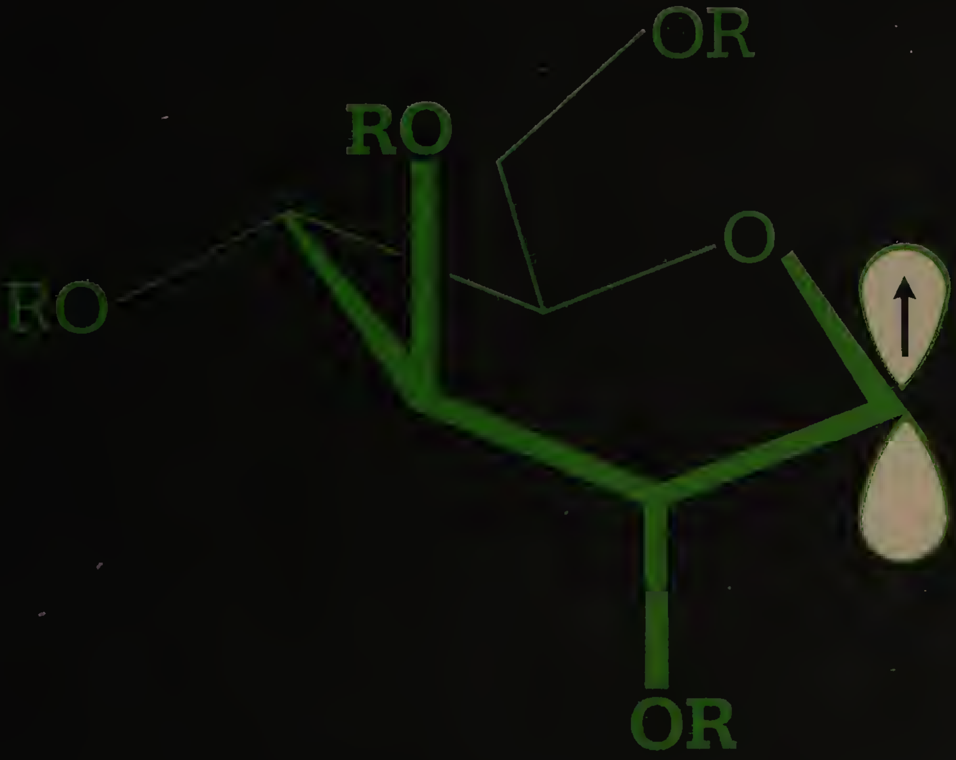
Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds

BERND GIESE



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Federal Republic of Germany

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Foreword

The past twenty years have witnessed an unparalleled development of new synthetic methods in the field of organic chemistry. Many of these new methodologies involve the same basic ionic processes which were involved in the early development of the mechanistic picture of organic chemistry. Although of great power these ionic processes do suffer from limitations, in particular the problems of compatability of functional groups. This is especially so in highly functionalised molecules.

Within the last decade however a new approach to bond formation has been emerging, namely the use of homolytic or radical reactions. It is already evident that these processes, well known of course in the polymer industry, have a great role to play in the synthesis of complex molecules. Professor Bernd Giese is a pioneer of this new development. In this book he describes in a masterly fashion the developments which have occurred and in particular how the practising synthetic chemist can make use of them in his work. The book will be of wide use to all chemists involved in synthesis both in industry and academia.

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Abbreviations

Ac	acetyl
AIBN	azoisobutyronitrile
Ad	adamantyl
Ar	aryl
Bn	benzyl
Bu	butyl
Bz	benzoyl
Cbz	carbobenzyloxy
Co(dmgH)$_2$py	cobaloxime (see p. 102)
DBU	diazabicycloundecane
DEAD	diethylazodicarboxylate
DHP	dihydropyran
DME	dimethoxyethane
DTBP	di-*t*-butylperoxide
e^-	electron
Et	ethyl
HMPA	hexamethylphosphortriamide
Im	imidazolyl
LDA	lithium diisopropylamide
MCPBA	m-chloroperbenzoic acid
Me	methyl
NBS	N-bromosuccinimide
OGlu(OAc)$_4$	tetraacetylglucoside
PCC	pyridinium chlorochromate
Pr	propyl
TBHP	*t*-butylhydroperoxide
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
THP	tetrahydropyranyl
TMS	trimethylsilyl
Tol	p-tolyl

Chapter 1

Introduction

Radical chemistry dates back to 1900 when Gomberg[1] investigated the formation and reactions of the triphenylmethyl radical. In the 1920's Paneth[2] showed that less stabilized alkyl radicals also exist and measured the lifetime of these radicals in the gas phase. Organic synthesis with radicals began in 1937 when Hey and Waters[3] described the phenylation of aromatic compounds by benzoyl peroxide as a radical reaction. The same year, Kharasch[4] recognized that the anti-Markovnikov addition of hydrogen bromide to alkenes proceeds via a radical chain process. In the following years, Mayo, Walling, and Lewis[5] discovered the rules of radical copolymerization reactions. The results of these early investigations were presented in two texts on radical chemistry.[6]

The deeper insights into the formation, structure, and reactions of radicals gained in the 1950's and 60's were collected (1973) in a two-volume work edited by Kochi.[7] In the following years, the work of Ingold and others made available the absolute rate constants of the major radical reactions in solution. These rate data have only recently been compiled in the Landoldt-Börnstein edited by Fischer.[8]

However, the 1970's also witnessed the start of new synthetic methods involving radicals, particularly in substitution reactions of aromatic compounds.[9,10] The last years have brought a rapid development in the use of alkyl radicals for the formation of aliphatic C-C bonds and in the synthesis of target molecules.[11]

This monograph is an attempt to bring together the principles that have to be followed when radicals are used in synthesis and to demonstrate how carbon-carbon bonds can be formed in radical reactions. Since radical chemistry provides mild reaction conditions for the formation of C-C bonds and these bonds constitute the backbone of organic compounds, this book will focus on this topic.

It is suggested that the chapter on the basic principles be read first, because one must have at least some knowledge of the reactivity of radicals in order to successfully apply radical reactions to synthesis.

REFERENCES

1. M. Gomberg, *J. Am. Chem. Soc.* **1900**, 22, 757; M. Gomberg *Chem. Ber.* **1900**, 33, 3150.
2. F. Paneth, W. Hofeditz, *Chem. Ber.* **1929**, 62, 1335.
3. D.H. Hey, W.A. Waters, *Chem. Rev.* **1937**, 21, 169.
4. M.S. Kharasch, E.T. Margolis, F.R. Mayo, *J. Org. Chem.* **1937**, 2, 393.
5. F.R. Mayo, F.M. Lewis, *J. Am. Chem. Soc.* **1944**, 66, 1594; F.R. Mayo, F.M. Lewis, C. Walling, *Discuss. Faraday Soc.* **1947**, 2, 285.
6. W.A. Waters: *The Chemistry of Free Radicals*, Clarendon Press, Oxford 1946; C. Walling: *Free Radicals in Solution*, Wiley, New York 1957.
7. J.K. Kochi (ed.): *Free Radicals*, Wiley, New York 1973.
8. H. Fischer (ed.), Landoldt-Börnstein, New Series, Vol. 13, Springer, Berlin since 1983.

9. J.F. Bunnett, *Acc. Chem. Res.* **1978**, 11, 413.

10. F. Minisci, *Top. Curr. Chem.* **1976**, 62, 1.

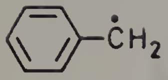
11. D.H.R. Barton, W.B. Motherwell in B.M. Trost; C.R. Hutchinson: *Organic Synthesis Today and Tomorrow*, Pergamon Press, Oxford 1981; D.J. Hart, *Science* **1984**, 223, 883; B. Giese, *Angew. Chem. Int. Ed. Engl.* **1985**, 24, 553; B. Giese (ed.): *Selectivity and Synthetic Applications of Radical Reactions*, Tetrahedron "Symposia-in-Print" Number 22, *Tetrahedron* **1985**, 41, 3887 ff.

Chapter 2

Basic Principles

A. General Aspects of Syntheses with Radicals

Radicals are species with at least one unpaired electron which, in contrast to organic anions or cations, react easily with themselves in bond forming reactions. In the liquid phase most of these reactions occur with diffusion controlled rates. Radical-radical reactions can be slowed down only if radicals are stabilized by electronic effects (stable radicals) or shielded by steric effects (persistent radicals). But these effects are not strong enough to prevent diffusion controlled recombination of, for example, benzyl radicals **1**[1] or tert-butyl radicals **2**.[2] Only in extreme cases, e.g. the triphenylmethyl radical **3** or the di-tert-butyl methyl radical **4**,[3] recombination rates are low. While the recombination rate of the triphenylmethyl radical **3** is reduced due to both steric and radical stabilizing effects, the steric effect alone slows down the recombination of the di-tert-butyl methyl radical **4**. Since **3** and **4** have no C-H bonds ß to the radical center, disproportionation reactions, in which the hydrogen atom is transferred, cannot occur.



1

$(CH_3)_3C\cdot$

2

$(C_6H_5)_3C\cdot$

3

$[(CH_3)_3C]_2\dot{C}H$

4

1. Reactions between radicals

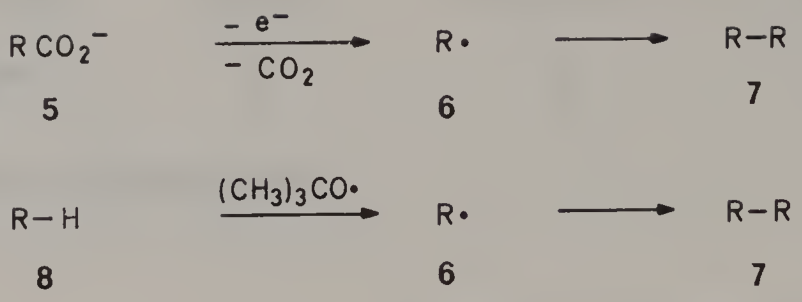
The fact that reactions between radicals are in most cases very fast could lead to the conclusion that direct radical-radical combination is the most synthetically useful reaction mode. This, however, is not the case because direct radical-radical reactions have several disadvantages:

- In the recombination reactions, the radical character is destroyed so that one has to work with at least equivalent amounts of radical initiators.

- The diffusion controlled rates in radical-radical reactions give rise to low selectivities which cannot be influenced by reaction conditions.

- The concentrations of radicals are so low that reactions with non-radicals, like the solvents, which are present in high concentrations, are often hard to prevent.

Nevertheless, there are useful synthetic applications in which new bonds are formed from radical-radical combination, for example, the Kolbe electrolysis of carboxylates (**5**→**7**), with the modern developments by Schäfer,[4] and the radical induced dehydrodimerization (**8**→**7**), which has been studied extensively in the last years by Viehe.[5]



2. Reactions between radicals and non-radicals

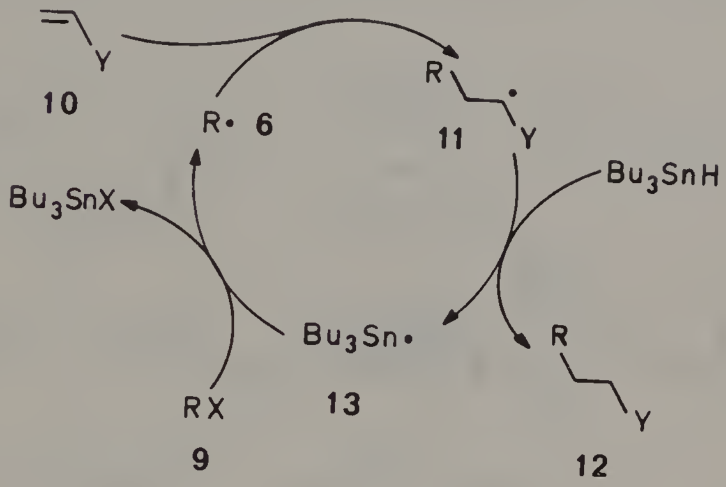
The second method for the synthesis of products using radical chemistry employs reactions between radicals and non-radicals. It possesses the following advantages:

- The radical character is not destroyed during the reaction; therefore, one can work with catalytic amounts of radical initiators.
- Most of the reactions are not diffusion controlled, and the selectivities can be influenced by variation of the substituents.
- The concentration of the non-radicals can be easily controlled.

In most cases, in order to apply reactions between radicals and non-radicals for syntheses, chain reactions have to be built up. For the successful use of radical chains two conditions must be obeyed:

- The selectivities of the radicals involved in the chain have to differ from each other.
- The reactions between radicals and non-radicals must be faster than radical combination reactions.

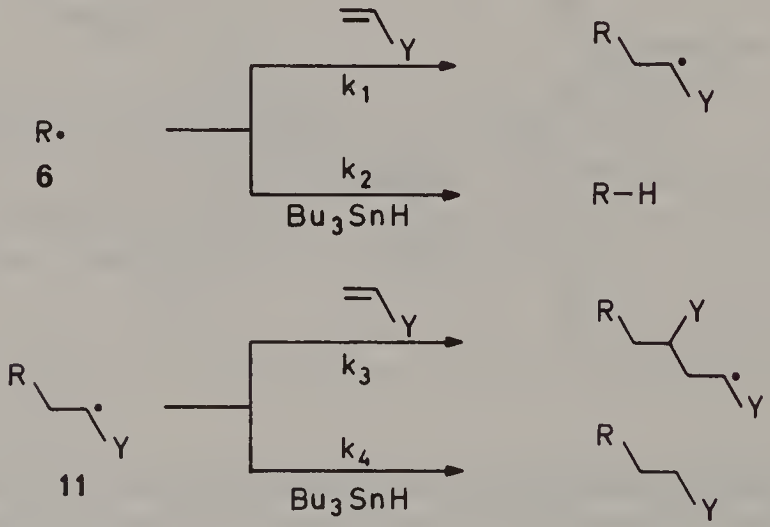
These rules can best be illustrated by a chain reaction that has gained increasing synthetic importance in the last years.[6] In this chain reaction, alkylhalides **9** and alkenes **10** react in the presence of tributyltin hydride to give products **12**.



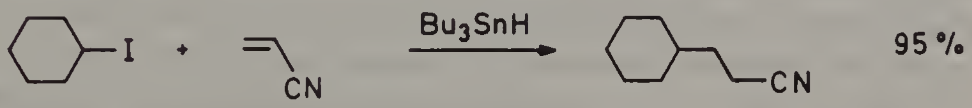
For a successful application of the tin-method, alkyl radicals **6** must attack alkenes **10** to form adduct radicals **11**. Trapping of **11** yields products **12** and tributyltin radicals **13**, which react with alkylhalides **9** to give back educt radicals **6**. The tin method can be synthetically useful only if these reactions are faster than all other possible reactions of radicals **6**, **11**, and **13**. Therefore, the radicals in the chain must meet certain selectivity and reactivity prerequisites.

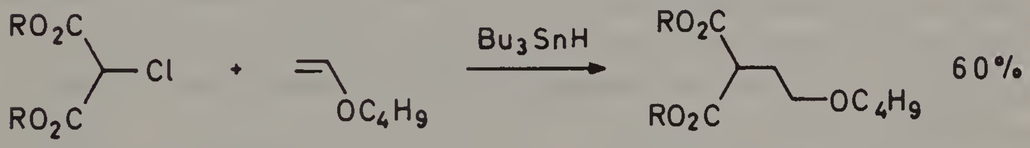
a. <u>Selectivity requirement</u>

Radicals **6**, **11**, and **13** are simultaneously present during the formation of product **12** from alkylhalides **9**, alkene **10**, and tributyltin hydride. The radicals face the same competition systems, but for a successful synthesis, each radical must react with a specific educt. Radical **6** must add to an alkene, adduct radical **11** has to abstract a hydrogen atom from tributyltin hydride, and tin radical **13** must react with an alkyl halide. This means, that the radicals in a synthetically useful chain reaction have to differ in selectivity. If, for example, adduct radicals **11** would possess the same selectivity as radicals **6** ($k_1/k_2 = k_3/k_4$), then either polymerization of alkenes ($k_1/k_2 >> 1$), reduction of alkylhalides ($k_1/k_2 << 1$), or formation of a product mixture ($k_1/k_2 \approx 1$) would result.



This can be prevented by choosing a suitable substituent on the alkene that changes the selectivity of radical **11** compared to radical **6**. Therefore, in planning syntheses one has to know at least something about the substituent influence on the selectivity of radicals. Fortunately, the mechanism of radical addition to alkenes is known in detail.[7] Alkyl radicals, substituted with electron-releasing groups (alkyl, alkoxy, amino etc.), behave like nucleophiles and react very fast with alkenes substituted by electron-withdrawing substituents (nitrile, ketone, ester etc.).[7,8] On the other hand, radicals with electron-withdrawing substituents behave like electrophiles and react fast with electron-rich alkenes.[7,9] The synthetic application of the tin-method is possible, therefore, only with those halides **9** and alkenes **10** which lead to radicals **6** and **11** with different or opposite polarity. For example, one can use the pairs cyclohexyl iodide/acrylonitrile[10] or chloromalonic ester/enolether.[11]

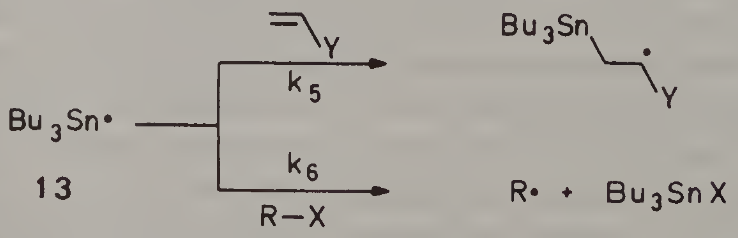




Of course, it is not sufficient that the selectivities of the radicals are merely different; they must differ to such a degree that the desired reaction dominates the various competitive reactions. At room temperature, alkyl radicals R• add to alkenes such as acrylonitrile with rate coefficients of about $10^5 - 10^6$ (l/mol•s),[8] whereas nitrile-substituted radicals react with acrylonitrile about 10^4 times slower.[12] Hydrogen transfer from Bu_3SnH to alkyl radicals also occurs with rate coefficients of $10^5 - 10^6$ (l/mol•s) at room temperature,[13] but these rates don't depend very much on the substituent at the radical center.[14] Therefore, the selectivities of alkyl radicals **6** and adduct radicals **11** in the competition system $H_2C{=}CHCN/Bu_3SnH$ are $k_1/k_2 = 1$ and $k_3/k_4 = 10^{-4}$. In order to form a C-C bond, the reaction between radical **6** and the alkene has to be faster than the reduction of **6** by Bu_3SnH. This is possible only with a $H_2C{=}CHCN/Bu_3SnH$

concentration ratio of at least 10-100, because the competition constant is about 1. Therefore, either one must work with an excess of acrylonitrile, or with low concentrations of Bu_3SnH. Low Bu_3SnH concentrations can be attained by slowly adding the tin hydride to the reaction mixture or by working with a catalytic amount of tin salts and equimolar amounts of $NaBH_4$, which generates the tin hydride in situ. When a $H_2C{=}CHCN/Bu_3SnH$ ratio of 10^2 is used, polymerization doesn't occur because the competition coefficient k_4/k_3 is about 10^4. The rate ratio r_4/r_3,which takes the concentrations into account, is 10^2; therefore, adduct radical **11** reacts predominately with Bu_3SnH to yield product **12**. If the excess of acrylonitrile is too large, then **11** reacts noticeably with acrylonitrile. An essential task, therefore, is to find the optimum concentration ratio for the synthesis in question. This is necessary because alkene substituents exert a strong influence on the rate. Thus, the rate of addition of the cyclohexyl radical increases by 8500 on going from 1-hexene to acrolein.[7,15]

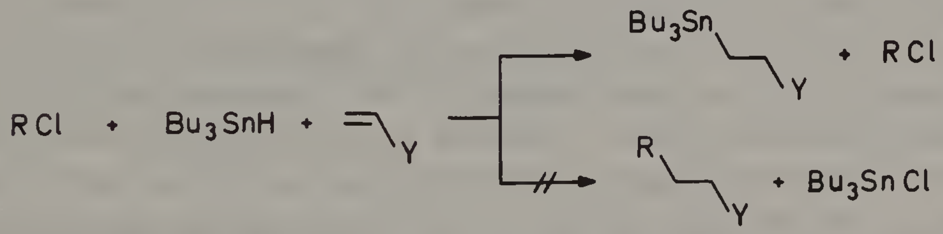
The third radical involved in the chain is the tributyltin radical **13**. For this radical the selectivity in the competition system alkene/tributyltin hydride is of no importance, because the reaction of **13** with tin hydride generates back the tin radical. However, the competition between alkene addition and halogen abstraction from the alkyl halide is synthetically important.



In fact, alkyl bromides and alkenes like acrylonitrile, react equally fast with the tin radical **13**.[16] Since a relatively large amount of acrylonitrile is already used in these syntheses, the undesired addition of tin radicals **13** to alkenes cannot be greatly influenced by varying the concentration ratio alkene/alkyl halide. Instead, it is better to switch from alkylbromides to the 10-100 times more reactive alkyl iodides.[16]

C-C bond formation doesn't take place when less reactive alkyl halides are used because alkyl radicals **6** are not regenerated in the chain. Therefore, not only alkyl chlorides, but also isonitriles that are reduced by tin hydride cannot be used as educts.[17] Syntheses with these educts in the presence of alkenes lead to tin hydride addition products on the alkenes.

$$RCl + Bu_3SnH \longrightarrow RH + Bu_3SnCl$$



This analysis is typical for the development of radical chain reactions in syntheses. In order to evaluate which reactions are synthetically useful, the magnitudes of the rate constants must be known. Many of these rate constants have been determined in recent years and most of the important ones are now known. Moreover, the solvent has little effect on the reaction rates of neutral radicals; therefore, the literature data can be used even if the synthesis is carried out in a different solvent.

b) Reactivity requirement

Chain reactions are terminated by combination of the radicals. Therefore, the rate of chain propagation between radicals and non-radicals (r_p) must be higher than that of chain termination between the radicals (r_t). Equations (a) and (b) are the analytical expressions for these reactions, where k_p and k_t are the rate constants for chain propagation and chain termination steps, respectively. R• represents all radicals that are present in the chain, and X the added reagents. The reactivity requirement that must be satisfied for the use of radical chains in syntheses is given by equation (c).

$$r_p = k_p \cdot [R\cdot] \cdot [X] \qquad (a)$$

$$r_t = k_t \cdot [R\cdot] \cdot [R\cdot] \qquad (b)$$

$$1 < \frac{r_p}{r_t} = \frac{k_p \cdot [X]}{k_t \cdot [R\cdot]} \qquad (c)$$

In most cases, carbon centered radicals react with each other with diffusion-controlled rates; the rate coefficients k_t, which have only a small temperature dependence, are $10^9 - 10^{10}$ (l/mol•s) in the liquid phase.[1,2] The concentration of the added reaction partner X depends on the reaction conditions, but in syntheses, these concentrations are often nearly one molar. The concentrations of radicals in chain reactions also depend on the reaction conditions, e.g. the rate of the decomposition of the initiator. Typically, radical concentrations in chain reactions are about $10^{-7} - 10^{-8}$ (mol/l).[18]

$$k_p > 10^2 \text{ (l/mol}\cdot\text{s)} \qquad (d)$$

According to expression (d), only those chain propagation steps whose rate coefficients k_p are larger than 10^2 (l/mol•s) can be used for syntheses. Thus, the homolytic cleavage of O-H and N-H bonds in aliphatic alcohols and amines by alkyl radicals, as well as the intermolecular addition to the C=O group of ketones and esters are so slow at room temperature that these reactions don't occur in synthetically useful chains. In other words, carbon-centered radicals exhibit high chemoselectivities and their employment in reactions with more complex molecules should be considered.

B. Elementary Reaction Steps between Radicals and Non-Radicals

2. Introduction

A radical chain is built up by different types of propagation steps all of which lead to new radicals

- Addition reactions.

$$R\cdot + AB \rightarrow RAB\cdot$$

- Substitution (abstraction) reactions.

$$R\cdot + AB \rightarrow RA + B\cdot$$

- Elimination (fragmentation) reactions.

$$RAB\cdot \rightarrow RA + B\cdot$$

- Rearrangement reactions.

$$RAB\cdot \rightarrow ARB\cdot$$

- Electron transfer reactions.

$$R^- + M^{n+} \rightarrow R\cdot + M^{(n-1)+}$$

or

$$RX^{\overline{\cdot}} + RY \rightarrow RX + RY^{\overline{\cdot}}$$

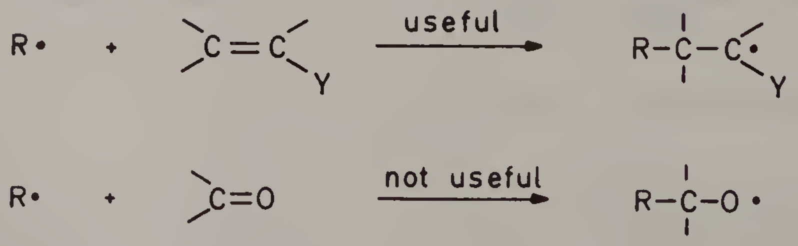
It is not the goal of this book to go into the mechanistic details of these elementary steps, but very often two simple rules can be applied to fast radical chain reactions:

- Most chain propagating steps are exothermic and one can use the strength of bonds that are broken and formed as a rough guideline for the rate of the reaction (thermodynamic parameter).
- Because of the early transition states in fast radical reactions, frontier molecular orbital (FMO) theory can be utilized for these reactions (kinetic parameter).

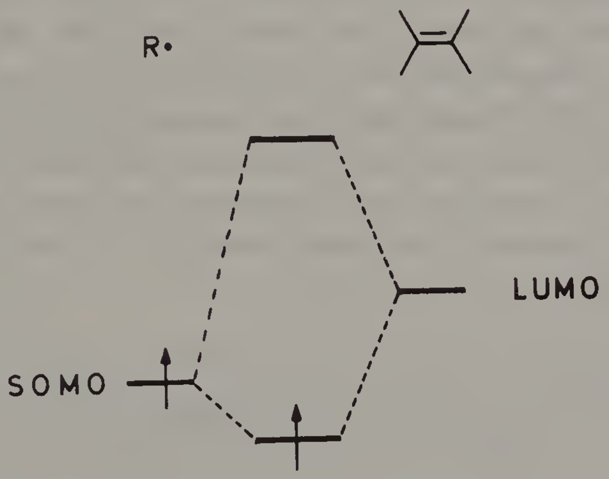
The applicability of these rules shall be demonstrated by some examples for the five different propagation steps.

2. Addition

Addition of alkyl radicals to alkenes is a useful C-C bond formation reaction in which a σ-CC bond is made from a π-CC bond in a very exothermic reaction. In contrast, π-CO bonds of ketones and aldehydes are nearly as strong as σ-CC bonds. Therefore, ketones and aldehydes cannot be used as intermolecular traps in syntheses.

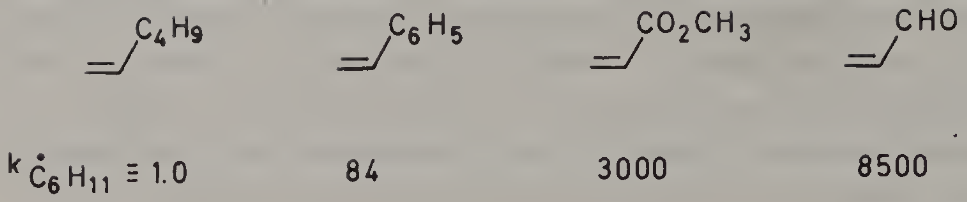


The rate of addition of a radical to an alkene depends largely on the substituents on the radical and the alkene. These substituent effects can be described by FMO theory.[7,19] The singly occupied orbital (SOMO) of the radical interacts with the lowest unoccupied orbital (LUMO) and/or the highest occupied orbital (HOMO) of the CC-multiple bond. Radicals with a high lying SOMO interact preferentially with the LUMO of the alkene.

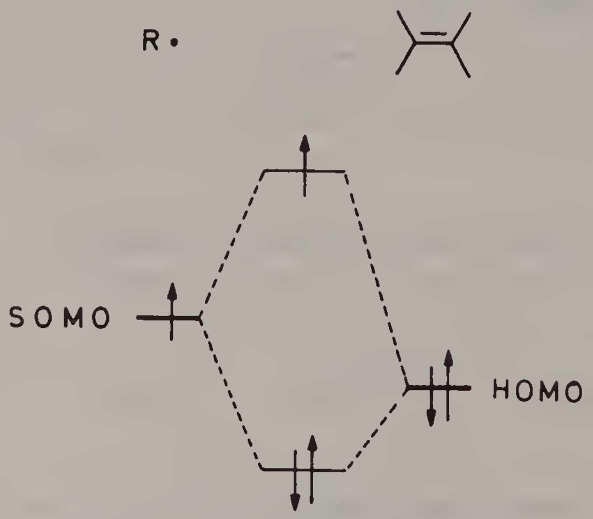


Orbital interaction between a nucleophilic radical and an electron-poor alkene

Electron withdrawing substituents at the alkene, which lower the LUMO energy, increase the addition rate by reducing the SOMO-LUMO difference. Therefore, cyclohexyl radicals react 8500 times faster with acrolein than with 1-hexene.[15]

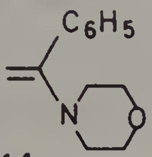


These orbital effects are so important that a tert-butyl radical reacts faster than prim. and sec. radicals with alkenes like vinylphosphonic ester or acrylonitrile.[20] Thus, the increase in the SOMO energy in going from prim. to tert. radicals has a larger effect on the rate than the decrease in the strength of the bonds that are formed. Alkyl, alkoxyalkyl, aminoalkyl, and other similar radicals are therefore nucleophiles. However, radicals with electron withdrawing substituents at the radical center have SOMO energies so low that the SOMO-HOMO interaction dominates.



Orbital interaction between an electrophilic radical and an electron-rich alkene

These radicals react like electrophiles; that is, electron donating substituents at the alkenes increase the rate. The malonyl radical, for example, reacts with enamine **14** 23 times faster than with acrylester 15.[11]



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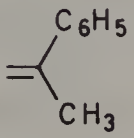
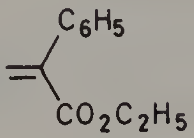


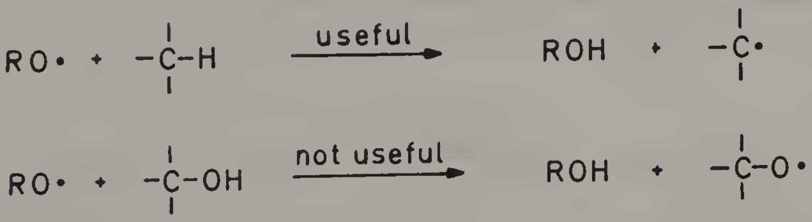


15

$k_{(EtO_2C)_2\dot{C}H}$ 23 3.5 $\equiv 1.0$

3. Substitution

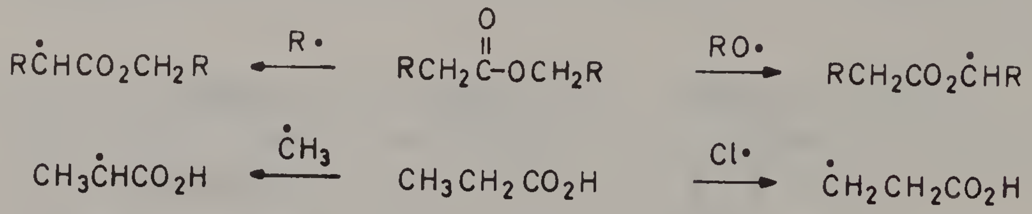
Since an O-H bond is much stronger than a C-H bond, a typical bimolecular reaction for alkoxy radicals is the H-abstraction from C-H bonds. However, OH-bonds of alcohols are attacked too slowly for synthetic applications because the reaction is thermoneutral.



$$RO\cdot + -\overset{|}{\underset{|}{C}}-H \xrightarrow{\text{useful}} ROH + -\overset{|}{\underset{|}{C}}\cdot$$

$$RO\cdot + -\overset{|}{\underset{|}{C}}-OH \xrightarrow{\text{not useful}} ROH + -\overset{|}{\underset{|}{C}}-O\cdot$$

Alkoxy radicals are electrophiles and they preferentially attack C-H bonds with high HOMO energies; for instance, the α-C-H bond of ethers and amines or the alkyl C-H bond of esters.[21] In contrast, nucleophilic alkyl radicals abstract a hydrogen atom from the acyl group of esters, because this C-H bond has a lower LUMO energy.



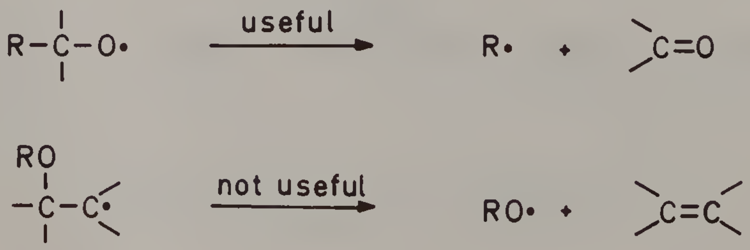
$$R\dot{C}HCO_2CH_2R \xleftarrow{R\cdot} RCH_2\overset{O}{\overset{\|}{C}}{-}OCH_2R \xrightarrow{RO\cdot} RCH_2CO_2\dot{C}HR$$

$$CH_3\dot{C}HCO_2H \xleftarrow{\dot{C}H_3} CH_3CH_2CO_2H \xrightarrow{Cl\cdot} \dot{C}H_2CH_2CO_2H$$

These differences also account for the preferential abstraction of the ß-hydrogen of propionic acid by the electrophilic chlorine atom and the abstraction of the α-hydrogen by the nucleophilic methyl radical.[21]

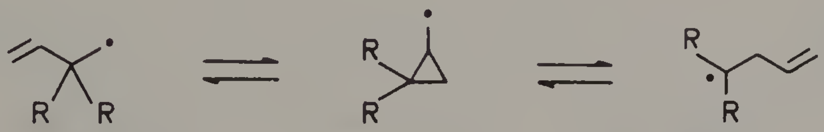
3. Elimination

In elimination reactions, two molecules are formed from one. Thus, these reactions are favored by activation entropies, and the free energy gain increases with increasing reaction temperature. Therefore, even alkoxy radicals undergo fast ß-elimination reactions, although the enthalpy differences between π-CO and σ-CC bonds are small.[22] But a C-OR bond α to a radical center is cleaved too slowly to be of synthetic use, because less stable π-CC bonds are formed. Only with the weaker C-Br, C-SR or C-SnR$_3$ bonds are ß-elimination reactions fast enough to be synthetically useful.[23]



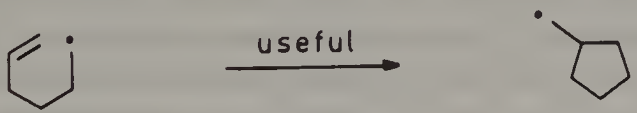
5. Rearrangement

Compared to their cationic counterparts, only a few radical rearrangements are fast enough to appear in syntheses.[24] An example is the vinyl migration in **16** which forms the more stable radical **18**.

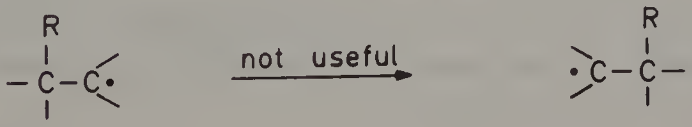


16 **17** **18**

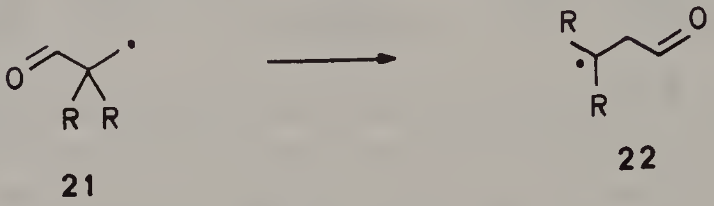
This reaction is a combination of an intramolecular addition (**16**→**17**) and an elimination reaction (**17**→**18**). The addition of the nucleophilic radical to the electron-rich alkene is fast because the loss in entropy is much smaller than in intermolecular reactions. The ß-C-C bond of **17** cleaves rapidly because of ring strain. The much smaller ring strain in **20** stops the rearrangement of the hexenyl radical **19** at the cyclopentylmethyl radical stage.



19 **20**

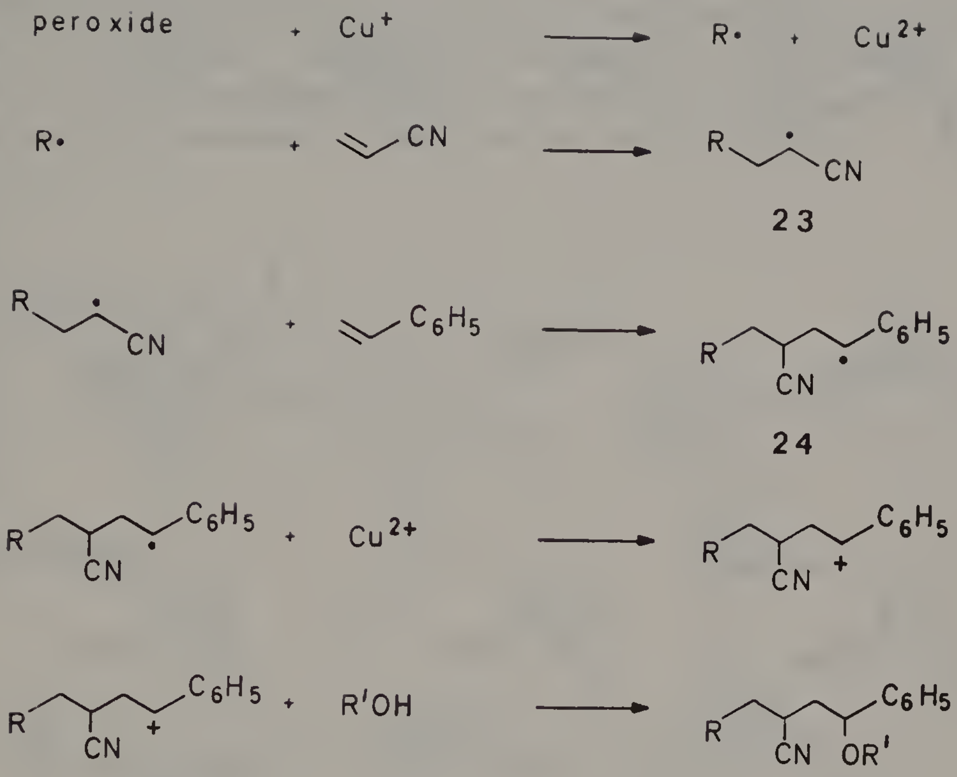


This is in accord with the very slow 1,2 alkyl or hydrogen shifts in radicals, which don't occur in syntheses because of the strong σ-bonds. An orbital effect presumably accounts for the formyl shift (**21**→**22**), which is nearly as fast as the vinyl shift of **16**,[25] even though a π-CO bond is much stronger than a π-CC bond.

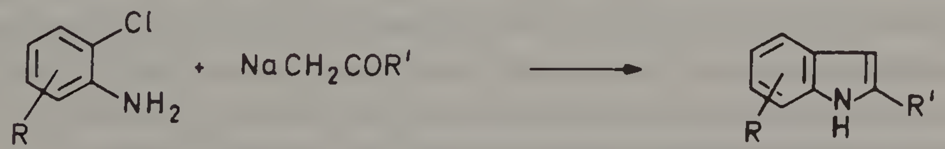


6. Electron transfer

The rate of electron transfer reactions depends on the difference in the reduction potentials of educts and products. Since alkyl radicals possess an unpaired electron in a nonbonding orbital, electron transfer reactions to many metal salts often occur with high rates.[26] The higher the SOMO energies of the radicals, the faster is the electron transfer. The alternating addition of alkyl radicals to olefin pairs, observed by Minisci, is a significant example of this behavior.[27] Alkyl radicals generated by electron transfer from Cu^+ to peroxides form adduct radicals **23** with acrylonitrile. The nitrile substituent at the radical center of **23** causes oxidation to be slower than addition to styrene and gives the 2:1 adduct radical **24**. Electron transfer from this benzylic radical is now faster than further addition to the alkene and products are formed via electron transfer and reaction with alcohols.



Compared to neutral radicals, electron transfer reactions with radical anions are so fast, that even neutral molecules can act as electron acceptors. This is the case in the $S_{RN}1$ reactions developed by Kornblum, Russell and Bunnett.[28] Thus, indoles **26** can be synthesized from aniline derivatives **25** in high yields via a multistep reaction sequence involving electron transfer reactions between radical anion **27** and the starting aniline **25** (see p. 252).



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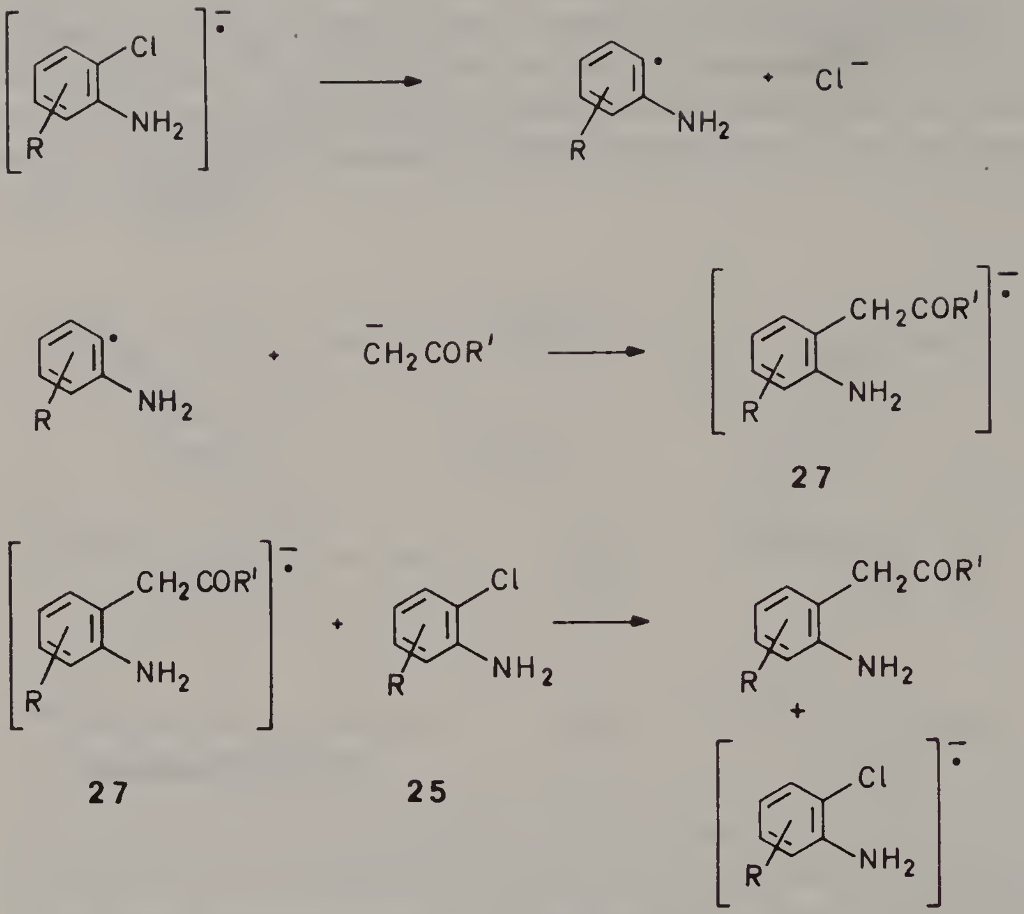
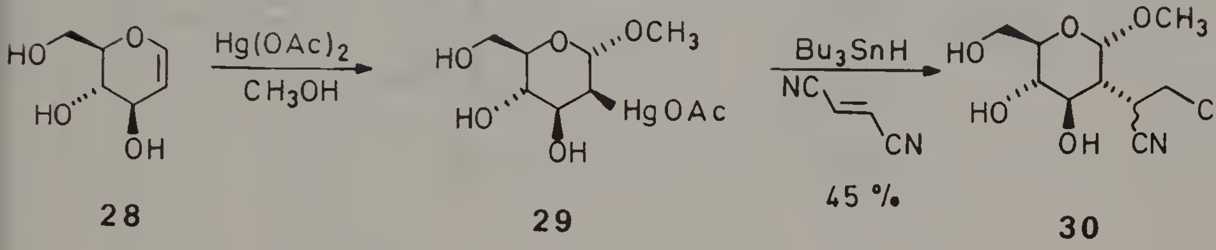


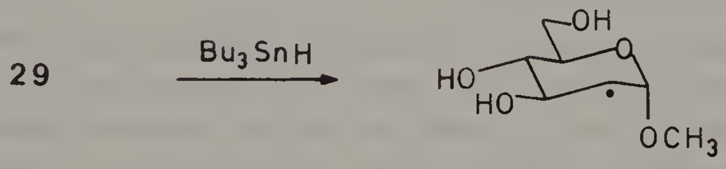
C. Comparison of Radicals and Ions in Syntheses

1. Chemoselectivity

Because of the reactivity requirement only functional groups that have bimolecular rate coefficients $k > 10^2$ (l/mol·s) are attacked by radicals. The limiting factor can be advantageous in the planning of syntheses because it means that a range of functional groups are tolerated without protection. Thus, the homolytical cleavage of O-H and N-H bonds in aliphatic alcohols and amines by alkyl radicals, as well as the intermolecular addition of alkyl radicals to C=O bonds of ketones and esters are so slow at room temperature that they don't occur in synthetically useful chains. In other words, carbon-centered radicals exhibit high chemoselectivities and their use in reactions with complex molecules should be considered.



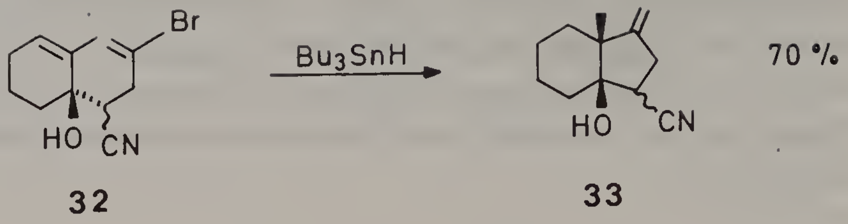
28 29 30

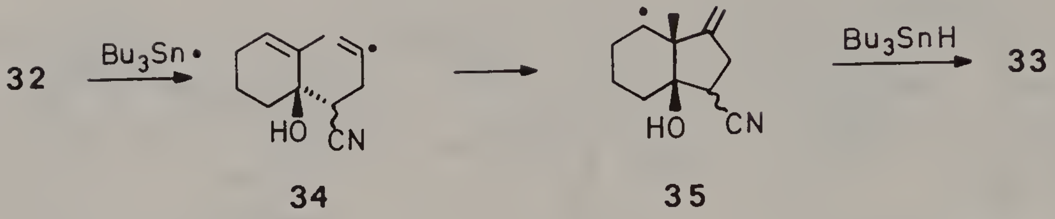


31

For example, the C-branched carbohydrate **30** can be synthesized from the glucal **28** without protection of the OH groups. The C-C bond formation occurs via homolysis of the C-Hg bond in **29**, attack of fumaronitrile at radical **31**, and subsequent hydrogen transfer, to yield product **30**.[29]

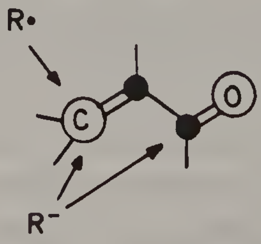
Another example is the cyclization of **32** to product **33** carried out by Stork.[30] Again there is no need to protect the OH group during the synthesis. It is also remarkable to note how facile the quaternary carbon atom in **33** is formed. The reaction occurs via the vinyl radical **34**, which exclusively cyclizes to a five-membered ring **35**; hydrogen abstraction then gives product **33**.





2. Regioselectivity

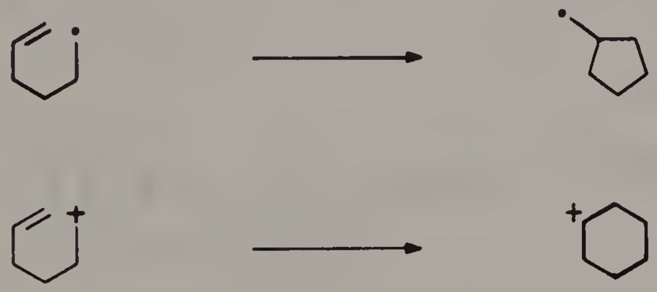
Radical reactions often show different regioselectivities than ionic reactions. Thus, α,ß-unsaturated aldehydes, ketones, and esters are attacked by carbon centered radicals exclusively at the olefinic carbon atom. In contrast, anionic species exhibit a competition between attack at the olefinic and the carbonyl C-atom.



Attack of radicals and anions at the LUMO of α, β-unsaturated carbonyl systems. The circles describe the quantity of the orbital coefficients.

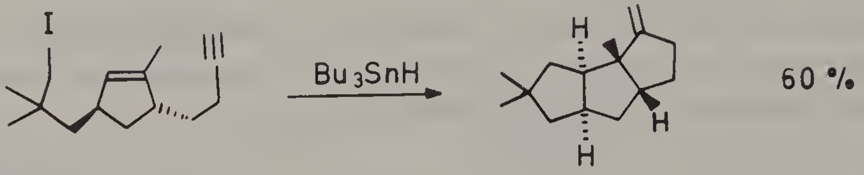
Radicals attack exclusively at the carbon atom with the largest LUMO coefficient. The resulting higher regioselectivity of radicals in addition reactions to α,ß-unsaturated carbonyl compounds demonstrates that orbital interactions are more important in radical than in ionic reactions.

Another special feature of radicals is the predominant cyclization of 1-hexenyl radicals to five-membered rings,[24,31] whereas cations yield six-membered rings.

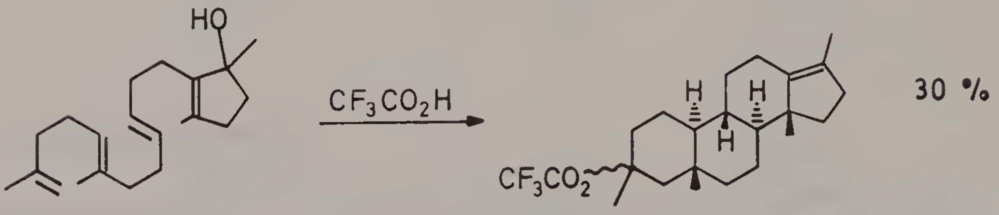


This differing behavior is caused by the different transition states for radical and cationic reactions. For radicals, kinetic measurements[7] and theoretical calculations[24] favor an unsymmetrical transition state in which the distances between the attacking radical and the two olefinic carbon atoms of the alkene are unequal.[32] In contrast, cations attack the center of the double bond where the electron density is high. Beckwith has shown that, because of ring strain effects, an unsymmetrical transition state leads to faster cyclization to a five-membered than to a six-membered ring.[31] This cyclization mode of radicals is also supported by the Baldwin-rules.[33]

The formation of five-membered rings during radical cyclization has been used extensively in the last years for the synthesis of target molecules. Thus, Curran[34] synthesized tricyclus **37** by homolytic iodine abstraction from **36**. The cationic cyclization of **38** yields the six-membered rings of **39**.[35]



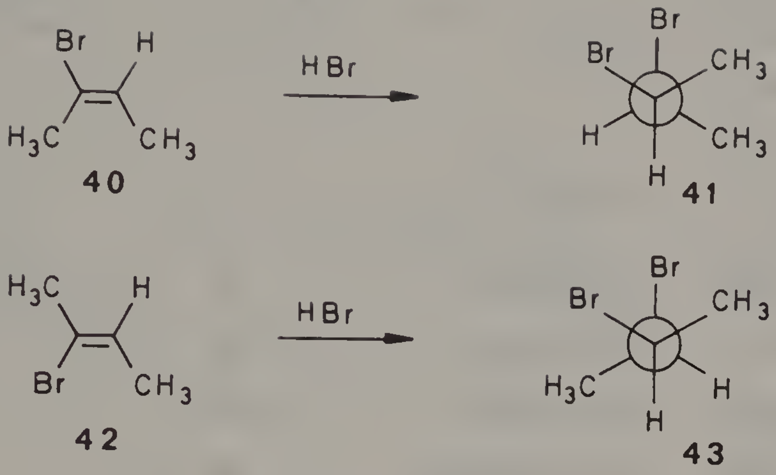
36 **37**



38 **39**

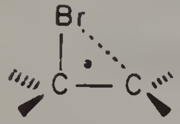
3. Stereoselectivity

Only a few examples of high stereoselectivities of acyclic radicals are known. For example, radical HBr addition to alkenes can occur in a *trans*-reaction, because of the bridging ability of the bromine located ß to the radical center. Thus, at -80°C the addition of HBr to *cis*- and *trans*-2-bromo-2-butene quantitatively gives products resulting from *trans*-addition: The *cis*-olefin **40** yields pure meso-2,3-dibromobutane **41** and the *trans*-alkene **42** gives pure d,l-dibromide **43**.[36]



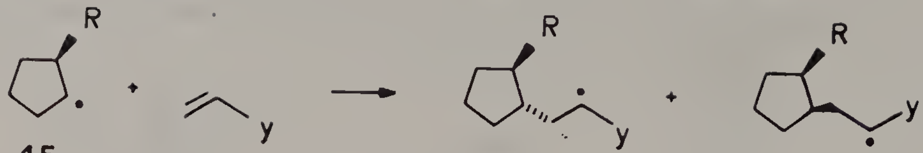
40 **41**

42 **43**

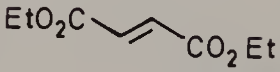


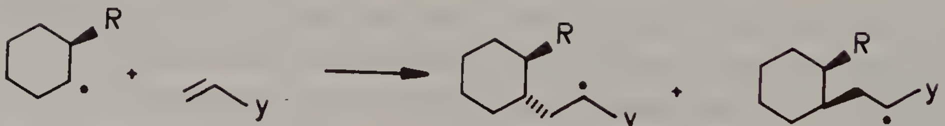
44

By raising the temperature, the stereoselectivity decreases so that at room temperature roughly the same mixture of products is obtained from each olefin. In general, the bridging of radicals like **44** is much less pronounced than that of cations;[36,37] thus, the stereoselectivity of acyclic radicals is often lower than that of cations. However, high stereoselectivities can be observed with cyclic radicals. For example, in C-C bond forming reactions, cyclopentyl radicals **45** give exclusively *trans*-adducts if the neighboring substituent is an amide group.[38] With less shielding CH_3 or OR groups, the stereoselectivity decreases, but it raises again if alkenes of low reactivity or with substituents at the attacked olefinic C-atom are used.[39] With cyclohexyl radicals **46**, the *trans*-stereoselectivity is less pronounced, but can also be relatively high.[38,39]

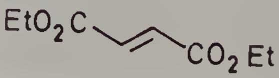


45

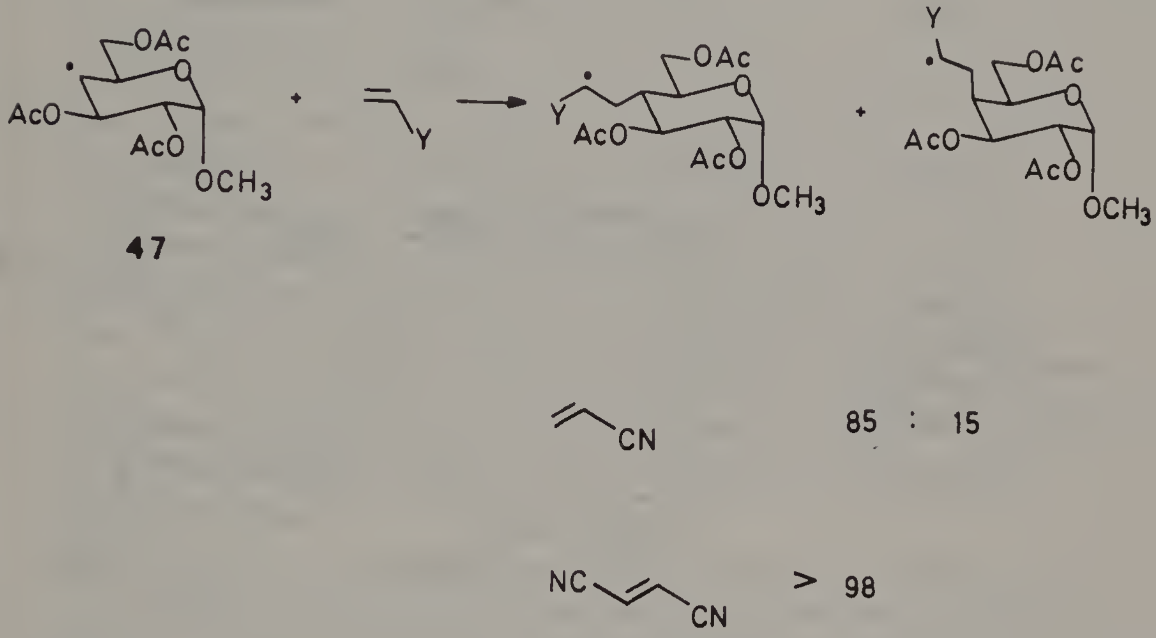
R	Alkene	
OCH_3	$H_2C=CHCN$	77 : 23
CH_3	$H_2C=CHCN$	92 : 8
NHAc	$H_2C=CClCN$	> 98
OCH_3	$H_2C=CHCO_2CH_3$	88 : 12
OCH_3	 EtO_2C CO_2Et	98 : 2



46

R	Alkene	
OCH_3	$H_2C=CHCN$	65 : 35
NHAc	$H_2C=CClCN$	> 95
OCH_3	$H_2C=CHCO_2CH_3$	70 : 30
OCH_3	 EtO_2C CO_2Et	92 : 8

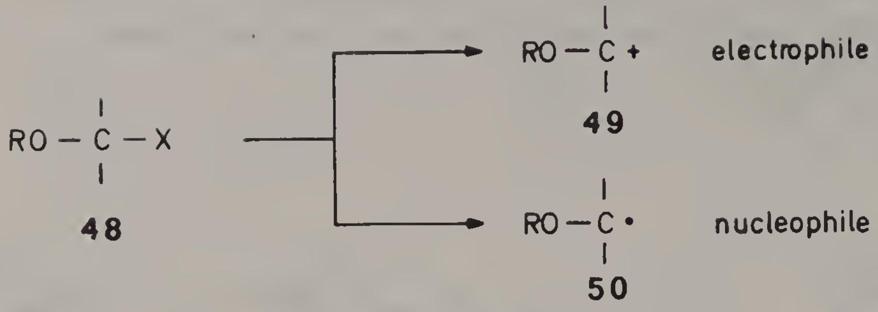
It is interesting to note that carbohydrate radicals, for example **47**, show higher selectivities than cyclohexyl radicals.[10,29]

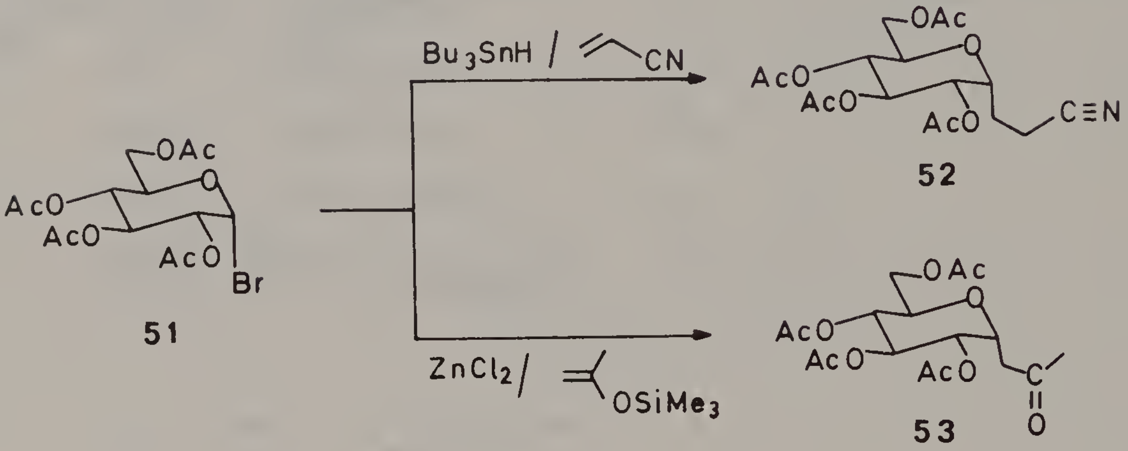


47

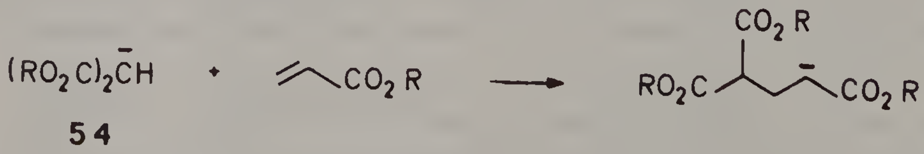
4. Umpolung

In radical reactions the product of "umpolung" of the reactivity can be often observed.[25,40] If one, for example, generates ions from α-haloethers **48**, cations **49** will be formed, because cations are stabilized by the alkoxy substituent. These cations are, of course, electrophiles and add easily to electron-rich alkenes like enolethers. The corresponding alkoxy alkyl radical **50**, however, is nucleophilic, and because of its high lying SOMO, it preferentially attacks electron-poor alkenes like acrylonitrile. Thus, α-bromoglucose **51** gives the 1,4-di-heterosubstituted product **52** in a radical reaction,[41] but the 1,3-di-heterosubstituted compound **53** in an ionic reaction.[42]





Carbanions 54, generated from malonates are stabilized by the ester substituents and are nucleophiles that undergo Michael addition with electron poor alkenes. But the corresponding malonyl radicals 55 are electrophiles, which, because of their low lying SOMO, easily attack enolethers.[11] Again radicals yield 1,4-di-heterosubstituted products, whereas ions form 1,5-di-heterosubstituted products.



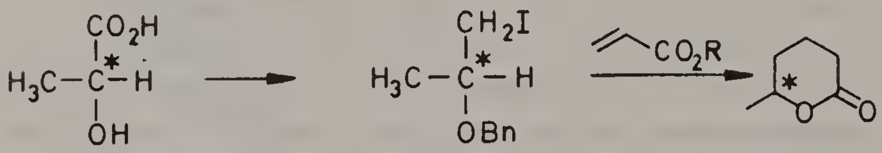
55

5. Racemization

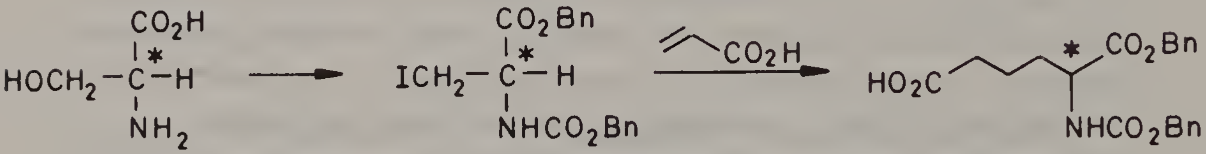
Since radical reactions used in syntheses are very fast,[6,43] side reactions, e.g. radical rearrangements, ß-elimination, and racemizations of chiral centers at adjacent or remote carbon atoms, are in most cases suppressed. Moreover, most radical reactions are carried out in the absence of strong acids and bases so that competing ionic reactions such as racemization don't occur. This means, that the radical methodology discussed here offers very mild reaction conditions under which chiral centers at the non-radical carbon atoms survive.

In many naturally occuring chiral molecules the chiral centers are substituted by OR or NR$_2$ groups. Ionic centers generated adjacent to an OR group can cause problems; a carbanion can induce heterolytic cleavage of the C-O bond, and with carbocations, rearrangement can occur.

These side-reactions make intermolecular reactions at ionic centers often impossible or lead to racemized products. In radicals with ß-OR or ß-NR_2 groups, elimination or racemization cannot compete with the fast chain reactions. This has been utilized, for example, in syntheses where the chiral centers are delivered from the chiral pool. Thus, from lactic acid **56**, the lactone **57**,[44] and from amino acid **58**, the aminoadipic acid **59**[45] can be synthesized without racemization. Radical C-C bond formation is the main step in these syntheses.



56 **57**



58 **59**

Elimination can compete with radical chain steps only if the ß-bonds are very weak, e.g. C-S, C-Br or C-metal bonds.[23,46]

REFERENCES

1. M. Lehni, H.Schuh, H. Fischer, *Int. J. Chem. Kinetics* **1979**, *11*, 705; H. Langhals, H. Fischer, *Chem. Ber.* **1978**, *111*, 543.

2. H.R. Dütsch, H. Fischer, *Int. J. Chem. Kinetics* **1981**, 13, 527.

3. D. Griller, K.U. Ingold, *Acc. Chem. Res.* **1976**, *9*,13; H.D. Beckhaus, G. Hellmann, C. Rüchardt, *Chem. Ber.* **1978**, *111*, 72; K. Schlüter, A. Berndt, *Tetrahedron Lett.* **1979**, 929.
4. H.J. Schäfer, *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 911.
5. H.G. Viehe, R. Merenyi, L. Stella, Z. Janousek, *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 917.
6. B. Giese, *Angew. Chem. Int. Ed. Engl.* **1985**, *24*,553.
7. B. Giese, *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 771.
8. A. Citterio, A. Arnoldi, F. Minisci, *J. Org. Chem.* **1979**, *15*, 2674; B. Giese, G. Kretzschmar, *Chem. Ber.* **1984**, *117*, 3160; K. Münger, H. Fischer, *Int. J. Chem. Kinetics* **1985**, *17*, 809.
9. J.M. Tedder, J.C. Walton, *Tetrahedron* **1980**, *36*, 701; K. Riemschneider, E. Drechsel-Grau, P. Boldt, *Tetrahedron Lett.* **1979**, 185.
10. B, Giese, J.A. González-Gómez, T. Witzel, *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 69.
11. B. Giese, H. Horler, M. Leising, *Chem. Ber.* **1986**,119,444.
12. R. Korus, K.F. O'Driscoll in J. Brandrup, E.H. Immergut: *Polymer Handbook*, Wiley, New York 1975, p. II-45.
13. C. Chatgilialoglu, K.U. Ingold, J.C. Scaiano, *J. Am. Chem. Soc.* **1981**, *103*, 7739.
14. H. Sakurai in J.K. Kochi: *Free Radicals*, Vol. 2, Wiley, New York 1973, p. 770.
15. B. Giese, G. Kretzschmar, *Chem. Ber.* **1983**, *116*, 3267.
16. K.U. Ingold, J. Lusztyk, J.C. Scaiano, *J. Am. Chem. Soc.* **1984**, *106*, 343.
17. D.H.R. Barton, G. Bringmann, G. Lamotte, R.S. Hay-Motherwell, W.B. Motherwell, *Tetrahedron Lett.* **1979**, 2291.
18. K.U. Ingold in J. Kochi: *Free Radicals*, Vol. 1, Wiley, New York 1973, p. 37.

19. I. Fleming: *Frontier Orbitals and Organic Chemical Reactions*, Wiley, London 1976.

20. T. Caronna, A. Citterio, M. Ghirardini, F. Minisci, *Tetrahedron* **1977**, *33*, 793; J.A. Baban, B.P. Roberts, *J. Chem. Soc. Perkin Trans. 2*, **1981**, 161.

21. J. Tedder, *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 401.

22. P. Brun, B. Waegell in R.A. Abramovitch: *Reactive Intermediates*, Vol. 3, Plenum Press, New York 1983, p. 392.

23. J.A. Kerr, A.C. Lloyd, *Quart. Rev. (London)*, **1968**, *22*, 549; T.E. Boothe, J.L. Greene, P.B. Shevlin, *J. Am. Chem. Soc.* **1976**, *98*, 951; G.E. Keck, E.J. Enholm, J.B. Yates, M.R. Wiley, *Tetrahedron*, **1985**, *41*, 4079.

24. A.L.J. Beckwith, K.U. Ingold in P. de Mayo: *Rearrangement in Ground and Excited States*, Vol. 1, Academic Press, New York 1980, p. 161.

25. B. Giese, H. Horler, *Tetrahedron Lett.* **1983**, *24*, 3221.

26. J.K. Kochi: *Organometallic Mechanism and Catalysis*, Academic Press, New York 1978; M. Julliard, M. Chanon, *Chem. Rev.* **1983**, *83*, 425.

27. F. Minisci, *Acc. Chem. Res.* **1975**, *8*, 165.

28. R.C. Kerber, G.W. Urry, N. Kornblum, *J. Am. Chem. Soc.* **1965**, *87*, 4520; G.A. Russell, W.C. Danen, *J. Am. Chem. Soc.* **1966**, *88*, 5663; J.K. Kim, J.F. Bunnett, *J. Am. Chem. Soc.* **1970**, *92*, 7463; R.A. Rossi, R.H. de Rossi, *ACS Monogr. 178*, **1983**.

29. B. Giese, K. Gröninger, *Tetrahedron Lett.* **1984**, *25*, 2743.

30. G. Stork, N.H. Baine, *J. Am. Chem. Soc.* **1982**, *104*, 2321.

31. A.L.J. Beckwith, C.H. Schiesser, *Tetrahedron* **1985**, *41*, 3925.

32. H. Fujimoto, S. Yamabe, T. Minato, K. Fukui, *J. Am. Chem. Soc.* **1972**, *94*, 9205; M.J.S. Dewar, S. Olivella. *J. Am. Chem. Soc.* **1978**, *100*, 5290.

33. J.E. Baldwin, *J. Chem. Soc. Commun.* **1976**, 734.

34. D.P. Curran, D.M. Rakiewicz, *Tetrahedron* **1985**, *41*, 3943.

35. W.S. Johnson, M.F. Semmelhack, M.U.S. Sultanbawa, L.A. Dolak, *J. Am. Chem. Soc.* **1968**, *90*, 2994.

36. P.S. Skell, K.J. Shea in J.K. Kochi: *Free Radicals*, Vol. 2, New York 1973, p. 809.

37. J.W. Wilt in J.K. Kochi: *Free Radicals*, Vol. 1, New York 1973, p. 333.

38. R. Henning, H. Urbach, *Tetrahedron Lett.* **1983**, *24*, 5343.

39. B. Giese, K. Heuck, H. Lenhardt, U. Lüning, *Chem. Ber.* **1984**, *117* 2132; B. Giese, H. Harnisch, U. Lüning, *Chem. Ber.* **1985**, *118*, 1345.

40. B. Giese, H. Horler, *Tetrahedron* **1985**, *41*, 4025.

41. B. Giese, J. Dupuis, *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 622; J. Dupuis, B. Giese, D. Rüegge, H. Fischer, H.-G. Korth, R. Sustmann, *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 896.

42. R.R. Schmidt, M. Hoffmann, *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 406.

43. C. Walling, *Tetrahedron* **1985**, *41*, 3887.

44. B. Giese, D.B. Gerth, *J. Org. Chem.* **1986**, in press.

45. R.M. Adlington, J.E. Baldwin, A. Basak, R.P. Kozyrod, *J. Chem. Soc. Chem. Commun.* **1983**, 944.

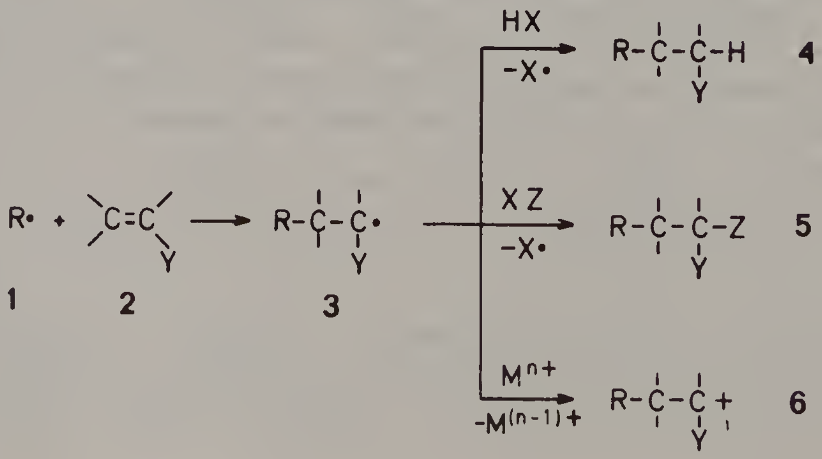
46. M.D. Johnson, *Acc. Chem. Res.* **1983**, *16*, 343; A. Gaudemer, K. Nguyen-Van-Duong, N. Shahkarami, S.S. Achi, M. Frostin-Rio, D. Pujol, *Tetrahedron* **1985**, *41*, 4095.

Chapter 3

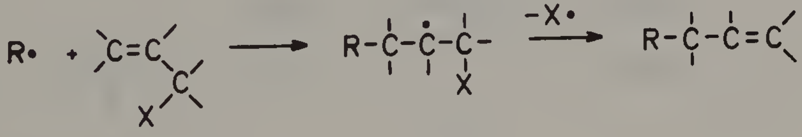
Intermolecular Formation of Aliphatic C–C Bonds

A. Introduction

The most important methodology for the synthesis of aliphatic C-C bonds via radical reactions is the addition of alkyl radicals **1** to alkenes **2**. This reaction leads to adduct radicals **3** that must be converted to non-radical products before polymerization occurs. Polymerization is avoided either by intermolecular trapping of adduct radicals **3** or by intramolecular, homolytic bond cleavage. Hydrogen atom donors X-H, heteroatom donors X-Z or electron donors M^{n+} are used as trapping agents.



In the alkene/radical trap competition system, educt radicals **1** must react faster with alkenes, and adduct radicals **3** must react faster with the radical traps. If this is not the case, either educt radicals are trapped before they can form a C-C bond or adduct radicals react with alkenes to give polymers. This selectivity requirement can be fulfilled by choosing suitably substituted alkenes. With nucleophilic alkyl radicals **1** one has to use alkenes **2** with electron-withdrawing groups Y (e.g. acrylonitrile) that reduce the nucleophilicity of the adduct radicals **3**, whereas with electrophilic radicals **1**, alkenes with electron-releasing substituents (e.g. enolethers) must be used. These selectivity changes reduce the amount of polymerization because the more nucleophilic the radical is, the faster is the reaction with an electron-poor alkene and vice versa.[1] If the adduct radicals give products by homolytic bond cleavage, this selectivity change is of less importance because now an intramolecular reaction competes with intermolecular reactions.



1 **7** **8** **9**

$X\cdot \longrightarrow R\cdot$

1

After adduct radicals **3** or **8** are converted to products the newly formed radicals X· must react with the radical precursor to give back the starting radicals R·. This condition severely limits the application of radical traps in syntheses. In some cases the newly formed radical X· is identical with the educt radical **1**. This simplifies the radical chain, but also reduces the flexibility of the synthesis.

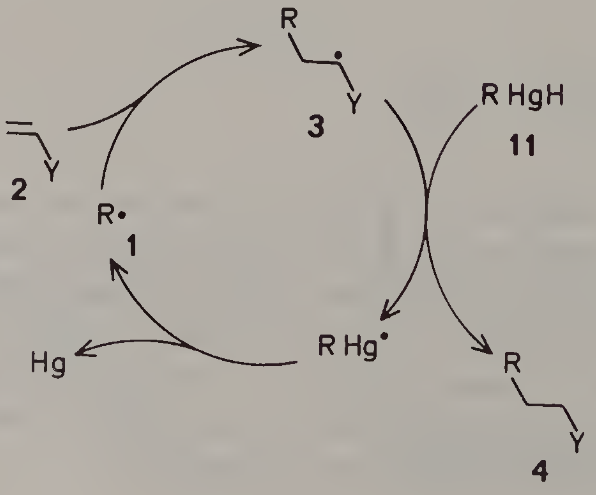
In spite of all these conditions, several methods for the formation of C-C bonds using radical chemistry have been worked out and successfully applied to the synthesis of target molecules. They are described in this chapter beginning with hydrogen donors as radical traps.

B. Trapping with Hydrogen Donors

1. Mercury hydride

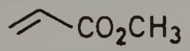
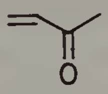
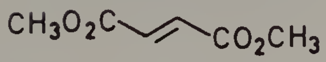
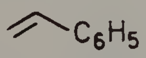
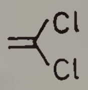
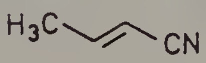
The reduction of alkylmercury salts **10** with hydrogen donors like $NaBH_4$ or Bu_3SnH leads to alkylmercury hydrides **11**. Although these hydrides have not yet been isolated, stereochemical,[2] polarographic,[3] and kinetic[4,5] studies indicate the existence of alkylmercury hydrides that trap alkyl radicals with rate coefficients of at least 10^7 $(l/mol \cdot s)^4$ at room temperature. Therefore, high yields of C-C bond formation occur with very reactive alkenes like acrylonitrile, vinyl ketones, acrylates, fumarodinitrile, or maleic anhydrides.[6,7]

$$\underset{\mathbf{10}}{RHgX} \xrightarrow{NaBH_4} \underset{\mathbf{11}}{RHgH}$$



Styrene, vinylidene chloride, and crotonic ester give low yields[8] because they are too unreactive[1] to compete with mercury hydrides. With these olefins, the amount of C-C bond formation products can be increased by using tin hydrides as hydrogen donors,[9] which react at least ten times slower with alkyl radicals than mercury hydrides.[4,10] An even slower hydrogen donor than a tin hydride is tributylgermanium hydride[11] which can also be used in syntheses.[12]

12 2 13

Alkene 2	Yield of 13	
	Mercury Method a)	Tin Method b)
	89	95
	80	85
	60	85
	55	78
	40	83
	35	90
	45	85

a) $C_6H_{11}HgOAc$ / $NaBH_4$; b) $C_6H_{11}I$ / Bu_3SnH

The advantage of the mercury method over the tin method lies on its very mild reaction conditions. High temperature initiators or photolytic conditions are not needed because the mercury hydrides start the chain by spontaneous decomposition and the chain length is very long. The reactions, which require only a few minutes, can be carried out at room temperature in CH_2Cl_2 and there is no need to work under N_2.

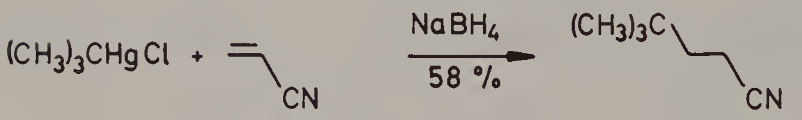
Functional groups like halides, alkenes, cyclopropanes, ketones, boro- and metallorganic compounds can be used as precursors for radical C-C bond formation reactions because they react easily to give organomercury compounds.

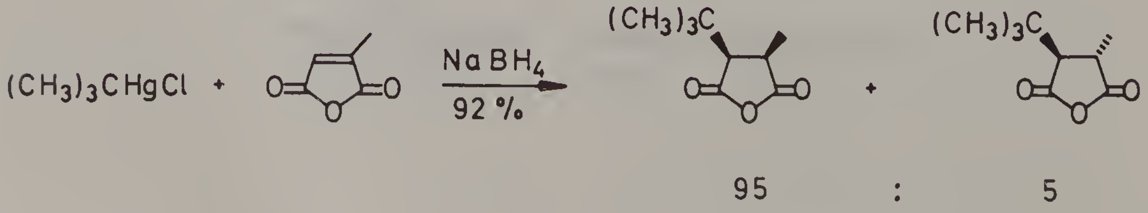
a. Halides

Halides can be easily transformed into alkylmercury salts via Grignard compounds and in situ mercuration.[8,13]

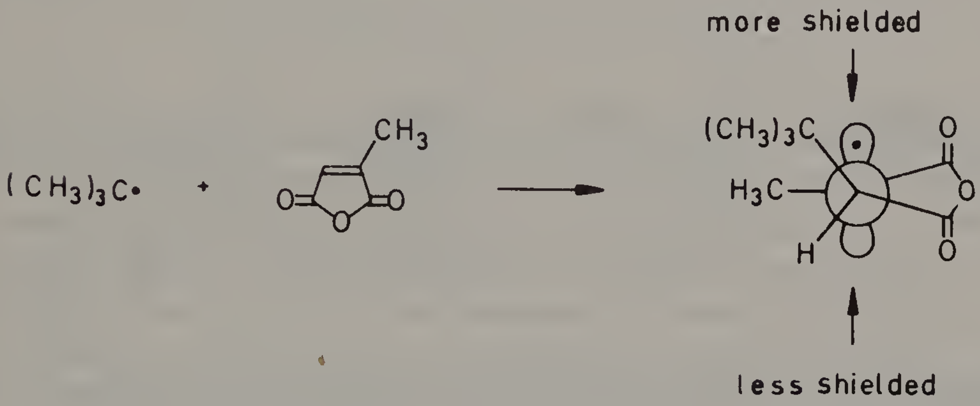
$$\mathrm{RHal} \xrightarrow{\mathrm{Mg}} \mathrm{RMgHal} \xrightarrow{\mathrm{Hg\,Hal_2}} \mathrm{RHgHal}$$

This route makes prim., sec., and tert. radicals accessible. A characteristic feature of radical reactions is that one can easily use a tert-butyl group in C-C bond formations.[14]



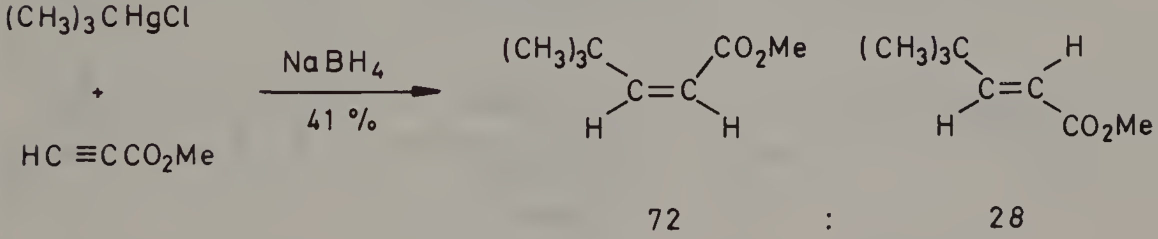


The yields are high because tert-butyl radicals are very nucleophilic (high lying SOMO) and, therefore, react very fast with electron poor alkenes.[1] The stereochemistry of the hydrogen abstraction step is influenced by the bulky tert-butyl group. For example, with methylmaleic anhydride the *cis*-isomer is formed predominately because in the π-radical **14** the tert-butyl group efficiently shields one side of the p-orbital.[14,15]



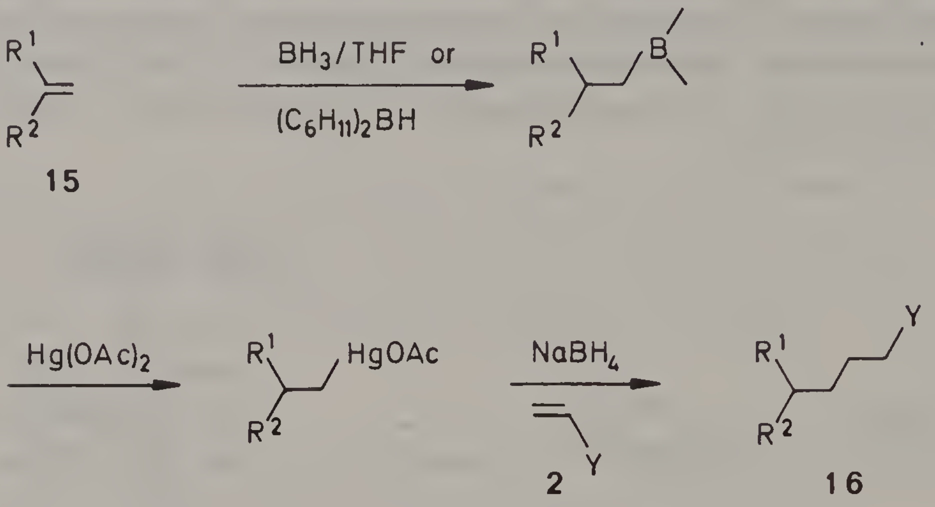
14

By similar reasoning, alkynes lead predominately to *cis*-alkenes in reactions with tert-butylmercury salts.[16]



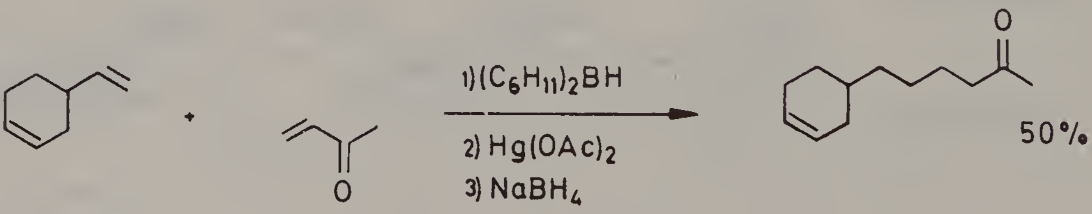
b. Alkenes

Alkenes with an electron-rich terminal double bond **15** can be coupled with electron-poor alkenes **2** in a one pot reaction.[17] The reaction proceeds via hydroboration of **15** and transformation of the boron-carbon bond into a mercury-carbon bond, which on reaction with $NaBH_4$ and alkene **2** gives product **16**.



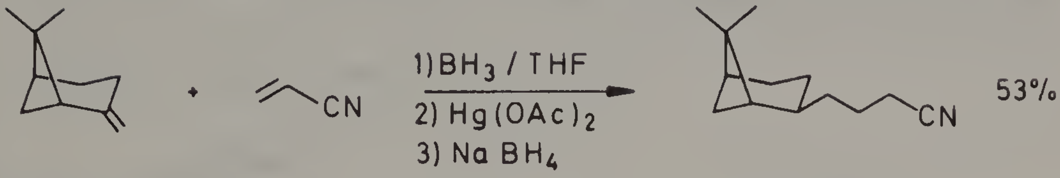
15 **2** **16**

These reactions tolerate substituents like Br, Cl, OH, OAc, OTs, OR, and CO_2R. Even alkenes with two different double bonds can be used. For example, vinylcyclohexene **17** reacts with **18** exclusively to give product **19** because the hydroboration step is faster at the terminal double bond, and prim. C-B bonds are mercurated faster than sec. ones.[17]



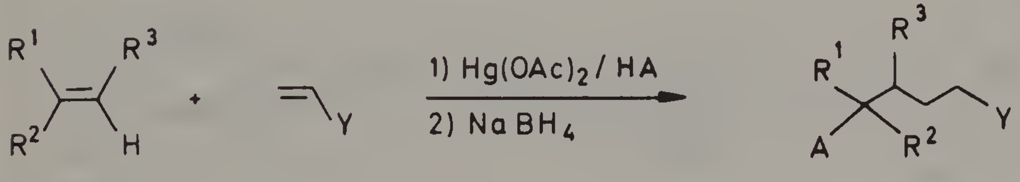
17 **18** **19**

The high regio- and stereoselectivity of this method is demonstrated by the reaction of ß-pinene **20**, which gives exclusively product **21**.[17]



20 **21**

The mercuration reactions of alkenes offer an even broader use of this system. Mono-, di-,and trisubstituted alkenes **22** are readily mercurated, according to the Markovnikov rule, with mercury salts in the presence of the solvent HA. Thus, alcohols are formed in the presence of water, ethers in alcohols, esters in acids, and amides in acetonitrile.[13] Combining the solvomercuration with radical C-C bond formation reactions offers a broad variety of synthetic possibilities.[18]

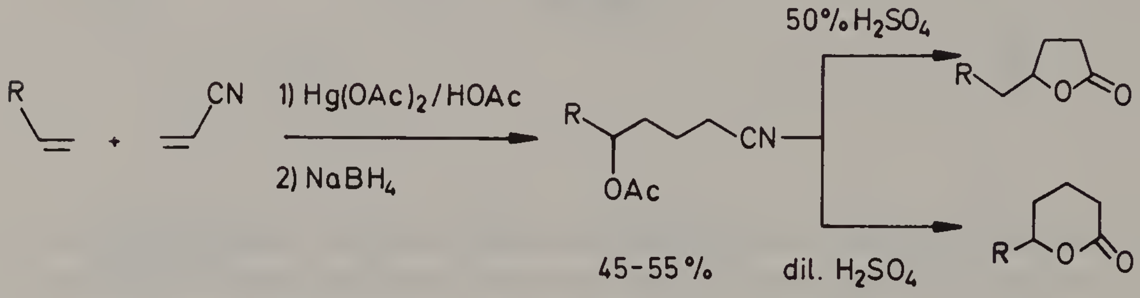


23

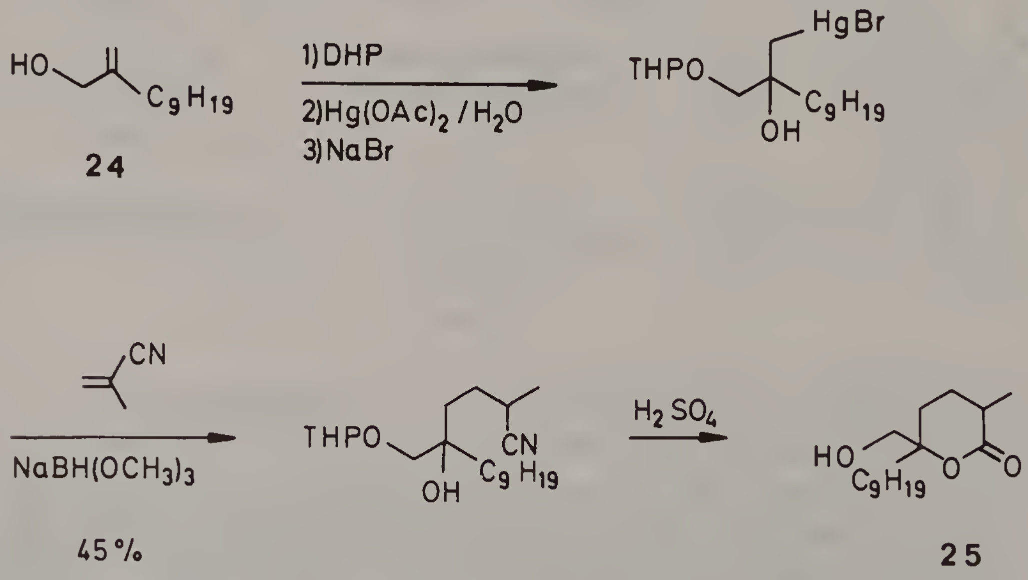
22 **2**

A = OH,OR,OAc,NHAc

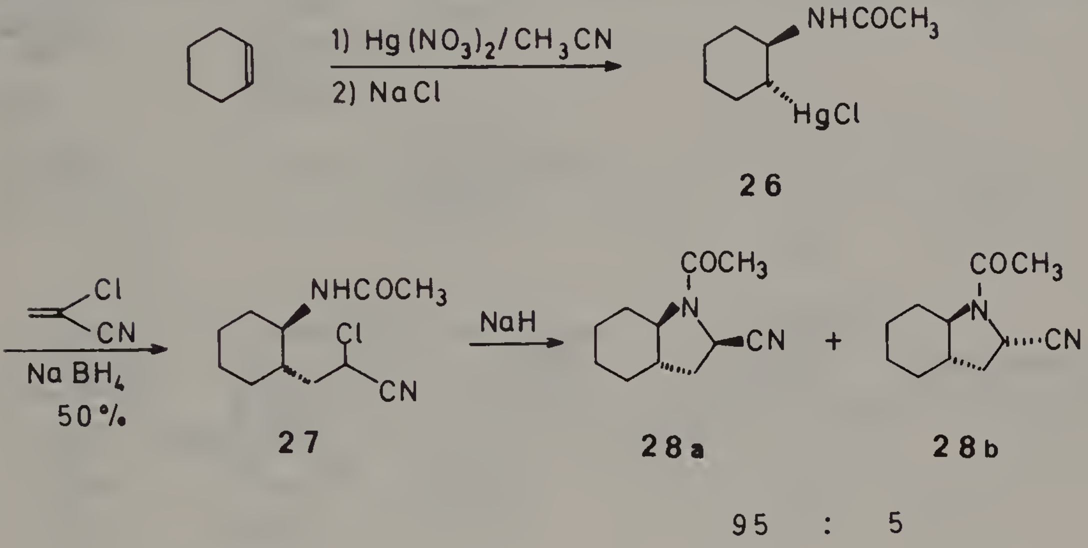
The synthesis can be carried out as a one-pot reaction: After solvomercuration, the reaction mixture is diluted with dichloromethane, the electron-poor alkene is added in about three- to tenfold excess, and finally $NaBH_4$ or $NaB(OCH_3)_3H$ is added to start the radical process.[18] Barluenga[19] has shown that it is often advantageous to carry out the synthesis as a phase transfer reaction in water/dichloromethane using Triton B as a phase transfer catalyst. The introduction of the additional functional group A in this reaction sequence permits subsequent reactions, e.g. lactonization.[20]



Kozikowski[21] has used this method to synthesize the antibiotic malyngolide **25**, as a racemic mixture of diastereomers, from allyl alcohol **24**.



With cyclic alkenes, the stereochemistry of the radical reaction can occur with high selectivity. Thus, Henning and Urbach[22] have synthesized α-aminonitriles **28** starting from cyclohexene, via solvomercuration, radical coupling with α-chloroacrylonitrile (**26**→**27**), and intramolecular substitution, which gave **28a** and **28b** in a 95:5 ratio.



26

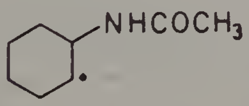
27

28a

28b

95 : 5

The C-C bond formation reaction of the cyclic radical **29**, and also the hydrogen abstraction of adduct radical **30** occur with high diastereoselectivity. This is presumably due to the preferred conformation of the radical **30**, which is attacked from the less hindered side.



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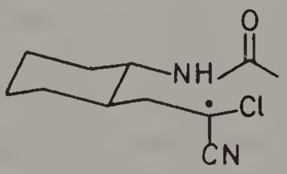
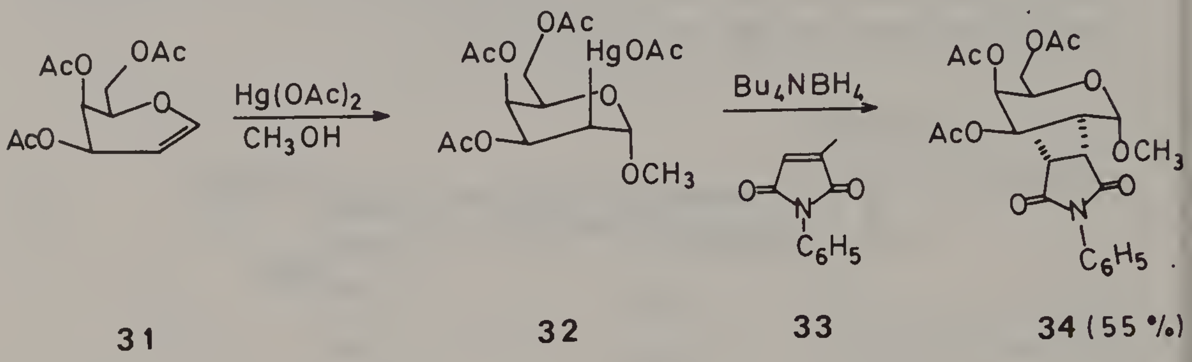
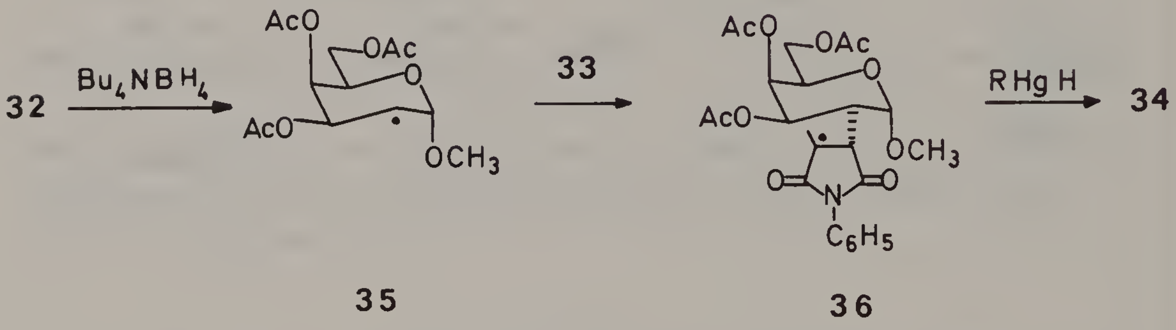


30

In the syntheses of **25** and **28**, two and three chiral centers are formed, respectively. Four chiral centers are introduced in the solvomercuration/reductive coupling sequence between galactal **31** and methylmaleic imide **33**.[6,23]



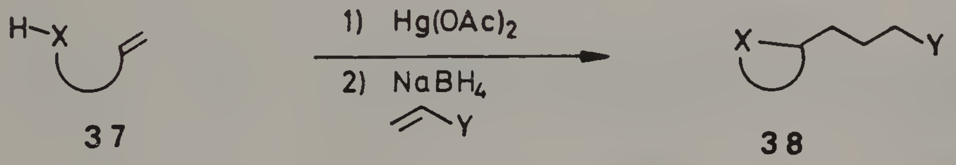


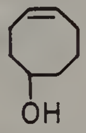
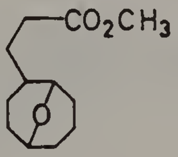
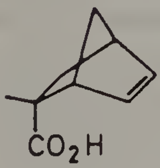
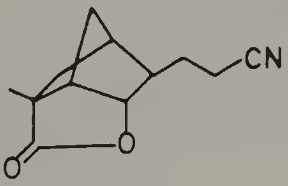
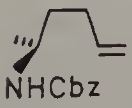
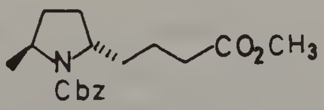
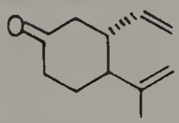
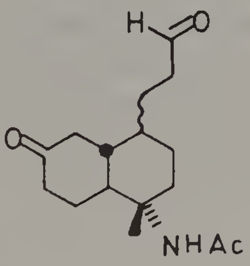
The four chiral centers in **34** are formed in three different steps:

- Electrophilic addition to an alkene.
- Radical addition to an alkene.
- Radical hydrogen abstraction from an alkylmercury hydride.

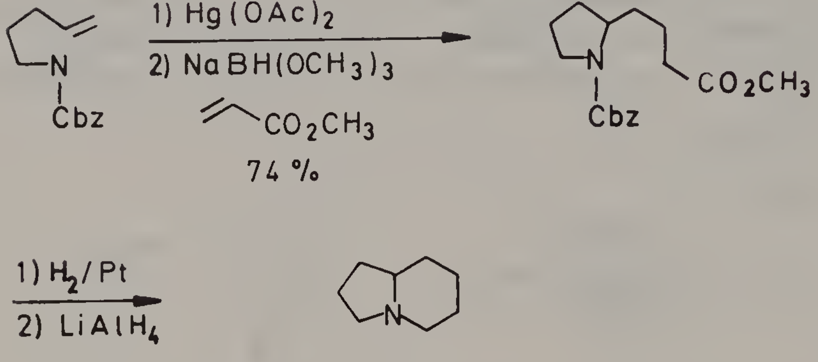
The mercuration of galactal **31** takes place *cis* to the complexing OAc substituents; subsequent *trans*-attack by the solvent CH_3OH leads to organomercuric salt **32**. Reduction of **32** gives carbohydrate radical **35** which is attacked at the equatorial side by methylmaleic imide (**35**→**36**).[23] In the cyclic radical **36**, the carbohydrate substituent shields the *cis*-side of the adjacent semioccupied p-orbital; therefore, the organomarcury hydride attacks from the *trans*-side giving rise to *cis*-product **34**. The diastereoselectivities of these reactions are higher than 95:5; only the diastereoface-differentiating reaction that generates the first chiral center at the maleic imide during the addition of **33** at **35** has a low selectivity of 55:45.

Alkenes **37**, with nucleophilic neighboring groups such as alcohols, carboxylates, amides, amines, and olefins, lead to cyclic products **38** in the mercuration/reductive coupling sequence.[24-26] The nucleophiles act as intramolecular traps for the mercurated olefins.



Educt **37**	Product **38**	Yield (%)
		62
		40
		41
		90

This reaction sequence was applied by Danishefsky for the synthesis of δ-coniceine **39** and indolizidinone **40**.[25]



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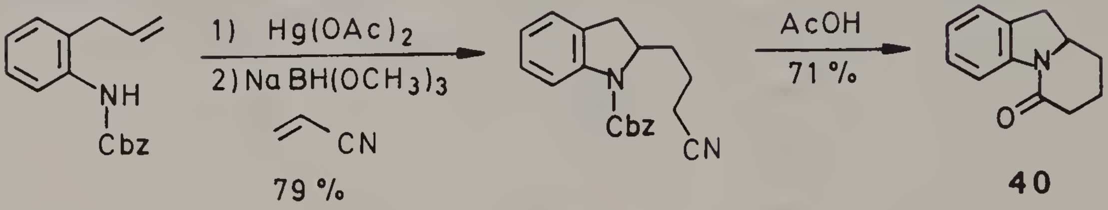
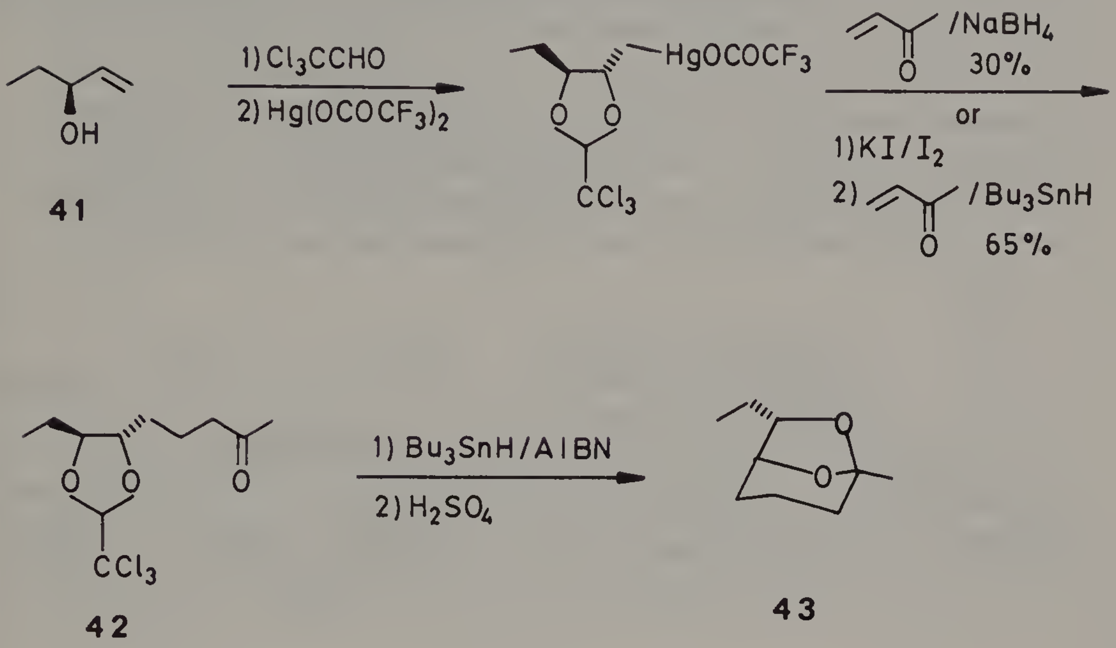


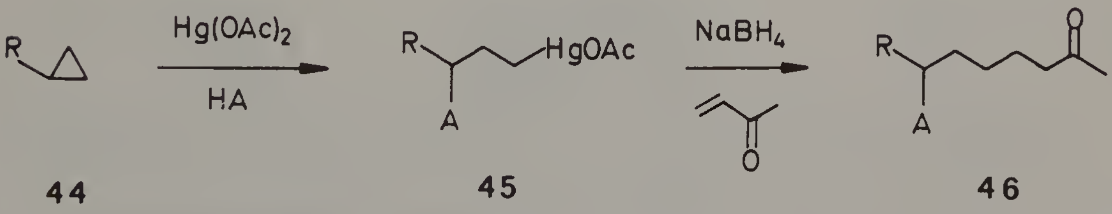
40

In the synthesis of brevicomin **43**, the first step is the mercuration of the chloral adduct of allylalcohol **41**, which occurs with a 85:15 diastereoselectivity.[27] Reductive coupling with methyl vinyl ketone yields product **42**, the precursor of brevicomin **43**. It should be noted that iodation of the mercurated intermediate and C-C bond formation using Bu_3SnH gives higher yields of **42**.[28]

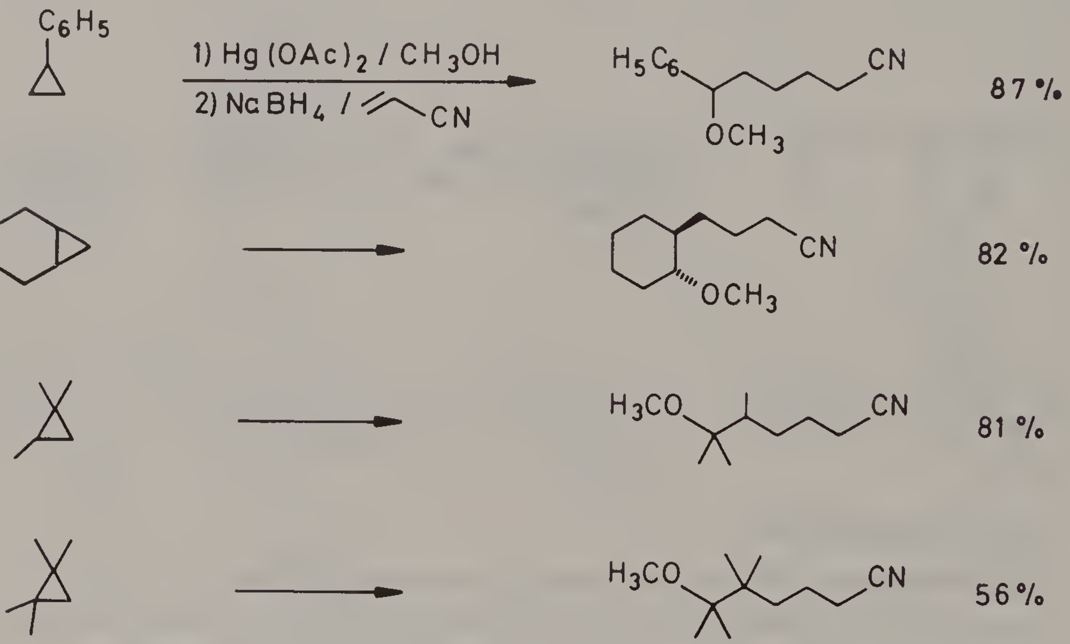


c. Cyclopropanes

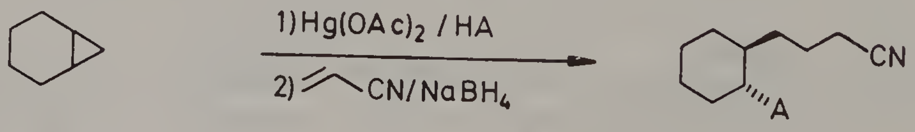
Cyclopropanes **44** can be readily solvomercurated [13] to give acyclic organomercury salts **45**. The radical C-C bond forming reaction with, for example, methylvinyl ketone leads to 1,6-disubstituted products **46**.[29]



In analogy to the mercuration of alkenes, the mercury ion attacks the lowest substituted C-atom of the cyclopropane, and the nucleophile reacts from the *trans*-side with the highest substituted cyclopropyl C-atom. Alkenes with electron-withdrawing substituents like CN, CO_2R, COR, Cl etc., and cyclopropanes with one to four alkyl or aryl groups can be used in these syntheses.[30] In most cases, the reactions are carried out without isolation of the organomercury salts.[30,31]

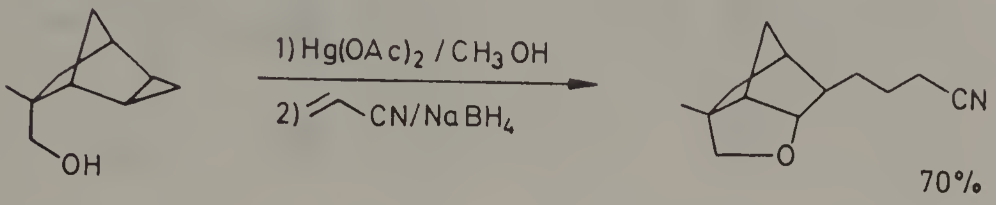


Different functional groups are introduced into the products by varying the solvents.[32]

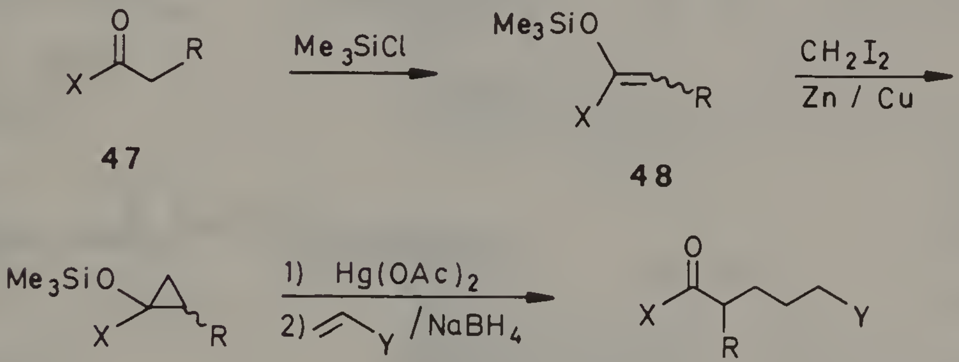


A :	OCH_3	OH	OAc	$NHCOCH_3(CH_3CN)$
yield :	82	62	65	65%

Also neighboring nucleophiles can trap the mercurated cyclopropane cation in an intramolecular reaction.[32]



The use of carbonyl compounds **47** as precursors for cyclopropanes broadens the application of this method considerably. Thus, silylation of carbonyl compounds **47** gives **48**, which leads to cyclopropanes **49** and C-C bond formation products **50**.[33]



47

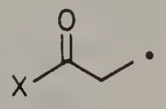
48

49

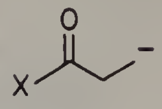
50

The intermediate radicals **51** are, because of their nucleophilicity, analogues to homoenolate anions **52**.[34] But, whereas anions **52** are mainly used in reactions with carbon-heteroatom double bonds, radicals **51** attack carbon-carbon double bonds. Both anions and radicals give products of umpolung of the reactivity.

ROS C

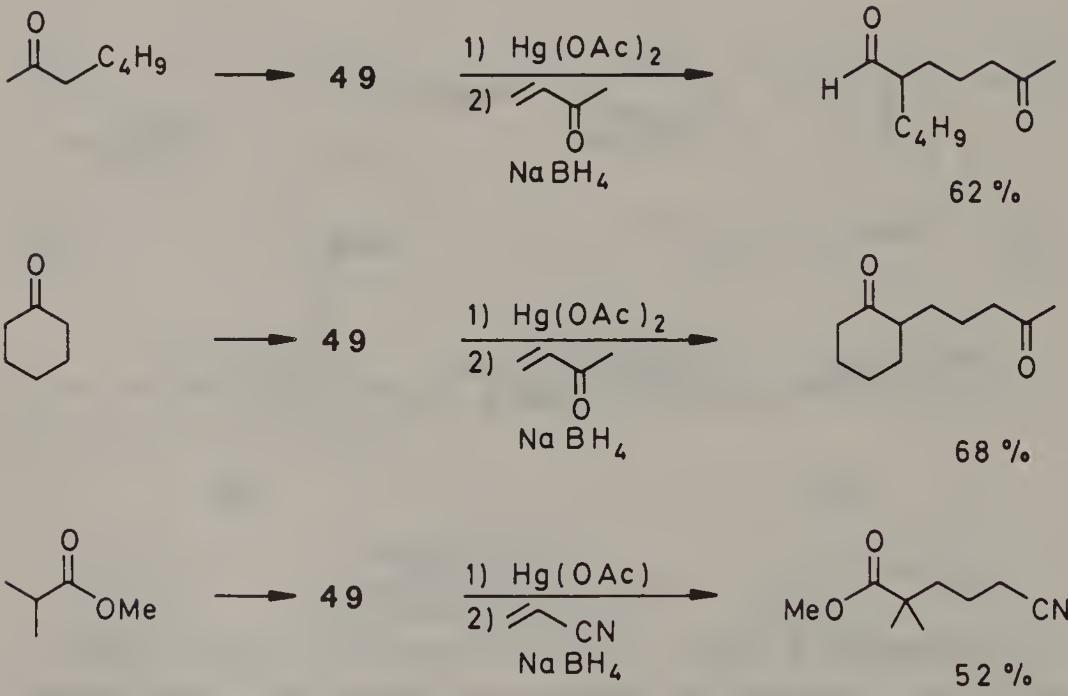


51

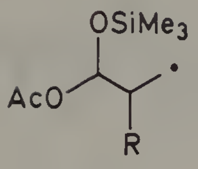


52

Aldehydes, ketones, and carboxylic esters can be used as carbonyl compounds. The examples shown below are one pot reactions after the cyclopropanation step.[33]



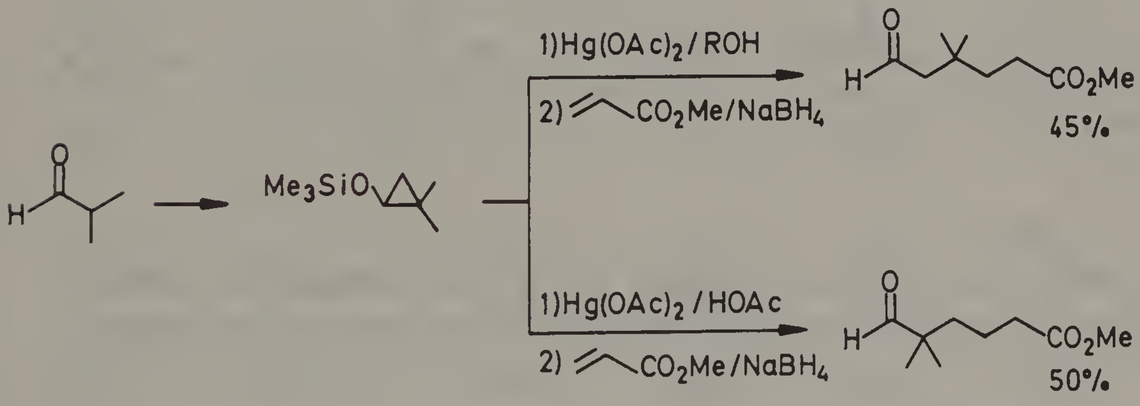
Solvomercuration of aldehydes in acetic acid leads, after reaction with $NaBH_4$, to radicals **53**. However, solvomercuration in alcohol or water/acetone gives radicals **54** which can easily rearrange.[35]



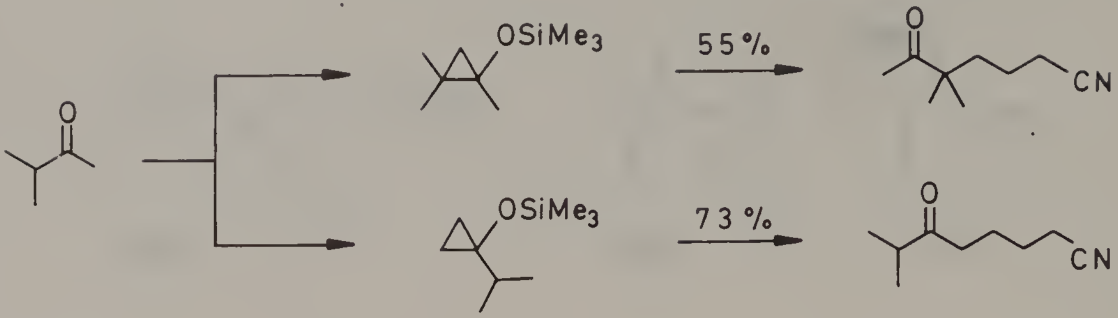
53

54a **54b**

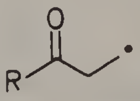
Under special conditions (different stability of the radicals, low concentration of the trapping alkene) one can also obtain C-C bond formation products from the rearranged radical intermediates. The very fast rearrangement of radicals **54**, which is on the order of $k = 10^6$ (s^{-1}) at 20°C,[36] makes this possible.



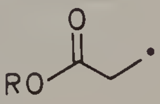
Starting from ketones, isomeric enolethers can be synthesized by the method of House.[37] This leads to isomeric cyclopropanes and C-C bond formation products.[33]



The rearrangement of radicals **55**[38] and **56**,[39] generated from ketones and carboxylic esters, respectively, is too slow to compete with the C-C bond formation reaction.



55

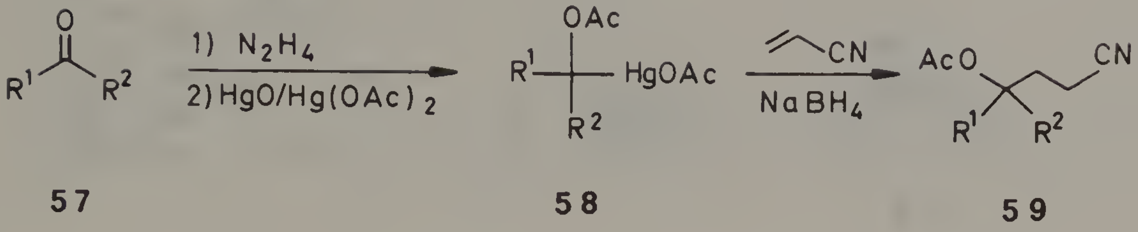


56

Therefore, no rearrangement occurs when ketones and carboxylic esters are used as educts for the cyclopropane route.[33]

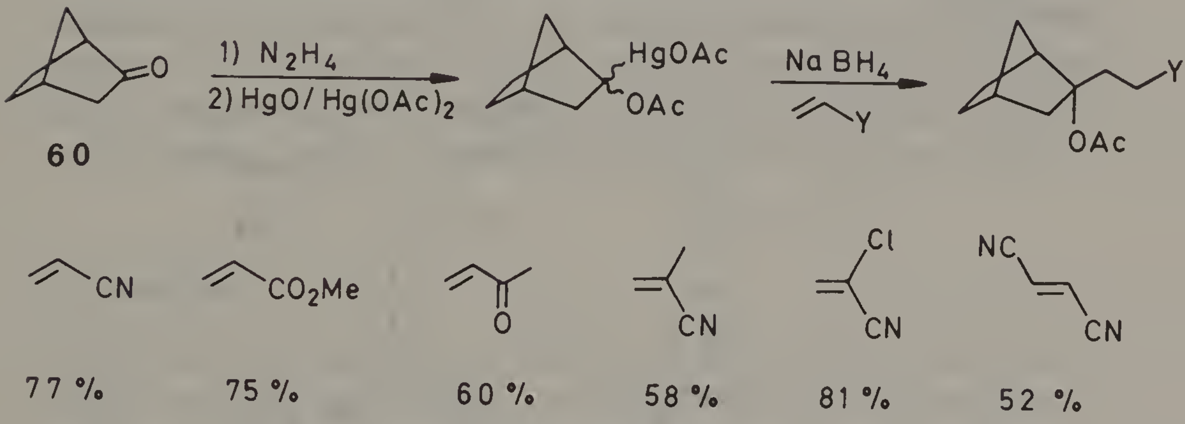
d. Ketones

Ketones **57** can be transformed via hydrazones into α-substituted organomercury salts **58**,[13] which after reduction in the presence of alkenes, e.g. acrylonitrile, give products **59**.[40] A large variety of ketones can be used; even a tert-butyl group is tolerated.[41]

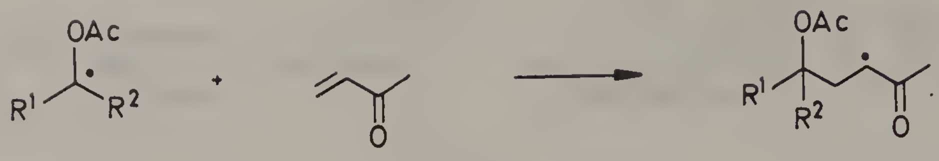


$R^1 = CH_3$; $R^2 = CH_3$ (70%), C_2H_5 (65%), $CH(CH_3)_2$ (62%), $C(CH_3)_3$ (46%)

Again, alkenes with electron-withdrawing substituents give good yields, as the reactions of norcampher **60** show.[41]



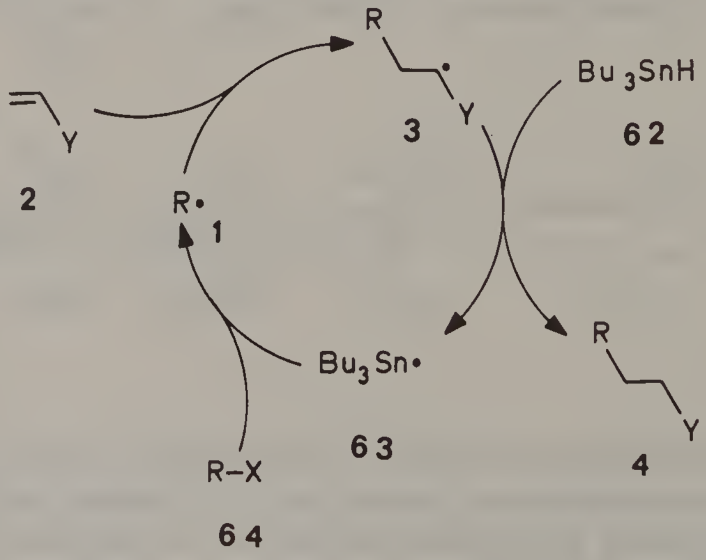
In these syntheses, C-C bonds between the electrophilic C-atoms of the carbonyl groups and the alkenes are formed. Therefore, this is another example of an umpolung reaction. The umpolung of the reactivity occurs in going from the ketone to the radical **61** which is a nucleophile, although the OAc group reduces the nucleophilicity a little bit.[42]



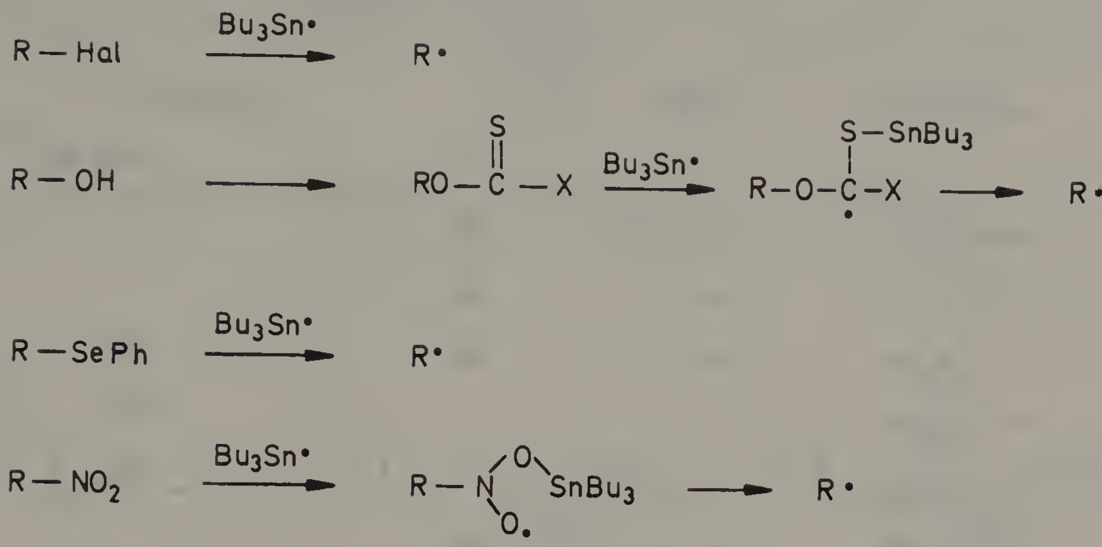
61

2. Tin hydride

Since the work of Kuivila[43] it has been known that alkyl radicals abstract hydrogen atoms from tin hydrides. Recently it has been shown that trialkyl or triaryltin hydrides, for example tributyltin hydride **62**, can also be used as traps for adduct radicals **3**.[44,45] The resulting tin radicals, for example **63**, don't decompose like the mercuric radicals, but react with suitable precursors **64** to give back the starting radical **1**.



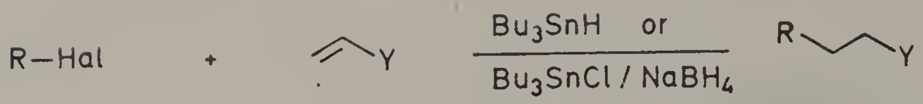
Halides,[44,45] alcohols,[9] selenides,[44,46] and tert. nitro compounds[47,48] can be used as radical precursors **64**.

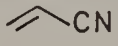
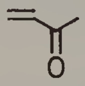
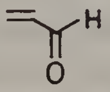
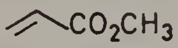
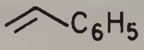
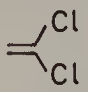
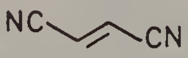
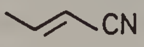


For a successful synthesis, it is important that the tin radicals react faster with the radical precursor **64** than with the alkene **2**. Therefore, most alkyl chlorides, prim. and sec. nitro compounds, and isonitriles, which are slowly reduced by tin hydride, cannot be used in C-C bond forming reactions.

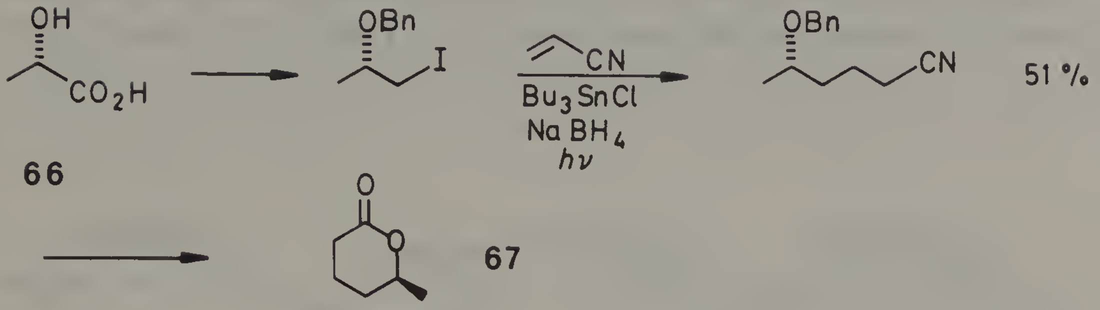
a. Halides

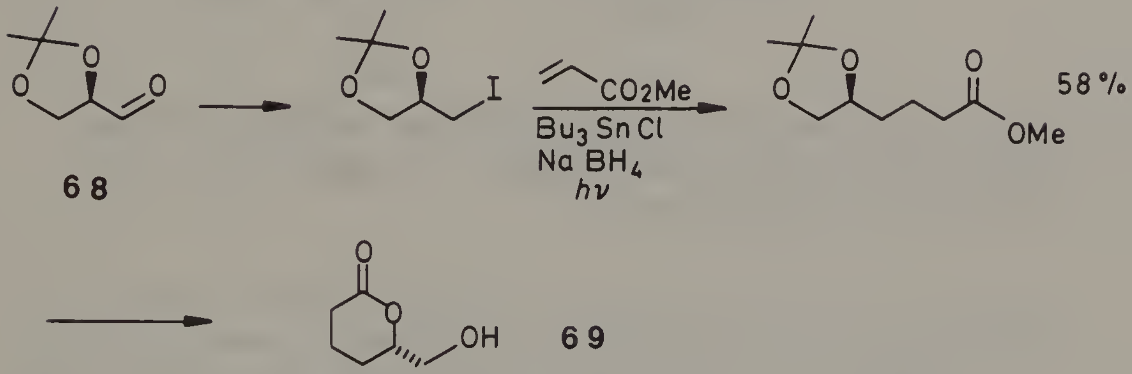
Reactions of halides with alkenes show that prim., sec., and tert. bromides and iodides, and alkenes with electron-withdrawing or radical-stabilizing substituents can be successfully used.[9] The reactions are carried out either photolytically at room temperature or thermally with radical initiators (e.g. AIBN). In some cases catalytic amounts of tin hydrides or even tin halides with an excess of $NaBH_4$ can be used. Working with low concentrations of tin hydrides lowers the amount of reduction products of starting material.



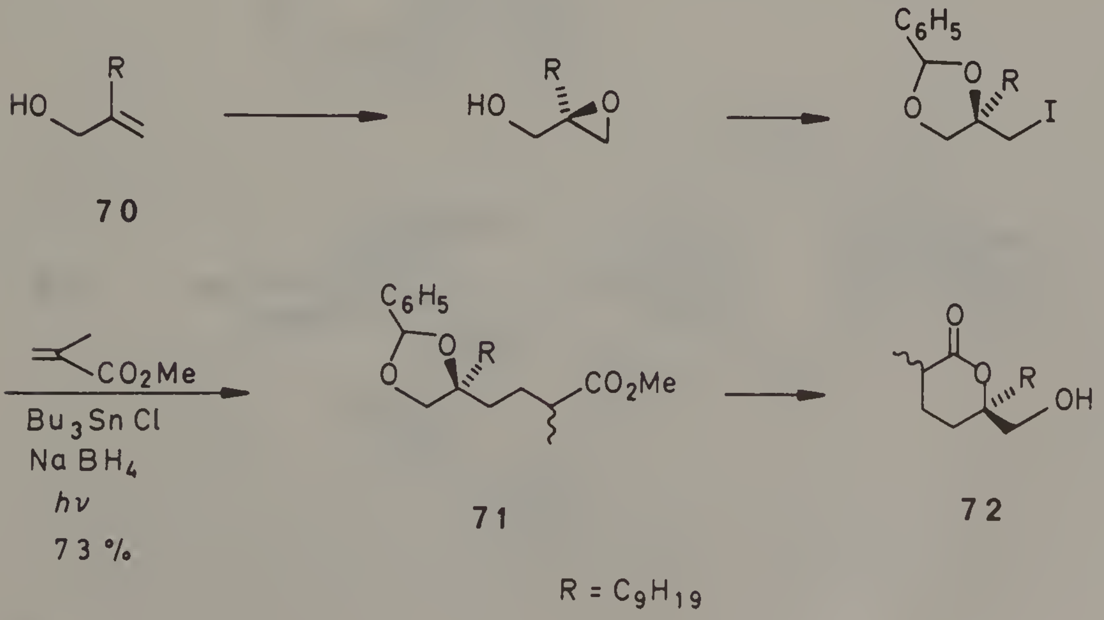
Alkylhalide	Alkene	Yield (%)	
		hν	Δ(AIBN)
$n-C_6H_{13}I$		80	
$c-C_6H_{11}I$	—"—	95	
$t-C_4H_9Br$	—"—	87	98
$n-C_6H_{13}Br$	—"—		68
$c-C_6H_{11}Br$	—"—		80
$t-C_4H_9Br$	—"—	62	
$c-C_6H_{11}I$		85	
—"—			90
—"—		85	
—"—		83	
—"—		87	
—"—			72
—"—		86	

CO and CN bonds located in ß-position to the radical center remain unchanged during the C-C bond formation. Therefore, this approach offers a suitable way to transfer the chirality of the starting material into the products. Thus, molecules from the chiral pool, like lactic acid **66** or the protected glyceraldehyde **68** are suitable precursors for the chiral lactones **67** and **69**, respectively.[49]

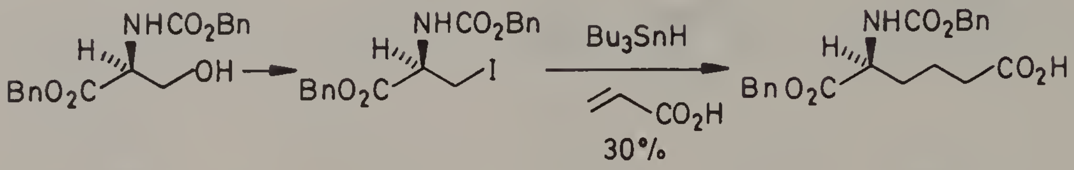




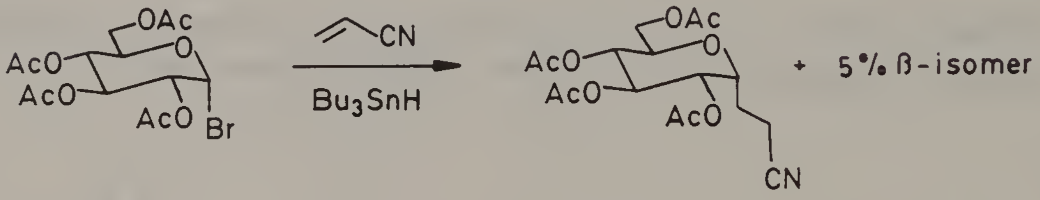
For the synthesis of malyngolide **72** the chiral center is introduced by Sharpless epoxidation of allylic alcohol **70**.[50]



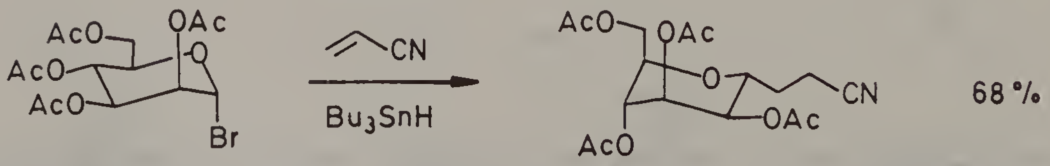
Baldwin has shown that also aminoacids can be used as precursors for these radical reactions.[51]



Because of the mild reaction conditions, radical C-C bond forming reactions have turned out to be suitable for the synthesis of C-glycosides.[45,52]

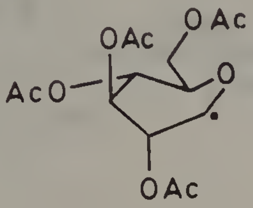


73 (70%)

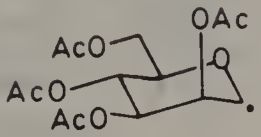


74

The predominant formation of α-C-glucosides **73** and **74** results from equatorial attack at the boat conformation of the glucosyl radical **75** and from the shielding effect of the axial substituent in the chair conformation of the mannosyl radical **76**, respectively.[46]

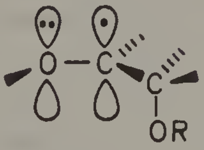


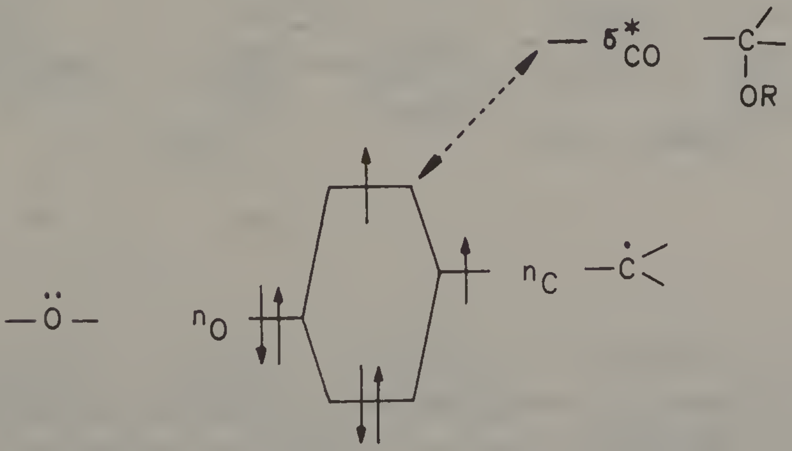
75



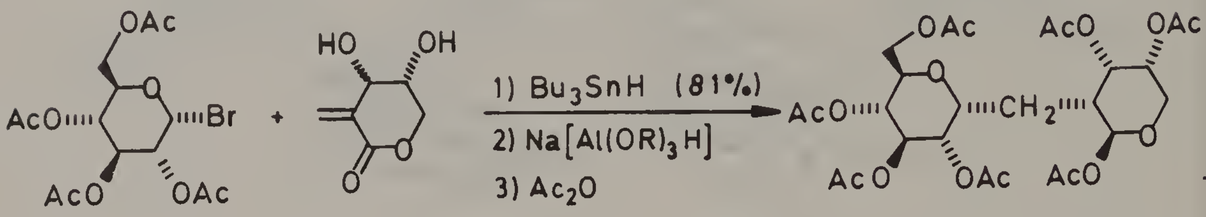
76

The glucosyl radical exists in the boat conformation because of the interaction between the high SOMO energy of the alkoxyalkyl radical and the low LUMO energy of the C-O bond.[46,53]



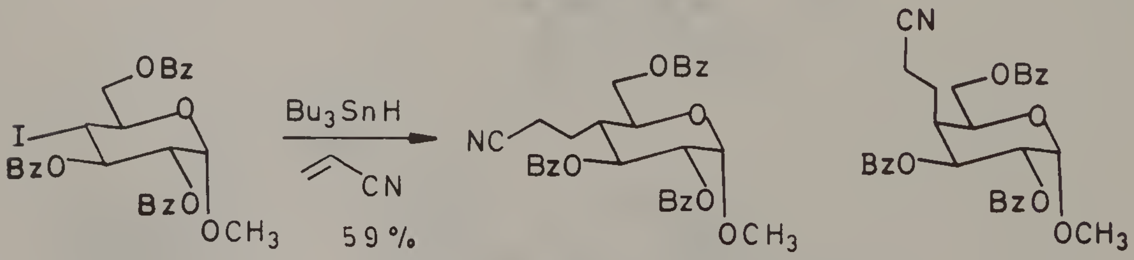


Using this methodology C-disaccharide **78**, in which the oxygen atom between the pyranosyl rings of the disaccharide is substituted by a CH_2 group, is readily available from alkene 77.[54]



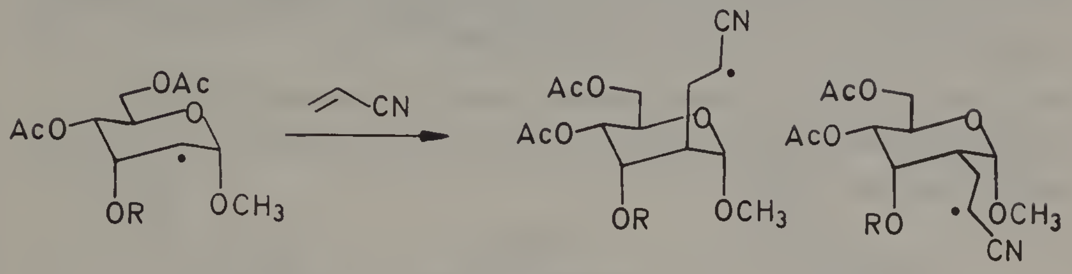
77 **78**

CC-bonds can be easily synthesized not only at the anomeric center, but also at all of the other carbohydrate ring positions, for example at C-4.[9]



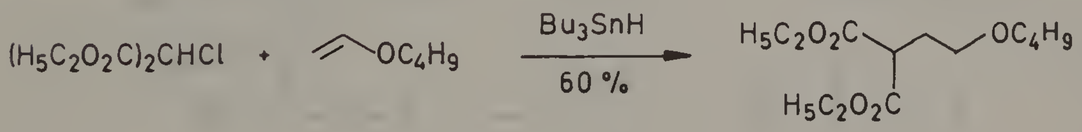
85 : 15

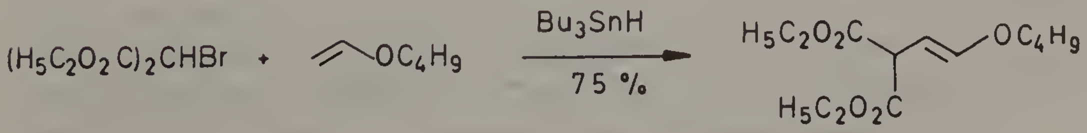
The newly formed C-C bonds in these C-branched sugars are predominately equatorial when the neighboring substituents are also equatorial.[55] Axial attack predominates only if both neighboring substituents are axial.[56]



R = H	65	:	35
CH_3	74	:	26
OAc	82	:	18
Li	96	:	4

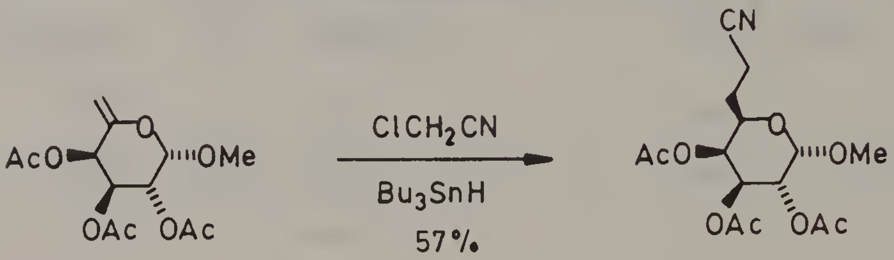
The tin hydride method also allows the use of electrophilic radicals in C-C bond forming reactions. Thus, the reaction of chloromalonic ester with enolethers gives addition products, but with bromomalonic ester, substitution products are formed.[57]





This different behavior is the result of the different rates of halogen abstraction. In the competition system $XCH(CO_2C_2H_5)_2$/ Bu_3SnH, the hydrogen donor reacts faster for X=Cl, but the halogen donor is faster for X=Br. Subsequent HBr elimination then gives the substitution products.[57]

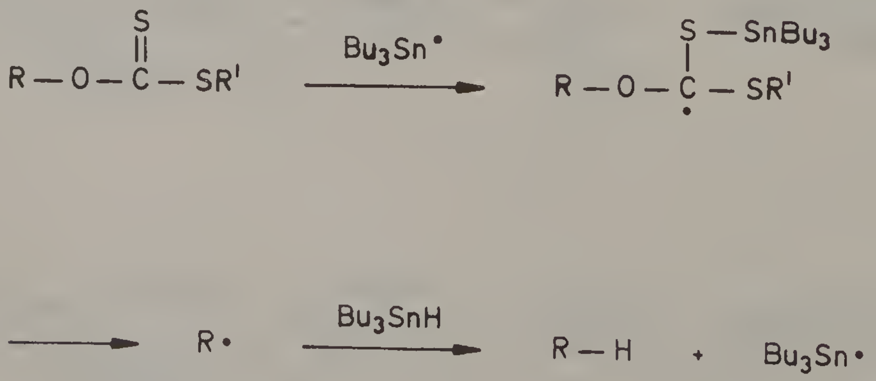
Chloroacrylonitrile can also be used as precursor for an electrophilic radical that reacts with enolether **79** to give deoxysugar **80**.[58]



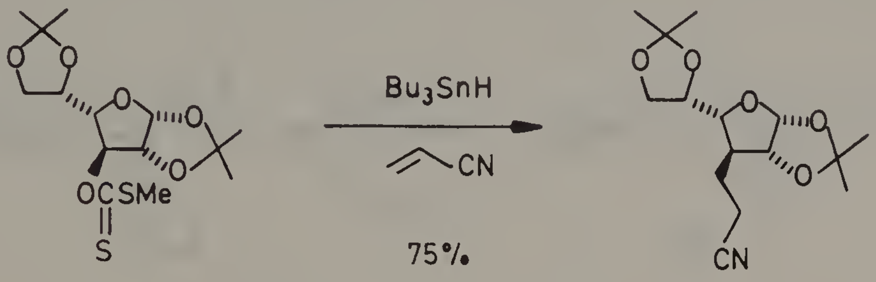
79 **80**

b. Alcohols and selenides

Barton[59,60] has shown that xanthates and similar thioacylated alcohols can be deoxygenated with tin hydrides.

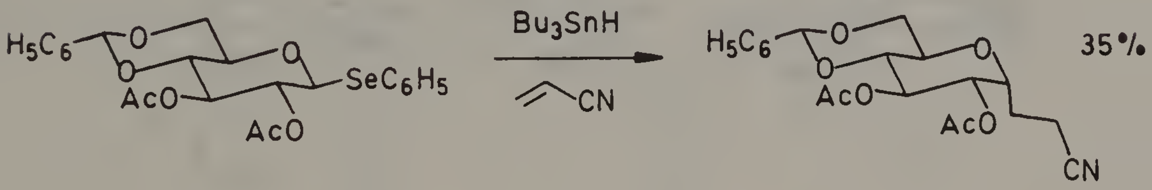


The attack of the tin radical at the sulfur atom is fast enough for a successful application of this method for C-C bond forming reactions. Thus, the C-branched deoxysugars **82** can be easily synthesized from xanthate **81**.[9]



81 **82**

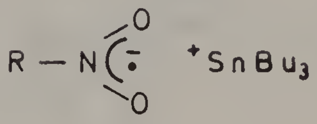
In the radical generated from **81**, both substituents shield one side of the radical center; therefore the C-C bond forming reaction occurs with high stereoselectivity. Selenides are also suitable precursors.[46]



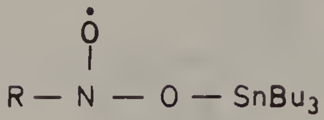
c. Nitro compounds

Nitro groups of sec. and tert. nitro compounds are very effectively replaced by hydrogen on treatment with tributyltin hydride.[61] Tight radical salts **83**[62] or nitroxide radicals **84**[48,63] have been proposed as intermediates in these reactions.

$$R{-}NO_2 \xrightarrow{Bu_3SnH} R{-}H$$



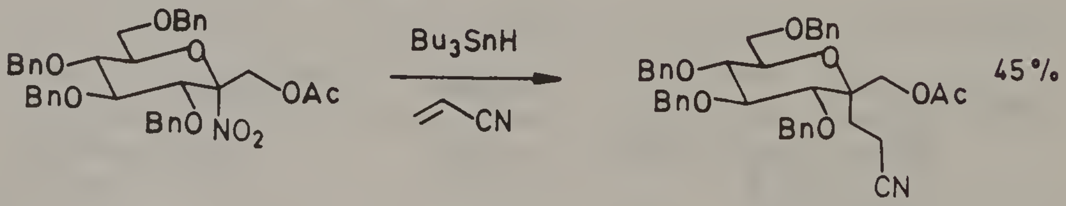
83



$R{-}\overset{\dot{O}}{N}{-}O{-}SnBu_3$

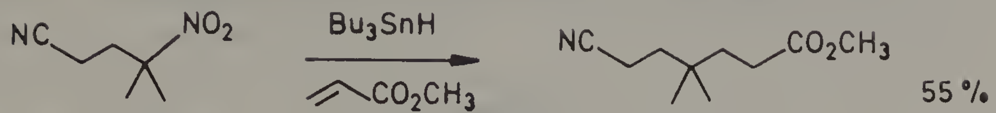
84

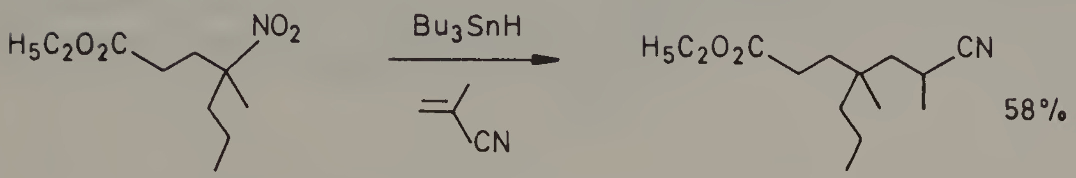
Tert. nitro compounds react with tributyltin hydride fast enough for a successful application of this method for C-C bond formation. Thus, **85** gives **86**, a C-glycoside of a keto sugar.[47,52]



85 **86**

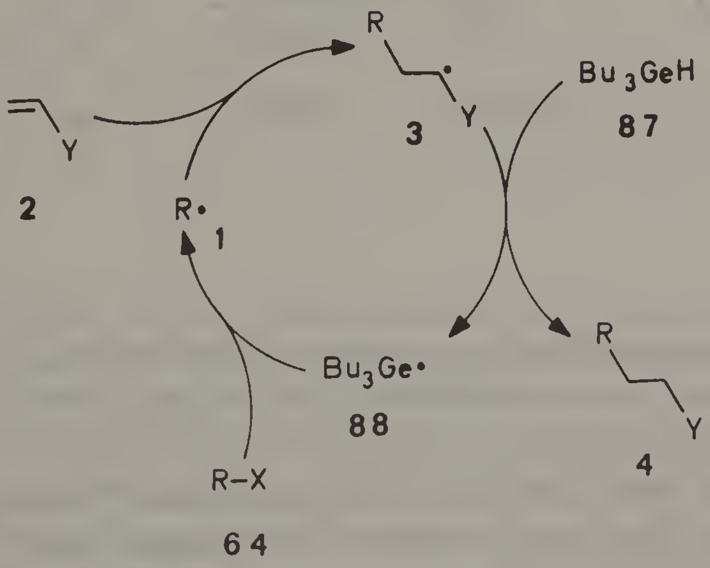
Ono[48] has shown that high yields in C-C bond forming syntheses with nitro compounds need high temperatures, long reaction times and large amounts of AIBN, because the radical chain is not very long. Nevertheless, several functional groups are tolerated under these conditions.



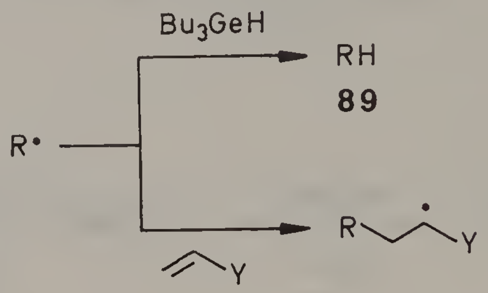


3. Germanium hydride

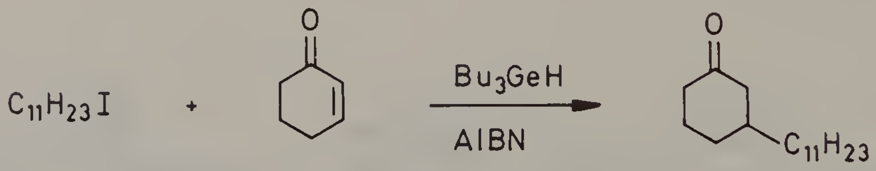
Trialkylgermanium hydride **87** is a less reactive hydrogen donor than trialkyltin hydride **62**.[11,64] But in reactions with alkyl halides **64** the germyl radical **88** is as reactive as the stannyl radical **63**.[11]



Therefore, in C-C bond forming syntheses with "unreactive" alkenes the amount of reduction product **89** should decrease by using germanium hydride instead of tin hydride.



Actually, Hershberger[12] has shown that cyclohexenone **90** gives the alkylated product **91** in good yields.



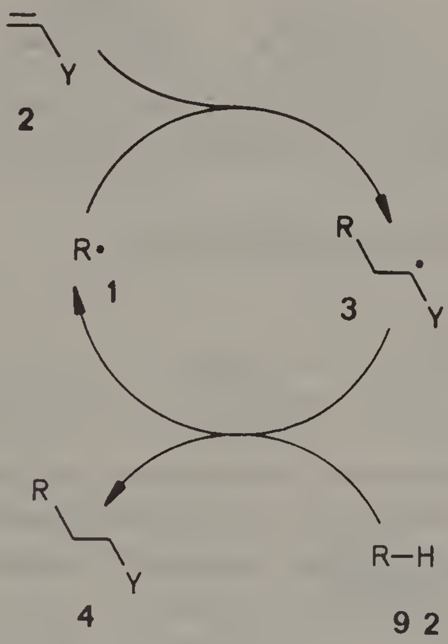
90 68% **91**

But this method needs long reaction times and one can often get similar results by working with low concentrations of tin hydride.[65]

Silanes are very unreactive hydrogen donors.[66] To build up a C-C bond forming chain reaction, high temperatures have to be used, and polymerization of electron-poor alkenes cannot be prevented.

4. "Carbon hydrides"

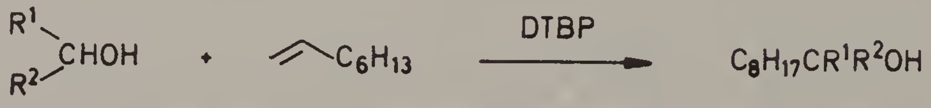
C-H bonds are much stronger than Hg-H, Sn-H, and Ge-H bonds. Therefore, C-H bonds can be used as traps for adduct radical **3** only if they are present in large excess and/or if substituents reduce the C-H bond strength. In contrast to mercury, tin, and germanium hydrides, an excess of the hydrogen donor **92** does not lead to side-products because hydrogen abstraction by educt radical **1** gives back the radical precursor **92**. A characteristic of this chain reaction is that hydrogen donation to adduct radical **3** directly leads to **1**.



Because of their radical stabilizing effects, both electron donating[67] and electron withdrawing groups[68] reduce the strength of C-H bonds.[69] Thus, alcohols, ethers, acetals, aldehydes, formic esters and amides, carboxylic esters, acids, lactones, amines, amides, and lactams can be used as hydrogen donors.[70] Under very special conditions even hydrocarbons add to alkenes. In most of these reactions, the formation of telomers plays a role and the chain lengths are relatively short.

a. Alcohols, ethers, and acetals

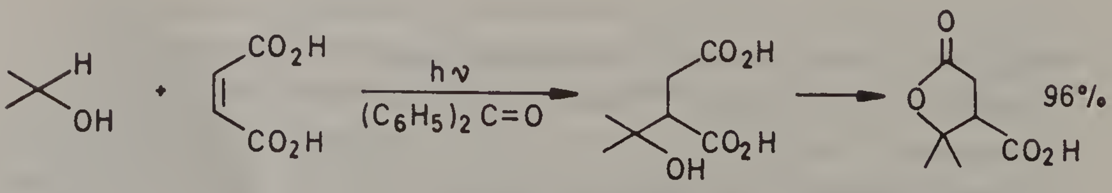
Alkyl radicals attack alcohols at the α-C-H bond, because this bond is much weaker than an O-H bond. The chain can be initiated photolytically or thermally with initiators like DTBP or Bz_2O_2. With electron-rich alkenes, the yields are not very high although they often increase in going from methyl via prim. to sec. alcohols.[71]



$R^1=R^2=H$: 16%; $R^1=CH_3, R^2=H$: 28%

$R^1=R^2=CH_3$: 46%.

Addition to electron-poor alkenes requires photolytical initiation with a sensitizer like benzophenone. Under these conditions, Schenck[72] added isopropyl alcohol to maleic acid in the synthesis of terebic acid **93**.



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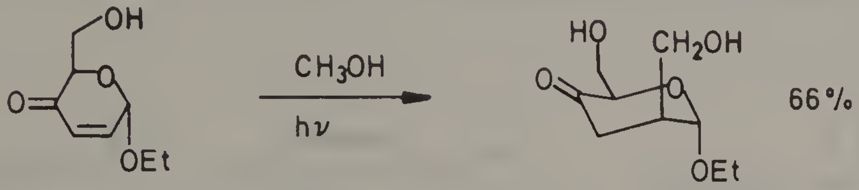
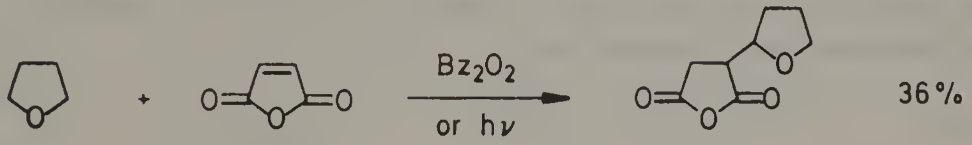
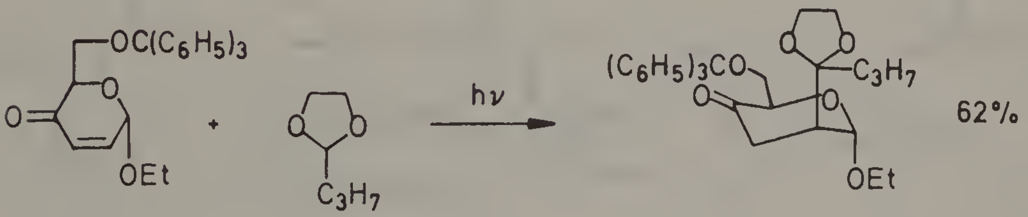
Fraser-Reid[73] introduced this method to carbohydrate chemistry and synthesized branched-chain sugars from enone **94**.



94

In addition reactions of ethers and acetals, electron-poor alkenes have been used predominately,[74,75] presumably because the educt radicals **95** have to be rapidly trapped to prevent ß-bond cleavage.[76]

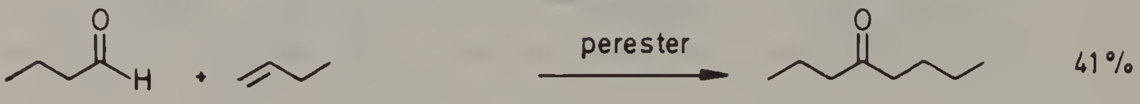


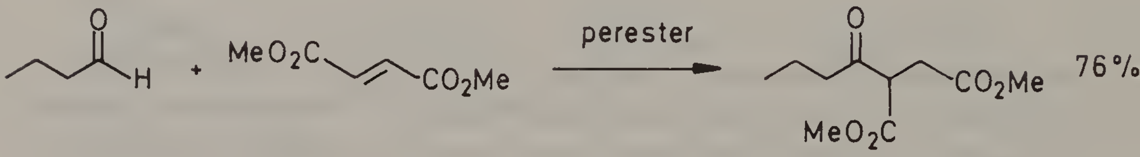


95

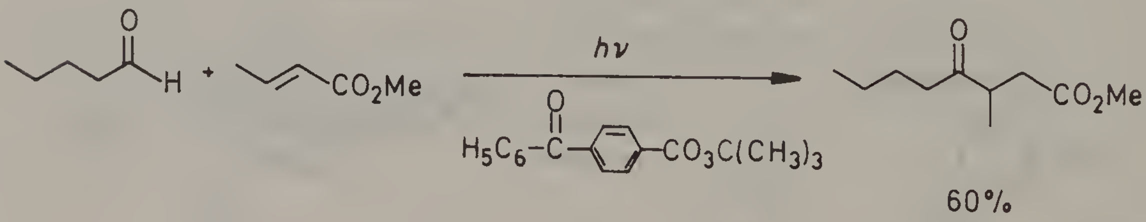
b. Aldehydes and formic acid derivatives

The radicals generated from aldehydes and formic acid derivatives are reactive σ-radicals which show nucleophilic behavior.[77,78] The yields of addition products are often fairly good, especially if electron-poor alkenes are used.[79]





The reactions can also be carried out under photolytical conditions with benzophenone as sensitizer[75] or with benzoylperbenzoate **96** as initiator.[78]



96

Like aldehydes, formic acid derivatives cleave the C-H bond of the carbonyl carbon atom. With formamides the yields are often higher than with formic esters.[80]

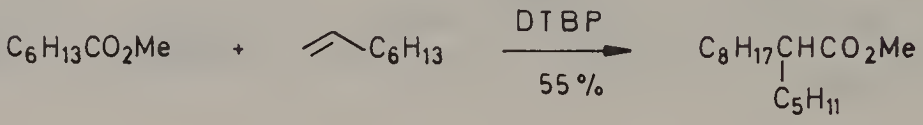
c. Ketones

Via electrophilic radicals ketones undergo addition reactions with electron-rich alkenes. In order to obtain good yields of 1:1 adducts, the reactions must be initiated with di-tert-butyl peroxide.[81]

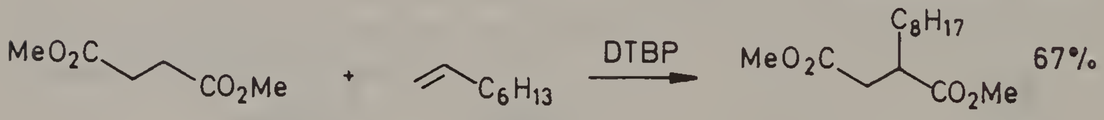
The presence of certain transition metal oxides can increase the yields.[82] Thus, without solvent, acetone and terminal alkenes in the presence of $Mn(OAc)_3$ afford mainly 1:1 adducts (see p. 89).[83]

d. Esters and lactones

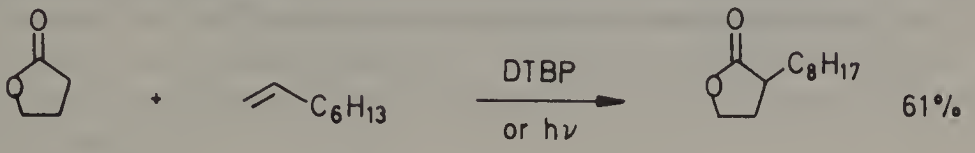
With carboxylic esters and lactones, hydrogen abstraction can occur either α to the carbonyl or at the alkoxy group, but generally esters have been predominately alkylated at the α-position of the acid moiety.[84]



For high regioselectivities and yields, esters with an additional electron-withdrawing substituent should be used. This leads to more electrophilic radicals which preferentially react with electron-rich alkenes.[85]



Lactones give also addition products with high regioselectivity.[81,86]

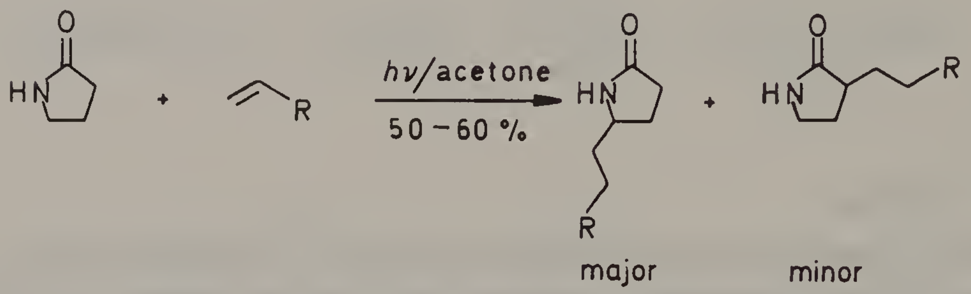


e. Amines

Amines react with electron-rich alkenes,[87] although the intermediate aminoalkyl radicals are very nucleophilic. The often observed high yields in these syntheses may be due to the weak α-CH bonds of amines.

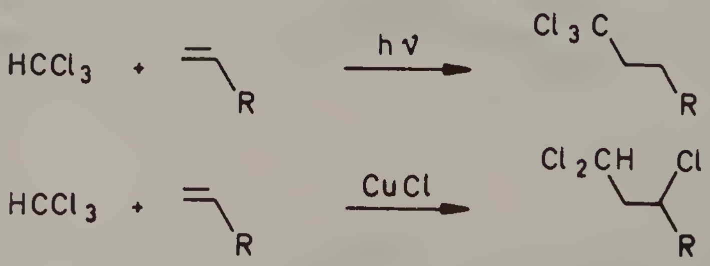
f. Amides and lactams

In contrast to esters and lactones, amides and lactams react predominately with the C-H bonds α to the nitrogen, presumably because nitrogen stabilizes radicals very effectively. The yields are acceptable mainly with lactams.[88]



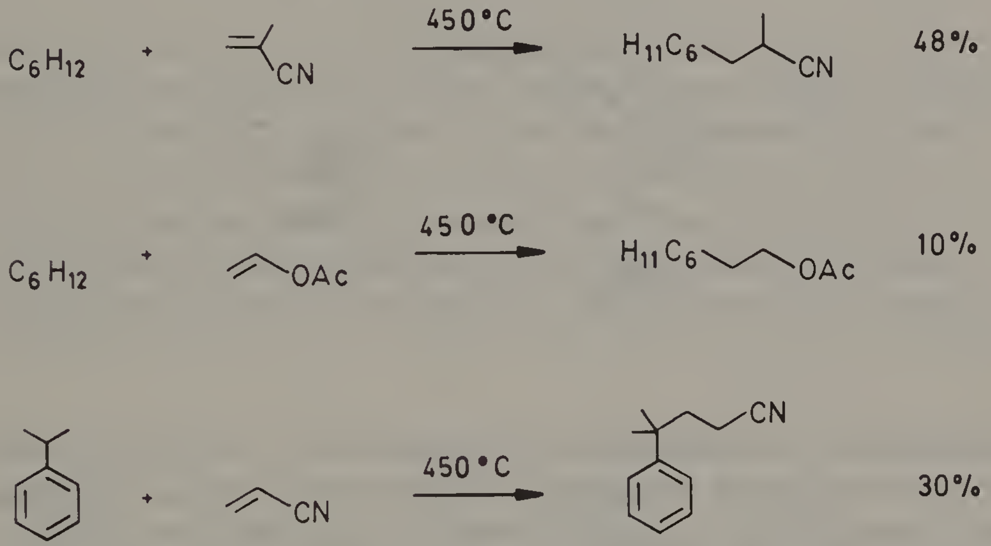
g. Chloroform

In contrast to other polyhaloalkenes, chloroform can act as a hydrogen donor because the C-H bond is cleaved by alkyl radicals faster than the C-Cl bond.[70] However, in the presence of CuCl or $FeCl_2$ chlorine is abstracted.[89]



f. Hydrocarbons

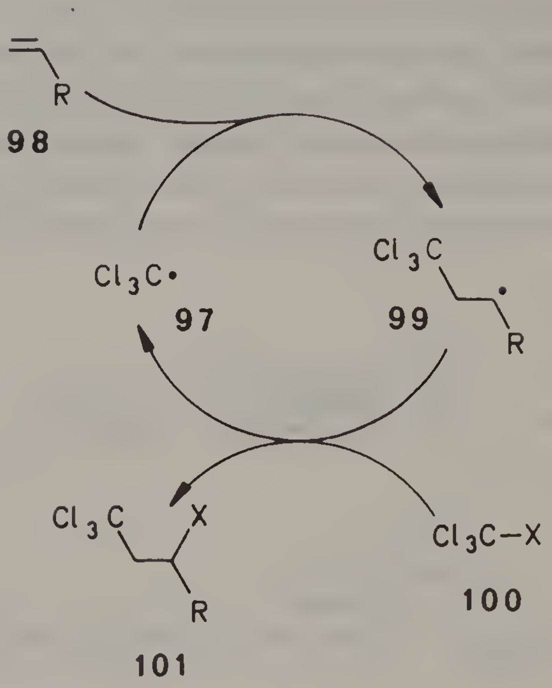
Under high pressure and with high temperatures, even hydrocarbons can be used as hydrogen donors. The temperatures of these reactions are so high (> 400°C) that no radical initiators are needed. To avoid further reactions of the products, the retention time in the hot zone should not be too long. Best yields are obtained in reactions with electron-poor alkenes.[90]



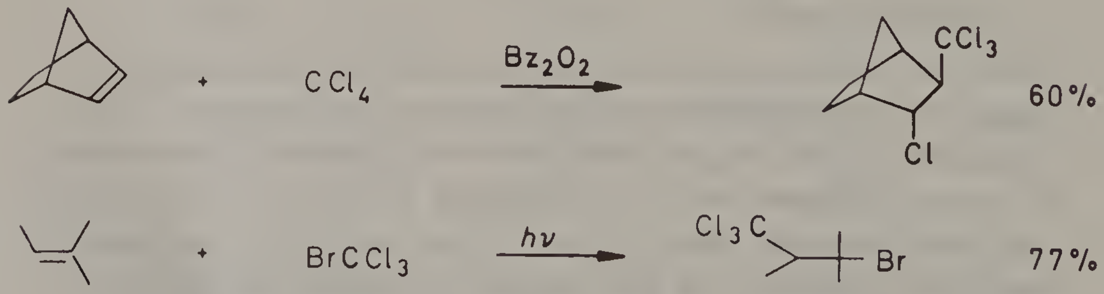
C. Trapping with Heteroatom Donors

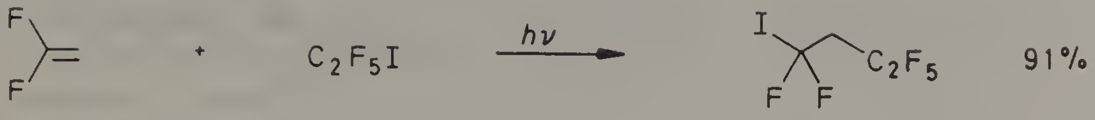
1. Halogen donor

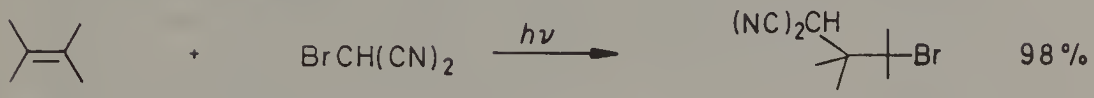
Light or peroxide initiated addition of polyhalogenated compounds to alkenes was first observed by Kharasch.[91] In these reactions, polyhalogenated alkyl radicals, for example **97**, attack alkenes **98** to give adduct radicals **99**. Since the C-X bond energies (X = Cl, Br, I) are low in polyhalogenated compounds, radicals **99** are trapped by polyhaloalkanes **100**, to give products **101** and the starting radicals **97**.[70,92]



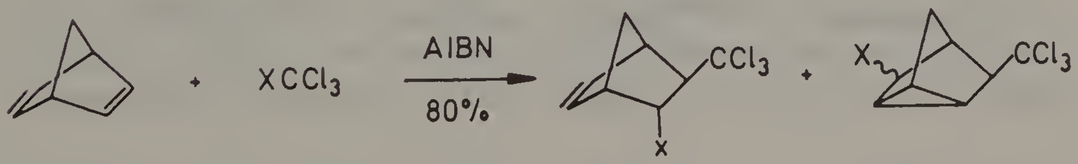
Halogenated radicals **97** are electrophiles[93] and react faster with electron-rich than with electron-poor alkenes. Bromides and iodides which are substituted by electron-withdrawing substituents like ester or nitrile groups can also be used in these syntheses.[94]



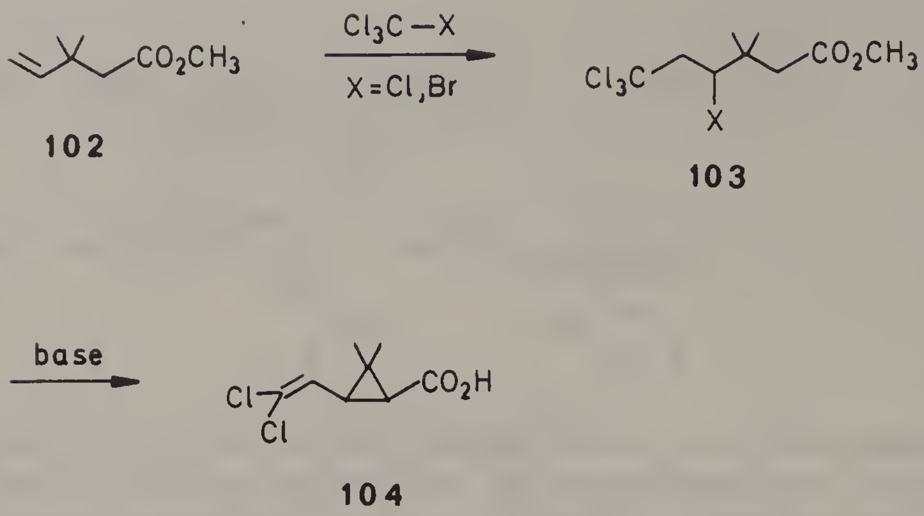




Depending upon the rate of halogen abstraction, intramolecular reactions can compete with the intermolecular product forming step. For example, ß-pinene[95] gives the ring-opened product with CCl_4 and norbornadiene[96] leads to a mixture of bi- and tricyclic adducts. The ratio of the cyclized versus the non-cyclized products depends on the concentration of the halogen donor, the halogen atom X, and the reaction temperature.[97]



This method was applied to the synthesis of permethrine acid **104**. Addition of $XCCl_3$ (X = Br, Cl) to alkene **102** gives **103**; base induced cyclization and elimination yields the target molecule **104**.[98]



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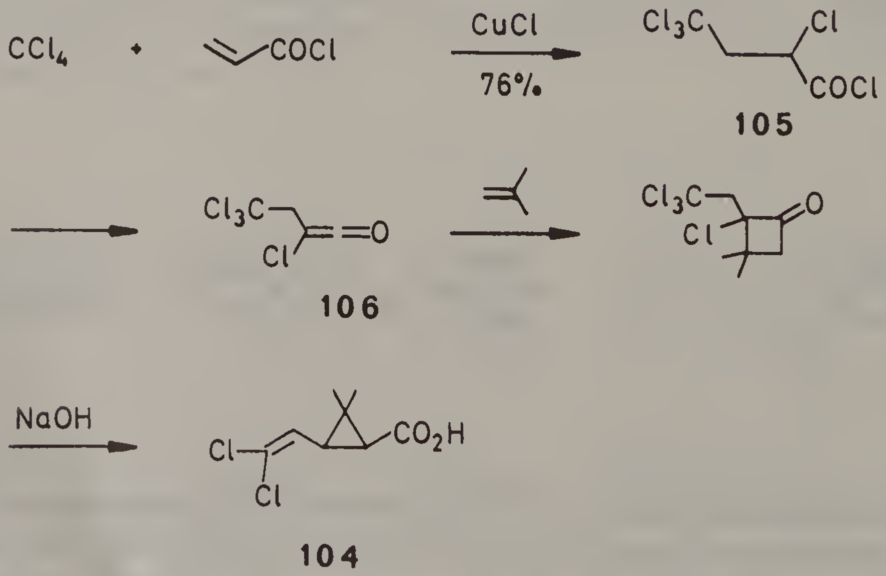
104

Reactions of perhaloalkenes can also be carried out with electron-poor alkenes in the presence of iron or copper salts. This approach has been used to synthesize permethrine acid **104** from acryloyl chloride.[99]



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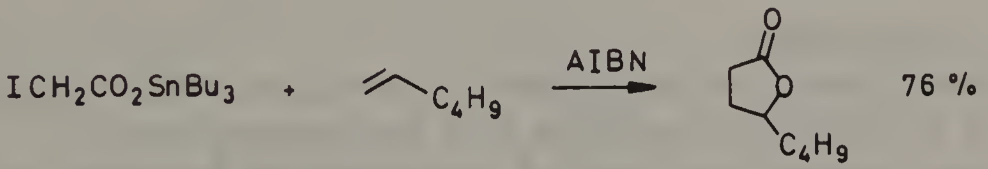
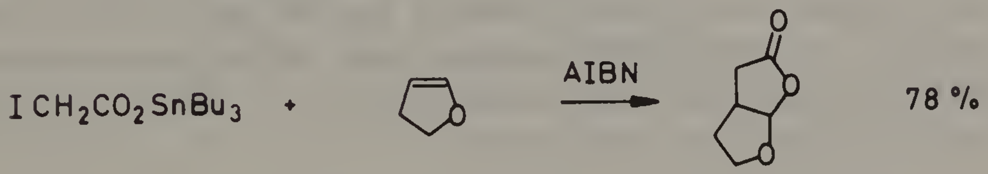
106

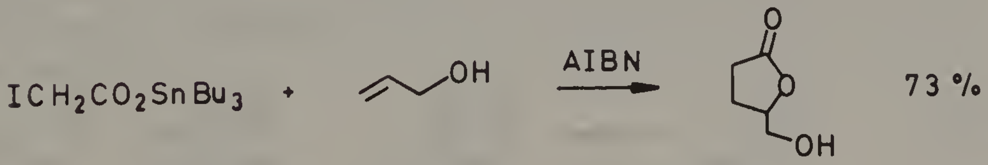
104

The addition product **105** is transformed into the ketene **106**, cycloaddition with isobutene, Favorskij rearrangement, and elimination then leads to **104**. The mechanistic details of the metal catalyzed addition reaction are not yet clear. It is, however, possible that an oxidative addition of Cu(I) to CCl_4 followed by a reaction with the electron-poor alkene occurs instead of a radical chain reaction.[100]

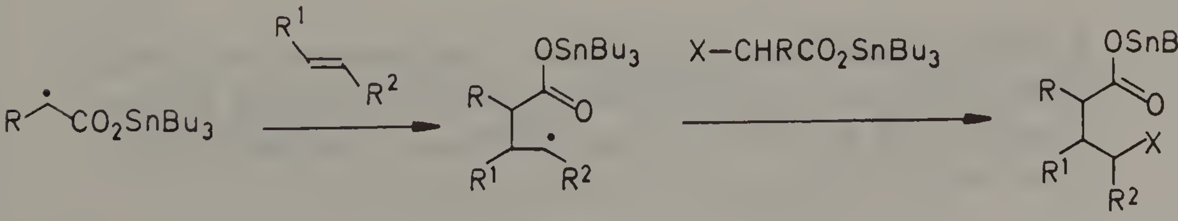
Kraus[101] has used tin salts of α-iodoacids and α-bromoacids for the synthesis of γ-lactones.





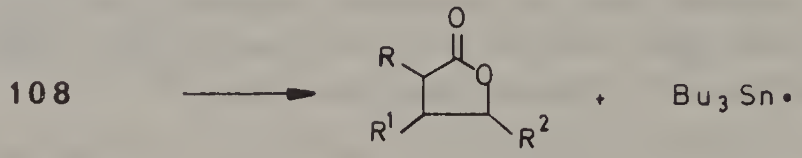


The reaction occurs presumably via addition of electrophilic radicals **107** to electron-rich alkenes and subsequent halogen abstraction (**108**→**109**). Cyclization then leads to the γ-lactone.



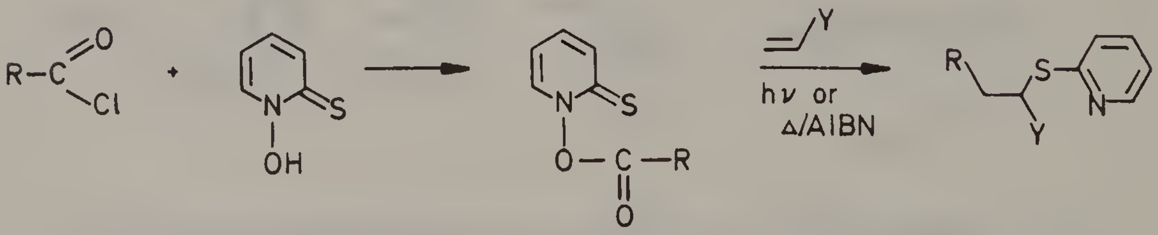
107 **108** **109**

This mechanism seems to be more likely than cyclization of radical **108**.



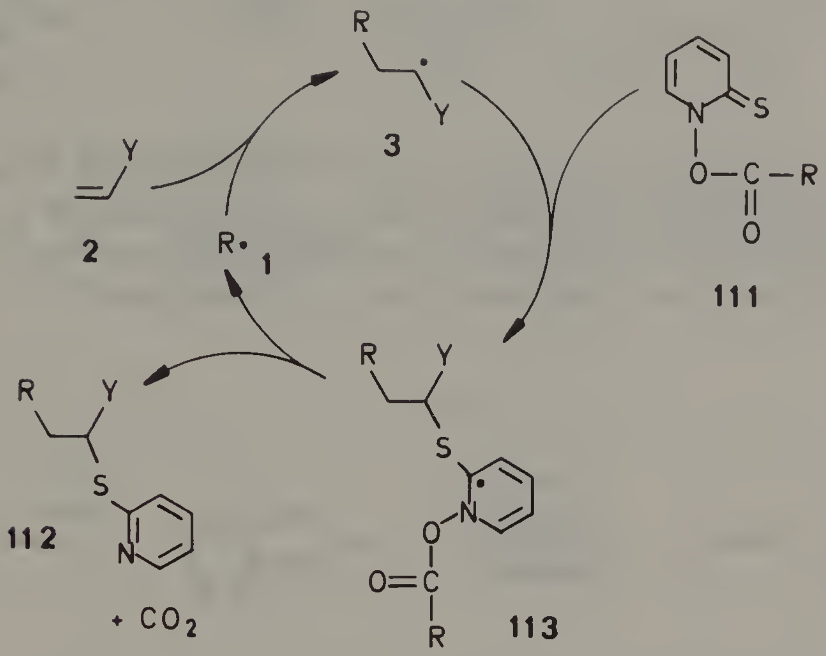
2. Thio donor

A very useful synthetic method in which radicals are trapped by a thiocarbonyl group has been developed by Barton.[102] Acid chlorides are converted with N-hydroxypiperidine-2-thione **110** to mixed anhydrides **111**, which are the radical precursors. Addition of electron-poor alkenes under either photolytical or thermal conditions leads to products **112** in which a C-C bond and a C-S bond have been formed.

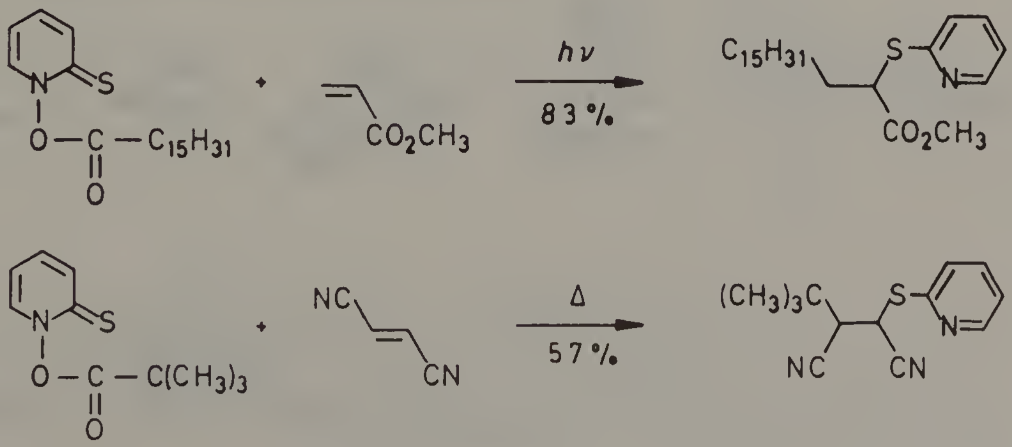


110 **111** **112**

In the reaction sequence radical **1** is generated and attacks alkene **2** to give adduct radical **3** that is trapped by the thio-compound **111**. Two successive ß-bond cleavages in **113** yield product **112** and the starting radical **1**.[103]



This reaction can be successfully carried out with a variety of different carboxylic acids as long as electron-poor alkenes are used.[102]



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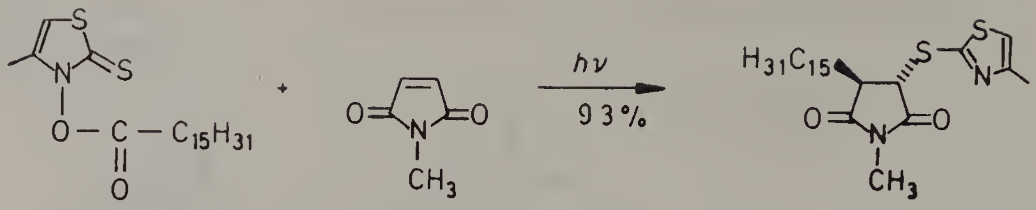
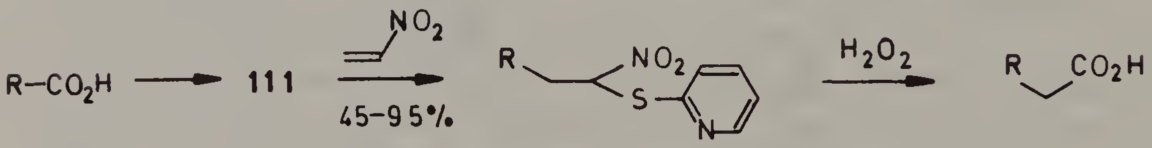
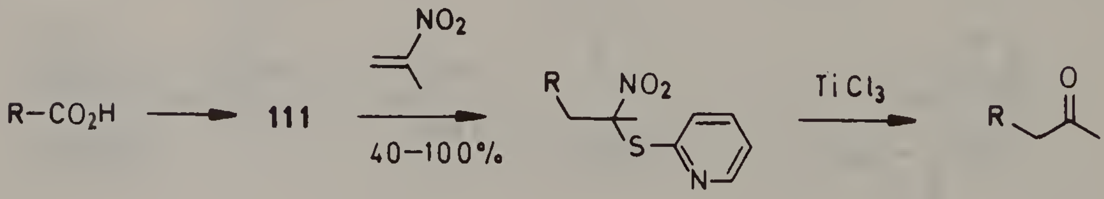


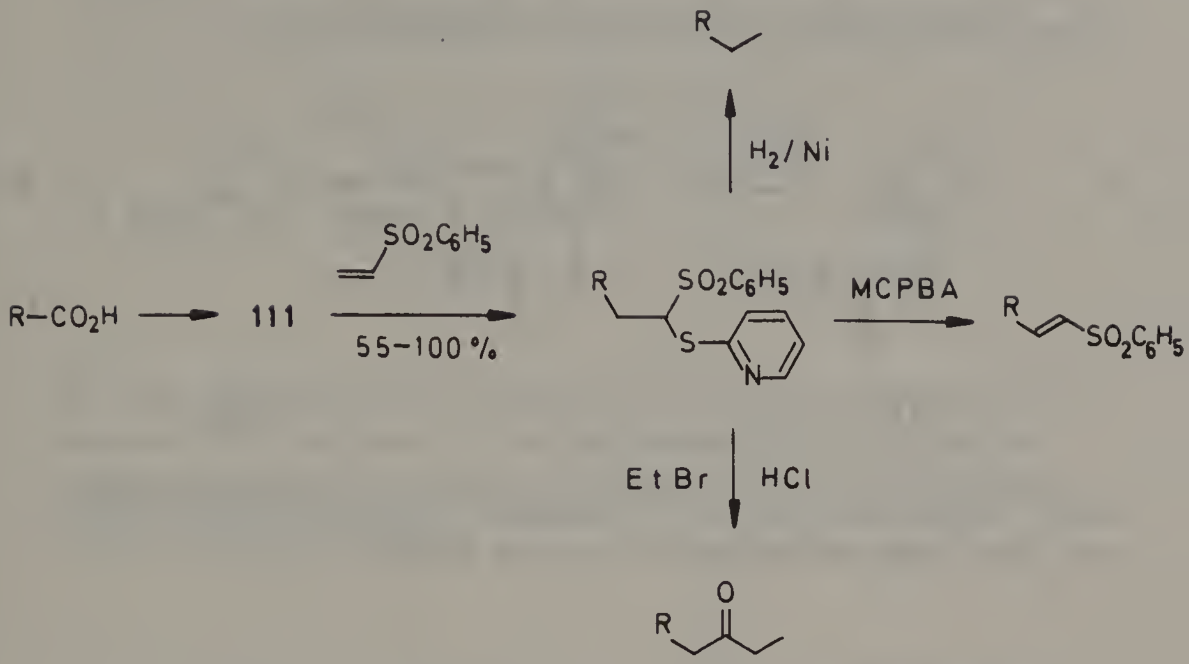
The reaction of nitroethylene with **111**, followed by oxidation, produces a carboxylic acid. Thus, in what could be a useful alternative to the classical Arndt-Eistert reaction, a carboxylic acid is transformed into the homologue.[104]



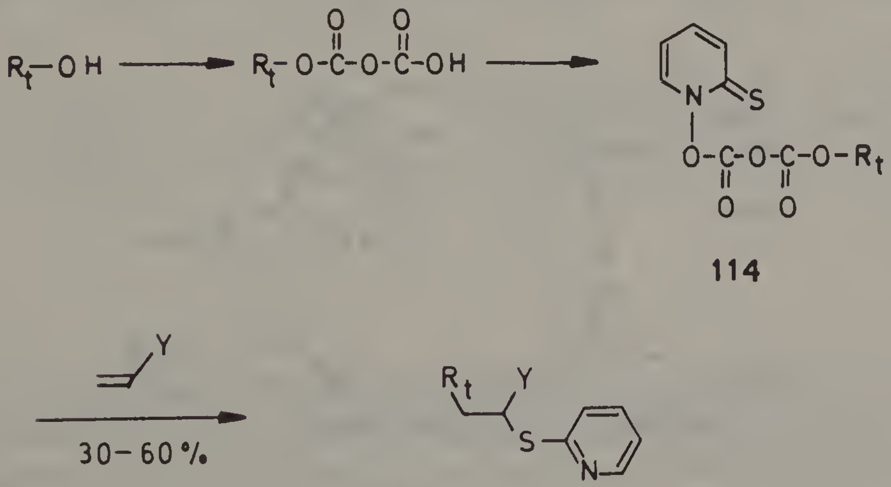
Radical C-C bond formation with 2-nitropropene and reductive cleavage with $TiCl_3$ leads to methyl ketones.[104]



Vinyl sulfones are also attractive alkenes because the adducts are versatile synthetic intermediates.[105]

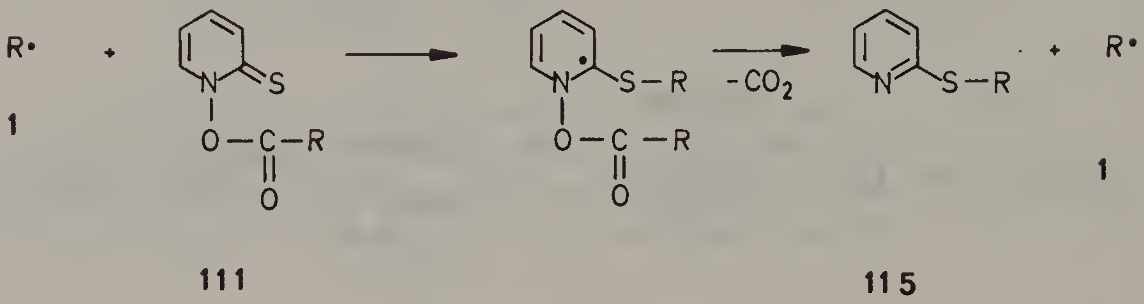


Alcohols can be used as radical precursors via their half oxalates and the thio compound **114**. Thus, reactions with tert. alcohols lead to quaternary carbon centers.[106]



114

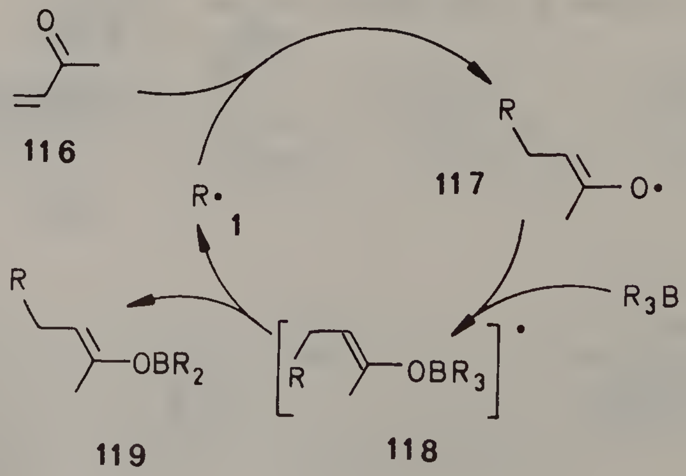
A side reaction, which involves the attack of alkyl radical **1** on the thio group of **111**, leads to thioether **115**.

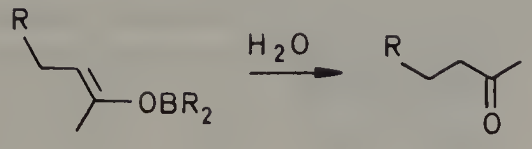


Since **111** is a fast radical trap, this C-C bond forming synthesis gives high yields only with very reactive alkenes.

3. <u>Borane donor</u>

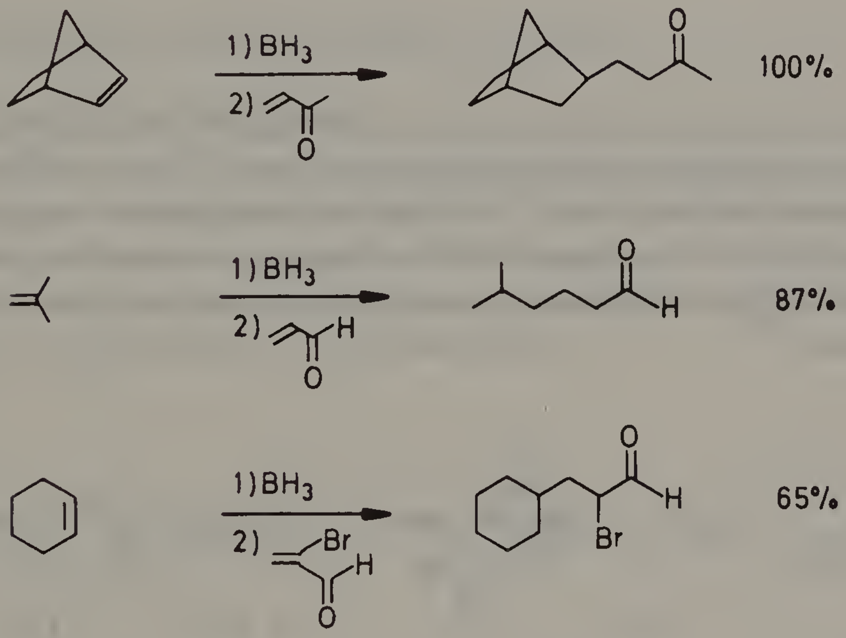
Brown[107] has shown that trialkylboranes are suitable precursors for alkyl radicals in C-C bond forming chain reactions with α,ß-unsaturated ketones and aldehydes. Adduct radicals **117** are generated by the addition of radicals **1** to alkene **116**. They are then trapped by trialkylboranes to give, in a synchronous displacement or via intermediate **118**, the starting radical **1** and **119**, which is hydrolysed to give product **120**.



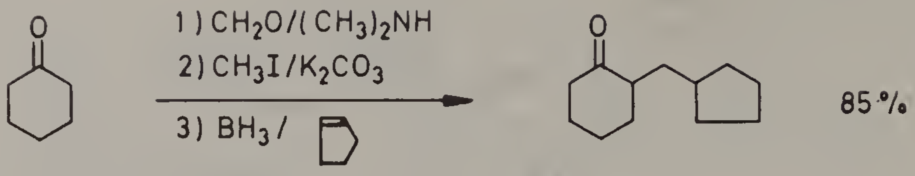


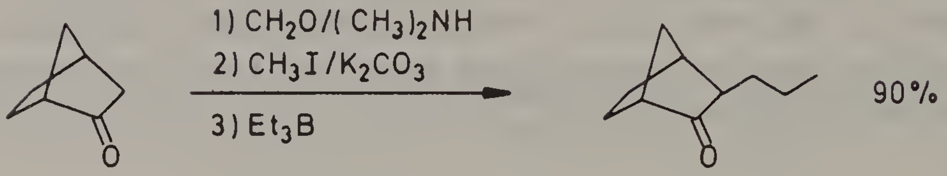
119 **120**

The trialkylboranes are generated by in situ hydroboration of alkenes. The reaction of trialkylboranes with O_2 produces peroxiboranes,and the radicals generated from these peroxiboranes start the chain.[107,108]

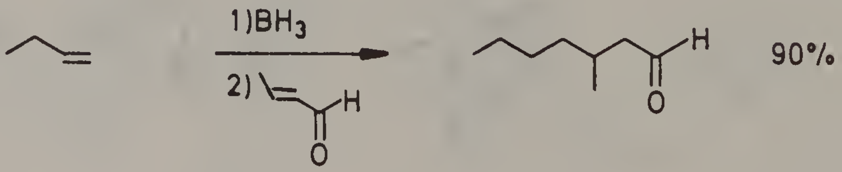


Mannich bases derived from cycloalkanones, quaternized in situ, react smoothly with trialkylboranes in alkaline solution, presumably via a methylene ketone, to give the products of a C-C bond forming reaction.[109]

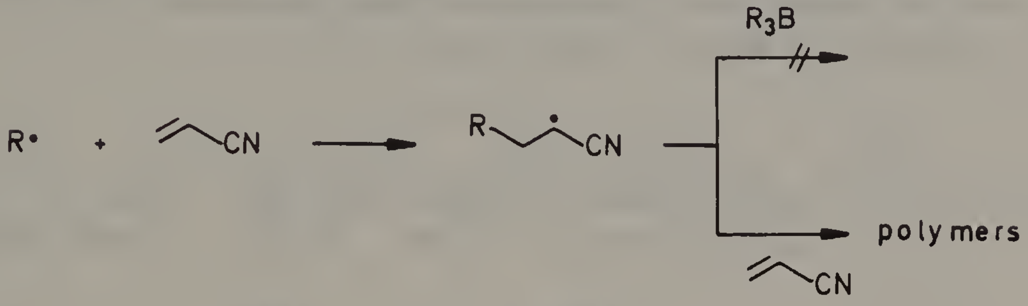




Also α,ß-unsaturated ketones and aldehydes with an alkyl group at the attacked C-atom of the double bond can be used in these syntheses. However, the reactions are successful only if enough radical initiators are present to restart the chains, which have short length because of the less reactive alkenes.[110]



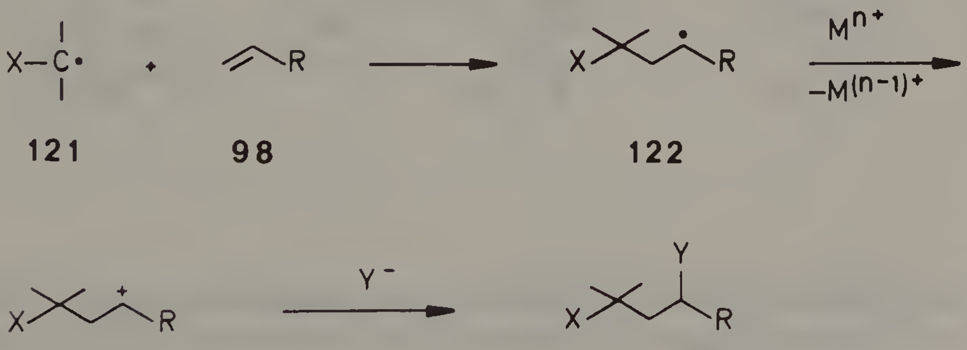
These syntheses are limited to α,ß-unsaturated aldehydes, ketones, and epoxides;[107] with ester or nitrile groups, the intermediate adduct radical cannot be trapped fast enough by the trialkylborane and polymerization occurs.



D. Trapping by Electron Transfer Reactions

1. Oxidation by metal ions

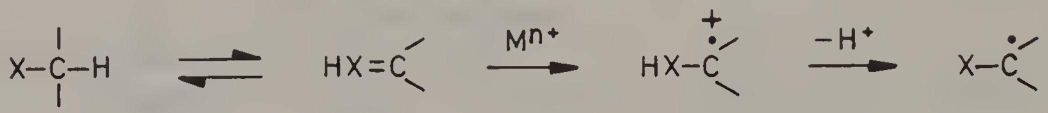
Cu^{2+}, Mn^{3+}, and Ce^{4+} ions are very efficient redox traps for nucleophilic alkyl radicals **122** [89,111] generated by addition of radicals **121** to alkenes **98**. These metal salts oxidize radicals with high lying SOMOs to cations **123**, which further react to give products, for example **124**.



121 **98** **122**

123 **124**

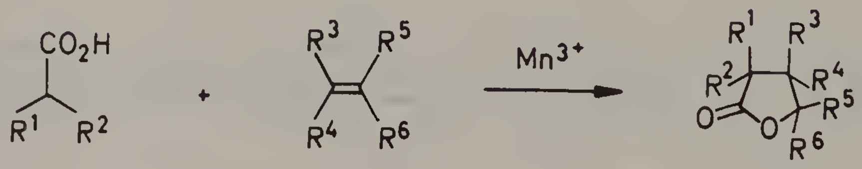
Since only nucleophilic radicals are oxidized fast enough, these syntheses are limited to electrophilic educt radicals **121** and electron-rich alkenes **98**. Acid, ester, acyl, nitro, and nitrile groups have been used as electron-withdrawing substituents X at the radical center of **121**. The preferred method for the generation of electrophilic radicals **121** involves the oxidation of hydrocarbons **125**, presumably via their tautomers **126** and the radical cation **127**.



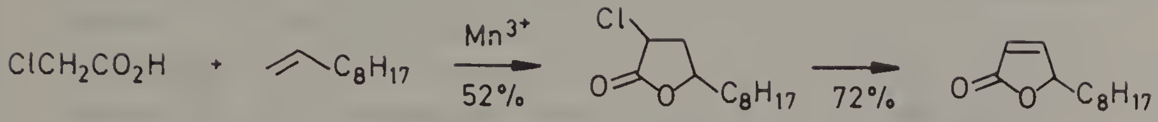
125 **126** **127** **121**

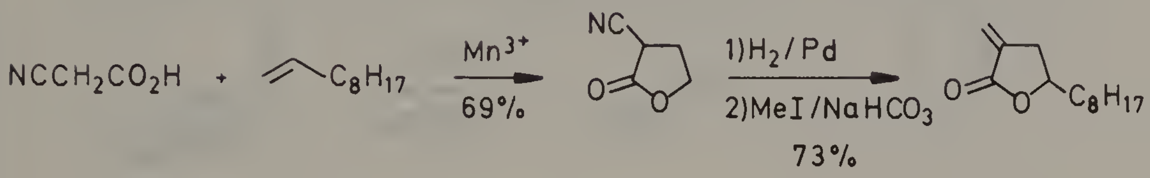
$X = CO_2H,\ CO_2R,\ COR,\ CN,\ NO_2$

Heiba[112] developed this method for the synthesis of γ-lactones, which are formed by intramolecular trapping of the cations **123**.

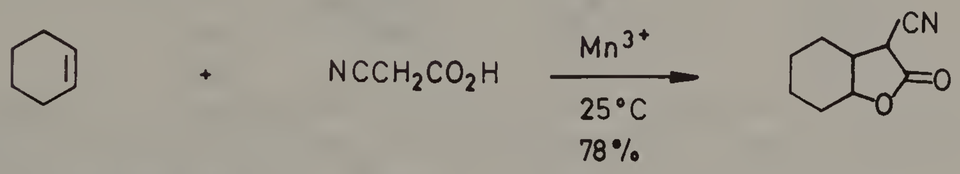


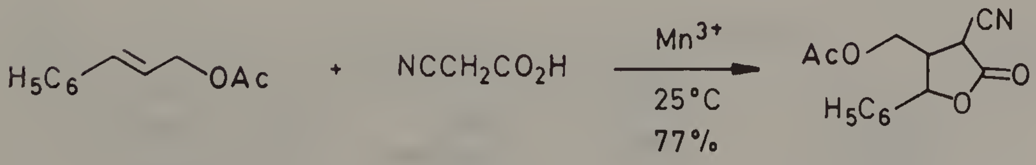
Chlorinated radical precursors give α,β-unsaturated γ-lactones after HCl-elimination, and methylene lactones can be synthesized from cyanomalonic acids.[113]



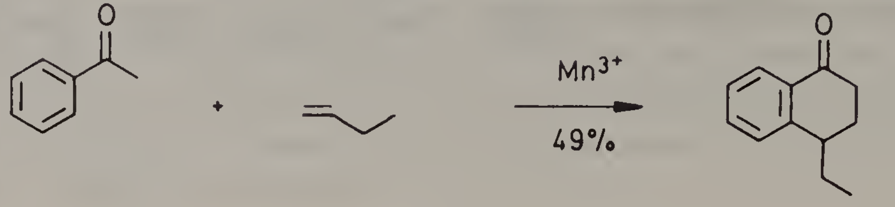


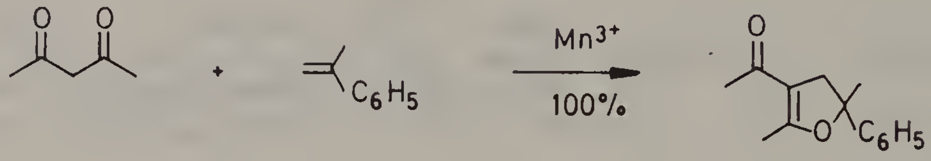
Temperatures of these reactions are often very high, but they can be reduced to 25°C if electron-withdrawing groups α to the carboxylic acid functions are present. This is, for example, the case with ß-keto,[114] cyanoacetic, and malonic acids.[115]

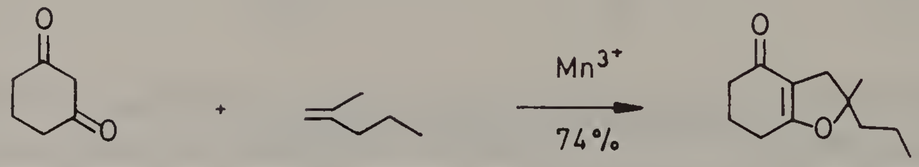




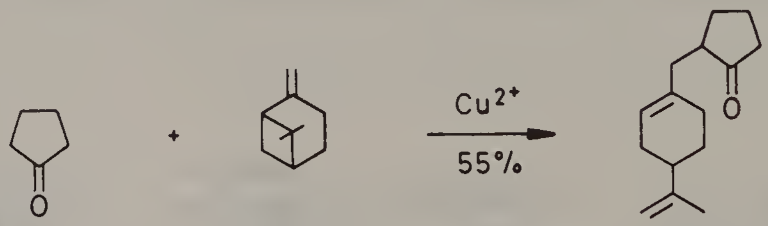
Ketones and phenyl rings can also trap the intermediate cations.[114]

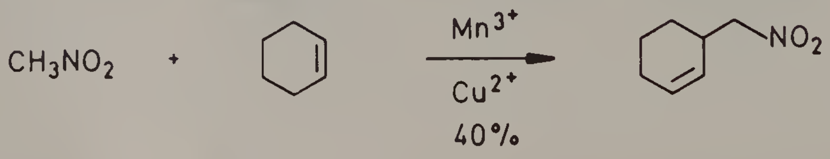


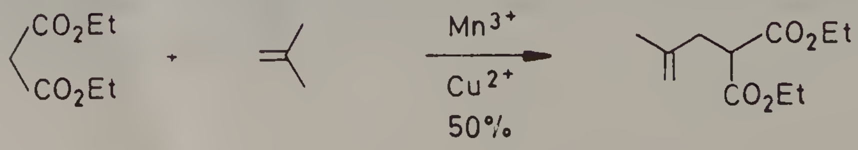




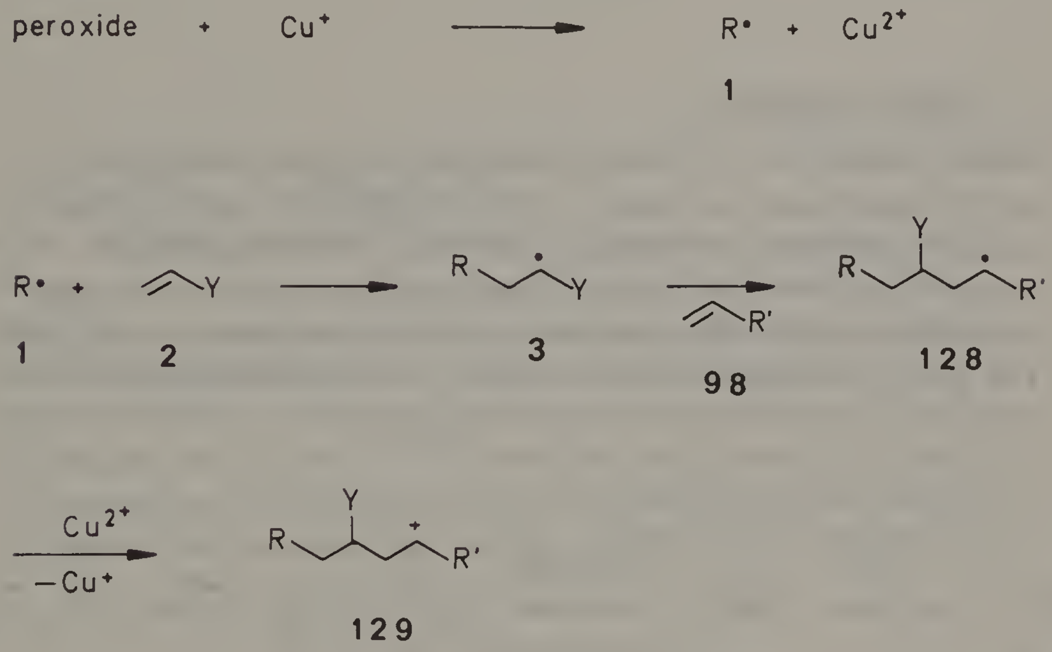
If the nucleophilic groups don't react fast enough, the cations are stabilized by deprotonation.[116]



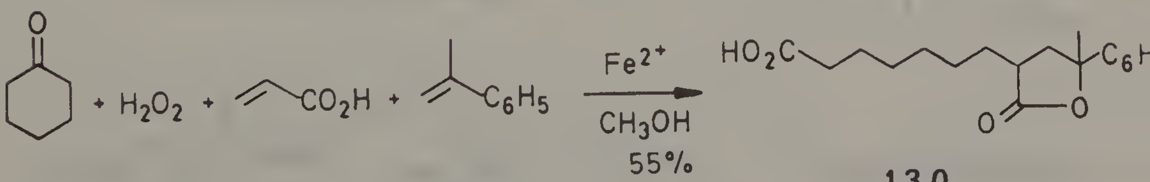




These C-C bond forming syntheses are not chain reactions because the Mn^{3+} ions are used up without being reoxidized. However, the reduced metal ions can be oxidized if peroxides are used as radical precursors. Thus, Minisci[89] generated radicals **1** from peroxides. Addition of **1** to electron-poor alkenes **2** gives adduct radicals **3** that are not oxidized because of the electron-withdrawing substituent Y and are therefore trapped by electron-rich alkenes **98**. Oxidation of **128** then gives cation **129** that reacts with electrophiles.

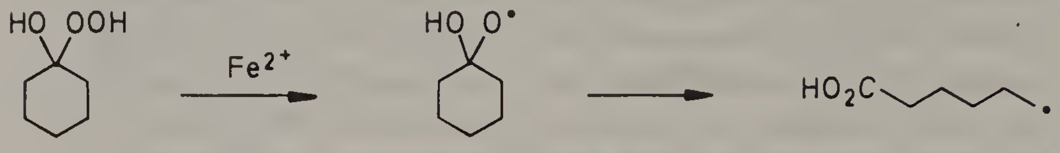


A synthetic application of this reaction sequence is the formation of γ-lactone **130** from cyclohexanone, acrylic acid, and α-methylstyrene.[117]



130

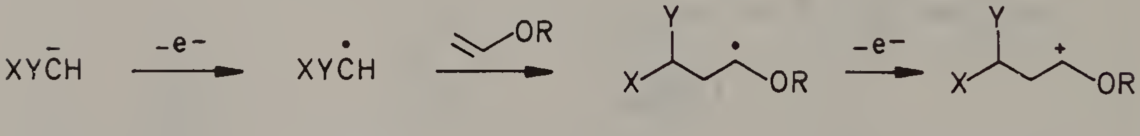
The reaction proceeds via the peroxide **131** which, after cleavage of the O-O bond, gives the nucleophilic alkyl radical **132**.



131 **132**

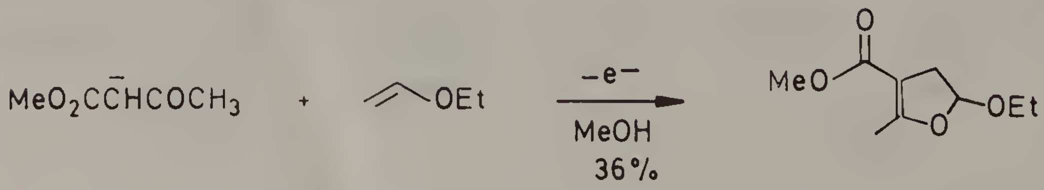
2. Anodic oxidation

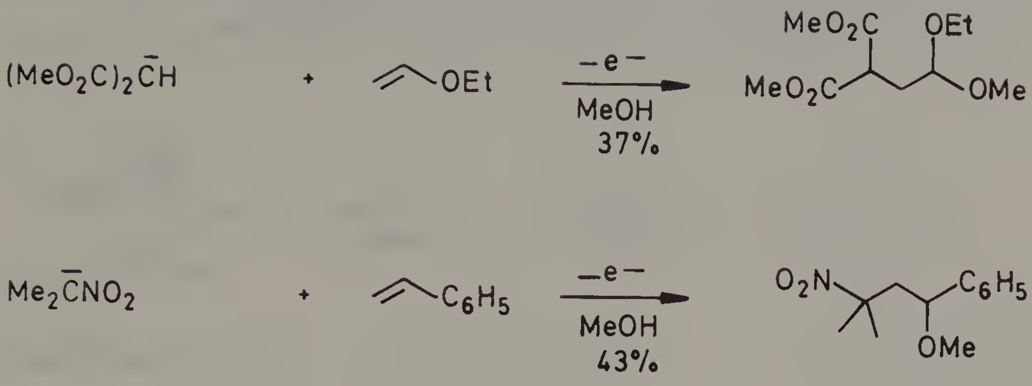
Anodic oxidation of anions **133** with electron-withdrawing substituents such as ester, acyl, nitrile, or nitro groups yields electrophilic radicals **134** that are resistent to further oxidation and react with enolethers. The so formed nucleophilic radicals **135** undergo rapid oxidation to cations **136** that are trapped either intra- or intermolecularly.[118]



133 **134** **135** **136**

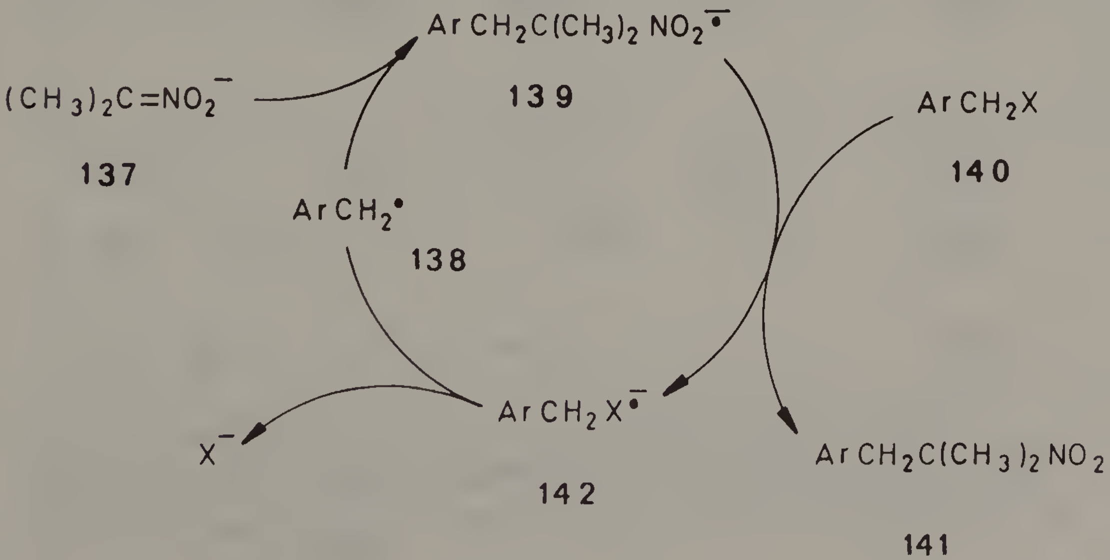
The products are formed in yields of about 40%, and even styrene can be used as alkene to trap the electrophilic radicals.[118,119]



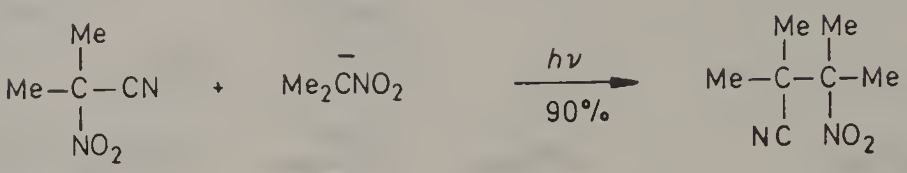


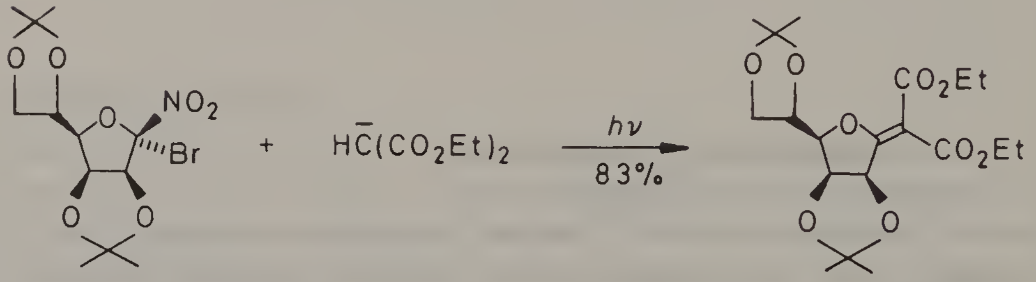
3. Syntheses via $S_{RN}1$ reactions

Alkyl radicals rapidly[120] attack nitroalkane anions, for example **137**, in a reaction that was first studied by Kornblum[121] with substituted benzyl radicals **138**. The reaction passes through the radical anion **139** which transfers an electron to the starting halide **140** to yield product **141** and the radical anion **142**.[121,122] Because **142** loses a halide ion in a monomolecular reaction step, the mechanism was termed "unimolecular nucleophilic radical substitution" ($S_{RN}1$).[123]

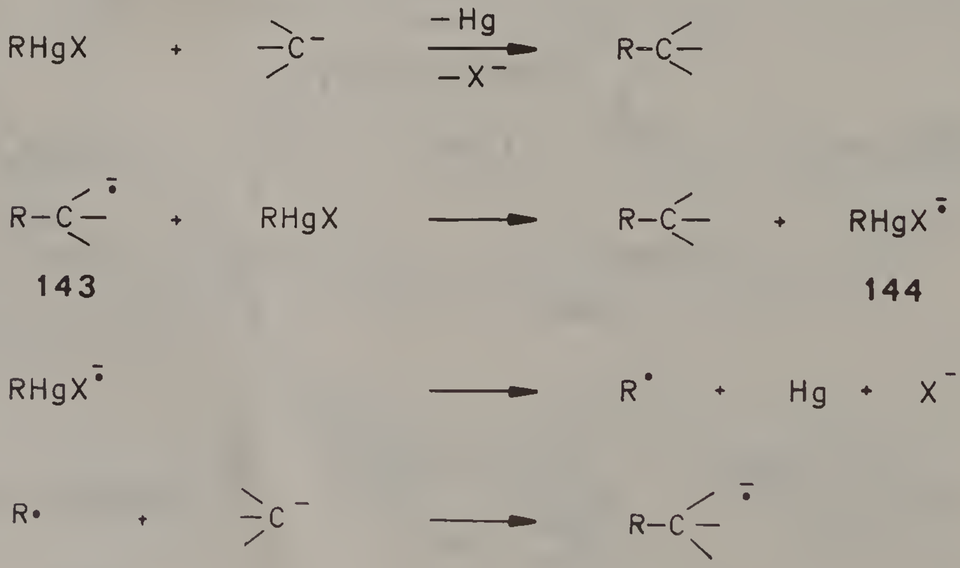


Alkylnitro radical ions can also be generated by reaction of nitro compounds with carbanions,[121] and Vasella[124] demonstrated the use of this method in carbohydrate chemistry.





Russell[125] has observed that alkylmercury salts react with nitrile, ester, acyl, and aryl substituted anions in aliphatic C-C bond formation reactions. The photoinitiated chain reaction occurs presumably via radical anions **143** and **144**.



143 **144**

143

The yields of several anions in their reactions with, for example, tert-butylmercury chloride are sufficiently high for a synthetic application of this methodology.[125,126]

$$(CH_3)_3CHgCl \quad + \quad R^- \quad \xrightarrow{h\nu} \quad (CH_3)_3C{-}R$$

$Me_2\overline{C}NO_2$ (69%) $H_2\overline{C}NO_2$ (68%) $(C_6H_5)_2\overline{C}CN$ (48%)

Fluorenyl$^-$ (44%) $C_6H_5\overline{C}(CO_2Et)_2$ (43%) $\overline{C}H_2COC_6H_5$ (54%)

E. Fragmentation

After construction of the C-C bond by radical addition to alkenes **145** the adduct radicals **146** can be transformed into non-radical products not only by intermolecular trapping reactions, but also by splitting off a radical, for example, in a ß-bond cleavage.

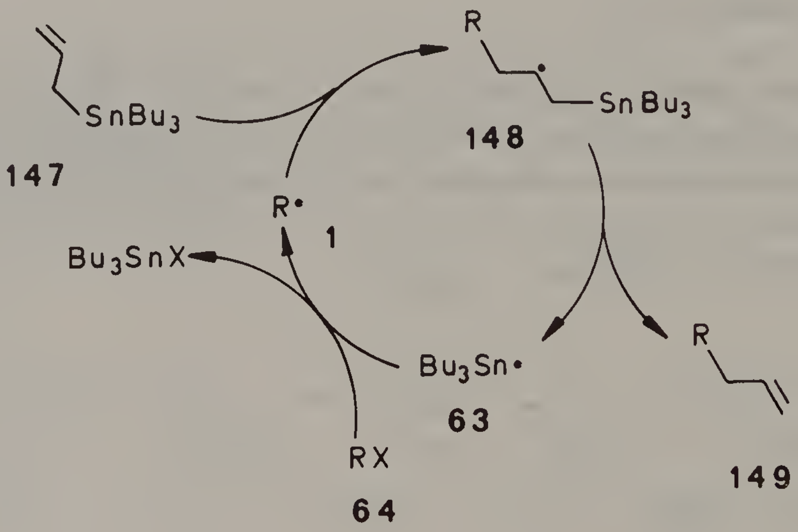
1 **145** **146**

In these synthetic methods, an intramolecular reaction prevents adduct radical **146** from reacting with alkenes **145**. If this fragmentation is fast enough, then radicals **1** and **146** need not to be of different polarity; that is, even electron-rich alkenes **145** can be used for C-C bond forming reactions with nucleophilic radicals. Various synthetic methods have been developed during the last years in which different radicals are split off in distinct reaction steps.

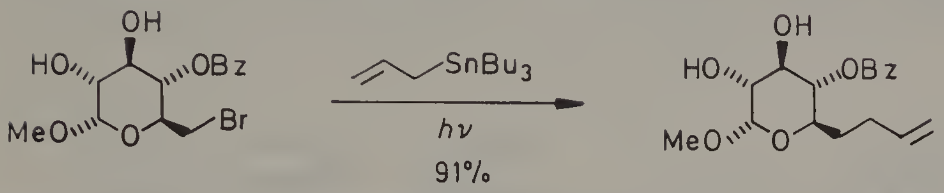
1. Cleavage of carbon-heteroatom bonds

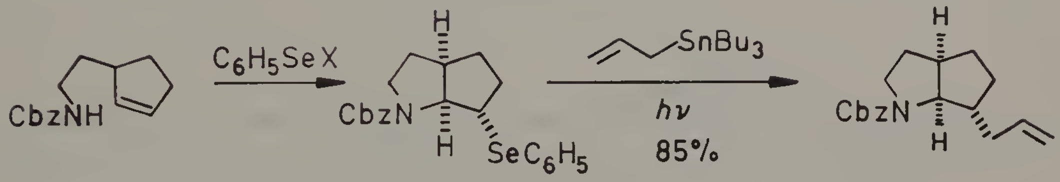
a. Carbon-tin bonds

Allylstannanes **147** have been used by Keck[127] for the synthesis of C-C bonds via addition reactions with alkyl radicals **1**. These syntheses benefit from the rapid cleavage of a C-Sn bond ß to a radical center. Therefore, adduct radicals **148** give allylsubstituted products **149** by splitting off a tributyltin radical **63** that reacts with **64** to give **1**. Compound **64** can be a halide, xanthate, thioether, or selenide.

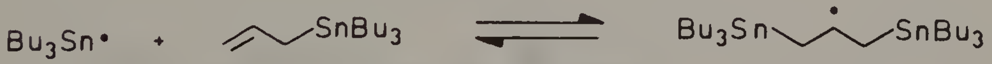


The radical chain is initiated by thermolysis of AIBN or irradiation. A variety of precursors **64**, including carbohydrate derivatives, can be used.[128,129]



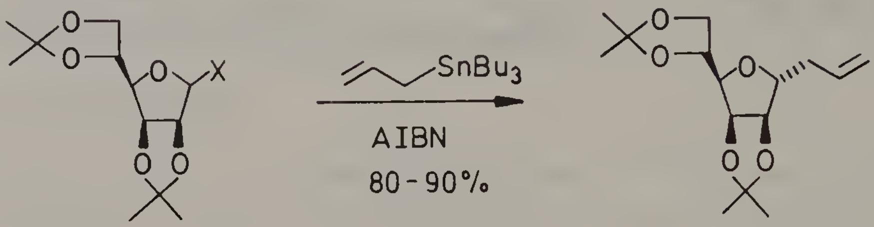


The advantage of this allyltin method is that hydrogen or heteroatom donors, which often also react with educt radical **1** to give by-products, are not needed. Furthermore, the side reaction involving the addition of tin radicals **63** to the alkenes destroys neither **147** nor **63**, because they are immediately regenerated by ß-bond cleavage of **148**.



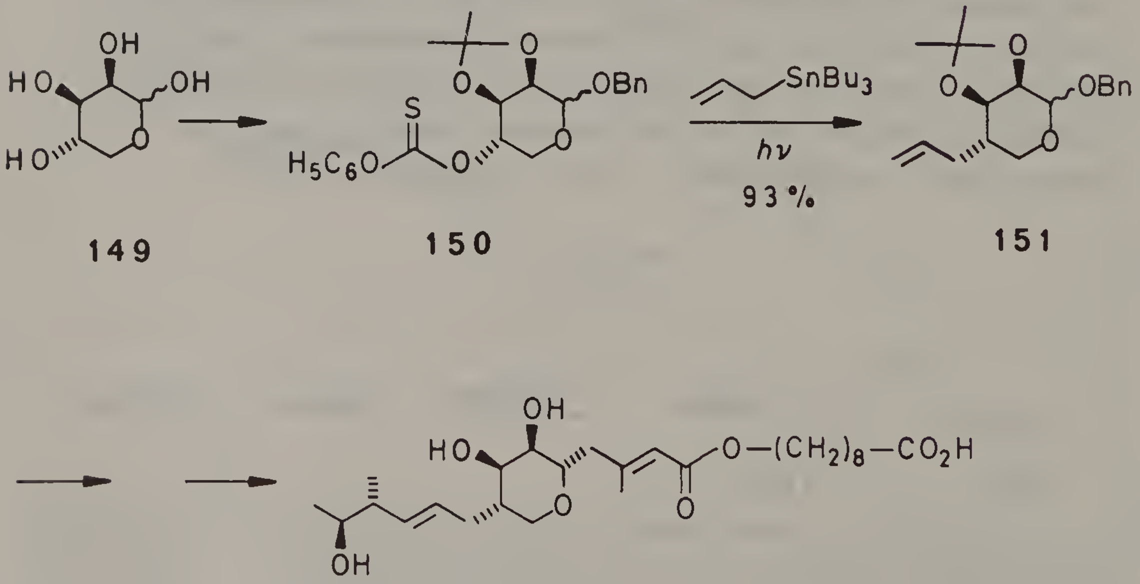
63 **147** **148**

Therefore, in syntheses with allyltin **147**, less reactive radical precursors like alkylchlorides and thioethers can be used.[128]



$X = Cl, SC_6H_5$

One application is the synthesis of pseudomonic acid C **152** from L-lyxose **149** in which the C-C bond forming step is carried out via radical allylation of **150**.[130]



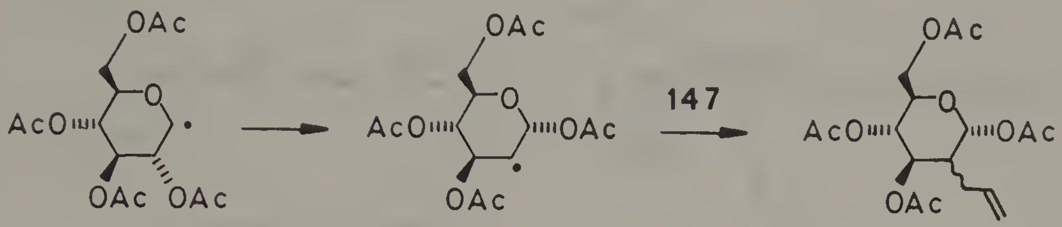
149

150

151

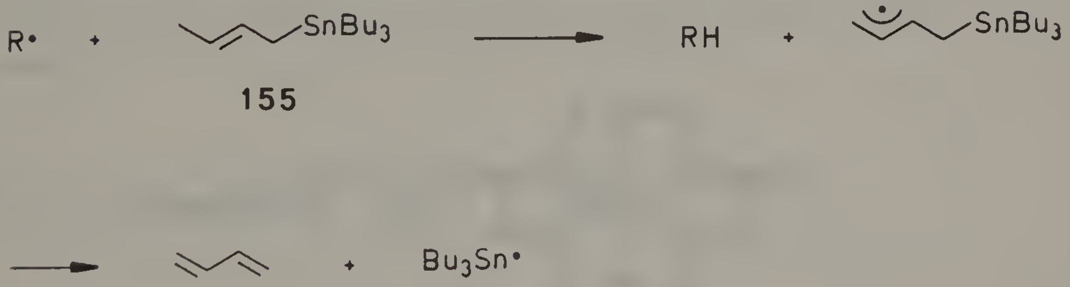
152

Compared to electron-poor alkenes like acrylonitrile, olefin **147** reacts slower with nucleophilic radicals. Therefore, intramolecular reactions, for example the acetyl migration **153→154**, can compete with the intermolecular trapping reaction.[131]



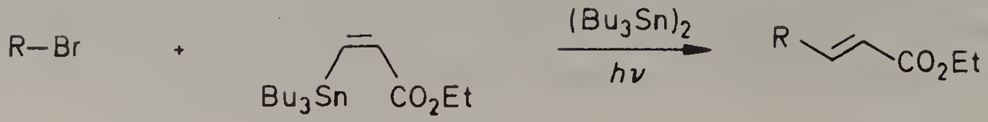
153 **154**

Unfortunately, this allylation method seems to be limited to allyl- and methallylstannanes. With crotylstannane **155**, for example, the synthesis fails because the alkene is too unreactive, and allylic hydrogen abstraction occurs.[128]



155

Baldwin[132] and Russell[133] have used vinylstannanes **156** and **157** for C-C bond forming reactions. The problem with these methods is that the alkyl radicals have to attack the tin-substituted olefinic C-atom in order to give products via ß-elimination of radical **158**.



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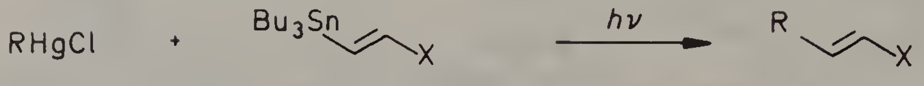

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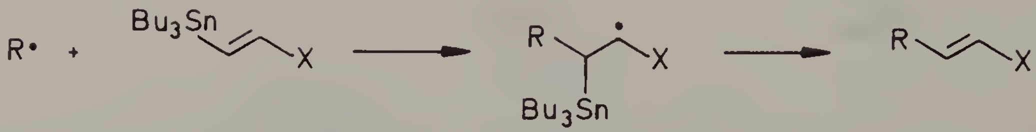

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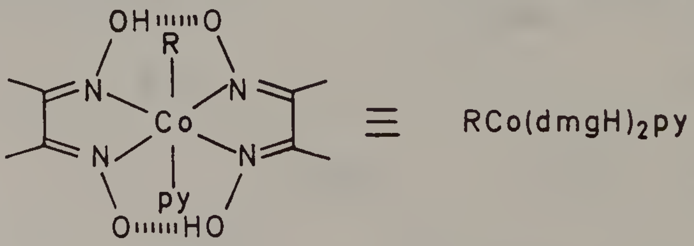
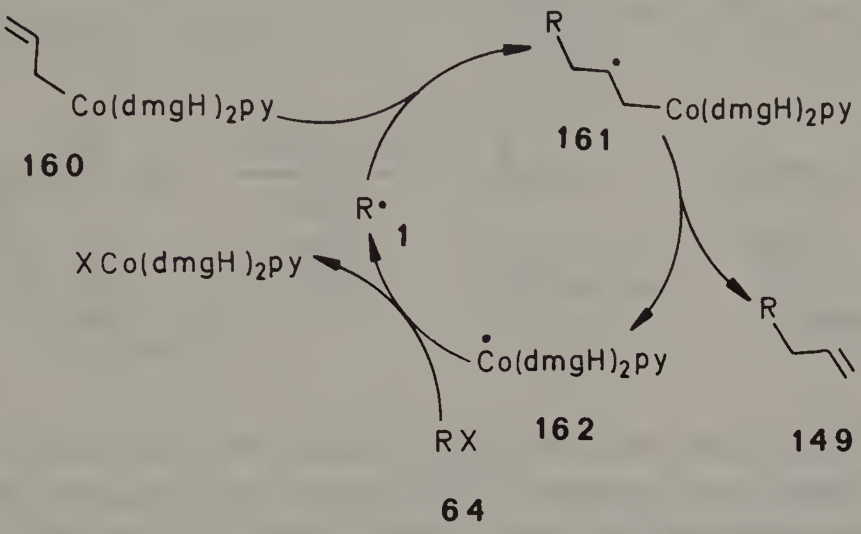
b. Carbon-cobalt bonds

Dissociation energies of C-Co bonds in organocobaloximes **159** are on the order of 20 kcal/mol for benzyl substituted compounds.[134]

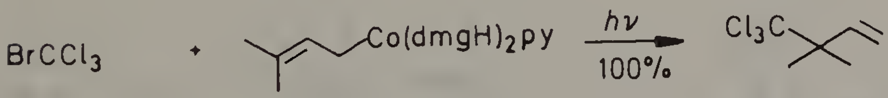


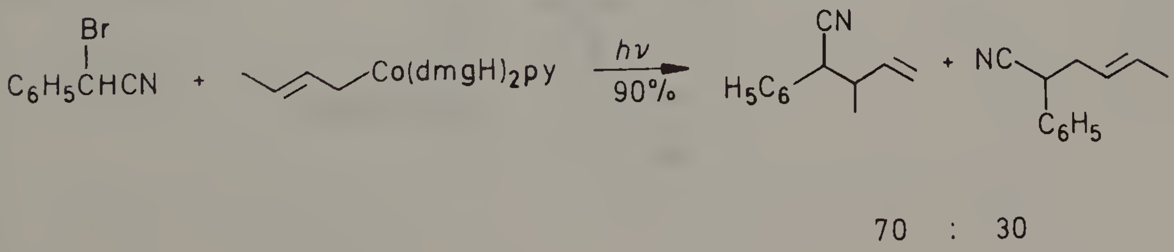
159

A radical center in ß-position leads to a rapid cleavage of the C-Co bond. Therefore, radical **161**, generated by addition of **1** to allylcobaloxime **160**, yields product **149** and the cobaloxime radical **162**. This radical abstracts a halogen from a suitable precursor and gives back the starting radical **1**.[135]



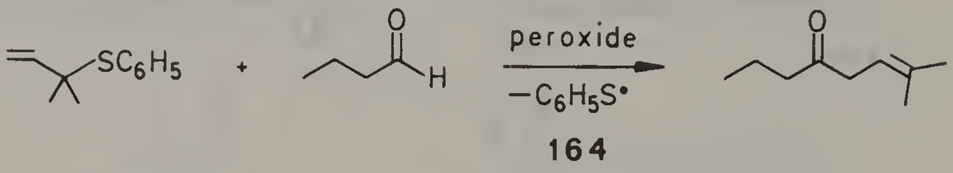
Syntheses with allylcobaloximes have been carried out mainly with electrophilic radicals. In contrast to the allyltin method, crotyl and higher alkylated systems can also be used.[136]





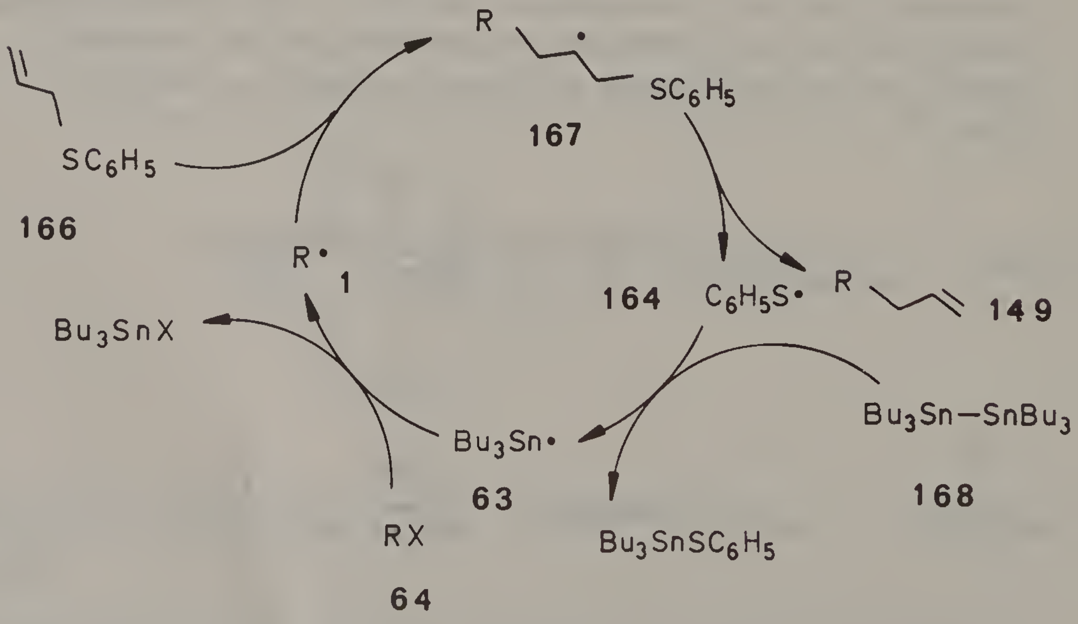
c. Carbon-sulfur bonds

Alkyl radicals with ß-C-S bonds undergo rapid ß-scission reactions. Thus, butyraldehyde adds to **163** and yields, as a side-product **165** after ß-elimination of phenylthio radical **164**.[137]

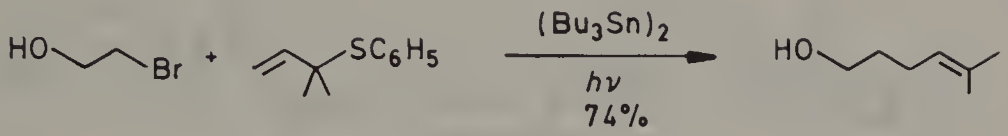


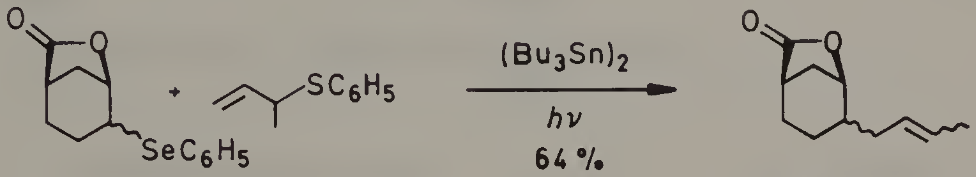
163 **165**

Keck[138] has shown how phenylthio radical **164** carries the chain reaction by trapping it with hexabutylditin **168**. The tributyltin radical **63** thus formed reacts with **64** and generates the starting radical **1**.

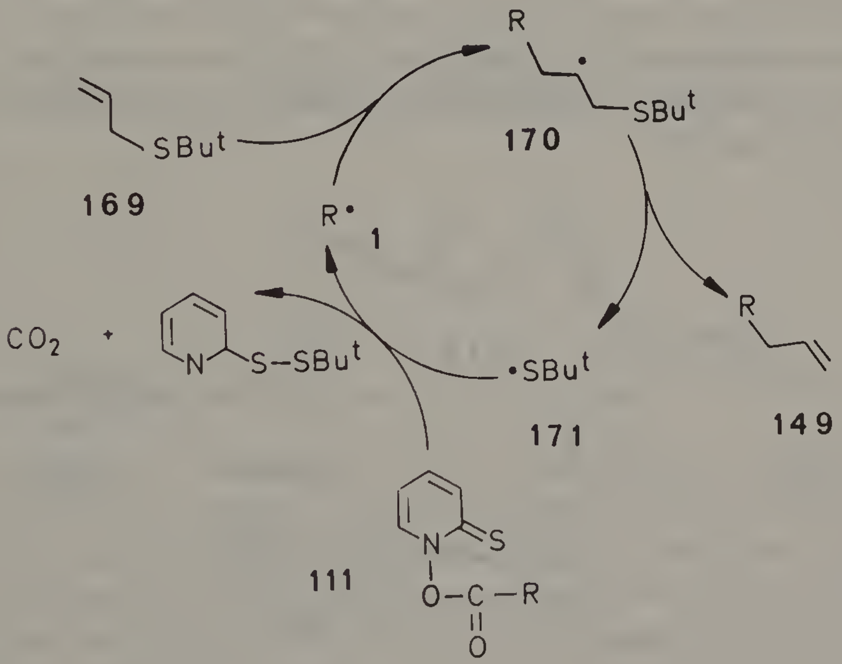


Halides and selenides are suitable precursors for educt radicals 1.[138]

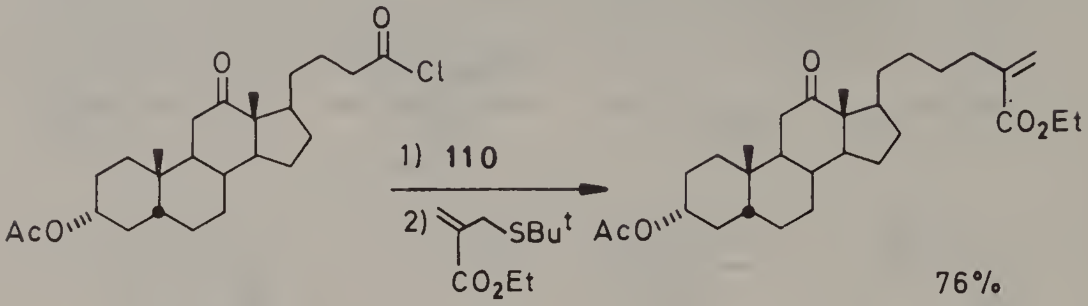


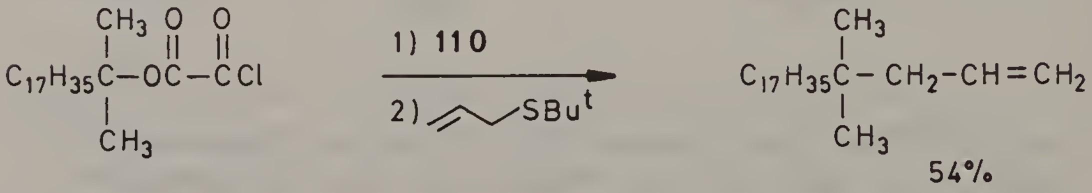


Barton[139] used thio compound **111** to trap tert-butylthio radical **171**. Radical **1**, thus generated, adds to **169** and gives product **149** via **170**.



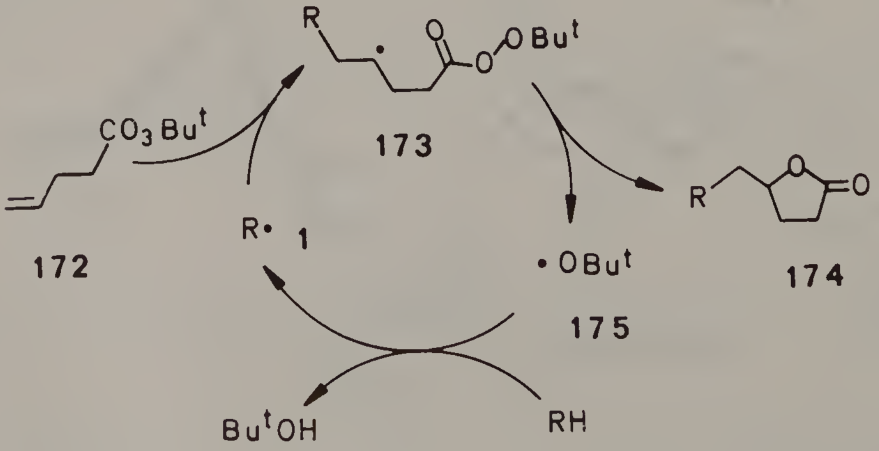
These syntheses can be carried out as one-pot reactions in boiling chlorobenzene.[106,139]





2. Cleavage of oxygen-oxygen bonds

Peresters can undergo radical induced decomposition.[140] Maillard[141] used this for the synthesis of γ-lactones **174** from homoallylperesters **172** via radical **173**. The tert-butoxy radical **175** regenerates the alkyl radical **1** by hydrogen abstraction from RH.

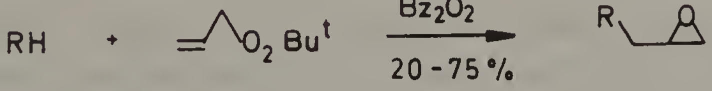


Hydrocarbons, ethers, ketones, nitriles, and even methylene chloride have been used as radical precursors.[141]

R = C_6H_{11} (73%), THP (65%), $C_2H_5\underset{\underset{\displaystyle O}{\|}}{C}CHCH_3$ (58%)

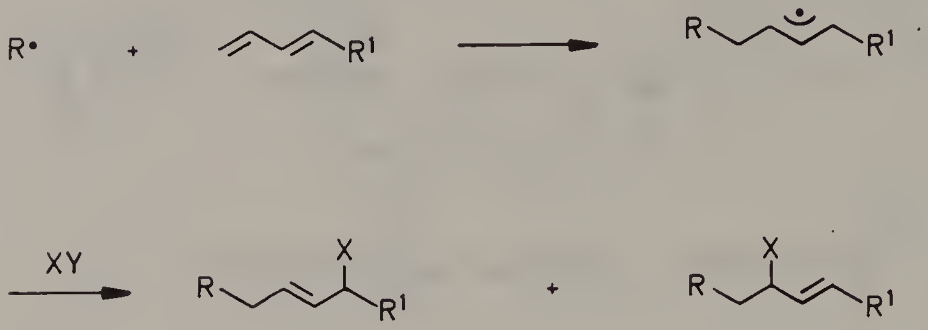
$CHCl_2$ (70%), CH_2CN (64%)

In an analogous reaction,[142] epoxides are formed from allylperoxides.[141]



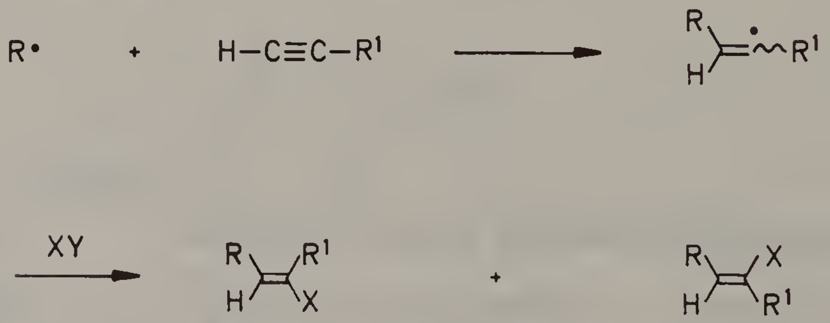
F. Miscellaneous Radical Addition Reactions

In the preceding sections of this chapter, mainly alkenes have been used as educts in the C-C bond formation reactions. For synthetic purposes alkenes are the most important traps, but 1,3-dienes or alkynes can also be utilized. The rates of radical addition to 1,3-dienes are slightly higher than those to alkenes.[143] However, since allyl radicals are the intermediates, mixtures are formed in the trapping reactions, although 1,4-adducts **176** are the main products in most cases.[70]



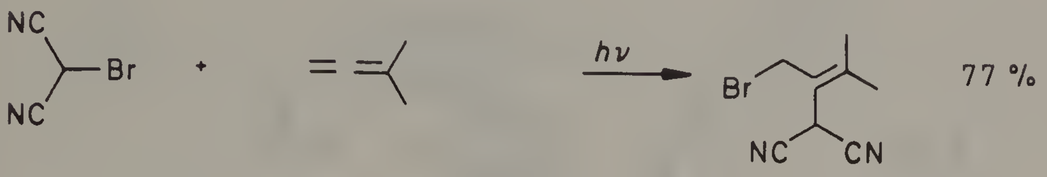
176

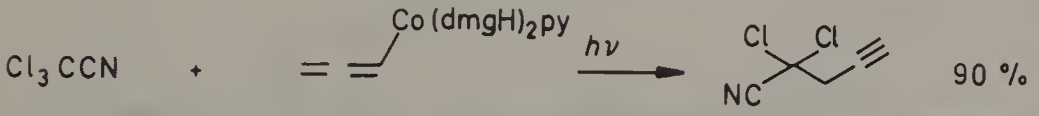
Alkynes are less reactive than alkenes.[1] Trapping of the intermediate vinyl radicals results in mixtures of *cis*- and *trans*-products. Since the semi-occupied orbital *trans* to substituent R is less shielded, *trans*-attack occurs faster, although the less stable *cis*-compound **177** is formed.[16]

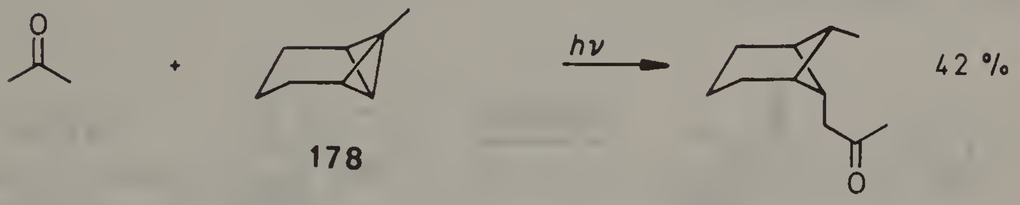


177

Allenes have been used in a few cases for intermolecular C-C bond forming reactions,[144] even the strained σ-bonds of cyclopropane **178** can trap alkyl radicals.[145]





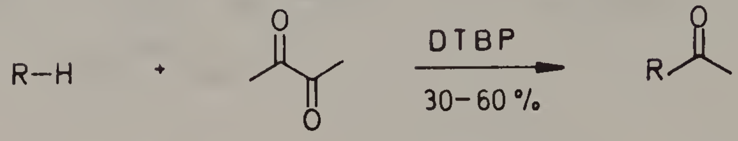


178

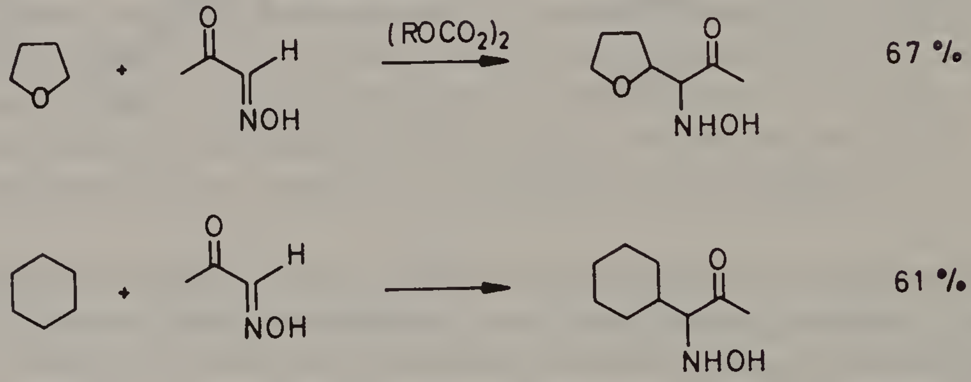
Carbon-oxygen π-bonds are as strong as carbon-carbon σ-bonds; thus, carbonyl groups react only slowly with alkyl radicals.[146] Furthermore, alkoxy radicals undergo rapid ß-bond cleavage. Nevertheless, several attempts have been made to use aldehydes and ketones as radical traps. Success can only be expected if the addition is favored by steric and polar effects. Thus, formaldehyde[147] and biacetyl[148] give products with moderate yields, but large amounts of peroxides were needed to restart the chain reactions.

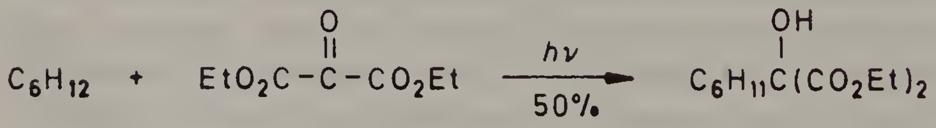
$$R\bullet + \rangle C{=}O \rightleftharpoons R{-}\overset{|}{\underset{|}{C}}{-}O\bullet$$

$$CH_3OH + CH_2O \xrightarrow[30\,\%]{DTBP} HO{-}CH_2CH_2{-}OH$$



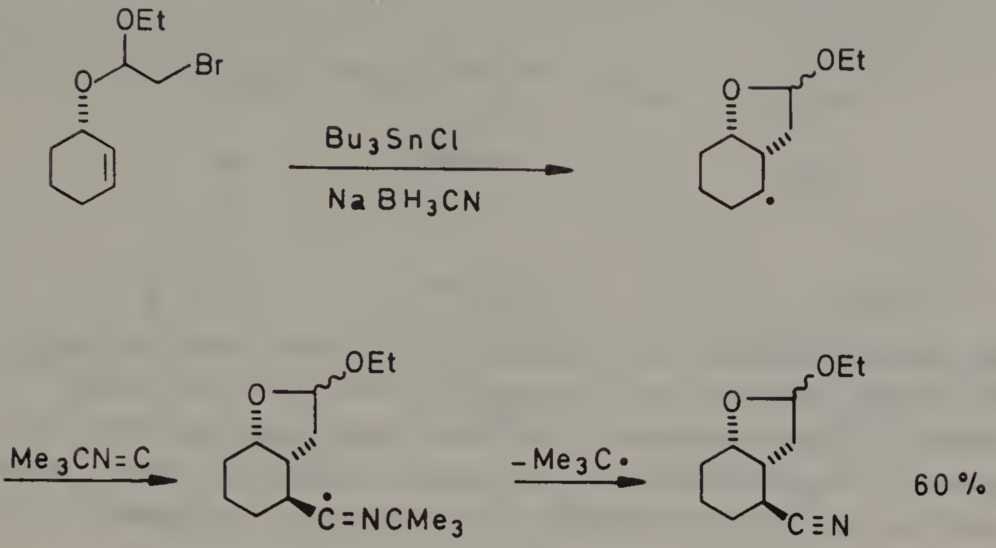
Aldoximes,[148] substituted by an acyl group, gives higher yields and diethyl mesoxalate[149] leads to products even under irradiation.





$$C_6H_{12} + EtO_2C{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}CO_2Et \xrightarrow[50\%]{h\nu} C_6H_{11}\overset{\overset{\displaystyle OH}{|}}{C}(CO_2Et)_2$$

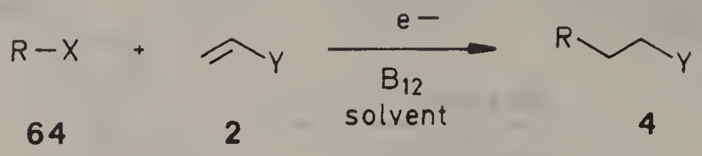
Stork[150] used tert-butylisonitrile in a multistep synthesis even though isonitriles react relatively slowly[151] with alkyl radicals.



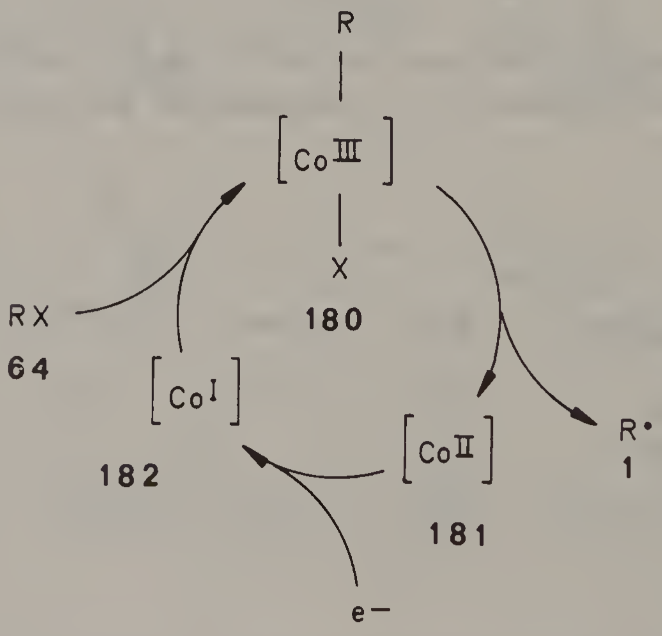
Many organometallics **179** (e.g. M = Li[152], Mg[153], Zn[154], Cu[155], Co[156]) react with alkenes **2** to form addition products **4**.

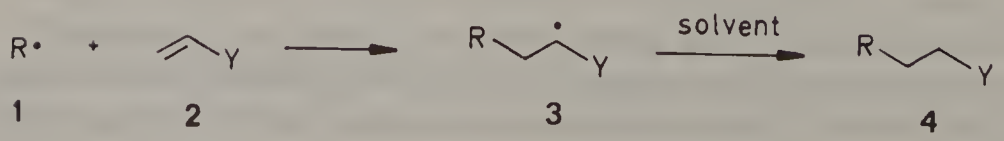
179 **2** **4**

In most of these reactions alkyl radicals are not involved. But Scheffold[157] has shown that the vitamin B_{12} catalyzed reaction of **64** with alkene **2** occurs via radicals which might be still in tight contact with the cobalt atom of vitamin B_{12}.

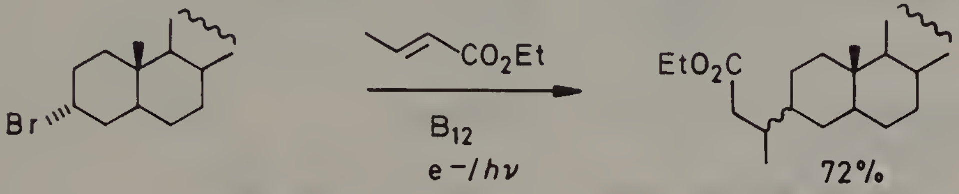


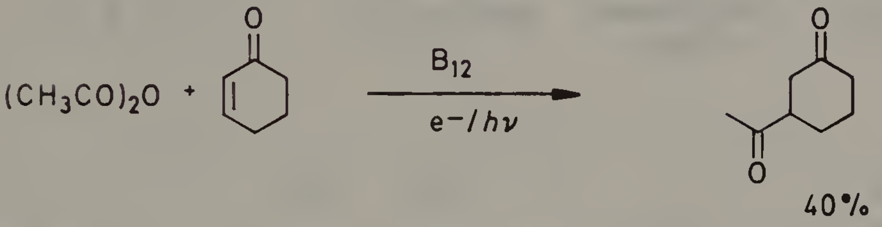
The reaction occurs via cleavage of the Co-C bond of alkyl cobalamine **180** leading to radical **1**, which is trapped by alkene **2**. Abstraction of a hydrogen atom, perhaps from the solvent, yields product **4**. The alkyl cobalamine **180** is regenerated by reduction (**181**→**182**) and alkylation (**182**→**180**).





As alkyl radical precursors alkyl halides[157,158] can be used, acid anhydrides[159] lead to acyl radicals. The reduction is carried out either at the cathode or with Zn, irradiation facilitates the Co-C bond cleavage.





G. Radical-Radical Reactions

In the preceding sections of this chapter the formation of C-C bonds took place in reactions between radicals and non-radicals. It is, however, also possible to use radical combination reactions to form C-C bonds. For a successful synthesis, it is important to work in the absence of reactive molecules other than those which form the combining radicals.

1. Oxidative coupling

a. Oxidation of anions

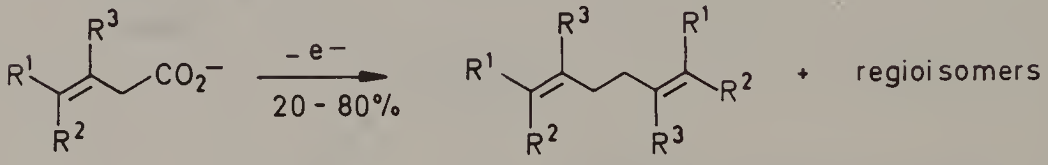
Kolbe electrolysis of carboxylates leads to radicals which yield dimers by recombination.[118,160] Substituents such as esters,[161] ketones,[162] and fluorides[163] are tolerated in these syntheses; polyhalogenated[164] and allylic acids[118,165] can also be used.

$$R{-}CO_2^- \xrightarrow[-\,CO_2]{-\,e^-} R^\bullet \longrightarrow R{-}R$$

$$X(CH_2)_nCO_2^- \xrightarrow{-\,e^-} X(CH_2)_{2n}X$$

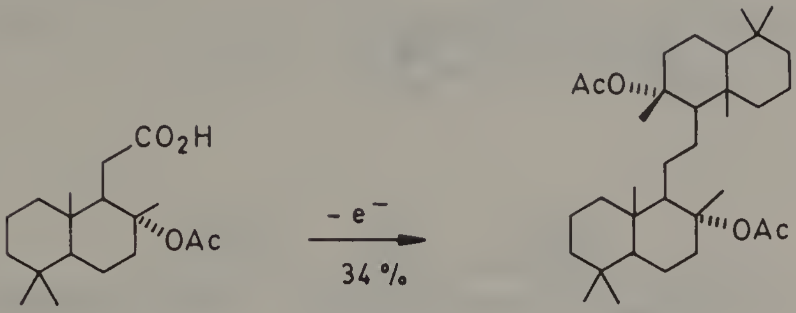
$X = CH_3, CO_2R, COR, OAc, F;\ n = 4 - 16 : 45 - 95\%$

$$FCCl_2CO_2^- \xrightarrow[45\%]{-\,e^-} FCCl_2{-}CCl_2F$$



With allylcarboxylic acids, the configuration at the alkene is retained to a large extent, but the radicals recombine from both sides of the allylic system.[118]

Kolbe electrolysis has been used in a variety of syntheses, for example, in the synthesis of a pentacyclosquallene[166] or α-onocerin.[167] Dimerization of **183** and **184**, respectively, are the main steps.



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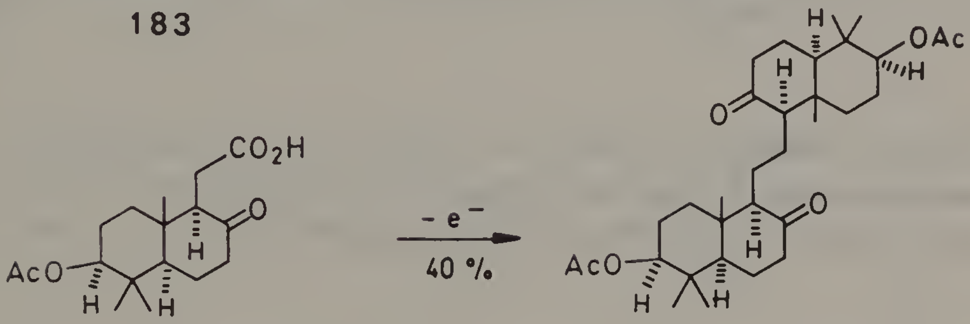
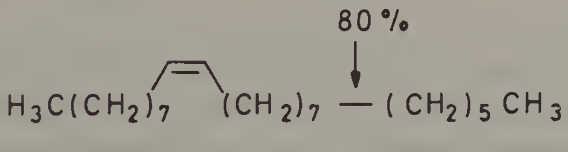
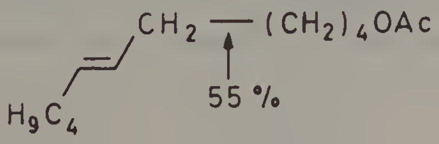
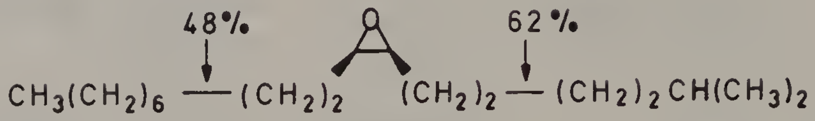


184

Mixed Kolbe electrolysis leads to unsymmetrical compounds, whose yields are increased if an excess of one of the acids is used. Schäfer[168] has synthesized pheromones under these conditions.





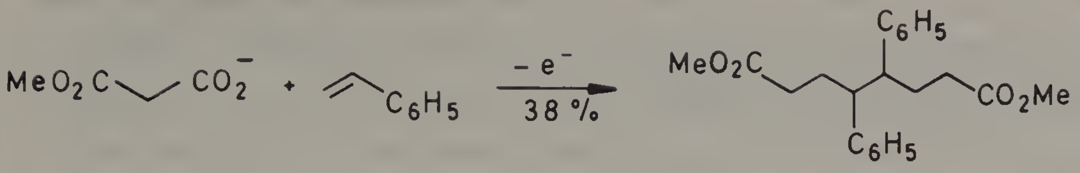


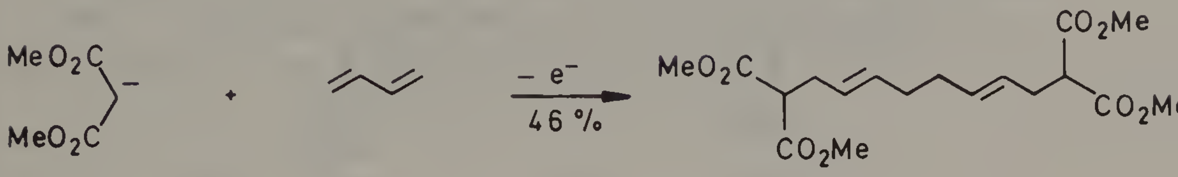
Not only carboxylic acids, but also anions of C-H acidic compounds like 1,3-dicarbonyls,[169] nitro compounds,[170] and acetylenes[171] undergo coupling reactions.

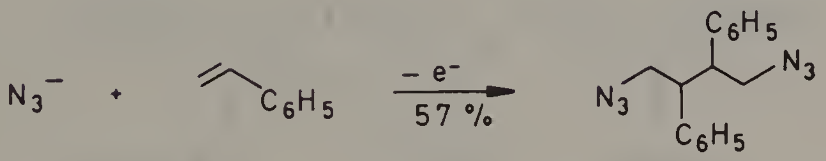
$$O_2N\overset{-}{C}H_2 \xrightarrow{-e^-} O_2NCH_2CH_2NO_2$$

$$RC{\equiv}C^- \xrightarrow{-e^-} RC{\equiv}C-C{\equiv}CR$$

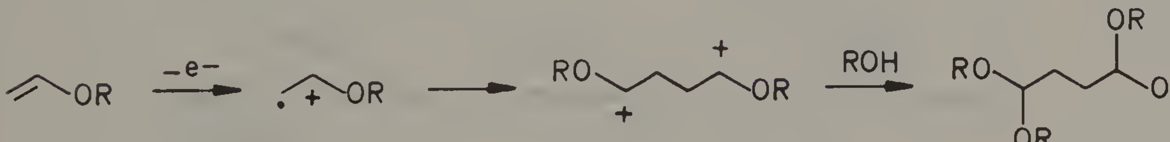
The radicals generated from carbanions by electrolysis can be trapped in the presence of electron-rich alkenes. With enolethers, the adduct radicals are rapidly oxidized to cations which react with the solvent to give the products.[119] Adduct radicals from styrene and butadiene, on the other hand, undergo dimerization faster than oxidation.[172]







Electron-rich alkenes, like enolethers, yield oxidized dimers presumably via recombination of radical cations **185** and subsequent reaction with alcohol.[173]



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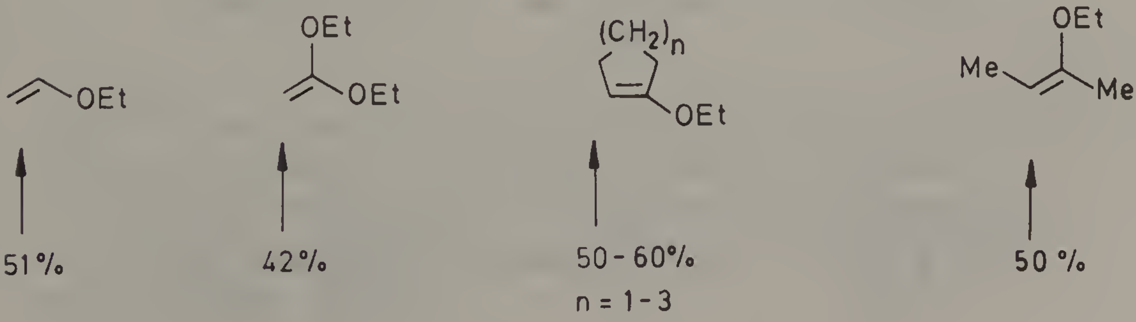
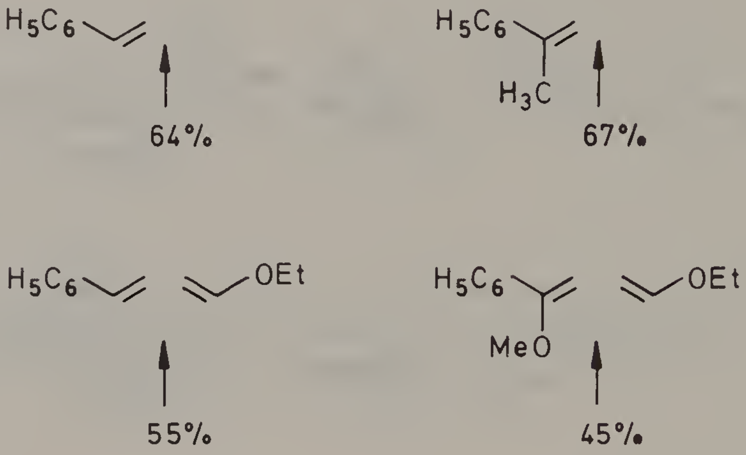
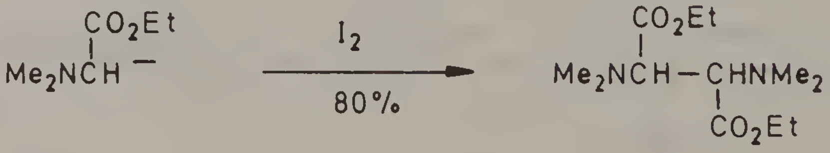


Phenylsubstituted or 1,1-dialkylated alkenes can also be used for these reactions.[118] Coelectrolysis of different alkenes gives unsymmetrical dimers.[174]

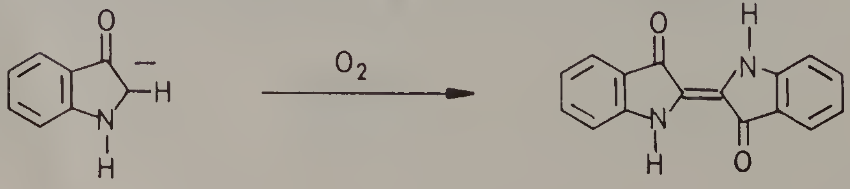


Oxidation of anions to radicals that recombine to dimers is accomplished not only by electrolysis, but also by oxidants like I_2,[175] O_2,[176] or metal salts.[177]



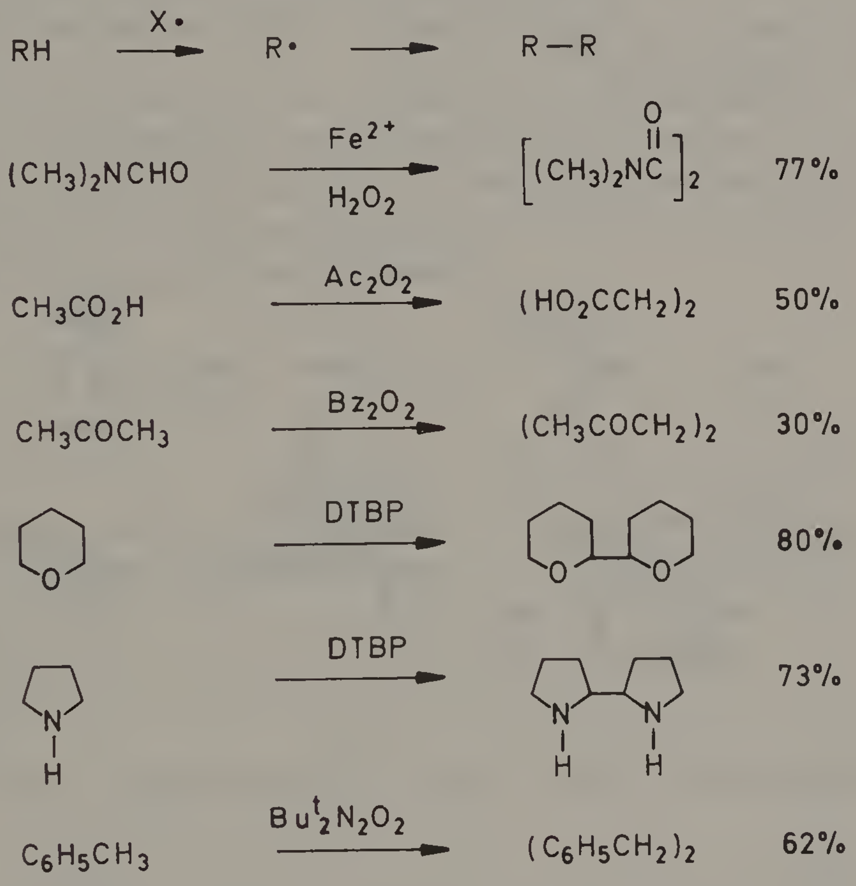
$$Me_2N\overset{CO_2Et}{\overset{|}{C}}H^- \xrightarrow[80\%]{I_2} Me_2N\overset{CO_2Et}{\overset{|}{C}}H{-}\underset{CO_2Et}{\underset{|}{C}}HNMe_2$$

$$(EtS)_3C^- \xrightarrow[86\%]{I_2} (EtS)_3C{-}C(SEt)_3$$

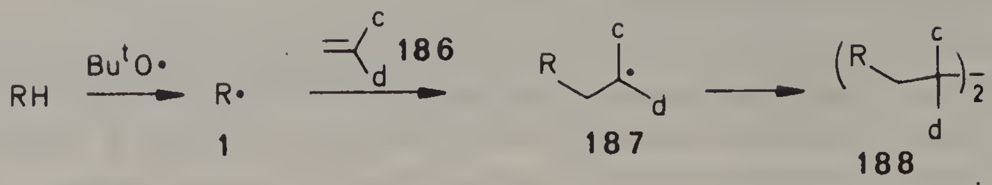


b. Dehydrodimerization

Formation of alkyl radicals from hydrocarbons is possible via hydrogen atom abstraction with initiators such as di-tert-butyl peroxide, benzoyl peroxide, acetyl peroxide, Fenton's reagent, or tert-butyl-hyponitrite. Hydrocarbons, alcohols, ethers, aldehydes, ketones, acids, and their derivatives have been used as hydrogen donors. Recombination reactions of the intermediate radicals yield the dimers.[178]



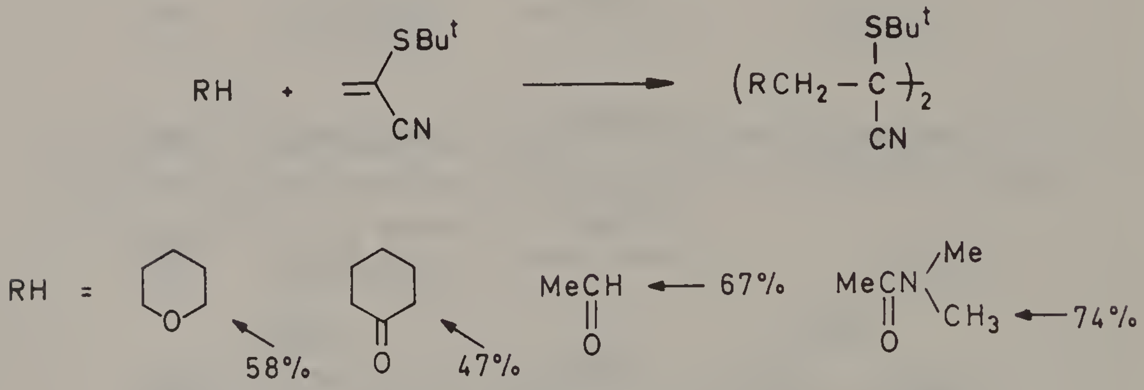
Viehe[179] has introduced a new synthetic method involving the trapping of radicals **1** with alkenes **186** to form captodative[179,180] substituted radicals **187**. These radicals are too unreactive for further attack at alkene **186** and, therefore, dimerize to **188**.



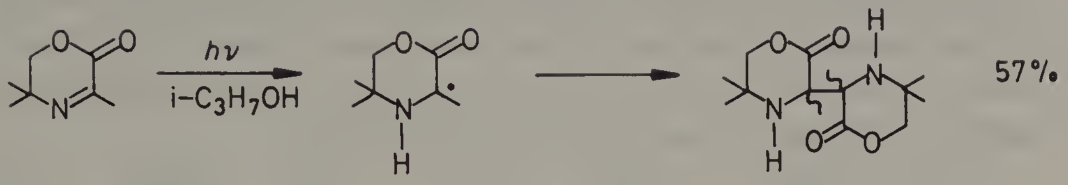
c = *capto (electron-withdrawing) substituent*

d = *dative (electron-donating) substituent*

Very effective in these syntheses is the combination of RS and CN substituents.[181]

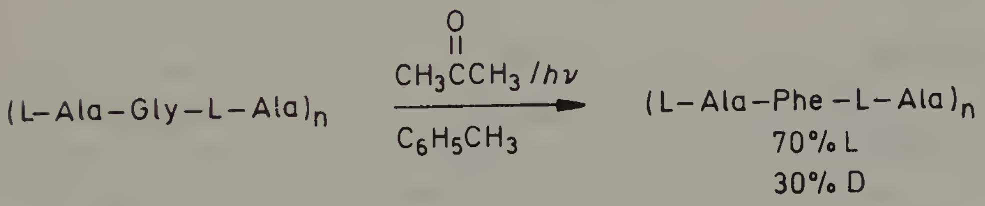


Hydrogen abstraction can also occur with photolytically excited ketones and imines. Thus, Koch[182] has shown that iminolactone **189** dimerizes to **191** via radical **190**, which is formed by hydrogen donation from isopropyl alcohol to the triplet state of **189**. At -15°C the DL:meso-ratio is 0.45.



189 **190** **191**

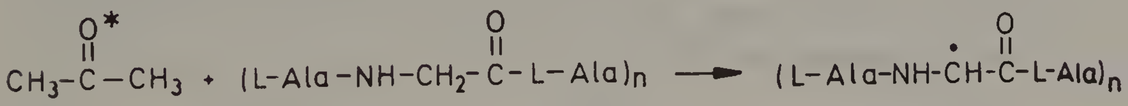
Elad[183] used photolytically excited ketones to abstract hydrogen from glycine, which combines with radicals to form new amino acids. In this way he synthesized peptide **193** from **192** via radicals **194** and **195** and observed a small optical induction of the C-C bond formation.



$$(\text{L-Ala-Gly-L-Ala})_n \xrightarrow[C_6H_5CH_3]{CH_3\overset{\overset{O}{\|}}{C}CH_3\,/h\nu} (\text{L-Ala-Phe-L-Ala})_n$$

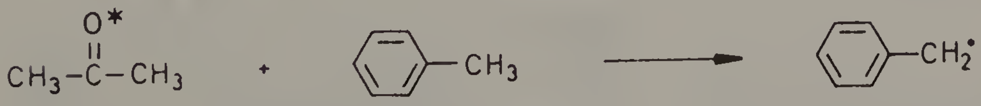
70% L
30% D

192 **193**



$$CH_3-\overset{\overset{O^*}{\|}}{C}-CH_3 + (\text{L-Ala-NH-}CH_2\text{-}\overset{\overset{O}{\|}}{C}\text{-L-Ala})_n \longrightarrow (\text{L-Ala-NH-}\dot{C}H\text{-}\overset{\overset{O}{\|}}{C}\text{-L-Ala})_n$$

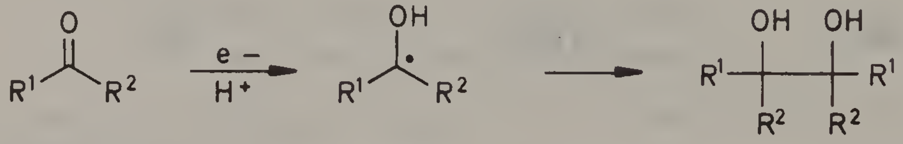
194



195

2. Reductive coupling

Reductive coupling of carbonyl compounds via radical-radical recombination is mainly accomplished either electrolytically at the cathode or by metals and metal ions. Thus, the cathodic reduction of ketones in an acidic solution yields hydroxyalkyl radicals **196** that dimerize to pinacols.[184]



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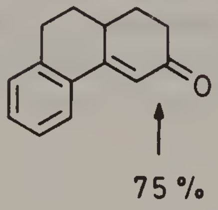
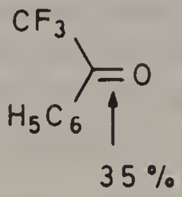
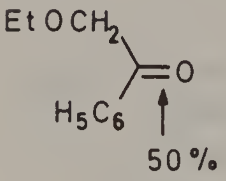
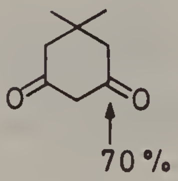
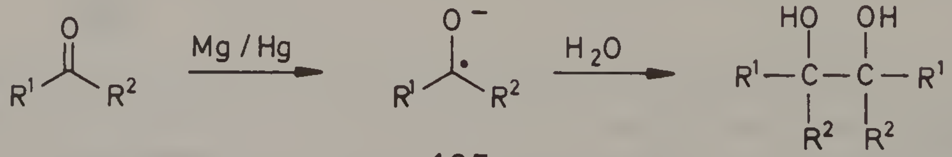








The pinacol dimerization can also be carried out with metals like Mg or Mg/Hg. Under these conditions, ketyl radicals **197** are the intermediates.[185]



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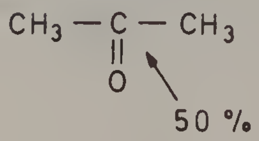
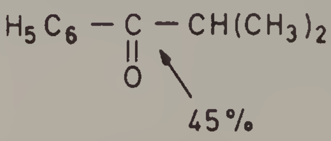
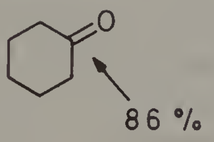


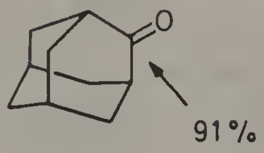
$CH_3-C(=O)-CH_3$

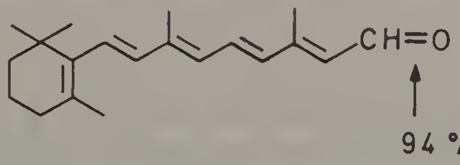


$H_5C_6-C(=O)-CH(CH_3)_2$

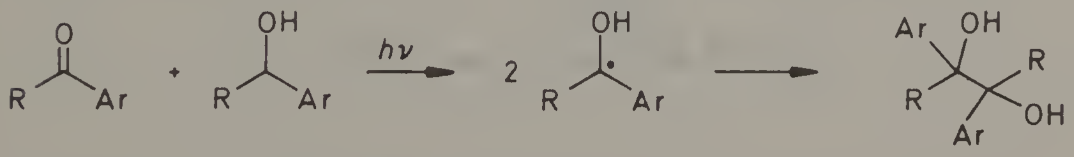
Ti(III) induced coupling of carbonyl compounds is believed to proceed via ketyl radical intermediates which dimerize to pinacol dianions to give alkenes after deoxygenation on the Ti(0) surface.[186]

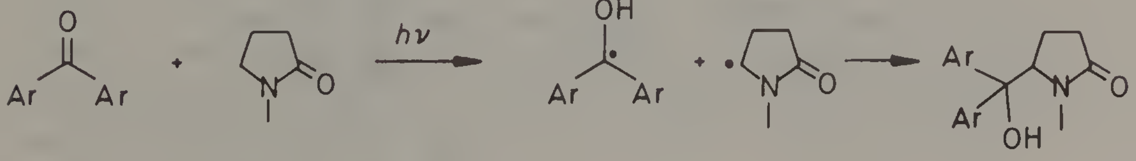




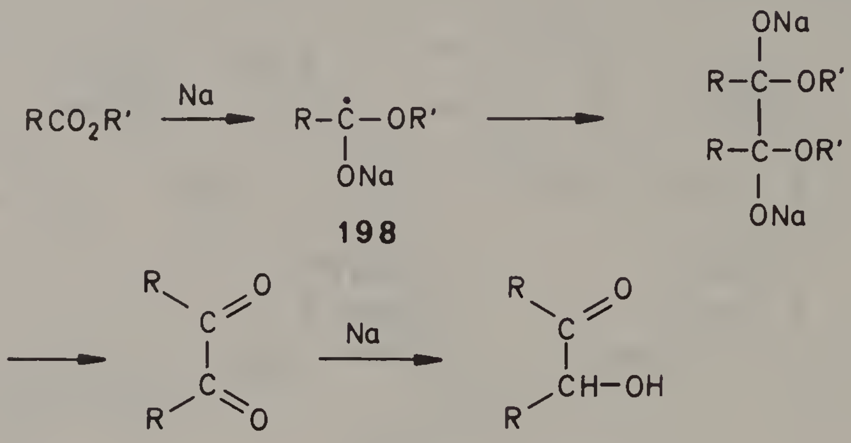


Pinacols are formed by the photoreduction of aryl ketones in the presence of suitable hydrogen donors.[187] Ketones in the triplet state abstract a hydrogen atom from the alcohol and recombination of the newly formed radicals gives the pinacols. The synthesis of mixed recombination products is also possible.[188]





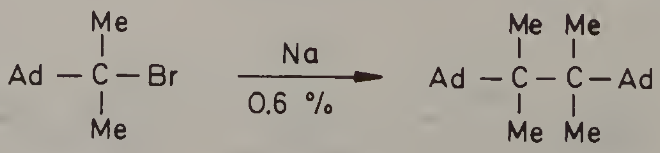
In the acyloin reaction, electrons are transferred from Na to esters. The resulting radical salts **198** recombine to give α-diketones which are reduced to acyloins.[189]



Cathodic dimerization of electron-poor alkenes, e.g. the synthesis of adipodinitrile from acrylonitrile, which often occurs via anions and Michael addition,[118] will not be discussed here.

The reductive coupling of alkyl halides with metals, for example the Wurtz reaction, or with anions occurs in some cases via radicals generated by single electron transfer steps.[190] These radical C-C bond forming reactions make possible the formation of very strained compounds.[191]

$$\mathrm{R{-}X} \xrightarrow{\mathrm{M}} \mathrm{R\cdot} \longrightarrow \mathrm{R{-}R}$$

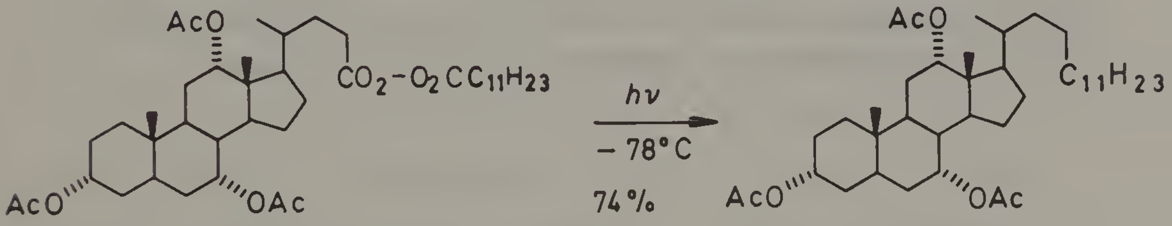


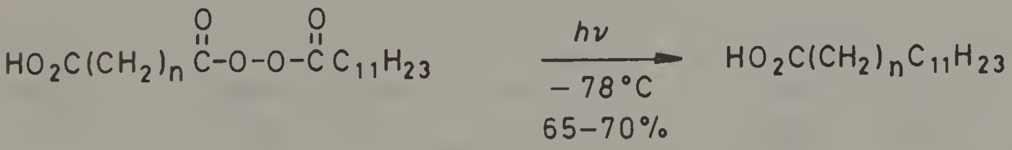
$$\mathrm{Ad{-}C(Me)_2{-}Br} \xrightarrow[0.6\ \%]{\mathrm{Na}} \mathrm{Ad{-}C(Me)_2{-}C(Me)_2{-}Ad}$$

In many cases the mechanism is not known in detail. Radical and ionic reaction steps compete with each other and product mixtures are formed.[190]

3. Diacylperoxides and azo compounds

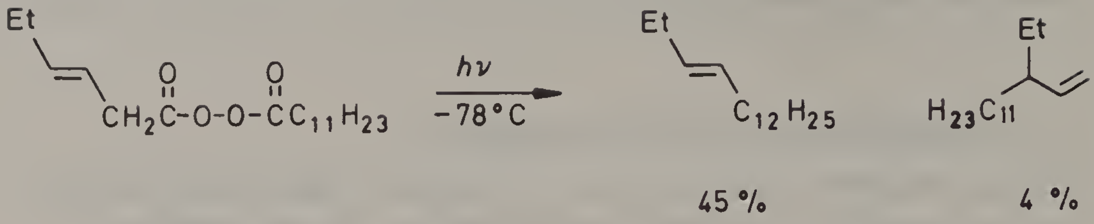
Photolysis and thermolysis of initiators like diacylperoxides or azo compounds produce radicals which, in the absence of suitable traps, give combination and disproportionation products. Synthetic applications of these reactions for intermolecular formation of C-C bonds are scarce because they have few advantages over other reactions such as the Kolbe electrolysis of acids. One advantage, however, is the greater selectivity of the low temperature photolysis of mixed diacylperoxides in the solid state.[192]

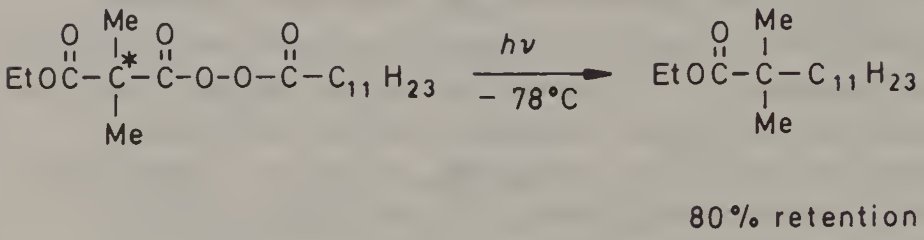




$$HO_2C(CH_2)_n\overset{O}{\overset{\|}{C}}-O-O-\overset{O}{\overset{\|}{C}}C_{11}H_{23} \xrightarrow[-78\,°C \;\; 65-70\%]{h\nu} HO_2C(CH_2)_nC_{11}H_{23}$$

Allyl radicals formed in the solid state have restricted mobility and react with a much higher regioselectivity than those formed under the conditions of the Kolbe electrolysis. Even radicals with three different substituents at the radical center react with high retention if chiral diacylperoxides are used as precursors.[192]



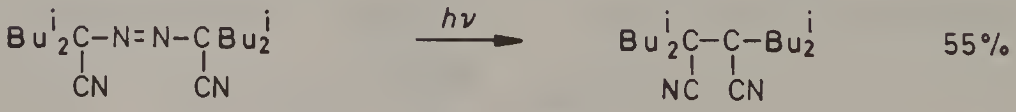


$$EtO\overset{O}{\overset{\|}{C}}-\underset{Me}{\overset{Me}{C^*}}-\overset{O}{\overset{\|}{C}}-O-O-\overset{O}{\overset{\|}{C}}-C_{11}H_{23}\xrightarrow[-78°C]{h\nu}EtO\overset{O}{\overset{\|}{C}}-\underset{Me}{\overset{Me}{C}}-C_{11}H_{23}$$

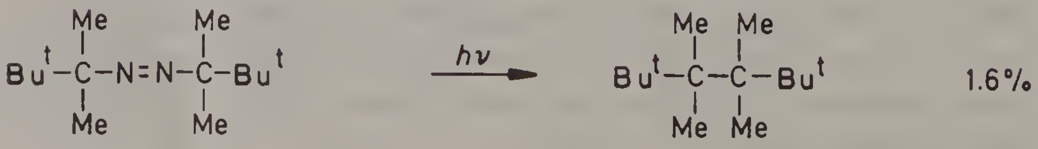
80% retention

Azo compounds are mainly used in cyclization reactions, but Rüchardt[193] has shown that in cases where other synthetic routes because of steric effects fail, azo compounds still give C-C bond formation products.

$$Bu^t_2CH-N{=}N-CHBu^t_2\xrightarrow{h\nu}Bu^t_2CH-CHBu^t_2\qquad 100\%$$



$$Bu^i_2\underset{CN}{C}-N{=}N-\underset{CN}{C}Bu^i_2\xrightarrow{h\nu}Bu^i_2\underset{NC}{C}-\underset{CN}{C}-Bu^i_2\qquad 55\%$$



$$Bu^t-\underset{Me}{\overset{Me}{C}}-N{=}N-\underset{Me}{\overset{Me}{C}}-Bu^t\xrightarrow{h\nu}Bu^t-\underset{Me}{\overset{Me}{C}}-\underset{Me}{\overset{Me}{C}}-Bu^t\qquad 1.6\%$$

The recombination of phenyl-substituted radicals with three different substituents often occurs with interesting diastereoselectivity [193] which is mainly caused by entropy effects. Porter[194] has demonstrated that the diastereoselectivity of the recombination of radicals with polar substituents can be increased in lipid bilayers.

REFERENCES

1. B. Giese, *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 771.
2. G.M. Whitesides, J. San Filippo, *J. Am. Chem. Soc.* **1970**, *92*, 6611; C.L. Hill, G.M. Whitesides, *J. Am. Chem. Soc.* **1974**, *96*, 870.
3. M. Devaud, *J. Organomet. Chem.* **1984**, *220*, C 27.
4. B. Giese, G. Kretzschmar, *Chem. Ber.* **1984**, 3160.
5. R.P. Quirk, R.E. Lea, *J. Am. Chem. Soc.* **1976**, *98*, 5973 ; G.A. Russell, D. Guo, *Tetrahedron Lett.* **1984**, *25*, 5239.
6. B. Giese, *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 553.
7. B. Giese, G. Kretzschmar, *Chem. Ber.* **1982**, *115*, 2012.
8. B. Giese, J. Meister, *Chem. Ber.* **1977**, *110*, 2588.
9. B. Giese, J.A. Gonzálex-Gómez, T. Witzel, *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 69.
10. C. Chatgilialoglu, K.U. Ingold, J.C. Scaiano, *J. Am. Chem. Soc.*, **1981**, *103*, 7739.
11. L.H. Johnston, J. Lusztyk, D.D.M. Wagner, A.N. Abeywickreyma, A.L.J. Beckwith, J.C. Scaiano, K.U. Ingold, *J. Am. Chem. Soc.* **1985**, *107*, 4594.
12. P. Pike, S. Hershberger, J. Hershberger, *Tetrahedron Lett.* **1985**, *26*, 6289.
13. H. Straub, K.P. Zeller, H. Leditschke in Houben-Weyl: *Methoden der Organischen Chemie*, Vol. 13/2b, Thieme, Stuttgart **1974**.

14. B. Giese, G. Kretzschmar, *Chem. Ber.* **1984**, *117*, 3175.

15. B. Giese, J. Meixner, *Tetrahedron Lett.* **1977**, 2783.

16. B. Giese, S. Lachhein, *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 768.

17. B. Giese, G. Kretzschmar, *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 965.

18. B. Giese, K. Heuck, *Chem. Ber.* **1979**, *112*, 3759; B. Giese, K. Heuck, *Tetrahedron Lett.* **1980**, *21*, 1829.

19. J. Barluenga, J. Lopez-Prado, P.J. Campos, G. Asensio, *Tetrahedron* **1983**, *39*, 2863; J. Barluenga, L. Ferrera; C. Nájera, M. Yus, *Synthesis* **1984**, 831.

20. B. Giese, T. Haßkerl, U. Lüning, *Chem. Ber.* **1984**, *117*, 859.

21. A.P. Kozikowski, T.R. Nieduzak, J. Scripko, *Organometallics* **1982**, 1, *675*.

22. R. Henning, H. Urbach, *Tetrahedron Lett.* **1983**, *24*, 5343.

23. B. Giese, K. Gröninger, *Tetrahedron Lett.* **1984**, *25*, 2743.

24. B. Giese, K. Heuck, *Chem. Ber.* **1981**, *114*, 1572.

25. S. Danishefsky, E. Taniyama, R.R. Webb, *Tetrahedron Lett.* **1983**, *24*, 11.

26. R.V. Stevens, K.F. Albizati, *J. Org. Chem.* **1985**, *50*, 632.

27. B. Giese, D. Bartmann, *Tetrahedron Lett.* **1985**, *26*, 1197.

28. B. Giese, D. Bartmann, unpublished results.

29. B. Giese, W. Zwick, *Chem. Ber.* **1979**, *112*, 3766; B. Giese, H. Horler, W. Zwick, *Tetrahedron Lett.* **1982**, *23*, 931.

30. B. Giese, W. Zwick, *Chem. Ber.* **1982**, *115*, 2526.

31. B. Giese, W. Zwick, *Tetrahedron Lett.* **1980**, *21*, 3569.

32. B. Giese, W. Zwick, *Chem. Ber.* **1983**, *116*, 1264; B. Giese, W. Zwick, unpublished results.

33. B. Giese, H. Horler, *Tetrahedron* **1985**, *41*, 4025.

34. D. Hoppe, *Angew. Chem. Int. Ed. Engl.* **1983**, *23*, 932.

35. B. Giese, H. Horler, *Tetrahedron Lett.* **1983**, *24*, 3221.

36. B. Giese, H. Horler, unpublished results.

37. H.O. House, L.J. Czuba, M. Gall, H.D. Olmstead, *J. Org. Chem.* **1969**, *34*, 2324.

38. D.A. Lindsay, J. Lusztyk, K.U. Ingold, *J. Am. Chem. Soc.* **1984**, *106*, 7087.

39. S. Wallowitz, J. Halpern, *J. Am. Chem. Soc.* **1984**, *106*, 8319.

40. B. Giese, U. Erfort, *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 130.

41. B. Giese, U. Erfort, *Chem. Ber.* **1983**, *116*, 1240.

42. B. Giese, R. Engelbrecht, U. Erfort, *Chem. Ber.* **1985**, *118*, 1289.

43. H.G. Kuivila, L.W. Menapace, C.R. Warner, *J. Am. Chem. Soc.* **1962**, *84*, 3584.

44. S.D. Burke, W.F. Fobare, D.M. Armistead, *J. Org. Chem.* **1982**, *47*, 3348.

45. B. Giese, J. Dupuis, *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 622.

46. J.Dupuis, B. Giese, D. Rüegge, H. Fischer, H.G. Korth, R. Sustmann, *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 896.

47. J. Dupuis, B. Giese, J. Hartung, M. Leising, H.G. Korth, R. Sustmann, *J. Am. Chem. Soc.* **1985**, *107*, 4332.

48. N. Ono, H. Miyake, A. Kamimura, I. Hamamoto, R. Tamura, A. Kaji, *Tetrahedron* **1985**, *41*, 4013.

49. B. Giese, D.B. Gerth, *J. Org. Chem.* **1986**, in press.

50. B. Giese, R. Rupaner, unpublished results.

51. R.M. Adlington, J.E. Baldwin, A. Basak, R.P. Kozyrod, *J. Chem. Soc. Chem. Commun.* **1983**, 944.

52. B. Giese, J. Dupuis, M. Leising, M. Nix, H.J. Lindner, *Carbohydr. Res.* **1986**, in press.

53. H.G. Korth, R. Sustmann, J. Dupuis, B. Giese, *J. Chem. Soc. Perkin Trans 2* **1986**, in press.

54. B. Giese, T. Witzel, *Angew. Chem. Int. Ed. Engl.* **1986**, in press.

55. B. Giese, K. Gröninger, *Tetrahedron Lett.* **1984**, *25*, 2743.

56. B. Giese, K. Gröninger, unpublished results.

57. B. Giese, H. Horler, M. Leising, *Chem. Ber.* **1986**, *119*, 444.

58. B. Giese, T. Witzel, unpublished results.

59. D.H.R. Barton, S.W. McCombi, *J. Chem. Soc. Perkin Trans.1* **1975**, 1574.

60. D.H.R. Barton, W.B. Motherwell in B.M. Trost, C.R. Hutchinson (Eds): *Organic Synthesis Today and Tomorrow*, Pergamon, Oxford 1981.

61. N. Ono, H. Miyake, R. Tamura, A. Kaji, *Tetrahedron Lett.* **1981**, *22*, 1705; N. Ono, R. Tamura, R. Tanikaga, A. Kaji, *J. Chem. Soc. Chem. Commun.* **1981**, 71.

62. D.D. Tanner, E.V. Blackburn, G.E. Diaz, *J. Am. Chem. Soc.* **1981**, *103*, 1557; G.A. Russell, D.F. Dedolph, *J. Org. Chem.* **1985**, *50*, 2498.

63. A.G. Davies, J.A.A. Hawari, C. Gaffney, P.G. Harrison, *J. Chem. Soc. Perkin Trans. 2* **1982**, 631.

64. J. Lusztyk, B. Maillard, D.A. Lindsay, K.U. Ingold, *J. Am. Chem. Soc.* **1983**, *105*, 3578.

65. B. Giese, B.E. Rückert, T. Witzel, unpublished results.

66. C.Chatgilialoglu, J.C. Scaiano, K.U. Ingold, *Organometallics* **1982**, 1, 466.

67. F.R. Cruickshank, S.W. Benson, *Int. J. Chem. Kinet.* **1969**, 1, 381; T.J. Burkey, A.L. Castelhano, D. Griller, F.P. Lossing, *J. Am. Chem. Soc.* **1983**, *105*, 4701; H. Birkhofer, H.D. Beckhaus, C. Rüchardt, *Tetrahedron Lett.* **1983**, *24*, 185.

68. D.F. McMillen, D.M. Golden, *Ann. Rev. Phys. Chem.* **1982**, *33*, 493; W. Barbe, H.D. Beckhaus, C. Rüchardt, *Chem. Ber.* **1983**, *116*, 1042.

69. K.W. Egger, A.T. Cocks, *Helv. Chim. Acta* **1973**, *56*, 1516.

70. C. Walling, E.S. Huyser, *Org. Reactions* **1963**, *13*, 91; D. Elad in O.L. Chapman: *Organic Photochemistry*, Vol. 2, Marcel Dekker, New York 1969, p. 168.

71. W.H. Urry, F.W. Stacey, E.S. Huyser, O.O. Juveland, *J.Am. Chem. Soc.* **1954**, *76*, 450.

72. G.O. Schenck, G. Koltzenburg, H. Grossmann, *Angew. Chem.* **1957**, *69*, 177.

73. B. Fraser-Reid, N.L. Holder, D.R. Hicks, D.L. Walker, *Can. J. Chem.* **1977**, *55*, 3978.

74. R.L. Jacobs, G.G. Ecke, *J. Org. Chem.* **1963**, *28*, 3036.

75. B. Fraser-Reid, R.C. Anderson, D.R. Hicks, D.L. Walker, *Can. J. Chem.* **1977**, *55*, 3986.

76. T.J. Wallace, R.J. Gritter, *J. Org. Chem.* **1962**, *27*, 3067.

77. F. Minsci, *Top. Curr. Chem.* **1976**, *62*, 1.

78. P. Gottschalk, D.C. Neckers, *J. Org. Chem.* **1985**, *50*, 3498.

79. M.S. Kharasch, W.H. Urry, B.M. Kuderna, *J. Org. Chem.* **1949**, *14*, 248; T.M. Patrick, *J. Org. Chem.* **1952**, *17*,1009.

80. W.H. Urry, E.S. Huyser, *J. Am. Chem. Soc.* **1953**, *75*, 4876; L. Friedman, H. Shechter, *Tetrahedron Lett.* **1961**, 238.

81. G.I. Nikishin, G.V. Somov, A.D. Petrov, *Izvest. Akad. Nauk* **1961**, 2065; G.I. Nikishin, G.V. Somov, A.D. Petrov, *Dokl. Akad. Nauk* **1961**, *136*, 1099.

82. M. Hájek, J. Málek, *Synthesis*, **1976**,*8*, 315.

83. M.G. Vinogradov, S.P. Verenchikov, G.I. Nikishin, *J. Org. Chem. USSR* **1972**, 8, 2515.

84. A.D. Petrov, G.I. Nikishin, Y.N. Ogibin, *Dokl. Akad. Nauk* **1960**, *131*, 580.

85. G.I. Nikishin, Y.N. Ogibin, A.D. Petrov, *Dokl. Akad. Nauk* **1961**, *136*, 1326; J.C. Allen, J.I.G. Cadogan, B.W. Harris, D.H. Hey, *J. Chem. Soc.* **1962**, 4468; M. Cazaux, R. Lalande, *Bull. Soc. Chim. Fr.* **1971**, 2, 461.

86. D. Elad, R.D. Youssefyeh, *J. Chem. Soc. Chem. Commun.* **1965**, 7.

87. W.H. Urry, O.O. Juveland, *J. Am. Chem. Soc.* **1958**, *80*, 3323.

88. J. Sinnreich, D. Elad, *Tetrahedron* **1968**, *24*, 4509.

89. F. Minisci, *Acc. Chem. Res.* **1975**, 165.

90. J. Metzger, J. Hartmanns, P. Köll, *Tetrahedron Lett.* **1981**, *22*, 1891.

91. M.S. Kharasch, E.V. Jensen, W.H. Urry, *Science* **1945**, *102*, 128.

92. G. Sosnovsky, *Free Radicals in Preparative Organic Chemistry*, Macmillan, London 1964.

93. M.M. Martin, G.J. Gleicher, *J. Am. Chem. Soc.* **1964**, *86*, 233; J.M. Tedder, *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 401.

94. P. Boldt, L. Schulz, J. Etzemüller, *Chem. Ber.* **1967**, *100*, 1281; M.H. Treder, H. Kratzin, H. Lübbecke, C.Y. Yang, P. Boldt, *J. Chem. Res. (S)* **1977**, 165.

95. D.M. Oldroyd, G.S. Fisher, L.A. Goldblatt, *J. Am. Chem. Soc.* **1950**, *72*, 2407; G. Dupont, R. Dulou, G. Clement, *Bull. Soc. Chim. Fr.* **1950**, 1056.

96. D.I. Davies in: *Essays on Free-Radical Chemistry*, Special Publication No. 24 of the Chemical Society, Burlington House, London 1970, p. 201.

97. B. Giese, K. Jay, *Chem. Ber.* **1977**, *110*, 1364.

98. D. Arlt, M. Jautelat, R. Lantzsch. *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 703.

99. P. Martin, E. Steiner, D. Bellus, *Helv. Chim. Acta* **1980**, *63*, 1947.

100. P. Martin, E. Steiner, J. Streith, T. Winkler, D. Bellus, *Tetrahedron* **1985**, *41*, 4057.

101. G.A. Kraus, K. Landgrebe, *Tetrahedron* **1985**, *41*, 4039.

102. D.H.R. Barton, D. Crich, G. Kretzschmar, *Tetrahedron Lett.* **1984**, *25*, 1055.

103. D.H.R. Barton, D. Crich, G. Kretzschmar, *J. Chem. Soc. Perkin Trans. 1* **1986**, 39.

104. D.H.R. Barton, H. Togo, S.Z. Zard, *Tetrahedron* **1985**, *41*, 5507.

105. D.H.R. Barton, H. Togo, S.Z. Zard, *Tetrahedron Lett.***1985**, *26*, 6349.

106. D.H.R. Barton, D. Crich, *Tetrahedron Lett.* **1985**, *26*, 757.

107. H.C. Brown, M.M. Midland, *Angew. Chem. Int. Ed. Engl.* **1972**, 11, 692.

108. H.C. Brown, E. Negishi, *J. Am. Chem. Soc.* **1971**, *93*, 3777; H.C. Brown, G.W. Kabalka, W.M. Rathke, M.M. Rogić, *J. Am. Chem. Soc.* **1968**, *90*, 4165.

109. H.C. Brown, M.W. Rathke, G.W. Kabalka, M.M. Rogić, *J. Am. Chem. Soc.* **1968**, *90*, 4165.

110. H. C. Brown, G.W. Kabalka, *J. Am. Chem. Soc.* **1970**, *92*, 712.

111. J.K. Kochi, *Acc. Chem. Res.* **1974**, *7*, 351.

112. E.I.Heiba,R.M. Dessau, W.J. Koehl, *J. Am. Chem. Soc.* **1968**, *90*, 5905; E. Heiba, R.M. Dessau, P.G. Rodewald, *J. Am. Chem. Soc.* **1974**, *96*, 7977.

113. W.E. Fristad, J.R. Peterson, A.B. Ernst, *J. Org. Chem.* **1985**, *50*, 3143.

114. E. Heiba, R.M. Dessau, *J. Org. Chem.* **1974**, *39*, 3456.

115. E.J. Corey, M.C. Kang, *J. Am. Chem. Soc.* **1984**, *106*, 5384; E.J. Corey, A.W. Gross, *Tetrahedron Lett.* **1985**, *26*, 4291; W.E. Fristad, S.S. Hershberger, *J. Org. Chem.* *1985*, *50*, 1026.

116. G.I. Nikishin, M.G. Vinogradov, T.M. Fedorova, *J. Chem. Soc. Chem. Commun.* **1973**, 693; J.Y. Lallemand, *Tetrahedron Lett.* **1975**, 1217; M.E. Kurz, L. Reif, T. Tantrarat, *J. Org. Chem.* **1983**, *48*, 1373.

117. F. Minisci, R. Galli, M.Cecere, V. Malatesta, T. Caronna, *Tetrahedron Lett.* **1968**, 5609; F. Minisci, P. Zammori, R. Barnardi, M. Cecere, R. Galli, *Tetrahedron* **1970**, *26*, 4153; F. Minisci, *Synthesis* **1973**, 1.

118. H.J. Schäfer, *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 911.

119. H.J. Schäfer, A. Al Azrak, *Chem. Ber.* **1972**, *105*, 2398.

120. D. Veltwisch, K.D. Asmus, *J. Chem. Soc. Perkin Trans. 2* **1982**, 1143; G.A. Russell, D. Guo, *Tetrahedron Lett.* **1984**, *25*, 5239.

121. R.C. Kerber, G.W. Urry, N. Kornblum, *J. Am. Chem. Soc.* **1965**, *87*, 4520; N. Kornblum, W.J. Kelly, M.M. Kestner, *J. Org. Chem.* **1985**, *50*, 4720; N. Kornblum, *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 734.

122. G.A. Russell, W.C. Danen, *J. Am. Chem. Soc.* **1966**, *88*, 5663.

123. J.K. Kim, J.F. Bunnett, *J. Am. Chem. Soc.* **1970**, *92*, 7463; R.A. Rossi, R.H. de Rossi, *Aromatic Substitution by the $S_{RN}1$ Mechanism*, ACS Monograph 178, Washington 1983.

124. B. Aebischer, R. Meuwly, A. Vasella, *Helv. Chim. Acta* **1984**, *67*, 2236.

125. G.A. Russell, J. Hershberger, K. Owens, *J.Am. Chem. Soc.* **1979**, *101* 1312; G.A. Russell, J. Hershberger, *J. Organomet. Chem.* **1982**, *225*, 43; G.A. Russell, R.K. Khanna, *Tetrahedron* **1985**, *41*, 4133.

126. See also: G.A. Russell, F. Ros, *J. Am. Chem. Soc.* **1985**, *107*, 2506; G.A. Russell, D.F. Dedolph, *J. Org. Chem.* **1985**, *50*, 2378.

127. G.E. Keck, J.B. Yates, *J. Am. Chem. Soc.* **1982**, *104*, 5829.

128. G.E. Keck, E.J. Enholm, J.B. Yates, M.R. Wiley, *Tetrahedron* **1985**, *41*, 4079.

129. R.R. Webb, S. Danishefsky, *Tetrahedron Lett.* **1983**, *24*, 1357.

130. G.A. Keck, D.F. Kachensky, E.J. Enholm, *J. Org. Chem.* **1985**, *50*, 4317.

131. B. Giese, K. Gröninger, R. Sustmann, H.G. Korth, unpublished results.

132. J.E. Baldwin, D.R. Kelly, C.B. Ziegler, *J. Chem. Soc. Chem. Commun.* **1984**, 133.

133. G.A. Russell, H. Tashtoush, P. Ngoviwatchai, *J. Am. Chem. Soc.* **1984**, *106*, 4622.

134. T.T.Tsou, M. Loots, J. Halpern, *J. Am. Chem. Soc.* **1982**, *104*, 623; H.B. Gjerde, J.H. Espenson, *Organometallics* **1982**, *1*, 435.

135. M. Veher, K.N.V. Duong, F. Gaudemer, A. Gaudemer, *J. Organomet. Chem.* **1980**, *177*, 231; A.Bury, M.D. Johnson, *J. Chem. Soc. Chem. Commun.* **1980**, 498; M.D. Johnson, *Acc. Chem. Res.* **1983**, *16*, 343.

136. A. Gaudemer, K. Nguyen-Van-Duong, N. Shahkarami, S.S. Achi, M. Frostin-Rio, D. Pujol, *Tetrahedron* **1985**, *41*,4095.

137. S.N. Lewis, J.J. Miller, S. Winstein, *J. Org. Chem.* **1972**, *37*, 1478.

138. G.E. Keck, J.H. Byers, *J. Org. Chem.* **1985**, *50*, 5442.

139. D.H.R. Barton, D. Crich, *Tetrahedron Lett.* **1984**,*25*, 2787.

140. T.T. Tidwell in W.A. Pryor: *Organic Free Radicals*, ACS Symp. Ser. 69, **1978**, p. 102.

141. B. Maillard, A. Kharrat, F. Rakotomanana, E. Montaudon, C. Gardrat, *Tetrahedron* **1985**, *41*, 4047.

142. K.U. Ingold, B.P. Roberts: *"Free Radical Substitution Reactions"*, Wiley, New York 1971; A.J. Bloodworth, A.G. Davies, I.M. Griffin, B. Muggleton, B.P. Roberts,

J. Am. Chem. Soc. **1974**, *96*, 7599; N.A. Porter, J.R. Nixon, *J. Am. Chem. Soc.* **1978**, *100* 7116; E.J. Corey, G. Schmidt, K. Shimoji, *Tetrahedron Lett.* **1983**, *24*, 3169.

143. P.I. Abell in C.H. Bamford, C.F.H. Tipper (ed): *Comprehensive Chemical Kinetics*, Vol. XVIII, Elsevier, Amsterdam, 1976, p. 111.

144. H.M. Bartels, P. Boldt, *Liebigs Ann. Chem.* **1981**, 40; A. Bury, C.J. Cooksey, T. Funabiki, B.D. Gupta, M.D. Johnson, *J. Chem. Soc. Perkin Trans. 2* **1979**, 1050.

145. P.G. Gassman, J.L. Smith, *J. Org. Chem.* **1983**, *48*, 4438.

146. H. Knoll, *Z. Chem.* **1982**, *22*, 245.

147. M. Oyama, *J. Org. Chem.* **1965**, *30*, 2429; J. Kollar, U.S. Patent 183537, **1980**.

148. W.G. Bentrude, K.R. Darnall, *J. Am. Chem. Soc.* **1968**, *90*, 3588; F. Minisci, R. Galli, M. Cecere, V. Malatasta, T. Caronna, *Tetrahedron Lett.* **1968**, 5609; A. Citterio, L. Filippini, unpublished results.

149. C. Pac, H. Sakurai, K. Shima, Y. Ogata, *Bull. Chem. Soc. Jap.* **1975**, *48*, 277.

150. G. Stork, P.M. Sher, *J.Am. Chem. Soc.* **1986**, *108*, 302.

151. D.M. Blum, B.P. Roberts, *J. Chem. Soc. Perkin Trans. 2* **1978**, 1313.

152. J. Luchetti, A. Krief, *Tetrahedron Lett.* **1978**, 2697; B. Dechamps, M.C. Roux-Schmitt, L. Wartski, *Tetrahedron Lett.* **1979**, 1377; C.A. Brown, A. Yamaichi, *J. Chem. Soc. Chem. Commun.* **1979**, 100; Y. Tamaru, T. Harada, H. Iwamoto, Z. Yoshida, *J. Am. Chem. Soc.* **1978**, *100*, 5221; M.R.Binns, R.K. Haynes, T.L. Houston, R. Jackson, *Tetrahedron Lett.* **1980**, 573; N. Seuron, L. Wartski, J. Seyden-Penne, *Tetrahedron Lett.* **1981**, *22*, 2175; J. Lucchetti, A. Krief *Tetrahedron Lett.* **1981**, *22*, 1623.

153. G. Stork, G.L. Nelsen, F. Rouessac, O. Gringore, *J. Am. Chem. Soc.* **1971**, *93*, 3091; J.E. McMurry, W.A. Andrus, J.H. Musser, *Synth. Commun.* **1978**, *8*, 53; M.P. Cooke, *Tetrahedron Lett.* **1979**, 2199; S.H. Liu, *J. Org. Chem.* **1977**, *42*, 3209.

154. J. Gilman, R.H. Kirby, *J. Am. Chem. Soc.* **1941**, *63*, 2046; T. Caronna, A. Citterio, A. Clerici, R. Galli, *Org. Prep. Proced. Int.* **1974**, 6, 299; M. Isobe, S. Kondo, N. Nagasawa, T. Goto, *Chem.Lett.*​**1977**, 679; T. Shono, I. Nishiguchi, M. Sasaki, *J. Am. Chem. Soc.* **1978**, 4314; C. Petrier, J.C. de Souza Barbosa, C. Dupuy, *100*, J.L. Luche, *J. Org. Chem.* **1985**, *50*, 5761.

155. G.H. Posner: *An Introduction to Synthesis Using Organocopper Reagents*, Wiley, New York 1980.

156. R. Scheffold, M. Dike, S. Dike, T. Herold, L. Walder, *J. Am. Chem. Soc.* **1980**, *102*, 3642.

157. R. Scheffold, *Chimia* **1985**, *39*, 203.

158. S. Albrecht, R. Scheffold, *Chimia* **1985**, *39*, 211; A. Ruhe, L. Walder, R. Scheffold, *Helv. Chim. Acta* **1985**, *39*, 1301.

159. R. Scheffold, R. Orlinski, *J. Am. Chem. Soc.* **1983**, *105*, 7200.

160. S.Torii: *Electroorganic Synthesis*, Verlag Chemie, Weinheim 1985.

161. L. Eberson, *Acta Chem. Scand.* **1959**, *13*, 40; B.C.L. Weedon, *Adv. Org. Chem.* **1963**, 1, 1; J. Haufe, F. Beck, *Chem. Ing. Tech.* **1970**, *42*, 170.

162. F. Fichter, S. Lurie, *Helv. Chim. Acta* **1933**, *16*, 885.

163. F.L. Pattison, J.B. Stothers, R.G. Woolford, *J.Am. Chem. Soc.* **1956**, *78*, 2255.

164. J.P. Waefler, P. Tissot, *Electrochim. Acta* **1978**, *23*, 899.

165. R.F. Garwood, N. ud Din, C.J. Scott, B.C.L. Weedon, *J. Chem. Soc. Perkin Trans. 1* **1973**, 2714.

166. E.J. Corey, R.R. Sauers, *J. Am. Chem. Soc.* **1959**, *81*, 1739.

167. G. Stork, A. Meisels, J.E. Davies, *J. Am. Chem. Soc.* **1963**, *85*, 3419.

168. W. Seidel, J. Knolle, H.J. Schäfer, *Chem. Ber.* **1977**, *110*, 3544; J. Knolle, H.J. Schäfer, *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 758; H. Klünenberg, H.J. Schäfer,

Angew. Chem. Int. Ed. Engl. **1978**, *17*, 47.

169. T. Okubo, S. Tsutsumi, *Bull. Chem. Soc. Jpn.* **1964**, *37*, 1794; R. Brettle, J.C. Parkin, *J. Chem. Soc. C.* **1967**, 1352; M. Lacani, I. Tabakovic, M. Vukicevic, *Croat. Chem. Acta* **1973**, *45*, 465.

170. H.J. Schäfer, *Chem. Ing. Tech.* **1969**, *41*, 179.

171. R. Bauer, H. Wendt, *J. Electroanal. Chem.* **1977**, *80*, 395.

172. M.Y. Fioshin, L.A. Salmin, L.A. Mirkind, A.G. Kornienko, *Zh. Obshch. Khim.* **1965**, *10*, 594; H.J. Schäfer, *Angew. Chem. Int. Ed. Engl.* **1970**, *9*, 158; H.J. Schäfer, R. Pistorius, *Angew. Chem. Int. Ed. Engl.* **1972**, *11*, 48.

173. H.J. Schäfer, E. Steckhan, *Angew. Chem. Int. Ed. Engl.* **1969**, 8, 518; D. Koch, H.J. Schäfer, E. Steckhan, *Chem. Ber.* **1974**, *107*, 3640; see also: B. Belleau, Y.K. Au-Young, *Can. J. Chem.* **1969**, *47*, 2117; M.A. Le Moing, G. Le Guillanton, J. Simonet, *Electrochim. Acta* **1981**, *26*, 139.

174. J.R. Falck, L.L. Miller, F.R. Stermitz, *Tetrahedron* **1974**, *30*, 931.

175. R. Schlecker, U. Henkel, D. Seebach, *Chem. Ber.* **1977**, *110*, 2880.

176. G.A. Russell, G. Kaup, *J. Am. Chem. Soc.* **1969**, *91*, 3851; see also: G. Eglington, W. McCrae in R.A. Raphael, E.C. Taylor, H. Wynberg (ed): *Advances in Organic Chemistry: Methods and Results* Vol. IV, Intercience, London 1963, p. 225.

177. P. Yates, Y.C. Toong, *J. Chem. Soc. Chem. Commun.* **1978**, 205.

178. For references see: J. Protasiewicz, G.D. Mendenhall, *J. Org. Chem.* **1985**, *50*, 3220.

179. H.G. Viehe, R. Merényi, L. Stella, Z. Janousek, *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 917.

180. H.G. Viehe, Z. Janousek, R. Merényi, *Acc. Chem. Res.* **1985**, *18*, 148.

181. S. Mignani, M. Beaujean, Z. Janousek, R. Merényi, H.G. Viehe, *Tetrahedron* (Woodward issue) **1981**, *37*, W 111.

182. R.W. Bennett, D.L. Wharry, T.H. Koch, *J. Am. Chem. Soc.* **1980**, *102*, 2345.

183. M. Schwarzberg, J. Sperling. D. Elad, *J. Am. Chem. Soc.* **1973**, *95*, 6418.

184. E. Kariv, E. Gileadi, *Collect. Czech. Chem. Commun.* **1971**, *36*, 476; C.P. Andrieux, J.M. Saveant, *Bull. Soc. Chim. Fr.* **1972**, 3281; C.P. Andrieux, J.M. Saveant, *Bull. Soc. Chim. Fr.* **1973**, 2090; E. Touboul, G. Dana, *J. Org. Chem.* **1979**, *44*, 1397.

185. H.O. House: *Modern Synthetic Methods*, Vol. II, Benjamin, Menlo Park 1972, p. 167.

186. J.E. McMurry, *Acc. Chem. Res.* **1983**, *16*, 405.

187. H.D. Becker, *J. Org. Chem.* **1967**, *32*, 2140.

188. J.C. Gramain, R. Remuson, Y. Troin, *J. Chem. Soc. Chem. Commun.* **1976**, 194.

189. J.J. Bloomfield, D.C. Owsley, J.M. Nelke, *Organic Reactions* **1976**, *23*, 259.

190. J.F. Garst, *Acc. Chem. Res.* **1971**, 4, 400; B.J. Wakefield: *The Chemistry of Organolithium Compounds*, Pergamon Press, New York 1974; W.C. Danen in E.S. Huyser (ed): *Methods in Free Radical Chemistry*, Vol. V, Dekker, New York 1974, p. 1; R.D. Guthrie in E. Buncel, T. Durst (ed): *Comprehensive Carbanion Chemistry*, Elsevier, Amsterdam 1980, p. 230; see also: W.A. Bailey, R.P. Gagnier, J.J. Patricia, *J. Org. Chem.* **1984**, *49*, 2098; E.C. Ashby, T.N.Pham, B. Park, *Tetrahedron Lett.* **1985**, *26*, 4691.

191. M.A. Flamm-ter Meer, H.D. Beckhaus, K. Peters, H.G. von Schnering, C. Rüchardt, *Chem. Ber.* **1985**, *118*, 4665.

192. M. Feldhues, H.J. Schäfer, *Tetrahedron* **1985**, *41*, 4213.

193. R. Winiker, H.D. Beckhaus, C. Rüchardt, *Chem. Ber.* **1980**, *113*, 3456; W. Barbe, H.D. Beckhaus, H.J. Lindner,

C. Rüchardt, *Chem. Ber.* **1983**, *116*, 3235 ; C. Rüchardt, H.D. Beckhaus, *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 529; see also: J.W. Timberlake, Y.M. Jun, *J. Org. Chem.* **1979**, *44*, 4729; P.S. Engel, *Chem. Rev.* **1980**, *80*, 99.

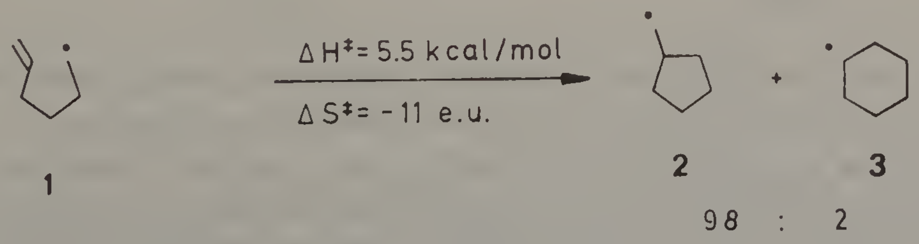
194. D.G. Wujek, N.A. Porter, *Tetrahedron* **1985**, *41*, 3973. W.J. Brittain, N.A. Porter, P.J. Krebs, *J. Am. Chem. Soc.* **1984**, *106*, 7652.

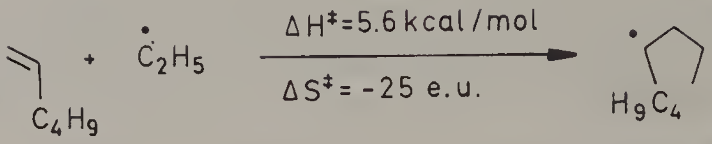
Chapter 4

Intramolecular Formation of Aliphatic C–C Bonds

A. Introduction

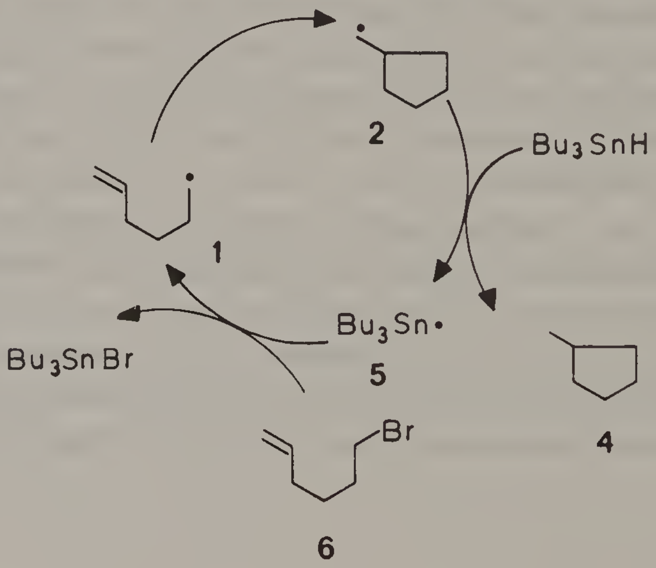
Radical cyclization reactions developed in the last years represent a breakthrough for synthetic radical chemistry.[1] These reactions exhibit interesting regioselectivities and stereoselectivities and can be carried out with a variety of functional groups as radical traps. Since their activation entropies are less negative than those of intermolecular reactions, not only carbon-carbon, but also carbon-oxygen and carbon-nitrogen multiple bonds efficiently react intramolecularly with radicals. Thus, the entropy of cyclization of the 5-hexenyl-radical **1** is 14 e.u. larger (less netagive) than that of the intermolecular addition of an ethyl radical to 1-hexene, but the activation enthalpies are not much different from each other.[2]





The cyclization of the 5-hexenyl radical **1** to cyclopentylmethyl radical **2** has a rate constant of about 10^6 (s^{-1}) at 20°C,[3] and is increased by electron-withdrawing substituents at the double bond.[4] Thus, cyclization reactions are fast enough for a successful application in syntheses.

Although radicals **1** and **2** have the same nucleophilicity, the selectivity requirement is also fulfilled because radical **1** reacts intramolecularly with the olefinic bond, whereas radical **2** reacts intermolecularly, e.g. with Bu_3SnH.



Since both the reactivity and the selectivity requirements for chain reactions are fulfilled, radical cyclization reactions are synthetically useful. But neither three- nor four-membered rings can be synthesized because the cyclopropylmethyl and cyclobutylmethyl radicals **8** and **10** cleave the rings with high rates to form the more stable acyclic radicals **7** and **9**, respectively.[5]

7 **8**

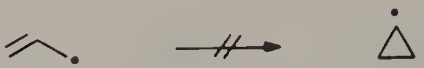
9 **10**

Cyclized products can be formed only in systems where a large proportion of the ring strain is already present in the non-cyclized radical, such as the norbornenyl radical **11**,[6] or if the cyclic radicals are stabilized by substituents, e.g. the phenyl substituted radical **14**.[7]

11 **12**

13 **14**

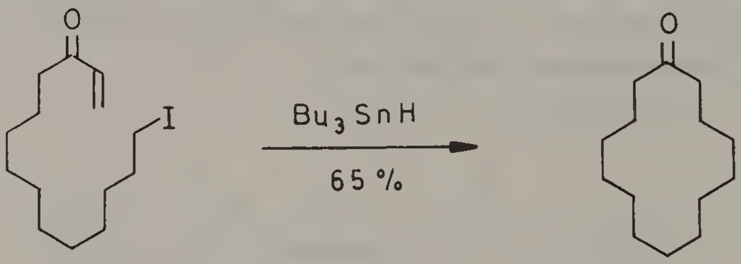
In contrast to cyclopropylmethyl and cyclobutylmethyl radicals **8** and **10**, cyclopropyl and cyclobutyl radicals **15** and **16** undergo ring cleavage very slowly,[8] but one cannot generate these radicals from allyl or homoallyl radical precursors.[5,9]



15

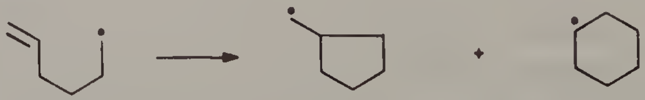
16

The formation of medium sized rings is also not a synthetically useful route,[10] but recently Porter[11] has shown that large rings can be synthesized via radical cyclization.



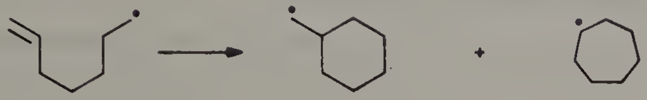
1. Regioselectivity

5-Hexenyl and 5-heptenyl radicals **1** and **17** cyclize predominately to the smaller rings **2** and **18**, respectively. Thus, the less stable prim. radicals are formed faster than the more stable sec. radicals.[10]



1 **2** **3**

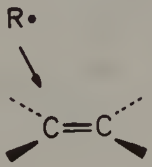
98 : 2



17 **18** **19**

90 : 10

According to the Baldwin rules,[12] the formation of **2** and **18** proceeds via a favored *exo*-cyclization, whereas **3** and **19** are formed in *endo*-cyclization reactions. Beckwith[10] has pointed out that stereoelectronic effects can explain these regioselectivities. Since the addition of alkyl radicals to alkenes proceeds via the unsymmetrical transition state **20**.[13] the same arrangement of atoms in the intramolecular addition favors transition states **21** and **22**.[10]



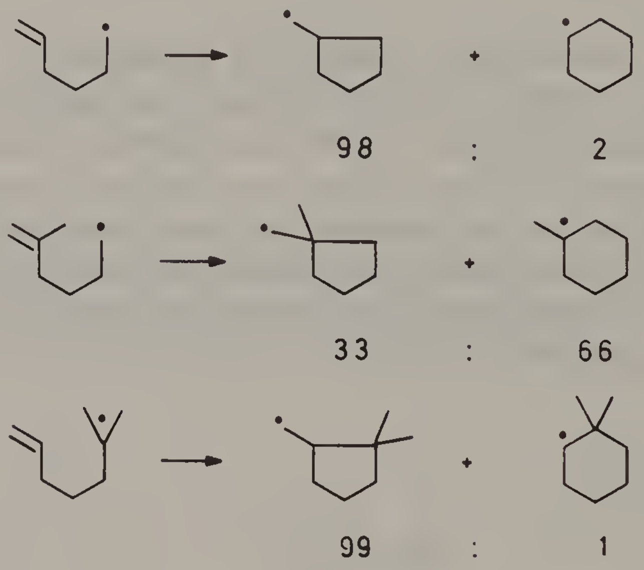
20

21

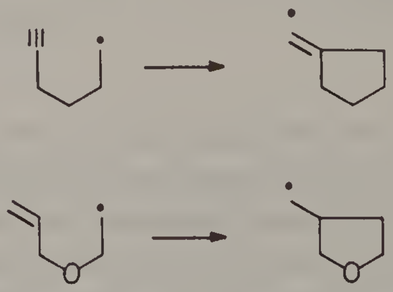
22

Additional steric effects[14] resulting from a 1,3-diaxial interaction in the transition state, as well as less favorable entropies[15] in the formation of cycloalkyl radicals compared to cycloalkyl methyl radicals, could also retard the *endo*-cyclization. Calculations using force field methods indicate that the smaller rings are formed because of less strained transition states.[10]

The ratio of the five- to six-membered rings depends on the substituents at the olefinic bond. A methyl group at the olefinic carbon atom reduces the attack at that C-atom due to steric effects; however, methyl groups at the radical center have only small effects.[10]

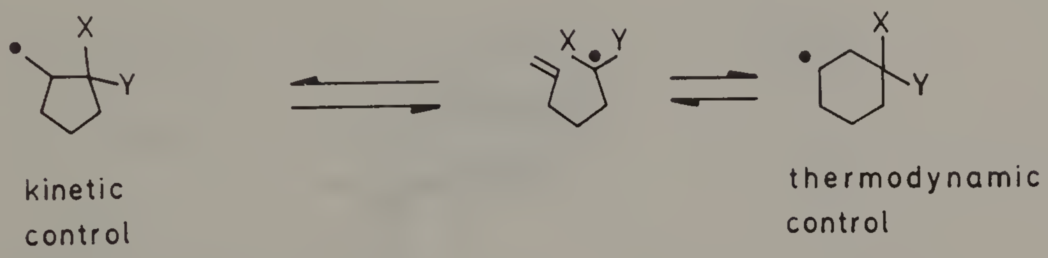


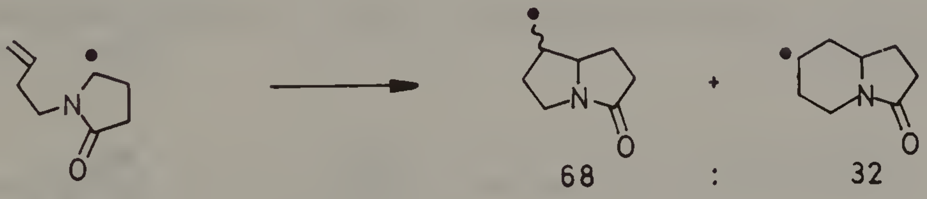
The formation of five-membered rings also predominates when CC-triple bonds are used as intramolecular radical traps or if an oxygen atom is within the chain.[10,16]



The situation changes, however, if the radical cyclization is reversible. Julia[17] has shown that under thermodynamic conditions six-membered rings are predominately formed.

A silicon group in the chain can also favor six-membered ring formation, as was observed by Wilt.[18] In a similar manner, systems containing amido groups [19,20] often yield to a considerable amount the larger ring.





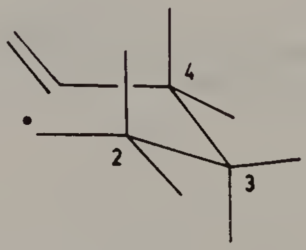
2. Stereoselectivity

Two useful guidelines governing the ring closure of substituted hexenyl radicals were formulated by Beckwith:[21]

- 1- or 3-substituted radicals preferentially give *cis*-disubstituted cyclopentyl products;

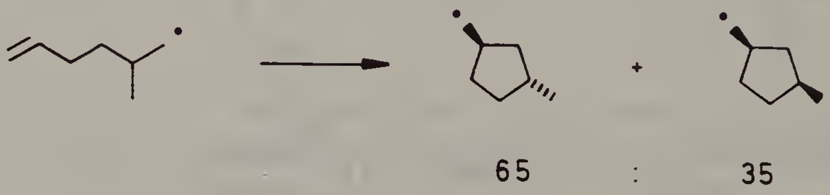
- 2- or 4-substituted radicals give mainly *trans*-disubstituted cyclopentyl derivatives.

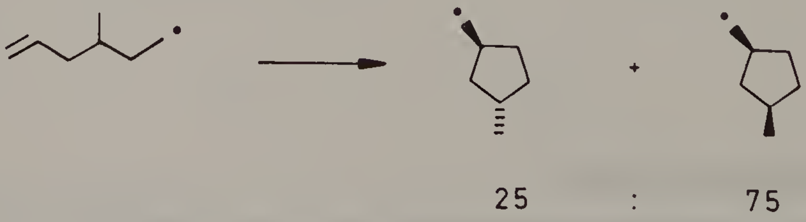
These rules can be explained by the transition state structure **23**, in which axial and equatorial positions are clearly distinguishable at C-2, C-3, and C-4. Thus, the more favorable conformer should contain the substituents in the equatorial position.

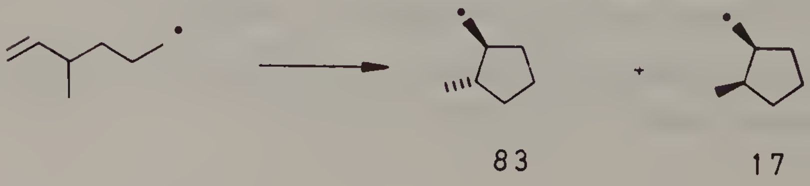


23

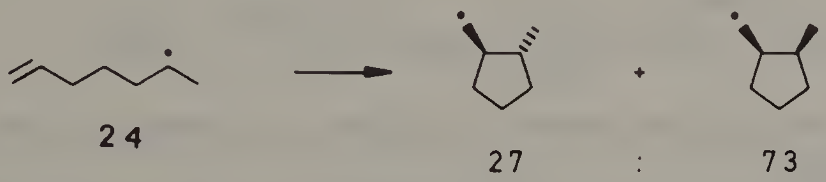
This effect is demonstrated by a series of radical cyclization reactions.[10]

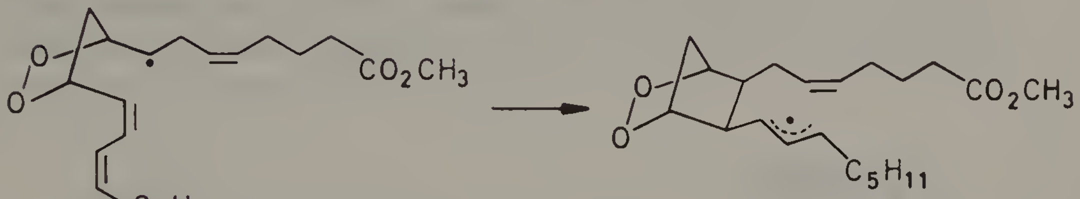






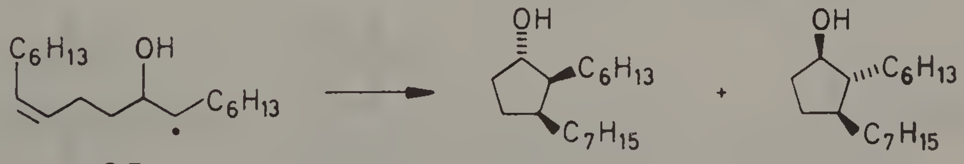
The preferred formation of the *cis*-cyclopentyl system from radical **24** cannot be so easily explained.[10] One possibility is that in the early transition states of radical additions to alkenes, in which the distance between the reacting C-atoms is about 2.3 Å,[13] attractive interactions between the methyl group and the π-bond exist. This explanation is backed by the observation of Corey that **25** cyclizes to the *cis*-isomer **26**.[22]





25 **26**

Porter[23] has shown that the ratio of cyclized radicals **28**:**29** depends on the solvent mixture. In the presence of micelles or bilayer forming tensides, the amount of *cis*-isomer **28** increases. This effect was explained by a special conformation of radical **27** at the water/benzene interphase.



27 **28** **29**

C_6H_6/H_2O	50	:	50
C_6H_6/H_2O / tenside	70	:	30

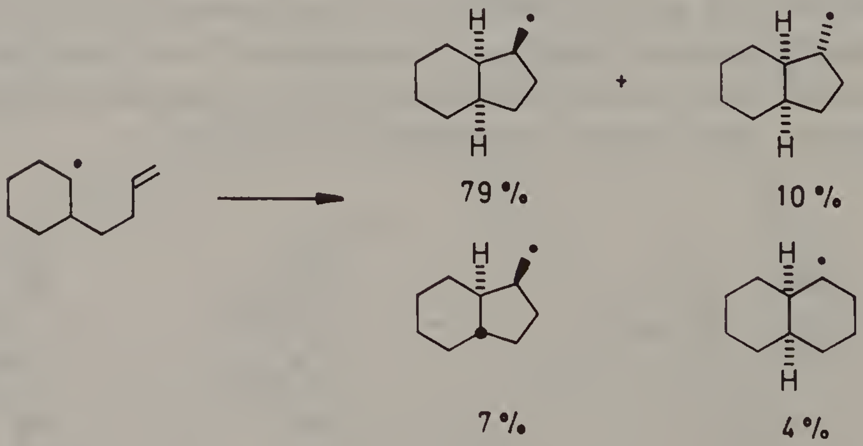
Interestingly, in the formation of a six-membered ring from the 1-methylheptenyl radical **30** the *cis*-product is again the main isomer.[10]

30

73 : 27

In radical cyclizations of cyclic alkenes *cis*-junction is the main reaction.[12]

n = 1,2 ; m = 2,3



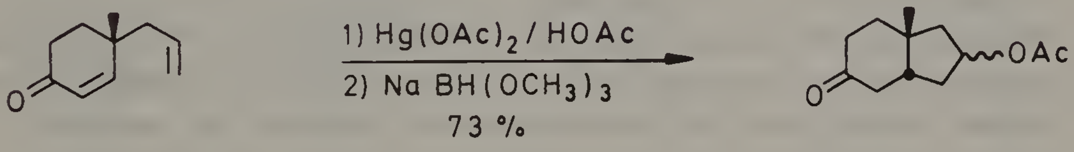
B. Trapping with Hydrogen Donors

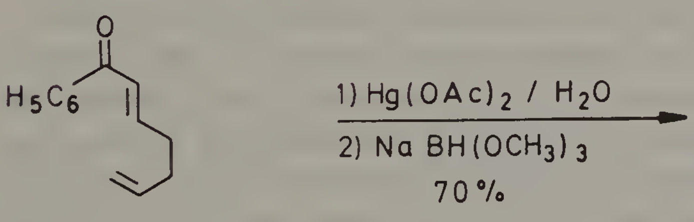
1. Mercury hydride

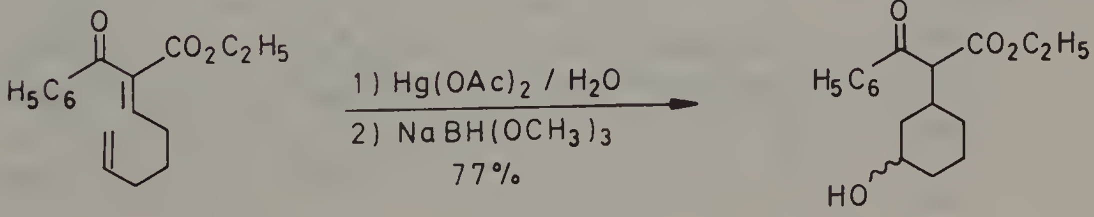
As described on page 38, the reduction of alkylmercury salts with inorganic hydrides like $NaBH_4$ or Bu_3SnH gives alkyl radicals via mercury hydrides and alkylmercury radicals.

$$RHgX \xrightarrow{NaBH_4} RHgH \xrightarrow[-HX]{+X\bullet} RHg\bullet \xrightarrow{-Hg} R\bullet$$

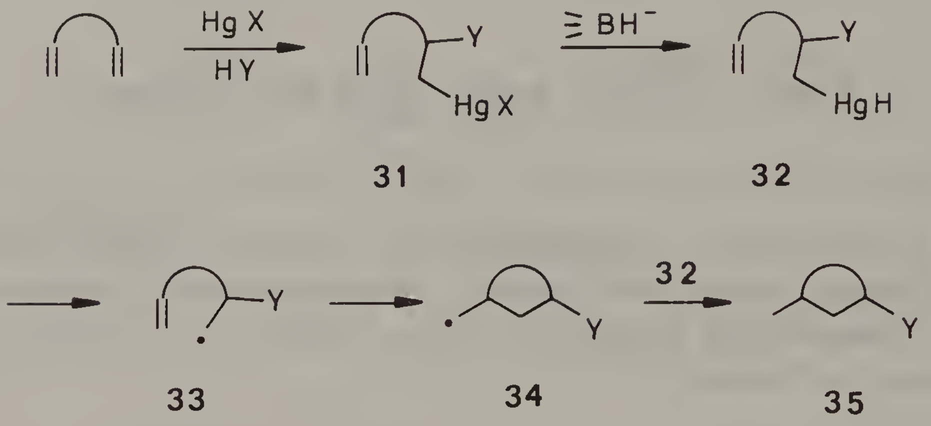
The flexibility of this method lies in the easy generation of alkylmercury salts, for example, by mercuration of alkenes. Thus, Danishefsky synthesized cyclic products via solvomercuration of dienes.[24]



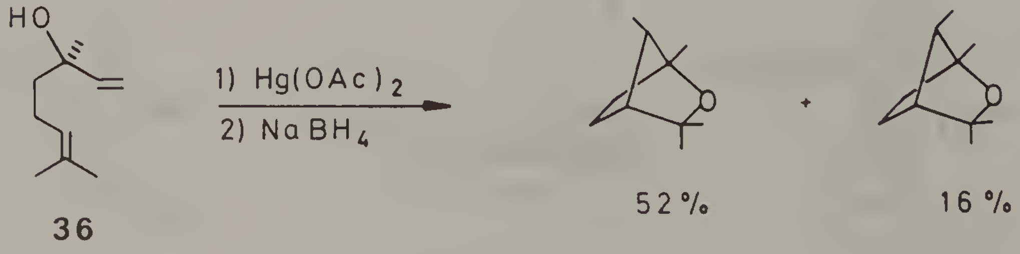


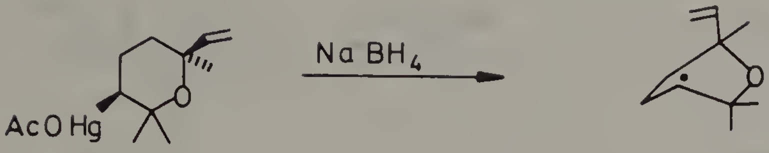


Organomercury salts **31**, which are formed as intermediates, are reduced without isolation to give radical **33**. After intramolecular addition to the CC-double bond, the cyclized radicals **34** are trapped by the organomercury hydride **32**, yielding products **35**.



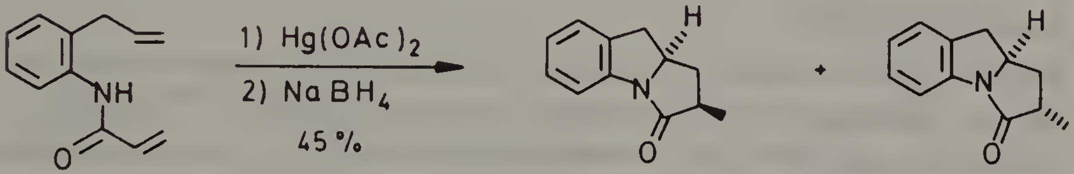
Dienes with suitable nucleophilic neighboring groups give bicyclic compounds because the intramolecular radical addition is preceded by ionic cyclization. Thus, bicyclic compounds are formed in 68% yield by mercuration of linalool **36**, and subsequent reduction. The reaction proceeds via the monocyclic organomercury compound **37**, which is formed by electrophilic attack of mercury acetate on the more electron-rich double bond in **36**, followed by intramolecular attack of the alcohol group. Reductive homolysis of the C-Hg bond gives radical **38**, which is converted into the bicyclic compounds by cyclization and hydrogen abstraction.[25]





37 **38**

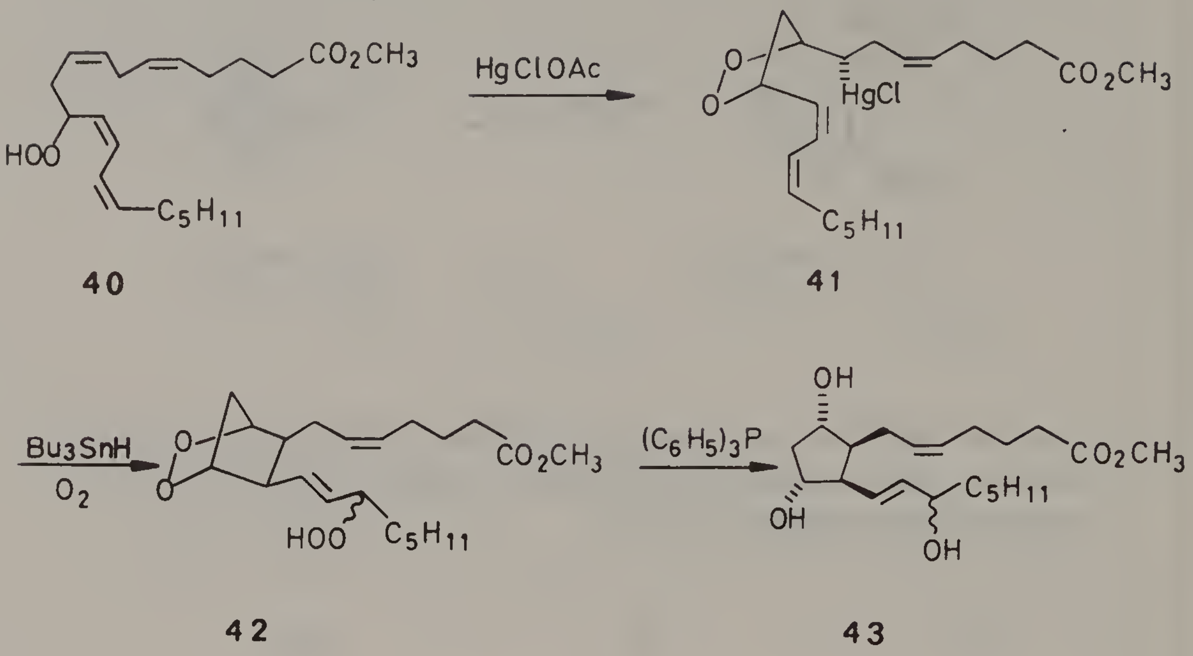
An amide function can also act as a nucleophile for the ionic reaction step; thus, benzannulated bicyclic compounds are formed from diene **39**.[24]



39

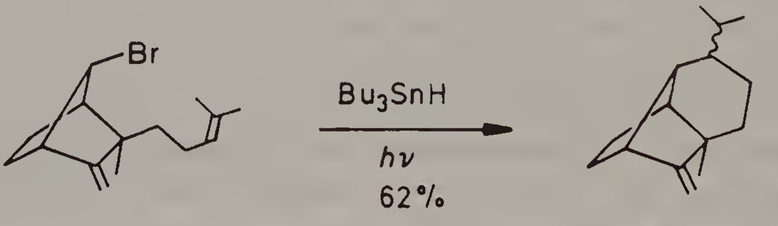
75 : 25

Corey has used this methodology in a prostaglandin synthesis.[22] Starting from the ester of arachidonic acid, the hydroperoxide **40** is synthesized, which, after an ionic mercuration reaction, yields the cyclic product **41**. Radical **25** (page 149), formed by reduction with Bu_3SnH, cyclizes to **26** which is trapped by O_2 and the mercury hydride to give **42**. The synthesis is completed by deoxygenation with $(C_6H_5)_3P$ and yields the *cis*-isomer **43**.

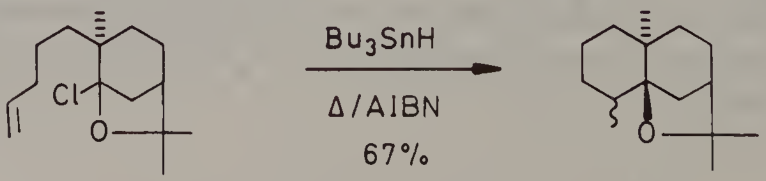


2. Tin hydride

Before 1980, studies of radical cyclizations centered mainly on the mechanistic aspects of the reaction.[1,5,17,18] Early synthetic applications include the synthesis of tepenoid **44** by Bakuzis and dihydroagarofuran **45** by Büchi.[26]

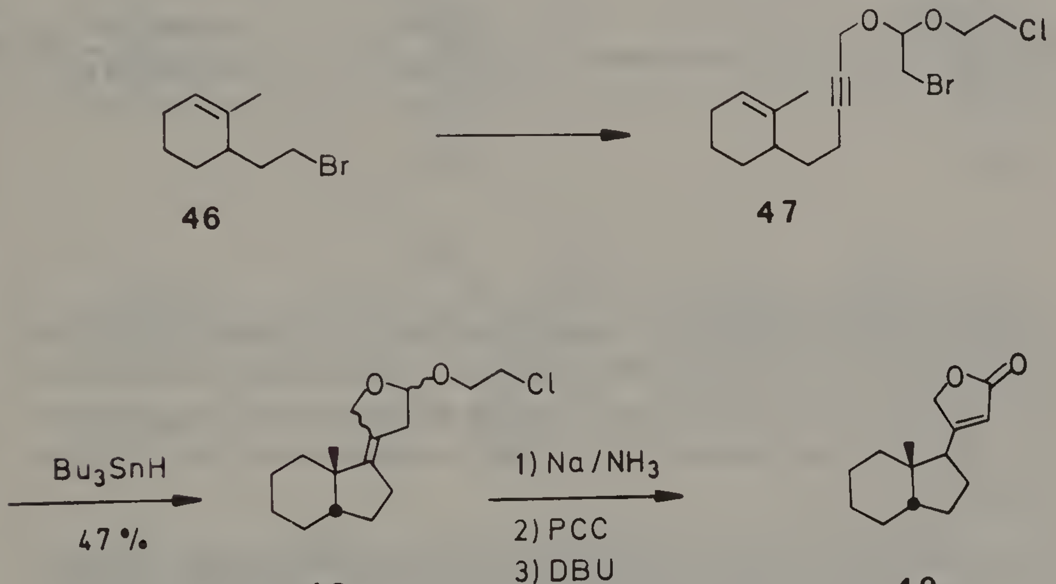


44



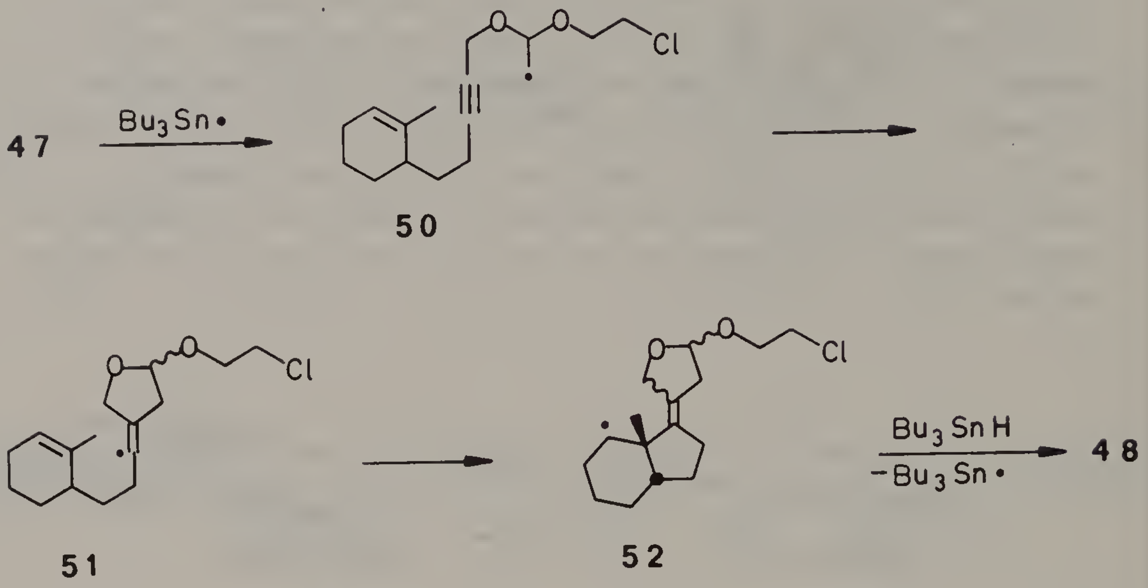
45

In these reactions, halides and tin radicals react to give alkyl radicals which, after cyclization, abstract a hydrogen atom from Bu_3SnH (see p. 56). In the last few years this reaction has been applied to syntheses of target molecules in several laboratories. Stork[27] has carried out pioneering work in which both alkyl and vinyl radicals were used in cyclization reactions with both acyclic and cyclic double- and triple-bonds. The synthesis of the butenolide **49** is an elegant example.[28]



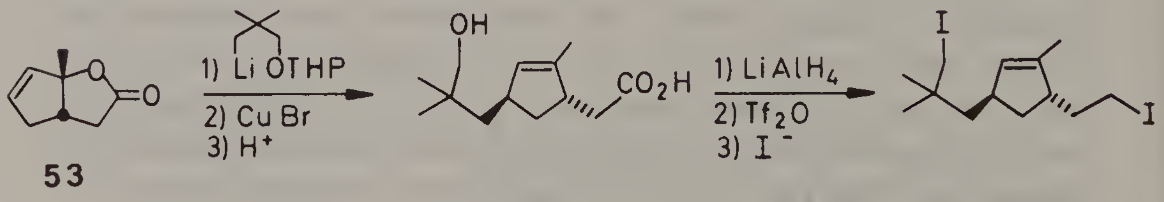
46 **47** **48** **49**

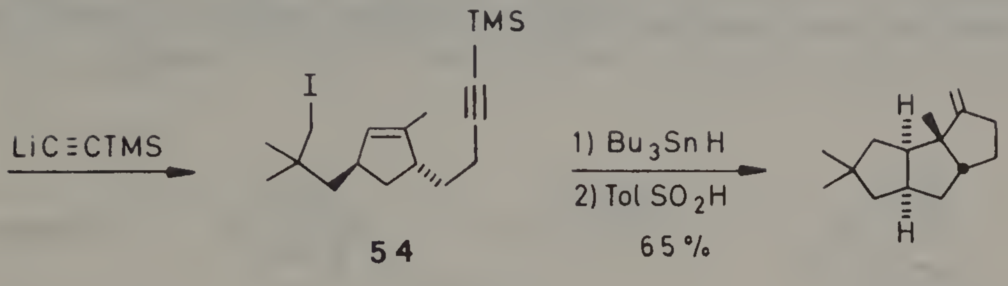
The radical chain reaction takes place in boiling benzene with bromide **47**, which is easily obtained from **46**. The tributyltin radical abstracts the bromine atom from **47**, leaving the less reactive C-Cl bond intact. The thus formed alkyl radical **50** attacks the triple bond in an *exo*-cyclization forming the vinyl radical **51**, which then reacts with the double bond of the cyclohexene ring. Radical **52** intramolecularly reacts with tributyltin hydride to give **48** and the tributyltin radical, which once again cleaves the C-Br bond of **47**.



During the synthesis, the radical center is transferred from a prim. alkyl to a vinyl, and then to a cyclohexyl position in two consecutive cyclizations. These reactions occur with very high rates, high yields, and a high stereoselectivity in the annulation step.

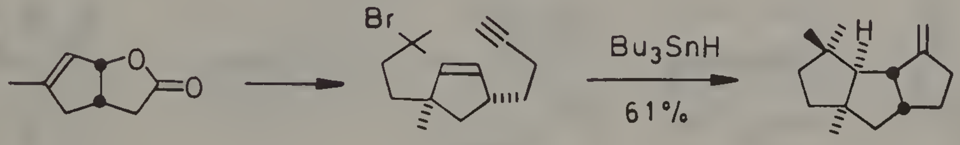
Other examples of such tandem cyclizations have been worked out by Curran[29] for the synthesis of cyclopentanoid natural products in which three cyclopentanes are annulated. The decisive radical cyclization in the synthesis of hirsutene 55 begins with iodide 54, which is synthesized from lactone 53.





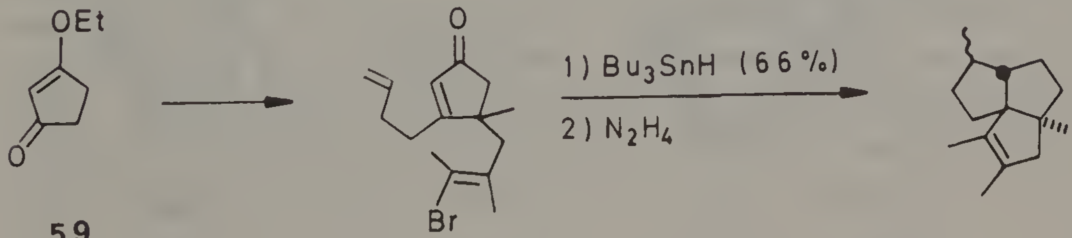
54 **55**

In the synthesis of capnellene **58**, lactone **56** is transformed into the bromide **57**; radical tandem cyclization with Bu_3SnH then gives capnellene **58**.[30]



56 **57** **58**

Radical precursor for the synthesis of silphiperfol-6-ene is bromide **60**, which is generated from **59** in three steps. Radical cyclization yields **61**, a mixture of silphiperfol-6-ene and 9-episilphiperfol-6-ene.[31]



59 **60** **61**

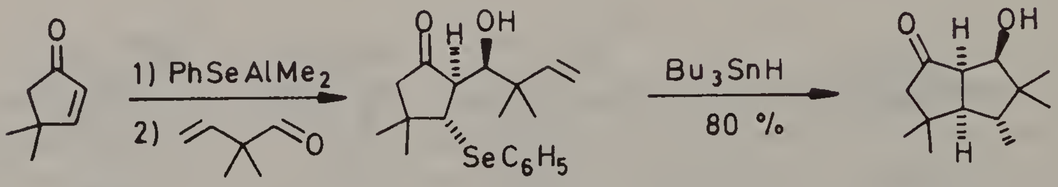
Beckwith[32] started with the acyclic precursor **62**. Cyclization with the less reactive germanium hydride (see p. 67) gave not only methyl triquinanes **63**, but also bicyclic isomers.

62

63

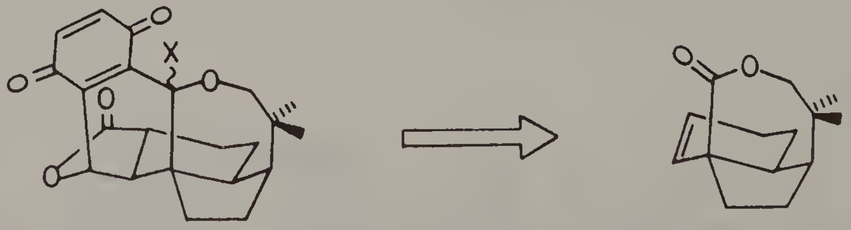
27%

A synthesis of bicyclic compound **64** has been carried out by Livinghouse.[33]



64

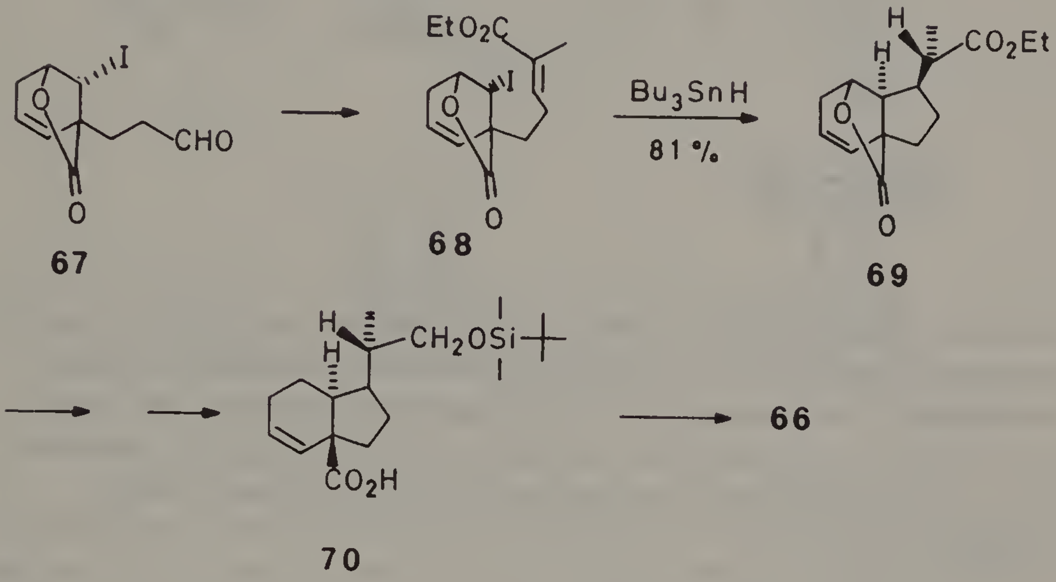
Hart[34] synthesized lactone **66** as a key intermediate for pleurotine **65a** and geogenine **65b**.



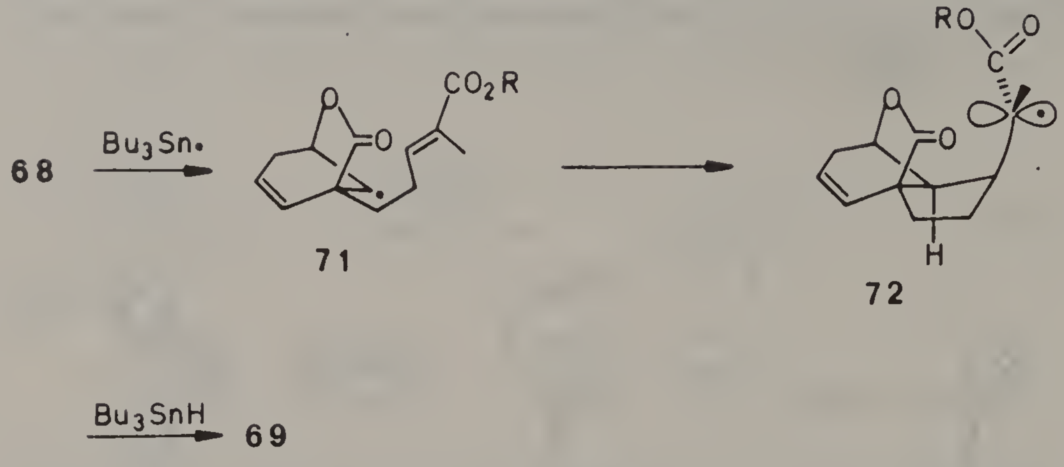
66

65a : X = ß - H
65b : X = α - H

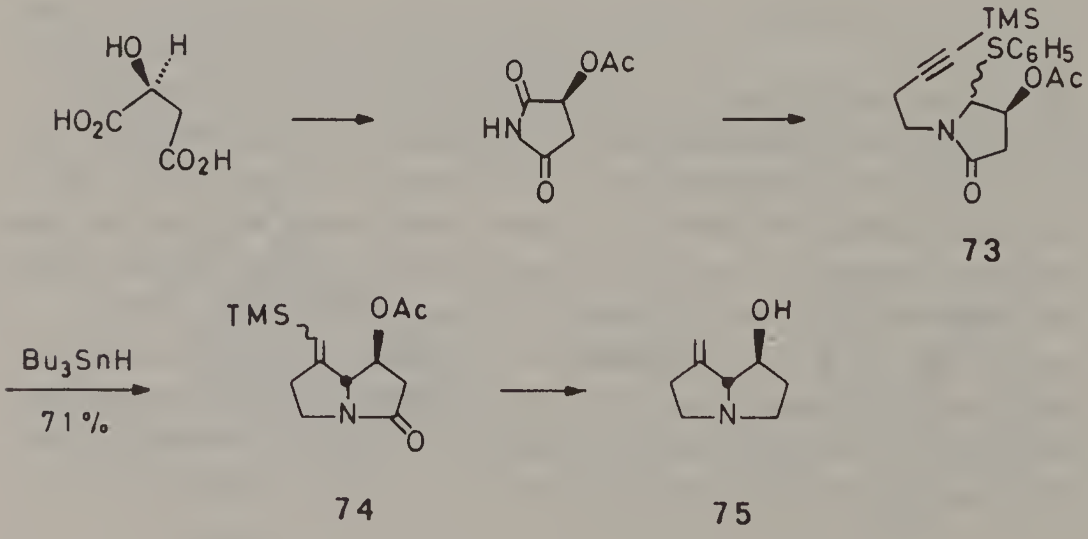
Aldehyde **67**, which can be made from benzoic acid, is converted to **68**. Cyclization of **68** gives tricyclus **69** which yields **70** in six steps.



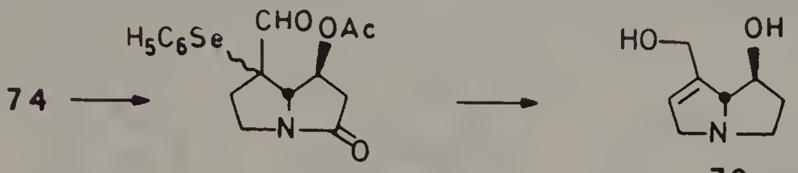
The predominant formation of **69** shows that the C-C and the C-H bonds are formed with high stereoselectivity. Because of the particular conformation of the bicyclic radical **71**, the C-C bond formation leads to a *trans*-annulation of the new ring. Remarkable also is the high diastereoselectivity of the hydrogen abstraction from the acyclic alkyl radical. The conformation **72**, in which the carbonyl groups of the lactone and the ester are far apart from each other, seems to be the preferred conformation of this acyclic radical. Hydrogen transfer from the least hindered side then gives the major isomer **69**.



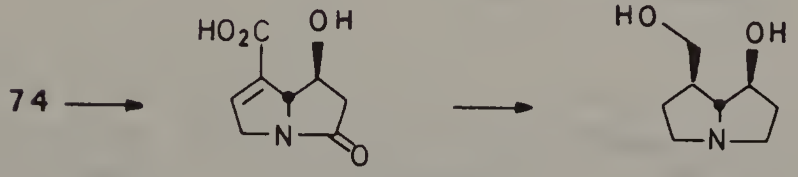
Another application of radical cyclization reactions, which was developed by Hart,[35] is for the formation of pyrrolizidine alkaloids. The synthesis of (-)-dehydrohastanecine **75** starts with malic acid, which is converted to the radical precursor **73**. Cyclization gives **74** and after two additional steps, alkaloid **75**.



The cyclized compound **74** is also a precursor for (+)-heliotridine **76** and (+)-hastanecine **77**.[35]

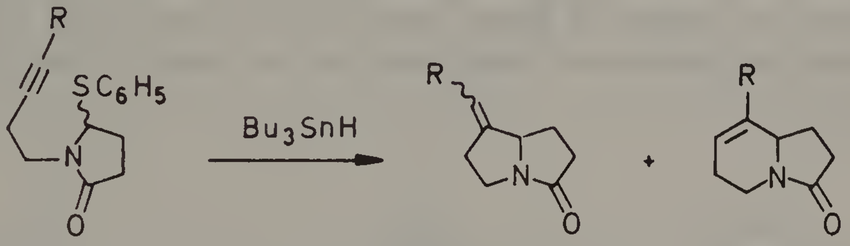


76



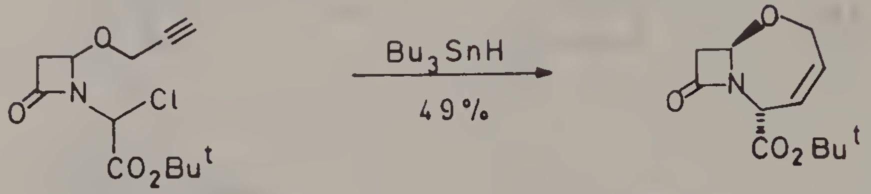
77

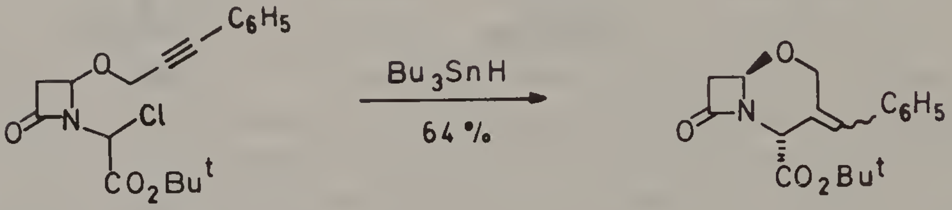
For the syntheses of alkaloids **75-77**, it is important that the alkyne **73** is substituted with a terminal Me_3Si-group because less bulky substituents lead to a considerable amount of six-membered ring formation.[35]



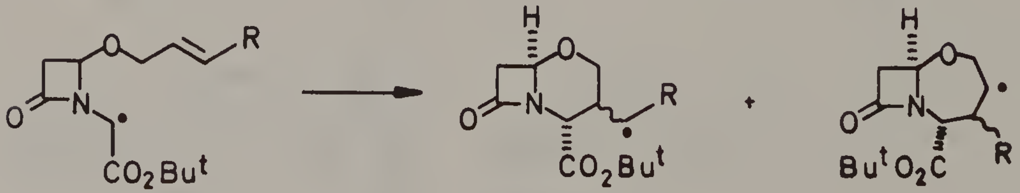
R = H	< 5	:	> 95
$n-C_3H_7$	56	:	44
$i-C_3H_7$	65	:	35
$t-C_4H_9$	> 95	:	< 5
$SiMe_3$	> 95	:	< 5

The formation of the larger ring was also observed in annulation reactions of ß-lactams carried out by Bachi.[36] But again, the size of the ring depends on the substitution. With a terminal triple bond, a seven-membered ring is formed, whereas a phenylated alkyne yields a six-membered ring.

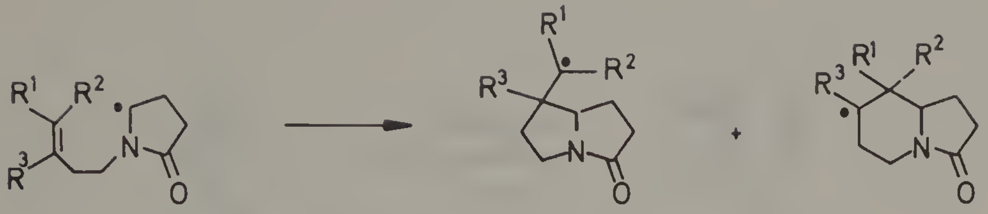




The larger amount of *endo*-cyclization is not caused by the triple bond because alkenes show a similar behavior. It is, therefore, the effect of amido substitution that leads to the successful competition of the formation of larger rings.[20,37]

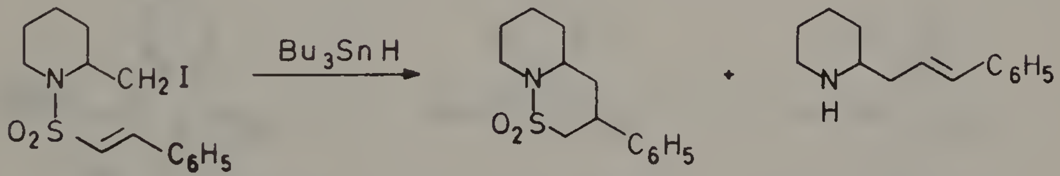


R = H < 5 : > 95
CO_2Me 68 : 4
C_6H_5 > 95 : < 5



R^1	R^2	R^3			
H	H	H	68	:	32
Me	Me	H	> 95	:	< 5
H	H	Me	< 5	:	> 95

Speckamp[38] has shown that *endo*-cyclization is also favored with sulfonamide **78**. However, the byproduct **79** may result from *exo*-cyclization, followed by fragmentation.

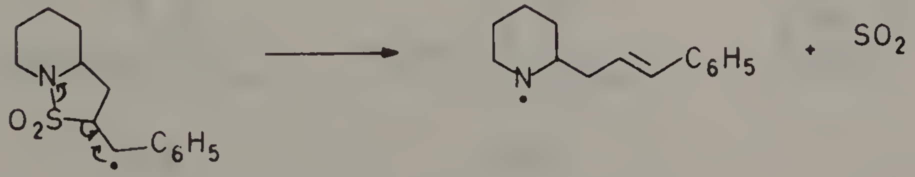


78

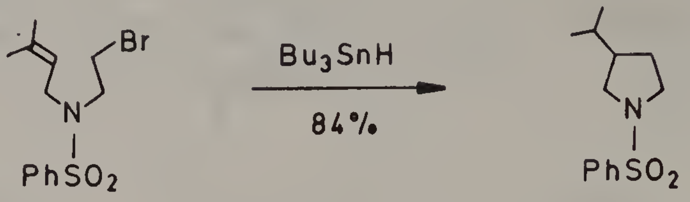
47 %

18 %

79

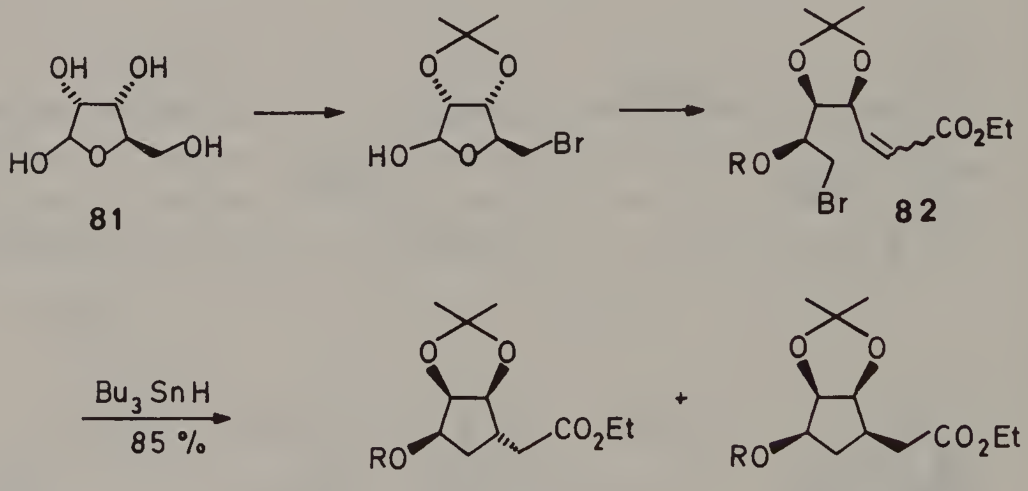


Pyrrolidins, for example **80**, were synthesized by Padwa[39] in high yields.



80

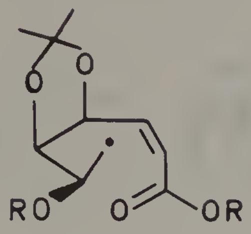
Cyclization reactions starting from carbohydrates have also been carried out. Thus, Wilcox[40] synthesized the cyclopentanoid compounds **83** from the pentose **81** which leads to the radical precursor **82** in four steps. Cyclization gave the five-membered rings in 85% yield.



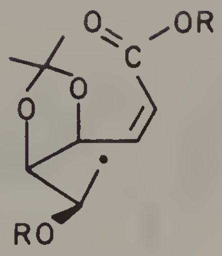
81 **82**

83a **83b**

The *trans*-isomer 83a is formed predominately, especially from the Z-isomer of 82. This shows that **84a** is favored over **84b**.



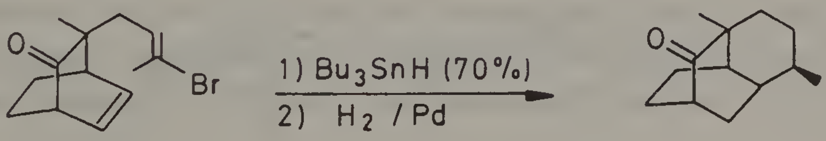
84a



84b

The synthesis of butenolide **49** by Stork[28] has already shown that not only alkyl, but also vinyl radicals can lead to cyclized products (see p. 155).

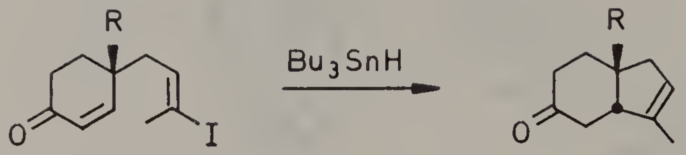
Another example is the synthesis of norseychellanone **86** by cyclization of bromide **85**.[41]



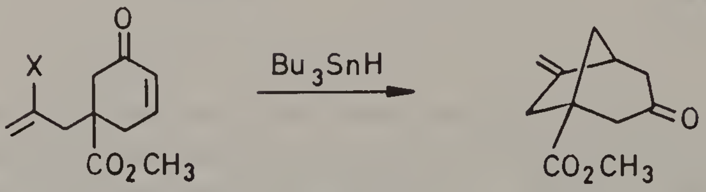
85

86

Additional work was carried out by Marinovic,[42] who also showed that the yield increases in going from chloride via bromide to iodide.

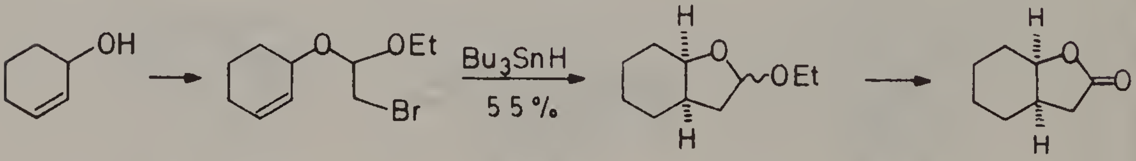


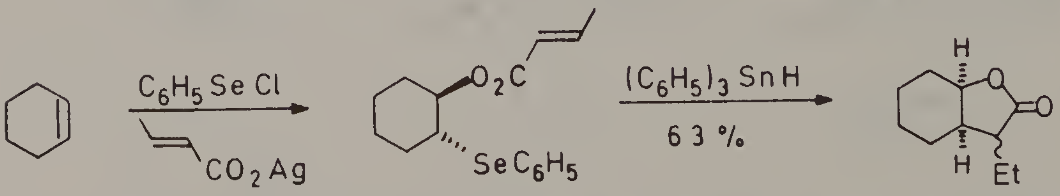
R = H (85 %)
CH_3 (83 %)

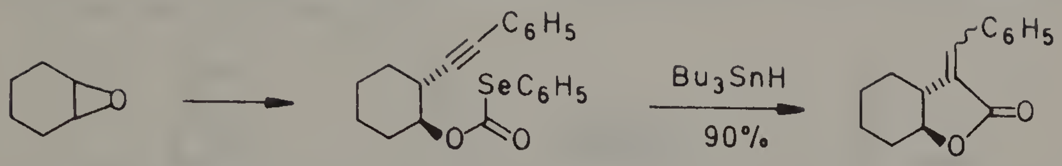


X = Cl (59 %)
Br (91 %)
I (93 %)

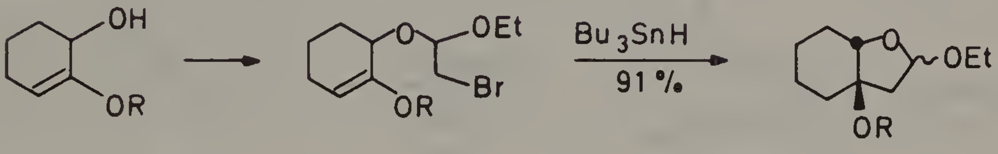
The tin method has turned out to be a suitable method for the synthesis of γ-lactones. Three different approaches have been worked out by Stork,[43] Clive,[44] and Bachi.[45]







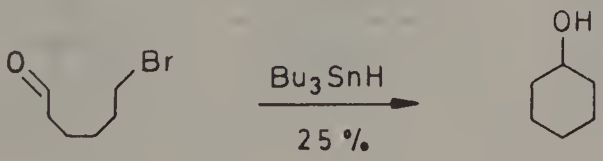
Pattenden[46] has shown that in these intramolecular reactions nucleophilic radicals can even add to the electron-rich double bond of an enolether.



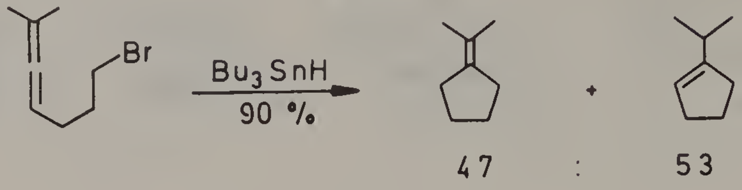
87

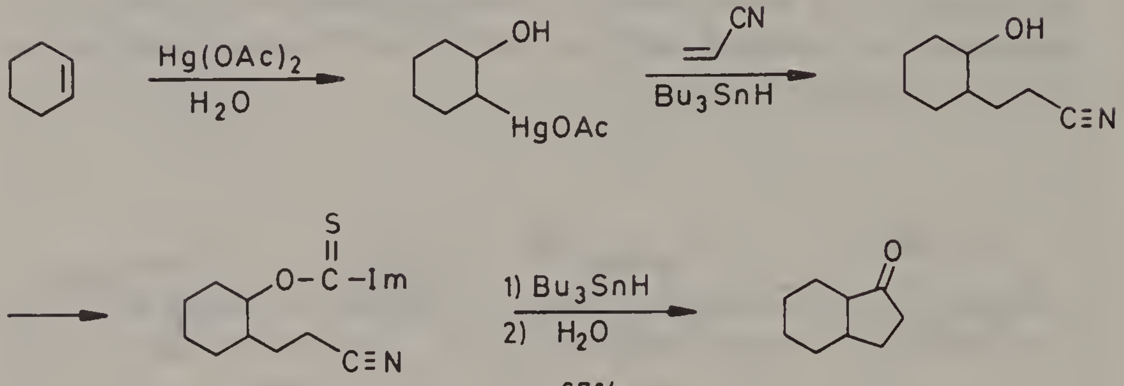
88

In the synthesis of **88**, the enolether function in **87** acts as a ketone equivalent. Ketones themselves are not good radical traps because the π-CO bond is too strong. Nevertheless, there are some examples of this kind in which products are formed in low yields.[47]



In contrast to ketones, allenes[48] and nitriles[49,50] are suitable radical traps for cyclization reactions.

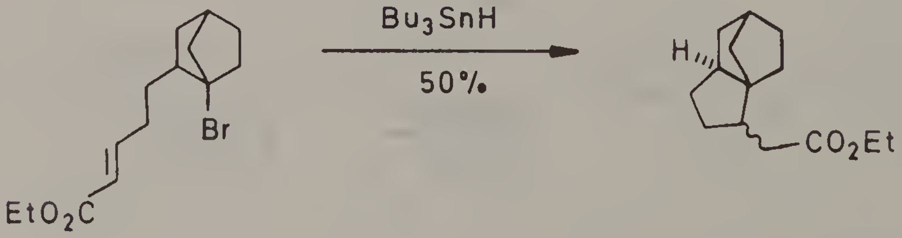




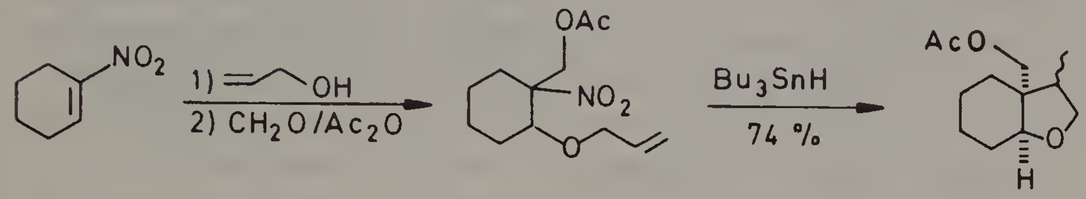
89 **90**

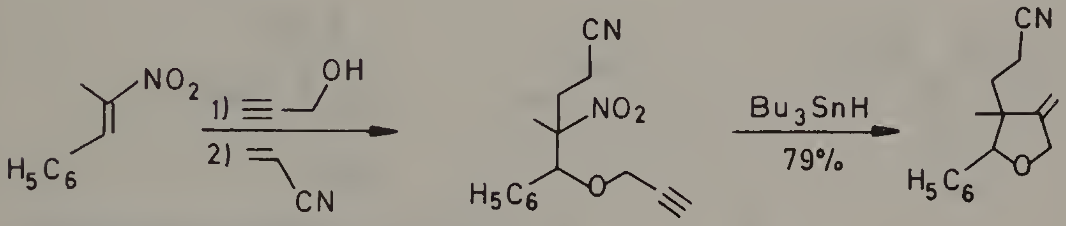
In Clive's[50] synthesis of ketone **90**, the carbon-centered radical is generated from **89** by attack of the tin radical on the sulfur atom.

Kraus[51] has demonstrated that radical precursors with a bridgehead C-Br bond can be also used.

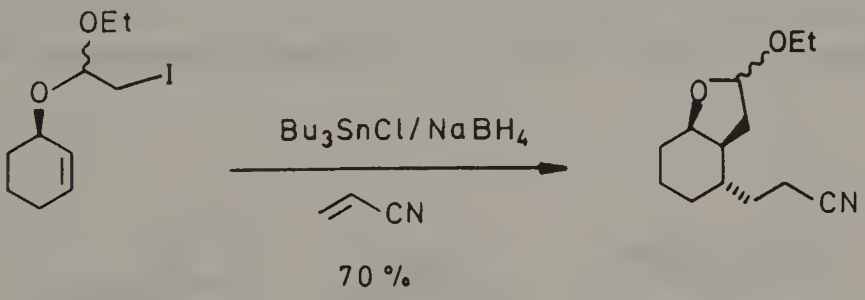


Nitro compounds are appropriate precursors for radical C-C bond forming reactions and Ono[52] has applied this methodology for cyclization reactions.



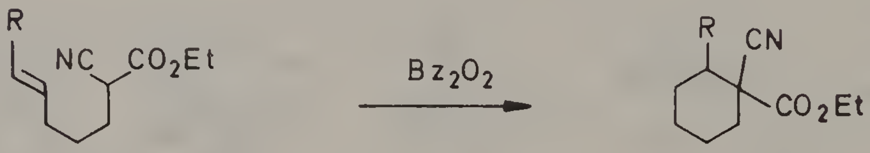


The often faster rate of cyclization compared to intermolecular C-C bond formation was used by Stork[53] to carry out both steps in one reaction sequence.



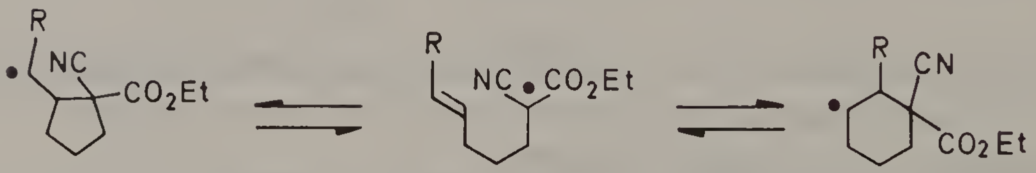
3. "Carbon hydride"

Examples for the trapping of cyclized radicals with C-H bonds as hydrogen donors are found in the earliest radical cyclization reactions performed by Julia[54] and his group. Hexenyl systems **91** give rise to cyclic products **92** if the radical chain is started by initiators which abstract a hydrogen atom from the tert. carbon atom. Since the cyclization is reversible with ester and nitrile substituted radicals, the more stable cyclohexyl radicals predominate yielding products **92**.

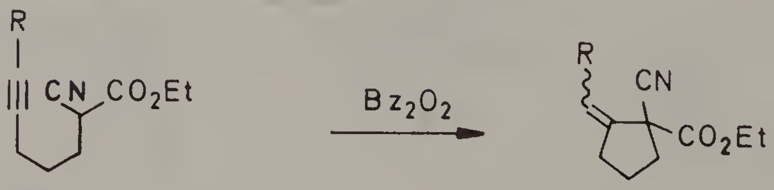


91 **92**

R = H (51%), CH_3 (65%), C_2H_5 (78%)



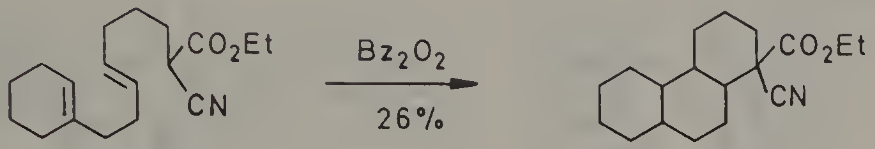
But alkyne **93** gives mainly the cyclopentyl derivative **94**.[55]

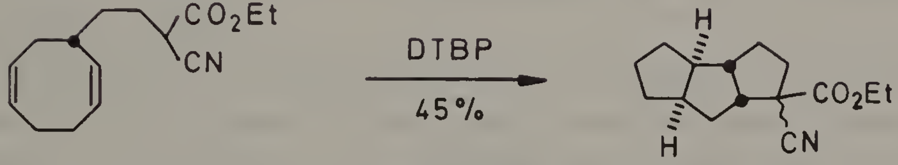


93 **94**

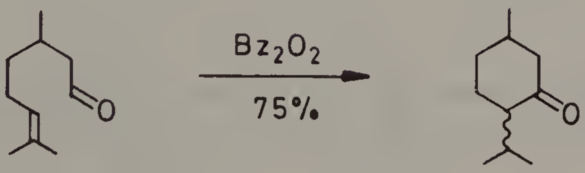
R = H (27%), CH_3 (63%)

This procedure can also be applied to tandem cyclization reactions.[56]

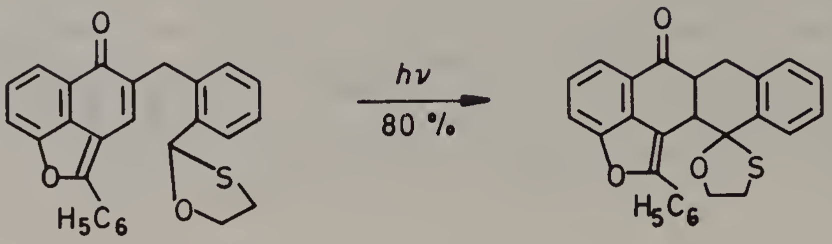




Hydrogen abstraction can also occur from aldehydes or their derivatives. Thus, citronellal gives a mixture of menthone (50%) and isomenthone (25%).[57]

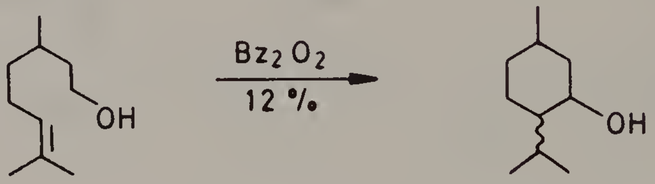


Barton[58] has photolytically cyclized **95** to the tetracycline derivative **96**.

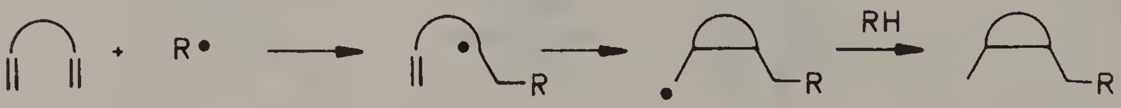


95 **96**

Alcohols don't effectively activate C-H bonds and give low yields of cyclization products, e.g. the cyclization of citronellol to isomeric menthols.[59]

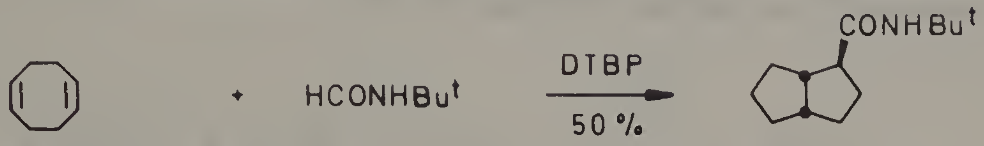


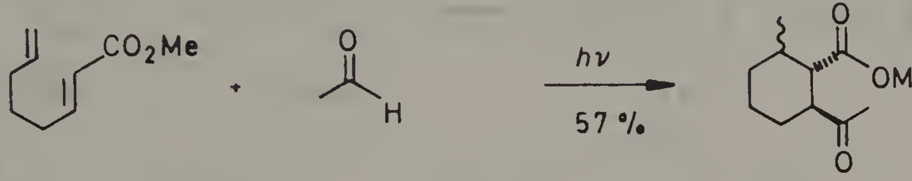
A different approach starts with dienes **97** which react with carbon centered radicals to give **98**. Cyclization yields radicals **99** which abstract a hydrogen atom from the added reagent RH.



97 **98** **99**

Formamide, esters, lactones, aldehydes, and chloroform can be used as the hydrogen donor RH.[5,60,61]

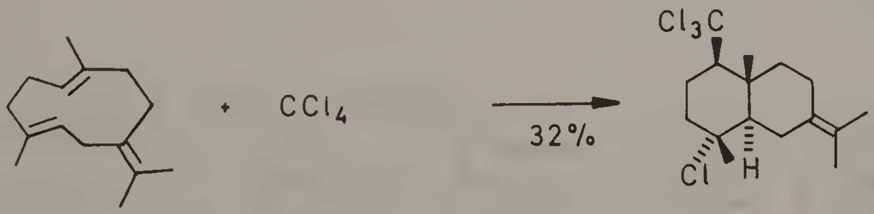


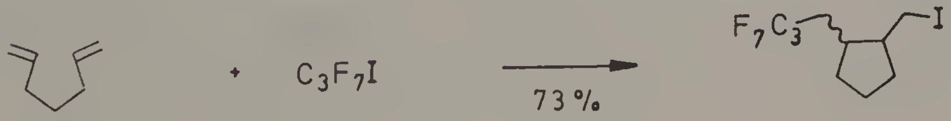


C. Trapping with Heteroatom Donors

1. Halogen donor

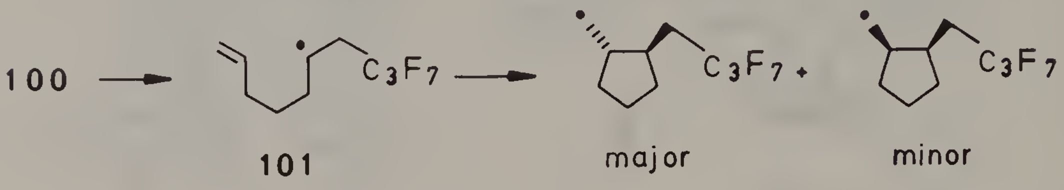
The addition of halogenated alkanes to dienes with suitably oriented double bonds yields cyclic products whose amount depends on the rate of halogen abstraction. The electrophilic alkyl radicals attack one of the double bonds, cyclization occurs, and finally, halogen abstraction gives the product and the chain carrying electrophilic radical (see p. 77).[5,60,62]

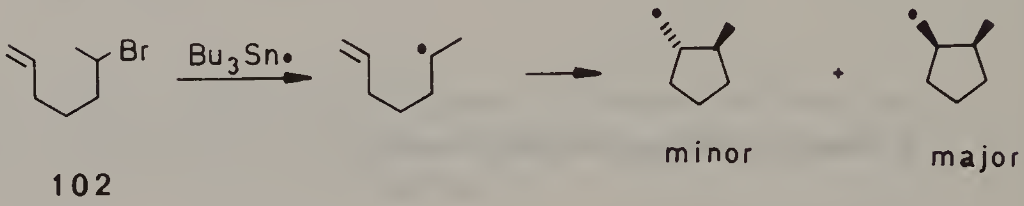




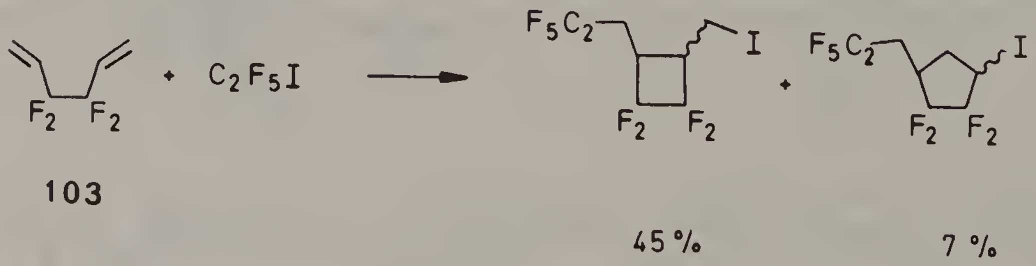
100

Brace[63] has reported that in the reaction of diene **100**, the *trans*-isomer is the major product. Thus, radical **101** shows a different stereoselectivity than the radical which is generated from halide **102** (see p. 149).

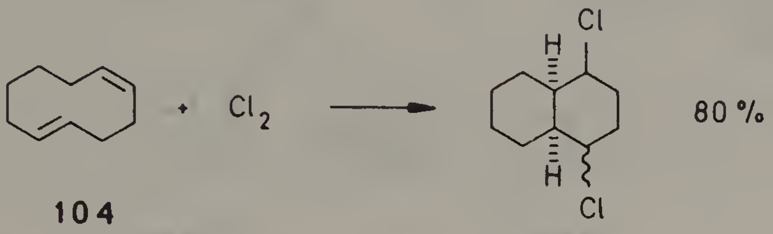




Another exceptional example is the formation of the four-membered ring from the thermally induced addition of pentafluoroiodoethane to diene **103**, observed by Modena.[64]



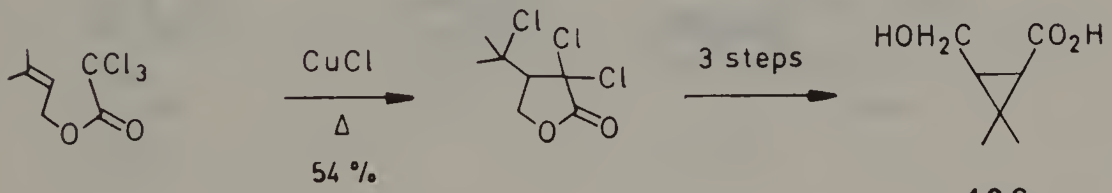
In cyclization reactions of dienes, carbon-free halogen donors can be used. Thus, Traynham[65] has shown that cyclodecadiene **104** gives **105** via radical chlorination.



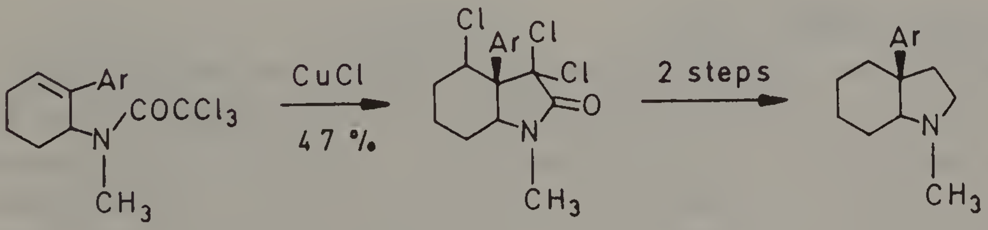
104

105

The alkene can also act as the halogen donor. This is, for example, the case if the halogen abstraction is facilitated by Cu-salts. Ogasawara[66] and Ito[67] have used this method for the synthesis of cyclopropane **106** and mesembrane **107**, respectively.

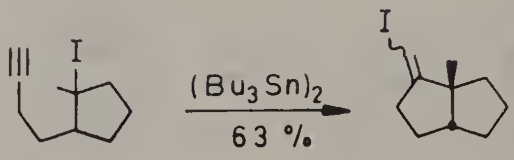


106



107

Weak tert. C-I bonds offer reaction possibilities in which the halogen donor is the molecule that cyclizes. Thus, Curran[68] has shown that iodide **108** yields **109** in the presence of radical initiators.



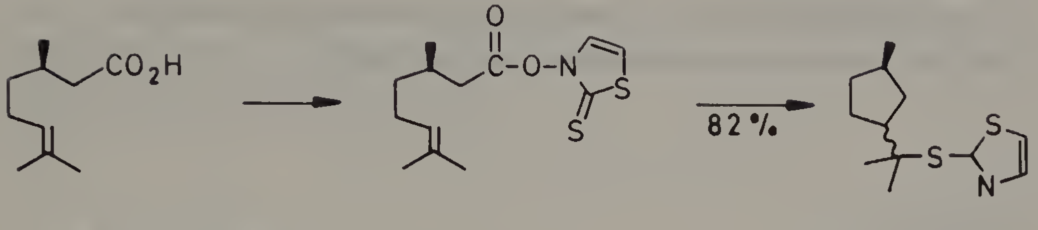
108 **109**

The synthesis of lactone **111** from iodide **110**, carried out by Kraus,[69] presumably occurs via iodine abstraction by the cyclized radical (see p. 81).

110 **111**

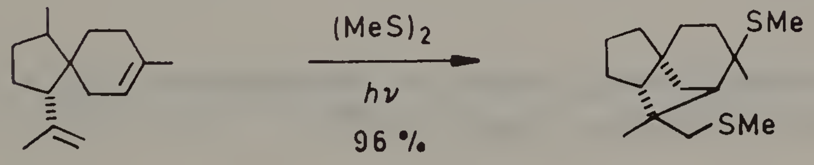
2. Thio donor

Barton[60] has applied his method of radical generation from carboxylic acids via thiohydroxamic acid derivatives (see p.82) to cyclization reactions. The radical precursor is synthesized, for example from citronellic acid, via the acid chloride and reaction with thiothiazole. Irradiation yields the cyclopentyl system **112**, which can be desulfurated to cedrene.

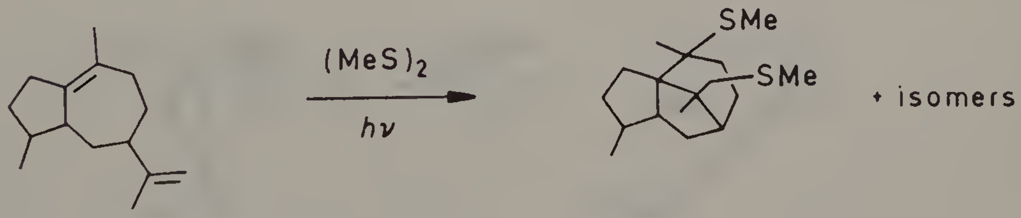


112

Starting with disulfides, cyclized radicals are trapped by thiyl radicals in a non-chain reaction. Thus, Kuehne[71] irradiated α-acoradiene **113** with dimethyl disulfide and obtained a nearly quantitative yield of **114**. Under similar conditions, α-bulnese **115** gives a product mixture containing **116**, which was desulfurated to dihydropatchulene.[71]



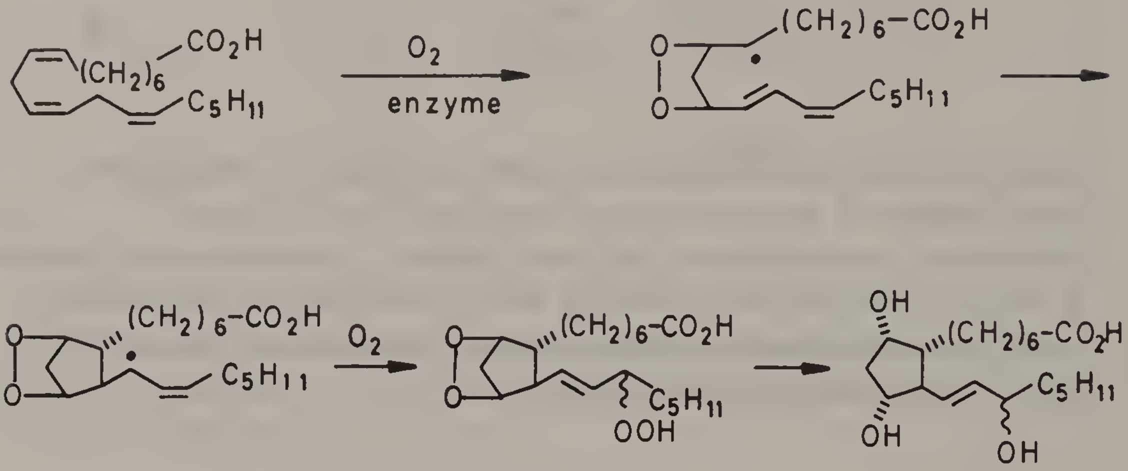
113 **114**



115 **116**

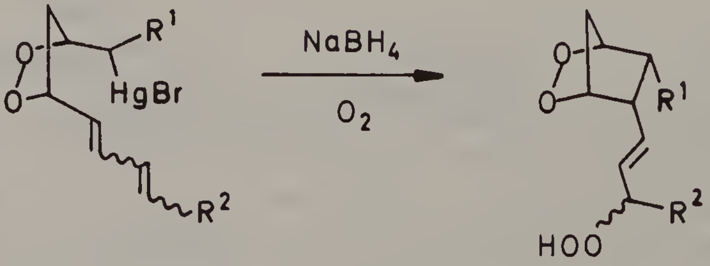
3. Oxygen donor

In the biosynthesis of prostaglandins molecular oxygen presumably traps the cyclized radical **117**.[72]



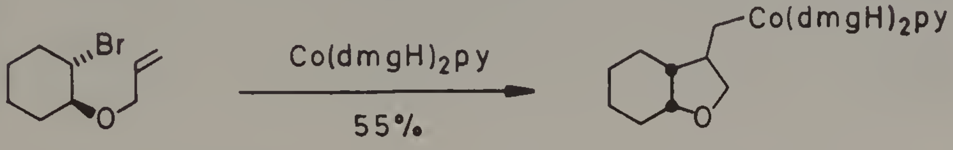
117

Porter[72] and Corey[22] have carried out syntheses that are similar to these in vivo reactions (see p. 154).



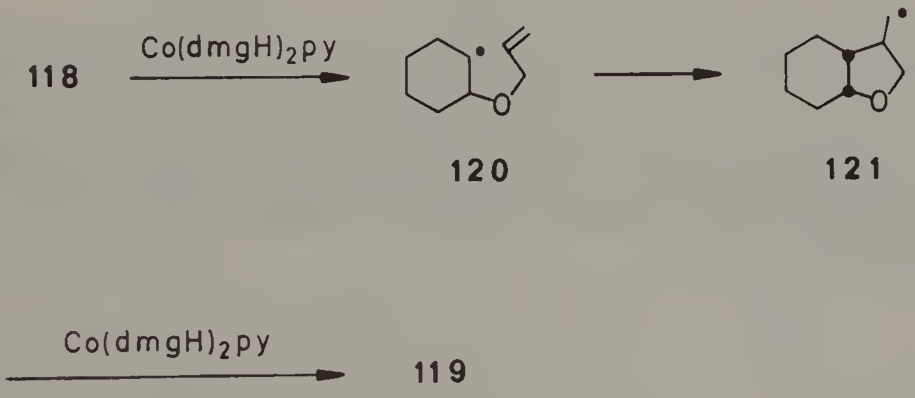
4. Metal donor

In the reaction of 2-allyloxycyclohexyl bromide **118** with cobaloxime (see p. 102), Tada[73] observed the formation of the cyclized organocobaloxime **119**.

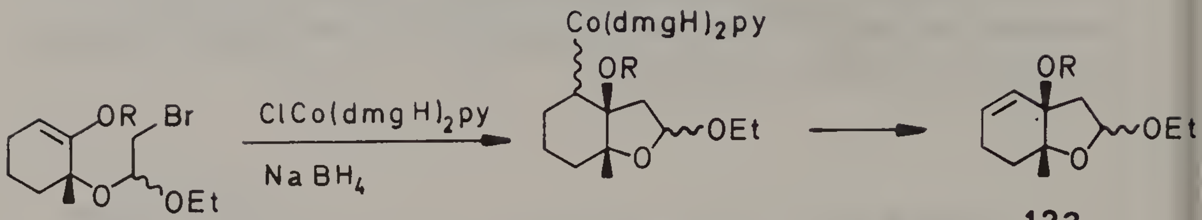


118 **119**

This reaction proceeds via radical **120**, which is formed by electron transfer from cobaloxime to bromide **118**. Radical cyclization and trapping of **121** with cobaloxime yields reaction product **119**.



Organocobaloximes of this kind can undergo 1,2-elimination reactions. Thus, Pattenden[74] cyclized bromide **122** to **123**.

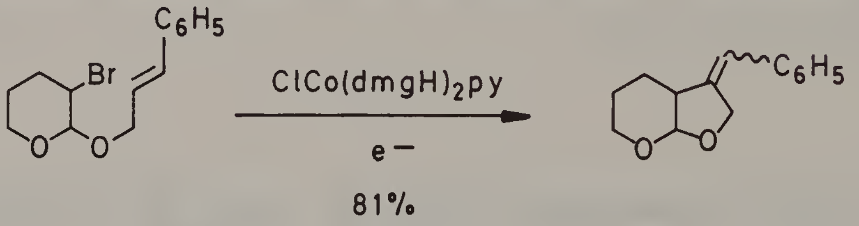


122

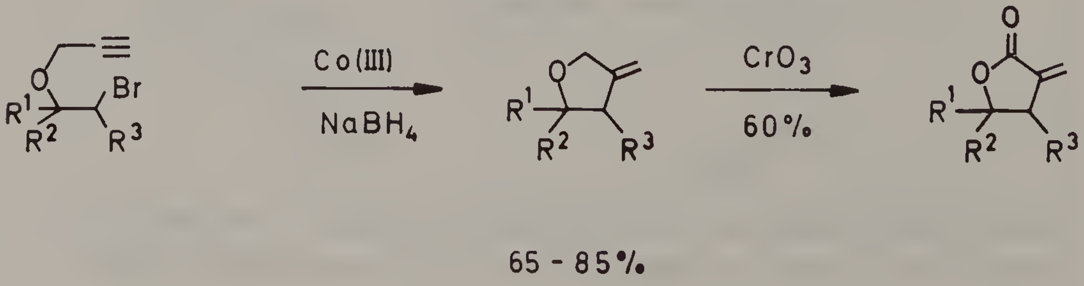
123

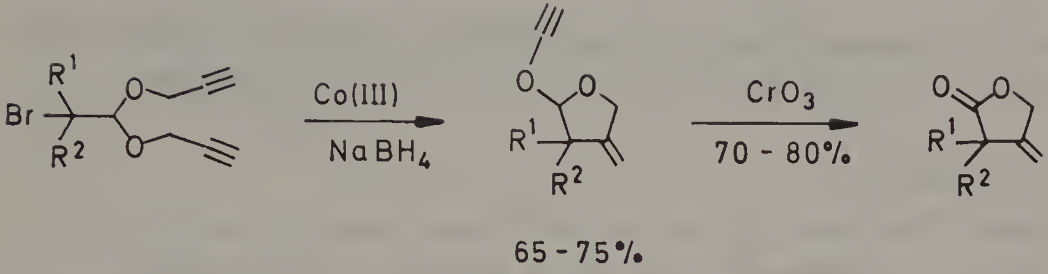
71 %

The cobaloxime is generated in these reactions from chlorocobaloxime with $NaBH_4$, but electrochemical reduction is also possible, as Torii[75] has shown.

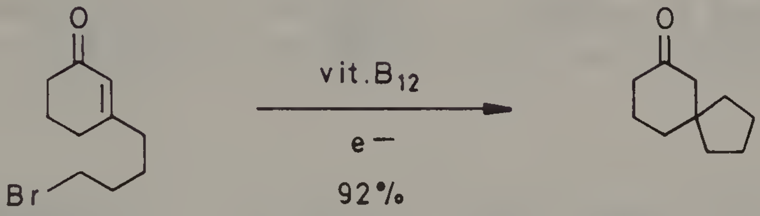


With C-C triple bonds, 1,2-elimination cannot occur and olefins are formed after the cyclization step under reductive conditions.[76]

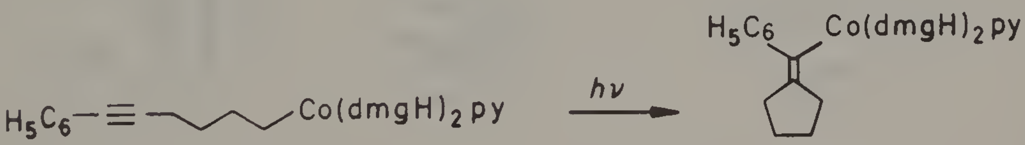




Scheffold[77] used vitamin B_{12} (see p. 111) in analogous reductive cyclization reactions.



These reactions are somewhat similar to the photolysis of hexynylcobaloxime **124** carried out by Johnson.[78] The reaction occurs via radical cyclization **126→127**.



124

125

126

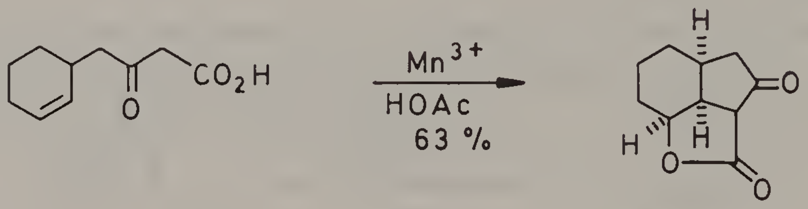
127

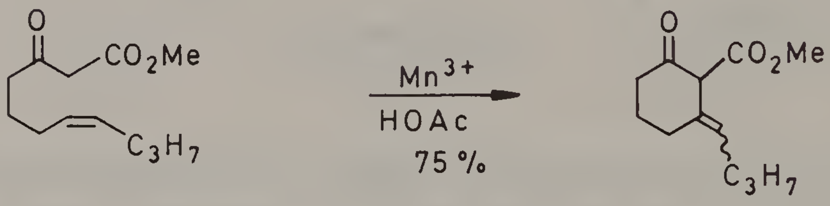
D. Trapping by Electron Transfer Reactions

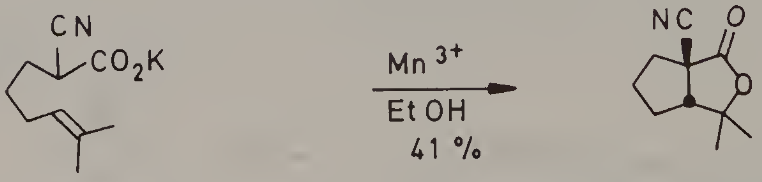
As in intermolecular C-C bond forming reactions, radicals can also be trapped after cyclization by electron transfer.

1. Oxidation

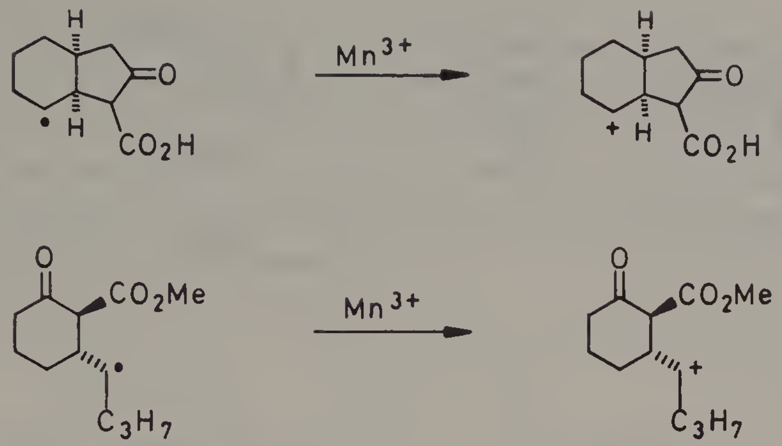
Corey,[79] Fristad,[80] and Snider[81] have used the oxidative addition of carboxylic acids to alkenes (see p. 90) for radical cyclization under mild conditions.



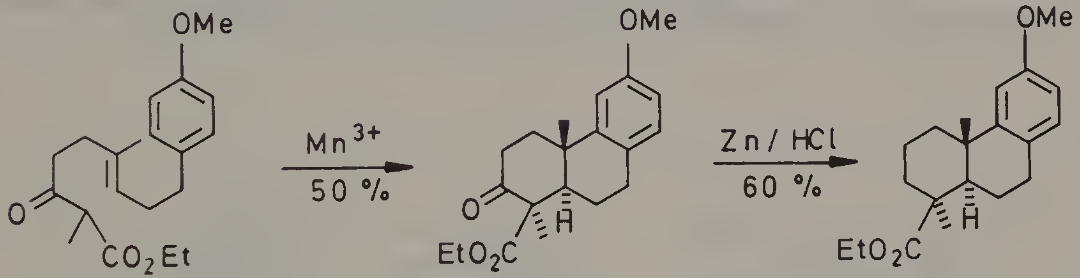




The cyclized radicals are oxidized to cations and either react with nucleophiles or are deprotonated to alkenes.

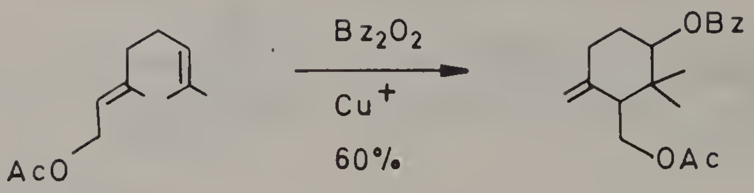


This reaction has been applied to the synthesis of podocarbic ester **129** by cyclization of **128** and Clemmensen reduction.[81]



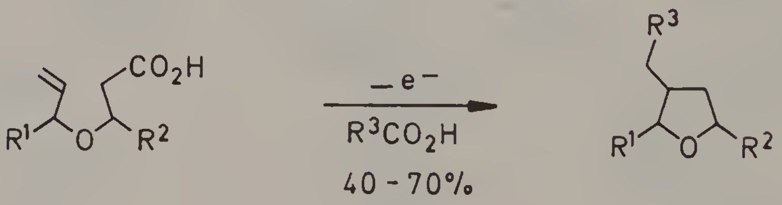
128 **129**

Benzoyloxy radicals, which are generated in a dibenzoyl peroxide/Cu^+ pair, add to one of the double bonds of dienes. Cyclization, followed by oxidation with Cu^{2+}, and finally deprotonation gives the product. Using this methodology, Breslow[82] transformed geranyl acetate to **130**, presumably via radical intermediates.

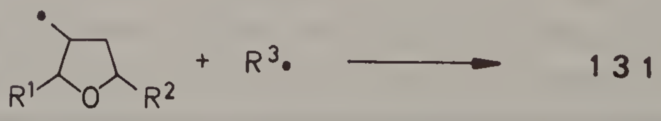


130

Kolbe electrolysis of unsaturated acids has been used by Schäfer[83] for the synthesis of tetrahydrofurans **131**. The products are formed via combination of the cyclized radical **132** with R^3·, generated from an excess of acid R^3CO_2H.



131



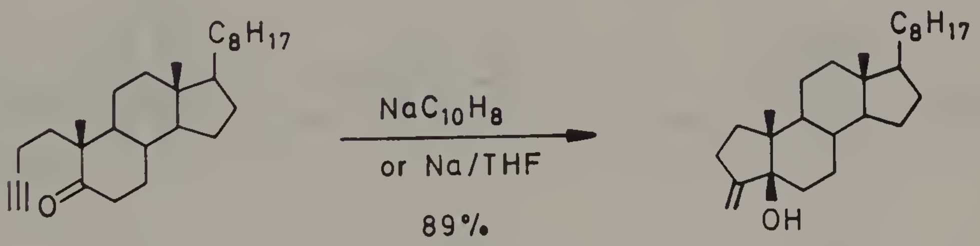
132

2. Reduction

Most of the precursors for radical cyclizations under reductive conditions are ketones which form ketyl radical anions **133**. Intramolecular additions to C-C multiple bonds give cyclized radical anions **134** that are further reduced and protonated. These reactions are not chain reactions and therefore require an excess of reducing agent.

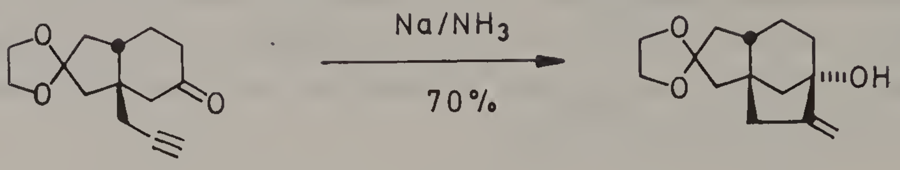
133 **134**

Pradhan[84] used alkali metals or sodium naphthalide for the cyclization of 4,5-secocholestan-5-one **135**.



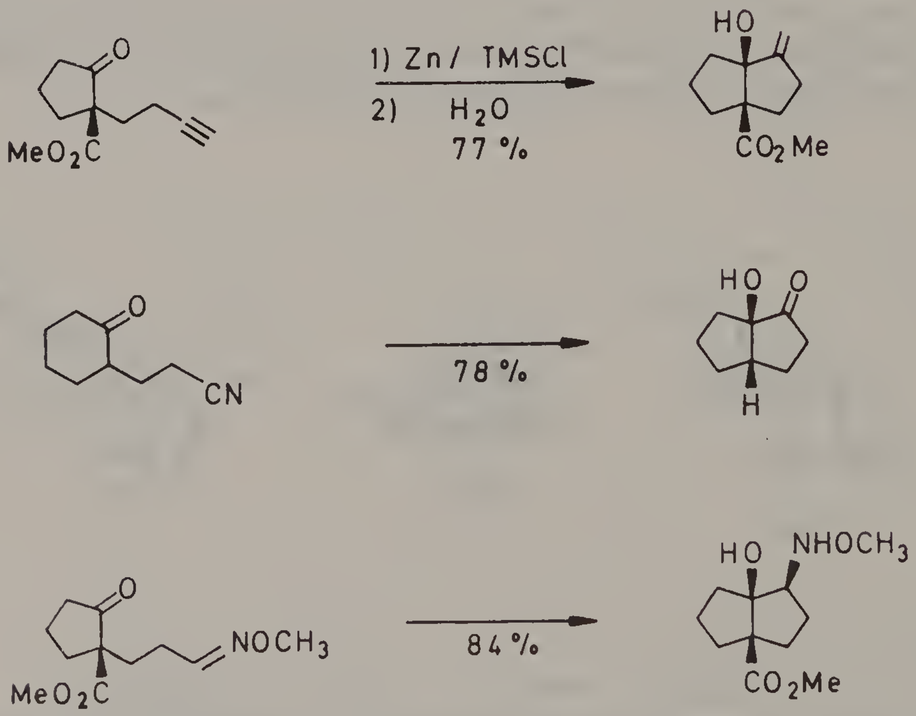
135

As a crucial step in the synthesis of gibberelic acid, Stork[85] treated ketone **136** with Na in liquid ammonia and obtained the cyclized product **137**.

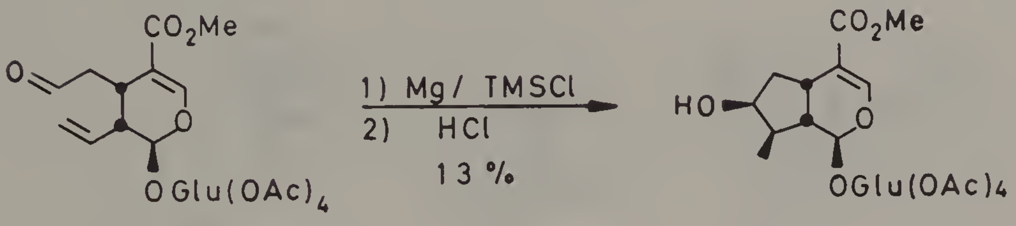


136 **137**

Using Zn as the electron donor, Corey[86] trapped acyclic radicals with various functional groups.

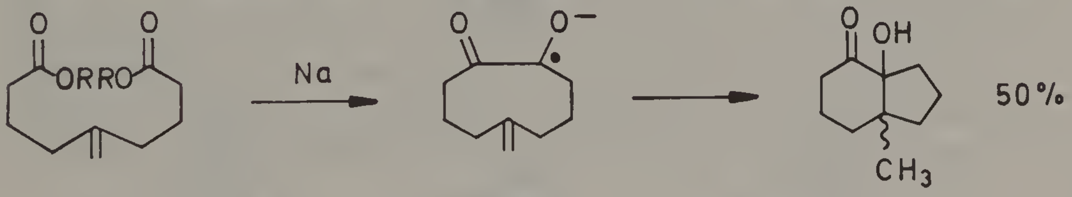


In the formation of loganin tetraacetate **139** from secologanin tetraacetate **138** Hutchinson[87] used Mg as electron donor.



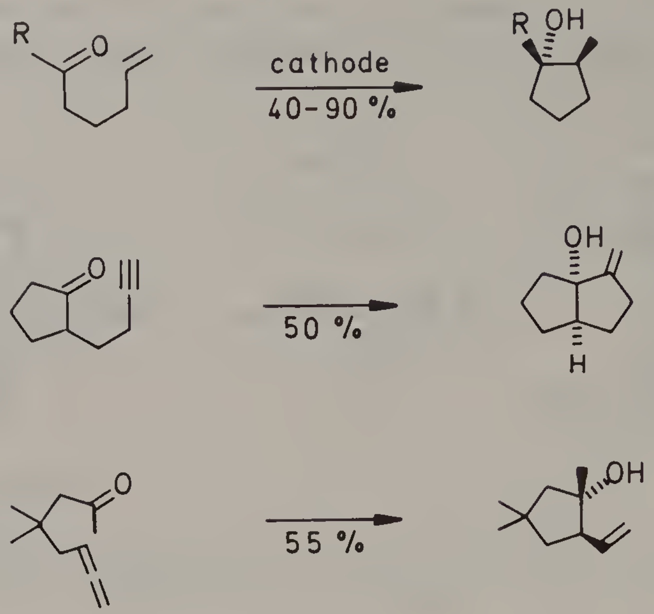
138 **139**

But it is not clear whether, under cyclization conditions with Zn or Mg, the cyclized radicals abstract a hydrogen atom from the solvent or an electron from the metals. The acyloin condensation of the diester **140** gives **142**, presumably via ketyl radical **141**.[88]

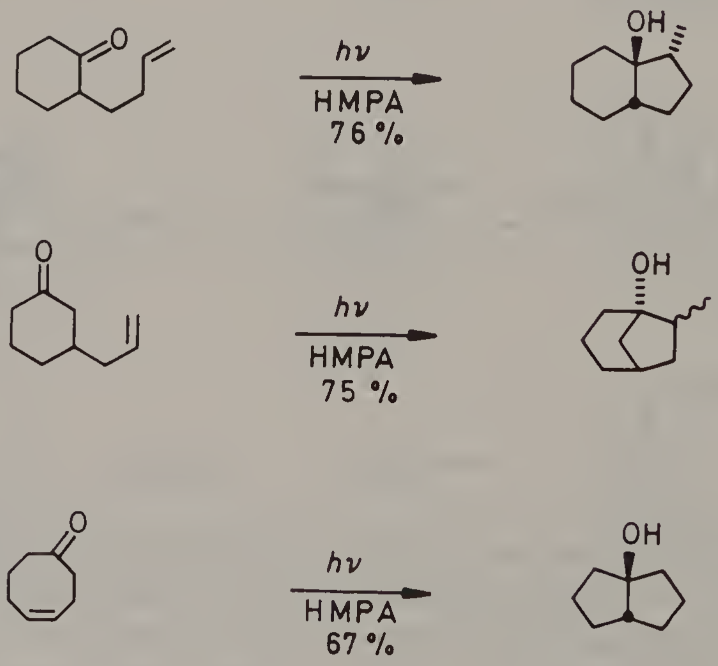


140 **141** **142**

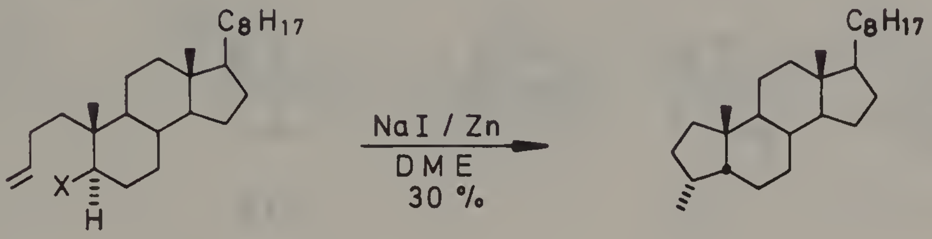
Reduction of ketones and radical cyclizations can also be carried out in an electrochemical cell at the cathode.[89] Alkenes,[90] alkynes,[91] and allenes [92] have been used as C-C multiple bonds to trap ketyl radicals under these conditions.



Photochemically induced electron transfer from tert. amines or hexamethylphosphortriamide to ketones can also lead to cyclized products.[93]



Pradhan[94] has demonstrated that not only ketones, but also iodides can be reductively cyclized. Starting from **143**, the iodide is generated in situ and cyclizes with Zn to give norcholestane **144**.



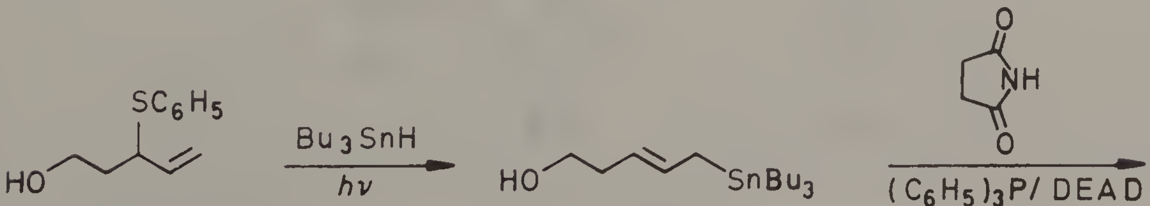
143

$X = OSO_2Me$

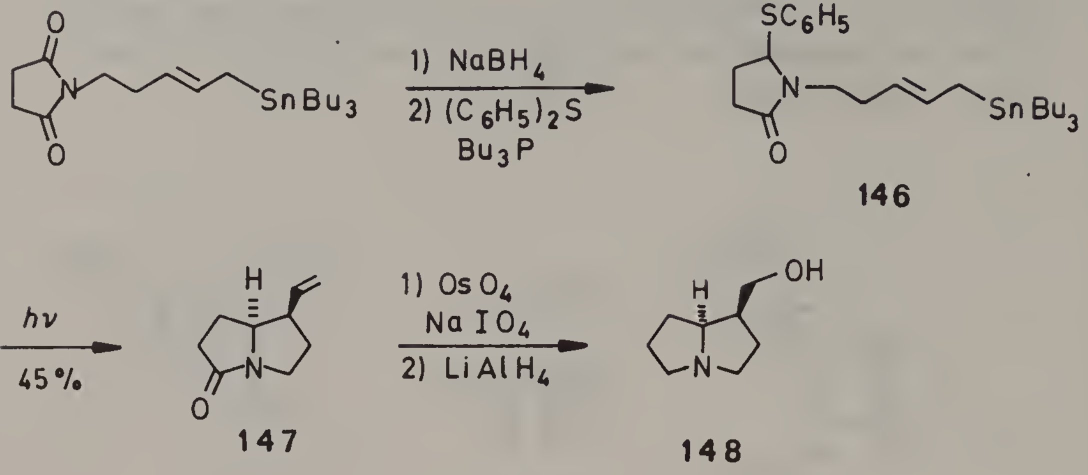
144

E. Fragmentation and Displacement

Reactions in which radicals undergo fragmentation after cyclization reactions have not been very frequently used in synthesis. In one example, Keck[95] has applied the allyltin method (see p. 98) to the synthesis of isoretronecanol **148**. The radical precursor **146** is synthesized from allylthioether **145** via Bu_3SnH addition, followed by phenylthiyl elimination, Mitsunobu coupling, reduction, and thiylation. After the radical cyclization (**146**→**147**), oxidation of the olefinic bond, and reduction of the amide yield the target molecule **148**.



145

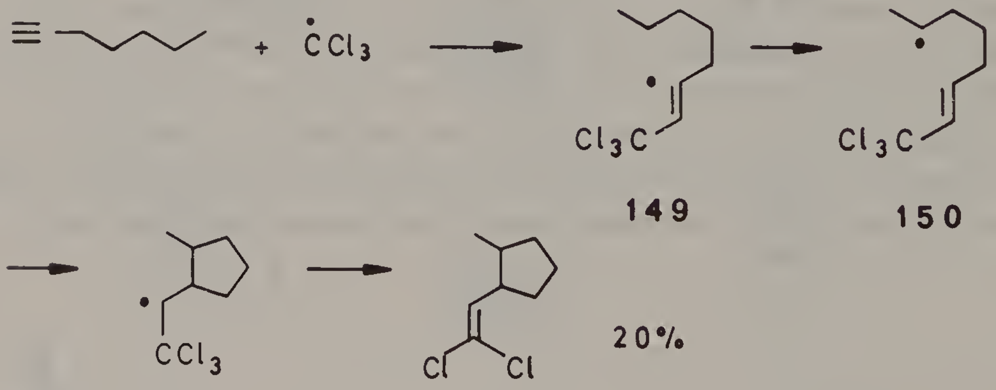


146

147

148

Carbon-halogen bonds ß to a radical center are also cleaved rapidly; thus, the addition of CCl_4 to heptyne gives **152** as a sideproduct via radicals **149**-**151**.



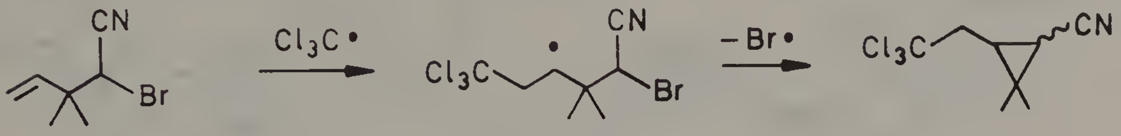
149

150

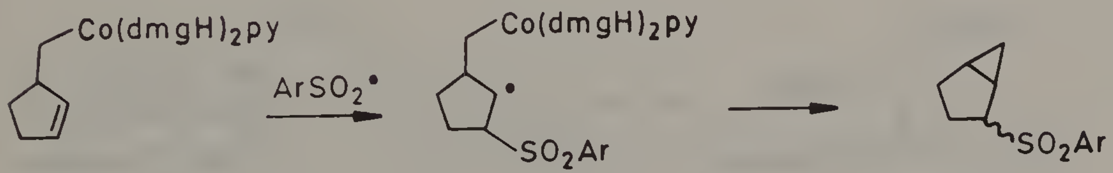
151

152

The displacement of radicals can occur simultaneously with the formation of the ring if the bonds broken are very weak. Thus, Johnson[78,97] has shown that compounds **153** and **155** cleave the C-Br and C-Co bonds concomitant with the radical attack and yield cyclopropanes **154** and **156**, respectively.

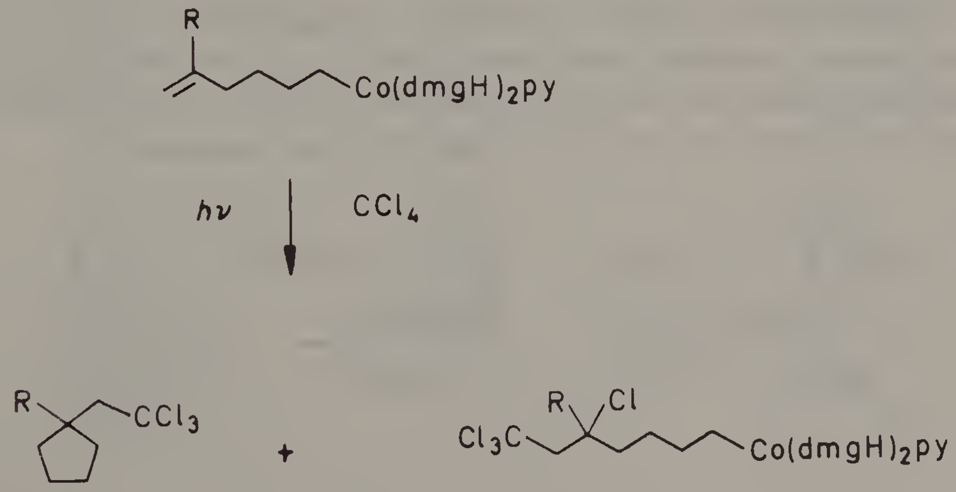


153 **154**



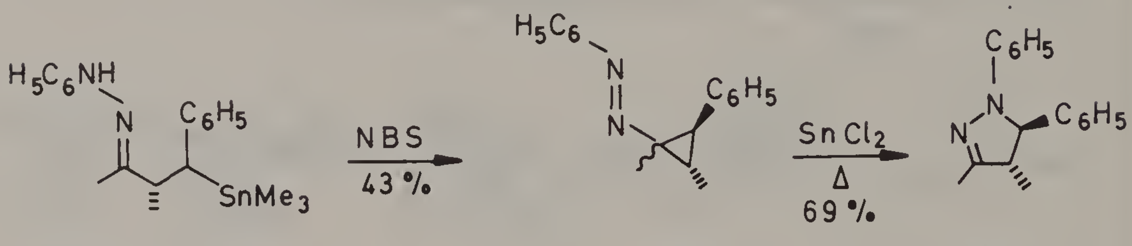
155 **156**

With low concentrations of the intermolecular radical traps, cyclopentanes can also be formed. The thermal and photochemical reaction between 5-hexenylcobaloxime and a large excess of CCl_4 gives mainly the acyclic product **158**; whereas in the presence of a low concentration of CCl_4, cyclopentane **157** is formed.[78]

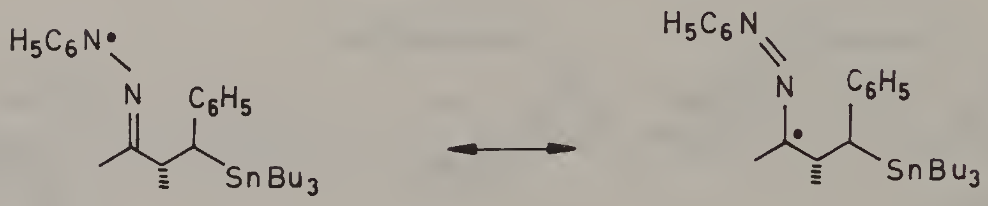


157 **158**

Replacement of a tin radical occurs during the formation of cyclopropane **160** from hydrazone **159**.[98] Radical **162** is the intermediate in this synthesis.



159 **160** **161**

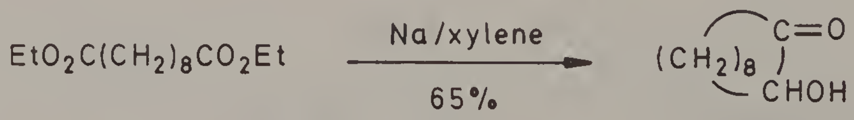


162

F. Biradicals

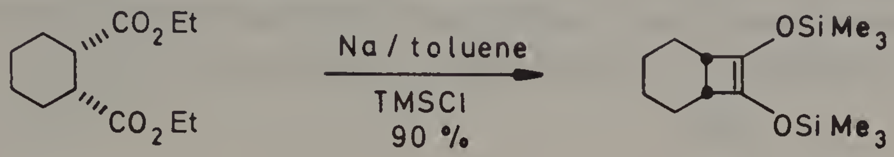
1. Reductive cyclization

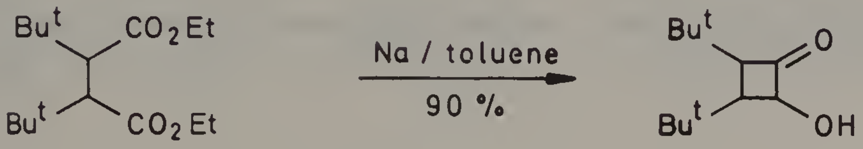
Acyloin condensation is a synthetically important reductive cyclization reaction involving biradicals. The reaction is especially useful for the synthesis of medium-sized rings that are often difficult to make by other methods.[99]



$$EtO_2C(CH_2)_8CO_2Et \xrightarrow[65\%]{Na/xylene} (CH_2)_8\begin{cases} C{=}O \\ CHOH \end{cases}$$

Carbocycles, suffering from angle strain, can also be synthesized.[100]

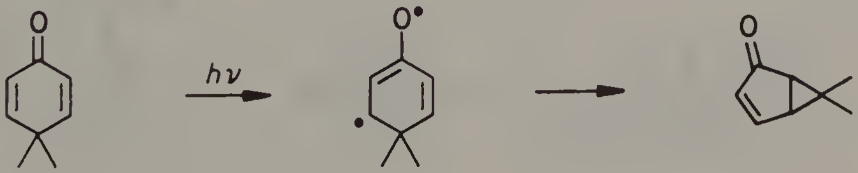




2. Photolytical cyclization of ketones

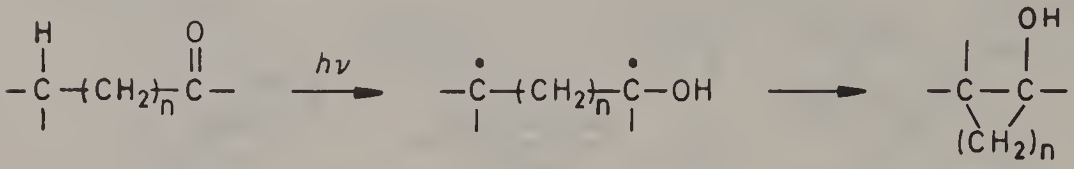
Many photolytical C-C bond forming cyclizations such as the di-π-methane rearrangement (**163→164**), the dienone-cyclopropylketone transformation (**165→166**), many intra- and intermolecular cycloadditions, as well as the Norrish I and Norrish II reactions of carbonyl compounds proceed via biradicals.

163 **164**

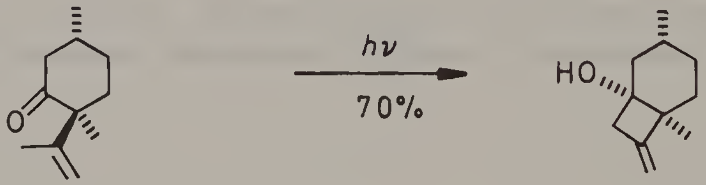


165 **166**

It is far beyond the scope of this text to include these photochemical reactions. There are several monographs and reviews which give excellent overviews of photochemistry.[101] In this chapter, mainly cyclizations are described in which biradicals are generated by intramolecular H-abstraction reactions.

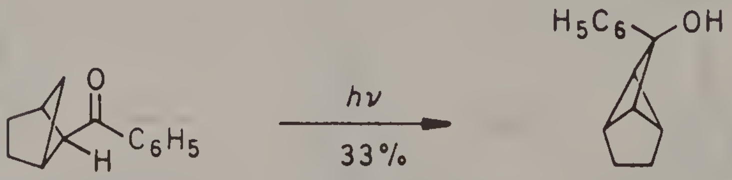


Cyclobutanes are formed following 1,5-hydrogen abstractions; thus, methylisopulegon **167** gives the bicyclic compound **168**,[102] and the strained tricyclic compound **170** is synthesized from **169**.[103]



167

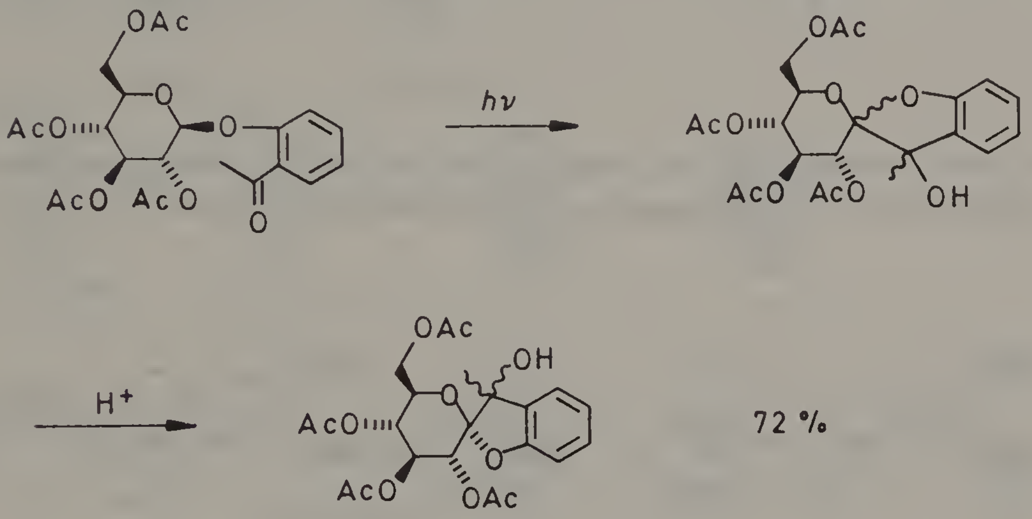
168



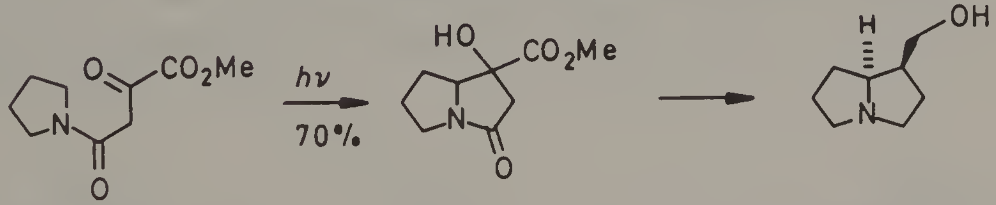
169

170

1,6-Hydrogen abstraction leads to five-membered rings. Descotes[104] used this method for C-C bond formation reactions at the anomeric center of carbohydrates.

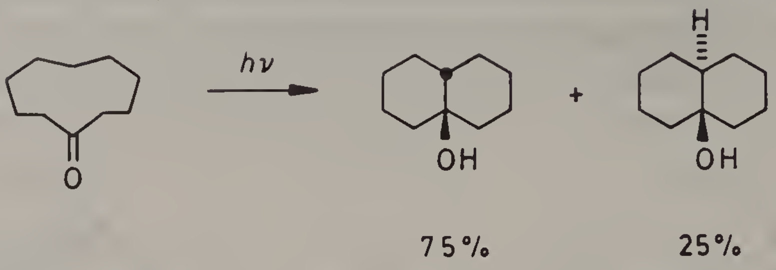


The pyrrolizidine alkaloid isoretronecanol **148** was synthesized from **171**, which cyclizes to **172**.[105]

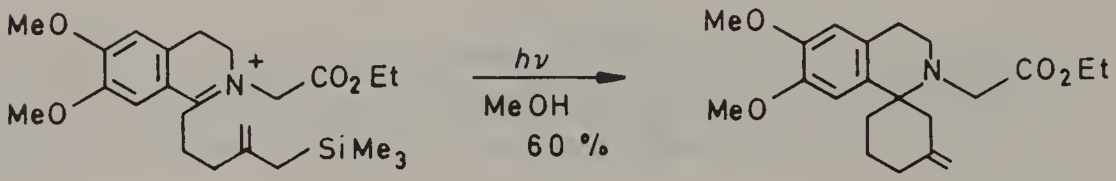


171 **172** **148**

Reactions involving 1,7-hydrogen abstraction form six-membered rings.



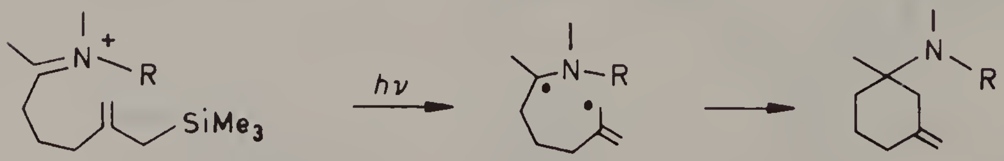
In the synthesis of alkaloids of the erythrina family, Mariano[107] cyclized the dihydroisoquinolinium salt **173** to **174**.



173

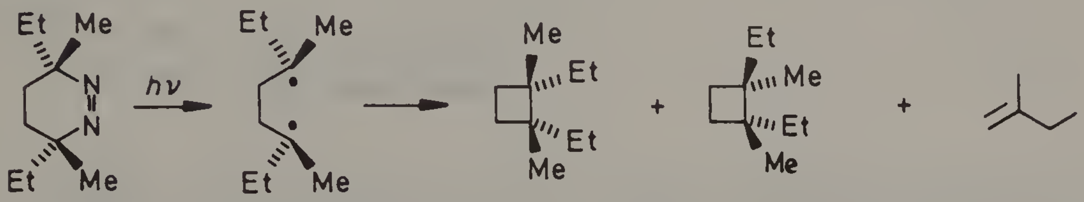
174

A biradical is presumably generated by a photostimulated electron transfer and desilylation step.



3. Diazenes

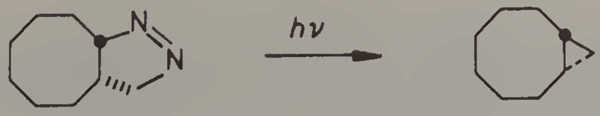
Nitrogen elimination of diazenes gives diradicals which competitively undergo intramolecular radical coupling to yield products of cyclization or disproportionation. Thus, from azo compound **175** cyclobutanes **177** and alkene **178** are formed via biradical **176**.[101]



175 **176** **177a** **177b** **178**

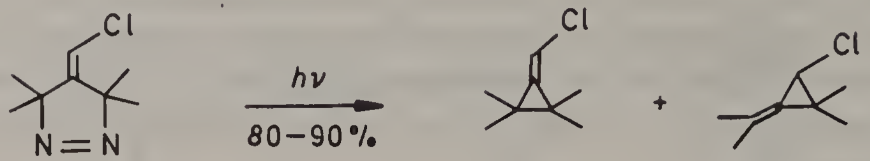
	177a	177b	178
direct :	35%	3,5%	60%
sensitized :	11%	8 %	77%

The amount of cyclized products **177** is relatively low and depends on the condition of the photolysis. The formation of three-membered rings **180** and **182** from pyrazoline derivatives **179** and **181** occurs with higher yields, although the product ratio **182a**:**182b** remains dependent on the photolytic conditions.[108]



96 %

179 **180**

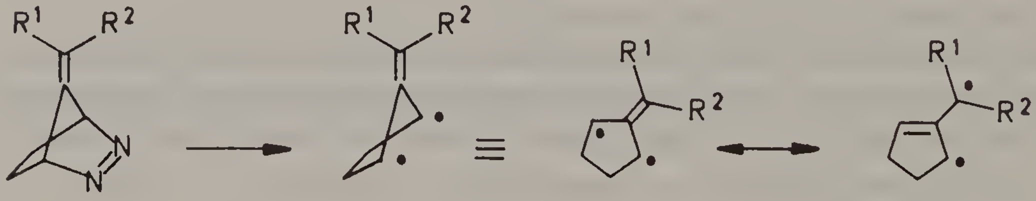


181 **182a** **182b**

direct : 77 : 23
sensitized: 25 : 75

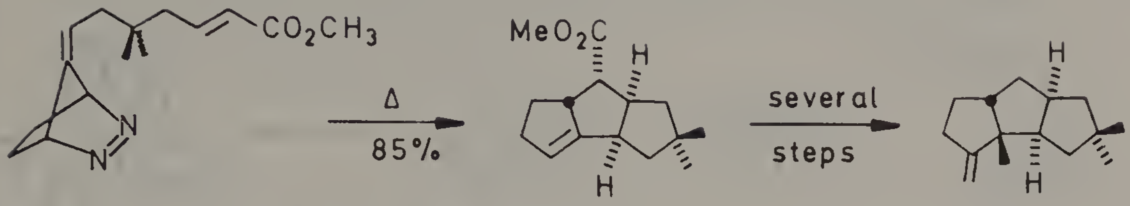
Sensitized photolysis leads to relatively long lived triplet biradicals that loose the stereo- and regiochemical information of the radical precursors **175** and **181**.

Little[109] elegantly applied trimethylenemethane biradicals **184**,[110] generated from cyclic azo compound **183**, in the synthesis of bi- and tricyclic target molecules.



183 **184**

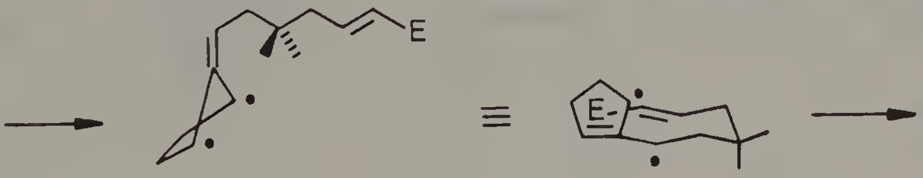
Intramolecular diyl trapping of trimethylenemethane derivatives leads to tricyclopentanoids of the hirsutene,[109,111] capnellene,[112] and coriolin[113] type. For the hirsutene synthesis, thermolysis of diazene **185** in boiling acetonitrile gives tricyclus **186**, which can be converted into hirsutene **55**.[111]



185 **186** **55**

The formation of **186** from diazene **185** proceeds via biradical **187** which reacts with the neighboring double bond. The high stereoselectivity of this reaction points to a preferred conformation, which could be caused by secondary orbital interactions between the ester group and the diyl ring carbon atoms.

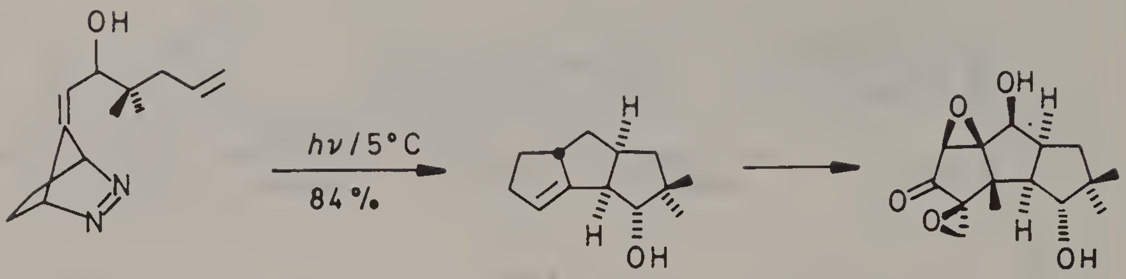
185



186

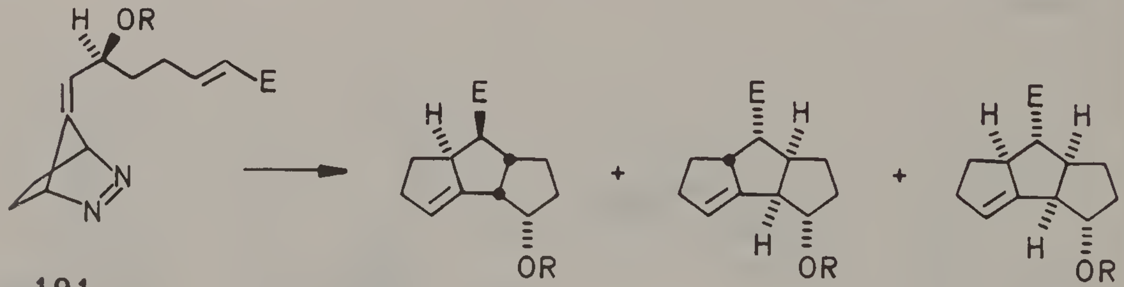
187 (E = CO_2Me)

The synthesis of coriolin **190** requires diazene **188**, which upon photolysis, gives **189**.[112]



188 **189** **190**

Detailed studies show that the stereochemistry of this diyl trapping reaction is temperature dependent.[114] Thus, the decomposition of diazene **191** gives products whose ratio changes by varying the reaction temperature.

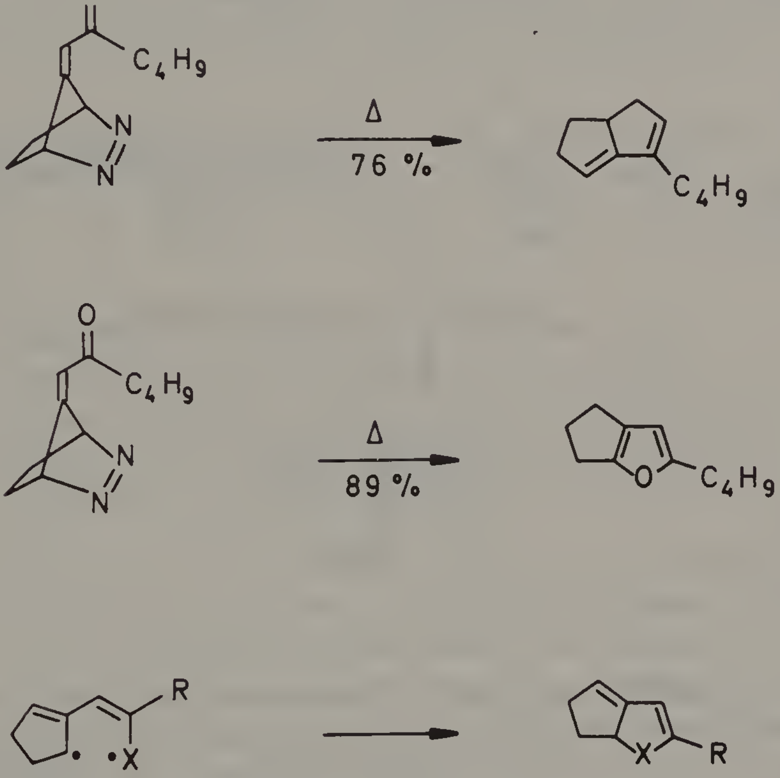


191

R : $SiMe_2Bu^t$
E : CO_2Me

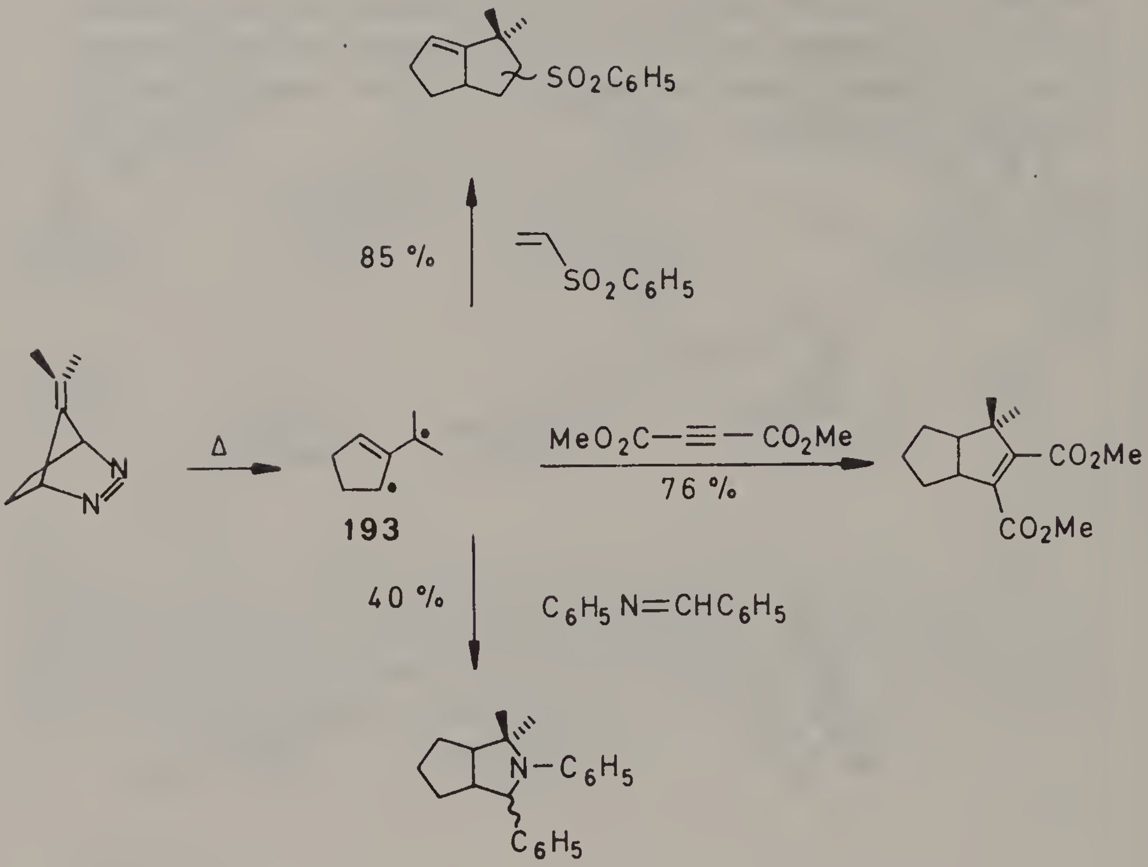
-31°C	1	:	48,5	:	2,4
+81°C	1	:	11,7	:	0,8

Bicyclic cyclopentanoids can be synthesized if the multiple bond is conjugated with the radical center. In these cases, even C-O double bonds can be used in direct combination reactions of diradical **192**.[115]



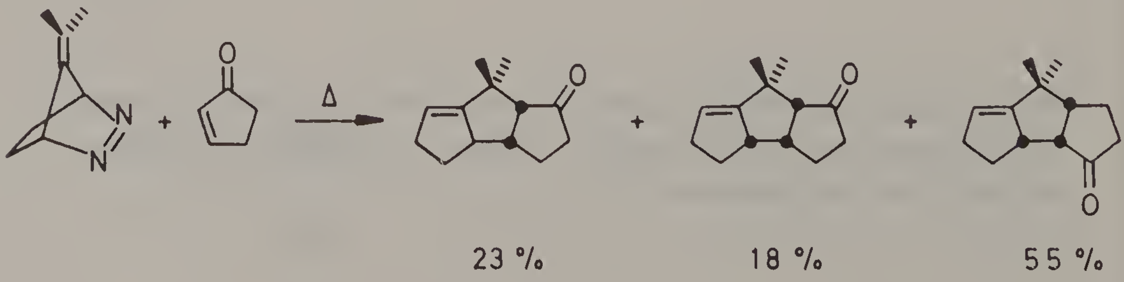
192

The trimethylenemethane derivatives **193** can also be trapped intermolecularly by alkenes, alkynes, aldehydes, ketones, imines, and thioketones.[116]



193

The low regioselectivity of these reactions limits their synthetic usefulness. Therefore, although the precursors are easily accessible and the total yields are high, the synthesis of complex tricyclopentanoids via intermolecular diyl trapping cannot compete with the intramolecular method.



REFERENCES

1. D.J. Hart, *Science* **1984**, *223*, 883; B. Giese, *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 553, B. Giese (ed.): *Selectivity and Synthetic Applications of Radical Reactions*, *Tetrahedron* **1985**, *41*, 3887.

2. P. Schmid, D. Griller, K.U. Ingold, *Int. J. Chem. Kinet.* **1979**, *11*, 333; P.I. Abell in C.H. Bamford, C.F.H. Tipper (ed.): *Kinetics* Vol. XVIII, Elsevier, Amsterdam 1976, p. 111.

3. C. Chatgilialoglu, K.U. Ingold, J.C. Scaiano, *J. Am. Chem. Soc.* **1981**, *103*, 7739.

4. S.U. Park, S.K. Chung, M. Newcomb, *J. Am. Chem. Soc.* **1986**, *108*, 240.

5. A.L.J. Beckwith, K.U. Ingold in P. de Mayo (ed.): *Rearrangements in Ground and Excetid States* Vol. 1, Academic Press, New York 1980, p. 161; J.M. Surzur in R.A. Abramovitch (ed.): *Reactive Intermediates*, Vol. 2, Plenum Press, New York 1982, p. 121.

6. D.I. Davies in D.H. Hey, W.A. Waters, R.O.C. Norman (ed.): *Essays on Free-Radical Chemistry* Burlington House, London 1970, p. 201; B. Giese, K. Jay, *Chem. Ber.* **1977**, *110*, 1364; P.C. Wong, D. Griller, *J. Org. Chem.* **1981**, *46*, 2327.

7. T.A. Halgren, M.E.H. Howden, M.E. Medorf, J.D. Roberts, *J. Am. Chem. Soc.* **1967**, *89*, 3051.

8. G. Greig, J.C.J. Thynne, *Trans Faraday Soc.* **1966**, *62*, 3338; S. Sustmann, C. Rüchardt, *Chem. Ber.* **1975**, *108*, 3043.

9. S.J. Christol, R.J. Daughenbaugh, *J. Org. Chem.* **1979**, *44*, 3434.

10. A.L.J. Beckwith, C.H. Schiesser, *Tetrahedron* **1985**,*41*, 3925; A.L.J. Beckwith, G.F. Meijs, *J. Chem. Soc. Perkin Trans. 2* **1979**, 1535; A.L.J. Beckwith, G. Phillipou, A.K. Serelis, *Tetrahedron Lett.* **1981**, *22*, 2811.

11. N.A.Porter, unpublished results.

12. J.E. Baldwin, *J. Chem. Soc. Chem. Commun.* **1976**, 734.

13. B. Giese, *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 753.

14. M. Julia, C. Descoins, M. Baillarge, B. Jacquet, D. Uguen, F.A. Groeger, *Tetrahedron* **1975**, *31*, 1737.

15. P. Bischof, *Tetrahedron Lett.* **1979**, 1291.

16. A.N. Abeywickreyma, V.W. Bowry, S.A. Glover, P.E. Pigou, unpublished results.

17. M. Julia, *Acc. Chem. Res.* **1971**, 4, 386; M. Julia, *Pure Appl. Chem.* **1974**, *40*, 553.

18. J.W. Wilt, *Tetrahedron* **1985**, *41*, 3979.

19. M.D. Bachi, F. Frolow, C. Hoornaert, *J. Org. Chem.* **1983**, *48*, 1841.

20. D.A. Burnett, J.K. Choi, D.J. Hart, Y.M. Tsai, *J. Am. Chem. Soc.* **1984**, *106*, 8201.

21. A.L.J. Beckwith, C.J. Easton, A.K. Serelis, *J. Chem. Soc. Chem. Commun.* **1980**, 482.

22. E.J. Corey, C. Shih, N.Y. Shih, K. Shimoji, *Tetrahedron Lett.* **1984**, *25*, 5013.

23. D.G. Wujek, N.A. Porter, *Tetrahedron* **1985**, *41*, 3973.

24. S. Danishefsky, S. Chackalamannil, B.J. Uang, *J. Org. Chem.* **1982**, *47*, 2231; S. Danishefsky, E. Taniyama. *Tetrahedron Lett.* **1983**, *24*, 15.

25. Y. Matsuki, M. Kodama, S. Ito, *Tetrahedron Lett.* **1979**, 4081.

26. P. Bakuzis, O.S. Campos, M.L.F. Bakuzis, *J. Org. Chem.* **1976**, *41*, 3261; G. Büchi, H. Wüest, *J. Org. Chem.* **1979**, *44*, 546.

27. G. Stork in H. Nozaki (ed.): *Current Trends in Organic Synthesis*, Pergamon Press, Oxford 1983, p. 359.

28. G. Stork, R. Mook, *J. Am. Chem. Soc.* **1983**, *105*, 3721.

29. D.P. Curran, D.M. Rakiewicz, *Tetrahedron* **1985**, *41*, 3943.

30. D.P. Curran, M.H. Chen, *Tetrahedron Lett.* **1985**, *26*, 4991.

31. D.P. Curran, S.C. Kuo, *J. Am. Chem. Soc.* **1986**, *108*, 1106.

32. A.L.J. Beckwith, D.H. Roberts, C.H. Schiesser, A. Wallner, *Tetrahedron Lett.* **1985**, *26*, 3349.

33. W.R. Leonard, T. Livinghouse, *Tetrahedron Lett.* **1985**, *26*, 6431.

34. C.P. Chuang, D.J. Hart, *J. Org. Chem.* **1983**, *48*, 1782;
D.J. Hart, H.C. Huang, *Tetrahedron Lett.* **1985**, *26*, 3749.

35. J.K. Choi, D.J. Hart, *Tetrahedron* **1985**, *41*, 3959.

36. M.D. Bachi, C. Hoornaert, *Tetrahedron Lett.* **1982**, *23* 2505.

37. M.D. Bachi, C. Hoornaert, *Tetrahedron Lett.* **1981**, *22*, 2689.

38. J.J. Köhler, W.N. Speckamp, *Tetrahedron Lett.* **1977**, 635.

39. A. Padwa, H. Nimmesgern, G.S.K. Wong, *J. Org. Chem.* **1985**, *50*, 5620.

40. C.S. Wilcox, L.M.Thomasco, *J. Org. Chem.* **1985**, *50*, 546.

41. G. Stork, N.H. Baine, *Tetrahedron Lett.* **1985**, *26*, 5927.

42. N.N. Marinovic, H.Ramanathan,*Tetrahedron Lett.* **1983**, *24*, 1871.

43. G. Stork, R. Mook, S.A. Biller, S.D. Rychnovsky, *J. Am. Chem. Soc.* **1983**, *105*, 3741.

44. D.L.J.Clive,P.L. Beaulieu, *J. Chem. Soc. Chem. Commun.* **1983**, 307.

45. M.D. Bachi, E. Bosch, *Tetrahedron Lett.* **1986**,*27*, 641.

46. M. Ladlow, G. Pattenden, *Tetrahedron Lett.* **1984**, *25*, 4317.

47. F. Flies, R. Lalande, B. Maillard, *Tetrahedron Lett.* **1976**, 439.

48. R. Gompper, D. Lach, *Tetrahedron Lett.* **1973**, 2687;
M. Apparu, J.K. Crandall, *J. Org. Chem.* **1984**, *49*, 2125.

49. D.D. Tanner, P.M. Rahimi, *J. Org. Chem.* **1979**, *44*, 1674.

50. D.L.J. Clive, P.L. Beaulieu, L. Set, *J. Org. Chem.* **1984**, *49*, 1313.

51. G.A. Kraus, Y.S. Hon, *J. Org. Chem.* **1985**, *50*, 4605.

52. N. Ono, H. Miyake, A. Kaminura, I. Hamamoto, R. Tamura, A. Kaji, *Tetrahedron* **1985**, *41*, 4013.

53. G. Stork, P.M. Sher, *J. Am. Chem. Soc.* **1986**, *108*, 302.

54. M. Julia, J.M. Surzur, L. Katz, *C.R. Acad. Sci. Ser. C* **1960**, *251*, 1030; M. Julia, *Rec. Chem. Progr.* **1964**, *25*, 3; M. Julia, *Pure Appl. Chem.* **1967**, *15*, 167.

55. M. Julia, C. James, *C. R. Acad. Sci. Ser. C* **1962**, *255*, 959.

56. M. Julia, F. Le Goffic *Bull. Soc. Chim. Fr.* **1964**, 1129; J.D. Winkler, V. Sridar, *J. Am. Chem. Soc.* **1986**, *108*, 1708.

57. J.P. Montheard, *C. R. Acad. Sci. Ser. C* **1965**, *260*, 577.

58. D.H.R. Barton, D.L.J. Clive, P.D. Magnus, G. Smith, *J. Chem. Soc. C* **1971**, 2193.

59. E. van Bruggen, *Rec. Trav. Chim. Pays-Bas* **1968,** *87*, 1134.

60. D. Elad in O.L. Chapman: *Organic Photochemistry*, Vol. 2, Marcel Dekkar, New York 1969, p. 168.

61. L. Freedman, *J. Am. Chem. Soc.* **1964**, *86*, 1885; P. Gottschalk, D.C. Neckers, *J. Org. Chem.* **1985**, *50*, 3498.

62. T.W. Sam, J.K. Sutherland, *J. Chem. Soc. Chem. Commun.* **1971**, 970; J.G. Traynham, H.H. Hsieh, *J. Org. Chem.* **1973**, *38*, 868; E.D. Brown, T.W. Sam, J.K. Sutherland, A. Torre *J. Chem. Soc. Perkin Trans. 1* **1975**, 2326.

63. N.O. Brace, *J. Org. Chem.* **1966**, *31*, 2879; N.O. Brace, *J. Org. Chem.* **1973**, *38*, 3167.

64. P. Piccardi, M. Modena, L. Cavalli, *J. Chem. Soc. C* **1971**, 3959; P. Piccardi, P. Massardo, M. Modena, E. Santoro, *J. Chem. Soc. Perkin Trans. 1* **1974**, 1848.

65. J.G. Traynham, H.H. Hsieh, *J. Org. Chem.* **1973**, *38*, 868.

66. S. Takano, S. Nishizawa, M. Akiyama, K. Ogasawara, *Synthesis* **1984**, 949.

67. H. Nagashima, K. Ara, H. Wakamatsu, K. Itoh, *J. Chem. Soc. Chem. Commun.* **1985**, 518.

68. D.P. Curran, M.H. Chen, D. Kim, *J. Am. Chem. Soc.* **1986,** *108*, 2489.

69. G.A. Kraus, K. Landgrebe, *Tetrahedron* **1985**, *41*, 4039.

70. D.H.R. Barton, D. Crich, G. Kretzschmar, *J. Chem. Soc. Perkin Trans. 1* **1986**, 39.

71. M.E. Kuehne, R.E. Damon, *J. Org. Chem.* **1977**, *42*, 1825.

72. N.A. Porter, M.O. Funk, *J. Org. Chem.* **1975**, *40*, 3614.

73. M. Okabe, M. Tada, *Chemistry Lett.* **1980**, 831.

74. M. Ladlow, G. Pattenden, *Tetrahedron Lett.* **1984**, *25*, 4317.

75. S. Torii, T. Inokuchi, T. Yukawa, *J. Org. Chem.* **1985**, *50*, 5875.

76. M. Okabe, M. Abe, M. Tada, *J. Org. Chem.* **1982**, *47*, 1775, 5382.

77. R. Scheffold, M. Dike, S. Dike, T. Herold, L. Walder, *J. Am. Chem. Soc.* **1980**, *102*, 3642; R. Scheffold, *Chimica* **1985**, *39*, 203.

78. M.D. Johnson, *Acc. Chem. Res.* **1983**, *16*, 343.

79. E.J. Corey, M. Kang, *J. Am. Chem. Soc.* **1984**, *106*, 5384.

80. A.B. Ernst, W.E. Fristad, *Tetrahedron Lett.* **1985**, *26*, 3761.

81. B.B. Snider, R. Mohan, S.A. Kates *J. Org. Chem.* **1985**, *50*, 3661.

82. R. Breslow, J.T. Groves, S.S. Olin *Tetrahedron Lett.***1966**, 4717; R.M. Coates, L.S. Melvin, *J. Org. Chem.* **1970**, *35*, 865.

83. R. Breslow, S.S. Olin, J.T. Groves, *Tetrahedron Lett.* **1968**, 1837.

84. S.K. Pradhan, S.R. Kadam, J.N. Kolhe, T.V. Radhakrishnan, S.V. Sohani, V.B. Thaker, *J. Org. Chem.* **1981**, *46*, 2622.

85. G. Stork, R.K. Boeckmann, D.F. Taber, W.C. Still, J. Singh, *J. Am. Chem. Soc.* **1979**, *101*, 7107.

86. E.J. Corey, S.G. Pyne, *Tetrahedron Lett.* **1983**, *24*, 2821.

87. T. Ikeda, S. Yue, C.R. Hutchinson, *J. Org. Chem.* **1985**, *50*, 5193.

88. P.Y. Johnson, M.A. Priest, *J. Am. Chem. Soc.* **1974**, *96*, 5618.

89. H.J. Schäfer, *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 911.

90. T. Shono, I. Nishiguchi, H. Ohmizu, M. Mitani, *J. Am. Chem. Soc.* **1978**, *100*, 545.

91. R. Pallaud, M. Nicolaus, *C. R. Acad. Sci. Ser.* **1968**, *C 267*, 1834; M.J. Allen, J.A. Siragusa, W. Pierson, *J. Chem. Soc.* **1960**, 1045.

92. G. Pattenden, G.M. Robertson, *Tetrahedron* **1985**, *41*, 4001.

93. D. Belotti, J. Cossy, J.P. Pete, C. Portella, *Tetrahedron Lett.* **1985**, *26*, 4591.

94. S.K. Pradhan, J.N. Kolhe, J.S.Mistry, *Tetrahedron Lett.* **1982**, *23*, 4481.

95. G.E. Keck, E.J. Enholm, *Tetrahedron Lett.* **1985**, *26*, 3311.

96. E.I. Heiba, R.M. Dessau, *J. Am. Chem. Soc.* **1967**, *89*, 3772; K.M. Kopchik, J.A. Kampmeier, *J. Am. Chem. Soc.* **1968**, *90*, 6733.

97. A. Bury, S.T. Corker, M.D. Johnson, *J. Chem. Soc. Perkin Trans. 1* **1982**, 645.

98. H. Nishiyama, H. Arai, Y. Kanai, H. Kawashima, K. Itoh, *Tetrahedron Lett.* **1986**, *27*, 361.

99. J.J. Bloomfield, D.C. Owsley, J.M. Nelke, *Org. Reactions* **1976**, *23*, 259.

100. J.J. Bloomfield, *Tetrahedron Lett.* **1968**, 587; J.M. Conia, J.M. Denis, *Tetrahedron Lett.* **1969**, 3545.

101. D.O. Cowan, R.L. Drisko: *Elements of Organic Photochemistry*, Plenum Press, New York 1976.

102. R.C. Cookson, J. Hudec, A. Szabo, G.E. Usher, *Tetrahedron* **1968**, *24*, 4353.

103. A. Padwa, W. Eisenberg, *J. Am. Chem. Soc.* **1970**, *92*, 2590.

104. C. Bernasconi, L. Cottier, G. Descotes, J.P. Praly, G. Remy, M.F. Grenier-Loustalot, F. Metras, *Carbohydr. Res.* **1983**, *115*, 105.

105. J.C. Gramain, R. Remuson, D. Vallée, *J. Org. Chem.* **1985**, *50*, 710.

106. M. Barnard, N.C. Yang, *Proc. Chem. Soc., London* **1958**, 302.

107. R.Ahmed-Schofield, P.S. Mariano, *J. Org. Chem.* **1985**, *50*, 5667.

108. S.D. Andrews, A.C. Day, *J. Chem. Soc. Chem. Commun.* **1966**, 667; T. Aratani, Y. Nakanisi, H. Nozaki, *Tetrahedron* **1970**, *26*, 4339.

109. R.D. Little, G.W. Muller, *J. Am. Chem. Soc.* **1979**, *101*, 7129.

110. J.A. Berson, *Acc. Chem. Res.* **1978**, *11*, 446.

111. R.D. Little, G.W. Muller, *J. Am. Chem. Soc.* **1981**, *103*, 2744.

112. R.D. Little, G.L. Carroll, *Tetrahedron Lett.***1981**, *22*, 4389.

113. L. Van Hijfte, R.D. Little, *J. Org. Chem.* **1985**, *50*, 3940.

114. K.J. Stone, R.D. Little, *J. Am. Chem. Soc.* **1985**, *107*, 2495.

115. K.D. Moeller, R.D. Little, *Tetrahedron Lett.* **1985**, *26*, 3417.

116. R.D. Little, H. Bode, K.J. Stone, O. Wallquist, R. Dannecker,*J. Org. Chem.* **1985**, *50*, 2400.

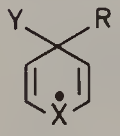
117. R.D. Little, A. Bukhari, M.G. Venegas, *Tetrahedron Lett.* **1979**, 305.

Chapter 5

C—C Bond Formation of Aromatic Systems

A. Introduction

Formation of C-C bonds by radical reactions involving neutral or charged, carbocyclic or heterocyclic aromatic systems can occur via radicals **1** - **4**.



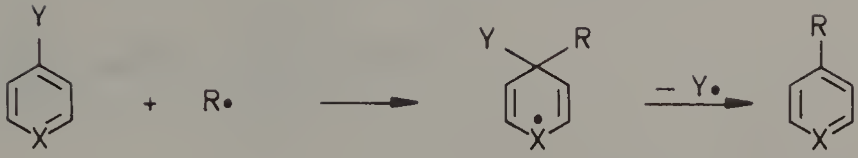
1

2

3

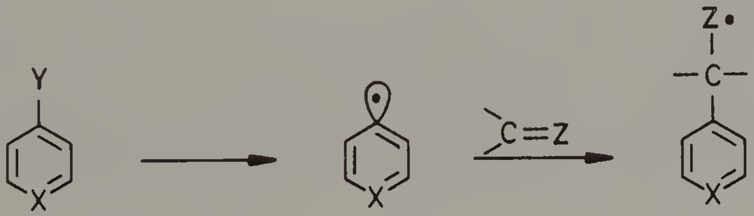
4

Radical **1** corresponds to the Wheland or Meisenheimer complex of ionic substitution reactions and is formed by radical attack at aromatic compounds. The aromaticity is regained by splitting off Y·.



1

Aryl radicals **2**, which have not lost aromaticity during their formation, are very reactive σ-radicals that rapidly attack unsaturated neutral or charged carbon atoms. They can be generated by several routes, including electron transfer reactions. The reaction products are formed from radical **5** via hydrogen abstraction, heteroatom donation, electron transfer, or fragmentation.

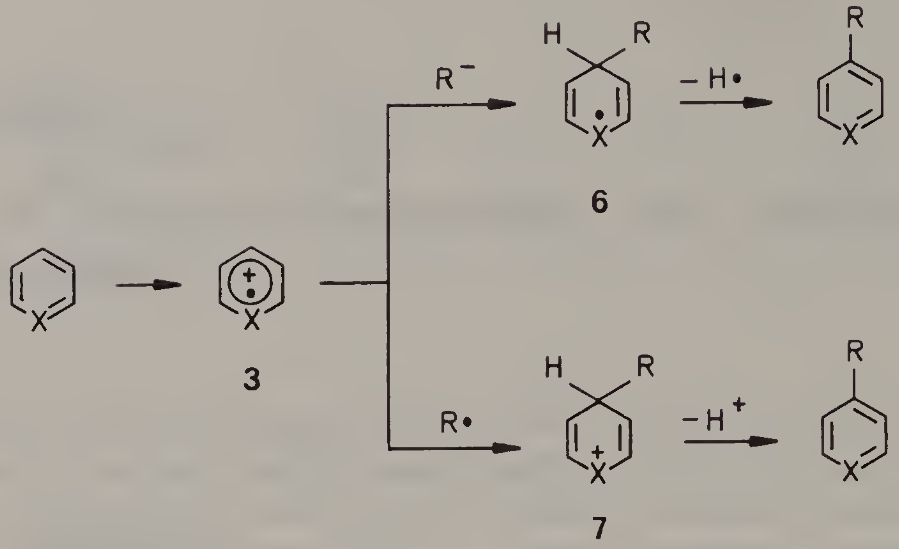


2

5

Radical ions **3** are formed by one-electron transfer reactions from the neutral aromatic compounds and react either with ions (**3** → **6**) or with radicals (**3** → **7**). The adduct radicals **6** and ions **7** yield products via hydrogen and proton abstraction, respectively.

ROS H

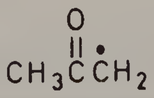


B. Reactions with Carbocyclic Aromatic Compounds

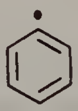
Benzene behaves like an electron-rich alkene and is attacked by nucleophilic alkyl radicals with rate coefficients of $10 - 10^3$ (l/mol·s) at 25-80°C.[1,2] This is slightly slower than the addition to alkylated alkenes[2,3] and is hardly fast enough for synthetic applications (see p. 12). However, electrophilic radicals such as **9**, or σ-radicals **10** and **11** are reactive enough[4] to be used in syntheses.

$R_3C\cdot$

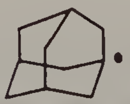
8


$CH_3\overset{O}{\overset{\|}{C}}\dot{C}H_2$

9



10

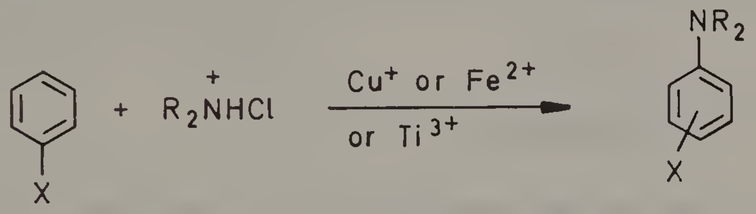


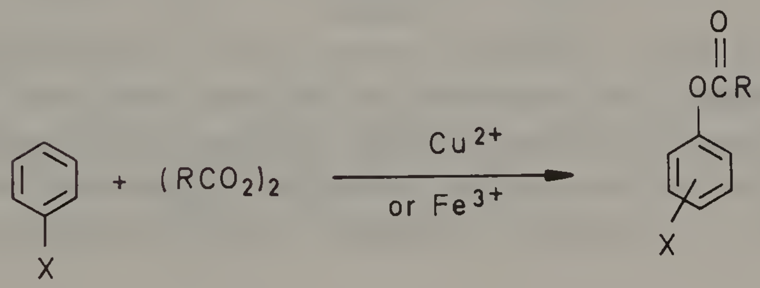
11

Nucleophilic π-radicals **8** are successful only if the aromatic compounds are substituted with electron-withdrawing groups or if electron-poor heterocyclic salts are used.[5]

1. Electrophilic radicals

Electron-rich aromatic compounds are readily attacked by electrophilic nitrogen- or oxygen-centered radicals generated from protonated N-chloroamines[5,6] and peroxides,[7] respectively. These syntheses involve radical chain reactions in which cyclohexadienyl radicals are trapped either by halogen abstraction or electron transfer.



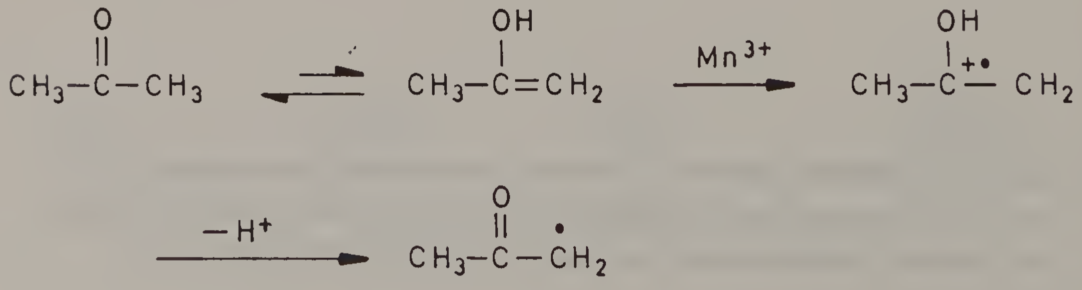


Carbon centered radicals exhibit electrophilic behavior if they are substituted by electron-withdrawing groups; this is clearly demonstrated by the ρ^+-values of Table 1.[8]

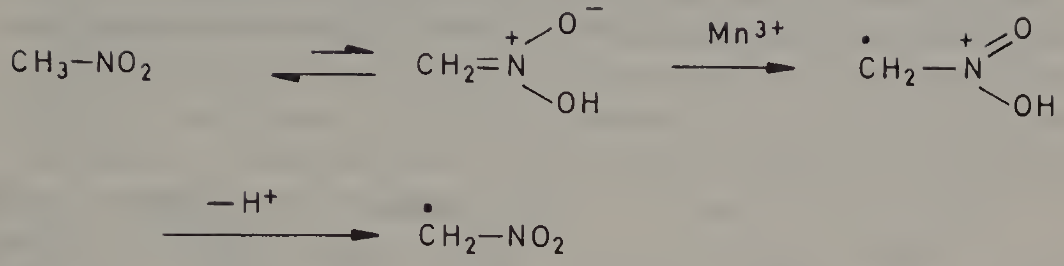
Table 1: Comparison of ρ^+-values of homolytic aromatic substitution by radicals X•

X•	ρ^+
C_6H_{11}•	1.1
CH_3•	0.1
C_6H_5•	0.1
H_3CCOCH_2•	-1.5
O_2NCH_2•	-2.1
$C_6H_5CO_2$•	-1.6
i-$C_3H_7OCO_2$•	-2.3

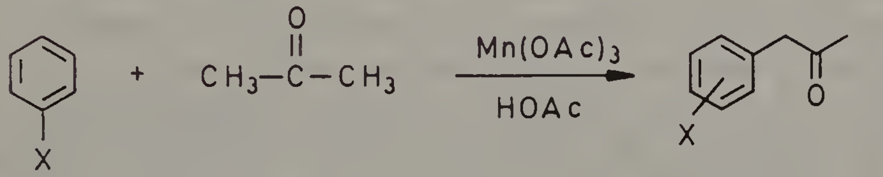
Because of their negative ρ^+-values, acyl- and nitro-substituted radicals are electrophiles and have found synthetic applications in C-C bond forming reactions with aromatic compounds. The radicals are generated by oxidation of acetone[8] or nitromethane[9] with Mn^{3+} or Ce^{4+} salts (see p. 89).



$$CH_3-\overset{O}{\overset{\|}{C}}-CH_3 \rightleftharpoons CH_3-\overset{OH}{\overset{|}{C}}=CH_2 \xrightarrow{Mn^{3+}} CH_3-\overset{OH}{\overset{|}{C}}\overset{+\bullet}{-}CH_2 \xrightarrow{-H^+} CH_3-\overset{O}{\overset{\|}{C}}-\overset{\bullet}{C}H_2$$

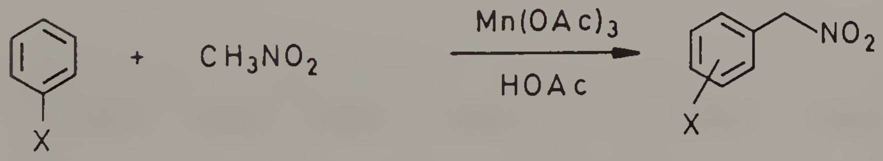


The yields are higher with anisole or toluene than with halobenzenes because of the electrophilic nature of acyl- and nitro-substituted radicals.



X : OCH_3 (74%; o:m:p = 84:3:13); CH_3 (51%; o:m:p = 66:20:14)

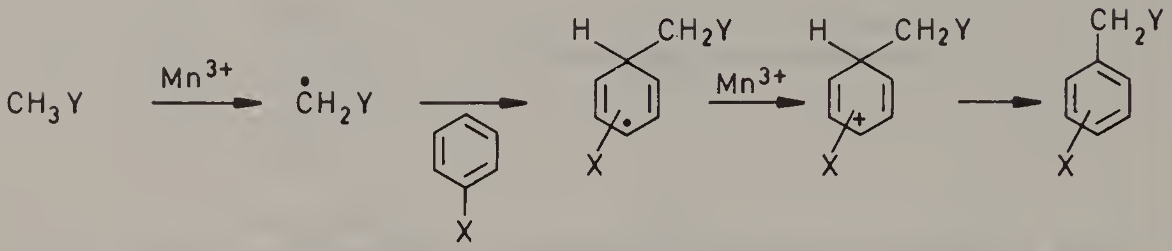
H (40%); F (29%; o:m:p = 71:9:20)



X : OCH_3 (77%; o:m:p = 71:5:24); CH_3 (77%; o:m:p = 52:27:21)

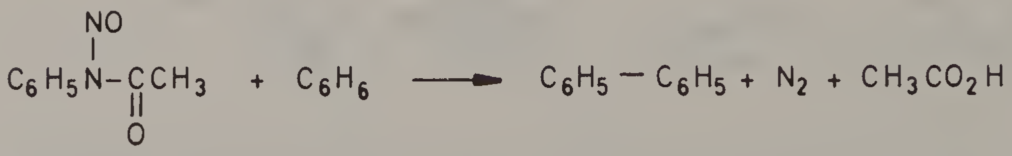
H (78%); Cl (20%; o:m+p = 52:48)

These radical alkylation reactions are not chain reactions because the formation of the attacking radicals, as well as the reaction of the cyclohexadienyl radicals, require stoichiometric amounts of Mn^{3+} or Ce^{4+} salts as oxidants.



2. σ-Radicals

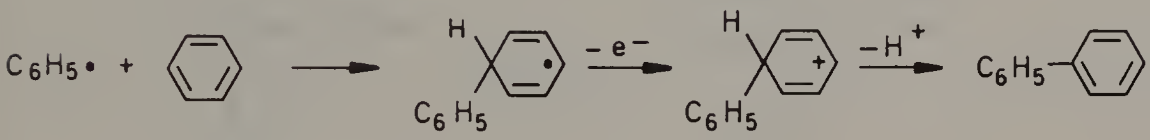
Besides electrophilic radicals, σ-radicals are also reactive enough to add to benzoic systems with synthetically useful rates. The phenyl radical attacks benzene with a rate coefficient $k = 4.5 \cdot 10^5$ (l/mol·s) at 25°C;[4] therefore, arylation of aromatic compounds can be carried out successfully. Actually, the phenylation of benzene using N-nitrosoacetanilide **12** was discovered by Bamberger[10] in 1896. Forty years later, Hey[11] proposed that the phenyl radical is a reaction intermediate.



$$C_6H_5\overset{\displaystyle NO}{\overset{|}{N}}-\underset{\underset{\displaystyle O}{\|}}{C}CH_3 + C_6H_6 \longrightarrow C_6H_5-C_6H_5 + N_2 + CH_3CO_2H$$

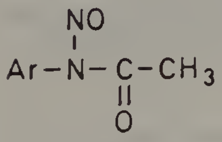
12

This reaction played a major part in the development of the concept and understanding of the transient existence of radicals in solution. From the extensive work of Hey,[11,12] Huisgen,[13] Rüchardt,[14] Perkins,[15] and Cadogan,[16] it seems that the following mechanism might be operative: The key step is the attack of the phenyl radical on benzene to give adduct radical **13**, which is oxidized either by nitroxide radicals or diazonium ions to the cyclohexadienyl cation **14**; deprotonation then gives biphenyl.



13 **14**

N-Nitrosoacetanilides **15**,[17] diazonium salts **16**,[18] azo compounds **17**,[19] triazenes **18**,[20] diacyl peroxides **19**,[21] carboxylic acids **20**,[22] arenecarbonyloximes **21**,[23] and arylhalides **22**[24] can be used as precursors for aryl radicals.



$Ar-\overset{\displaystyle NO}{\overset{|}{N}}-\underset{\underset{\displaystyle O}{\|}}{C}-CH_3$

15

$ArN_2^+X^-$

16

$Ar-N=N-C(C_6H_5)_3$

17

$Ar-N=N-NR_2$

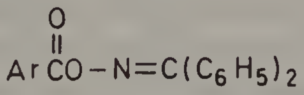
18

$(ArCO_2)_2$

19

$ArCO_2H$

20



$Ar\overset{\overset{\displaystyle O}{\|}}{C}O-N=C(C_6H_5)_2$

21

$Ar-Hal$

22

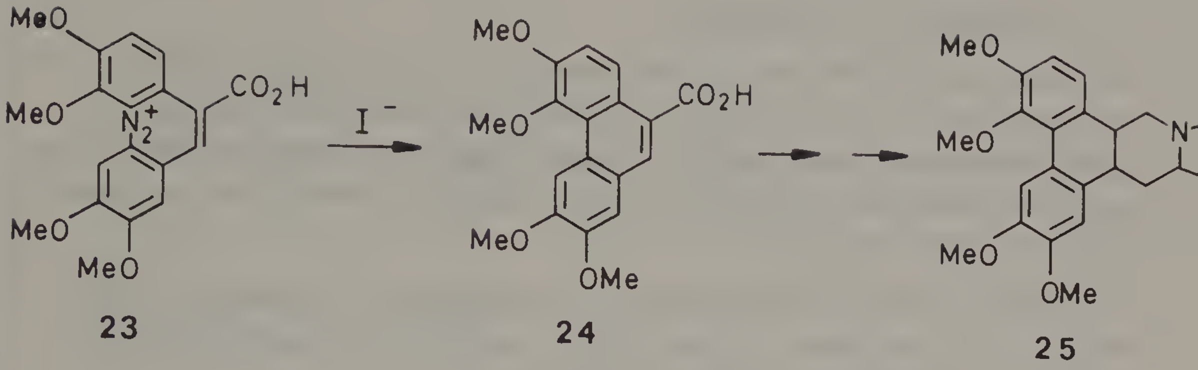
Radical arylations of aromatic compounds are more of mechanistic than of synthetic interest because in most cases positional and substrate selectivities (regioselectivity and chemoselectivity) are quite low. Generally, all of the free positions of an aromatic substrate are substituted,[25] and at higher conversion polysubstitution occurs.

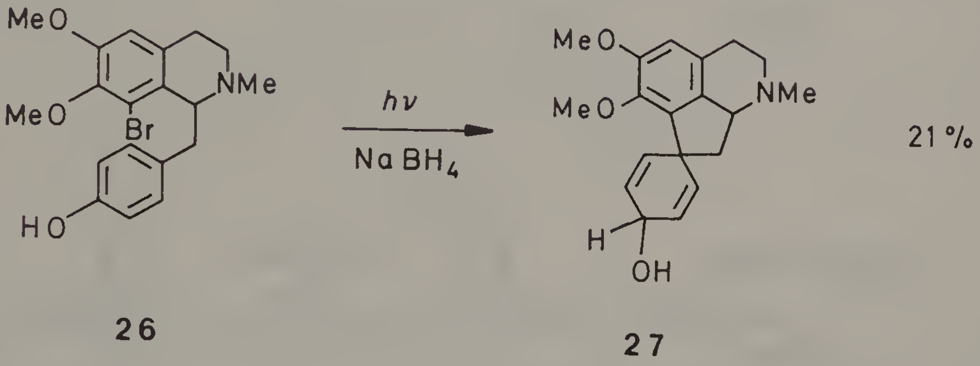
o : m : p = 69 : 18 : 13

o : m : p = 62 : 8 : 30

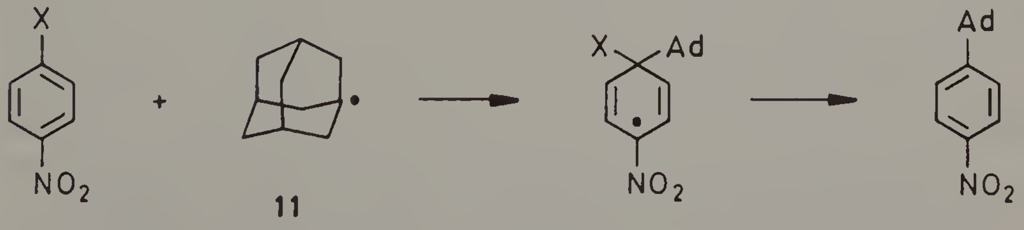
The ρ-values of table 1 (see p. 214) show that this low selectivity is due to the small polar effects of arylation reactions.

Intramolecular reactions are governed less by polar than by ring strain effects. Therefore, intramolecular arylation, like the Pschorr synthesis of phenanthrene systems, occurs with higher selectivity. The cyclization **23** → **24**, which is the key step in the synthesis of the alkaloid tylocrebrine **25**,[26] and also the formation of spiro compound **27** by photolysis of bromide **26**[27] demonstrate this selectivity.





Tiecco[28] has shown that in reactions with σ-radicals such as the 1-adamantyl radical **11** ipso substitution can also occur. Thus, nitro, acyl, nitrile, and sulfonyl groups are substituted by σ-radicals if the aromatic compounds are made strongly electron-deficient by the presence of other electron-withdrawing substituents.

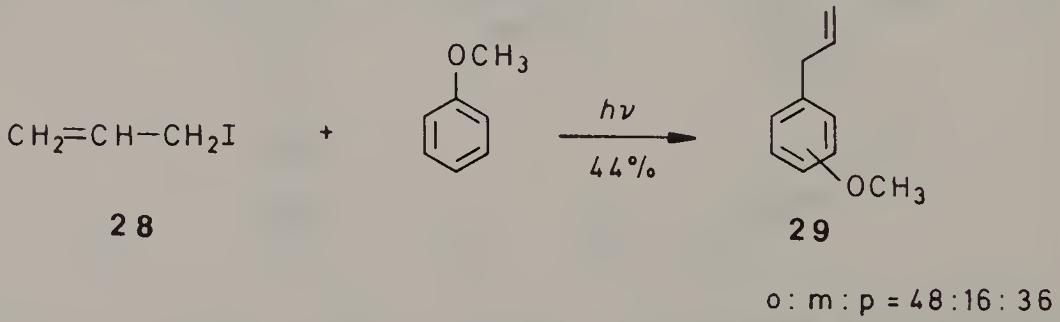


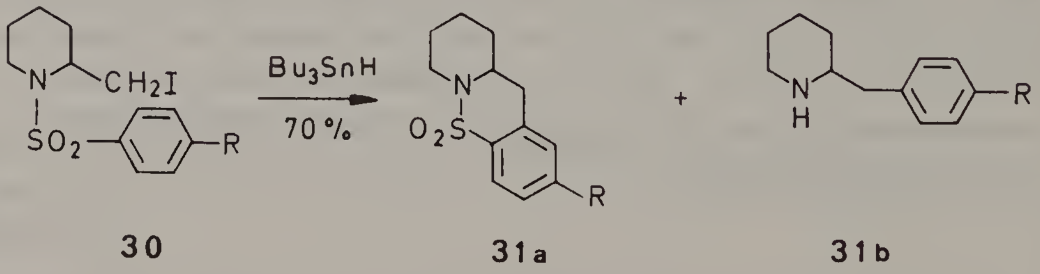
$X = NO_2, CN, COR, CHO, CO_2R, SO_2R$

3. Nucleophilic π-radicals

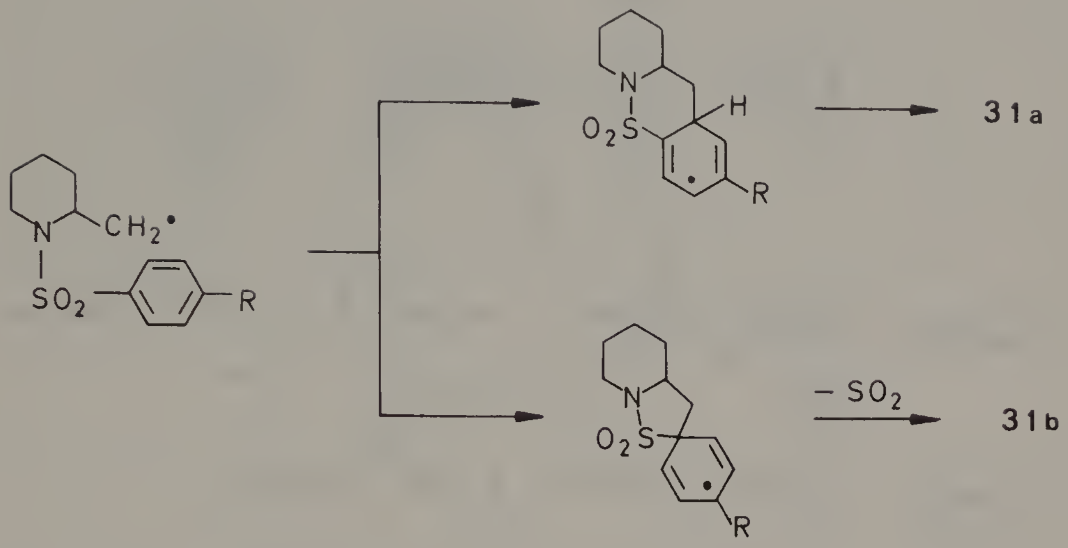
Substitution reactions of nucleophilic alkyl radicals with π-character are synthetically important mainly in reactions with protonated heterocyclic bases. Synthetic applications with benzoid compounds are rare because addition rates and position selectivities are low.

Therefore, only a few synthetically interesting cases exist in which alkyl radicals of this type, generated from for example iodides, react with benzoid systems.[29,30]



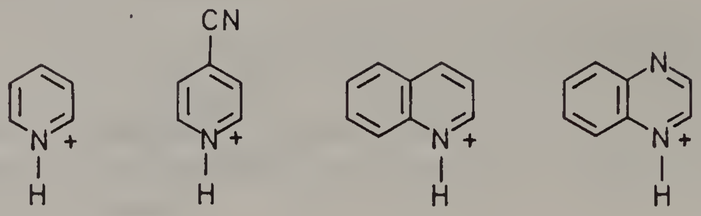


It is believed that the synthesis of **29** and **31** proceeds via attack of the alkyl radical at the aromatic ring.[30] The formation of **31b** is an example of an intramolecular ipso substitution.



C. Reactions with Heterocyclic Aromatic Compounds

Alkylations and acylations of heterocyclic aromatic compounds developed by Minisci[5,6] and his group are very useful substitution reactions that proceed by radical addition at the aromatic ring. These reactions are equivalent to Friedel-Crafts alkylations and acylations, but in contrast to Friedel-Crafts reactions, they are carried out with electron-poor aromatic systems. Thus, radical chemistry makes possible C-C bond formation reactions which are difficult to accomplish using ionic methods. The rates are particularly high in the presence of strong acids which protonate heterocyclic bases. Prim. butyl radicals attack protonated pyridine with a rate coefficient of $4.4 \cdot 10^4$ (l/mol·s) at 57°C.[31] Electron-withdrawing groups, annulation with aromatic rings, and introduction of heteroatoms in the ring increase the reactivity. In an analogous manner, electron-donating substituents at the radical center, e.g. alkyl groups, in most cases raise the reactivity of radicals.[31]

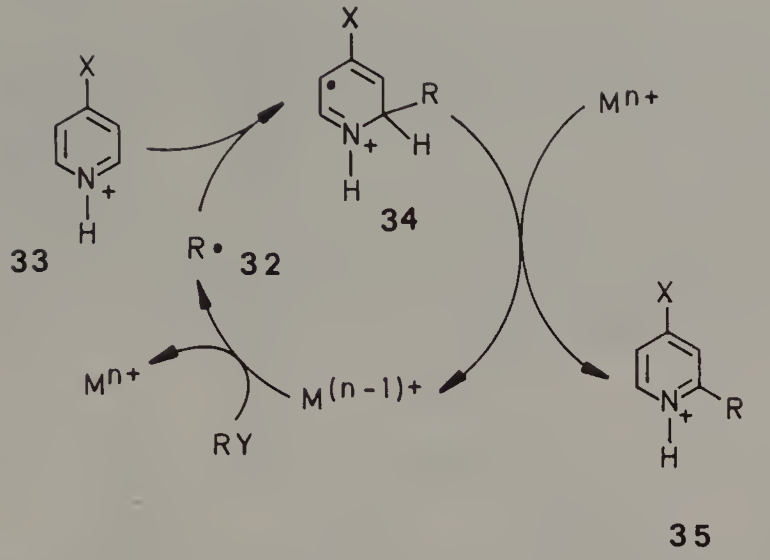


$k_{C_3H_7CH_2^\bullet}$	$4.4 \cdot 10^4$	$8.9 \cdot 10^5$	$8.5 \cdot 10^5$	$1.8 \cdot 10^7$ (l/mol·s)
$k_{(CH_3)_3C\bullet}$	$3.3 \cdot 10^4$	$6.3 \cdot 10^7$	$4.1 \cdot 10^6$ (l/mol·s)	

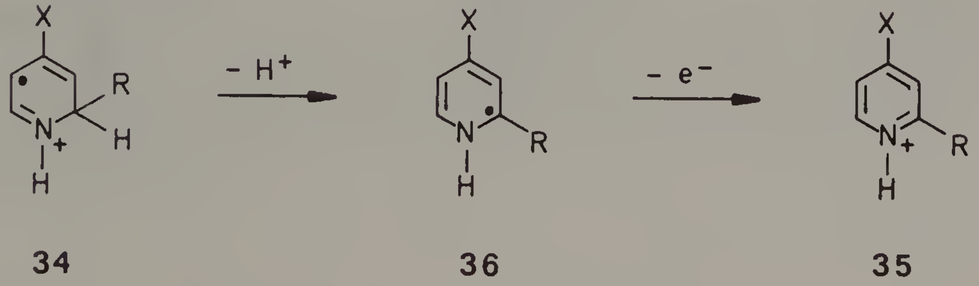
These substituent effects demonstrate the nucleophilic behavior of alkyl radicals in their reactions with protonated heterocyclic aromatic compounds. The polar effects can be explained by an interaction between the SOMO of the radical and the LUMO of the aromatic compounds (see p. 15).

Acyl radicals are σ-radicals which also behave like nucleophiles and attack protonated pyridines with a rate coefficient of 10^5 - 10^6 (l/mol·s).[32] Therefore, not only alkylation, but also acylation of heteroaromatic compounds can be successfully carried out.

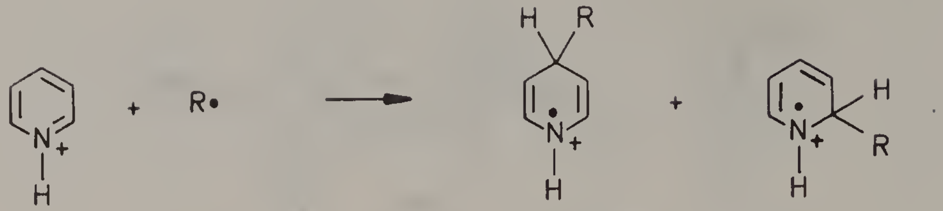
The chain reaction proceeds via addition of radical **32** at the protonated heteroaromatic ring **33**, to give the azacyclohexadienyl radical **34** which is oxidized, e.g. by metal ions, to give product **35**. The reduced metal ion regenerates the starting radical **32** by reaction with suitable precursors.



The rearomatization of **34** proceeds presumably via radical **36**, which is rapidly oxidized to **35**.[33]

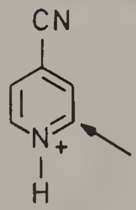


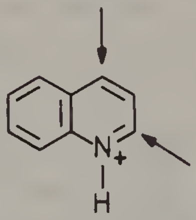
In general, the regioselectivity increases with increasing polar effects. Thus, tert-butyl radicals are slightly more selective than cyclohexyl and ethyl radicals.[6]

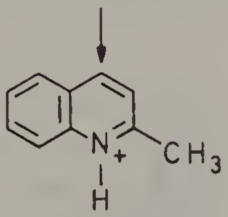


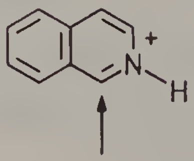
R = C_2H_5	56	:	44
$c-C_6H_{11}$	63	:	37
$t-C_4H_9$	68	:	32

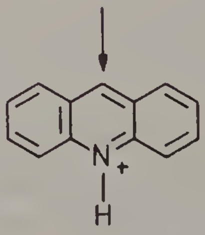
Very high regioselectivities are achieved if the heteroaromatic compounds are further substituted or annulated with aromatic rings.[6]









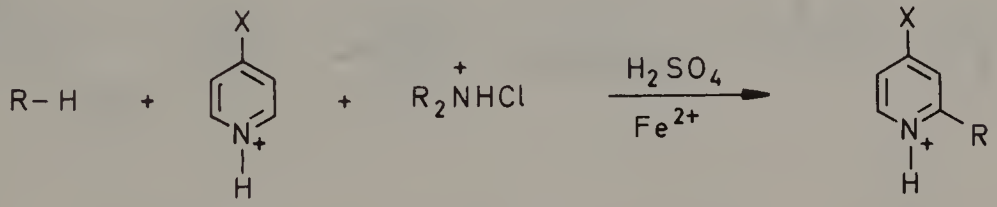


1. Alkylation

A large variety of unsubstituted and substituted alkyl radicals are readily available from hydrocarbons, alkyl halides, alcohols, ethers, ketones, acids, and formamides.[6]

a. Hydrocarbons

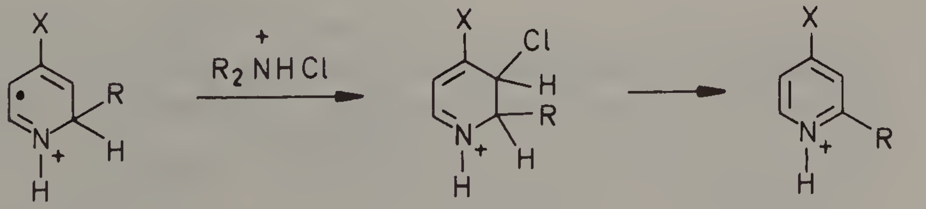
Hydrogen abstraction from unactivated hydrocarbons can be achieved with dialkylammonium radical cations, which are generated from chloroammonium ions with Fe^{2+} salts.[34]



$$R_2\overset{+}{N}HCl + Fe^{2+} \longrightarrow R_2\overset{+\bullet}{N}H + Fe^{3+} + Cl^-$$

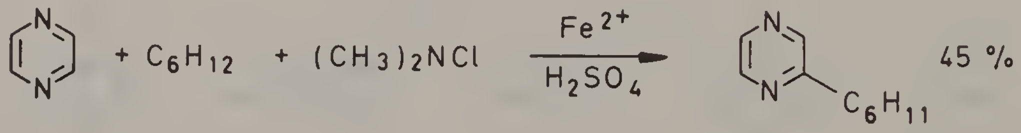
$$R_2\overset{+\bullet}{N}H + R{-}H \longrightarrow R\bullet + R_2\overset{+}{N}H_2$$

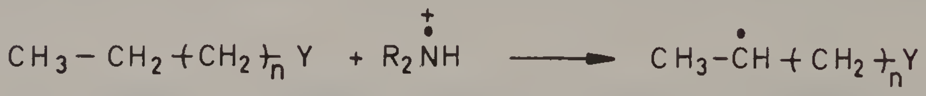
It is believed that the cyclohexadienyl radical cation **34**, formed after radical attack, abstracts a chlorine atom from the chloroammonium ion and yields product **35** by dehydrochlorination.[34]



34 **35**

The difficulty with hydrocarbons lies in the regioselectivity of the hydrogen abstraction step. With cyclic hydrocarbons like cyclohexane there is, of course, no selectivity problem, and in acyclic systems the selectivity question can be solved by introducing electron-withdrawing substituents, which direct the attack of the electrophilic radical to the ω-1 position.[34] Thus, the acyclic hydrocarbons **37** react with high regioselectivities that increase with the bulk of the substituents R at the nitrogen centered radicals.[34,35]





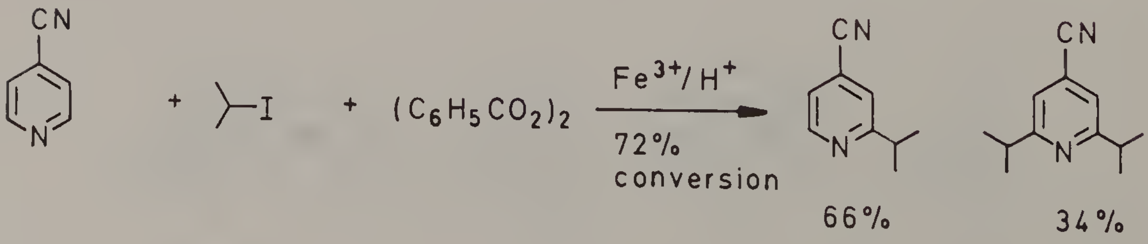
$$CH_3-CH_2{+}CH_2{+}_nY + R_2\overset{+\bullet}{N}H \longrightarrow CH_3-\overset{\bullet}{C}H{+}CH_2{+}_nY$$

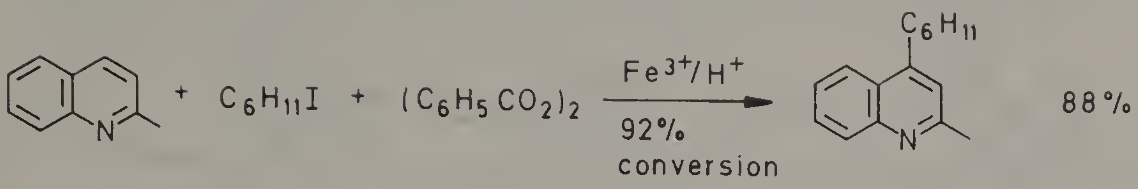
37

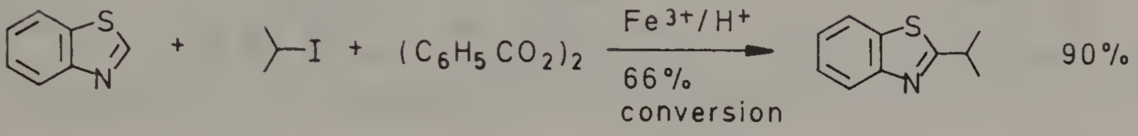
$Y = CO_2R$, Cl, OCH_3, NH_2, $n = 3, 4$

b. Alkyl iodides

In the presence of dibenzoyl peroxide, alkyl iodides are suitable precursors for radical substitution reactions of heteroaromatic compounds.[36]







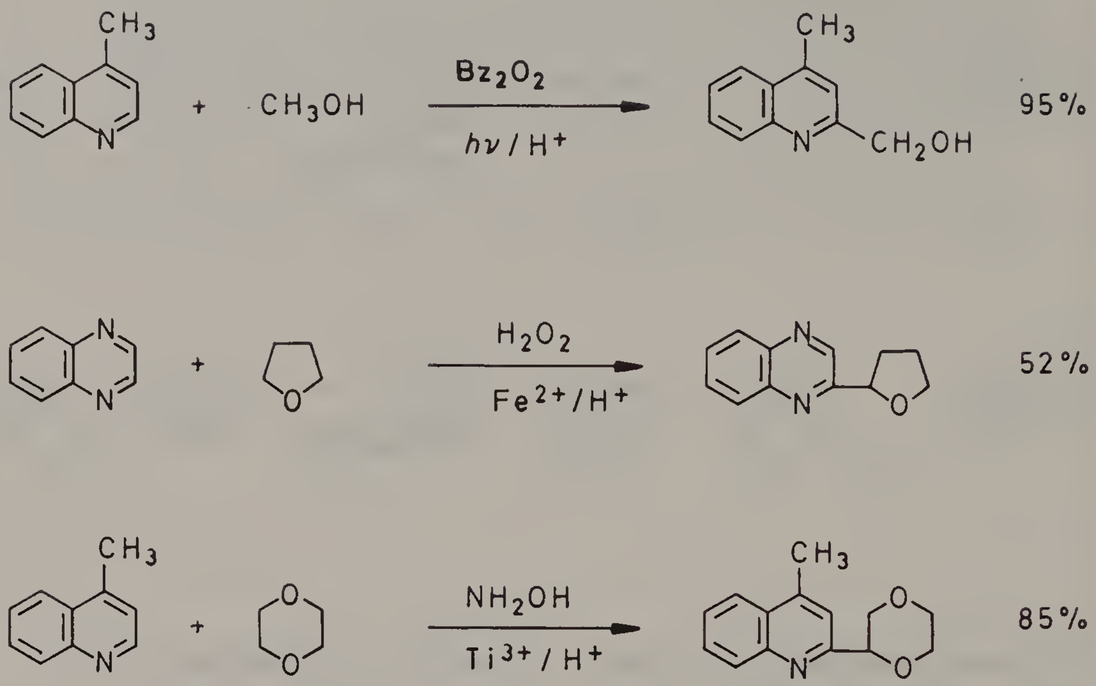
Dibenzoyl peroxide oxidizes radical **34** to the product **35**. The benzoyloxy radical, thus formed, loses CO_2 and gives phenyl radicals which abstract iodine from alkyl iodides.[35]

$$\mathbf{34} + (C_6H_5CO_2)_2 \longrightarrow \mathbf{35} + C_6H_5CO_2^{\bullet} + C_6H_5CO_2^{-}$$

$$C_6H_5CO_2^{\bullet} \xrightarrow{-CO_2} C_6H_5^{\bullet} \xrightarrow{R-I} R^{\bullet} + C_6H_5I$$

c. <u>Alcohols and ethers</u>

α-Oxyalkyl radicals can be easily obtained by hydrogen abstraction from alcohols and ethers with redox systems like H_2O_2/M^{n+}, t-BuOOH/M^{n+}, $\overset{+}{N}H_3OSO_3^{-}/M^{n+}$, $S_2O_8^{\ 2-}/M^{n+}$ ($M^{n+} = Fe^{2+}$, Ti^{3+}), $\overset{+}{N}H_3OH/Ti^{3+}$, or oxidants like $S_2O_8^{\ 2-}$ and dibenzoyl peroxide.[37]

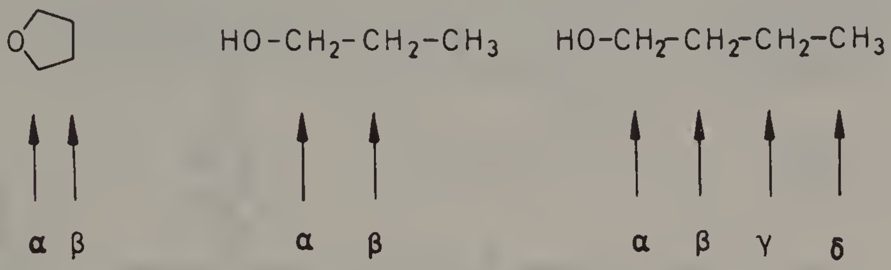


Intermediates which abstract hydrogen atoms from alcohols and ethers are heteroatom centered radicals or phenyl radicals.

The formation of oxygen centered radicals from peroxides is a well known reaction that occurs via electron transfer from the metal ion to the peroxide and cleavage of the O-O bond. The oldest reagent of this type is Fenton's reagent (H_2O_2/ Fe^{2+}).[38]

$$RO{-}OR + M^{n+} \longrightarrow RO^{\bullet} + RO^{-} + M^{(n+1)+}$$

These very reactive radicals attack not only α-CH bonds of alcohols and ethers, a considerable amount results also from abstraction of more remote hydrogen atoms. The regioselectivity depends very much on the reaction conditions.[37]

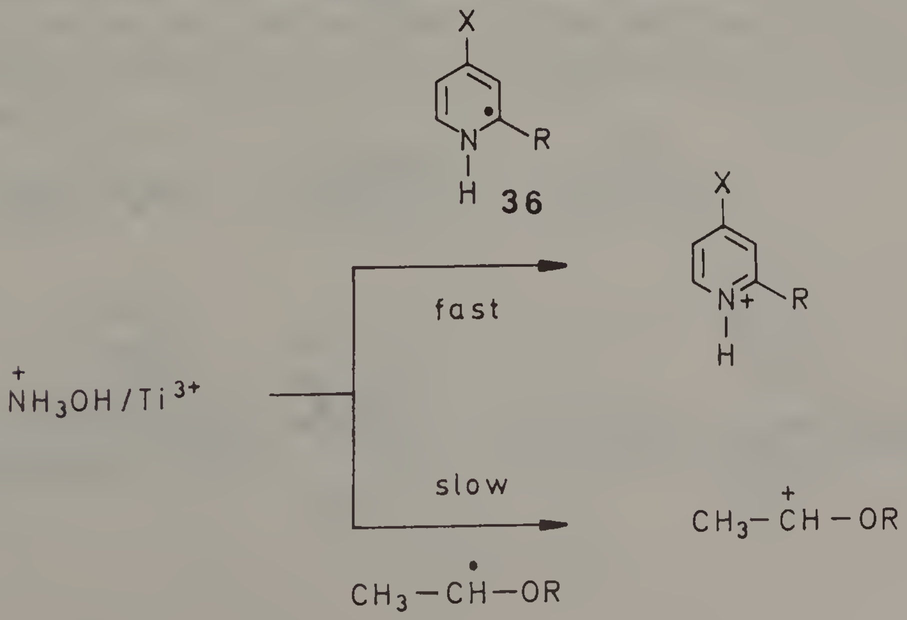


	α	β
$\overset{+}{N}H_3OH/Ti^{3+}$	97	3

	α	β
DTBP/98°C	65	35
DTBP/hν	> 95	5

	α	β	γ	δ
$\overset{+}{N}H_3OH/Ti^{3+}$	43	12	42	3
TBHP/Fe^{2+}	6	17	70	7
DTBP/ 80°C	60	12	28	

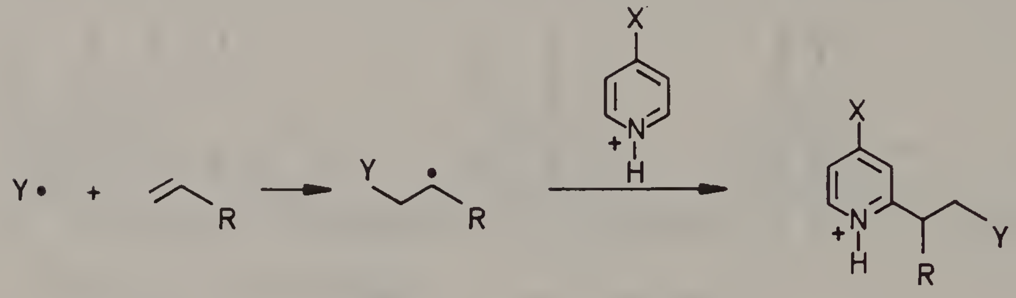
A problem also arises from the oxidizability of alkoxyalkyl radicals, especially if further alkyl groups make the oxidation even easier. Therefore, mild oxidants should be used in these cases, but their oxidizing power must be large enough for the rearomatization of the heterocyclic intermediate **36**. The $\overset{+}{N}H_3OH/Ti^{3+}$ redox system fulfills these requirements.[37]



36

d. Alkenes

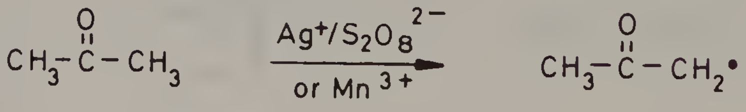
Electron-rich alkenes can be used as radical precursors because they are easily attacked by electrophilic radicals Y• to give nucleophilic alkyl radicals **38**, which react with heterocycles in acidic solution to give substitution products **39**.



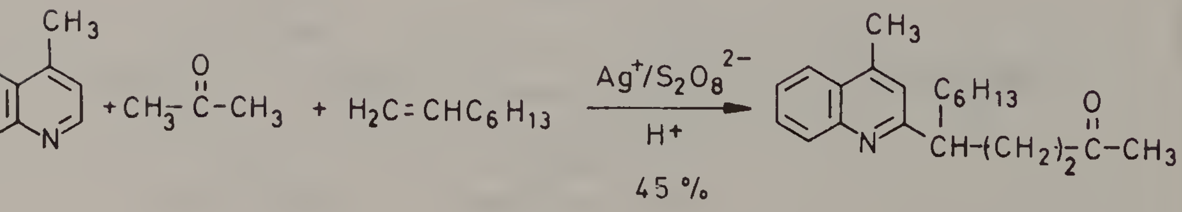
38 **39**

Electrophilic radicals are generated by oxidation of ketones or azides.[6,39]

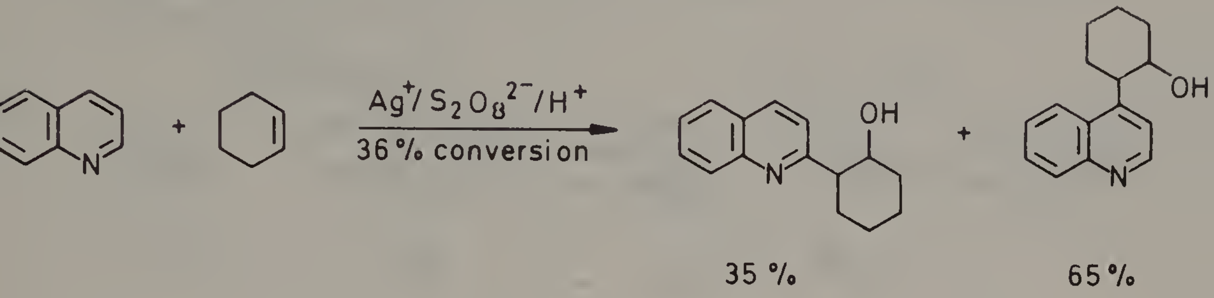
$$Fe(N_3)^{2+} \xrightarrow[Fe^{2+}]{H_2O_2} N_3^{\bullet}$$

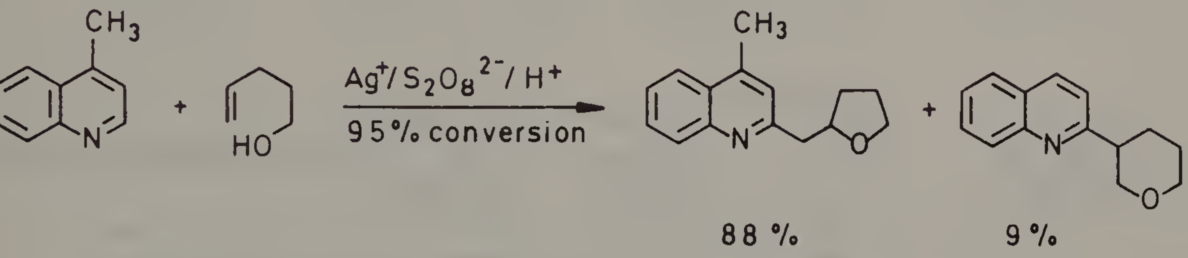


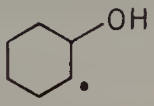
$$CH_3-\overset{O}{\overset{\|}{C}}-CH_3 \xrightarrow[\text{or } Mn^{3+}]{Ag^+/S_2O_8^{2-}} CH_3-\overset{O}{\overset{\|}{C}}-CH_2^{\bullet}$$



Treatment of alkenes like cyclohexene and 1-pentenol with $Ag^+/S_2O_8^{2-}$ gives hydroxylated cyclohexyl radical **40** and radicals **41**, respectively.[40]







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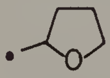

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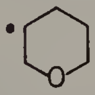
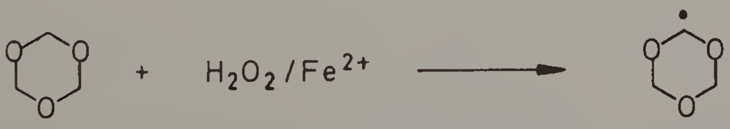


41b

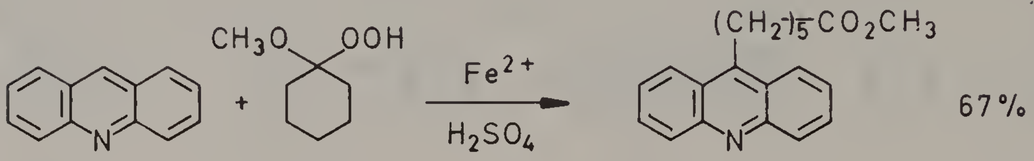
e. Derivatives of aldehydes and ketones

Cyclic acetals of formaldehyde like trioxane can be used to introduce dialkoxyalkyl groups, via radical **42**, into heterocycles.[6]

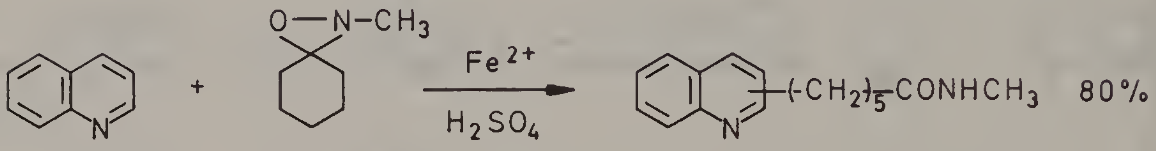


42

Ketone derivatives **43** and **45** undergo ring cleavage under oxidative conditions to give substitution products **44** and **46**, respectively.[41]



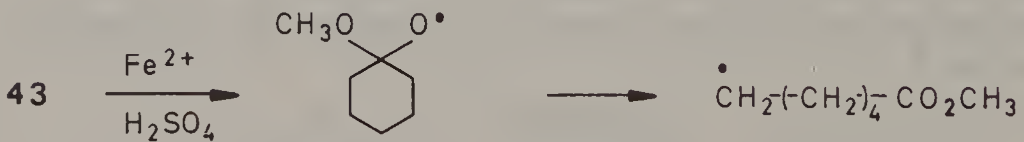
43 **44**



46 (2 : 4 = 53 : 47)

45

The ring cleavage occurs as a result of ß-fragmentation of radicals **47** and **48**.[41]



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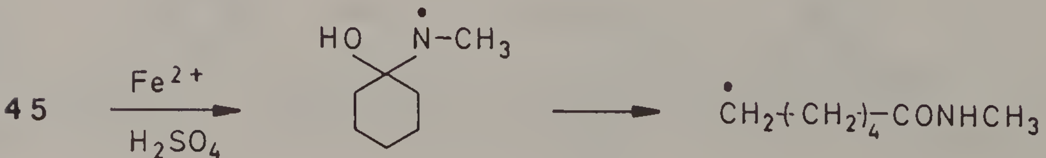


48

f. Carboxylic acids

A large number of prim., sec., and tert. alkyl radicals can be obtained from the corresponding carboxylic acids by reaction with $Ag^+/S_2O_8^{2-}$.[6,42]

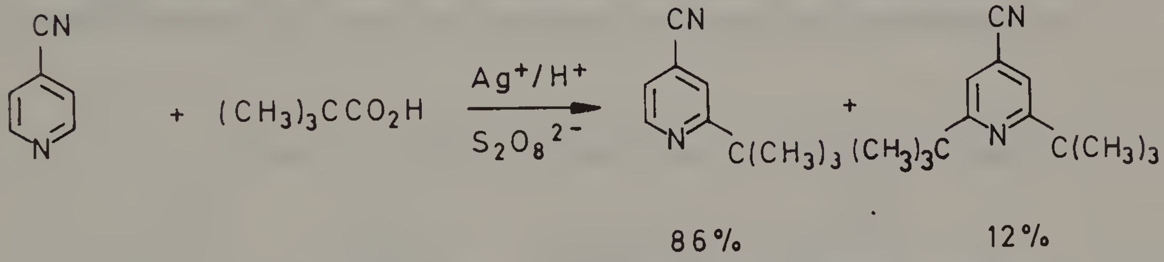
$$S_2O_8^{2-} + Ag^+ \longrightarrow SO_4^{\overline{\bullet}} + SO_4^{2-} + Ag^{2+}$$

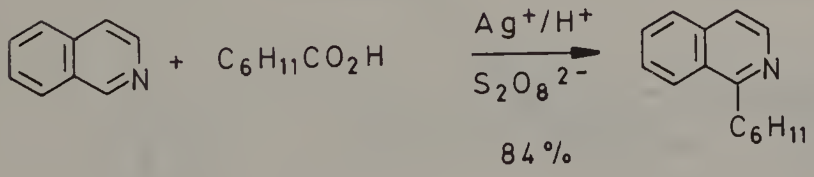
$$SO_4^{\overline{\bullet}} + Ag^+ \longrightarrow SO_4^{2-} + Ag^{2+}$$

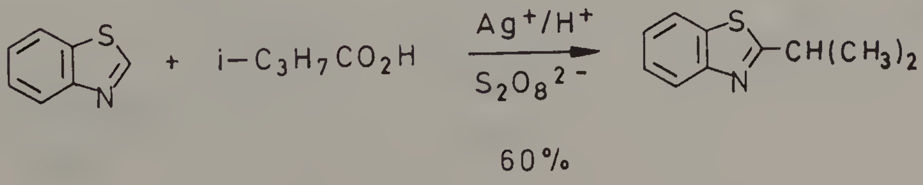
$$RCO_2H + Ag^{2+} \longrightarrow RCO_2^\bullet + H^+ + Ag^+$$

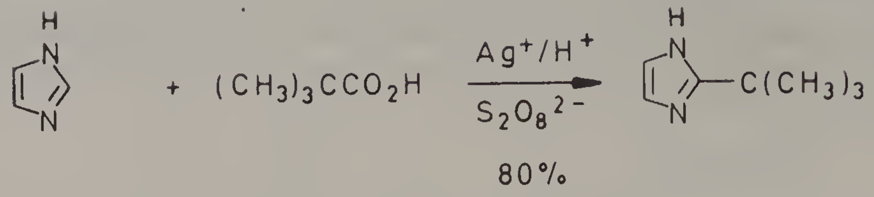
$$RCO_2^\bullet \longrightarrow R^\bullet + CO_2$$

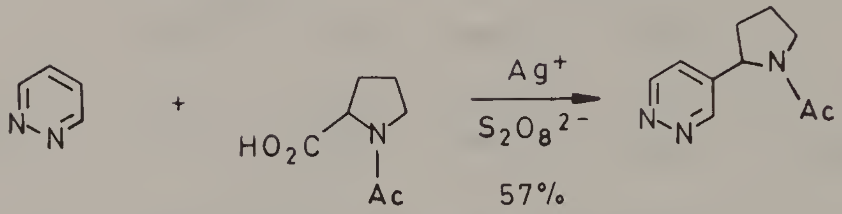
Substitution reactions with these alkyl radicals are very useful in heterocyclic chemistry.[6,43,44]







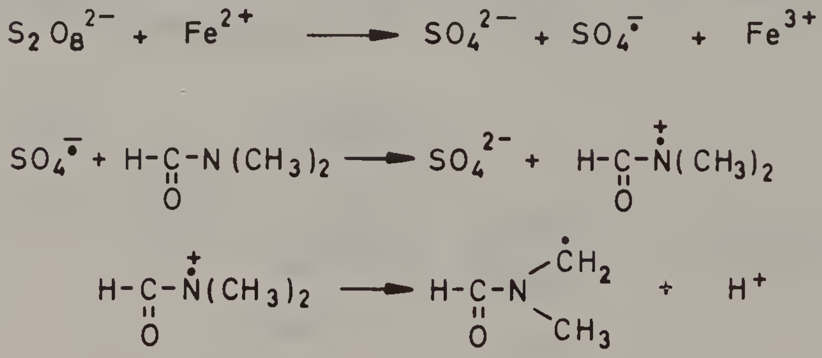




Arylperoxides, alkylpercarbonates, and perborates can be used in place of peroxydisulfate to oxidize Ag^+ to Ag^{2+}.[45]

g. Dialkylamides

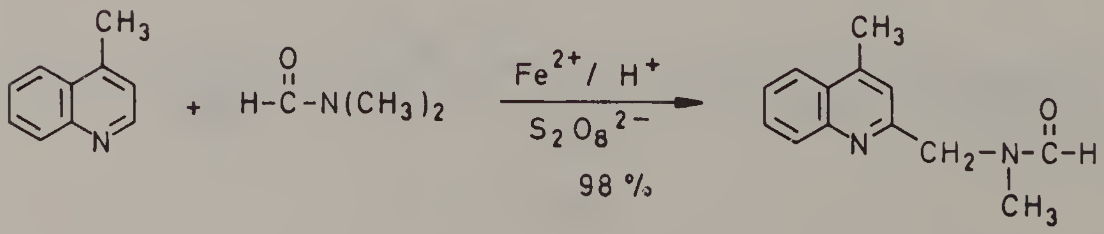
Dialkylformamides are oxidized with $Fe^{2+}/S_2O_8^{2-}$ predominately to amidoalkyl radicals via electron transfer reactions.[46]



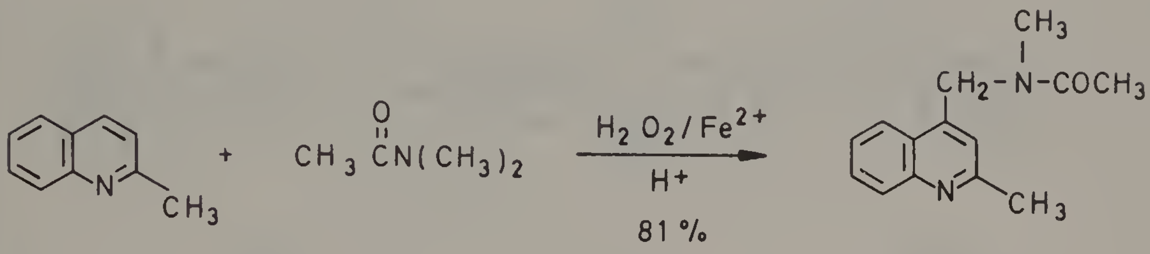
$$S_2O_8^{2-} + Fe^{2+} \longrightarrow SO_4^{2-} + SO_4^{\bullet-} + Fe^{3+}$$

$$SO_4^{\bullet-} + H\text{-}C(=O)\text{-}N(CH_3)_2 \longrightarrow SO_4^{2-} + H\text{-}C(=O)\text{-}\overset{\bullet+}{N}(CH_3)_2$$

$$H\text{-}C(=O)\text{-}\overset{\bullet+}{N}(CH_3)_2 \longrightarrow H\text{-}C(=O)\text{-}N(\dot{C}H_2)(CH_3) + H^+$$



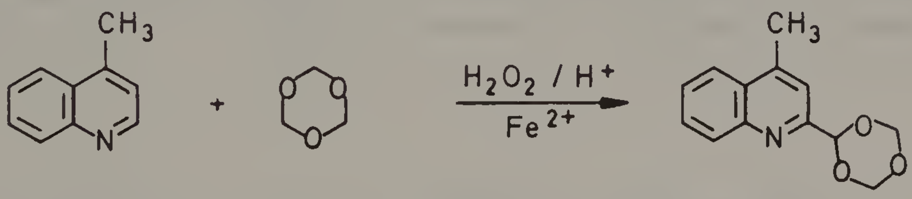
Alkoxy radicals abstract a hydrogen atom from the carbonyl carbon atom of formic amides, but N-alkylamides from other carboxylic acids give rise to α-N-amidoalkylation.[47]

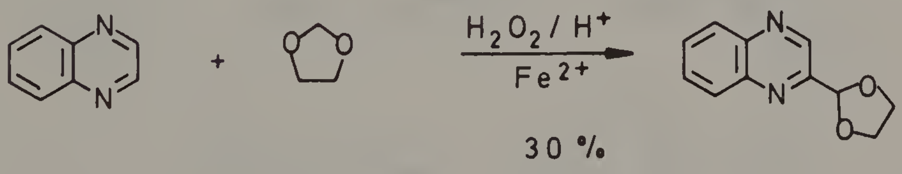


2. Acylation

a. Formation of aldehydes

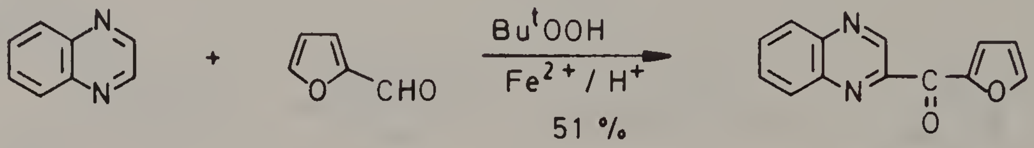
The introduction of a formyl group into a heteroaromatic compound can best be carried out with trioxane or 1,3-dioxolane, which after undergoing the C-C bond formation give formylated heterocycles.[48]

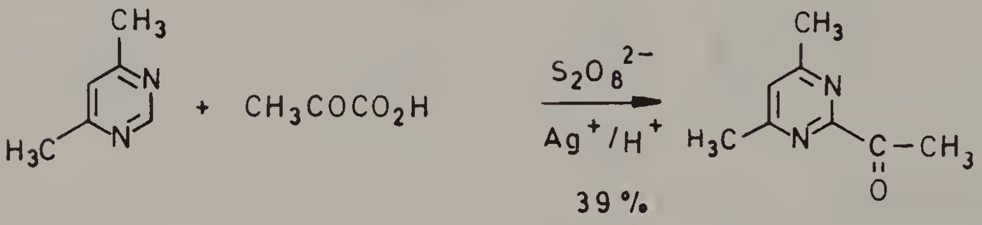




b. Formation of ketones

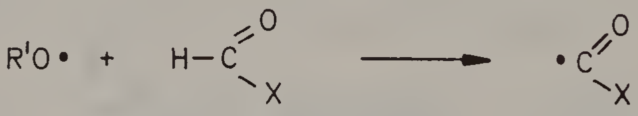
Heterocyclic ketones are synthesized via hydrogen abstraction from aldehydes[49] or oxidative decarboxylation of α-ketoacids.[50]





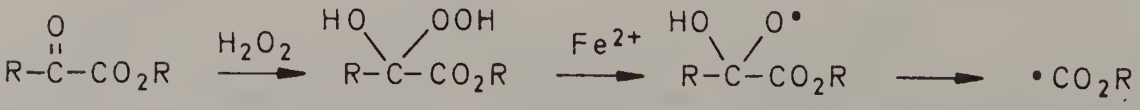
c. Formation of carboxylic acids

Formic acid derivatives, keto ester or oxalic ester precursors are used to introduce carboxylic acid derivatives into heteroaromatic compounds.[51]



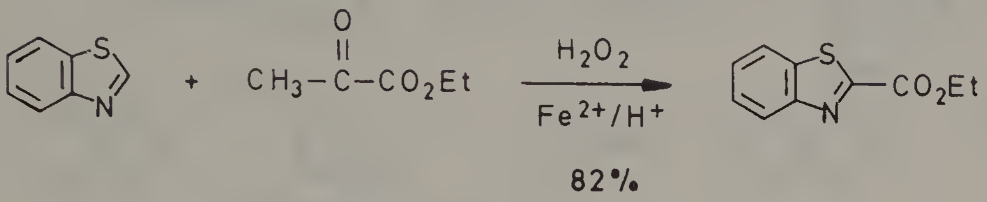
$$R'O\cdot + H-C(=O)X \longrightarrow \cdot C(=O)X$$

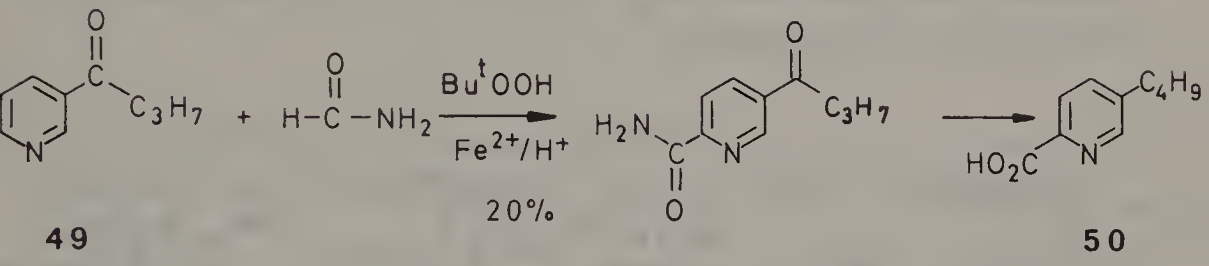
$$HO_2C-CO_2R \xrightarrow{S_2O_8{}^{2-}} \cdot CO_2R$$



$$R-\overset{O}{\overset{\|}{C}}-CO_2R \xrightarrow{H_2O_2} R-C(OH)(OOH)-CO_2R \xrightarrow{Fe^{2+}} R-C(OH)(O^\bullet)-CO_2R \longrightarrow \cdot CO_2R$$

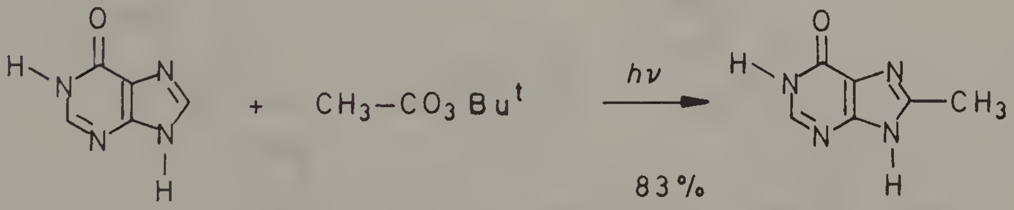
Various syntheses have been carried out using these methods. For example, Rüchardt[52] synthesized fusarinic acid **50** from pyridine derivative **49**.



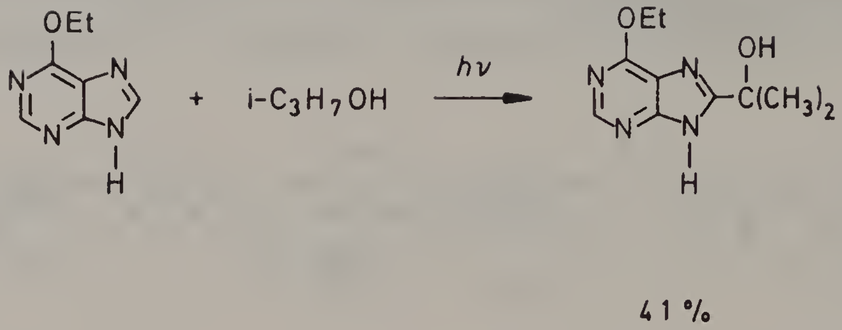


3. Miscellaneous C-C bond formations

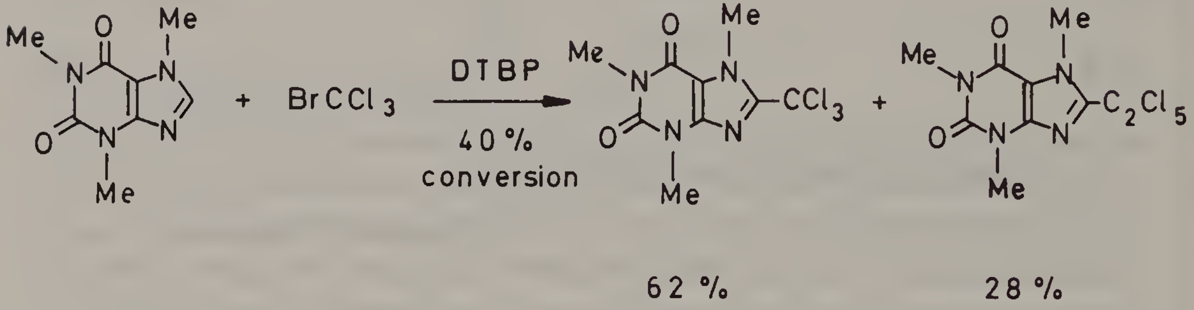
Although alkylation and acylation reactions of Minisci and his group are the most important radical C-C bond forming reactions with heterocycles, some other methods have also been used. Thus, purines can be methylated with tert-butyl peracetate.[53]



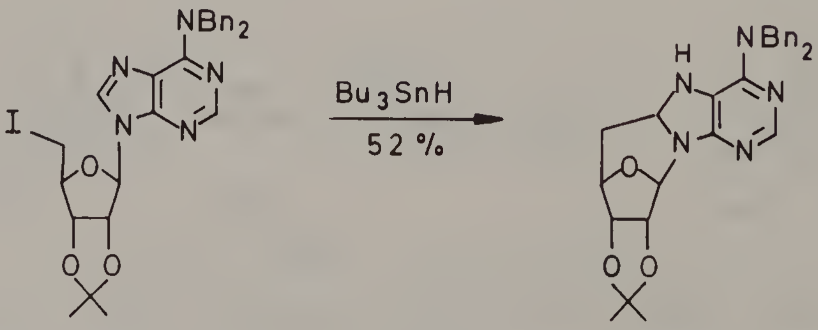
Photolysis of isopropylalcohol in the presence of 6-ethoxypurine gives a mixture of mono- and disubstituted products.[54]



Peroxide initiated reactions of $BrCCl_3$ introduced perchloroalkyl substituents into purines.[55]



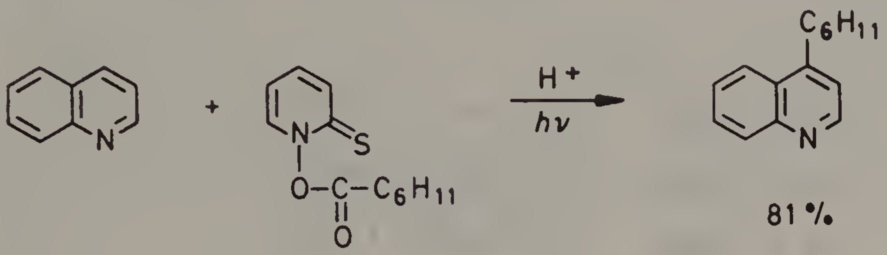
In an intramolecular reaction stannane reduction of the adenosine derivative **51** leads to product **52**.[56]



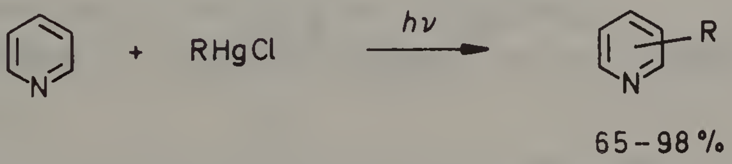
51

52

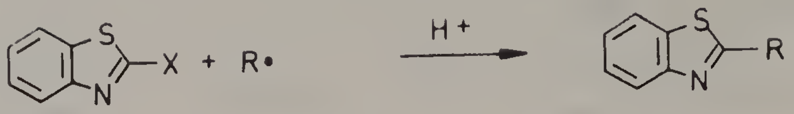
Radicals generated from acids by the method of Barton[57] (see p. 82) also lead to substitution reactions with heteroaromatics.



In a photostimulated reaction, Russell[58] produced alkyl radicals from alkylmercury salts (see p. 96) that add to unprotonated pyridine.



Heterocyclic aromatic compounds also undergo radical ipso substitution reactions, especially with σ-radicals and heterocycles that are protonated or substituted with electron withdrawing substituents.[28,59] Efficient leaving groups are RCO, NO_2, and RSO_2.



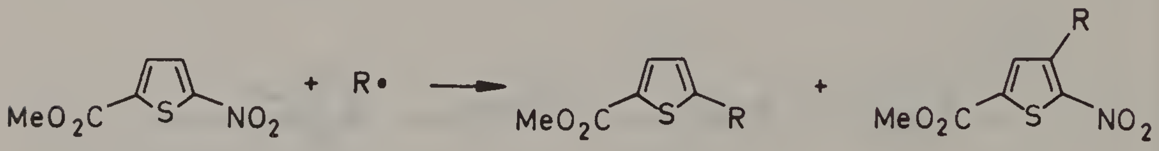
X = NO_2, R = Ad (95 %)

X = COEt, R = Ad (60 %)

X = COEt, R = MeCO (73 %)

X = $SO_2C_6H_5$, R = Ad (80 %)

The amount of ipso substitution is always lower with π-radicals than with σ-radicals. According to Tiecco,[60] the substituted thiophene **53** gives ipso substitution product **54** with adamantyl radicals, but product **55** with methyl radicals.

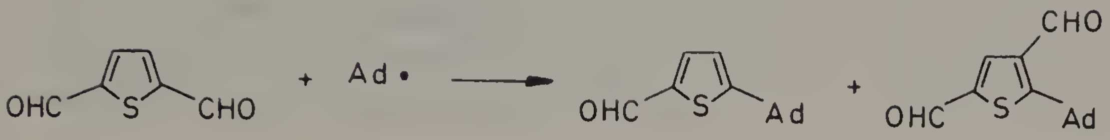


53 **54** **55**

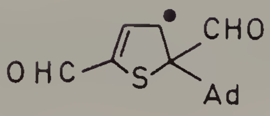
R = Ad : formed not formed

R = CH_3 : not formed formed

Ipso substitution can also lead to rearranged products if 1,2-shifts of ipso intermediates occur. Thus, thiophene **56** reacts with adamantyl radicals to give **57** and **58**. The intermediate for both products is presumably radical **59**, which either loses the formyl group or undergoes rearrangement.[61]



56 **57** **58**

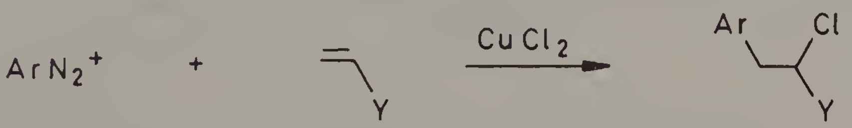


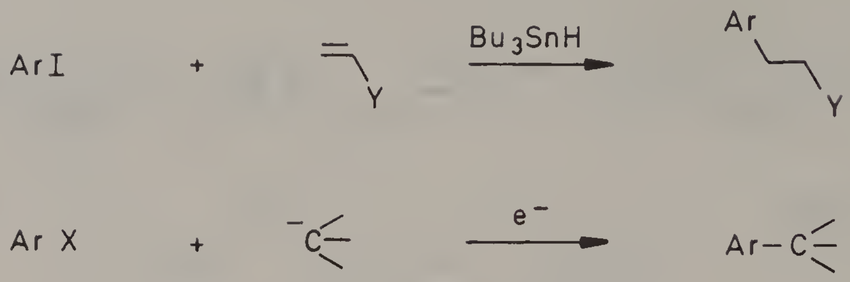
59

D. Reactions of Aryl Radicals

Although aryl radicals can be generated in various reactions, three methods have turned out to be most useful for synthetic C-C bond forming purposes:

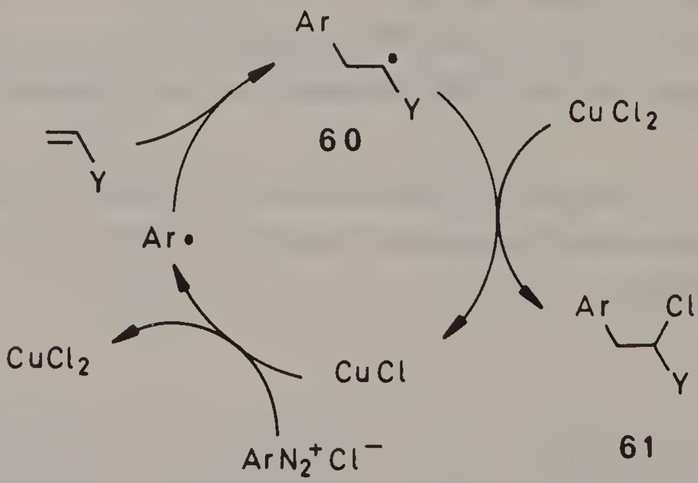
- Reactions of diazonium salts with cuprous chloride in the presence of alkenes (Meerwein reaction).
- Reaction of halides with stannane in the presence of alkenes.
- Reaction of halides, phosphonates, sulfides, or ammonium salts with carbanions under electron transfer conditions ($S_{RN}1$ reaction).



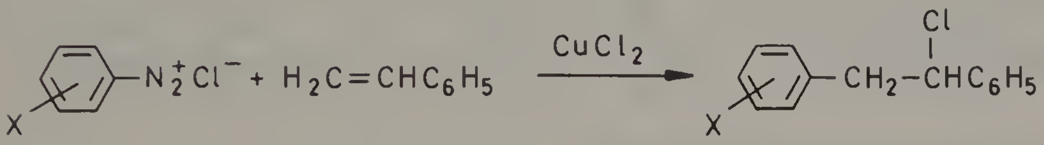


1. Aryldiazonium salts/metal ions

The reaction of aryldiazonium salts with CuCl produces aryl radicals which are trapped by alkenes to give adduct radicals **60**. These radicals abstract a chlorine atom from $CuCl_2$ to give product **61** and CuCl. Thus, the Meerwein reaction is a chain reaction in which catalytic amounts of Cu(I) and Cu(II) salts are involved as electron and halogen donors.[62]

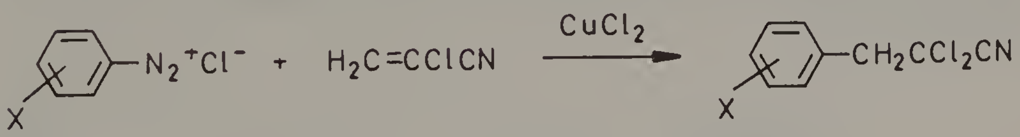


Carbocyclic aromatic compounds containing electron-withdrawing or electron-donating substituents have been used as diazonium salts. In reactions with styrene, the yields of C-C bond formation reactions depend only slightly on the nature of the substituent of the phenyldiazonium salts.[63]



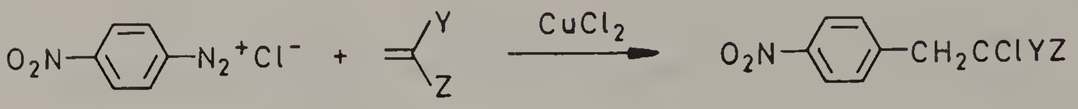
X = p-NO_2(80%), m-NO_2 (56%),
o-NO_2(46%), p-Cl (68%),
p-Br (74%), H (44%),
p-CH_3(52%), p-OCH_3(42%)

With more polar alkenes like α-chloroacrylonitrile, the same substituent independence of the diazonium salt is observed.[64]



X = p-NO_2(65%), o-NO_2(62%), p-Cl (68%),
p-Br (68%), H(53%),
p-CH_3(52%), p-CH_3O (53%)

Aryl radicals are so reactive that a large variety of alkenes is suitable for these syntheses. Alkenes substituted with chlorine, acetoxy, phenyl, pyridyl, aldehyde, ketone, carboxylic acid, ester, amide, nitrile, sulfone, and phosphonate substituents have been used; even ethylene itself reacts.[62]



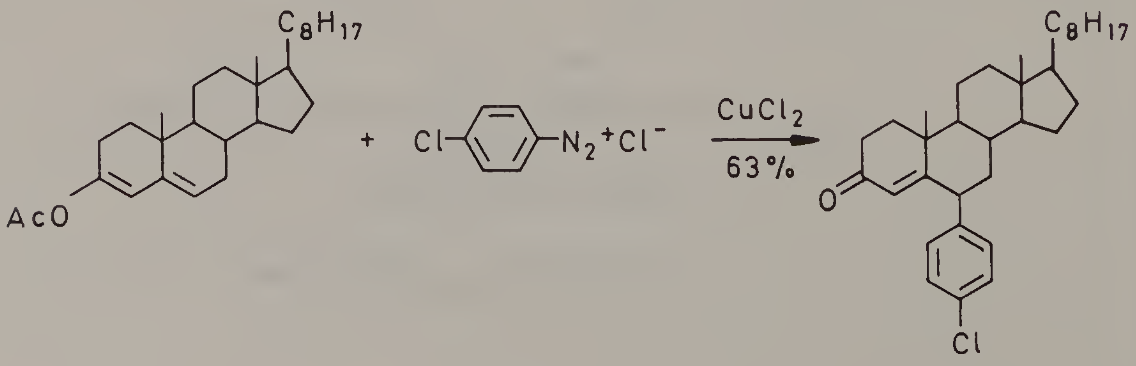
X = Y = H (50%) ; X = H, Y = Cl (62%) ; X = Y = Cl (70%) ; X = H, Y = OAc (41%) ;

X = H, Y = C_6H_5 (80%) ; X = H, Y = $COCH_3$ (41%) ; X = H, Y = CO_2CH_3 (56%) ;

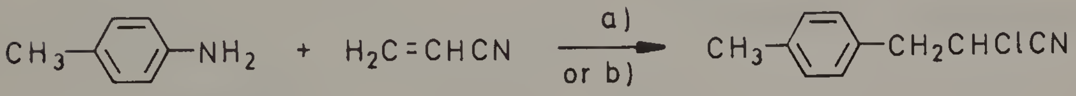
X = H, Y = $CONH_2$ (64%) ; X = CH_3, Y = CN (55%) ; X = H, Y = $PO(OEt)_2$ (17%) ;

X = H, Y = SO_2CH_3 (48%)

In reactions with 1,2-disubstituted alkenes and alkynes, regioisomers and stereoisomers, respectively, are formed. In some cases, elimination reactions occur during or after the radical steps.[62] With cyclic alkenes the yields are often low, but with the more reactive dienes, reasonable yields can be obtained.[62,65]



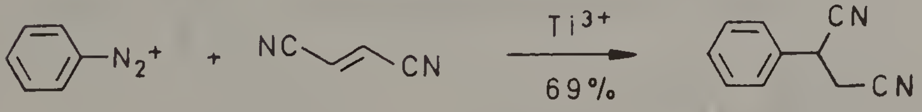
In most cases, the diazonium salts are prepared in situ from aromatic amines either in aprotic solvents with alkylnitrites[66] or in acidic aqueous medium with $NaNO_2$.[67] Generally, the yields of the Meerwein reaction are higher in aprotic organic solvents than in mixtures containing water.



a) $(CH_3)_3CONO/CuCl_2/CH_3CN$ (73%)

b) $NaNO_2/HCl/CuCl_2/H_2O$ (40%)

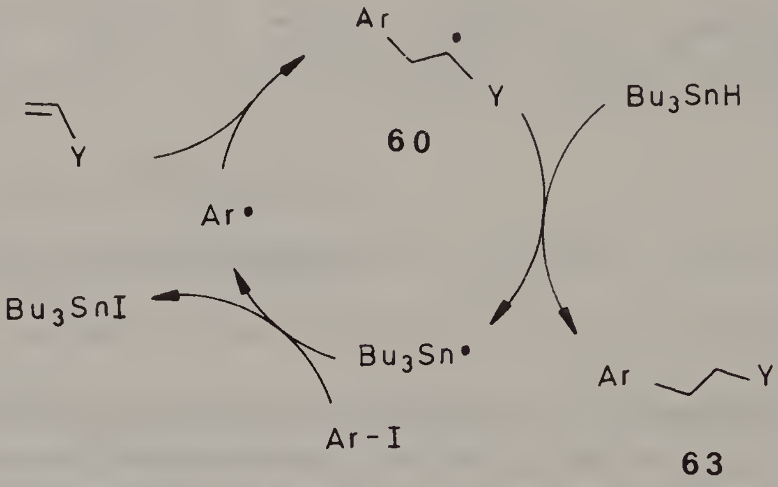
In an alternative to the Meerwein reaction, Citterio[68] used Ti^{3+} salts as reagents. The Ti^{3+} salts reduce diazonium salts to aryl radicals, and adduct radicals **60** to anions **62** which are protonated to give product **63**. Thus, Ti^{3+} is not a catalyst and has to be used in excess.



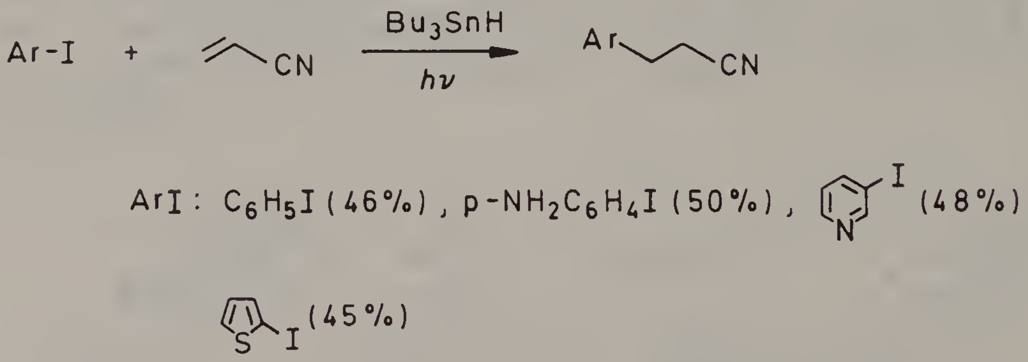
60 **62** **63**

2. Arylhalide / tin hydride

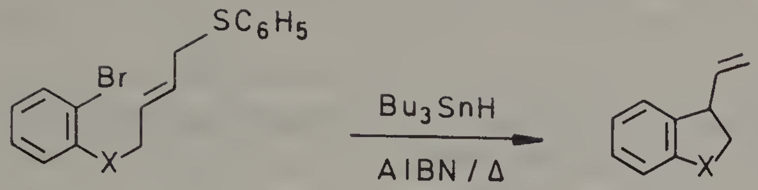
The radical chain reaction using Bu_3SnH (see p. 56) has also been established with aryl halides.[69] Trapping of aryl radicals with electron-poor alkenes leads to adduct radicals **60** which react with stannane to give products **63**.



The yields of these reactions are often not very high.[69]

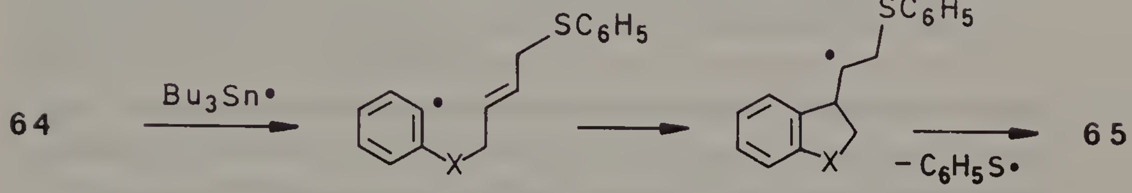


Bromides can be used in cyclization reactions. Thus, the reaction of bromide **64** with Bu_3SnH gives **65**. The product forming step is the ß-bond cleavage of radical **67**.[70]



64 **65**

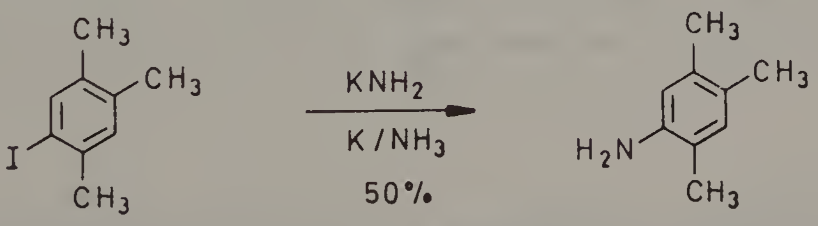
X = NH (96%), X = O (75%)



66 **67**

3. $S_{RN}1$ reaction

In 1970 Bunnett[71] observed that the amination of 5- and 6-iodopseudocumene in liquid amonia with catalytic amounts of potassium yields almost exclusively substitution products **68** and **69**, respectively.



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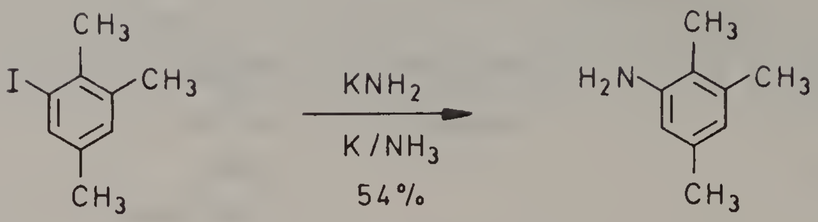
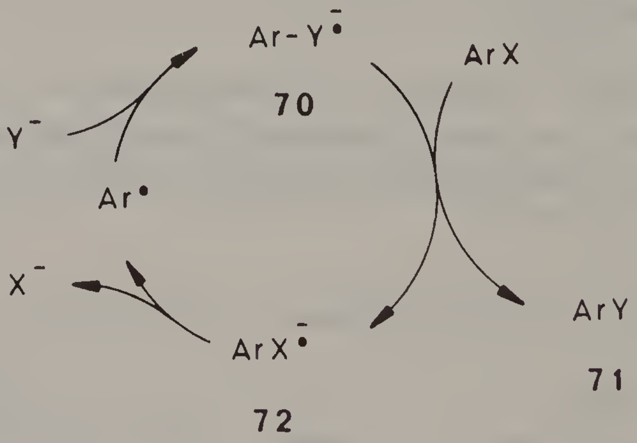


69

This very high regioselectivity, which is not in accord with an aryne intermediate, can be explained by a chain reaction in which aryl radicals attack nucleophiles Y^- to give radical anions **70**. These radical anions transfer an electron to the educts and yield substitution products **71**. Cleavage of the C-X bond of the newly formed radical anions **72** regenerate the aryl radicals.[71]



This $S_{RN}1$ scheme is analogous to that proposed by Kornblum[72] and Russell[73] for reactions of nucleophiles with certain p-nitrobenzyl halides and 2-halo-2-nitropropanes. Reactions with carbanions offer a wide variety of C-C bond formation possibilities with carbo- and heteroaromatic systems.

Halogens, phosphates, phenylsulfides, and trimethylammonium groups have been used as nucleofugic groups which can be substituted in these syntheses. These reactions also occur in the presence of substituents like alkyl, alkoxy, phenyl, carboxylate, and benzoyl groups, but nitrile and hydroxy groups are incompatible.[74]

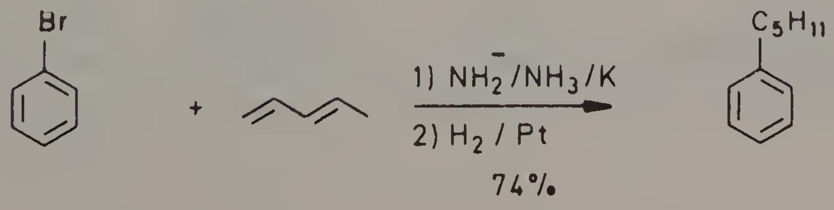
A variety of carbo- and heteroaromatic substrates, equipped with suitable nucleofugic groups, participate in $S_{RN}1$ reactions. These include benzenes, naphthalenes, anthracenes, phenanthrenes, pyridines, pyrimidines, pyrazines, quinolines, isoquinolines, and thiophenes.[74]

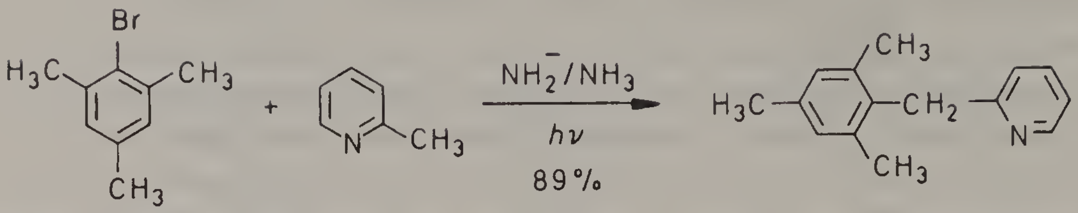
Liquid ammonia has turned out to be the most suitable solvent, but dimethyl sulfoxide, tetrahydrofuran , and aqueous tert-butyl alcohol have also been employed with some success. The syntheses are promoted by electron donation by potassium metal or, in few cases, from electrodes, and irradiation to stimulate the electron transfer steps.[74]

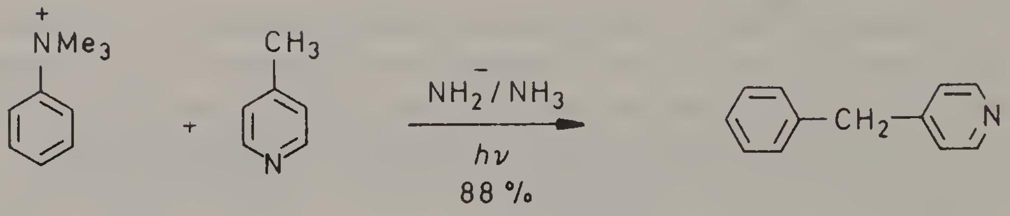
The carbanions used as nucleophiles in these C-C bond forming reactions shall be discussed in detail.

a. Conjugated hydrocarbons

Conjugated hydrocarbons that have lower pK_a values than ammonia (pK_a = 32.5) are converted into their carbanions by reaction with amide ions in liquid ammonia. Many of these carbanions can be used for C-C bond formation reactions if they are soluble in liquid ammonia. Thus, 1,3-pentadiene reacts with phenylbromide to give, after hydrogenation, 1-phenylpentane;[75] picolines can be arylated at the methyl group.[76]



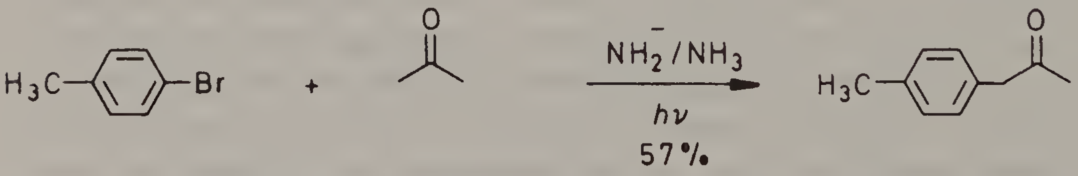


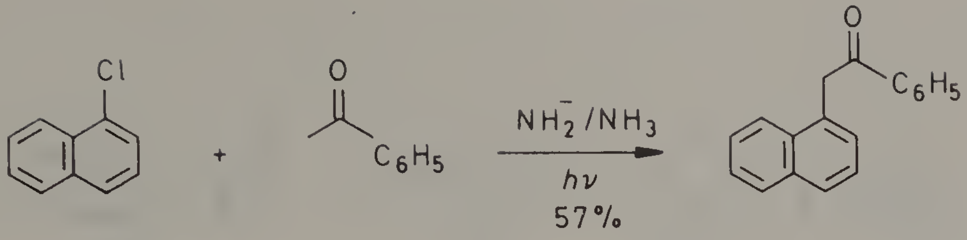


The reaction with 2-bromomesitylene shows that $S_{RN}1$ reactions are not hindered by small ortho substituents.

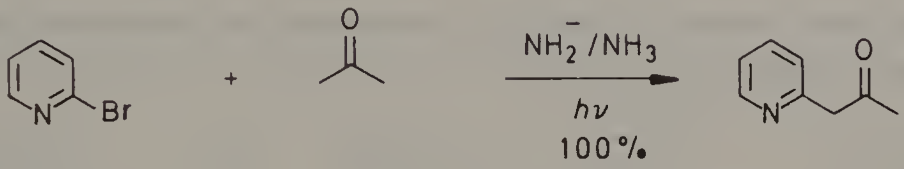
b. Ketones

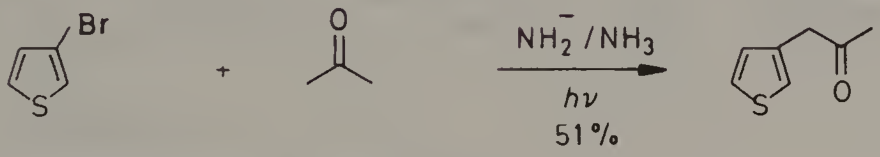
The best procedure for conducting arylation reactions of ketones involves the generation of carbanions with potassium amide or potassium tert-butoxide in liquid ammonia, followed by addition of the aromatic substrate and photolysis.[74,77]

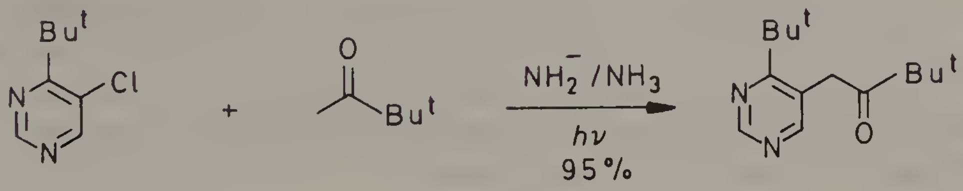




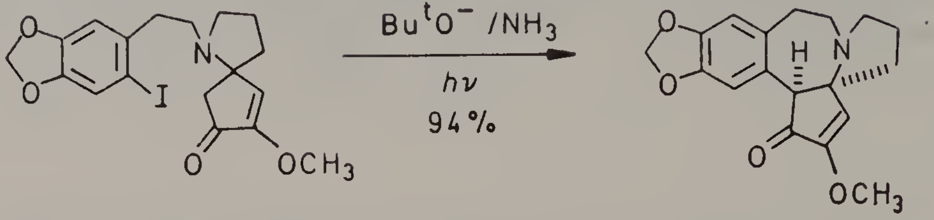
Heterocyclic halides give comparable yields of C-C bond formation products.[78]





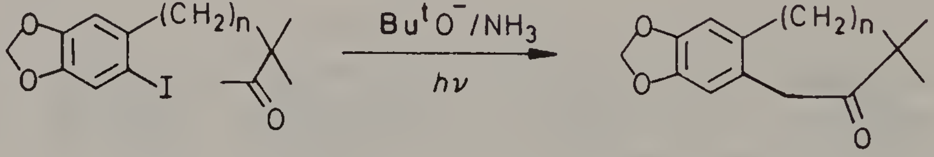


Cyclization reactions can also be carried out using the $S_{RN}1$ method. Thus, (±) cephalotoxinone **74** has been synthesized from iodide **73**.[79]



73 **74**

Medium sized rings can also be synthesized in intramolecular C-C bond forming reactions.[80]

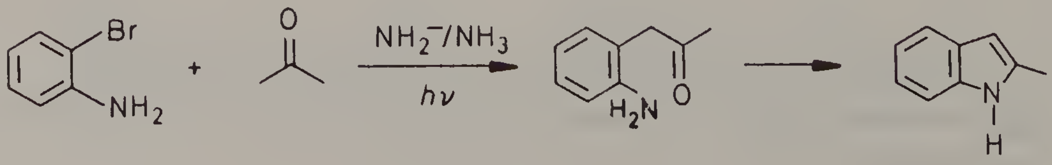


n = 1 (99%)

n = 3 (73%)

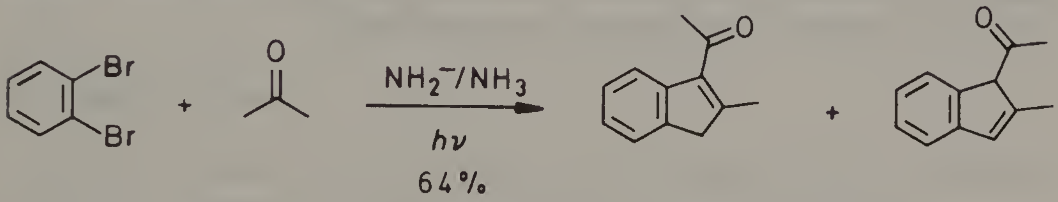
n = 5 (35%)

Ortho-substituted aromatic compounds give rise to cyclic products by successive reactions.[81]



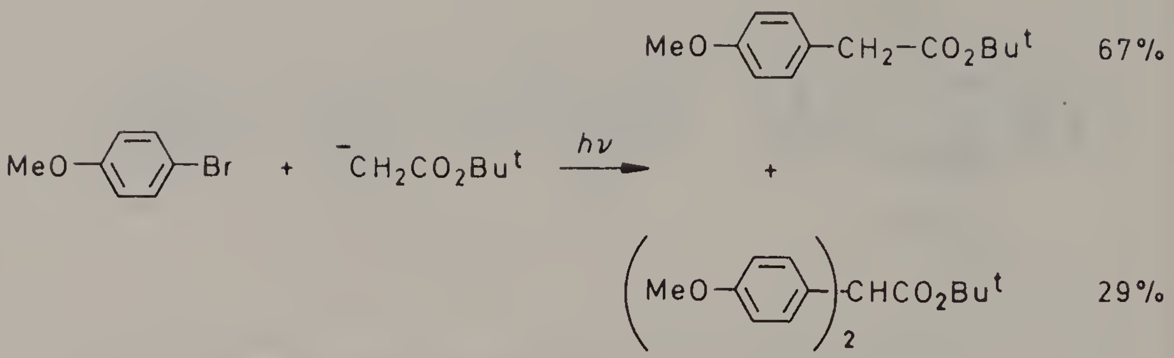
93%

In a reaction involving o-dibromobenzene, the product of two $S_{RN}1$ reactions cyclizes to isomeric indenes.[82]

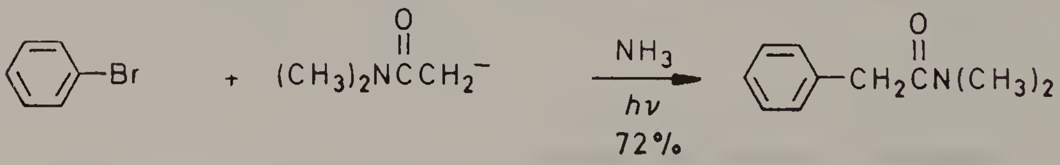


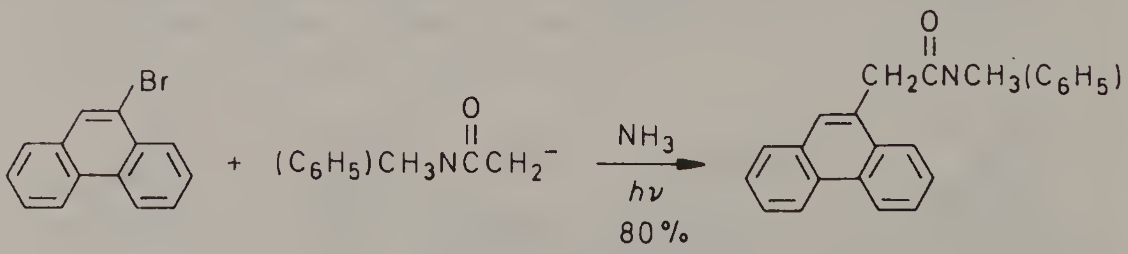
c. Aldehydes, esters, and amides

Aldehydes and esters are not as useful in $S_{RN}1$ syntheses as ketones. Reduction of the halobenzene with aldehydes and disubstitution with esters severely limits these reactions.[80,83]

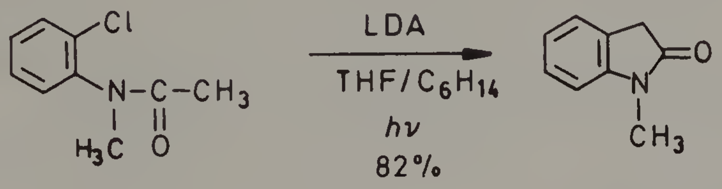


The acetamide anion fails to react with arylhalides in liquid ammonia; however, the enolate ions of N,N-disubstituted amides give high yields of substitution products.[84]





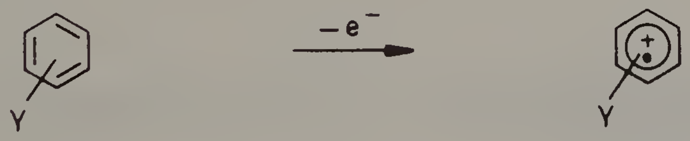
Intramolecular C-C bond formation reactions are also possible with N,N-disubstituted amides. These reactions have been used for the synthesis of oxindole **76** from **75** in a tetrahydrofuran/hexane mixture, with lithium diisopropyl amide as base.[85]



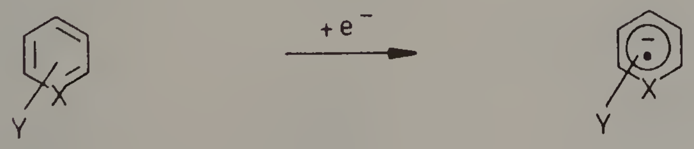
75 **76**

E. Radical Ions

Electron transfer to or from benzoid systems leads to radical ions **77** and **78** with 5 and 7 π-electrons, respectively.



77



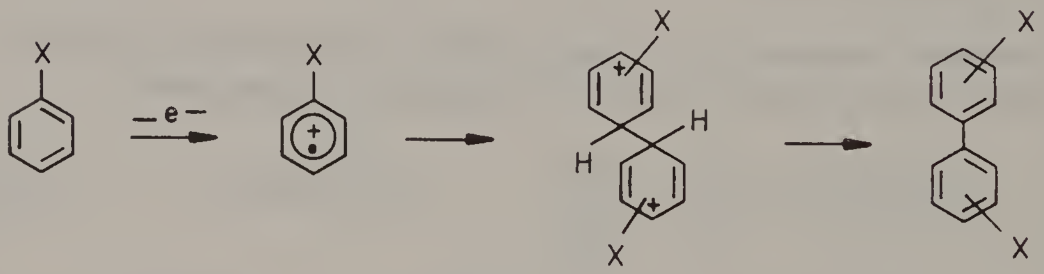
78

Radical cations **77** are intermediates in most side chain oxidations carried out at the anode or with metal salts.[86] Some electrophilic aromatic substitution reactions are also believed to proceed via these cations.[87] The formation of C-C bonds occurs via recombination or reaction of **77** with carbon nucleophiles.

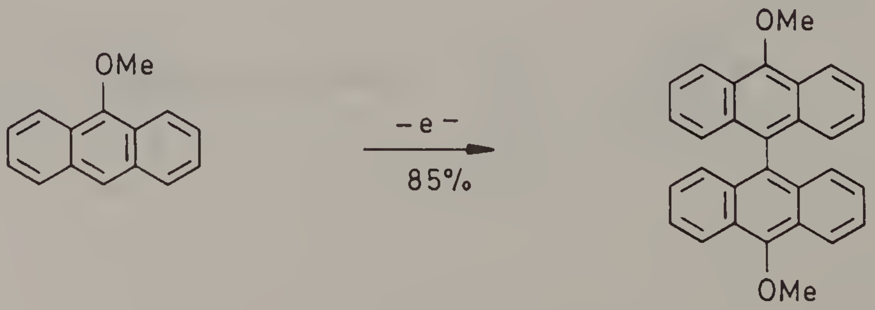
Radical anions **78** are intermediates of $S_{RN}1$ reactions which lead, with suitable nucleofugic groups Y, to C-C bonds via phenyl radicals. Direct formation of C-C bonds from radical anions **78** occurs mainly via radical recombination.

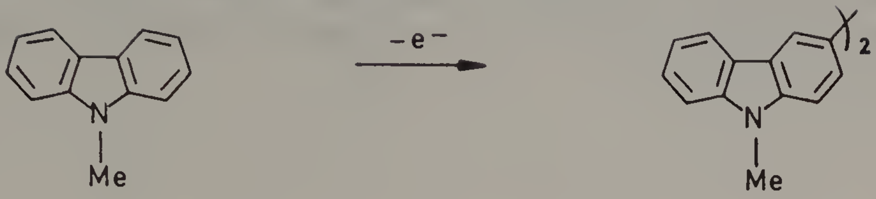
1. Radical cations

Anodic oxidation of electron-rich aromatic systems leads to aromatic radical cations which recombine to give biphenyls after deprotonation.[88]

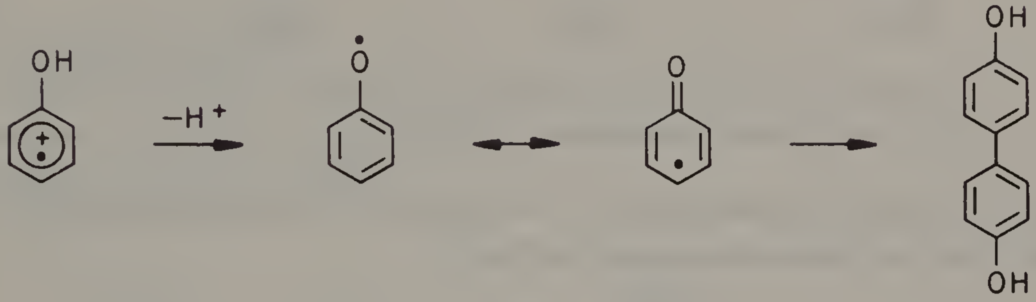


Thus, 9-methoxyanthracene and N-methylcarbazole can be oxidatively coupled.[89]

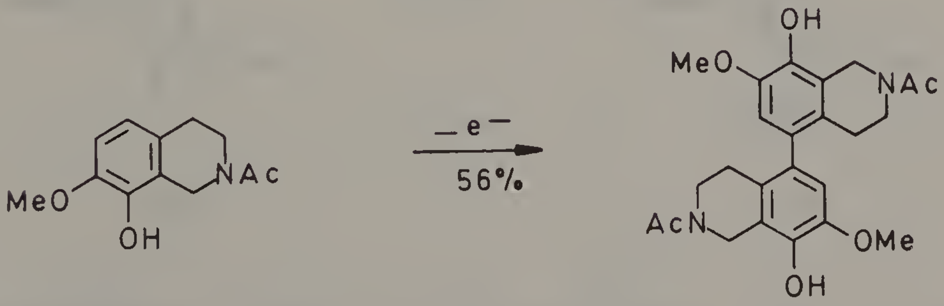




With phenols, radical cations deprotonate to give phenoxy radicals which combine to give dimers.[88]



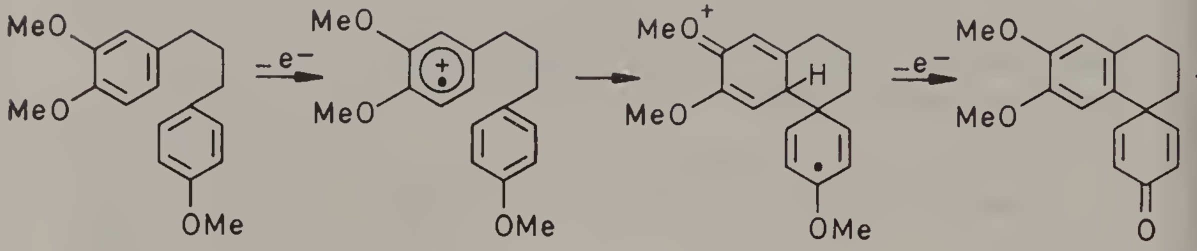
Thus, tetrahydroisoquinoline **79** was coupled to give the dimer **80**.[90]



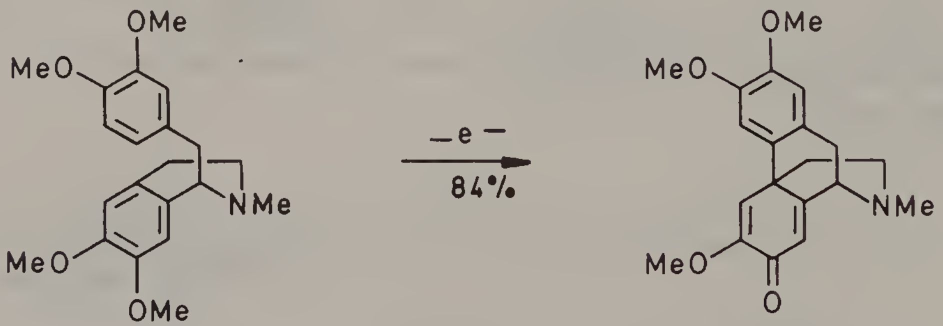
79

80

Intramolecular C-C bond formation reactions between aromatic rings occur by trapping the radical cations with suitably situated aromatic compounds. The newly formed radical is then further oxidized; if aromatization is not possible, quinoid systems are formed.[91]

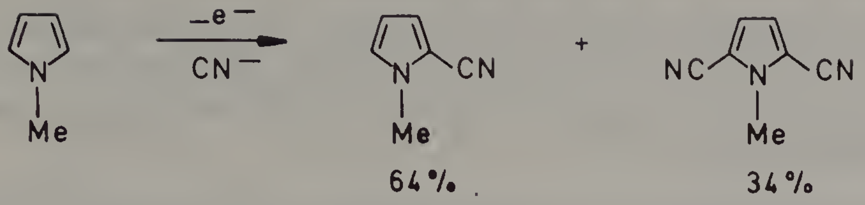


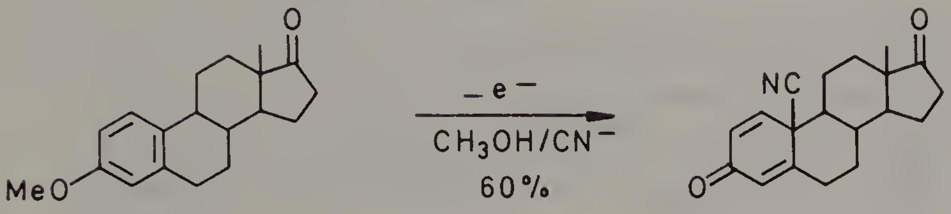
This method has been used in the synthesis of morphinandienone **82** from tetrahydroisoquinoline **81**.[92]



81 **82**

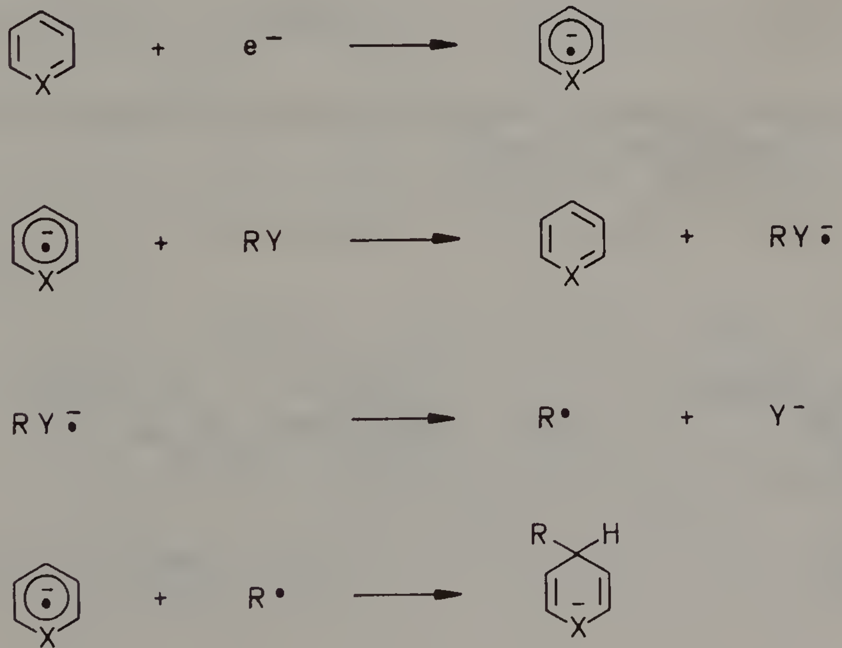
Aromatic radical cations can also be trapped intermolecularly by anions; thus, nitriles are formed in the presence of cyanide ions.[93]





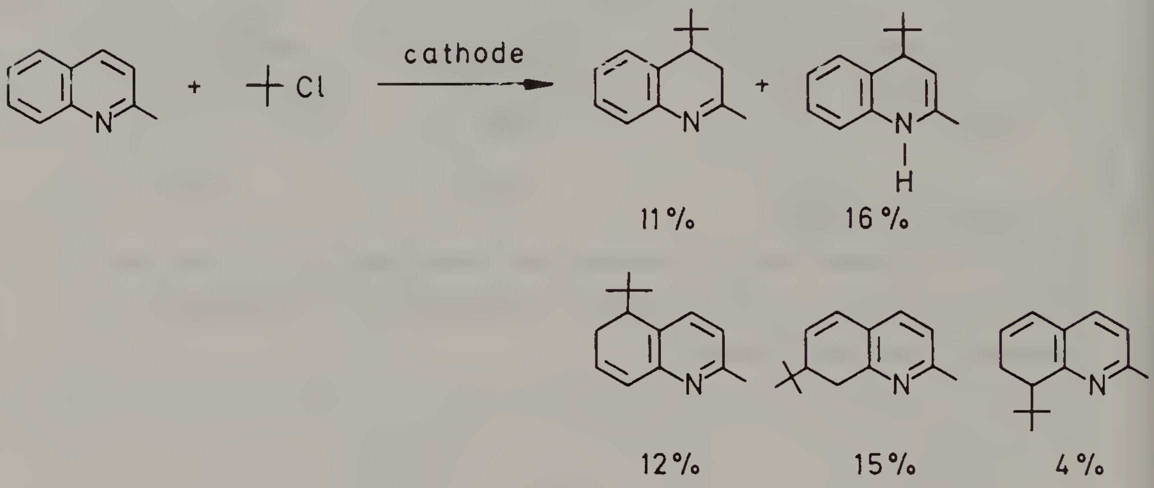
2. Radical anions

Direct C-C bond forming reactions from radical anions are scarce. They occur via radical combination reactions in a complex reaction scheme.

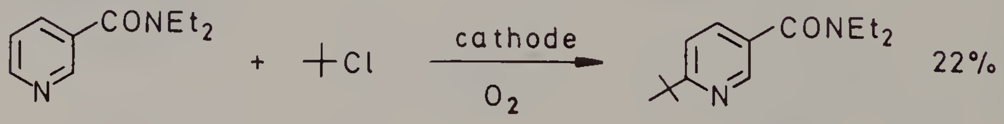


The radical anion, formed at the cathode or with a metal, transfers an electron to an alkyl halide. The newly formed alkylhalide radical anion decomposes to an alkyl radical which recombines with the aromatic radical anion; protonation then yields the product.[94]

Tertiary alkyl halides are mainly used and the radical combination often occurs with a low selectivity. Thus, α-methylquinoline leads to a mixture of products.[95]



The reaction of nicotinic amide **83** is more selective, but the yield of product **84** is low.[96]



83 **84**

REFERENCES

1. A. Citterio, F. Minisci, O. Porta, G. Sesana, *J. Am. Chem. Soc.* **1977**, *99*, 7960.
2. K. Münger, H. Fischer, *Int. J. Chem. Kinetics* **1985**, *17*, 809.
3. B. Giese, *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 771.
4. T.J. Burkey, D. Griller, L. Lunazzi, A.S. Nazran, *J. Org. Chem.* **1983**, *48*, 3704.
5. F. Minisci, A. Citterio in G.H. Williams (ed.): *Advances in Free-Radical Chemistry* Vol. VI, Heyden, London 1980, p. 65.
6. F. Minisci, *Synthesis* **1973**, 1; F. Minisci, *Top. Curr. Chem.* **1976**, *62*, 1.
7. M.E. Kurz, P. Kovacic, A.K. Bose, J. Kugajevsky, *J. Am. Chem. Soc.* **1968**, *90*, 1818; M.E. Kurz, E.M. Steele, R.L. Vecchio, *J. Org. Chem.* **1974**, *39*, 3331.
8. M.E. Kurz, V. Baru, P.N. Nguyen, *J. Org. Chem.* **1984**, *49*, 1603.
9. M.E. Kurz, P. Ngoviwatchai, T. Tantrarant, *J. Org. Chem.* **1981**, *46*, 4668.
10. E. Bamberger, *Ber. Dtsch. Chem. Ges.* **1897**, *30* 366.
11. W.S.M. Grieve, D.H. Hey, *J. Chem. Soc.* **1934**, 1797.
12. D.H. Hey, C.J.M. Stirling, G.H. Williams, *J. Chem. Soc.* **1956**, 1475.
13. R. Huisgen, G. Horeld, *Liebigs Ann. Chem.* **1949**, *562*, 137; R. Huisgen, H. Nakaten, *Liebigs Ann. Chem.* **1951**,*573*, 181.
14. C. Rüchardt, B. Freudenberg, *Tetrahedron Lett.* **1964**, 3623; G. Binsch, E. Merz, C. Rüchardt, *Chem. Ber.* **1967**, *100*, 247.
15. M.J. Perkins in J.K. Kochi (ed.): *Free Radicals*, Wiley, New York 1973, p. 231.

16. J.I.G. Cadogan, *Acc. Chem. Res.* **1971**, *4*, 186.

17. J.I.G. Cadogan in G.H. Williams (ed.): *Advances in Free Radical Chemistry*, Heyden, London 1980, p. 185.

18. J.I.G. Cadogan, *Pure Appl. Chem.* **1967**, *15*, 153

19. D.H. Hey, M.J. Perkins, G.H. Williams, *J. Chem. Soc.* **1965**, 110.

20. C.S. Rondestvedt, H.S. Blanchard, *J. Am. Chem. Soc.* **1955**, *77*, 1769.

21. M.J. Perkins in J.K. Kochi (ed.): *Free Radicals* Vol. II, Wiley,New York 1973, p. 231.

22. P.J.Bunyan, D.H. Hey, *J. Chem. Soc.* **1960**, 3787.

23. M. Hasebe, K. Kogawa, T. Tsuchiya, *Tetrahedron Lett.* **1984**, *25*, 3887.

24. R.K. Sharma, N. Kharasch, *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 36; I. Grimshaw, A.P. de Silva, *Chem. Soc. Rev.* **1981**, *10*, 181.

25. R. Ito, T. Migita, N. Morikawa, O. Simamura, *Tetrahedron* **1965**, *21*, 955.

26. B. Chauncy, E. Gellert, *Aust. J. Chem.* **1970**, *23*, 2503.

27. M. Sainsbury, *Tetrahedron* **1980**, *36*, 3327.

28. M. Tiecco, *Acc. Chem. Res.* **1980**, *13*,51.

29. C.M. Camaggi, R. Leardini, P. Zanirato, *J. Org. Chem.* **1977**, *42*, 1570.

30. J.J. Köhler, W.N. Speckamp, *Tetrahedron Lett.* **1977**, 631.

31. A. Citterio, F. Minisci, V. Franchi, *J. Org. Chem.* **1980**, *45*, 4752.

32. M. Bellati, T. Caronna, A. Citterio, F. Minisci, *J. Chem. Soc. Perkin Trans. 2* **1976**, 1835.

33. C. Giordano, F. Minisci, V.Tortelli, E.Vismara, *J.Chem.Soc. Perkin Trans. 2* **1984**, 293; F. Minisci, C. Giordano, E. Vismara, S. Levi, V. Tortelli, *J. Am. Chem. Soc.* **1984**, *106*, 7146.

34. T. Caronna, A. Citterio, T. Crolla, F. Minisci, *Tetrahedron Lett.* **1976**, 1731.

35. T. Caronna, A. Citterio, T. Crolla, F. Minisci, *J. Chem. Soc. Perkin Trans.1* **1977**, 865.

36. G. Castaldi, F. Minisci, V.Tortelli,E.Vismara,*Tetrahedron Lett.* **1984**, *25*, 3897.

37. F. Minisci, A. Citterio, E. Vismara, C. Giordano, *Tetrahedron* **1985**, *41*, 4157.

38. C. Walling, *Acc. Chem. Res.* **1975**, *8*, 125.

39. A. Citterio, A. Gentile, F. Minisci, *Tetrahedron Lett.* **1982**, *23*, 5587.

40. A. Clerici, F. Minisci, K. Ogawa, J.M. Surzur, *Tetrahedron Lett.* **1978**, 1149.

41. F. Minisci, R. Galli, V. Malatesta, T. Caronna, *Tetrahedron* **1970**, *26*, 4083.

42. F. Minisci, A. Citterio, C. Giordano, *Acc. Chem. Res.* **1983**, *16*, 27.

43. F. Minisci, R. Bernardi, F. Bertini, R. Galli, M. Perchinummo, *Tetrahedron* **1971**, *27*, 3575.

44. G. Heinisch, A. Jentzsch, I. Kirchner, *Tetrahedron Lett.* **1978**, 619.

45. F. Minisci, E. Vismara, U. Romano, *Tetrahedron Lett.* **1985**, *26*, 4803

46. G.P. Gordini, F. Minisci, G. Palla, A. Arnone, R. Galli, *Tetrahedron Lett.* **1971**, 59.

47. A. Arnono, M. Cecere, R. Galli, F. Minisci, M. Perchinummo, O. Porta, G.P. Gardini, *Gazz. Chim. Ital.* **1973**, *103*, 13.

48. G.P. Gardini, *Tetrahedron Lett.* **1972**, 4113

49. G.P. Gardini, F. Minisci, *J. Chem. Soc. C* **1970**, 929; M. Bellati, T. Caronna, A. Citterio, F. Minisci, *J. Chem. Soc. Perkin Trans. 2* **1976**, 1835.

50. T. Caronna, G. Fronza, F. Minisci, O. Porta, *J. Chem. Soc. Perkin Trans. 2* **1972**, 2035; T. Sakamoto, S. Konno, H. Yamanaka, *Heterocycles* **1977**, *6*, 1616.

51. F. Minisci, G.P. Gardini, R. Galli, F. Bertini, *Tetrahedron Lett.* **1970**, 15; R. Bernardi, T. Caronna, R. Galli, F. Minisci, M. Perchinunno, *Tetrahedron Lett.* **1973**, 645; A. Citterio, A. Gentile, F. Minisci, M. Serravalle, S. Ventura, *J. Org. Chem.* **1984**, *49*, 3364.

52. E. Langhals, H. Langhals, C. Rüchardt, *Liebigs Ann. Chem.* **1982**, 930.

53. M.F. Zady, J.L. Wong, *J. Org. Chem.* **1979**, *44*, 1450.

54. H. Steinmaus, I. Rosenthal, D. Elad, *J. Org. Chem.* **1971**, *36*, 3594.

55. J. Zylber, N. Zylber, A. Chiaroni, C. Riche, *Tetrahedron Lett.* **1984**, *25*, 3853.

56. K.N.V. Duong, A. Gaudemer, M.D. Johnson, R. Quillivic, J. Zylber, *Tetrahedron Lett.* **1975**, 2997.

57. D.H.R. Barton, B. Garcia, H. Togo, S.Z. Zard, *Tetrahedron Lett.* **1986**, *27*, 1327.

58. G.A. Russell, D. Guo, R.K. Khanna, *J. Org. Chem.* **1985**, *50*, 3423.

59. M. Fiorentino, L. Testaferri, M. Tiecco, L. Troisi, *J. Chem. Soc. Chem. Commun.* **1977**, 316; M. Fiorentino, L. Testaferri, M. Tiecco, L. Troisi, *J. Chem. Soc. Perkin Trans. 2* **1977**, 1679; T. Caronna, A. Citterio, M. Belatti, *J. Chem. Soc. Chem. Commun.* **1976**, 987.

60. L. Testaferri, M. Tiecco, M. Tingoli, M. Fiorentino, L. Troisi, *J. Chem. Soc. Chem. Commun.* **1978**, 93.

61. P. Cogolli, L. Testaferri, M. Tiecco, M. Tingoli, *J. Chem. Soc. Perkin Trans. 2* **1980**, 1336.

62. C.S. Rondestvedt, *Org. Reactions* **1976**, *24*, 225.

63. K.G. Tashchuk, A.V. Dombrovskii, *J. Org. Chem. USSR* **1965**, 1, 2034.

64. N.O. Pastushak, A.V. Dombrovskii, L.I. Rogovik, *J. Gen. Chem. USSR* **1964**, *34*, 2254.

65. M. Allard, J. Levisalles, *Bull. Soc. Chim. France* **1972**, 1926.

66. M.P. Doyle, B. Siegfried, R.C. Elliott, J.F. Dellaria, *J. Org. Chem.* **1977**, *42*, 2431.

67. C.F. Koelsch, *J. Am. Chem. Soc.* **1943**, *65*, 57.

68. A. Citterio, *Org. Synthesis* **1984**, *62*, 67; A. Citterio, E. Vismara, *Synthesis* **1980**, 291.

69. B. Giese, J.A. Gonzalez-Gomez, unpublished results.

70. Y. Ueno, K. Chino, M. Okawara, *Tetrahedron Lett.* **1982**, *25*, 2575.

71. J.K. Kim, J.F. Bunnett, *J. Am. Chem. Soc.* **1970**, *92*, 7463.

72. N. Kornblum, R.E. Michel, R.C. Kerber, *J. Am. Chem. Soc.* **1966**, *88*, 5662.

73. G.A. Russell, W.C. Danen, *J. Am. Chem. Soc.* **1966**, *88*, 5663.

74. R.A. Rossi, R.H. de Rossi: *Aromatic Substitution by the $S_{RN}1$ Mechanism*, ACS Monograph 178, Washington 1983; J.F. Wolfe, D.R. Carver, *Org. Prep. Proc.* **1978**, *10*, 225.

75. R.A. Rossi, J.F. Bunnett, *J. Org. Chem* **1973**, *38*, 3020.

76. J.F. Bunnett, B.F. Gloor, *J. Org. Chem.* **1974**, *39*, 382.

77. R.A. Rossi, J.F. Bunnett, *J. Am. Chem. Soc.* **1972**, *94*, 683; R.A. Rossi, R.H. de Rossi, A.F. Lopez, *J. Am. Chem. Soc.* **1976**, *98*, 1252; J.F. Bunnett, J.E. Sandberg, *J. Org. Chem.* **1976**, *41*, 1702.

78, J.F. Bunnett, B.F. Gloor, *Heterocycles* **1976**, *5*, 377; A.P. Komin, J.F. Wolfe, *J. Org. Chem.* **1977**, *42*, 2481; E.A. Oostveen, H.C. van der Plas, *Rec. Trav. Chim. Pays-Bas* **1979**, *98*, 441.

79. S.M. Weinreb, M.F. Semmelhack, *Acc. Chem. Res.* **1975**, *8*, 158.

80. M.F. Semmelhack, T.M. Bargar, *J. Org. Chem.* **1977**, *42*, 1481.

81. R.R. Bard, J.F. Bunnett, *J. Org. Chem.* **1980**, *45*, 1546; R. Beugelmans, H.J. Ginsburg, *J. Chem. Soc. Chem. Commun.* **1980**, 508.

82. J.F. Bunnett, P. Singh, *J. Org. Chem.* Ref. 74, p. 113.

83. R. Beugelmans, G. Roussi, *Tetrahedron* **1981**, *37*, 393.

84. R.A. Rossi, R.A. Alonso, *J. Org. Chem.* **1980**, *45*, 1239.

85. J.F. Wolfe, M.C. Sleevi, R.R. Goehring, *J. Am. Chem. Soc.* **1980**, *102*, 3646.

86. C.J. Schlesener, C. Amatore, J.K. Kochi, *J. Am. Chem. Soc.* **1984**, *106*, 3567; C. Walling, G.M. El-Taliami, K. Amarnath, *J. Am. Chem. Soc.* **1984**, *106*, 7573; E. Baciocchi, T. Del Giacco, C. Rol, G.V. Sebastiani, *Tetrahedron Lett.* **1985**, *26*, 541; F. Minsci, A. Citterio, *Acc. Chem. Res.* **1983**, *16*, 27.

87. F. Effenberger, *Chem. in unserer Zeit* **1979**, *13*, 87.

88. S. Torii: *Electroorganic Syntheses, Part I, Oxidations*, VCH, Weinheim 1985.

89. S.N. Frank, A. Bard, A. Ledwith, *J. Electrochem. Soc.* **1968**, *90*, 4645; O. Hammerich, V.D. Parker, *Acta Chem. Scand.* **1982**, *B36*, 519.

90. J.M. Bobbitt, H. Yagi, S. Shibuya, J.T. Stock, *J. Org. Chem.* **1971**, *36*, 3006.

91. E. Kotani, N. Takeuchi, S. Tobinaga, *J. Chem. Soc. Chem. Commun.* **1973**, 550.

92. L.L. Miller, F.R. Stermitz, J.R. Falck, *J. Am. Chem. Soc.* **1971**, *93*, 5941; E. Kotani, S. Tobinaga, *Tetrahedron Lett.* **1973**, 4759.

93. K. Yoshida, *J. Am. Chem. Soc.* **1979**, *101*, 2116; K. Ponsold, H. Kasch, *Tetrahedron Lett.* **1979**, 4465.

94. J.F. Garst, *Acc. Chem. Res.* **1971**, 4, 400; T. Lund, H. Lund, *Tetrahedron Lett.* **1986**, *27*, 95.

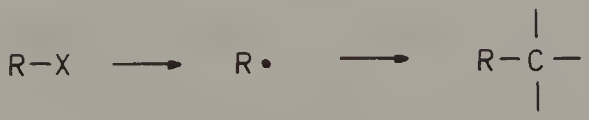
95. C. Degrand, H. Lund, *Acta Chem. Scand.* **1977**, *B31*, 593.

96. C. Degrand, D. Jacquin, P.L. Compagnon, *J. Chem. Research (S)* **1978**, 246.

Chapter 6

Methods of Radical Formation

This chapter gives a concise collection of methods, which lead to carbon centered radicals via rupture of C-X bonds and which are used in the formation of C-C bonds.



$$R{-}X \longrightarrow R\bullet \longrightarrow R{-}\overset{|}{\underset{|}{C}}{-}$$

Detailed discussions and examples of these methods are found in this book on the pages cited in brackets.

A. Carbon-Halogen Bonds

1. Alkylhalides and arylhalides

$$\mathrm{R{-}Hal} \longrightarrow \mathrm{R}\cdot$$

a) Bu_3SnH, AIBN or hν (p. 7 - 11, 39, 57 - 64, 111, 142, 154 - 169, 220 - 221, 238, 246 - 247); $(Bu_3Sn)_2$, hν (p. 102, 176); allyltin (p. 98 - 101); vinyltin (p. 102).

b) Bu_3GeH, AIBN (p. 39, 67 - 68, 158).

c) $XCo(dmgH)_2py$, $NaBH_4$ or cathode (p. 179 - 181); $Co(dmgH)_2py$ (p. 102 - 103, 191).

d) Vitamin B_{12}, Zn or cathode (p. 112 - 113, 181).

e) Na or K (p. 124, 247 - 249); Zn (p. 189).

f) Anions (p. 95 - 97, 247 - 255, 259 - 260).

g) Bz_2O_2, Fe^{3+} (p. 226 - 227).

h) hν or AIBN (p. 77 - 82, 173 - 176, 220).

B. Carbon-Oxygen Bonds

1. Alcohols

$$\mathrm{R{-}OH} \longrightarrow \mathrm{R}\cdot$$

a) CS_2, MeI, Bu_3SnH, AIBN (p. 57, 64 - 65).

b) $(COCl)_2$, N-hydroxypiperidine-2-thione, hν or AIBN (p. 85).

c) $ClPO(OEt)_2$; $S_{RN}1$ conditions (p. 249).

2. Aldehydes, ketones, and esters

a) N_2H_4; Hg^{2+}, $NaBH_4$ (p. 54 - 56).

b) Cathode, H+ (p. 122, 187 - 188).

c) R-H, hν (p. 123, 194 - 196).

d) Zn, TMSCl (p. 186); Mg, TMSCl (p. 187).

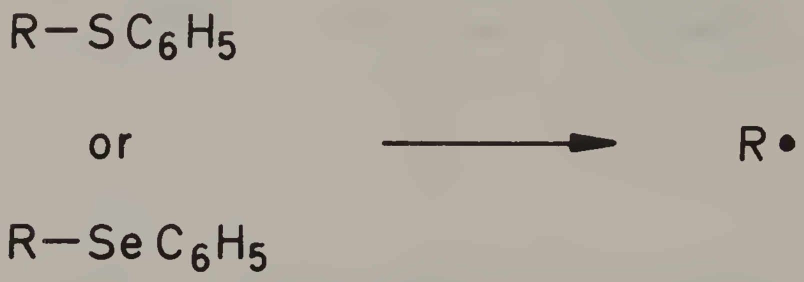
a) Na (p. 124, 185 - 187, 192 - 193);
Mg (p. 122); Ti(III) (p. 123).

b) R_3N or HMPT, hν (p. 188).

c) Cathode (p. 187 - 188).

C. CARBON-SULFUR AND CARBON-SELENIUM BONDS

1. Alkylsulfides, arylsulfides, alkylselenides, and acylselenides



a) Bu_3SnH, AIBN or hν (p. 57, 65, 158, 160 - 161, 166 - 167).

b) Anions, hν (p. 249).

D. CARBON-NITROGEN BONDS

1. Amines

$$R{-}NH_2 \longrightarrow R\bullet$$

a) MeI, anion, hν or Na (p. 249 - 250).

2. Nitro compounds

$$R{-}NO_2 \longrightarrow R\bullet$$

a) Bu_3SnH, AIBN (p. 57, 65 - 67, 169).

b) Anion, hν (p. 95 - 97).

3. Diazonium salts

$$\mathrm{Ar{-}N_2^{+}X^{-}} \longrightarrow \mathrm{Ar}\bullet$$

a) Cu^{+}, Ti^{3+} (p. 217 - 219, 242 - 245).

4. Azo compounds

$$\mathrm{R{-}N{=}N{-}R} \longrightarrow \mathrm{R}\bullet$$

a) Δ or $h\nu$ (p. 126 - 127, 197 - 202, 217).

E. Carbon-Carbon Bonds

1. Carboxylic acids

$$R{-}CO_2H \longrightarrow R\cdot$$

a) N-Hydroxypiperidine-2-thione, hν (p. 82 - 86, 176 - 177, 239).

b) M^{n+}, peroxide (p. 233 - 234, 236).

c) SO_2Cl_2, H_2O_2 or RO_2H, Δ (p. 125 - 126, 237).

d) Anode (p. 113 - 117, 184).

2. Ketones

a) H_2O_2, Fe^{2+} (p. 93 - 94, 232, 236 - 237).

3. Cyclopropanes

a) Hg^{2+}, $NaBH_4$ (p. 49 - 54).

4. Alkenes

a) Hg^{2+}, $NaBH_4$ (p. 43 - 49, 151 - 154).

b) B_2H_6, O_2 (p. 86 - 89); B_2H_6, Hg^{2+}, $NaBH_4$ (p. 41 - 43).

c) Peroxide, M^{n+} (p. 21, 230 - 231).

d) Capto dative alkenes (p. 119 - 120).

e) Cyclization of dienes (p. 172 - 175, 177 - 178, 183 - 184; tandem cyclization (p. 26, 155 - 158, 170); combination of intramolecular and intermolecular reactions (p. 111, 169).

5. Alkenes and aromatic compounds

a) Anode (p. 117 - 118, 255 - 259).

a) Cathode (p. 124, 259 - 260).

F. Carbon-Hydrogen Bonds

$$R{-}H \longrightarrow R\bullet$$

a) Peroxides (p. 6, 17 - 18, 69 - 76, 106 - 107, 109 - 110, 119 - 120, 170 - 173, 227 - 231, 234 - 237).

b) Ketone/hν or hν (p. 69 - 76, 120 - 121, 123, 172 - 173, 194 - 196).

c) M^{n+} (p. 89 - 93, 182 - 183, 214 - 216).

d) $R_2\overset{+}{N}HCl$, Fe^{2+} (p. 225 - 226).

e) Δ (p. 69).

G. Carbanions

$$R^{-} \longrightarrow R\cdot$$

a) Anode (p. 94 - 95, 116 - 117).

b) I_2 or O_2 (p. 118).

H. Carbon-Boron Bonds

a) O_2 (p. 86 - 89).

b) Hg^{2+}, $NaBH_4$ (p. 41 - 43).

I. Carbon-Mercury Bonds

$$\mathrm{R{-}HgX} \longrightarrow \mathrm{R}\bullet$$

a) $NaBH_4$ or Bu_3SnH (p. 23, 38 - 56, 151 - 154, 178).

b) Anions, hν (p. 98); heteroaromatic, hν (p. 239).

J. Carbon-Cobalt Bonds

$$\mathrm{R{-}Co} \longrightarrow \mathrm{R}\bullet$$

a) Δ (p. 111 - 113, 179 - 181).

Author Index

Bold figures refer to the pages on which the authors are cited in the text, roman figures refer to pages on which references are listed at the end of each article.

Subject Index

C

Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds

The past twenty years have witnessed an unparalleled development of new synthetic methods in the field of organic chemistry. Many of these new methodologies involve the same basic ionic processes which were involved in the early development of the mechanistic picture of organic chemistry. Although of great power, these ionic processes do suffer from limitations, in particular the problems of compatibility of functional groups. This is especially so in highly functionalised molecules.

Within the last decade, however, a new approach to bond formation has been emerging, namely the use of homolytic or radical reactions. It is already evident that these processes, well known in the polymer industry, have a great role to play in the synthesis of complex molecules. In this book the author, who is a pioneer of this new development, describes in a masterly fashion the developments which have occurred and in particular how the practising synthetic chemist can make use of them in his work. The book will be of wide use to all chemists involved in synthesis both in industry and academia.

Contents:

Introduction. Basic Principles. Intermolecular Formation of Aliphatic C–C Bonds. Intramolecular Formation of Aliphatic C–C Bonds. C–C Bond Formation of Aromatic Systems. Methods of Radical Formation. Author Index. Subject Index.

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