Pergamon

Tetrahedron Vol. 51, No. 28, pp. 7579-7653, 1995

0040-4020/95 $29.00+0.00

0040-4020(95)00434-3

TETRAHEDRON REPORT NUMBER 376

Redox Induced Radical and Radical Ionic Carbon-Carbon Bond Forming Reactions

Peter I. Dalko

Laboratoire de Synthèse des Substances Naturelles,*
URA CNRS N°478
Université Paris XI, Bât. 410,
91405 Orsay Cedex, France.

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* Current address: Department of Chemistry, Harvard University, 12 Oxford Street, Cambridge, MA 02138, USA.

Dedicated to Professor Sir Derek H. R. Barton, F.R.S.

I. Introduction

Electron transfer (ET) is a basic phenomenon in chemistry that provides the ground for mechanistic arguments of molecular reactivity. A couple of decades ago, electron-pair centred mechanisms were considered as the exclusive approach for chemical reactions. This picture is now changing: with the advent of electron transfer chemistry, there is growing evidence that the electron-pair mechanism is more an extreme case than a general process. An important reason why one electron processes have not been postulated in the past is because it is often difficult to identify the radical or radical ionic intermediate[1]. Recent techniques, however, have allowed the consideration of one-electron transfer pathways in a number of reactions. These reactions fall into one of two categories:

(1) It is believed that one electron transfer is implicated in the vast majority of chemical reactions to a greater or lesser extent. A large number of "established" polar reactions have been shown to proceed in fact by the single electron transfer (SET) pathway[2]. In these cases electron transfer occurs spontaneously between diamagnetic reagents. The classical S_N2 substitution[3] or the Wittig reaction[4] may be viewed in several cases as proceeding by a single electron-transfer. Evidence has been provided that aromatic ketones, aldehydes and esters can react by a SET process in several instances: in AlH_3, and $LiAlH_4$ reductions; in the Meerwein-Ponndorf-Verley reduction[5]; in the aldol condensation[6]; in the Cannizzaro reaction and the Claisen condensation[7]. In a number of cases, anions can be powerful one electron reductants, and thus initiate radical reactions. Thiol anions are notoriously powerful nucleophiles but also strong reducing agents owing to the facile $RS^- \rightarrow RS\cdot$ transformation[8]. Also, Me_3Sn^- is a powerful one-electron donor, producing alkyl radicals upon reaction with alkyl halides[9]. Diaryl phosphide anions of alkali metals (Li, Na, K) also react with aryl and alkyl halides *via* an electron transfer mechanism[10]. Lithium-alkyl derivatives, enolates and cuprates (R_2CuLi) appear to act as one electron donors[11] as well. Charge transfer polymerisation has also become an important process. While the vast majority of organic ET reactions proceed *via* the inner sphere electron transfer mechanism (*vide infra*), complexation patterns play an important role. It is not surprising therefore, that many Lewis acids were found to promote one electron transfer (e.g. $ZnCl_2$, $Mg(ClO_4)_2$, $AlCl_3$, and BF_3)[12]. On the other hand, it would be interesting to examine how general the Brønsted and Lewis acids are in promoting one electron transfer reactions[13].

In these reactions, the one electron mechanism cannot be assigned to a specific process. The mechanism (polar *vs* SET) can change within the reaction type depending on the nucleophile-electrophile or donor-acceptor couple, and also, but to a lesser extent, on the solvent. In other terms, the generality of this type of mechanism is always in question. Moreover, the transient free radical character of the reacting molecules can be hardly exploited, because the diradicals produced undergo fast recombination.

(2) It is in agreement with empirical observations that chemical interactions between paramagnetic and diamagnetic species, particularly when the interacting nuclei have substantial electronegativity differences, often occur by one electron transfer. There are a great number of stable paramagnetic molecules[14], which are known to be potent one electron transfer agents. This type of reaction may result in the formation of synthetically useful, reactive high spin organic intermediates. These intermediates undergo typical radical / radical ionic reactions. A plethora of such electron transfer *mediated* organic reactions have been developed in the last decade.

It is easy to anticipate the nature of the electron transfer mechanism (i.e. one or two electron transfer) in redox mediated reaction systems, at least in theory, by knowing the initial and final degree of oxidation level of the electron transfer agent. If the change in oxidation state is one, the reaction sequence involves a single electron transfer in at least one of the steps. In such reactions, a one electron mechanism is predictable. It is also believed that the electron transfer mechanism in the same type of reaction is far more general (in contrast to case (1)). However, if the change in the oxidation state of the electron transfer agent is different from one in the overall reaction, a SET process cannot be excluded. Of course, this prediction does not give information about the nature (radical or polar) of the crucial coupling step (in our case the C-C-bond forming step).

Such redox reactions are among the first ones that students meet in introductory chemistry: the Fehling test and the silver mirror reactions. It was believed for a long time, but only recently demonstrated, that reactions of alkyl or aryl halides with metals (Frankland, Grignard, Rochow, Wurtz reactions, or Ullmann coupling for example)[15] proceed *via* one electron transfer mediated free radical pathways. There is a disagreement, however, whether these one electron transfer intermediates (i.e. radicals or radical anions) are adsorbed on the metal surface or diffuse freely in solution. The Clemmensen[16] and Birch reductions also proceed *via* radical anionic intermediates. Different biomimetic oxidations and nitrogen conversion reactions take place *via* well documented one electron transfer pathways. These one electron transfer reactions, however, occur rarely with concomitant formation of a new carbon-carbon bond. Other typical one electron reactions are the acyloin condensation and the Kolbe electrolysis, discovered nearly a century and a half ago, which represented important steps in the formation of C-C bonds *via* radical / radical ionic intermediates.

In the last few years, many reviews and monographs have appeared on this topic, covering a broad area of chemistry[11, 17-26, 48]. Surprisingly, little attention has been given to the one electron transfer mediated C-C bond forming reactions in the condensed phase and in the dark, and those in which no electrochemical methods were used. Undoubtedly, these reactions have an enormous impact on chemo- and stereoselective reactions used in synthesis. Addition of one electron to a molecule usually results in an increase of its reactivity because the bond dissociation energies in radical anions are much smaller than those in the corresponding neutral molecules[27]. In addition, many of the radical cationic reactions were found to proceed on a nearly flat activation energy hypersurface, allowing fast and selective processes. Under mild conditions, the electron transfer can be directed selectively from the most ionisable functionality in a multifunctional molecule. Coordination patterns also play an important role in this selectivity, due to the "intimate" nature (inner sphere ET) of most electron transfer steps in organic chemistry. Strategically, in multistep organic sequences, a frequently mentioned advantage of radical/radical ionic reactions is their capacity to generate reactive intermediates with inverted polarity (umpolung). Recent developments of mild reagents, reaction conditions and new methodologies promise forthcoming breakthroughs in this area. Their utility in synthetic strategies is only now just beginning to be exploited.

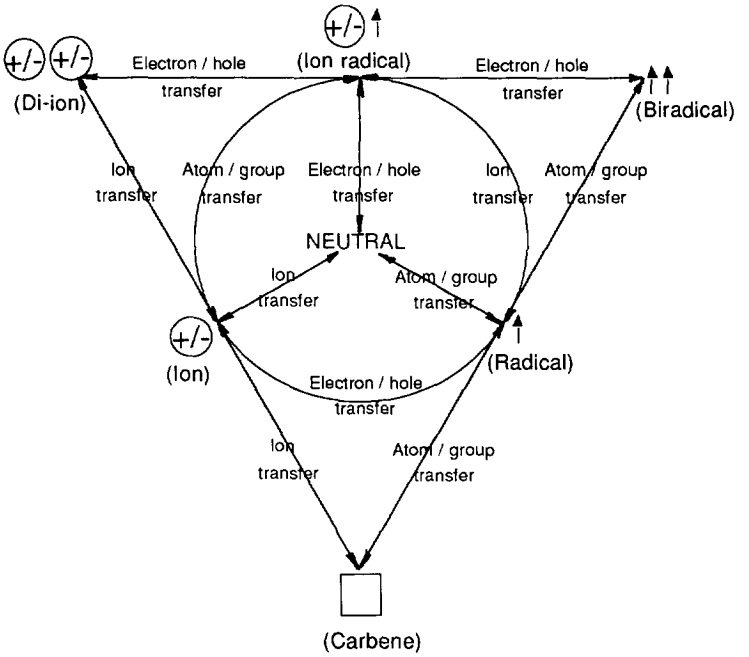
The subject of this review is to give an account of redox mediated radical/radical ionic reactions in the condensed phase, and in the dark, leading to carbon-carbon bond formation. This review aims to provide a comparative study of the different methods which allow similar transformations. Due to space considerations, the goal of this review is more to describe the general synthetic methodology than to provide a detailed account of each reaction. The paper thus discusses the proposed mechanisms and attempts to illustrate the usefulness of the reaction by providing preparative applications.

Characteristics of redox induced C-C bond forming reactions

In a multicomponent reaction, in general, distinction between polar, ligand coupling, group/atom- and electron transfer mechanisms is difficult[3c-e, 11]. There is more evidence that in many (if not in all) organic reactions these mechanisms are in competition with each together, to a greater or a lesser extent. The "pure" polar or electron transfer/radical mechanisms in this context, are the extreme cases. The question is to establish which is the predominant pathway.

The probability of a SET reaction depends on the one electron donor ability of the reductant (oxidation potential), the electron acceptor ability of the oxidant (reduction potential), on the steric factors of the reactants and, to a lesser extent, on the nature of the solvent[3d, 34]. Various experimental methods have been applied so far to find evidence for the ET process[11, 28-33].

Scheme 1 shows the possible transformations which an electronically neutral molecule in the ground state may undergo. The graph is highly symmetric. According to this graph, an electronically neutral molecule and also every reactive intermediate may undergo electron transfer, as well as homo- and heterolytic bond dissociation or association. In the points of intersection there are the products of every transformation. The lines represent the operations. These lines are bi-directional, corresponding to the addition-elimination processes (i.e. bond dissociation-bond formation or one electron reduction-one electron oxidation). Usually the term electron transfer (ET) is employed both for oxidation and reduction processes. However, for one electron oxidation the term hole transfer (HT) has also been proposed although it is not largely followed.

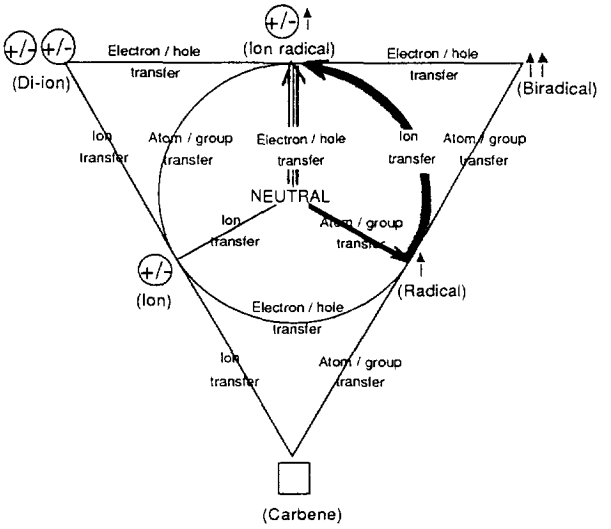


Possible pathways for C-C bond forming reactions in the ground state

Scheme 1

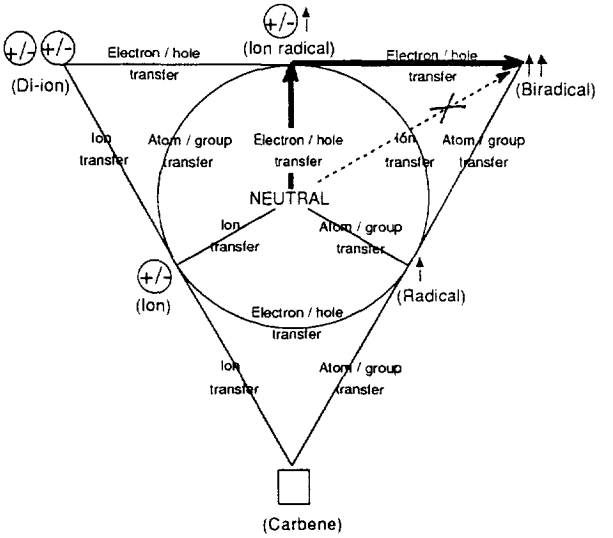
Among the conclusions which can be drawn from this graph, only two will be mentioned.

1) From electronically neutral species, electron transfer yields radical ionic species. Scheme 2 illustrates well that the same transformation can be formally accomplished in two steps: atom / group transfer followed by ion transfer.



Scheme 2

2) Scheme 3 suggests that, for example, the neutral molecule to biradical transformation is not allowed in a single step in an *intermolecular* reaction.



Scheme 3

As Scheme 1 indicates, single electron transfer to or from electronically neutral molecules results in the formation of radical ions: radical anions and radical cations respectively. The unpaired spin and the charged site can be located on the same atom, or spatially separated (distonic species). Carbogenic radical ions are (generally) highly reactive intermediates, with a short half life. Surprisingly, some examples show that these radical ions cannot be treated either as conventional radical species or even as their ionic counterparts[35]. They are characterised by their own *unique chemical behavior*. Moreover, and beyond the "classical" chemical reactivity of this class of compounds (addition, rearrangement, dissociation), molecules of unstable configuration can also break down by disproportionation or other electron transfer reactions, or even undergo a subsequent electron transfer. This second electron transfer leads to a doubly charged species. Due to the highly reactive nature of such intermediates, there is little evidence for this process[36, 37] in the condensed phase.

Radical ions:

Basically, there are three types of transformations illustrated in the literature whereby new carbon-carbon bonds are formed:

- Addition reactions of radical ions represent a special class in terms of chemical reactivity. An extraordinarily low activation energy has been found for the cation radical / neutral cycloadditions, including both the Diels-Alder and cyclobutanation reactions. Moreover, radical cation cycloadditions allow the obtention of thermally forbidden adducts. This type of reaction has been reviewed recently[19f-g] and will therefore not be discussed here, with the exception of the dimerisation of phenyldiazomethane.

- The radical ion may rearrange. Although radical cationic rearrangements in the gas phase are well documented, only a few examples of such C-C bond forming reactions have been observed in condensed phase.

- Radical ions may undergo a fragmentation reaction, forming a radical entity and an ionic species. The general reactivity of carbon centred radicals is abundantly illustrated and detailed in many excellent monographs and reviews, to which interested readers are referred[21].

Radicals:

Theoretically all radical species undergo similar transformations. However, in practice, the selectivity of the reactions depend strongly on the method by which this reactive intermediate was prepared. Some common features of redox radical reactions are noteworthy, and illustrate the differences as compared to other atom/group transfer reactions:

1) Complexation plays an important role in redox mediated reactions. This complexation has stereochemical consequences. Many of these types of reactions show enhanced acyclic diastereoselectivity: a) in freely diffusing (free-radical) reactions by formation of a solvated complex (template effect); b) in heterogeneous media, where radicals are adsorbed on the metal-surface, by orienting the immobilised active species. In fact, many synthetically useful SET reactions proceed in heterogeneous media. In such systems mechanistic problems related to the electron transfer process are coupled with the question of the surface activation. Moreover, in many circumstances, the exact structure of the reagents is unknown.

2) The elementary steps (initiation, propagation and termination) are different in many respects compared to non-redox "atom/group transfer" radical reactions. The initiation step, i.e. the formation of the primary radical, can be synchronous or stepwise with regard to the ET step. In the former case, the mechanism is similar to that of the atom/group transfer radical chain-reactions. If chain propagation occurs, usually the chains are shorter than those

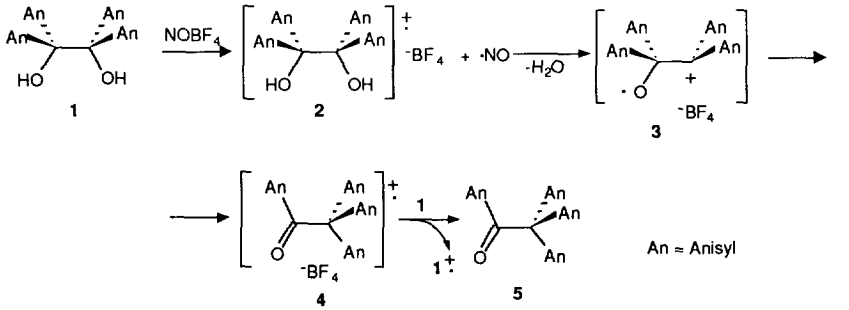
of the atom/group transfer free radical chain reactions. The reason is that the free radical intermediates can undergo fast one electron oxidation or reduction in the presence of a redox system (second electron transfer prior to chemical reaction, metallation, etc.), terminating the chain mechanism. The consequence of this type of termination is the creation of competing and often dominant polar reaction channels. Free-radical chain reactions are terminated usually by functional group transformations, such as atom transfer (hydrogen, halogen, aryl-selenyl etc.) fragmentation or oxidation. Redox coupling can also be terminated in another way, i.e. C-C bond forming dimerisation. Selective cross couplings can be obtained if one of the radicals is persistent or if the radicals are forming simultaneously (in the same solvent shell or they are close enough on the metal surface). Surprisingly, despite the persistent nature of the metal promoted radical reaction telomerisation is minimised in most cases. This phenomenon is presumably due to the fact that metal-coordinated radicals are intermediates, the net result being that the termination step is faster than the telomerisation.

As Scheme 1 shows, SET reactions are not only related to neutral species: anions or cations etc. may also undergo electron transfer reactions.

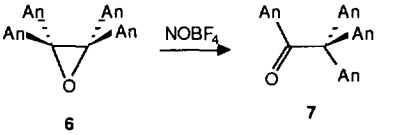
II. Reactivity

1. One electron transfer mediated rearrangements

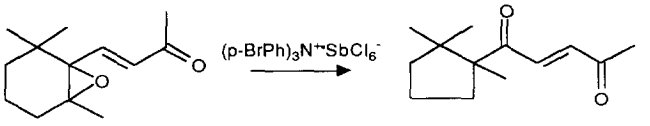
Pinacolones are obtained from electron rich benzopinacols in quantitative yields[38] using catalytic amounts of $NOBF_4$, as a one electron oxidant. The proposed operating mechanism is the radical chain sequence shown below. Since $NOBF_4$ is a weak electrophile, an outer sphere mechanism was assumed for the ET process, which forms a radical cation-radical anion pair. The radical anion dissociates to the gaseous ·NO free radical and the ion pair having $^-BF_4$ anion, which is a poor nucleophile and has no tendency for back electron transfer. In the absence of efficient electron donors, the radical cation rearranges to the corresponding pinacolone.



Similar observations with radical cations[38] derived from epoxides have also been described.

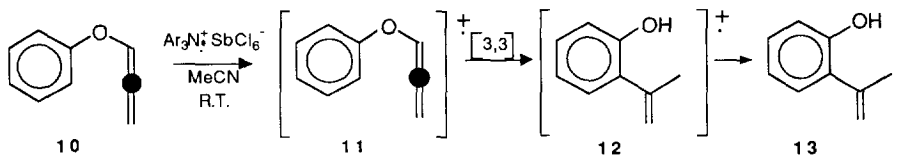


Aminium or trityl hexachloroantimonate react[39] at room temperature, under air and/or oxygen saturated methylene chloride solutions with epoxides. This result is somewhat surprising, since this reaction should be endergonic (thermodynamically unfavorable). Epoxides such as **8** show oxidation potentials in the range 1.9-2.1 V *vs.* Ag/Ag$^+$. The reducing potential of the aminium salt is E°=1.17 *vs.* SCE (standard calomel electrode). The driving force for the reaction could be the isomerisation of the ring closed radical cation into the corresponding ring opened one, followed by migration and subsequent electron transfer with the neutral substrate. Traces of acid, which may also catalyse the rearrangement were carefully eliminated.



8 **9**

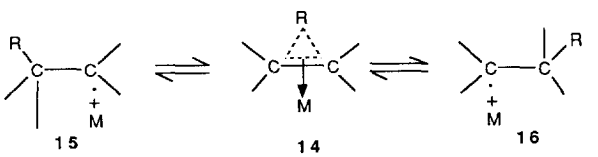
Cation radical initiated Cope, Claisen and related reactions have attracted considerable interest[40], as shown for the [3,3]-sigmatropic rearrangement of aryl allenylmethyl ether[40e] **10** in the presence of tris(4-bromophenyl)aminium hexachloroantimonate:



10 **11** **12** **13**

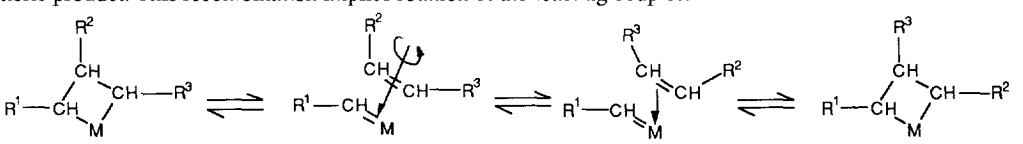
Often the intermediate generated by one electron transfer undergoes a second electron transfer prior to the critical carbon-carbon formation. This cationic (and not radical ionic) pathway was postulated for example in the 1,2-migration of the 1- and 1,4-disubstituted naphthalenes[41] by oxidation with ceric ammonium sulfate, manganese(III) salts and also by anodic oxidation.

At elevated temperatures 1,2-bond shift isomerisation of paraffins occurs on transition metal catalyst surfaces. Two possible mechanisms have been considered. The first is closely akin to that of a carbonium ion rearrangement: a radical cationic rearrangement. According to this mechanism, the alkyl radicals **15** and **16** are generated[42] at the metal surface by C-H bond scission which then isomerises *via* π-complexed intermediate **14**.



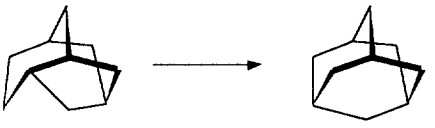
15 **14** **16**

The alternative mechanism involves an olefin metathesis type cleavage, where the moieties recombine to give the isomeric product. This recombination implies rotation of the reacting couples.



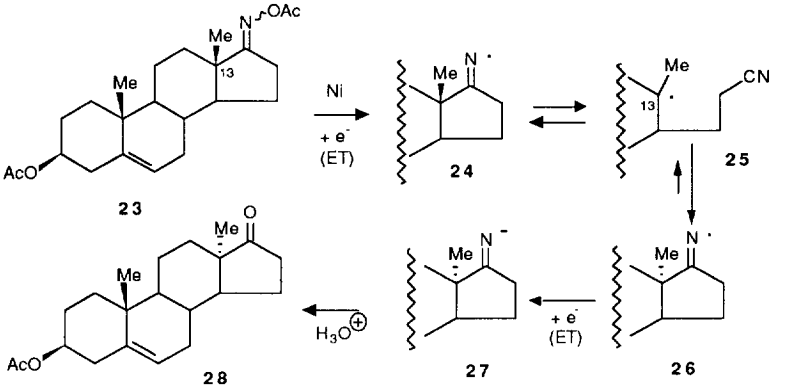
17 **18** **19** **20**

In the rearrangement of caged compounds *e.g.* protoadamantane **21** to adamantane **22**, which occurs in excellent yield over platinum and palladium catalysts, the metathesis mechanism must be excluded since the intermediate alkene-metallacarbene complex cannot rotate. A similar behaviour was observed using MoO_3/Al_2O_3 and Pt/SiO_2 catalysts which were reduced at elevated temperatures[42].



21 **22**

A novel approach to 13-epi-17-ketosteroid **28** was developed from 17-acetoxy iminosteroid **23** by heating with nickel powder in acetic acid-octane[43]. The mechanism of this process is believed to involve fragmentation of the 17-iminyl radical **24** which undergoes ring opening followed by ring closure with inversion at position 13. Other metals, such as iron in hot acetic anhydride or cobalt, tin and samarium also gave the 13α epimeric ketone product, but the reactions were somewhat less satisfactory.



The authors made an observation concerning the modulation of the electron transfer rate. If acetic acid is used alone, the reduction of the intermediate iminyl radical becomes too fast with respect to D-ring opening and the product which has natural configuration is then obtained. In octane the desired reaction proceeds smoothly and the 13-epi-ketone **28** is produced directly by spontaneous hydrolysis of the intermediate imine in good yield.

2. Reductive electron transfer mediated fragmentation-recombination reactions

2.1 Reductive alkylation via σ-bond cleavage. General considerations.

One of the most important group of reductive coupling reactions is the reductive coupling of halides. Electron transfer rate constants for the carbon-halogen bond cleavage as well as the radical formed can be obtained from the numerous studies of Savéant[3a, 44] and others[45].

Other electrophiles, most notably sulphones, nitro- and carbonyl compounds, having less negative electrode potential than the reducing agent may undergo reduction and fragmentation reactions in the presence of one electron donors. The fragmentation can be stepwise (formation of a complex) or synchronous (dissociative one electron

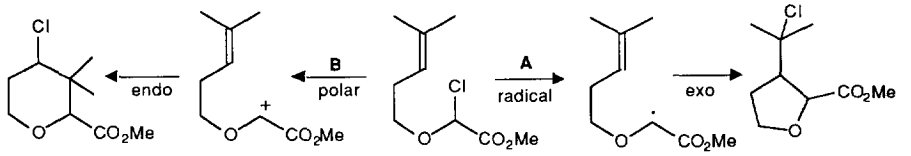
transfer), with regard to the electron transfer step.

Although some aspects of reductive alkylation induced by the use of low valent transition metal complexes were reviewed recently,[19 l, 46-50] considerable progress has been achieved since, particularly in the ET area.

2.1.1 Reductive alkylation via fragmentation of a C-heteroatom bond

The Kharasch-type alkylation reaction

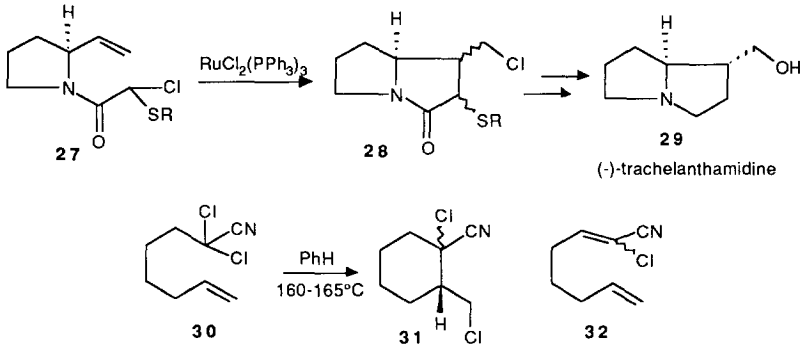
The generation and subsequent intermolecular reaction of acyl radicals with alkenes was reported nearly fifty years ago by Kharasch[51]. More recent advances in this area are based on the observation that a number of transition metal complexes catalyse the reaction. It is thought that the reaction proceeds *via* metal-coordinated radicals[52]. The efficiency of α,α–dichlorocarboxylates- or α,α–dichloronitrile-olefin cyclisation has been recognised for a long time.The reaction is particularly well suited for the preparation of five membered carbo- or heterocycles. It was shown that the choice of ligand for the metal complex was very important for the regiochemical outcome of the cyclisation reactions[53]. This was explained in terms of change in the nature of the metal-complex promoting either the halogen atom transfer *via* radical mechanism **A** or Lewis-type reaction *via* carbocation (polar) pathway **B** (Scheme 4).



Scheme 4

For example, Cu(I), Ru(II), Fe(II) and Co(0) were found to catalyse effectively the inter[54]- or intramolecular[53, 55, 56] radical addition of α-trichloro esters and amides to olefins. With these catalysts, the overall transformation is a halogen translocation with a concomitant cyclisation *via* radical pathway. The reaction requires elevated temperatures (155-160°C in benzene (sealed tube) or in refluxing *tert*-butylbenzene).

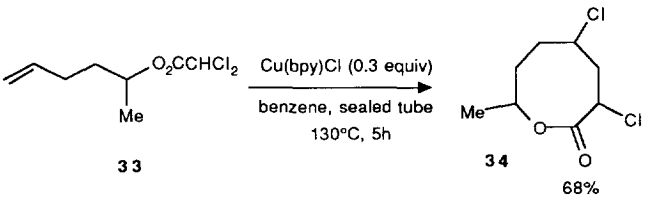
Ruthenium(II) complex mediated radical cyclisation was featured in a synthesis of the pyrollizidine alkaloid (-)-trachelanthamidine[55g] **29**.



$RuCl_2(PPh_3)_3$, (4%), 20h	-	98%
$FeCl_2[P(EtO)_3]_3$, (5%), 23h	89%	-
CuCl / PPh_3, (1%), 17h	91%	-

Carbocycles larger than five membered may also be prepared in these metal complex mediated radical reactions. Particularly good results were obtained in the metal-catalysed α,α-dichloro nitrile **30** addition to alkenes[56].

In a recent variant, eight- and nine-membered lactones have been prepared through Cu(I) chloride 2,2'-bipyridine complex catalysed cyclisation of ω-alkenyl-α,α-dichlorocarboxylates in benzene[53a]. The regioselectivity of this process corresponds to the pattern followed in medium- and large-ring radical cyclisations.



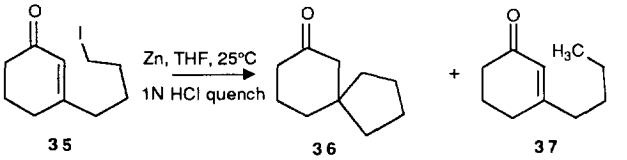
33 **34** 68%

Proline derivatives were also prepared by this copper(I)-catalysed chlorine transfer radical cyclisation[53b].

Reductive alkylation using zinc-copper couple

Among the main group elements, the use of zinc[57] in different redox couples must be mentioned. In fact the use of Zn in different redox systems is very popular because of its relatively high redox potential and its compatibility with a great number of functional groups and co-catalysts. Applications have been found with a plethora of salts such as CuI, $TiCl_4$, $CoCl_2$, $LaCl_3$. The nature of the electron transfer in Zn mediated reductive coupling reactions has been the subject of recent debate[58] . Organometallic electrophilic ligand coupling *versus* electron transfer mediated radical coupling mechanisms were proposed and tested for structurally close but not identical molecules.

To establish polar *vs* radical pathway, different experiments have been made. Simple treatment of **35** with zinc dust promotes cyclisation[58a] in dry THF at room temperature. Aliquots were quenched at intervals with 1N HCl and analysed. A mixture of the cyclisation product **36** and the reduction product **37** was obtained. Upon further reaction, the amount of reduction product decreased, while the amount of cyclisation product increased concomitantly. This result suggests, that under these conditions, only a small part, at most, of the cyclisation product can result from a radical mediated pathway. It was shown also that the success of the cyclisation is highly sensitive to the type of zinc metal used for the reaction.

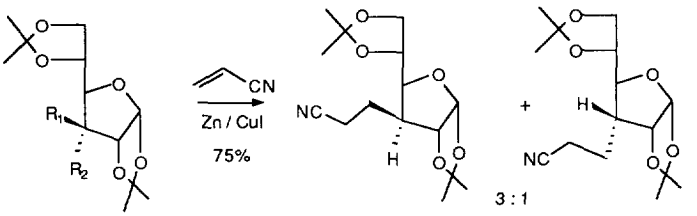


35 **36** **37**

On the other hand, several features of the mechanism at work in zinc promoted reductions in aqueous media and in the presence of catalytic amounts of copper salt have been reported by the Luche group. In these reactions, the reductive addition of alkyl halides to α,β,-unsaturated carbonyl derivatives and nitriles have been studied[59]. In most cases, addition reactions were carried out in a mixture of ethanol/water, using a Zn/CuI suspension in the protic solvent mixture. They concluded that the *free radical* mechanism is highly improbable, however, it seemed also to be unlikely that the reaction follows a purely ionic mechanism *via* an organometallic species. An alternative pathway was proposed[60] where the radical is tightly adsorbed on the *surface of the metal*. The best yields were obtained in water rich solvents, which suggests an important degree of structural organisation in the solvent shell. The solvent cage around the radical formed should be rigid and sensitive to ultrasonic breakage[61]. It was observed

that sonication accelerates the addition reaction to olefins, at the expense of side reactions such as hydrogen abstraction from the solvent or Wurtz-type coupling, which generally take place close to the metal surface.

This zinc-copper method has been used to prepare branched chain sugar derivatives[62]. Both stereoisomer **38** and **39** underwent slow reductive conjugate addition[62a] with acrylonitrile, in the presence of Zn/CuI mixture, giving virtually the same ratio of **40 / 41**.



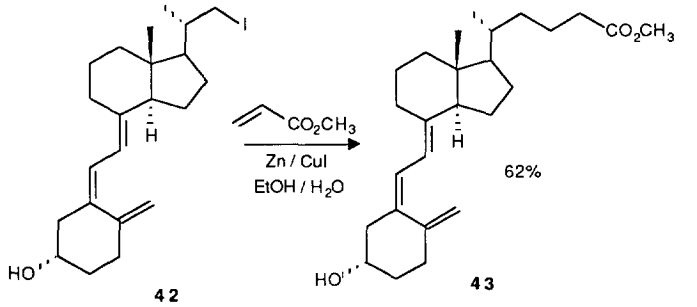
38 $R_1 = H; R_2 = I$
39 $R_2 = H; R_1 = I$

40 **41**

This reaction was also shown to be useful for preparing intermediates for unnatural amino acids[63b].

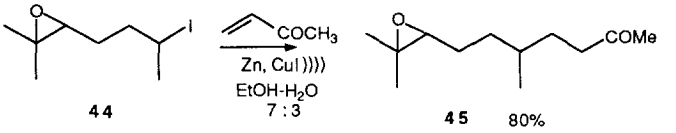
The same group studied[62c] the effect of the electron mediator in related systems. They found that $NiCl_2$ (the Zn/Ni^{2+} system[63] is inefficient), ferric(III) chloride, and cobalt(II) chloride gave a modest yield unless pyridine was used as solvent. The addition of sodium iodide to the reaction mixture interestingly raised the yields (up to 60%). Surprisingly the reaction did not work in acetonitrile. Ferrous(II) chloride was absolutely ineffective in the absence of zinc.

The same reaction was used to prepare vitamin D_3 analogue[64] **43**. The procedure allows the introduction of different side chains without disruption of the labile vitamin D triene system.



42 **43**

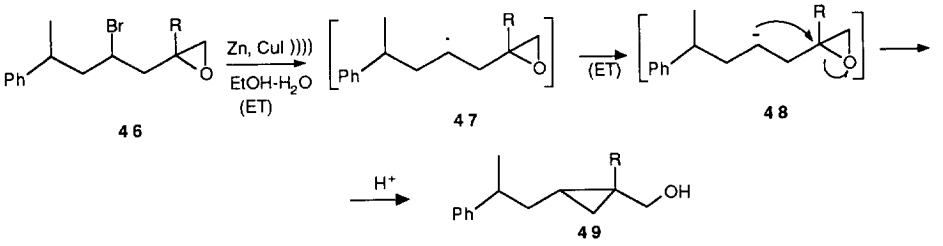
Epoxy alkyl halides, in which the reducible groups (i.e. the halogen and the oxirane cycle) are separated by at least two carbons as in **44**, undergo[65] conjugate addition presumably *via* one electron transfer. It is assumed that this process takes place at the surface of the reducing metal. It has been shown that the electron transfers are strongly influenced by ultrasonic waves.



44 **45** 80%

Sonication of epoxy halide **46** in the presence of zinc-copper couple and an α,β-unsaturated carbonyl

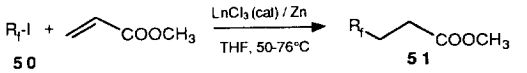
compound gave rise to the cyclopropyl alcohol **49**. The ring opening-ring forming process involved is to some extent analogous to the recently reported[66] Lewis acid catalysed 1,3-elimination-cyclisation of 3,4-epoxyalkylstannanes in which the conformation and configuration of the initially formed radical are important in determining the outcome.



a) R = H 30%

b) R = Me 58%

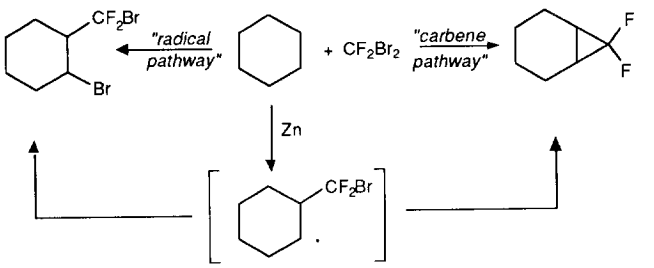
Perfluoroalkyl iodides may be added[67] to electron poor olefins (acrylic esters) under protic conditions. The electron source is Zn. It was found that the $LnCl_3$ / Zn system (Ln = La, Sm, Dy, Yb) gave hydroperfluoroalkylated products[68] in higher yields than Zn alone. Although the reaction mechanism is not clear at present, the reaction may involve a radical mechanism.



50 **51**

65-80%

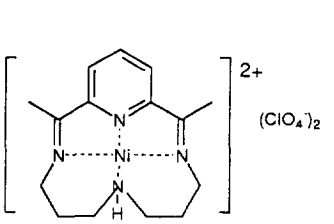
An interesting analysis has been made by Wu[69] comparing the reactivity of the zinc induced addition of dibromodifluoromethane to olefins under different conditions. In general, 1:1 adducts are considered to be forming *via* a radical mechanism, while cyclopropane products are believed to form *via* addition of carbenes (in most cases). On the basis of the results, however, a reductive debromocyclopropanation mechanism was suggested, which proceeds on the zinc metal surface (Scheme 5).



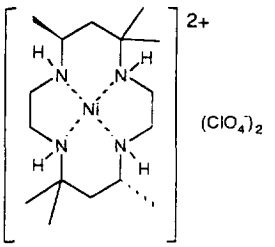
Scheme 5

Low valent nickel mediated radical coupling reactions

Nickel(II) complexes **52** and **53** are relatively weak reducing agents. They exhibit Ni^{II}/Ni^{I} redox couples at -0.70 and -1.38 V *vs.* SCE respectively. Despite this limiting factor, a number of one electron transfer applications have been found.

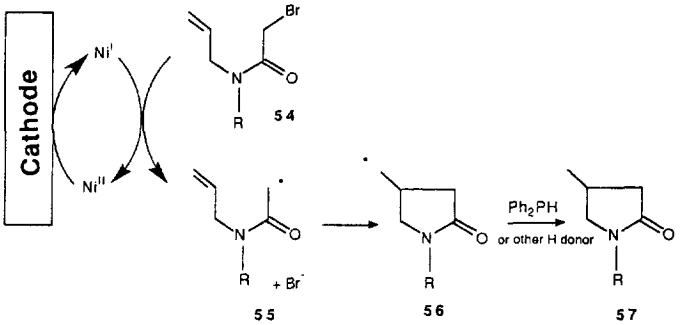


52

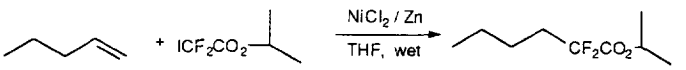


53

These complexes have been used[70] as electron transfer catalysts to mediate cyclisation of N-allylic and N-propargyl bromo amides as well as *o*-bromoacryloylanilides. The reaction of bromo amide **54** in acetonitrile containing 2 mol equiv. of diphenylphosphine (Ph_2PH), as hydrogen atom donor produced pyrrolidinone **57** as the sole cyclised product in 58% yield. It was shown that the substituent on the nitrogen atom has a considerable influence on the selectivity of the cyclisation. The reason is that the cyclisation involving an amide group in the linking chain attains the required conformation for the cyclisation[71] with more difficulty than the all carbon counterpart because of the restricted rotation around the amide [C(O)-N] bond. It was shown that tosylation is better for the protection of the nitrogen than benzylation.



A general synthetic methodology for preparing α,α-difluoroesters has been recently described[72] *via* nickel dichloride-zinc couple. Although the mechanism of this reaction has not been investigated, it was proposed that Ni(0), produced from the reaction of $Zn/NiCl_2$, initiated the addition of iododifluoroacetate **59** to the alkene **58**, to afford an adduct (c.f. Raney-Ni catalysed addition of perfluoroalkyl iodides to alkenes[73]) followed by reduction of the adduct with Ni(0) in wet THF to give the corresponding α,α-difluoro functionalised ester **60**.



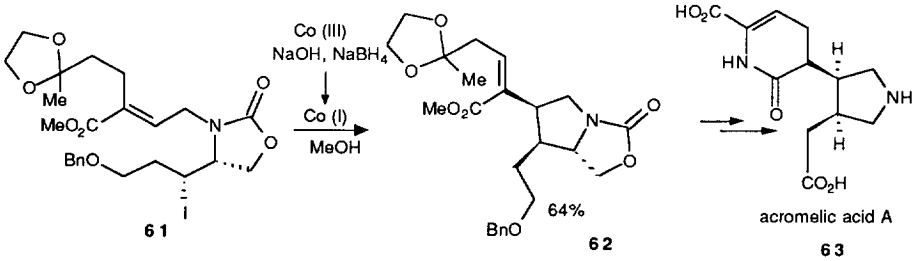
58 59 60

Low valent cobalt mediated radical coupling reactions

It is well established that alkyl-cobalt species can undergo thermal or photochemical homolysis[74] allowing the formation of carbon centred radicals. These reactions which are formally different from the redox system mediated free radical reactions have found broad application. In the dark, the reaction requires heating for the homolytic cleavage of the Co-C bond to occur. Mediation by a redox system allows the reaction to be carried out at room

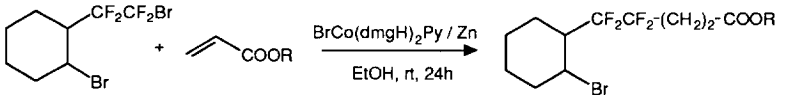
temperature. The active low valent Co species can be prepared from cobalt(III) salts by reduction with metal hydrides ($NaBH_4$) or with metals (Zn).

By way of example, the Baldwin group reported[75a] a powerful radical cyclisation reaction based on chlorocobaloxime, in the presence of sodium borohydride. The Co(I) was postulated as an active species in the reaction. This methodology was used to prepare[75b] acromelic acid A **63**, by an enantiospecific route.



61 62 63

The addition of per(poly)fluoroalkyl halides to electron deficient alkenes (such as ethyl acrylate) is not easy due to the electrophilic nature of the fluorinated radicals. The bimetallic redox system, cobaloxime(III)(cat.)/Zn, could efficiently initiate[76] the addition of per(poly)fluoroalkyl halides to both electron-rich and -deficient alkenes.



64 65

Samarium based methods

Low valent samarium chemistry has evolved as a most dynamic branch in preparative organic chemistry in the last few years. Undoubtedly, the reaction has enormous synthetic potential in terms of mild conditions, and chemo-, regio-, and stereoselectivity. Barbier-type reactions, pinacol couplings, and α-ketol and vicinal carbonyl compound preparations are the most frequently used transformations. Samarium (II) has also been applied in acyl-chloride coupling and Simmons-Smith cyclopropanation. However, only a few of these transformations can be considered to proceed *via* a characteristic radical pathway. An inherent advantage of the radical processes is to incorporate it in tandem reactions.

Much of SmI_2 chemistry has been summarised in various reviews[47, 48]. This report will only deal with new developments in this field, related to the ET carbon-carbon bond forming reaction.

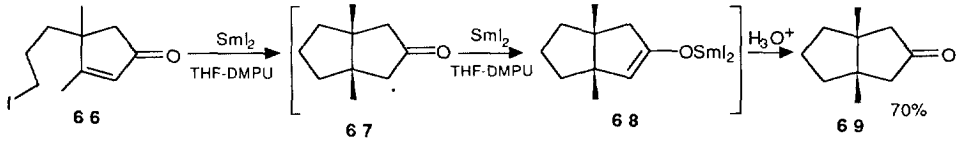
The method used for the preparation of samarium diiodide strongly influences the reactivity of the species. It can be prepared in THF from metallic samarium in the presence of diiodoethane under an inert atmosphere. Other solvents such as acetonitrile[77] can be used too, since the nitrile group is inert towards the reagent. In this solvent, reductive coupling of acyl halides with ketones gave enhanced yields, probably because the competing hydrogen abstraction of the intermediate radical from the solvent (THF) was diminished, or probably because a polar mechanism and not a radical one is operating. Other procedures recommend the preparation of a samarium(II) iodide equivalent from metallic samarium and Me_3SiCl / NaI reagent in acetonitrile under ambient conditions[78]. This reagent promotes reductive carbonyl coupling and yields pinacol dimers in about a 1:1 ratio of *threo* and *erythro* isomers. Interestingly, bis(cyclopentadienyl)samarium ($SmCp_2$) gives a stable organosamarium derivative at -10°C, in contrast to SmI_2, and this complex is reactive towards electrophiles[79].

Mechanism

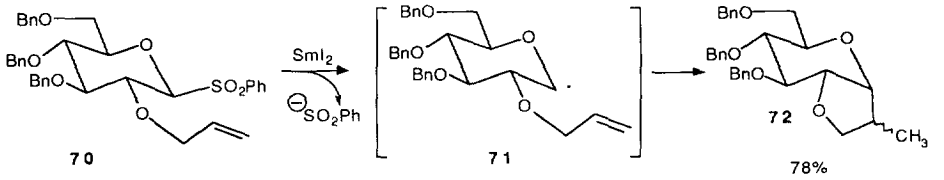
The mechanism of the SmI_2-promoted reactions has been the subject of much study and speculation. In general, the reactivity of Sm (II) iodide is characterised by a single electron transfer from the samarium (II) to a suitable substrate to yield an anion radical intermediate and samarium (III)[80a]. The role of donor ligands (such as HMPA, DMPU, or other Lewis bases)[80b] is to increase the reducing power of Sm(II) (the reduction rates increase until about 4 equiv. of HMPA are added) and also to modify the structure of the activated complex and change the mechanistic pathway. By virtue of this high reducing potential, and in the presence of HMPA, organic halides, carbonyls, α-hydroxy esters, P-O and P-Cl bonds, sulfoxides, sulfones and nitro compounds can be reduced effectively [81].

The radical intermediates may undergo reaction, either in an inter- or intramolecular mode, or they may be converted to anions by electron transfer from another equivalent of samarium (II) iodide. The question is whether the crucial C-C bond forming step is the result of radical or organometallic coupling, or alternatively an alkyl radical addition to a samarium(III)-activated carbonyl. Despite extensive studies, not one proposed mechanistic pathway is in complete agreement with all of the experimental results[48], probably because different mechanisms are at work affording identical products. Good approximation can be made for potentially competing reactions by comparing the relative rates. The reduction rate constants for a primary alkyl radical[82] by SmI_2 vary from $5x10^5$ to $7x10^6$ $M^{-1}s^{-1}$, depending on the amount of HMPA used. Even subtle changes in the nature of the reaction (inter or intramolecular reaction, catalyst, etc.) or in the structure of the substrates may change the main mechanism. The same reaction can be conducted by a Sm-carbenoid[83], radical, or Sm-nucleophilic pathway.

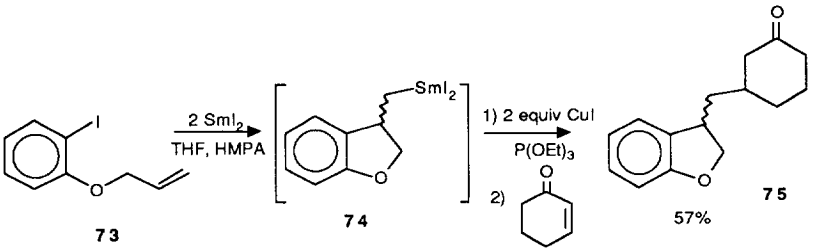
Samarium(II) iodide promotes intramolecular conjugate addition reactions[84] leading to five membered rings such as **69**. The samarium enolate intermediate **68** can also be trapped in an aldol condensation with aldehydes.



α–D-Glucopyranosyl bromide and β-D-glucopyranosyl phenyl sulfone **70** undergo reductive fragmentation[85] in the presence of SmI_2. When adequate leaving groups, such as acetoxy or benzyloxy functions were present at C-2, the corresponding glucals were obtained in high yield. When the C-2 position was allylated, a reductive 5-*exo*-trig radical cyclisation (**72**) took place.

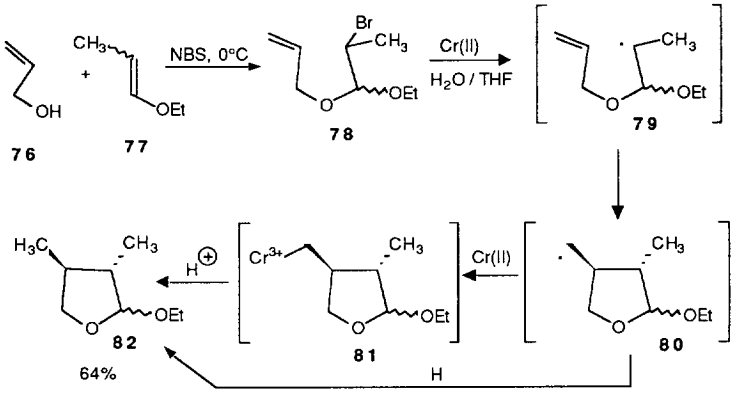


Aryl iodides also undergo one electron induced fragmentation[48b] in the presence of SmI_2. It is noteworthy that the organosamarium intermediate **74** can be trapped or transmetallated *in situ*, which extends the usefulness of these reagents. The use of 2 equiv. of halide, 4 equiv. of SmI_2, 1 equiv. of CuI·P(OEt)$_3$ complex, and 1 equiv. of 1,4 -enone provides 1,4-conjugate addition products as **75** in moderate to good yield.



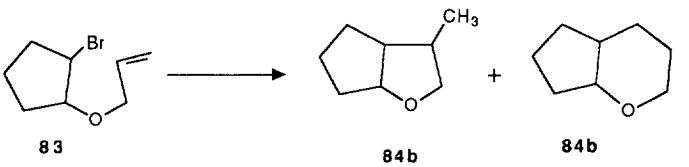
Low valent chromium mediated radical coupling reactions

α-Bromoacetals undergo free-radical cyclisation[86] in the presence of activated chromium(II)-acetate complexed with ethylenediamine or 2,2'-dipyridyl ligands. It is possible to use only catalytic amounts of the complex and regenerate it with $LiAlH_4$ or electrochemically.



The α-bromoacetals **78** react in aqueous THF at room temperature with the *in situ* prepared activated chromium(II) complexes to form tetrahydrofurans **82** in good to excellent yields. The mechanism presumably involves alkyl free radicals which undergo intramolecular cyclisation. After cyclisation, the radical can be quenched by hydrogen abstraction from the solvent or by trapping with another Cr(II) complex to afford the organochromium species **81**, which is subsequently hydrolysed to **82**. The low concentration of the Cr(II) species (to prevent premature trapping) is assured by the low solubility of the complex in the organic phase.

The reaction is generally *trans* selective. However, the diastereoselectivity of the 5-*exo*-trig cyclisations **83** → **84a** varies with the Cr(II) ligand and the solvent. For reactions leading to bicyclic tetrahydrofurans a high regioselectivity was observed which was better than the corresponding tin hydride mediated free-radical cyclisation.



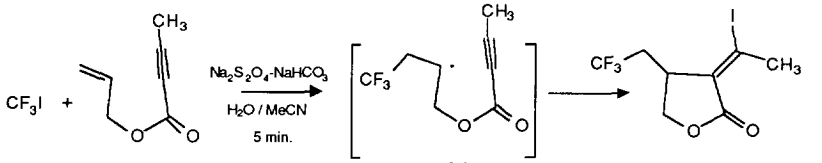
Cr(II)	18-54	:	1
Bu_3SnH	8	:	1

Sulfinate mediated radical reactions

In the presence of sodium dithionite and sodium bicarbonate, perfluoroalkyl iodides smoothly react with allylic alkynoates[87] in aqueous acetonitrile to give cyclic products. A proposed mechanism is outlined in the following scheme:

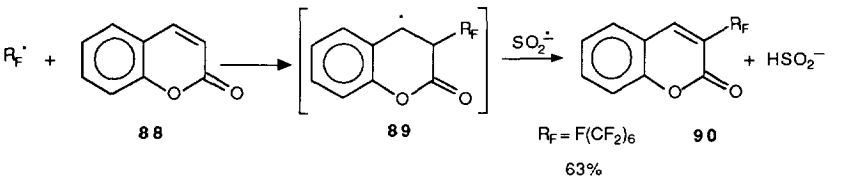
$$S_2O_4^{2-} \rightarrow 2\ SO_2^{\bullet -}$$
$$SO_2^{\bullet -} + R\text{-}I \rightarrow R\text{-}I^{\bullet -} + SO_2$$
$$R\text{-}I^{\bullet -} \rightarrow R^{\bullet} + I^-$$

Sodium dithionite generates the perfluoroalkyl radical by transferring an electron to R_f-I, thus initiating the reaction.



Perfluoroalkyl-containing compounds can also be prepared using Rongalite as initiator of the free radical process[88]. The reaction was explained in term of the following mechanism:

$$HOCH_2SO_2^- \rightarrow HSO_2^- + CH_2O$$
$$R_FI + HSO_2^- + OH^- \rightarrow R_F^{\bullet} + SO_2^{\bullet -} + I^- H_2O$$

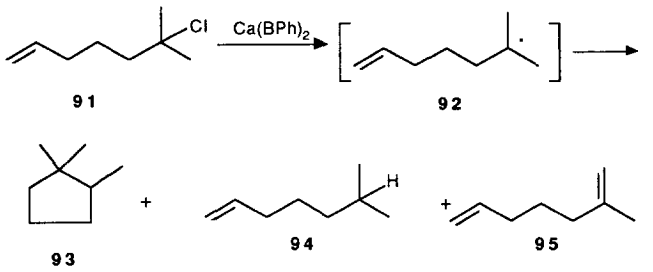


Metal-aromatic complexes

Aryl-alkali metal complexes are reported to be strong one electron reducing agents. However, the consecutive one electron reductions / metallation occur so fast that it is difficult to trap the transient free radical[89]. Preparative applications include reductive lithiation of alkyl halides, thioethers and tetrahydrofurans by means of radical anions[90]. This method was shown to be fairly general for preparing organolithium compounds.

Among alkaline earth metals, calcium-aromatic complexes are also powerful one electron reducing agents[30]. The reaction of organic halides with calcium-aromatic complexes such as calcium-biphenyl ($Ca(BPh)_2$) and calcium-naphthalene takes place by a single electron transfer mechanism which provides free radicals in solution as intermediates. An intramolecular trapping experiment gave some evidence for this radical pathway. Reduction of 6-chloro-6-methyl-1-heptene **91**, with a calcium aromatic anion radical in THF at -60°C yielded the cyclised product, along with the reduced acyclic olefin, and a trace of a diene. The large amount of cyclic product obtained is in agreement with an electron transfer process involving free radicals in solution. This cyclisation reaction has,

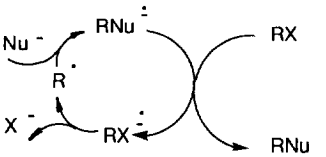
however, limited preparative importance.



The $S_{RN}1$ electron transfer substitution reaction

A nucleophilic substitution, in which Nu^- displaces X, could proceed as a multistage sequence involving radical anions and free radicals as intermediates[91]. This so-called $S_{RN}1$ reaction is believed to proceed *via* a unimolecular radical chain reaction and occurs with some aromatic[92a-b] and aliphatic[23, 92c-e] substrates.

According to this mechanism, the initial step is the formation of an organic radical anion by addition of an electron to the electron acceptor, which can be a nitro-, halo-, or sulphonate group. The second step is the dissociation of the radical anion to the X^- anion and the corresponding radical. The radical then combines with the nucleophile (α-nitro, α-keto or α-sulphonyl derivatives) to give a radical anion which, in turn, transfers one electron to the starting material to yield the product and a radical anion to continue the chain (Scheme 6). This chain mechanism is supported in a number of cases by experimental observations which include 1) calculated chain lengths are longer than one; 2) inhibition by addition of a catalytic amount of radical acceptor or radical scavenger; 3) significant electrocatalytic effects; 4) insensitivity to steric effects and 5) complex kinetics.



Scheme 6

In some cases, a non-chain radical mechanism[93] has been proposed. Thus, no inhibition or only partial inhibition effects have been observed by addition of different radical scavengers. The fact that no dimers derived from the homocoupling of the radicals have ever been found may arise from a nonchain mechanism. Kinetic studies also support this hypothesis.

Recently, the existence of the $S_{RN}1$ mechanism was questioned by Denney[94], and an $S_{RN}2$ mechanism was proposed instead. However, it was promptly rebutted by Bunnett[95], Rossi[96], and Savéant[97].

The $S_{RN}1$ reaction appears to be controlled by three main factors: 1) the presence of an appropriate LUMO level to accept an electron for the generation of the radical anion $RX\cdot^-$, 2) the ease of the fragmentation, and 3) the degree of SOMO-HOMO and SOMO-LUMO interaction between the free radical intermediate R·, and the nucleophile Nu^-, in the propagation step to allow them to couple[98, 99] easily. In most cases, the coupling reaction

between R· and the Nu^- is the rate determining step in the dark[100]. This reaction has found considerable synthetic applications, especially for the preparation of hindered compounds with quaternary centres.

Confusion often arises from the similarity in the products obtained by electron transfer radical pathway and by ionic mechanism. According to the classical picture, halides *ortho* or *para* to an EWG (e.g. nitro) group are activated for a nucleophilic aromatic substitution *via* an addition elimination mechanism[101]. The reactions of *o*- and *p*-nitroaryl halides with various anions are representative examples of this mechanism. The mechanistic criteria for the S_NAr process is first order in both reagents, exhibits a leaving group effect (F>>Cl), a positional effect (lack of reactivity of the *meta* isomer) and is insensitive to radical traps. Interestingly, the mechanistic pathways (i.e. S_{RN} *vs* S_NAr mechanism) can be different even with identical substrates under seemingly similar conditions (e.g. when the electron source is RS^- *versus* RO^-) or by changing the leaving group (e.g. I *versus* Br, Cl, F)[102]. It has been suggested[103] that in S_NAr reactions, the Meisenheimer complex forms by radical coupling of the products of an initial electron transfer step between the two reactants, the nucleophile and the aromatic substrate. The occurrence of such a two-step sequence taking place within the solvent cage and with no possibility of intercepting the radical intermediates has only theoretical significance in differentiating radical from polar reaction pathways.

The initiation step of the electron transfer reaction can be spontaneous[104] or induced by light[99], by various redox systems such as solvated electrons in liquid ammonia[92, 97, 105], Na(Hg) amalgam in ammonia[106] which interestingly does not provide solvated electrons, certain inorganic salts[107, 108] or cathodically generated electrons[22].

Diazonium salts can be easily reduced with aqueous solutions of hypophosphorous acid[109]. The driving force of this reaction is the low reduction potential of the diazonium salt and the irreversible fragmentation of the formed radical:

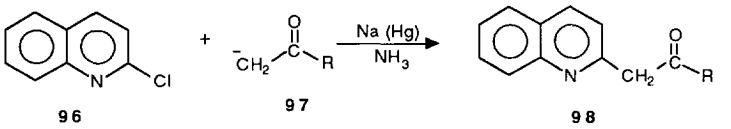
$$ArN_2^+ + H_2PO_2^- \rightarrow ArN_2\cdot + H_2PO_2\cdot$$
$$ArN_2\cdot \rightarrow Ar\cdot + N_2\uparrow$$
$$Ar\cdot + H_3PO_2 \rightarrow ArH + H_2PO_2\cdot$$

This old reaction has generated interest[110] again recently. Arenediazonium salts can also be reduced by other electron donors, for example by hydroquinones[111]. Addition of divalent metals (Cu^{2+}, Zn^{2+}, Mg^{2+}) considerably accelerate the rate of the decomposition. On the other hand, arenediazonium ions are reduced with sodium dithionite, in the presence of Ti(III) and hydrogen peroxide[112] or with a Ti(III)-persulfate redox system[113] and undergo fragmentation to produce aryl radicals. The radicals thus formed can be trapped with anions of nitroalkanes (nitromethane, nitroethane, 1- and 2-nitropropane)[114]. However, the radical anion formed in the coupling of an aryl radical with nitromethane anion fragments faster[115] than the electron transfer, producing stable benzylic radicals:

$$ArN_2^+ \rightarrow ArN_2\cdot \rightarrow Ar\cdot + N_2 \rightarrow [Ar\text{-}CH_2\text{-}NO_2]\cdot^- \rightarrow Ar\text{-}CH_2\cdot + NO_2^-$$

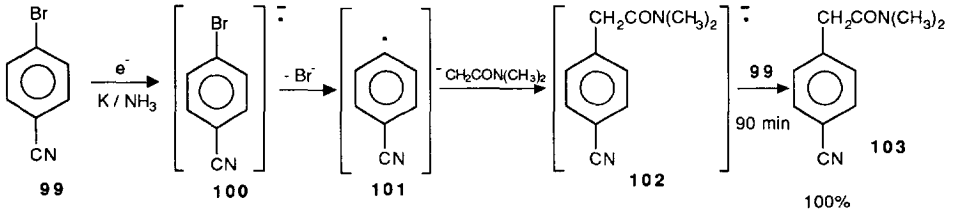
Na(Hg) is an efficient reagent for initiating $S_{RN}1$ reactions of aryl halides and carbanions in liquid ammonia[116]. 2-Chloroquinoline reacts with the anion derived from acetone[106] in the presence of Na(Hg) and gives 48% of the substitution product **98a**, together with a substantial amount of dimeric biquinoyl. In the reaction of 2-

chloroquinoline, however, with the more reactive ketone **97b**, the substitution product **98b** is obtained in a near quantitative yield.

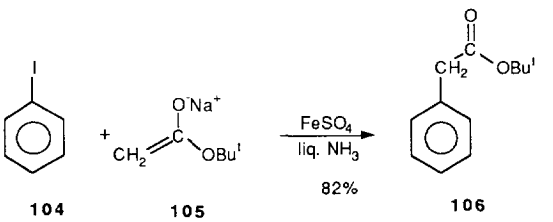


a) R = CH_3 (48%)
b) R = Ph (98%)

Solvated electrons obtained from dissolution of potassium metal in liquid ammonia initiate $S_{RN}1$ reactions[117] of aromatic compounds substituted with EWG.

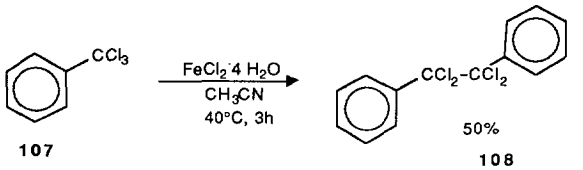


In 1984 Galli and Bunnett[107] reported a preparatively useful substitution reaction catalysed by ferrous ion. Surprisingly this redox system initiated $S_{RN}1$ reaction seemed to be abandoned until recently. The apparent unique catalytic activity of simple iron(II) salts was confirmed by the results of a limited study with other metal salts[108] which can formally act as one electron transfer agents. For the conversion of **104** into **106** the following salts, arranged in the order of increasing redox potential, gave the product (yield %): CuCl (11), $RuCl_3$ (21), $FeCl_2$ (73), Hg_2SO_4 (12), $Ce_2(SO_4)_3$ (9), and $CoSO_4$ (7). As Galli and Bunnett tentatively suggested, there are three possible functions of the ferrous ion: (a) electron transfer from Fe(II) to ArI; (b) iron-mediated electron transfer from the nucleophile to ArI; or (c) direct capture of iodine from ArI, with formation of Ar·. In accordance with the general mechanism of $S_{RN}1$ reactions, it was shown that iodides react faster and more efficiently than bromides, and that electron rich substrates react sluggishly.



Low valent iron mediated radical coupling reactions

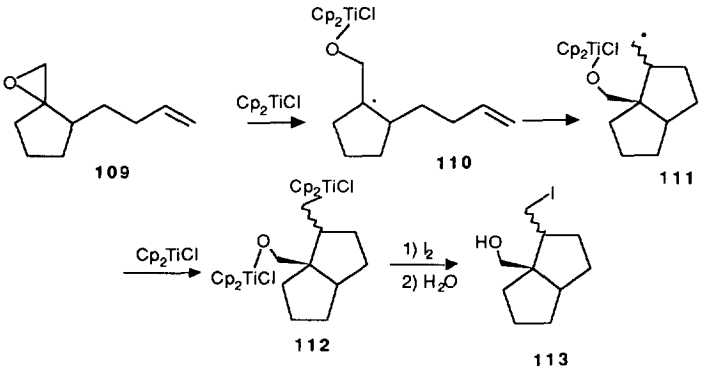
The reductive dimerisation of halomethyl organic derivatives using $FeCl_2$ in acetonitrile has been described[118] recently. The radicals formed from trichloromethyl compounds underwent a coupling reaction and proton abstraction after further reduction to a carbanionic species. It was also shown that sterically crowded reaction centres are preferentially involved in coupling rather than mere reduction. Lowering the reducing power of the Fe(II) salt by adding water makes the homocoupling more efficient.



107 108

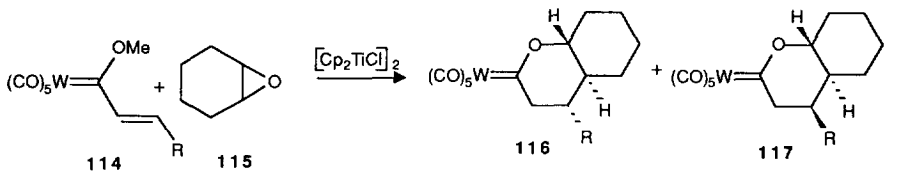
Low valent titanium mediated radical coupling of epoxides

Bis(cyclopentadienyl)titanium (III) chloride promotes radical cyclisation[119] of epoxides to olefins. The reaction tolerates ester and acetal functions, and is especially well suited for the introduction of quaternary centres. The intermediate organotitanocene compound can be quenched with a proton or with other electrophiles[119a-b].



109 110 111 112 113

Alternatively, the intermediate free-radical can be trapped with unsaturated Fischer carbene complexes[119c-d] in an intermolecular reaction. The reaction affords tetrahydropyranylidene complexes **116** and **117** with good diastereoselectivity. The equatorial isomer is obtained when the β-substituent is sterically demanding, but the axial isomer predominates when the substituent is methyl.



114 115 116 117

R = iPr 74% 3.6 : 1

R = Me 60% 1 : 3.3

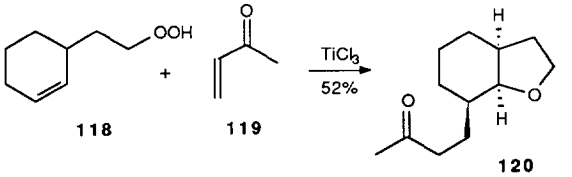
2.1.2 Alkylation via reduction of a heteroatom-heteroatom bond

Reduction of a heteroatom-heteroatom bond using low valent titanium

Decomposition of hydroperoxides in the presence of transition metal ions has been extensively investigated[120]. They are classically reduced by Cu(I) salts or other low valent transition metal salts such as Fe(II), Mn(II), Ag(I), Co(II), Cr(II), Ti(III), etc.

$$\text{R-OOH} + \text{Ti(III)} \rightarrow \text{R-O}\cdot + \text{Ti(IV)(OH)}$$

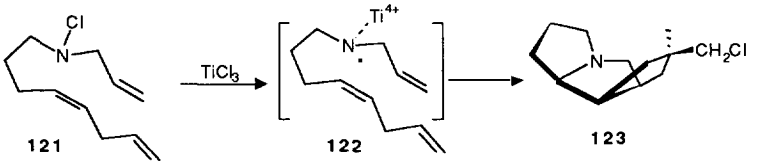
An interesting combination of peroxide based tandem radical cyclisation has been reported[121] using Ti(III).



118 119 120

Formation of R· radical from the corresponding peroxy radical by a homolytic deoxygenation is rare but it can be the major reaction pathway if the radical formed is highly stabilised[122].

N-Chloroamine **121** reacts with titanium trichloride producing iminyl radical intermediates[123]. This radical intermediate was exploited in tandem cyclisation to form *cis-syn-cis* aza-triquinane **123** as the main product.



121 122 123

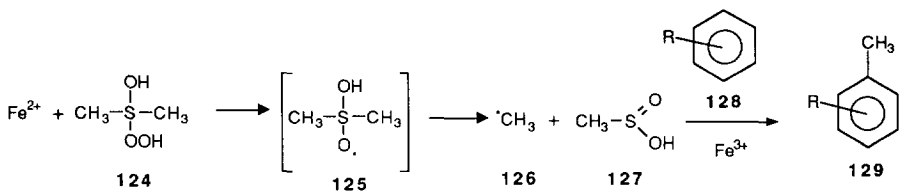
Carbon-carbon bond formation by Fenton chemistry

The mechanism of the Fenton reaction has been the subject of controversy[124] for more than a hundred years. It is generally presumed that free hydroxyl radicals are produced from the one-to-one combination of iron(II) salt and hydrogen peroxide in acidic medium.

$$[(H_2O)_6Fe^{II}]^{2+} + HOOH \rightarrow [(H_2O)_5Fe^{III}OH] + HO\cdot + H_2O$$

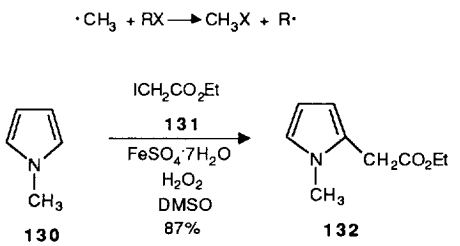
The free hydroxyl radical can react with hydrocarbons, generating carbon centred radicals which may dimerise or undergo other typical free radical transformations.

Methyl radicals are formed in the Fenton induced decomposition of hydrogen peroxide in DMSO[125], and these add to reactive substrates such as quinones, nitroaromatic compounds, thiophenes, furans, pyridines, and quinolines[126] . Benzene, benzoic acid, indole and simple alkenes are hardly alkylated.



124 125 126 127

The methyl radical can be exploited to generate other radicals[127].

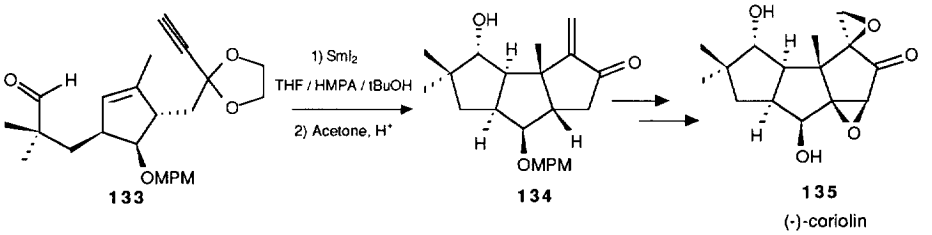


2.2 Reductive coupling of two π bonds

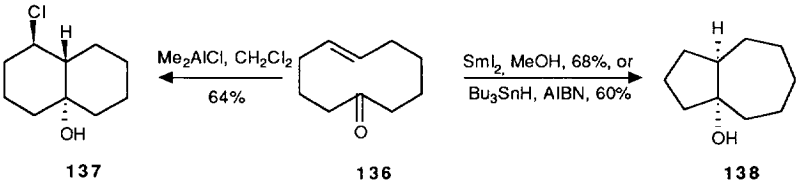
2.2.1. Ketyl-olefin coupling and related reactions

Ketyl radicals generated by SmI_2 efficiently add to electron rich and electron poor olefins in intramolecular reactions. The newly formed radical can be exploited in a tandem radical sequence or can be trapped by a second equivalent Sm(II) to form an organosamarium derivative.

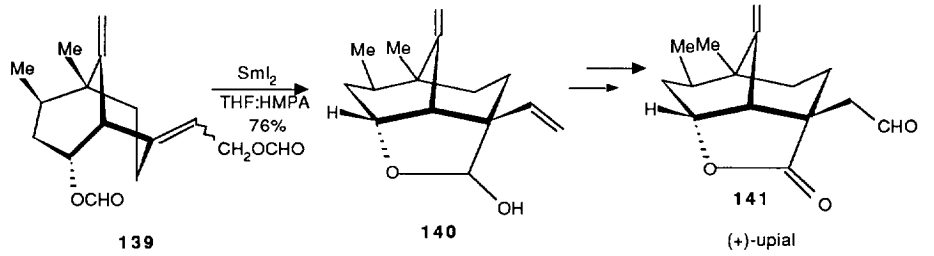
Based essentially on the work of the Curran group[128a], (-)-coriolin was prepared in an enantioselective sequence[128b]. The key step of the synthesis is a samarium(II) mediated tandem radical cyclisation of **133** in a mixture of THF / HMPA / *tert*-butanol. After the transformation of the dioxolane moiety to the corresponding ketone, the triquinane derivative **134** was isolated in 60% yield.



An interesting selectivity has been observed in the transannular cyclisation[129] of unsubstituted 5-cyclodecenones in radical versus Lewis acid catalysed electrophilic addition conditions[130]. Two sets of radical reaction conditions, Bu_3SnH / AIBN and SmI_2 / MeOH, were found to induce clean cyclisation, and both conditions gave exclusively the bicyclo[5.3.0]decan-1-ol **138**, with the *cis* ring fusion. The corresponding *cis* alkene was far less reactive than its *trans* isomer, but the radical cyclisation resulted in the same regio- and stereoisomer. This regio- and stereoselectivity was shown to be opposite to the Lewis acid mediated cyclisation which gave preferentially *trans* fusion from the E isomer and *cis* fusion from the Z isomer in a 1,6-cyclisation.

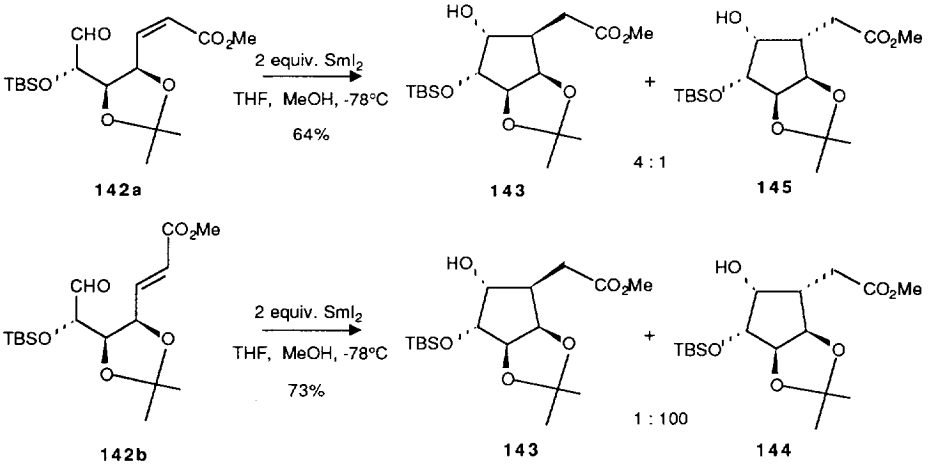


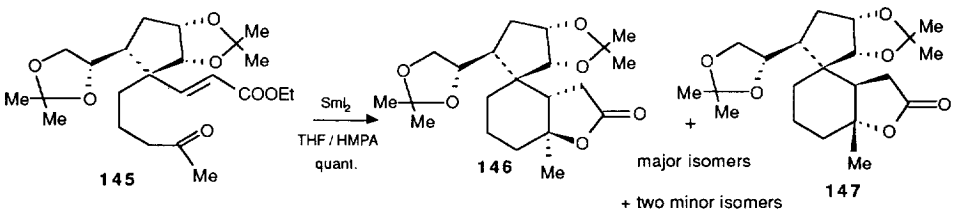
A crucial step in the total synthesis[131] of the marine sesquiterpene (+)-upial **141** was conducted with samarium(II) iodide. In the presence of 3 equiv. of SmI_2 in 2:1 THF-HMPA at 25°C, for 30 min., the biformylated intermediate **139** underwent cyclisation followed by subsequent metallation and β-elimination to the tricyclic hemiacetal in a 76% yield.

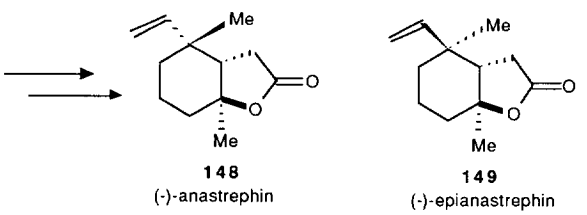


139 140 141 (+)-upial

Carbohydrate templates have been studied extensively by the Enholm group[132]. Stereoselective preparation of highly oxygenated cyclopentane substrates has been achieved using SmI_2. It was found that the selectivity of the cyclisation depends mostly on the Z/E geometry of the double bond[133]. It would appear that a *cis*-olefin **142a** in the starting substrate favors the *anti* product **143** and a *trans*-olefin **142b** favors the *syn* product **144**. The predominance of the *syn* product from the *trans*-olefin has also been reported[134] in several related noncarbohydrate cases.

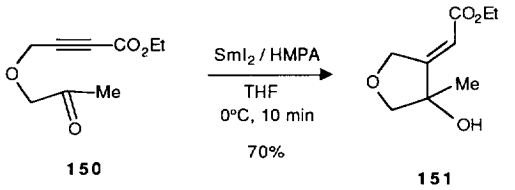






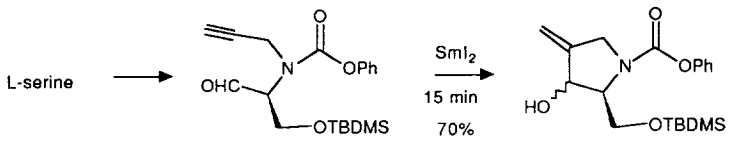
SmI_2 mediated reductive coupling reactions were explored in the total synthesis of the insect sex attracting pheromones[135] (-)-anastrephin **148**, (-)-epianastrephin **149**. In the key step of the sequence, the intermediate ketyl radical attacks the β-carbon of the unsaturated ester with an interesting stereochemical outcome. Using either Z or E olefins, two *trans* lactones (**146** and **147**) were predominant in both cases, in almost the same ratio. These facts indicate that there is no conformational bias with regard to the chairlike transition state. This is probably due to the sterically unfavorable interaction of the methyl group adjacent to the bulky ketyl-SmI_2 complex. In the absence of HMPA, only the reduced product (i.e. the corresponding secondary alcohol) was obtained.

Intramolecular carbonyl-alkyne coupling reactions promoted by SmI_2 have also been reported[136]. Five-membered carbocycles were produced in modest yields, unless the alkyne was activated[137] with phenyl, silyl or ethoxycarbonyl groups. Ketones generally provided slightly better yields than aldehydes, and E stereoisomers were isolated in all cases. Oxygen and nitrogen containing heterocycles were also prepared in this way:



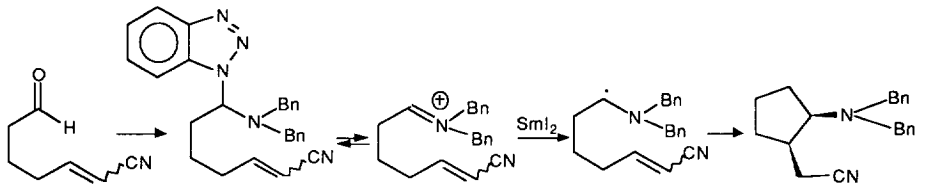
150 **151**

Precursors of the neurotoxic kainoid group of amino acids have been prepared[138] by a Sm(II) mediated construction of the trisubstituted pyrrolidine ring. The propargyl derivative **152** undergoes a rapid and efficient ring closure, to give the corresponding alkene **153** in high yields. The diastereoselectivity of the reactions were not reported, however.



152 **153**

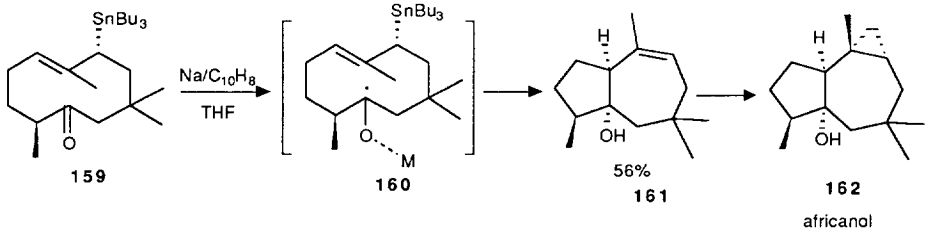
Iminium cations, derived from dissociation of α-dialkylaminoalkyl benzotriazole derivatives **155**, readily accept an electron[139a] from SmI_2. The generated 2-aza-alkyl radical may dimerise or be trapped through an intramolecular 5-*exo* (**158**) or 6-*exo* cyclisation[139b] in moderate to good yield.



154 (E : Z = 65 : 35) **155** **156** **157** **158** 63% (cis : trans = 67 : 33)

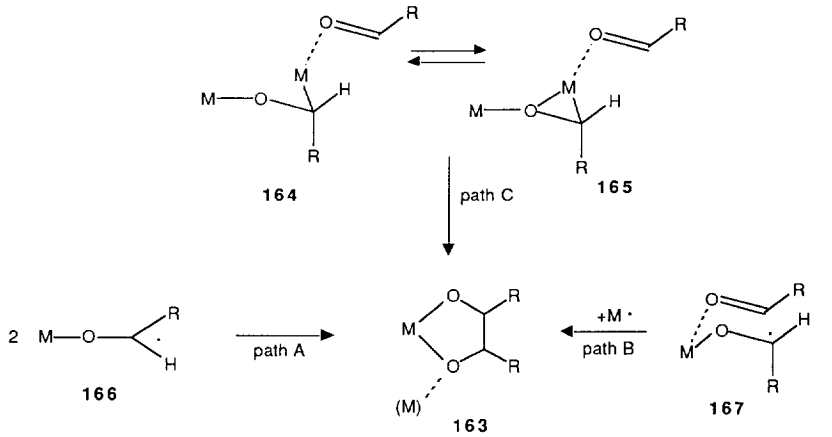
Redox systems other than Sm(II) / Sm(III), have also been tested, for example in the stereocontrolled synthesis of the sesquiterpene africanol **162** and its congeners[130b]. The stereochemistry of the transannular cyclisation was controlled through the choice of reaction conditions. In this case, $Na/C_{10}H_8$ appeared to be very selective to obtain

the *cis* ring fusion regardless of the stereochemistry of the cyclodecenone.



2.2.2. The one electron transfer mediated pinacol coupling, and related reactions

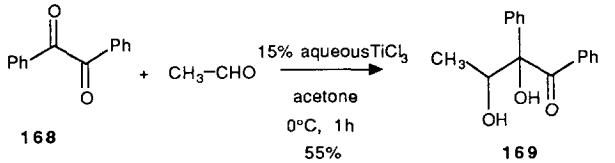
The pinacol coupling promoted by low valent metals may proceed *via* 3 different kinds of mechanisms: the dimerisation of two ketyl radicals (path A); attack of the ketyl radical an coordinated aldehyde (path B); or *via* the formation of an organometallic intermediate (metallaoxiranes) (path C).



Generally, the reaction is conducted under polar conditions. However, in intramolecular cases in which the free-radicals can react fast, and in heterogeneous media where the intermediate radicals are adsorbed and stabilised on the surface of the metal, an alternative radical pathway may be reasonable. In aprotic solvents, aromatic aldehydes and ketones generally have a reduction potential in the range of -1.8 to -2.0 V (*vs.* SCE)[140d] while aliphatic examples are in the range of -2.2 to -2.8 V (*vs.* SCE)[140d]. Coordination of a Lewis acid is expected to lower the reduction potential of the carbonyl compound[141], thereby facilitating the subsequent SET step.

The titanium method

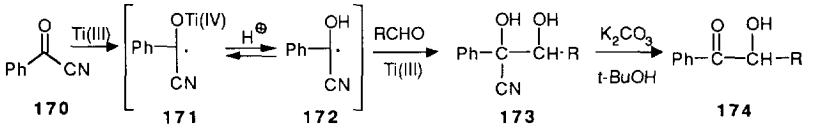
Aqueous Ti(III) was reported to convert carbonyl compounds into the corresponding carbon centred radicals, which could add to aldehydes and ketones to afford dihydroxy compounds[142]. Cyano, hydroxy, methoxy and chloromethyl functional groups were tolerated under these conditions. A further advantage of this methodology is that the intermediate alkoxy radical undergoes rapid reduction by Ti(III) ion, making the addition step practically irreversible. Hence the intermediate alkoxy radical does not suffer β-bond cleavage, an often encountered problem in heteroatom centred radical chemistry. The reaction allows the synthesis of α,β-dihydroxy ketones **169** starting from α,β-dicarbonyl compounds[143] **168**, aldehydes, and aqueous $TiCl_3$.



168 169

A similar transformation was reported[144] using SmI_2. The reaction between the diketone and the aldehyde occurred with almost complete lack of the self coupling of the aldehyde. In this case, the reaction is believed to proceed *via* a samarium 1,2-diphenylethene-1,2-diolate followed by the aldol reaction.

One of the oldest reactions in organic chemistry is the benzoin condensation. Generally, the reaction is performed under ionic conditions. A recent variant describes an electron transfer mediated coupling[145] between benzoyl cyanide and aryl or aliphatic ketones. When benzoyl cyanide is allowed to react with aqueous acidic $TiCl_3$ solution in acetic acid, a dicyanohydrin is produced by reductive coupling. When the reaction is carried out in the presence of acetone or acetaldehyde, the corresponding 1,2-diols (**173**) are observed. This reaction is an interesting example of radical umpolung. The intermediate α-cyano-ketyl radical **171** formed by inner sphere electron transfer from Ti(III) to **170**, can be regarded as a masked benzoyl radical. In general, benzoyl radicals (σ-type) add to the carbonyl O-atom, but the masked benzoyl radical (a π-type) adds to the carbonyl C-atom. Thus the reactivity of the masked functionality is reversed compared to that of the unmasked one.

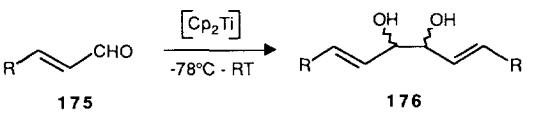


170 171 172 173 174

a) R = 4-OCH_3-C_6H_4 49%
b) R = C_2H_5 28%

Aliphatic ketones were found to be poor substrates and reasonable yields of products were obtained only when they were used as solvents or co-solvents.

Reactive titanocene can be prepared by reducing titanocene dichloride with one equiv. of magnesium (Brintzinger-van Tamelen procedure). Simple carbonyl functions, esters, and olefins as well as ethers and acetals are inert *vis à vis* this complex. α,β-unsaturated aldehydes **175**, however, react rapidly[146] at -78°C to give the corresponding vicinal bis(allyl alcohols) **176**, which are formed as a diastereomeric mixture with a diastereomeric excess of 30% in favor of the threo-racemate.



175 176

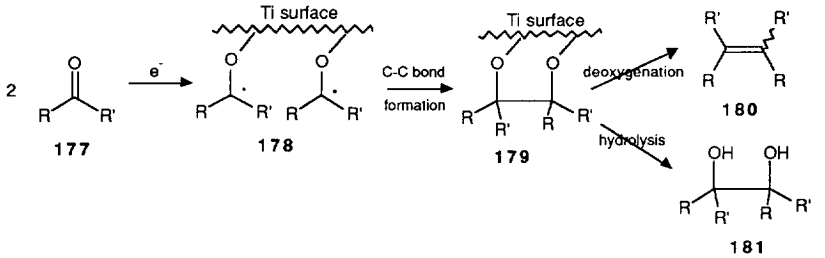
a) R = CH_3 y:89%
b) R = n-C_3H_7 y:84%

The McMurry type pinacol coupling and related reactions

The reductive coupling of carbonyl derivatives using low valent Ti species is referred to as the McMurry reaction[49]. The applications of the McMurry reaction have been reviewed in many recent articles and reviews[49, 50], so only the SET aspects and some recent developments of this reaction will be described here.

The reaction is believed to proceed by dimerisation of the ketyl radical anion, followed by deoxygenation when

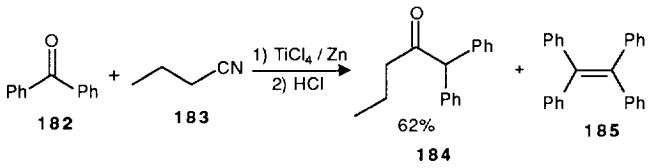
the reaction is carried out at an elevated temperature.



It was also found that, by lowering the temperature (at or below room temperature), the reaction can be stopped at the *vic*-diol **181** level. However, the alkene **180** remains a more or less important side product.

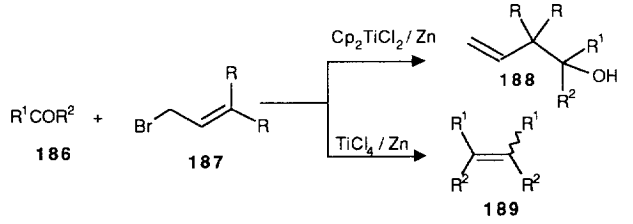
In its simplest form, the reaction affords symmetrical olefins or diols from the corresponding ketones or aldehydes by homocoupling. Coupling reaction between two different carbonyl compounds[147] can also be carried out. However, in order to avoid self coupling in these reactions, the simultaneous slow addition and/or the use of an excess of one of the reagents is usually necessary. Using this technique, intermolecular reductive coupling can be performed between two different functionalities. For instance, coupling reactions of nitriles with carbonyl and nitro compounds[148] have been described.

When a mixture of ketone **182** and nitrile **183** is treated with $TiCl_4$/Zn (1:2), the desired ketone **184** was obtained in the presence of the symmetrical olefin **185**. Aldehydes afford the olefin as the major product.

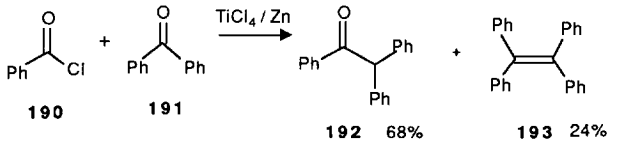


It is believed, that the first SET process reduces the carbonyl to give the ketyl radical anion, which reacts with the nitrile. Aromatic aldehydes or ketones give[149] higher yields.

Interestingly, polar *versus* radical reactivity can be tuned by using different Ti compounds. Allyl bromides, which are considered to react principally *via* an electrophilic polar pathway can couple with aldehydes or ketones in the presence of Cp_2TiCl_2/Zn to afford the homoallylic alcohol with a good regioselectivity (Cp_2Sm is reported[79] also to react *via* an electrophilic mechanism). By way of contrast, use of the $TiCl_4$/Zn redox system, which is presumed to generate persistent ketyl radicals, affords the McMurry olefin.



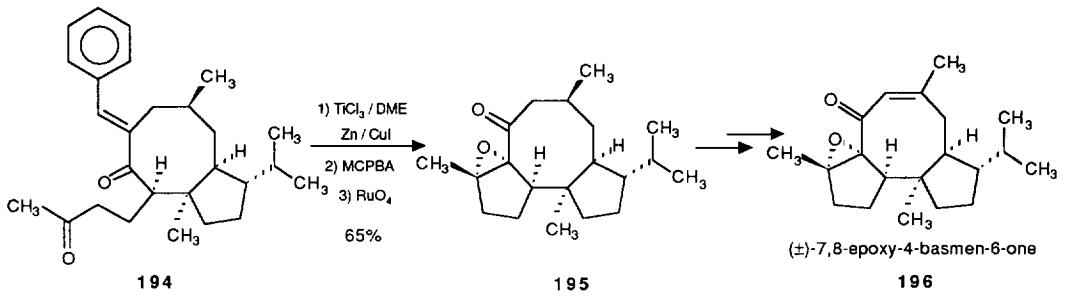
Low valent Ti promotes the reductive coupling reactions[150] of carboxylic derivatives with aromatic ketones. When acyl chloride **190**, and benzophenone **191** were treated with $TiCl_4$/Zn, the ketone cross coupling product **192** was obtained along with olefin **193**, arising from reductive self-coupling of benzophenone.



Unfortunately, the McMurry reaction suffers from some limitations. Neither halogen substituents nor NO_2 groups are tolerated. The high oxophilicity of Ti complicates the reaction with oxygenated molecules. In spite of these handicaps, several variants of this process have been applied to the synthesis of natural products.

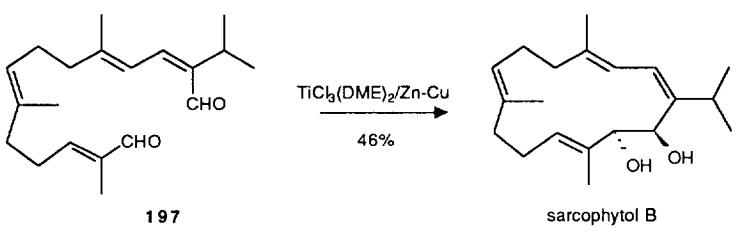
The stereochemistry of the low valent Ti mediated intramolecular pinacol coupling reaction was investigated for a variety of ring sizes[151] and with a variety of stereogenic centres. Calculations, predicting the stereochemical outcome of the reaction using MM2 force field methods agreed well with the experimental results. Accordingly, small rings (up to six membered cycles) preferentially give the *cis*, whereas larger rings (10 membered or larger) preferentially give the *trans* diol.

The Ti(III) / Zn-Cu redox system mediated coupling reaction was one of the key steps in the synthesis[152] of diterpenoid **196**. Treatment of advanced intermediate **194** with $TiCl_3$-dimethoxyethane complex (19 equiv.) and zinc-copper couple (75 equiv.) in refluxing dimethoxyethane for 1.5 h led to smooth carbonyl coupling affording a sensitive diene, which was transformed into **195** in two steps.



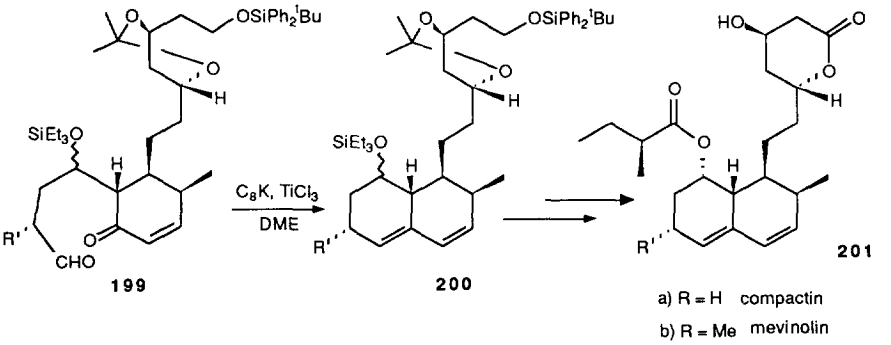
In an example of the dialdehyde pinacol coupling in the presence of a Mg(Hg)-$TiCl_4$ reagent, Corey and coworkers[153] obtained *cis*-1,2-cyclohexane diol in 32% yield.

Titanium induced pinacol coupling was the key step in the synthesis of sarcophytol B[154]. Dialdehyde **197** was added *via* syringe pump over 30 hours at -40°C to a stirred slurry of a low-valent titanium reagent prepared by reduction of $TiCl_3(DME)_2$/Zn-Cu in DME, and led to **198** in 46% yield.

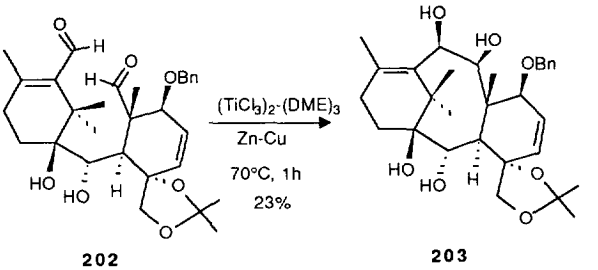


A similar McMurry type approach was used[155, 156] to prepare other members of the cembrenoid family.

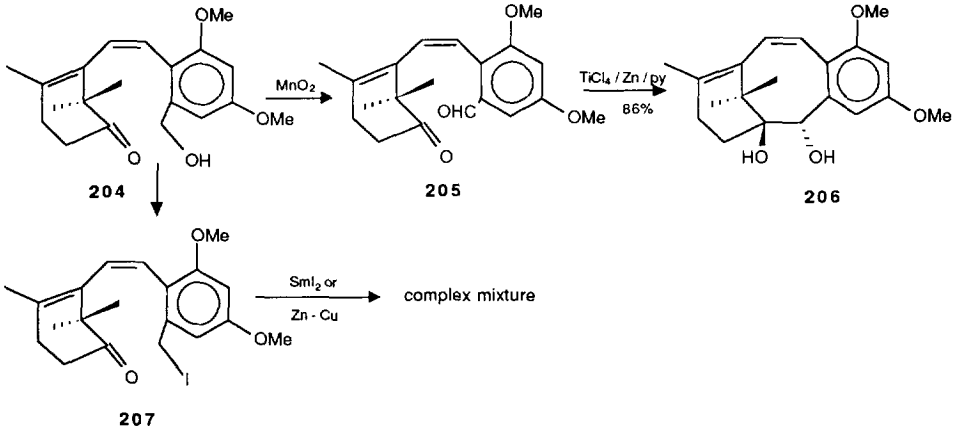
In the total synthesis[157] of (+)-compactin **201a** and (+)-mevinolin **201b**, the advanced intermediate **200** was prepared by a modified McMurry reaction, using C_8K and $TiCl_3$.



Taxol is currently one of the most popular synthetic targets, because of its challenging structure and clinically significant antitumor activity. McMurry type coupling has been shown to be particularly well suited to assemble the highly oxygenated ABC ring system, as in Nicolaou's total synthesis[158]. The suitably functionalised dialdehyde **202** was subjected to $TiCl_3$/Zn-Cu coupling and afforded the *cis*-diol **203** in 23% yield.

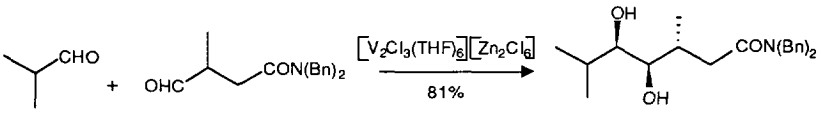


A recent approach towards the taxan structure involves a pinacol closure[159] of the B ring. The paper notes the failure of the Barbier chemistry in the cyclisation, using samarium(II)-mediated methods or a Zn-Cu couple.



The vanadium method

Pedersen et al. described[160] a well-characterised and homogeneous vanadium(II) halide reagent ($(V_2Cl_3(THF)_6)_2(Zn_2Cl_6)$), which promoted intermolecular pinacol cross coupling reaction. The reagent was prepared from $VCl_3(THF)_3$ and zinc dust. The high stereoselectivity and reaction rate observations indicated that chelation may play important role in this reaction.

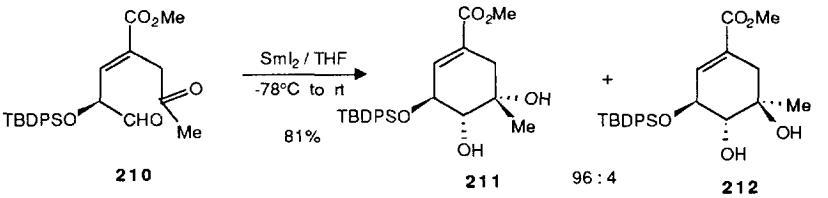


208 **209**

syn / anti 14 : 1

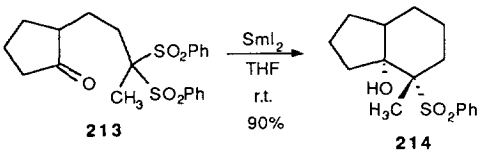
The samarium method

The first example of an intramolecular pinacol coupling using SmI_2 was reported by Kagan and co-workers[161]. Since then, extensive studies of related couplings of ketoaldehydes[162a] and dialdehydes[162b,c] with SmI_2 have been reported. An interesting feature of this pinacol coupling is the preponderance of *vic. cis*-diols, when 5 and 6 membered cycles are formed. When alkoxy substituents are present on each of the carbon atoms adjacent to the carbonyl groups, the major *cis*-diol will have an orientation opposite to the two substituents. This stereoselectivity can be the result of steric and dipolar effects, possibly involving the ketyl radical and the adjacent alkoxy group (β-effect[163]). In the presence of only one substituent, the major product is still the *cis*-diol, with variable amounts of the *trans* byproduct, as shown in the conversion of **210** into **211** and **212**.



210 **211** 96 : 4 **212**

Reductive pinacol-type cyclisation of keto bis-sulfone **213** in the presence of freshly prepared SmI_2 (kept in the presence of excess Sm) in THF at room temperature afforded **214** as a single diastereomer[164]. The *cis* stereochemistry of the hydroxyl and sulfone substituents in this and in other examined products suggest that, in spite of the widespread belief that sulfones are poor Lewis bases, samarium coordinates to both the carbonyl and sulfone oxygens in the transition state of the cyclisation. Reductive coupling of **213**, using low valent titanium reagents was reported to be unsuccessful.

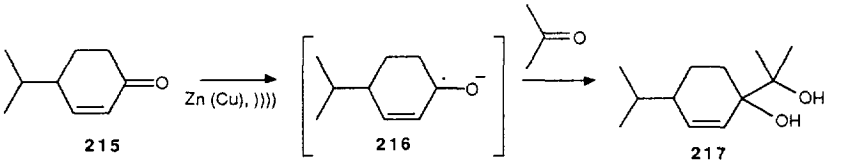


213 **214**

The zinc-copper method

Reductive coupling of diaryl, arylalkyl, and α,β-unsaturated ketones in the presence of Zn metal has been studied[165] extensively. It has been shown that carbon-carbon bond formation occurs frequently in the classical Clemensen reduction and in its modifications. Radical and radical ionic species are likely to be involved. In a recent

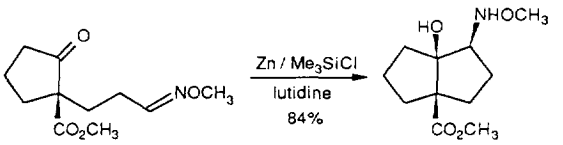
study[165e], it was postulated that the formation of these species, (i.e. the electron-transfer processes) occur at the *surface of the metal*, where the ketyl **216** should be tightly adsorbed. According to this mechanism, the initial step is a single electron transfer from the metal to the conjugated carbonyl **215**. The next step can be either reaction with acetone, which gives an unstable radical, rapidly stabilised by the second SET step, or the reduction of **216** to a dianion which reacts with acetone. It is not known, however, whether the catalyst salt used acts as an electron carrier by its capacity to bind to the Zn bulk and the organic compound. It was shown that sonication accelerates the reaction.



215 **216** **217**

85%

In 1973, Motherwell reported[166] a novel reaction for the transformation of ketones to olefins involving the use of Zn / Me_3SiCl as reagent. Recognising the potential usefulness of this methodology, the same reaction was used to induce radical cyclisation with δ,ε-π-systems (olefins, ketones and imines)[167]. A number of *cis* fused five membered rings were thus prepared with a high tolerance of numerous functional groups.



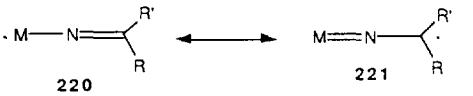
218 **219**

2.2.3 C-C coupling reactions via α-amino- and α-imino radical intermediates

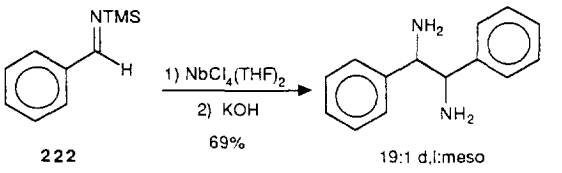
The niobium method

d^1 Niobium reagents [Nb(IV) compounds, $NbCl_4(THF)_2$] promote reductive coupling[168] of N-(trimethylsilyl)imines or nitriles. This reaction has a considerable synthetic potential because of the relatively few methods for preparing vicinal diamines. For example, unlike the carbonyl analogs, N-alkyl (or aryl) imines show little or no reactivity[169] with low-valent titanium reagents.

The coupling mechanism in the presence of Nb(IV) can be rationalised by the resonance structure **220**-**221**.



220 **221**



222 19:1 d,l:meso

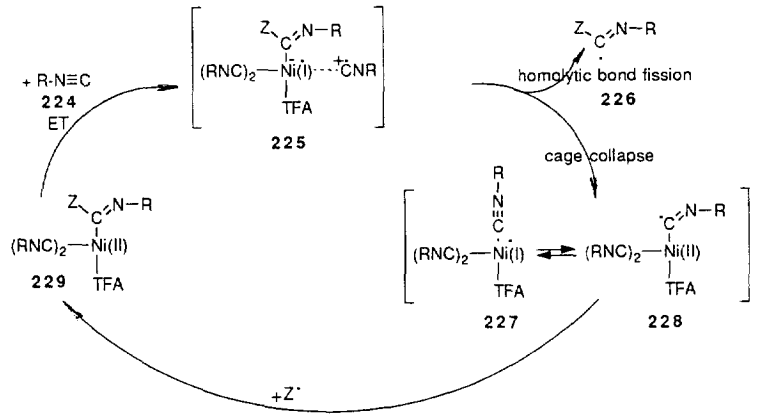
223

Dimerisation of this metal protected α-amino radical leads to the diimido compound. Hydrolysis then gives the unsubstituted vicinal diamine.

Reductive pinacol coupling of carbonyl compounds was recently also described[170] using Nb(III) chloride. However, this Nb reagent is considered as a two- and not a one-electron reductant.

The nickel method

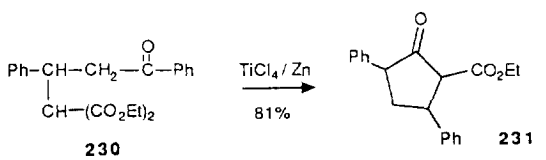
Polyisocyanides have many interesting properties: they adopt an extended helical structure, and show nonlinear optical and ion channel properties. Homogenous living polymerisation[171] based on catalysis by $[(\eta^3\text{-}C_3H_5)Ni(OC(O)\text{-}CF_3]_2$ allows the preparation of polyisocyanides in a very controlled fashion. Careful mechanistic investigations using ESR, cyclic voltammetry, and bulk magnetic susceptibility measurements produced evidence for the reduction of nickel (II) to nickel(I) by the isocyanides, implying a one electron transfer mechanism. Chain transfer proceeds differently under N_2 and O_2. The most probable chain transfer process has been determined to be the homolytic nickel-iminoacyl bond breakage followed by reinitiation at the metal centre. There are several literature precedents for homolytic bond fission; in fact, it is the most generally accepted route for organonickel decomposition[172]. The proposed chain transfer under nitrogen is depicted in Scheme 7.



Scheme 7

2.2.4 Reactions of esters and amides

Cyclisation of ketoesters is a powerful tool for the preparation of cycloalkanones[173]. In the presence of Ti-Zn couple, the mechanism of this reaction appears to be an exact analogue of the cyclisation of carboxylic derivatives with aromatic ketones[174]. The reaction allows the formation of cyclic β-ketoesters in good yield.



The reaction can be extended to the synthesis of the acyloxycarbocycles and various heterocycles. The cyclisation of acyl-amides[175] is particularly noteworthy:

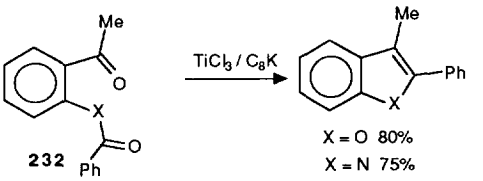
1) the reaction can be applied to a large variety of amides (aliphatic, aromatic, heteroaromatic, and tolerates other ester functions);

2) the chemoselectivity is high[176]: the keto-amide cyclisation is preferred over the keto-ester coupling;

3) the reaction does not require high dilution, in contrast to other derivatives;

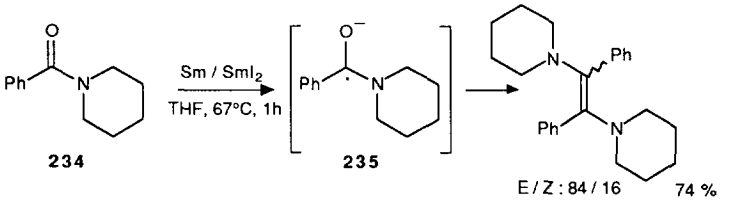
4) in line with free radical reactions, the cyclisation is not sensitive to steric factors[177].

Extension of the original ketoester cyclisation to the closely related acyloxycarbonyl- and acylamidocarbonyl compounds affords benzofurans and indoles, respectively[178].



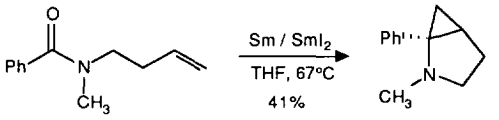
232 233

The samarium / samarium (II) diiodide system mediates deoxygenative coupling[179] of aryl amide derivatives. The coupling reaction proceeds even in the presence of a catalytic amount of SmI_2. Remarkably, the samarium metal can be replaced by Mg, which has a similar reducing power. Two mechanistic pathways were proposed for this coupling reaction, each beginning with a one-electron reduction of the amide to afford an radical anion of type **235**. The first alternative postulates dimerisation followed by deoxygenation to provide the *vic*-diaminoalkene **236**. The second hypothesis suggests that the initially formed radical anion undergoes further reduction to give an α-aminocarbene intermediate.



234 235 236

Amides containing an olefin at an appropriate position (**237**) undergo cyclopropanation[179].



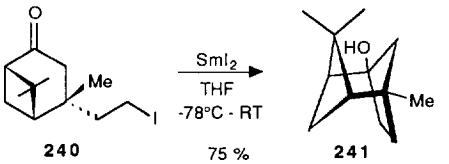
237 238

2.3. Ketyl-halide coupling; The radical Barbier reaction, does it exist?

One of the most useful and notable applications of samarium chemistry is the samarium-Barbier coupling between ketones and halides. The possibility to control the tandem coupling increases the synthetic utility of the reaction. In spite of intensive mechanistic investigations, no unified mechanism has been proposed. Evidence was found that, in the intermolecular reactions, the polar pathway (i.e. the formation of an organosamarium

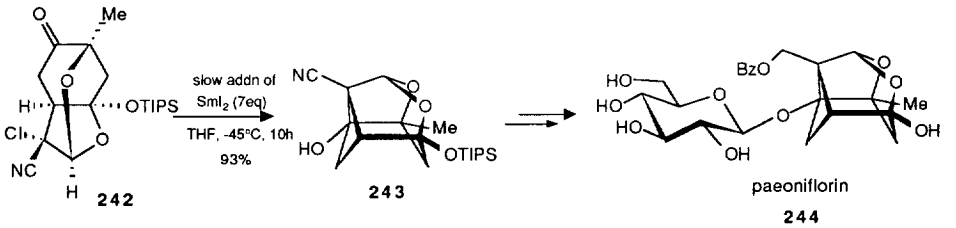
intermediate) is dominant. However, in intramolecular reactions, radical/radical anion intermediates may operate. Other metals, (for example: Na, used in particular in acyloin condensation) act in a similar way.

The ability to generate highly strained ring systems is one of the most promising features of the samarium-Barbier strategy. The reaction necessitates fairly high dilution (15 mM), and an initiation at -78°C. Anhydrous or hydrated iron complexes and salts, including $FeCl_3$, $FeCl_2$, $Fe(acac)_3$, $Fe[DBM]_3$ appear to catalyse the process effectively[180]. Iodoketone precursors (**240**) give higher yields than the bromo counterparts and chlorides are inert in most cases.



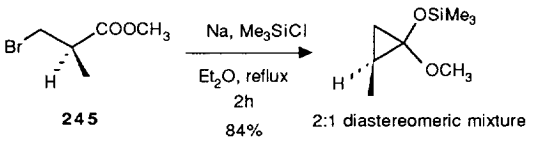
240 75 % **241**

Paeoniflorin, a complex terpenoid-β-glucoside widely used in traditional Chinese medicine, has defied chemical synthesis for almost three decades. The SmI_2 induced cyclisation[181] of **242** to **243**, corresponding to a normally unfavorable aldol cyclisation, proceeded in excellent yield to give the core substructure of paeoniflorin **244**.



242 **243** paeoniflorin **244**

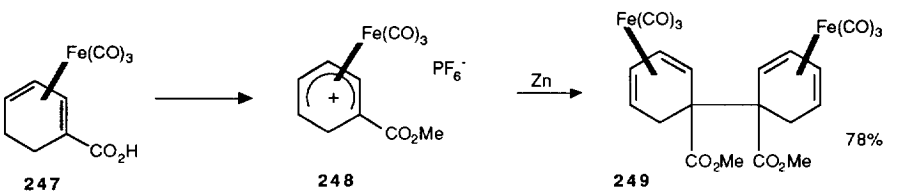
It was shown that optically active diesters and some β-halo esters undergo sodium induced cyclisation without loss of optical purity[182]. Sonication allows a lower reaction temperature and thus access to strained cycles, which are in some cases, inaccessible by conventional techniques.



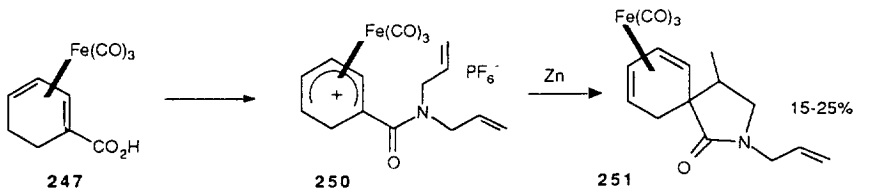
245 2:1 diastereomeric mixture **246**

2.4. One electron reduction of carbocations

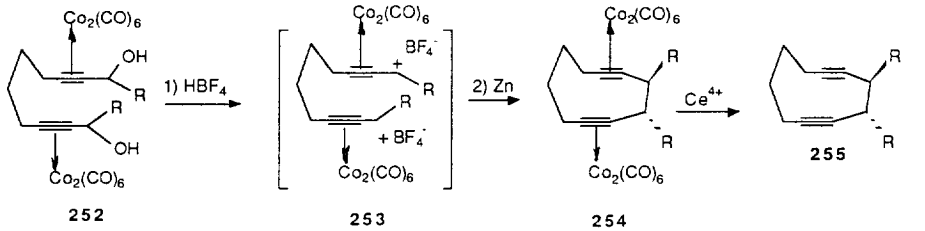
Zinc dust efficiently mediates the reductive dimerisation of dienyl tricarbonyliron cations[183], such as **248**, which proceeds in good yield (78%). However in the intramolecular radical trapping experiment, cyclisation afforded only 15-25% of the lactam **251**, nevertheless indicating that radical intermediates might be involved.



247 **248** **249**

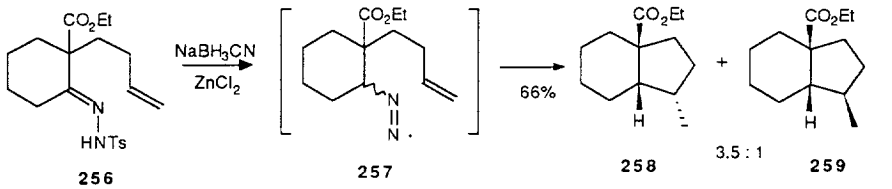


Propargylium salts provide a novel and convenient source of radicals *via* Co cluster intermediates[184]. This method is particularly useful in an intramolecular process to prepare the cyclic 1,5-diyne **255** with high stereoselectivity (de=80%).

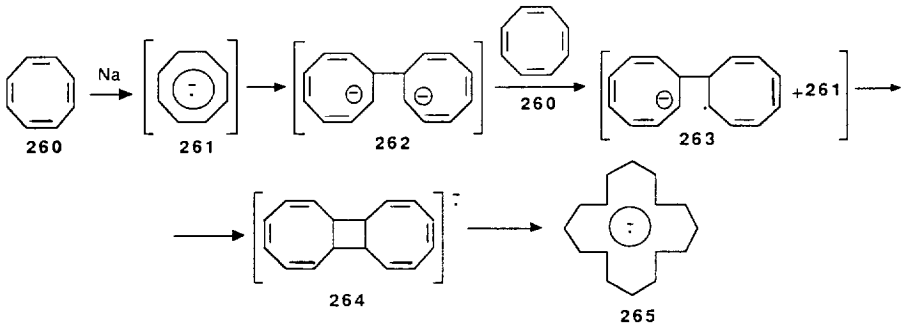


2.5. Miscellaneous

A radical mechanism has been suggested for the reduction of a ketone tosylhydrazone **256** with $NaBH_3CN$ / $ZnCl_2$. In an intramolecular radical trap experiment[185] the reaction affords the *endo* methyl isomer, typical of a free radical cyclisation.



Sodium [8]-annulene radical anion **261**, prepared from [8]-annulene **260** in HMPA with freshly distilled sodium metal mirrors, readily dimerises to form the anion radical of [16]annulene[186] **265**. Kinetic studies revealed that the reaction is of second order in **261**, and an ET mechanism was proposed. Interestingly, the corresponding potassium derivative does not give the dimerised product. This intriguing difference in reactivity was explained by ion association, which inhibited the formation of **265**.



19 Electron complexes emerge as powerful one electron reducing agents[24] which have been used in organo-transition metal chemistry. For example, $[Fe^{I}(\eta^5\text{-}C_5H_5)(C_6R_6)]$ complexes, having E° values (*vs.* SCE) in DMF of -1.36 V (R=H) and -1.57 V (R=Me)[187a], mediate CO_2 reduction to oxalic acid and other carbonates. Synthetically useful processes can be also achieved with organic halides[187b] which alkylate the sandwich complexes *via* ET process. This reaction allows access to crowded compounds which are otherwise difficult to prepare[187c].

3. Carbon-carbon bond formation *via* oxidative electron / hole transfer reactions

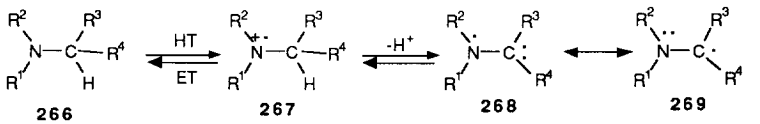
3.1 General considerations

Among one electron oxidation processes, autoxidation is a well known transformation which may also result in C-C bond formation. However oxidation in general, especially using high valent metal salts, has found many synthetic applications. Among the metal salts, Mn(III) $[Mn(OAc)_3{\cdot}2H_2O]$ and Ce(IV) [especially ceric ammonium nitrate, CAN, $[(NH_4)_2Ce(NO_3)_6]$ have emerged as powerful one electron oxidising agents. The use of peroxydisulfate ion in the presence of Ag^{2+} salts is particularly effective in electron transfer reactions. Vanadium (V) as well as lead (IV), thallium(III), iron (III) and Ir(VI) salts have also been used (*vide supra*).

Halogens and halogen derivatives have also been used in oxidation processes, to prepare carbon centred radicals. The most thoroughly studied reactions of ClO_2 with organic compounds are those involving oxidation of amines in aqueous solutions[188], yielding radical cations[189]. In most cases, a single mechanism involving the rate determining formation of a cation radical is operative.

Under mild oxidising conditions, electron transfer can be directed selectively from the most ionisable functionality of a multifunctional molecule. While the reactions proceed almost exclusively *via* inner sphere mechanism, coordination patterns play also an important role in this selectivity.

1) Tertiary amines are among the most easily oxidised neutral organic substances since their oxidation potentials are between +0.8 to +0.5 V. The E° changes on substitution, and the tendency can be predicted; for example amides have larger E° than carbamates. SET oxidation of amines leads to the formation of amine radical cations (aminium radicals, **267**), which, may undergo different transformations. Among these reactions the most common is the α-CH deprotonation, to produce α-amino radicals. This deprotonation is important in the presence of base (which can even be the solvent) or other nucleophiles. Since the radical cations of tertiary amines are much more acidic than the amines themselves, they can also be deprotonated competitively by the unoxidised starting tertiary amine.



266 **267** **268** **269**

Other electrofugal groups, (R_3M where M=Si, Sn, or Ge etc.) at the α-position may also undergo heterolytic fragmentation. Silane cation radical fragmentations are exceptionally fast. These fragmentations are favored by increasing the solvent polarity (more importantly by protic solvents) and by the addition of coordinating salts (e.g. $LiClO_4$).

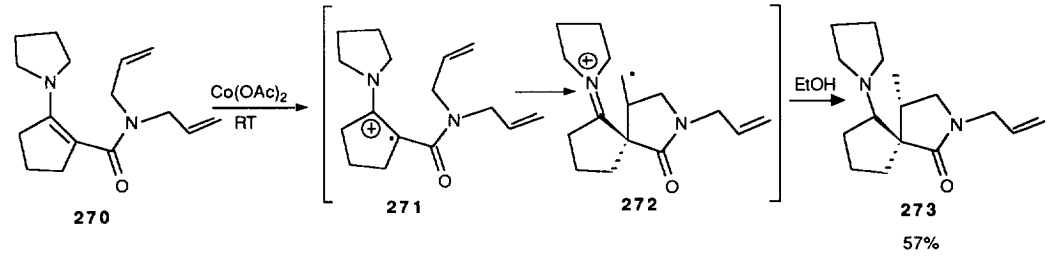
2) Among the electron-rich Π-systems, enolates are moderately easy to oxidise. The oxidation potentials for phenyl vinyl sulfide, phenyl vinyl ether, and N-methyl-N-vinyl acetamide have been recorded as 1.42, 1.62 and 1.55 V *vs.* SCE[140]. Enolisable dicarbonyl compounds, enol ethers and conveniently substituted cyclopropanes also can be easily oxidised.

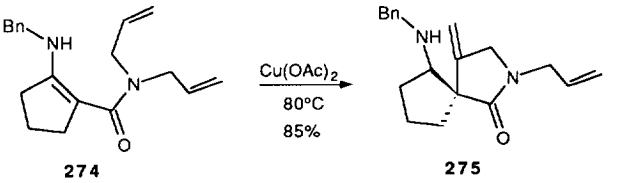
3) Olefins and aryls cannot be oxidised, unless activated, by any of the common one electron oxidisers (methylcyclohexene E°=1.77 V *vs.* SCE)[190]. Electrofugal substituents may render the reaction possible.

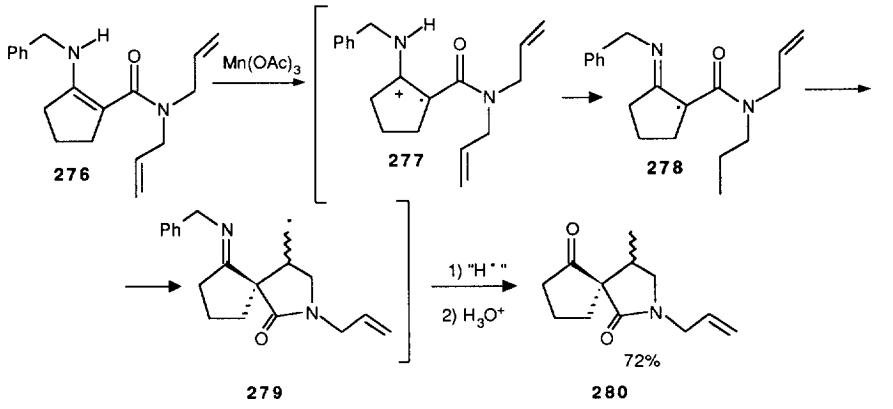
3.2 One electron oxidation of nitrogen-compounds

Oxidation of enamines

Enamines **270** and **274** can be oxidised[191] by metal salts such as $Co(OAc)_2$, AgOAc, CuCN, or by $Cu(OAc)_2$. For the overall transformation, logically, if no radical chain mechanism is operating, two equivalents of one electron transfer oxidiser is required, except when Cu(II) is used. In this case, less than two equivalents of reagent is allowed, because the formed Cu(I) undergoes disproportionation to Cu(II) and Cu(O), thus partly regenerating the oxidising agent. The radical cation which is formed reacts intramolecularly with unactivated olefins, producing cyclised azaspiro products **273** and **275** in good yields. The exocyclic radical is reduced by the solvent (EtOH), or undergoes formal hydride elimination[192] when $Cu(OAc)_2$ is used.

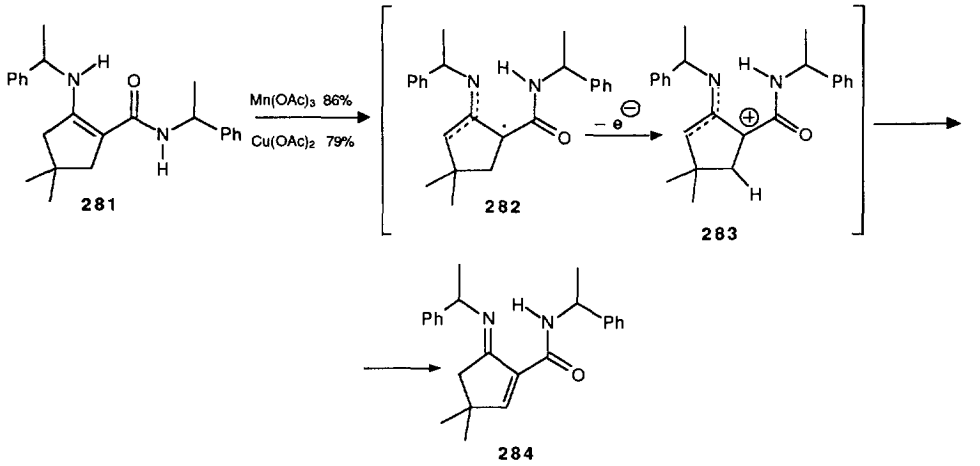




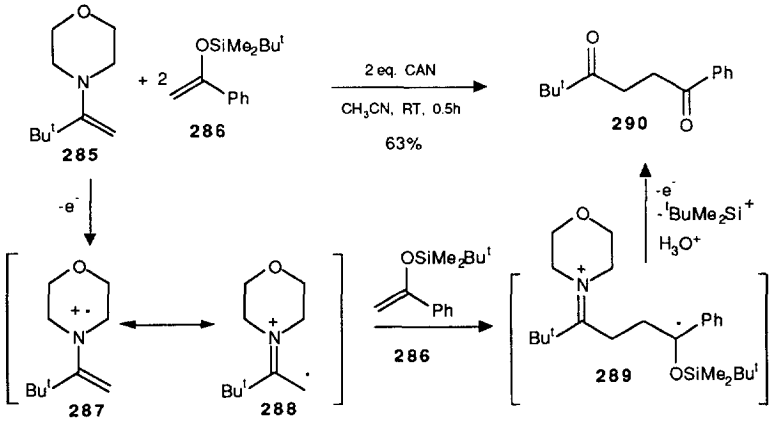


Azaspiranic systems were prepared by Mn(III) oxidation[193], from N-alkyl-N-unsaturated alkyl-β-carboxamidoenamines (**276**). The reaction was explained by the formation of radical cation **277**, which equilibrates with the corresponding radical-imine of type **278**. Spirolactam **280** was formed selectively. The diastereoselectivity is opposite to that observed in the case of β-ketoamides[194].

Typical secondary, but synthetically useful reactions are observed when overoxidation of the radical is faster than the addition reaction. In the absence of olefins or of an alkene substituent, the oxidation of ketoesters by $Mn(OAc)_3$ leads to the formation of C-C and/or C-O dimers[195]. When enamines of β-ketoamides are oxidised by $Mn(OAc)_3$ or $Cu(OAc)_2$ in the absence of radical acceptors, dimers were not produced, but α,β-dehydrogenated compounds were isolated instead in good yields[196].

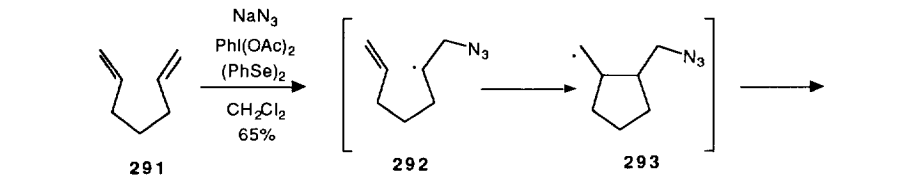


The reaction of pinacolone enamine **285** and electron rich olefins such as α-(*tert*-butyldimethylsiloxy) styrene **286** was examined[197] in the presence of 2 molar equivalents of various metallic oxidants such as Mn(III), Ag(II), Fe(III), and Ce(IV) compounds. Among these oxidants, Ce(IV) nitrate (CAN) gave the best result and afforded product **290** in a 63% yield.

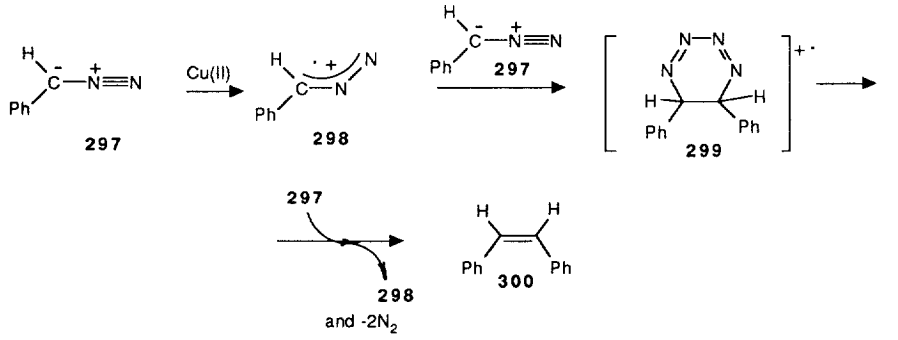


Oxidation of diazo- and azido-compounds

Hypervalent iodine reagents react principally *via* a two electron, polar mechanism in the dark. In the presence of easily oxidisable azide anions (E_{ox}=0.78 V *vs* SCE)[198], however, the reaction follows a radical cation pathway[199]. It was suggested that the fastest process occurring under the employed reaction conditions is the oxidation of the azido anion to the corresponding azido radical by $PhI(OAc)_2$. Addition of this radical to the double bond leads to a carbon radical that is rapidly trapped by radicophiles. Application of this reaction to azido-phenylselenylation gave the expected product with anti-Markownikoff regioselectivity. Evidence for the proposed mechanism was found in an experiment starting from 1,6-heptadiene. Three products were isolated, in a ratio 1:1:1 (65%). The fact that open chain products **294** and **295** were formed in considerable amounts indicates that the trapping of carbon radicals by diphenyl diselenide is a fast process which occurs at a rate comparable to that of the cyclisation.



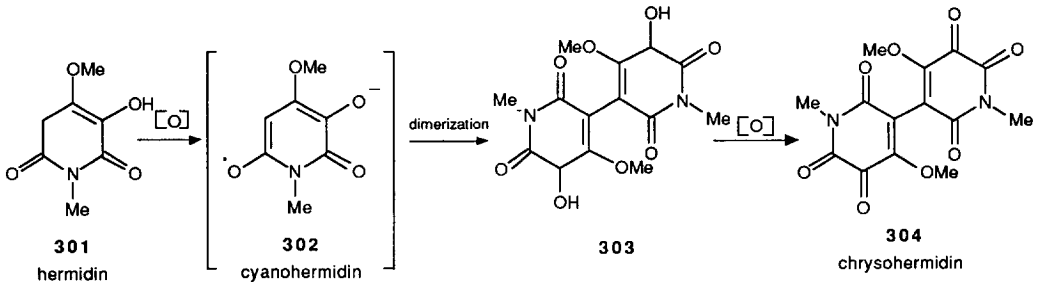
The formation of dimeric olefins from phenyldiazomethane **297** has been studied extensively. The electrocatalytic reaction was initiated using ceric[200] and cupric salts[201], lithium bromide, rhodium complexes, and chloranil. Although a chain sequence involving radical cation **298** was proposed for the case of cerium(IV), an alternative carbenoid mechanism has often been written for these reactions. Recently, it was shown[202] that the mechanism involves a concerted [4+2] cycloaddition between phenyldiazomethane **297** and 298. The preferential formation for *cis*-olefins was explained by the preferred transition state for the cycloaddition. One of the most interesting aspects of the reaction is that a forbidden [3+3] cyclodimerisation of 1,3 dipolar species is turned into an allowed [4+2] process by one electron removal.



3.3 Oxidation of active methylene compounds

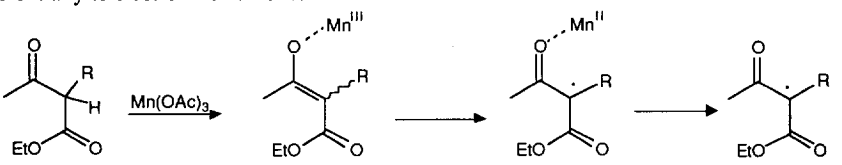
Oxidative coupling *via* autoxidation

The *Mercurialis perennis L.* plant alkaloid hermidin **301**, undergoes dimerisation[203] by autoxidation *via* the transient blue radical-anion cyanohermidin, **302**, and forms chrysohermidin **304**.



Manganese(III) mediated oxidative coupling

Essentially due to the extensive work of the Snider group, the manganese(III)-induced oxidative addition of enolisable carbonyl compounds to alkenes has received renewed attention in recent years[19i, 204-229]. It is presumed that the reaction begins with a one electron oxidation[206] to produce an electrophilic radical which adds to an alkene. The slow step in this process is the formation of Mn(III) enolate **306**, which rapidly loses Mn(II) to give the acyclic manganese free-radical **308**. This free radical may undergo an inter- or more frequently an intramolecular addition, preferentially to electron rich alkenes.



It is well recognised that the nature of the termination step has a determinant influence on the selectivity and yield. Mn(III) acetate (but not $Mn(pic)_3$) is not an effective quench for carbon centred radicals, so that the process must be terminated in different ways:

1) The reaction may be terminated by hydrogen abstraction. The hydrogen source may be the solvent. Ethanol quenches primary and alkenyl radicals efficiently, but acetic acid is less reactive. The starting material also can serve as the hydrogen source, and in an ideal chain process, a catalytic amount of Mn(III) would be sufficient. Using $Mn(OAc)_3 \cdot 2H_2O$, complete consumption of the starting material was observed in the presence of 0.5 equivalent of Mn(III) salt which indicates a chain length of around 2.

2) To suppress H abstraction, which in some cases is not a desired process, the termination of the reaction can be the reduction or oxidation of the last formed carbon radical.

i) Mn(II) salts produced in the reaction can also reduce alkyl radicals[207]. In some cases, supplementary addition of Mn(II) considerably increases the yield, which indicates that this terminating procedure may be operating.

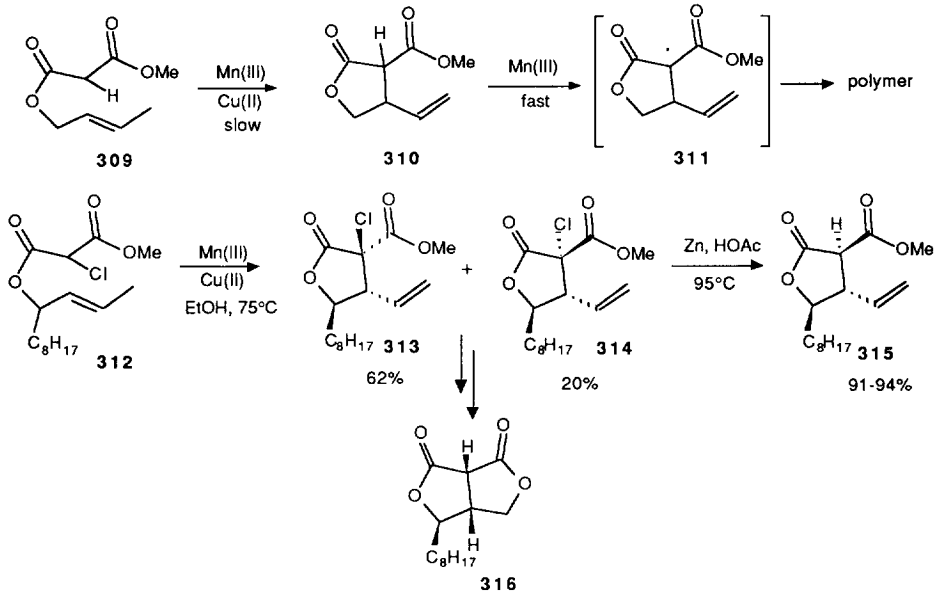
ii) The reaction can be terminated by a formal oxidative β-hydride elimination[208] to give an alkene with

$Cu(OAc)_2 \cdot H_2O$. The amount of Cu(II) is of no importance, if the cyclisation is much faster than oxidation of radical by Cu(II). This is often the case, particularly when the initial radicals are centred on tertiary carbon and would, on oxidation, form an unstable α-carbonyl cation. Radicals on a secondary carbon however, appear to be oxidised more readily than on a tertiary one. For this reason, and to prevent premature oxidation, the use of a catalytic amount of Cu(II) is suggested. The second equivalent of Mn(III) reoxidises Cu(I) to Cu(II).

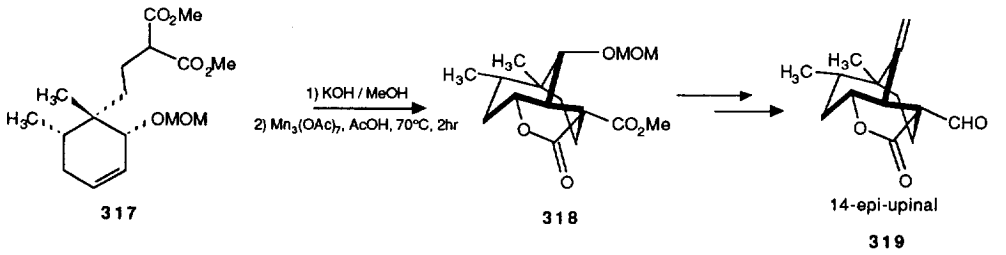
The γ-lactone synthesis

The "one step" γ-lactone synthesis was among the first applications[209] of the Mn(III) mediated oxidative cyclisations. As discussed above, complexation occurs in the first step between the Mn salt with the oxo-oxygen, followed by ET, enolisation and addition of the carbon centred radical to the olefin. Removal of the second electron converts the adduct radical to the corresponding cation, which undergoes electrophilic cyclisation. Recently, it was shown that sonication accelerates the reaction, and that Mn(II) formed is reoxidised under the reaction conditions to Mn(III), allowing the lactonisation to proceed with only a catalytic amount of Mn(III)[210].

Unsubstituted malonate esters (malonates having α-hydrogens, e.g. **309**) generally do not afford the desired lactone since the product oxidises more rapidly[211] than the starting material. For instance, reaction of α-alkyl or α-chloro (**312**) substituted derivatives with two equivalents of $Mn(OAc)_3 \cdot H_2O$ and one equivalent of $Cu(OAc)_2 \cdot H_2O$ in ethanol provides 62% of **313** and 20 % of **314**, which were reduced to a single isomer **315** with Zn / acetic acid. Both isomers **313** and **314** were converted into the avenaciolide precursor **316** in a short sequence.

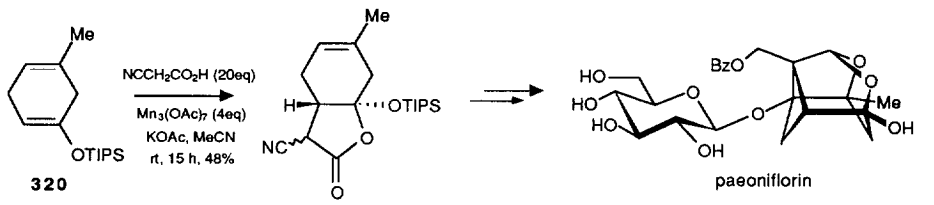


An elegant example of this oxidative cyclisation is Paquette's 14-*epi*-upinal synthesis[212]. Under typical conditions, the cyclisation of **317** afforded the complex structure of **318** in good yield and selectivity.



317 318 319

There are some exceptions, however, to the use of unsubstituted malonate derivatives for γ-lactone synthesis. A Mn(III) promoted lactonisation was used in the synthesis of paeoniflorin[181]. The annulation step of a suitably protected dihydro-*m*-cresol derivative **320** with cyanoacetic acid provided **321**, which contains all 10 carbons of the terpenoid part of the natural product.

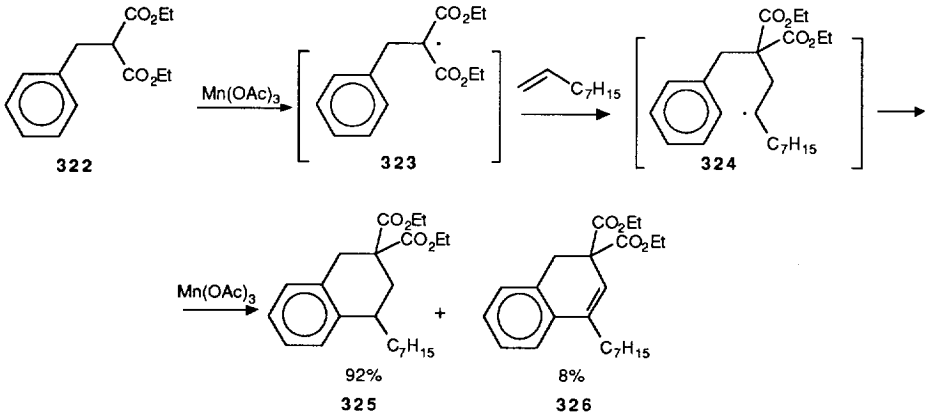


320 321 244

Synthesis of carbocycles

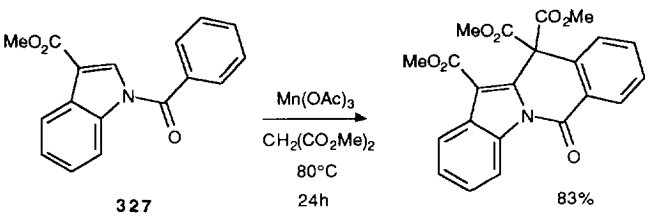
The Mn(III) based oxidative free radical mono, tandem and triple cyclisations have been applied in a wide variety of carbocyclic products.

The oxidation of diethyl benzylmalonate **322** by high-valent metal [Mn(III), Ce(IV), Pb(IV), Ni(III) or Co(III)] salts[213a, b] in acetic acid in the presence of substituted alkenes or alkynes affords tetrahydronaphthalene **325** and a small amount of dihydronaphthalene **326**. The reaction requires a stoichiometric amount of metal salt. Alternatively, the metal salt can be electrogenerated[213c] allowing its use in catalytic amount. Among the tested salts, the Mn(II)/Mn(III), Co(II)/Co(III) and Ce(III)/Ce(IV) systems were the most efficient.



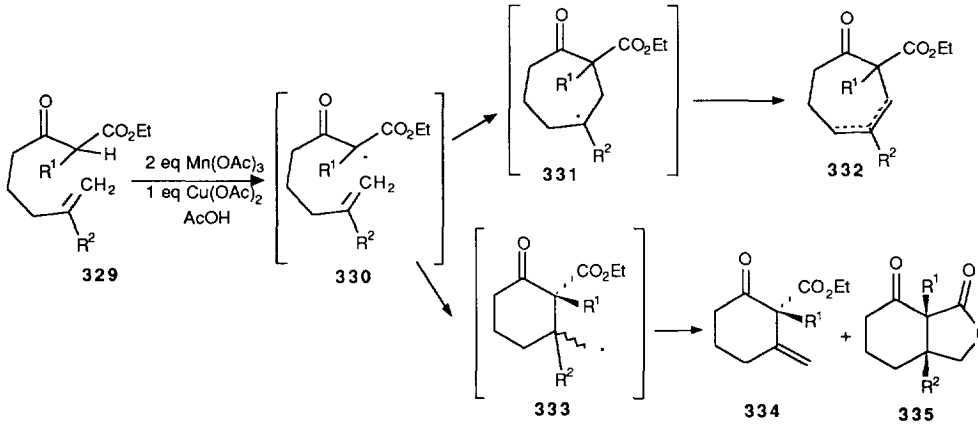
322 323 324 325 326

Another interesting combination of Mn(III) mediated inter- / intramolecular cyclisation of **327** was described recently[214].



327 328

Mn(III) based oxidative free radical cyclisation[215] of enolisable β-dicarbonyl compounds has been used to prepare cycloheptanes and cyclooctanes in modest to good yields. Attempts to synthetise larger rings by this method were unsuccessful. The regiochemistry of the cyclisation is very substrate dependent: using simple 6-heptenyl derivative like **329**, (R^1, R^2=H) the parent radical gives almost exclusively the cyclohexanemethyl radical **333**, while some more complex 6-heptenyl radicals (R^1 and/or R^2 = alkyl) exclusively give the cycloheptyl radical **331**.

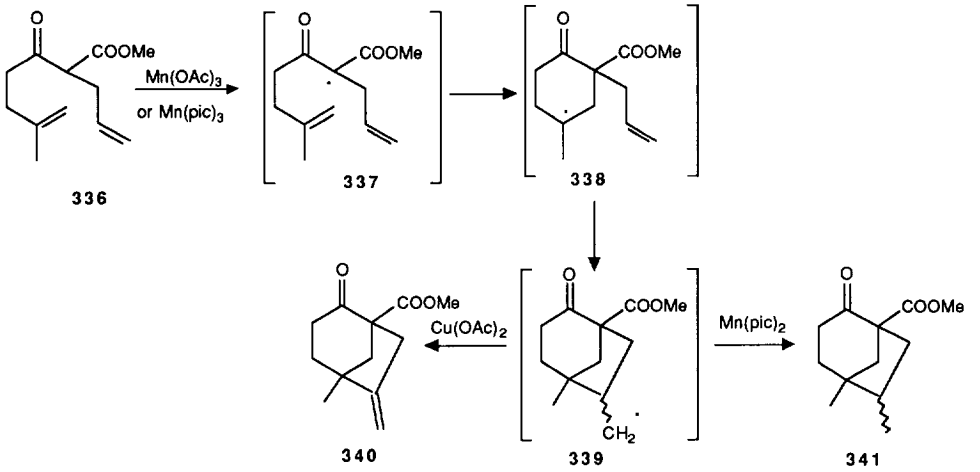


329 330 331 332 333 334 335

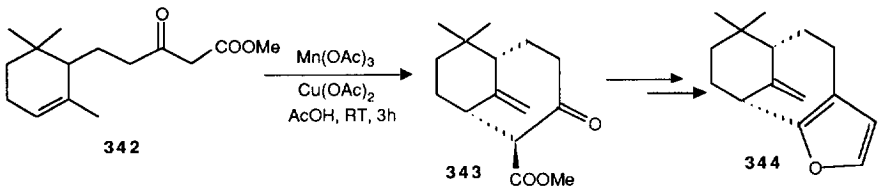
Alkyl substitution (R_2) also improves the yield since the more nucleophilic alkene adds more rapidly to the electrophilic radical.

Oxidative tandem cyclisation of acetoacetates **336** by Mn(III) gives radical **339**. This intermediate can be oxidised in the presence of a Cu(II) salt and gives alkene **340**. The asymmetric variant of this reaction was also described[216] where chiral esters or amides were used or the carboxylic function was replaced by a chiral sulfoxide group, which completely controls the stereochemistry of the cyclisation. Narasaka recently reported[217] that Mn(III) picolinate [$Mn(pic)_3$] in DMF is suitable for the same oxidation (i.e. to convert **336** to **341** *via* **339**). This methodology can be also used for the oxidative cleavage of cyclopropanols to give β-keto radicals and for the oxidation of O-silyl derivative of a nitronate to give cation radicals. He also noted that β-keto acids afford different mixtures of products with $Mn(pic)_3$ and $Mn(OAc)_3$ (i.e. **340** *cf.* **341**).

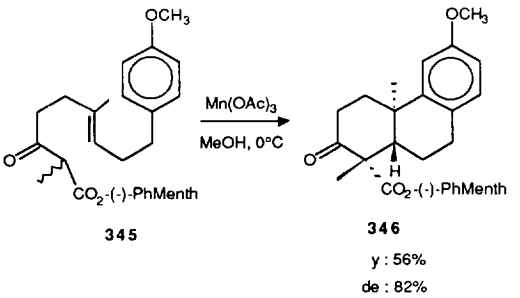
Surprisingly, in the same reaction, using 2 equiv. of $Mn(pic)_3$ and 1 equiv. of $Cu(OAc)_2$ in AcOH no alkene **340** was formed[218]. This reaction afforded bicycloalkane **341**, probably because the $Mn(pic)_2$ formed in the reductive elimination step reacts faster with the primary radical than $Cu(OAc)_2$.



The marine derived furanosesquiterpene, dihydropallescensin **344**, was the goal of a recent synthesis by White et al[219]. Treatment of the keto-ester **342** with Mn(III) and an equal amount of Cu(II) allowed the formation of the bridged system with exclusive 7-*endo* cyclisation, in good yield.



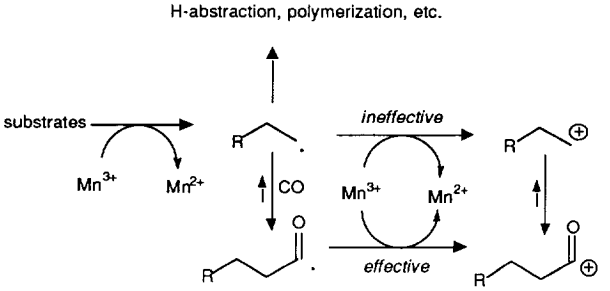
Oxidative Mn(III) mediated free radical cyclisation can also provide synthetically useful asymmetric induction[220]. (+)-O-methylpodocarpic acid derivative, **346**, was prepared[221] using phenylmenthol as the optimal chiral auxiliary . It was found that the extent and *direction* of the diastereoselectivity depends on the size of the α-substituent and also, on the double bond substitution pattern. This complex selectivity was rationalised by the formations of different complexes in the transition state, depending on the substituents.



Oxidative carbonylation

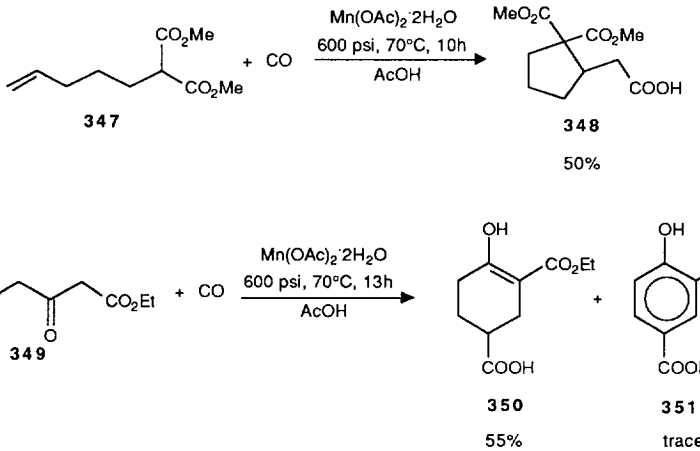
The inefficient termination step of the Mn(III) acetate mediated radical cyclisation can be exploited for the preparation of carboxylic acids *via* carbon monoxide trapping[222] under high pressure. This free radical CO addition

leads first to an acyl radical, then to an acyl cation, and finally to a carboxylic acid. The overall transformation involves the oxidative carbonylation of organic compounds (Scheme 8).



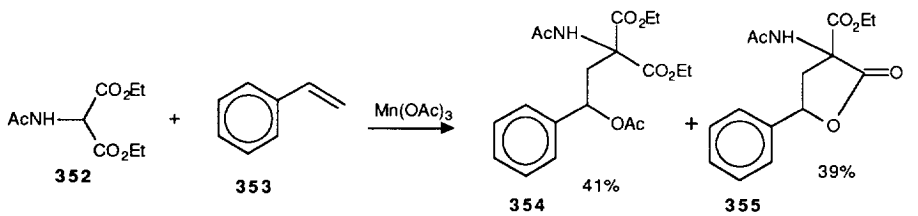
Scheme 8

The selectivity of this cyclisation is surprising. While the malonyl derivative **347** affords the 5-*exo* product[222] **348**, the ketoester **349** furnishes the 6-*endo* products **350** and **351**.

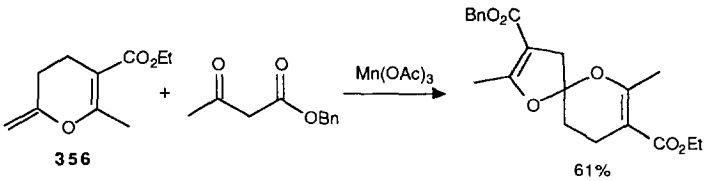


Intermolecular reactions

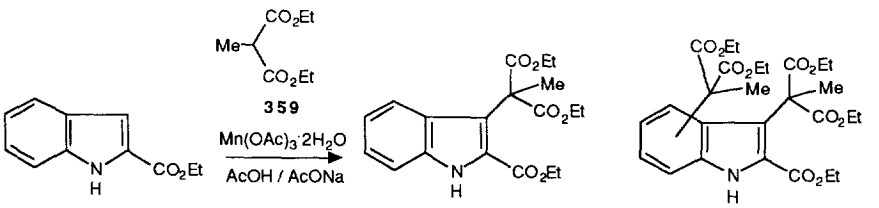
The Mn(III) mediated *inter*molecular alkylation is considered to be inefficient in most cases. However, some exceptions have been reported. Substituted α-amidomalonyl radicals can be trapped by conjugated olefins[223] such as **353** in the Mn(III) acetate oxidation to give the addition-acetoxylation/lactonisation products **354** and **355**. This method represents a new non-ionic approach to the synthesis of α-amino acids.



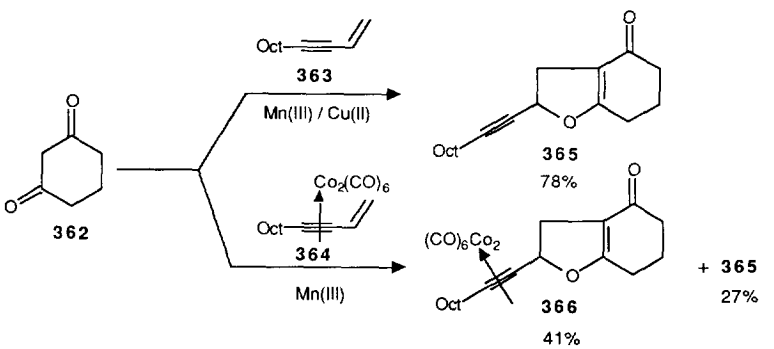
Oxaspirolactones[224a], fused acetal derivatives[224b], and spirocyclic acetals[224c] can also be prepared *via* the intermolecular Mn(III) mediated free radical reaction.



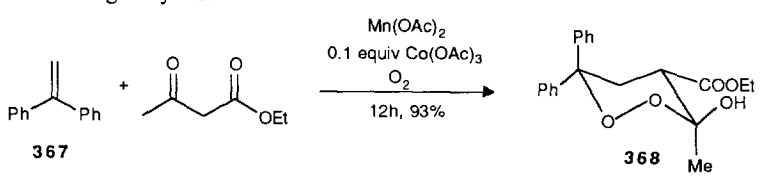
Methylmalonation of electron-rich pyrroles and indole derivatives, except for those substituted with electron withdrawing groups, was unsuccessful[233] due to the incompatibility of the substrate with the oxidation conditions. Strong electron withdrawing groups render the molecule **358** less easily oxidisable and allow the methylmalonation.



The reaction of the Co-complexed substrate **364** proceed with Mn(III) promotion alone[225], whereas the free enyne **363** require combined Mn(III)/Cu(II) mediation to produce significant yields of dihydrofurans **365** and/or **366**.



Similarly, cyclisations of alkene **367** with 1,3-diones or acetoacetesters or amides and molecular oxygen afford 1,2-dioxan-3-ols[226] **368** in good yield.

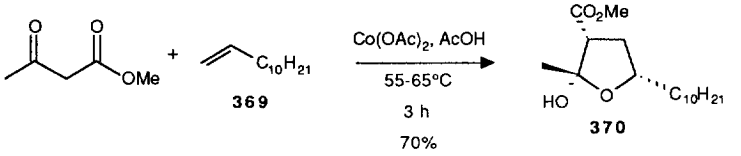


It has been shown, however, that the combination of manganese (II) and manganese (III) acetates is a far more effective reagent for 1,2-dioxan-3-ol formation than either reagent used separately[227]. A great number of co-

oxidants [$Co(OAc)_3$, $KMnO_4$, $Pb(OAc)_4$, $Cu(OAc)_2$, CrO_3, $Tl(OAc)_3$, CAN, $Fe(ClO_4)_3$] were tested and shown to be efficient in a 0.1 ratio with 1 equiv. of $Mn(OAc)_2$ and O_2 in the reaction.

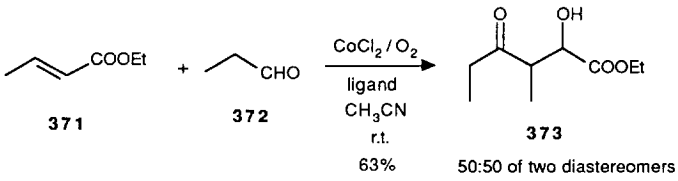
Cobalt(II) mediated alkylation

The Co(II) acetate mediated addition[228] of acetoacetates are similar in many respects to the Mn(III) acetate promoted reaction. It is an efficient method for the synthesis of substituted tetrahydrofurans, using acetoacetate and terminal olefins.



Interestingly, under a N_2 atmosphere, unchanged starting materials were mainly recovered. A similar lack of reactivity was observed by careful exclusion of oxygen. The stereoselectivity of the reaction is remarkable: only one diastereoisomer was obtained.

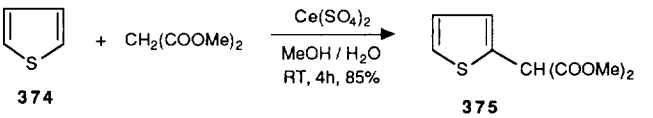
Cobalt (II) acetate or chloride promotes the radical chain addition[229] of an aldehyde **372** to electron deficient alkenes **371**. The reaction was successful when an excess of the olefin was used (otherwise aldehydes gave the corresponding carboxylic acid and 1,2-diketone). From a mechanistic point of view, the formation of radicals is facilitated by the fragile nature of the intermediate carbon-cobalt bond which undergoes homolytic cleavage in the presence of molecular oxygen. Interestingly under similar conditions, unactivated alkenes furnish epoxides.

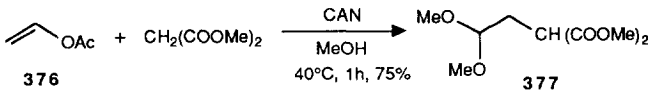


Oxidation with cerium(IV) salts

CAN [ceric ammonium nitrate, $(NH_4)_2Ce(NO_3)_6$] and other Ce(IV) compounds[48c] are often compared to the Mn(III) salts since they perform similar transformations. It is considered, however, that Ce(IV) reactions give higher yields and also prove superior in their control of the regiochemistry in 2-alkanone coupling reactions. They can also be applied efficiently in intermolecular reactions, which is not the case with Mn(III) promoted coupling.

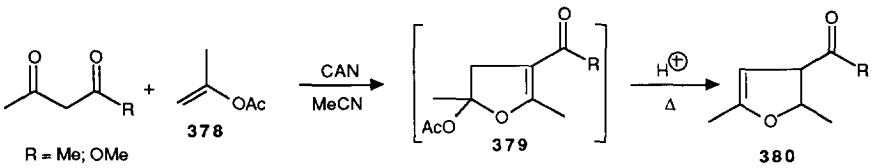
One important variant is the generation of α-ketoalkyl free-radicals from enolisable carbonyl compounds. These radicals add to electron rich alkenes allowing access to a variety of polyfunctionalised carbonyl compounds. An often cited example is the regioselective addition of the malonyl free-radical to thiophene[230] **374** and to vinyl-acetate[231, 232] **376**.





376 377

Other 1,3-dicarbonyl derivatives offer a convenient route to various furans[234]. Thus 1,3-diketones afford 2-alkyl-3-acylfurans, and β-keto esters give 2-alkyl-3-carboalkoxy-furans (**380**).

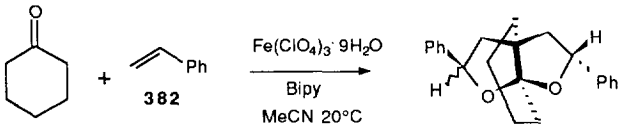


378 379 380

An often mentioned limitation of the reaction is the fact that a large excess of the carbonyl-compound is required (usually it is the solvent) due to the slow initial oxidation step.

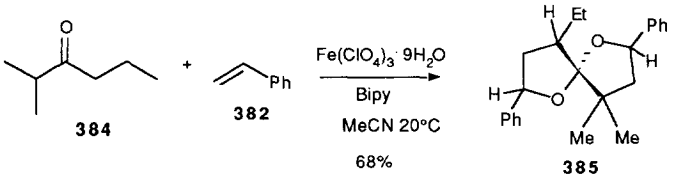
Oxidation with iron(III) salts

Oxidative addition reactions of iron (III) salts, which have counteranions of low nucleophilicity [$Fe(ClO_4)_3 \cdot 9H_2O$, (FEP)], in acetonitrile, are similar to those carried out with Mn(III) acetate in acetic acid[235]. In both cases, ligated water plays a specific role, as it was seen, for example, in the lactonisation of malonic ester in the presence of olefins. The nature of the ligands has, however, a subtle consequence in the reactivity. For example, cyclohexanone **381**, in the presence of FEP in acetonitrile undergoes oxidative addition[236] to styrene, and forms a furo[2,3-*b*]furan **383**. Basic additives, i.e. water in excess and pyridine only marginally affect the yield, but increase the oxidation time. A definitive improvement of this reaction was achieved by addition of a stoichiometric amount of 2,2'-bipyridine.



381 382 383

However, alkene radical traps such as oct-1-ene are inefficient, and only α–hydroxylated ketones are observed. Strong substrate dependence was also observed: the presence of a basic nitrogen in the carbonyl starting material was found to lower the yield and methyl ketones (i.e. acetone, acetophenone, methyl-tert-butyl ketone) were markedly less reactive than derivatives having a longer alkyl chain. α,α-Dialkyl substituted ketones (i.e. 2-methylcyclohexanone and 2-methylhexan-3-one) are also easily oxidised in the presence of aryl conjugated olefins but the products are the spiroketals.

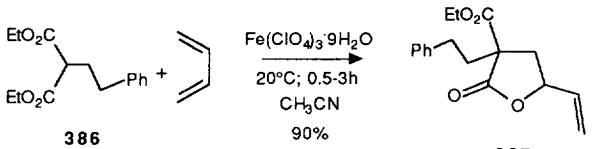


384 382 385

It is interesting to compare the selectivity of these different one electron oxidation-addition reactions. A prominent preference for the less substituted carbon was observed with Mn(III)[237] and Pb(IV)[238] acetates,

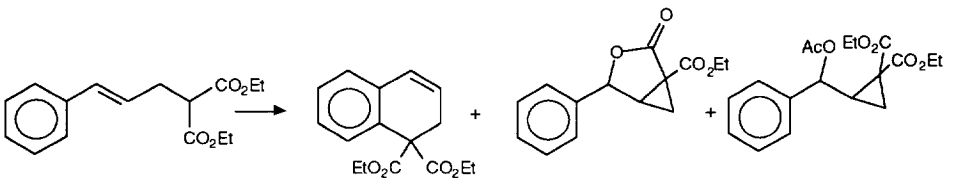
whereas oxidation by CAN[232] and by FEP[239] occur at the more substituted carbon atom.

γ-Lactones can be prepared[240] by oxidation of dialkyl malonates **386** with ferric perchlorate (FEP) in acetonitrile in the presence of olefins and dienes.



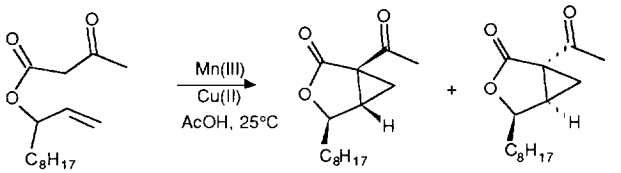
Cyclopropanation reactions

Intramolecular cyclopropanation of ω-phenylalkenylmalonates by Mn(III) acetate and/or Fe(III) perchlorate was investigated by Citterio et al[241].

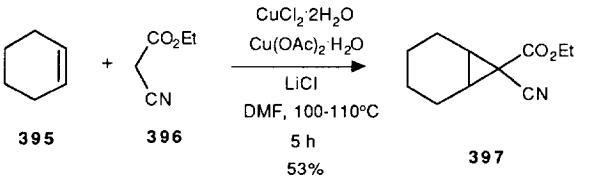


$Mn(OAc)_3$/ $Cu(OAc)_2$ in AcOH	70%		28%
$Fe(ClO_4)_3 \cdot 9H_2O$ in CH_3CN	48%	12%	

Cyclopropanation can also be achieved using manganese(III)[218]. In this reaction the alkyl side-chain of **392** controls the stereochemistry of the cyclisation.

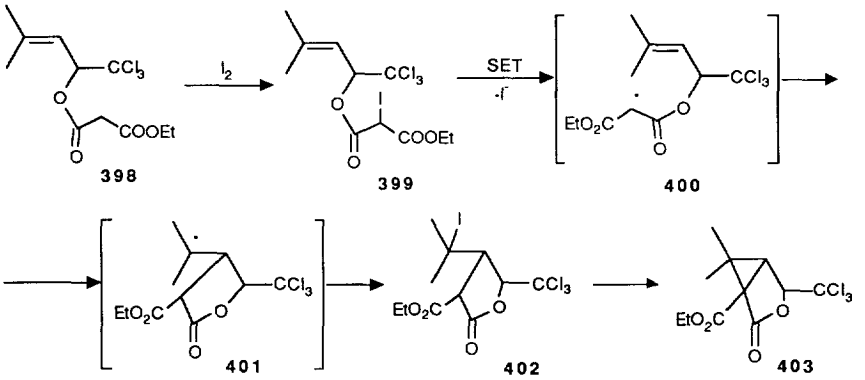


Ethyl cyanoacetate **396** undergoes cyclopropanation[242] in the presence of an olefin and a mixture of $CuCl_2$-$Cu(OAc)_2$ and LiCl. A free radical mechanism has been proposed, even though the intermediacy of radicals has not been completely established.



Substituted cyclopropanes can be prepared under phase transfer conditions using malonate derivatives, iodine, solid potassium carbonate and a quaternary ammonium salt (TCMC, Aliquat®) in the presence of an olefin[243]. A

particularly interesting application has been found in the synthesis of cyclopropane γ-lactones, versatile starting materials for pyrethroid type insecticides and other natural products. The initial attack of iodine at the olefinic double bond and the "triplet carbene route" were ruled out, on the basis of synthetic, NMR and ESR experiments, and a single electron transfer / radical mechanism was proposed.

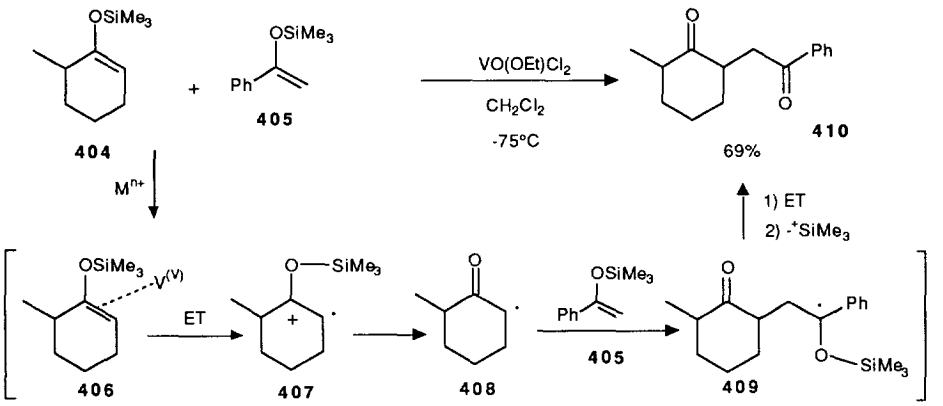


3.4 Oxidation of enol ethers, enolates and other metallated compounds

Oxidation of silyl-enol ethers

One-electron oxidation of organosilicon compounds accompanied by desilylation are potentially useful in radical reactions. Silyl-enol ethers are much more readily oxidised[244] than their ketone precursors, and react at reasonable rates. When the two reagents are vinyl-ethers, the success of the method lies in preferential oxidation of one of the two components. Nevertheless, in order to prevent the homocoupling reaction, the acceptor silyl-enol ether should be used in excess.

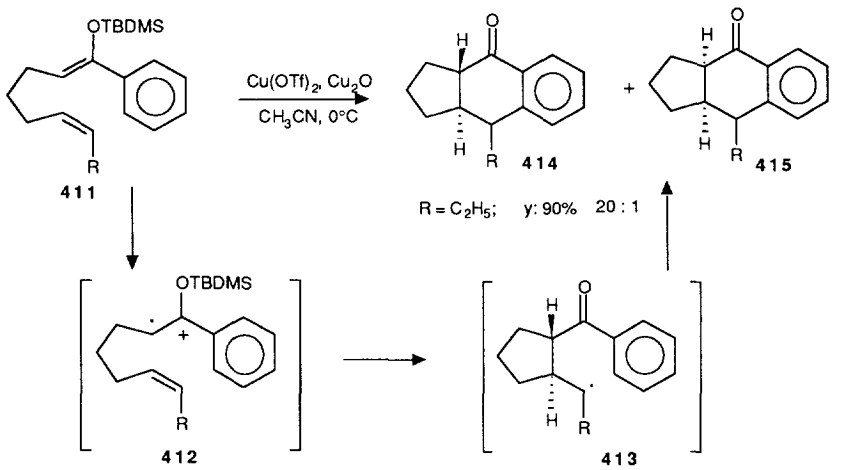
Efficient CAN promoted cross-coupling occurs between silyl dienol ethers and silyl enol ethers to give dicarbonyl compounds with high regio- and stereoselectivity[245]. Using $VO(OEt)Cl_2$, the corresponding reaction proceeds[246] at a lower temperature in general to that compared with other metal oxidants, depending on the starting silyl enol ether.



The desilylation of silyl enol ethers by oxovanadium(V) compounds is considered to be related to the difference in their redox potential, a difference which can be exploited in the synthesis of unsymmetrical 1,4-diketones. The

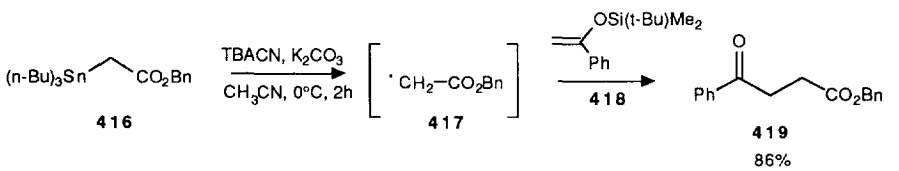
mechanism of the reaction can be rationalised by one electron oxidation of the silyl-enol ether by the metal complex leading to the radical cation **407**. Desilylation followed by cross coupling, subsequent oxidation, and finally a second desilylation affords the product.

Treatment of silyl enol ether **411** with 2 equiv. of $Cu(OTf)_2$ and an excess of Cu_2O in CH_3CN at 0°C, as described by Kobayashi[247] for the oxidative coupling of trimethylsilyl enol ethers gives 90% of a 20:1 mixture[248] of **414** and **415**. Similarly, treatment of **411** with 2 equiv. of CAN and excess $NaHCO_3$ in acetonitrile at 25°C gives 73-88% yield of a 20:1 mixture[249] of **414** and **415**. No tricyclic products were obtained from treatment of **411** with $TiCl_4$, $Fe(ClO_4)_3$, $Mn(OAc)_3$, PhIO and HBF_4. Reaction with terminal alkenes (R=H), however, gave complex mixtures. Also, the oxidative cyclisation with disubstituted olefins proceeded in lower yield. The mechanism of this tandem cyclisation is complex. Formation and cyclisation of a free enol radical is unlikely since Curran and Chang[250] have shown that cyclisation of the enol radical gives a mixture of 5-*exo* and 6-*endo* products. Formation of an enol cation is unlikely since cyclisation of enol cation leads preferentially to the 6-*endo* product[251] while only the 5-*exo* product is obtained from **411**. The formation of cation radical **412** has been proposed as the first step in the photoinduced desilylation of enol silyl ethers[252].



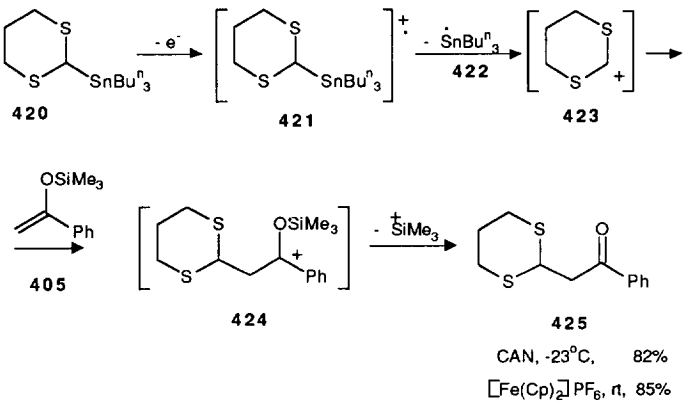
Oxidation of organotin compounds

For the asymmetric cross coupling of silyl enol ethers, one of the silyl ethers has to be employed in large excess. An alternative approach in order to prevent homocoupling, is to replace one of the enol ethers with another derivative which is oxidised faster than the corresponding silyl derivative. Oxidation of α-stannyl acetates was reported[253a] to give α-radicals of acetates with elimination of the stannyl group. The treatment of **416** with tetrabutylammonium hexanitrocerate(IV) (TBACN) in the presence of K_2CO_3 at 0°C gave the cross addition product **419** exclusively and none of the succinate was detected.



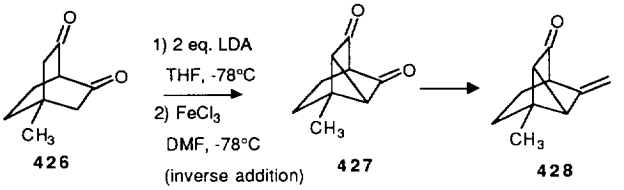
It was postulated, however, that the tributyltin-dithianyl radical-cation **421** undergoes a fragmentation reaction

to give the tributylstannyl radical **422** and the 1,3-dithian-2-yl cation **423** respectively[253b]. Accordingly, the carbocation reacts with olefinic nucleophiles and affords the corresponding ketone **425** in high yield.

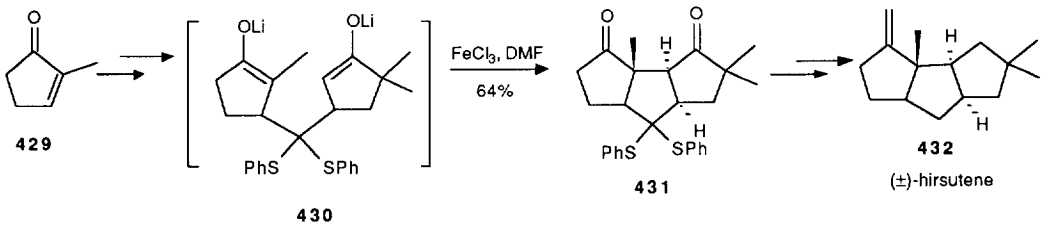


Oxidation of organolithium compounds and other anions

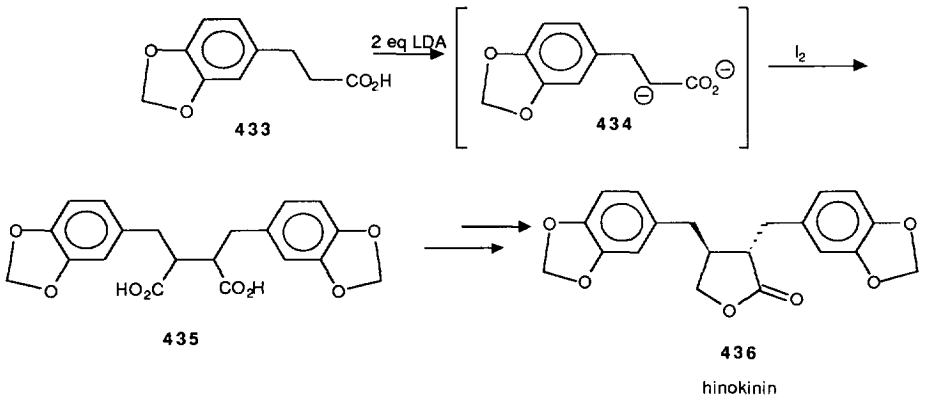
Paquette has reported an intramolecular oxidative coupling[254] using ferric chloride to prepare an advanced intermediate **428** for the synthesis of cerorubenic acid-III. In this synthesis, addition of dienolate of **426** to $FeCl_3$ in DMF at -78°C during 30 min., produced cyclopropane intermediate **427** in 54% yield. The latter possesses a plane of symmetry and thus allows the synthesis of either enantiomer of the natural product. The mechanism of this oxidative cyclisation is not discussed in the paper, but it is likely that a one electron transfer pathway is involved. Cu(II) salts have also been utilised for intramolecular enolate coupling, but were somewhat less effective in the present context.



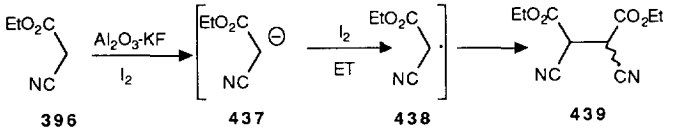
An elegant synthesis of (±)-hirsutene **432** was developed by Cohen et al.[255]. The key step of the synthesis is a one pot, completely stereoselective oxidative cyclopentannulation of dienolate **430** with two equivalents of ferric chloride in DMF. Cupric chloride was also tested, but proved inferior. The formation of a single diastereoisomer of the triquinane is useful and suggests that stereochemical equilibration may occur at some stage. This annulation procedure can also be extended to cyclohexanone enolates.



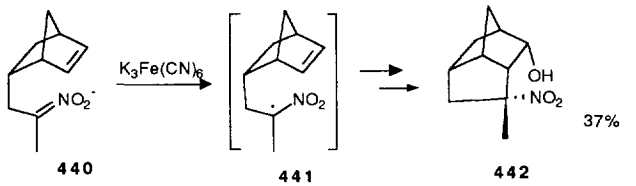
An electron transfer coupling mechanism was proposed for the diiodine coupling[256] of carboxylic acid dianions. Oxidative dimerisation of phenylpropionic acid dianion **434** to succinic acid derivative **435** constitutes an efficient way to construct the basic lignan skeletal framework. A practical application of this methodology[257] is the synthesis of hinokinin **436**, a cytotoxic metabolite isolated from the human gastrointestinal tract.



A recent variant of this reaction was described for activated methylene compounds in the presence of potassium fluoride on alumina[258]. The first step of the oxidative coupling reaction is the deprotonation of the acidic compound **396** by the solid base. Oxidation by diiodine can occur *via* a one or two electron oxidation step. It seems probable that radicals are involved in this reaction. Although ultrasound greatly improved the yields of coupling[259], the selectivity remained low and a mixture of dimers, trimers and olefinic compounds was obtained.

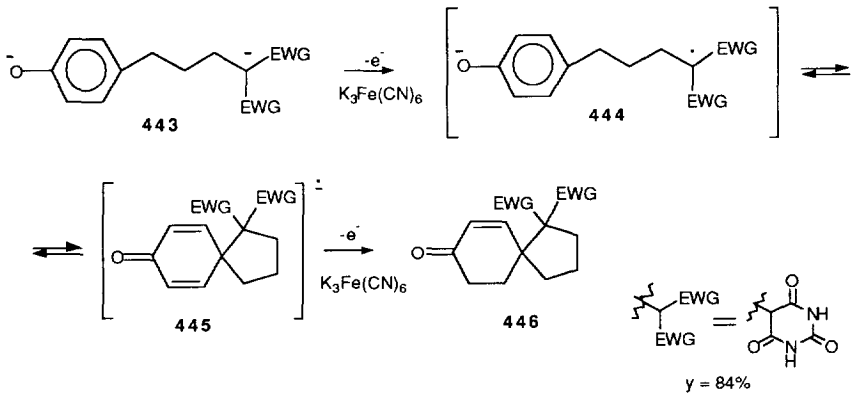


α-Nitroalkyl radicals can be generated by one electron oxidation of various nitronate anions[260], using Fe(III). The strongly electrophilic nature of these radicals is well known and they can thus be reacted with various nucleophiles. The reaction, however, has only limited synthetic potential, due to competing reactions, which are generally faster than C-C bond formation. Cyclisation of α-nitroalkyl radicals for synthetic purposes will only be useful if more electron rich groups than simple alkenes are present.



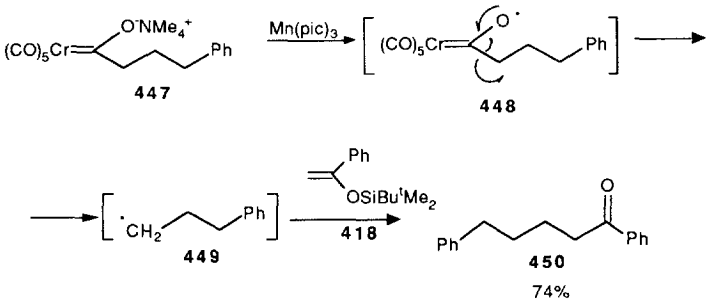
The phenolate-enolate cyclisation of various aromatic compounds was examined by Kende[261] using $K_3Fe(CN)_6$ (+0.48V) or K_2IrCl_6 (+0.89V) as one electron oxidising agents, and dilute base (KOH, Na_2CO_3 etc.). Oxidative coupling occurs in the *para* or *ortho* position to the phenolic oxygen and preferentially forms five membered spiro systems. The one-electron oxidation of the enolate unit of the reactant molecule to the corresponding enol radical rather than the oxidation of the phenoxide to phenoxy radical was postulated. It is this enol radical which

subsequently reacts with the phenolate ring, as illustrated in the following scheme. This reaction allows the cyclisation of carbocyclic-, heterocyclic-, acyclic enols and phenolic nitronates in moderate to good yields. Attempts to modify the cyclisation regiochemistry by the use of higher pH or other oxidants (e.g. MnO_2, $FeCl_3$, VOF_3-TFA, $VOCl_3$, $Tl(CF_3CO_2)_2$, $CuCl_2$) failed to produce cyclisation products.



Oxidation of Fischer-carbenes

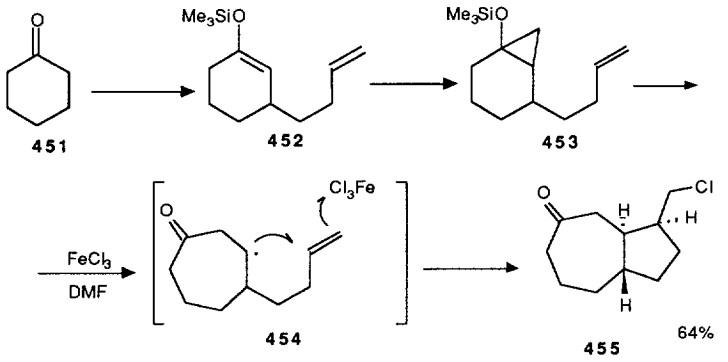
Chromium(0) complexes can be oxidised with $Mn(pic)_3$, giving carbon centred radicals[262] with decomplexation. When **447** and 3 molar equivalent of **418** in DMF were treated with 2.5 molar equivalent of $Mn(pic)_3$, the addition product **450** was obtained in 74% yield without any formation of the self coupling product. By considering the nucleophilic character of the alkyl radicals, this method affords satisfactory yields with electron rich olefins.



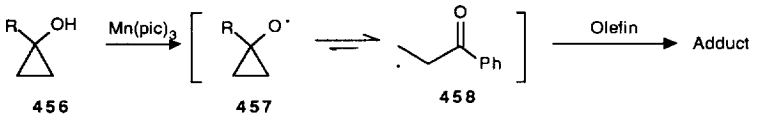
3.5 Oxidative fragmentation of strained carbocycles

There are many examples on the oxidative fragmentation of strained cyclic alcohols, silyl ethers and ketones in the literature. The transient free radical can be trapped with different radicophiles. However, only a few examples of oxidative fragmentation leading to C-C bond formation have been reported.

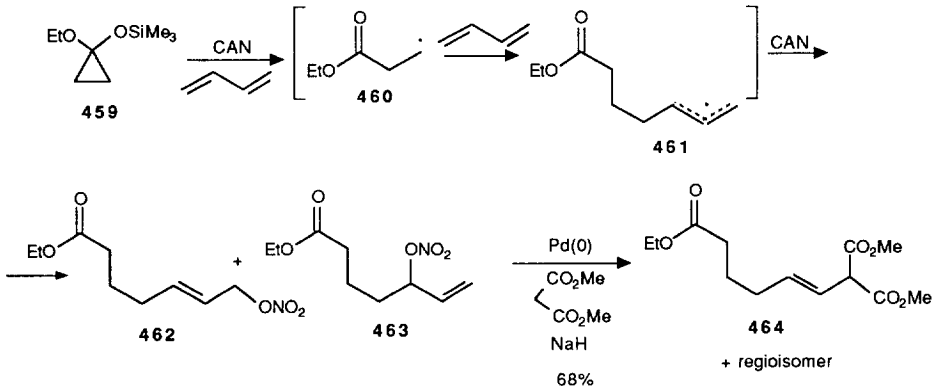
Based on the ring expansion method of the Saegusa group[263], a tandem free radical ring expansion-cyclisation sequence was developed by Booker-Milburn[264]. It was found that slow addition of a DMF solution of ferric chloride (2.2 equiv.) to a solution of the cyclopropane **453** afforded the *trans* fused chloro ketone **455** (64%) as a single diastereoisomer. The reaction is thought to proceed *via* β-scission of the cyclopropyl alkoxy radical followed by intramolecular trapping of the intermediate carbon centred radical.



In similar fashion, the oxygen centred radical **457**, generated by $Mn(pic)_3$ oxidation is converted to the carbon centred radical, **458**, by a fragmentation reaction[265].



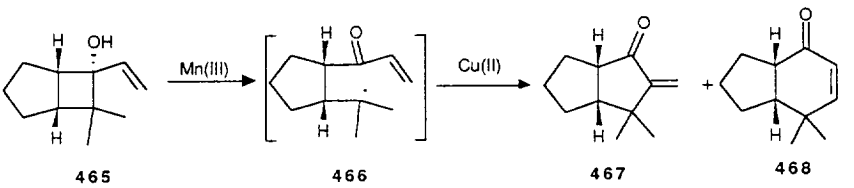
By virtue of the similarity in chemical behavior of silyloxycyclopropanes with trimethylsilyl enol ethers, the CAN promoted oxidative fragmentation-addition of silyloxycyclopropane **459** to diene was developed[266]. The synthetic potential of the reaction was further increased by realising that the allyl-nitrates, **462** and **463**, thus formed, could undergo palladium(0) catalysed allylic substitution.



Similarly, cyclobutanones and diketene undergo one-electron oxidative ring opening[267] to generate radical species at the α or γ position with respect to the carbonyl group, which add to electron deficient alkenes.

Ring opening reactions of cyclopropylcarbinyl radicals are also facile. Oxidative fragmentation of cyclobutanols with Mn(III) picolinate[265] give β-keto radicals which can add inter- or intramolecularly to alkenes. Oxidation of cyclopropyl silyl ethers with cupric tetrafluoroborate affords radicals[249] that add to alkenes. The one electron oxidation of cyclobutanols using $Mn(OAc)_3$ in the presence of $Cu(OAc)_2$ gives γ-keto radicals[268] which can be trapped by cyclisation onto a proximate double bond to give a new cyclic structure. Transient tertiary radicals are particularly interesting intermediates. The reaction of **465** under usual conditions affords 83% of methylenecyclopentanone **467** and a trace amount of cyclohexenone **468**. The same reaction with other oxidants

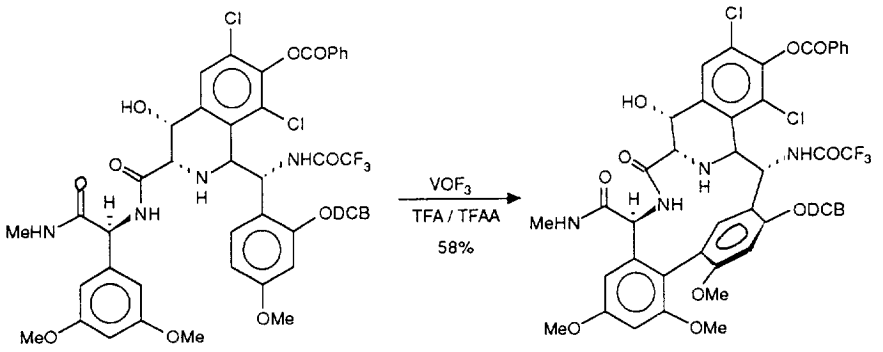
that generate alkoxy radicals, such as CAN, $Pb(OAc)_4$, or (diacetoxyiodo)benzene-iodine were not promising. Interestingly, the oxidation of **465** with $Mn(pic)_3$ / $Cu(OAc)_2$ in DMF gives 17% of cyclohexenone **468** and no methylenecyclopentenone **467**.



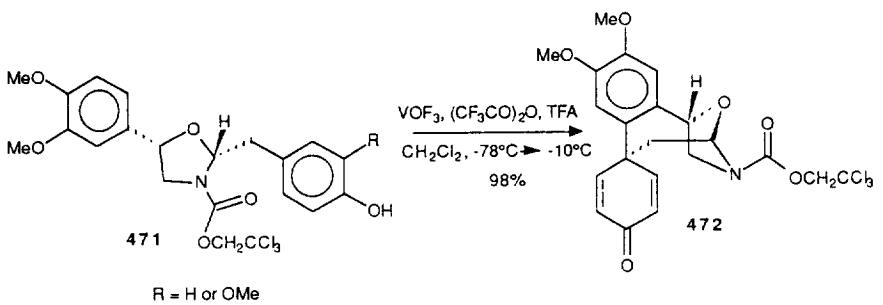
465 **466** **467** **468**

3.6 Oxidative coupling of aromatic rings

Pentavalent oxovanadium compounds have been shown to serve as Lewis acids with a one electron oxidation capacity[269]. One of the most thoroughly studied coupling reactions of these reagents is the inter and intramolecular biaryl coupling, especially of substrates which contain hydroxy or alkoxy substituents. Evans's elegant biomimetic oxidative coupling approach to the tripeptide macrocycle, a structural subunit common to all member of the vancomycin antibiotics[270] characterises the synthetic power of this reaction well. The coupling was performed with VOF_3 / $BF_3.OEt_2$ (7 / 15 equiv.) in TFA/TFAA solvent mixture, followed by addition of excess activated zinc, and afforded 58% of a single atropoisomer **470**. The addition of $BF_3.OEt_2$ was found to be critical in preventing competitive attack of oxygen nucleophiles on the presumed radical cation intermediate, while the zinc reduction step was necessary to quench the radical cation intermediate, which is also prone to nucleophilic attack. The use of other one electron oxidants either met with modest success [$Mn(acac)_3$] or failed to induce cyclisation [$Tl(TFA)_3$, $FeCl_3$, $VOCl_3$, CoF_3, Pt anode).



469 **470**

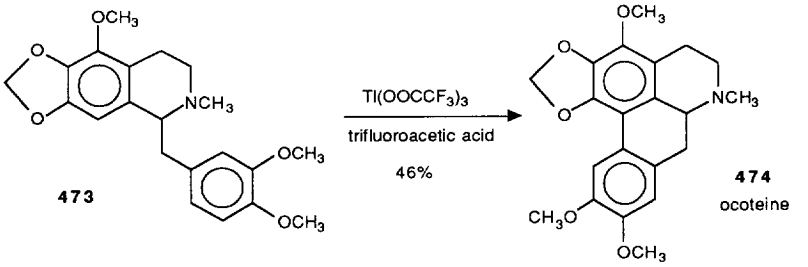


471 **472**

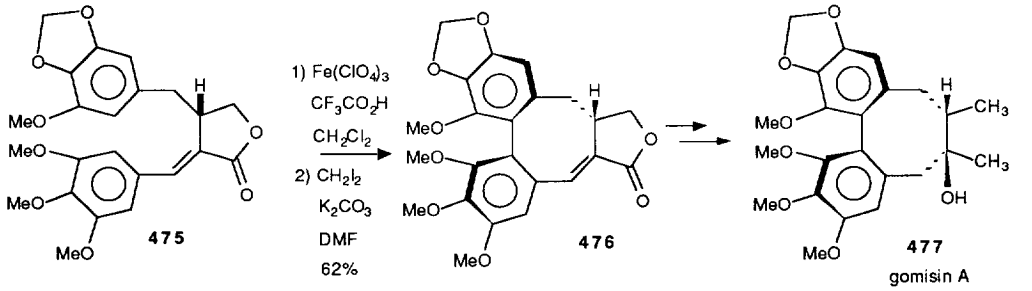
Sterically favorable *para-para* phenolic coupling was achieved[271] in the synthesis of a secoisosalutaridine framework, **472**, using vanadium oxytrifluoride and trifluoroacetic acid in dichloromethane.

The oxidative coupling of **471** could also be accomplished with $VOCl_3$ and $PhI(OCOCF_3)_2$ but neither reagent approached the efficiency of VOF_3.

Regiospecific oxidative dehydrodimerisation of electron rich aromatic compounds can be achieved by thallium (III) trifluoroacetate ($E°_{Tl(III)/Tl(I)}$=+1.26V *vs.* SCE)[17d]. The arylation gives good to excellent yields in trifluoroacetic acid or in carbon tetrachloride or acetonitrile containing $BF_3{\cdot}OEt_2$.The reaction is postulated to proceed via generation of the radical cation $Ar^{+\cdot}$ by the thallium salt followed by subsequent reaction of this electrophile with the aromatic substrate and rearomatisation. Other salts such as Hg(II) or Fe(III) generally gave lower yields in comparative experiments with Tl(III) trifluoroacetate. Pb(IV) and Co(III) oxidations were even better than the reference Tl(III) reaction in many instances. Among other alkaloids, the apoporphine alkaloid (±)-ocoteine **474** was prepared by Tl(III) mediated biaryl coupling. Although the thallium procedure[272] is very mild and efficient, the toxicity of thallium salts presents problems in large scale use.

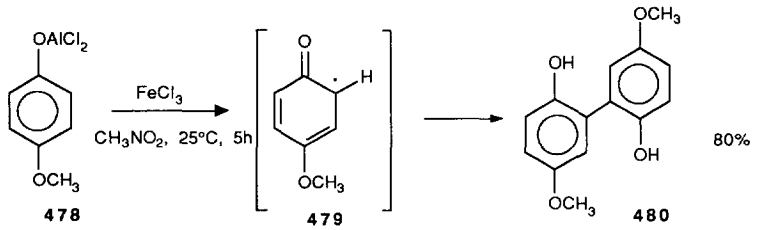


Aromatic compounds undergo oxidative coupling in the presence of iron (III) perchlorate[273] in trifluoroacetic acid. This reaction was exploited in the preparation[274] of optically pure gomisin A **477** and schizandrin, the anticancer steganacin analogs. Interestingly, ruthenium dioxide ($E°_{Ru(IV)-Ru(III)}$=0.86V *vs.* SCE) in trifluoro acetic acid medium[275] proved to be equally efficient in the non-phenolic oxidative coupling reaction in the synthesis of bis(benzo)cyclooctadiene lignan lactone congeners.

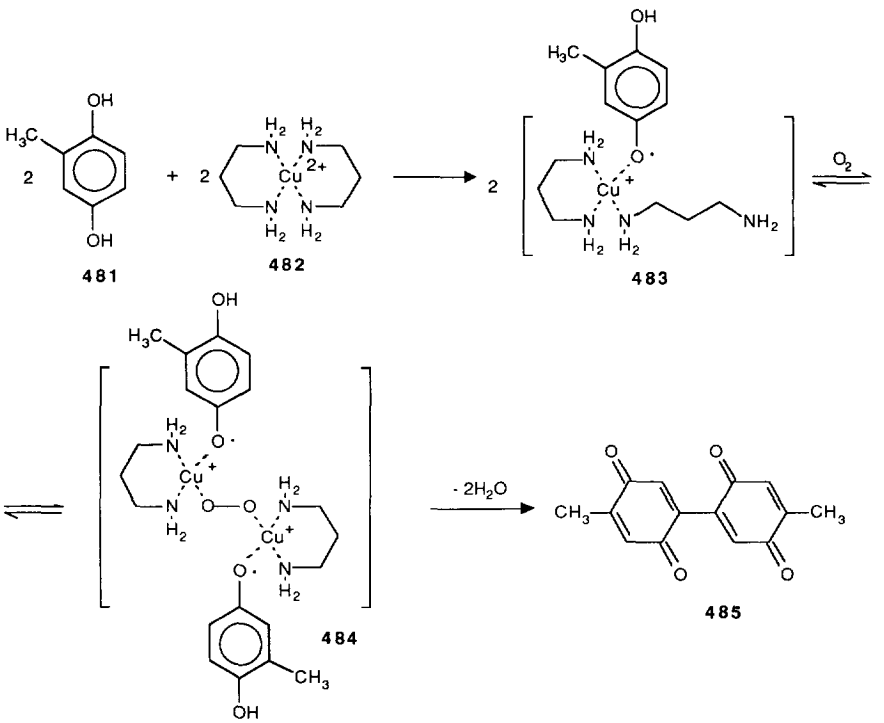


Dichloroaluminium phenolates (**478**) undergo highly selective oxidative coupling[276] in the presence of stoichiometric amounts of $FeCl_3$. Heterogeneous reagents such as MnO_2 and $CuBr_2$ were shown to be less efficient. The process involves a radical mechanism; in the presence of $AlCl_3$, the extraction of a second electron from the complexed aryloxy radical **479** seems unlikely. It was found that the process was of general applicability with respect to the *p*-substituted phenolic substrate. Electron withdrawing substituents on the phenol ring reduce the reactivity, and the reaction is highly sensitive to steric hindrance. The outcome of the reaction is dependent

upon the nature of the solvent. Solvents with a low donor number, such as nitromethane and methylenechloride, are particularly favored. Biaryl coupling of **478** to **480** is sluggish in THF and inhibited in DMF.

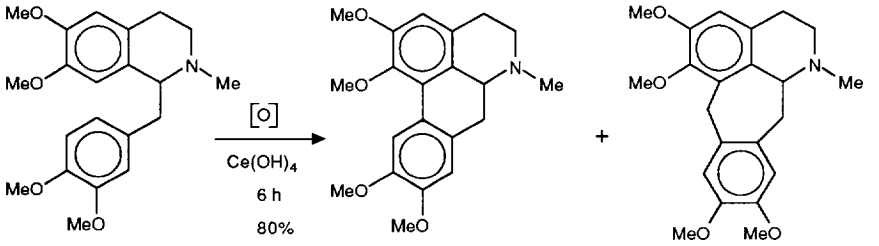


Diamine-copper complexes are known to catalyse the oxidative coupling of substituted phenols by means of air or oxygen[277]. In the presence of oxygen, in boiling ethanol containing an equimolar amount of bis(1,3-propanediamidato) copper (II) chloride and a trace of acetic acid, hydroquinones undergo oxidative coupling and form biquinones in yields of 50-75%. ESR studies concluded that the reaction proceeds *via* copper-complexed aryloxy radical intermediates probably as outlined below:



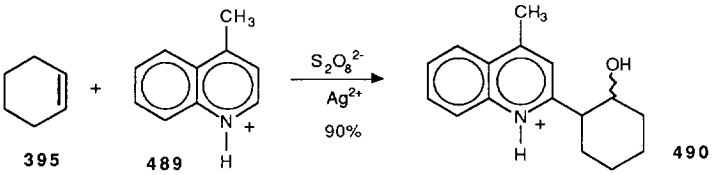
A great number of redox systems were tested by Robin and co-workers[278] to develop non-phenolic oxidative coupling of lignan and alkaloid precursors. In their exhaustive examples, there were no attempts to distinguish between one-electron transfer *vs* polar (Friedel-Crafts) coupling mechanisms. All the experiments were carried out in trifluoroacetic or pentafluoropropionic acids. A Lewis acid such as $BF_3{\cdot}Et_2O$ activates the *para* position of the coupling aryl group, and favors the aryl-aryl (**487**) *vs.* aryl-alkyl (**488**) coupling. In the oxidative coupling of laudanosine **486** to glaucine **487**, three metallic salts gave good results: $Ce(OH)_4$, $RuO_2{\cdot}2H_2O$ and

$Fe(OH)(OAc)_2$ The benzocycloheptisoquinoline **488** probably formed *via* Friedel-Crafts reaction with the solvent, CH_2Cl_2, in oxidative medium.



486 **487** **488**

Due to the high redox potential of silver(II) ($E°_{Ag2+/Ag+}$=1.98 V *vs.* SCE)[279], Ag(II) salts are particularly effective for electron transfer reactions. The catalytic use of the salt is preferred because of the high cost of the metal. The parallel use of peroxydisulfate ion, $S_2O_8^{2-}$, which is one of the strongest oxidising agents ($E°_{S2O8^{2-}/SO4^{2-}}$=2.01 V *vs.* SCE) allows the regeneration of the metal salts in their higher oxidation form, which is the actual oxidant of the organic substrate. This high oxidation potential allows the conversion of olefins and aryl compounds to the corresponding radical cation. The reaction is often referred to as the Minisci reaction[19h]. Another advantage of the reaction is that in spite of its high electrode potential, Ag(II) does not quench the carbon centred radicals efficiently. The persistent radicals can thus dimerise or undergo addition to radical traps such as olefins. Among the numerous selective syntheses that have been accomplished[19h], only the alkylation of the heteroaromatic base **489**, is shown here.

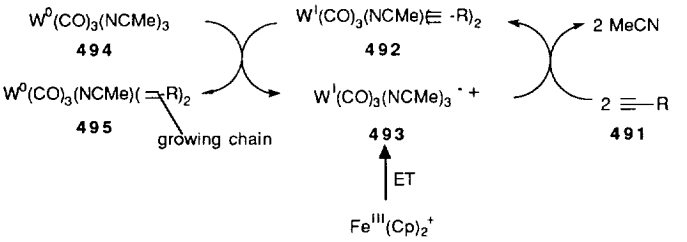


395 **489** **490**

3.7. Miscellaneous

Electron transfer mediated polymerisation

Tungsten catalysis is a well known way to catalyse polymerisation of terminal alkynes **491** by the Katz mechanism involvolving metal-vinylidene intermediates. The initiation of polymerisation using $W(CO)_3(NCMe)_3$ (**494**) is very slow at 20°C (one week). However, addition of a catalytic amount of the one electron oxidant, $[FeCp_2]^+PF_6^-$ as activator, renders the process rapid[280] due to initiation of efficient redox cycles.

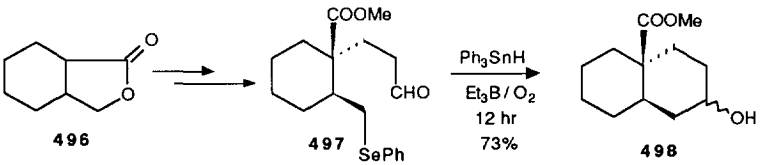


Formation of carbon radicals by trialkylborane autoxidation

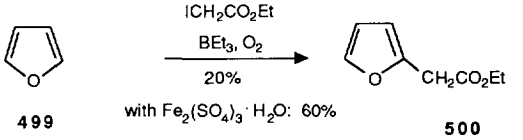
The formation of carbon radicals by trialkylborane autoxidation is a well known reaction. In most cases, the primary radical formed is used as an initiator in free radical sequences.

$$R_3B + O_2 \rightarrow R_2BO_2\cdot + R\cdot$$

Based on this fragmentation reaction, trialkylboranes may be jointly used with tin hydrides in classical free radical chain reactions[281].

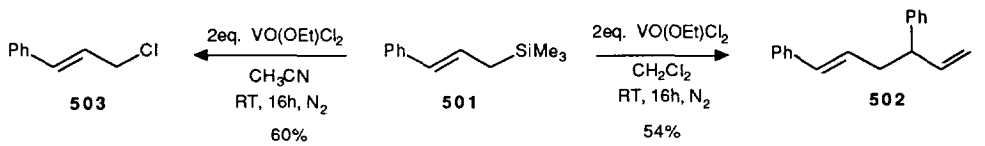


The BEt_3/RX system has been employed to obtain malonyl radicals from the corresponding iodides and bromides. These undergo addition to electron rich heterocycles[282] and/or vinyl ketones[283]. It was shown that, in a number of cases, the addition of an equimolar amount of $Fe_2(SO_4)_3 \cdot H_2O$ increases the yields. It is presumed that the role of Fe^{3+} is to facilitate oxidation of the intermediate radical σ-complex to the final substitution product.



Oxidation of allylic and benzylic silanes

Versatile cross coupling of allylic and benzylic silanes[284] can be achieved. Treatment of cinnamyltrimethylsilane **501** with $VO(OEt)Cl_2$ in dichloromethane led to the 1,5-hexadiene derivative **502** regioselectively by an oxidative coupling in 54% yield. The choice of the solvent drastically influences the reaction products. Oxidation of **501** in acetonitrile instead of dichloromethane resulted in chlorination (**503**) without the formation of **502**. Coordination of acetonitrile to the oxovanadium species seems to prevent C-C bond formation.



III. Summary

The aim of this review was to provide a comprehensive analysis and comparison of different methods of redox reactions in the ground state, for which open shell intermediates were found or postulated in the critical C-C bond formation step. Among these redox reactions, the overwhelming majority proceed *via* a single electron transfer, non-chain mechanism. The main factors which control these reactions are:

(1) the redox potential differences (ergocity) of the interacting redox couples;

(2) the chemical affinity between the electron donor and electron acceptor molecules is a factor in inner-sphere

cases (the most frequent ones);

(3) the variation of the redox properties of the metal reagents by the ligands (solvent molecules, added ligands);

(4) the regio- and stereochemistry imposed by the preexisting ligand-metal framework and the interacting substrates in the metal coordination shell.

As illustrated in this review, and contrary to the general belief, redox induced radical and radical ionic reactions often feature high diastereoselectivity. These new, and in most cases, particularly mild reactions are beginning to be exploited in multistep syntheses and this strategy promises forthcoming breakthroughs.

This review summarises redox radical reactions in the ground state, up to the first month of 1994.

Acknowledgments

This overview was initiated by Prof. Sir Derek H.R. Barton during my stay at Texas A&M University. His encouragement and comments are acknowledged. The manuscript was finished at Harvard where Prof. Yoshito Kishi made it possible to complete the text. Thanks for this help. Friendly thanks are due to Prof. Didier Astruc. His remarks and competence helped me a lot. Warm wellcomes to Dr Sam Z. Zard for corrections in the initial text and to Prof. Willy B. Motherwell for his advices. Thanks to Profs. Yves Langlois, Joe Cs. Jászberényi, Drs. Michael A. Gray and Arnaud Haudrechy who helped me to complete the manuscript. I am grateful to Profs. Henry Kagan, Michel Chanon and to Dr René Beugelmans for sending me reprints, manuscripts and notes relevant to the topic. The CNRS, France, and the NATO (grant No 12B93FR) are acknowledged for financial support.

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(*Received* 5 *May* 1995)