REVIEW

Organic syntheses through free-radical annulations and related cascade sequences

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1 Introduction

Multiple step chemical transformations that are linked together in one pot, *i.e.* cascade or domino processes, are continually growing in popularity and many new sequences have been published recently. One reason behind this is the stereocontrol achievable *via* tightly scripted reaction coordinates programmed into suitable precursors. Another is the sheer elegance of terpenoid, steroid and alkaloid natural product syntheses, accomplished by these means, that have gained widespread approbation, and stimulated the wish to emulate, in many research groups. In addition, cascade methodology has the potential to streamline laboratory and large-scale preparations, and decrease environmental impact, because the number of manipulations can be reduced with consequent savings in solvents, reagents, hardware, operator and instrument time.

1.1 Classification of cascade processes

Individual cascade sequences may combine anionic, cationic, radical, pericyclic and other types of steps. A useful framework for classifying cascades, according to the mechanisms of their principal steps, has been devised by Tietze and Beifuss[1,2] who also reviewed major types of cascades with cationic, anionic, radical, pericyclic, carbene, transition metal catalysed, and other processes, as their primary steps. Cascades having all steps unimolecular are especially auspicious because their in-built entropic advantage allows large effective molarities to be achieved. However, cascades in which one of the main propagating steps is bimolecular, are also well documented, and entail good yields, provided the bimolecular step is fast enough to compete with alternative reaction pathways. A book,[3] compilations of synthetic applications,[4] and reviews of other aspects of cascade processes have appeared.[5–8] An issue of *Chemical Reviews* was devoted to aspects of cascade reactions including tandem reactions of carbon monoxide and nitriles,[9] processes mediated with samarium iodide,[10] Mn(III)-based free-radical cyclisations,[11] cascade cyclisations involving enediynes, and related systems,[12] and others.[13]

We recently reviewed cascade reactions that proceed exclusively by intramolecular sequences of free-radical reactions.[14] Only four elementary rearrangement types are commonly included in free-radical cascades; cyclisations (**C**), hydrogen migrations (**H**), group migrations (**M**) and ring fissions (**F**). A convenient system for classifying free radical cascades was devised. This indexed each cascade by a code consisting of a letter string that designated the type and order of the individual mechanistic steps involved. For example, a 3-stage cascade consisting of sequential 6-*endo*-, 5-*exo*- and 5-*exo*-cyclisations would be designated $\mathbf{C^{6n}C^{5x}C^{5x}}$. These classification codes display the component steps and indicate the reaction course. One advantage of their use is that they provide shorthand descriptions of the paths of cascades. They can therefore be employed in place of intermediate structures, thus enabling mechanistic schemes to be significantly compacted.

1.2 Free radical annulations and cascade processes

Cascades of intramolecular radical steps are undoubtedly of great synthetic utility. However, the incorporation of intermolecular radical steps into free-radical cascades opens further possibilities to the organic chemist. The term "annulation" was defined by Danheiser *et al.* as a "ring forming process in which two molecular fragments are united with the formation of two new bonds,"[15] and this definition has generally been adopted, especially by radical chemists. The possibility of a radical cycloaddition, consisting of an intermolecular addition followed by a sequential cyclisation, is especially appealing. A cyclic product could thereby be prepared from acyclic precursors and the 2-stage cascade would amount to an annulation. In practical terms, an attacking radical would itself have to contain an appropriately placed radical acceptor moiety.

Most frequently, the initial radical is a but-3-en-1-yl, but-3-yn-1-yl or analogous species that adds to a double or triple bond (X=Y) to produce a hex-5-en-1-yl type of radical, well adapted for a favourable *5-exo* type of ring closure (Scheme 1).

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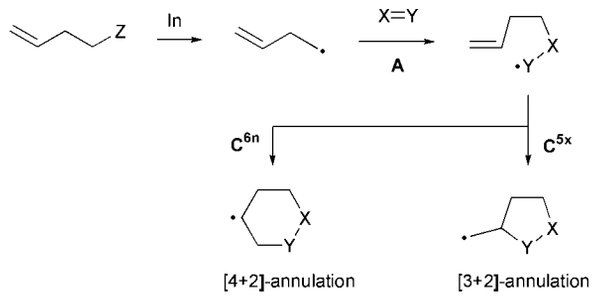
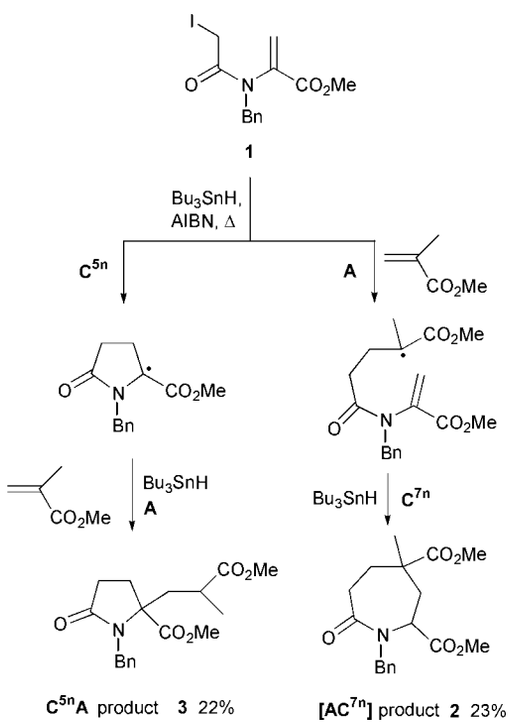


Scheme 1

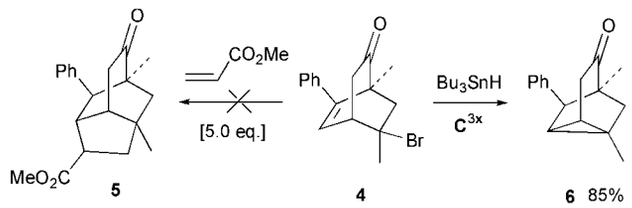
The classification of cascade processes recently introduced[14] is easily extended by using the letter **A** to designate intermolecular additions. Thus, the processes of Scheme 1 would be classified as 2-stage **AC**^{5x} and **AC**^{6n} cascades. Other types of cycloadditions may be set up by generating alk-*x*-en-1-yl, or analogous alkynyl, aromatic, *etc.* radicals. Of course, the alk-*x*-en-1-yl radical may also contain substituents and heteroatoms. The **AC**^{5x} sequence amounts to a [3+2]-annulation and the **AC**^{6n} sequence is a [4+2]-annulation. It is important to distinguish between annulative sequences, and those that just involve the same steps but do not conform to the definition given above. To aid this distinction, overall annulative sequences will be indicated by brackets. For example, the annulation yielding ε-lactam **2**, shown in Scheme 2, would be



Scheme 2

designated [**AC**^{7n}]. Any subsequent steps, in a longer cascade, would be displayed outside the brackets.

This article reviews and evaluates free radical cascades containing intermolecular addition steps. Intermolecular reactions have to proceed without the entropic advantage of intramolecular processes, and require favourable conditions to compete efficiently in a cascade. The radical acceptor needs to contain β-substituents of opposite polarity to that of the attacking radical to facilitate the addition step. A large excess of the radical acceptor is also usually required. In designing sequences involving intermolecular additions, the position of the intermolecular step is crucial. If the intermolecular process is the last step in the sequence, then there is usually little problem. Intramolecular processes will occur first, and then addition will take place, when there is no other option. The main problems occur when functionality in the developing molecule (*e.g.* double bonds) prevent intermolecular reaction from being the most favourable pathway at the desired stage. 5-*exo*-Cyclisations are the most obvious examples, but other intramolecular interceptions can be less expected. Srikrishna *et al.* were anticipating a radical annulation of bicyclic bromide **4** with methyl acrylate, that would have led to the pupukeanone skeleton **5**.[16] Instead, 3-*exo* cyclisation to tricyclo-ketone **6** took place in high yield (Scheme 3). The formation of a cyclopropyl

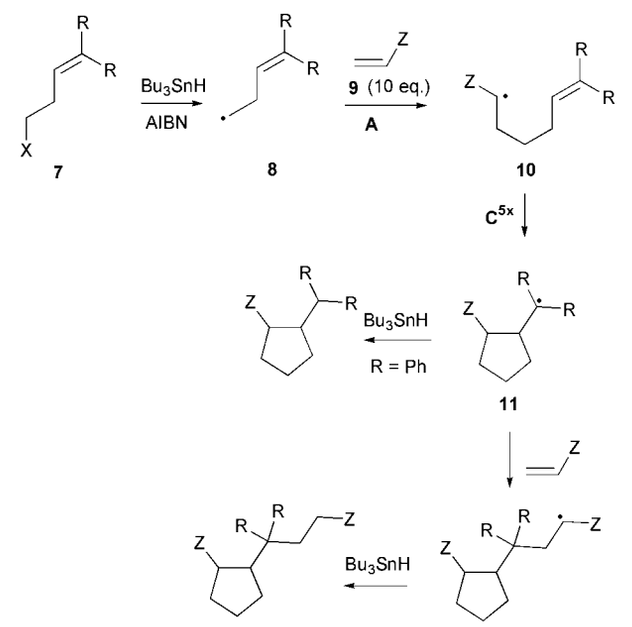


Scheme 3

ring is not normally observed in radical processes because the high strain in the product ensures that the reverse ring opening is much more rapid. In this example the strain is already partly present due to the architecture of the starting material and closure of the three-membered ring is favoured.

An intermolecular addition may compete successfully with a slow cyclisation step. For example, the unsaturated amidomethyl radical derived from **1**, underwent intermolecular addition to methyl methacrylate [**AC**^{7n}], in preference to cyclisation, and gave significant quantities of oxazepane **2** rather than the desired pyroglutamate **3**.[17] (Scheme 2). Ring closure to pyroglutamate **3** involved an initial *5-endo*-cyclisation of the amidomethyl radical. Such cyclisations are slow and disfavoured,[18] and hence the intermolecular addition supervened.

The main experimental problems are associated with radical cascades in which a fast cyclisation is required to occur subsequent to an addition step. This difficulty is especially apparent when alkyl radicals are involved. The work of Angoh and Clive,[19] Saičić and Čeković[20] and of Barton *et al.*[21] provided insight into the problems and solutions (Scheme 4).



Scheme 4

In a prototype annulation, but-3-enyl radical **8** underwent addition to acceptor **9**, which was present in excess.[20] As expected, the subsequent *5-exo* cyclisation was fast and resulted in the cyclised species **11**. Unfortunately, the alkyl radicals **8**

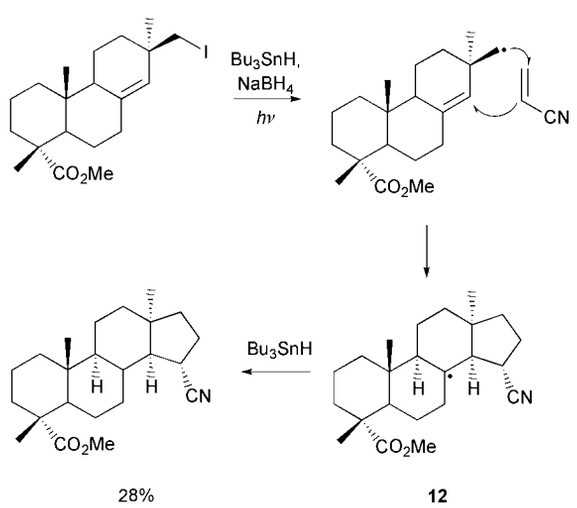
and **11** were very similar in character, hence radical **11** underwent addition in the presence of excess alkene **9**. The oligomerisation that resulted is a common problem for **AC** sequences. An exception occurred for R = Ph. In that case, the cyclised radical was a resonance stabilised benzyl type that abstracted hydrogen from the organotin hydride in preference to addition.[22]

There are two main ways to counter these oligomerisation problems. First, it must be ensured that the initial radical is sufficiently different in character from the cyclised radical so as to disfavour further addition. Second, the cyclised species may be intercepted by a terminating step that is faster than intermolecular addition. The most obvious choice is a fragmentation step ($\mathbf{F}_2$) but other terminations, such as oxidation to a cation, have also been employed. Another useful ploy is cyclisation onto an aromatic ring, which usually results in termination by re-aromatisation.

2 Steric differentiation of initial and rearranged radical reactivity

The above illustration[20] (Scheme 4) demonstrated that oligomerisation could be prevented when cyclisation resulted in the formation of resonance-stabilised benzyl radicals, because addition by these radicals was much slower. Unfortunately, this is an exceptional result. Alkyl radicals, whether primary, secondary or tertiary, abstract hydrogen from tributyltin hydride at virtually the same rate.[23] Gratifyingly, this lack of specificity can be rendered advantageous in certain circumstances, because steric factors do affect the rates of addition to double bonds. Hence, annulations involving only alkyl radicals can be successful if the cyclised intermediate contains a much more crowded environment than the initial radical.[24] Intermolecular hydrogen transfer to the cyclised radical becomes the favoured pathway.

This type of differentiation is exemplified in a steroid skeleton synthesis reported by Maillard and Delmond (Scheme 5).[25] Radical **12** was too sterically hindered to undergo



Scheme 5

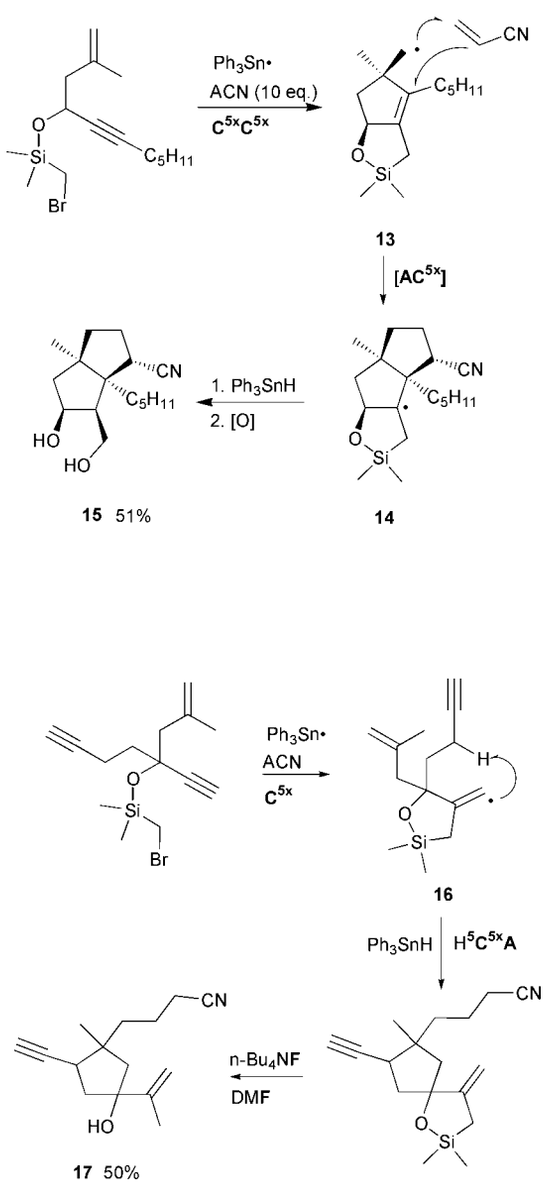
intermolecular addition, so abstraction took place to give the desired steroid skeleton in an isolated yield of 28%. The newly formed ring had *cis*-geometry in accordance with Clive's guidelines,[26] while the hydrogen abstraction from tributyltin hydride occurred from the least hindered face. The formation of two other major products, probably resulting from ring-expansion followed by further oxidation, were responsible for the moderate yield.

The technique can readily be applied to longer sequences, both prior to and after the annulation step, provided basic guidelines are followed regarding the prevention of unwanted reactions:[27]

1. All cyclisation steps must be so rapid that intermolecular addition or termination is not competitive.
2. When intermolecular addition is required, intramolecular steps should not be possible. This is a greater problem in longer sequences where more functionality is present. Competing cyclisations are obvious problems, but unexpected hydrogen abstractions can also disrupt a cascade.
3. The radical designed to undergo intermolecular hydrogen abstraction should be much more sterically hindered than the radical undergoing intermolecular radical addition.

These guidelines all refer to rates relative to competing reactions. For example, slow cyclisations may be permitted, if the unwanted intermolecular addition is slower. While guideline 3 refers only to hydrogen abstraction, this is because the only examples of steric differentiation annulations involve this termination method, due to the comparatively small size of the tributyltin hydride moiety. Other effectively small terminating agents could be used instead. It is conceivable that a 'reverse steric annulation' could be developed, in which a crowded initial radical undergoes addition to a 'small' acceptor, such that the final radical after annulation would not be sterically crowded and could react intermolecularly with a large terminating agent.

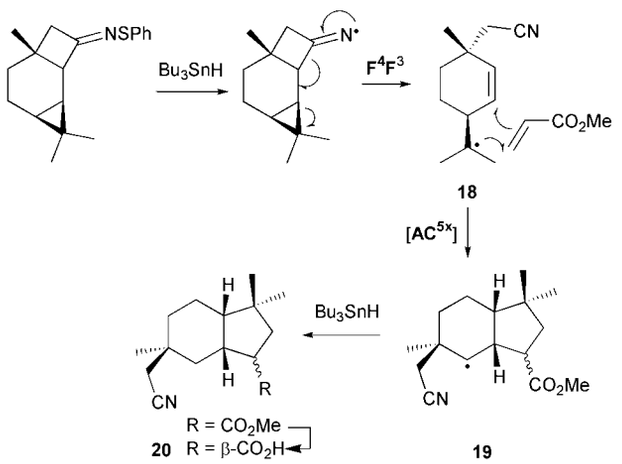
A $\mathbf{C^{5x}C^{5x}[AC^{5x}]}$ sequence leading to a diquinane framework **15** was described by Malacria and co-workers (Scheme 6).[28]



Scheme 6

Such was the design of the reaction that all the radicals in the sequence (not shown) apart from **13** and **14** could undergo rapid cyclisations. Radical **13**, which was less sterically hindered, added to acrylonitrile, but tertiary, bridgehead radical **14** abstracted hydrogen from triphenyltin hydride. Further work from the same laboratory illustrated some of the pitfalls that can occur, especially in longer sequences.[29] Vinyl type radical **16** underwent a [1,5]-H shift (**H**^{5}), rather than a 5-*exo* cyclisation, leading to undesired product **17**, isolated in 50% yield as a mixture of stereoisomers.

Zard and co-workers combined a radical annulation with two prior regioselective fragmentations, starting from an iminyl radical.[30] The product was the functionalised bicyclo[4.3.0]-nonane derivative **20**. Subtle steric effects appeared to be at work to prevent oligomerisation, because radical **18** was tertiary and thus both more thermodynamically stable and seemingly less sterically accessible than secondary radical **19** (Scheme 7).



Scheme 7

The nitrile group in **19** was too far away to have a significant electronic effect, but presumably blocked the approach of methyl acrylate to the concave face of the bicycle, while the molecular shape prevented approach to the convex face. The isomeric mixture **20** (R = CO_2Me) was epimerised under basic conditions and hydrolysed to yield solely the β-isomer of carboxylic acid **20**.

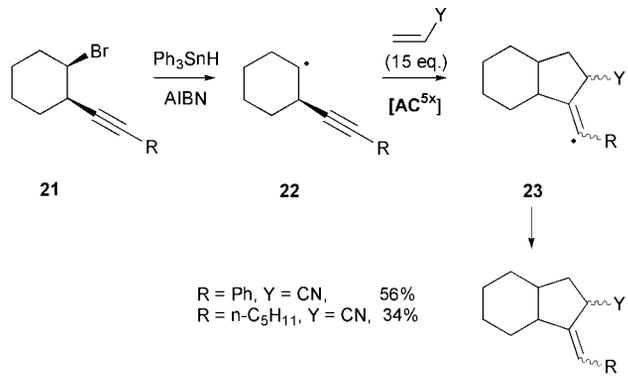
3 Electronic differentiation of radical reactivity

3.1 Cascades started by nucleophilic radicals: annulations of halo-butenes and -butynes with alkenes

The most common technique to differentiate two radicals at different stages in an annulation cascade has been to ensure that they are different in electronic character. It is well established that radical additions are frontier orbital controlled, and that nucleophilic radicals add most efficiently to electron-poor double bonds, while electrophilic radicals add best to electron-rich acceptors. The presence of two electronically similar alkyl radicals, both unable to undergo cyclisations, is the cause of the oligomerisation problem in radical annulations, as shown in Scheme 4. In an early annulation Angoh and Clive[19] described the use of alkyne radical acceptors **21** as a way of distinguishing cascade propagating radicals (Scheme 8).

The resulting vinyl radical **23** is sufficiently different in character to the initial alkyl radical **22** to prevent oligomerisation, and this distinction is enhanced when R = Ph in a manner similar to that observed for alkyl radicals (Scheme 4).[20]

In fact, guidelines for implementing radical annulations with electronic differentiation are very similar to the guidelines



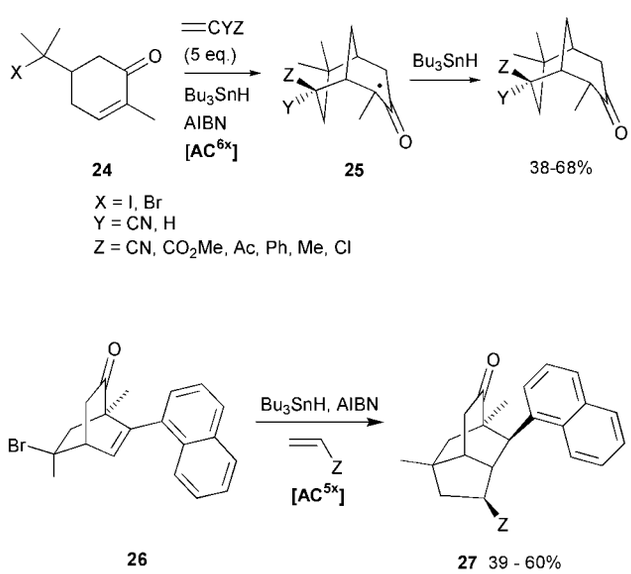
Scheme 8

for the steric annulations; the main difference being in guideline 3.[31]

3′. The final radical must be electronically more suited to undergo a termination step than the starting radical, and less suited toward intermolecular addition.

An interesting corollary can be deduced. Electronic differentiation between the initial and final radicals is not required if the intermolecular addition step is slow and the premature termination prior to addition is degenerate, *i.e.* returns the starting material. As long as termination is more rapid than oligomerisation, annulation will occur.

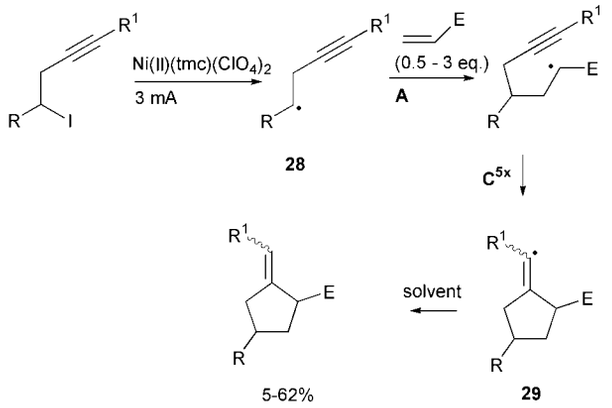
Srikrishna and co-workers synthesised a variety of chiral bicyclo[3.3.1]nonan-3-ones, a common natural product ring system, *via* a radical annulation strategy (Scheme 9).[32] The final



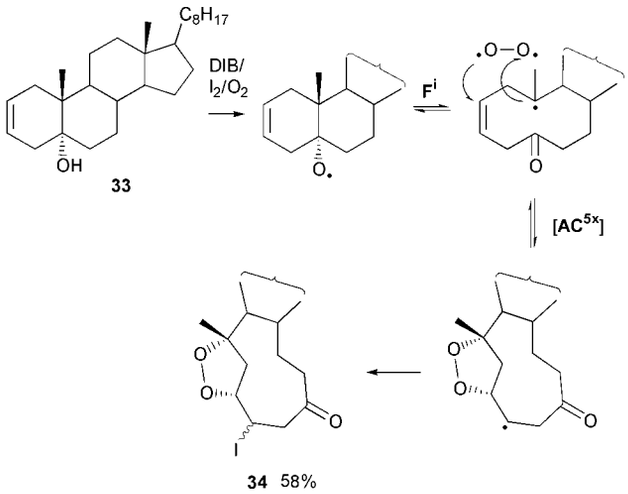
Scheme 9

tertiary α-acyl radical **25** was apparently sufficiently different from the initial tertiary alkyl radical derived from **24** to prevent oligomerisation, although steric factors may play a part. Steric effects were certainly responsible for the stereoselectivity of the final hydrogen abstraction; tributyltin hydride could only approach from the less hindered side. The problem of the unexpected 3-*exo* cyclisation of bicyclo[2.2.2]octenyl radical **4** (Scheme 3) was overcome by using a bulkier radical stabilising group, such as naphthyl (**26**⟶**27**).[16,32,33] This unusual result was attributed to steric crowding that prevented good overlap of olefin and aromatic orbitals and reduced the electrophilicity of the double bond.

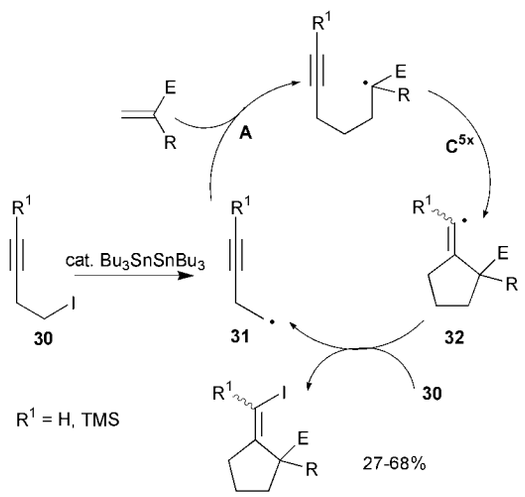
Ozaki and co-workers described a radical annulation conducted under electroreductive conditions[34] (Scheme 10). The reaction succeeded because hydrogen atom transfer from the solvent to the initial alkyl radical **28** was not fast enough to



tmc = 1,3,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane
E = electron-withdrawing group



Scheme 11



Scheme 10

prevent intermolecular addition, whereas transfer to the vinyl radical **29** was fast enough to terminate the reaction. Even so, oligomer formation and direct reduction still caused loss of yield in many examples.

3.2 Radical differentiation in iodine and hydrogen atom transfer reactions

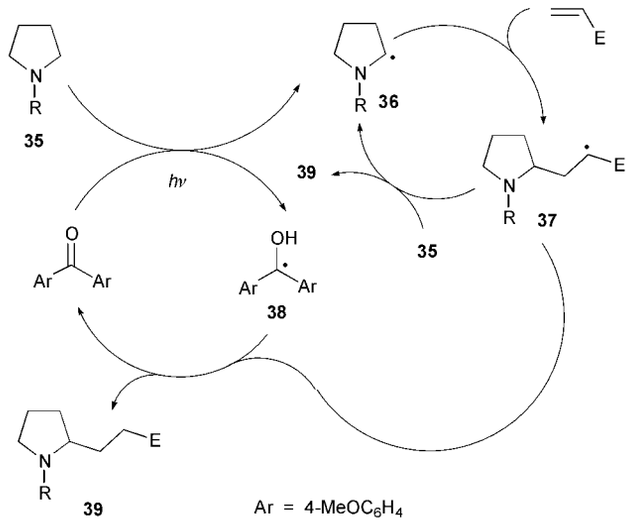
Curran and co-workers have described the use of iodine atom transfer reactions in radical annulations (Scheme 10).[35] Owing to the nature of the propagation steps, the lifetime of an alkyl radical in iodine transfer sequences is effectively longer than when a tin hydride is present. Premature atom abstraction by alkyl radical **31** is degenerate, *i.e.* regenerates the starting material. In these examples annulation resulted in vinyl radical **32**, which abstracted iodine from **30**, to regenerate the alkyl radical **31**. Iodine abstraction was a faster process than addition of the vinyl radical to alkynyl iodide **30**. Only a small excess of alkynyl iodide was required, further aiding successful annulation. Often, co-product resulting from a 6-*endo* cyclisation was observed. The low efficiency of the process, and the requirement that iodides be used, has meant that applications of the technique have been limited. Curran has briefly illustrated the use of a chiral auxiliary in an iodine transfer annulation,[36] and annulations of electrophilic radicals have also been described (Section 3.7).

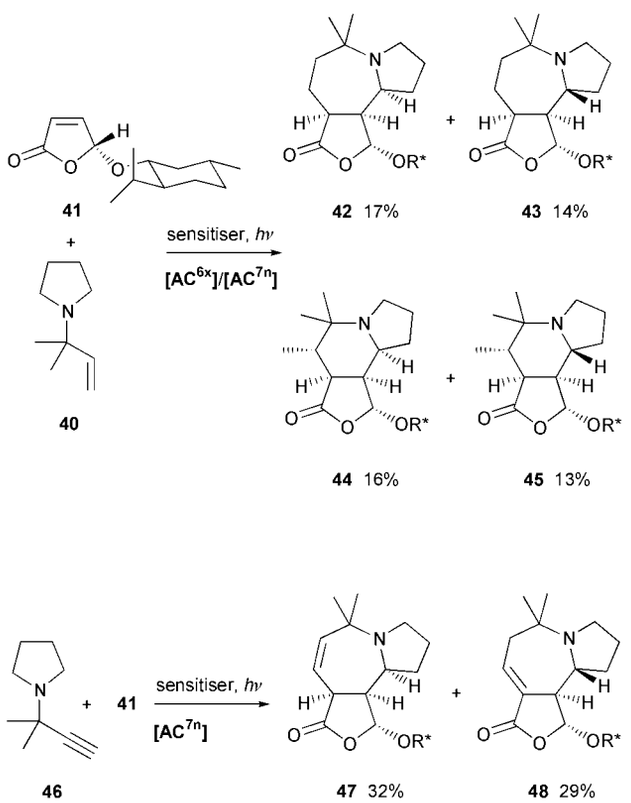
1,2-Dioxolanes have been prepared by an unusual atom transfer type methodology by the group of Suárez.[37–40] In most of their preparations, for example conversion of steroid **33** to ring-expanded dioxolanyl derivative **34** (Scheme 11), an alkoxyl radical was generated using (diacetoxyiodo)benzene (DIB)–iodine. Initially, a hypoiodite was formed and the O–I bond then cleaved photolytically to afford an alkoxyl radical. The latter underwent a rapid β-scission to form a ring-expanded carbon-centred radical that picked up molecular oxygen. The resulting peroxyl radical could cyclise onto a lactone, resulting in extended sequences[39] or, as in the displayed example, onto a carbon–carbon double bond.[40] Radicals for these sequences have also been generated by addition of thiyl radicals to double bonds.[37]

3.3 Radical differentiation in hydrogen atom abstractions: annulations with alkenyl-pyrrolidine and lactone acceptors

Significant advances have been made towards the use of α-aminoalkyl radicals by way of a technique well suited to radical annulations, although the scope is somewhat limited.[41] Photolysis of a tertiary amine in the presence of a sensitiser was known to generate an α-aminoalkyl radical by photoelectron transfer (PET), although with sensitisers such as benzophenone, stoichiometric quantities were required, and side reactions lowered yields of the desired products. Hoffmann and co-workers showed that 4,4′-dimethoxybenzophenone acted as a catalytic sensitising agent for these PET reactions. The catalytic cycle proposed (Scheme 12) has interesting implications for radical annulation chemistry. Most importantly, some hydrogen abstraction occurred from intermediate **38**, regenerating the sensitiser. If α-aminoalkyl radical **36** also took part in abstraction, pyrrolidine starting material (and catalyst, if abstraction was from **38**) would be regenerated, so the abstraction was effectively degenerate. Crucially, the catalyst was not used up by this side reaction.

This sequence can become an annulation if radical **37** is designed to undergo a cyclisation prior to abstraction. The major difference is that the cyclised radical is likely to be less suitable for hydrogen abstraction from the pyrrolidine starting material. Photosensitised addition of alkenylpyrrolidine **40** to chiral lactone acceptor **41** produced a mixture of four tricyclic products **42**–**45**. Compounds **44** and **45** were formed *via* 6-*exo*-cyclisations, while 2-oxa-6-azacyclopentazulene derivatives **42** and **43** were formed *via* 7-*endo* mode ring closures. Cyclisation of alkynyl variant **46** resulted in just two isomers, both formed *via* 7-*endo* cyclisations. Use of the chiral menthol auxiliary in **41** enabled high levels of stereoselectivity to be achieved. The difference in conjugation in the products was ascribed to the enol form of **47** not being readily accessible, in contrast to the enol form of the intermediate leading to **48**. It is also worth noting that the success of the reaction depended on blocking the allylic position of the starting pyrrolidine, by bismethyl substitution, to prevent unwanted abstraction.

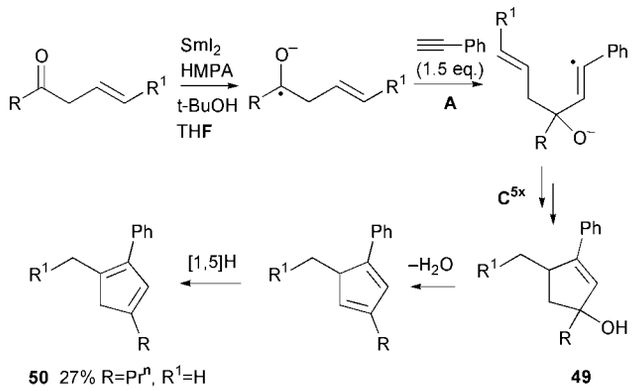




Scheme 12

3.4 Radical differentiation in samarium(II) iodide mediated cascades: annulations with but-3-enones and alkynes

Samarium(II) iodide is a versatile reagent that has been used in many tandem reactions,[10] although few of these consisted solely of radical steps.[14] However, it appears to be a very promising reagent for mediating radical annulations. Ketyl radicals, generated from substituted but-3-en-1-ones, are highly nucleophilic and can undergo intermolecular addition to activated double or triple bonds without the need for a large excess of the radical acceptor. Alkyl radicals formed as a result of the annulation would not readily undergo further intermolecular additions. Results from our laboratory indicated that such annulations did indeed take place, although isolated yields were poor (Scheme 13).[42] The initially formed cyclopentenols **49** underwent facile dehydration and [1,5]-hydrogen shifts leading



Scheme 13

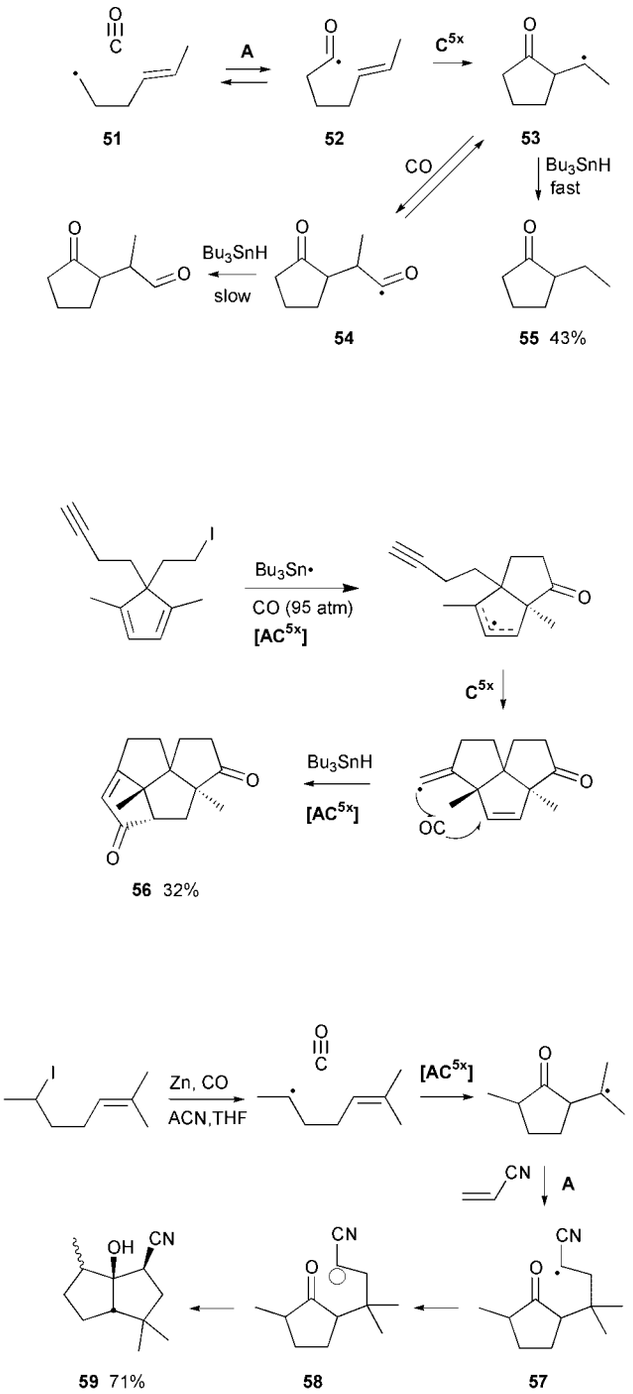
to the formation of cyclopentadienes **50**. The propensity of the latter to undergo Diels–Alder dimerisations may explain the low isolated yields; the best was 27% for R = *n*-Pr, R^1 = H.

3.5 Annulations with carbon monoxide and pent-4-enyl iodides: preparation of cyclopentanones and polycyclic analogues

Carbon monoxide is isoelectronic with isonitriles (see Section 5), and acts as a geminal radical acceptor/radical donor synthon.[9] The principal annulation, therefore, involves addition of a pent-4-enyl or pent-4-ynyl type radical to CO followed by a $\mathbf{C^{5x}}$ ring closure of the resulting acyl radical to produce a cyclopentanone derivative (Scheme 14). Electronic differentiation comes about between the adduct acyl radical **52** and the initial and cyclised alkyl radicals and disfavours certain unwanted reactions. A key factor in the success of these reactions is the reversibility of the carbon monoxide addition and hence the pressure of CO may be critical. The simple [4+1] annulation shown in Scheme 14 is illustrative.[43] Pent-4-enyl radical **51** added to carbon monoxide because the pressure was sufficient to prevent competitive hydrogen abstraction from tributyltin hydride. The subsequent 5-*exo* cyclisation rendered the reaction irreversible to this point. Cyclopentylmethyl-type radical **53** could undergo either further addition to carbon monoxide, or hydrogen abstraction. The second carbon monoxide addition, yielding **54**, was reversible. Hydrogen abstraction from tributyltin hydride is much more rapid by alkyl radicals such as **53** than for acyl radicals (**52** or **54**), so kinetic resolution ensured that 2-ethylcyclopentanone (**55**) was the major product. The $\mathbf{C^{3x}F^{3i}}$ ring expansion of **53**, leading to cyclohexanones, can be competitive in these types of reactions, but if the cyclised radical contains stabilising groups in the α-position then this is prevented. A recent comprehensive review of the chemistry of acyl radicals has appeared which describes in more detail such annulations.[44] In addition, Ryu *et al.* have also described annulations, and have given guidelines on the design of successful tandem radical reactions involving carbon monoxide.[9]

Curran and co-workers described a double-annulation-containing sequence in their investigations towards a synthesis of Crinipellin A (Scheme 14).[45] Both intermolecular additions to carbon monoxide were followed by rapid 5-*exo* cyclisations, leading to tetracycle **56**.

An elegant advance was made with a CO-annulation–addition–ionic cyclisation sequence (Scheme 14).[46] The method used zinc as an one-electron reductant. Carbon monoxide annulation was followed by a further radical intermolecular addition to acrylonitrile. Adduct radical **57** was then reduced to the corresponding anion **58** and nucleophilic ring closure onto the carbonyl group yielded bicyclo[3.3.0]octan-1-ol derivative **59**, which contained four new carbon–carbon bonds. This approach provides a neat complement to samarium(II) iodide methodology, which is usually the primary choice for sequences involving both radicals and anions.[10] It is noteworthy that the

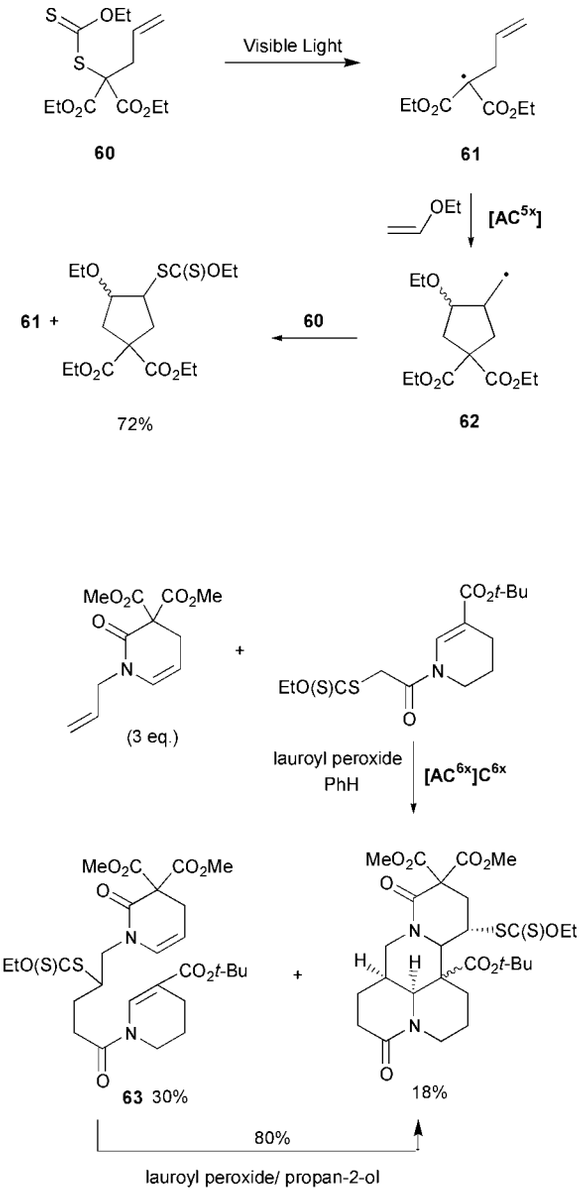


Scheme 14

zinc was used as received, and also that samarium(II) iodide is unsuitable for the annulation of alkyl radicals, because their reduction to anions would be too rapid to allow intermolecular addition to occur.

3.6 Electrophilic alkenyl radicals derived from xanthates

Another way to ensure divergent selectivity of initial and final radicals is to arrange that one is electrophilic in nature. Initial generation of an electrophilic radical is often easier, and an added advantage is that electrophilic radicals generally add to unactivated double bonds. Electronic differentiation is important when the final radical is nucleophilic, and hence xanthates, which are good acceptors for nucleophilic radicals, are useful substrates for this type of annulation, as demonstrated by the group of Saičić (Scheme 15).[47] The 'unwanted' early interception of initial radical **61** was unimportant, because addition to **60** was degenerate. This meant that radical



Scheme 15

61 effectively had a longer lifetime, and radical addition steps that would normally be too slow could take place here. The final cyclopentylmethyl radical (**62**) was nucleophilic and added efficiently to the starting xanthate, maintaining the chain. Conversely, radical **62** did not add to the electron rich alkene and so oligomer formation was avoided.

Xanthate chemistry has been employed in a synthesis of (±)-matrine, a naturally occurring alkaloid with possible anti-ulcerogenic and anticancer properties. A radical annulation based on the same principles as described above was the key step (Scheme 15).[48] In this case, the disfavoured **C**^{6x} cyclisations were the troublesome steps, but such is the nature of xanthate chemistry that these steps could be forced to completion. Intermediate compound **63** was amongst the products obtained but was also a xanthate and underwent further radical cyclisation. Five contiguous chiral centres were created in one operation with fair stereoselectivity. Only two isomers were isolated, and the major stereomer was the desired product that could be converted to (±)-matrine.

3.7 Iodine atom transfer annulations of electrophilic alkenyl radicals

Several iodine transfer annulations have been reported involving electrophilic alkenyl radicals.[49–52] In the previous

examples of atom transfer reactions (Section 3.2) in which nucleophilic radicals were generated by iodine abstraction, the necessary differentiation occurred because ring closure formed vinyl radicals that were unsuited for further intermolecular additions. If the radical generated by iodine abstraction is electrophilic then the required electronic distinction will occur, even when cyclisation leads to alkyl radicals.

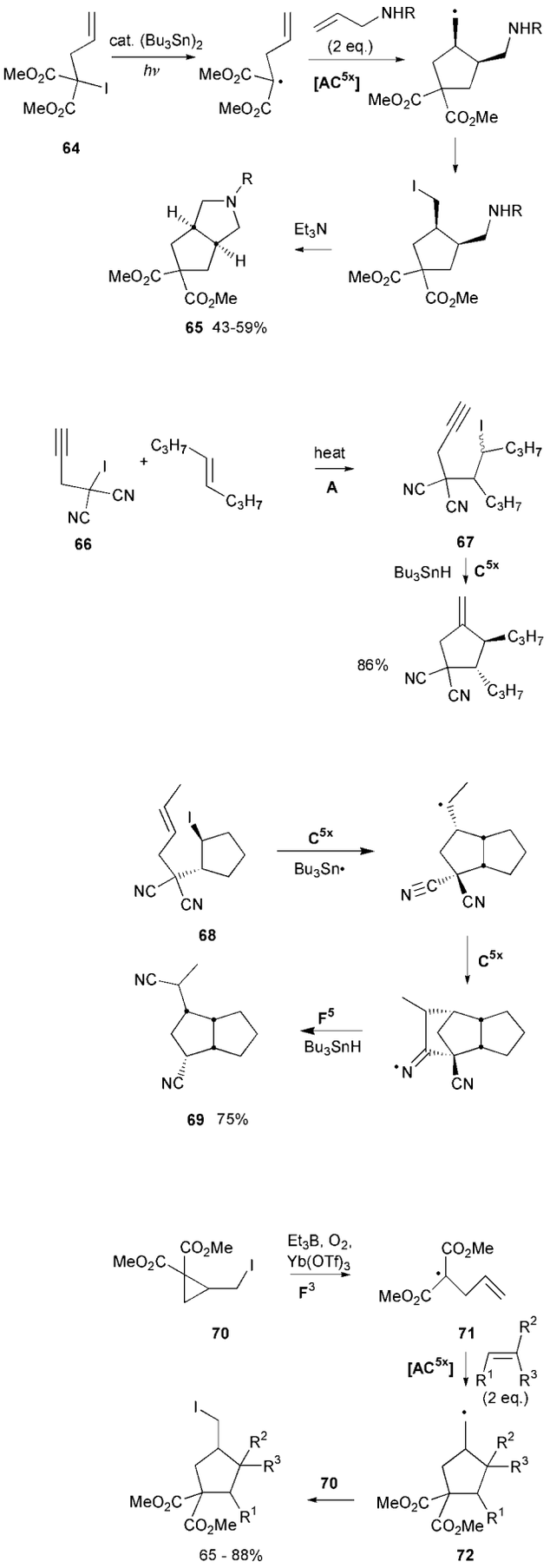
Flynn and Zabrowski showed that iodomalonate **64** underwent annulations with allylic amines, leading to azabicyclo-[3.3.0]octane systems **65**, provided that the amine had low nucleophilic character.[49] Curran and Seong described annulation reactions of allyl[51] and propargyl (prop-2-ynyl)[50] iodomalonitriles, and iodomalonates.[52] The optimised procedure for the reaction of iodomalonitriles such as **66** contained two steps. First, the electrophilic radical underwent intermolecular addition to an unactivated alkene. Tin compounds were not only unnecessary, they were deleterious in the case of propargyl iodomalonitriles, and the reactions proceeded best under thermal conditions in the dark. The annulation was not complete, because iodine atom abstraction competed effectively with cyclisation. The second step involved treatment of intermediates such as **67** with tributyltin hydride and resulted in the formation of methylenecyclopentanes in good yields (Scheme 16).

Allyl iodomalonitriles behaved slightly differently. Treatment of the product of atom-transfer addition (**68**) with tributyltin hydride led to cyclisation, and the resulting alkyl radical was suitably situated to undergo a nitrile transfer ($\mathbf{C^{5x}F^{5}}$) forming bicyclo[3.3.0]octane derivative **69** in good yield. These malonate and malonitrile radical cascades are perhaps slightly deceptive because they are in fact two reactions conducted by different techniques, but they can still be performed in one pot, and the adoption of the two-stage process is merely an optimisation of a tandem sequence.

In a recent development, Taguchi and co-workers have improved the efficiency of the process to a synthetically feasible level by using a masked homoallylic iodide in the form of an iodomethylcyclopropyl derivative (Scheme 16) (see also the section on round-trip annulations, Section 7).[53] There are several notable advantages of the system. Unwanted intermolecular addition to the radical precursor **70** does not occur, because there is no unsaturated moiety. Premature iodine abstraction by homoallylic radical **71** is degenerate, and addition to the alkene acceptor is efficient with just a two-fold excess of the acceptor. This contrasts with other round-trip type annulations, and has been attributed to the extended lifetime of radical **71** under these conditions. Ytterbium(III) triflate† facilitated the reaction, which was shown to work efficiently with less reactive alkenes such as cyclopentene. This methodology opens routes to a wide range of bicyclic and spirocyclic cyclopentane derivatives that could not be obtained using previous homolytic methods.

3.8 Annulations with electrophilic alkenyl radicals generated oxidatively

Numerous reports of manganese(III) acetate initiated sequences show that this technique is well suited for annulations.[11,54,55] Manganese(III) acetate creates electrophilic radical centres adjacent to the carbonyl groups of alkenyl esters and related compounds. The alkyl radicals formed after annulation are rapidly intercepted and converted to cations, usually by a copper co-oxidant, and hence cycloalkenes are the normal products. In a different approach, a second cyclisation onto an aromatic ring is incorporated into the reaction design, and the oxidative conditions facilitate re-aromatisation. The mechanisms, and the nature of radical generation, have been reviewed.[9]



Scheme 16

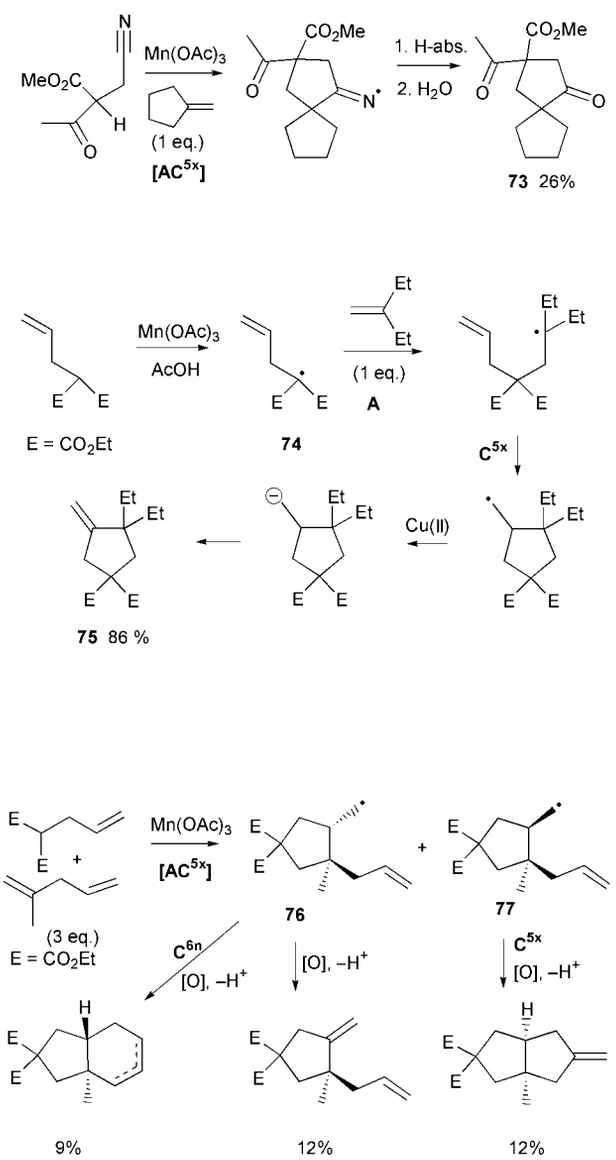
In a few examples termination by hydrogen abstraction occurred. The different characters of the malonyl starting radical, and the final iminyl radical formed by cyclisation onto

† The IUPAC name for triflate is trifluoromethanesulfonate.

a nitrile group, were brought into play.[56] The product imines were hydrolysed, producing spirocyclic ketones, such as **73**, in moderate yields.

As mentioned earlier, copper co-oxidants distinguish between electrophilic radicals and product alkyl radicals, which are further oxidised. In a representative example, addition of allylmalonyl radical **74** to unactivated 2-ethylbut-1-ene, was followed by cyclisation and further oxidation, producing the methylenecyclopentane derivative **75** in excellent yield.

Snider and Buckman have described an annulation which may be followed by a further cyclisation, leading to a mixture of products (Scheme 17).[55] The stereochemistry of the first 5-*exo*



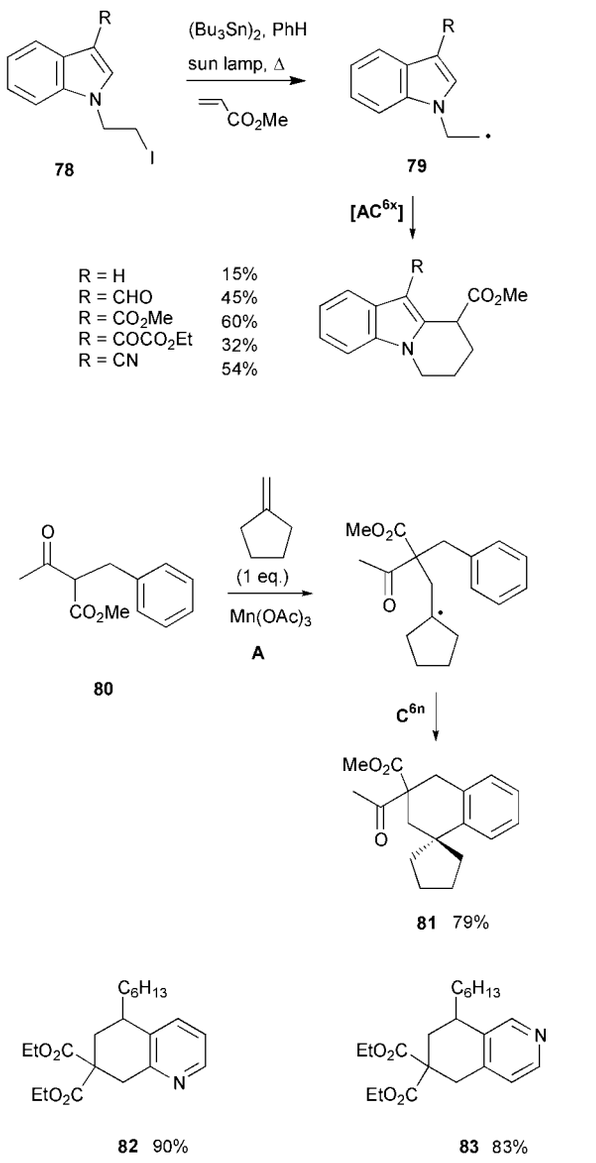
Scheme 17

cyclisation was not well controlled, and while *cis*-radical **77** underwent a rapid 5-*exo* cyclisation, *trans*-radical **76** could not do this, and was either intercepted by copper(II), or underwent a slow 6-*endo* cyclisation (Scheme 17).

In contrast to other cascade sequences initiated by manganese(III) acetate,[11,14] analogous annulative sequences have not been employed in steroid or other natural product syntheses.

4 Prevention of oligomerisation by cyclisation onto aromatic rings

Radical annulations may also be facilitated by including in the designs steps that terminate the cascades by means of radical addition to aromatic rings. Re-aromatisation is often very rapid and can bring the cascade to a successful endpoint. An annulation terminated by cyclisation onto an aromatic ring has recently been described using tin chemistry (Scheme 18).[57] Use



Scheme 18

of tributyltin hydride led to low yields of cyclised products, because 1-(2-iodoethyl)indoles **78** were reduced directly, without undergoing addition. When hexabutylditin was employed, hydrogen transfer to the indolylethyl radical **79** was excluded, and annulation took place fairly well. The product benzoindolizidine derivatives were obtained in reasonable yields, provided that the 3-position was activated.

Terminations by cyclisation onto phenyl rings have also been incorporated into manganese(III) acetate mediated annulation sequences.[55,58] For example, spiro-tetralin derivative **81** was formed in good yield (79%) from annulation of ethyl benzylacetoacetate **80** with methylenecyclopentane.[55] Premature oxidation did not occur provided copper(II) acetate was not present and the manganese(III) acetate was added slowly. Both alkynes and alkenes have been shown to be suitable radical acceptors in the addition steps of similar annulations.[59] Other metal oxidants, notably ceric ammonium nitrate and iron(III) perchlorate, have also been employed successfully.[58,60]

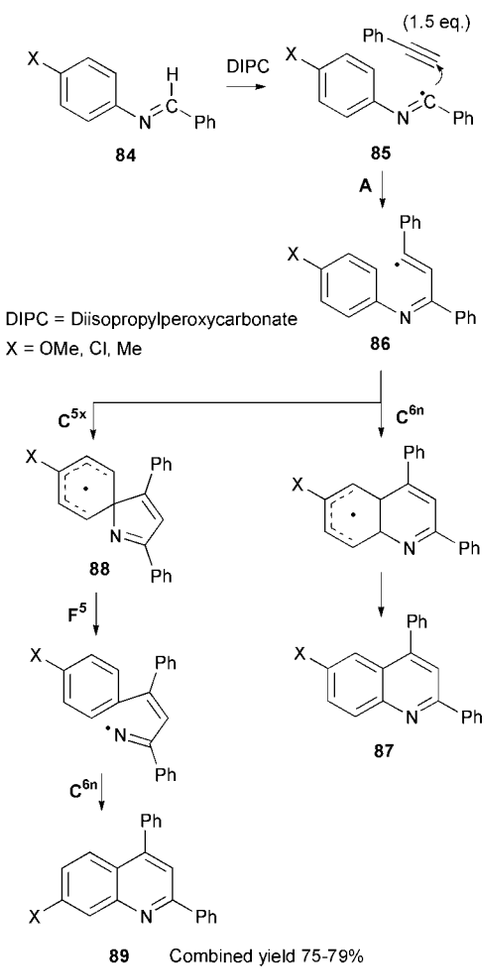
Tetrahydroquinolines, such as **82**, and tetrahydroisoquinolines, such as **83**, were prepared in high yields from the corresponding 2- and 4-picolyl malonates.[61] However, 3-picolyl

malonates led to product mixtures because the intermediate radical could cyclise in two different ways.

5 Syntheses of aza-heterocycles by radical annulations

Although [3+2] and [4+2] radical annulation techniques have been underused in organic synthesis as a whole, the field of heterocyclic synthesis, especially aza-heterocycle preparation, is an exception. The procedures developed combine many of the features and controls that have been described in the preceding sections to ensure that annulation is successful. These reactions are virtually always terminated through a cyclisation onto an aromatic ring, but the intermediates all have very different characteristics. No troublesome design features have to be artificially incorporated (such as electron withdrawing groups) to achieve success; intermediates such as imidoyl and iminyl radicals inherently contain sufficient distinction.

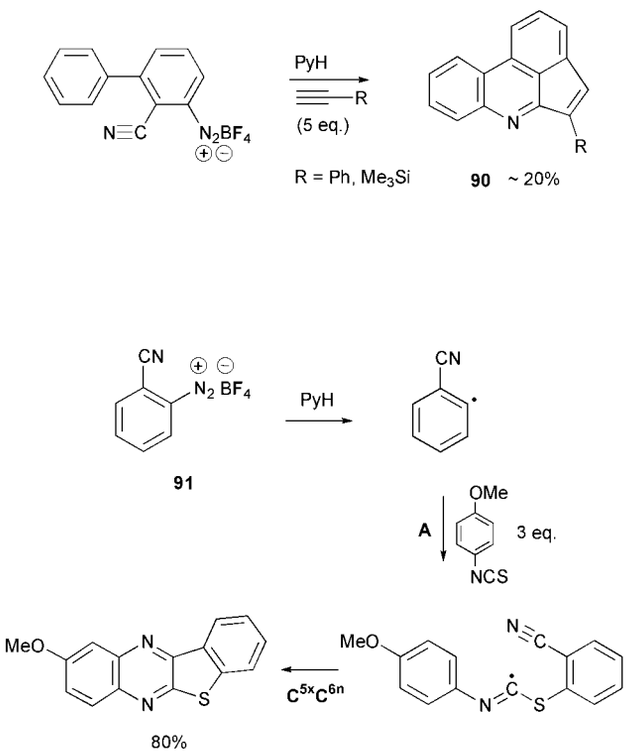
In 1986, Zanardi and co-workers described the intermolecular addition of arylimidoyl radicals **85**, generated by hydrogen abstraction from the corresponding imine **84**, to phenylacetylene (Scheme 19).[62] Vinyl radical **86** cyclised rapidly



Scheme 19

onto the aromatic ring. Unfortunately, a mixture of products was obtained because ring closure could occur either directly in 6-*endo* fashion to give the desired quinoline **87**, or in 5-*exo* mode to give the spirocyclic intermediate **88**, that then fragmented and re-substituted the ring to produce isomeric quinoline **89**. It is worth noting that iminyl radical **85** could alternatively have been generated by addition of a phenyl radical to an aryl isonitrile. Related reactions, in which diethyl azodicarboxylate was used as the radical acceptor instead of phenylacetylene, have also been described, leading to benzotriazines.[63] In these circumstances, no rearrangement products were observed.

The same research group utilised diazonium tetrafluoroborates as aryl radical precursors in annulations leading to aza-polycyclics. Various phenanthrenes and chrysene,[64] as well as novel nitrogen heterocycles **90**,[65] have been prepared by related annulations followed by further cyclisations onto aromatic rings (Scheme 20).



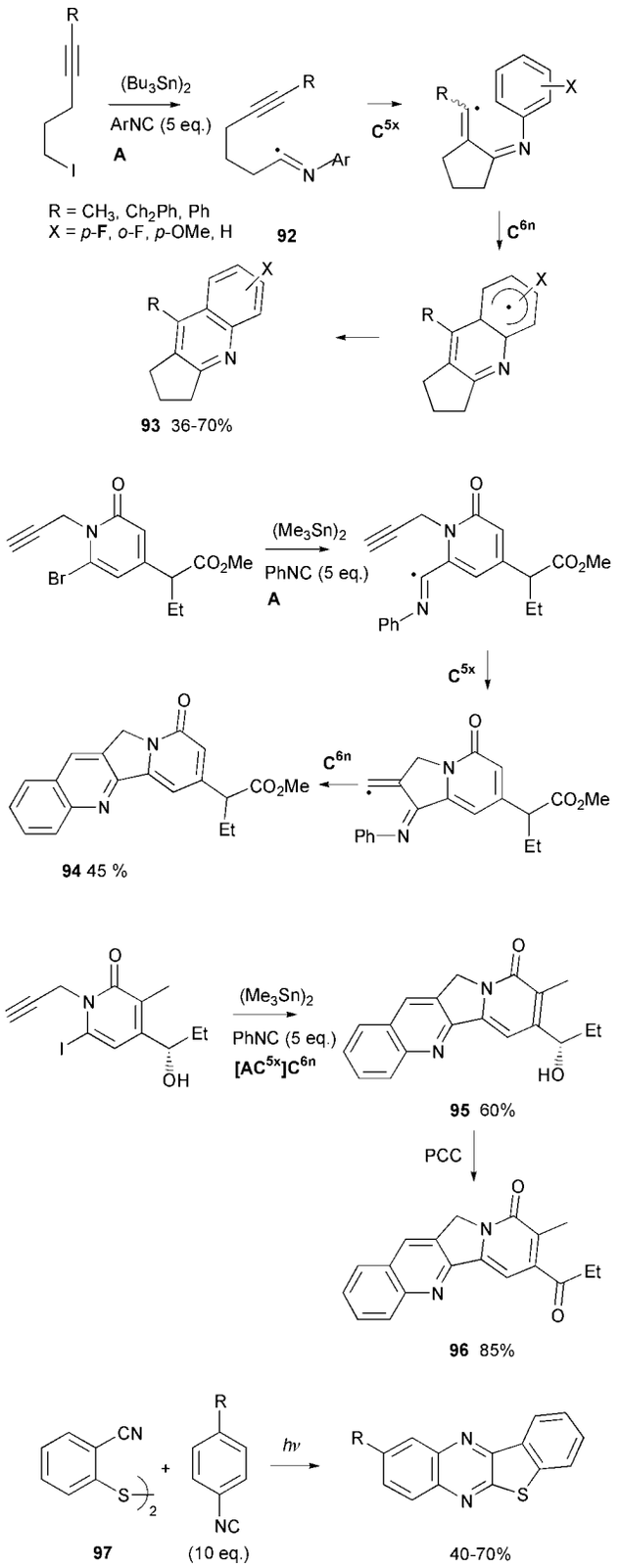
Scheme 20

Sulfur-containing heterocycles have also been prepared from 2-cyanodiazonium tetrafluoroborates **91**.[66] The procedure utilised isothiocyanates as good radical acceptors, and an example is shown in Scheme 20. The final cyclisation onto the aromatic ring was demonstrated to occur primarily *via* direct attack, rather than through a spiro-intermediate, but was substituent-dependent. The aryl radicals could also be generated from the tetrafluoroborates in ethyl acetate in the presence of potassium acetate and [18-crown-6]. This technique gave similar, or in some cases improved, yields to the pyridine method.

Isonitriles are examples of geminal radical acceptor/radical donor synthons.[9] In other words, owing to their unusual electronic structure, the site at which an incoming radical attacks (the terminal carbon) is also the site on which the unpaired electron resides after addition. As such, they are suitable for [4+1] annulations. They are excellent radical acceptors, and have been the subject of several synthetic studies. Curran and Liu developed the method, showing that cyclopenta-fused quinolines **93** could be prepared from simple aryl isonitriles and haloalkynes.[67] Imidoyl radicals **92** exclusively underwent cyclisation (although with some imidoyl radicals fragmentation to a nitrile occurred) and a second cyclisation onto the aromatic ring yielded substituted quinoline products (Scheme 21).

This annulation technique has also been applied to the synthesis of camptothecin precursor **94** (Scheme 21).[68] The method was later developed to enable camptothecin, and related structures, to be prepared stereoselectively.[69]

Mappicine ketones are structurally very similar to camptothecin, and display antiviral activity. The most common syntheses, from camptothecin, are not ideal because they involve a decarboxylation and do not provide a good route to



Scheme 21

analogues. The radical annulation technique using isonitriles has been employed not only to make (−)-mappicine **95**, and hence mappicine ketone **96**, but has been combined with combinatorial techniques to create a library of mappicine and mappicine ketone analogues.[70,71] The very fact that this was possible illustrates the efficiency and generality of the process, and perhaps indicates how homolytic annulation methodology might develop.

Nanni and co-workers conducted a detailed investigation into the products obtained from annulations with isonitriles, enabling several mechanistic questions to be answered.[72] As before, product mixtures due to rearrangements *via* spirocyclohexadienyl radicals can occur in some cases. However, this rearrangement is not a significant pathway in the annulation of disulfide **97** with aryl isonitriles.[73] This [**AC**^{5x}]**C**$^{6n/6x}$ annulation was only successful with aromatic precursors; after addition of aliphatic thiyl radicals to isonitriles, β-scission led to the isolation of isothiocyanates as major products.

One of the major reasons for the success of these reactions is the different nature of all the radicals involved. However, attempts to perform two intermolecular addition steps prior to cyclisation were largely unsuccessful, due to the perceived reversibility of vinyl radical addition to isonitriles.[72,74]

Annulations leading to 7-membered rings have also been accomplished using appropriate heteroaromatic xanthates together with allyl acetate as the radical acceptor.[75]

6 Annulations terminated by dissociative fragmentations: assembly of triquinane and related structures

Appropriate placement of a good radical leaving group enables a cascade to be terminated by a rapid dissociative fragmentation, with which intermolecular addition cannot compete. Suitable leaving groups are stannyl, thiyl and silyl. An advantage of this method is that the expelled radical may be involved in maintaining the chain. The rapidity of fragmentation enables large excesses of radical acceptors to be employed. Again, simple guidelines can be drawn up to promote the design of such annulations.

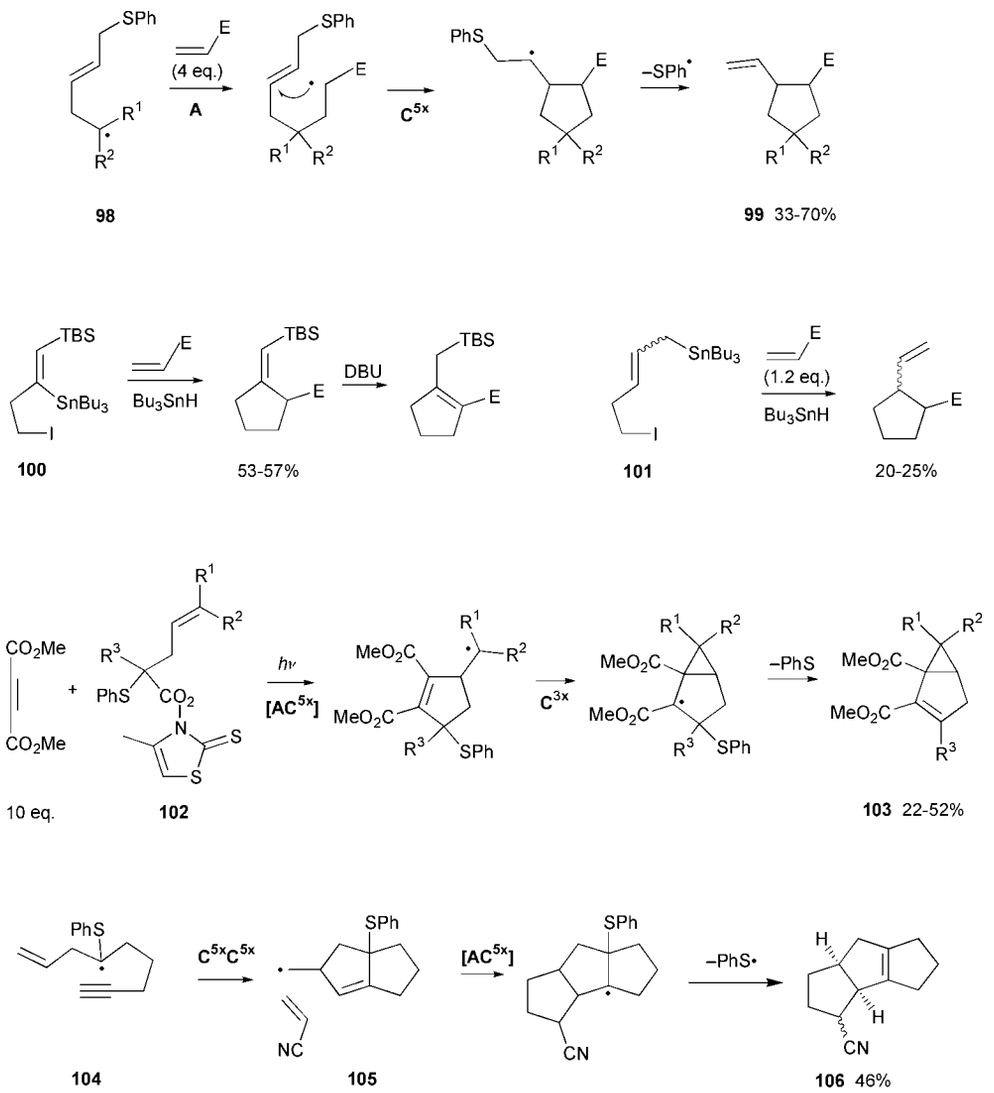
1. All cyclisation steps must be so rapid that intermolecular addition and termination are not competitive.
2. When intermolecular addition is required, intramolecular steps should not be possible.
3. The fragmentation should be rapid enough to prevent oligomerisation.
4. The reaction design must be such that premature fragmentation cannot occur.

Saičić and Čeković demonstrated that simple vinylcyclopentanes **99** could be prepared by this technique, using phenylthiyl as the expelled radical (Scheme 22).[76] The initial substituted butenyl radicals **98** were generated from thiohydroxamic esters, so the reactions did not proceed by chain mechanisms and hence the possibility of unwanted interception by hydrogen abstraction was precluded. A wide range of substituents was tested, and it was also shown that alkyne precursors resulted in the formation of allenes.

Curran and van Elburg established that vinylstannanes **100** and allylstannanes **101** were also viable reagents for this technique.[77] Vinylstannanes resulted in better yields. The desired position of the resulting double bond is also a consideration when applying the methodology.

The reversibility of the radical expulsion step sometimes enables unfavourable radical equilibria to be driven to completion. An example may be drawn from the equilibrium between a homoallylic and a cyclopropylmethyl radical. Saičić and co-workers showed that radical annulations could lead to bicyclo[3.1.0]hex-2-enes **103** when a well-placed phenylthiyl leaving group trapped a 3-*exo* cyclisation.[78] Dimethyl acetylenedicarboxylate acted first as an intermolecular, and then as an intramolecular, radical acceptor in the space of three steps (Scheme 22).

The fragmentation approach was also employed to assemble linear triquinane skeletons.[79] Radical **104** was generated from a thiohydroxamic ester and underwent a double cyclisation, followed by annulation and fragmentation, to construct triquinane skeleton **106** in an acceptable 46% yield. Expulsion of the phenylthiyl radical was sufficiently rapid to allow 22 equivalents of radical acceptor to be used without unwanted additions interrupting the sequence. This excess of acrylonitrile limited the amount of unwanted 3-*exo* cyclisation of the



Scheme 22

phenylsulfyl-substituted butenyl radical **105**, in contrast to the above example (**102**⟶**103**).

A remarkable annulation–cascade sequence has also been discovered which results in the formation of the linear triquinane skeleton **109** (Scheme 23).[80] The sequence terminates with the expulsion of a silyl radical, thus maintaining the chain, and preventing the further addition of acrylonitrile to **108**. It is remarkable that such a long and complicated sequence can occur in good yield, given that unwanted addition would potentially be competitive with several of the intermediate steps. A significant amount of side-product resulting from 3-*exo* cyclisation of **107** (trapped by rapid 5-*exo* cyclisation) was isolated.

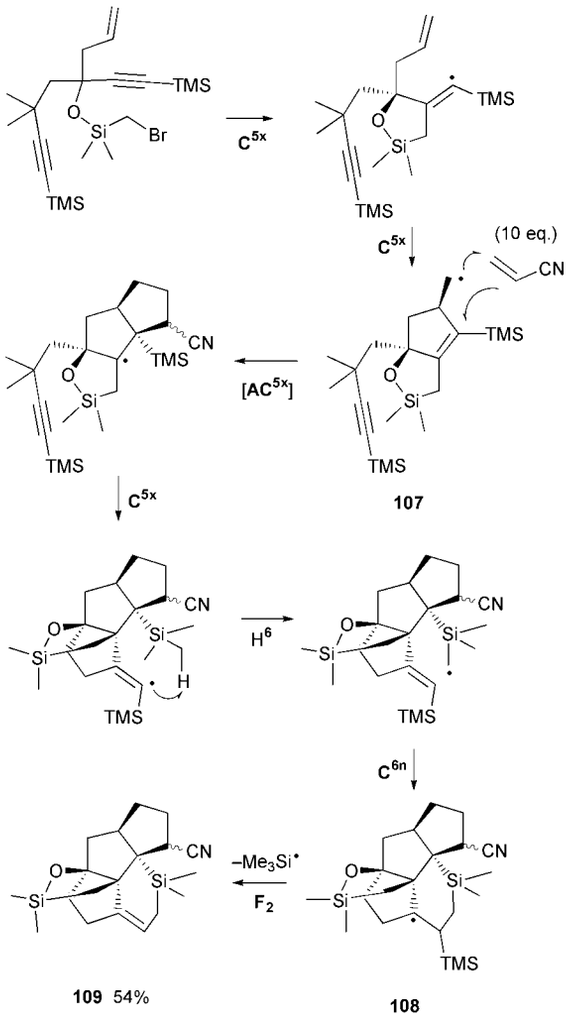
7 'Round trip' radical sequences based on vinylcyclopropanes

In a typical radical annulation, a homoallylic radical undergoes an intermolecular addition to an alkene double bond, and cyclisation follows. The groups of Feldman, Oshima, Singleton and Chuang have developed sequences in which the homoallylic radical is generated by radical addition to a vinylcyclopropane (or oxirane) followed by cleavage of the three-membered ring (Scheme 24). The design of the system is such that the final radical is situated on the same carbon as the first generated radical (a 'round-trip' annulation).[81] The chain is maintained by expulsion of the same radical that initially underwent addition, thus ending the cascade sequence. The reactions are, theoretically at least, catalytic in the radical sources, and provide an atom-efficient route to vinylcyclopentanes (and heterosubstituted variants).

Feldman *et al.* reported archetype annulation processes of vinylcyclopropanes **110** and demonstrated that when substituent R^1 was an ester, stereoselectivity could be improved by inclusion of trimethylaluminium in the reaction medium.[82] The sequence was catalysed by phenylthiyl radicals, which are highly suitable for use in these annulations, because they add reversibly to alkenes. 2,2-Dihalovinylcyclopropanes such as **111** also underwent efficient annulations,[83] but good yields were only obtained when electron deficient alkenes were employed. Interestingly, the reaction of the dibromo analogue of **111** did not require diphenyl disulfide to proceed, but was probably catalysed by bromine atoms.

Oshima[84] and Feldman[85] investigated the electronic requirements of the reaction in more detail. Substituted vinylcyclopropanes containing two strongly electron-withdrawing groups, such as **112**, only underwent successful annulation with electron rich alkenes. However, when only one electron-withdrawing substituent was present (**113**) annulations were successful with both electron poor and electron rich alkenes–a potentially vital piece of information in synthetic design. Chuang and Ngoi showed that 5-*exo* cyclisation was more rapid than β-elimination of a tosyl group or chlorine atom, increasing the range of compatible functionality.[86]

The analogous annulations with vinylepoxides were shown to give tetrahydrofurans (**114**) provided appropriate aromatic substituents were present to ensure C–O bond fragmentation.[87]



Scheme 23

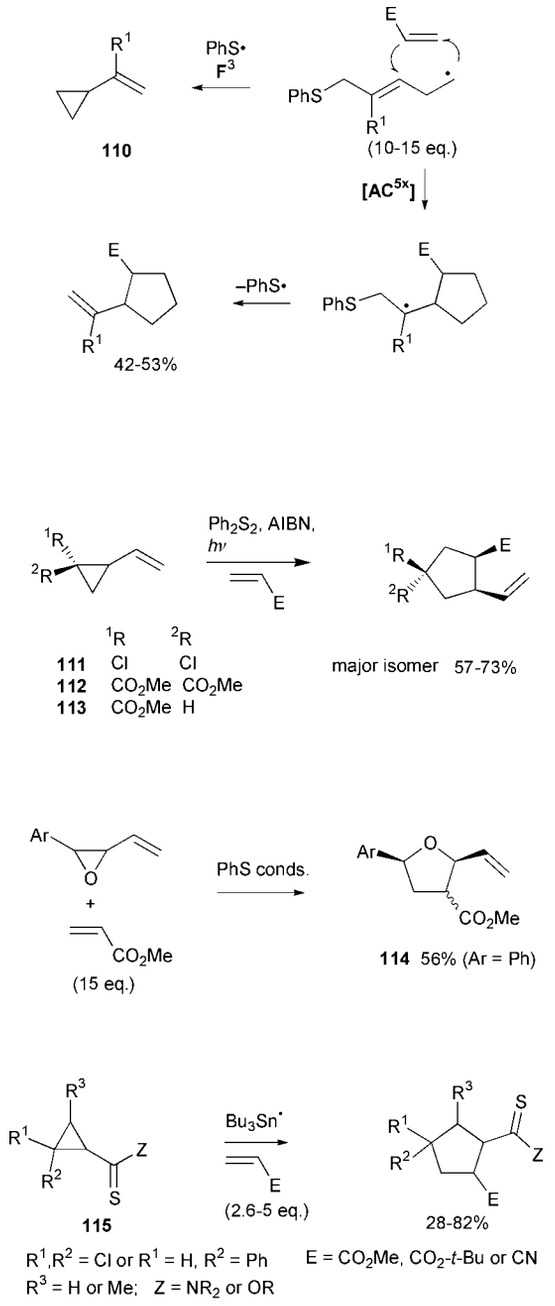
Thioamide- and thioester-substituted cyclopropanes (**115**) have also been used in radical annulations.[88] The principle is the same but in this case tributyltin radicals, which add efficiently to thiocarbonyl groups, were used to mediate the reactions (Scheme 24).

An example of a double annulation (**F**^{3}**F**^{3}[**AC**^{5x}][**AC**^{5x}]) has been described using the above methodology.[82] Cyclopropylcyclopropane **116** underwent double fragmentation on addition of a thiyl radical to give dienyl radical **117**. Subsequent double annulation proceeded smoothly, forming biscyclopentane **118** as a mixture of isomers in 58% yield (Scheme 25).

Closely related annulation sequences were described by Singleton and co-workers using methylenecyclopropanes, for which radical addition is selective for the ring carbon of the double bond.[89,90] The technique can be employed for both electron rich[89] and electron poor alkenes[90] and an example affording methylenecyclopentanes (**119**⟶**120**) is shown in Scheme 25. The method did not require a large excess of alkene acceptor, but the reaction with electron rich alkenes was suspected to proceed *via* a non-chain mechanism.

Most synthetic radical reactions are carried out under oxygen-free conditions, as oxygen is a good radical acceptor. The initial product of radical addition to oxygen is a peroxyl radical, which can cyclise onto appropriately placed unsaturation. The products are often 1,2-dioxolanes, and the round-trip methodology has been used to control the reaction, providing a facile, stereoselective route to 1,3-diols.[91] The method has been employed using catalytic diphenyl diselenide or diphenyl disulfide, as shown in Scheme 26 (**121**⟶**122**).[92]

The ring substituents were of great importance in controlling the stereochemistry, and unexpected isomers could be obtained.



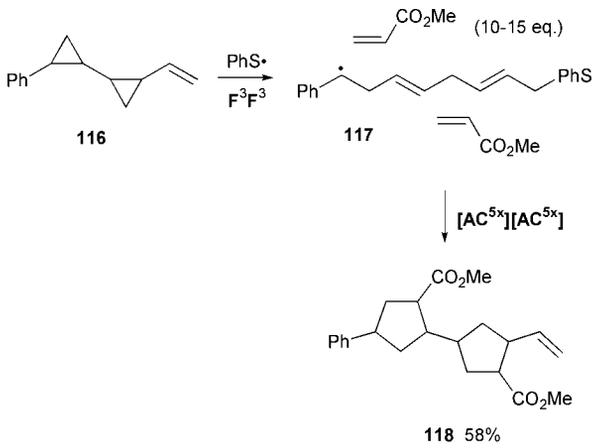
Scheme 24

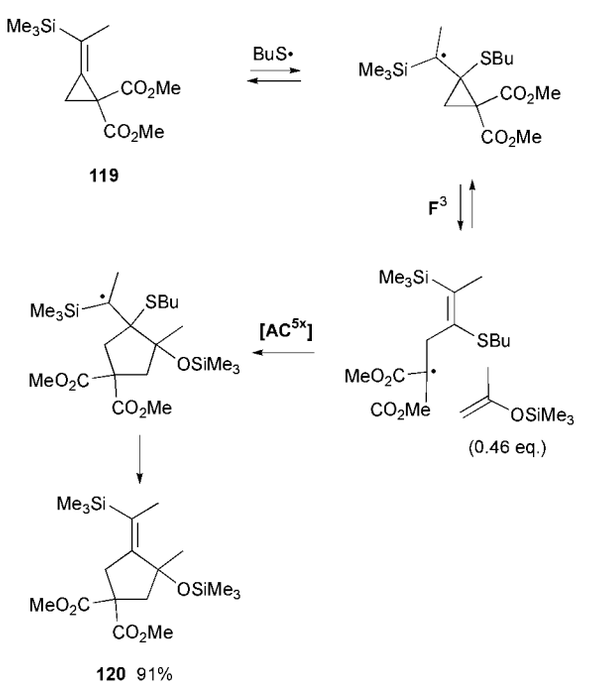
Ester-containing substrates led predominantly to dioxolanes, such as **123**, with *anti* stereochemistry.[93,94] When the process resulted in the formation of an internal double bond, as with vinyldioxolane **124**, the geometry was greatly influenced by the properties (*i.e.* the rate of expulsion) of the chain carrying radical.[95] Ph_2S_2 favoured *trans*-stereochemistry whereas Ph_2Se_2 was less selective. The plant metabolite, (±)-yashabushitriol, was synthesised to demonstrate the utility of the technique.

Double and triple annulations with oxygen have been performed.[92] For the triple annulation (**125**⟶**126**) two possible sequences to the same product are possible, depending on the regioselectivity of the initial ring opening. Use of diphenyl diselenide enabled isolation of monoannulated product **127**, indicating that the triple annulation proceeded *via* a **F**^{3}[**AC**^{5x}]-**F**^{3}**F**^{3}[**AC**^{5x}][**AC**^{5x}] sequence (rather than by initial double ring opening).

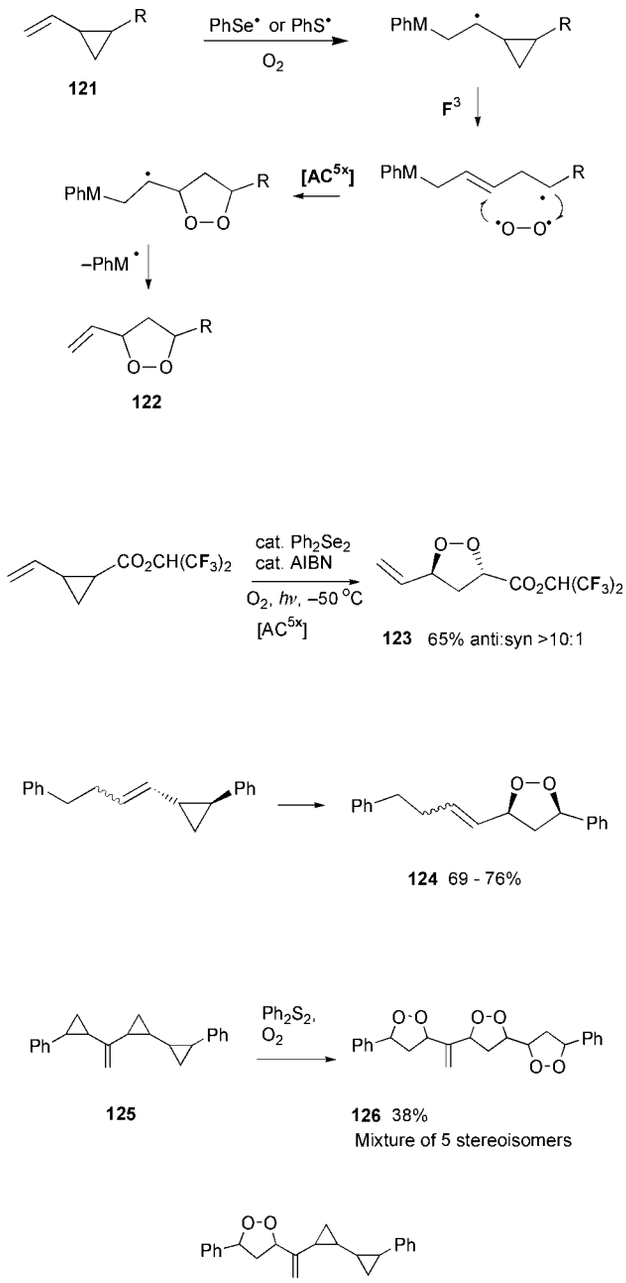
8 Conclusions

This survey of recent literature has shown that the basic free radical annulation process succeeds with an impressive range of





Scheme 25



Scheme 26

but-3-enyl, pent-4-enyl and alkynyl radical types. The alkenyl or alkynyl radical can contain a wide range of functionality and can be linear or cyclic. The main methods of generating these radicals include: conventional reactions of the corresponding halides or selenides with tin or silicon hydrides, treatment of but-3-en-1-ones with SmI_2, photolyses of unsaturated xanthates, rearrangements of cyclopropylmethyl radicals derived from vinylcyclopropanes or cyclopropylmethyl halides, and treatment of allyl esters and ketones with Mn(III) acetate. Similar annulations succeeded for butenyl analogues in which the unsaturation formed part of an aromatic ring, for example, annulations of aryl-iminyl radicals. In addition, aryl radicals containing 2-cyano-substituents functioned as the 4-atom unit in annulations with various acceptors.

Alkenes, particularly acrylate esters and acrylonitrile, and alkynes, were the most popular radical acceptors leading to many functionalised cyclopentanes, methylenecyclopentanes, vinylcyclopentanes, diquinanes, bicyclo[4.3.0]nonanes and aza-analogues. Carbon monoxide can act as a geminal radical acceptor, *i.e.* addition of a pent-4-enyl radical (or analogue) generates an unsaturated acyl radical (1-oxohex-5-enyl) that subsequently cyclises. Annulations of this type with CO afforded several types of functionalised cyclopentanones and polycyclic analogues. Isonitriles also behave as geminal radical acceptors, giving rise to unsaturated imidoyl radicals, that cyclise to produce a range of aza-heterocycles. Numerous annulations in which dioxygen couples with but-3-enyl type radicals to yield unsaturated peroxyl radicals that ring close to vinyldioxolanes have also been studied.

Several successful strategies for overcoming problems of oligomerisation have been devised. Apart from controlling the relative concentrations of the alkene (or other acceptor) and the initial radical precursor, the reactivities of the initial and cyclised radicals need to be differentiated either sterically or in terms of their nucleophilic/electrophilic character. Another useful tactic is to arrange for the ring closure step to be onto an aromatic or heteroaromatic ring. Rapid re-aromatisation of the resulting species then ensures that oligomerisation does not compete.

The science of 'programming' organic precursor molecules to achieve particular target structures is progressing steadily. Various types of homolytic annulations have been combined with additional rearrangement steps, particularly additional

cyclisations, in numerous intricate cascade sequences leading to stylish syntheses of polycyclic molecules. In this way mild and straightforward syntheses of a number of steroid, alkaloid and terpene natural products have been achieved, often with good stereocontrol. These highlight the potential of annulative cascades and point to a bright future for them.

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