O4 Reactive Intermediates - 1 (Radicals)

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***Recommended texts**:*
"An Introduction to Free Radical Chemistry", A.F. Parsons, Blackwell, Oxford, 2000.
"Reactive Intermediates", C.J. Moody and G.H. Whitham, OUP (Primer No.8), 1992.
"Radical Chemistry: The Fundamentals", M.J. Perkins, OUP (Primer No. 91), 2000: mostly concentrates on mechanistic / physical organic aspects
"Free Radical Chain reactions in Organic Synthesis", W.B. Motherwell and D. Crich, Academic Press, 1992.
"Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds", B. Giese, Pergamon Press, Oxford, 1986.
"The Design and Application of Free Radical Chain Reactions in Organic Synthesis", D.P. Curran, *Synthesis,* **1988**, 417 and 489.

Course content:

1. Introduction to Radical Chemistry:
   Advantages, reactivity; chain reaction processes

2. Functional Group Transformations involving Radicals:
   Dehalogenation, deoxygenation, deamination, decarboxylation, desulfurisation etc.

3. Radicals in Carbon-Carbon Bond Formation
   Inter- and intramolecular processes; stereochemical aspects

4. Synthetic Applications of Radical Chemistry
   Examples of the application of radical chemistry to total synthesis

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Lecture 1

Introduction

What is a reactive intermediate? A reactive intermediate corresponds to a shallow dip in a diagram of free energy *versus* reaction coordinate; generally, the rate of conversion of this intermediate into the reaction product is fast compared to the rate of its formation (otherwise, the intermediate would be an isolable compound, or a species in rapid equilibrium with the reactants).
The Handout summarises the main types of reactive intermediate of interest to organic chemists. In this course, we will be concentrating on the chemistry of radicals. (Other species, such as carbenes and nitrenes, will feature in Dr. Smith's course next term).

Radicals

Radicals are species with an unpaired electron. Up until relatively recently, radicals were regarded as highly reactive species whose reactions were unselective and difficult to control (remember the radical chlorination of methane!). The last 20 years have seen the field develop to such an extent that it is now recognised that radicals can take part in highly useful and selective reactions, and their chemistry offers a viable alternative to traditional, ionic methods.

Advantages of *radicals*

(i) Radicals are neutral and so are far less solvated than carbocations or carbanions. Therefore, they are smaller and can operate in polar, hindered environments where ionic chemistry fails.

(ii) Unlike carbocations, radicals are not prone to rearrangements.

(iii) Unlike carbanions, alkoxy- and sulfonyloxy- groups β-to a radical centre do not undergo elimination. However, halogen, sulfur and selenium groups β-to radicals *are* eliminated. Thus, radical elimination chemistry can be complementary to that of anions.

(iv) Protection of OH and NH_2 groups is unnecessary in radical reactions. (Unlike carbanions, radicals are not basic.)

One disadvantage of radical chemistry (there are others that we will see later) is that they readily react with O_2, so their reactions must be carried out under an inert atmosphere.

Relative Reactivity of Radical Species

Not all radicals show the same reactivity.....broadly speaking, the character of radicals is affected by (i) the nature of the atom that is the radical centre; (ii) the electronic properties of the groups attached to the radical.

The importance of the atom bearing the unpaired electron is nicely illustrated by the different reactivities of group 6 radicals, and is rationalised by the hard / soft nature of the radical centre. Thus, alkoxy radicals ($RO^\bullet$) are small and hard; they typically undergo H-atom abstraction and β-scission reactions. However, they rarely add to C=C. Thiyl ($RS^\bullet$) and selenyl ($RSe^\bullet$) radicals, however, are larger and softer. They do not usually abstract H, but they do readily add to C=C. This is useful for *Z/E* isomerisation of alkenes.

Within radicals centred on the same element, the groups attached can also influence reactivity. For example, consider carbon centred radicals ($R_3C^\bullet$). These species do undergo addition to C=C bonds (in fact this is an extremely useful C-C bond forming reaction, as we'll see later in the course).

Simple alkyl radicals ($R_3C^\bullet$) are generally considered to be nucleophilic radicals: they react fastest with electron-poor alkenes *(e.g.* α,β-unsaturated carbonyl compounds; cyanoalkenes).

However, when R=electron withdrawing group, the radicals are electrophilic and react fastest with electron rich alkenes *(e.g.* enol ethers, enamines).

This leads to the concept of ***radical umpolung*** (reverse polarity): for example, malonates are traditionally used as carbon nucleophiles; however, the malonyl radical is electrophilic. Similarly, α-halo ethers are regarded as electrophiles in ionic chemistry, but the derived radicals are nucleophilic.

Next time*,* we will rationalise this behaviour in terms of frontier molecular orbital theory, and move on to consider the main features of chain reaction processes.

Reactive Intermediates

	C	**N**	**O**
-onium ion	R_5C^+ carbonium ion	R_4N^+ ammonium ion	R_3O^+ oxonium ion
neutral molecule	R_4C	R_3N	R_2O
anion	R_3C^- carbanion	R_2N^- amide anion	RO^- alkoxide
radical	$R_3C^\bullet$ carbon radical	$R_2N^\bullet$ aminyl radical	$RO^\bullet$ oxyl radical
-enium ion	R_3C^+ carbenium ion	R_2N^+ nitrenium ion	RO^+ oxenium ion
-ene	$R_2C:$ carbene	$RN:$ nitrene	$:O:$ oxene

Lecture 2

Last time, we saw that radicals can be considered to be either nucleophilic (reacting fastest with electron poor alkenes), or electrophilic (reacting fastest with electron rich alkenes).

These tendencies can be nicely rationalised in terms of frontier molecular orbital theory.
Recall the key ideas of this theory:

- Best overlap (and maximum stabilisation) results from interaction of a filled orbital (the HOMO of one reactant) and an unoccupied orbital (LUMO of the other reactant) which are close together in energy. For radicals, we need to consider the interactions with a singly-occupied orbital (SOMO).
- Electron withdrawing groups lower orbital energies; electron donating groups raise them.

As shown in the Handout:
Electrophilic radicals have low energy SOMOs, and the dominant interaction is with the HOMO of an electron rich alkene.
Nucleophilic radicals have high energy SOMOs and the dominant interaction is with the LUMO of an electron poor alkene.

In general, nucleophilic radicals are more discriminating in their reactions since ΔE_1 is inherently larger than ΔE_2.

Chain Reaction Processes
Most synthetically useful radical reactions involve chain reactions. The main features of a chain reaction can be illustrated by considering the reduction of haloalkanes by tributyltin hydride. The key types of step are initiation, propagation (molecule + radical to give another molecule and another radical) and termination. Termination of the chain process can occur by combination of two radicals, a process that has a very high rate constant (often approaching diffusion control). However, the concentration of radicals is very low in the chain process, leading to low actual rates of radical combination.

In many chain processes, as we shall see, careful consideration of relative rates of various competing reactions is needed in order to determine the optimum experimental conditions.

Initiation
Iodoalkanes often do not require use of external initiators - initiation is achieved by the presence of a trace of iodine or oxygen, and the reaction of $Bu_3Sn^\bullet$ and RI is almost always productive, allowing the chain process to proceed efficiently.
For chloroalkanes, however, a larger proportion of collisions between $Bu_3Sn^\bullet$ and RCl is non-productive, and so it is necessary to have continuous regeneration of $Bu_3Sn^\bullet$ by addition of an initiator. It is best to add the initiator slowly, in portions - if it is added all at once, the resulting flood of radicals can lead to a higher chance of recombination.

Typical initiators are compounds with weak bonds that undergo decomposition at a convenient rate at < 150ºC. Commonly used examples are azobisisobutyronitrile (AIBN) and dibenzoyl peroxide.
Functional Group Transformations involving Radicals

1. Dehalogenation
- of haloalkanes (R-X) using trialkyltin hydrides.
Reactivity: RI > RBr > RCl (R-F inert).
R tertiary > secondary > primary > aryl or vinyl

2. Deoxygenation
- of alcohols.
Traditional methods (*e.g.* conversion of the alcohol into the tosylate and reduction with $LiAlH_4$) are ineffective for hindered, polar substrates. A highly effective alternative was developed in the mid-1970s in this Department by Professor Sir Derek Barton (Nobel Prize, 1969).
The *Barton-McCombie reaction* involves formation of a thiocarbonyl derivative (*e.g.* a xanthate ester) followed by reaction with tributyltin hydride. The mechanism involves attack of the tin radical on the sulfur of

the thiocarbonyl group; Bu_3SnH is best added slowly to the reaction mixture to allow fragmentation of the resulting intermediate to an alkyl radical, rather than direct hydride abstraction.

The Barton-McCombie reaction works well for primary and secondary alcohols. For tertiary alcohols, it is sometimes necessary to use other thiocarbonyl derivatives since xanthates can undergo competing Chugaev elimination.

The Barton-McCombie reaction has proved to be extremely powerful and is particularly useful in carbohydrate chemistry, allowing the preparation of deoxysugars.

Next time, we will examine other examples of radical methods for FG removal where ionic methods are largely unsuccessful.

Lecture 3

Last time, we started looking at **Functional Group Transformations involving Radicals** and considered 1. Dehalogenation; 2. Deoxygenation.

3. Deamination

- removal of the NH_2 group.

Direct homolytic cleavage of the C-N bond of a primary amine is energetically unfavourable, so it is necessary to convert the amine into a suitable derivative first.

Isocyanides undergo the desired conversion to alkanes with tributyltin hydride under radical conditions. Isocyanides can readily be prepared by dehydration of formamides which can themselves be prepared from primary amines.

The ease of isocyanide reduction follows the usual order of radical stability: tertiary > secondary > primary. Reduction of primary isocyanides requires very vigorous conditions and a large amount of initiator.

Like deoxygenation, this deamination procedure has proved to be extremely useful in carbohydrate chemistry.

4. Denitration

The nitro group is an extremely useful anion-stabilising group in synthesis, and the ability to remove it presents some powerful synthetic possibilities. Again, this transformation is difficult with ionic methods, but tributyltin hydride reduction of tertiary- or secondary nitro compounds leads efficiently to alkanes.

5. Desulfurisation / Deselenation

Again using tributyltin hydride, proceeding by a similar mechanism to the dehalogenation process we saw in the last lecture. *Aryl* sulfides or selenides are usually used since the S-Ph or Se-Ph bonds are not cleaved, leading to selective cleavage of the other C-S or C-Se bond.

6. Decarboxylation

It has long been known that the carboxyl radical readily loses CO_2 to give an alkyl radical. However, an efficient way of making the carboxyl radicals was not known until the late 1970s when Barton developed the chemistry of O-acyl thiohydroxamates. These compounds are readily prepared from acid chlorides and undergo reaction with Bu_3SnH/AIBN to give carboxyl radicals, which lose CO_2 to give alkyl radicals which are then trapped by Bu_3SnH to give the alkane.

Alternatively, it is possible to trap the alkyl radical with other reagents, leading to useful, functionalised products. For example:

(a) *Decarboxylative halogenation* is effected by thermal or photochemical reaction of the O-acylthiohydroxamate with CCl_4, $BrCCl_3$, or CH_2I_2. This chemistry provides a more efficient alternative to the venerable Hunsdiecker reaction, which involves low-yielding reaction of a silver carboxylate salt with iodine in a non-chain free radical process.

(b) *Hydrodecarboxylation* occurs upon heating the O-acylthiohydroxamate with *tert*-butyl thiol in the presence of oxygen. Overall, this allows transformation of a carboxylic acid to the alcohol with one less carbon.

Next time, we will start to consider the use of radical reactions in carbon-carbon bond forming processes.

Lecture 4

Carbon-Carbon Bond Forming Reactions involving Radicals

Carbon-carbon bond forming reactions are of course of prime importance in organic synthesis. Radical reactions again allow the formation of C-C bonds in situations where ionic chemistry gives poor results.
The most useful radical C-C bond forming process is addition to alkenes. Like nucleophilic addition to carbonyl groups, this is subject to a *stereoelectronic* requirement: attack occurs at approximately 109° to the alkene.

We will consider both intermolecular and intramolecular addition of radicals to alkenes.

Intermolecular Addition
Commonly, addition of a haloalkane to an electron-poor alkene in the presence of Bu_3SnH/AIBN. Consideration of the mechanism of the chain process suggests several requirements for efficient reaction:
(a) The alkyl radical ($R^\bullet$) must add to the electron deficient alkene faster than it reacts with Bu_3SnH (which would lead to undesired formation of RH).
(b) The intermediate radical must react with Bu_3SnH faster than it reacts with the starting alkene (a process that would lead to polymerisation).
Therefore, best results are obtained when $R^\bullet$ is a nucleophilic radical and the starting alkene is electron deficient, thereby (i) making the initial addition fast; (ii) making the intermediate radical (after addition) electrophilic (since the radical centre is next to an electron withdrawing group), so that it will not react rapidly with the starting alkene. Experimentally, in order to avoid reaction of $R^\bullet$ with Bu_3SnH, it is best to keep the concentration of the electron deficient alkene high (use an excess) and to keep the concentration of Bu_3SnH low by adding it slowly to the reaction mixture.

Intermolecular addition can also proceed by non-tin hydride chain processes. **Halogen atom transfer** can be a useful chain process: for example, addition of halocarbons to alkenes, involving highly electrophilic, halogenated radicals.

The presence of a leaving group on the alkene can lead to useful transformations *via* **addition-elimination**. The overall process is effectively substitution of the leaving group.

Intramolecular Addition

This is particularly favourable (“proximity effect”), and has fewer limitations than its intermolecular counterpart with respect to substitution on the alkene.

The most important process (which accounts for the majority of the uses of radical cyclisations in synthesis) is the selective **5-exo-cyclisation of the 5-hexenyl radical** to give the cyclopentyl methyl radical.

This occurs even though the alternative - a 6-endo cyclisation to give a more stable, cyclohexyl radical - is thermodynamically more favourable. Thus, the 5-exo-cyclisation is proceeding under kinetic control. The preference for 5-exo cyclisation is explained by an early transition state with little product character. The transition state is a strain free, chair-like arrangement which nicely accommodates the stereoelectronically-required attack angle on the alkene.

This model also nicely explains the stereochemical outcome of the cyclisation reaction. Assuming that substituents prefer to adopt *pseudo*-equatorial positions in the chair-like transition state, we see why:

- The 2-methyl-5-hexenyl radical (and the 4-methyl-5-hexenyl radical) cyclise to give predominantly the ***trans***-dimethyl product

- The 3-methyl-5-hexenyl radical cyclises to give mostly the ***cis***-dimethyl product.

The 1-methyl-5-hexenyl radical also gives predominantly the ***cis***-product, due to a combination of steric and stereoelectronic factors.

5-Exo-cyclisation proceeds with a variety of substituents on the chain. However, substituents in the 5-position can retard 5-exo reaction so that 6-endo predominates.

Next time: we will see some spectacular examples of the use of radical cyclisations in synthesis!

Lecture 5

Carbon-Carbon Bond Forming Reactions involving Radicals **- continued**

Last time, we met one of the most important C-C bond forming reactions in radical chemistry: the **5-*exo* cyclisation of the 5-hexenyl radical.**
The stereochemistry of this process can be rationalised in terms of a chair-like TS where substituents prefer to occupy a *pseudo*-equatorial orientation.

As well as being a very powerful method for making 5-ring carbocycles, the 5-*exo* cyclisation can also provide a route to 5-ring heterocycles.

Although there is a strong kinetic preference for cyclisation of the 5-hexenyl radical to give *5-exo* rather than *6-endo*-ring closure, the 6-*endo* pathway can compete or even predominate under some circumstances:

(a) When the alkene has substitution at the 5-position: 6-*endo* cyclisation is then faster than 5-*exo*.
(b) When the starting radical is stabilised: this results in the cyclisation being reversible, leading to formation of the thermodynamically more stable 6-ring product.
(c) In the cyclisation of vinyl radicals. Here, the 6-ring product is formed by rearrangement of the kinetic 5-ring, *via* a cyclopropyl methyl radical. The ratio of 5-*exo* to 6-*endo* products can be controlled to some extent by altering the concentration of Bu_3SnH.

What about using radical cyclisations to make larger rings than cyclopentanes?

Cyclisation of the 6-Hexenyl radical could conceivably be used to make cyclohexanes via 6-*exo* ring closure. However, this reaction is far less widely used in synthesis than the 5-hexenyl radical cyclisation since:
(a) It is *ca.* 40 times slower, hence reduction of the non-cyclised radical with Bu_3SnH can compete with cyclisation, leading to formation of the reduced starting material as a by-product.
(b) k_{exo}/k_{endo} is only about 7 at 25°C, so *endo* ring closure competes to a greater extent.
(c) **1,5-H abstraction** is a competing process. This leads to formation of a resonance-stabilised, allylic radical.

However, this 1,5-H abstraction process can be useful - it has been incorporated into some ingenious reaction sequences, for example the “tandem” 1,5-H abstraction - 5-*exo* process.

Formation of medium rings by radical reactions suffers from the same difficulties as with ionic chemistry (cyclisations are enthalpically and entropically disfavoured). However, as with ionic chemistry, useful syntheses of medium rings can be accomplished by ring expansion reactions.

Macrocyclisation (formation of large rings) can be achieved by *endo*-cyclisation of radicals onto terminal alkenes.

Much current research is focused on **tandem radical processes** where a sequence of two or more successive radical reactions can provide extremely rapid routes to highly complex ring systems. Impressive examples include Curran’s synthesis of hirsutene, and Pattenden’s recent work on the formation of steroid-like systems (see Handout).

Many of the reactions we have seen in this course involve the use of Bu_3SnH. While this reagent participates in some extremely efficient radical chain processes, there is a major problem….Sn reagents are highly toxic and *e.g.* for the synthesis of pharmaceuticals, the presence of even tiny amounts of Sn residues is unacceptable. Therefore, another major area of research is the development of alternatives to the use of Sn, or systems that use Sn in catalytic amounts. For example:

(a) **Atom transfer**: we met the idea of halogen atom transfer earlier (Lecture 4: section on Intermolecular Addition). This concept can also apply to Sn chemistry: see the Handout for the use of catalytic $(Bu_3Sn)_2$ as alternative conditions for Curran’s hirsutene synthesis. An advantage over Bu_3SnH

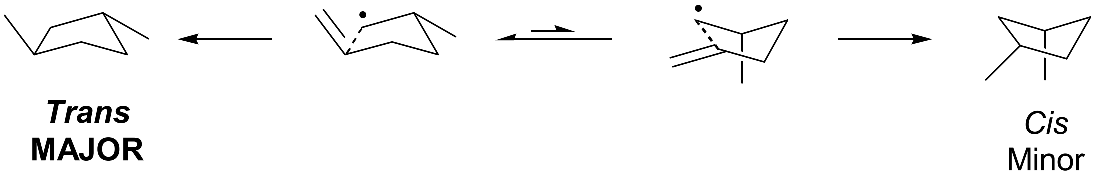
chemistry is that the product contains a potentially useful vinyl iodide unit.

(b) It is possible in some cases to use catalytic Bu_3SnCl + stoichiometric $NaBH_3CN$ to prepare Bu_3SnH *in situ*.

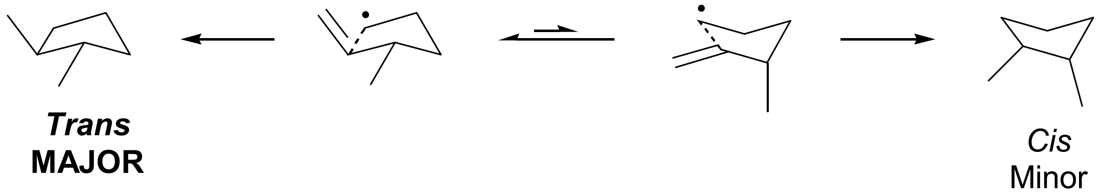
(c) $(Me_3Si)_3SiH$ has similar properties to Bu_3SnH (and can be used in catalytic amounts with stoichiometric $NaBH_4$).

Stereochemistry of Cyclisation of Substituted 5-Hexenyl Radicals

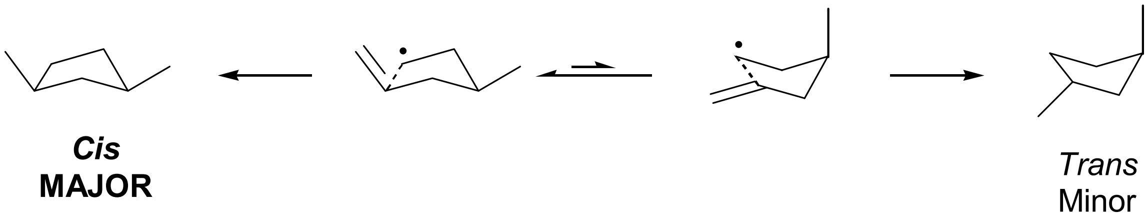
2-methyl:



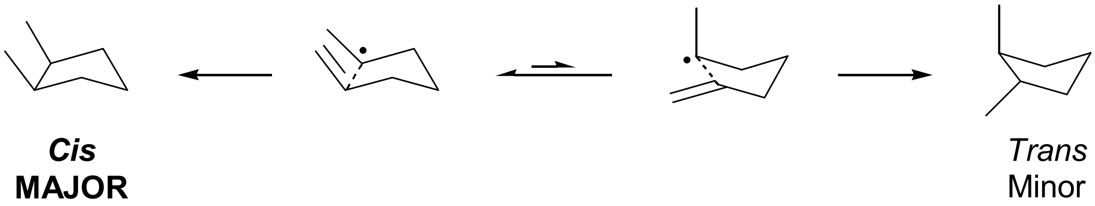
4-methyl:



3-methyl:

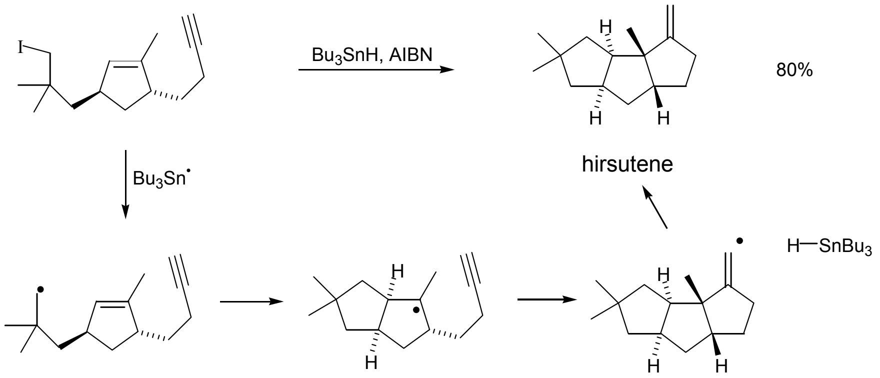


1-Methyl-5-hexenyl:

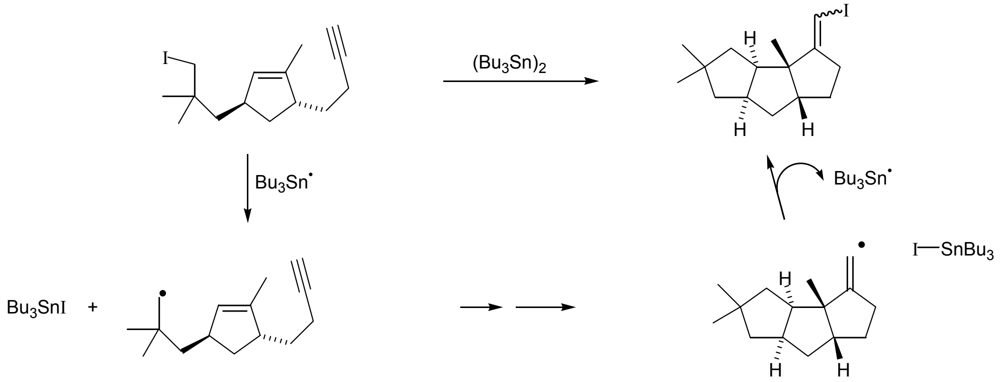


Tandem Radical Cyclisations

Hirsutene synthesis (Curran, *Tetrahedron,* **1985**, *41*, 3943).

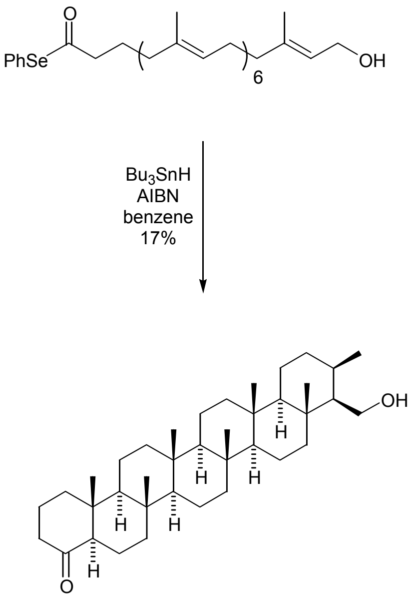


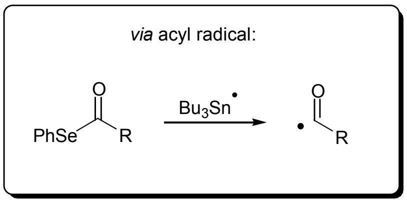
Atom transfer conditions:



Tandem Radical Cyclisations

Pattenden, *J. Chem. Soc., Perkin Trans.* 1, **1999**, 843.




via acyl radical: