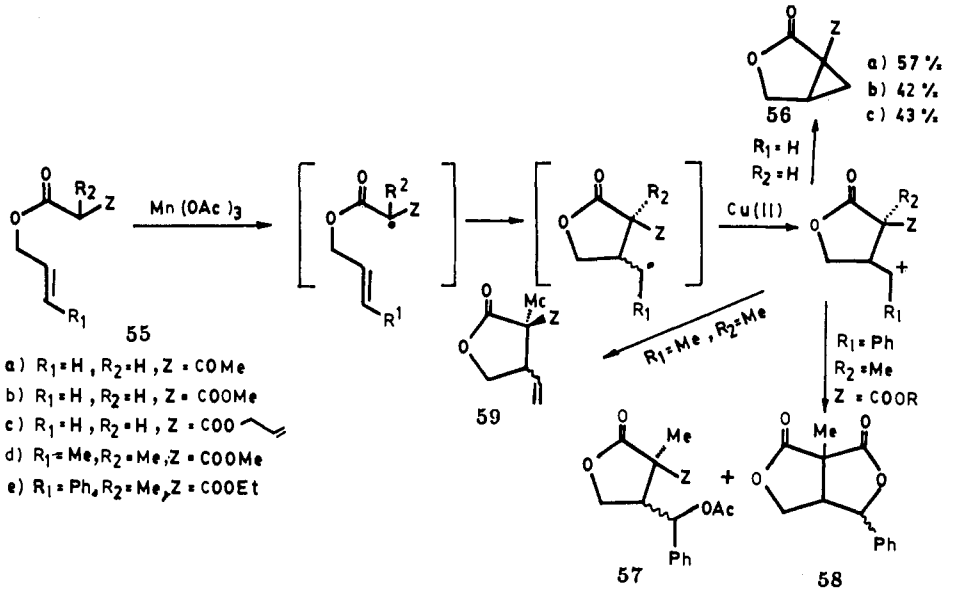
Manganese(III) acetate-promoted intermolecular addition of β-keto esters to alkenes leads to the formation[116–117] of dihydrofurans. Thus enol ethers **85–87**, β-dicarbonyl compounds **88**, and the manganese(III) acetate react under mild conditions to form 1-alkoxy-1,2-dihydrofurans (**89–91**) in good yields. The latter are readily converted to furans **92–94** by acid-catalyzed elimination of ROH (Scheme 23).

Manganese(III)-promoted reaction of 2-substituted dihydropyrans **95** with potassium methyl malonate (**96**) gives the corresponding[125] γ-lactone **97** in good yields. The reaction with phenylacetic acid or cyanoacetic acid did not yield any γ-lactone under these conditions (Scheme 24).

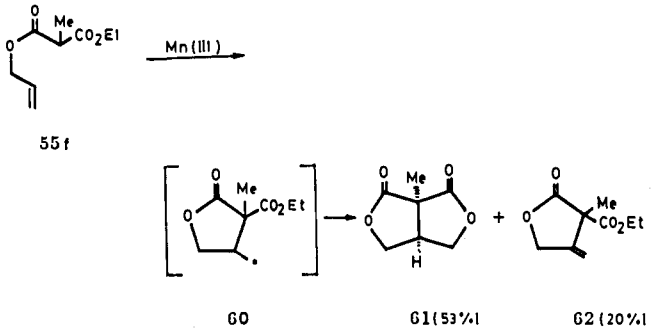
Recently, Mellor and Mohammad have reported a general route[126] to oxospirolactones **99** and spiroacetals **101** by manganese(III) acetate-promoted addition of β-dicarbonyl compound **88** to exocyclic enol lactones **98** and vinylogous enol esters **100**, respectively. Similarly, the addition to endocyclic ethers **102** gave fused acetals and ketals **103** (Scheme 25). These workers have also developed a novel route to thiaspirocycles **105**, **107**, and **109** by manganese(III) acetate-promoted addition of β-dicarbonyl compounds **88** to thiazole and thiazine derivatives **104**, **106**, and **108**, respectively (Scheme 26). This methodology establishes a general route to a series of unusual spirocyclic system in which a three-atom unit is added via radical chemistry in order to create the five-membered oxacycle.

Narasaka and co-workers have carried out the addition[127a] reaction of β-keto carboxylic acids to olefinic compounds in the presence of manganese(III) tris(2-pyridinecarboxylate) [Mn(pic)$_3$]. The reaction of 3-oxo-3-phenylpropionic acid (**110**) with various silyl enol

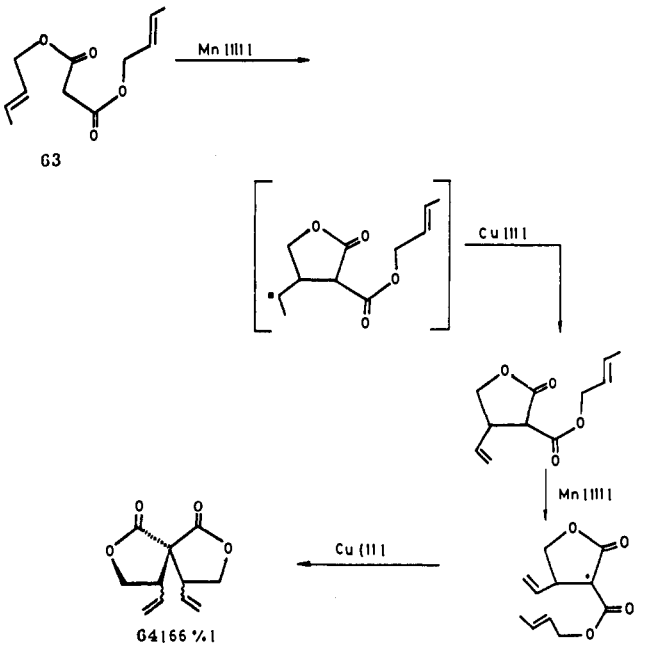
Scheme 16



Scheme 17



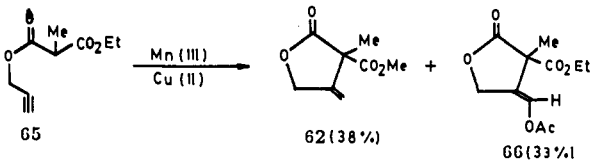
Scheme 18



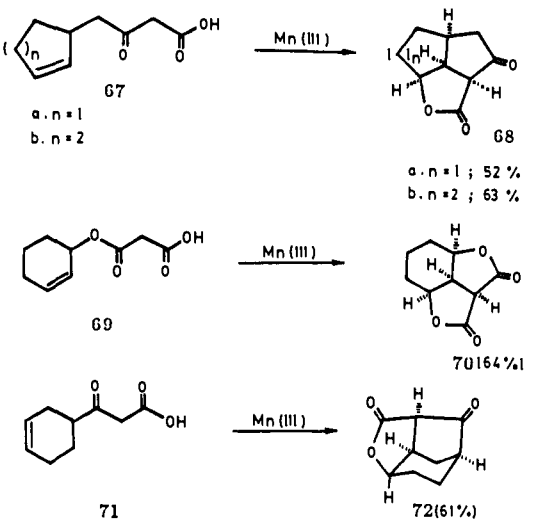
ethers **111** in the presence of $Mn(pic)_3$ leads to 1,4-dicarbonyl compounds **112** (Scheme 27).

Similarly, **110c** reacted with ketene dithioacetal (**113**), allyltin (**114**), and enamine **115** to give the corresponding coupled products **116**, **117**, and **112c**, respectively, in moderate yields (Scheme 27).

Scheme 19



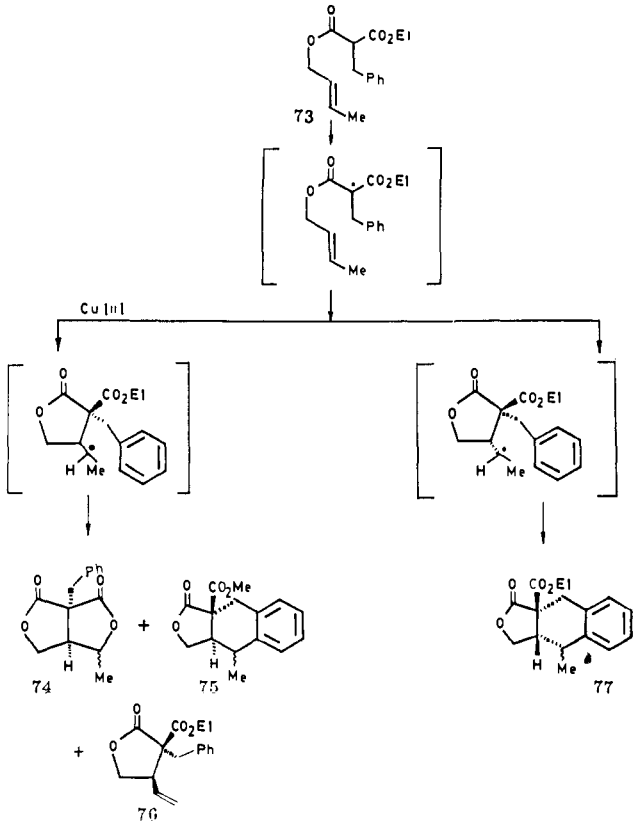
Scheme 20



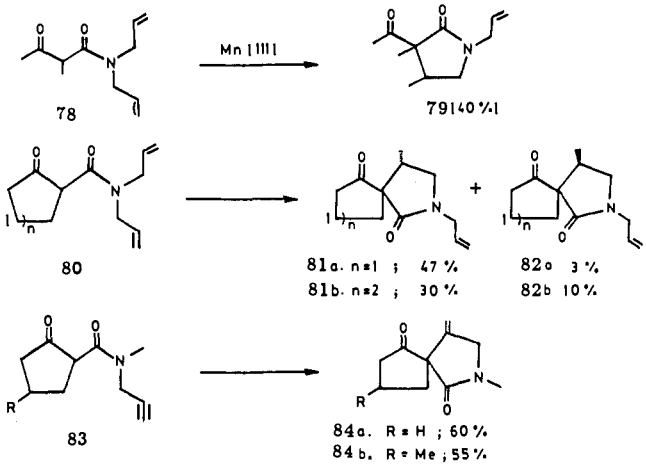
Silyl derivatives of *aci*-nitroalkanes **118** react with silyl enol ether **111b** in the presence of $Mn(pic)_3$ to give the intermolecular[127b] addition products leading to the formation of β-nitro ketones **119** and enones **120** in good yields (Scheme 28).

$Mn(pic)_3$-promoted reaction of cyclopropanol derivatives with electron-rich olefins leads[127c] to cross-addition products in good yields. The reaction between various silyl enol ethers **111** and cyclopropanols **121** provides a novel general synthesis of 1,5-dicarbonyl compounds **122**. Interestingly, a secondary cyclopropanol and a cyclopropanone hemiacetal **123** could be employed as β-formyl and β-alkoxycarbonyl radical sources in this reaction, and the corresponding aldehydes and esters **124** were obtained in good to high yields (Scheme 29). It is also notable that bicyclo[4.1.0]-

Scheme 21



Scheme 22

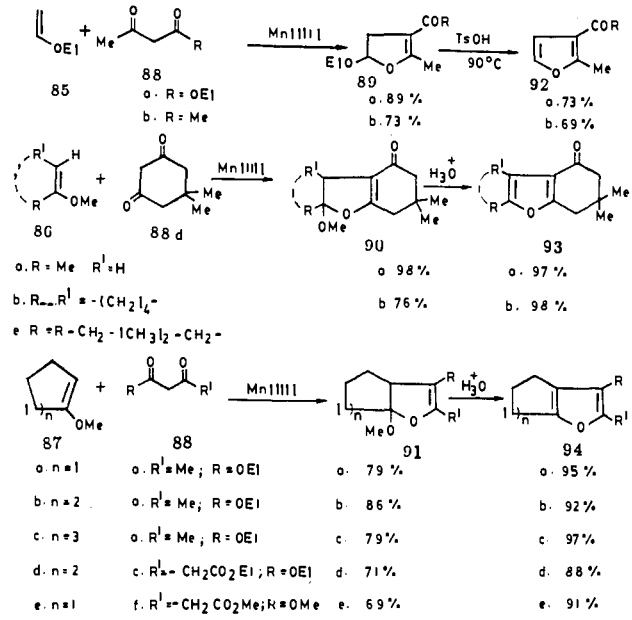


heptan-1-ol (**125**) was oxidized to give the ring-expanded radical, affording the seven-membered adducts **126** and a major product (Scheme 30).

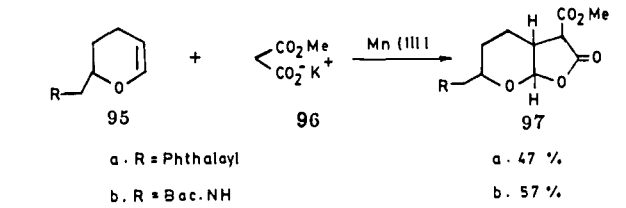
The mechanism of this reaction is explained by the formation of a β-keto radical **121a** generated oxidatively from the cyclopropanol **121**. Reaction of **121a** with electron-rich olefin **111** gave a radical intermediate **121b** which was further oxidized to **121c** by $Mn(pic)_3$ affording eventually the 1,5-dicarbonyl compound **122** (Scheme 31).

The bicyclo[4.1.0]heptan-1-ol derivative **123** having[127d] 3-butenyl group at C_5 position is oxidized with $Mn(pic)_3$ to give ring-expanded bicyclo[5.3.0]decan-3-one **124** as a single diastereomer in more than 90% purity (Scheme 32). These transformations proceed via ring-expanded β-keto radicals **123a**, which cyclize intramolecularly affording bicyclic radical intermediate **123b**.

Scheme 23



Scheme 24

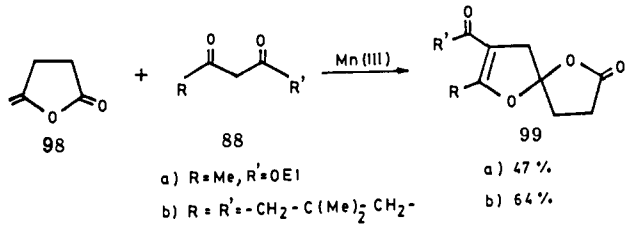


The cyclized radicals are trapped with various radical-trapping reagents such as electron-deficient olefins, tributyltin hydride, and diphenyl diselenide to give the corresponding functionalized products **125–127** (Scheme 32).

Fristad et al. have demonstrated that manganese(III) acetate promoted-addition[111] of aroylacetate **128** to substituted styrene **129** leads to the formation of dihydrofurans **130** which may be easily opened by stannic chloride and cyclized onto the electron-rich aromatic ring to form tetralones **131** (Scheme 33). They have reported an interesting route[128] to the highly oxygenated, 4-arylnaphthalene family of naturally occurring lignans, as exemplified by podophyllotoxin (**132**). Thus oxidation of keto ester **128c** in the presence of substituted cinnamate **133** afforded the *trans*-dihydrofuran **134** exclusively (Scheme 34). This reaction occurs by an initial addition of electrophilic radical from aroylacetate to cinnamate to give a stabilized radical **133a** which on rapid oxidation to cation **133b** followed by intramolecular trapping by ketone affords the dihydrofuran **134**. Treatment of **134** with $SnCl_4$ provides the desired tetralone **135** in good yields.

In recent years, Snider and co-workers[129–147] have carried out elegant studies on the Mn(III)-promoted oxidation of unsaturated β-keto esters and have demonstrated the formation of carbocyclic products via a free-radical cyclization. Their findings have resulted into the development of a novel method for the synthesis of a wide variety of fused and spirocyclic products. They have carried out the oxidative cyclization[129] of several simple unsaturated β-keto esters **136** and **138** and have

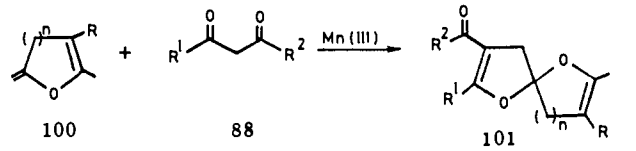
Scheme 25



98 88 99

a) R=Me, R'=OEt a) 47 %

b) R = R'= -CH2-C(Me)2-CH2- b) 64 %

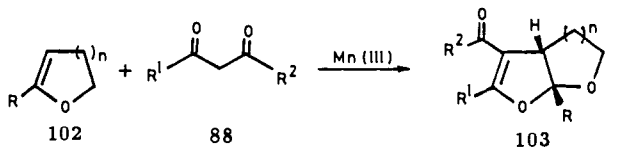


100 88 101

a) R=COOEt, n=1 a) R¹=Me, R²=OEt a) 37 %

b) R=COOEt n=1 d) R¹=R²= -CH2-C(Me2)-CH2- b) 43 %

c) R=COOEt, n=2 c) R¹=Me, R²=OCH2Ph c) 61 %



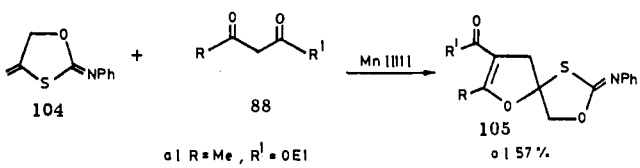
102 88 103

a) R=Me, n=1 a) R¹=Me, R²=OEt a) 51 %

b) R=H, n=1 b) R¹=R²=Me b) 26 %

c) R=H, n=2 d) R¹=R²= -CH2-C(Me2)-CH2- c) 43 %

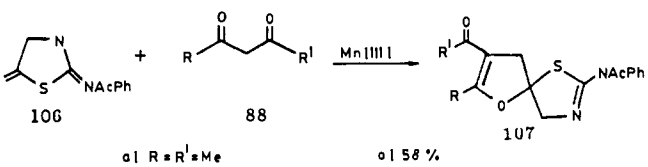
Scheme 26



104 88 105

a) R=Me, R¹=OEt a) 57 %

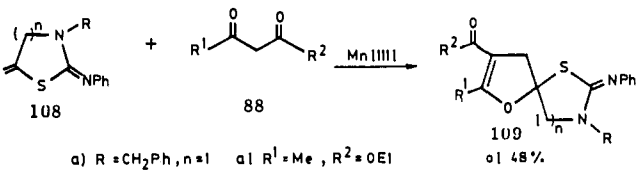
b) R=R¹= -CH2-C(Me2)-CH2- b) 65 %



106 88 107

a) R=R¹=Me a) 58 %

b) R=R¹= -CH2-C(Me2)-CH2- b) 76 %



108 88 109

a) R=CH2Ph, n=1 a) R¹=Me, R²=OEt a) 48 %

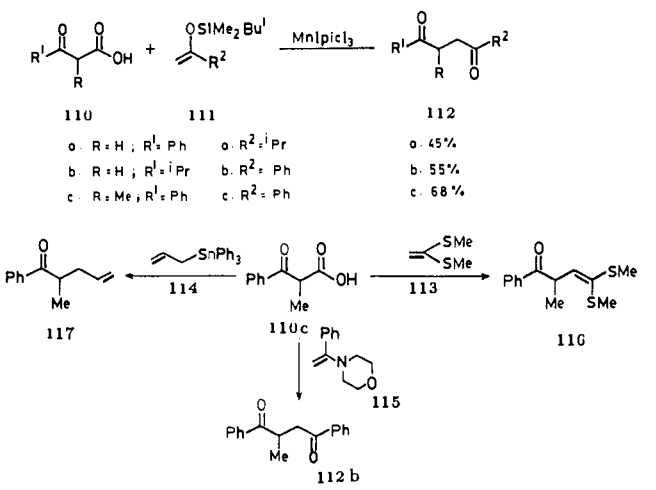
b) R=CH2Ph, n=1 d) R¹=R²= -CH2-C(Me2)-CH2- b) 59 %

c) R=H, n=2 a) R¹=Me, R²=OEt c) 60 %

shown that this reaction is useful for the formation of cyclohexanones **137** and cyclopentanones **139** and **140** containing unsaturated substituents in the 3-position (Scheme 35).

This methodology is applied during a formal total synthesis of ester of (±)-podocarpic acid (**143**) by using the appropriate β-keto ester **141** and subjecting it to the Mn(III)-promoted[130] oxidative cyclization leading

Scheme 27



110 111 112

a. R=H; R¹=Ph a. R²=iPr a. 45%

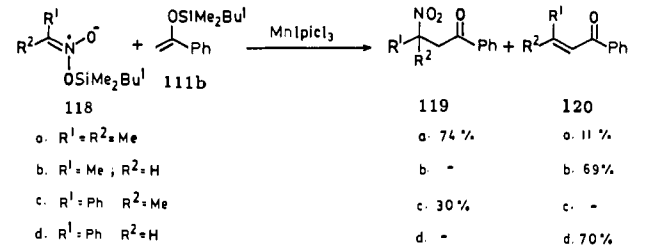
b. R=H; R¹=iPr b. R²=Ph b. 55%

c. R=Me; R¹=Ph c. R²=Ph c. 68%

117 114 110 113 110

110c 115 112b

Scheme 28



118 111b 119 120

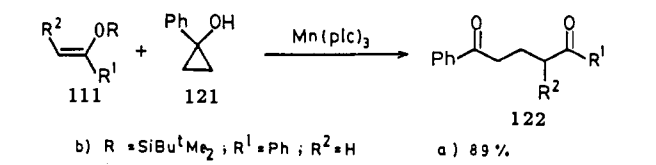
a. R¹=R²=Me a. 74 % a. 11 %

b. R¹=Me; R²=H b. - b. 69%

c. R¹=Ph R²=Me c. 30% c. -

d. R¹=Ph R²=H d. - d. 70%

Scheme 29



111 121 122

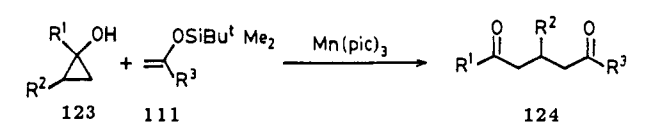
b) R =SiBu^tMe2; R¹=Ph; R²=H a) 89 %

c) R =SiBu^tMe2; R =-n-Bu^n; R=H b) 88 %

d) R =SiMe3; R¹=Me; R²=H c) 14 %

e) R =SiMe3; R¹=Ph; R²=Me d) 41 %

f) R =SiBu^tMe2; R¹=SPh; R²=H e) 66 %



123 111 124

a) R¹= -(CH2)2-Ph; R²=H b) R³=Ph a) 80 %

b) R¹= -(CH2)2-Ph; R²=H h) R³=SPh b) 59 %

c) R¹=Ph; R²=Me b) R³=Ph c) 78 %

d) R¹=OEt; R²=H h) R³=SPh d) 85 %

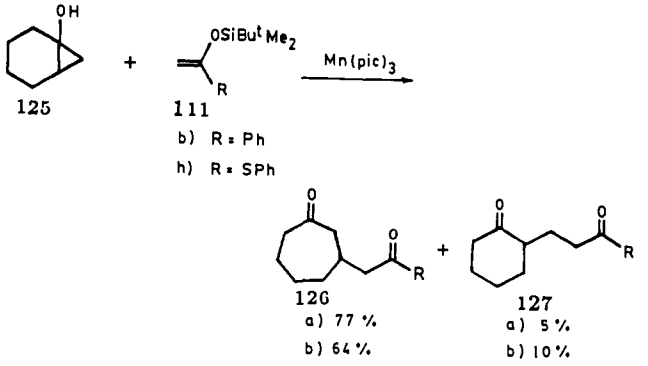
e) R¹=OEt; R²=H b) R³=Ph e) 63 %

f) R¹=H; R²= -CH2Ph h) R³=SPh f) 33 %

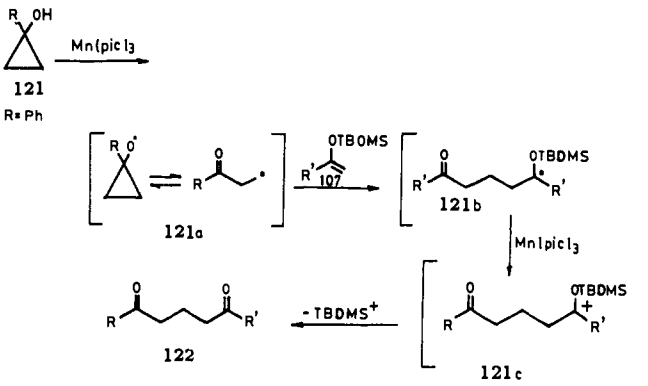
to the formation of the key intermediate **142** (Scheme 36).

Peterson and co-workers have demonstrated a remarkable control of the mode of ring closure[148] during Mn(III)-promoted oxidative radical cyclization by variation of the nature of the radical terminus. They have shown that the substituents of double bond made the kinetically favored exo-cyclization mode of the 5-hexenyl radical reversible, a circumstance that resulted in six-membered-ring product formation. Thus

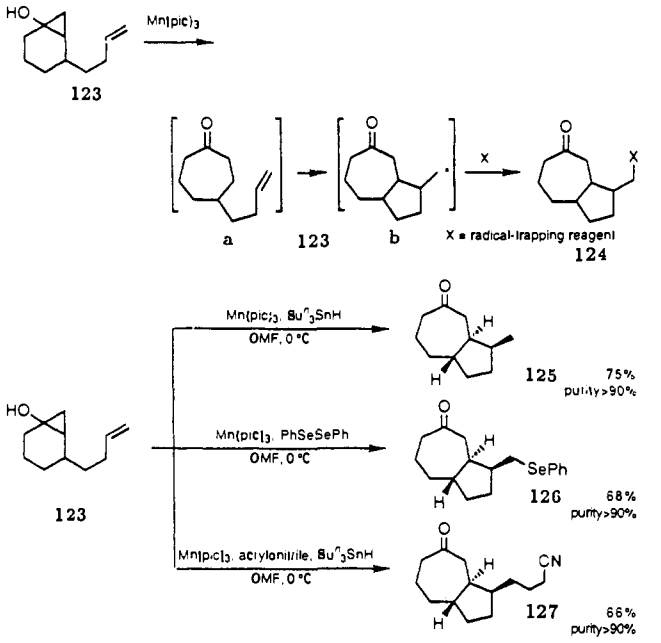
Scheme 30



Scheme 31



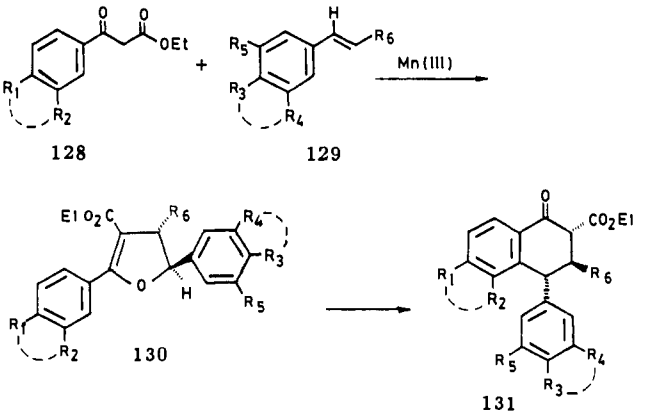
Scheme 32



methyl 3-oxo-6-heptenoate (**144**) provided an excellent probe to the reversibility of these cyclizations as only methyl salicylate (**145**) was obtained when the reaction was performed according to the published procedure. In contrast the oxidative ring closure of **146** proceeded through a secondary benzylic radical intermediate that not only rendered the cyclization irreversible, but provided sufficient impetus to the reaction to deliver cyclopentanone **147** in high yields (Scheme 37).

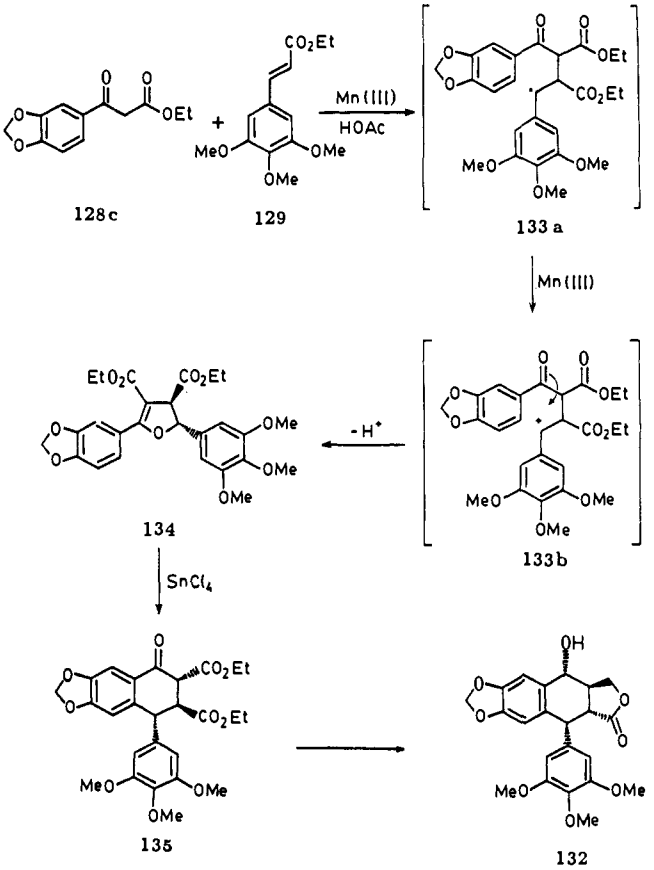
Snider and co-workers have also showed that treatment of 3-oxo-6-heptenoate esters **148a,b** with 4 equiv of manganese(III) acetate and 1 equiv of copper(II) acetate gave salicylate esters **149a,b** respectively in

Scheme 33



	R_1	R_2	R_3	R_4	R_5	R_6	Yield (%) 130	Yield (%) 131
a.	OMe	OMe	OMe	H	H	Me	52	84
b.	OMe	OMe	-O-CH_2-O-		H	CH_2OAc	58	84
c.	-O-CH_2-O-		-O-CH_2-O-		H	CO_2Et	71	86

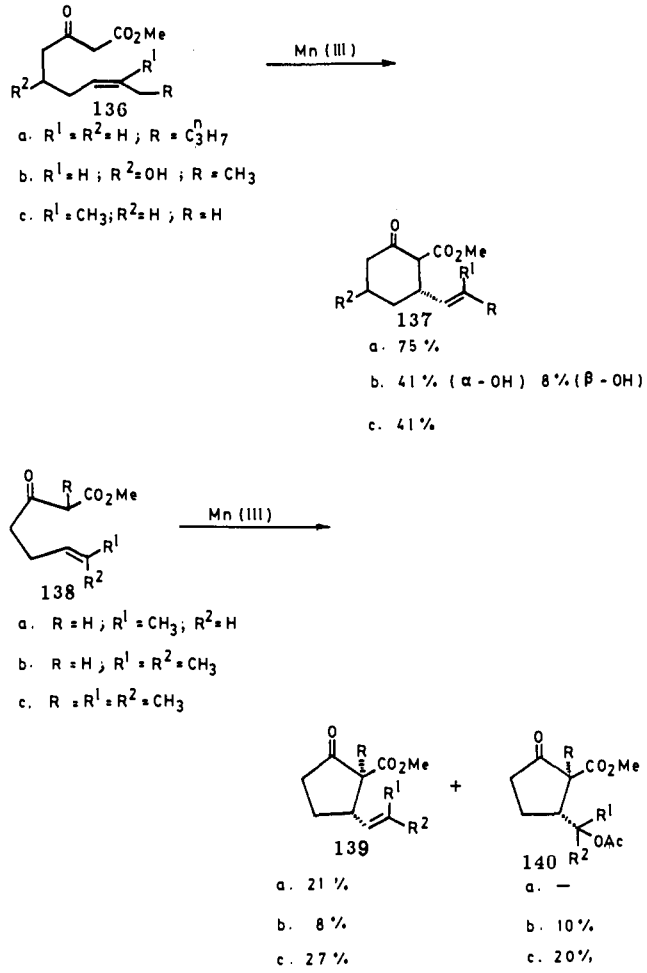
Scheme 34



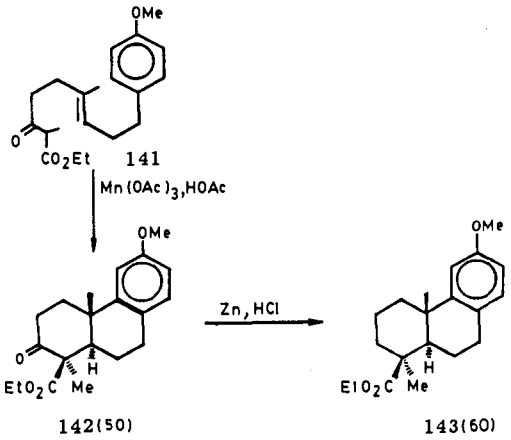
yields of 17–87% (Scheme 38). Similar treatment with 4 equiv of manganese(III) acetate and excess LiCl gave mixture of salicylate esters and chlorides which could be converted[136] to the salicylate ester by heating at reflux in acetic acid containing excess LiCl in overall yield of 40–90%.

In an interesting study, Snider and co-workers have demonstrated that Mn(III)-initiated oxidative free-radical cyclization of unsaturated β-keto esters with a benzyl group is controlled[131] by the nature of the monocyclic radical. The secondary monocyclic radical **150a** derived from **150** undergoes cyclization with the

Scheme 35



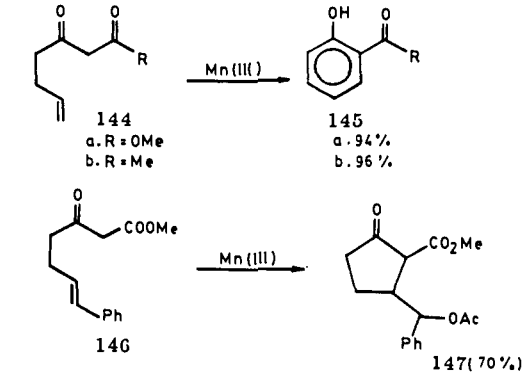
Scheme 36



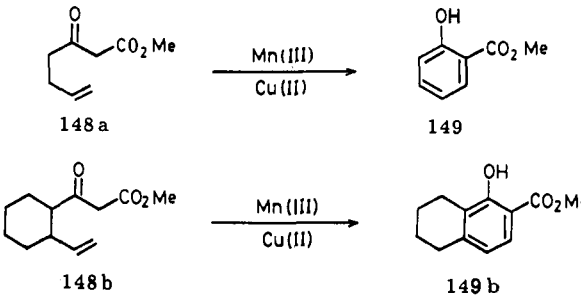
aromatic ring to form the second ring **151**, via radical **150b** prior to oxidation to give a secondary cation **150c** as evidenced by the absence of any olefinic monocyclic product **152** or **153**. Surprisingly, the reaction of **150** in the presence of manganese(III) and copper(II) acetate also did not show any traces of **152** or **153**. The later results clearly reveal that cyclization is faster than oxidation by copper(II) acetate (Scheme 39).

In a similar study these workers have shown that oxidation[129] of **154** with 2 equiv of manganese(III) acetate gave a 74% yield of a diastereomeric mixture of tricyclic adduct **155**. On the other hand, the oxidative cyclization of **154** in the presence of copper(II) acetate

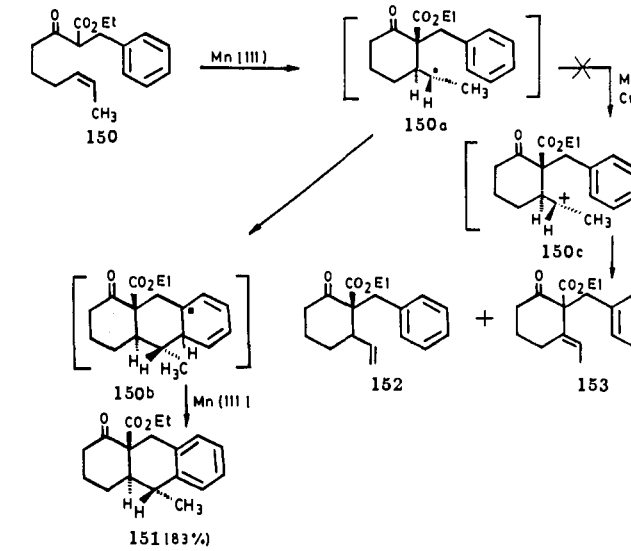
Scheme 37



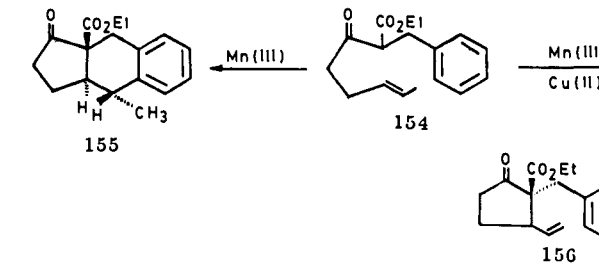
Scheme 38



Scheme 39

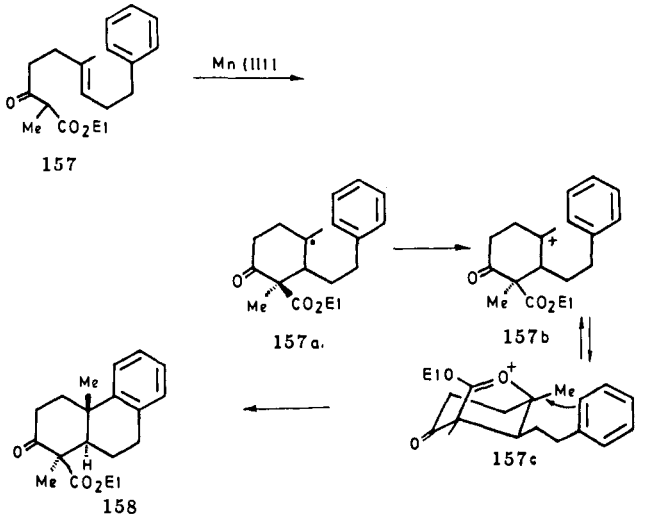


Scheme 40

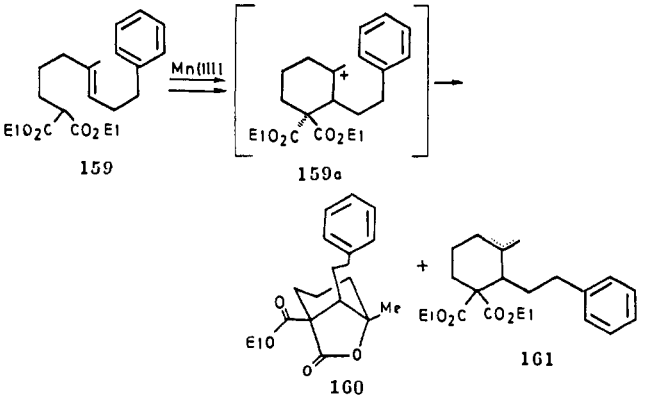


gave a 50% yield of the olefinic product **156** (Scheme 40). This result indicates that the oxidation of the intermediate radical is much faster than the second cyclization reaction. This result is the opposite of that obtained in the oxidative cyclization of **150**, in which cyclization of **150a** to **150b** is much faster than oxidation to give **152** or **153**. The copper(II) acetate oxidations

Scheme 41



Scheme 42

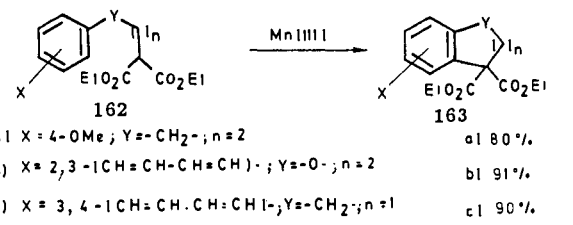


to give **152** and **153** should occur at similar rates. On the other hand, the cyclization to give **155** is slower than cyclization of **150** to give **151** since a relatively strained trans-fused indanone is being formed.

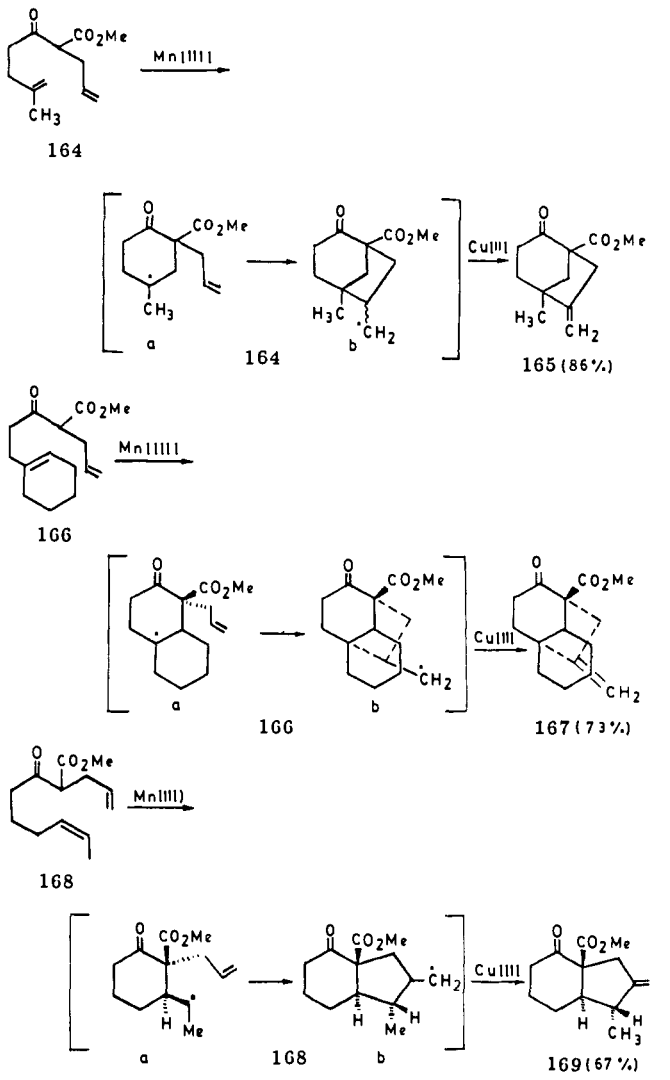
Alternatively, if the monocyclic radical[129] is tertiary (i.e. **157a**) then the oxidation of the latter to the cation **157b** precedes the second cyclization as shown by Mn(III)-promoted oxidation of **157** to the corresponding tricyclic product **158** (Scheme 41). Oxidation of **157a** affords the cationic intermediate **157b** which reacts reversibly with the carbonyl group to give oxonium ion **157c** which can then cyclize with inversion to give **158**. The intermediacy of a carbocation is demonstrated by performing the oxidative cyclization with malonate diesters **159** or acid where an intramolecular capture of carbocation **159a** by ester or acid group predominates over the intermolecular Friedel–Crafts cyclization. Thus manganese(III) acetate-promoted oxidation of **159** leads to lactone **160** and olefin **161**. No tricyclic adduct like **158** were obtained from the cyclization of either **159** and the corresponding carboxylic acid (Scheme 42).

Citterio et al. have carried out the manganese(III) acetate-promoted intramolecular cyclization to aromatic ring by converting substituted α-arylalkyl or α-(aryloxy)alkyl-β,β-dicarbonyl compound **162** to the corresponding bicyclic aromatic compound **163** (Scheme 43). High yield and selectivity are observed[149] in six-membered-ring closures, whereas five- and seven-membered-ring closures are associated with side products of dimerization and/or hydrogen abstraction. The

Scheme 43



Scheme 44

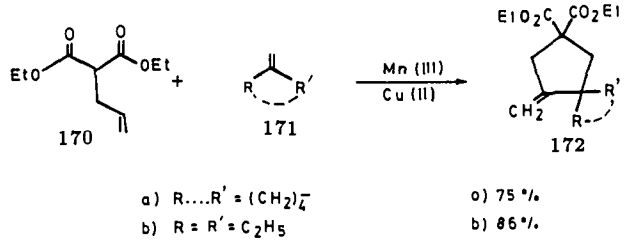


aromatic substitution is favored in all the cases by a high electron density of the aromatic carbon atom α to the carbonylalkyl substituent.

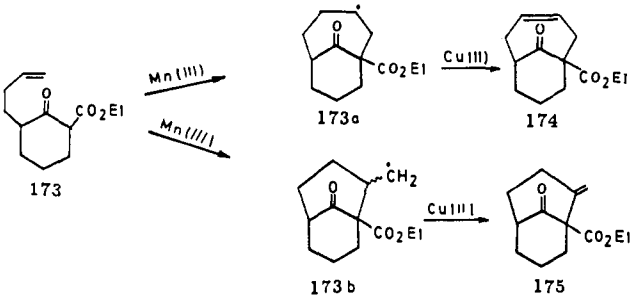
Snider and Dombroski have reported[132] a new class of oxidative cyclization in which two sequential cyclizations to double bonds generates a bicyclic cyclopentylmethyl radical (i.e. **164b**) which is then oxidized to generate an *exo*-methylenecyclopentane. Thus the reaction of **164**, **166**, and **168** with manganese(III) and copper(II) acetates resulted in the formation of the bicyclic products **165**, **167**, and **169**, respectively, in which a six- and a five-membered ring are formed in one step (Scheme 44). Similarly, the bicyclic product consisting of a seven- or eight-membered and a five-membered ring can be obtained in low yield from the corresponding unsaturated β-keto esters.

Manganese(III) acetate-promoted oxidative free-radical annulation have been achieved by intermolec-

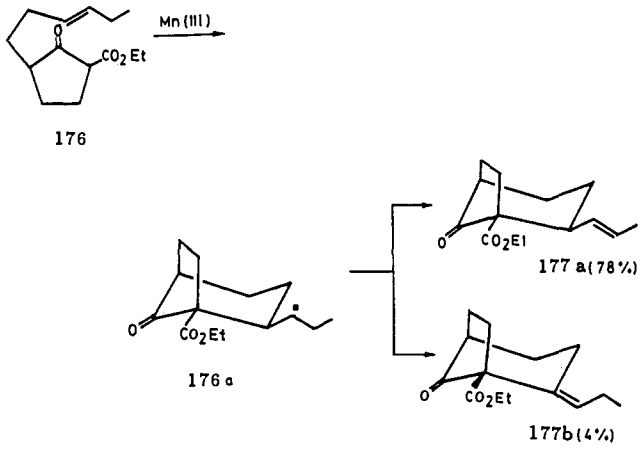
Scheme 45



Scheme 46



Scheme 47



ular addition of diethyl allylmalonate (**170**) to sterically accessible nucleophilic alkenes **171** leading to the formation[135] of methylenecyclopentanes **172** in high yields. The reaction with methylenecyclopentane (**171a**) and 2-ethyl-1-butene (**171b**) gives high yields of the annulated products **172a,b**, respectively (Scheme 45).

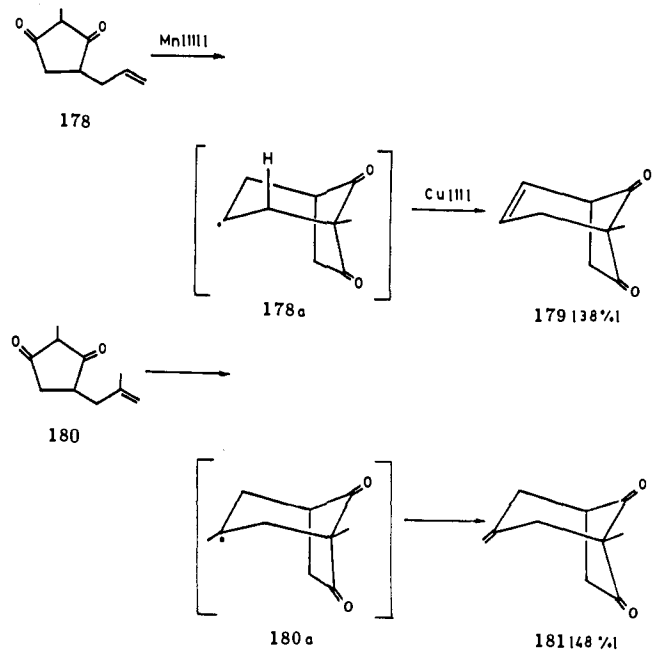
Oxidative cyclization of unsaturated cyclic β-keto esters provides a simple route to highly functionalized bicyclic compounds. Thus, alkenylated ethyl 2-oxocyclohexanecarboxylate (**173**) can be converted via a 7-endo (i.e. **173a**) and 6-exo (i.e. **173b**) cyclization to the corresponding[137] bicyclic products **174** and **175** in approximately equal amounts (Scheme 46).

On the other hand, the ethyl 2-oxocyclopentanecarboxylate derivative **176** undergoes 6-exo cyclization to give **177a** with an equatorial side chain in the exclusive process (Scheme 47).

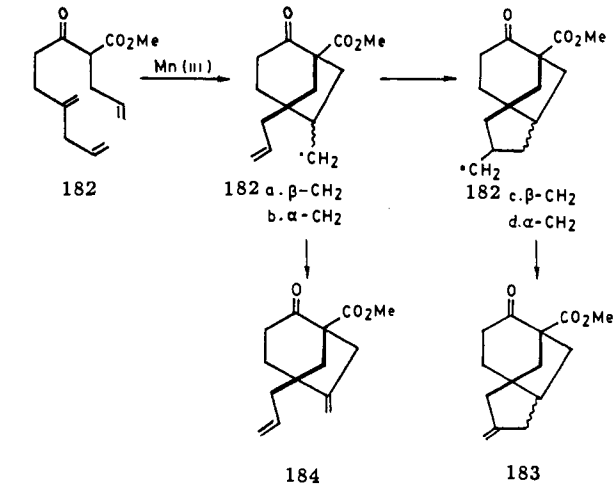
The oxidative cyclization of unsaturated 2-methylcyclopentane-1,3-diones **178** and **180** provides an efficient route to bicyclic[3.2.1]octane-6,8-diones **179** and **181** respectively (Scheme 48).

Manganese(III) acetate-promoted triple oxidative free-radical cyclizations[139] have been performed using the triene which has been converted to the corresponding tricyclic product in moderate yields. Cyclization of

Scheme 48



Scheme 49

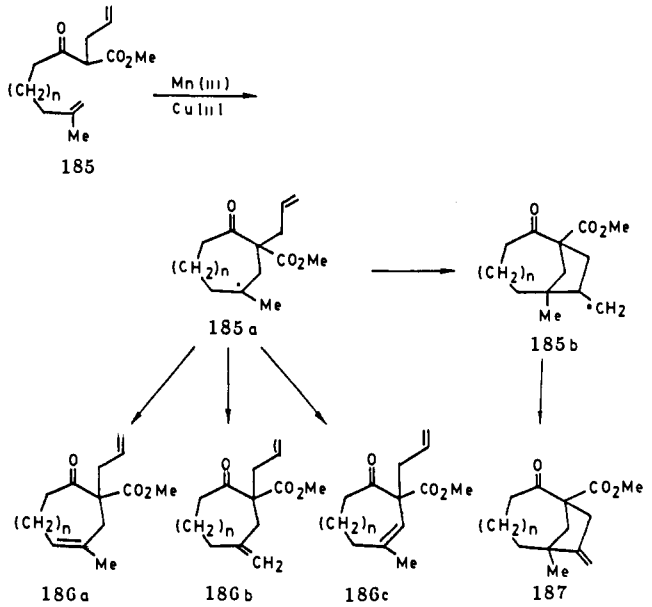


182 gives a 2:1 mixture of **183** and **184**. The major isomer **182** cyclizes rapidly to **182c** which reacts with copper(II) acetate to give **183** after oxidative elimination. The minor isomer **182b** cyclizes slowly to **182d** which contains a highly strained *trans*-bicyclo[3.3.0]octane. Radical **182b**, therefore, reacts with the cupric ion to give **184** after oxidative elimination (Scheme 49).

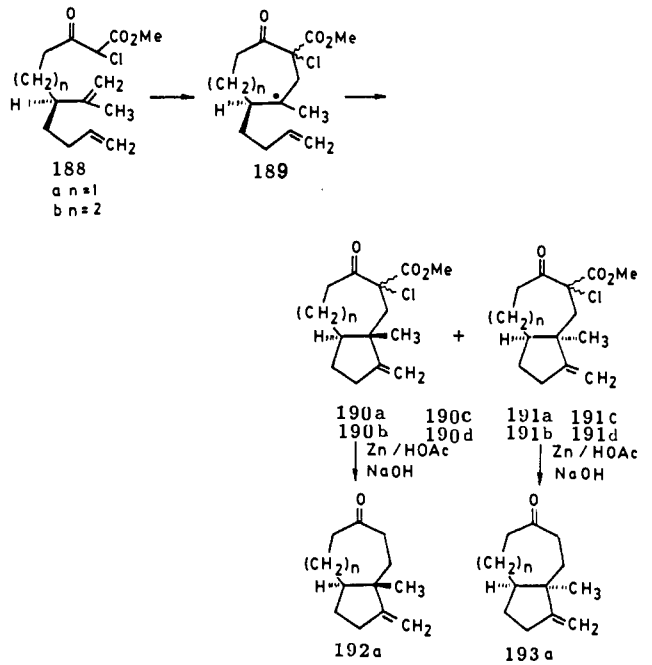
Manganese(III)-promoted tandem oxidative cyclization of unsaturated α-allylacetoacetates **185** provides a versatile[141] route to bicyclo[4.2.1]nonanes and bicyclo[5.2.1]decanes **187** (n = 1 or 2), respectively. Oxidative cyclization of **185** (n = 1) gives exclusively the cyclic tertiary radical **185a**, which cyclizes to give **185b**, and the latter radical is oxidized by Cu(II) to afford **187**. Cyclization of a tertiary cycloheptyl radical **185a** (n = 1) is much faster than its oxidation by Mn(III) or Cu(II), whereas oxidation of tertiary cyclooctyl radical **185a** (n = 2) is competitive with cyclization to give **186a–c** as well as **187** (Scheme 50).

Tandem cyclizations have also been used for the synthesis[141] of bicyclo[5.5.0]decanes **192** and bicyclo[6.3.0]undecanes **193**. Thus the chlorinated β-keto ester **188a** (n = 2) reacts with 2 equiv of $Mn(OAc)_3 \cdot 2H_2O$ and

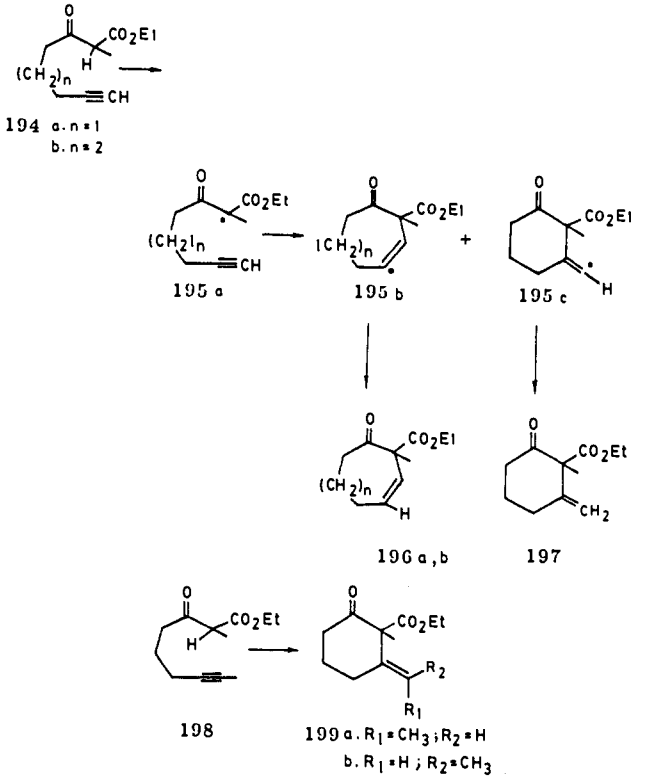
Scheme 50



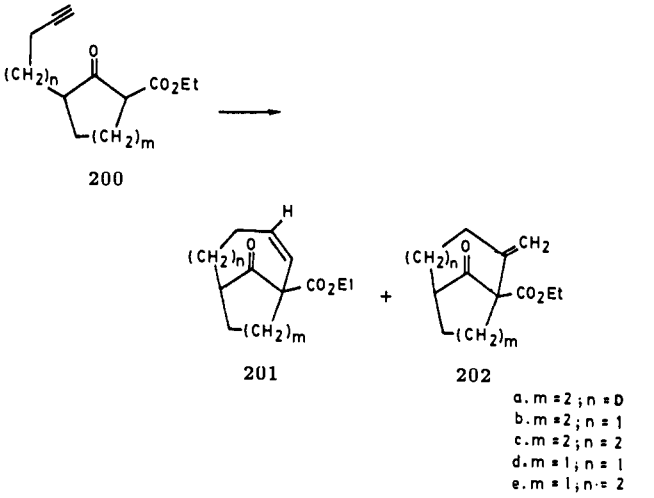
Scheme 51



Scheme 52



Scheme 53

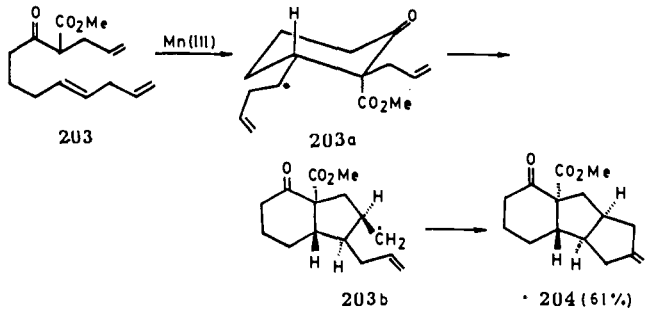


1 equiv of $Cu(OAc)_2 \cdot H_2O$ in acetic acid to afford a mixture of two trans-fused isomers **190a** (36%) and **190b** (9%) and the two cis-fused isomers **191a** (10%) and **191b** (10%), respectively (Scheme 51). Reductive dechlorination of a 1:2.3 mixture of **190b** and **191b** with zinc dust in acetic acid followed by hydrolysis with NaOH in aqueous methanol and decarboxylation provides a 1:2.3 mixture of trans-fused bicyclo[5.3.0]decane **192a** and **193a**, respectively. Similarly the oxidative cyclization of **188b** leads to a mixture of two trans fused isomers **190c** (48%) and **190d** (9%) and two cis-fused isomers **193c** (17%) and **193d** (2%). Reduction, hydrolysis, and decarboxylation of **190c–d** and **191c–d** furnished a 3:1 mixture of **192b** and **193b**, respectively.

Snider and co-workers have also conducted anhydrous $Mn(OAc)_3$-promoted intramolecular cyclizations to alkynes to form medium-sized rings. Treatment of **194a** with 2 equiv of anhydrous $Mn(OAc)_3$ in ethanol gave 35% of cycloheptenone **196a** and 0.2% of methylenecyclohexenone **197**. Similar treatment of **194b** yielded 34% of cyclooctenone **196b**. In order to encourage 6-exo over 7-endo cyclization, a terminal methyl group was introduced as evidenced[141] by the oxidative cyclization of β-keto ester **198** to the corresponding cyclohexanone derivative **199a,b** (Scheme 52). They have also demonstrated that acetylenic β-keto esters **200** can be oxidized to a mixture of bicyclo[3.3.1]nonane **201** and methylenebicyclo[3.2.1]octane **202** (Scheme 53).

Similarly, a stereoselective synthesis of linearly fused tricyclic compound **204** can be achieved by a Mn(III)-promoted triple oxidative free-radical cyclization of the triene **203**. Oxidative cyclization of **203** gives monocyclic radical **203a** which cyclizes[139] to **203b** with the allyl and methylene group cis to each other and trans to axial ester group to avoid severe steric interactions. Cyclization of 5-hexenyl radical **203b** followed by oxidative

Scheme 54



203 203a 203b 204 (61%)

elimination with Cu(II) ion gave **204** in 61% yield (Scheme 54).

The tandem radical cyclization strategy has been used for the synthesis of *trans*-hydrindanones as evidenced[139] by the oxidative cyclization of **205** to the corresponding bicyclic products **207** and **209**. A 6-exo cyclization of **205** proceeds through a chair transition state with an equatorial side chain to give **206a** or through a chair transition state with an axial side chain to give **208a**. Cyclization of 5-hexenyl radicals **206b** and **208b** followed by oxidative elimination with Cu(II) ion gives **207** and **209**, respectively. Cyclization to give **209** is the major process since there is severe interaction between the methyl group and axial hydrogen in **207** (Scheme 55).

Similar tandem cyclization reactions in which both double bonds are on the same chain provides access[139] to *cis*-hydrindans. Oxidation of **210** gives (*E*)-enol radical **211a** which cyclizes to give monocyclic tertiary radical **211b**. 5-Exo cyclization of **211b** gives cis-fused radical **211c** which reacts with Cu(II) ion to give **212** (Scheme 56). In a related study Snider et al. have observed[147] that oxidative free-radical cyclization of dimethyl 4(*E*),8-nonadiene-1-ylmalonate (**213a**) and ethyl 4(*E*),8-nonadiene-1-ylcyanoacetate (**213b**) in the presence of Mn(III) and Cu(II) affords the expected dienyl–cyclopentane (Scheme 57). On the other hand the oxidative cyclization of **213a** with Mn(III) in ethanol affords a mixture of the stereoisomers of methylhydrindan **215**. The formation of diene **214** in the presence of Cu(II) indicates the kinetically controlled cyclization of radical **214a** leads to the cyclopentylalkyl radical **214b**. The latter reacts with Cu(II) much faster than it undergoes ring opening to regenerate a stabilized radical. The formation of **215** rather than **216** indicates that, as expected, the cyclization of the stabilized acyclic radical **214a** is reversible but the cyclization of the unstabilized cyclohexyl radical **215a** to give hydrinanylmethyl radical **215b** is not reversible, since the primary radical abstracts a hydrogen atom from ethanol faster than it reverts to give cyclohexyl radical **215a**. These results have unambiguously established that benzoyl peroxide promoted cyclization of **213a** also affords methylhydrindan **215** instead of decalin **216** as reported earlier by Julia and co-workers.

Recent studies by Snider and Dombroski have illustrated[143] that oxidative free-radical cyclization of γ,γ-bisallylic acetoacetates **217** proceeds via a boat cyclohexyl radical **217c,d**. It is interesting to note that radical **217c** (x = allyl) cyclizes exclusively to the allyl group α to the ester to give **219b** while radical **217d** (x = $PhCH_2$) cyclizes equally to the benzyl group α to the ester and the allyl group γ to the ester to give mixture of **219d** and **219e** even though cyclization to the allyl group should be 10–100 times faster (Scheme 58). A plausible explanation has been offered which invokes the formation of a chair cyclohexane radical **217a** with an axial ester group. The inversion of chair **217a** will give chair cyclohexane **217b** with axial allyl and X substituents, however, if X = H this chair is relatively stable so that cyclization can occur to give **218**. If X $\neq$ H, this conformation is very unstable owing to a 1–3 relationship of two axial substituents and this situation makes boat conformers **217c** and **217d** lower in energy than chair conformers. Thus bicyclo[3.2.1]octanes **219a,b** are formed from boat cyclohexyl radical **217c** and tandem cyclization product **219c** is obtained from boat cyclohexyl radical **217d**.

Snider et al. have also used β-keto sulfoxides and β-keto sulfones as substrates to Mn(III)–Cu(II)-based oxidative free-radical cyclizations. Oxidative cyclization of racemic sulfoxide **220** affords **221** as a single diastereomer whereas the cyclization[142] of enantiomerically pure sulfoxide (*S*)-**222** gives **223** as a single enantiomer. Similarly cyclization of **224** gives indanone **225**, which spontaneously loses toluenesulfonic acid to give indanone **226** (Scheme 59).

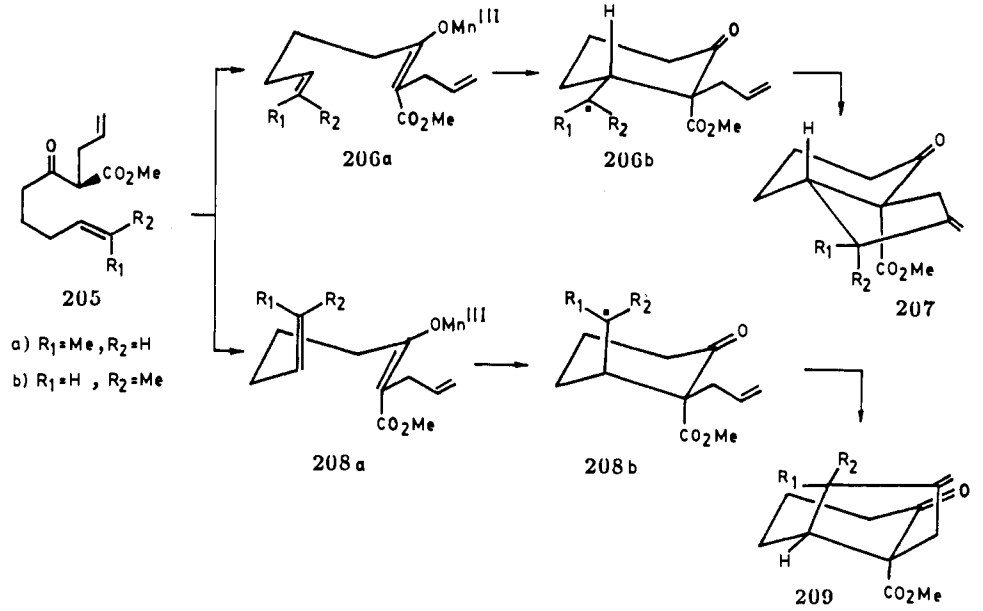
A recent study has established that Mn(III)-based oxidative free-radical cyclizations and annulations can be terminated by addition to nitriles and this provides[146] a novel route to cyclopentanones and cyclohexanones. Oxidative cyclization of **227** with 2 equiv $Mn(OAc)_3 \cdot 2H_2O$ in ethanol gave 51% of **229**. Oxidation gives radical **227a** which cyclizes to afford the tertiary δ-cyano radical **227b**. The later cyclizes to iminyl radical **227c** which either abstracts a hydrogen atom from the solvent or another molecule of **227** to give **228**. Alternatively **227c** may be reduced and protonated to give imine **228** and hydrolysis of latter leads to the ketone **229** (Scheme 60).

Similarly, this reaction has been used for the synthesis[146] of indandione **231** which can be obtained by Mn(III)-promoted oxidation in acetic acid from the corresponding acetoacetate **230**. These cyclizations are largely solvent and pH dependent, and the yield of **231** can be enhanced in ethanol containing 5 equiv of trifluoroacetic acid. The low yields of **231** in nonacidic solution have been explained owing to the possible side reaction that might lead to the formation of the olefin **232** derived by the oxidation of the corresponding radical anion **230b**. The formation of **230b** may be encouraged by the presence of the radical **230a** which should significantly enhance the acidity of the proton adjacent to the cyano group (Scheme 61).

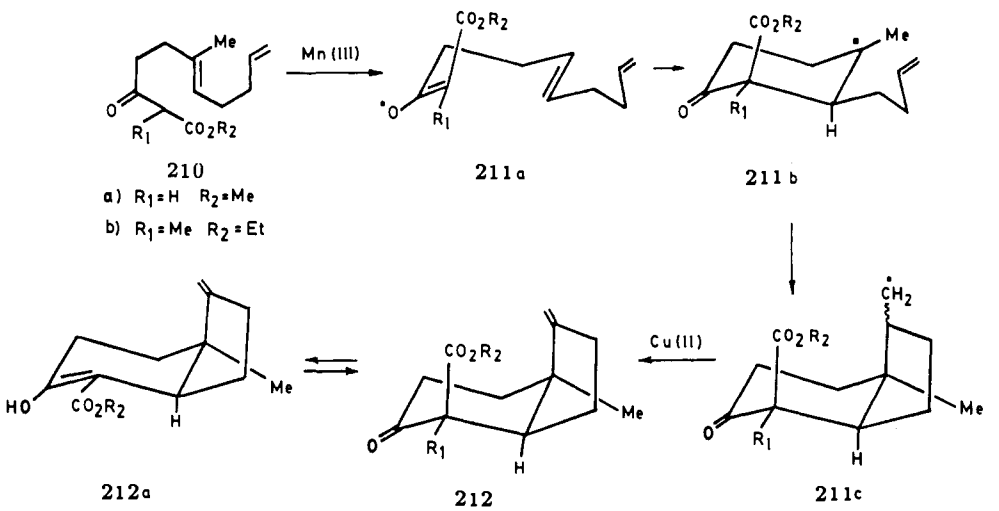
Annulation to give cyclopentanones **235a** and cyclohexanones **235b** have been performed[146] by the oxidation of methyl (cyanomethyl)acetoacetate (**233a**) and methyl (cyanoethyl)acetoacetate (**233b**), respectively, in presence of 2 equiv of $Mn(OAc)_3 \cdot 2H_2O$ and 1 equiv of methylenecyclopentane in ethanol containing trifluoroacetic acid. The yield of **235** can be enhanced significantly in the presence of 2 equiv of $Mn(OAc)_3 \cdot 2H_2O$ and 1 equiv of $Mn(OAc)_2 \cdot 4H_2O$ in ethanol medium (Scheme 62).

The development of Mn(III)-promoted oxidative free-radical cyclization strategy has been applied to the synthesis of some natural products. Paquette and coworkers have[150] synthesized (±)-14-epiupial, and the

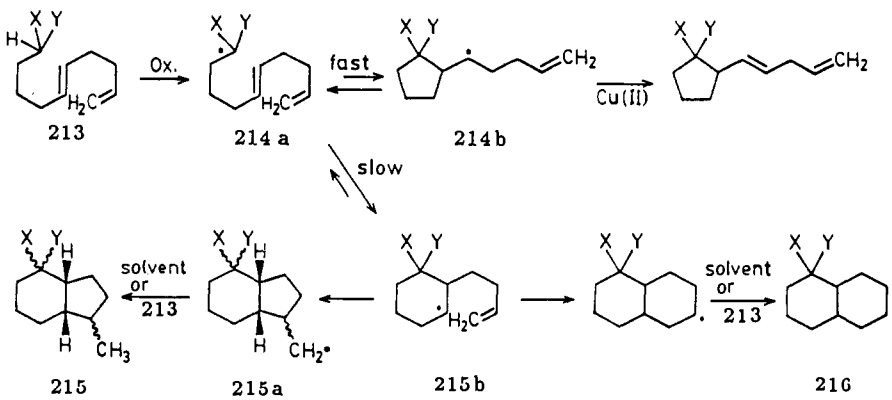
Scheme 55



Scheme 56



Scheme 57[a]



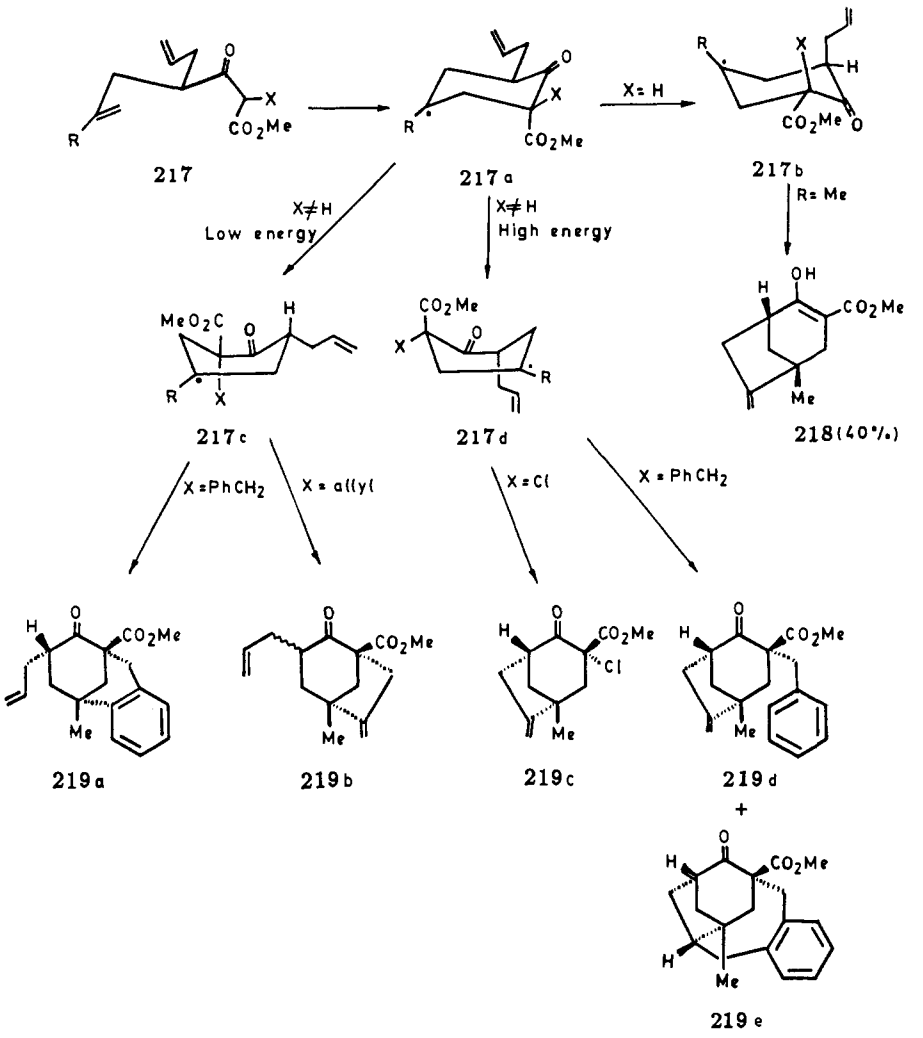
[a] (a) X = Y = CO_2Me. (b) X = CO_2Et, Y = CN.

key step is the Mn(III)-promoted concurrent formation of the bicyclic[3.3.1]nonane and lactone rings **237** from the corresponding malonate derivative **236** (Scheme 63).

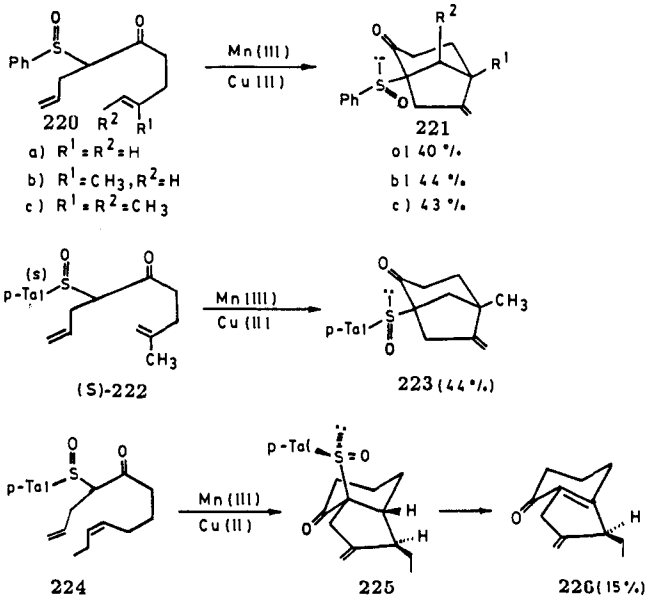
Rama Rao and co-workers have developed[151] a convenient route for constructing the spiro[4.4.0]-nonane system **239** of fredericamycin A using a Mn-(III)-based oxidative free radical cyclization of the 1,3-dione **238** as the key step (Scheme 64). Zoretic and co-workers have demonstrated a Mn(III)-mediated oxidative cyclization of β-keto ester **240** leading to the formation[154] of *D*-homo-5α-androstan-3-one **241** in which seven asymmetric centers have been established in one step (Scheme 64).

White and co-workers have performed[152] the elegant

Scheme 58

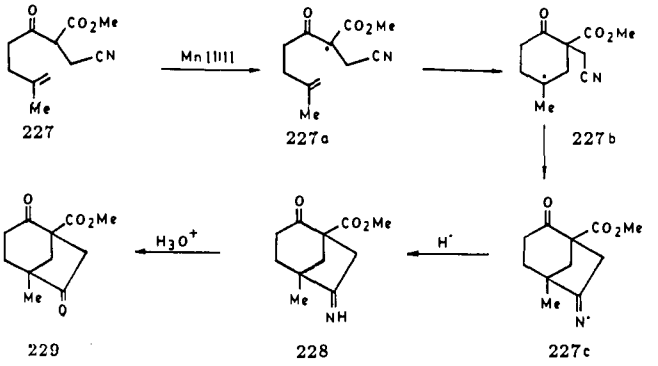


Scheme 59



oxidative cyclization of keto ester **243** en route to dihydropallesconsin (**245**) a marine-derived furanosesquiterpene. The desired keto ester **243** was prepared in two steps involving Li/NH_3 reduction of the olefin **242** and carbomethoxylation of the resulting methyl ketone. An exclusive 7-endo cyclization was performed

Scheme 60

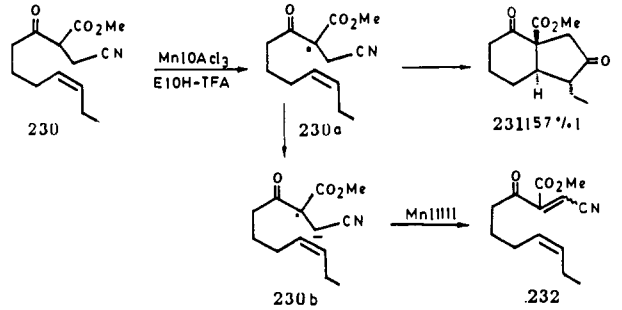


on **243** in the presence of Mn(III) and Cu(II) to give the bridged bicyclic keto ester **244** which was transformed to the natural product in six steps (Scheme 65). Ruveda et al. have observed the incorporation of oxygen[153] in a similar transformation using **243**.

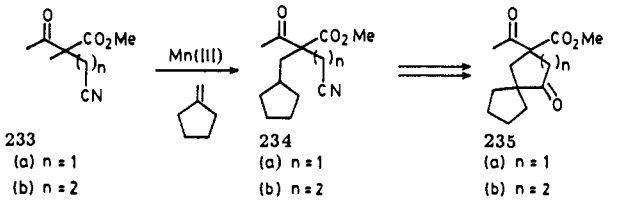
D. Iron

Iron(III) salts are known to oxidize electron-rich centers to provide the formation of radical species. They are particularly efficient in the oxidation of aromatic systems or a carbanion to the corresponding carbon-centered radical which undergoes carbon–carbon bond formation to yield the coupled products. Oxidative coupling of a variety of aromatic compounds **246**, **248**, and **250** to the corresponding coupled products **247**,

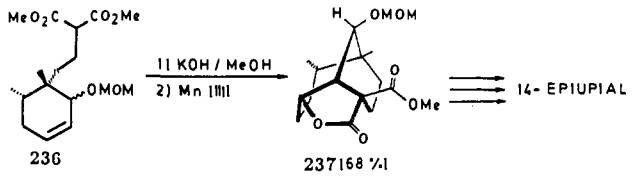
Scheme 61



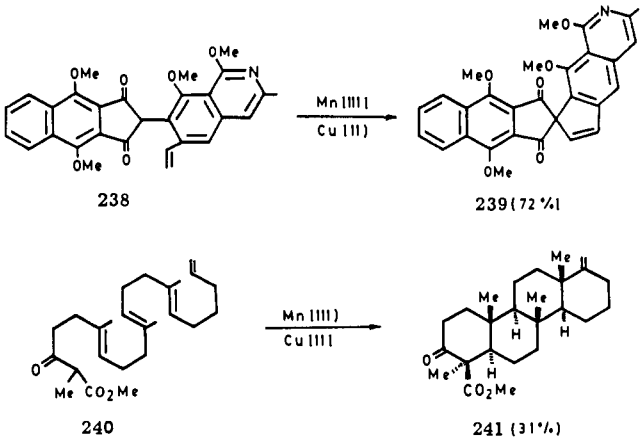
Scheme 62



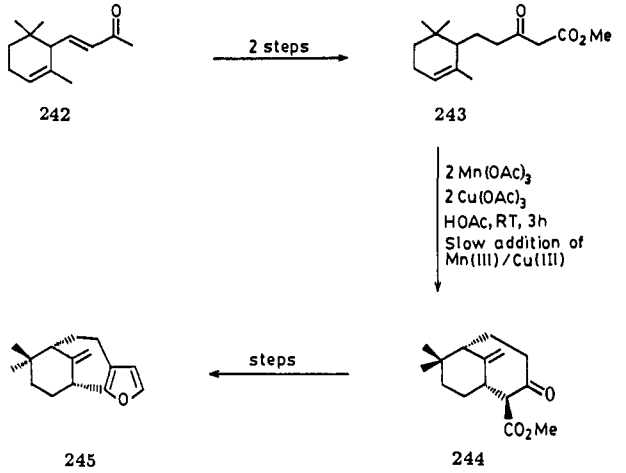
Scheme 63



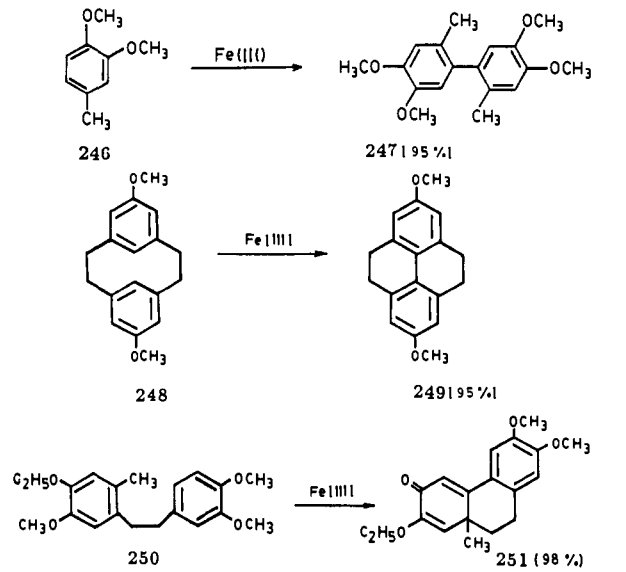
Scheme 64



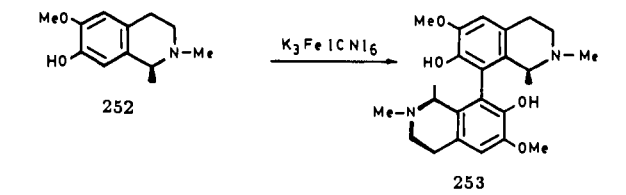
Scheme 65



Scheme 66



Scheme 67



249, and 251, respectively, have been achieved by $FeCl_3$ supported on silica gel[155-158] (Scheme 66).

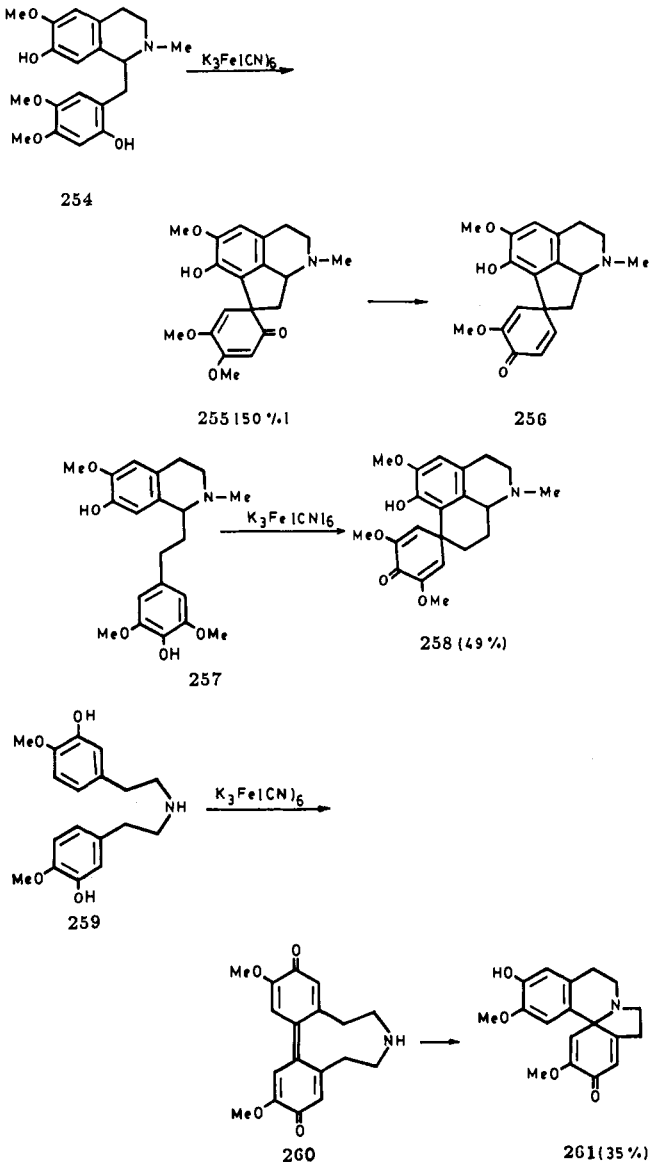
Alkaline potassium ferricyanide has been used to promote the coupling of totaral to podototorin in moderate[159] yields. Similarly, (±)-tetrahydroisoquinoline **252** on oxidation with potassium ferricyanide afforded three stereoisomers of **253**, whereas[160] separate oxidations of (*S*)- and (*R*)-enantiomers of **252** provided only the (*S*,*S*)- and (*R*,*R*)-isomers of **253**, both as a single rotamer (Scheme 67).

The 4′,7-dihydroxy compound (±)-benzyltetrahydroisoquinoline **254** was coupled using potassium ferricyanide to the spiroketone **255** as a pair of diastereomers.[161] One stereoisomer on reduction of carbonyl and aqueous acid treatment was converted to the alkaloid orientalone **256**. A similar treatment affected the ortho,para-coupling on the corresponding 6′,7-dihydroxy compound 1-(2-arylethyl)tetrahydroisoquinoline **257** and led to the formation of **258**, a precursor[162] for (±)-multifloramine. The biomimetic synthesis of crysodienone (**261**) was achieved by ferricyanide-promoted oxidative coupling[163] of bis(arylethyl)amine **259**. The reaction proceed via para,para-coupling, oxidation to diphenoquinone **260** followed by an intra-Michael addition (Scheme 68).

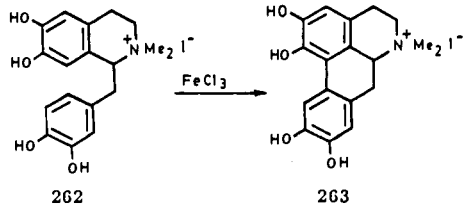
Iron(III) chloride has found widespread use in the oxidative coupling of a variety of phenols leading to the synthesis of a large number of natural products. Thus laudanosoline methiodide (**262**) was converted[164] to **263** via preferential ortho,para-coupling, with aqueous iron(III) chloride at room temperature (Scheme 69).

In the *o*- or *p*-hydroxystyryl subunit, the radical from phenolic oxidation is delocalized through the aromatic ring and the side chain and couplings may thus involve the β-carbon and products can be derived from C_β–C_β coupling of two units. Iron(III) chloride is known to

Scheme 68

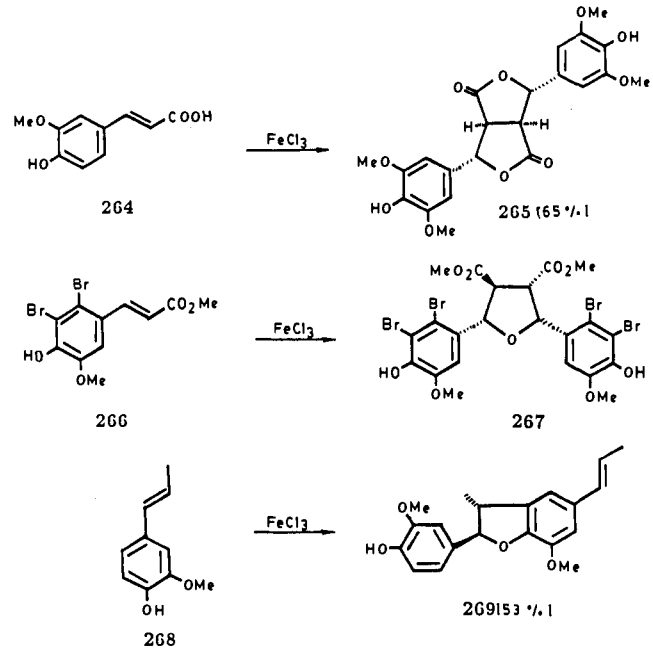


Scheme 69

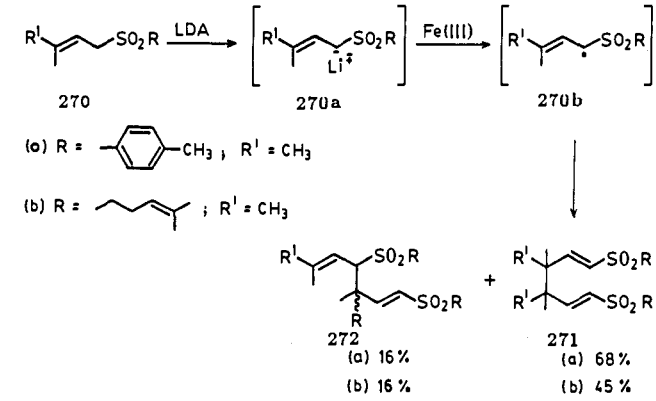


affect this type of coupling as evidenced by hydroxycinnamic acid conversion to bisaryl dilactone. Thus the oxidation of sinepic acid (**264**) to the dilactone **265** is mediated[165,166] by iron(III) chloride in presence of oxygen. If a *p*-hydroxycinnamate ester is employed, rather than acid, then C_β–C_β coupling can be followed by trapping of quinone methide intermediates with water, as in the formation[167] of the tetrahydrofuran **267** from methyl dibromoferulate (**266**), with iron(III) chloride in aqueous acetone. Iron(III) chloride also encourages the coupling of C_β–C_{AR} bonds as illustrated by the generation[168] of dehydrodiisoeugenol (**269**) from (*E*)-isoeugenol (Scheme 70). The mechanism for the formation of coupled products can be rationalized in

Scheme 70



Scheme 71

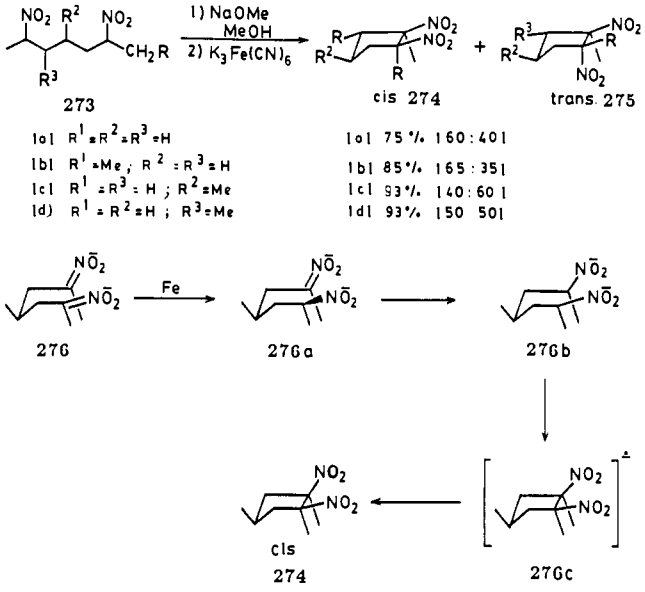


terms of electron-transfer oxidation and C–C coupling ortho or para to the hydroxy or methoxy group.

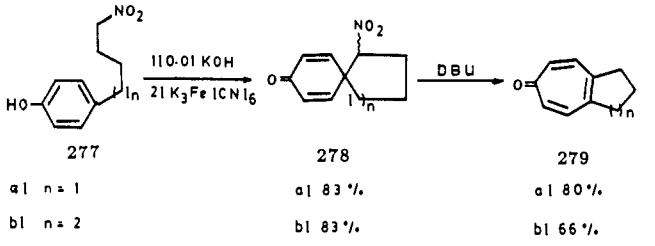
Lithium salts of allylic sulfones **270a** are oxidized with $FeCl_3$–DMF complex mainly to 1,6-disulfones **271** by 3,3-coupling. The dimerization proceeds with considerable regioselectivity, and the preference for coupling[169,170] at either α- or γ-position could be controlled by the choice of oxidant. The mechanism of these reactions can be explained by the oxidation of sulfonyl anions **270a** with ferric salts to the corresponding allyl radicals **270b** which undergo coupling[171–174] to give the observed products (Scheme 71).

Bowman and Jackson have recently shown[175,176] that dinitro dianions of 2,6-dinitroalkanes **273** can be oxidized with $K_3Fe(CN)_6$ to give a mixture of 1,2-dinitrocyclopentanes **274** and **275**, respectively. According to the mechanism the dianion **276** may give α-nitroalkyl radical **276a** which undergoes stereoselective cyclization to 1,2-dinitrocyclopentanes **274** and **275**. The high diastereoselectivity have been explained using the Beckwith's model where the intermediate radical anions **276b** react via transition states which have cyclohexane chair conformation with 3- or 4-methyl substituent in the equatorial position to yield the cyclized products (Scheme 72).

Scheme 72



Scheme 73

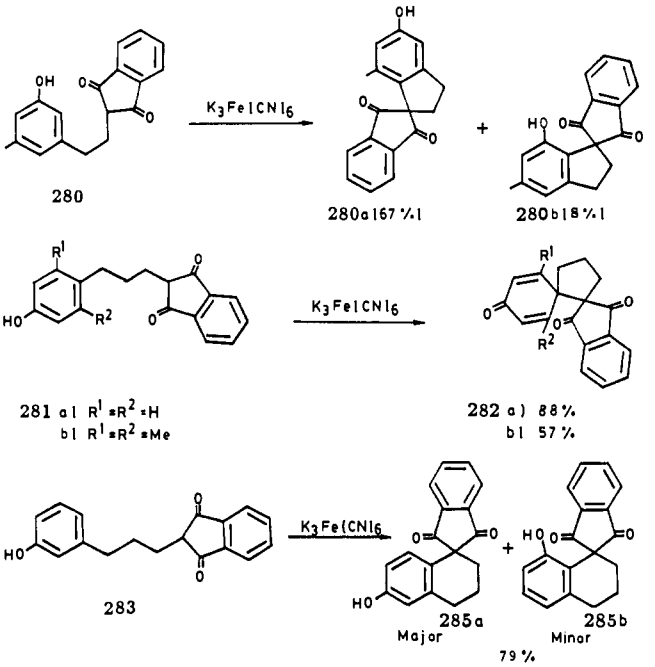


Recently Kende and co-workers have developed an interesting $K_3Fe(CN)_6$-mediated oxidative intramolecular cyclization of a phenolate with a stabilized enolate. They have shown that treatment of the phenolic nitroalkanes **277** in dilute base with $K_3Fe(CN)_6$ results in the formation[177] of spirocyclic nitro dienones **278** which undergo facile rearrangement to annelated tropone or tropolone derivatives **279** (Scheme 73). No cyclization is observed below pH 11, indicating that deprotonations of both the phenol (pK_a = 10.1) and of the nitroalkane (pK_a = 8.8) are required. When the reaction of **277** is carried out with 2.1 equiv of base, the spirocyclic intermediate **278** can be isolated in good yields and a dilute alkaline solution of the latter on acidification rapidly produces tropone **279** in high yields.

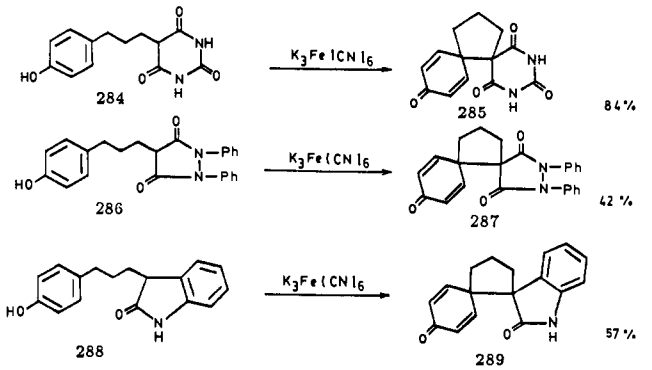
Ferricyanide oxidation of the dianions of phenolic β-diketones affects intramolecular phenoxy–enoxy radical coupling to form spiro systems derived from carbon–carbon bond formation[178,179] para or ortho to the phenolic oxygen. Thus a variety of indandione substrates undergo cyclization in the presence of $K_3Fe(CN)_6$ to yield spirocyclic products (Scheme 74). The phenolic enolate systems **280** and **281** tethered by a three-carbon chain cyclize in good yield to give cyclopentane rings **280a,b** and **282**, whereas for the generation of a cyclohexane ring, the spirocyclization of para-substituted case proceeds in very poor yields. However, the meta-substituted phenol **283** cyclizes in good yield to a 2:1 ratio of para to ortho cyclization products **283a** and **283b**, respectively.

Ferricyanide oxidations are quite facile with substrates having heterocyclic carbon acids attached by a chain to the para position of a phenol, e.g. **284**, **286**, and

Scheme 74



Scheme 75

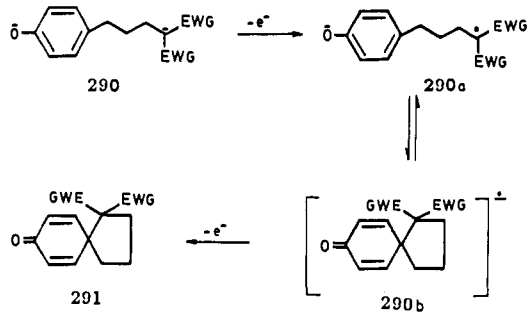


288. Since such cyclic enolate species are stabilized by one or more CONH groups, they undergo rapid[180] cyclization with alkaline $K_3Fe(CN)_6$ to yield spirocyclic dienones **285**, **287**, and **289**, respectively (Scheme 75). Closure to a cyclopentane again is superior to formation of a cyclohexane. The success of these reactions depends upon the pK_a values of the enolic segments which range from 4–5 for the barbituric acids **284** and pyrazolinedione **286** to an estimated 12–14 for the oxindole **288**.

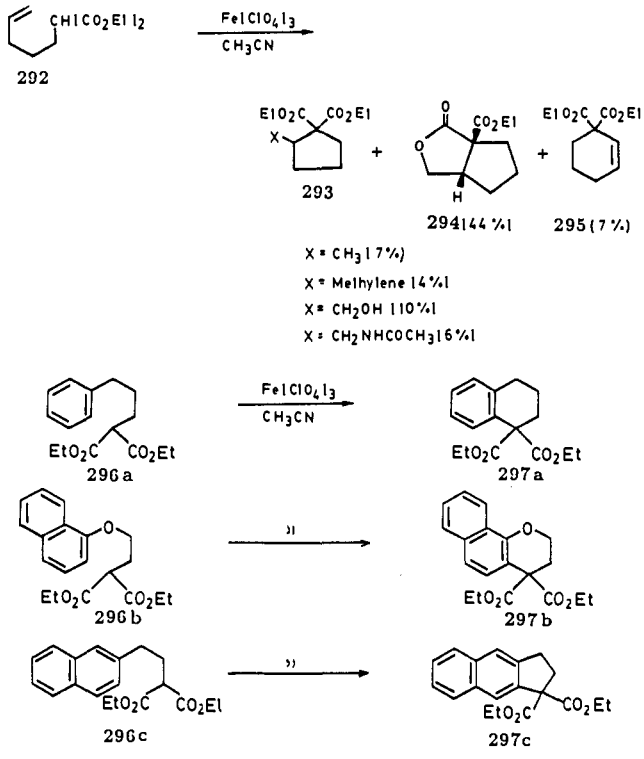
A mechanism for this cyclization has been proposed by Kende by assuming the formation of a dianion **290** which undergoes one-electron oxidation to an open-radical anion **290a** which is in equilibrium with a cyclized radical anion **290b**. A rapid second one-electron oxidation of the cyclized intermediate yields the product **291** (Scheme 76).

Citterio and co-workers have carried out oxidative deprotonation[181] of carbonyl compounds by Fe(III) salts of weakly nucleophilic anions. They have shown that the iron(III) perchlorate in acetonitrile at 0–50 °C oxidizes the α-position of malonic esters to give the corresponding radicals which, in the presence of olefins, undergo inter- or intramolecular free-radical chain or oxidative additions to give cyclic products. Thus diethyl α-(4-pentenyl)malonate (**292**) undergoes intramolecular

Scheme 76



Scheme 77



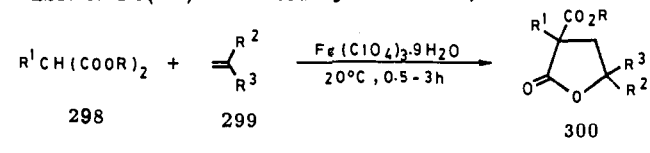
radical cyclization in the presence of iron(III) perchlorate to give a mixture of five-membered cyclization products **293** and **294**. Similarly, the aromatic malonate derivatives **296a–c** lead to the formation of five- or six-membered products **297a–c** (Scheme 77).

Iron(III) perchlorate nonahydrate (FEP) in acetonitrile promotes the inter- and intramolecular addition[182] of dialkyl malonates **298** to conjugated olefins **299** to furnish γ-lactones **300** in high yields (Table 3). The reaction can also be carried out under heterogeneous conditions in aromatic or chlorinated aliphatic solvents using FEP adsorbed on silica gel. The mechanism of these reactions seems to be similar to Mn(III)-promoted oxidative addition reactions.

E. Cobalt

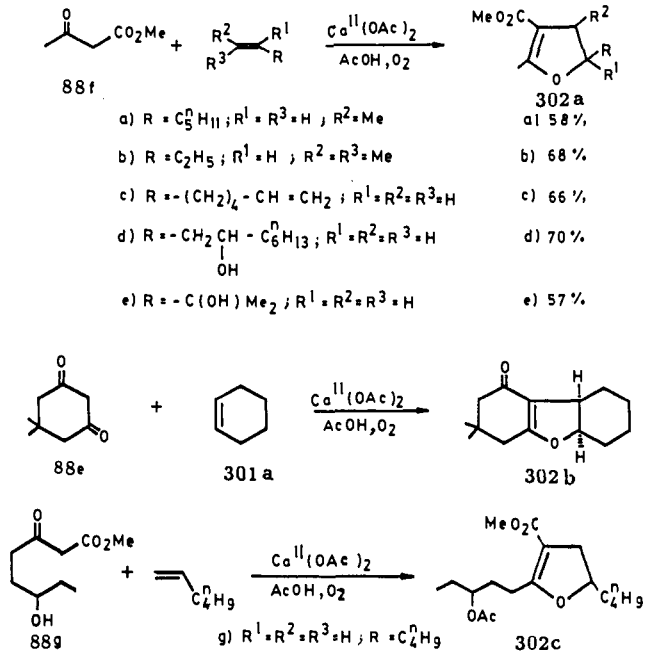
The generation of radicals by an oxidative process using cobalt complexes is relatively unexplored compared to Mn(III)-promoted oxidations. However, the oxidation of alkyl aromatics by cobalt complexes is a well-known process,[183–189] and it involves the intermediacy of carbon-centered radicals. Aldehydes can be oxidized with cobalt(III) complexes to the corresponding acyl radicals, and accordingly Nikishin and co-

Table 3. Fe(III)-Promoted Synthesis of γ-Lactones



R	R^1	R^2	R^3	Yield (%)
Et	Me	H	Ph	90
Et	4-$ClC_6H_4CH_2$	H	Ph	89
Et	4-Cl.$C_6H_4CH_2$	Me	Me-C(=CH_2)-	89
Me	H	H	Ph	65
Et	Me	H	4-MeO-C_6H_4	78

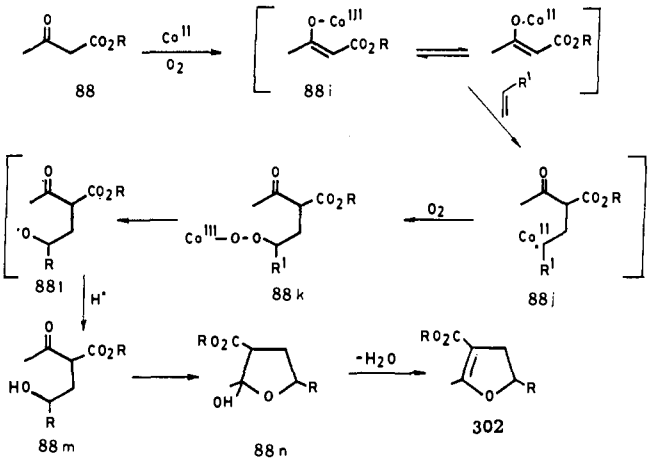
Scheme 78



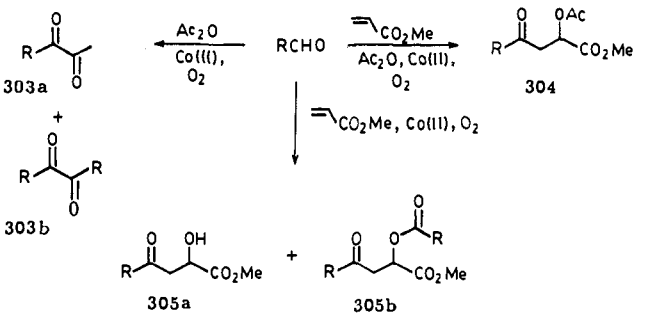
workers have shown that cobalt(II) acetate promotes the addition[190,191] of aldehydes to monosubstituted olefins in the presence of oxygen to give the corresponding ketones. The reactions with Co(II) complexes in the presence of oxygen are believed to involve the formation[192] of Co(III) species, however; no mechanistic details are available on these reactions.

The reaction of 1,3-dicarbonyl compounds **88** with various alkenes **301** in the presence of cobalt(II) acetate under aerobic[193a–c] conditions gives dihydrofurans **302** in moderate to good yields (Scheme 78). These reactions are believed to proceed[193c] via a radical process and are terminated by incorporation of dioxygen. It is proposed that cobalt(II) acetate will oxidize β-dicarbonyl compound to give a cobalt(III) enolate **88g** which is likely to behave as an enol radical. The latter radical will add to alkene to yield another radical **88h** which will undergo insertion of dioxygen to give a peroxycobalt complex **88i**. The latter on homolytic cleavage of oxygen–oxygen bond followed by hydrogen-atom abstraction may give rise to the corresponding hydroxy compound **88k**. The intramolecular ketalization will yield **88l** which on water elimination will yield dihydrofurans **302** (Scheme 79). Cobalt(II) chloride-catalyzed oxidative coupling[193d–e] of enolizable aliphatic

Scheme 79



Scheme 80



aldehydes with excess of acetic anhydride affords a mixture of 1,2-diones **303a,b** in acetonitrile medium under aerobic conditions. These reactions are proceeding via an acyl radical which can be trapped with excess of methyl acrylate to yield 2-acetoxy-4-oxo esters **304** (Scheme 80). Trapping of the acyl radical can also be achieved in the absence of acetic anhydride to afford the corresponding 2-hydroxy and 2-(acyloxy)-4-oxo esters **305a** and **305b**, respectively.

F. Copper

Carbon-centered radicals can be generated from the corresponding stabilized anions by an oxidative process using copper(II) halides. Copper-promoted dimerization of carbanions, which are stabilized by sulfonyl, phosphoryl, imidoyl,[194-195] and alkoxycarbonyl[196] groups, are well known in organic synthesis. Mislow and coworkers have carried out a one-pot synthesis[197] of optically pure 1,2-ethanobis(phosphine oxide) **307** and sulfoxide **309** via the copper-promoted oxidative dimerization of chiral phosphinyl **306** and sulfinyl **308** carbanions (Scheme 81).

Ito and co-workers have developed a novel route to 1,4-diketones by oxidative coupling of lithium enolates[198] with $CuCl_2$ in DMF (Table 4). They have also carried out the cross-coupling of the different methyl ketones leading to the formation of a specific 1,4-diketone (Table 5). Interestingly, the oxidative coupling[199] of enolates of vinylogs of methyl ketones and acetate produced γ,γ-coupling dimers and α,γ-coupling dimers predominantly (Table 6).

Kobayashi and co-workers have reported a simple method for the preparation of 2,2-dialkyl-1,3-cyclopentanedione (**311**) and functionalized spiro[4.4.0] ring

Scheme 81

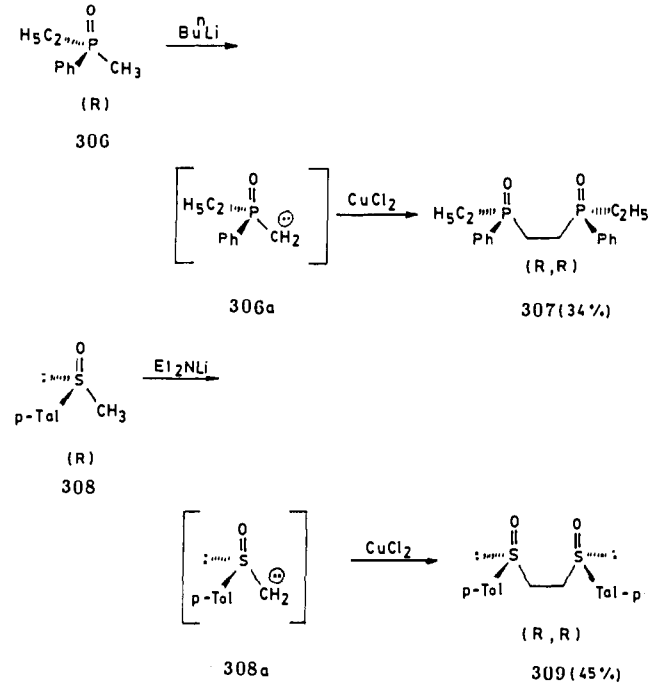
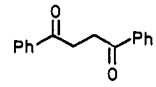
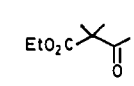
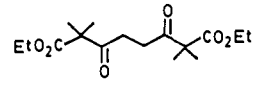
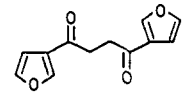
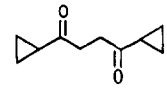
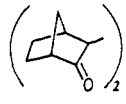
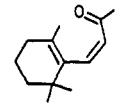
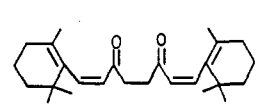


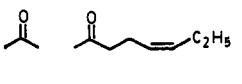
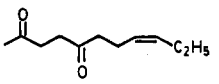
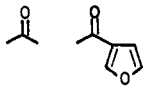
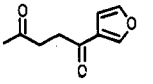
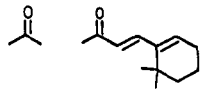
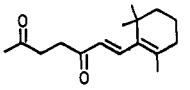
Table 4. Synthesis of 1,4-Diketones by Oxidative Coupling of Ketone Enolates

Entry	Ketone	1,4-diketones	Yield(%)
1			95
2			64
3			41
4			46
5			73
6			82

systems **311c,d** through intramolecular oxidative[200,201] coupling of dilithium enolates of 3,3-dialkyl-2,4-pentanedione (**310**) by means of $Cu(OTf)_2$ (Scheme 82). The oxidative coupling procedure has been applied[202] to construct the 1,4-cyclohexanedione **313** from the diketone **312** leading to the part structure of an intermediate used in the synthesis of C_{16}-hexaqunacene.

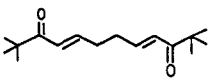
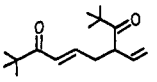
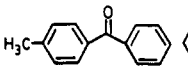
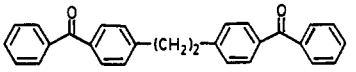
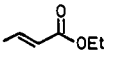
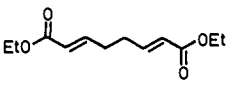
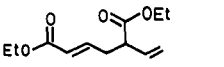
The oxidative cyclization of dimethyl glutarate (**314**) to dimethyl cyclopropanedicarboxylate (**315**) have been achieved by the oxidation of dianion[203] of the former with $CuBr_2$. Similarly Babler and Serussi have achieved the synthesis[204] of cyclopentane derivative by $CuCl_2$-promoted coupling of the corresponding enolate of *tert*-butyl ester of pimelic acid. Hiyama has developed a

Table 5. Cross-Coupling of Lithium Enolates of Acetone and Methyl Ketones

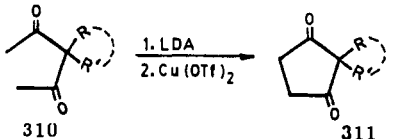
Entry	Ketones	Coupling products[a]	Yield (%)
1			68
2			59
3			65

a. Only major product is shown here

Table 6. Oxidative Coupling of Vinylogs of Carbonyl Compounds

Vinylogs of carbonyl compounds	Dimeric products	Yield (%)
		33
		32
		48
		27
		40

Scheme 82



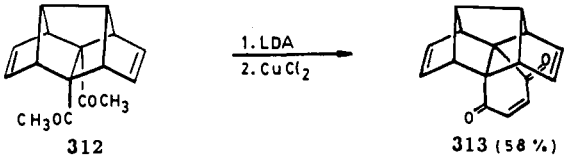
310 311

a. R = R' = Me — a. 32 %

b. R = Me, R' = -CH_2Ph — b. 38 %

c. R.... R' = -$(CH_2)_4$- — c. 27 %

d. R..... R' = -$(CH_2)_5$- — d. 47 %

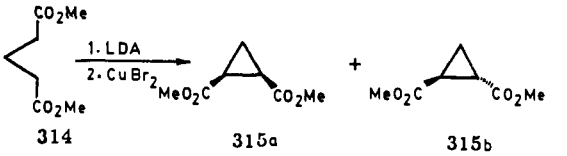


312 313 (58 %)

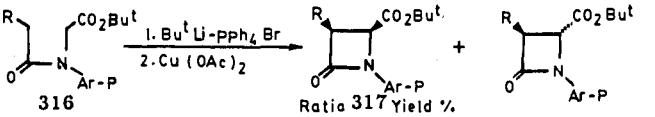
new synthesis of β-lactams **317** and **318** through stereoselective[205] oxidative coupling of the dianions of acyclic amides **316** (Scheme 83).

Oxidative addition of 1,3-dicarbonyl compounds **88d** to conjugated olefins in the presence of $CuCl_2$–pyridine leads to the formation of dihydrofurans **319**. Alternatively, the reaction[206] could be carried out with $CuCl_2$–pyridine–oxygen system and in this case only catalytic amount of copper(II) chloride is required (Scheme 84).

Scheme 83



314 315a 315b

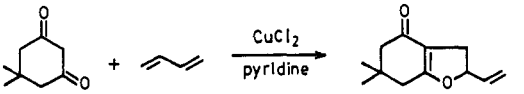


316

	Ratio 317	Yield %
a. R = Et	a. 3:2	40
b. R = OMe	b. 1:2	43
c. R = Bn_2N	c. 1:2	72

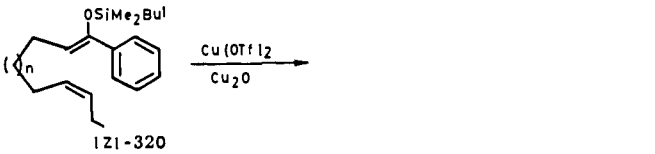
318

Scheme 84



319

Scheme 85



IZI-320

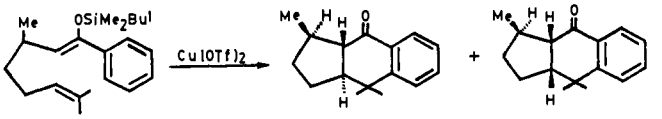
a. n = 1

b. n = 2

321 322

a. 90 % (20:1)

b. 37 % (20:1)

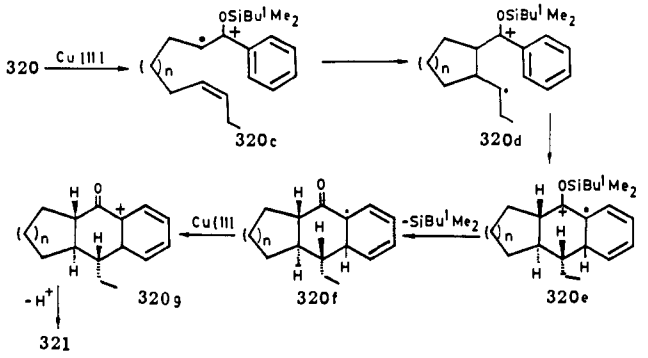


323 324a 324b

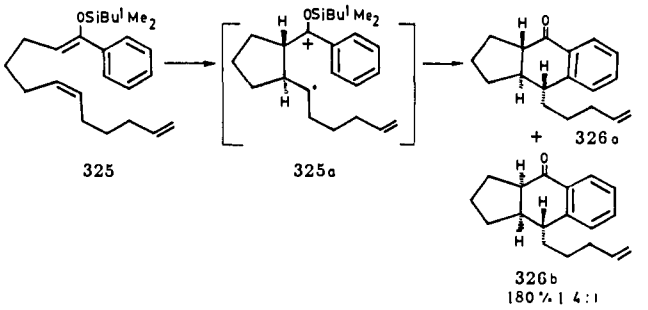
90 % (3.2:1)

A detailed investigation on the oxidative cyclization of δ,ε- and ε,ζ-unsaturated enol silyl ethers and unsaturated siloxycyclopropanes have been recently reported[207] by Snider and Kwon (Schemes 85–89). They have shown that oxidative cyclization of silyl enol ethers of unsaturated aromatic ketones **320** with cupric triflate and cuprous oxide provides the tricyclic ketones **321** and **322** stereoselectively (Scheme 85). The stereochemistry of the cycloadduct is controlled by the stereochemistry of the enol ether as indicated by the conversion of (*Z*)-**320** to mainly the tricyclic ketone **321**. In order to determine the effect of a methyl substituent on the stereochemistry[208] of the product, the (*Z*)-silyl enol ether **323** was subjected to oxidative cyclization with $Cu(OTf)_2$. However, the selectivity in this cyclization was poor and a 3.2:1 mixture of tricyclic ketones **324a** and **324b** were observed. These cyclizations proceed by oxidation of **320** to the cation radical **320c** followed by cyclization of the latter to another cation radical **320d**. This cation radical undergoes a second

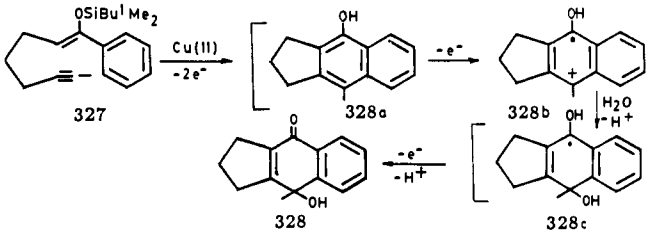
Scheme 86



Scheme 87



Scheme 88

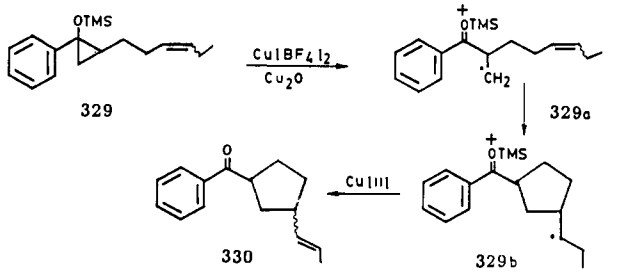


cyclization to give cation radical **320e** which loses the silyl group, undergoes a second oxidation, and loses a proton (i.e. **320f,g**) to give **321** (Scheme 86). The oxidation of a *Z* and *E* mixture of silyl enol ether **325** in which the double bond is positioned so as not to interfere with the first cyclization, with $Cu(OTf)_2$ afforded a mixture of tricyclic ketones **326a** and **326b**. Surprisingly, the benzene ring participates in the second cyclization instead of the double bond. This observation again proved that the second cyclization is also taking place through cation radical intermediate **325a** (Scheme 87).

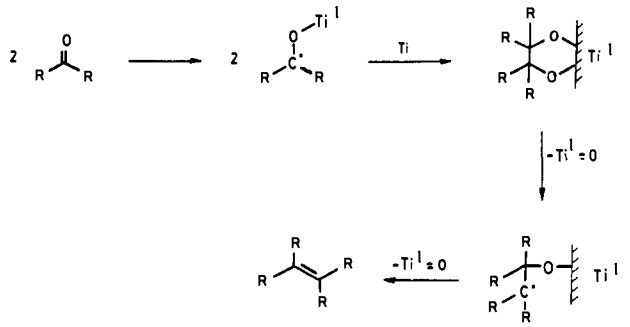
The oxidative cyclization of silyl enol ethers **327** containing triple bonds with $Cu(OTf)_2$, excess Cu_2O, and 3 equiv H_2O gives **328** in 70% yield. A complex mixture of products were obtained under anhydrous condition. This observation is accounted for by oxidative cyclization of **327** to give naphthol **328a** which may be oxidized to cation radical **328b**. The latter can react with water and lose a proton to give radical **328c**, which can be oxidized to give **328** (Scheme 88).

The oxidative cleavage of (oxosilyl)cyclopropanes **329** with $Cu(BF_4)_2$ and Cu_2O gives a moderate yield of **330**. The formation of this product is explained by oxidation of **329** by $Cu(BF_4)_2$ to generate radical **329a**. The latter undergoes 5-exo cyclization to give cyclopentane alkyl radical **329b** which is oxidized by $Cu(BF_4)_2$ to give **330** (Scheme 89).

Scheme 89



Scheme 90



III. Reactions of Radicals Generated by a Reductive Process

The survey of the reactions of radical generated by a reductive process is arranged according to the increasing atomic number of the metal. The following section describes the generation and the reactivity of the carbon-centered radicals derived from the various transition metals (Ti, V, Cr, Co, Cu, Nb, Ru) and organic molecules interactions.

A. Titanium

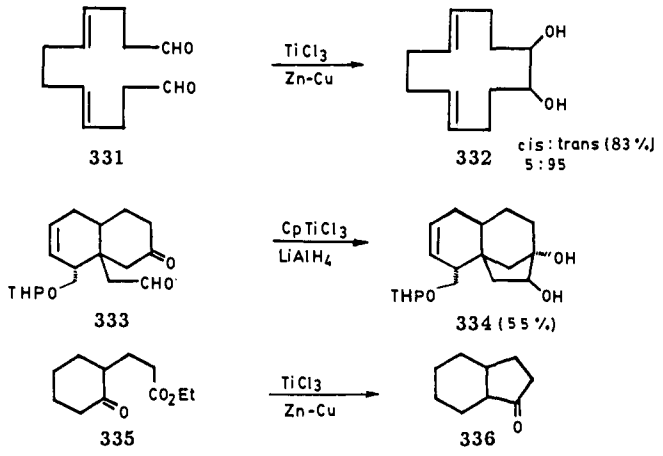
The reactions using titanium complexes can be broadly divided into the following two categories: carbonyl coupling reactions and epoxide–carbonyl coupling reaction. A third category, δ-enone coupling reactions, will be briefly mentioned.

a. Carbonyl Coupling Reactions

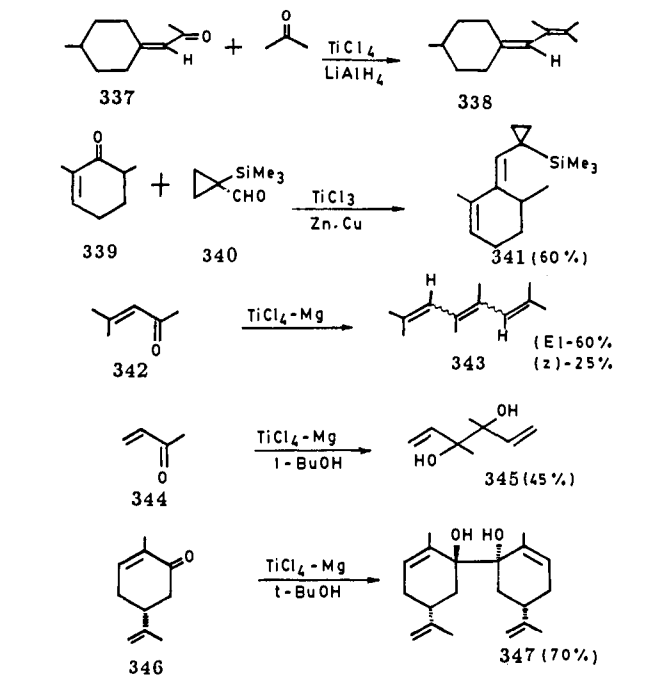
There are approximately 10 titanium-based reagents commonly used for the reductive coupling of carbonyls to alkenes: they include $TiCl_4$–Mg(Hg),[209] $TiCl_4$–Zn,[210] $TiCl_3$–Mg,[211] $TiCl_3$–$LiAlH_4$,[212] $TiCl_3$–K(Li), $TiCl_3$–Zn–Cu, $TiCl_3$–C_8K, $TiCl_4$–Al–$AlCl_3$, $TiCl_2$–Zn, and Cp-$TiCl_3$–$LiAlH_4$.[213] The most widely used reagent is the McMurry reagent,[212,214] $TiCl_3$–$LiAlH_4$, and this system produces Ti^0 or Ti^I depending on the molar ratio of $TiCl_3$ and $LiAlH_4$. These couplings proceed through an intermediate titanium pinacolate which undergoes deoxygenation to yield the alkene (Scheme 90). Pinacols have been isolated from these reductive couplings after short reaction time. It is widely recognized that both these processes occur via a radical pathway.

McMurry and others have shown that ketones and aldehydes undergo reductive dimerization to yield olefins. The titanium reagent is prepared by reaction of $TiCl_3$ and $LiAlH_4$ in the ratio 2:1 and the active coupling species is considered to be Ti(0) as shown by Giese and co-workers.[215,216]

Scheme 91

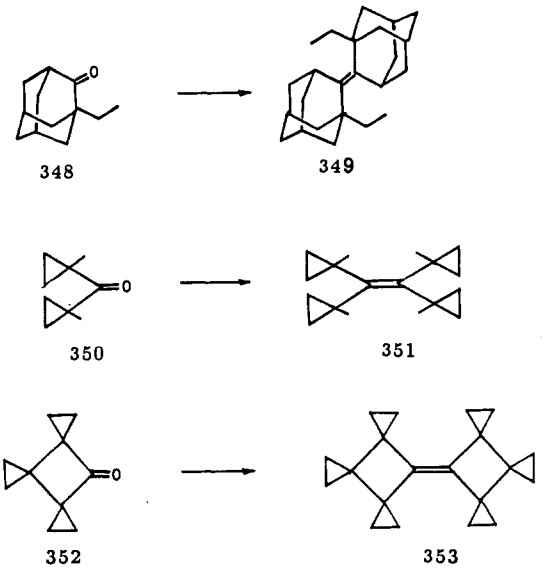


Scheme 92



A variety of carbonyl compounds undergo reductive coupling in inter- or intramolecular fashion to give the corresponding pinacols or olefins. Various aspects of the Ti(0) coupling has been reviewed[217,218] by McMurry, and it is quite clear that these reactions are extremely versatile as practically any carbonyl compound can undergo mixed coupling inter- or intramolecularly. Titanium-promoted intramolecular coupling of carbonyl compounds have been particularly fascinating as it leads to the formation of novel intermediates **332**, **334**, and **336** for the synthesis of various natural products via a pinacol coupling of[219] dialdehydes **331**, keto[213] aldehydes **333**, and keto[220] esters **335**, respectively (Scheme 91). Intermolecular mixed coupling of a variety of carbonyl compounds can be achieved, however, they are generally useful only if one component is used in excess and if the products are easily separable. For example, mixed coupling of acetone with chiral (*R*)-(−)-(4-methylcyclohexylidene)acetone (**337**) has been[221] used to prepare diene **338** (Scheme 92). Similarly, reactions of equimolar amounts of 2,6-dimethyl-2-cyclohexenone (**339**) and formyl(trimethylsilyl)cyclopropane (**340**) with Ti(0) gave mixed coupled[222] product **341** in 60% yield. The reductive homo coupling of α,β-ethylenic ketones **339** and **342** by $TiCl_4$–Mg reagent leads to 1,3,5-trienes **343** and bisillylic pinacols **345**. Similarly, carvone (**344**) undergoes homocoupling to the corresponding[223–227] pinacol **347** in good yields (Scheme 92). Recently Banerji and Nayak have reported[228] a novel one-pot synthesis of phenanthrenes by coupling of *o*-alkoxyaromatic aldehydes or ketones in a dealoxylation process using $TiCl_3$–Li–THF system.

Scheme 93



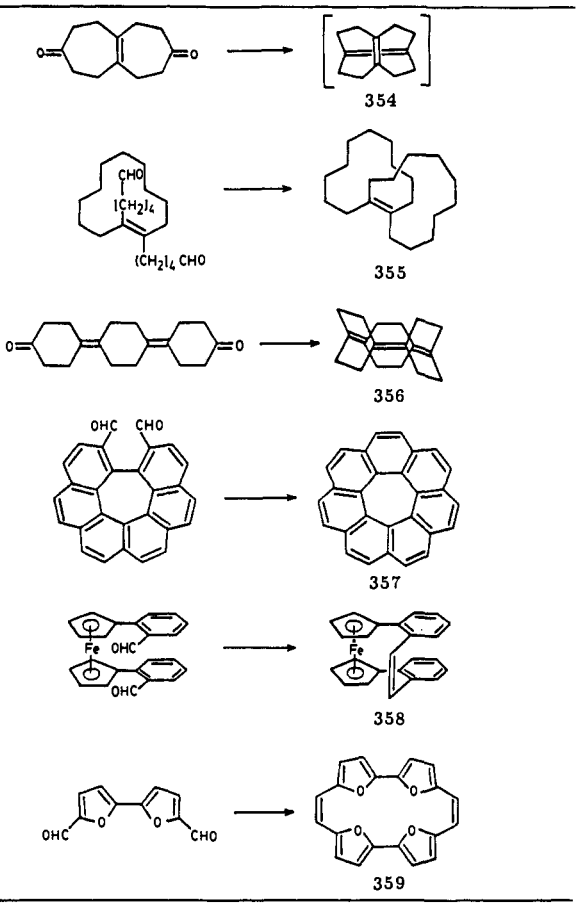
The large thermodynamic driving force provided by the formation of titanium–oxygen bond has been exploited to build high strain into the product during carbonyl coupling reactions. This has allowed a remarkably[229–231] easy synthesis of highly strained molecules. Lenoir's coupling of ethyladmantanone (**348**) provides the synthesis of "tied-back" compound **349** and similarly **351** and **353** can be synthesized from the corresponding ketones **350** and **352**, respectively (Scheme 93).

Another very interesting use of the carbonyl coupling reaction has been for the synthesis of molecules with unusual structures. The remarkable ability of this reaction to form medium and large rings in high yields has led to the use of the reaction in a wide variety of transformations. Noteworthy among the many transformations are McMurry's synthesis[232–234] of crossed diene **354** and bicyclo[4.4.4]tetradecene (**355**), Marshall's synthesis[235] of betweenanenes **356**, Yamamoto's synthesis[236] of [7]circulene (**357**), Shimizu's synthesis[237] of ferrocene cyclophane **358**, and Vogel's synthesis[238] of tetrafuranoid (**359**, Table 7).

The titanium-promoted carbonyl-coupling reaction is extremely valuable in the synthesis of natural products containing a variety of different ring sizes (Table 8). Five-membered rings[239,240] are formed during strigol (**360**) and hirsutene (**361**) synthesis, and six-membered rings are formed during estrone (**362**), compactin (**363**), and isokhusimone (**364**) synthesis.[241–243] Similarly, eight-membered rings are formed in the taxane (**365**), fusicoccane (**366**), and ceroplastol (**367**) synthesis,[244–246] and ten-membered rings are formed during helminthogermacrene (**368**), bicyclogermacrene (**369**) or lipidozene[247–249] synthesis (Table 8).

The titanium-promoted coupling reaction has been also used for the synthesis of macrocyclic rings (Table

Table 7. Titanium-Promoted Synthesis of Some Unusual Molecules

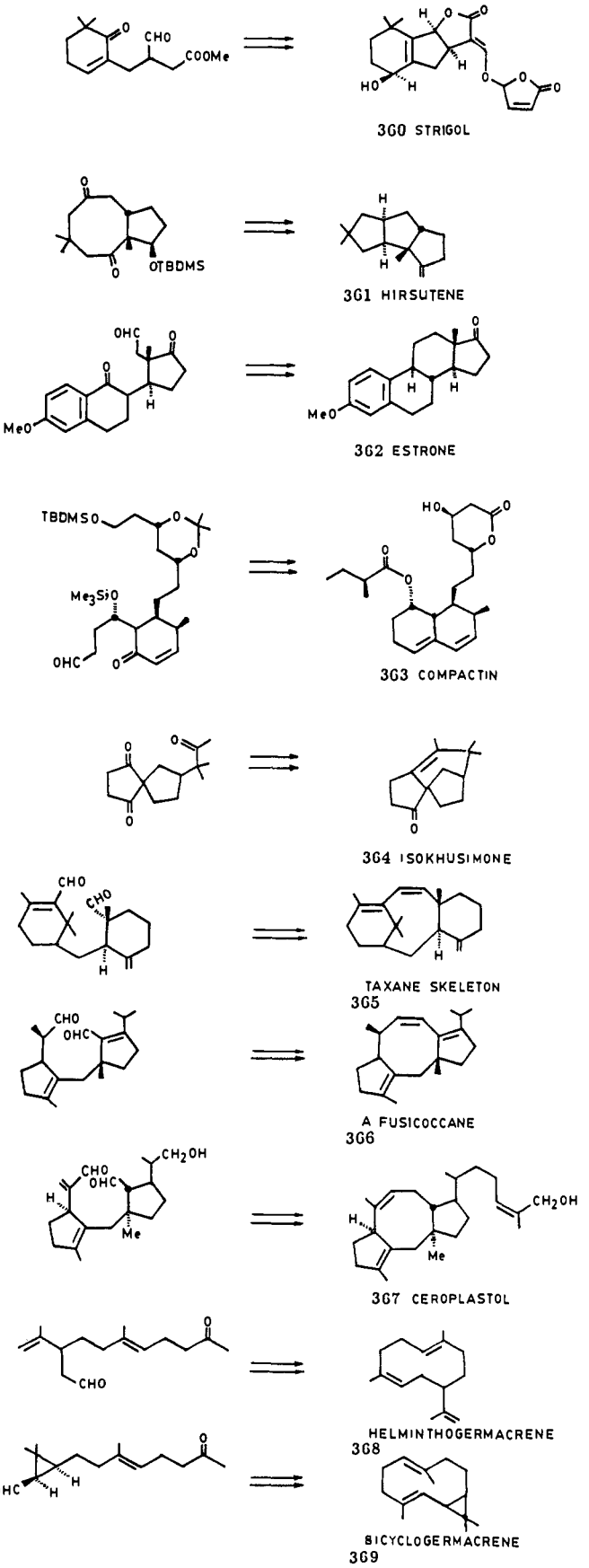


9). An eleven-membered ring is formed in humulene (**370**) synthesis,[250] a twelve-membered ring is formed[251] in verticillene (**371**) synthesis; fourteen-membered rings are formed[249] in the casbene (**372**) and sarcophytol B (**373**) synthesis,[219] whereas a fifteen-membered ring is formed[252] in the flexibilene (**374**) synthesis (Table 9).

The keto ester **375** and **377** coupling reactions have been used in synthesis[220,253] of capnellene (**376**) and isocaryophyllene (**378**), respectively (Scheme 94). It is interesting to note that the olefin isomerization occurs during the carbonyl coupling for the synthesis of isocaryophyllene.

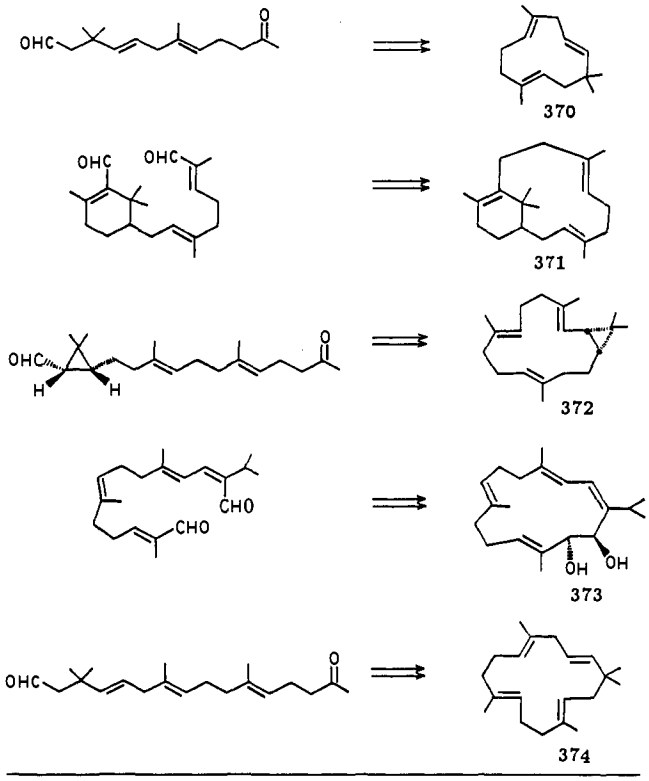
An aqueous acidic 15% solution of $TiCl_3$ is a mild reducing agent ($E°$ = −0.1 V). This reagent has no effect on aliphatic or aromatic ketones and aldehydes; however, it easily couples carbonyl compounds **379** activated toward reduction by an electron-[254,255] withdrawing group. Thus, benzoyl cyanide, when allowed to react with aqueous $TiCl_3$ in acetic acid affords the expected benzyl dicyanohydrin **380**. On changing the medium[256,257] from acetic acid to acetone, a novel reaction occurs between benzoyl cyanide and acetone to give mixed 1,2-diol **381** as the main product (Scheme 95). Electron-withdrawing substituted carbonyl compounds **382** selectively[258] add in the presence of aqueous $TiCl_3$ to the carbonyl carbon atom of α,β-unsaturated aldehydes **383** to give allylic pinacols **384** in high yields (Scheme 95). A strong interaction between the LUMO of the aldehydic carbonyl group and the SOMO of the alkyl radical has been proposed for the selective formation of the pinacols.

Table 8. Titanium-Promoted Synthesis of Natural Products

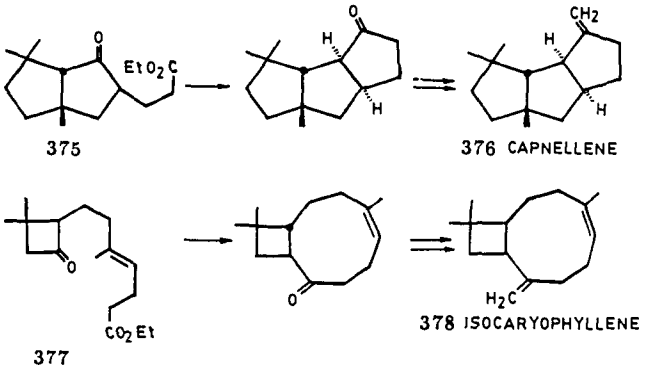


The mixed coupling of aliphatic compounds can be achieved by use of excess of one of the reactants. This

Table 9. Titanium-Promoted Synthesis of Macrocyclic Rings



Scheme 94



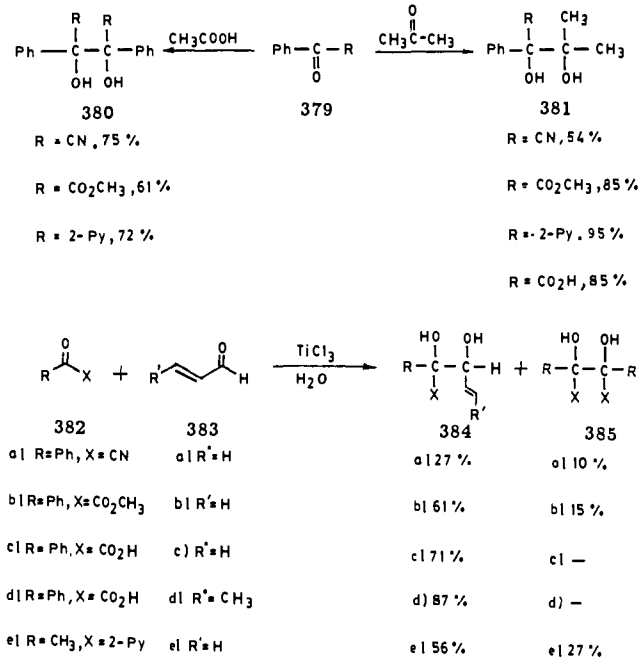
protocol was first developed[259] by Corey and then applied by Li et al. to the synthesis of the alkaloids isoharringtonine **386** and **387** by titanium-promoted cross-coupling between methyl glyoxaldehyde and **386** (Scheme 96).

b. Epoxide–Olefin Coupling Reactions

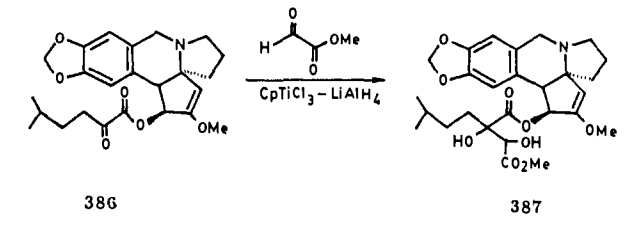
Nugent and Rajanbabu have recently shown[260] that epoxy olefins undergo a Cp_2TiCl-promoted titanium-centered radical-induced intramolecular addition to the olefins to give cyclopentanemethanols (Table 10). The reaction conditions are compatible with carbonyl functionality, and the procedure is well suited to the introduction of quaternary centers. The ring fusion is generally cis and the endo isomer is the major product in each case.

These reactions are terminated by quenching with water, however, if the iodine is used as a quenching agent then the iodo alcohol **389** may be isolated in an isomerically pure form from the epoxy olefin **388** (Scheme 97).

Scheme 95



Scheme 96

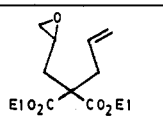
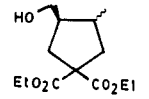
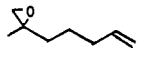
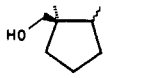
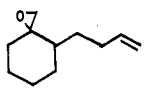
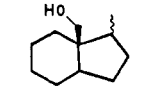
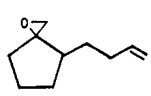
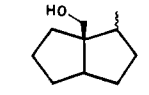
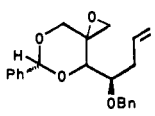
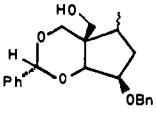
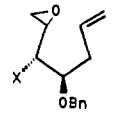
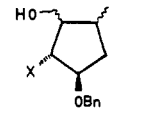


Cp_2TiCl also promotes the intermolecular addition of epoxides to activated olefins to give hydroxy esters or lactones (Table 11). The acrylate adducts can be readily converted[261] into δ-valerolactone, this overall scheme represents a novel [3 + 3] annulation to prepare such lactones from epoxides. The carbohydrate epoxide **390** can be readily added to activated olefin in the presence of Cp_2TiCl to give axial adduct **391** as the major isomer. It appears that the regioselectivity of the ring opening is affected by the stereoelectronic stabilization of the incipient radicals, however, the possibility of a reversible ring opening followed by slow addition to the olefin cannot be ruled out (Scheme 98).

These reactions are believed to proceed via carbon-centered radicals which may be formed by the homolysis of the epoxide C–O bond (Scheme 99). The latter process is known to occur from the σ-complex of an epoxide with a paramagnetic transition metal having a half-filled (π-symmetry) d orbital.

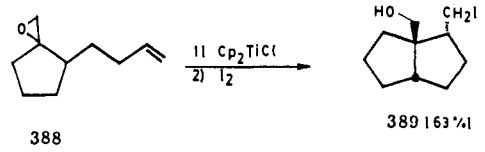
The alkyl radicals generated by the reaction of titanocene monochloride and epoxides **393** undergo intermolecular reactions[262a] with α,β-unsaturated Fisher carbene complexes **394** to give cyclic ethers **395–399** (Scheme 100). Owing to their highly electrophilic nature, the α,β-unsaturated Fisher carbenes are a much better trap for alkyl radicals. Cyclohexene oxide **393c** leads to the exclusive formation of trans-fused bicyclic systems **397** or **399**. The equatorial isomer is obtained as the major product when the β-substituent is phenyl, but the axial isomer predominated[262b] when the substituent is methyl.

Table 10. Ti(III)-Induced Cyclization of Epoxyolefins to Cyclopentanemethanols

Epoxyolefins	Product	Yield [%]	Isomer ratio
		68	85:15 [cis:trans]
		94	1:1
		82	55:45 [endo:exo]
		88	90:10 [endo:exo]
		72	83:17 [endo:exo]
		74 [X=OAc] 44 [X=OBn]	45:30:15:10[a]

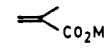
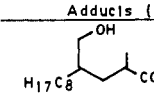
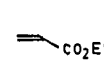
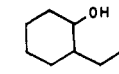
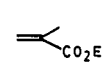
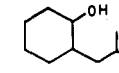
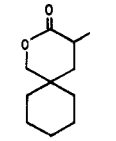
[a] ratio in order: 1,2-trans; 1,5-cis; 1,2-trans; 1,5-trans; 1,2-cis; 1,2-cis; 1,5-trans.

Scheme 97



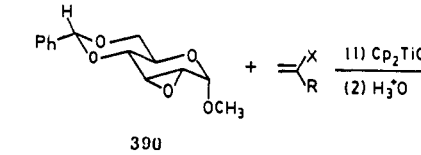
388 389 [63%]

Table 11. Addition of Epoxides to Activated Olefins

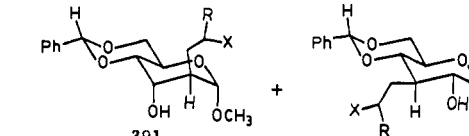
Epoxides	Olefins	Adducts (Yield %)
		 79
		 70 cis:trans 3:5
		 82 cis:trans 1:2
		 81

The mechanism of the above reaction involves generation of a β-alkoxy radical, addition to the unsaturated carbene complex, and trapping of a novel metal carbene α-radical by a second equivalent of titanocene monochloride. Quenching of the latter with ethereal HCl followed by the intramolecular attack of the secondary hydroxyl group to the carbene leads to

Scheme 98



390



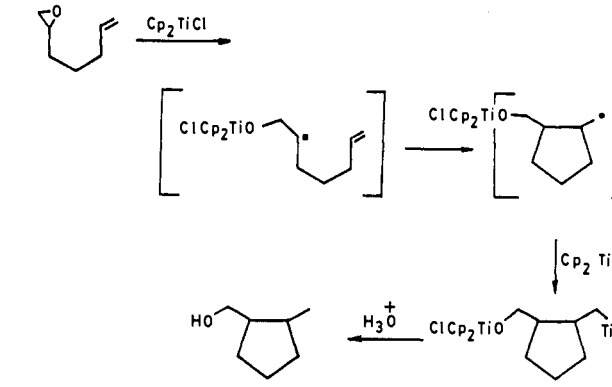
391 392

a) X=H, R=CN — a) 32% — a) 3%

b) X=H, R=$COCH_3$ — b) 45% — b) 7%

c) X=CH_3, R=CO_2CH_3 — c) 73% — c) –

Scheme 99



an intermediate which upon loss of methanol gives the cyclic carbene ether (Scheme 101).

c. δ-Enone Coupling Reactions

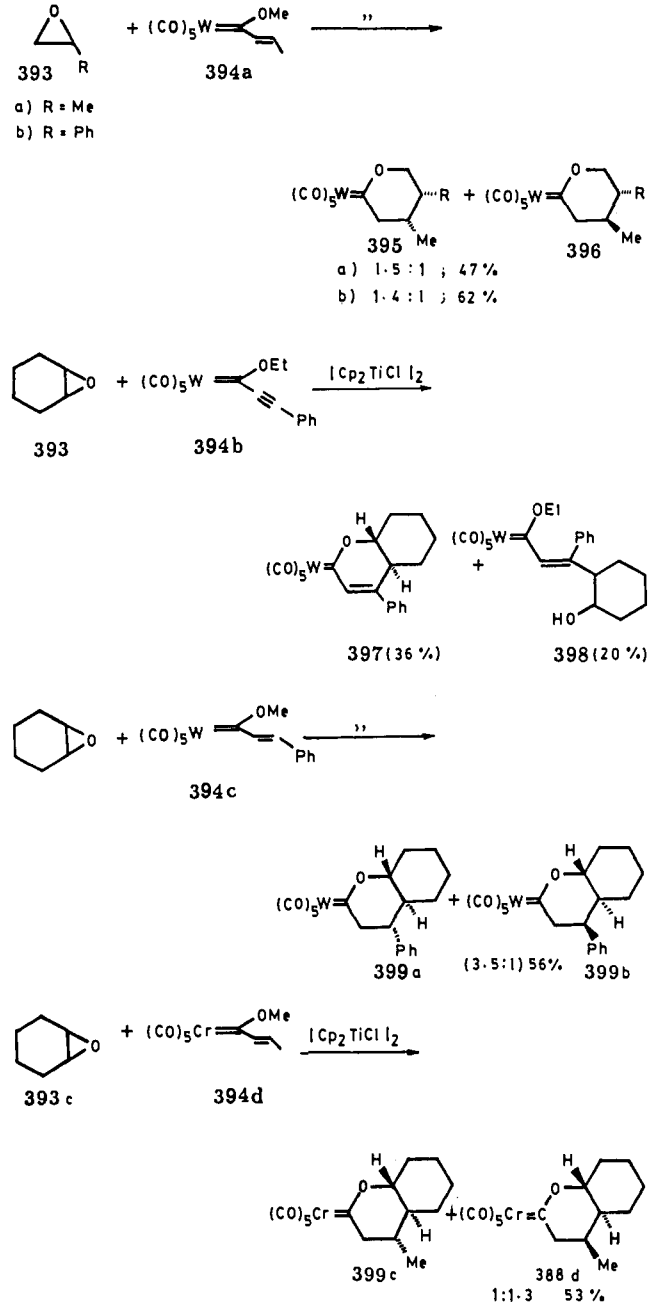
The cyclization of δ-enone **400** promoted by the $TiCl_4$–Mg(Hg) complex leads to the trans isomer of the corresponding[263] cyclopentanol **401** (Scheme 102).

B. Vanadium

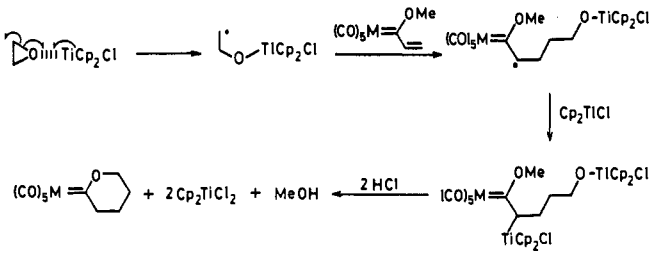
The complexes of vanadium(II) are good reducing agent and they mediate the coupling of benzyl, allyl, or alkyl halides by a reductive[264] process.

Paderson and co-workers have shown that the vanadium(II) reagent $[V_2Cl_3(THF)_6]_2[Zn_2Cl_4]$ promotes the cross-coupling of electronically similar aldehydes to give pinacol. In an impressive study they have shown[265] that the reagent couples aryl aldehydes in high yield and with high diastereoselectivity. However, non-aryl aldehydes do not couple at any appreciable rate and aryl as well as dialkyl ketones give little or no coupling products under the same conditions. However, coupling of non-aryl aldehydes is accelerated if they contained an appropriately placed chelating group capable of forming six- and seven-membered chelate rings with a vanadium center. Such aldehydes were referred to as chelation-accelerated aldehydes or CA aldehydes. Accordingly, the intramolecular coupling between a CA aldehyde and less reactive aldehydes have been achieved in high yields (Table 12). The major diastereomer in all of the cross-coupling reactions is a threo diol and the threo–erythro ratio increases as α-branching in either aldehyde increases.

Scheme 100



Scheme 101



Two possible radical mechanisms have been proposed for these couplings. One involves the dimerization of the ketyl radical (path A) and the other involves the ketyl radical attack on a coordinated aldehyde (path B) (Scheme 103).

Vanadium dichloride induces the regioselective addition of bromotrichloromethane to olefinic compounds to give[266] the 1,2-addition products **402**. 1-Hexen-5-ol

Scheme 102

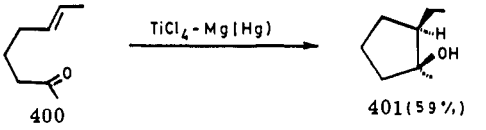
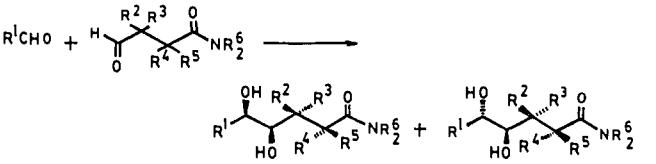
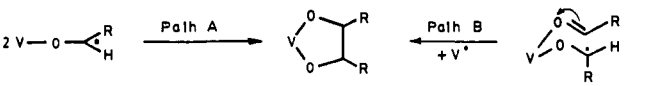


Table 12. Vanadium-Promoted Pinacol Cross-Coupling

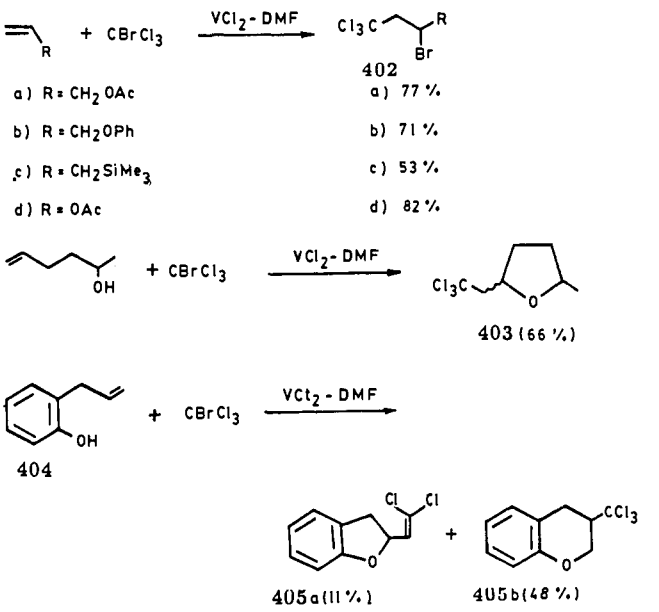


R^1	R^2	R^3	R^4	R^5	R^6	ds	Yield (%)
$PhCH_2CH_2$	H	H	H	H	Bn	4:1	57
i-Pr	H	H	H	H	Bn	8:1	73
t-Bu	H	H	H	H	Bn	100:1	42
i-Pr	H	Me	H	H	Bn	14:1	81
i-Bu	H	H	H	Me	Bn	4:1	80
$PhCH_2CH_2$	Me	Me	H	H	Me	>50:1	81

Scheme 103



Scheme 104



reacted with bromotrichloromethane in presence of VCl_2 to produce the tetrahydrofuran **403**. Similarly, 2-allylphenol (**404**) cyclized to the benzofuran **405a**. The major product, however, was the benzodihydropyran **405b** formed via an unusual endo-type ring closure (Scheme 104).

C. Chromium

Chromium(II) complexes are useful reagents for the reductive[267-270] coupling of allyl, benzyl, or alkyl halides. The alkyl radicals can be generated from alkylnyl halides **406** by $Cr(ClO_4)_2$, and they can undergo intramolecular cyclization to give[271] methylenecycloalkane (**407**, Scheme 105). Five- and six-membered rings are formed more readily and the iodides give more cyclic products than the corresponding bromides. The alkyl-

Scheme 105

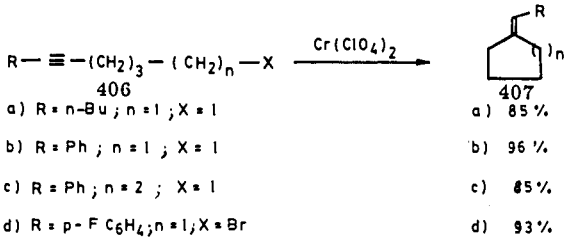
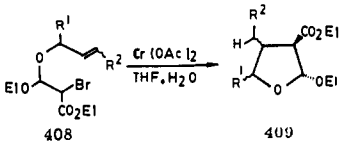
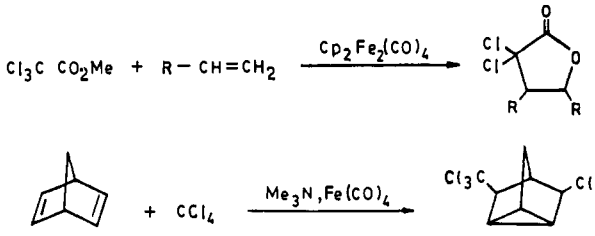


Table 13. Cr(II)-Promoted Synthesis of Substituted Tetrahydrofurans



	R^1	R^2	isomer ratio	yield (%)
a	H	H	2t 4c : 2t 4t (1:3.9)	79
b	CH_3	H	2t 4c 5t : 2t 4t 5c (1:0.89)	83
c	H	CH_3	2t 4c : 2t 4t (1:1.68)	83
d	$-(CH_2)_3-$		2t 4c 5c : 2t 4t 5t (1:1.04)	78

Scheme 106



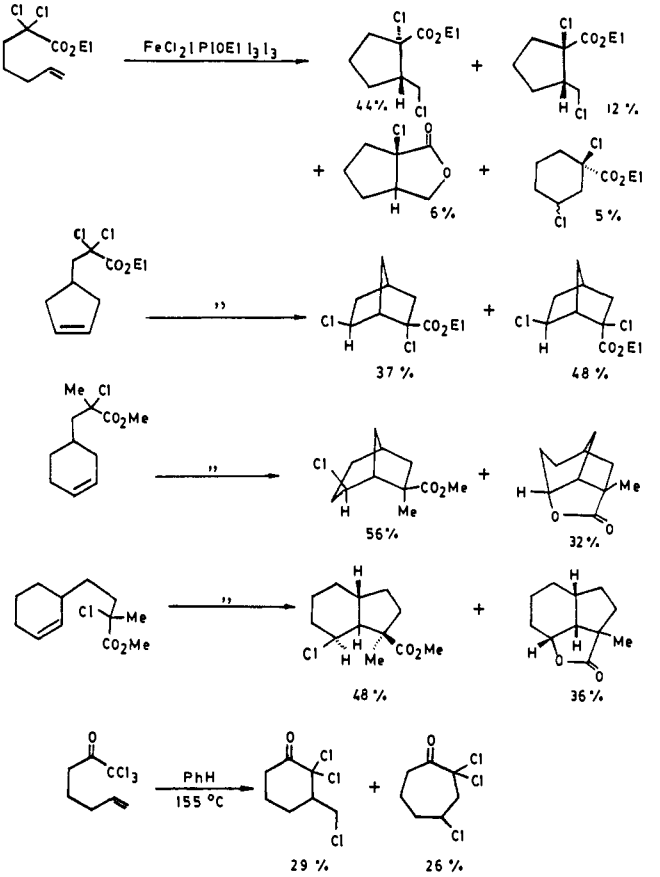
substituted compounds give only a trace of cyclic products upon direct addition to Cr(II) reagent, however, an inverse addition and prolonged addition time brings about a dramatic change in these cyclizations. The Cr(II)-based method for radical generation gives results comparable to those obtained with tin hydrides. Similarly, β-(allyloxy)-α-bromo esters **408** undergo intramolecular[272] cyclization in the presence of $Cr(OAc)_2$ to give the substituted tetrahydrofurans **409** (Table 13).

D. Iron

Fe(II) complexes act as good catalysts in promoting the Kharash reaction[273-282] with various halocarbons and olefins (Scheme 106). These reactions proceed via a radical-chain process and their synthetic utility is due to the fact that metal-coordinated radicals are intermediates, the net result being that the rate of halide abstraction becomes faster than that of telomerization.

$FeCl_2[P(OEt)_3]_3$ is an efficient catalyst for intramolecular[283-286] Kharash cyclization of unsaturated α,α-dichloro esters or ketones leading to the formation of cyclopentanes, cyclohexanes, lactones, and bridged carbocycles (Scheme 107). Fe(II) complex-catalyzed reaction generates a radical by a reductive process, and

Scheme 107



it proceeds via a radical-chain mechanism which is terminated by chlorine atom transfer.

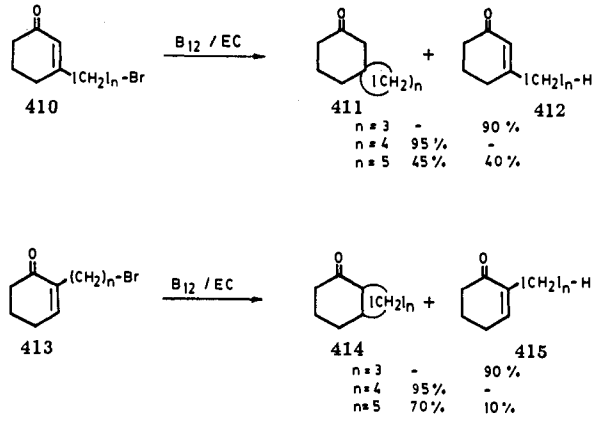
E. Cobalt

Carbon-centered radicals can be efficiently generated by homolysis of alkylcobalt(III) species. The later species can be synthesized by a reductive process from[287-291] an alkyl halide and nucleophilic Co^I reagent. The cobalt-mediated free-radical reactions can be divided into the following two categories.

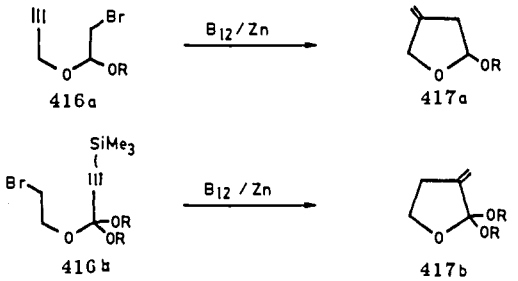
a. Vitamin B_{12}-Catalyzed Radical Reactions

Vitamin B_{12}-promoted radical reactions in organic synthesis has been pioneered by Scheffold. Vitamin B_{12} can be reduced chemically ($Zn-NH_4Cl$) or electrochemically (−0.8 V) to afford Cob(I)alamin (B_{12s}) which can be converted[292,293] to the corresponding alkyl analogs on reaction with various alkyl halides. The ability of vitamin B_{12} and its analogs to form alkylcobalt derivatives in combination with the ease of homolysis of the carbon–cobalt bonds in these molecules, has led to the development of novel synthetic routes to various natural products. Vitamin B_{12} is used in catalytic quantities and is an efficient catalyst in electroorganic synthesis since it acts as a mediator in the transfer of electrons from cathode to electrophilic organic substrates. The two useful B_{12}-catalyzed reactions are the reductive β-elimination and the conjugate addition of R–X to activated olefins. The B_{12}-catalyzed cyclization by electrolysis at −1.4 to −1.6 V in the presence of 5 mol % hydroxocobalamin hydrochloride (electrocatalysis EC) of α,β-unsaturated ketones **410** and **413** bearing a bromo side chain occurs in excellent yields. The

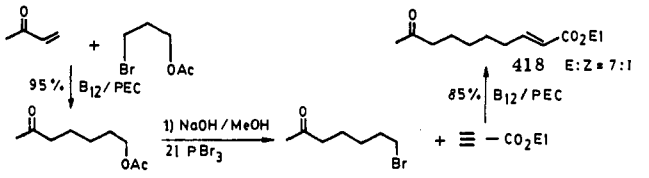
Scheme 108



Scheme 109



Scheme 110



cyclization is dependent upon the number of carbon atoms present in the side chain, and the reaction usually proceeds via 5-exo-trig or 6-endo-trig arrangement to give **411** and **414**, respectively (Scheme 108).

2-(Bromoethyl)propargylic ethers **416** undergo facile 5-exo-dig cyclization to yield precursors for α- and β-methylene lactones **417** (Scheme 109).

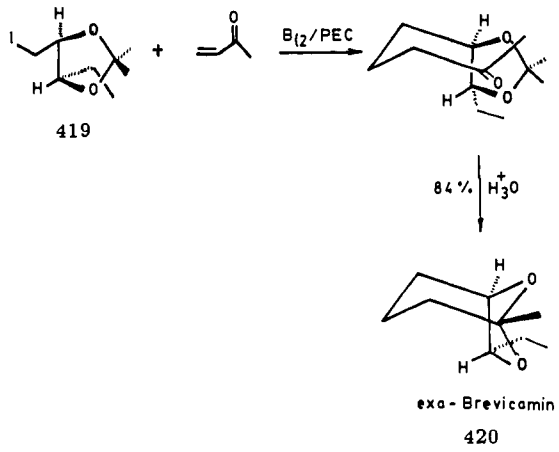
The consecutive addition of alkyl halide to activated[293] olefins by photoelectrocatalysis (PEC) of hydroxocobalmin hydrochloride allows the construction of extended carbon chains as shown for the synthesis of pheromones Queen substance **418** (Scheme 110).

The mild conditions of the B_{12}/PEC reaction are suited for the addition of primary alkyl halides **419** containing a potential leaving group. This is illustrated by synthesis of *endo*- and *exo*-brevicomin (**420**, Scheme 111).

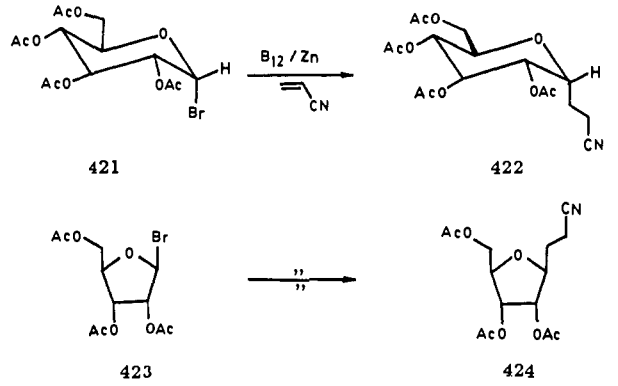
The synthesis of c-glycosides may be achieved by B_{12}-catalyzed C–C bond formation. Thus, 3-(2,3,4,6-tetra-*O*-acetyl-α-D-glucosyl)propionitrile (**422**) can be prepared from acetobromoglucose **421** by reduction with Zn in DMF in the presence of acrylonitrile and 3 mol % of hydroxocobalmin hydrochloride. Similarly, the ribofuranosyl derivative **424** can be prepared from the corresponding acetobromofuranose **423** (Scheme 112).

Acid anhydrides **425** react under B_{12}/PEC conditions with α,β-unsaturated carbonyl compounds[294] to give the corresponding 1,4-addition products **426** which may be converted to cyclopentenones **427** (Scheme 113).

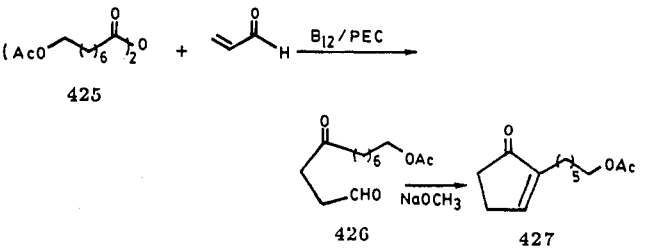
Scheme 111



Scheme 112



Scheme 113

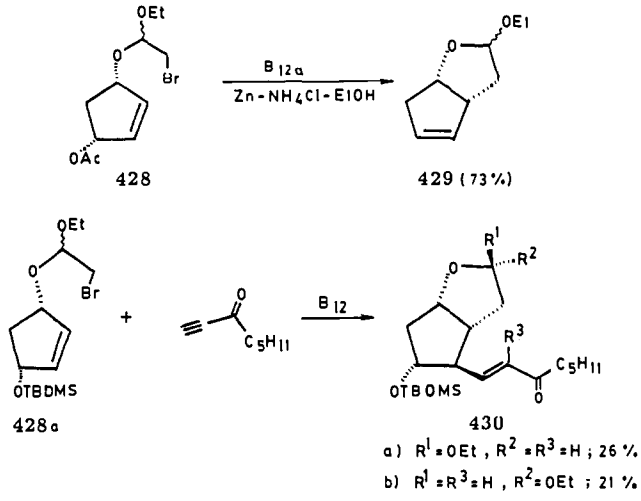


The B_{12}-catalyzed electrolysis of acetoxy bromo acetal **428** in DMF at −1.0 V afforded the diastereomeric acetal **429** as product of the cyclization–elimination sequence. Starting from a chiral cyclopentene bromo acetal **428a** and 1-octyn-3-one, a prostaglandin $F_{2\alpha}$ precursor **430**, containing all structural features from C_6 to C_{20} with 8*R*, 11*R*, and 12*R* chirality, is obtained by the one-step formation of two carbon–carbon bonds in the B_{12}-catalyzed radical cyclization[295] addition sequence (Scheme 114).

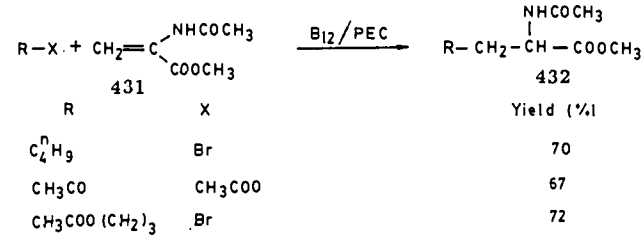
2-Amino esters **432** can be synthesized by B_{12}-catalyzed photoelectrochemical 1,4-hydroaddition of alkyl halides[296] or carboxylic anhydrides to 2-acetomidoacrylate (**431**, Scheme 115).

In studies directed toward forskolin, Pattenden et al., have observed dichotomous reactivity in stannane- and cobalt-mediated radical cyclization. In one instance, it was shown that the radical cyclization[297] or the bromo acetal **433** initiated by $Bu_3Sn^\bullet$ (Bu_3SnH, AIBN) led (95%) to predominantly the equatorial-oriented side-chain isomer **434a**, whereas use of catalytic vitamin B_{12} (MeOH, $LiClO_4$, −1.9 V, 24 h) produced

Scheme 114



Scheme 115



(70%) almost entirely the corresponding axial epimer **434b** of the bicyclic epimer (Scheme 116). The vitamin B_{12}-catalyzed reaction of the corresponding bromoacetal **433a** with an ethoxy group led to a 1:1 mixture of ethyl acetal **434c** and ethylene acetal **434d** in a combined yield of 70%, furthermore, both were produced with their side chains oriented exclusively axial. This led to the suggestion that the cyclization in the presence of vitamin B_{12} most likely to occur via the transient organocobalt **435**. 1,2-Elimination of Co–H from **435** would then lead to the observed ethylene acetal, whereas C–Co bond cleavage accompanied by hydrogen-atom addition would produce the corresponding ethyl acetal (Scheme 116).

The mechanism for vitamin B_{12}-catalyzed electrochemical reaction can be explained by the following catalytic cycle. One-electron reduction of organocobalt(III) complex gives Co(I) and generates[295] the alkyl radical. Nucleophilic attack of Co(I) complex regenerates the organocobalt(III) complex (Scheme 117).

b. Organocobalt-Mediated Radical Reactions

Recent studies of cobalt-mediated radical reactions have demonstrated the facile homolytic cleavage (thermal or photochemical) of a range of alkyl and acyl cobalt reagents and the addition of the resulting carbon-centered radical to carbon–carbon double bond. The required organocobalt reagents have been prepared by single-electron transfer from a nucleophilic Co^I reagent to the alkyl or acyl halides. Johnson and co-workers have demonstrated[298-301] that the allyl organocobaloximes **436** undergo an S_H2' displacement with trichloromethyl radical. Cyclopropane **438** can be synthesized from homoallylic cobaloximes **437** and a suitable radical precursor by an intramolecular homolytic displacement at the α-carbon (Scheme 118).

Fused and spiro cyclopropane systems **440** and **442** can also be synthesized by the reaction of appropriate cycloalkenyl cobaloximes **439** and **441** with free-radical precursors like toluenesulfonyl iodide (Scheme 119).

The thermal and photochemical reactions of hex-5-enyl cobaloximes **443** with a large excess of CCl_4 gives mainly the pentachloroheptane **444** (path A) (Scheme 120). The photochemical reaction in presence of low concentration of CCl_4 gives mainly the cyclopentylmethyl chloride **445a** through homolysis of the carbon–cobalt bond, cyclization of the hexenyl radical, and chlorine atom abstraction (path B). However, the thermal reaction[301] in the presence of a low concentration of CCl_4 gives a higher yield of (trichloroethyl)cyclopentane **445b** through attack of a trichloromethyl radical at the terminal unsaturated carbon followed by the intramolecular homolytic displacement of cobalt by attack of the secondary radical center on the α-carbon (path C) (Scheme 120).

Pattenden and co-workers have synthesized a variety[302-319] of organocobalt compounds using salen and salophen ligands. These workers have elegantly exploited the weakness of C–Co bond to initiate carbon-centered radical formation which underwent a new carbon–carbon bond formation to give a product radical. The latter carbon-centered radical can be trapped with Co^{II} to give a carbon–cobalt bond which can be manipulated to introduce functionality (i.e. C=C and OH) into the product. This process is termed as a cobalt group-transfer reaction and is formally related to atom-transfer reactions because of the nature of the transformation that they effect; however, the mechanistic pathway for these differ considerably. They have demonstrated the wide applicability of this new cobalt-initiated cyclization–trap functional group interconversion strategy for the synthesis of a very wide range of OH-substituted aromatic and heterocyclic molecules.

Reaction between the Co(I) species derived from Co(III)salen or Co(II)salophen and (*O*-allyl)- or (*O*-but-3-enyl)iodophenols **446** lead to an isolatable cobalt complex **447** which can be converted into substituted benzofuran **447a–e** upon treatment with variety[303] of reagents (Scheme 121).

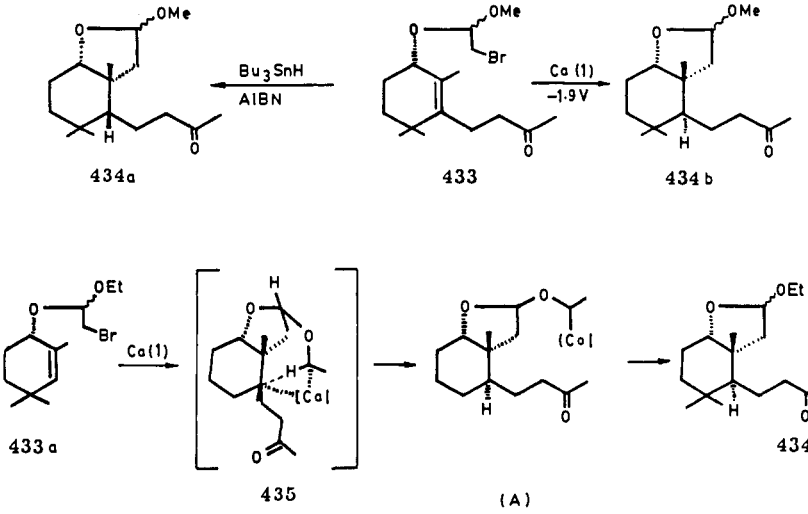
Radical cyclization of acetal **448** in the presence of Co(I) cobaloxime leads to the cis-ring fused alkyl–cobalt complex **449** which can be converted in a preparative manner into lactone **450** following 1,2-elimination and hydrolysis/oxidation and into lactone **451** following insertion of molecular oxygen and hydrolysis/oxidation (Scheme 122).

These reactions are believed to proceed via a reductive process to give an organocobalt complex **446a** which undergoes an intramolecular cyclization of the radical **446b** generated by homolytic cleavage of carbon–cobalt bond (Scheme 123).

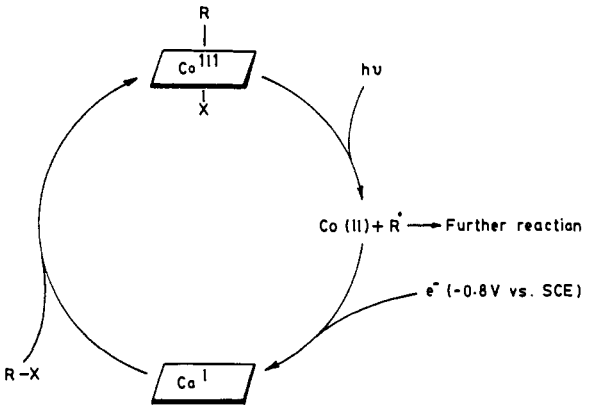
The intermolecular addition reactions between organocobalt reagents **452** and **447** and a variety of deactivated C=C bonds led to new alkene products **453** and **454**, which resulted from radical addition to the C=C bonds followed by "dehydrocobaltation" from the presumed[304] organocobalt intermediates (Scheme 124).

The organocobalt reagents can be prepared with remarkable regiospecificity by hydrocobaltation of alkenes. Thus electron-deficient olefins can be con-

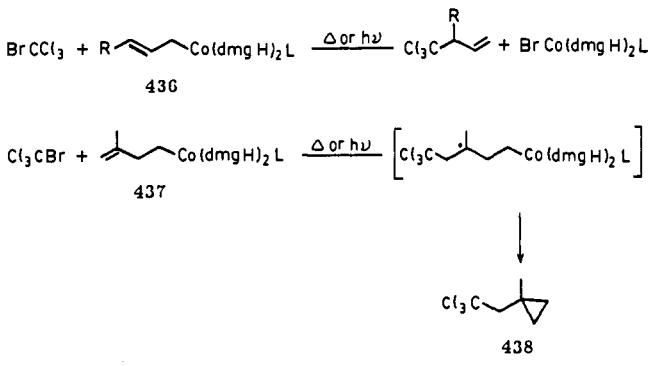
Scheme 116



Scheme 117



Scheme 118

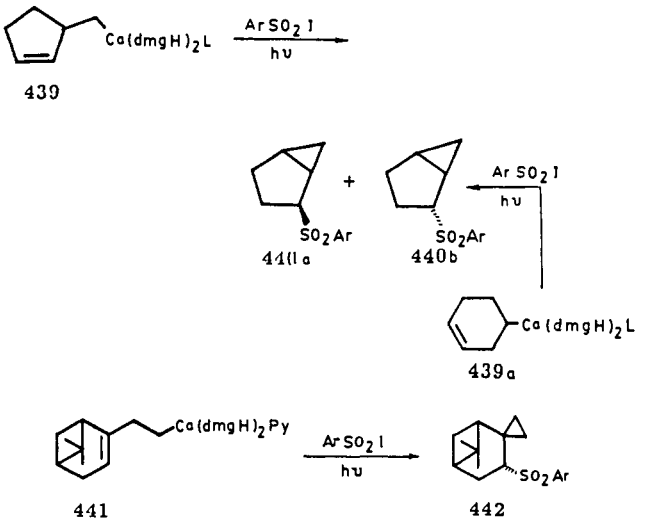


verted to either of the regioisomeric organocobalt complexes by suitably manipulating the reaction conditions (Scheme 125).

The cross-coupling of sp^2 carbon centers by the hydrocobaltation–radical addition–dehydrocobaltation sequence has been achieved by coupling of any electron-deficient alkene to a second alkene at either of their α- or β-sites leading to several[305,306] types of cross-coupled products **455** (Scheme 126).

Pattenden and co-workers have proposed a range of acylcobalt salophen compounds, precursors to the corresponding acyl radicals. Irradiation of de-aerated, refluxing solutions of the acylcobalt salophens **456** in methylene dichloride, in the presence of deactivated C=C bonds, similar to the reactions with alkylcobalt compounds, led to good yields of the corresponding[307,308]

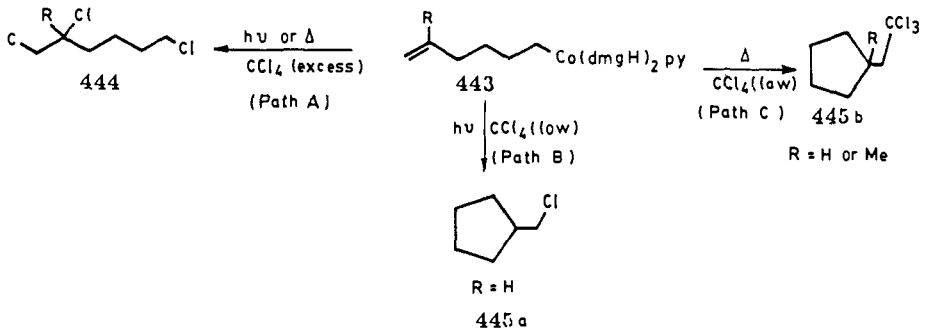
Scheme 119



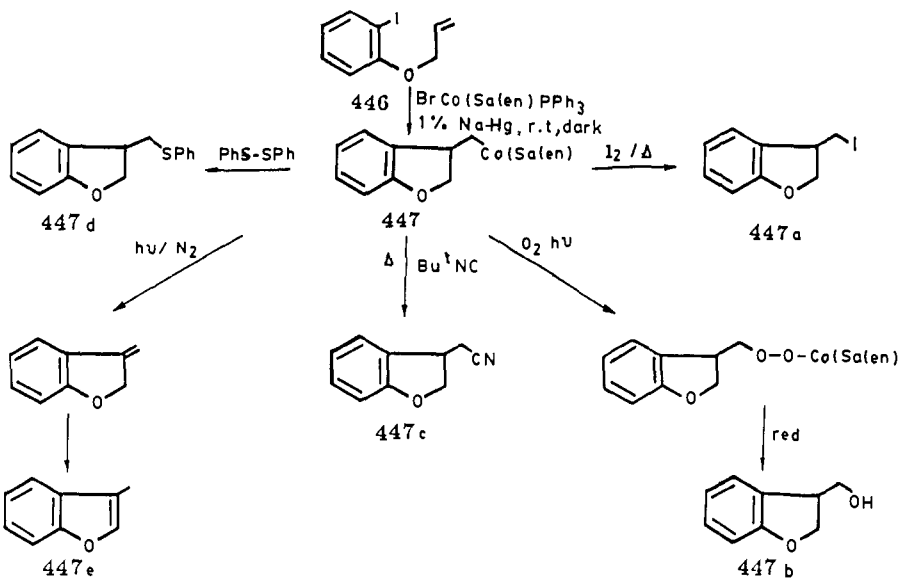
highly functionalized alkene products **453** and **457** resulting from the familiar: homolysis (to RCo)–addition–elimination (dehydrocobaltation) sequence (Scheme 127).

Branchaud and co-workers have developed an alkyl equivalent[320–329] to the Heck reaction via a novel cobalt-mediated radical–olefin coupling (Scheme 128). They have also achieved a novel cobaloxime-mediated radical alkyl–heteroaromatic cross-coupling, replacing a C–H in the protonated heteroaromatic with C–alkyl via anaerobic visible-light photolysis of 95% ethanol solutions of primary and secondary alkyl cobaloximes and pyridinium, quinolinium, 4-methylpyridenium, benzothiazolium *p*-toluenesulfonates (Scheme 129). They have recently demonstrated that radical alkyl–styryl coupling can be catalyzed by in situ generated cobaloxime[328] in the presence of zinc (Scheme 130). A variety of alkyl bromides can be coupled with styrene provided (a) the concentration of styrene is high, (b) there is a low catalyst concentration (pyridine + dimethylglyoxime + $CoCl_2$) to avoid premature β-H elimination, and (c) there is a low (50–100 mM) concentration of alkyl bromide. A mechanism has been proposed for the catalytic process using $Co^{II}(dmgH)_2$-py during the coupling of alkyl bromide with styrene (Scheme 131).

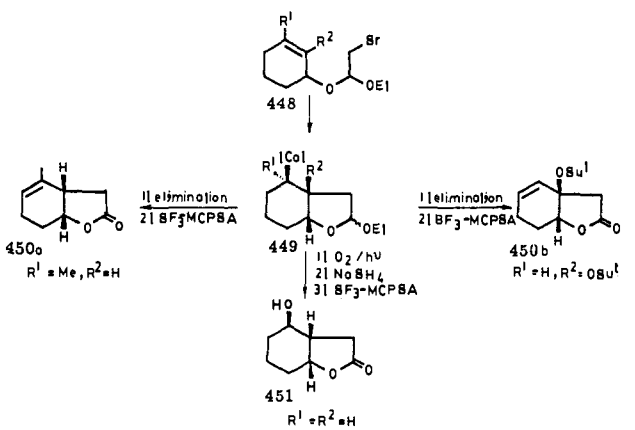
Scheme 120



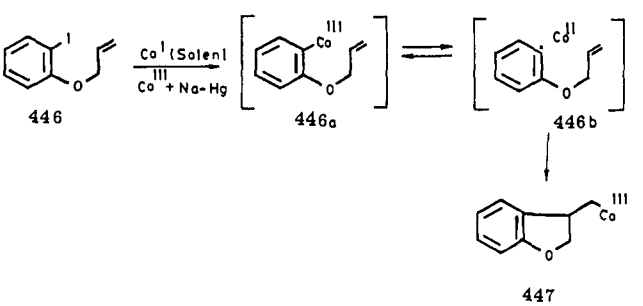
Scheme 121



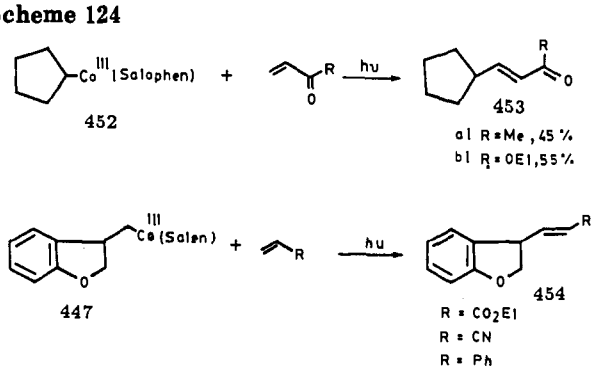
Scheme 122



Scheme 123



Scheme 124

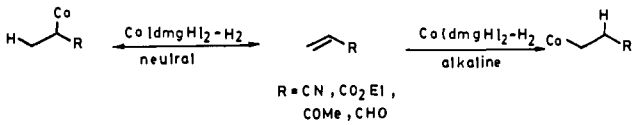


In another elegent study, Branchaud and co-workers have demonstrated an efficient cross-coupling between alkyl cobaloximes **458** and nitroalkyl anions **459** to give nitroalkanes **460** (Scheme 132).

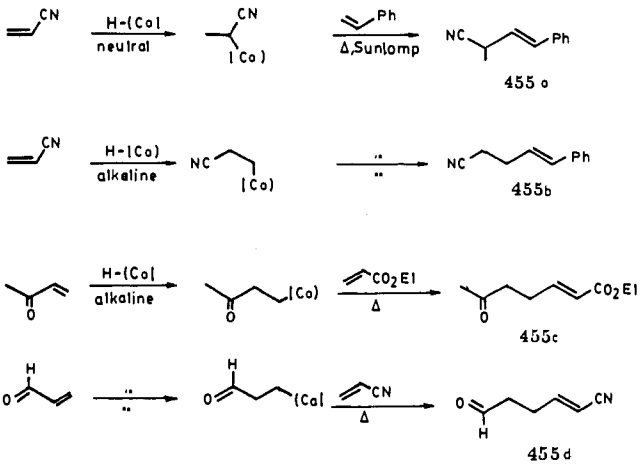
The alkyl–cobalt addition–elimination (cobalt group transfer) sequence has been used by Baldwin and Li during the enantiospecific synthesis of (−)-α-kainic acid and (−)-α-allokainic acid. These reactions proceed via the carbon-centered radicals which are generated from the corresponding[330–333] organocobalt(III) intermediate formed by a reductive process using **461** as the substrate (Scheme 133).

In a similar manner, these workers have also synthesized[333] a C-8 side-chain analog **462a** of domoic acid using a cobalt-mediated cyclization–elimination sequence on the iodide **462** (Scheme 134). They extended this methodology to an enantiospecific total synthesis[331] of acromelic acid A, a potent neurotoxin obtained from poisonous mushrooms. The cornerstone of their syn-

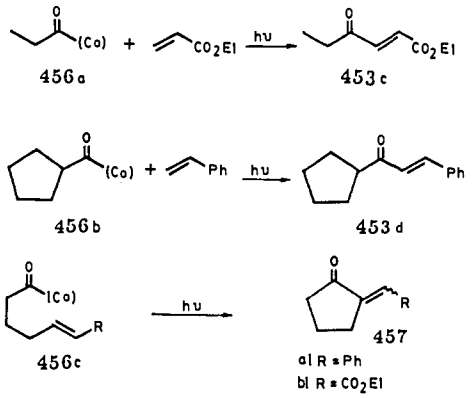
Scheme 125



Scheme 126



Scheme 127



thetic strategy was a cobalt-mediated radical cyclization of substrate which was prepared from the epoxy alcohol in optically pure form. Treatment of **463** with cobalt(I) afforded **463a** which was converted to the natural product by pyridone formation and routine functional group manipulation (Scheme 135).

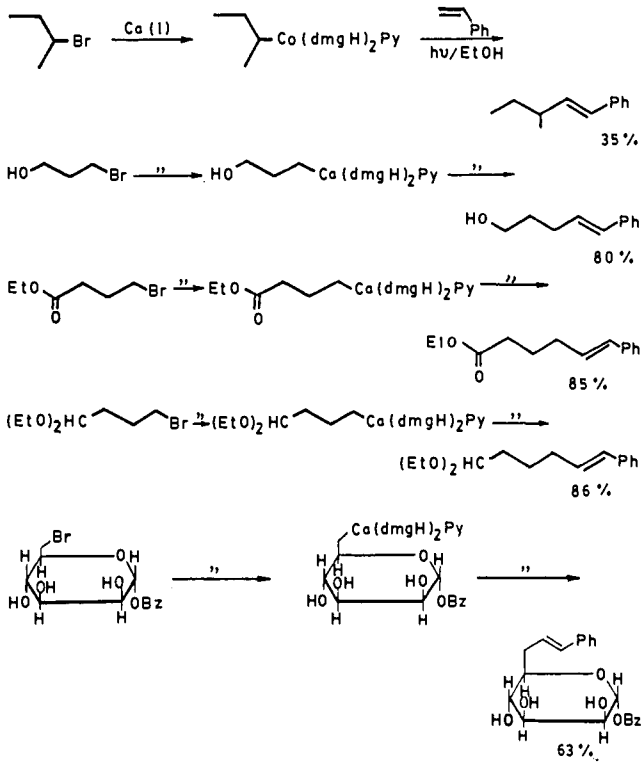
Pattenden and co-workers have shown that unsaturated carbonylcobalt salophens **464a–c** undergo homolytic cleavage producing[309] carbamyl radicals, which then undergo cyclization, accompanied by trapping (with Co^{II} or TEMPO) or dehydrocobaltation leading to functionalized β-, γ-, and δ-lactams **465a–g** (Scheme 136).

The key intermediate **465h** for the synthesis of (±)-thienamycin has been prepared by heating a solution of carbamylcobalt[310] salophen **464d** in toluene (Scheme 137).

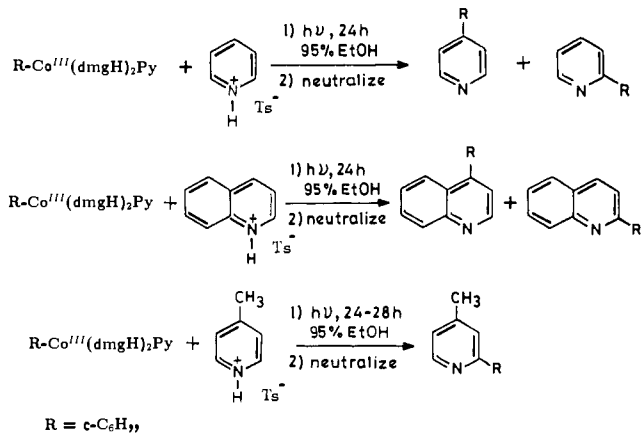
Epoxy olefins **466** can be converted to cycloalkanols **468** on treatment with cobalt(I) dimethylglyoxime using a sunlamp. These reactions proceed via the cyclization of the intermediate β-hydroxycobaloximes **467** which are produced by a nucleophilic[311,312] opening of epoxides with cobalt(I) (Scheme 138).

Pattenden and co-workers have recently developed a cascade cobalt group transfer reaction by effecting

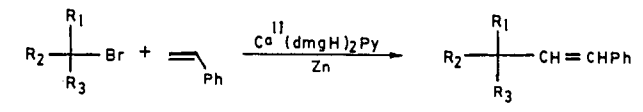
Scheme 128



Scheme 129



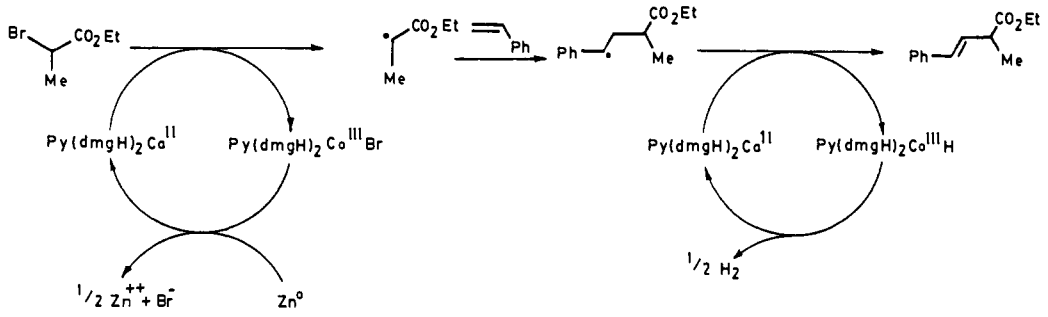
Scheme 130



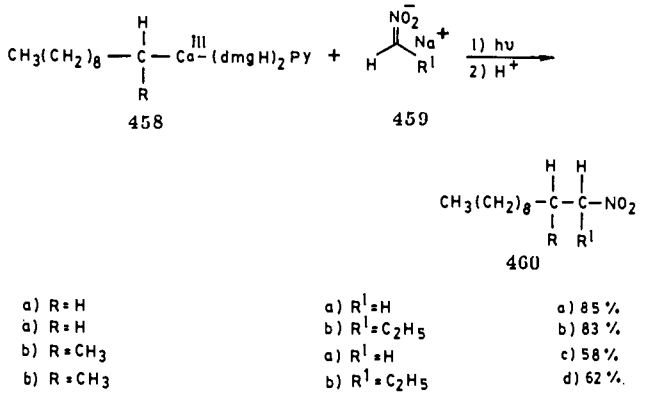
a) R_1=H; R_2=Me; R_3=CO_2Et	a) 60 %
b) R_1=R_2=H; R_3=CO_2Et	b) 20 %
c) R_1=R_2=Me; R_3=CO_2Et	c) 0 %
d) R_1=R_2=H; R_3=CO_2Et	d) 45 %
e) R_1=R_2=H; R_3=$(CH_2)_2CO_2Et$	e) 37 %
f) R_1=R_2=H; R_3=$(CH_2)_8CH_3$	f) 42 %

consecutive cobalt-mediated radical cyclization in a controlled manner, allowing trapping and interception of intermediate organocobalt intermediates leading to functionalized[319] mono and bicyclic systems. Treatment of a mixture of diastereomers of **469a** with cobaloxime resulted in exclusive 5-exo-trig cyclization leading to tetrahydrofuranyl methyl cobaloxime **470a** (Scheme 139). The later irradiation with ultraviolet sunlamp, was then found to undergo a second, equally

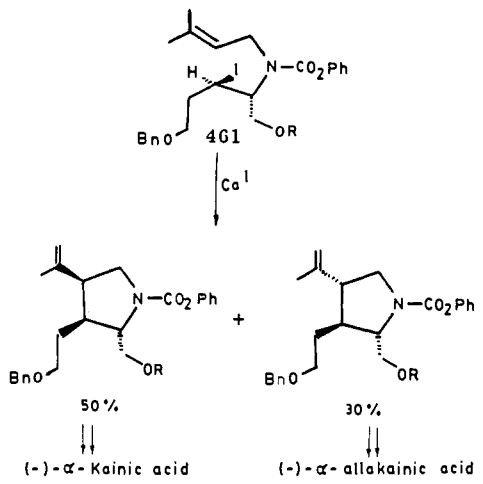
Scheme 131



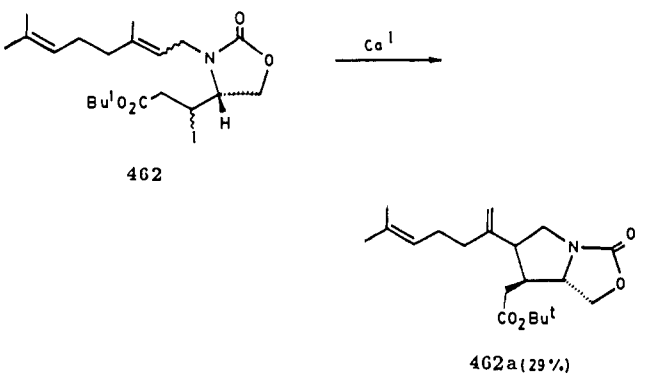
Scheme 132



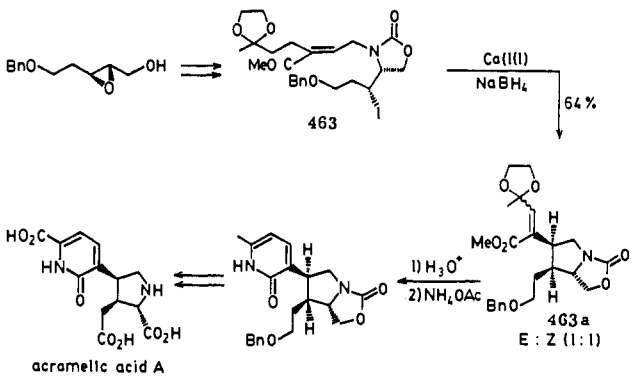
Scheme 133



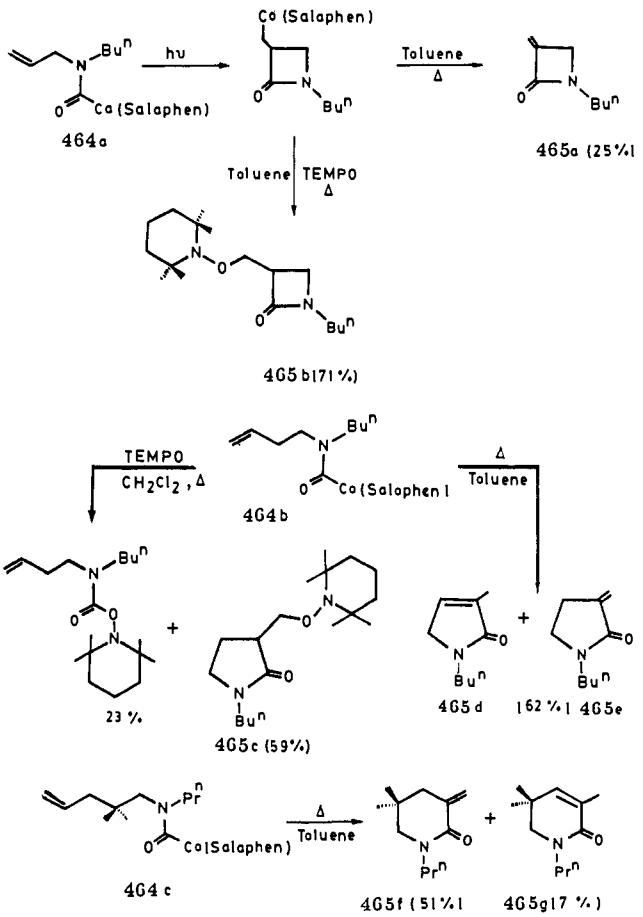
Scheme 134



Scheme 135

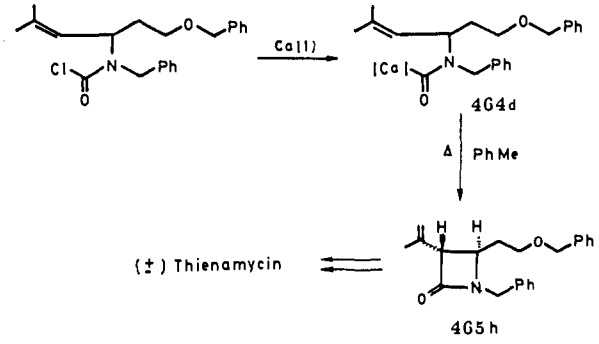


Scheme 136

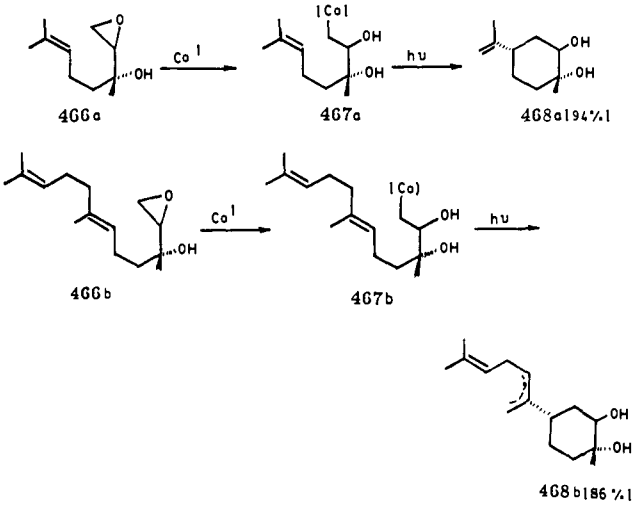


smooth, 6-exo-trig cyclization, which was accompanied by dehydrocobaltation, producing the trans-ring fused bicycle **471** in high yields. A similar treatment of vinyl iodide **469b** led to the formation of the intermediate cobalt salophen **470b** which on irradiation gave the corresponding bicyclic product **471b**. The tandem cyclization and radical trapping of substrate **469** which incorporates only monosubstituted carbon-to-carbon double bonds first led to the corresponding furan cobaloxime **470c**, however, the later irradiation un-

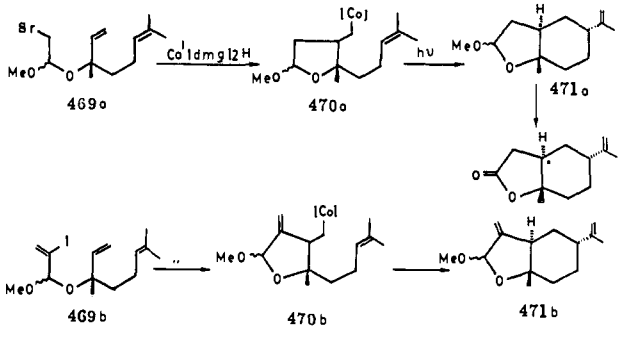
Scheme 137



Scheme 138



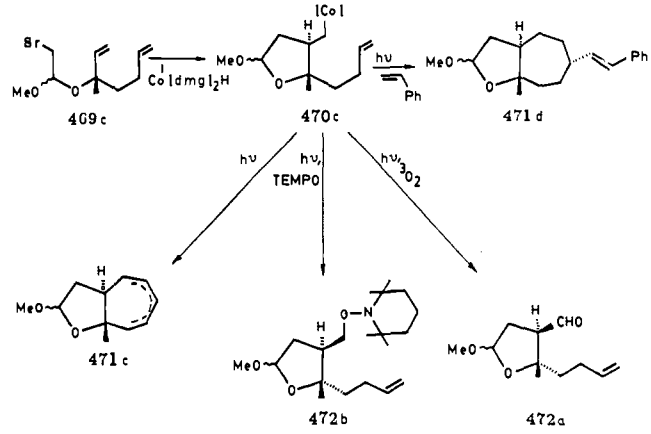
Scheme 139



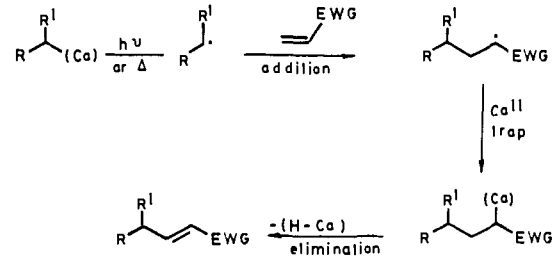
derwent exclusive 7-endo-trig cyclization to give the bicyclic product **471c** in good overall yield (Scheme 140). Hydrolysis and in situ oxidation of **471** in the presence of Jones reagent gave the bicyclic lactones. When a solution of cobaloxime **470c** was irradiated in the presence of oxygen, the only product isolated was the aldehyde **472a**, which is presumably formed by oxidative elimination involving a peroxycobalt intermediate. Irradiation of **470c** in the presence of tetramethylpiperidine oxide led to the substituted hydroxylamine **472b**. Similarly, irradiation of cobaloximes **470c** in the presence of styrene led to the product **471d** resulting from tandem 5-exo-7-endo cyclization with in situ product radical trapping by styrene terminating in dehydrocobaltation (Scheme 140).

The mechanism for the radical addition–elimination, promoted by alkyl- or acylcobalt reagent, can be explained by Michael addition followed by dehydrocobaltation (Scheme 141).

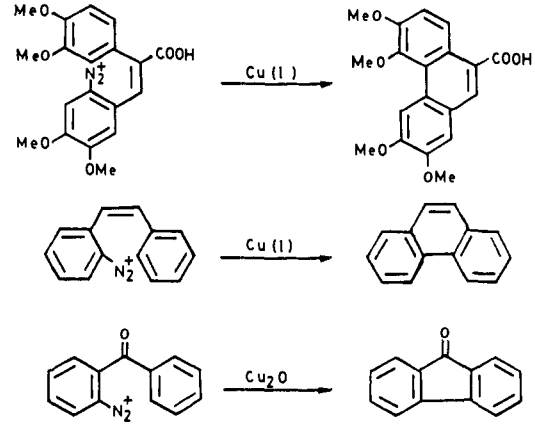
Scheme 140



Scheme 141



Scheme 142



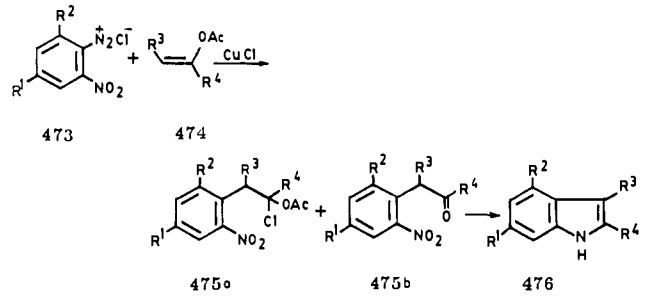
F. Copper

The classical Sandmeyer reaction, which involves copper(I) catalyzed dediazonization of arene diazonium salts, is believed to proceed[334–337] via a radical process. In their pioneering work Kochi and co-workers have demonstrated the Cu(I)Cl-mediated addition of arene diazonium compound to variety of olefins led to the formation[338–340] of arylethyl chloride. These reactions are believed to proceed via generation of radical by reductive processes which are terminated by chlorine atom transfer.

The Cu(I)-promoted intramolecular cyclization of arene diazonium compounds have led to the synthesis of a variety[341,342] of polycyclic aromatic compounds (Scheme 142).

Substituted indoles **476** can be prepared via Meerwein arylation involving a radical addition between 4- and 6-substituted 2-nitrobenzenediazonium chloride **473** and vinyl acetate **474** or vinyl bromide followed by a reductive cyclization of the resulting[343] intermediate **475** (Table 14).

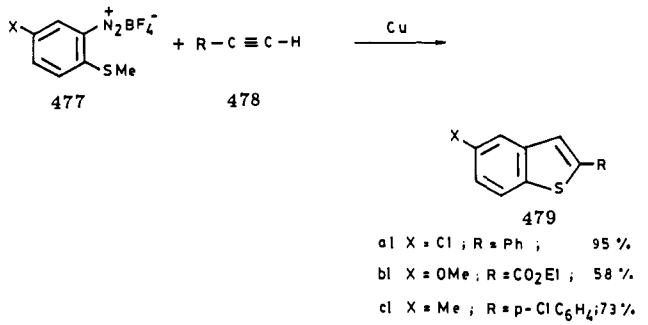
Table 14. Cu(II)-Promoted Synthesis of Indoles



473 474 475a 475b 476

				yield (%)	
R_1	R_2	R_3	R_4	475	476
H	H	H	H	79	90
MeO	H	H	H	66	83
Cl	H	H	H	53	74
CF_3	H	H	H	32	72
H	H	Me	Me	13	62

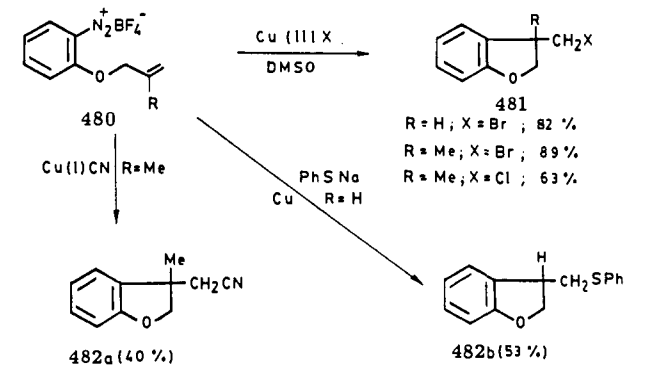
Scheme 143



477 478 479

a) X = Cl ; R = Ph ; 95 %
b) X = OMe ; R = CO_2Et ; 58 %
c) X = Me ; R = p-ClC_6H_4 ; 73 %

Scheme 144



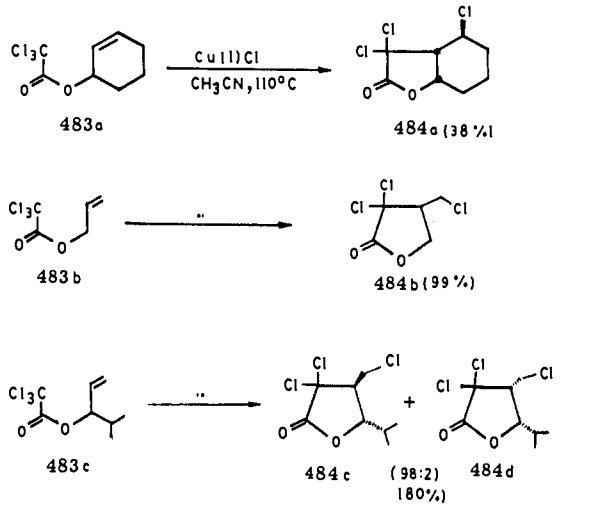
480 481 482a (40 %) 482b (53 %)

R = H ; X = Br ; 82 %
R = Me ; X = Br ; 89 %
R = Me ; X = Cl ; 63 %

The reaction of *o*-(methylthio)arenediazonium tetrafluoroborates **477** with alkynes **478** in the presence of freshly prepared Cu powder leads to the formation of 2-substituted benzo[*b*]thiophenes **479** via an annelation process[344] involving an S_Hi substitution at sulfur (Scheme 143).

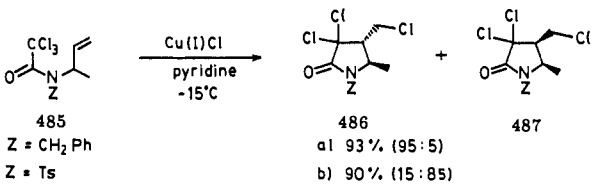
Beckwith and Meys have elegantly demonstrated the synthesis of dihydrobenzofurans **481** and **482** by radical cyclization of arenediazonium tetrafluoroborates **480** with copper(II) bromide or chloride. They have also shown that these radical cyclizations can be carried out[345,346] in the presence of copper(I) cyanide–pyridine or benzenethiolate, leading to the incorporation of the cyanide (i.e. **482a**) or the thiolate (i.e. **482b**) group respectively in dihydrobenzofurans (Scheme 144). The mechanism for the Cu(I)-promoted radical formation from aryl diazonium salts follows a radical-chain mechanism. Such a mechanism has salient features

Scheme 145



483a 484a (38 %) 483b 484b (99 %) 483c 484c (98:2) 484d (80 %)

Scheme 146



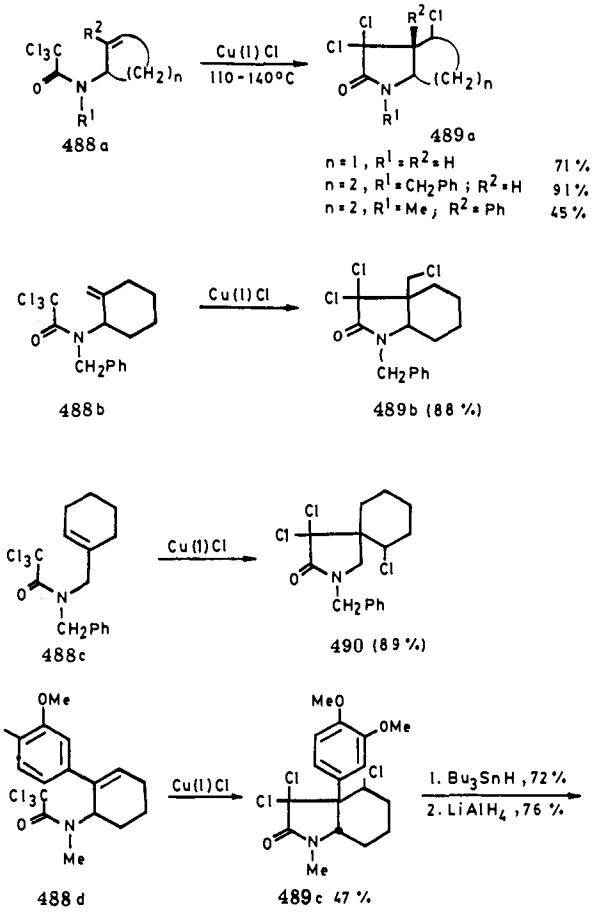
485 a) Z = CH_2Ph b) Z = Ts 486 a) 93 % (95:5) b) 90 % (15:85) 487

similar to those originally postulated by Kochi for the Sandmayer and Meerwein arylations.

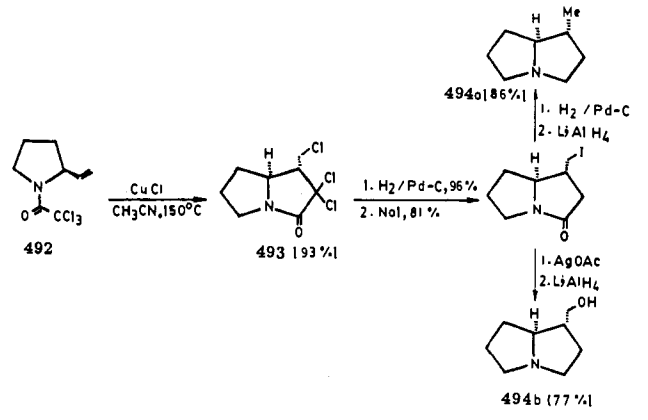
Ito and co-workers have shown that cuprous salt catalyzed the cyclization of allyl trichloroacetal to trichlorinated γ-lactones by way of an intramolecular atom-transfer radical[347-350] cyclization. The stereochemical outcome was dependent on the structure of the starting trichloroacetates. 2-Cyclohexyl trichloroacetate (**483a**) gave the corresponding cis-fused bicyclic lactone **484a**, whereas the reaction of acyclic trichloroacetates **483b,c** derived from 1-butene-3-ol and its analogs generally provided the trans-substituted lactones **484b,d** (Scheme 145). The stereoselectivities observed at −15 °C in Cu(I)-catalyzed cyclization of N-substituted *N*-(1-buten-3-yl)trichloroacetamides **485** were dependent on the protecting group. Cyclization of either the *N*-benzyl- or *N*-methyl-*N*-allyltrichloroacetamide **485a** afforded the corresponding trans isomer **486a** predominantly (trans/cis = 7:3–9:1) (Scheme 146). On the other hand, the cyclization of *N*-tosyl, *N*-mesyl, *N*-Cbz, or *N*-*t*-Boc analogues **485b** provided the corresponding cis isomers **487b** with good stereoselectivity (trans/cis = 2:8–1:9). A similar effect is also observed for the $RuCl_2(PPh_3)_3$-catalyzed reaction of trichloroacetamides. Similarly cyclization of certain *N*-allyltrichloroacetamides **488** provided a stereoselective preparative method for several bicyclic lactams **489** which possess the pyrrolidine alkaloid skeletons. Accordingly, mesembrane (**491**) has been synthesized in good yields by Cu(I)-catalyzed cyclization[350] of *N*-allyltrichloroacetamide **488d** (Scheme 147).

The synthesis of pyrrolidizine alkaloids pseudohaliotridane (**494a**) and trichelantamidine (**494b**) have been achieved via 5-exo-trig cyclization of a radical derived from homolysis of C–Cl bond in (2*S*)-*N*-(trichloroacetyl)-2-vinylpyrrolidine (**492**) by a copper(I)-catalyzed cyclization (Scheme 148). This cyclization provides[351] a diastereoface selection in an atom-transfer annulation,

Scheme 147

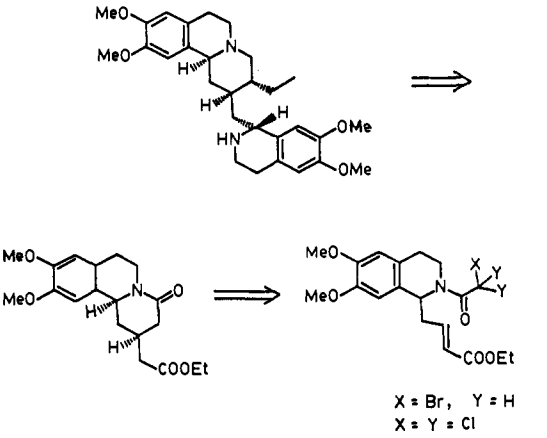


Scheme 148

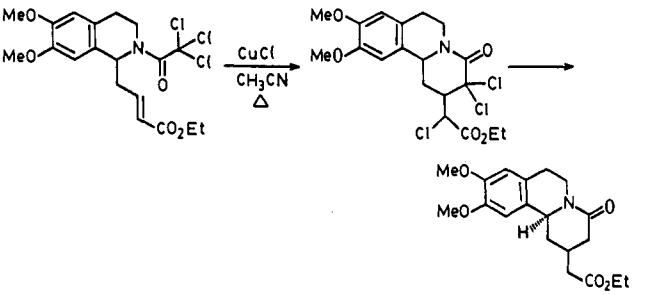


which induces the chirality present at C-2, affording only one diastereomer **493** due to the steric hindrance of the pyrrolidine nucleus. Yamazaki and co-workers have achieved[352] the formation of a six-membered ring by halogen atom transfer cyclization as a model reaction toward the synthesis of alkaloid emitine (Scheme 149). Thus the treatment of trichloroacetamide with CuCl

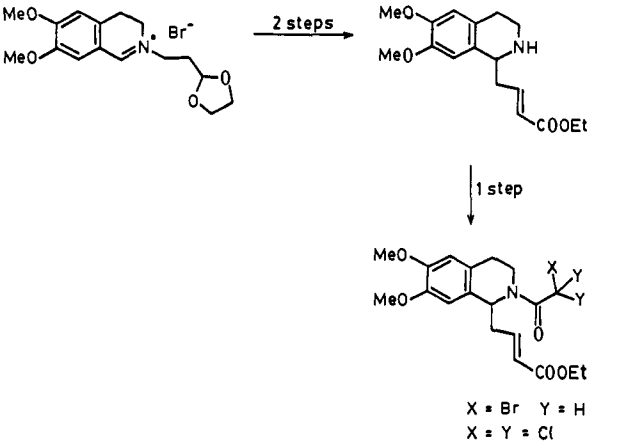
Scheme 149



Scheme 150



Scheme 151

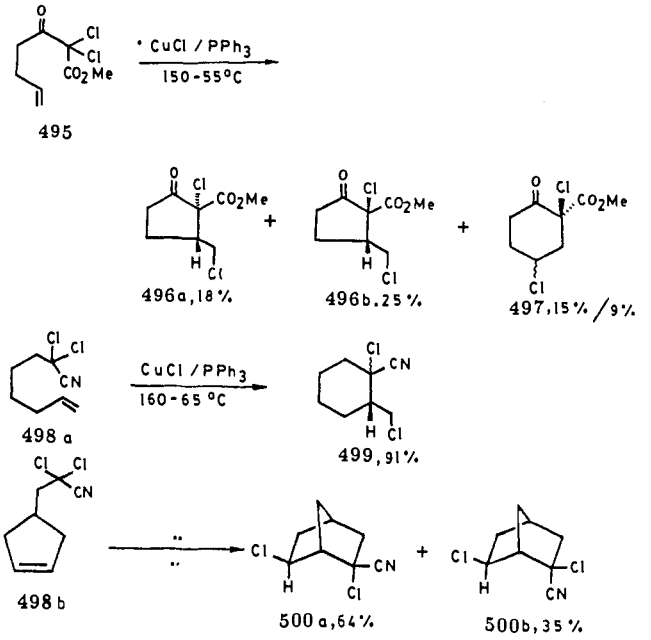


in CH_3CN in a sealed tube at 140 °C formed the intermediate by a 6-exo radical cyclization. Reductive removal of the chlorine atoms afforded the key precursor tricyclic lactam ester in 93% yield as an 82/18 mixture of α and β epimers (Scheme 150). The synthesis of radical precursor is shown in Scheme 151.

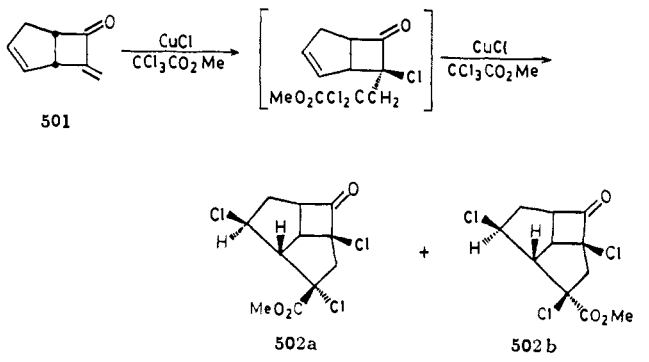
The cyclization of α,α-dichloro-β-keto esters **495** with CuCl–PPh_3, proceeds to give a mixture of exo products **496a** (18%), **496b** (25%), and two endo cyclization[284] products **497** (15%/9%). α,α,-Dichloronitriles **498** also undergo cyclization with Cu(I) catalyst to give cyclohexane **499** or norbornane α-chloro nitriles **500**. Since these nitriles can be hydrolyzed to ketones, the overall transformation is equivalent[285] to acyl radical/alkene addition (Scheme 152).

Copper(I)-catalyzed addition of CCl_3CO_2Me to α-methylidenecyclobutanone **501** gives 2*H*-cyclobuta[*cd*]-pentalene **502** by a successive inter- and intramolecular radical addition. The intramolecular cyclization[353]

Scheme 152



Scheme 153



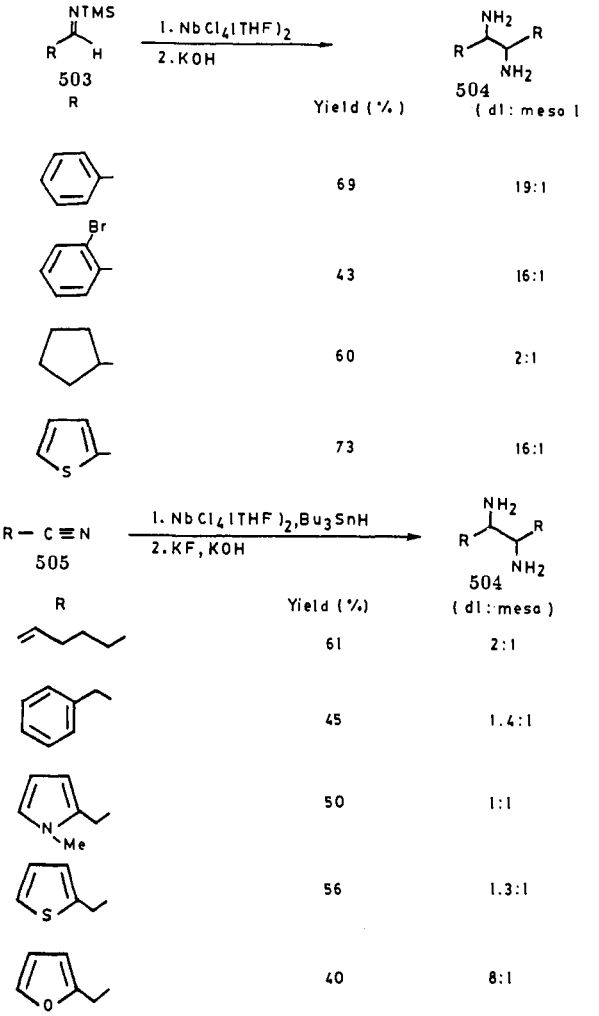
takes place by trans addition of the *endo*-CH_2CCl_2-CO_2Me moiety across the cyclopentene double bond (Scheme 153). The mechanism for these reactions is proposed by a initial electron transfer from Cu(I) to the substrate leading to the formation of a dichloromethane radical which undergoes addition to the double bond to generate a new radical and the process is terminated by a halogen atom transfer.

G. Niobium

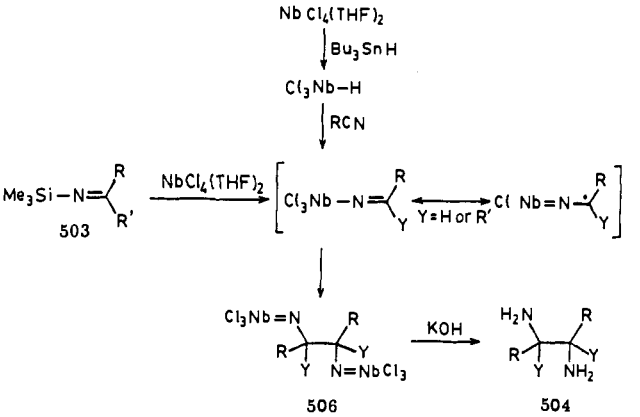
The free-radical reactions promoted by niobium are rare, however, a recent elegant work of Pederson and Roskamp have demonstrated the use of d^1 niobium reagent during[353] the coupling of imines or nitriles. Thus, $NbCl_4(THF)_2$ has been used for the coupling of *N*-(trimethylsilyl)imines **503** or nitriles **505** to give the corresponding vicinal diamines in good yield (Scheme 154).

The mechanism for the vicinal diamine synthesis has been explained by considering the resonance structure for a simple d^1 *N*-metal imine derivative (A and B). The dimerization of metal-protected α-amino radical (i.e. B) would lead to a diimido compound **506** which upon hydrolysis gives the vicinal diamine **504**. The generation of niobium imines directly from nitrile insertion can be achieved by reacting the latter with

Scheme 154



Scheme 155

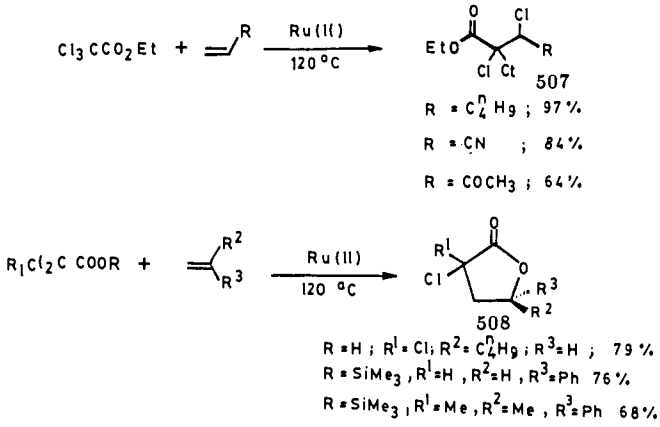


niobium(IV) hydride C which is generated from Bu_3SnH reduction of $NbCl_4(THF)_2$ (Scheme 155).

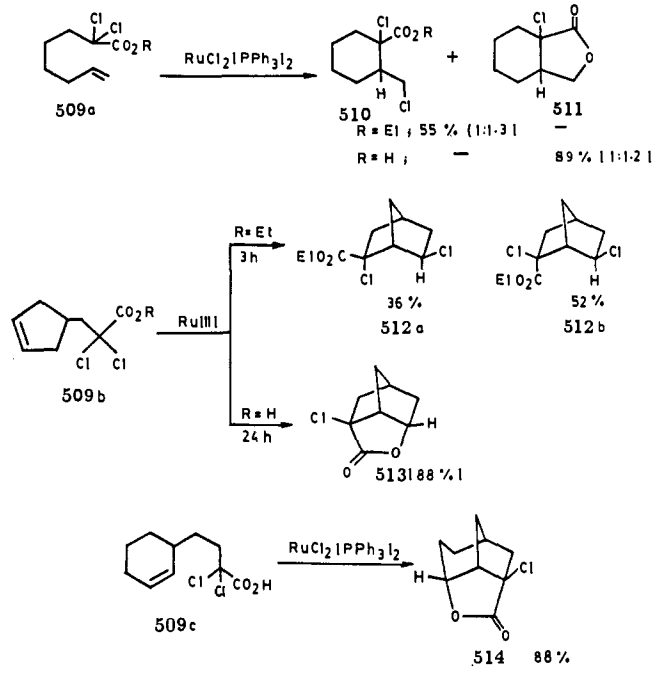
H. Ruthenium

The synthetic utility of the radical reactions brought about by interaction of dichlorotris(triphenylphosphine)ruthenium(II) with an organic halide has found widespread use in organic synthesis. The Ru(II)-catalyzed addition of polychloroacetic acid with 1-olefins gives high yields of adducts. This reaction is particularly useful for additions involving easily polymerizable olefins such as styrene, methyl methacry-

Scheme 156



Scheme 157

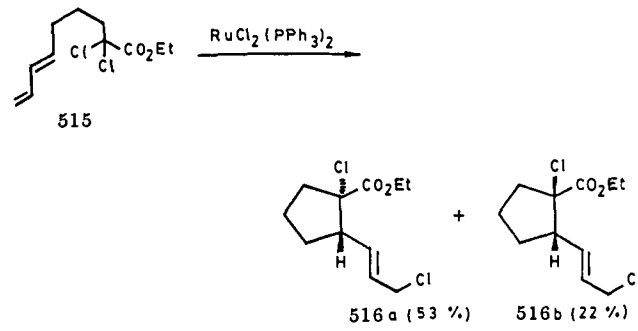


late, etc. Thus, Matsumoto and co-workers have shown that trichloro- and dichloroacetic esters and acid undergo efficient addition[354-359] to variety of 1-olefins in the presence of Ru(II) complex to give the corresponding chloroesters **507** and lactones **508** (Scheme 156).

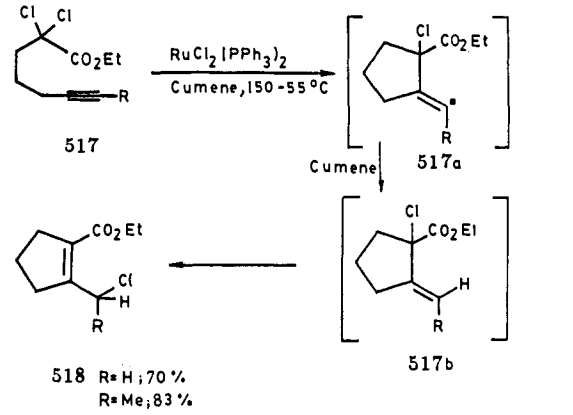
Ru(II)-catalyzed intramolecular version of these reactions has been recently developed by Wienreb and co-workers into a useful[283-266] synthetic methodology. Several unsaturated mono- and di-α-halo esters and acids **509** can be efficiently transformed via Kharasch cyclization to γ-halocarboxyl and γ-lactone carbocycles **510** and **511** via exo closure of a 5-hexenyl-type radical intermediate (Scheme 157). The same transformation can also be performed by an iron complex as mentioned in section II.D. This cyclization methodology can also be used to produce bridged carbocyclic compounds **512** and **513**. It is also possible to synthesize the bridged [3.2.1] system **514** from the corresponding α,α-dichloro acids **509c** (Scheme 157).

The Ru(II)-catalyzed intramolecular Kharasch addition to 1,3-diene **515** gave only 1,4-addition products **516** with *E* double-bond geometry (Scheme 158).

Scheme 158



Scheme 159

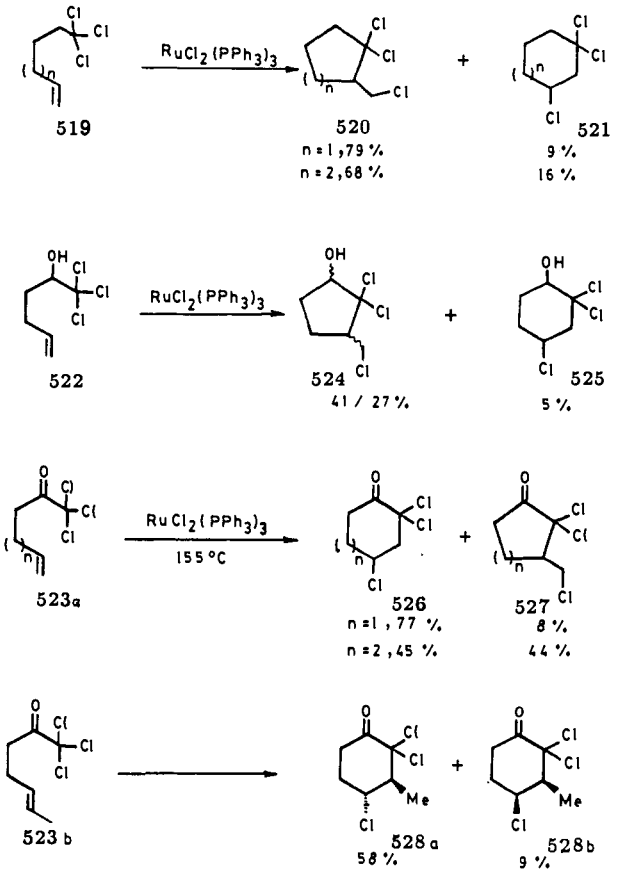


The Ru(II)-catalyzed intramolecular cyclization of α,α-dichloro ester alkynes **517** in the presence of toluene or cumene do not yield any Kharasch product, but rather α,β-unsaturated γ-chloro esters **518** are produced in good yields. These reactions are believed to proceed via a hydrogen-atom abstraction by vinyl radical **517a** followed by a rearrangement of the double bond using **517b** (Scheme 159).

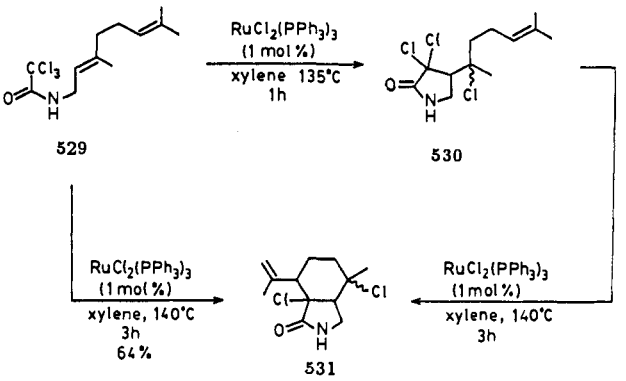
(Trichloromethyl)olefins (**519**) undergo intramolecular cyclization to the corresponding products **520** and **521** obtained by an exo closure. Similarly, trichloromethyl alcohols **522** and ketones **523** are efficiently converted to the corresponding cyclic products **524**–**528** by Ru(II) complex. A reversal of regiochemistry is observed during the cyclization of trichloromethyl ketones **523b**, since cyclohexanones **528** rather than cyclopantanone are obtained as the major product (Scheme 160). Double cyclization of *N*-geranyltrichloroacetamide (**529**) afforded bicyclic lactam **531** as a mixture of two diastereomers. This transformation is interpreted as two independent reactions occurring stepwise (Scheme 161). The initial ruthenium-catalyzed monocyclization of **529** affords **530**, whereas the second reaction from **530** to **531** proceeds via ruthenium-catalyzed addition of a carbon–chlorine bond at the α position to the olefinic bond. The precursor **533** for the synthesis of (±)-pretazettine (**532**) has been synthesized[360] by chlorine-atom transfer cyclization of a chloroacetamide **534**. Treatment of **534** with 20 mol % of $RuCl_2(PPh_3)_3$ afforded the lactam **535** in 57% yield. Subsequent sulfide oxidation followed by Pummerer rearrangement/hydrolysis produced ketolactam **536**. This was dehydrochlorinated, reduced, and acylated to give the precursor **533** (Scheme 162).

Kamigata et al. have developed a novel Ru(II) catalyzed reaction[361-363] of alkenylsulfonyl chlorides

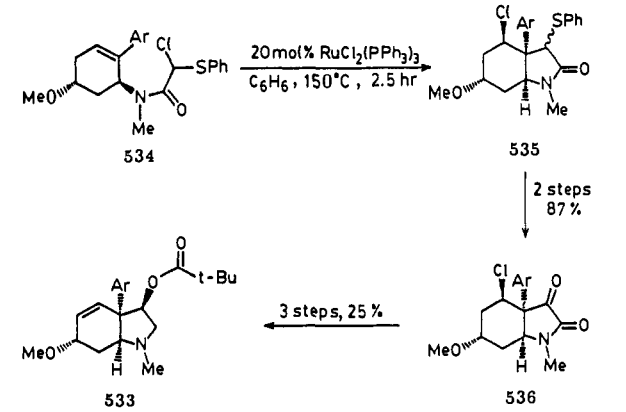
Scheme 160



Scheme 161

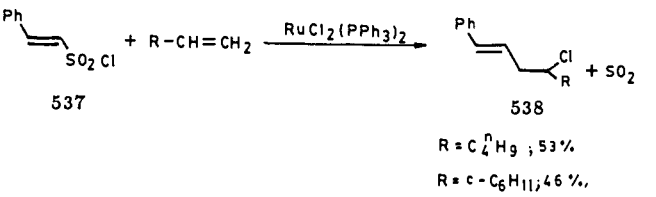


Scheme 162

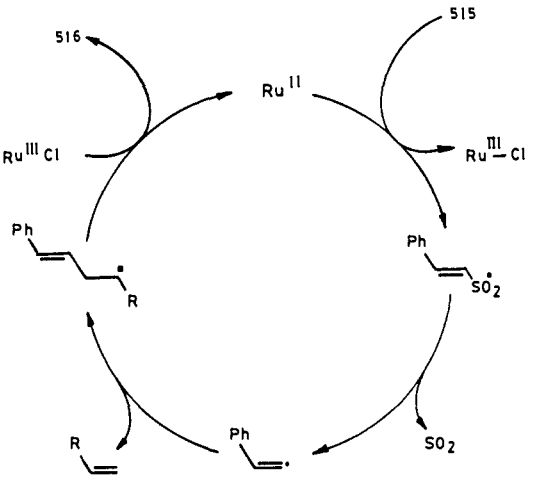


with olefins. The reaction between (*E*)-2-phenylethanesulfonyl chloride (**537**) with alkyl olefin gave (*E*)-4-alkyl-4-chloro-1-phenyl-1-butene (**538**) with extrusion

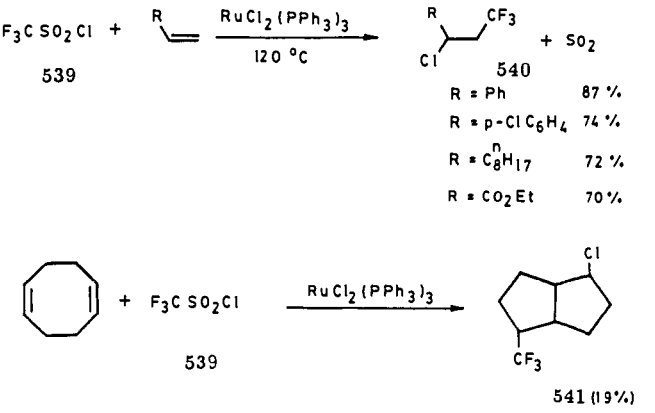
Scheme 163



Scheme 164



Scheme 165



of sulfur dioxide (Scheme 163). The reaction with vinyl arenes follows a different[361] course and (*E*,*E*)-1,4-diaryl-1,3-butadienes are formed in high yields.

Mechanistically the above reactions are very interesting as the sulfonyl radical formed by the interaction of (*E*)-2-phenylethenesulfonyl chloride and Ru(II) catalyst releases the sulfur dioxide to form vinyl radical. The vinyl radical reacts with the alkyl olefin to give the radical intermediate which abstracts the chlorine atom from $Ru^{III}Cl$ to afford the final product (Scheme 164).

The perfluoroalkylation of acyclic and cyclic alkenes by perfluoroalkanesulfonyl chlorides **539** have been carried out in the presence of Ru(II) catalyst. The addition reactions proceeded smoothly[363] with extrusion of SO_2, in alkenes possessing an electron-donating or an electron-withdrawing group, at 12 °C, to give the corresponding chloroperfluoroalkylated compounds **540** and **541** in high yield (Scheme 165).

The mechanism of this reaction is similar to the one proposed for the alkenylsulfonyl chloride addition to olefins.

IV. Conclusion

The synthetic potential of these findings is beginning to show tremendous promise as evidenced from its application in the synthesis of complex organic molecules. The pioneering efforts of Heiba and Corey, and lately by Snider, has clearly demonstrated that manganese(III)-promoted oxidative free-radical reactions are emerging as an outstanding methodology for the construction of complex cyclic structures. Copper(II)- and iron(III)-promoted oxidative reactions of aromatic substrates, carbanions, or silyl enol ethers show good promise as a viable tool during the construction of complex organic compounds. Initial studies of Hirao and co-workers indicates that vanadium-promoted radical reaction of carbonyl compounds may potentially be a useful route to carbon–carbon bond formation under mild conditions. McMurray's pioneering efforts have already established titanium-mediated bond formation as a truly outstanding methodology whose utility is clearly seen in the synthesis of a variety of complex natural products. It is interesting to note that this elegant reaction has found its use during the strategy-level bond construction as evidenced in the results compiled in the table. Sheffold's pioneering efforts culminated in establishing vitamin B_{12} as a versatile catalyst in promoting bond formation on sensitive molecules and the application of this strategy in the synthesis of compounds incompatible with basic or acidic conditions has clearly illustrated the uniqueness of this approach. Pattenden's efforts using organocobalt complexes has laid a solid foundation for exploitation of this remarkable reaction via cobalt group transfer reactions. The application of this novel reaction has already been demonstrated by Baldwin and Li. Nagashima's work on copper(I)-catalyzed cyclization of trichloroacetamides has opened new vistas for exploitation for the synthesis of alkaloids and related molecules. An initial progress made in ruthenium-catalyzed atom transfer cyclization also holds good promise for future exploitation in synthesis. Apart from these well-established methods there are also some potentially useful methodologies based on titanium-promoted alkene–epoxide coupling, cobalt-catalyzed oxidative coupling of aldehydes, and niobium-promoted vicinal diamine synthesis, whose application to organic synthesis awaits exploitation.

It has become quite evident from the foregoing sections that the transition metal-promoted radical reactions are valuable additions to the repertoire of the new synthetic methodology. This development is quite significant and has far-reaching consequences in the domain of the synthesis of complex organic molecules. Clearly a new era has dawned upon the frontiers of organic synthesis.

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VI. References

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