Classroom

In this section of *Resonance*, we invite readers to pose questions likely to be raised in a classroom situation. We may suggest strategies for dealing with them, or invite responses, or both. "Classroom" is equally a forum for raising broader issues and sharing personal experiences and viewpoints on matters related to teaching and learning science.

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An Appreciation of Free Radical Chemistry
Part 5: Free Radicals in Organic Synthesis

Part 1. Introduction, *Resonance*, Vol.10, No.2, pp.72-78, 2005.
Part 2. Free Radical Reactions in Industry, *Resonance*, Vol.10, No.3, pp.71-79, 2005.
Part 3. Free Radicals in Diseases and Health, *Resonance*, Vol.10, No.4, pp.65-74, 2005.
Part 4 Free Radicals in Atmospheric Chemistry, *Resonance*, Vol 10, No.7, pp.61-72, 2005.

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A Brief Recollection

The idea of trivalent carbon was introduced in 1900 by Gomberg when he discovered triphenylmethyl. However, trivalent carbon free radicals did not receive much attention in organic synthesis till almost eight decades later, though major contributions to the development of the polymer industry were made during the 1940's and later.

For a synthetic sequence to be useful, the reactions should be efficient and selective in new bond formation and functional group transformation. The reaction should be such that one should be able to confidently predict the regio- and stereochemical outcomes, and takes place under the mildest possible conditions. However, until recently, free radical reactions were difficult to control. The common experience was that they led to polymers or complex mixtures or intractable tars. Therefore, early free radical chemistry remained only in the domain of physical organic chemistry and polymer chemistry.

As described in Part 1 of this series, a free radical chain reaction consists of three stages – (i) initiation, (ii) propagation, and (iii)

termination. The spectacular success achieved in free radical mediated organic synthesis in recent times is due to the discovery of new initiators, substrates that produce radical centres at the desired positions in spite of the presence of multiple functional groups, and a wide variety of reagents for allylation, vinylation, alkylation and so forth. In addition, a good understanding of the free radical reaction mechanism and of the influence of factors such as solvents, electronic effects, conformational and stereochemical relationships between the substrates and the products, the neighbouring groups, the presence of Lewis acids, etc., has led to the realisation of unprecedented control over the chemo, regio- and diastereospecificity. The free radical chemistry has transformed from the intractable to the predictable. In certain systems, radical chemistry can deliver results that are far superior to those obtained from conventional ionic or organometallic methods. Thus, radical reactions are occupying important positions in multi-step organic synthesis or functional group interconversions, including natural products in which key steps involve free radical reactions resulting in great simplification of their total synthesis. Consequnetly, the application of free radicals in organic synthesis, which was only a trickle in the 1970's has now acquired the proportion of a flood.

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In this part, we will consider just a few syntheses involving free radicals. They are not necessarily the most important or the most interesting, but they give a good insight into the heart and soul of the working of free radical syntheses. It is hoped that they are sufficient to appreciate and enjoy the flavour of the underlying principles.

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Free Radical Reactions in Synthesis

Free radical reactions are by nature chain reactions, and an efficient chain reaction requires that each collision between a neutral free radical and the reagent or substrate in the propagation sequence is an effective one. A fine balance among the competing processes has to be maintained for the overall success of the synthesis, which involves one or more of the following elementary

It should also be noted that in most cases the acyclic radicals follow the same rules of stereoselectivity as non-radicals.

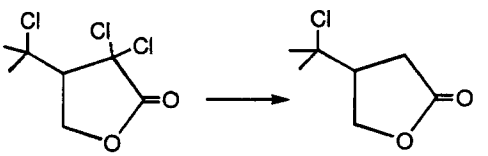
processes – (i) homolysis, and its reverse, i.e., radical coupling, (ii) homolytic substitution, S_H2, (iii) addition to multiple bonds, and its reverse, i.e., β-cleavage, and (iv) electron transfer.

It should also be noted that in most cases the acyclic radicals follow the same rules of stereoselectivity as non-radicals. But, the stereochemistry of cyclic radicals is simpler as they exist in a reduced number of conformations relative to acyclic ones, and the outcome is easier to predict or control.

Addition-Cyclisation

By far the most important free radical reaction is the addition of carbon radicals to carbon-carbon double bonds. Cyclisation following radical addition has provided a remarkably facile approach to polycyclic compounds, which is rarely observed in ionic chemistry, and its share in such synthetic protocol is rapidly growing.

Let us look at a very simple conversion, that of trichlorolactone **1** to chlorolactone **2**, which is a reduction reaction involving the substitution of chlorines by hydrogen.



1 **2**

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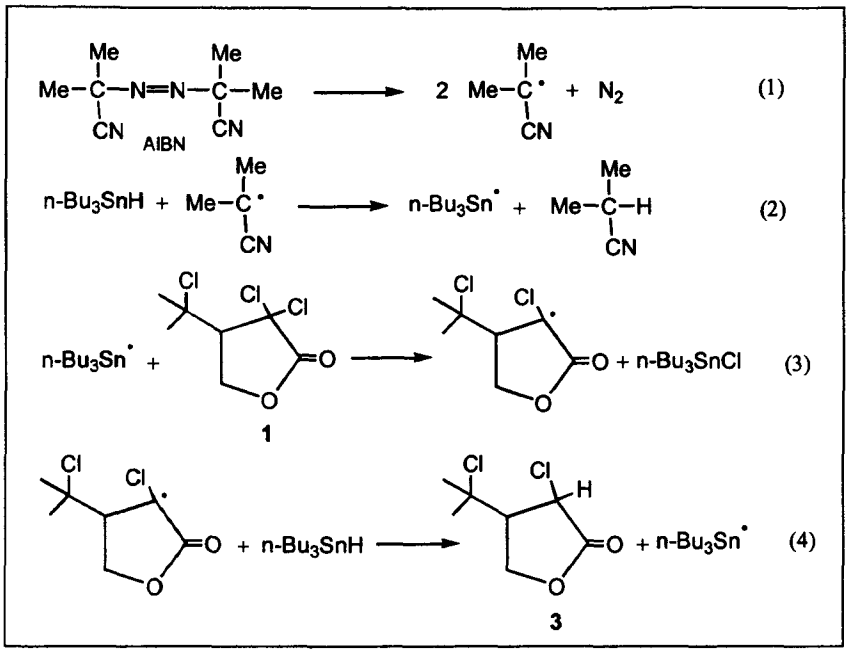
1. The lactone functional group is sensitive to most of the reducing reagents. One cannot use such common methods as dissolving metal reduction or lithium aluminium hydride, or catalytic hydrogenation, as they would destroy the lactone ring. However, refluxing **1** in benzene with n-Bu_3SnH and AIBN (azobisisobutyronitrile) will bring about the desired conversion very smoothly. This involves free radical mechanism and the reaction is highly chemoselective, (*Scheme* 1).

Reactions of the type shown in (3) and (4) repeated once more with **3** leads to the removal of the second chlorine atom and



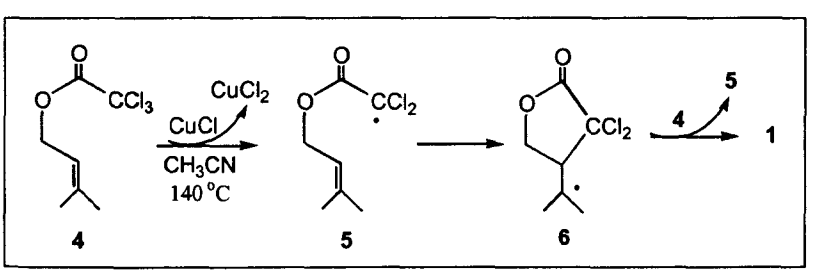
Scheme 1.

formation of **2**. The exocyclic chlorine at the tertiary position is spared under this condition because of steric hindrance of the adjoining methyl groups.

2. Compound **1** itself is a product of a very simple free radical cyclisation. (*Scheme* 2)

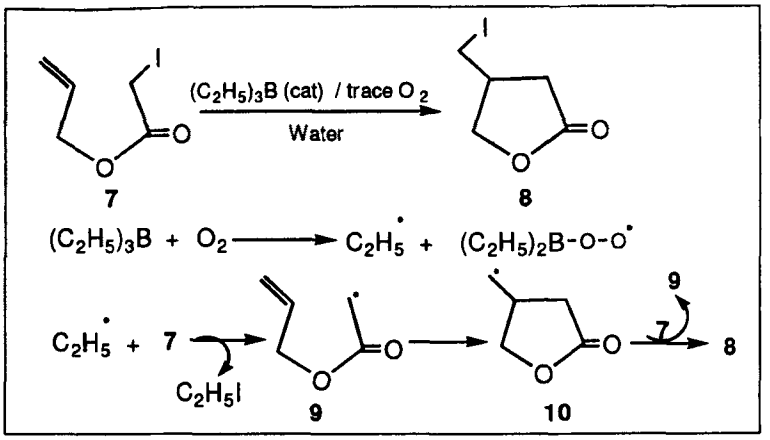
(Note that **4** is an ester of CCl_3-COOH and $Me_2C{=}CH\text{-}CH_2OH$).

The first step in *Scheme* 2 is initiated by transfer of an electron from the catalyst CuCl to chlorine of $-CCl_3$ group in **4**. Such reactions in which an atom (here Cl) is relocated are called *atom transfer* reactions. Another very simple atom transfer reaction is depicted in *Scheme* 3.



Scheme 2.

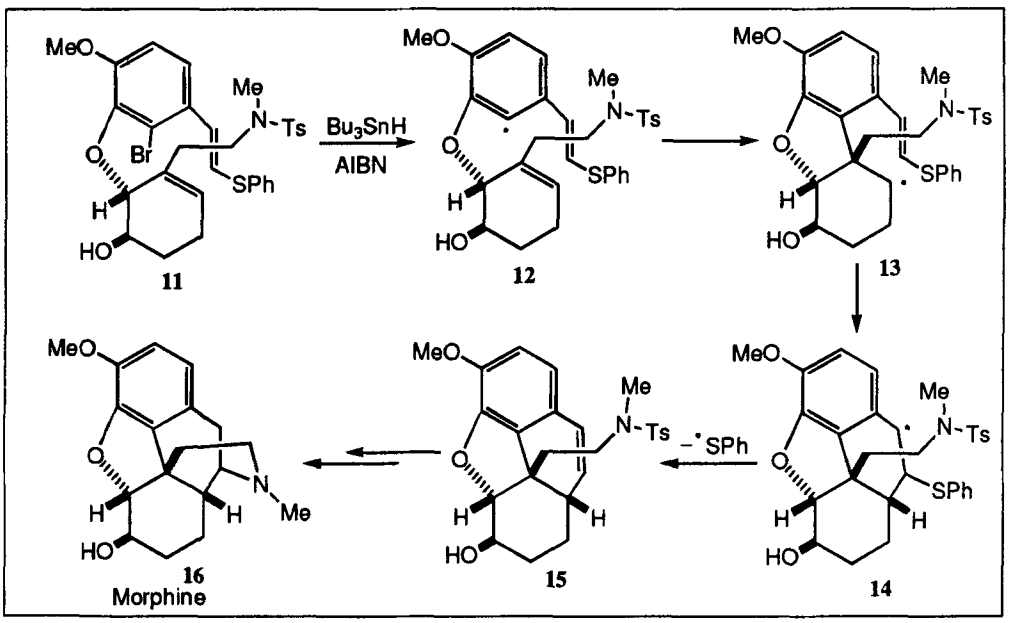
Scheme 3.

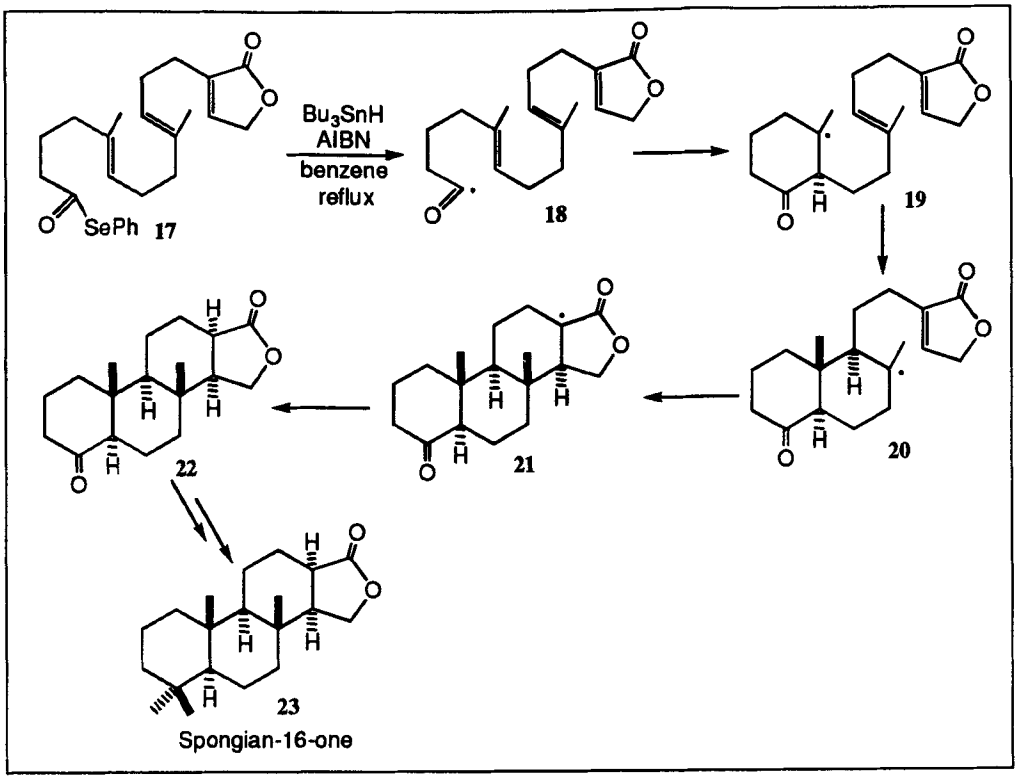


The Addition-Cyclisation Cascade in Natural Product Synthesis

If there are two or more double bonds in the substrate and are situated in suitable positions, the radical addition-cyclisation would link up all the double bonds resulting in a polycyclic end product with amazingly high chemo-, regio-, and stereoselectivity. Such processes have become powerful weapons in the armoury of organic chemists undertaking natural product synthesis, for example, morphine **16** (*Scheme* 4), spongian-16-one **23**

Scheme 4.

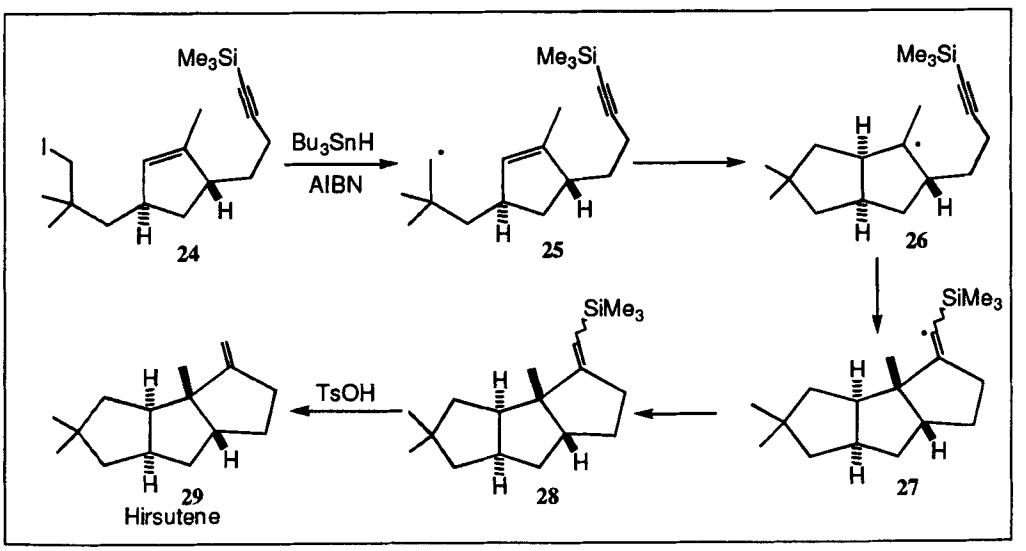


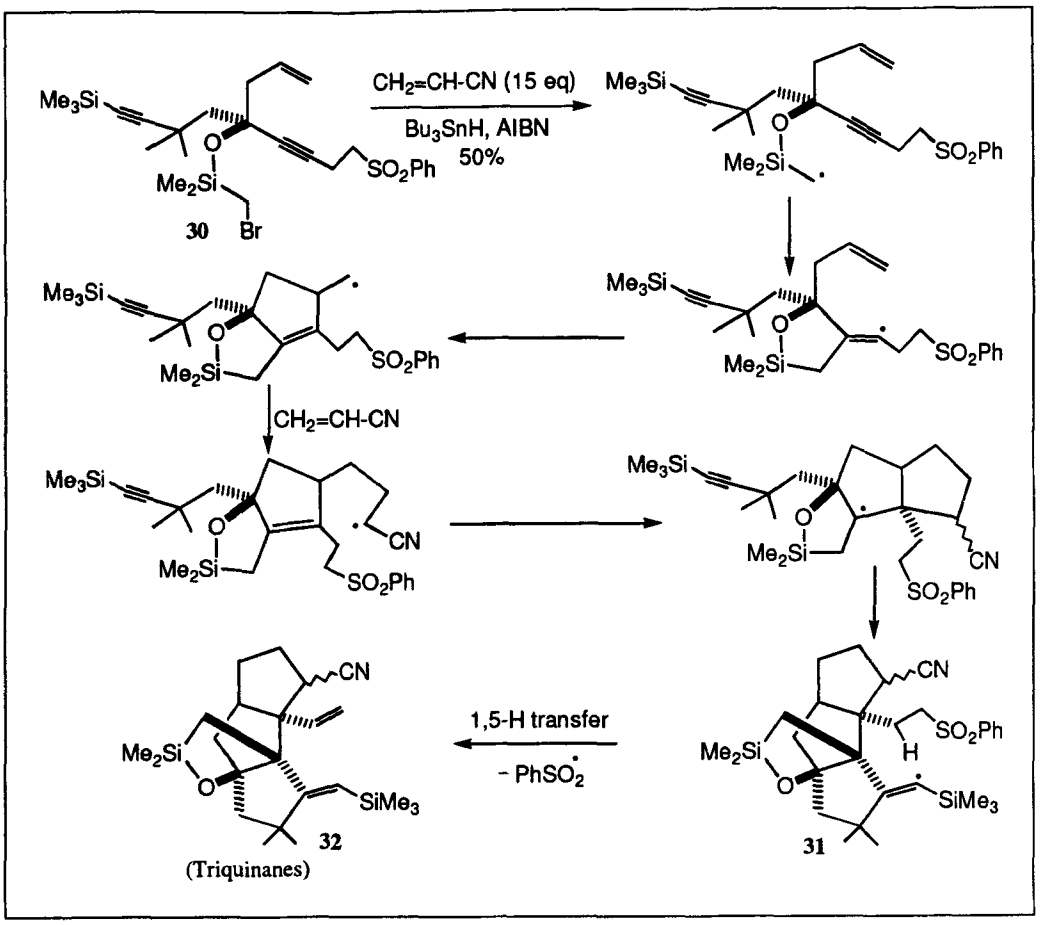


(*Scheme* 5), and hirsutene **29** (*Scheme* 6). Comprehensive explanations about the mechanism of these reactions are avoided here with a view to give the reader an opportunity to work out the problems.

Scheme 5.

Scheme 6.





Scheme 7.

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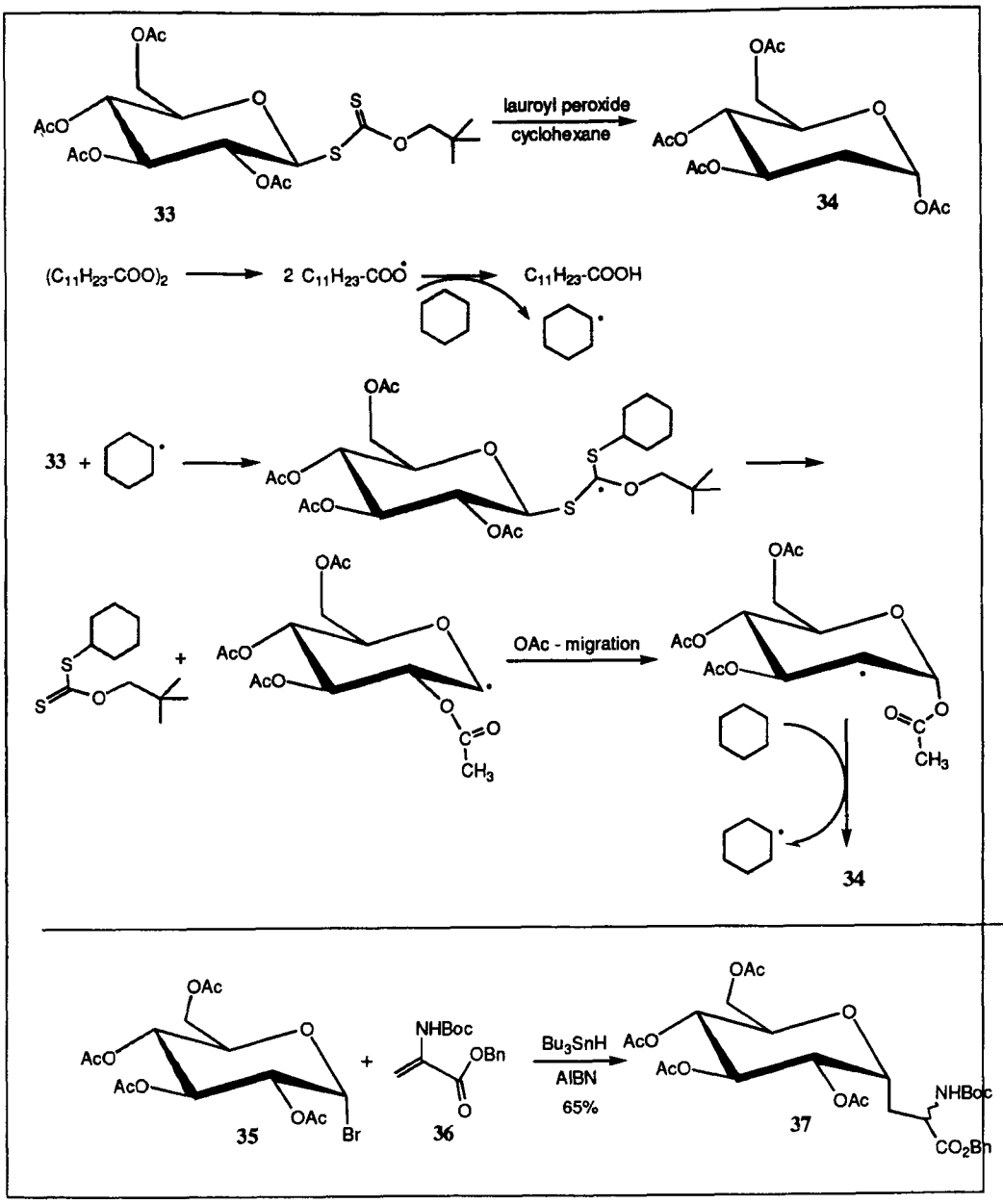
Even more complex cyclisation products have been obtained by very simple free radical reaction protocols. An example is the synthesis of linear triquinanes from starting compounds that can be easily assembled from readily available compounds (*Scheme* 7). Such fantastic reactions involving conventional ionic processes cannot even be visualised let alone realised.

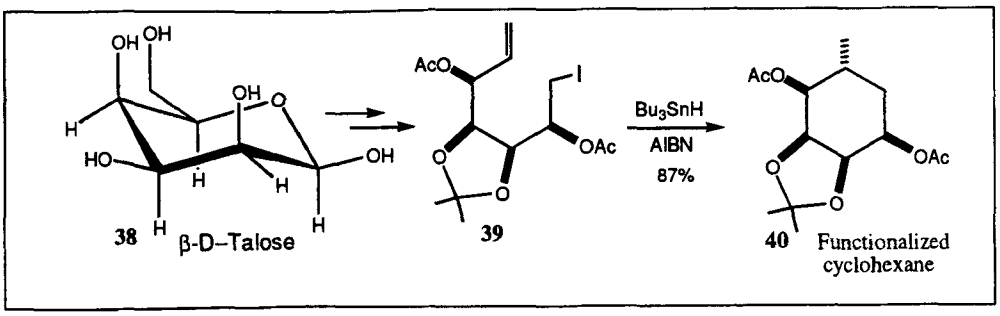
The readers are urged to work out the interesting mechanism involved in this fascinating reaction. (In case of any specific difficulty, the author may be contacted).

Carbohydrates in Enantiospecific Transformations

Modification of carbohydrates and using these inexpensive naturally occurring optically active substances to synthesise compounds with chiral centres of known stereochemistry have become popular. A few examples are shown in *Schemes* 8–10.

Schemes 8 and 9.





Scheme 10.

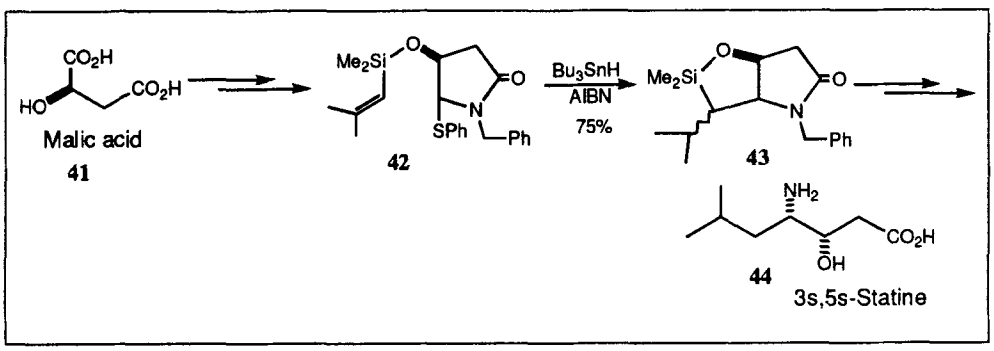
Stereoselective Synthesis of Acyclic Compounds

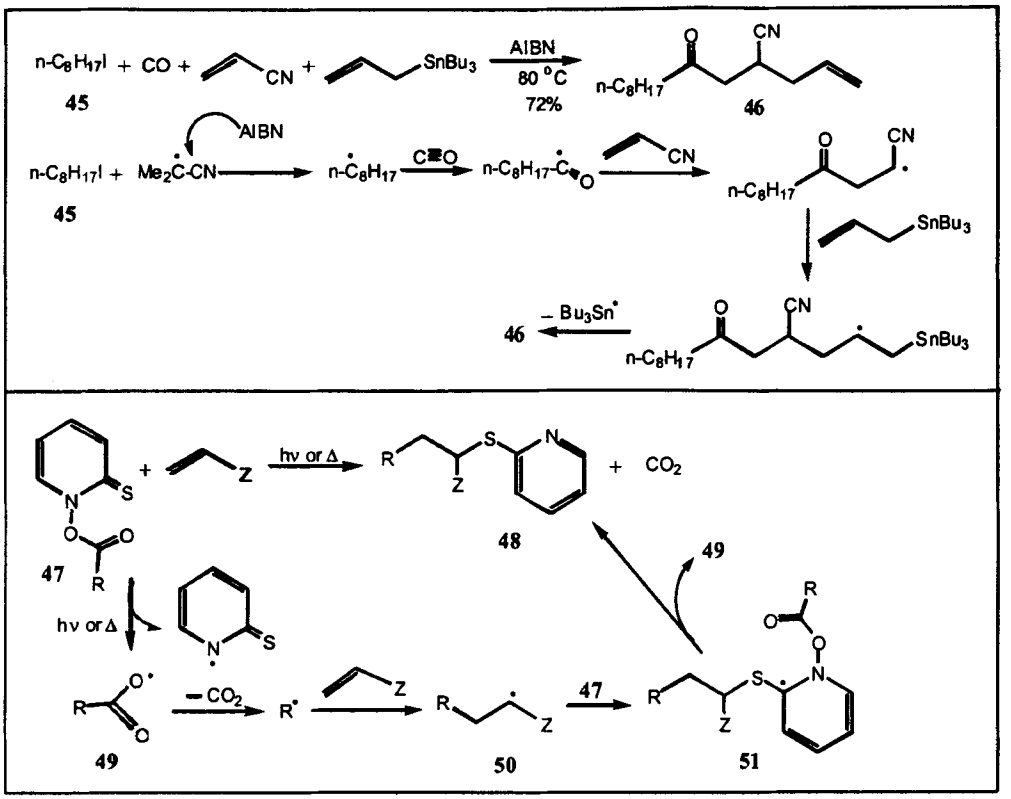
Stereochemical control achieved during cyclisation by employing substrates with appropriate stereochemistry has been utilized to synthesize cyclic compounds of defined geometry. For example, *Scheme* 11 shows the synthesis of biologically important g-amino acid statine.

Remarkable Intermolecular Multistep Addition Cascade Reactions

Cascade or sequential addition in an intramolecular fashion is relatively less complicated as the generated radical centre is close to the double bond and conformational requirements for such additions are met. On the other hand, intermolecular radical cascade involving several molecules is expected to be highly unfavourable as stringent kinetic and thermodynamic conditions for each step are to be fulfilled to connect the substrate molecules in correct order. However, surprisingly many intermolecular multistep free radical reactions are observed to take place smoothly. *Schemes* 12 and 13 show two such cases.

Scheme 11.



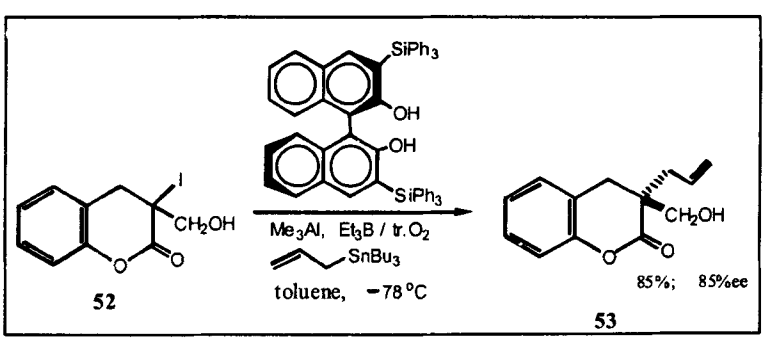


Schemes 12 and 13.

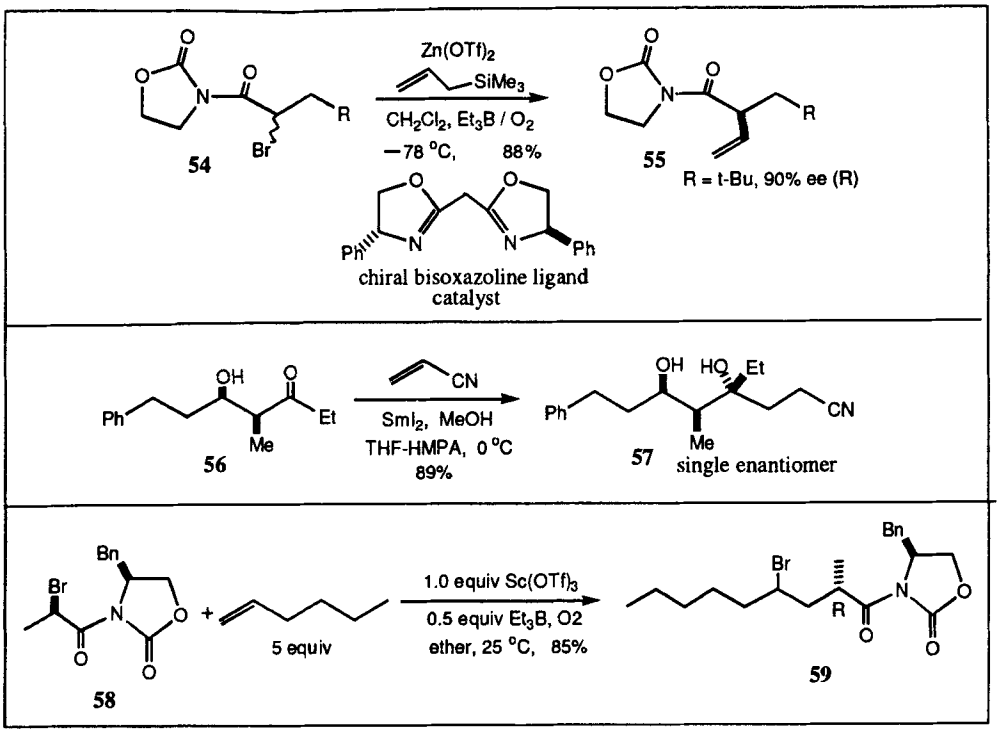
Free Radical Asymmetric Induction

A high degree of stereoselectivity has been achieved through asymmetric induction by using chiral auxiliaries as catalysts or utilising asymmetric centres in the substrate molecules. Further assistance for this purpose may be secured from Lewis acid initiators or other Lewis acids that control the stereochemistry by complexation. A few examples are given in *Schemes* 14 –17.

Scheme 14.



Here, Et_3B is the initiator (a trace of O_2 is necessary), and Me_3Al is the Lewis acid. Low temperature is also important to accomplish the stereoselectivity. This has been possible because Et_3B (with a trace



Schemes 15-17.

of O_2) is a good initiator even at that low temperature.

SmI_2 acts as both an initiator and a complexing agent. The solvent supplies the hydrogen in the final step.

Addition – Atom Transfer (Br)

$Sc(OTf)_3$ is Lewis acid used for complexation which is responsible for the observed stereoselectivity.

Conclusion

Free radical synthetic methodology has grown by leaps and bounds in just about two decades. The limit to which the scope of free radical synthesis can go is restricted only by the imagination of the synthetic chemist. It greatly simplifies a synthetic sequence, makes use of readily available, relatively inexpensive reactants and reagen-ts; the transformations are selective, involve fewer steps, the yields are good, the reaction conditions are mild, etc. Therefore, such free radical reactions truly qualify to be called "Green Chemistry".

Suggested Reading

[1] A F Parsons, *An Introduction to Free Radical Chemistry*, Blackwell Science, Oxford, 2000.

[2] B Giese, *Free Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*, Pergamon, Oxford, 1986.

[3] P Renaud and P Sibi (Eds), *Radicals in Organic Synthesis*, Vols. 1 and 2, Wiley-VCH, 2001.