PERKIN 2 REVIEW

The use of free radical initiators bearing metal–metal, metal–hydrogen and non-metal–hydrogen bonds in synthesis

Bruce C. Gilbert and Andrew F. Parsons *

Department of Chemistry, University of York, Heslington, York, UK YO10 5DD

Received (in Cambridge, UK) 20th September 2001
First published as an Advance Article on the web 28th January 2002

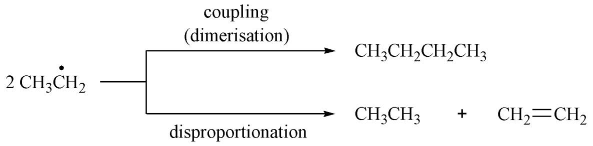
Covering: up till end of September 2001

1 Introduction

The free-radical reaction is an important tool for the modern organic chemist and within the last twenty to thirty years the use of radicals in synthesis has grown enormously. We are now at the point where radicals are routinely considered for the preparation of even the most complex target molecules.[1] This reflects the fact that radical reactions offer a number of advantages over ionic transformations. For example, whereas reactions involving cations or anions generally proceed under conditions of either high or low pH, radical reactions typically proceed under mild and neutral conditions. This allows acid-sensitive and chiral substrates to be transformed without fear of decomposition or racemisation. Although reactions involving ions are often dependent on the nature of the solvent, this is usually less of a problem for radical reactions: radicals are generally not solvated and so they tend to react similarly in a range of different solvents (unlike ions). As radicals are not solvated they are also generally highly reactive, which means that radical reactions can be used to assemble even sterically hindered centres within complex target molecules. This may involve a variety of flexible tandem and cascade sequences, which have been developed to form a number of carbon–carbon bonds in remarkably effective "one-pot" transformations.

The ability to design predictable and high-yielding radical transformations builds on the important contributions made by physical organic chemists in the 1960's and 1970's.[2] This fundamental work not only characterised the main pathways by which radicals react but also provided information on the relative rates of these processes. The rate constants of a variety of initiation, propagation and termination steps are now available and these can be used to help understand why radicals react in a particular manner, which is crucial for the design of efficient radical reactions.[3] For example, it is only when radical rate constants are known that appropriate concentrations of reagents can be calculated before a given radical reaction is undertaken.

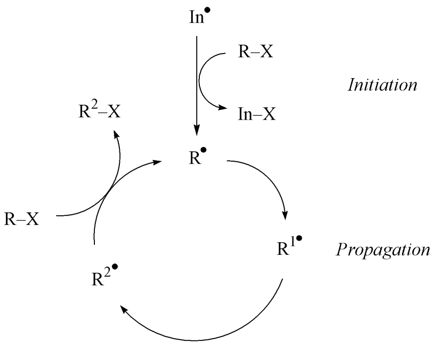
Radical reactions can be divided into those which display non-chain and chain mechanisms. For non-chain reactions the intermediate radical reacts with another radical in a disproportionation step or, more commonly, in a coupling reaction (Scheme 1). These termination reactions produce non-radical products and if the radical starting materials are identical, then symmetrical dimers can be formed extremely rapidly: in solution at rt the rate constant for reaction between two carbon-centred radicals is typically around 10^8–10^9 dm^3 mol^{-1} s^{-1} unless bulky substituents hinder the approach of the radical centres.[4] This type of dimerisation process has found application in well-known Wurtz and Kolbe reactions.[1]



Scheme 1

Most synthetically important radical reactions involve chain processes and a classic example involves the photolysis of alkanes and chlorine to form alkyl chlorides.[1] Following initiation, the first-formed radical ($R^\bullet$) reacts through a series of propagation steps to produce new radical products ($R^{1\bullet}$ and then $R^{2\bullet}$), which ultimately lead to regeneration of the initial radical (Scheme 2). For the majority of radical reactions a

DOI: 10.1039/b102044g



Scheme 2

peroxide or azo compound is used as an initiator to form $\mathrm{In}^{\bullet}$ and start the chain. In theory, the reactant (RX) could be completely converted to product (R^2X) using only one molecule of the initiator radical ($\mathrm{In}^{\bullet}$). In practice, however, more than one molecule is usually required because of competing radical–radical reactions, which terminate the chain. This can be a major problem as termination reactions are very fast, essentially diffusion-controlled, processes. As a consequence, typically 0.1 equivalents of the initiator are used and this is often added slowly to the reaction mixture (using a syringe pump). Slow addition of the initiator helps the chain reaction to continue because this generates a low concentration of the radical intermediates ($R^{\bullet}$, $R^{1\bullet}$ and $R^{2\bullet}$) which, in turn, reduces the rate of termination processes. In other words, the radicals ($R^{\bullet}$, $R^{1\bullet}$, $R^{2\bullet}$) will now have more chance of reacting with a non-radical substrate (*i.e.* RX), to continue the chain, rather than with another radical (*i.e.* $R^{1\bullet}$ or $R^{2\bullet}$), which would stop the chain.

An efficient chain process not only requires slow termination steps, but fast propagation steps (typically with rate constants of $>10^2$ dm^3 mol^{-1} s^{-1}). If the desired propagation steps are slow (*e.g.* rate constants of $<10^2$ dm^3 mol^{-1} s^{-1}) then this increases the likelihood of the radical intermediates ($R^{1\bullet}$, $R^{2\bullet}$) undergoing terminations or alternative propagation reactions (*e.g.* reaction with the solvent) leading to a reduced yield of the desired product (R^2X).[5]

As a rule of thumb, these propagation reactions involve the formation of strong bonds at the expense of much weaker bonds. The bond dissociation energies (BDE) of the bonds which are broken and formed can therefore provide a guide as to whether the reaction will proceed. Bond dissociation energies can also tell us which radicals are most likely to be generated in initiation steps; the weaker the bond, the more easily the radicals are likely to be formed.

However, if bulky substituents surround a radical centre then these groups will reduce the rate at which the radical reacts (in propagation and termination reactions) because of steric hindrance.[6] For example, whereas dimerisation of the methyl radical typically has a rate constant of ~3×10^{10} dm^3 mol^{-1} s^{-1}, the considerably more hindered trityl radical ($Ph_3C^{\bullet}$) dimerises with a rate constant of only ~3×10^2 dm^3 mol^{-1} s^{-1} (at rt in low viscosity solvents).[4] Steric hindrance therefore increases the lifetime of radicals, which are often reported as half-lives ($t_{1/2}$) at a given concentration.[6]

This review will discuss some synthetically important radical reactions (non-chain and chain) mediated by a variety of initiators bearing metal–metal, metal–hydrogen or non-metal–hydrogen bonds. The use of these types of initiators in a variety of radical reactions will be outlined and the rate constants of the elementary steps will be discussed in detail to provide a rationale of why many of these reactions work particularly well.

2 Metal–metal bond initiators

A number of metal-centred radicals can be prepared by homolysis of weak metal–metal bonds in metal dimers of the type $R_nM–MR_n$. Radicals can usually be formed on photolysis or thermolysis and, as highlighted in this review, the efficiency of the homolysis depends on both the nature of the metal (M) and the substituents (R) attached to the metal. Of particular synthetic importance are tin-centred radicals, although radicals centred on other group 14 elements, notably silicon, are of increasing interest (Section 2.1). Transition-metal dimers can also undergo homolysis to generate metal-centred radicals as illustrated by the reactions of manganese or rhenium carbonyls (Section 2.2).

2.1 Organoditin (R_6Sn_2) and related group 14 compounds

2.1.1 Radical generation

Tin-centred radicals are used routinely to initiate a variety of radical transformations. These radicals can be prepared from hexaalkylditin or hexaarylditin compounds ($R_3Sn–SnR_3$) as the weakest bond in these compounds is the tin–tin bond and this can be homolytically cleaved by heating above 200 °C or by photolysis (Scheme 3).

$$\mathrm{R_3Sn{-}SnR_3} \xrightarrow[\text{or } h\nu]{\text{heat}} \mathrm{R_3Sn}^{\bullet} + {}^{\bullet}\mathrm{SnR_3}$$

Scheme 3

Photolysis provides the mildest method of radical generation: the absorption of light by organoditin compounds leads to a $\sigma \longrightarrow \sigma^*$ transition and the excited state has a weaker Sn–Sn bond. Although ditin compounds do not have an absorption maximum in the normal UV region (for Bu_6Sn_2, $\lambda_{max} = 236$ nm) they have a strong absorption that tails to around 250–260 nm. Hence, laser-flash photolysis of hexabutylditin (Bu_6Sn_2) at 266 nm produces tributyltin radicals.[7] More recently, tin-centred radicals have been generated on UV irradiation of Bu_6Sn_2 in the presence of triplet sensitisers including acetone.[8]

The bond dissociation energies of the tin–tin bonds in these types of compound are usually similar and, for example, the Sn–Sn bond in hexamethylditin (Me_6Sn_2) is around 258 kJ mol^{-1}.[9] Changing from alkyl to aryl substituents on the tin atoms does not significantly change the Sn–Sn bond strength.[10] This presumably reflects the pyramidal shape of the trialkyl and triaryltin radicals, which prevents extensive conjugation of the unpaired electron (in an sp^3 orbital) with the π-electrons in the benzene rings.[11] This is in stark contrast to the majority of carbon-centred radicals, which are effectively planar and so can be stabilised by neighbouring aryl substituents.[1]

Steric effects are generally less important for tin-centred radicals than for carbon-centred radicals because the covalent radius of the tin is considerably larger (*i.e.* 0.140 nm for Sn *versus* 0.077 nm for C) and this places the alkyl or aryl substituents further away from the radical centre. However, the size of the groups is still important as illustrated by the different rates of trapping of $Bu_3Sn^{\bullet}$ and $Ph_3Sn^{\bullet}$ radicals by the 2,2,6,6-tetramethylpiperidin-1-yloxyl (TEMPO) radical (*i.e.* 6.2×10^8 and 1.9×10^7 dm^3 mol^{-1} s^{-1}, respectively).[12] Extremely bulky groups can significantly influence the longevity of the tin-centred radical as these groups can protect the radical from reacting (thereby increasing its lifetime). For example, whereas the ${}^{\bullet}SnMe_3$ radical dimerises at an essentially diffusion-controlled rate ($2k_t = 2.8 \times 10^9$ dm^3 mol^{-1} s^{-1} at −65 °C),[13] the radical ${}^{\bullet}Sn[CH(SiMe_3)_2]_3$ has been reported to have a half-life of *ca.* 1 year at 20 °C because steric hindrance effectively reduces the rate of dimerisation.[14]

Dimers of other group 14 elements can also undergo homolysis to give radicals. In hexamethyl compounds of the type Me_6M_2, where M is a group 14 element, the strength of the M–M bond decreases as the size of the element increases and so lead-centred radicals are generally more easily formed than silicon-centred radicals (Table 1).[9] However, it should be noted that silyl radicals can be generated on photolysis of a variety of silanes including tetrakis(trimethylsilyl)silane, $Si[SiMe_3]_4$.[15]

Table 1 The influence of covalent radii on metal–metal bond dissociation energies (BDE) in group 14 dimers[9]

M–M in Me_6M_2	E/kJ mol^{-1}	Covalent radius/nm
Si–Si	285	0.117
Ge–Ge	248	0.122
Sn–Sn	163	0.140
Pb–Pb	139	0.144

Heteronuclear compounds such as $Me_3Sn–SiMe_3$ can also decompose to give tin- and silicon-centred radicals and the strength of the Sn–Si bond ($E \approx 235$ kJ mol^{-1}) is in-between those of Sn–Sn and Si–Si. The strength of M–carbon bonds follows a similar trend: C–Si > C–Ge > C–Sn > C–Pb. Hence, tetraethyllead ($PbEt_4$) has a particularly weak Pb–C bond ($E \approx$ 129 kJ mol^{-1}), which accounts for the ease of homolysis and hence the effectiveness of this reagent as an anti-knock agent in petrol.[16]

An alternative approach to tin-centred radicals involves reaction of dialkylditins with oxygen- or selenium-centred radicals produced on thermolysis of peroxides or diselenides, respectively (Scheme 4).[13,17,18] These bimolecular homolytic substitution (S_H2) reactions involve radical attack at a tin atom leading to cleavage of the relatively weak Sn–Sn bond and the formation of, for example, a stronger tin–oxygen bond. This is a synthetically attractive method for preparing tin-centred radicals as it avoids the use of high-energy UV light, which is normally required for direct homolysis of the Sn–Sn bond.

$$RO^{\bullet} + R_3Sn{-}SnR_3 \xrightarrow{S_H2} RO{-}SnR_3 + {}^{\bullet}SnR_3$$

Scheme 4

2.1.2 Abstraction and addition reactions

Tin-centred radicals have played a central role in the development of both synthetic and mechanistic organic radical chemistry. One important reason for this is the fact that these radicals can react with a diverse range of organic substrates as illustrated by reaction of trialkyltin radicals with a variety of organohalides, selenides, sulfides or xanthates to form carbon-centred radicals (Scheme 5). A considerable range of alkyl and aryl iodides, bromides and to a lesser extent chlorides will react in bimolecular homolytic substitution (S_H2) reactions with tin-centred radicals and this method is commonly used, for example, to form carbon-centred radicals in EPR spectroscopy studies (designed to identify the radicals formed and their rates of reaction).[19]

$$R_3Sn^{\bullet} + X{-}R \xrightarrow{S_H2} Bu_3Sn{-}X + R^{\bullet}$$

Scheme 5

The rate of reaction of a tin radical with an organohalide depends on both the nature of the halogen group and to a lesser extent, the alkyl or aryl group[20] (Table 2). In general, the weaker the carbon–halogen bond the faster the rate of halogen-atom abstraction, hence iodides react faster than bromides and chlorides: R–I > R–Br > R–Cl. As a rough guide, the rate constant for halogen-atom abstraction is usually greater than 10^9 dm^3 mol^{-1} s^{-1} for alkyl iodides, around 10^7–10^8 and 10^5 dm^3 mol^{-1} s^{-1} for alkyl bromides and chlorides, respectively, while alkyl fluorides tend not to react. This is because the driving force for these halogen-atom abstraction reactions relies on the formation of a relatively strong tin–halogen bond (*e.g.* BDE = 356 and 423 kJ mol^{-1} for $Me_3Sn–Cl$ and $Me_3Sn–Br$,[21–28] respectively) at the expense of a weaker carbon–halogen bond [*e.g.* BDE ≈ 250 and 290 kJ mol^{-1} for $Br–CH_2Ph$ and $Br–C(CH_3)_3$, respectively]. The importance of the alkyl or aryl group is evident from the following general trend in reactivity: benzyl ≈ allyl > alkyl > aryl ≈ vinyl. Once again, this is expected from bond strengths as, for example, benzyl bromide has a much weaker C–Br bond than bromobenzene (BDE ≈ 250 *versus* 340 kJ mol^{-1}). However, it should be noted that the tri-*n*-butyltin radical reacts only approximately six times faster with 2-bromo-2-methylpropane than with 1-bromopentane and so it shows relatively little discrimination between primary, secondary or tertiary alkyl halides.

Table 2 Absolute rate constants (k) for reaction of organohalides and related compounds with the tributyltin radical ($^nBu_3Sn^{\bullet}$) at rt[29–31]

Compound	k/dm^3 mol^{-1} s^{-1}
$I–CH_3$	4.3×10^9
$Br–CH_2Ph$	1.5×10^9
$Br–C(CH_3)_3$	1.5×10^8
$PhSe–CH_2CO_2Et$	1.0×10^8
$Br–CH_2(CH_2)_3CH_3$	2.6×10^7
$Cl–CH_2CO_2Et$	1.0×10^6
$Cl–CH_2Ph$	1.1×10^6
$PhS–CH_2CO_2Et$	2.0×10^5
$Cl–C(CH_3)_3$	2.7×10^4

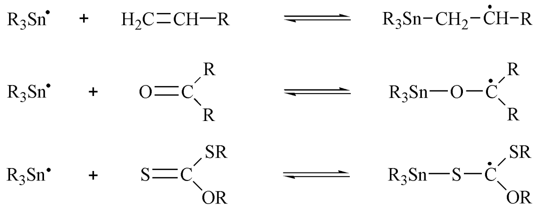
Table 3 Absolute rate constants (k) for reaction of organohalides with tin ($^nBu_3Sn^{\bullet}$), germanium ($^nBu_3Ge^{\bullet}$) and silicon radicals [$Et_3Si^{\bullet}$ and $(Me_3Si)_3Si^{\bullet}$] at rt[29–31]

	k/dm^3 mol^{-1} s^{-1}			
Compound	$^nBu_3Sn^{\bullet}$	$^nBu_3Ge^{\bullet}$	$Et_3Si^{\bullet}$	$(Me_3Si)_3Si^{\bullet}$
$Br–CH_2Ph$	1.5×10^9	8×10^8	2.4×10^9	9.6×10^8
$Br–C(CH_3)_3$	$1.7–1.4 \times 10^8$	8.6×10^7	1.1×10^9	1.2×10^8
$Cl–CH_2Ph$	1.1×10^6	1.9×10^6	2.0×10^7	4.6×10^6

Sulfides, and particularly selenides, undergo similar (concerted) S_H2 reactions and the order of reactivity of organohalides, selenides, xanthates and sulfides towards tin radicals is typically as follows: R–I > R–Br > R–SePh ≈ R–OC(=S)SMe > R–Cl > R–SPh.[29,30]

Similar reactions are observed for related germanium- and silicon-centred radicals (Table 3).[29,31] For halogen-atom abstraction, $^nBu_3Ge^{\bullet}$ and $^nBu_3Sn^{\bullet}$ have essentially equal reactivity whereas the $Et_3Si^{\bullet}$ radical is slightly more reactive. As predicted, the introduction of bulkier substituents on the tin, germanium or silicon reduces the rate of halogen-atom abstraction because of steric effects. Thus, tris(trimethylsilyl)silyl, $(Me_3Si)_3Si^{\bullet}$, is around 4–10 times less reactive than $Et_3Si^{\bullet}$ towards halogen-atom abstraction.[22] This is also apparent in S_H2 reactions with sulfides and selenides, which may occur *via* a synchronous or stepwise process involving λ^4-sulfanyl or λ^4-selanyl radicals [of the type ${}^{\bullet}SR_2(SiR_3)$ or ${}^{\bullet}SeR_2(SiR_3)$, respectively].[22] The rate constants for reaction of $Et_3Si^{\bullet}$ with fluoren-9-yl phenyl sulfide and for $(Me_3Si)_3Si^{\bullet}$ with *n*-decyl phenyl sulfide are 2.4×10^8 and $\leq 5 \times 10^6$ dm^3 mol^{-1} s^{-1}, respectively (at rt).[22,32]

Trialkyltin radicals can also add to a variety of C=C, C=O and C=S double bonds as shown in Scheme 6. Addition to



Scheme 6

Table 4 Absolute rate constants (k) for addition of tin, germanium and silicon radicals to alkenes between 21–29 °C[29–31]

	k/dm^3 mol^{-1} s^{-1}			
Alkene	^{n}Bu$_3$Sn$^•$	^{n}Bu$_3$Ge$^•$	Et$_3$Si$^•$	(Me$_3$Si)$_3$Si$^•$
$H_2C{=}CH{-}CN$	8.8×10^7	1.8×10^8	1.1×10^9	6.0×10^7
$H_2C{=}C(CH_3)CO_2CH_3$	1.2×10^8	1.2×10^8	4.6×10^8	$9.7 \times 10^{7\,a}$
$H_2C{=}CH{-}Ph$	9.9×10^7	8.6×10^7	2.2×10^8	5.9×10^7

[a] Reaction with ethyl acrylate not methyl methacrylate.

electron-poor alkenes is usually favoured (over electron-rich alkenes) because trialkyltin radicals are considered to be nucleophilic radicals (*i.e.* in the transition state of the reaction, a positive charge on tin is stabilised by electron-donating alkyl groups). These reactions are generally reversible because of the formation of a relatively weak carbon–tin bond (the Sn–Me bond strength in Me$_4$Sn is only 278 kJ mol^{-1}).[9] However, the rate of fragmentation of the adduct radical does depend on the alkyl (R) substituents and the reaction temperature; the introduction of radical stabilising groups will generally reduce the rate of fragmentation while higher reaction temperatures will favour elimination over addition.

The reaction of ^{n}Bu$_3$Sn$^•$ with aldehydes or ketones involves addition of the tin radical to the oxygen, rather than carbon atom so as to form a stronger tin–oxygen rather than a tin–carbon bond. It interesting to note that, although trialkyltin radicals are usually considered as being nucleophilic, in these reactions, the tin radicals behave as electrophilic radicals and so the "philicity" depends on the nature of the acceptor double bond. This regioselectivity has also been observed when tin radicals react with α,β-unsaturated substrates such as maleic anhydride.[33–35]

Addition of ^{n}Bu$_3$Sn$^•$ to aldehydes or ketones is usually reversible, as fragmentation to regenerate the strong C=O bond is normally fast. Indeed, the formation of a strong C=O bond is a key driving force in the reaction of xanthates with tin radicals.[36] The tin radical adds (reversibly) to the relatively weak C=S bond leading to an intermediate radical which fragments to form a stronger C=O bond rather than regenerate the xanthate starting material (Scheme 6). The rate of fragmentation of the intermediate radical depends on the stability of the leaving group. Hence, fragmentation to form primary radicals is generally much slower than that to form (more stable) secondary radicals.

Although tin radicals generally do not add to the carbonyl bond of carboxylic acid derivatives (*e.g.* esters, amides), benzoate esters have proved to be an exception[37] (presumably because the benzene ring can stabilise the adduct radical). A related addition–fragmentation reaction has also been observed when secondary or tertiary nitro derivatives react with ^{n}Bu$_3$Sn$^•$; this leads to the formation of a strong Sn–O bond at the expense of a weaker C–N bond.[38]

Germanium- or silicon-centred radicals also add to C=C double bonds (the rate constants are compared with those for ^{n}Bu$_3$Sn$^•$ in Table 4).[21,22] These nucleophilic radicals add rapidly particularly to electron-poor alkenes and, as for halogen-atom abstractions, Et$_3$Si$^•$ is the most reactive. The rate of fragmentation of the radical adducts (of the type $^•CH_2{-}CH_2{-}MR_3$) is slower for trialkylsilyl radicals as the C–Si bond (~377 kJ mol^{-1}) is stronger than the C–Ge (~318 kJ mol^{-1}) or C–Sn bonds (~272 kJ mol^{-1}). This means that silyl radicals can even add irreversibly to alkenes. However, the introduction of bulkier substituents on silicon can weaken the Si–C bond and so reactions using the tris(trimethylsilyl) radical can be reversible at ordinary temperatures.[23] It has also been shown that triple bonds are only slightly less reactive toward addition of the Et$_3$Si$^•$ radical than alkenes (*i.e.* 2.3×10^6 *versus* 3.7×10^6 dm^3 mol^{-1} s^{-1} for addition to HC≡C^{t}Bu and H$_2$C=CH^{t}Bu).

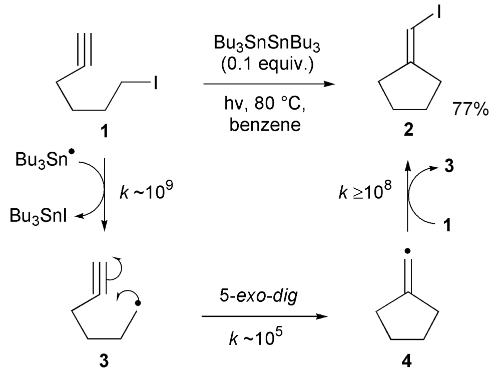
Silyl radicals can also add to carbonyls so as to form a stronger silicon–oxygen rather than a carbon–oxygen single bond. As for halogen-atom abstractions, Et$_3$Si$^•$[24] reacts more rapidly than (Me$_3$Si)$_3$Si$^•$[25] and the rate of addition to ketones is around 10^4–10^5 dm^3 mol^{-1} s^{-1}. Rates of addition of silyl radicals to related functional groups, including thioketones,[26] isocyanates,[27] isonitriles, nitriles and nitro compounds[28] are also known. For example, Et$_3$Si$^•$ adds to ^{t}BuN=C=O, ^{n}BuN=C, ^{t}BuC≡N and MeNO$_2$ with rate constants of 5.5×10^6, 1.6×10^8, $\le 3 \times 10^5$ and 4.3×10^7 dm^3 mol^{-1} s^{-1}, respectively (at rt).[28]

2.1.3 Applications in synthesis

As shown above, the use of hexaalkylditin and related compounds offers an approach to a wide variety of carbon-centred radicals from organohalides and related compounds. The carbon-centred radicals can then undergo a number of reactions including intra- or inter-molecular addition to alkenes or other multiple bonds, leading to a variety of carbon–carbon bonds. The real challenge in designing efficient syntheses using these types of reagents lies in deciding the fate of the radical formed after the cyclisation or intermolecular addition. For a chain reaction, this radical would ideally react with another molecule of starting material to regenerate the initial radical and this tactic has been utilised as described below.

2.1.3.1 Atom-transfer cyclisations

An atom-transfer cyclisation leads to the formation of a cyclic product on transfer of an atom in an acyclic starting material. A typical iodine-atom transfer cyclisation is shown in Scheme 7, in which photolysis of 6-iodohex-1-yne **1** with 0.1 equivalents of hexabutylditin at 80 °C for 0.5 h affords (iodomethylene)-cyclopentane **2** in 77% yield.[39] In this reaction, the tri-*n*-butyltin radical abstracts an iodine atom from iodide **1** (at a rate constant of ~10^9 dm^3 mol^{-1} s^{-1}) to form primary radical **3**, which can then undergo a 5-*exo-dig* cyclisation to form a new C–C σ-bond at the expense of a C≡C π-bond. The rate constant for this type of cyclisation is around 10^5 s^{-1} at 25 °C and this generates vinyl radical **4**, which is able to abstract an iodine atom



Absolute rate constants at r.t. (in s^{-1} or dm^3 mol^{-1} s^{-1} where appropriate)

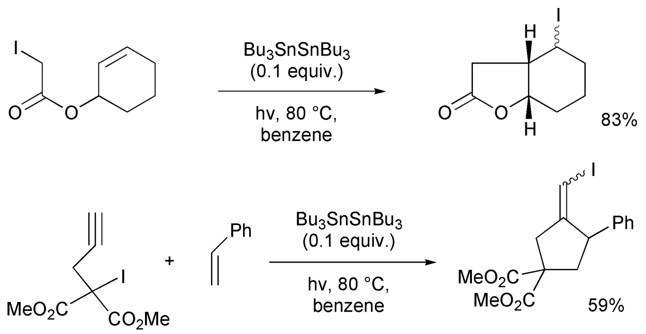
Scheme 7

from iodide **1**. In the process, another radical **3** is produced and the chain reaction continues. Hence, the requirement for only a small quantity (*i.e.* 0.1 equivalents) of hexabutylditin. This process is synthetically attractive because the reaction produces a cyclic compound, which contains a versatile vinyl iodide functional group.

The key to the success of this reaction lies in the rate of iodine-atom abstraction by vinyl radical **4** from primary iodide **1**. Fast cyclisation of **3** produces cyclic radical **4** and if the rate of iodine-atom abstraction by **4** had been slow, then this reactive vinyl radical would undergo other undesirable reactions. This could include hydrogen-atom abstraction from **1** or reaction of **4** with the solvent to give a number of products. Although the rate constants for these processes are not known they are expected to be similar to the corresponding phenyl radical reactions as both phenyl and vinyl radicals are sp^2 hybridised: the phenyl radical abstracts hydrogen atoms from alkanes/toluenes at rates of around 10^4–10^5 dm^3 mol^{-1} s^{-1} and adds to benzene with a rate constant of 4.5×10^5 dm^3 mol^{-1} s^{-1} at rt.[40]

In the cyclisation of **1** to **2**, these side reactions are not a major problem because the rate of iodine-atom abstraction by radical **4** is very fast and it is estimated to be $\geq 6 \times 10^8$ mol dm^{-3} s^{-1} at 30 °C. The iodine-atom transfer to radical **4** is irreversible because this produces a more stable primary radical (**3**) at the expense of a vinyl radical (**4**). In other words, a stronger C–I bond is formed in vinyl iodide **2** than that broken in alkyl iodide **1**. This is a fundamental requirement for these types of reactions and iodides are the precursors of choice because the weak C–I bond ensures high rates of iodine-atom abstraction.

Iodine-atom cyclisations can be used to form heterocycles, including bicyclic lactones,[41] while more challenging tandem (inter- followed by intra-molecular) radical sequences can be utilised to give substituted cyclopentanes in reasonable yields (Scheme 8).[42] There are three key features of the second example that deserve particular attention. (1) The use of iodomalonates in inter-/intra- sequences is found to work well because the C–I bond in the precursors is particularly weak (as the esters can mesomerically stabilise the radical that is formed) leading to high rates of iodine-atom abstraction. (2) The first-formed carbon-centred radical is electrophilic (as it is adjacent to two electron-withdrawing esters) and for intermolecular additions it is important that the polarity of the radical and alkene are matched (see Section 3.3); this ensures a relatively high rate of addition (k is typically 10^5–10^6 dm^3 mol^{-1} s^{-1}) and so these reactions involve addition to the less hindered end of electron-rich alkenes (*e.g.* styrene). (3) The 5-*exo* radical cyclisation is accelerated by the presence of two bulky ester groups in the side chain due to the Thorpe–Ingold effect (see Section 3.3).[43] Therefore, careful design of the precursors ensures sufficiently fast propagation rates ($\geq 10^5$ s^{-1} or dm^3 mol^{-1} s^{-1}) can be maintained resulting in an efficient radical transformation.



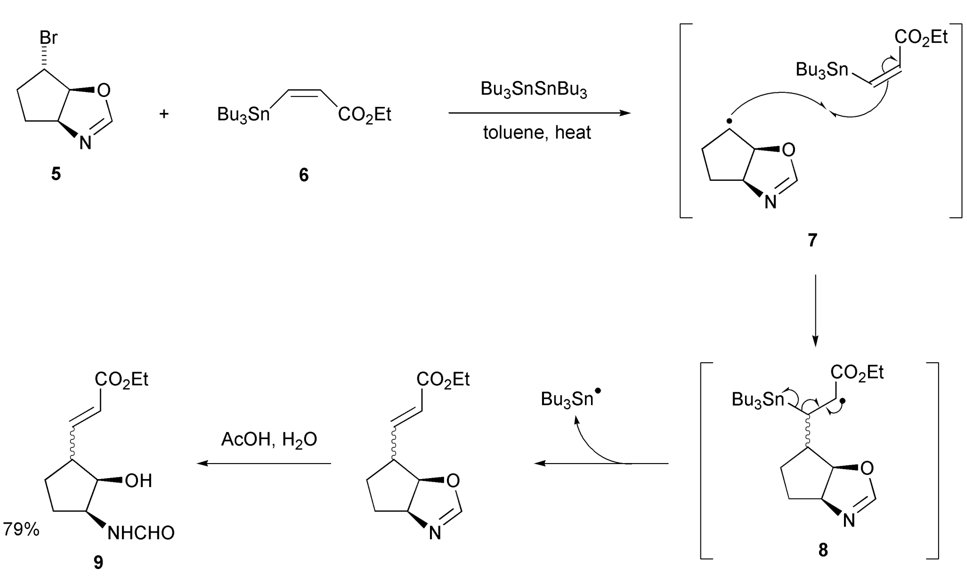
Scheme 8

Related transformations involve intermediate oxiranylmethyl radicals, which undergo epoxide fragmentation, radical translocation followed by iodine-atom transfer cyclisation.[44]

2.1.3.2 Chain reactions using allyl- and vinyl-stannanes

Hexabutylditin has also been employed as an initiator for radical reactions involving allyl- or vinyl-stannanes. Radical addition to the double bond of allyl- or vinyl-stannanes can produce radical adducts which are able to undergo β-elimination, and cleavage of the weak carbon–tin bond (~270 kJ mol^{-1}) leads to expulsion of the tri-*n*-butyltin radical (in an S_H2' reaction). This means that unsaturated stannanes have a built-in chain carrier, namely the tri-*n*-butyltin radical, and the reaction can be regarded as an auto-propagation system. From a synthetic perspective, these reactions are useful because they lead to the introduction of an allyl or vinyl group into a starting material.

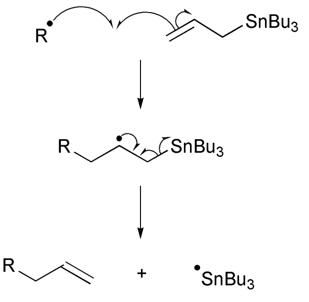
For example, thermolysis of secondary bromide **5** and vinylstannane **6** in the presence of hexabutylditin produces, after hydrolysis, the cyclopentane **9** (Scheme 9).[45] The nucleophilic cyclopentyl radical **7** (produced on bromine-atom abstraction by $^n Bu_3Sn^•$) adds to the electron-poor double bond of **6**, to generate radical **8**, which can undergo β-elimination to regenerate the tri-*n*-butyltin radical. It is important that the polarity of the alkene and radical are matched in these reactions to ensure a sufficiently fast rate of radical addition to the alkene double bond. This is particularly important in this case because the alkene is sterically hindered and radical attack (which can be retarded by large alkene substituents) needs to occur at the carbon atom bearing the bulky $^n Bu_3Sn$ group. Therefore, the introduction of an electron-withdrawing ester group on the



Scheme 9

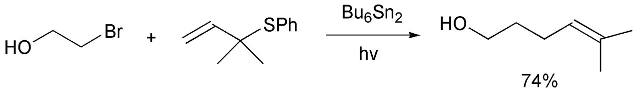
double bond accelerates the rate of addition of the nucleophilic cyclopentyl radical **7**.

For allylstannanes, steric hindrance is less of a problem as the alkene is mono-substituted and even nucleophilic alkyl radicals are able to add sufficiently rapidly ($k \approx 10^4$–10^5 dm^3 mol^{-1} s^{-1} at 50–80 °C)[46] to the electron-rich double bond to maintain a chain reaction (Scheme 10). It should be noted, however, that carbon-centred radicals (generated from AIBN or Et_3B–O_2) are now routinely used to initiate these types of reactions rather than tin-centred radicals.[47]



Scheme 10

Alternative S_H2' reactions can also be carried out using allylic sulfides or sulfones, which possess weak carbon–sulfur bonds (*e.g.* the C–S BDE in Me–SPh is ~240 kJ mol^{-1}).[48] Addition of $HOCH_2CH_2^•$ to the less hindered end of the double bond produces a radical adduct that can fragment to form thiyl ($PhS^•$) (Scheme 11) or sulfonyl ($PhSO_2^•$) radicals. It is interesting to note that the $PhS^•$ radical, but not the $PhSO_2^•$ radical, is stabilised by extensive delocalisation of the unpaired electron around the benzene ring.[49,50] The resulting sulfur-centred radicals can then react with hexabutylditin in an S_H2 reaction to form, for example, $^nBu_3Sn$–SPh and the chain carrying $^nBu_3Sn^•$ radical. In the process, a much stronger Sn–S bond is formed. It should be noted that for these reactions, carbon–carbon bond formation and generation of $^nBu_3Sn^•$ occur as discrete steps in the chain.

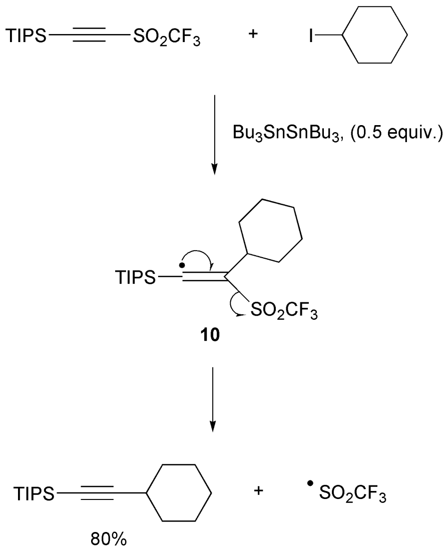


Scheme 11

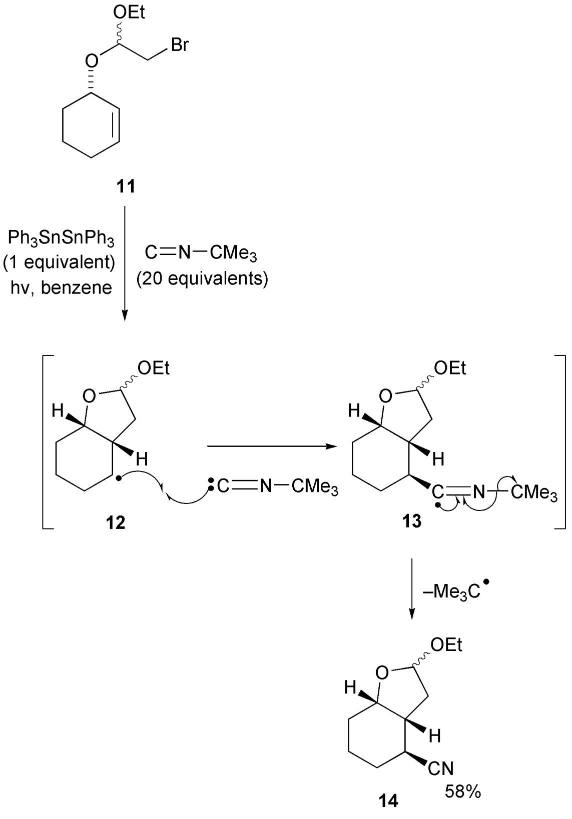
2.1.3.3 Non-chain reactions

Hexabutylditin has also found application as an initiator in non-chain free-radical reactions. For example, irradiation of iodocyclohexane with triisopropylsilylacetylenylsulfonyltrifluoromethane and hexabutylditin leads to a chemospecific alkynylation reaction (Scheme 12).[51] The cyclohexyl radical adds to the alkyne to generate an intermediate vinyl radical **10**, which undergoes β-elimination (which is faster than intermolecular iodine-atom transfer) to give the desired alkyne. Although carbon radicals usually add slowly to triple bonds the introduction of a strongly electron-withdrawing sulfonyl group is crucial for addition of the nucleophilic cyclohexyl radical.[52] This method then relies on β-elimination of the trifluoromethylsulfonyl radical ($^•SO_2CF_3$), which undergoes fragmentation to sulfur dioxide and the trifluoromethyl radical.[53] The trifluoromethyl radical does not efficiently abstract an iodine atom from iodocyclohexane [as this would form a weak (~235 kJ mol^{-1}) I–CF_3 bond] and so probably reacts with the solvent (benzene). As the cyclohexyl radical is not (efficiently) regenerated in this non-chain reaction, 0.5 equivalents of hexabutylditin are required to ensure the alkyne product is formed in good yield.

Organoditin compounds can also be used to initiate the addition of carbon radicals to other acceptors including alkyl nitrites[54] or isocyanides. For example, Stork and Sher have shown that photolysis of bromoacetal **11** and hexaphenylditin in the presence of excess *tert*-butylisocyanide produces the bicyclic nitrile **14** in 58% yield (Scheme 13).[55] Cyclisation of the first-formed carbon radical (k ~10^5 s^{-1}) is faster than reaction with the isocyanide and so bicyclic radical **12** is formed, which can then add to the isocyanide. The resulting imidoyl radical **13** then fragments to expel the *tert*-butyl radical, which presumably takes no further part in this (non-chain) reaction.

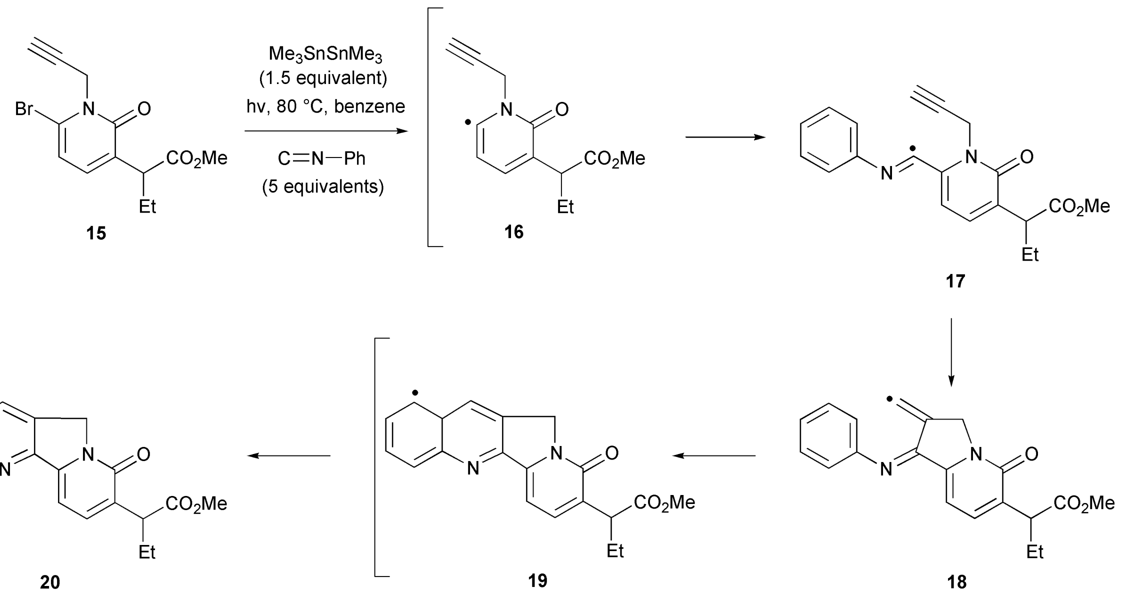


Scheme 12

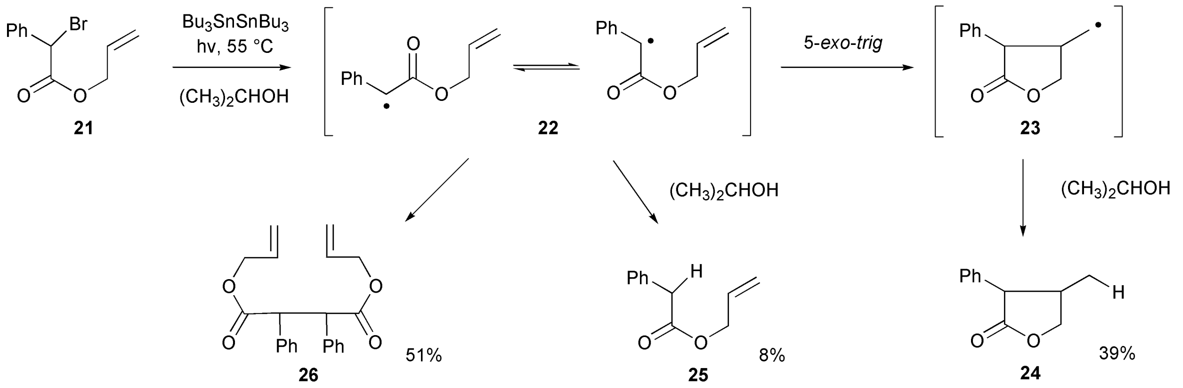


Scheme 13

Curran and others have extended this method to the preparation of the tetracyclic ring system of camptothecin and related natural products.[56] Photolysis of hexamethylditin in the presence of bromide **15** produces radical **16** which can add to phenylisocyanide to generate imidoyl radical **17** (Scheme 14). As a phenyl, rather than a *tert*-butyl group is present, radical **17** does not fragment but it adds to the alkyne to produce vinyl radical **18** which cyclises on to the aniline ring to generate



Scheme 14



Scheme 15

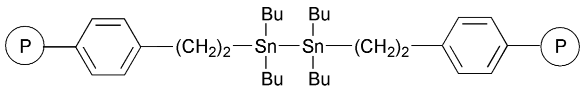
cyclohexadienyl radical **19**. Oxidative rearomatisation of **19** produces tetracycle **20** in 45% yield and although the mechanism of the rearomatisation is unclear, one equivalent of the hexamethylditin is required for the transformation and so a chain reaction is unlikely.[57]

Hexabutylditin-initiated radical reactions have also been carried out in the presence of hydrogen-atom donors including isopropanol, toluene or cyclohexa-1,4-diene which all have relatively weak C–H bond(s) ($\leq$380 kJ mol^{-1}).[58] Carbon-radical reactions typically involve cyclisations to form cyclic primary radicals that can abstract a hydrogen atom from these donors (*e.g.* the rate constant for reaction of the ethyl radical with cyclohexa-1,4-diene at rt is 5.8×10^4 dm^3 mol^{-1} s^{-1}).[59] These types of reaction can be strongly influenced by polar effects and, for example, electrophilic radicals react most readily with the most electron-rich double bonds in potential hydrogen-atom donors.

For example, irradiation of bromo-ester **21** and hexabutylditin in isopropanol at 55 °C produces butyrolactone **24** in 39% yield (Scheme 15).[60] Following 5-*exo-trig* cyclisation of **22**, the resulting cyclic primary radical **23** can abstract a hydrogen atom from isopropanol to form **24** and the $^{\bullet}CMe_2OH$ radical. This radical only slowly adds to electron-rich alkenes (*e.g.* the rate constant for addition to $H_2C{=}CH^tBu$ is only 1×10^3 dm^3 mol^{-1} s^{-1})[61] and so presumably undergoes combination and/or disproportionation reactions.[62,63]

The success of this reaction relies on a relatively fast hydrogen-atom transfer step from isopropanol to radical **23** and so the yield of **24** will depend on the concentration of the isopropanol: the greater the number of equivalents of isopropanol the faster the rate of hydrogen-atom transfer. However, the situation is complicated by the fact that the cyclisation of α-ester radicals is relatively slow (because of restricted rotation about the ester bond)[41,64] and so the first-formed radical **22** can also abstract a hydrogen atom from isopropanol to form the simple reduced compound **25** (in 8% yield). In addition, as acyclic radical **22** is more stable than cyclic radical **23**, the rate of hydrogen-atom abstraction from isopropanol is expected to be lower and so the main product from this reaction is diester **26**, which is produced from dimerisation of radical **22**.

Similar reactions can also be mediated using polymer-supported distannanes such as **27**.[65] The use of a polymer-supported reagent not only simplifies the reaction work-up but also leads to products with only low levels of toxic tin by-products (0.02 to 0.1 mol%).



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2.2 Dimanganese decacarbonyl [$Mn_2(CO)_{10}$] and related group 7 compounds

2.2.1 Radical generation and reaction

Dimanganese decarbonyl [$Mn_2(CO)_{10}$] consists of two $Mn(CO)_5$ units linked by a relatively weak manganese–manganese single bond (estimates in solution and the gas phase range from ~94–154 kJ mol^{-1}).[66] There are no bridging carbonyl groups and each manganese atom has octahedral coordination. Homolytic bond cleavage of the Mn–Mn bond can be achieved by heating or by photolysis.[67,68] In cyclohexane, $Mn_2(CO)_{10}$ has λ_{max} at 324 nm (ε = 21 400 dm^3 mol^{-1} cm^{-1}) and so visible light will lead to promotion of an electron from the σ to the σ* orbital of the Mn–Mn bond.[69] The excited state undergoes efficient homolysis of the Mn–Mn bond to form $^\bullet Mn(CO)_5$ (Scheme 16) although loss of carbon monoxide to form $Mn_2(CO)_9$ has also been observed.[66–68]

$$(OC)_5Mn{-}Mn(CO)_5 \longrightarrow (OC)_5Mn^\bullet + {}^\bullet Mn(CO)_5$$

Scheme 16

The manganese pentacarbonyl radical has been detected using EPR spectroscopy and spin-trapping techniques. Hence, irradiation of dimanganese decacarbonyl and the spin-trap nitrosodurene† (in THF at −30 °C) produces an 18-line EPR spectrum consistent with the formation of the adduct $ArN(O^\bullet)Mn(CO)_5$ derived from $^\bullet Mn(CO)_5$.[70] A variety of flash photolysis and pulse radiolysis experiments have also clearly established the formation of the manganese pentacarbonyl radical and estimated that the rate of recombination of this radical (to reform the dimer) is around 10^9 dm^3 mol^{-1} s^{-1}.[66–68,71] Photolysis of $Mn_2(CO)_{10}$ in the presence of phosphines, nitriles or amines has resulted in ligand exchange reactions. For example, photolysis in the presence of PPh_3 has led to $Mn_2(CO)_9PPh_3$ and $Mn_2(CO)_8(PPh_3)_2$, which are likely to be derived from radical combination reactions of the $^\bullet Mn(CO)_4PPh_3$ radical.

Once formed, the manganese pentacarbonyl radical can undergo hydrogen- or halogen-atom abstraction reactions (Scheme 17). For example, in the presence of hydrogen-atom donors including thiols and triethylsilane, the $^\bullet Mn(CO)_5$ radical abstracts a hydrogen atom to form pentacarbonylhydridomanganese [$H{-}Mn(CO)_5$].[72] The driving force for this reaction is the formation of a stronger H–Mn bond (~250–270 kJ mol^{-1})[73] at the expense of a much weaker Mn–Mn bond. Novel metal complexes, including $Bu_3Sn{-}Mn(CO)_5$ and $Et_3Si{-}Mn(CO)_5$ have been isolated from reactions with tributyltin hydride and triethylsilane although these are not necessarily formed by a radical mechanism.[74]

$$RS{-}H + {}^\bullet Mn(CO)_5 \longrightarrow RS^\bullet + H{-}Mn(CO)_5$$
$$R{-}X + {}^\bullet Mn(CO)_5 \longrightarrow R^\bullet + X{-}Mn(CO)_5$$

Scheme 17

The manganese pentacarbonyl radical abstracts halogen atoms from a variety of organohalides with weak carbon–halogen bonds (Scheme 17).[75] These reactions produce manganese complexes with stronger manganese–halogen bonds [*e.g.* the BDEs for $Cl{-}Mn(CO)_5$ and $Br{-}Mn(CO)_5$ are 294 and 242 kJ mol^{-1}, respectively][73] and, under some conditions, alkylmanganese complexes [*e.g.* $PhCH_2Mn(CO)_5$] have also been detected.[76] The weaker C–Br bond ensures that bromides react more rapidly than chlorides and reaction with CBr_4 approaches the diffusion-controlled limit (Table 5).

Similar abstractions take place with manganese radicals bearing ligands other than CO, although the electronic properties and particularly the size of the ligands (measured in terms of the cone angle) does affect the rate of the reactions (Table 6).[75] The introduction of bulky phosphine substituents weakens the Mn–Mn bond and the resulting manganese radicals will react more slowly in halogen-atom abstraction (and recombination) reactions due to steric hindrance.[76] Steric effects are also important for reactions involving $^\bullet Mn(CO)_5$. Hence, when using alkyl halides, primary carbon-centred radicals are generally easier to form than secondary radicals, while tertiary radicals are even more difficult to prepare and this usually requires iodide rather than bromide or chloride precursors.[77] This pattern of reactivity is in contrast to the order of stability of carbon radicals (3° > 2° > 1° > methyl) and the fact that tertiary carbon radicals are usually easier to prepare than primary radicals.

Table 5 Rate constants (k) for reaction of organohalides with $^\bullet Mn(CO)_5$ at 21 °C[75]

Compound	k/dm^3 mol^{-1} s^{-1}
$Br{-}CBr_3$	1.5×10^9
$Br{-}CHBr_3$	1.0×10^7
$Br{-}CH_2Ph$	4.8×10^5
$Br{-}CH_2Br$	7.0×10^3
$Cl{-}CCl_3$	1.4×10^6

Table 6 Rate constants (k) for reaction of CCl_4 with $^\bullet Mn(CO)_5$ and related radicals at 24 °C[75]

Radical	k/dm^3 mol^{-1} s^{-1}
$^\bullet Mn(CO)_5$	1.4×10^6
$^\bullet Mn(CO)_4P(i\text{-}Pr)_3$	2.8×10^4
$^\bullet Mn(CO)_4P(C_6H_{11})_3$	2.0×10^4
$^\bullet Mn(CO)_3[P(i\text{-}Pr)_3]_2$	1.0×10^3

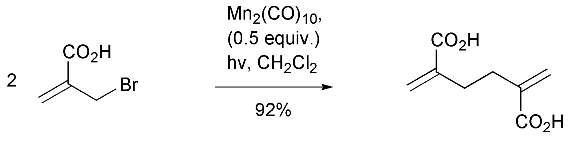
Some mononuclear manganese complexes can also form $^\bullet Mn(CO)_5$ on photolysis or thermolysis. For example, photolysis of pentacarbonylhydridomanganese [$H{-}Mn(CO)_5$] in a solid CO matrix at 10–20 K[78] or reaction of $H{-}Mn(CO)_5$ with carbon-centred radicals (including $Ar_3C^\bullet$) can produce $^\bullet Mn(CO)_5$.[79] Carbon–manganese bonds in benzyl- and acyl-manganese carbonyls can also be cleaved homolytically (although competitive loss of CO has also been observed). For example, photolysis of $PhCH_2{-}Mn(CO)_5$ has been shown to produce bibenzyl and dimanganese decacarbonyl, derived from radical combination reactions, while $Cl{-}Mn(CO)_5$ is formed on photolysis of $PhCH_2{-}Mn(CO)_5$ in the presence of CCl_4.[80]

The rhenium–rhenium bond in dirhenium decacarbonyl [$Re_2(CO)_{10}$] can also undergo homolysis to generate the rhenium pentacarbonyl radical [$^\bullet Re(CO)_5$].[81] Like $^\bullet Mn(CO)_5$, $^\bullet Re(CO)_5$ can rapidly recombine or abstract halogen atoms from alkyl halides and reaction with CCl_4, Ph_3CCl or $PhCH_2Cl$ produces carbon-centred radicals together with $Cl{-}Re(CO)_5$. The Re–Re bond (~213 kJ mol^{-1}) is stronger than the Mn–Mn bond and $^\bullet Re(CO)_5$ tends to be more reactive than $^\bullet Mn(CO)_5$.[82] For example, $^\bullet Re(CO)_5$ abstracts a chlorine atom from CCl_4 over 60 times faster (in ethanol at rt) than does $^\bullet Mn(CO)_5$ (*i.e.* with rate constants of 3.9×10^7 *versus* 6.1×10^5 dm^3 mol^{-1} s^{-1}).[83]

2.2.2 Applications in synthesis

2.2.2.1 Couplings

Dimanganese decacarbonyl has found application in the coupling of allylic and benzylic bromides (Scheme 18).[84,85]



Scheme 18

These reactions involve the efficient generation and coupling of carbon-centred radicals produced on bromine-atom abstraction by the manganese pentacarbonyl radical. High concentrations of the carbon-centred radicals are produced which ensures efficient coupling reactions leading to generally good-to-excellent yields of homo- or cross-coupled products. The by-product $BrMn(CO)_5$ is also easily removed using a DBU work-up procedure followed by column chromatography.

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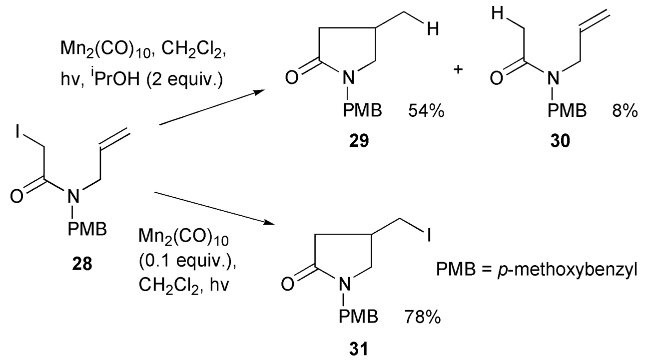
† The IUPAC name for durene is 1,2,4,5-tetramethylbenzene.

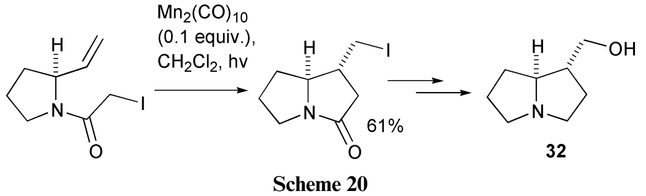
2.2.2.2 Reductions and atom-transfer cyclisations

The intermediate carbon-centred radicals produced from halogen-atom abstractions can undergo hydrogen-atom abstractions when photolyses are carried out in the presence of compounds with particularly weak C–H bonds.[86] For example, trichlorinated alkanes ($\mathrm{RCCl_3}$) can be selectively reduced to dichlorinated products ($\mathrm{RCHCl_2}$) on photolysis with dimanganese decacarbonyl in the presence of isopropanol (which acts as a hydrogen-atom donor).

Radical cyclisation reactions have also been carried out in the presence of hydrogen-atom donors (Scheme 19).[77,87] Photolysis of iodide **28** with dimanganese decacarbonyl in the presence of isopropanol affords pyrrolidinone **29** in 54% yield together with the simple reduced compound **30** in 8% yield. The first-formed carbamoylmethyl radical can undergo cyclisation onto the allyl double bond (the rate constant for this type of cyclisation is around 0.5–1.0 × 10^6 $\mathrm{s^{-1}}$ at rt)[88] to give a primary radical, which can abstract a hydrogen atom from isopropanol (see Scheme 15 for a related reaction). Simple reduction to form amide **30** is in competition with the cyclisation and so the ratio of **29** : **30** depends on the number of equivalents and rate of addition of the isopropanol. Under some conditions, iodine-atom transfer cyclisation is observed and for example, the chain reaction of iodide **28** with 0.1 equivalents of dimanganese decacarbonyl affords primary iodide **31** in 78% yield. This type of reaction has been used as the key step in an enantioselective synthesis of the pyrrolizidine alkaloid (−)-trachelanthramidine **32** (Scheme 20).[89] The iodine-atom transfer cyclisation proceeds in 61% yield, which compares to a yield of 58% when using hexabutylditin.[90]

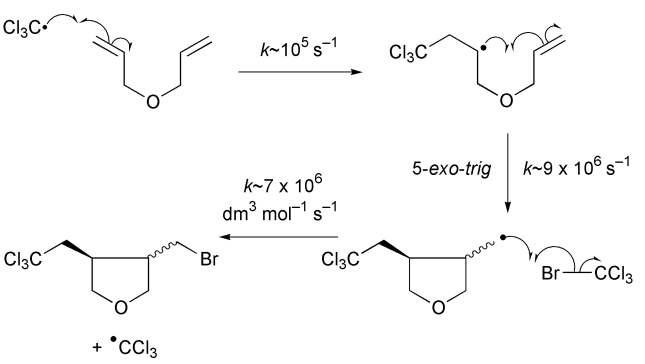


Scheme 19



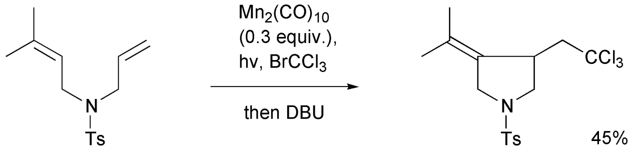
Scheme 20

Related bromine-atom transfer reactions can also be carried out using bromotrichloromethane and 1,6-dienes in the presence of 0.1 equivalents of dimanganese decacarbonyl (Scheme 21).[77] Bromine-atom abstraction by the manganese pentacarbonyl radical generates the electrophilic trichloromethyl radical on cleavage of the weak Br–C bond (~234 kJ $\mathrm{mol^{-1}}$) in $\mathrm{BrCCl_3}$. The $^\bullet\mathrm{CCl_3}$ radical adds to the least-hindered end of one of the electron–rich double bonds (the rate constant for addition of $^\bullet\mathrm{CCl_3}$ to alkenes, including styrene and methyl acrylate is ~10^4–10^5 $\mathrm{dm^3\ mol^{-1}\ s^{-1}}$ at rt).[91] Following 5-*exo* cyclisation, the resultant cyclic primary radical can abstract a bromine atom from $\mathrm{BrCCl_3}$ to produce the cyclic halide and $^\bullet\mathrm{CCl_3}$ (with a rate constant of ~10^6 $\mathrm{dm^3\ mol^{-1}\ s^{-1}}$ at rt),[92] which continues the chain reaction. The rate of cyclisation is sufficiently fast (~9 × 10^6 $\mathrm{s^{-1}}$)[93] that premature bromine-atom abstraction by the first-formed secondary carbon radical does not compete. Cyclisation of unsymmetrical dienes is also possible to give products derived from addition of $^\bullet\mathrm{CCl_3}$ to the less-hindered double bond. On basic (DBU) work-up, elimination of HBr can lead to cyclic products bearing an unsaturated side chain (Scheme 22).[89]



Absolute rate constants are at r.t.

Scheme 21

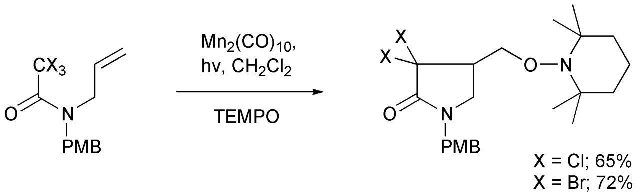


Scheme 22

It should also be noted that $\mathrm{Mn_2(CO)_{10}}$ has been used as an initiator for free-radical polymerisation. Bamford demonstrated that photolysis of methyl methacrylate and $\mathrm{Mn_2(CO)_{10}}$ in the presence of $\mathrm{CCl_4}$ leads to efficient polymerisation.[94] Alternative organohalides (*e.g.* alkyl bromides and iodides) can also be used[95] and recently, Yagci and Hepuzer have found that $\mathrm{Mn_2(CO)_{10}}$ in combination with onium salts is an effective initiator for cationic polymerisation reactions.[96]

2.2.2.3 TEMPO reactions

Dimanganese decacarbonyl-mediated cyclisations can also be carried out in the presence of the long-lived aminoxyl TEMPO (Scheme 23).[77,87] This has proved to be an effective method for forming cyclic hydroxylamines from haloamides; cyclisation of carbamoylmethyl radicals can produce pyrrolidinones derived from trapping of the intermediate cyclic primary radical with TEMPO. TEMPO reacts rapidly with most carbon-centred radicals and the rate of trapping of the intermediate primary carbon radical is expected to be around 1 × 10^9 $\mathrm{dm^3\ mol^{-1}\ s^{-1}}$ at rt.[97,98] Slow addition of the TEMPO ensures that the cyclisation occurs prior to TEMPO trapping, while the introduction of halogen substituents is expected to lower the rate of trapping of the first-formed carbamoylmethyl radical by TEMPO on steric and/or thermodynamic grounds (the rate constant for reaction of the *tert*-butyl radical with TEMPO is 7.6 × 10^8 $\mathrm{dm^3\ mol^{-1}\ s^{-1}}$ at rt).[98]



Scheme 23

3 Metal–hydrogen and non-metal–hydrogen initiators

Metal-centred radicals, generated from a range of metal dimers, can react with organohalides (and related compounds) to

Table 7 Absolute rate constants (k) for reaction of group 14 hydrides with the *tert*-butoxyl radical (^{t}BuO$^•$) at rt[11,113]

Metal hydride	k/dm^3 mol^{-1} s^{-1}
H–SnPh$_3$	4.3×10^8
H–SnBu$_3$	1.9×10^8
H–Si(SiMe$_3$)$_3$	1.1×10^8
H–GeBu$_3$	9.2×10^7
H–GePh$_3$	9.2×10^7
H–Si(SMe)$_3$	4.4×10^7
H–SiPh$_3$	1.1×10^7
H–SiEt$_3$	5.7×10^6

Table 8 Absolute rate constants (k) for reaction of carbon-centred radicals with tributyltin hydride (^{n}Bu$_3$SnH)[11,100,117,118]

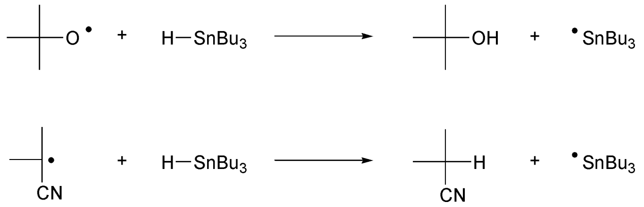
Carbon-centred radical	k/dm^3 mol^{-1} s^{-1}	Temperature/°C
$^•$Ph	5.9×10^8	25
$^•$CH=C(CH$_3$)$_2$	3.5×10^8	30
$^•$CH$_2$CH$_2$CH$_2$CH$_3$	2.5×10^6	27
$^•$CH$_2$CH$_3$	2.3×10^6	27
$^•$C(CH$_3$)$_3$	1.7×10^6	30
$^•$CH(CH$_3$)$_2$	1.5×10^6	27
$^•$CH$_2$Ph	3.6×10^4	25
$^•$CH(CH$_3$)Ph	1.1×10^4	25

produce carbon-centred radicals. These radicals can also readily be generated using radical reagents bearing metal–hydrogen or non-metal bonds. In these reactions, the carbon-centred radicals can abstract a hydrogen atom from the metal or non-metal reagent to continue the chain reaction: the net effect is reduction. Mercury hydrides (RHgH),[99] which possess an extremely weak Hg–H bond (~60 kJ mol^{-1}), have proved useful in this respect but their high toxicities have limited their widespread use and, at present, the most important reagents are group 14 hydrides and particularly tri-*n*-butyltin hydride.[100,101]

3.1 Tributyltin hydride (Bu$_3$SnH) and related group 14 hydrides

3.1.1 Radical generation

The tri-*n*-butyltin radical (^{n}Bu$_3$Sn$^•$) can easily be prepared, photochemically or thermally, from reaction of ^{n}Bu$_3$SnH with peroxides or azo compounds (Scheme 24): the resulting carbon- or oxygen-centred radicals react rapidly with ^{n}Bu$_3$SnH to break the weak Sn–H bond (~310 kJ mol^{-1}).[11] For example, thermolysis of AIBN produces $^•$CMe$_2$CN, which abstracts the hydrogen atom from ^{n}Bu$_3$SnH with a rate constant of ~10^6 dm^3 mol^{-1} s^{-1}.[102] As the Sn–H bond is much weaker than C–H bonds, $^•$CMe$_2$CN selectively abstracts a hydrogen atom from ^{n}Bu$_3$SnH in the presence of a variety of organic compounds. When using peroxides, the reactive alkoxyl radicals (RO$^•$) tend to react less discriminately than $^•$CMe$_2$CN and so even though the rate of hydrogen-atom abstraction from Sn–H compounds is fast (2.0×10^8 dm^3 mol^{-1} s^{-1} at 25 °C)[103] hydrogen-atom abstraction from organic compounds (to make an O–H bond at the expense of a weaker C–H bond) can be a problem. In comparison, hydrogen-atom abstraction by peroxyl radicals (ROO$^•$) is much slower (~10^3 dm^3 mol^{-1} s^{-1} at 55 °C).[104,105] Ethyl radicals, generated from Et$_3$B–O$_2$, can also be used to prepare ^{n}Bu$_3$Sn$^•$ at room temperature or below (even down to −78 °C)[106–108] as can diethylzinc–air[109] or 9-borabicyclo[3.3.1]nonane.[110] Similar reactions occur with other organotin hydrides including Me$_3$SnH[111] and Ph$_3$SnH and the alkyl/aryl substituents have only a small effect on the rate constant of hydrogen-atom abstraction.



Scheme 24

Silicon and germanium hydrides undergo related hydrogen-atom transfer reactions (Table 7). The stronger Ge–H bond (~370 kJ mol^{-1} for ^{n}Bu$_3$GeH) and particularly the Si–H bond (~398 kJ mol^{-1} for Et$_3$SiH) ensure that these reactions proceed at lower rates than the corresponding tin hydride reactions.[112] The introduction of bulky substituents can, however, weaken the Ge–H and Si–H bonds and the rate constants for hydrogen-atom abstraction by ^{t}BuO$^•$ decrease in the order: Ph$_3$SiH > Ph$_2$Si(H)Me > PhSi(H)Me$_2$ > Me$_3$SiH, and Ph$_3$SiH > Ph$_2$SiH$_2$ > PhSiH$_3$.[112] An exceptional case is tris(trimethylsilyl)silane for which hydrogen-atom abstraction is accelerated by the presence of trimethylsilyl groups on the silicon atom, and the rate constant for reaction with ^{t}BuO$^•$ is 1.1×10^8 dm^3 mol^{-1} s^{-1} (at rt).[113,114] The Si–H bond strength in this compound is only ~351 kJ mol^{-1} and the stability of the (Me$_3$Si)$_3$Si$^•$ radical has been mainly attributed to through-space (hyperconjugation) interaction between the bonding and/or antibonding β-Si–C bonds.[115] It should also be noted that the introduction of alkylthio substituents can weaken the Si–H bond.[116] For example, the strength of the Si–H bond in (MeS)$_3$SiH is predicted to be ~345 kJ mol^{-1} and the rate constant for hydrogen-atom abstraction by the ^{t}BuO$^•$ radical has been determined as 4.4×10^7 dm^3 mol^{-1} s^{-1} at 27 °C. The introduction of these electron-withdrawing substituents also affects the polarity of the silicon-centred radical (*i.e.* making the radical more electrophilic), which can influence the rate of subsequent propagation reactions.

3.1.2 Radical reactions

Tri-*n*-butyltin hydride and related compounds readily act as hydrogen-atom donors in free-radical reactions: the weak Sn–H bond ensures that a tremendous variety of carbon-centred radicals can abstract a hydrogen atom from Bu$_3$SnH to produce Bu$_3$Sn$^•$, which can continue the chain reaction (see, for example, Table 8).[11,100,117,118] The rate constants for these reactions depend on the nature of the carbon-centred radical; reactive aryl and vinyl radicals abstract a hydrogen atom around 10^4 times more rapidly than the stabilised benzyl radical. Similar reactions can also be carried out using tributyltin deuteride and this represents an important method for introducing deuterium into organic compounds.

Reactions of related germanium and silicon hydrides with carbon-centred radicals are usually slower than for tin hydrides because of the increased strength of the Ge–H[117] and Si–H[119] bonds (Table 9). However, the introduction of three bulky trimethylsilyl groups in tris(trimethylsilyl)silane sufficiently weakens the Si–H bond so that it is only marginally stronger than the Sn–H bond in tri-*n*-butyltin hydride. The rate of hydrogen-atom transfer to alkyl halides using this reagent is therefore only around 10 times slower than that for tri-*n*-butyltin hydride.[120] Silicon hydrides bearing alternative (bulky) substituents have also been investigated including 9,10-dihydro-9,10-disilaanthracenes,[121,122] diphenylsilanes,[123–126] tetraaryldisilanes (Ar$_4$Si$_2$H$_2$)[127] and tris(alkylthio)silanes.[128,129] For example, 9,10-dihydro-9,10-silaanthracene reacts with primary carbon radicals at similar rates to tris(trimethylsilyl)silane (*i.e.* 2.1×10^6 dm^3 mol^{-1} s^{-1} at 80 °C).[130]

Bulky substituents have also been shown to weaken the Ge–H bond and facilitate hydrogen-atom abstraction reactions. For example, primary alkyl radicals abstract the hydrogen atom from Ph$_3$GeH (3.8×10^6 dm^3 mol^{-1} s^{-1}) around 10 times faster than from ^{n}Bu$_3$GeH (3.8×10^5 dm^3 mol^{-1} s^{-1}) at 80 °C.[131] The Ge–H bond in tris(trimethylsilyl)germane is even weaker than that in Ph$_3$GeH and the rate of hydrogen abstraction from (Me$_3$Si)$_3$GeH by a primary carbon radical is even faster than

Table 9 Rate constants (k) for reaction of carbon-centred radicals with group 14 hydrides. The reaction temperature is given in brackets[117–120]

	k/dm^3 mol^{-1} s^{-1}			
Carbon-centred radical	^{n}Bu$_3$SnH	^{n}Bu$_3$GeH	Et$_3$SiH	(Me$_3$Si)$_3$SiH
Ph	5.9×10^8 (30)	2.6×10^8 (29)	—	~1.9×10^8 (r.t.)
Primary	2.3×10^6 (25)	1.0×10^5 (27)	7.0×10^2 (25)	3.7×10^5 (25)
Secondary	1.5×10^6 (25)	1.8×10^4 (25)	—	1.4×10^5 (25)
Tertiary	1.8×10^6 (25)	2.0×10^4 (25)	3.0×10^3 (50)	2.6×10^5 (25)

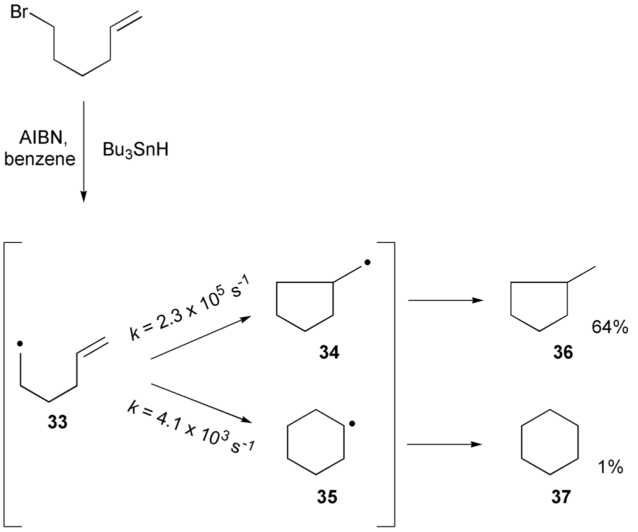
that from ^{n}tributyltin hydride (*i.e.* 1.5×10^7 dm^3 mol^{-1} s^{-1} at 80 °C).[131,132] Trifuran-2-ylgermane[133] has also been employed in radical reduction reactions while bulky thio substituents have been introduced to form chiral germanium hydrides.[134]

3.1.3 Applications in synthesis

It is not possible to review exhaustively the tremendous number of radical transformations, particularly cyclisations,[135] which have been mediated using tri-*n*-butyltin hydride. Instead, some important types of reaction will be discussed in detail so as to illustrate a number of important points which need to be considered when using tri-*n*-butyltin hydride, or related group 14 hydrides, to effect efficient carbon–carbon bond formation.

3.1.3.1 Cyclisations

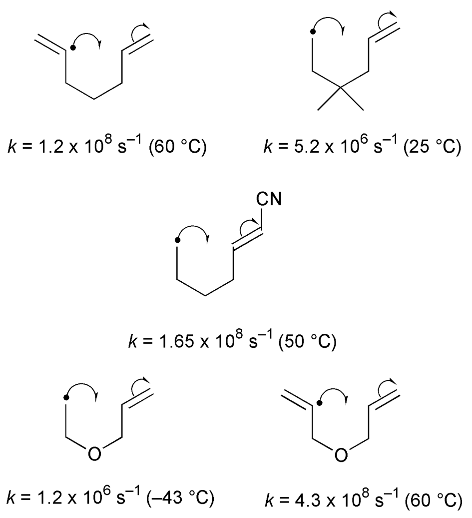
Probably the most popular and useful transformation mediated by tri-*n*-butyltin hydride is the radical cyclisation of unsaturated halides (and related compounds) to form, particularly, 5- and 6-membered rings. For example, the cyclisation of the hex-5-en-1-yl radical **33** is irreversible and forms the primary radical **34**, derived from 5-*exo* cyclisation, in preference to the thermodynamically more stable secondary radical **35** (Scheme 25). In both cases, the reaction leads to the formation of a C–C σ-bond at the expense of a much weaker C=C π-bond. At 25 °C, the rate of 5-*exo* cyclisation is 2.3×10^5 s^{-1} compared to a much slower rate of 4.1×10^3 s^{-1} for 6-*endo* cyclisation.[136] The preference for 5-*exo* cyclisation has been explained on the basis of stereoelectronic effects favouring a chair-like transition state (which is sometimes known as the "Beckwith model"). Following cyclisation, the cyclic radicals **34** and **35** abstract a hydrogen atom from ^{n}Bu$_3$SnH (at approximately the same rate) to form cycloalkanes **36** and **37**, respectively, together with ^{n}Bu$_3$Sn$^\bullet$ which re-enters the chain reaction. The major process in competition with cyclisation of radical **33** is reaction with ^{n}Bu$_3$SnH to form hex-1-ene, which is generally known as the product of "simple" or "direct" reduction. The rate constant for this reaction is around 10^6 dm^3 mol^{-1} s^{-1} at 25 °C. As the rate of simple radical reduction depends on the concentration of ^{n}Bu$_3$SnH, the formation of the by-product (hex-1-ene) would be a significant problem if ^{n}Bu$_3$SnH was added to the starting organohalide in one portion. In other words, as the rate of cyclisation is 2×10^5 s^{-1}, the concentration of ^{n}Bu$_3$SnH must be less than 10^{-2} mol dm^3 in order to minimise the rate of simple reduction (which is equal to $10^6 \times$ [Bu$_3$SnH]). However, the yield of hex-1-ene can be minimised by slow addition of ^{n}Bu$_3$SnH (often known as the syringe-pump technique), which increases the lifetime of radical **33** allowing more time for cyclisation (which does not depend on the ^{n}Bu$_3$SnH concentration). Other competitive processes include addition of the tin radical to the double bond, although this is a not a major problem because, unlike halogen-atom abstraction, this is reversible and so rapid fragmentation can regenerate the tin radical and alkene (see Scheme 6). Radical coupling reactions can also be minimised by using a low concentration of reactants (typically 10^{-7}–10^{-8} mol dm^{-3}) in a (non-halogenated) solvent such as benzene, toluene or cyclohexane.



Scheme 25

As ^{n}Bu$_3$GeH is a slightly less reactive hydrogen-atom donor than ^{n}Bu$_3$SnH, competitive simple reduction to form hex-1-ene is less of a problem. The rate constant of the reaction of ^{n}Bu$_3$GeH with radical **33** at 23 °C has been found to be 9.3×10^4 dm^3 mol^{-1} s^{-1},[120,137] which is around 20 times slower than for the corresponding ^{n}Bu$_3$SnH reaction. Simple reduction is also less of a problem when using silanes and reaction of radical **33** with (Me$_3$Si)$_3$SiH proceeds with a rate constant of 3.82×10^5 dm^3 mol^{-1} s^{-1} at 25 °C.[120] The same reaction using the deuteriosilane, (Me$_3$Si)$_3$SiD, has a similar rate constant of 5.87×10^5 dm^3 mol^{-1} s^{-1} at 90 °C.[78] The slower rate of hydrogen-atom donation when using silanes is a distinct advantage over tin hydrides and syringe-pump techniques are usually unnecessary for even "slow" radical cyclisation reactions. However, on the downside, some silicon-centred radicals, unlike tin-centred radicals, can add irreversibly to alkenes. So if the rate of addition of the silicon-centred radical to the alkene (Table 4) is faster or similar to the rate of halogen-atom abstraction (Table 3), then this can lead to undesired (hydrosilylated) products.

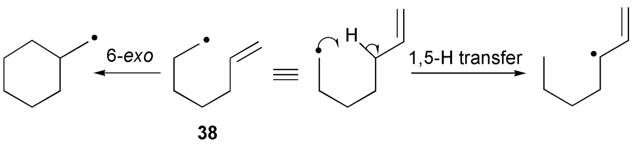
Radical cyclisation mediated by ^{n}Bu$_3$SnH (and related hydrides) has proved to be a very flexible method for making both 5-membered carbacycles and heterocycles. The rate of 5-*exo* radical cyclisation (and hence the yield of cyclised product) can be increased by either: (1) using vinyl/aryl radical precursors; (2) introducing alkyl groups, particularly geminal dialkyl groups, within the carbon chain; (3) introducing an oxygen or nitrogen atom within the carbon chain; or (4) placing an electron-withdrawing group on the acceptor bond. These effects are illustrated in Scheme 26. The high reactivity of sp^2-hybridised vinyl and aryl radicals ensures particularly rapid C–C bond formation (~10^8–10^9 dm^3 mol^{-1} s^{-1})[138,139] whilst the introduction of alkyl groups or a heteroatom affects the bond angles and/or lengths of the chain: this leads to the radical being closer to the alkene carbon atom in the 5-*exo* (chair-like) transition-state resulting in faster cyclisation (1.2×10^6 dm^3 mol^{-1} s^{-1} at −43 °C).[140,141] The fact that an electron-withdrawing nitrile group can increase the rate of cyclisation (1.65×10^8 dm^3 mol^{-1} s^{-1} at 50 °C)[142] can be explained on the basis of polarity; the high-energy SOMO of the nucleophilic alkyl radical can interact more effectively with the LUMO orbital of the electron-poor double bond.[1] It should also be



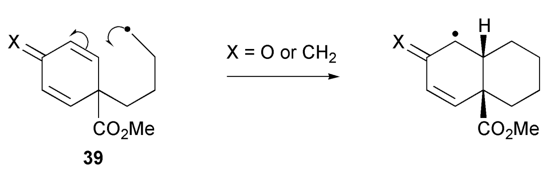
Scheme 26

noted that the introduction of a nitrile group leads to the formation of cyclic secondary radical which is mesomerically stabilised by the nitrile triple bond. However, tri-*n*-butyltin hydride is such an efficient hydrogen-atom donor that the introduction of a nitrile group does not significantly reduce the rate constant of hydrogen-atom donation (~10^5 dm^3 mol^{-1} s^{-1})[143] and so the chain reaction can be continued. For these types of reactions slow addition of tri-*n*-butyltin hydride is often not required because of the particularly rapid rates of cyclisation.

Similar ^{n}Bu$_3$SnH reactions take place using 1-halohept-6-ene precursors to form 6-membered rings. Unfortunately, the rate of 6-*exo* cyclisation is around 40 times slower[144] than 5-*exo* cyclisation and so simple reduction of the hept-6-en-1-yl radical **38** is more problematic (Scheme 27). In addition, the hept-6-en-1-yl radical **38** can undergo a competitive 1,5-hydrogen-atom abstraction to form a more stable (resonance-stabilised) allylic radical.[145] Therefore, for efficient 6-membered ring formation heteroatoms or alkyl groups can be introduced into the chain or electron-withdrawing substituents positioned onto the acceptor double bond, and slow addition of tri-*n*-butyltin hydride is desirable. For example, the presence of a ketone substituent (X = O) in cyclohexadiene **39** increases the rate constant for radical cyclisation from 5.8 × 10^3 s^{-1} (for X = H$_2$) to 2.5 × 10^6 s^{-1} at 70 °C (Scheme 28).[144] This strategy can also be used effectively in the formation of cyclobutanes,[146] large rings (11–14 membered)[147] and even medium-sized rings.[148]



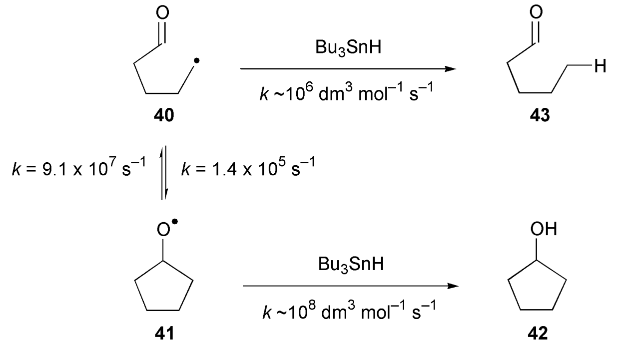
Scheme 27



Scheme 28

Tin hydride-mediated cyclisation using alternative precursors to alkenes including alkynes, nitriles, imines, oximes and hydrazones is also possible. Whereas radical cyclisation onto alkynes and nitriles[149] is slightly slower than for alkenes (*e.g.* 5-*exo* cyclisation of the hex-5-yn-1-yl radical occurs with a rate constant of 2.8 × 10^4 s^{-1} at 25 °C),[136] imines and related compounds usually undergo faster cyclisation (~10^6–10^8 s^{-1} for 5-*exo* cyclisation and 10^5–10^6 s^{-1} for 6-*exo* cyclisation).[150] This trend largely reflects the stability of the cyclic radicals produced, as indicated by the order of C–H and N–H bond dissociation energies.

Radical cyclisation onto carbonyls is reversible and the intermediate cyclic alkoxyl radical **41** can fragment to regenerate the initial carbon-centred radical **40** (Scheme 29). The rate of fragmentation (k = 9.1 × 10^7 s^{-1} at 25 °C) is higher than 5-*exo* cyclisation (1.4 × 10^5 s^{-1} at 25 °C) and yet reaction with tri-*n*-butyltin hydride can afford cyclopentanol **42** as well as pentanal **43** (the simple reduced product).[151] This is because the rate constant for reaction of the alkoxyl radical **41** with tri-*n*-butyltin hydride (~10^8 dm^3 mol^{-1} s^{-1} at 25 °C) is around 100 times faster than the corresponding reaction of carbon radical **40** (~10^6 dm^3 mol^{-1} s^{-1} at 25 °C). The electrophilic alkoxyl radical is able to abstract a hydrogen atom much more quickly from tri-*n*-butyltin hydride than the nucleophilic alkyl radical, so as to make a stronger O–H rather than C–H bond.

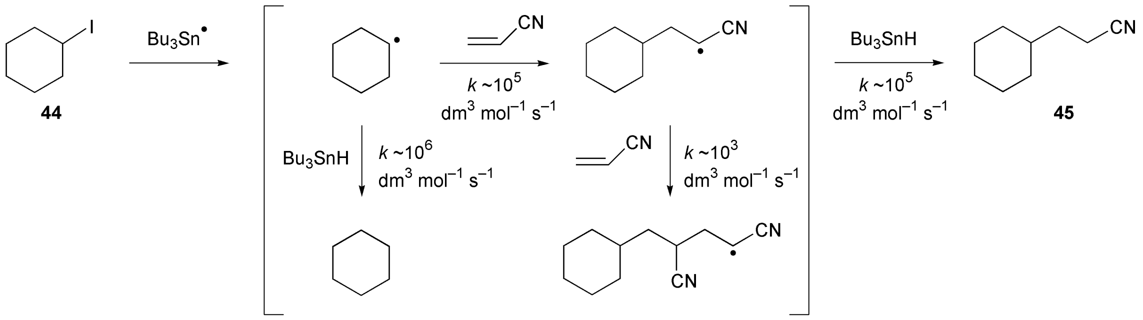


Scheme 29

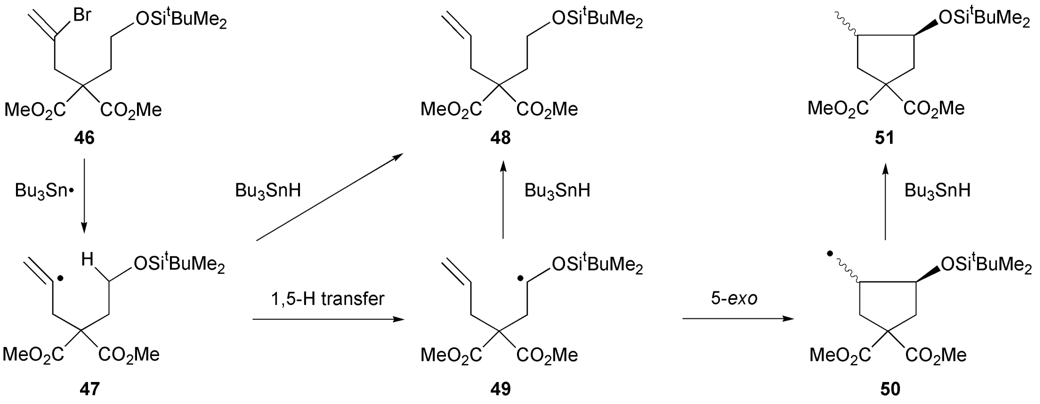
3.1.3.2 Intermolecular additions

Intermolecular radical additions mediated by ^{n}Bu$_3$SnH, to make a range of carbon–carbon bonds, commonly involve addition of carbon-centred radicals to alkenes to form stronger C–C σ-bonds at the expense of C=C π-bonds.[152] Unfortunately, these reactions are more difficult to conduct than comparable cyclisations because of entropic factors, and reactions mediated by tri-*n*-butyltin hydride can be plagued by simple reduction of the alkyl halide. Alternatively, if the rate of hydrogen-atom donation is too low, then alkene polymerisation can occur. For efficient radical addition, the polarity of the radical and alkene should be matched; nucleophilic radicals add faster to electron-poor double bonds because of a more efficient SOMO–LUMO interaction while electrophilic radicals add faster to electron-rich alkenes because of a more efficient SOMO–HOMO interaction. This explains why the *tert*-butyl radical adds to the double bond of acrolein (k = 2.8 × 10^6 dm^3 mol^{-1} s^{-1}) over 3000 times faster than to propene (0.92 × 10^3 dm^3 mol^{-1} s^{-1}) at room temperature.[152] The size of the alkene substituent is also important as this governs both the regioselectivity of the addition and the rate at which the radical will add; the greater the number of bulky substituents, the slower the rate of radical addition. In general, radical addition rates of around 10^5–10^6 dm^3 mol^{-1} s^{-1} are required for successful carbon–carbon bond formation using tin hydrides. In some cases, the size of the substituents may also influence the stereoselectivity of a radical addition reaction. Most reactions of Bu$_3$SnH with a prochiral (planar) carbon-centred radical lead to hydrogen-atom transfer to both faces of the radical in equal amounts. However, steric effects can lead to stereoselectivity (*i.e.* preference for attack from one face of the radical), particularly when using cyclic radicals or carrying out acyclic radical reactions at low temperature (to slow down the rate of bond rotation).

Pioneering work by Giese *et al.*[153] showed, for example, that the rate of addition of the cyclohexyl radical to a range of substituted alkenes, depends on the electronic properties of the



Scheme 30



Scheme 31

substituent; in general, the more electron-withdrawing the substituent(s) the greater the rate of addition. This explains the efficient (95% yield) formation of nitrile **45** from reaction of cyclohexyl iodide **44** and acrylonitrile in the presence of Bu_3SnCl (0.2 equiv.)–$NaBH_4$ (Scheme 30).[154] The use of only 0.2 equivalents of Bu_3SnCl ensures a low concentration of Bu_3SnH is generated (from reduction[155] using $NaBH_4$), which in turn, minimises the amount of simple reduction leading to cyclohexane (which has a rate constant of around 10^6 dm^3 mol^{-1} s^{-1} at rt). Hence, radical addition to the double bond ($k \approx 10^5$ dm^3 mol^{-1} s^{-1} at rt) occurs followed by hydrogen-atom abstraction (~10^5 dm^3 mol^{-1} s^{-1} at rt) in preference to slower radical addition to another molecule of the alkene (~10^3 dm^3 mol^{-1} s^{-1} at rt) leading to a polymer.[143] The same reaction using tris(trimethylsilyl)silane–AIBN (added over 2 h at 80 °C) afforded **45** in a comparable yield (90%).[22] It should also be noted that $^{\bullet}CMe_2CN$ (derived from AIBN) prefers to abstract the hydrogen atom from $(Me_3Si)_3SiH$ or Bu_3SnH rather than add to the acrylonitrile double bond (2×10^3 dm^3 mol^{-1} s^{-1} at 42 °C).[156]

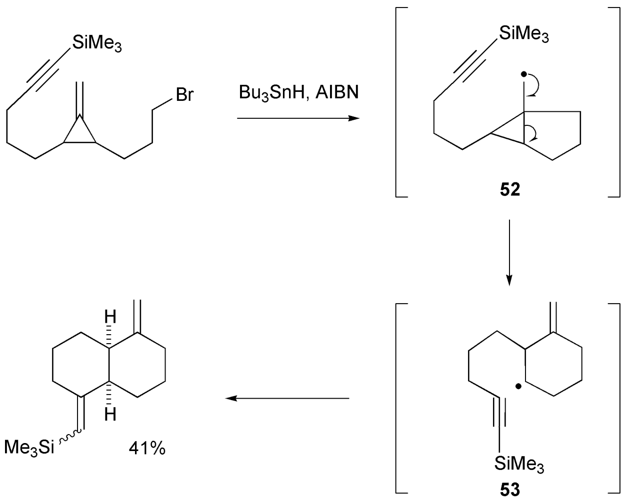
As for intramolecular reactions, intermolecular radical addition to alkynes is slower than that for alkenes; this reflects the fact that vinyl radicals are less stable than alkyl radicals. Hence the *tert*-butyl radical adds to the double bond of methyl acrylate ($k = 1 \times 10^6$ dm^3 mol^{-1} s^{-1} at 26 °C) around 5.5 times faster than to the triple bond of methyl propiolate (1.8×10^5 dm^3 mol^{-1} s^{-1} at 24 °C).[157] Simple reduction of the organic halide is, therefore, even more of a problem using tin hydride or related compounds.

3.1.3.3 Radical rearrangements

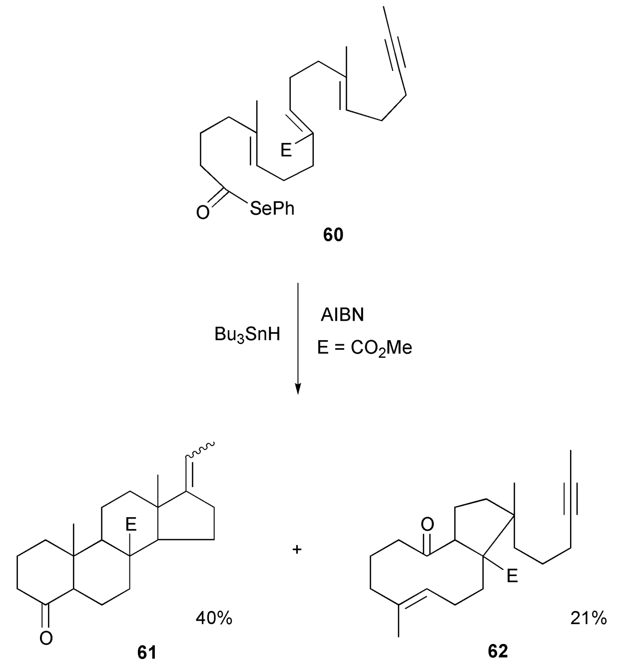
Intramolecular hydrogen-atom transfers mediated by $^nBu_3SnH$ have also found application in synthesis. Of particular importance are intramolecular 1,5- and 1,6-hydrogen-atom transfers (also known as translocations), which lead to relocation of the first-formed radical prior to, for example, carbon–carbon bond formation.[158] For stereoelectronic reasons, the first-formed radical prefers to attack a hydrogen atom at an angle approaching 180° (typically 150–160°), which explains the preference for 1,5- and 1,6-hydrogen-atom transfers, that proceed through 6- and 7-membered transition states, respectively. In competition with intramolecular translocation is hydrogen-atom abstraction from tri-*n*-butyltin hydride (or related hydrides) as illustrated in Scheme 31.[159] Hence, reaction of bromide **46** with $^nBu_3SnH$–AIBN affords reactive vinyl radical **47**, which could form the simple reduced product **48** or, alternatively, undergo a 1,5-hydrogen-atom abstraction to form the more stable radical **49** (which is stabilised by the electron-donating oxygen atom of the silyl ether). Radical **49** could then react with tributyltin hydride to form **48** or attack the alkene double bond in a 5-*exo* cyclisation leading to cyclic primary radical **50**, which could then form cyclopentane **51** on hydrogen-atom abstraction. When $^nBu_3SnH$–AIBN was added to **46** over 8 h, a 10 : 1 mixture of **51** : **48** was formed. Vinyl radical **47** is expected[139] to rapidly abstract a hydrogen atom from $^nBu_3SnH$ ($k \approx 1 \times 10^8$ dm^3 mol^{-1} s^{-1}) and so tin hydride must be added slowly to bromide **46** to ensure 1,5-hydrogen-atom abstraction leading to **49**. For fast hydrogen-atom abstraction, a more stable radical must be generated after translocation (*i.e.* a stronger C–H bond must be formed) and in this case, the rate constant of the 1,5-hydrogen-atom abstraction is around 1×10^6 dm^3 mol^{-1} s^{-1}. Following hydrogen-atom abstraction, slow addition of $^nBu_3SnH$ encourages cyclisation of **49** in preference to reduction.

Radical ring-expansion reactions have also been successfully employed in the preparation of a variety of cyclic target molecules as illustrated by the ring expansion of β-keto esters by Dowd and co-workers.[160] Related $^nBu_3SnH$ reactions have been developed by Kilburn and co-workers using methylenecyclopropane derivatives (Scheme 32).[161] For example, following 5-*exo* cyclisation the cyclopropylmethyl radical **52** is formed, which rapidly ring-opens (~10^8 s^{-1} at rt)[162] to form the much less strained cyclohexane radical **53** prior to 6-*exo* cyclisation and hydrogen-atom abstraction.

Combined ring expansion–intramolecular hydrogen-atom abstraction reactions, with fast propagation steps, can also be designed to afford an elegant approach to bicyclic molecules as illustrated in Scheme 33.[163,164] Addition of the tri-*n*-butyltin radical to thiocarbonylimidazole **54** affords secondary radical **55**, which could ring-open the strained 3-membered epoxide ring



Scheme 32



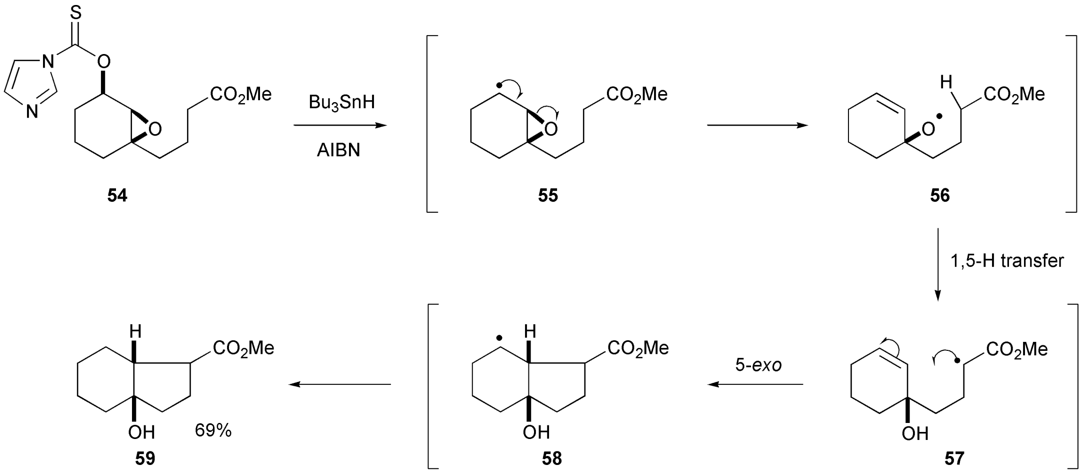
Scheme 34

by either C–C or C–O bond cleavage.[165,166] In this case, the C–O bond breaks to form alkoxyl radical **56**, which rapidly undergoes a 1,5-hydrogen-atom abstraction ($k > 10^8$ s^{-1})[167–169] so as to form a strong O–H bond (~435 kJ mol^{-1}) at the expense of a much weaker C–H bond (~385 kJ mol^{-1}); the presence of the ester substituent facilitates the abstraction by stabilising radical **57**. Secondary radical **57** can then undergo 5-*exo* cyclisation leading to the bicyclic radical **58**, which forms product **59** on abstraction of a hydrogen atom from ^{n}Bu$_3$SnH.

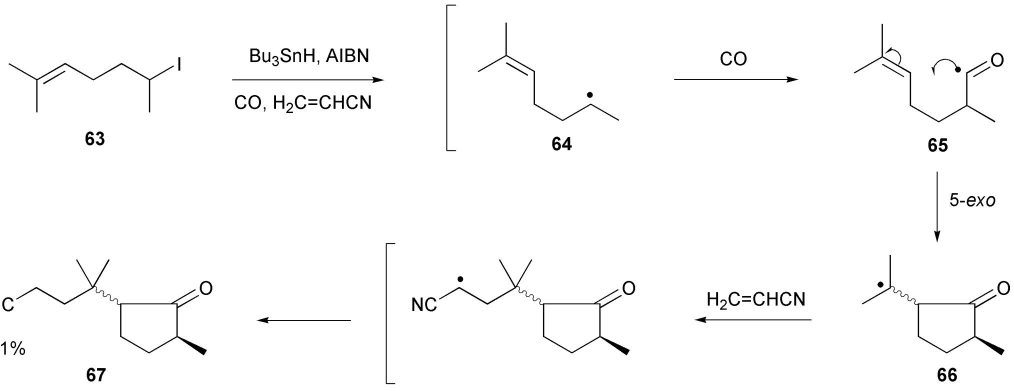
3.1.3.4 Cascade reactions

The high reactivity of radical intermediates has elegantly been exploited in a variety of tandem and cascade reaction sequences mediated by ^{n}Bu$_3$SnH.[170] These reactions are synthetically attractive as they can proceed to form a number of carbon–carbon bonds in a "one-pot" reaction. This represents a "clean" method of synthesis as a large number of reactions can be carried out with only one product purification, thereby reducing chemical waste. Efficient conversions require careful design of the starting material(s) and reaction conditions so as to ensure fast and desirable propagation steps. The challenge is to control the fate of each individual radical in the reaction sequence. A particularly impressive example, reported by Pattenden and co-workers, involves serial 6-*endo-trig* cyclisations from polyene precursors leading to steroids (Scheme 34).[171] Hence slow addition (8 h) of ^{n}Bu$_3$SnH to polyene selenoate **60** produces an acyl radical, which undergoes three successive 6-*endo-trig* cyclisations followed by a final 5-*exo-dig* cyclisation onto the alkyne. Reaction of the resultant vinyl radical with tri-*n*-butyltin hydride affords the tetracycle **61** in an excellent 40% yield (as a mixture of four diastereoisomers). This reaction also demonstrates the difficulty in preventing side-reactions in some polyfunctional precursors as a competitive 10-*endo-trig* followed by 5-*exo-trig* reaction sequence also produced bicycle **62** in 21% yield. The appreciable formation of **62** *via* an unusual 10-*endo-trig* cyclisation is explained on the basis of polarity; the electron-withdrawing ester substituent is expected to facilitate the 10-*endo-trig* cyclisation as acyl radicals are nucleophilic and prefer to add to electron-poor double bonds.

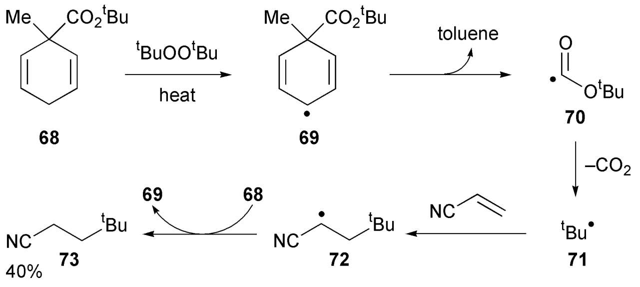
A combination of intra- and inter-molecular reactions can also be employed in synthesis and, in many cases, a fast (entropically favoured) intramolecular reaction is followed by a slower intermolecular reaction. For example, acyl radicals can be generated on formylation of alkyl radicals in the presence of carbon monoxide (Scheme 35).[172] Reaction of iodide **63** and ^{n}Bu$_3$SnH under a high pressure of carbon monoxide (*e.g.* 80 atm) ensures that the initial alkyl radical **64** is formylated, rather than reduced with tin hydride, and the resultant acyl radical **65** can undergo 5-*exo* cyclisation to give cyclic radical **66**. This nucleophilic radical can then add intermolecularly to electron-poor alkenes, including acrylonitrile to give cyclopentanone **67** in 71% yield. Once again, the polarity of the alkene is matched to that of the radical **66** so as to minimise competitive formylation of **66** or reaction with tin hydride. It should also be noted that radical **66** is tertiary and so is less



Scheme 33



Scheme 35



Scheme 36

prone to carbonylation (by another molecule of CO) than the initial, more reactive, secondary radical **64**. Related reactions mediated by tri-organogermanes or tris(trimethylsilyl)silane have also been used and as these reagents are less effective hydrogen-atom donors, the formylation reactions can proceed at lower CO pressures.[172]

3.2 Cyclohexadienes, thiols, phosphites, boranes and related compounds

There is no doubt that tin and related hydrides can be used to mediate a diverse range of important radical reactions on a small scale. However, none of these reagents is particularly inexpensive and so this could be a problem for large-scale reactions.[173] There are further problems with tri-*n*-butyltin hydride because not only is this compound toxic but the tin halide by-products (from radical reactions) are notoriously difficult to separate from the organic products. A number of modifications have been developed[174] to overcome these problems including using water- or acid-soluble stannanes,[175] fluorous tin reagents [*e.g.* $(C_6F_{13}CH_2CH_2)_3SnH$],[176] polymer-supported tin reagents,[177] different work-up procedures[178] or catalytic tin methods.[179]

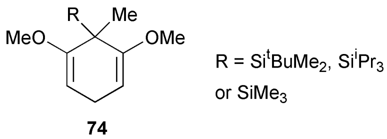
An alternative strategy to overcoming the problems associated with these reagents is to develop new metal hydrides (*e.g.* $HGaCl_2$)[180] or to use a combination of an alternative metal initiator together with a non-metal hydrogen-atom donor. Recent examples of metal initiators which have been used in this way include nickel macrocyclic complexes,[181] manganese(0)[182] and iron(III) salts.[183] Finally, (toxic) metals could be avoided completely if non-metal hydrides, bearing a weak non-metal–hydrogen bond (or bonds), could replace ^{n}Bu$_3$SnH in radical chain reactions. Suitable non-metal–hydrogen bonds include carbon–hydrogen, sulfur–hydrogen, phosphorus–hydrogen or boron–hydrogen and some reagents of current interest are highlighted below.

3.2.1 Cyclohexa-1,4-dienes

Cyclohexa-1,4-diene is known to be a good hydrogen-atom donor because the resultant cyclohexadienyl radical is stabilised by resonance. The weak methylene C–H bonds (~305 kJ mol^{-1}) ensure reasonably fast rates of hydrogen-atom abstraction by primary carbon radicals ($k = 2.3 \times 10^5$ dm^3 mol^{-1} s^{-1} at 50 °C),[119] while tertiary carbon radicals react around 20 times slower (9.4×10^3 dm^3 mol^{-1} s^{-1} at 27 °C).[59] The resonance-stabilised cyclohexadienyl radical cannot propagate a chain reaction by, for example, abstracting a halogen atom from an alkyl halide. As a consequence, cyclohexa-1,4-diene is often used in non-chain radical processes.

To overcome this problem, Walton and co-workers have recently explored alkyl radical generation from cyclohexa-1,4-diene-3-carboxylates as illustrated in Scheme 36.[184] Following hydrogen-atom abstraction from the cyclohexadiene ring of **68** (using ^{t}BuO$^•$) the resultant cyclohexadienyl radical **69** can fragment to generate the alkoxycarbonyl radical **70** and an aromatic ring (this is a strong driving force for the fragmentation). Radical **70** can then undergo β-scission, to lose carbon dioxide (with a rate constant of ~10^4 s^{-1} at rt),[185] and the resultant *tert*-butyl radical **71** can then add to the electron-poor double bond of acrylonitrile to generate a new radical adduct **72**. The chain reaction can be completed by radical **72** abstracting a hydrogen atom from another molecule of cyclohexadiene **68** (this occurs at a rate of around 0.82×10^5 s^{-1} at 140 °C).[184] Although the desired adduct **73** is formed, the reaction is complicated by the formation of oligomers, isobutane and also *tert*-butyl benzoate, which is derived from competitive loss of the methyl radical from cyclohexadienyl radical **69**. The rate of hydrogen-atom transfer from **73** is slower than from ^{n}Bu$_3$SnH and so direct reduction of the *tert*-butyl radical [which has a rate constant of around 2×10^6 dm^3 mol^{-1} s^{-1} at rt for tributyltin hydride (Table 8)] is less of a problem. However, the lower rate of hydrogen-atom transfer leads to the formation of oligomers and the chains were found to be short and so relatively large amounts of the peroxide initiator had to be employed. Fragmentation of **69** to give the methyl radical also reduces the yield of **73** although this process can be used beneficially and alkyl radicals have been generated in good yield from 1-alkylcyclohexa-2,5-diene-1-carboxylic acids.[186] More recently, the same group have used 1-carbamoyl-1-methylcyclohexa-2,5-dienes to generate aminoacyl radicals *via* a similar radical fragmentation approach.[187] In this case, the greater stability of aminoacyl radicals [of the type $^•$C(O)NR$_2$] in comparison to alkoxyacyl radicals [$^•$C(O)OR] ensures that the intermediate cyclohexadienyl radical fragments to give only aminoacyl radicals.

Studer and Amrein have employed a similar strategy in the design of silylated cyclohexadienes **74**.[188] Following hydrogen-atom abstraction, the resultant cyclohexadienyl radicals fragment to form silyl radicals ($^•$SiMe$_2$^{t}Bu or $^•$Si^{i}Pr$_3$), which can



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react with alkyl halides to form carbon-centred radicals. The chain is completed by hydrogen-atom abstraction from the silylated cyclohexadiene, which, for a primary carbon radical, has been estimated to have a rate constant of around 1 × 10^5 dm^3 mol^{-1} s^{-1} at 70 °C. In general, therefore, the rates of hydrogen-atom donation from these cyclohexadienes are lower than for $^nBu_3SnH$.

3.2.2 Thiols and related compounds

Alkylthiols generally react rapidly with alkyl radicals in hydrogen-atom transfer reactions so as to break the relatively weak sulfur–hydrogen bond (~370 kJ mol^{-1}) and form a stronger carbon–hydrogen bond (≥400 kJ mol^{-1}). For example, primary alkyl radicals abstract a hydrogen atom from *tert*-butylthiol at a rate of around 7 × 10^6 mol dm^{-3} s^{-1} at 25 °C.[189] The resulting thiyl radical ($RS^\bullet$) can add reversibly to alkenes[190] but is unable to abstract a halogen atom from alkyl halides at a sufficiently high rate to maintain a chain reaction. Roberts and co-workers, who introduced triethylsilane into the reaction mixture, devised an ingenious solution to this problem using *polarity reversal catalysis* (Scheme 37).[191,192] On introduction of triethylsilane the electrophilic thiyl radical abstracts the electron-rich hydrogen atom from the silane to generate a triethylsilyl radical (step i). This reacts very rapidly with alkyl halides to generate carbon-centred radicals ($k \approx 10^6$ dm^3 mol^{-1} s^{-1}) that can participate in carbon–carbon bond forming reactions (step ii). The chain is completed by rapid abstraction of a hydrogen atom from the thiol by the (nucleophilic) alkyl radical to regenerate $RS^\bullet$ (step iii). This strategy is therefore based on replacement of a slow propagation step (*i.e.* $RS^\bullet$ + RX) with two fast consecutive propagation steps (*i.e.* steps i and ii).

$$\begin{array}{lllll}
\text{(i)} & RS^\bullet + H\text{–}SiEt_3 & \longrightarrow & RS\text{–}H + {}^\bullet SiEt_3 \\
\text{(ii)} & Et_3Si^\bullet + X\text{–}R & \longrightarrow & Et_3Si\text{–}X + {}^\bullet R \\
\text{(iii)} & R^\bullet + H\text{–}SR & \longrightarrow & R\text{–}H + {}^\bullet SR
\end{array}$$

Scheme 37

A similar effect has been accomplished using the silanethiol $(Me_3Si)_3SiSH$ (Scheme 38).[193] Abstraction of a hydrogen atom generates a thiyl radical (step i) that can undergo a 1,2-shift (step ii) to produce a silicon-centred radical capable of halogen-atom abstraction (step iii). A related silanethiol (Ph_3SiSH) has recently been shown to behave in a similar manner by catalysing the organosilane reduction of thiocarbonyl compounds.[194]

3.2.3 Phosphites and related compounds

A variety of organophosphorus compounds contain weak P–H bonds (*e.g.* the strength of the P–H bond in dialkylphosphines is only around ~310 kJ mol^{-1}) and so these reagents can act as effective hydrogen-atom donors. The rate constants for hydrogen-atom abstraction by a primary carbon-centred radical from dicyclohexylphosphine [$(cyclo\text{-}C_6H_{11})_2P\text{–}H$] and diphenylphosphine ($Ph_2P\text{–}H$) are 7 × 10^5 and 1.5 × 10^7 dm^3 mol^{-1} s^{-1} at 50 °C, respectively.[119] Phosphites [$(RO)_2P(O)H$] behave similarly and the rate constant for hydrogen-atom abstraction from $(MeO)_2P(O)H$ and $(EtO)_2P(O)H$ by a primary carbon-centred radical has recently been determined to be 1.2 × 10^5 dm^3 mol^{-1} s^{-1} at 130 °C.[130]

Table 10 Rate constants (*k*) for reaction of the diphenylphosphinoyl radical with organohalides at 23 ± 2 °C[196]

Halide	k/dm^3 mol^{-1} s^{-1}
$Cl_3C\text{–}Br$	8.3 × 10^8
$CH_2\text{=}CHCH_2\text{–}Br$	6.8 × 10^6
$PhCH_2\text{–}Br$	1.1 × 10^6
$Cl_3C\text{–}Cl$	1.4 × 10^6
$Me_3C\text{–}Br$	4.0 × 10^5

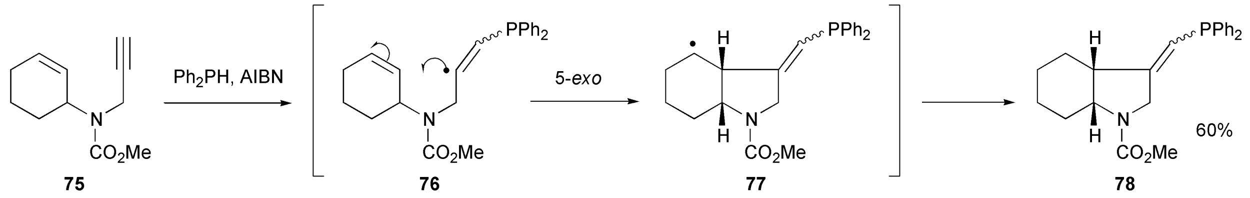
Phosphorus-centred radicals are known to add rapidly to alkene double bonds.[195] Thus, for example, the phosphinoyl radical, $Ph_2P(O)^\bullet$ adds to electron-poor double bonds with a rate constant of around 10^7 dm^3 mol^{-1} s^{-1} at rt.[196] This type of reaction has been exploited by Simpkins who has reacted diphenylphosphine with enyne **75** to produce bicycle **78** in a radical chain process (Scheme 39).[197] The $Ph_2P^\bullet$ radical adds to the terminal alkene to produce an intermediate vinyl radical **76**, which undergoes 5-*exo-trig* cyclisation to produce **77**. Bicyclic compound **78** is then formed on hydrogen-atom abstraction from Ph_2PH, which continues the chain reaction.

Halogen-atom abstraction is also possible from alkyl halides bearing particularly weak carbon–halogen bonds (Table 10).[196] As predicted, the rate of halogen abstraction using the diphenylphosphinoyl radical [$Ph_2P(O)^\bullet$] reflects the carbon–halogen bond strength and the rate constants decrease with increasing bond strength. This has been exploited in radical dehalogenation reactions and dialkyl phosphonates reduce alkyl halides (and also xanthates) *via* a radical-chain mechanism.[198] Dialkyl phosphonates also have application in radical addition–cyclisation reactions involving carbon tetrachloride and 1,6-dienes (Scheme 40).[199] This involves chlorine-atom abstraction by the phosphonyl radical [$(EtO)_2P(O)^\bullet$] to generate the electrophilic trichloromethyl radical, which adds to one of the double bonds of diene **79**. The resultant secondary radical cyclises onto the double bond to form a primary radical, which abstracts a hydrogen atom from diethyl phosphonate to give cyclopentane **80** (in 72% yield). In competition with the formation of **80** is halogen-atom abstraction leading to tetrachloride **81**. More recently, related intermolecular reactions have also been carried out.[200]

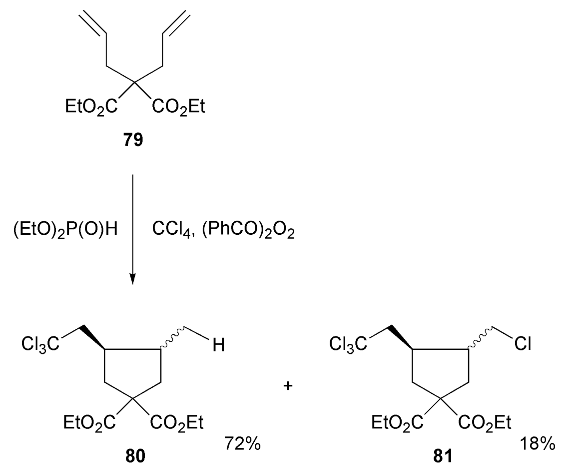
Hypophosphorous acid (phosphinic acid, H_3PO_2) and its salts can act as hydrogen-atom donors in alkyl halide reductions and deoxygenations[198,201] and, more recently, these reagents have been used to mediate carbon–carbon bond formation.[202] Murphy and co-workers have used hypophosphorous acid and its corresponding 1-ethylpiperidine salt to mediate

$$\begin{array}{lllll}
\text{(i)} & R^\bullet + H\text{–}SSi(SiMe_3)_3 & \longrightarrow & R\text{–}H + {}^\bullet SSi(SiMe_3)_3 \\
\text{(ii)} & {}^\bullet SSi(SiMe_3)_3 & \longrightarrow & (Me_3Si)_2\overset{\bullet}{S}i\text{–}SSiMe_3 \\
\text{(iii)} & (Me_3Si)_2\overset{\bullet}{S}i\text{–}SSiMe_3 + X\text{–}R & \longrightarrow & (Me_3Si)_2Si(X)\text{–}SSiMe_3 + {}^\bullet R
\end{array}$$

Scheme 38

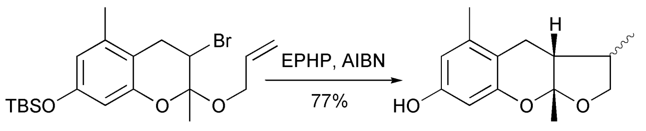


Scheme 39



Scheme 40

radical cyclisations in both aqueous and organic media.[203] For example, 1-ethylpiperidine hypophosphite (EPHP) was used to mediate a key 5-*exo-trig* cyclisation reaction leading to the synthesis of the natural product alboatrin (Scheme 41).[204] Related radical cyclisations of hydrophobic alkyl halides have been carried out using EPHP in water (in the presence of a water-soluble initiator and the surfactant cetyltrimethylammonium bromide)[205] or in aqueous alcohol (in the presence of a base).[206]



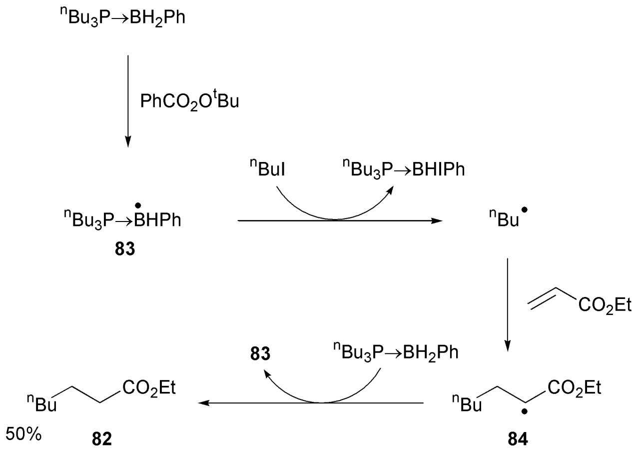
Scheme 41

3.2.4 Ligated boranes

Roberts and co-workers were to the first to recognise the ability of ligated-borane complexes, L ⟶ BH_3 (where L = NR_3, PR_3, SR_2), to act as hydrogen-atom donors in radical reactions.[207] Due to the polarity of the $^{\delta+}$B–H$^{\delta-}$ bond, electrophilic radicals are expected to abstract the (electron-rich) hydrogen atom from these types of complexes even though the B–H bond is not particularly weak (the B–H bond strength in H_3NBH_3, H_2SBH_3 and H_3PBH_3 is 416–431, 381 and 374–389 kJ mol^{-1}, respectively).[208] Thus, the *tert*-butoxyl radical abstracts a hydrogen atom from Me_3NBH_3, Et_3NBH_3, Bu_3PBH_3 or Ph_3PBH_3 with rate constants of ~10^7 dm^3 mol^{-1} s^{-1} at 25 °C.[209] In contrast, nucleophilic alkyl radicals only slowly abstract hydrogen atoms from these complexes. Primary alkyl radicals abstract a hydrogen atom from Bu_3PBH_3 at a rate of only 3×10^3 dm^3 mol^{-1} s^{-1} at 80 °C, while aminoboranes (Me_3NBH_3 and Et_3NBH_3), with stronger B–H bonds, are less reactive ($<1 \times 10^3$ dm^3 mol^{-1} s^{-1} at the same temperature).[209] This means that for efficient chain-reaction sequences, reaction of these ligated boranes with electrophilic radicals is preferable. With a view to increasing the rate of hydrogen-atom abstraction, a variety of boranes have been prepared including ligated phenylboranes, L ⟶ BH_2Ph and L ⟶ $BHPh_2$. The introduction of radical-stabilising phenyl substituents was expected to weaken the B–H bond(s) and so increase the rate of hydrogen-atom abstraction.[208]

The ligated boryl radicals, L ⟶ $B^{\bullet}H_2$, can abstract halogen atoms from simple alkyl halides and, as predicted, alkyl iodides react much more rapidly than alkyl chlorides. The rate constants for bromine-atom abstraction from ethyl bromide (at −96 °C) by $(CD_3)_2SB^{\bullet}H_2$ and $^{i}Pr_2EtNB^{\bullet}H_2$ are 6.2×10^5 and 2.8×10^6 dm^3 mol^{-1} s^{-1}, respectively.[208] Reactions are faster with tertiary bromides and the rate constant for reaction of *tert*-butyl bromide and $^{i}Pr_2EtNB^{\bullet}H_2$ is ~5×10^7 dm^3 mol^{-1} s^{-1} at 25 °C.[210] Therefore, amino- and sulfanyl-boryl radicals are less reactive to halogen-atom abstraction than, for example, $^{n}Bu_3Sn^{\bullet}$ or $Et_3Si^{\bullet}$ (see Tables 3 and 4), whereas the phosphanylboryl radicals are thought to be even less reactive.[211] It should also be noted that some boryl radicals, including $R_2SB^{\bullet}H_2$, can undergo competitive β-scission to form alkyl radicals ($R^{\bullet}$) together with $RSBH_2$.

These reagents have been shown to have application in the addition of alkyl radicals to electron-poor alkenes (Scheme 42).[207] For example, heating *tert*-butyl perbenzoate with *n*-butyl iodide, ethyl acrylate and $^{n}Bu_3PBH_2Ph$ produced ester **82** in 50% yield. Following rapid hydrogen-atom abstraction by the $^{t}BuO^{\bullet}$ radical, the phosphanylboryl radical **83** is expected to abstract the iodine atom from *n*-butyl iodide to generate $^{n}Bu^{\bullet}$. Intermolecular addition to the least hindered end of the double bond produces the electrophilic radical adduct **84**, which is capable of abstracting a hydrogen atom from $^{n}Bu_3PBH_2Ph$ to continue the chain reaction. As the butyl radical is nucleophilic, the rate of simple reduction is relatively slow, which means that the phosphanylborane does not need to be added dropwise to the reaction mixture (in contrast to related $^{n}Bu_3SnH$ reactions, see Section 3.1.3.).



Scheme 42

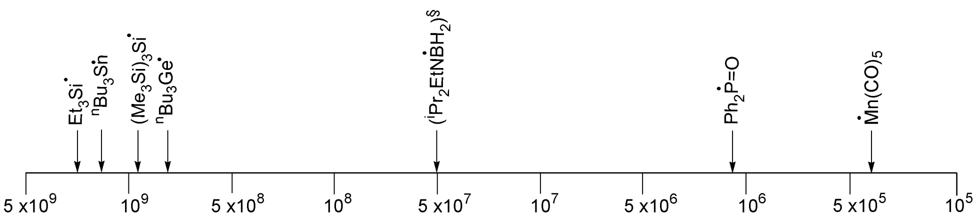
More recently, Barton and Jacob have shown that phosphanylboranes can mediate radical deoxygenation reactions.[212] Selective reduction of xanthates occurred in the presence of organo-chlorides or -bromides and yields of deoxygenation products were found to depend on the nature of the phosphorus compound ligated to the borane [*e.g.* $^{n}Bu_3PBH_3$ was found to react more rapidly than $(MeO)_3PBH_3$].

4 Conclusions

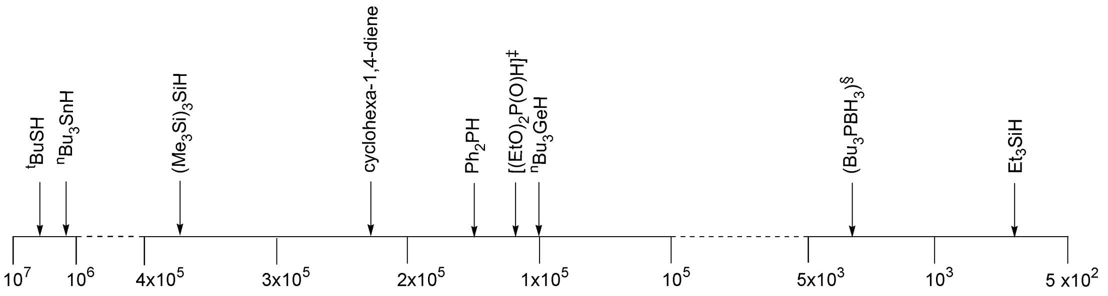
Overall, we have shown how metal–metal and metal–hydrogen compounds can be successfully employed to mediate a wide range of radical transformations. Thermodynamic and kinetic considerations have been shown to underpin the success of efficient radical-chain reactions, which require rapid and selective radical generation together with selective propagation reactions (rather than radical–radical or radical–solvent reactions).

The synthetic chemist will need to choose conditions and reagents in order to optimise the desired transformation and consideration of kinetic data should be particularly helpful in this respect. Scheme 43 summarises data relevant to the choice of metal-centred species to bring about halogen-atom abstraction. The particularly rapid reactions of group 14-centred radicals reflect their widespread use in carbon–carbon bond formation. The less reactive species (boron, manganese and phosphorus-centred radicals), nevertheless, have specific synthetic uses as noted above.

The information in Scheme 44, which shows absolute rate constants for reaction of primary carbon-centred radicals with group-14 and non-metal hydrides, should be useful in designing



Scheme 43 Absolute rate constants (in $dm^3\ mol^{-1}\ s^{-1}$) for reaction of various radicals with benzyl bromide (or § = *tert*-butyl bromide) at rt.



Scheme 44 Absolute rate constants (in $dm^3\ mol^{-1}\ s^{-1}$) for reaction of primary carbon radicals with various hydrides at rt (or § = 80 °C; ‡ = 130 °C).

radical reduction reactions, for which the rate of hydrogen-atom abstraction is crucial. The importance of tin and silicon hydrides in reduction is indicated by their extremely rapid reaction with carbon radicals. Compounds bearing C–H, P–H or B–H bonds are generally slower radical reducing agents than $^nBu_3SnH$ which means that simple reduction can be less of a problem (than for $^nBu_3SnH$) in carbon–carbon bond forming reactions. These reagents may well find increased application in, for example, mediating slow radical addition reactions.

5 Acknowledgements

We would like to thank past and present members of our research groups together with research councils, industry and charities that have supported our research programmes.

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