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Radicals in organic synthesis. Part 1

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Contents

Abbreviations: (*S*,*S*)-BDPP, (2*S*,4*S*)-2,4-bis(diphenylphosphino)pentane; ABCVA, 4,4′-azobis(4-cyanovaleric acid); ACCN, 1,1′-azobis(cyclohexanecarbonitrile); AIBN, azobisisobutyronitrile; AMBN, azobismethylisobutyronitrile or 2-(1-cyano-1-methyl-propylazo)-2-methyl-butyronitrile; ATRA, atom transfer radical addition; ATRC, atom transfer radical cyclisation; ATRP, atom transfer radical polymerisation; BDPP, 2,4-bis(diphenylphosphino)pentane; bipy, 2,2′-bipyridine; BPO, benzoyl peroxide; BTAC, benzyltriethylammonium chloride; CAN, cerium(IV) ammonium nitrate or ceric ammonium nitrate or diammonium cerium(IV) nitrate; Cat, catechol; COD, 1,5-cyclooctadiene; Coll, collidine or 2,4,6-trimethylpyridine; CTAB, cetyltrimethylammonium bromide; DBPB, 2,2-bis(*tert*-butylperoxy)butane; DCP, dicumyl peroxide; DEPO, diethylphosphine oxide; dHbipy, 4,4′-di-*n*-heptyl-2,2′-dipyridyl; DLP, dilauroyl peroxide or lauroyl peroxide or dodecanoyl peroxide; DMA, *N*,*N*-dimethylacetamide; DMDO, dimethyl dioxirane; DMF, dimethylformamide; DMP, 1,4-dimethylpiperazine; DMSO, dimethylsulfoxide; DPPB, 1,4-bis(diphenylphosphino)butane; DPPE, 1,2-bis(diphenylphosphino)ethane; DPPP, 1,3-bis(diphenylphosphino)propane; DTBP, di-*tert*-butyl peroxide; EH, 2-ethylhexanoate; EPHP, 1-ethylpiperidinium hypophosphite; HMDS, hexamethyldisilazane or bis(trimethylsilyl)amine; HMPA, hexamethylphosphoramide; HWE, Horner–Wadsworth–Emmons; IBX, 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide; MAP, 4-methoxyacetophenone; MOM, methoxymethyl; MW, microwave; NHPI, *N*-hydroxyphthalimide; PMB, *para*-methoxybenzyl; PMDETA, *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine; PMP, *para*-methoxyphenyl; PRC, polarity-reversal catalyst/catalysis; PRE, persistent-radical effect; PTOC-OMe, *N*-methoxycarbonyloxypyridine-2-thione; quin, quinuclidine; SET, single electron transfer; SEM, 2-(trimethylsilyl)methoxymethyl; TAHP-1, hexadecanyltrimethylammonium hypophosphite; TBADT, tetrabutylammonium decatungstate; TBDPS, *tert*-butyldiphenylsilyl; TBHN, di-*tert*-butyl hyponitrite; TBHP, *tert*-butyl hydrogen peroxide; TBPP, *tert*-butyl peroxypivalate; TBS, *tert*-butyldimethylsilyl; TBST, tri-*tert*-butoxysilanethiol; TBTH, tributyltin hydride; TEMPO, 2,2,6,6-tetramethylpiperidine-1-oxyl radical; Tf, trifluoromethanesulfonyl or triflyl; THP, tetrahydropyran; TMEDA, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine; TMS, trimethylsilyl; TPA, tripyridylamine; Tr, trityl; Ts, toluenesulfonyl or tosyl; TSE, 2-tosylethyl; TTMSS, tris(trimethylsilyl)silane; xantphos, 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene.

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1. Introduction

From its humble origins as a mere 'chemical curiosity,' radical chemistry has developed into one of the most powerful tools for preparative organic synthesis. Initially considered too reactive to be of use in synthesis, to quote Chatgilialoglu, '…most chemists have avoided radical reactions as messy, unpredictable, unpromising, and essentially mysterious,'[1] radicals now play a dominant role in the development of novel methodology and have found widespread use in the synthesis of complex natural products. In fact, far from being too reactive to give clean reactions, it is clear that radicals are frequently more selective and predictable than ionic reactions. Radical processes show numerous advantages over their ionic counterparts, including greater functional-group tolerance, the frequent use of pH-neutral conditions and a capability to be incorporated into elaborate reaction cascades that rapidly increase molecular complexity. Furthermore, radical chemistry is amenable to 'green' chemistry; there are many examples of radical reactions being performed in water and with a variety of cheap, environmentally benign reagents. Research into radical chemistry continues to blossom and, with the move away from tin-based methodologies, its future is well assured.

The aim of the following two articles is to highlight recent developments in the use of radical reagents and reactions in organic synthesis; as such, it is not intended to be an all-inclusive review. The review is loosely based on the material covered by the author's contributions to *Annual Reports on the Progress of Chemistry: Section B*,[2a–f] covering the literature from 2002 to 2007; key publications from 2008 have been included, but the year was not meticulously surveyed. The review concentrates on radical reactions that aid the synthetic chemist and can be performed in any standard organic research laboratory; discussion of both electro- and photochemistry, with the exception of simple UV-light initiation, is limited. Photochemical reactions that do not proceed by a chain process, i.e., the combination of biradicals, have not been included. Similarly, due to the intended practical bias, there is little discussion of fundamental research on the physical properties of radicals and their reactions, such as kinetic experiments. Regrettably, these restrictions mean that many elegant publications are not included; hopefully, the review will stimulate the reader to seek these papers out.

There have been a number of specialist reviews providing comprehensive coverage of various aspects of radical chemistry published over the last five years; topics covered include free-radical cascade processes,[3] the synthesis of heterocycles by radical cyclisations,[4] the synthesis of five- and six-membered heterocycles,[5a,b] 5-*endo-trig* cyclisations,[6] the formation of five-membered rings by translocation–cyclisation,[7] unusual radical cyclisations,[8] radical reactions in aqueous media,[9] the chemistry of ketyl radical anions formed by photoinduced electron transfer,[10] the addition of radicals to C=N bonds,[11,12] 'clean' radical reagents,[13] phosphorus-based radical methodology,[14] indium and indium reagents in organic synthesis,[15a,b] dichloroindane as a versatile reducing agent,[16] titanocene-mediated radical reactions,[17a,b] copper(I)-catalysed atom transfer radical cyclisations,[18] atom transfer radical polymerisations (ATRP),[19a,b] samarium(II) iodide in organic synthesis,[20–22] samarium(II) iodide in asymmetric synthesis,[23] transition metal generated radicals,[24] cerium regents in synthesis,[25] the persistent radical effect,[26a,b] cyclohexa-1,4-diene-based radical reagents,[27] radical additions to aromatic systems,[28] diastereoselective radical reactions,[29a,b] enantioselective radical reactions,[30–32] stereoselective conjugate additions.[33,34] radical carbonylations,[35] *O*-centred radicals in C–O bond formation,[36] inorganic radical reagents,[37] radical chemistry of organoboranes,[38a,b] the addition of phosphorus compounds to unactivated hydrocarbons,[39] nitrogen-directed radical rearrangements,[40] thiol-mediated radical cyclisations,[41] the chemistry of *N*-centred radicals,[42] chirality control in photochemical reactions[43] and the carbometallation of unactivated alkenes by zinc enolate derivatives.[44] An issue of *Tetrahedron: Asymmetry* was dedicated to stereoselective radical reactions.[45] The nature of the current review means there will be overlap with some of these publications; in all cases, the interested reader is directed towards the specialist review for a more detailed insight.

It is impossible to organise such a substantial body of work to please every reader, or even the author; the original draft of this review was over 350 pages and considerable editing has led to its current structure. To emphasise the synthetic uses of radicals, the review has been divided into two sections; reagents and transformations. Due to the size of the topic, there is an uneven division of material over two issues of *Tetrahedron*, with reagents and intermolecular additions following this introduction whilst radical cyclisations and rearrangements are found in a forthcoming issue. The first section is not a comprehensive list of every radical initiator and hydride source available, but concentrates on new technologies that aid clean radical reactions. Examples of the utility of each reagent will be given in this section, but the majority of the chemistry will be contained in the subsequent sections. The ability of radicals to partake in cascade reactions and multi-component couplings results in potential overlap between the various sections; for example, a cyclisation could also involve a conjugate addition. Regrettably, this is unavoidable and the author has organised such reactions by the 'key' step. A lenient definition of the term 'radical reaction' has been employed and, thus, a number

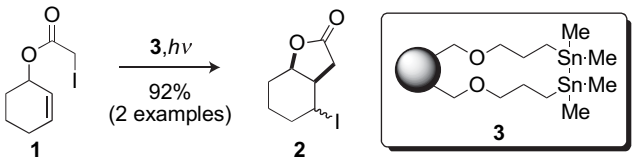
of transformations for which the mechanism has either not been determined or may not be 'free radical' have been included when deemed appropriate. It is hoped that the review offers a timely overview of the current state of free-radical chemistry in organic synthesis and encourages other researchers to utilise radical chemistry in their own work and, more auspiciously, to further develop this vibrant field.

2. Radical reagents

2.1. 'Clean' tin reagents and procedures

Organotin reagents have been central to the development of free-radical chemistry and their use still underpins many endeavours in this field. Unfortunately, these reagents are plagued by shortcomings; they are toxic, a problem compounded by the recurring difficulty in their complete removal. These deficiencies have severely limited the use of radical chemistry in industrial settings. Considerable effort has been expended attempting to alleviate these failings, or to eliminate the use of tin completely. Many alternatives to 'traditional' tin reagents have been disclosed, but none match the versatility of the original trialkyltin reagents. A single replacement for tributyltin hydride is unlikely, but there are a number of useful alternatives, depending upon the reaction being undertaken. A review by Studer and Amrein summarises both tin hydride substitutes and the use of 'clean' tin procedures in reductive radical chain reactions up to 2002.[13] Therefore, only advances since the end of 2001 will be covered.

Due to the known utility of tin hydride reagents in radical chemistry, modified variants that facilitate simple purification have long been a major goal. Polymer-supported reagents are readily removed by filtration and this has led to the synthesis of a number of supported tin hydrides; a comprehensive list can be found in Ley's extensive review of polymer-supported methodologies.[46] There have been limited reports of polymer-supported distannanes for use in atom transfer cyclisations, with Kilburn's polystyrene-bound distannane reagent **3** being one of the few examples (Scheme 1).[47a,b] Employing 10 mol % of the ditin reagent **3** allowed cyclisation of **1** to **2** in a yield comparable to standard solution-based reagents. Direct reduction of the iodide was only a minor by-product, indicating that hydrogen-atom abstraction from the polymer was not a problem. The reagent could be removed by filtration to leave the isolated product with a low residual tin level (<5–34 ppm). Direct recycling of the reagent resulted in a dramatic reduction in yield (25 compared to 92%). This shortcoming could be overcome by regeneration of the distannane resin via a two-step process that gave a polymer-supported reagent capable of forming **2** in 79% yield.



Scheme 1.

A number of drawbacks are often cited with polymer-supported reagents; the insoluble nature of most polymers means reactions are performed under heterogeneous conditions and an excess of both reagent and initiator is often required. Furthermore, leaching of the tin residues is frequently observed. Many of these deficiencies can be circumvented by the use of solution-based tin reagents containing an additional functionality to facilitate purification. Three examples of such reagents are given in Figure 1. Unfortunately, direct comparisons cannot be made, as no common reaction has been reported. Both **4**[48a,b] and **5**[49] are relatively stable stannanes that can be stored at low temperature for extended periods. Their activity is comparable to that of tributyltin hydride and they mediate standard radical cyclisations and reductions. Pyrene derivative **4** is removed by treatment with activated charcoal, which removes 99% of the tin by-products. Unfortunately, the strong π-stacking interactions that allow such excellent separation complicate recovery of the reagent. Stannane **5** is readily removed from the reaction medium by mild base or acid hydrolysis followed by extraction of the resulting base-soluble tin compounds with aqueous $NaHCO_3$ to leave the desired products with a high level of purity. The greatest drawbacks of both these reagents are the length of syntheses and the inability to recycle the reagents.

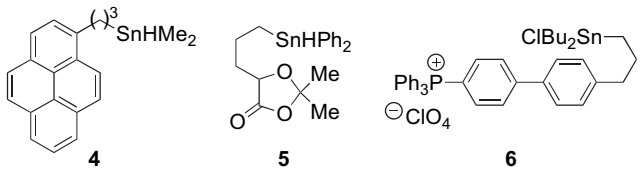


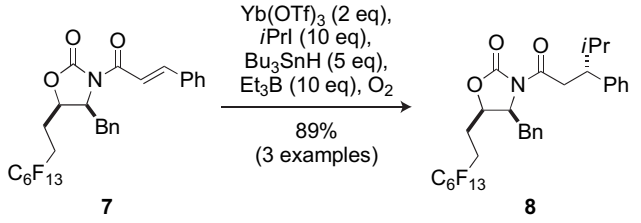
Figure 1.

A potential solution to these shortcomings lies in attaching a phosphonium moiety. Phosphonium reagents are frequently very soluble in chlorinated solvents, yet can be precipitated out of solution by the addition of ether, hexane or toluene. Charette has reported a number of variants for use in radical chemistry.[50] Tin chloride **6** is readily prepared and can be used as a pre-reagent in radical reductions and cyclisations; the hydride itself is unstable and so is formed in situ. The tin residues can be quantitatively removed by filtration following dilution of the reaction mixture with ether/hexanes. The concentration of residual tin in the final product was reported to be just 5 ppm. For the reduction of various alkyl and aryl bromides, **6** could be used as a catalyst (0.1 equiv) with the hydride formed in situ by reduction with stoichiometric sodium cyanoborohydride. The phosphonium-supported tin reagent could be recovered and recycled up to six times with minimal loss of effectiveness. This ameliorates the fact that the reagent requires a lengthy synthesis.

The difficulty in preparing modified tin reagents means that a simple and inexpensive method to remove tin impurities is still an attractive proposition. Harrowven has reported that elution of the concentrated reaction mixture with dichloromethane through a flash column with a stationary phase comprising 10% w/w of finely ground KF and 90% w/w silica gives the product with the level of tin impurity below 30 ppm.[51] Potentially, this facile process could have far-reaching implications for free-radical methodology.

A complementary method for the separation of tin residues involves modification of the *substrate* and not the reagent. Previously, this has been achieved by attaching the substrate to a polymeric support, but such methodology is not without its disadvantages.[52] Alternatively, the substrate can be attached to a fluorous support; this permits standard solution-phase reaction conditions to be utilised, but facilitates purification. Fluorous compounds are readily purified due to the fact that many preferentially partition into a fluorous phase during organic/fluorous liquid/liquid extraction.[53] The fluorous oxazolidinone **7** was utilised in diastereoselective conjugate radical additions (Scheme 2).[54] With this substrate, an excess of tributyltin hydride could be employed and the product still obtained in high purity after simple purification by fluorous solid-phase extraction with FluoroFlash™; product **8** was contaminated with just 0.054% w/w of residual tin, compared to 6.6% w/w for the non-fluorous analogue. Comparable diastereoselectivities are observed for the fluorous and

non-fluorous analogues. This impressive ability to remove tin impurities bodes well for future applications of this technology in other radical reactions.



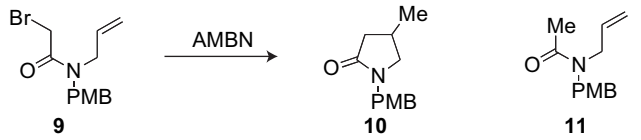
Scheme 2.

The effectiveness of organostannanes in radical chemistry still makes them the reagent of choice for many applications, but their value is tempered by their toxicity. Thus, strategies that can harness tin's potency, whilst mitigating contamination issues will continue to play a vital role in the development of radical chemistry.

2.2. Germanium hydrides

Triorganogermanes are potential replacements for their toxic Group 14 kin. They are perceived to be less harmful than tin hydrides, although full toxicology studies have yet to be performed. Whilst the use of germanium hydrides in radical reactions has been long known,[55a–d] it is only recently that systematic studies of their reactivity have begun. The two most common germanium hydrides are tributylgermanium hydride and tri-(2-furyl)germanium hydride. Unfortunately, a direct comparison of the two reagents is impossible, as the author has been unable to find a common reaction mediated by both reagents.

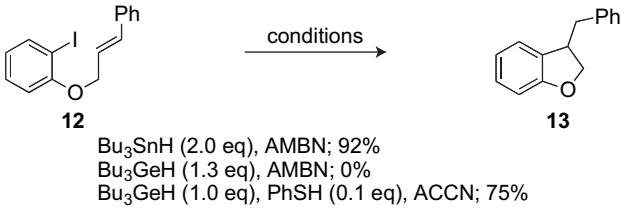
Tributylgermanium hydride is readily prepared in one step from germanium(IV) chloride and is now commercially available. It is more stable than its tin counterpart and can be stored indefinitely at low temperature under a nitrogen atmosphere. Bowman[56] has found that the slower rate of hydrogen abstraction from tributylgermanium hydride, compared to tributyltin hydride, facilitates specific reactions, but reduces its generality. Transformations that suffer from premature reduction (**11**), such as the cyclisation of amide **9** to lactam **10** are enhanced by the use of tributylgermanium hydride (Scheme 3). Similarly, the radical deoxygenation of thiocarbonylimidazolides by the Barton–McCombie reaction is also more efficient with the less reactive germanium hydride. Further uses of germanium hydrides have been reported including the reduction of bromides[57] and aromatic azides to amines.[58]



Scheme 3.

Tri-(2-furyl)germane has been developed by Oshima and is a relatively stable liquid that is readily handled under air, but should be stored under an inert atmosphere.[59] It appears to be easier to prepare than tributylgermane, but, until comprehensive studies have been performed, it is unclear whether it is a superior reagent. Tri-(2-furyl)germane readily mediates standard radical reductions, deoxygenations and cyclisations. A highly attractive feature of this reagent is its ability to reduce both water-soluble and -insoluble primary, secondary and tertiary alkyl halides as well as xanthates in pure water.

The reduced reactivity of germanium hydrides can be ameliorated by the addition of polarity-reversal catalysts (see Scheme 10; Section 2.5). Cyclisation of iodide **12** to heterocycle **13** occurs in an excellent 92% yield when the reaction is mediated by tributyltin hydride, but fails in the presence of tributylgermanium hydride (Scheme 4).[56] Chain propagation is curtailed as the stable benzylic adduct radical is unable to abstract hydrogen from the germane. Addition of just 10 mol % of thiophenol, a polarity-reversal catalyst,[60] overcomes this limitation by reacting with the intermediate benzylic radical to give **13** and a thiyl radical, which is responsible for hydrogen abstraction from the germanium hydride and propagation of the chain.



Scheme 4.

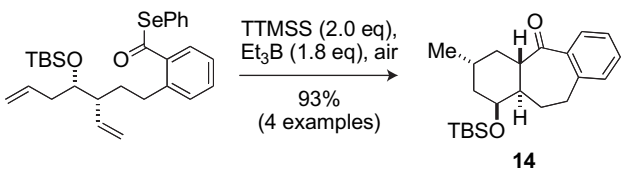
Even though germanes show reduced toxicity, compared to stannanes, it is still beneficial to remove all traces of organogermanium impurities from the final products and, as a result, Bowman has investigated two solid-phase germanium hydrides; one based on the Merrifield resin and the other on Quadragel™.[61] Both reagents mediated standard radical reactions, although with reduced activity, compared to tributylgermanium hydride. Generally, the Quadragel™-supported germane gave the best results, but these reagents still require further study before they can compete with their supported tin counterparts.

Whilst these examples demonstrate the potential of organogermanes, it is unlikely that they will ever be widely accepted; germanium is possibly too expensive to make it commercially viable, although its price has seen a marked decrease over the last 7 years, and the low radical activity of these compounds coupled with their propensity to react directly with alkenes is unappealing in most applications.

2.3. Organosilanes

Ascending Group 14, organosilanes have been a popular, if expensive, alternative to tin hydrides for nearly twenty years. They have seen widespread use in radical chemistry and, as they cannot be considered new developments in radical methodology, discussion in this section will be terse; interested readers are directed towards an early review on the subject[1] and a recently published book.[62] The example below is included only to highlight one of the advantages of organosilane-mediated radical reactions.

Compared to tin hydrides, organosilanes are less effective hydrogen-atom donors and this makes them ideal reagents for reactions that are plagued by premature reduction. The first example of a cascade 7-*exo* acyl radical cyclisation followed by 5- or 6-*exo* radical cyclisation was facilitated by the use of tris-(trimethylsilyl)silane (TTMSS) (Scheme 5).[63] Cyclisations to form seven-membered rings are often problematic, due to unfavourable entropic factors, and, therefore, such cyclisations invariably involve

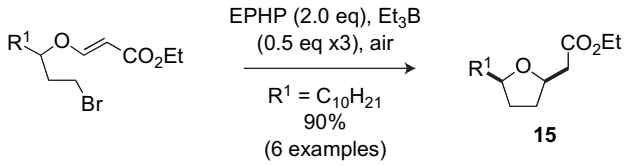


Scheme 5.

radical donors and acceptors that are tethered by an aryl ring to restrict the degree of conformational freedom. Furthermore, acyl radicals are used as they exhibit a slower rate of reduction than alkyl radicals. Even with these biases, a complex mixture of products was obtained when TBTH was used. On the other hand, the cyclisations were found to be high yielding when TTMSS was employed as the hydride donor giving fused systems such as **14** in good yield and with complete diastereoselectivity. Vigorous stirring of the reaction was essential for reproducibility; presumably, the rapid stirring increases the surface area of the solution that is exposed to oxygen thus facilitating more efficient radical initiation via the interaction of air and triethylborane. The reaction is equally effective for the formation of a fused 5,6-ring system. Many examples of the use of silanes can be found throughout Section 3 and Part 2 of this review.

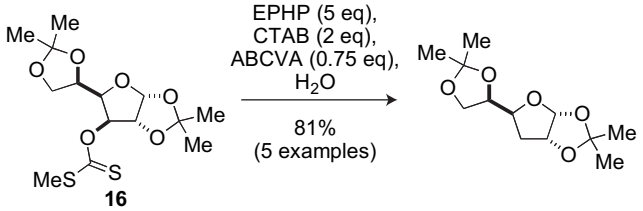
2.4. Organophosphorus (P–H) reagents

Arguably, phosphorus reagents show the most promise as a substitute for traditional tin hydrides. They have had a long and productive association with radical chemistry, stretching back to the seminal work of Barton.[64] Their attraction arises from their relatively low cost, reduced toxicity and ease of removal. As a result, the last ten years has seen a dramatic increase in the use of such reagents and an excellent overview of this area has recently been published.[14] Probably the most commonly employed phosphorus reagent is the salt, 1-ethylpiperidinium hypophosphite (EPHP),[64,65a–c] as exemplified by the formation of tetrahydrofuran **15** (Scheme 6) under relatively mild and clean conditions.[66]



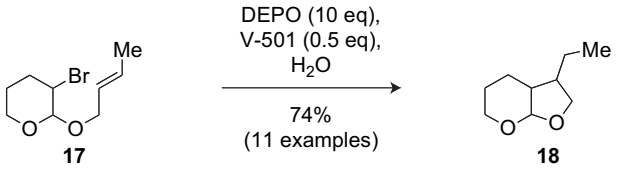
Scheme 6.

An attractive feature of many phosphorus-based reagents is their water solubility, which permits radical reactions to be performed in aqueous media. Jang has developed an aqueous variant of the Barton–McCombie reaction, which uses xanthates in the deoxygenation of alcohols.[67] Whilst the radical-chain carrier, EPHP hypophosphite, is water soluble, many organic compounds are not and, as a result it, is often crucial that a surfactant or phase-transfer reagent is added. The optimum conditions appear to be cetyltrimethylammonium bromide (CTAB) in conjunction with the water-soluble radical initiator, 4,4′-azobis(4-cyanovaleric acid) (ABCVA or V-501). Even so, only secondary alcohol derivatives, such as carbohydrate **16**, that are miscible in the reaction medium are deoxygenated in good yield (Scheme 7); highly hydrophobic substrates, such as steroid derivatives, still give poor results and should be performed in ethanol. The reactions can either be performed in water at 80 °C with ABCVA as the initiator or in ethanol at room temperature with triethylborane as the initiator with little variation in the yield.



Scheme 7.

Whilst the use of water as a solvent is attractive, the requirement for excess EPHP and surfactant is far from ideal. To overcome these limitations, Murphy has introduced diethylphosphine oxide (DEPO) as a novel chain carrier;[68] it is soluble in both water and a number of organic solvents and shows sufficient lipophilicity to negate the need for a phase-transfer reagent. Additionally, with a pK_a value of 6, it is effectively neutral, yet can be removed via a base wash. If diethylphosphine oxide is used in conjunction with a water-soluble initiator, such as V-501, then essentially pure products can be isolated after a simple basic work-up. Acid-sensitive bromide **17** was readily cyclised using 10 equiv of DEPO and 0.5 equiv of V-501 in water, to give **18** in excellent yield (Scheme 8). Not only does this result indicate that DEPO mediates cyclisations under relatively mild conditions, with no trace of acetal hydrolysis, in yields comparable to tributyltin hydride-mediated reactions, but that the potential problem of phosphorus radical addition to alkenes (see Section 3.1.8) is not an issue.



Scheme 8.

One of the most exciting developments in phosphorus-based radical chemistry combines the advantages outlined above with the ability to perform enantioselective radical reactions. The chiral quaternary ammonium hypophosphite **19** and its pseudo-enantiomer **20** (Fig. 2) are readily prepared from cinchona alkaloids and mediate the formation of amino acids (**23**) by the addition of alkyl radicals to oxime ether **22** (Scheme 9).[69] In this reaction, **19** and **20** play a multitude of different roles; they act as the radical-chain carriers, as surfactants and as chiral additives, capable of inducing high enantioselectivity (up to 98% ee). The optimum reaction medium is a mixture of dichloromethane and water; use of either pure water or pure dichloromethane results in greatly reduced yields. Presumably, this is a result of the insolubility of the substrate in water and the salts in dichloromethane. The enantioselectivity is thought to arise due to hydrogen bonding between the ammonium salt and the bidentate glyoxylate oxime ether coupled with π-stacking of the aryl groups organising the substrate prior to attack, as depicted in **21**. The reaction has many advantages over conventional nucleophilic additions; it utilises no metal reagents, all reagents are cheap and readily available, the use of aqueous

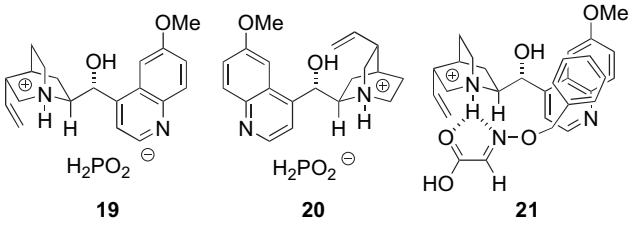
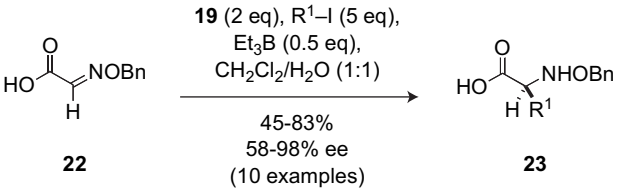


Figure 2.



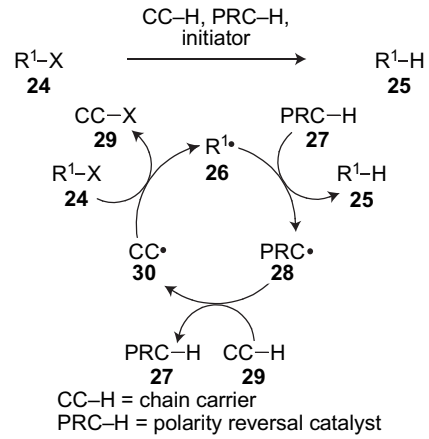
Scheme 9.

solvent mixtures is preferable to pure halogenated solvents and the chiral amine can be readily recycled. With these benefits in mind, it is anticipated that other applications of this and analogous systems will be reported in the future.

It is clear that the use of phosphorus-based radical reagents will continue to grow; the reagents are cheaper, less toxic and more readily removed than their tin counterparts. In this age of environmental concern, their activity in aqueous reaction media is highly attractive. All these beneficial features, combined with their ability to perform enantioselective reactions, should encourage the use of phosphorus-based radical reactions in an industrial setting.

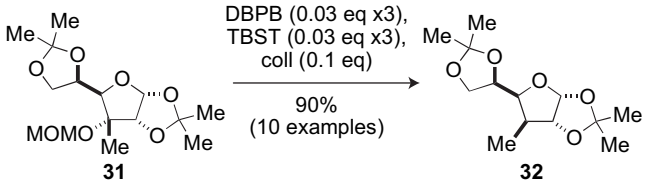
2.5. Thiols

Thiols have a venerable history in radical chemistry having been employed as both radical precursors and radical-chain carriers; their use was reviewed in 2008.[41] An increasingly important role for thiols is that of polarity-reversal catalysts (PRCs). It is often forgotten that radical-chain reactions rely on polarity effects for efficient propagation; smooth hydrogen-atom transfer only occurs if an electrophilic radical interacts with a nucleophilic source of hydrogen or vice versa. If the polarities are mismatched, the reaction will be sluggish at best or a non-chain process. PRCs alleviate this problem, facilitating hydrogen-atom transfer by the addition of an extra propagation step; Scheme 10 outlines this principle. In this generalised example, the desired reaction involves the reduction of a radical precursor **24** via a nucleophilic alkyl radical, $R^1\cdot$**26**, with a hydrogen source to give R^1–H (**25**) and a new radical-chain carrier, CC·**30**. A potential problem with the reduction occurs if **30** is also nucleophilic, in which case the transition state for hydrogen-atom abstraction will not benefit from charge-transfer stabilisation and thus will be slow. This problem can be overcome by the addition of a suitable polarity-reversal catalyst PRC–H **27** that allows **26** to abstract a hydrogen atom to give a new, electrophilic radical **28** that can then be reduced by the CC–H **29** to give the chain carrier **30**. Thus, one direct abstraction step is replaced by a series of transformations that permit the desired reaction to occur with the benefit of charge stabilisation.[60]



Scheme 10.

The use of PRC enables the deoxygenation of methoxymethyl (MOM)-protected secondary and tertiary alcohols.[70] An informative example is the deoxygenation of carbohydrate **31** (Scheme 11). Treatment of the methoxymethyl-protected alcohol with 2,2-bis(*tert*-butylperoxy)butane (DBPB) as radical initiator and tri-*tert*-butoxysilanethiol (TBST) as the polarity-reversal catalyst in the presence of collidine (coll) furnishes the desired deoxy compound **32**. The reaction fails to give any product in the absence of thiol. These conditions work for a wide range of substrates, although they appear to give low yields with secondary alcohols derived from carbohydrates. The reaction offers a number of advantages over the more traditional Barton–McCombie process, in that the radical precursor is considerably easier to prepare and there is no need to use tin-based radical reagents.



Scheme 11.

A thiol-based PRC has permitted a mild reduction of aromatic azides to amines under tin-free conditions to be developed.[71] Aromatic azides are normally inert towards triethylsilane under thermal conditions, but, in the presence of catalytic quantities of *tert*-dodecanethiol, they are readily reduced to anilines in virtually quantitative yields. PRC overcomes the polarity mismatch observed between the nucleophilic silane and the nucleophilic *N*-centred radical, which inhibits hydrogen transfer.

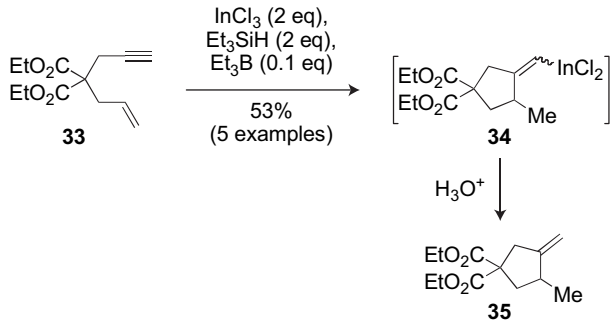
Sulfur-based reagents continue to play an important role in radical chemistry; their ease of synthesis and stability make them attractive as both radical-chain carriers and polarity-reversal catalysts.

2.6. Indium hydride reagents

Indium is without any known toxicity, making it an attractive precursor for the synthesis of radical reagents. This section will concentrate on the use of indium hydride reagents; indium metal-initiated or -mediated radical reactions are covered in Section 2.7.3. The most prevalent indium hydride reagent is dichloroindane ($HInCl_2$) and whilst this reagent appears to be stable in solution at ambient temperature,[72] it readily decomposes in water and is prepared immediately prior to reaction[73] or in situ. Baba and Shibata have published an overview of their contribution to the development of dichloroindane as a versatile reducing agent.[16]

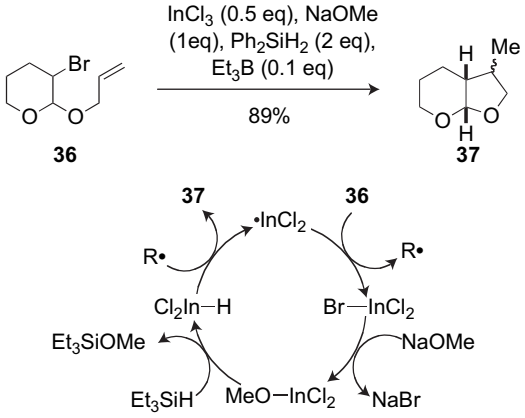
All methods for the preparation of dichloroindane are based on the reduction of indium(III) chloride. Initially, this reduction was achieved via transmetallation with tributyltin hydride, but, as this negates all the inherent advantages of indium chemistry, the method has rapidly been superseded by milder and more environmentally benign syntheses. A variety of different reagents reduce indium(III) chloride to dichloroindane including diisobutylaluminium hydride[73] and sodium borohydride.[74a,b] Both of these methods have limited substrate compatibility, due to the strongly reducing conditions employed; both diisobutylaluminium hydride and sodium borohydride are excellent reducing agents, whilst indium(III) chloride is a good Lewis acid. In the case of sodium borohydride, the problem is compounded by the fact that borane is produced during the transmetallation step.

A less-reactive hydride source is triethylsilane and the use of this reagent to generate dichloroindane enables standard radical cyclisations to be achieved.[75] Cyclisation of enyne **33** proceeds without reduction of the ester moiety to furnish, after acidic hydrolysis of alkenylindium **34**, cyclopentane **35** in 53% yield compared to a mere 12% obtained with the indium(III) chloride/sodium borohydride conditions (Scheme 12). The possible reasons for the low yield when sodium borohydride is employed include reduction of the ester moiety and hydroboration mediated by the borane by-product. Unfortunately, the reaction suffers from low yields when catalytic indium(III) chloride is used. The exact reason for this is unclear but, is probably due to a slow transmetallation step.



Scheme 12.

Whilst the use of triethylsilane as a hydride source has overcome a number of the disadvantages associated with earlier methodologies, the by-product of transmetallation is chlorotriethylsilane and this, in combination with indium(III) chloride, produces a strong Lewis acid. In order to circumvent the formation of such reactive species, methodology involving the in situ formation of an alkoxyindium species prior to reduction has been developed.[76] Indium(III) chloride is reacted with sodium methoxide to give the alkoxyindium species, which undergoes 'transmetallation' to give the indium hydride. Finally, reaction with triethylborane forms the desired indium radical and initiates the chain process. This methodology permits the cyclisation of enynes and unactivated halides, including the acid-sensitive acetal **36**, which failed to give the desired bicyclic acetal **37** under other indium-based conditions (Scheme 13). The use of just 50 mol % in this reaction shows that a catalytic variant is possible.



Scheme 13.

Whilst indium hydrides have a number of advantages over their tin counterparts, it is unlikely that they will gain widespread acceptance, due to the need to prepare them either directly prior to the reaction or in situ. This, coupled with the general utility of indium(0) metal in radical processes, means it is the latter reagent that is likely to become more popular.

2.7. Single electron transfer (SET) reagents

Without doubt, this is the most ambiguous section of the review; it is often hard to categorically state whether a reaction is occurring via a purely radical mechanism or via an organometallic species or via a combination of the two, with a radical formed within the ligand coordination sphere of the metal. The author has tried to restrict the discussion to reactions and reagents for which there is empirical data supporting the involvement of radicals. SET reagents can initiate radical reactions either by the donation of a single electron from the metal to the substrate (a reductive process) or by the transfer of an electron from the substrate to the reagent (an oxidative process). Reagents in this section commonly facilitate reactions that have no hydride-mediated equivalents.

2.7.1. Titanium-based reagents

An increasingly popular reagent for the generation of radicals is titanocene(III) chloride (Cp_2TiCl). This reagent is predominantly employed in the generation of radicals by the reductive ring opening of epoxides, although its utility is gradually extending to include other precursors. Like any low-valent titanium species it is not stable and is normally prepared prior to the reaction by the reduction of the commercially available titanocene(IV) chloride. Alternatively, catalytic titanocene(III)-mediated reactions involving in situ reduction have been developed. The reagent itself exists as an equilibrium between the monomeric **39** or **40** and dimeric species **38** (Fig. 3). The general mechanism for titanocene(III)-mediated reactions is believed to proceed via coordination of **40** to an epoxide **41** followed by homolytic scission of a C–O bond to give the more stable β-titanoxyl radical **42** (Scheme 14). Radical **42** participates in standard reactions. Alternatively, it can interact with another equivalent of the titanium reagent to produce an alkyltitanium complex that can participate in ionic reactions. The radical chemistry of titanocene(III) chloride-mediated transformations has recently been reviewed;[17a,b] therefore, detailed coverage is avoided.

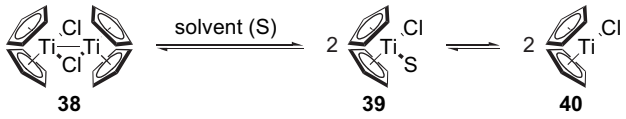
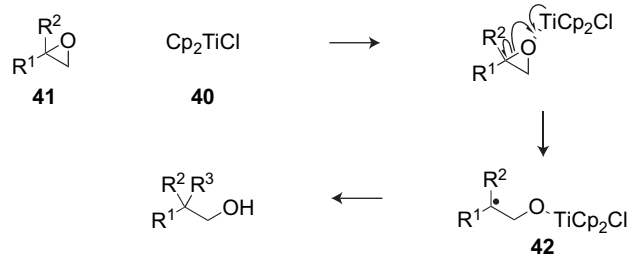


Figure 3.



Scheme 14.

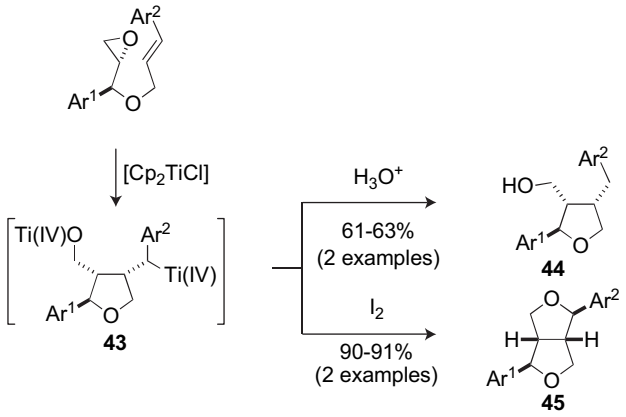
The reasons for the singular efficacy of titanium-based reagents in the reductive ring opening of epoxides, compared to other low-valent single electron transfer reagents, have been elucidated.[77] In a series of comparison experiments between titanocene(III) chloride, samarium(II) iodide, chromium(II) chloride and $[V_2Cl_3(THF)_6]_2[Zn_2Cl_6]$ it became clear that the optimum reagent showed a good balance of Lewis acidity versus reducing power. If the Lewis acidity of the metal reagent is too high, then ring opening of the epoxide via an S_N1 or S_N2 reaction becomes a problem; this is typical of the reactions of samarium(II) iodide. Alternatively, if the metal is too efficient a reductant, then the β-metalloxy radical (e.g., **42**) is prematurely reduced to an alkylmetal species before the radical reaction can occur. This side reaction is particularly prevalent with the vanadium reagent, even though this reagent is not a particularly powerful reductant. It is believed that the dimeric nature of this species is the cause of this anomalous behaviour. Only chromium(II) chloride and titanocene(III) chloride showed the necessary balance of properties to allow C–C bond formation, with the former reagent displaying a lower reactivity. It is interesting to speculate that the development of the correct ancillary ligand

might allow the reactivity of the chromium to be increased and thus this deficiency could be corrected.

The majority of titanocene(III) chloride-promoted reactions require an excess of titanium and this results in issues of practicality as large quantities of titanium salts are precipitated. A number of catalytic variants have now been developed; the earliest employed the combination, Cp_2TiCl_2/Mn/coll·HCl.[78] In this system, the Ti–O and Ti–C bonds formed during the reaction are protonated by the collidine hydrochloride to give the alcohol (H–O) and the alkane (H–C). Subsequently, an aprotic variant was developed which utilises Cp_2TiCl_2/Mn/coll·TMSCl. This reagent system prevents the reduction of the putative alkyltitanium(IV) species to the simple alkane and allows β-elimination to occur to furnish alkenes.[79] A second non-reductive (in terms of the alkene) catalytic system was recently introduced that utilises the mixture, Cp_2TiCl_2/Mn/lutidine·HCl/BEt_3. The borane is believed to reduce the Cp_2Ti(IV)HCl species to the active titanium(III) species, thus enabling alkyl radical disproportionation to give an alkene, rather than reduction to the simple alkane.[80]

An intriguing new catalytic system has been developed that employs hydrogen gas (H_2) as the hydrogen-atom source in the reduction of the terminal radical.[81] This reaction effectively combines the catalytic Cp_2TiCl_2/Mn/lutidine·HCl conditions with catalytic hydrogenation mediated by Wilkinson's catalyst. The radical generated by epoxide ring opening first abstracts a hydrogen from the rhodium dihydride species to give the alkoxytitanocene(IV) species and a monohydride complex. A second equivalent of the radical then abstracts the second hydride to furnish more alkoxytitanocene(IV) and regenerate Wilkinson's catalyst. Protonation of the alkoxytitanocene(IV) and reduction of the rhodium propagate the catalytic cycle. The conditions are compatible with the enantioselective ring opening of *meso* epoxides. Such a system is attractive in terms of atom economy and because it opens up the possibility of combining radical chemistry with the vast arsenal of methods available for catalytic hydrogenation.

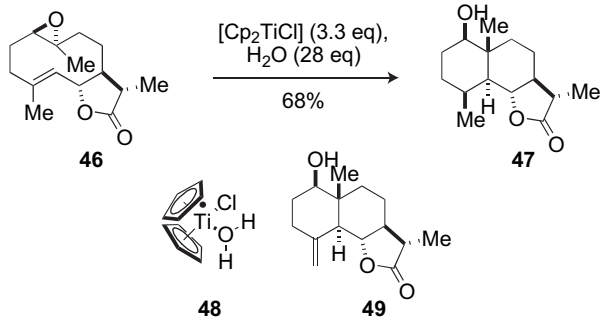
Titanocene(III)-mediated epoxide ring opening–radical cyclisation can be utilised to form most ring-sizes.[82] The simplest rings to create are, of course, five-membered rings such as **44** (Scheme 15).[83] The reaction can furnish either the monocyclic alcohol **44** via protonation of the intermediate Ti–C bond (**43**) or the bicyclic furofuran **45** by a cascade radical cyclisation–ionic cyclisation. The latter reaction is achieved by quenching the intermediate organotitanium species with iodine followed by an intramolecular S_N2-like cyclisation. Such methodology has been employed in the synthesis of a number of natural products.[84]



Scheme 15.

Under the correct conditions, the addition of iodine is unnecessary and a radical cascade yields the bicyclic furans directly. When sub-stoichiometric quantities of titanocene(III) are employed, the initial radical cyclisation generates a long-lived *C*-centred radical that preferentially undergoes a Ti–O bond-breaking 5-*exo*-*tet* radical cyclisation onto the oxygen atom. The substitution of the titanocene moiety regenerates the active titanocene(III) species; formally the process is a catalytic redox isomerisation.[85] Significantly, the optimum yields are only obtained when the reaction is performed with catalytic titanocene(III) (Cp_2TiCl_2/Mn/Coll·HCl), the use of stoichiometric quantities resulting in a decrease in yield, due to reductive trapping of the intermediate radical.

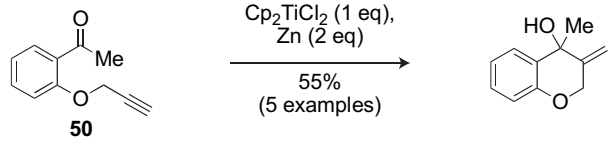
It is often stated that water is an inert medium for radical reactions; it is assumed that the strength of the H–OH bond prevents hydrogen transfer. It is becoming apparent that activation of water by a Lewis acid can result in the formation of excellent hydrogen-atom donors c.f. use of BMe_3–H_2O in reductions (see Section 2.11). The use of water as a hydrogen donor in radical transformations is highly desirable as conventional hydrogen-atom donors such as 1,4-cyclohexadiene, tributyltin hydride or thiols are either toxic and/or foul smelling; obviously, water has none of these issues. Treatment of a range of epoxides with titanocene(III) chloride and a large excess of water permits the efficient reductive ring opening of the epoxides to give alcohols.[86] The reaction can be performed with a sub-stoichiometric quantity of the titanocene reagent with only a marginal drop in yield. The use of D_2O allows the selective incorporation of deuterium and confirms the proposed mechanism. The reaction is believed to proceed via the aqua complex **48** (Scheme 16), with computational studies suggesting an extraordinary lowering of the O–H dissociation energy in this complex; the calculated value for water is 452.6 kJ mol^{-1} (experimental value is 492.4 kJ mol^{-1}), whilst the calculated reaction energy for O–H bond dissociation in **48** is a mere 206.8 kJ mol^{-1}. Water can be used to quench tandem radical ring opening–cyclisation sequences, although premature reduction prior to cyclisation is sometimes observed. The earliest example of the use of water as a hydrogen source for radical reactions appears to be in the cyclisation of **46** to **47** (Scheme 16); if the reaction is carried out in the absence of water, then the *exo*-alkene **49** is predominantly isolated.[87] This methodology in conjunction with the results described in Section 2.11 indicate that water can be a useful source of hydrogen atoms in radical reactions.



Scheme 16.

Epoxides are no longer the sole radical precursors in titanocene(III)-mediated reactions. Alkyl bromides are suitable precursors, as long as they are activated by a group capable of stabilising the resulting radical via either resonance stabilisation or inductive effects. This has permitted the radical-promoted conjugate addition of allylic, propargylic or benzylic bromides to reactive conjugated ketones or esters.[88] Non-activated alkynes and alkenes can be employed in the cyclisations of α-bromoesters and this allows the preparation of highly functionalised tetrahydrofurans.[89] It is also possible to use non-activated iodides in cyclisations achieved under photoirradiation conditions.[90]

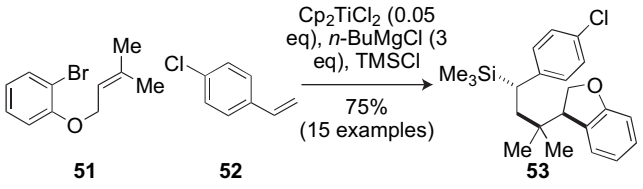
Considering that titanium-ketyl radicals have long been postulated as intermediates in reactions such as pinacol and McMurry couplings, it is somewhat surprising that a titanocene(III) reagent has not been utilised in an intramolecular ketyl radical addition earlier than 2006.[91] A range of aldehydes and ketones, such as **50**, undergo cyclisation onto alkenes and alkynes (Scheme 17). The rate of reaction of the ketone appears to be much slower than that of the corresponding aldehydes and the yield is lower. It is essential that the carbonyl substrate be added to an excess of the titanium reagent to prevent intermolecular dimerisation (pinacol-like coupling).



50

Scheme 17.

Titanocene(III) acts like other SET reagents and promotes reactions such as the carbomagnesation of alkenes.[92] In this process, the radical coupling of alkyl or aryl halides with an alkene is followed by a second reduction step to give an organometallic species that can be trapped in an ionic electrophilic process (Scheme 18). The reaction shows impressive generality; the radical donor can be a primary, secondary or tertiary alkyl halide or an aryl halide. The ionic electrophilic trap can be an alkyl halide, acyl chloride or a silane. A remarkable three-component transformation highlights the power of this reaction; SET reduction of bromide **51** initiates cyclisation to give a tertiary radical that adds to alkene **52**, before being reduced to a benzylic anion equivalent that undergoes ionic addition to chlorotrimethylsilane to give **53** as the sole product.



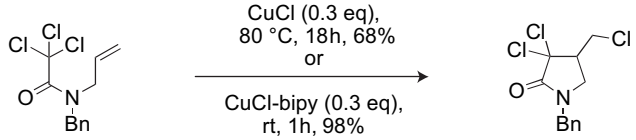
51 **52** **53**

Scheme 18. Bonds formed by a radical process are in bold; bonds formed by an ionic process are dashed.

The titanocene(III)-mediated methodology is a powerful addition to the gamut of radical chemistry. The titanocene(III) reagents are readily accessible, easily removed from the reaction medium at the end of a transformation and are not toxic. Utilising epoxides as radical precursors has a number of attractive features, compared to the more conventional precursors; they are readily prepared for alkenes or carbonyls, they can be formed in enantiomerically pure form and retain functionality on generation of the radical. Additionally, it is becoming clear that titanocene(III)-mediated reactions can compete with the ubiquitous samarium(II) iodide SET reagent. The fact that titanium(III) reagents can be used in sub-stoichiometric quantities, should guarantee that they will see far greater use over the coming years and this is an area of radical chemistry that will become of great importance.

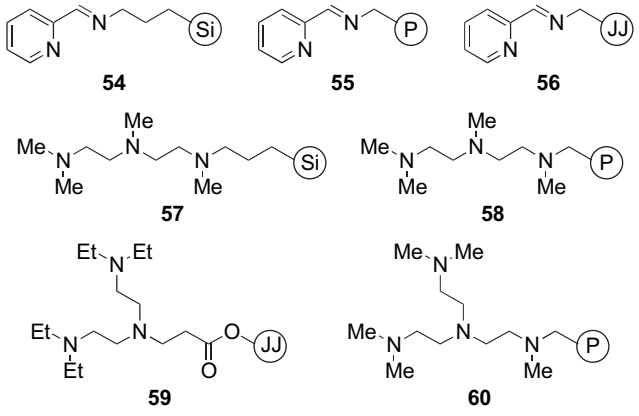
2.7.2. Copper-based reagents

Copper(I) salts have a venerable history as catalysts for atom transfer radical cyclisation (ATRC) (Part 2, Section 2.8). The popularity of copper(I) salts has undoubtedly arisen, due to their low cost, reduced toxicity and the mild reaction conditions associated with such reagents. In the majority of copper-mediated atom transfer radical cyclisations, the reactive halide is adjacent to a carbonyl group. This is necessary to activate the halide by lowering the LUMO of the C–X bond. Simple copper(I) chloride can catalyse the atom transfer radical cyclisation, but it requires high catalyst loadings and high temperatures to obtain satisfactory yields (Scheme 19). The situation is ameliorated by the addition of amine ligands, which greatly increase the reactivity of the catalyst, cutting the reaction times from several hours at elevated temperatures to less than one hour at room temperature.[93] Whilst the standard ligand for ATRC is 2,2′-bipyridine (bipy), which offers an ideal combination of activity, availability and practicality, there are a number of more effective ligands that permit reduced catalyst loadings, reaction times and temperature as well as facilitating the use of less activated halides.[94a–g] It is not clear how these ligands aid the reaction; they might help solubilise the copper(I) or they could alter its redox potential. A general mechanism for transition metal-mediated atom transfer processes is given in Part 2, Section 2.8 and, whilst this is undoubtedly a simplification, it explains most observations. An excellent review of copper(I)-mediated radical cyclisations covers this area in detail.[18]



Scheme 19.

Although copper(I) salts are far less problematic than their tin counterparts, there is still a desire to remove all copper residues from the final products. Surprisingly, few examples of solid-supported systems have been evaluated; Clark has rectified this shortcoming and has studied solid-supported variants of some of the most reactive amine-based ligands for copper-mediated ATRC **54**–**60** (Fig. 4).[95] As is commonly the case when reagents are introduced onto a solid-support, both the activity and the stereoselectivity of all the polymer-bound reagents was less than that of their solution-based counterparts. More surprising was the reversal in the normal reactivity of the various reagents. When the reactions are carried out in solution, the polyamine catalysts analogous to **57**–**60** are invariably more reactive than the pyridylmethanimines analogous to **54**–**56**, yet, in these studies, the supported pyridylmethanimine ligands were generally more effective. The only exception was ligand **59**, which was the only solid-supported ligand to mediate the cyclisation of deactivated bromide derivatives. The potential recyclability of the reagents was studied with the catalyst based on **58**; whilst it was possible to re-use the catalyst up to seven times, the activity was found to decrease with each



54 **55** **56**

57 **58**

59 **60**

Si = silica; P = cross-linked polystyrene; JJ = *J*anda*J*el

Figure 4.

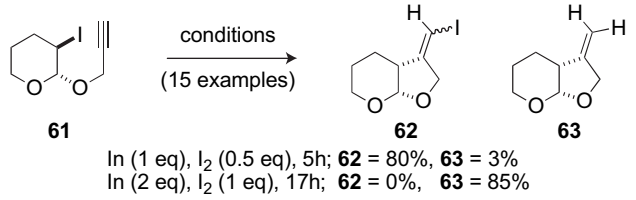
successive run. This was largely believed to be the result of copper leaching and oxidative deactivation forming the unreactive copper(II) species.

The use of copper(I)-mediated radical reactions will continue to escalate, due to its cheapness and versatility in ATRC and ATRP. Whilst it is possible that new ligands will be developed, the combined simplicity and effectiveness of those that already exist means they are unlikely to be supplanted.

2.7.3. *Indium metal-based reagents*

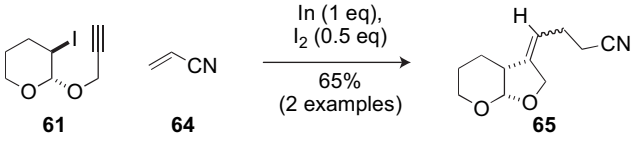
Indium metal is an attractive reagent; not only does it have no known toxicity, but it is also unaffected by air or oxygen at room temperature and can be used in water without detriment. It has a low first ionization potential, comparable with that of the alkali metals, and is thus a suitable reagent for single electron transfer processes. Two general reviews on the use of indium and indium reagents in organic synthesis are recommended.[15a,b]

A low-valent indium species, prepared in situ from indium powder, can be employed in either ATRCs or reductive radical cyclisations of iodoalkynes (Scheme 20).[96,97] Treatment of iodide **61** with 1 equiv of indium and 0.5 equiv of iodine gives the alkenyl iodide **62** in good yield. The reaction permits the synthesis of a range of mono- and bi-cyclic heterocycles. Simple alkyl-disubstituted alkynes are tolerated, but, if the substituent is a phenyl group, then only reductive cyclisation is observed. Indium can be used as a catalyst; just 0.1 equiv of indium and 0.05 equiv of iodine give the product with only a slight reduction in yield. Increasing the amount of indium results in reductive cyclisation to give **63**. The generality of this methodology has recently been extended to allow the cyclisation of alkenes and aromatic iodides.[98]



Scheme 20.

The reaction is believed to proceed via SET to the alkyl iodide to form a *C*-centred radical. The evidence for the intermediacy of a radical comes from the success of a cyclisation–conjugate addition sequence; cyclisation of **61** in the presence of acrylonitrile **64** gives nitrile **65** in 65% yield (Scheme 21).[96] Alternatively, under reductive cyclisation conditions, an alkenylindium species is a good substrate for palladium-catalysed arylations. These results can be explained if a low-valent indium species (In, In^{+} or In^{2+}) is formed in situ and this species abstracts the iodine from **61** to give the initial radical; in the absence of excess reducing agent, cyclisation gives an alkenyl radical that has sufficient time to undergo conjugate addition to activated alkenes. If there is a high concentration of the indium species present, the radical is trapped to give the alkenylindium, which is either protonated to give the reduced product or utilised in palladium chemistry.



Scheme 21.

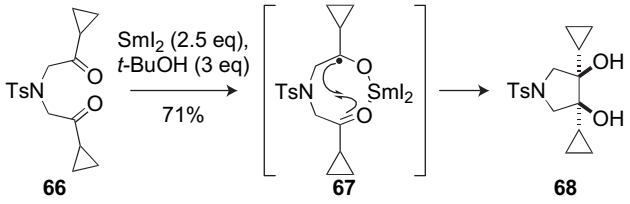
The stability of indium in water makes it a promising reagent for performing radical reactions in aqueous media. Naito has exploited indium as a radical initiator in the addition of alkyl radicals to imines in aqueous media.[99a,b] Both a glyoxylic oxime ether and a glyoxylic hydrazone were shown to be excellent radical acceptors with sufficient water stability to be of practical value. Curiously, water is essential for reactivity and it is assumed that it helps to activate indium and that it acts as a proton donor. An ionic mechanism has been discounted, as the addition of a radical scavenger inhibits the reaction. This control experiment does not rule out the possibility that an organoindium species is formed by sequential SET prior to addition. The reaction proceeds at a slower rate than those initiated by triethylborane, but it is cleaner, resulting in less side products, and requires fewer equivalents of the radical precursor to achieve good yields. The same reaction conditions can be used for the intermolecular addition of alkyl radicals to activated alkenes in aqueous media.

Low-valent indium compounds and indium hydrides (see Section 2.6) are rapidly becoming valuable reagents for radical reactions. With a greater understanding of the radical chemistry of indium, it is anticipated that the utility of these reagents will increase.

2.7.4. *Samarium(II) iodide*

Of all the reagents introduced for the formation of radicals, samarium(II) iodide is possibly the most versatile and widely used after tributyltin hydride. It has been employed in most forms of radical reactions, including ketyl–alkene couplings, conjugate additions, pinacol-like coupling reactions, deoxygenations, desulfonylations, dehalogenations and many other reduction reactions; its uses have been extensively reviewed[20–22] and many examples are discussed in the appropriate sections of this report.

Despite their ubiquity, the mechanism of many samarium(II) iodide-mediated reactions is still debatable; it is unclear whether the active species is a radical, an anion or an organosamarium species. Often, cyclopropyl ketones are employed as probes to ascertain the intermediacy of a ketyl radical anion; ring opening of the cyclopropane is seen as evidence of a radical process, whilst a lack of ring scission indicates either an anion or an organosamarium species exists. It appears that this assumption is misleading. Whilst investigating intramolecular pinacol couplings, Handa noted that **66** reacts to give **68** without any observable cyclopropane ring opening (Scheme 22).[100] The paper suggests that the rate of 5-*exo*-*trig* cyclisation of the ketyl radical **67** is considerably faster than the rate of ring opening. The ease of cyclisation is thought to arise due to the nucleophilic nature of the ketyl radical, combined with the increased electrophilicity of the ketone caused by chelation to the samarium(III) cation found in **67**. Even more interesting is the fact that the ketone reduction appears to require chelation; in competition experiments between the diketone **66** and a monoketone, the latter is unreactive, suggesting that inner-sphere SET is important.

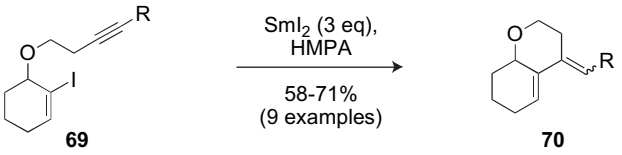


Scheme 22.

The role of hexamethylphosphoramide (HMPA) in samarium(II) iodide-mediated ketyl radical cyclisations is poorly understood. Coordination of HMPA to samarium forms a more powerful reductant that promotes the formation of the ketyl radical, but it appears that coordination of the ketyl radical anion to the sterically congested samarium(III)–HMPA complex stabilises the radical to such an extent that it can inhibit the reaction. Thus, it is necessary

to liberate the contact ion pair through displacement of the anion by yet another equivalent of HMPA to furnish the solvent-separated ion pair with concomitant release of the steric constraint to cyclisation.[101] Clearly, the mechanism of samarium(II)-promoted cyclisations is more complex than was originally thought.

Samarium(II) iodide has been used to synthesise a variety of heterocycles via numerous different bond-forming processes. One route that has been taxing to achieve by other radical methods is the cyclisation of alkenyl radicals, such as those derived from **69**, onto alkynes to form tetrahydropyrans with two *exo* alkenes such as **70** (Scheme 23).[102] Whilst analogous dienes can be formed by 5-(π-*exo*)-*exo*-*dig* cyclisations, the corresponding 6-(π-*exo*)-*exo*-*dig* process is unfavourable, with only two examples being known prior to this study. In order to obtain good yields, it appears that the alkyne must be substituted with either an aromatic ring or an alkene; when the substituent is either an alkyl group or a silyl group, cyclisation occurs in less than 30% yield. Presumably the reason for this observation is the stability of the alkenyl radical formed during the cyclisation, compared to the initial alkenyl radical. Unfortunately, the stereoselectivity of the reaction is poor, giving essentially a 1:1 mixture of the *E*- and *Z*-alkenes. Samarium(II) iodide has also been used to generate radicals from aryl iodides.[103a,b]



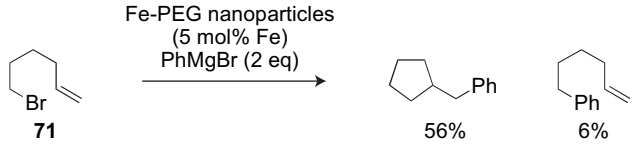
69 **70**

Scheme 23.

The popularity of samarium(II) iodide continues to increase as more uses are found for this versatile and user-friendly reagent. There is no reason to think that research into samarium(II) iodide will diminish in the foreseeable future.

2.7.5. Transition metal-catalysed radical couplings

One of the most exciting developments in radical chemistry is the use of sub-stoichiometric quantities of transition metal complexes and nanoparticles for the generation of alkyl radicals. Whilst the majority of this research has been driven by the desire to overcome the limitations of traditional palladium-catalysed cross-coupling technologies, it is rapidly becoming apparent that these results will have a profound impact on the field of radical chemistry. The background material, the cross coupling of sp^3-centres without β-hydride elimination or prohibitively slow oxidative addition, is beyond the scope of this review; interested readers are referred to more authoritative reviews.[104a–c] For operational simplicity, the use of iron nanoparticles offers the greatest potential; these are simply generated by the reduction of iron(III) chloride with an aryl Grignard reagent in the presence of polyethylene glycol (PEG). The latter polyol is necessary to stabilise the nanoparticles. The nanoparticles can either be pre-formed or prepared in situ and they catalyse the coupling of a range of primary and secondary alkyl iodides, bromides and chlorides with non-hindered aryl Grignards.[105] The reaction is believed to proceed by SET from the iron to the alkyl halide followed by fragmentation of the radical anion to give an alkyl radical and a halide anion. The alkyl radical can then undergo standard radical reactions before either attacking an iron-aryl complex or being trapped as an iron species that can undergo reductive elimination. Evidence for the radical nature of this reaction originates from the cyclisation of **71** prior to cross coupling (Scheme 24) as well as the ring opening of suitable cyclopropanes. The simplicity of this procedure is a considerable advantage, compared to the use of pre-made well-defined metal complexes, and it offers comparable and, in a number of examples, improved activity.[106a–c] It should be stressed that the mechanism has not been conclusively delineated; Fürstner has also prepared low-valent iron complexes and employed them in the coupling of alkyl halides and aryl Grignard reagents. The results of these reactions showed that, whilst some halides underwent 5-*exo*-*trig* cyclisations, in agreement with the postulated radical mechanism, many others did not.[107]



71

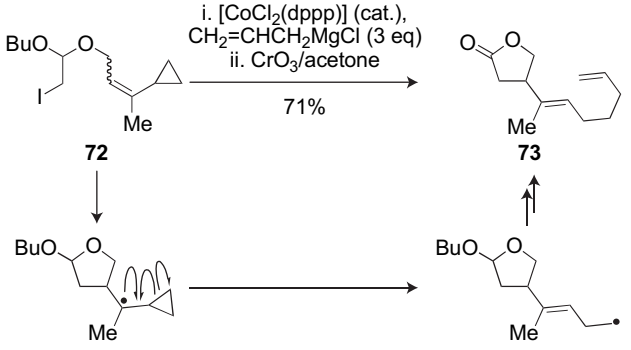
Scheme 24.

An analogous coupling reaction has been developed utilising cobalt(II) phosphine complexes[108] and cobalt(II) amine complexes.[109] Both systems permit the coupling of a range of primary bromides and iodides with aryl Grignard reagents. Once again, substrates with pendant alkenes cyclise prior to the cross-coupling reaction. The amine system appears to be more general than the phosphine system, allowing secondary substrates to react as efficiently as their primary counterparts. The amine-based system gives superior yields for direct intermolecular couplings, whilst the phosphine system is better suited to tandem cyclisation–coupling reactions. The transformation appears to be rapid, as both systems permit the use ester-containing substrates without any nucleophilic addition being observed.

Aryl Grignard reagents are not the only coupling partners that can be utilised; purportedly radical variants of both the Stille[110] and the Suzuki[111] couplings have been developed employing aryl monoorganotin and arylboronic acid reagents, respectively. Both reagents are more attractive than Grignard reagents, due to their increased stability and functional-group tolerance. The tin-based side products of the monoorganotin compounds are inorganic species that generally do not suffer from the purification and toxicity problems observed with the triorganotin compounds. In both examples, nickel(II) complexes are utilised as catalysts; the Stille coupling employs 2,2′-bipyridine as a ligand, whilst the Suzuki coupling utilises simple amino alcohols. Of the two protocols, the Suzuki reaction appears to be more general, allowing the coupling of both primary and secondary alkyl bromides, iodides and chlorides. These conditions also show greater tolerance to substituents in the *ortho* position of the aryl-coupling partner than the Grignard-based methodologies. Similar to the iron-catalysed reactions, cyclisation of alkene substrates prior to coupling suggests that a radical mechanism is involved. This hypothesis is further reinforced by the observation that the Stille reaction gave the same diastereoselectivities independently of the ligand used (2,2′-bipyridine, bathophenanthroline or 4,4′-dimethoxy-2,2′-bipyridine) and the diastereoselectivities were essentially identical to those obtained in both the radical Suzuki coupling and the tributyltin hydride-mediated cyclisations. The radical nature of the reaction has gained further support from both practical and theoretical studies.[112]

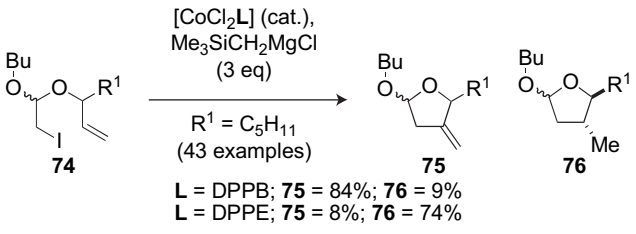
The cobalt-based system is the most developed and permits the coupling of alkyl halides with allyl,[113a,b] alkenyl and alkynyl[114] Grignard reagents as well as with aryl reagents. The allylation reaction proceeds smoothly with primary, secondary and tertiary halides, although ligand optimisation is required for each substrate. The cyclisation of **72** with concomitant ring opening of the cyclopropane and subsequent allylation to give **73** allude to a radical mechanism (Scheme 25).[113a,b] An early investigation of enantioselective allylation has been made, but with little success, and the highest enantioselectivity is currently 22% ee. Curiously, the

alkenylation and alkynylation is limited to the coupling of trimethylsilyl-substituted Grignard reagents.[114] At present, the reason for this restriction is unclear; other silyl substituents gave poor yields, as did non-silylated reagents. The greatest drawback of the current methodology is the need to perform the reactions with *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) as the solvent.



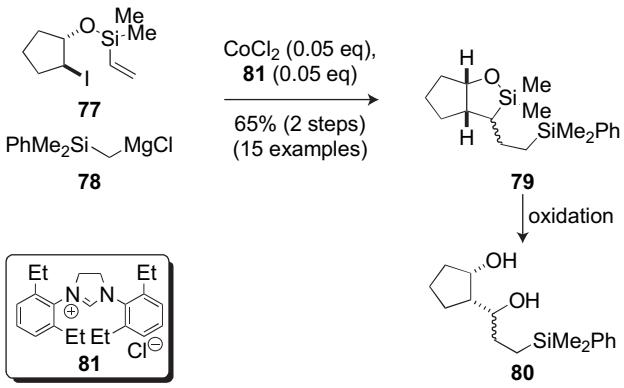
Scheme 25.

The cobalt methodology forms the basis of a radical-based alkenylation reaction analogous to the Heck reaction.[115a,b] The putative active low-valent cobalt species is formed by the reduction of a cobalt salt with trimethylsilylmethylmagnesium chloride; no other Grignard reagent appears to form the active species, again illustrating an interesting dependence on silyl reagents. A variety of alkyl halides can be employed in the reaction; tertiary halides require higher temperatures than primary and secondary halides, whilst iodides generally give lower yields than both bromides and chlorides. Curiously, in this reaction, esters and other reactive functionalities were no longer tolerated unlike previous coupling conditions. Additionally, amine ligands fail to give products and only phosphine ligands generate the active species. An intriguing result is found with the cyclisation of iodide **74**; if 1,4-bis(diphenylphosphino)butane (DPPB) is the ligand, the major product is the alkene **75**, resulting from a Heck-like transformation. If 1,2-bis(diphenylphosphino)ethane (DPPE) is used, reductive cyclisation to furnish **76** is observed (Scheme 26). This methodology complements the Heck reaction, as it permits alkyl substrates to be utilised that would normally suffer β-hydride elimination. With alkyl halide substrates, the reaction is believed to proceed by a radical intermediate, whilst, in both alkenyl and aryl halide substrates, a more conventional oxidative addition step is postulated.



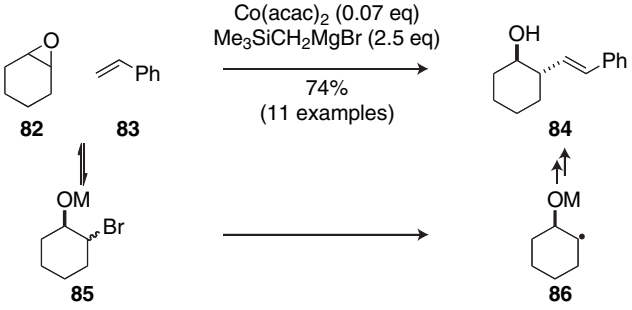
Scheme 26.

The combination of cobalt(II) chloride and various *N*-heterocyclic carbene ligands, such as **81**, promotes the synthesis of cyclic ethers and amines by radical cyclisation followed by cobalt-mediated coupling with α-silyl, alkyne or aryl Grignard reagents.[116] The most impressive application of this technology is the synthesis of diols such as **80** (Scheme 27). In these reactions, the radical formed from iodide (**77**) cyclises on to a silicon-tethered alkene to give a primary radical that is trapped by a cobalt complex. Interaction of **78** with the complex followed by reductive elimination gives the bicycle **79**, which can be subjected to Tamao–Fleming oxidation to give **80**.



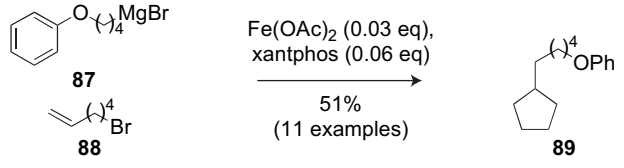
Scheme 27.

An alternate cobalt system permits the Mizoroki-Heck-like coupling of styrene **83** with a range of epoxides such as **82** to give homocinnamyl alcohols **84** (Scheme 28).[117] The exact nature of the catalyst is unclear, but a silylated Grignard reagent is again a requirement. Unlike titanocene(III)-mediated reactions, the coupling does not proceed via reductive ring opening of the epoxide (see Section 2.7.1); instead, magnesium bromide formed through the Schlenk equilibrium affects ring opening to give a bromoalkoxide **85**. SET then occurs to give the radical **86**, which adds to styrene. Not only can a range of epoxides be used in the reaction but two phenylsulfonyl-protected aziridines also undergo ring opening and addition to styrene. An overview of cobalt-based couplings can be found in a recent article.[118]



Scheme 28.

The majority of these couplings involve the reaction of an alkyl or aryl halide with an sp^2-hybridised organometallic reagent; the coupling of sp^3–sp^3 centres is still relatively rare. A simple iron-based system has achieved the latter coupling, permitting the addition of alkyl Grignard reagents **87** to alkyl halides **88** (Scheme 29).[119] Once again, the evidence for the intermediacy of a radical species comes from the 5-*exo*-*trig* cyclisation of **88** prior to coupling to give **89** and from the ring opening of bromomethylcyclopropane. Currently, this methodology is limited to primary halides, giving poor yields with secondary halides, but it clearly shows the potential of transition metal-mediated radical chemistry.

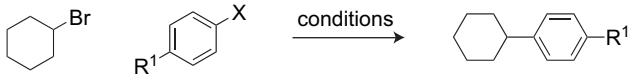


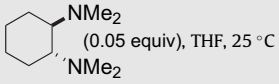
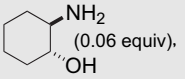
Scheme 29.

An accurate comparison of the different methodologies is not possible, as different examples are used in each report, but some valuable information can be gleaned from Table 1. Whilst the

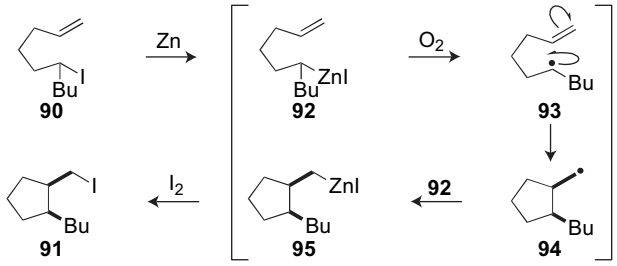
highest yield is obtained with a well-defined iron complex, the experimental ease of the other methodologies makes them more attractive. In terms of the substrate scope, either the radical Suzuki reaction[111] or the cobalt-catalysed[109] systems currently display the most versatility.

Table 1
Comparison of metal-catalysed radical couplings



R^1	X	Conditions	Yield (%)	Ref.
Me	MgBr	$FeCl_3$ (0.05 equiv), PEG (M_W 14,000), Et_2O, 35 °C	78	105
H	MgBr	$[Li(TMEDA)]_2[Fe(C_2H_4)_4]$ (0.05 equiv), THF, −20 °C	94	107
H	MgBr	$CoCl_2$ (0.1 equiv), DPPP (0.12 equiv), THF, −15 °C	24 95	108 109
H	MgBr	$CoCl_2$ (0.06 equiv),  (0.05 equiv), THF, 25 °C		
H	$SnCl_3$	$NiCl_2$ (0.1 equiv), 2,2′-bipy (0.15 equiv), KO*t*-Bu (7.0 equiv), *t*-BuOH/*i*BuOH, 60 °C	83 70	110 111
SMe	$B(OH)_2$	NiI_2 (0.06 equiv),  (0.06 equiv), NaHMDS (2 equiv), *i*PrOH, 60 °C		

Organozinc reagents often show 'unusual' reactivity, adding to unactivated alkenes despite their inability to add to a carbonyl functionality unaided by a catalyst. It has previously been shown that dialkylzinc compounds can donate an electron to oxygen and thus generate alkyl radicals. Through a series of comparison reactions with tin-mediated atom transfer cyclisations, it has been elucidated that alkylzinc halides react in a similar manner and can be employed as radical precursors.[120] Thus, when iodo-alkenes, such as **90**, are reacted with zinc metal followed by iodine they give cyclopentanes **91** with the same stereoselectivity as the tin-mediated cyclisations (Scheme 30). Interestingly, the mechanism for this reaction would appear to involve the reduction of the alkyl halide to an alkyl radical that is probably reduced on the surface of the metal faster than it can cyclise, thus generating an alkylzinc halide **92**. The latter is oxidised by oxygen to give an alkyl radical **93** that is identical to the first radical *except* for its chemical environment. Intramolecular cyclisation then furnishes a primary radical **94**, which participates in zinc group transfer with a second equivalent of organozinc **92** to give **95**. Rigorous removal of oxygen from the solvent precludes cyclisation. Undoubtedly, there is renewed interest in organozinc compounds due to their functional-group tolerance, and they have a healthy future in radical chemistry, as highlighted by a recent *Perspective*.[44]

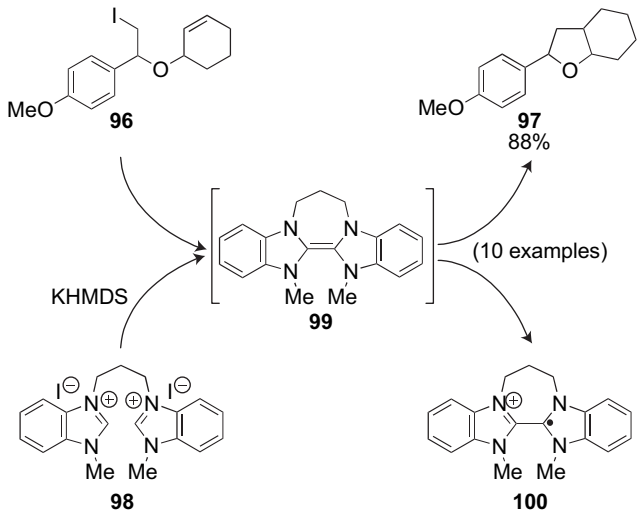


Scheme 30.

It is clear that the development of new metal-mediated methods for the formation of alkyl radicals will have a great impact on future research.[121a,b] Whilst the current methods have not yet been successfully employed in enantioselective synthesis, it is anticipated that it is only a matter of time before this shortcoming is addressed. It should be remembered that, twenty years ago, few researchers believed that any enantioselective radical reactions could be achieved and this clearly is no longer the case.

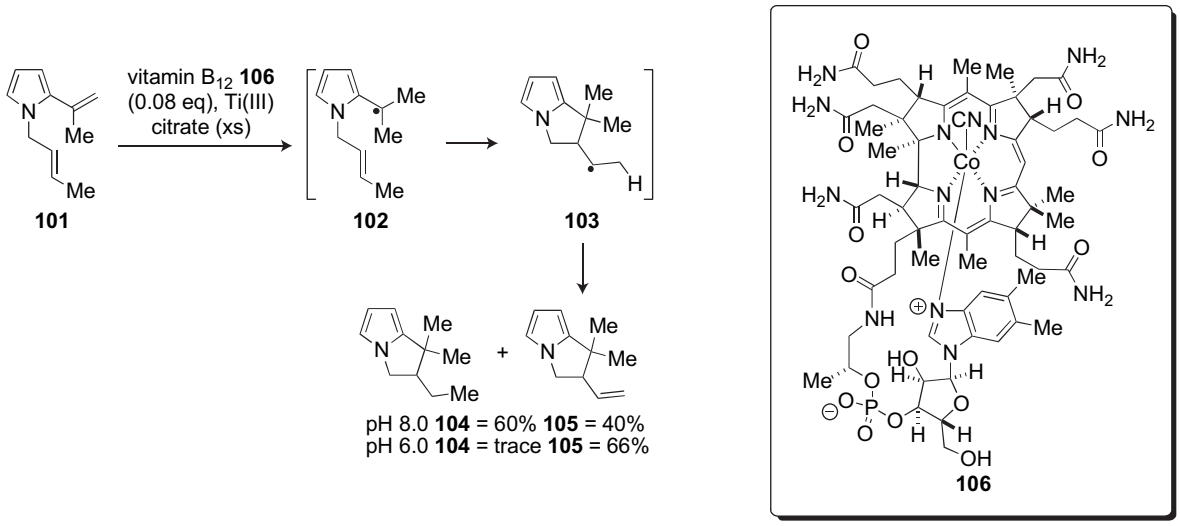
2.7.6. *Miscellaneous single electron donors*

One of the most exciting alternatives to metal-based SET reagents is the tetraazaalkene **99**, a neutral ground-state organic molecule that can act as a super single electron donor (Scheme 31).[122] Electron donation from **99** is promoted by two stabilising factors acting in concert; first, considerable aromatic stabilisation energy resides in the formation of the, radical cation **100** and secondly, further stability is imparted on both the cation and the radical by the adjacent nitrogen atoms. These combined forces allow **99** to reduce unactivated aryl iodides and alkyl iodides, such as **96**, to a radical that cyclises to give **97**. The major drawback of this methodology arises from the high reactivity of **99** towards air and, as a result, the optimum yields are obtained when **99** is made immediately prior to reaction by simple deprotonation of the stable salt **98**. This reaction proceeds under mild, essentially neutral conditions and therefore has a potentially wide functional-group tolerance. It is anticipated that further uses of this, and related, reagents will be reported in the future. In fact, more reactive variants, based on simple bisimidazolylidenes, have already been reported, but these have been utilised in the formation of aryl anions and desulfonylation instead, of in radical chemistry.[123a,b]



Scheme 31.

Another similarly attractive radical initiator is formed from the combination of sub-stoichiometric vitamin B_{12} **106** and stoichiometric titanium(III) citrate.[124] The reagent is highly chemoselective and only activates mono- or 1,1-disubstituted arylalkenes. Monosubstituted derivatives invariably undergo dimerisation, whilst the 1,1-disubstituted arylalkenes readily participate in cyclisation reactions with non-activated alkenes. Both pyrrolizines, such as **104** and **105**, and substituted tetrahydrofurans can be prepared in good yields (Scheme 32). One of the advantages of this system is that the product distribution is strongly influenced by the pH of the reaction medium; at pH 8.0, alkene **101** furnishes the reduced compound **104** as the major product, whilst, at pH 6.0, alkene **105** predominates. Whilst the mechanism for alkene activation is not fully understood, it is thought that the alkyl radicals **102** are generated



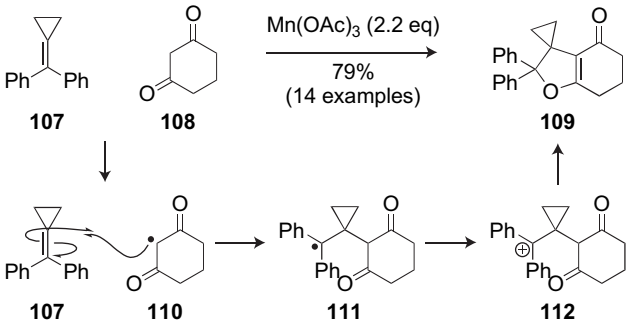
Scheme 32.

by the addition of a low-valent cobalt(I) species across the appropriately substituted alkene **101** to give an organocobalamin that undergoes homolytic cleavage to produce **102**. Cyclisation to give **103** is followed by one of two processes; at pH 6.0, the Ti(III)-mediated reduction of the cob(II)alamin species produced during the activation of the alkene is very slow and, thus, it has sufficient time to abstract a β-hydrogen from **103** to yield **105** and a hydridocobalamin. The latter is rapidly deprotonated to regenerate the active cob(I)alamin species. Alternatively, at higher pH, the cob(II)alamin is reduced before it can abstract the hydrogen and radical **103** is reduced to **104**, presumably via hydrogen abstraction from the solvent. The current methodology offers a mild method for the initiation of radical cyclisations; it is particularly attractive that the product can be selectively formed in either the reduced or non-reduced form, depending upon the pH. The same system has been used in the dimerisation of a variety of styrene derivatives as well as benzylic bromides and chlorides. A second publication includes a more detailed mechanistic exploration.[125]

2.8. Manganese-based reagents

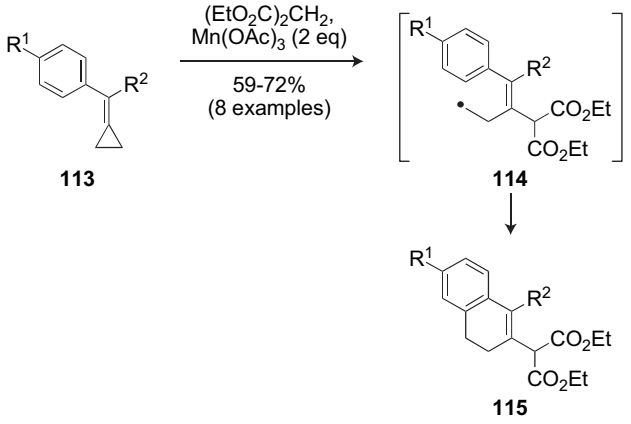
An attractive method for the generation of *C*-centred radicals is the oxidation of acidic C–H positions utilising transition metal complexes such as manganese(III) acetate. The advantages of such systems are manifold; primarily, C–H activation precludes the need to synthesise specific radical precursors. Invariably, radical formation occurs adjacent to an enolisable carbonyl group, with the rate of radical generation correlating with the enolisability of the substrate. Thus, electron-withdrawing groups at the α-position greatly increase the ease of radical generation. The exact mechanism of radical generation is still a matter of contention; it is possible that the reaction proceeds via the slow formation of the manganese(III) enolate followed by a rapid loss of manganese(II) with concomitant formation of the radical. Alternatively, SET occurs from the enol to give a radical cation that then loses a proton to give the required α-carbonyl radical. Radicals formed by this methodology are invariably electrophilic due to the presence of the electron-withdrawing groups and they readily add to electron-rich acceptors. More background material is available in a review of transition metal-generated radicals.[24]

The use of manganese(III)-mediated radical reactions for the formation of C–C bonds has been extensively developed over the last two decades; many of these reactions involve consecutive radical–ionic processes to form heterocycles. This is exemplified by the following annulation process; treatment of diphenylmethylenecyclopropane **107** with 1,3-cyclohexanedione **108** in the presence of 2.2 equiv of manganese(III) acetate gives **109** (Scheme 33).[126] The reaction proceeds via the formation of the α-carbonyl radical **110**, which adds to the alkene to furnish the intermediate **111**. The radical is stabilised by the two phenyl rings and, thus, does not participate in cyclopropane ring-opening rearrangement, instead being oxidised by another equivalent of manganese(III) acetate to the cation **112**. Finally, cyclisation of the carbonyl on to the cation gives **109**. A variety of methylenecyclopropanes can be used in this reaction but they must possess an aryl substituent to stabilise the radical or unidentified side products are formed. A disadvantage of this reaction, as with many manganese(III) acetate-promoted transformations, is that the reaction must be performed in acetic acid or only a trace of product is observed.



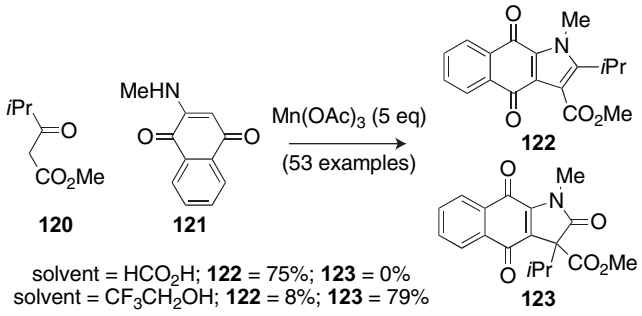
Scheme 33.

Conflicting results have been reported;[127] treatment of a series of mono-substituted aryl methylenecyclopropanes **113** with diethyl malonate and manganese(III) acetate gave the substituted 3,4-dihydronaphthalenes **115** (Scheme 34). Strikingly, the report includes examples of di-substituted methylenecyclopropanes as well. The dihydronaphthalenes **115** arise from radical fragmentation of the cyclopropane to give intermediate **114** that undergoes intramolecular addition to the aryl ring. At present, it is unclear why changing from a diketo species to a diester alters the reactivity so dramatically. It is hoped that the extraordinary differences in reactivity between the two systems are explained in due course.



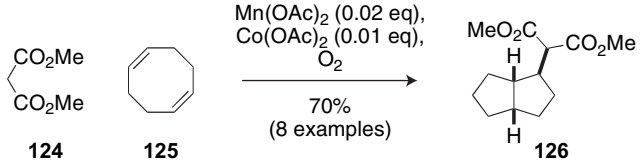
Scheme 34.

Both the solvent and the addition of copper salts can influence the fate of the initial adduct radical, as illustrated in Scheme 35.[128] Cyclisation of **116** in the presence of 2 equiv of manganese(III) acetate and 1 equiv of copper(II) triflate in acetonitrile gave the bicycle **117**. It is essential for the solvent to be deoxygenated in order to obtain impressive yields. When the copper oxidant was omitted and a protic solvent used, the methyl-substituted cyclopentane **118** was formed via a reductive process. Finally, a mixture favouring the alkene **119** over the lactone **117** was obtained if the reaction was performed with copper(II) acetate and dimethyl sulfoxide. A similar additive effect has been reported in the synthesis of carbocycles tethered to oxygen heterocycles.[129]

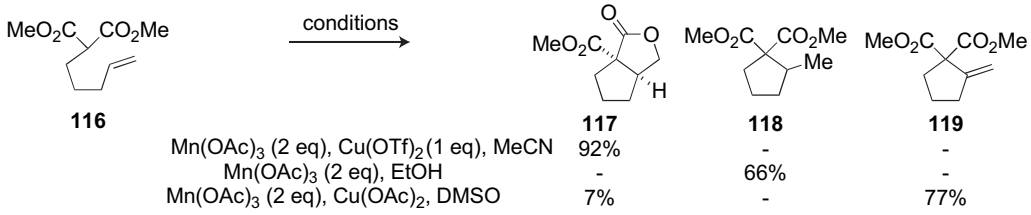


Scheme 36.

One of the main drawbacks of the manganese(III) methodology is that the metal is normally employed in excess. A catalytic variant has been developed that utilises just 0.02 equiv of manganese(II) acetate and 0.01 equiv of cobalt(II) acetate with oxygen as the terminal oxidant.[131] Under these conditions, a variety of malonates (**124**) or their equivalents add to non-activated alkenes such as **125** to give adduct **126** in good yield (Scheme 37). A plausible mechanism involves oxidation of the cobalt(II) species by the oxygen to give an intermediate that can convert the manganese(II) into the



Scheme 37.



Scheme 35.

Manganese(III)-mediated oxidative radical reactions can occur in a range of solvents, although acetic acid appears to be the most common. The solvent has little effect on the initial radical reaction, but it can influence the fate of the radical adduct. Reaction of 2-(methylamino)-1,4-naphthoquinone **121** with β-keto ester **120** can give two products, indole **122** and lactam **123** (Scheme 36).[130] Both are generated by the radical addition of **120** to **121** to form a C–C bond; the solvent then controls the second step. When the reaction was performed in formic acid, indole **122** was formed exclusively as the acid catalyses amine condensation. When the solvent was 2,2,2-trifluoroethanol, lactam **123** became the predominant product. This was formed by oxidation of the enamine to form an aminyl radical that cyclised onto the enol form of the β-keto ester moiety. After a third oxidation, this time forming a cation, there is an alkyl-group migration and generation of **123**. Formation of **123** was considerably slower than the synthesis of **122** in the acidic medium (16 h vs 30 min). This methodology proves highly versatile, a common radical-mediated C–C bond-forming reaction is followed by the chemoselective synthesis of one of two compounds, depending upon the acidity of the reaction medium.

active manganese(III) species. Unfortunately, the current methodology still employs acetic acid at elevated temperatures as the reaction medium; more promise is shown by the one example that is performed under solvent-free conditions. This methodology has been extended to permit the formation of radicals from acid anhydrides and thus allow the synthesis of carboxylic acids.[132] The reaction is performed utilising the anhydride as the solvent and it is vital that the concentration of oxygen is carefully controlled; too much oxygen results in polymerisation. The optimum conditions required a mixture of oxygen (0.1 atm) and nitrogen (0.9 atm), although it is more practical to simply perform the reaction open to the air, which results in only a minimal decrease in yield. Interestingly, the use of stoichiometric manganese(III) gives considerably lower yields.

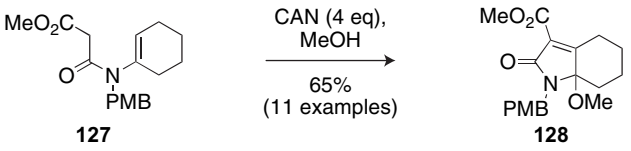
The oxidative nature of the manganese(III)-mediated reactions, with the inherent retention of functionality, is highly attractive in the functionalisation of complex molecules.

2.9. Cerium-based reagents

High-oxidation-state cerium(IV) species are capable of the oxidative generation of radicals from enolisable carbonyls; a recent

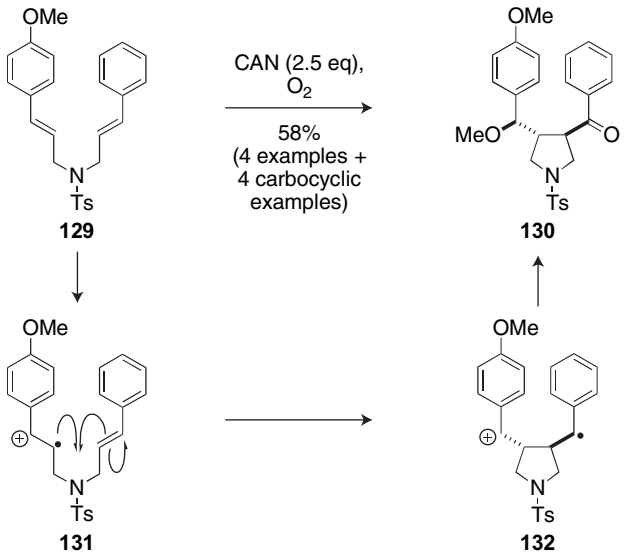
review details the use of cerium(IV) reagents in synthesis.[25] For further mechanistic insight into the formation of radicals and radical cations from β-diketones and β-keto silyl enol ethers interested readers are directed towards a recent publication by Flowers;[133] this paper suggests that some C–C bond-forming reactions mediated by cerium(IV) may, depending upon the solvent, proceed via a radical cation, rather than by the postulated radical pathways.

Cerium(IV) ammonium nitrate (CAN) mediates a reaction analogous to the classic copper(I)-catalysed ATRC of α,α,α-trichloro acetamides (see Part 2, Section 2.8).[134] In this variant, simple β-amido esters, such as **127**, are the radical precursors and not halides (Scheme 38). Interestingly, when the same reaction is performed with manganese(III) acetate, a diene is formed, instead of aminol **128**. Both reactions are believed to proceed via radical cyclisation followed by the formation of an iminium ion. It is possible that methanol adds to the iminium species to give **128** in both reactions and the milder CAN-mediated reactions allow isolation of the adduct, whilst the acidic manganese(III) reaction conditions catalyse elimination. Alternatively, the manganese(III) system promotes deprotonation before alkoxy addition can occur.



Scheme 38.

Cerium(IV) reagents are capable of oxidizing electron-rich alkenes to give radical cations like **131** that can participate in a 5-*exo*-*trig* radical cyclisations. Thus, diene **129** undergoes oxidative cyclisation to give the saturated nitrogen heterocycle **130** (Scheme 39).[135] Cyclisation is followed by oxidation of the radical **132** to give a ketone, whilst the cation undergoes nucleophilic attack to give the ether. The reaction works equally well for the synthesis of cyclopentanes. In these examples, a malonate group replaces the nitrogen moiety; undoubtedly, the Thorpe-Ingold effect plays an important role in the success of this reaction. Both piperidines[136] and tetrahydropyrans[137] can also be prepared by the CAN-mediated oxidative ring opening of suitably substituted epoxides.



Scheme 39.

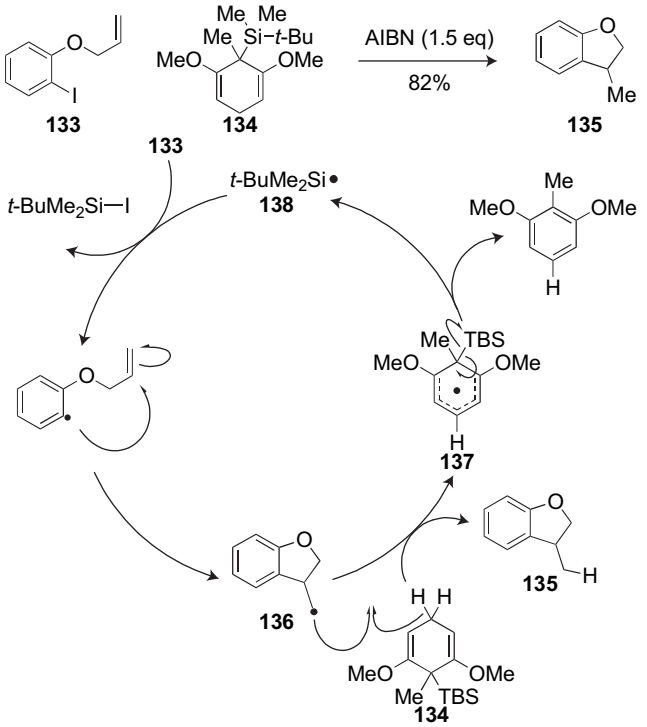
2.10. Organic radical reagents

This section outlines three disparate topics; the use of cyclohexadiene derivatives as hydride donors and two general methodologies for performing radical reactions. The first of these general methodologies is the use of alkoxyamines and the persistent-radical effect (PRE), whilst the second is the use of xanthates in a comparable reaction manifold; both methods are based around the long half-life of specific radicals.

2.10.1. Cyclohexadiene-based radical reagents

Amongst the most elegant alternatives to organotin hydrides are functionalised cyclohexa-1,4-dienes as hydrogen-donor reagents. The success of these reagents arises from the activation of the bis(allylic) C–H bond so that hydrogen abstraction is as easy as that from tin hydrides ($DH°$(R–H)=318.2 kJ mol^{-1}, compared to $DH°$(Sn–H)=326.6 kJ mol^{-1} for tin reagents). Furthermore, if a neutral radical is expelled from the resulting bis(allylic) *C*-centred radical intermediate, re-aromatisation occurs with all the inherent gain in resonance stabilisation energy that this entails (ca. 138.2 kJ mol^{-1} for benzene). Designing reagents based on cyclohexa-1,4-dienes has the additional benefit that the carbocyclic ring structure offers unparalleled potential for fine tuning of the electronics via the addition of substituents. The two leading proponents, Walton and Studer, have outlined the realisation of this concept in an edifying account.[27]

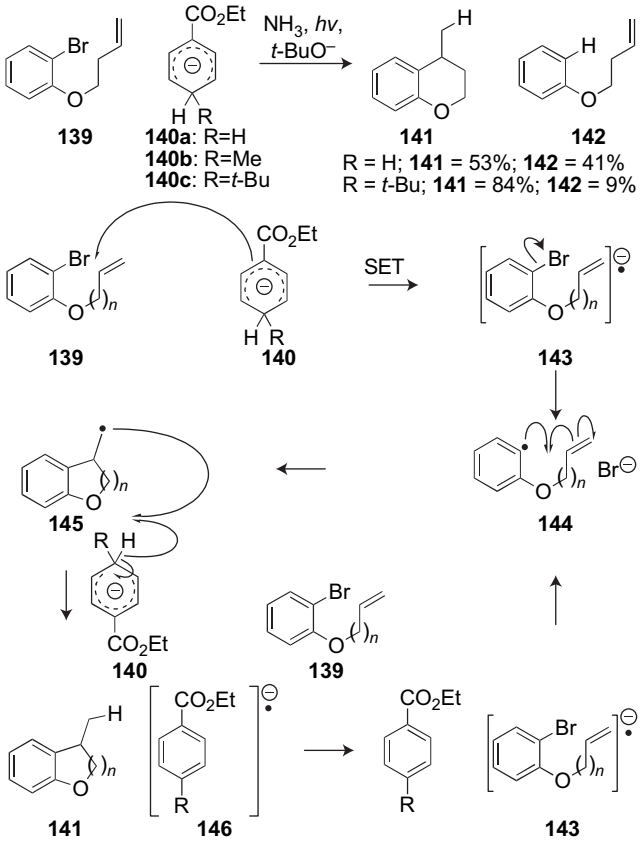
Silylated cyclohexa-1,4-dienes such as **134** appear to be the best examples of these reagents yet synthesised (Scheme 40).[138] These can be readily prepared on a large scale (30–40 g) in a 'one-pot' procedure and are stable solids. The methoxy substituents on the carbocyclic ring play two important roles; firstly, they enhance the rate of H donation by extending the resonance stabilisation of the cyclohexadienyl radical and secondly, they are thought to augment the rate of re-aromatisation or silyl-radical expulsion. Dienes without the methoxy substituents required alkoxy radicals to initiate chain reactions. Diene **134** is an excellent reagent for the reduction of a variety of functional groups, including primary,



Scheme 40.

secondary, and tertiary alkyl halides and aryl halides as well as xanthates and selenides. The reaction is very practicable; bromoadamantane can be reduced with no initiator, simply by performing the reaction under an atmosphere of air. Diene **134** can also be employed as a hydrogen source in a range of standard reductive radical reactions including the cyclisation of iodides such as **133** (Scheme 40), Beckwith–Dowd ring enlargement and Giese-type intermolecular radical additions. Diene **134** donates a hydrogen to radical **136** to afford the product and the cyclohexadienyl radical **137**, which undergoes re-aromatisation with expulsion of the corresponding silyl radical **138** that propagates the chain processes by reacting with the substrate **135**. The hydrogen-transfer step is the rate-limiting step and it is approximately 10-fold slower than that from tris(trimethylsilyl)silane and 55-fold slower than that from tributyltin hydride. As has been discussed in Section 2.2, a slow rate of hydrogen transfer can often be an advantage in radical reactions, especially those that involve either intermolecular couplings or tandem processes, both of which are prone to premature reduction. It is anticipated that such reagents will gain popularity over the coming years, due to their impressive reactivity, reduced toxicity and ease of purification.

A conceptually similar approach utilises the mono-anion of reduced ethyl benzoate **140** as both a source of electrons and of hydrogen (Scheme 41).[139,140] Irradiation of aryl halide **139** and reagent **140** results in the transfer of one electron from **140** to the cyclisation precursor to generate a radical anion **143** that fragments to afford the radical **144** and a halide anion. Cyclisation yields **145** that reacts with **140** to give the product and form the radical anion **146**, which propagates the chain. Like the previous methodology, the driving force for the fast hydrogen transfer is the re-aromatisation of **140**. One of the advantages of this system is that both bromides and aryl chlorides are effective precursors. Unfortunately, there are a number of disadvantages, namely the



Scheme 41.

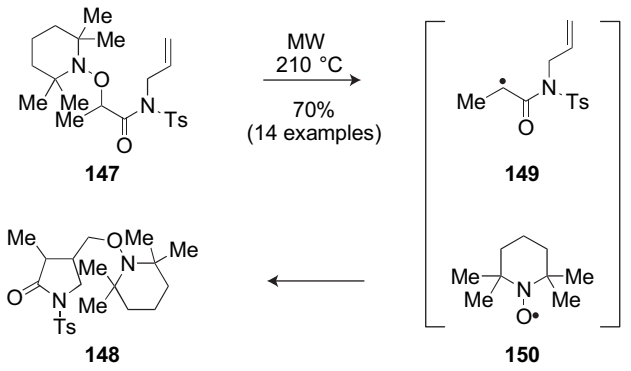
reagent **140** is generated via the reduction of ethyl benzoate by dissolving sodium in ammonia and the resulting NH_2^- ions have to be neutralised with *tert*-butanol. This generates highly basic alkoxide anions that preclude the use of base-sensitive molecules. Furthermore, whilst liquid ammonia may be a useful ionizing solvent, it is far from practical, requiring temperatures below −33 °C. Finally, the hydrogen-transfer step is very fast, near the diffusion-limit rate, meaning that only very rapid reactions give good yields; in all other processes, premature reduction becomes a competing pathway. Attempts to overcome this latter problem and to reduce the reactivity of the anion have centred on the addition of substituents to the *para*-position of the aromatic ring (**140** R≠H).[140] Such a change reduces the rate of hydrogen transfer in two ways; firstly, it removes one hydrogen atom and, secondly, it introduces steric congestion. Thus, **140b** (R=Me) is approximately half as reactive as **140a** (R=H), whilst **140c** (R=*t*-Bu) is a quarter as reactive as **140a**. The benefit of reducing the rate of hydrogen abstraction is apparent when the reagents are employed in a slow 6-*endo*-*trig* cyclisation; the non-substituted reagent **140a** furnishes 53% of **141** and 41% of **142**. When the *tert*-butyl derivative **140c** is utilised, an impressive 84% yield of the cyclised product **141** is obtained with only 9% of the reduced material **142**.

Even though **140** is readily prepared, it is anticipated that the cyclohexadiene reagents of Studer and Walton will become more popular due to their stability and mild reaction conditions. These derivatives offer great potential for clean, green radical chemistry and it is anticipated that their use should become more widespread.

2.10.2. Alkoxyamines and the persistent-radical effect

The persistent-radical effect (PRE) covers a class of reactions in which two different radicals, one long-lived or persistent, and the other transient or with a relatively short half-life react in a highly specific manner to give the cross-coupling product. Non-selective statistical reaction between the two radicals is suppressed, due to the inefficacy of the persistent radical to undergo homo-coupling. A more in-depth analysis of this effect and its use in organic synthesis can be found in two recent reviews.[26a,b] The success of this strategy is based on the thermal homolysis of certain alkoxyamines to give persistent nitroxide radicals and transient *C*-centred radicals. The transient radicals then undergo traditional radical chemistry, either cyclisation or intermolecular addition, before recombining with the nitroxide radical to give the product. Frequently, the initial homolysis generates a stabilised transient radical in a reversible process; this then reacts to give a new, non-stabilised radical that is irreversibly trapped by reaction with a nitroxide radical. The most common radical precursors are based on 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) and have been utilised in radical cyclisations and polymerisations.

The PRE strategy is exemplified by the cyclisation of alkoxyamine **147** to lactam **148** (Scheme 42). Reversible thermal homolysis of **147** gives the stabilised radical **149** and TEMPO **150**; cyclisation and subsequent irreversible trapping of the ensuing primary radical gives lactam **148**, formally the product of isomerisation.[141] Under standard thermal heating, the reaction takes 24 h; however, utilising microwave heating, the reaction can be performed in 2.5 min! A similar staggering acceleration was observed for the intermolecular variant; previously, under standard thermal conditions, the reactions took 3 days to go completion. Microwave heating allowed complete conversion in 10 min, a 430-fold acceleration, finally making this methodology practicable. It should be noted that this is one of only a few examples of microwave heating being utilised to accelerate radical reactions.



Scheme 42.

Microwave heating is not the only strategy to improve the efficiency of PRE reactions; altering the structure of the nitroxide moiety can also have a dramatic effect on the rate of reaction.[142] The activation energy for C–O bond homolysis depends upon the stability of both radicals and the structure of the nitroxide. Increasing the steric bulk of the nitroxide results in a far more efficient C–O bond homolysis; 2,6-di-*tert*-butyl nitroxide reacts over 4-fold faster than the standard TEMPO nitroxide, whilst one of the most effective nitroxides is the ethyl derivative **151** (Fig. 5). The intermolecular addition of TEMPO-derived malonyl radicals to simple alkenes can take three days to give good conversion; derivatives of **151** add in just 1.5 h and furnish the product in higher yield.

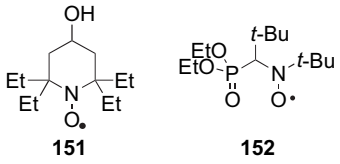
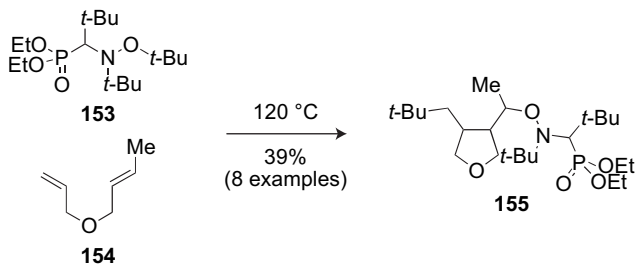


Figure 5.

Altering the nitroxide structure can overcome other problems inherent with the TEMPO-based methodology. The synthesis of lactones and lactams is often plagued by competitive hydrogen-atom abstraction and/or competitive intramolecular hydrogen-transfer processes. The use of SG1 (*N*-*tert*-butyl-*N*-(1-diethylphosphono-2,2-dimethylpropyl) nitroxide) **152**-based alkoxyamines (Fig. 5) can overcome these problems and permits the synthesis of lactams analogous to **148** to be achieved without recourse to microwave heating.[143] Presumably, the steric bulk of **152** permits a more efficient C–O bond scission, whilst the lack of readily abstracted hydrogens avoids other side reactions.

The majority of PRE-based transformations involve the use of pre-formed alkoxyamines; an elegant exception is the multi-component reaction sequence shown in Scheme 43.[144] In this reaction, a 1:1 mixture of *tert*-butyl-alkoxyamine **153** and diene **154** is heated in a sealed tube, facilitating an intermolecular radical addition, which is followed by cyclisation to furnish the tetrahydrofuran **155**. The reaction occurs with complete regioselectivity; the initial *tert*-butyl radical adds exclusively to the least-hindered alkene. Whilst the yield is far from satisfactory, the reaction offers a highly atom economical merger of two reagents, resulting in the formation of two new C–C bonds and the introduction of an oxygen functionality that can be utilised to further elaborate the molecule.

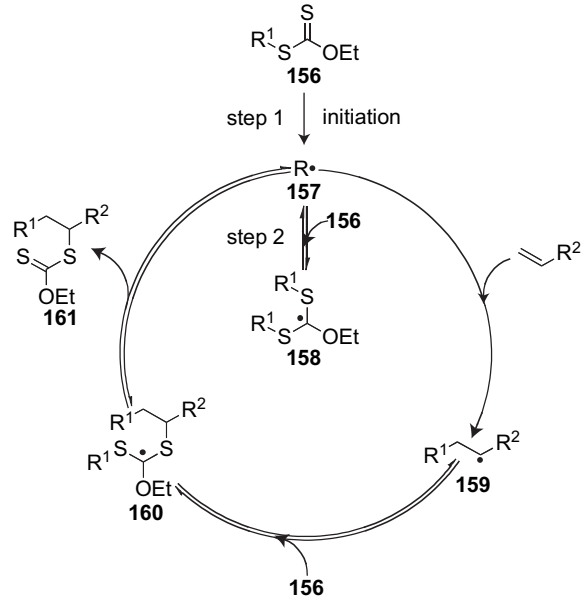


Scheme 43.

The use of the PRE is comparable to the radical chemistry of xanthates in many respects (see Section 2.10.3), as the long lifetime of the radicals involved allows additions to non-activated alkenes to occur without premature reduction. Thermal initiation means the methodology is atom economical and green. In cyclisation reactions, both xanthates and alkoxyamines permit reactions that are effectively isomerisations and, as a result, products retain useful functionality. In an analogous fashion to the xanthates, it is believed that this class of transformation will see increased use.

2.10.3. Xanthates in radical reactions

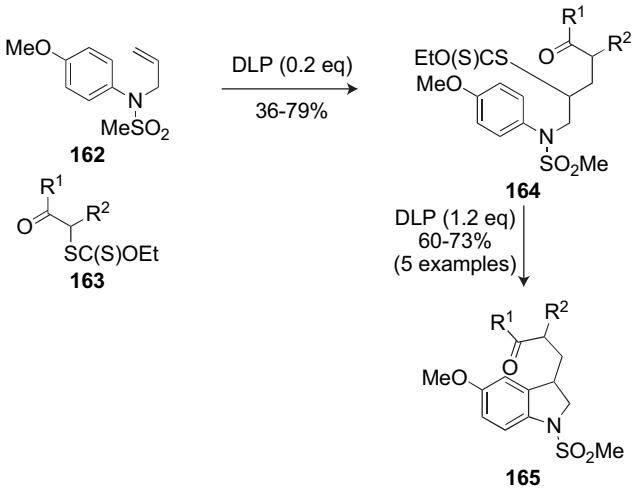
The radical chemistry of the xanthate group offers one of the most powerful and general tin-free methodologies for the formation of C–C bonds including many additions that are difficult to achieve via standard methods. The major advantage of xanthate chemistry arises from the reversible addition–fragmentation of alkyl radicals to xanthates and other related thiocarbonyls as outlined in the general mechanism (Scheme 44). Radical initiation (step 1) gives an alkyl radical **157** that has two possible fates; profitable addition to a suitable acceptor, or addition to a second equivalent of xanthate **156** to give the stabilised radical **158** (step 2). This radical is either too hindered to dimerise or it does so reversibly. Whilst **158** can fragment via cleavage of either the C–S or C–O bond, the latter type is rare, due to the strength of the C–O bond and the instability of the resulting ethyl radical. Therefore, C–S homolysis is the only productive pathway and, thus, addition of **157** to **156** is both reversible and degenerate. This effectively gives the radical **157** a protracted lifetime and allows it to react with non-activated acceptors. Addition of radical **157** to the appropriate acceptor gives **159**, which can be thought of as the chain carrier. Subsequent reaction with another equivalent of **156** results in the intermediate **160** that can either return to **159** or give the product **161** and the alkyl radical **157**. For a successful chain reaction, the alkyl radical **157** must be at least as, and preferably more, stable than the adduct **159** in order to drive the equilibrium in the last two steps. If **159** is less stable, then the reaction can still be forced to completion by utilising a stoichiometric amount of initiator.



Scheme 44.

The advantages conferred by this mechanism are manifold; the apparent prolongation of the lifetime of the alkyl radical **157** allows slow or reluctant reactions, including taxing intermolecular additions, to proceed without competitive side reactions. Group transfer of the xanthate moiety means additional radical and non-radical transformations allow elaboration of the product. Simple organic peroxides can be used as radical initiators avoiding the production of toxic waste. Furthermore, a number of methods exist for the introduction of the xanthate, including nucleophilic substitution, the use of electrophilic bis(xanthates) and conjugate additions. There have been a vast number of reports on the use of xanthates and it would be impossible to comment on them all; interested readers are directed towards a number of authoritative reviews written by Zard and co-workers, who are undoubtedly the pre-eminent researchers in this field.[145a–c,146] One example is included to highlight the power of xanthate chemistry.

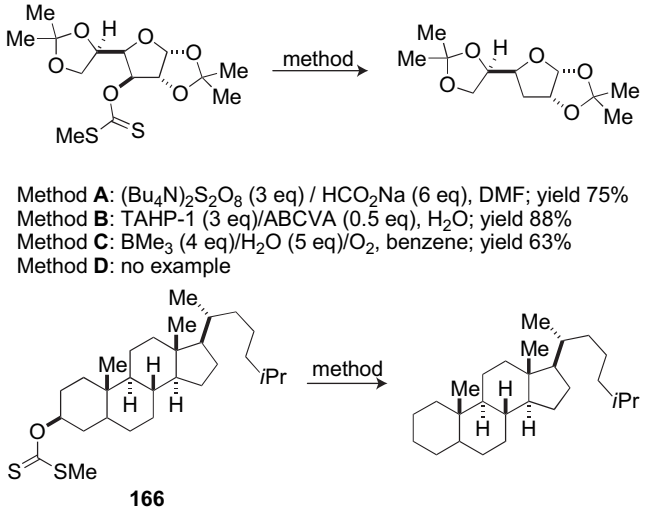
The xanthate-group transfer permits multiple radical reactions to be performed consecutively and this has led to an elegant, convergent synthesis of 2-substituted-5-methoxyindolines **165** (Scheme 45).[147] The reaction has two distinct steps; the first is the intermolecular addition of xanthate **163** to methanesulfonyl-protected allylaniline **162** to give **164**. A second radical reaction results in ring closure to give the indoline **165**. The first radical addition is a chain reaction, requiring only sub-stoichiometric quantities of peroxide initiator; the latter step is not a chain process and requires stoichiometric peroxide. Cyclisations onto aromatic rings can be problematic (see Part 2, Section 2.5) as they involve disruption of aromaticity. Undoubtedly, the lengthened lifespan of the alkyl radical generated from **164** aids the cyclisation. Additionally, the stoichiometric peroxide probably facilitates the oxidation–re-aromatisation step. This methodology was employed in a simple synthesis of melatonin. An analogous strategy has been employed in the synthesis of *C*-arylglycosides;[148a,b] in this sequence, a series of xanthates were coupled with alkenyl carbohydrates prior to cyclisation of the resultant secondary xanthates onto an aryl ring. Once again, the first reaction utilises dilauroyl peroxide (DLP) as an initiator, whilst the second requires a stoichiometric amount of DLP.



Scheme 45.

2.11. Miscellaneous reducing agents

The Barton–McCombie reaction is one of the most widely employed methods for the deoxygenation of primary and secondary alcohols. Classically, the reaction utilises tributyltin hydride; as a result, considerable effort has been focussed towards developing more environmentally benign and operationally facile variants. Whilst the following reagents have only been employed in deoxygenation reactions, it is not unreasonable to assume that they could be of value in other radical processes if the rate of hydrogen transfer is appropriate. Deoxygenation of a variety of primary, secondary and tertiary xanthates has been achieved by the carbon dioxide radical anion formed by the oxidation of sodium formate with tetrabutylammonium peroxydisulfate (method A; Scheme 46).[149] Tetrabutylammonium peroxydisulfate has advantages over other peroxydisulfates in that it is soluble in organic solvents. Phosphorus-based reagents are popular alternatives to tin hydrides (see Section 2.4); one practical derivative is hexadecanyltrimethylammonium hypophosphite (TAHP-1), which has been utilised as both a surfactant and as a phosphorus hydride radical chain carrier, thus permitting xanthate deoxygenations to be performed in neat water in the presence of a suitable water-soluble radical initiator, such as 4,4′-azobis(4-cyanovaleric acid) (ABCVA) (method B).[150] The long alkyl chain on TAHP-1 promotes the substrate solubility in water and the formation of a micellar system that accelerates the reaction. The majority of substrates were deoxygenated in excellent yields, with the exception of hydrophobic compounds such as the cholestanyl derivative **166**. Water can be employed as a hydrogen-atom source in deoxygenation reactions. Bubbling trimethylborane and air through a solution of xanthate in benzene and water furnishes the deoxygenated product in moderate-to-excellent yield after a simple work-up involving evaporation of the volatile by-products (method C).[151] The method enables simple deuteration by the substitution of D_2O for water. The authors believe that the hydrogen is abstracted from a complex formed between water and the trialkylborane; the resulting *O*-centred radical dissociates to give an alkyl radical chain carrier and a dialkylborinic acid. Tris(trimethylsilyl)methane (TMS_3CH) has been reported to promote standard radical reductions and cyclisations of primary, secondary, and tertiary alkyl halides as well as aryl halides and xanthates (method D).[152] A recent publication has questioned the validity of this paper; a combined practical and theoretical investigation of the utility of TMS_3CH in radical reductions by Coote and Sherburn found it to be completely ineffectual.[153]



Method **A**: $(Bu_4N)_2S_2O_8$ (3 eq) / HCO_2Na (6 eq), DMF; yield 75%
Method **B**: TAHP-1 (3 eq)/ABCVA (0.5 eq), H_2O; yield 88%
Method **C**: BMe_3 (4 eq)/H_2O (5 eq)/O_2, benzene; yield 63%
Method **D**: no example

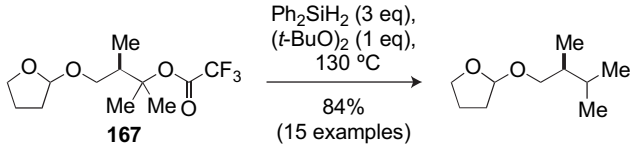
166

Method **A**: $(Bu_4N)_2S_2O_8$ (3 eq)/HCO_2Na (6 eq), DMF; yield 96%
Method **B**: TAHP-1 (3 eq)/ABCVA (0.5 eq), H_2O; yield 7%
Method **C**: BMe_3 (4 eq)/H_2O (5 eq)/O_2, benzene; yield 71%[a]
Method **D**: TMS_3CH (2 eq)/AIBN (0.5 eq), benzene; yield 89%[b]

Scheme 46. [a]Cholesterol derivative; [b]a later reference questions these results.[153]

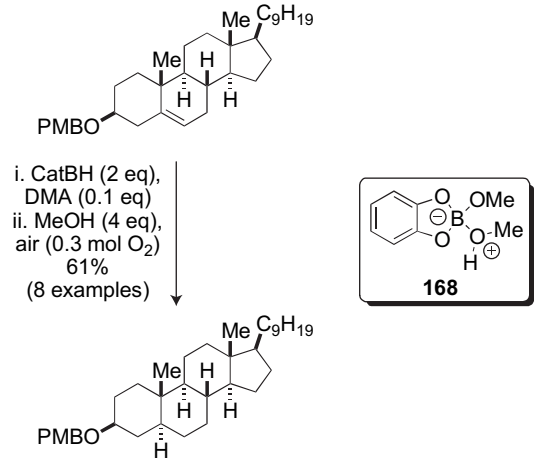
The deoxygenation of tertiary alcohols can be problematic as their thiocarbonyl/xanthates derivatives are rarely thermally stable and, thus, other radical precursors have been sought. Roberts has

shown that methoxymethyl (MOM) ethers can act as good precursors if the reduction is mediated by a thiol that acts as a polarity-reversal catalyst (see Section 2.5).[154] Alternatively, trifluoroacetate derivatives of tertiary alcohols such as **167** can be deoxygenated with diphenylsilane and di-*tert*-butyl peroxide (Scheme 47).[155] Good yields can be obtained with a variety of tertiary alcohols and it appears that reducible groups such as epoxides, ketones and esters are untouched by these reaction conditions.



Scheme 47.

B-Alkylcatecholboranes can be employed in the reduction of alkenes. The reduction is a two-step process involving hydroboration followed by radical reduction mediated by methanol and the slow introduction of oxygen (Scheme 48).[156] The methodology reduces a range of alkenes including those that give rise to primary, secondary and tertiary alkylboranes. Interestingly, a series of labelling experiments suggest that methanol is the source of the hydrogen atom that reduces the alkyl radical with zwitterion **168** as the active reagent. Propagation of the chain reaction occurs by ejection of a methoxy radical from the boronate derived from **168**. This mechanism is supported by the fact that other alcohols give far less efficient reactions.

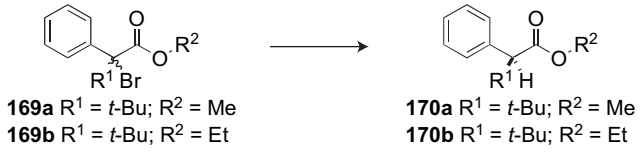


Scheme 48.

There is a perpetual demand for new hydrogen sources for radical reactions that are cleaner, more efficient, less toxic, and more highly selective and practical than tin hydrides; the reduction of alcohol derivatives offers an excellent testing ground for these reagents. Only time will tell if any of these have more general value in radical chemistry.

2.12. Chiral radical reagents

A multitude of chiral reagents exist for standard ionic transformations, yet the use of chiral reagents in radical chemistry is still woefully inadequate. Reagent control, utilising chiral hydrogen sources, is a challenging area. This section discusses reagents utilised exclusively in radical chemistry and does not cover the use of chiral complexing reagents or Lewis acids that can be employed in ionic as well as radical transformations. Three groups have reported related approaches to the chiral reagent-mediated reduction of α-bromo esters (Scheme 49).[157–160]



Scheme 49.

Metzger prepared the binaphthyl tin hydride **171** (Fig. 6)[159] and showed that, at low temperature (−100 °C), it reduced the bromide **169a** in excellent yield with 64% ee. The reagent was substrate specific, and reducing the steric bulk of R^1 lowered the enantioselectivity. Interestingly, the addition of magnesium-based Lewis acids to the system made little difference to the enantioselectivity (see below), but the use of the chiral tin bromide **172** led to considerable rate enhancements, reducing the reaction time from hours to minutes, and increasing the selectivity (68% ee at −78 °C). The exact role of **172** is unclear, and experiments show that the chirality of the hydride is responsible for the enantioselectivity and that the chirality of the bromide is unimportant. The data suggest an interaction between the bromide and the hydride, but its role in the reaction is uncertain. A catalytic variant has been developed employing just 1 mol% of **171** and 3 equiv of sodium cyanoborohydride to yield **170a** quantitatively with 30% ee. Whilst there is an appreciable drop in selectivity, this is the first example of a catalytic enantioselective reduction of this kind and bodes well for the future.

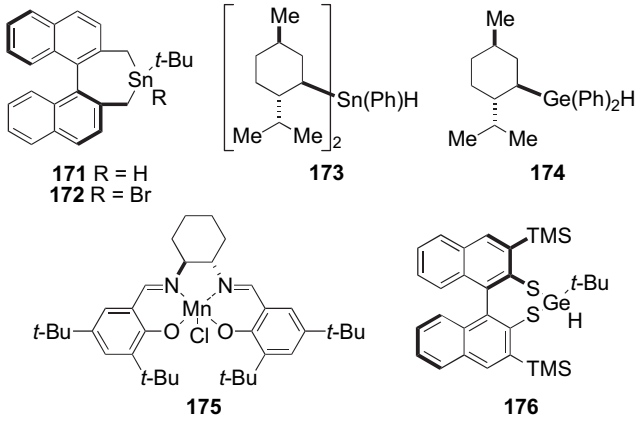


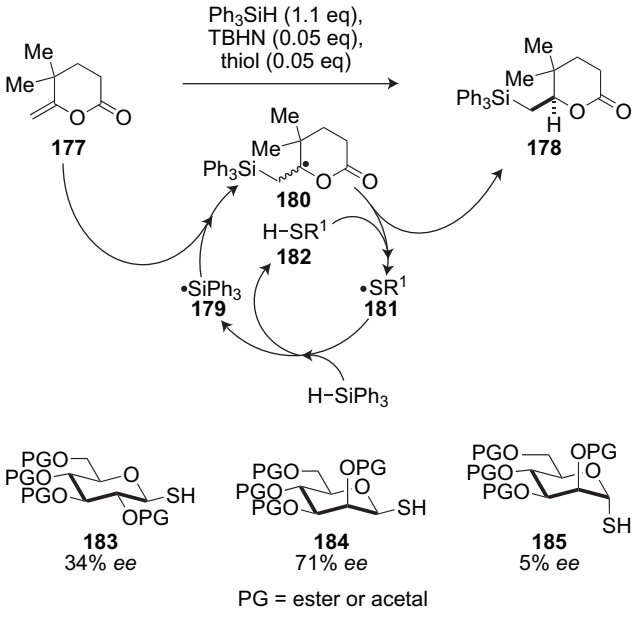
Figure 6.

Schiesser's results, utilising a menthyl-substituted stannane **173**, contradict some of Metzger's findings.[158] The presence of 1 equiv of a bulky Lewis acid had a dramatic effect on the reduction of ester **169b**. Selectivity as high as 83% ee could be achieved in the presence of the manganese–salen complex **175**, compared to the formation of a virtually racemic product when no Lewis acid was added; all bulky Lewis acids led to improved selectivities. Using the enantiomer of **175** gave an equally high selectivity of the *same enantiomer* of **170b**. Therefore, the sense of induction is controlled by stannane **173** and is independent of the Lewis acid. The Lewis acid is assumed to simply increase the effective bulk of the substrate. Even more remarkable was the dramatic effect that the relatively small magnesium ions have on the reaction; selectivities as high as 96% ee could be obtained for the reduction of **169a** in the presence of magnesium(II) triflate. It is possible that the magnesium allows dimeric ester complexes to form that increase the effective bulk of the substrate, but this has not been confirmed. The methodology was extended to the reduction of α-bromo amino

esters with spectacular results; protected amino acids could be formed in 99% ee. Presumably, this dramatic increase in selectivity arises due to the bidentate nature of the substrate that permits a rigid chelate to form that enhances facial selectivity. Schiesser has also prepared the germanium derivative **174**;[157] whilst this furnishes excellent enantioselectivities when used in conjunction with magnesium salts, the yields of the reactions are far from satisfactory. It is thought that the slow rate of hydrogen transfer from germanes results in poor radical chain propagation.

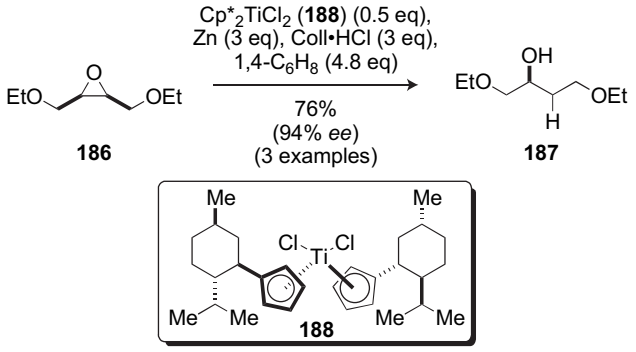
Curran reported the synthesis of the dithiogermane **176** as an alternative chiral hydrogen source.[160] This germanium hydride is a stable solid that, as a result of the two Ge–S bonds, is a significantly better hydrogen donor than tributyltin hydride. Reduction of the ester **169a** initiated by triethylborane at −60 °C proceeded in 42% ee.

Of the reagents employed in enantioselective hydrogen-atom transfer reactions, the most interesting are the chiral thiols developed by Roberts.[161] The carbohydrate-derived thiols **183**–**185** serve as enantiomerically pure hydrogen-atom donors and polarity-reversal catalysts (PRCs). Radical initiation with di-*tert*-butyl hyponitrite (*t*-BuON=NO*t*-Bu; TBHN) results in the formation of a silyl radical **179** that can add to alkene **177** to give the prochiral tertiary *C*-centred radical **180** (Scheme 50). Hydrogen abstraction from the chiral thiol (**182**) then occurs stereoselectively to yield the enantiomerically enriched **178** and a thiyl radical **181**, which abstracts a hydrogen from the silane to regenerate **179**. It appears that there are two main factors that affect the enantioselectivity: the orientation of the thiol in relation to the pyranose ring, β-glucose thiols **185** being active, whilst α-glucose thiols give no selectivity, and the orientation of the C-2 substituent, β-mannose **184** being far more effective than β-glucose **183**. Other factors are also important, but these are not fully understood. There is a large stereoelectronic component to the selectivity; when the hydroxyl groups are protected with esters, better enantioselectivities are observed than when acetal-based protecting groups are employed. The optimal thiol has yet to be elucidated, but these preliminary results are highly promising, indicating it should be possible to develop a powerful asymmetric thiol-based radical chemistry. It will be interesting to see if this work could be combined with the Stetter-like chemistry found in Part 2, Section 2.2, Scheme 27.

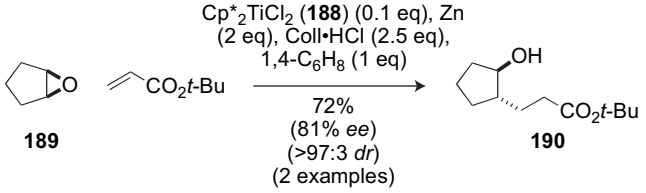


Scheme 50.

Chiral titanium pre-catalysts, such as **188**, allowed the first example of catalytic enantioselective radical *generation*.[162] Initial studies looked at the simple reductive desymmetrisation of *meso*-epoxides **186** to alcohols **187**, which could be achieved in good yield and selectivity (94% ee; Scheme 51). Such a reaction does not constructively utilise the full potential of the alkyl radical. A more exciting example involved tandem ring opening–radical addition of **189** to give **190** in good yield and excellent stereoselectivity (94% de; 81% ee; Scheme 52). The authors showed that bulkier catalysts induce higher diastereoselectivities, but to the detriment of the yield. This is a remarkable reaction, employing catalytic enantioselective radical generation to form two stereocentres and a new C–C bond, and is an exciting step in the development of stereoselective radical reactions. This work has recently been summarised in an informative 'concepts' article.[163]



Scheme 51.



Scheme 52.

Whilst chiral reagents are still relatively uncommon in radical chemistry, there are an increasing number of enantioselective radical reactions that rely on either stoichiometric or sub-stoichiometric quantities of a chiral catalyst. Many of these reagents will be discussed along with the appropriate transformations in the following sections. Interested readers are directed towards an excellent collection of reviews, which include diastereoselective radical reactions,[29a,b] enantioselective radical reactions,[30–32] asymmetric additions to C=N bonds[12] and stereoselective conjugate additions.[33,34] An issue of *Tetrahedron: Asymmetry* was also dedicated to stereoselective radical reactions.[45]

3. Radical reactions

There have been a vast number of publications on radical reactions in the last six years; the author cannot discuss the majority of them and will just highlight the most pertinent. Even so, there is still a large array of reactions and it is hard to organise these in a manner that will please all. The review is very simplistically divided into the following sections; intermolecular additions are found in this issue and then a subsequent issue of *Tetrahedron* will include cyclisations and rearrangements. Each section will be further sub-divided, depending upon the nature of the radical donor and acceptor. Unavoidably, tandem or cascade processes muddy the categories and examples are placed where the author deems the most creative step

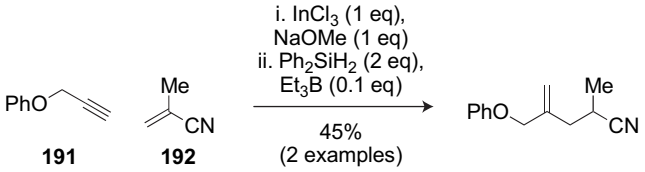
of the reaction to lie; obviously, this is open to interpretation. For the purpose of this review, cascade reactions will involve consecutive intramolecular reactions, whilst tandem reactions will comprise both an intermolecular and an intramolecular step. Radical transformations involving a series of intermolecular additions will be considered to be multi-component couplings.

3.1. Intermolecular addition reactions

3.1.1. Radical conjugate addition reactions of C-centred radicals

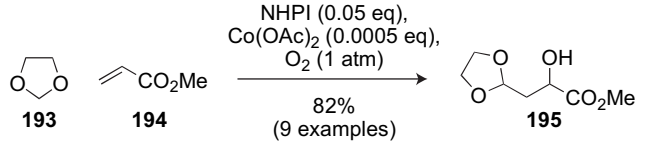
Radical conjugate (1,4-) additions present a powerful tool for the synthetic chemist; they show a far greater functional-group tolerance than ionic reactions and display exceptional chemoselectivity for 1,4- over 1,2-addition. Such useful methodology has been the focus of two excellent reviews; advances in radical conjugate additions covering the literature from 2001 to 2005[33] and a review on catalytic asymmetric tandem transformations triggered by conjugate additions.[34] As a result, this review will concentrate on examples since 2005.

Considerable research has been expended on increasing the range of radical precursors that can be employed in conjugated additions. Under standard tin hydride conditions, the intermolecular addition of radicals derived from alkynes to alkenes has proven impossible; premature reduction of the alkenyl radical intermediate is the probable complication in these reactions. Using dichloroindane, generated in situ, has overcome this limitation and allowed the first example of an *intermolecular* radical coupling of an alkyne **191** and an alkene **192** (Scheme 53).[76] The reduced reactivity of the indium system gives the alkenyl radical a sufficient lifespan to permit C–C bond formation.



Scheme 53.

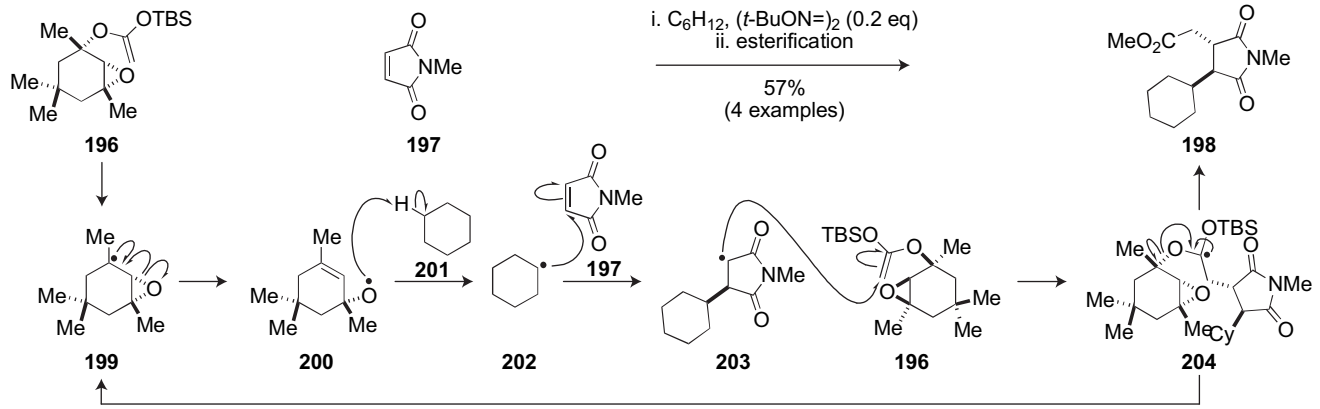
C–H activation and functionalisation is an important aspiration of synthetic chemists and it is clear that the high reactivity of radicals shows potential in this area. The radical-mediated addition of acetals to activated alkenes has been known for a long time,[164] but it is only in the last few years that it has gained widespread acceptance. Reaction of 1,3-dioxolane **193** with methyl acrylate **194** mediated by *N*-hydroxyphthalimide (NHPI) and cobalt(II) acetate under an oxygen atmosphere gave **195** in good yield (Scheme 54).[165a–c] A plausible mechanism involves activation of oxygen by cobalt(II) to give a cobalt(III)–dioxygen complex that abstracts a hydrogen from NHPI to form an *N*-oxyl radical. The latter species abstracts a hydrogen from the acetal to give a highly nucleophilic acetal-based radical that readily adds to the alkene. The resulting alkyl radical is trapped by oxygen to give a hydroperoxide, which undergoes cobalt-mediated redox decomposition to give an alkoxy radical that is eventually reduced to the alcohol. A number of different activated alkenes can be employed in the reaction, although crotonates are not tolerated, presumably due to steric factors. 1,3-Dioxalane **193** can be replaced by 2-methyl-1,3-dioxolane to permit the incorporation of a masked acetyl group.



Scheme 54.

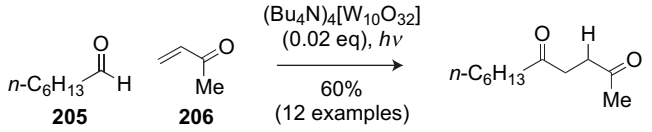
The energetically favourable rearrangement of *C*-centred oxiranylcarbinyl radicals to allyloxy radicals generates *O*-centred radicals that possess a superior ability to abstract hydrogen atoms than their *C*-centred counterparts. Harnessing this property permits a fascinating method for the activation of simple alkanes.[166] Key to the success of this methodology is the judicious choice of substrates so that the electronics of each component are matched. Thus, treatment of **196** with initiator results in the formation of *C*-centred radical **199** that rearranges to the electrophilic allyloxy radical **200** (Scheme 55). This radical can abstract a hydrogen from any electron-rich C–H position, including alkyl C–Hs, such as **201**, to give a nucleophilic secondary carbon radical **202**. Polarity effects disfavour the addition of electron-rich **202** to the equally nucleophilic **196** and, thus, it selectively adds to electron-deficient alkene **197**. The resulting electrophilic radical **203** adds to the ketene to give **204**, which undergoes β-fragmentation to yield the product **198** after esterification and regenerate the chain carrier **199**. Remarkably, with only minor modifications, this methodology can also be used to functionalise electron-deficient C–H positions. As allyloxy radical **200** is electrophilic, it is ill-disposed towards abstracting an electron poor hydrogen and thus, it is necessary to add a PRC. These noteworthy processes allow C–H functionalisation without the use of heavy metals or the need for specific radical precursors and offer great potential for the metal-free functionalisation of simple compounds.

Acyl radicals are valuable intermediates for the synthesis of ketones. Unfortunately, the formation of acyl radicals is fraught with problems, many of which arise from the use of unattractive precursors (see Part 2, Section 2.2). Ideally, such radicals would be generated by the direct abstraction of hydrogen from the aldehyde, but the inefficiency of this step inhibits radical chain reactions. Photo-excited tetrabutylammonium decatungstate (TBADT) is an effective catalyst for the intermolecular addition of aldehydes **205**



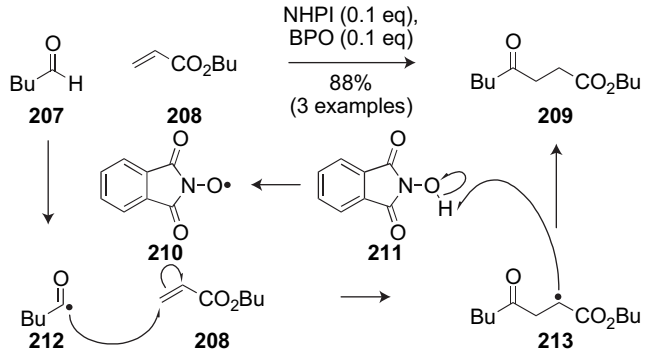
Scheme 55.

to activated alkenes **206** (Scheme 56).[167] Not only does excited TBADT abstract the carbonyl hydrogen, but it also permits back hydrogen transfer to the adduct radical, completing the catalytic cycle. The reaction proceeds with good yields for simple primary aldehydes, but is ineffective with aromatic aldehydes as these competitively absorb light. Furthermore, secondary and tertiary aldehydes are also plagued by decarbonylation to give relatively stable alkyl radicals. This problem can be ameliorated slightly by lowering the temperature of the reaction, but, whilst this helps secondary aldehydes, the yields from tertiary aldehydes are still far from acceptable. This methodology shows considerable potential, as it allows the facile coupling of aldehydes and alkenes with only catalytic quantities of the tungsten reagent; furthermore, the fact that equimolar amounts of substrates can be coupled is a considerable advance on many of the older radical technologies. Of course, the large molecular weight of TBADT ($C_{64}H_{144}N_4O_{32}W_{10}$; MW=3320) means that, even with such low catalytic loadings, a large mass of material is required.



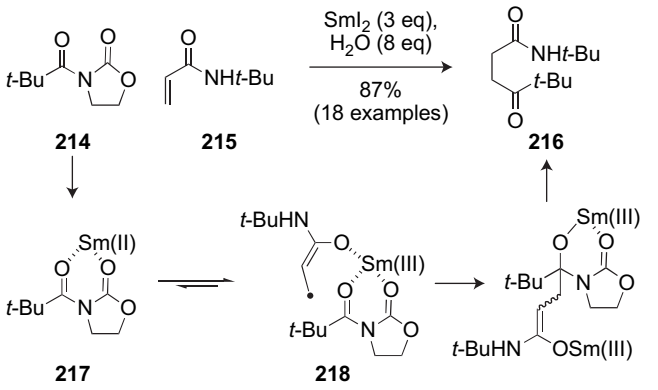
Scheme 56.

A more attractive variant of this reaction utilises PRC, *N*-hydroxyphthalimide (NHPI) **211**, and benzoyl peroxide (BPO) (Scheme 57).[168] Thus, pentanal **207** will add to electron-deficient alkenes, such as **208**, in good yields under operationally simple conditions. The initiator abstracts a hydrogen from **207**, forming an acyl radical **212** that adds to the alkene **208** to give an electron-deficient secondary radical **213**. Abstraction of a hydrogen from NHPI **211** gives the product **209** and the chain propagator **210**. To obtain good yields, the alkene must be added slowly to an excess of aldehyde to prevent polymerisation. The methodology can also be applied to acetals, permitting the formation of protected ketones or aldehydes; this reaction is more sensitive and substituted activated alkenes must be employed to prevent polymerisation. The potential of this methodology was demonstrated in a three-component coupling reaction between an acetal, an activated alkene and a non-activated alkene; it is anticipated that this reaction will see further development.



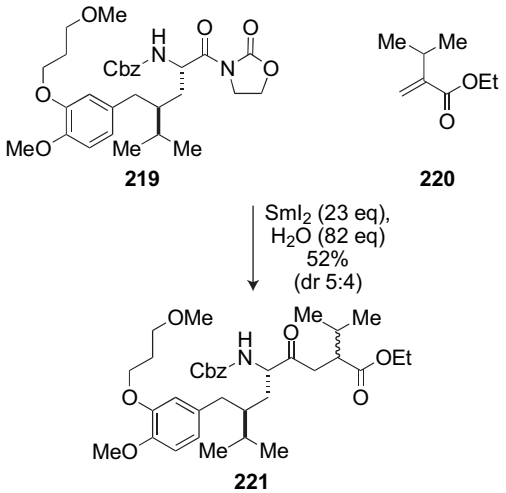
Scheme 57.

Skrydstrup has developed a powerful methodology for the coupling of *N*-acyl oxazolidinones to acrylates and acrylamides.[20] At first glance, this chemistry appears to permit the conjugate addition of an acyl radical equivalent **214** to an activated alkene (**215**) to furnish a γ-keto amide **216** (Scheme 58). The transformation is quite remarkable, as decarbonylation is not a competing process; this is especially unusual for substrates, such as **214**, where fragmentation would lead to a stable tertiary radical. It was initially believed that the reaction involved the addition of a metallated ketyl radical anion equivalent to the activated alkene. Evidence is mounting that this hypothesis is erroneous and that Skrydstrup has uncovered a new mode of reactivity for samarium(II)-mediated radical reactions.[169a,b] It appears that the reaction proceeds via coordination of the oxazolidinone to the samarium(II) iodide to give **217**, activating the samarium(II) species in an analogous fashion to hexamethylphosphoramide (HMPA). This complex then reduces the *acrylate*/*acrylamide* to furnish the chelated radical anion **218** that adds to the carbonyl moiety of **217**. The samarium serves a number of roles; it tethers the two substrates together to give a favourable intramolecular reaction, it acts as a hard Lewis acid, activating the carbonyl to radical attack, and, finally, it traps the alkoxy radical formed by the addition, preventing premature fragmentation.



Scheme 58.

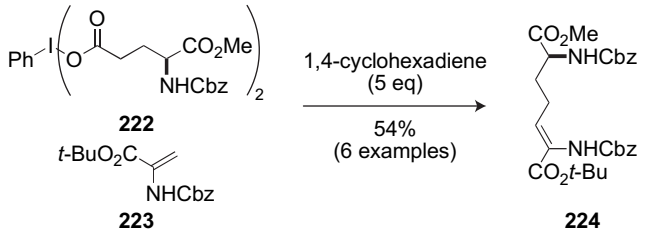
The *N*-acyl oxazolidinone methodology is a versatile process for the preparation of a range of γ-keto esters or amides including peptidyl ketones,[170] overcoming many of the shortcomings found with an earlier thiopyridyl ester-based reaction.[171a–d] Under optimum reaction conditions, samarium(II) iodide (4 equiv) and water (8 equiv), α-substituted acrylates and acrylamides can be coupled to appropriate *N*-acyl oxazolidinones.[172] β-Methyl acrylates can also be employed in the reaction, although they only undergo successful coupling with unhindered oxazolidinones. The range of oxazolidinones has been expanded to include those based on sterically demanding, Boc-protected amino acids. Currently, the only drawback with these reactions is the low diastereoselectivity observed in the addition of chiral oxazolidinones to α-substituted acrylates. The power of this methodology is best illustrated with the synthesis of **221** (Scheme 59); bulky acrylate **220** with an isopropyl group in the



Scheme 59.

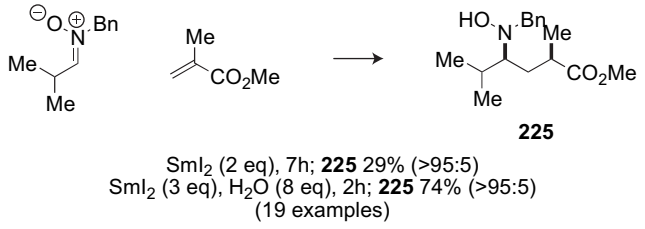
α-position can be coupled to the sterically demanding amino acid derivative **219** in good yield, but with poor diastereoselectivity.

An alternative approach to similar compounds is based on deliberate radical decarbonylation. Decomposition of bis((2*S*)-*N*-benzyloxycarbonyl-2-aminopentan-5-carboxy-1-methyl ester)-iodobenzene **222** followed by conjugate addition of the resulting alkyl radical to a series of selectively protected dehydroamino acids, such as **223**, gives **224** (Scheme 60).[173] The diacyloxyiodobenzenes are readily prepared from the corresponding acids and (diacetoxyiodo)benzene; the reaction is reversible, but the equilibrium can be shifted in favour of **222** by removal of the acetic acid. Due to the surprising stability of **222**, prolonged thermolysis in the presence of the activated alkene and 1,4-cyclohexadiene is required to achieve the desired conjugate addition. In the majority of reactions, only the unsaturated product **224** was isolated; hydrogen-atom abstraction from the substrate competed with reduction by interaction with 1,4-cyclohexadiene.



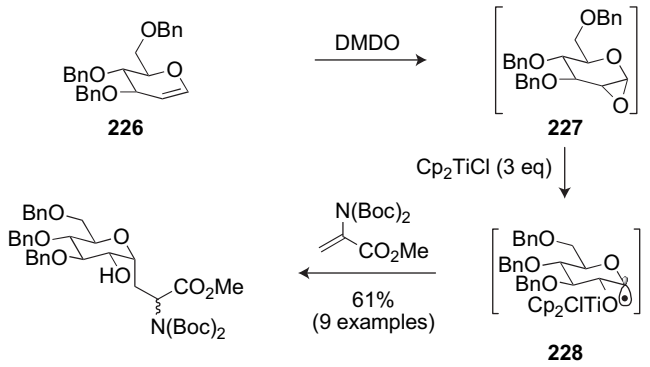
Scheme 60.

Nitrones have proved to be good precursors to the nitrogen equivalent of the ketyl radical.[174] Addition to give γ-amino esters such as **225** occurs to a range of acrylates, including α- and β-substituted acrylates, but not β,β-disubstituted esters (Scheme 61). Remarkably, this methodology has facilitated one of the first examples of *intermolecular* radical addition to α,β-disubstituted acetylenic esters. Curiously, the reaction is accelerated by the addition of a small quantity of water, which is suggestive of a radical mechanism, rather than the alternate ionic mechanism.



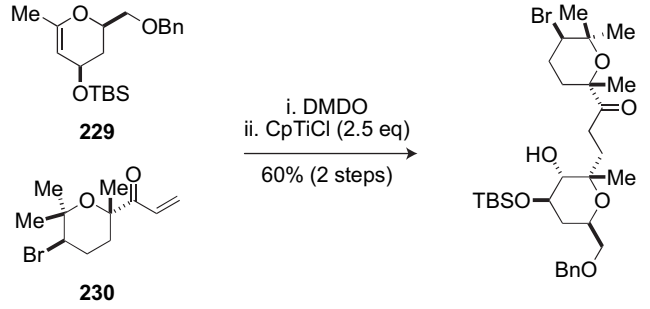
Scheme 61.

Titanocene(III)-promoted reductive ring opening of epoxides such as **227** has been applied to the synthesis of *C*-glycosides. The methodology involves the in situ epoxidation of a glycal, such as **226**, followed by treatment with titanocene(III) chloride and addition to an activated alkene.[175] The reactions proceed with excellent regio- and stereo-chemistry via the formation of the stabilised anomeric radical **228** that reacts to give the α-glycoside (Scheme 62). The methodology offers a number of advantages over more conventional routes to *C*-glycosides, as a range of substituents can be incorporated into the sugar at the C-1 position with concomitant formation of a free hydroxyl group at C-2. Furthermore, the excellent stereoselectivity for the α-glycoside is complementary to organometallic reagents, which tend to ring open 1,2-anhydro sugars to give β-glycosides. A variety of radical traps can be employed, but it appears that they must have the correct reduction potential, ≈−2.7 to −2.9 (vs $Ag/AgNO_3$); simple aldehydes like acrolein are reduced by the titanocene(III) reagent before the anomeric radical is formed, whilst simple alkenes are insufficiently electrophilic to react with the radical.



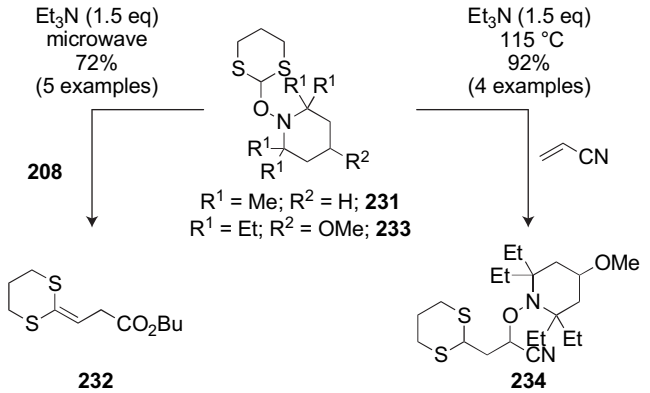
Scheme 62.

This methodology permits the coupling of two highly functionalised tetrahydropyrans **229** and **230** as part of an approach towards thyrsiferol (Scheme 63).[176] It is essential that the dimethyl dioxirane (DMDO) was dried with 4 Å molecular sieves immediately before the reaction. If this precaution was not taken, then the reaction was highly capricious, due to the instability of the intermediate epoxide. The titanocene(III)-mediated ring opening of epoxides and subsequent conjugate addition to activated alkenes has also been employed in the diastereoselective preparation of quaternary centres.[177]



Scheme 63.

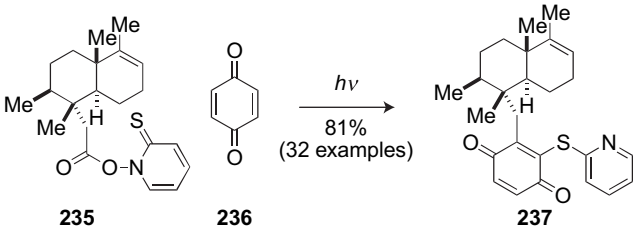
Dithiane-derived alkyloxyamine **231** was an attempt to employ the persistent-radical effect (PRE) to acyl radicals and their equivalents; direct formation of an acyl radical from an alkyloxyamine ester is hard due to the activation energy of C–O bond homolysis, which, at 150 kJ mol^{-1} is too high for clean thermal homolysis. Reaction of **231** with activated alkenes results in the formation of alkene **232** (Scheme 64).[178] The double bond of **232** arises from thermolysis of the C–O bond of **231** followed by radical addition to the acrylate and recombination of the resulting alkyl radical with



Scheme 64.

TEMPO. Finally, elimination of TEMPOH and isomerisation furnishes **232**. The optimum conditions require heating in a microwave to avoid decomposition. Utilising the dithiane derived from the sterically demanding *N*-oxide **233** stopped the elimination, even under conventional heating, and permitted the formation of the desired alkyloxyamine **234**. This product is not stable under the reaction conditions and dissociates to form a second radical that can result in the formation of telomers.

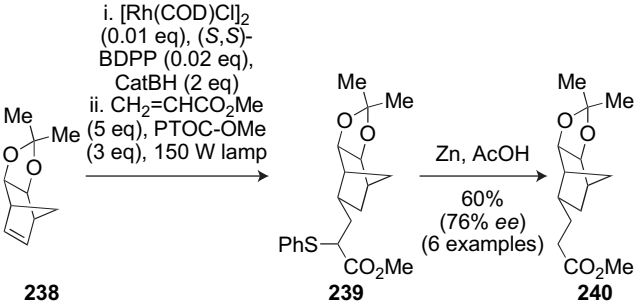
Group transfer has been employed in a highly convergent synthesis of a family of quinone sesquiterpenes.[179a,b] The key step in this synthesis was the radical decarboxylation–quinone addition step that couples **235** and **236**, whilst transferring the sulfide moiety to give **237** (Scheme 65). The coupling was remarkably chemoselective, taking place only at conjugated, unsubstituted double bonds on functionalised quinines and was highly regioselective, with the decalin portion adding *para*- to any electron-donating substituents. The sulfide moiety can be utilised to further elaborate the quinone ring or it can simply be removed. This methodology was used to prepare ilimaquinone, smenospongidine and derivatives of avarone as well as a large number of simple quinone derivatives.



235 **236** **237**

Scheme 65.

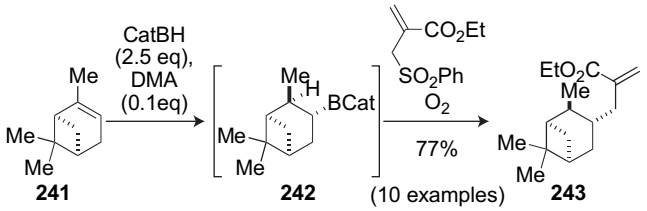
Halides are probably the most common radical precursors, but they are not without their disadvantages; they are frequently hard to prepare and are often unstable. Therefore, the search for alternative precursors that overcome these shortcomings continues. Alkylboranes have proven versatile halide substitutes. Foremost in this area is Renaud, who has published two useful reviews on the radical chemistry of organoboranes.[38a,b] One of the principal advantages of organoboranes as radical precursors is their facile synthesis; one of the simplest methods involves *N*,*N*-dimethylacetamide-catalysed hydroboration of alkenes.[180,181] The resulting organoborane can be used in subsequent radical reactions without purification or isolation. The methodology is amenable to large-scale preparation, as long as high-quality catecholborane is employed.[182] Furthermore, it is possible to introduce the borane moiety in an enantioselective fashion.[183] In an elegant three-step procedure, catalytic enantioselective hydroboration of acetal **238** was followed by conjugate radical addition to an activated alkene employing the Barton carbonate (*N*-methoxycarbonyloxypyridine-2-thione (PTOC-OMe)) as a radical trap and chain-transfer reagent. Finally, desulfurisation of **239** gave **240** in good yield and 76% ee (Scheme 66). Whilst acyclic examples currently give poor selectivities (41% ee), it is clear that this methodology has great potential.



238 **239** **240**

Scheme 66.

The radical-mediated hydroallylation of alkenes demonstrates all the inherent advantages of the borane methodology.[181,182,184] Hydroboration of (+)-α-pinene **241** with catecholborane occurs with the anticipated regio- and stereoselectivity to give the alkylborane **242** (Scheme 67). In situ reaction with an allyl sulfone and a radical initiator (di-*tert*-butyl hyponitrite) then gave the allylated product **243**. The reaction proceeds via radical addition to the allyl sulfone followed by β-elimination of the benzenesulfonyl radical, which acts as the radical chain carrier. The reaction works for a wide range of allyl sulfones and can readily be scaled up (45 mmol of α-pinene); for large-scale reactions efficient initiation can simply be achieved by the controlled addition of air. Catecholborane is the optimum borane for these reactions, as it is highly reactive towards oxygen-centred radicals and its reaction with heteroatom-centred radicals results in the irreversible formation of the desired alkyl radical. Employing ethyl 2-(benzenesulfonylamino)acrylate in place of the allyl sulfone gives an ethyl pyruvate equivalent that permits the formation of α-alkylated ketones.[185]

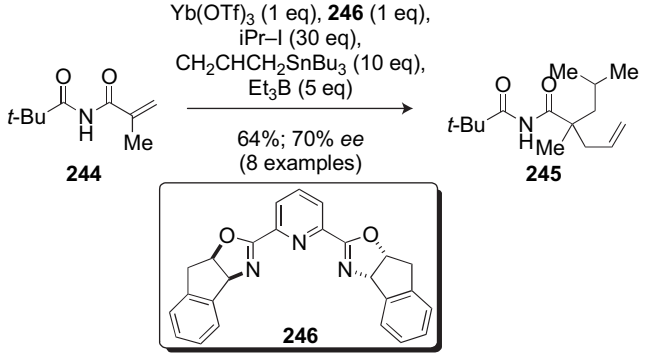


241 **242** **243**

Scheme 67.

3.1.2. Stereoselective radical conjugate addition reactions

Sibi is undoubtedly in the vanguard of research into enantioselective radical reactions to activated alkenes and has written a number of reviews covering this area.[30,31] Additionally, there are reviews highlighting other aspects of stereoselective radical reactions[29a,b,32] and conjugate additions.[33,34] The almost ubiquitous nature of the 2-oxazolidinone auxiliary seems to have curtailed research into alternative auxiliaries, even though many show greater promise. Imides have been tested in the demanding task of enantioselective formation of chiral quaternary centres, such as **245**; one strategy for the preparation of such molecules involves the non-stereoselective conjugate addition of a nucleophilic radical to give an intermediate α-radical that is stereoselectively trapped by an allylstannane (Scheme 68).[186] The best results were obtained when an isopropyl radical was added to the *tert*-butyl-substituted imide **244** in the presence of a chiral Lewis acid derived from ytterbium triflate and ligand **246**. The use of other imides led to a reduction in selectivity. The structure of the initial nucleophilic radical makes a marked difference to the selectivity of the reaction; *tert*-butyl gives the highest enantioselectivities whilst, non-branched alkyls give poor selectivity. Whilst the reaction could be performed with a sub-stoichiometric quantity of Lewis acid, both

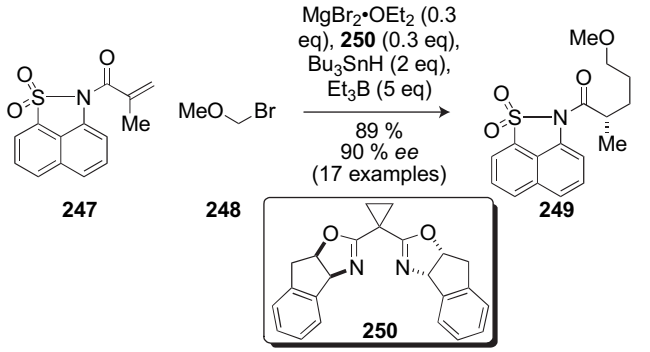


244 **245** **246**

Scheme 68.

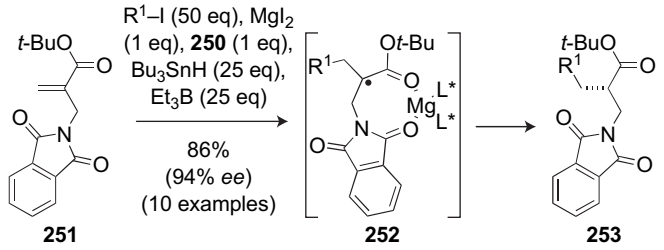
the yield and the enantioselectivity decreased (52 vs 70% ee). Shockingly, this is still one of the few studies on the formation of quaternary centres by radical conjugate addition.

Far more common is the study of enantioselective hydrogen transfer to install a stereogenic centre at the α-position of α,β-unsaturated carboxylic acid derivatives. Auxiliaries that allow amplification of stereochemical information appear to be better suited to this reaction than simple oxazolidinones. Sibi has found that one of the optimal achiral templates is the 1,8-naphthosultam moiety of **247** (Scheme 69).[187] It appears that the tetrahedral geometry of the sulfone is the key to the success of this template; it is thought that this allows amplification of the stereochemical information inherent in the chiral Lewis acid via selective coordination to one of the diastereotopic sulfone oxygens. Thus, the prochiral radical formed from the addition of **248** to **247** participates in a highly enantioselective hydrogen abstraction in the presence of the chiral Lewis acid formed from magnesium bromide and **250** to give **249** in good yield and enantioselectivity. Other groups have observed similar findings; benzimidazolyl sulfone-based auxiliaries give good results in analogous reactions.[188] This, coupled with the versatility of the sulfone moiety towards further synthetic elaboration, should make this methodology very attractive in the future.



Scheme 69.

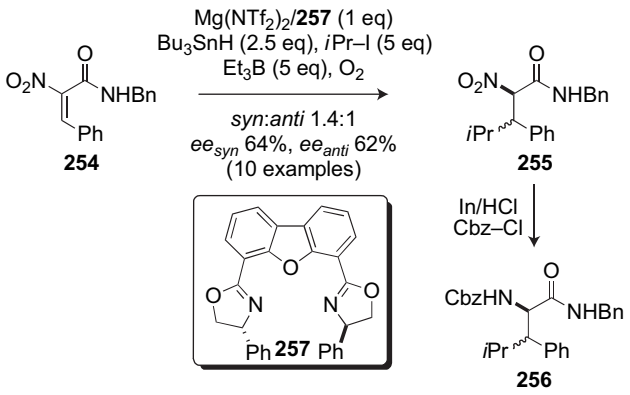
Enantioselective hydrogen-atom transfer to a stabilised tertiary radical was key in the synthesis of α-substituted β-amino acids (β^2-amino acids) such as **253**.[189a,b] A number of different nitrogen-protecting groups were assessed, the best of which was the phthalimido group, presumably due to the formation of a suitable chelate **252** (Scheme 70). It is important that the bulky *tert*-butyl ester is used; the smaller methyl ester shows poor enantioselectivities. Due to the high reactivity of the substrate **251**, the reaction requires the use of a stoichiometric amount of a chiral Lewis acid in order to achieve moderate-to-good enantioselectivities; with smaller amounts, a non-stereoselective background reaction competes. In an analogous reaction, Sibi has investigated enantioselective hydrogen abstraction in the preparation of 'formaldehyde aldol' products in which the phthalimido moiety was replaced by a hydroxyl group.[190] The structure of the radical acceptor was highly influential in the outcome of the reaction; the benzyl ester gave higher yields than either the methyl or the *tert*-butyl ester, but



Scheme 70.

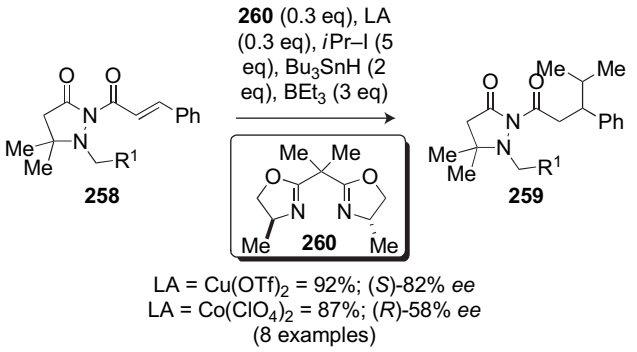
with reduced enantioselectivity. In contrast to the amino acid synthesis, the methyl ester furnished the highest enantioselectivities. Interestingly, the *tert*-butyl ester reversed the selectivity, although there is no clear rationale for this observation.

Similar chemistry has been explored by Castle in order to synthesize β-substituted α-amino acids (Scheme 71).[191] The reaction is highly sensitive to a range of factors including the nature of the β-substituent on the acceptor **254**, which must be aromatic in order to obtain good yields. The properties of the various activating groups must be balanced for good yields and stereoselectivity; amides are plagued by reduction of the alkene, whilst their ester counterparts are untainted by this side reaction. Paradoxically, higher enantioselectivities are normally obtained with the amide substrates. For any stereoselectivity to be observed, a reductive work-up procedure was required to convert the nitro group of **255** into amine **256** and thus minimise epimerisation of the acidic α-stereocentre. Under the optimal conditions, the reaction proceeds with high enantioselectivity, but low diastereoselectivity. The problem appears to be that the initial addition occurs with little selectivity (ee of β-stereocentre 12–25%) whilst the hydrogen-abstraction step, which installs the α-stereocentre, proceeds with fair-to-good selectivity (ee of α-stereocentre 63–83%). Formation of the α-stereocentre is believed to be reagent (**257**) controlled, rather than substrate controlled.



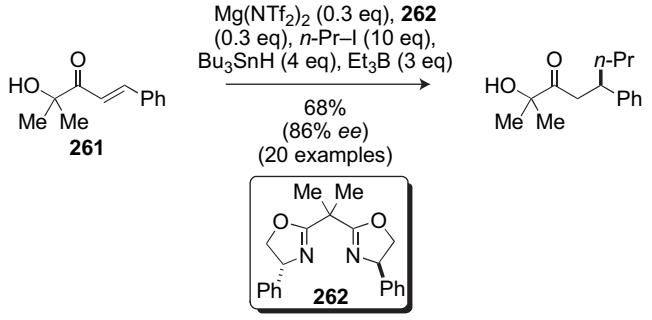
Scheme 71.

The majority of enantioselective radical conjugate additions create a β-stereocentre with research focusing on the ability of different auxiliaries to transmit stereochemical information from a chiral Lewis acid to the substrate. The concept of a fluxional substituent on the auxiliary is best illustrated by the substituent of the non-acyl nitrogen on pyrazolidinones such as **258**. The theory behind fluxional substituents is that the group on the nitrogen can reside on either face of the template due to pyramidal nitrogen inversion; on complexation to a chiral Lewis acid, the fluxional group relays the chiral information from the ligand to the substrate. Thus 'weak' chiral differentiation can be amplified to a large observed enantioselectivity. Sibi found that good enantioselectivity could be achieved, even with the normally ineffective ligand **260** if large fluxional groups R^1 were used (Scheme 72).[192] Equally interesting was the effect of the Lewis acid; copper(II) triflate gave *S*-**259**, whilst all other metal complexes gave *R*-**259**, with the most effective being cobalt(II) perchlorate. The reversal of selectivity probably arises as a result of the different geometries of the various complexes; the copper(II) species is square planar, whilst all the other metals tested form tetrahedral or octahedral complexes. It is apparent that the amplification of enantioselectivity through the fluxional group is greatest when the ligand is coplanar to the substrate, as found in square planar complexes, and is reduced when other geometries predominate.



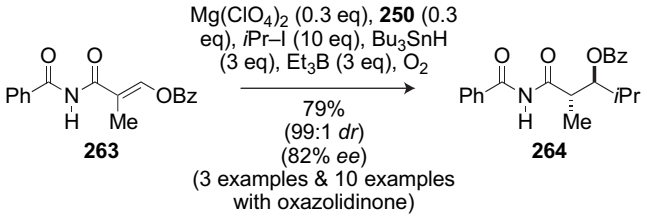
Scheme 72.

The majority of enantioselective conjugate radical additions involve carboxylic acid-derived substrates and two-point coordination via the lone pair of the carbonyl group and a lone pair on the auxiliary. Invariably these auxiliaries involve 1,5-coordination, forming a six-membered chelate; it is much rarer to see examples of 1,4-cordination (five-membered chelate). α′-Hydroxy enones, such as **261**, are an interesting exception; firstly, they involve a ketone, not a carboxylic acid derivative, and, secondly, they form a five-membered chelate.[193] The optimum results were obtained with ligand **262** and magnesium triflamide (Scheme 73). There is little difference in the enantioselectivity observed when using either 30 mol % of the Lewis acid or a stoichiometric amount, although, in the latter cases, the yield is higher. The potential of this auxiliary arises through its versatile elaboration; simple procedures allow it to be converted into aldehydes, ketones or esters.[194]



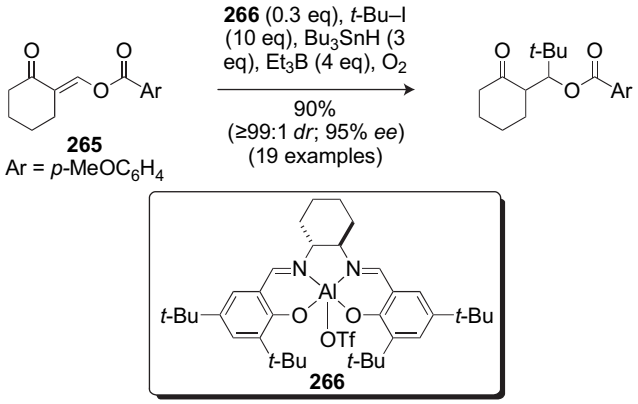
Scheme 73.

The aldol reaction remains one of the most important reactions in synthetic organic chemistry and the synthesis of aldol-like products via radical transformations is an attractive goal. One route to such compounds involves the addition of alkyl radicals to β-oxygen-substituted α,β-unsaturated imides such as **263** (Scheme 74).[195,196] The β-substituent must be an acyloxy group, as simple ethers are unreactive. The optimum results are obtained when the achiral oxazolidinone[196] auxiliary is replaced by an N–H imide.[195] Imides give good results with α,β-disubstituted enoyl substrates and, thus, enable two stereocentres to be created in one reaction. The more conventional oxazolidinone auxiliary frequently results in poor reactions, due to rotation of the C–C bond of the enoyl moiety in order to reduce $A^{1,3}$ strain. Reaction of **263** with secondary or tertiary alkyl radicals in the presence of a sub-stoichiometric amount of a Lewis acid led to the formation of **264** in good yield and selectivity; oxazolidinone-based systems require stoichiometric amounts of Lewis acid. It is thought that the chiral Lewis acid is responsible for the control of the β-stereocentre, but that the α-stereocentre is formed under substrate control. This methodology shows great potential in the formation of *anti*-propionate aldols and is thus complementary to ionic methods, the majority of which form the *syn*-aldol products.



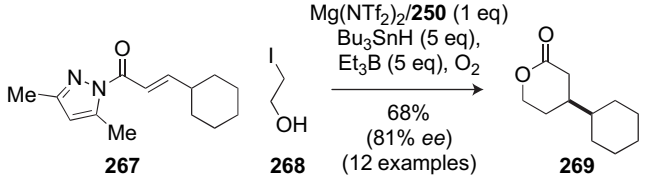
Scheme 74.

It is now possible to perform similar chemistry on cyclic ketones, such as **265**, that do not posses an auxiliary and are only 'single-point' donors (Scheme 75).[197] The optimum results were obtained with a salen-based Lewis acid **266**, which does not require the formation of a bidentate chelate. The nature of the acyl group also affects both the yield of the reaction and the enantioselectivity, with the electron-rich *p*-methoxybenzoate giving the best results. Once again, the Lewis acid controls the enantioselectivity of the initial radical addition, whilst substrate control influences hydrogen transfer to the α-position.



Scheme 75.

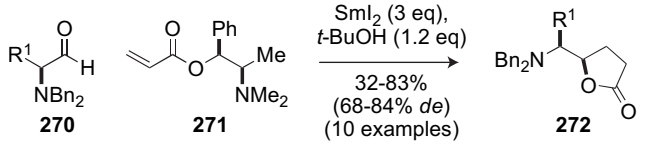
One of the key advantages of radical chemistry is the opportunity to utilise a reactive functionality without protection and this property has been exploited in the enantioselective conversion of pyrazoles (**267**) into lactones (**269**) (Scheme 76).[198] The synthesis of six- and seven-membered lactones (**269**) can be achieved in good yields and enantioselectivity by a 'one-pot' radical conjugate addition–nucleophilic cyclisation sequence. A range of iodo alcohols participate in the reaction, allowing the rapid preparation of a variety of substituted lactones. Interestingly, the yields and selectivity are higher for the formation of the seven-membered lactone, compared to the six-membered ring analogues. It is clear that the reaction proceeds via the coordination of the alcohol **268**, pyrazole **267** and Lewis acid prior to addition, as the enantioselectivity is considerably lower when the hydroxyl functionality of the nucleophile is omitted. Furthermore, the increased selectivity observed for the formation of the seven-membered lactones indicates that the length of the tether might play an important role in determining the enantioselectivity.



Scheme 76.

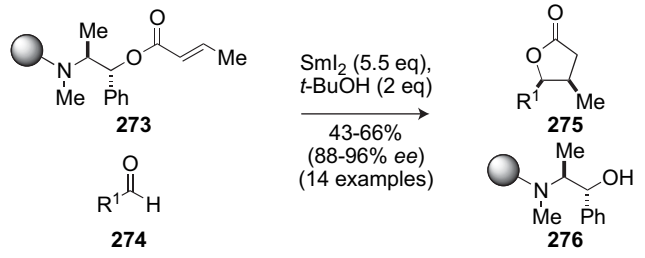
One of the most common strategies for the synthesis of enantiomerically enriched compounds via radical reactions is the use of a chiral auxiliary to allow a diastereoselective transformation followed by cleavage of the auxiliary. It would be impossible to include all examples published in the last five years and the interested reader is directed towards a number of specialised reviews.[29a,b,31,33]

A highly diastereoselective samarium-mediated ketyl radical–alkene coupling reaction has been developed for the synthesis of γ-butyrolactones **272** (Scheme 77).[199] The ketyl radicals are prepared by the reaction of enantiomerically pure amino aldehydes, such as **270**, with samarium(II) iodide and add to acrylate **271** to give, after ionic cyclisation, γ-aminoalkyl γ-butyrolactones **272** in good yield and excellent diastereoselectivity. The use of the enantiomer of **271** results in a non-stereoselective coupling–cyclisation sequence, implying that the stereogenic centres must be 'matched' for profitable reaction; the use of achiral acrylate also leads to little stereoinduction. The reaction proceeds via the coordination of the samarium alkoxy ketyl radical and the carbonyl group of the acrylate; the amino nitrogen of **270** does not coordinate to the samarium. Addition of HMPA disrupts the coordination and results in a loss of stereoselectivity. The ephedrine-based acrylates have also been employed in the synthesis of γ-amino acids via the addition of nitrone-derived ketyl-like radicals to the α,β-unsaturated esters.[200]



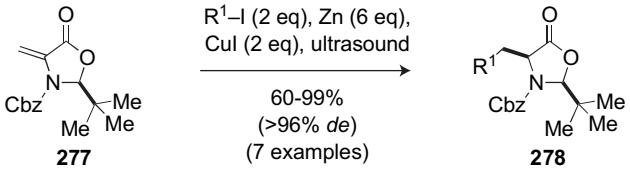
Scheme 77.

Building upon Fukuzawa's results, Procter has demonstrated an elegant solid-phase asymmetric resin-capture—release strategy for the synthesis of γ-butyrolactones **275** (Scheme 78).[201a,b] (1*R*,2*S*)-Ephedrine was immobilised on Wang resin (**276**) and then used to 'capture' crotonyl chloride to give **273**. The crotonate resin **273** was reacted with a variety of aldehydes **274** in the presence of samarium(II) iodide and a proton source to give the γ-butyrolactones **275** in moderate yield and good enantioselectivity, whilst simultaneously regenerating the chiral resin **276**. In some cases, the resin could be reused in a number of cycles with only minimal loss of selectivity.



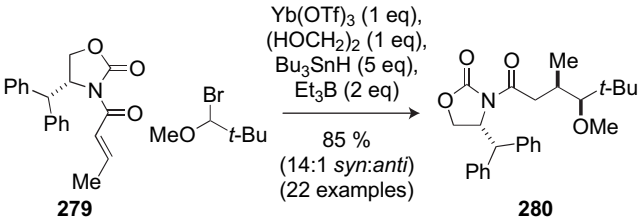
Scheme 78.

A simple enantioselective synthesis of α-amino acids in aqueous media has been developed, starting from the activated alkene **277** (Scheme 79).[202] Ultrasound-induced conjugate addition of an alkyl radical, formed from the action of copper(I) iodide and zinc powder on an iodide, to the cysteine-derived **277** results in the formation of **278** in good yield and diastereoselectivity. Primary, secondary and cyclic iodides are all tolerated in the reaction and all give 98% de. The choice of nitrogen-protecting group is important; benzamides give variable results, whilst benzyl carbamate results in consistently high diastereoselectivities. The reaction is believed to progress via single electron transfer from the surface of the metal to generate an adsorbed radical that undergoes 1,4-radical addition. Addition of a second electron and protonation of the resultant enolate gives the product. The beauty of this synthesis is the simplicity of the reactions, which are performed in aqueous ethanol using readily handled materials.



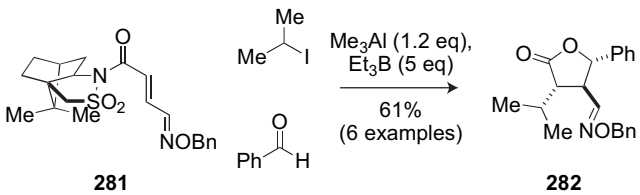
Scheme 79.

Sibi continues to test the limits of diastereoselective radical conjugate additions and has investigated the induction of stereocontrol to the γ-centre of alkenoates.[203] This can be achieved by adding prochiral radicals to substituted alkenes, as shown in Scheme 80. Moderate *syn* selectivity (≤6:1) was obtained in the additions of alkyl and α-alkoxy radicals to oxazolidinone crotonate. Interestingly, an excellent *anti* diastereoselectivity between the β- and γ- centres was achieved with less reactive halogenated radicals, suggesting a subtle stereoelectronic effect in a late transition state could be involved. The use of lanthanide Lewis acids in the presence of achiral additives was also found to improve the selectivity. Combining all the information garnered, an elegant example utilising **279** was reported to give **280** with good selectivity. Considering the separation of the existing stereocentre with the incoming radical, this induction is quite remarkable and bodes well for the future.



Scheme 80.

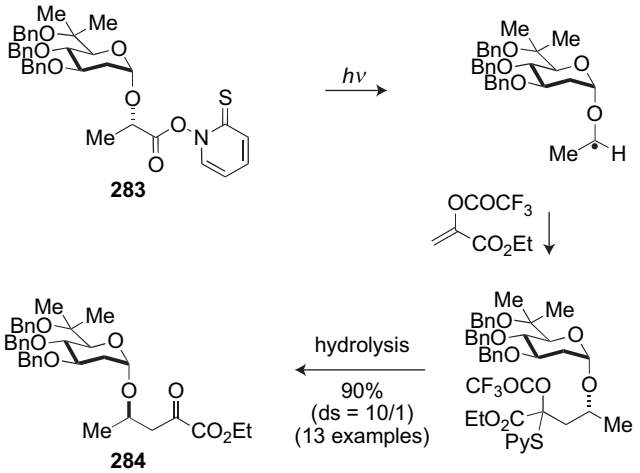
Regio- and stereoselective addition to a doubly activated alkene has permitted the development of a promising tandem radical–polar crossover sequence that involves radical conjugate addition followed by aldol-type coupling as a route to functionalised lactones (**282**; Scheme 81).[204] Treatment of α,β-unsaturated oxime ether **281** with triethylborane, isopropyl iodide, trimethylaluminium and benzaldehyde resulted in the formation of lactone **282** in good yield and stereoselectivity. Under these conditions, the triethylborane acts as a radical initiator to form the isopropyl radical by iodine-atom transfer. Radical addition occurs with complete regioselectivity for the α-carbonyl position to give an *N*-centred intermediate radical that is trapped by the excess triethylborane to afford a boryl enamine and regenerate the ethyl radical as chain



Scheme 81.

carrier. The benzaldehyde is activated by the trimethylaluminium and partakes in an aldol-type reaction. Finally, lactonisation gives the product **282**. Under the 'one-pot' reaction conditions, the diastereoselectivity of the radical conjugate addition is slightly lower than it would be if the reactions were performed stepwise, due to the high temperatures required for the aldol–lactonisation step. Overall, this is an elegant route to an attractive building block. Conceptually related reactions have been developed by Bertrand,[205] who investigated a radical–polar crossover reaction employing C_2 symmetric diimide fumarate derivatives and Sibi has performed additions to non-symmetrical oxazolidinone-based fumarates.[206]

Attaching the chiral auxiliary to the radical *donor* is a less-common strategy. The development of a chiral hydroxyalkyl radical equivalent is an attractive goal, as it would permit the formation of enantiomerically enriched secondary alcohols. Acetal-based chiral auxiliaries appear to be ideal candidates, as a number are readily available, they are easily functionalised with an appropriate radical precursor and they are simple to remove after diastereoselective reaction. Garner has studied a range of tetrahydropyran (THP) and sugar derivatives.[207] The results indicate that the C-6 substituent is vital for good selectivity. The simple C-6-*tert*-butyl THP gave excellent diastereoselectivity, but resulted in only moderate isolated yields. This was overcome by exploiting more robust sugar-derived auxiliaries. Utilising **283** allowed the formation of the protected 'aldol' product **284** with excellent diastereoselectivity (Scheme 82). Whilst the carbohydrate-based auxiliaries result in good control of the stereochemistry, they are not without their drawbacks; lengthy syntheses, lability problems and poor atom economy make them far from ideal. Attempts to improve these auxiliaries have led to the synthesis of the fluorinated derivatives **285** and **286** (Fig. 7).[208a,b] Unfortunately, both auxiliaries are still not optimal and, whilst they address a number of the problems encountered above they are not without their own shortcomings. It is clear that this methodology shows great potential to offer a complementary route to aldol-like products and it is anticipated that further improvement and applications will be forthcoming.



Scheme 82.

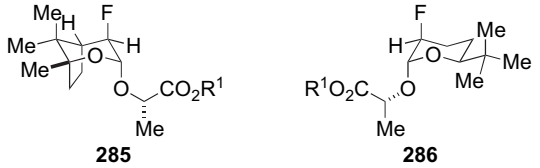
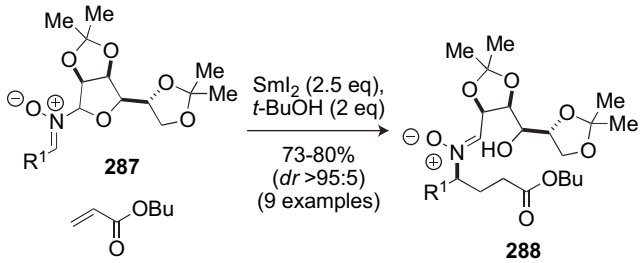


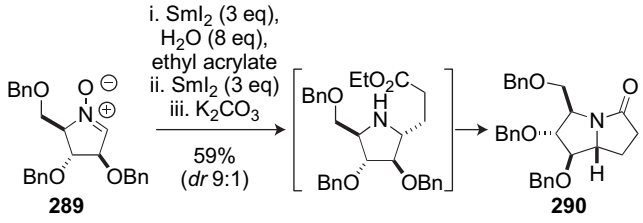
Figure 7.

Carbohydrate derivatives can also be employed as chiral auxiliaries for the reaction of nitrone-derived radicals (Scheme 83).[209] Alkyl nitrone **287** must have an α-substituent in order to obtain good yields and diastereostereoselectivities, but, this limitation notwithstanding, the reaction is highly promising, furnishing the coupled products **288** in excellent yields as almost exclusively one diastereoisomer. Interestingly, ring opening of the sugar residue occurs in the reaction, resulting in the formation of a new nitrone. Cleavage of the auxiliary is easily achieved by simple acid hydrolysis.



Scheme 83.

The nitrone methodology has been applied to the synthesis of (+)-hyacinthacine A_2 (Scheme 84).[210] Umpolung-like chemistry of nitrone **289** permits the rapid formation of the B-ring of the pyrrolizidine skeleton **290** in an elegant 'one-pot' addition–reduction–cyclisation sequence. The convergent nature of this synthesis should permit the preparation and evaluation of a range of analogues.

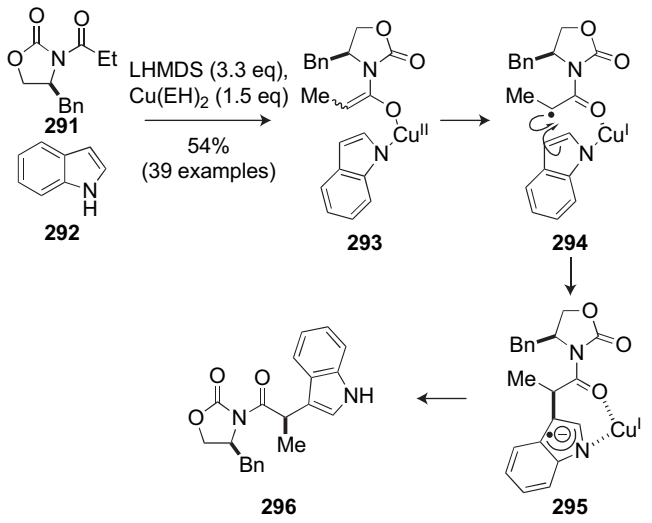


Scheme 84.

Stereoselective radical conjugate additions have blossomed in the preceding twenty years with a number of remarkable examples being reported, but considerable research is still required, including the evaluation of effective achiral auxiliaries, the development of more effective methods for the formation of quaternary centres and the lowering of chiral Lewis-acid loadings. It is hoped that the advent of novel organocatalytic Lewis acids, hydrogen-bond donors and Brønsted acids might facilitate these advances.

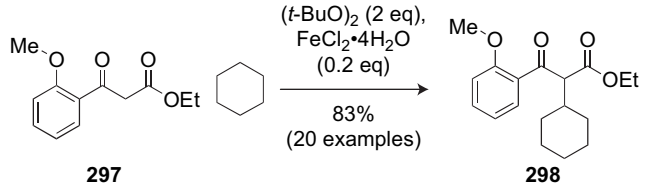
3.1.3. Addition of C-centred radicals to non-activated multiple bonds

Relatively few ionic process can compete with radicals for the formation of C–C bonds with unactivated multiple bonds, with palladium(0)-type couplings being the obvious exception. An exciting area of research is C–H activation without pre-functionalisation; the obvious advantages of this strategy include atom economy and the potential use of cheap, readily available starting materials. The use of highly reactive carbenoids derived from diazo species goes some way towards achieving this goal, as do a number of recent reports detailing the use of palladium and related metal catalyst systems, but all these methodologies fall short of the results achieved with radical chemistry. Radicals have been employed in a truly remarkable strategy that permits the direct coupling of indoles and pyrroles to the α-position of carbonyl compounds without recourse to pre-functionalisation/derivatisation of either

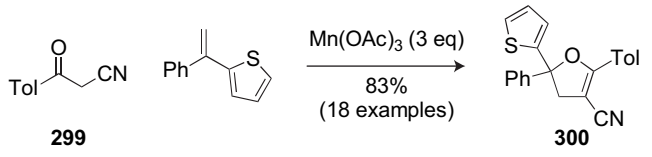


Scheme 85.

component (Scheme 85).[211] Considering the outcome of this transformation, the reaction conditions are straightforward; the carbonyl compound **291** and the indole **292** are treated with a base and then the resulting anions are oxidised with copper(II) 2-ethylhexanoate [$Cu(EH)_2$]. Studies suggest that the reaction proceeds by the formation of the copper chelate **293** followed by SET, which results in oxidation of the carbonyl to give an α-keto radical **294**. Due to its proximity to the indole anion, this radical is attacked to give a radical anion **295**. Finally, a second oxidation, followed by tautomerisation, furnishes the coupled product **296**. The reaction appears to be general, working for a range of substrates with few limitations, except that the indole or pyrrole moiety must have a free N–H, presumably to allow deprotonation and chelation. Obviously, the carbonyl group needs to be chosen so that regioselectivity in the enolate formation step is not an issue. What is notable about this reaction is that dimerisation of the carbonyl species is only observed when methyl ketones are employed. The reaction tolerates many functional groups including halides and epoxides. Furthermore, incorporation of a chiral auxiliary onto the carbonyl substrate permits diastereoselective variants to be performed. The development of methodology that allows the coupling of complex substrates without pre-functionalisation is undoubtedly going to be an important area in organic synthesis over the coming years, due to its manifest advantages over current technologies.[212]



Scheme 86.

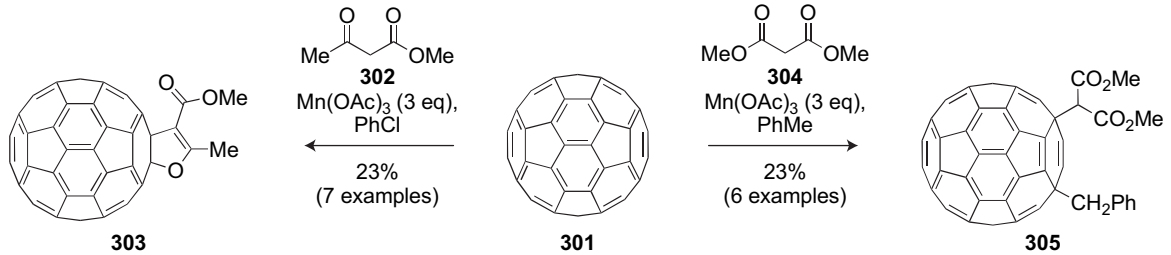


Scheme 87.

Radical reactions show considerable promise for other C–C bond formations. Whilst the direct alkylation of 1,3-dicarbonyl compounds by radical processes has been known for many years, the majority of these methodologies have involved alkenes or similar radical acceptors (see Sections 2.8 and 2.9). It is now possible to couple 1,3-dicarbonyls with *simple alkanes*. This chemistry builds upon Gif and Fenton reactions for the activation of C–H bonds and enables the formation of C–C bonds from simple, non-functionalised compounds. Thus, treatment of β-keto ester **297** and cyclohexane in the presence of iron(II) chloride and *tert*-butyl peroxide gave the product **298** in an excellent 83% yield (Scheme 86).[213] The reaction is relatively general for a range of cyclic alkanes, but there are issues of regiochemistry when linear alkanes are employed. Curiously, diketones give poor yields in this reaction. The reaction is thought to proceed by the iron-catalysed decomposition of the peroxide to give an alkoxy radical that abstracts a hydrogen from the alkane and an iron(III) alkoxide, which enolises the β-keto ester. A combination of these two intermediates gives the product and regenerates an iron(II) species. Related methodology also facilitates the activation of benzylic C–H bonds, thus permitting benzylic alkylation of both β-keto esters and 1,3-diketones.[214] The success of the latter (yields of up to 85%) makes the failure of 1,3-diketones to react with cyclic alkanes even more inexplicable.

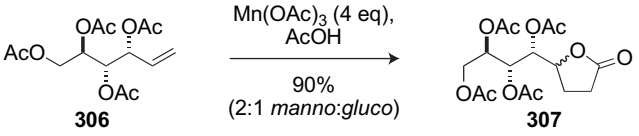
Oxidative manganese(III)-mediated radical reactions offer an attractive methodology for the coupling of non-activated alkenes. The majority of radical precursors used in these reactions are dicarbonyl compounds (see Section 2.8), but this is not a pre-requisite and alternative electron-withdrawing groups can replace one of the carbonyl moieties. Thus 3-oxopropanenitriles such as **299** readily undergo intermolecular radical addition followed by ionic cyclisation to give 4,5-dihydrofuran-3-carbonitriles **300** (Scheme 87).[215] The optimum yields are obtained in substrates in which the adduct radical is stabilised. Thus, 1,1-disubstituted alkenes generally give higher yields than 1,2-disubstituted alkenes.

Radical reactions are one of the most effective methods for the functionalisation of [60]fullerene (C_{60}) **301**. Manganese(III)-mediated reactions can be employed to couple β-dicarbonyl compounds with C_{60} (Scheme 88).[216a,b] Interestingly, β-keto esters such as **302** form heterocycles such as **303**, whilst malonates **304** deliver a 1,4-bisadduct **305** derived from the addition of 1 equiv of the malonate followed by interaction with the solvent. Similar results have been found for the manganese(III)-mediated addition of other carbonyl substrates to C_{60}[217] including the use of malonic acids to yield fused lactones.[218]



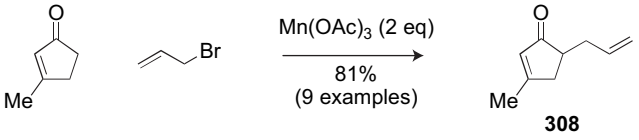
Scheme 88.

A comparable methodology has been employed in the preparation of precursors for 3-deoxy-D-*manno*-oct-2-ulosonic acid (KDO).[219] Simple treatment of alkene **306** with manganese(III) acetate in acetic acid results in the formation of the two diastereoisomers of lactone **307** in excellent combined yield and moderate stereoselectivity (Scheme 89). It is argued that the reaction proceeds by the formation of a *C*-centred radical on acetic acid that adds to **306** to give a secondary alkyl radical that undergoes rapid radical C–O bond-forming cyclisation. All processes occur within the manganese(III) ligand sphere, thus preventing oligomerisation, although it should be stressed that cationic cyclisation cannot be ruled out.



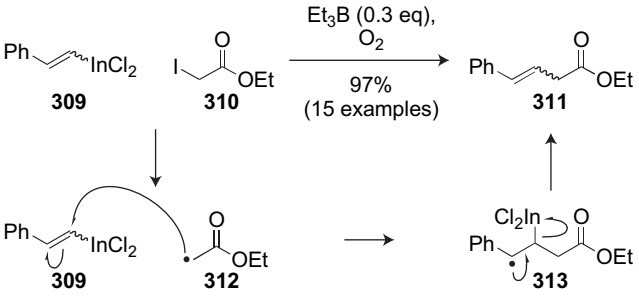
Scheme 89.

Manganese(III) acetate also permits the α′-allylation of α,β-unsaturated ketones.[220] The reaction is believed to proceed via the formation of a manganese(III) enolate that undergoes one-electron oxidation to give an α′-keto radical, which adds to allyl bromide to give the product **308** (Scheme 90). The reaction is general, giving the desired product for a range of cyclic unsaturated ketones with varying substitution patterns. No acyclic precursors have been reported, which suggests that the reaction is more problematic with such substrates.



Scheme 90.

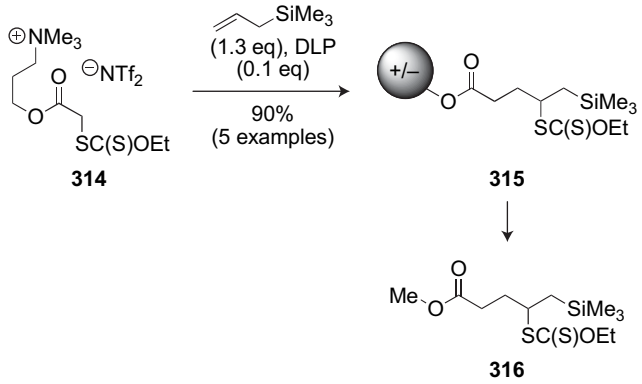
More conventional radical chemistry employs allyl- and alkenylindium reagents as attractive alternatives to organostannanes for the functionalisation of α-halo esters (Scheme 91).[221] The reagents are prepared from indium(III) chloride and Grignard reagents. In both cases, iodides are more effective precursors than bromides and the reactions proceed in good yield. The allylation reaction is effectively identical to the standard tin reactions, except that it is accelerated by the addition of water. Interestingly, the indium-based alkenylation reaction is far superior to the analogous tin processes. The coupling of **310** and β-styrylindium **309** is thought to proceed by the formation of the carbonyl-stabilised radical **312** that adds to the carbon bearing the indium atom to give the stabilised radical **313**. Elimination of the dichloroindium radical gives the product **311** and an indium chain carrier that abstracts iodine from **310**. The reaction works efficiently for a variety of α-iodo and α-bromo carbonyl compounds, but gives poor results with chlorides. The alkenyl reagents must be able to stabilise the adduct



Scheme 91.

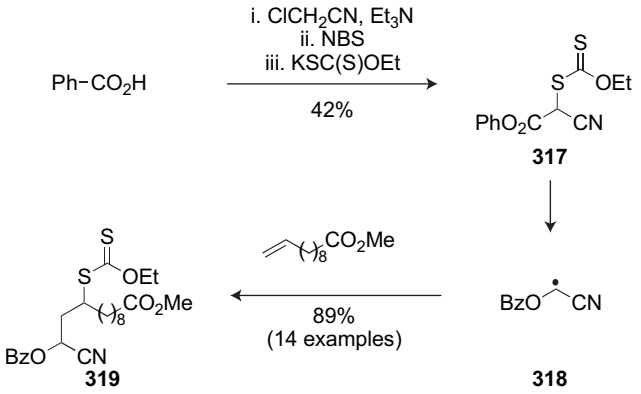
radical and therefore have a substituent at the 2-position. In addition to allylindium and alkenylindium reagents, both alkynylindium and arylindium reagents can be employed in similar coupling reactions.[221]

Xanthate-derived radicals are excellent candidates for coupling reactions with non-activated alkenes, due to the prolonged lifespan of the radical (see Section 2.10.3).[145a–c] Whilst xanthate chemistry can generally be considered to be environmentally benign, it would be attractive to be able to perform such reactions on a solid supports and thus facilitate facile purification. Unfortunately, radical reactions on solid support are often problematic, requiring excess initiator and extended reaction times. 'Task-specific onium salts' (TSOSs) are versatile functionalised ionic liquids that can act as soluble supports and they offer considerable potential in radical chemistry.[222] This is highlighted by the use of **314**, which reacts with a small excess of alkene (1.3 equiv) and only 0.1 equiv of DLP to give **315** (Scheme 92). Simple hydrolysis gives **316** and the support that can be recycled. Cleavage of the product from a support with a long linker is markedly less efficient than from those with a linker of three carbons such as **314**. With this proviso in mind, TSOSs appear to be effective soluble supports, showing comparable or better results than other soluble supports.



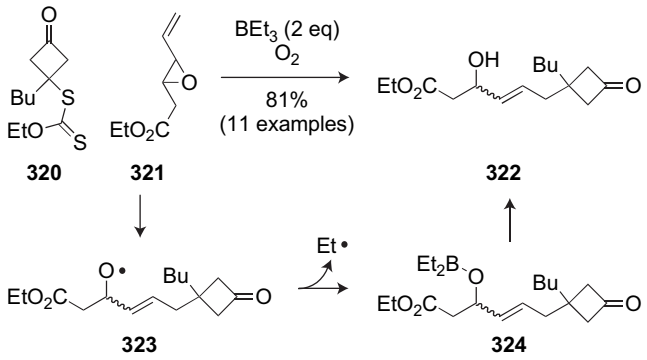
Scheme 92.

Umpolung or the inversion of polarity of a functional group is an important strategy in organic synthesis; in its most common form, it permits normally electrophilic aldehydes to behave as nucleophiles. The most prevalent example of umpolung involves the conversion of an aldehyde into a 1,3-dithiane followed by deprotonation. The xanthate derived from 1,3-dithiane has been studied as an equivalent of the formyl radical or a simple one-carbon radical equivalent, but it is of limited value, due to its highly electron-rich character, which necessitates the use of highly activated acceptors.[223] Slightly more promising is the radical chemistry of the mono-sulfoxide of 1,3-dithiane; this adds to a variety of alkenes under standard conditions, but its utility is severely limited by the formation of multiple diastereoisomers. Currently, the most promising xanthate-based one-carbon radical equivalent is cyano(ethoxythiocarbonylthio)methyl benzoate **317**.[224] This reagent is readily prepared from benzoic acid and is stable for several months under an inert atmosphere (Scheme 93). As a result of the degenerate nature of the addition of acyl radical equivalent **318** to **317**, it has a long effective lifetime and readily adds to a wide range of unactivated alkenes and the resulting products, such as **319**, contain much exploitable functionality. Related umpolung chemistry allows radicals to be generated from aldehydes via an *O*,*S*-acetal xanthate.[225] The radical precursors are readily prepared in two, high-yielding, steps and the resultant radicals add to a variety of non-activated alkenes to give protected 1,3-hydroxyxanthates; these compounds are useful precursors to a variety of structural motifs.



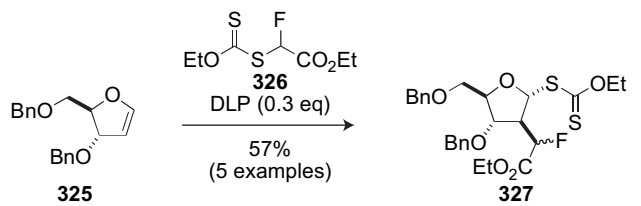
Scheme 93.

Peroxides are invariably the radical initiator of choice with xanthate chemistry, but it is becoming apparent that other initiators offer a number of benefits.[226a–c] One interesting example is the use of triethylborane in the coupling of xanthate-derived radicals with alkenyl epoxides **321** to give alcohols such as **322** (Scheme 94).[227] Addition of the alkyl radical derived from **320** to **321** results in ring opening and the formation of an alkoxy radical **323**. The latter is rapidly trapped by oxophilic triethylborane to give a borinate **324** and an ethyl radical that propagates the chain reaction. This methodology provides a useful route to functionalised allylic alcohols. Xanthates are ideally suited for highly modular approaches to elaborate structures, due to their ability to undergo group-transfer reactions with non-activated alkenes prior to being employed in the reaction with alkenyl epoxides.



Scheme 94.

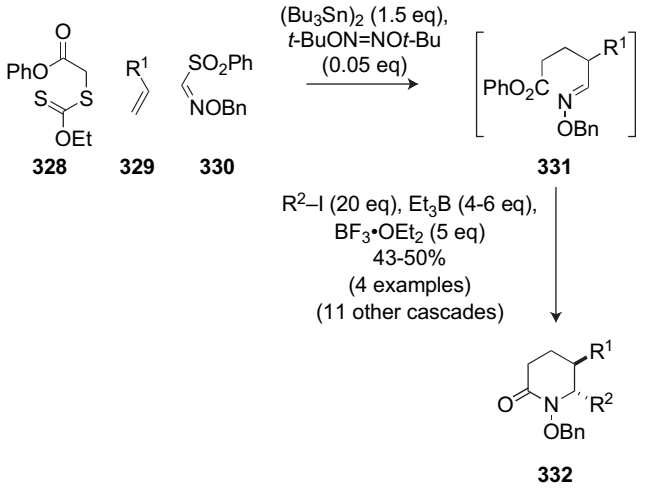
Xanthates are not only useful in radical reactions, but are also readily used in a range of ionic transformations. Lequeux has developed an elegant two-step radical group transfer–nucleophilic substitution sequence for the convergent synthesis of nucleoside analogues.[228] A variety of electron-deficient xanthates, such as **326**, undergo radical addition to dihydrofurans, such as **325**, to give anomeric dithiocarbonates **327** with complete regiocontrol (Scheme 95); two diastereoisomers are observed, differing only at the stereogenic centre bearing the fluorine atom. Nucleophilic substitution of the anomeric dithiocarbonate occurs analogously to



Scheme 95.

standard glycosidation chemistry. The stereoselectivity of this latter, ionic, step is frequently less impressive than that observed in the radical coupling. Notwithstanding this general trend, when both coupling partners are sterically encumbered, nucleotides can be formed with complete diastereoselectivity as single isomers.

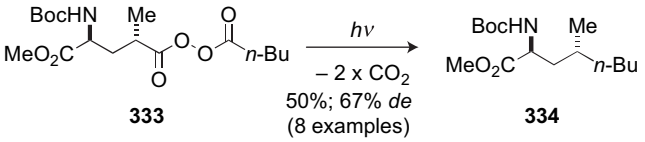
One of the many advantages of radical reactions is their ability to facilitate numerous carbon–carbon bond-forming processes in one synthetic operation. This permits multi-component reactions to rapidly build complex molecules. An elegant example enables piperidinones to be prepared by a formal [2+2+2] process (Scheme 96).[229] Homolytic scission of xanthate **328** generates an ambiphilic radical that adds to the electron-rich alkene **329** faster than it does to the electron-poor **330**. The resulting *nucleophilic* radical selectively adds to the sulfonyl oxime **330** before undergoing a rapid β-fragmentation to give the unactivated oxime **331**. In situ radical alkylation with a fourth component followed by irreversible ionic ring closure gives the desired **332**. Considering the increase in complexity, the moderate yields are more than acceptable. Substituting an iodide for xanthate **328** and removing the sulfone leaving group from **330** permitted the development of a 'green,' tin-free variant. Similarly, radical additions mediated by the persistent radical effect are also amenable to elegant 'one-pot' reactions; the clean nature of the PRE allows it to be combined with palladium-catalysed Trost–Tsuji reactions, facilitating the rapid synthesis of carbocycles.[230]



Scheme 96.

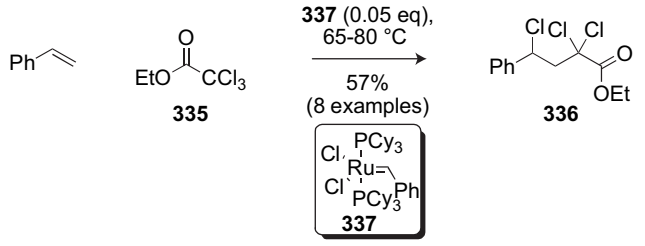
A new clean method for the coupling of alkyl radicals employs diacyl peroxides. Whilst the reactions of these species have been extensively studied on a mechanistic level, their use in C–C bond formation is not widespread, due to the perception that all diacyl peroxides are explosive; in fact, it appears that only small diacyl peroxides, namely those with less than 7 carbons on each side, can be detonated. Of course, care should be taken, as the scrambling of acyl groups can occur during the preparation of diacyl peroxides and therefore small acyl groups should be avoided.[231] Yet, as this simple methodology shows, diacyl peroxides exhibit great potential.[232] Both symmetrical and unsymmetrical **333** diacyl peroxides are readily prepared from protected amino acids via 1,3-dicyclohexylcarbodiimide (DCC)-mediated couplings and the resultant peroxides are stable at −20 °C for several weeks. A range of bis-(amino acids) were prepared by low-temperature photolysis utilising neat (solid or oil) substrates to prevent the formation of complex mixtures or crossover products and this makes the procedure very simple: the substrates are placed in a flask, cooled and a light is shone in from above! Surprisingly, there is considerable retention of stereochemistry (**334**, 67% de; Scheme 97), with no

evidence to implicate substrate control. This, and the fact that there is no observable formation of crossover products, suggests that cage recombination is enhanced, due to the restricted movement of the radicals at low temperature. The ratio of surface area to layer thickness is important, as it appears that the outer strata can offer photo-protection to the inner layers. Similarly, certain structural features hinder the reaction; the Fmoc protecting group and aromatic acyl groups attached directly to the peroxide are incompatible with the present reaction conditions. With the operational simplicity of this methodology, it is somewhat surprising that it has not gained further acceptance.



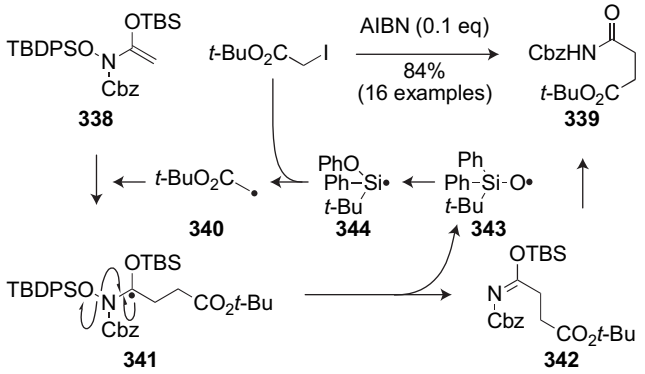
Scheme 97.

One of the earliest radical couplings was the Kharasch reaction or atom transfer radical addition (ATRA). It is apparent that Grubbs's alkylidene pre-catalyst **337** is one of the most active reagents known for ATRA and can facilitate the intermolecular additions of a wider range of substrates than can be achieved with traditional ATRA catalysts such as $(Ph_3P)_3RuCl$. High yields can be obtained for a range of alkenes, as long as they are not prone to metathesis or polymerisation. Even more advantageous is the range of trichloro substrates that can be utilised; the reaction is not restricted to simple trichloroalkanes such as chloroform, but allows functionalised compounds such as trichloroacetates **335** to add to styrene to give **336** in reasonable yields (Scheme 98).[233]



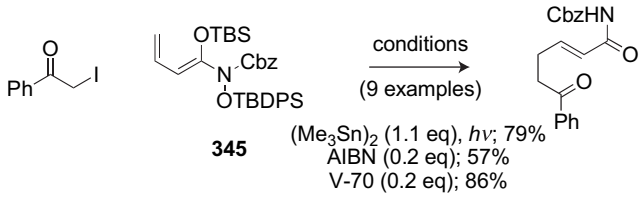
Scheme 98.

The radical chemistry of silyl groups is key to the α-alkylation of amide derivatives **338** to generate **339** (Scheme 99).[234] The coupling proceeds via the addition of an alkyl radical **340** to the functionalised ketene *O*,*N*-acetal **338** to give a ketyl-like radical **341**, which fragments via homolytic cleavage of the N–O bond to furnish the imine **342** and a silyloxy radical **343**. The latter undergoes a 1,2-phenyl transfer to generate the silyl radical **344** that propagates the chain. Simple initiation with AIBN permits the addition of alkyl radicals bearing electron-withdrawing groups under tin-free conditions. Unfortunately, these conditions do not give any product with neutral alkyl or electron-rich radicals; these substrates require the use of hexamethylditin. It is currently unclear why the tin-free conditions only work for electron-deficient alkyl radicals.



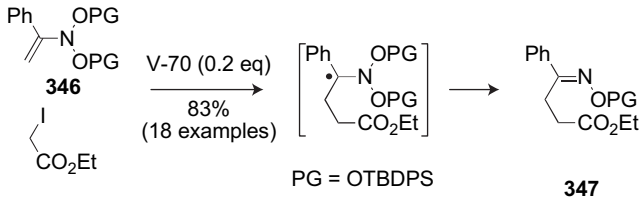
Scheme 99.

This methodology has been elaborated to allow γ-alkylation of α,β-unsaturated amide equivalents, **345** (Scheme 100).[235] Normally, the γ-functionalisation of α,β-unsaturated carbonyl compounds is a taxing endeavour and this is the first example of the addition of a range of alkyl radicals exclusively at the γ-position with no observable addition to the α-position. The complete regiocontrol is thought to arise, due to the nature of the two potential radical intermediates; γ-attack gives rise to an allylic radical with all the stability that this inherently entails, whilst α-attack gives a ketyl-like radical. Optimum conditions employ either hexamethylditin or the low-temperature initiator V-70 (2,2′(4-methoxy-2,4-dimethylvalerontrile)) that facilitates tin-free addition; AIBN gives poor yields, due to thermal decomposition of the starting materials. In this reaction, only electrophilic radicals undergo clean addition to **345**, and electron-rich or nucleophilic radicals give poor results, even when tin reagents are utilised. Notwithstanding this limitation, this tin-free coupling methodology still presents an elegant route to these valuable synthetic building blocks.



Scheme 100.

A conceptually similar addition–fragmentation protocol has been employed in the synthesis of oximes **347** from organonitro derivatives **346** (Scheme 101).[236] The tin-free version shown was only performed on a simple enamine **346**, whilst a tin-based variant was tested on a large range of bis(silyloxy)enamines; the reaction proved to be very general and allowed the formation of a wide range of oximes such as **348**–**350** (Fig. 8). These species are useful intermediates in the synthesis of ketones, enones, enals, thio esters, α-keto esters, isoxazoles, esters, nitriles and isoxazolines. As with the methodology described above, the only real limitation is that only electrophilic radicals will add to **346**.



Scheme 101.

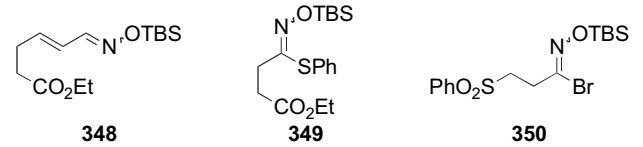
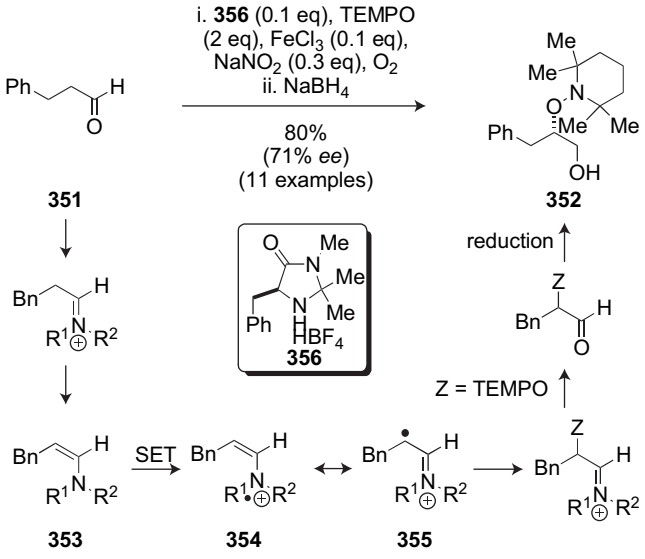


Figure 8.

The last few years have seen considerable resources invested in developing transition metal-mediated coupling reactions of sp^3 carbon centres; whilst many of these show considerable promise, it is slightly surprising that radical chemistry has not been exploited more in this arena. Not only do radical processes already exist for these transformations, as illustrated in this section, but it is becoming increasingly apparent that many of the transition metal-mediated processes are, in fact, radical (see Section 2.7.5).

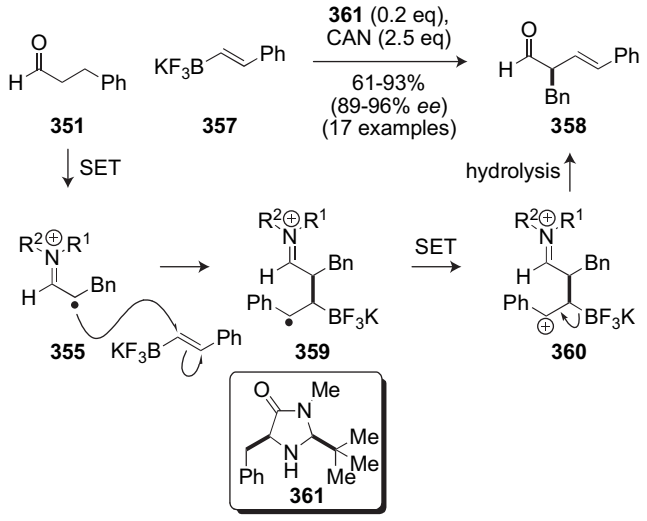
3.1.4. Stereoselective coupling reactions of C-centred radicals

One of the most exciting advances in enantioselective radical reactions is the effective combination of radicals and enamine organocatalysis that has been independently reported by MacMillan[237–239] and Sibi.[240,241] Both groups have built on precedent laid over the last 15 years[242,243] to develop methodology for the enantioselective functionalisation of the α position of aldehydes. The initial step of both methodologies is condensation of an aldehyde **351** with a chiral secondary amine to give an enamine **353** that is then oxidised by an SET process to furnish the iminium radical cation **354** (Scheme 102). It is the fate of the alkyl radical **355** that differentiates the two methodologies; in Sibi's reaction, the radical is trapped with the persistent *O*-centred radical, TEMPO, resulting in the α-oxyamination **352** of the initial aldehyde.[240] Chiral imidazolidinone **356** gives moderate-to-excellent enantioselectivities for a range of aldehydes; a variety of aryl-substituted aldehydes were tolerated, but simple alkyl aldehydes containing no aromatic rings or double bonds gave no selectivity, suggesting that π-interactions are important. The benefit of this system is that oxidation is achieved with a catalytic quantity of iron(III) chloride in conjunction with a stoichiometric amount of a co-oxidant comprised of sodium nitrite and oxygen. The disadvantage is that products of the type **352** are accessible by more conventional chemistry.



Scheme 102.

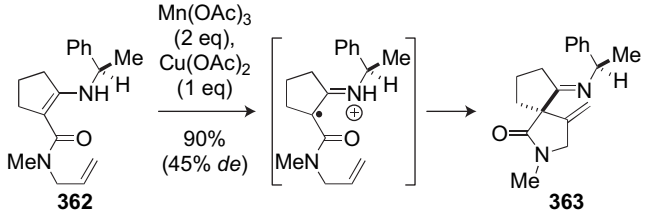
MacMillan's methodology is more versatile and permits the reaction of the radical cation **355** with a host of electron-rich acceptors including allylsilanes,[238] silyl enol ethers,[237] heteroaromatics[238] and alkenyl potassium trifluoroborate salts.[239] Reaction with alkenyl potassium trifluoroborate **357** gives **358** in good yield and selectivity when **361** is employed as the catalyst (Scheme 103). In MacMillan's reactions, two distinct oxidation steps occur; the first gives the radical cation **355**, whilst the second is required to oxidise radical **359** to the cation **360**. As a result, the methodology needs an excess of the metal-based oxidant, CAN. The reaction is quite general; a range of aldehydes can be employed in the reaction, whilst the alkenyl component **357** can be alkyl or aryl substituted with little variation in the yield or selectivity. Not only does this methodology permit the facile synthesis of enantiomerically pure homoallylic aldehydes that would be difficult to form by conventional means, but it is also undoubtedly just the tip of the iceberg; it is easy to imagine this general strategy, the formation of a chiral radical cation from enamines, being employed in a wide range of novel transformations and it will be fascinating to see how this work progresses.



Scheme 103.

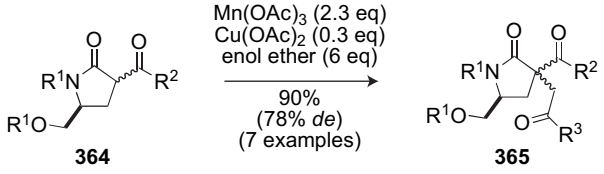
Currently, neither methodology is ideal; Sibi's system involves a single oxidation and so appears to be limited to the addition of persistent radicals. MacMillan's method is far more impressive in scope but uses an excess of metal oxidant. A combination of the two would have a major impact on both radical chemistry and organocatalysis and this is undoubtedly being investigated along with the use of photoredox chemistry.

Most stereoselective radical couplings of electron-rich or electron-neutral alkenes involve diastereoselective processes based around the use of chiral auxiliaries and not enantioselective processes. Considering the versatility of radicals formed by manganese(III)-mediated oxidation of carbonyl compounds, it is somewhat surprising that there have been few reports of their use in stereoselective synthesis. Arguably, Cossy reported the first diastereoselective oxidation–radical cyclisation of an enamine (Scheme 104).[242] Chiral β-carboxamido enamine **362** was oxidised with manganese(III) acetate/copper(II) acetate to give a radical cation that cyclised to give spirocycle **363** with moderate diastereoselectivity (45% de). The enamine was formed from a primary amine and, whilst it is possible that an iminium cation formed from a secondary amine would have less rotational freedom, thus giving higher diastereoselectivity, the added bulk unfortunately prevents condensation.



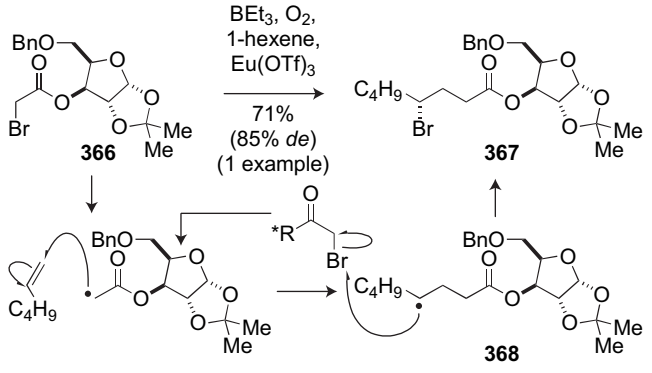
Scheme 104.

Shockingly, it was as late as 2003 that Parsons reported the first investigation of the diastereoselective intermolecular addition of dicarbonyl substrates to electron-rich alkenes (Scheme 105).[244] Initial studies employed a benzyl-protected lactam (**364**; R^1=Bn), but gave poor results, possibly due to the benzyl group undergoing a competitive oxidative reaction. Use of the inert methyl group (**364**; R^1=Me) led to good yields and stereoselectivities of the desired compounds **365**. Not unsurprisingly, increasing the steric bulk of the substituents on either the 1,3-dicarbonyl substrate (R^2) or the radical acceptor (R^3) resulted in improved diastereoselectivity. Clearly these results show great potential for future work. Currently, one major limitation is the nitrogen-protecting group; methyl groups are not easy to remove!



Scheme 105.

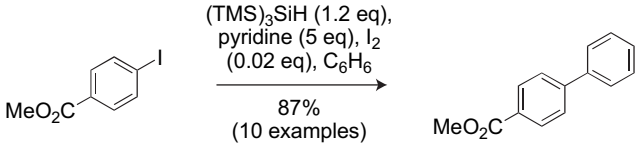
Examples of stereoselective ATRA are limited. One particular obstacle to achieving stereocontrol is the distance between the new stereocentre and the most obvious point of attachment of any chiral auxiliary, the ester moiety of the radical precursor. Enholm has reported an example of 1,6-stereoinduction utilising a carbohydrate-derived precursor **366** (Scheme 106).[245] Crucial to the success of this protocol is the use of a Lewis acid, which probably plays two roles: firstly, it coordinates to the ester **366**, resulting in activation of the α-bromo ester and facilitating bromide transfer from **366** to secondary radical **368**, and secondly, the authors propose that the Lewis acid tethers the chain-transfer reagent **366** and the product radical **368** together, thus allowing induction of stereochemical information via a pseudo-intramolecular bromine-atom transfer. The optimum conditions utilised europium(III) triflate and form **367** in a yield of 71% and 85% de. Omission of the Lewis acid resulted in no product formation. The long-range induction, across six atoms, suggests that the carbohydrate auxiliaries on both the acceptor and donor contribute to the selectivity. It is also highly likely that the oxygenated nature of the auxiliary plays an important function in stereochemical induction, although there is not enough experimental evidence to confirm this. Oxazolidinones have also been employed as the chiral auxiliaries for Lewis acid-mediated Kharasch-type additions.[246] In this reaction, the bromoacetyl moiety was added to norbornadiene with excellent selectivity when ytterbium(III) triflate was used as the Lewis acid.



Scheme 106.

3.1.5. Addition of C-centred radicals onto aromatic rings

Intermolecular radical additions to aromatic rings are rare, but attractive, as they permit the formation of compounds such as biaryls without recourse to transition-metal catalysts or harsh reaction conditions. Radicals have been implicated in the oxidative coupling of phenols and naphthols to form biaryls; whilst not all of these reactions are radical dimerisations, all lie outside the scope of this review. The majority of free-radical additions to aromatic rings are performed under reductive conditions, yet still conclude with *oxidative* re-aromatisation. Virtually every component of these reactions has been implicated in this step, from the solvent and initiator[247] to other radical intermediates. Curran has recently reported that oxygen is an excellent reagent for promoting re-aromatisation.[248] Delightfully, this finding stems from a control experiment during studies on the addition of aryl radicals to arenes that gave superior results to the planned reaction (Scheme 107). These investigations found that, on a small scale, sufficient oxygen was present in the non-degassed solvent to give excellent yields of the biaryl product; large-scale reactions require more oxygen and it appears that these are best performed in a flask open to the air! It is essential that pyridine is used to neutralize the hydrogen iodide formed during the reaction and that TTMSS is employed as the hydride source as tributyltin hydride gives no product. Whilst the intermolecular reaction suffers from some limitations including the need for a large excess of the arene acceptor and poor regioselectivity, these can be overcome by performing the intramolecular variant. The reaction is believed to proceed by the abstraction of a hydrogen from the intermediate cyclohexadienyl radical by the dioxygen radical to give the aromatic ring and a peroxide radical. Amusingly, rigorous degassing of solvents prior to radical reactions may, in certain cases, actually hinder their efficiency. It is interesting to speculate whether many of the previous reports of radical additions to arenes over the preceding decade have been aided by 'adventitious oxygen.'

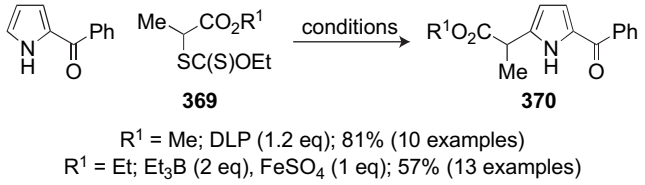


Scheme 107.

Another possible mechanism operates in certain examples.[249] The efficient addition of bromide- and selenide-derived radicals to aromatic systems often requires stoichiometric quantities of initiator, whilst those derived from iodides frequently furnish good yields with only sub-stoichiometric quantities; this difference can be explained if two propagation sequences are in operation and that the dominant sequence is dictated by the substrate structure. The first mechanism requires the initiator (or oxygen) to abstract a hydrogen in the re-aromatisation step. The second mechanism involves standard radical addition followed by loss of a *proton* to form a radical anion species. This participates in SET between the intermediate and the radical precursor to give the product and a new, halo radical anion, which can lose a halide anion to generate the aryl radical. As SET to bromides and selenides is much less facile than to iodides, this would explain the difference in reactivity of these substrates.

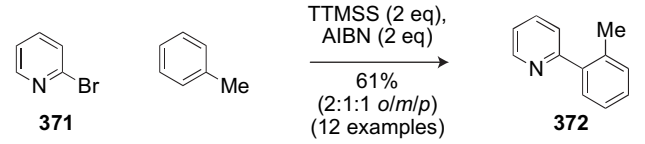
The scarcity of reports of intermolecular radical additions to aromatic systems is probably a result of the premature reduction of the radical prior to the relatively slow addition step. The comparatively long lifetime of radicals generated from xanthates **369** can overcome this problem. Oxidative re-aromatisation is presumably facilitated by either a DLP-promoted oxidative chain process or by an alkyl radical derived from the fragmentation of the peroxide in a non-chain reaction; both mechanisms require a stoichiometric amount of peroxide to complete the reaction. Alternatively, an external oxidant can be added; Miranda has used both

methodologies, stoichiometric DLP,[250] or triethylborane in the presence of iron(II) sulfate hydrate[251] in the electrophilic alkylation of heteroaromatic systems (Scheme 108). Whilst both reaction conditions allow the synthesis of substituted heteroaromatic systems **370** under relatively mild conditions, they both suffer from the same drawback, namely that the initiator must be added dropwise over 12–14 h. The same methodology has been employed in the regioselective radical alkylation of 3-substituted pyrroles to yield 2,3-disubstituted derivatives.[252]



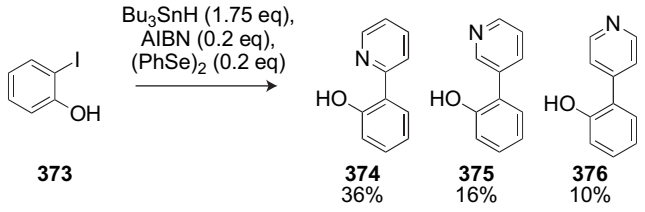
Scheme 108.

A problem with intermolecular radical additions to aromatic rings is the control of regiochemistry. Bromopyridine **371**-derived radicals add to benzene in good yield, but the addition to substituted benzenes is more problematic; for example, there is only a slight preference for the *ortho* adduct **372** when toluene is the acceptor, with the other regioisomers also being formed (Scheme 109).[253] The use of an excess of initiator in these reactions suggests that it may be involved in the re-aromatisation step.



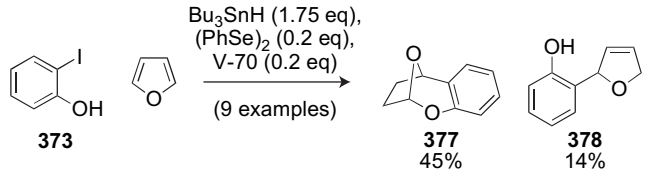
Scheme 109.

Addition to heteroaromatics is often more efficient, due to the directing effect of the heteroatom and, thus, addition of an aryl radical to pyridine furnishes biaryl compounds with predominantly 2-substitution analogous to **374**.[253] This selectivity is best explained by the stability of the intermediate radical. Interestingly, the optimum yields are obtained in the presence of sub-stoichiometric diphenyl diselenide, a reagent that should hamper the re-aromatisation of the intermediate radical. Normally, under such reductive conditions, diphenyl diselenide is reduced to benzeneselenol, which traps the cyclohexadienyl radical and *prevents* re-aromatisation. It is not clear why this reagent assists this coupling reaction or what role it is playing, but, in its absence, the yields of **374**, **375** and **376** from **373** are 9, 4 and 1% respectively (Scheme 110).[254]



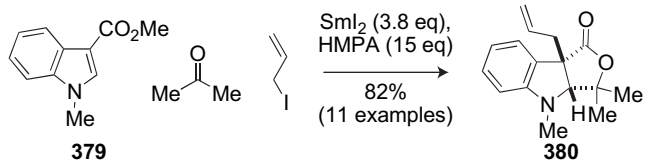
Scheme 110.

By altering the radical acceptor, this reaction can be utilised to synthesise a variety of complex heterocycles. Addition of *o*-iodophenol **373** to furan gives a mixture of the acetal **377** and the alkene **378** (Scheme 111).[254] Initial radical attack is favoured at the 2-position of the furan, with the resultant oxyallyl radical preferentially reacting with benzeneselenol at the distal terminus to the oxygen atom (C-5 in original furan numbering) to give the 2,3-dihydro-2-arylfuran **378**. When an *ortho*-phenol group is present, the 2,3-dihydro-2-arylfurans are not isolated, but spontaneously undergo acetal formation to give **377**; either the phenol or the selenol are acidic enough to catalyse this reaction. As a practical consideration, AIBN cannot be employed as the initiator, as it only decomposes at temperatures >80 °C; furan boils at 32 °C. As a result, V-70, which has a half-life of 10 h at 30 °C, is used. Interestingly, when thiophene is utilised in the reaction, instead of furan, the opposite selectivity is observed, with the 2,5-dihydro-2-arylthiophene being the major product.



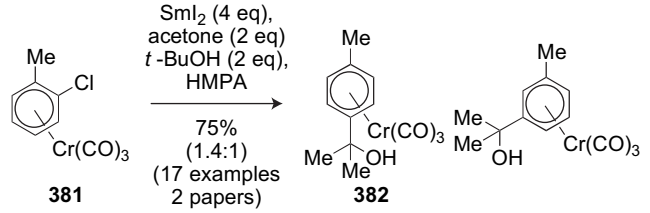
Scheme 111.

Ketyl radicals formed by the action of samarium(II) iodide readily add to activated indoles **379**,[255] facilitating a highly convergent radical addition–ionic allylation–lactonisation sequence to give functionalised derivatives such as **380** in excellent yield (Scheme 112). The ester moiety is essential; indoles missing this functionality fail to react. Simple two-component addition reactions, missing the allyl reagent, occur with complete diastereoselectivity for the trans compound, the opposite result to that observed with the intramolecular reactions (see Part 2, Section 2.6, Scheme 72). Yet, in the three-component coupling reaction, the cis adduct was the only product formed. These results can be explained if a samarium enolate that is allowed to equilibrate is formed.



Scheme 112.

Another nucleophilic aromatic radical substitution reaction of ketyl radicals permits the functionalisation of chloro- and fluoro-η^6-chromium–arene complexes.[256a,b] The reaction does not proceed with the expected *ipso* substitution; the regiochemical outcome of the substitution reaction of methyl chloroarene complex **381** shows that *meta*-tele substitution **382** is preferred (Scheme 113). *ipso* Substitution is possible if both *meta* positions are blocked. There is no discernable pattern to suggest that either fluorine or chlorine is the better leaving group, with the yields for each being comparable. It is anticipated that this methodology will gradually be developed so that it is complementary to conventional nucleophilic aromatic substitution.



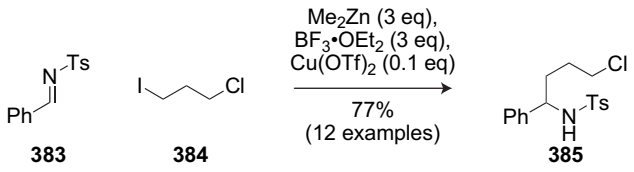
Scheme 113.

Radical chemistry offers a route to substituted aromatic rings that is complementary to the more conventional transition metal-mediated or ionic processes. Presently, radical couplings are not as

versatile, but this is due to the comparative lack of study, rather than any inherent inferiority; these limitations should be ameliorated in the coming years.

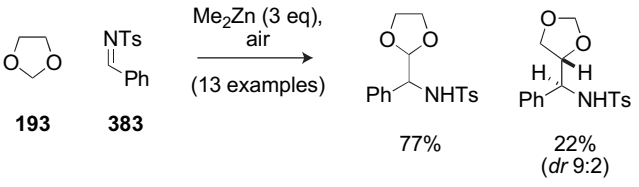
3.1.6. Radical additions to C=X bonds

The addition of radicals to the C=N bond of imines and related functionality is well known; a typical example is given in Scheme 114. In this reaction, dimethylzinc–air replaces the more common initiator, triethylborane–air;[257] the reaction proceeds in a similar manner with the homolytic scission of the zinc–carbon bond to give a methyl radical that can abstract an iodide to form the desired alkyl radical. The advantage of dimethylzinc is that it can form primary alkyl radicals in addition to secondary and tertiary radicals. Triethylborane cannot achieve this goal due the energy of ethyl radicals being similar to that of most primary radicals, whilst the methyl radical is far less energetically stable, making iodine abstraction more profitable. Selective abstraction of the iodine from **384** permits the addition to **383** and the formation of the chloroamine **385** in good yield. The latter is readily cyclised by standard nucleophilic substitution to give a pyrrolidine. Good yields for the addition to the imine are only obtained in the presence of boron trifluoride etherate and copper(II) triflate. The boron reagent is probably a simple Lewis acid that activates the imine, but the role of the copper(II) salt is less clear and further research is required to elucidate its mode of action.



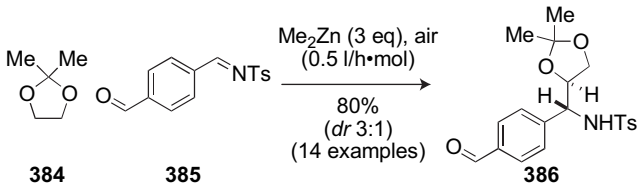
Scheme 114.

Direct C–H activation is an important goal in organic synthesis. One method to achieve this is via selective hydrogen abstraction of the α-C–H of ethereal substrates. A number of different reagents promote this reaction and it offers an excellent method for the rapid assembly of oxygenated molecules. Treatment of a variety of oxygenated compounds with excess dimethylzinc–air facilitates hydrogen-atom abstraction and radical addition to activated imines such as **383** (Scheme 115).[258] Often, the addition step is reversible, due to the strength of the C=N bond and the stability of the initial α-ethereal radical; dimethylzinc acts as both a Lewis acid and a radical trap to prevent the reverse fragmentation process from occurring. A variety of different ethers including tetrahydrofuran, tetrahydropyran and 1,4-dioxane as well as linear ethers, such as diethyl ether, react efficiently. Quite remarkably, 1,3-dioxolane **193** adds to **383** with high stereo- and regio-chemistry. The success of the reaction is independent of the nitrogen-protecting group, which can be either electron donating or electron withdrawing.



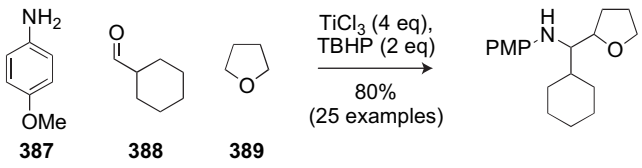
Scheme 115.

Successful introduction of a C1 fragment would allow the development of a form of umpolung chemistry complementary to the more common dithiane chemistry.[259] Whilst the 1,3-dioxolane addition shown in Scheme 115 succeeds in this venture, the regioselectivity makes it less than ideal. Using 4,4,5,5-tetramethyl-1,3-dioxolane overcomes the regioselectivity issue, but hydrolysis of the resultant acetal proved to be problematic. More successful was the use of *tert*-butyl methyl ether, which added to the imine in an acceptable 59% yield and could be unmasked to give the free alcohol by treatment with trifluoroacetic acid. Equally successful was the addition of a C2 diol unit; 2,2-dimethyl-1,3-dioxolane **384** adds to a range of electron-rich and electron-poor imines in excellent yields and can readily be hydrolysed to a diol (Scheme 116). For the most part, addition occurs with satisfactory stereoselectivity; low selectivity was found only with aliphatic imines. One advantage of this reaction over the ionic additions is its high chemoselectivity for addition to imines over aldehydes. Thus, reaction of **385** only gives one product, the amine **386**. Such selectivity with organometallic reagents is hard to imagine.



Scheme 116.

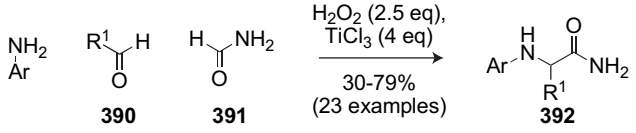
Analogous chemistry can be mediated by a combination of titanium(III) chloride and *tert*-butyl hydrogen peroxide in aqueous media;[260] the latter fact is quite remarkable considering that many imines readily undergo hydrolysis. The methodology involves the three-component coupling of an amine **387**, an aldehyde **388** and an ether **389** (Scheme 117). The reaction is operationally simple, involving the dropwise addition of *tert*-butyl hydrogen peroxide to a mixture of the other reagents and watching for the sudden colour change of the blue titanium(III) species to a yellow colour, which indicates that the reaction has gone to completion. Key to the success of this reaction is the multifarious role played by the titanium reagent; as titanium(III), it acts as the initiator and as the radical terminator, preventing fragmentation of the aminyl radical, whilst, in the higher oxidation state, it acts as a Lewis acid and a dehydrating agent. The reaction works well for a combination of secondary amines and formaldehyde, but can be problematic with primary amines, as these give a mixture of the mono- and bis-adducts; the selectivity could be improved by using *p*-methoxyaniline as the primary amine component and reducing the amount of formaldehyde used. Secondary amines fail to react with any aldehyde other than formaldehyde, presumably due to steric factors. Only the use of *p*-methoxyaniline permitted higher aldehydes such as **388** to be incorporated in good yields. Whilst the transformation can be considered environmentally benign, as the reaction is carried out in water, and no chromatography is required when volatile amines are employed, it is potentially limited, due to the acidic conditions required.



Scheme 117.

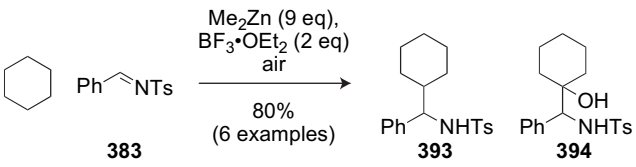
C–H activation of substrates other than ethers and acetals can be achieved under similar reaction conditions. The titanium(III) chloride methodology activates formamide **391** and, thus, facilitates the synthesis of amino amides **392** (Scheme 118).[261] A wide range of aldehydes **390** can be employed in the reaction, including aromatic, aliphatic and alkenyl aldehydes. The reaction is independent of the

electronics of the aldehyde. This offers an attractive route to these important compounds.



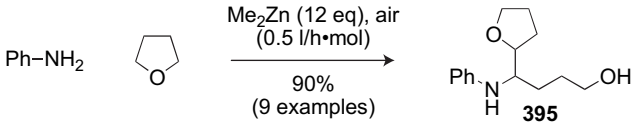
Scheme 118.

One of the most exciting developments in this field has been the direct activation of non-functionalised C–H compounds. Simple cycloalkanes can be aminoalkylated by treatment with dimethylzinc, boron trifluoride etherate and the appropriate imine to give **393** (Scheme 119).[262] Without the Lewis acidic boron trifluoride etherate, the formation of 1,2-amino alcohols **394** via aerial oxidation was observed. Other radical initiators, such as diethylzinc and triethylborane, result in lower yields, due to competitive addition of an ethyl radical to the imine; it is only the highly active, non-stabilised, methyl radical that gives good yields. This is one of a select group of reactions that permits the functionalisation of unactivated C–H bonds.



Scheme 119.

Equally remarkable is the finding that the C=N/carbonyl component of the these reactions is not required and that amino alcohols **395** can be prepared simply by treating aniline and tetrahydrofuran with dimethylzinc under a continuous stream of air (Scheme 120).[263] Dimethylzinc is unique in its ability to initiate this reaction effectively, both diethylzinc and triethylborane giving inferior results. A range of primary anilines can be employed as well as alkoxyamines and *N*,*N*-dialkylhydrazines, but secondary amines fail to react. The mechanism of the reaction is believed to involve generation of the α-alkoxyalkyl radical by α-C–H abstraction followed by oxidation to give an oxonium ion. The latter species is attacked by the amine to give an aminal that is in equilibrium with the imine. The imine is then attacked by a second equivalent of the α-alkoxyalkyl radical to give **395**.



Scheme 120.

Considerable effort has been directed towards developing diastereoselective additions to C=N π bonds, due to the ubiquity of chiral α-branched amines in Nature, medicinal chemistry and biochemistry. Naito has extensively studied intermolecular radical additions to many variants of the C=N moiety including chiral nitrones. The addition of alkyl radicals under tin-free conditions to four different nitrones **396**–**399** (Fig. 9) was investigated.[264] Triethylborane was employed as both the radical initiator and the chain-transfer agent. Addition to nitrone **396**, bearing Oppolzer's camphorsultam, occurred with moderate yield (47%) and excellent diastereoselectivity (>95% de). The major by-products were formed by the competitive addition of an ethyl radical derived from triethylborane and by the alkylation of the oxygen of the nitrone moiety. More promising results were achieved with the cyclic nitrone **397**, which gave the desired product in good yields (72–82%) and excellent diastereoselectivity (>95% de).[265] The amount of triethylborane and oxygen required to initiate the reaction had to be carefully controlled; too little triethylborane or too much oxygen resulted in the formation of a substituted nitrone **400** devoid of a new stereocentre. Interestingly, the acyclic variant of this reaction, employing **398**, gave unsatisfactory results. Finally, it was found that acetal **399** could be selectively converted into either diastereoisomeric product. Conducting the radical addition in the absence of a Lewis acid gave predominantly the *anti* diastereoisomer (85%) in moderate yield (46%). Performing the addition in the presence of a Lewis acid reversed the selectivity to give the *syn* product (97%) in the same yield (47%).

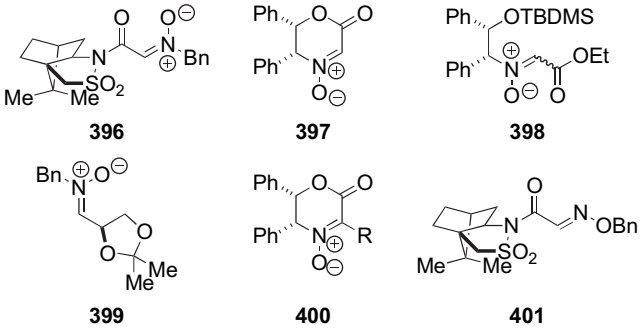
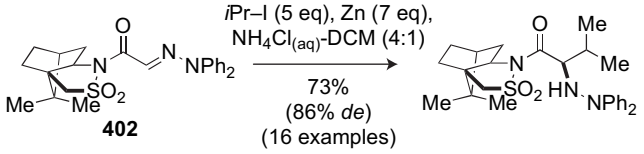


Figure 9.

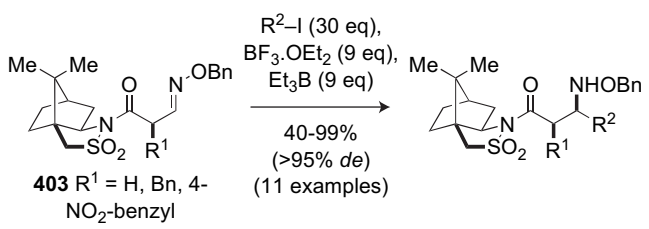
Radical alkylation of oxime ethers can be achieved using zinc as the initiator in aqueous–alcohol media.[266] The reaction protocol is highly practicable; the substrates and zinc powder are simply suspended in methanol and then saturated aqueous ammonium chloride solution is added and the reaction stirred at room temperature. Whilst the exact role of the ammonium chloride is unclear, it must activate the zinc, as no reaction occurs in its absence. The reaction proceeds well with secondary and tertiary alkyl iodides, but fails with bromides and primary iodides. The zinc is believed to reduce the iodide to an alkyl radical and zinc(I) iodide via SET; the radical then adds to the oxime ether to give an aminyl radical that is reduced to an anion by a second equivalent of zinc. The diastereoselective variant employs the glyoxylic acid derivative of Oppolzer's camphorsultam **401** and requires a biphasic system with dichloromethane replacing methanol in order to obtain good yields and selectivity. If the oxime ether moiety was replaced with a diphenyl hydrazone group (**402**), then the reaction was slower, with decreased yield, but proceeded with improved diastereoselectivity (Scheme 121). Alternatively, indium metal promotes allylation or alkylation of oxime ethers in aqueous media; the reaction is slower than the zinc variant, but proceeds with higher diastereoselectivities.[267]



Scheme 121.

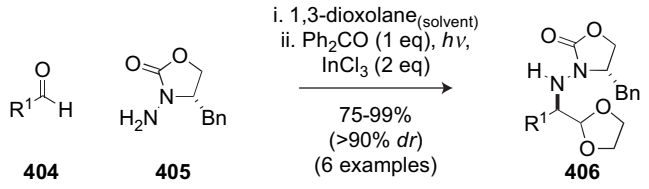
Intermolecular radical addition to glyoxylic oxime ethers proceeds efficiently due to activation of the C=N bond by the electron-withdrawing amide functionality. Non-activated examples, where the oxime is separated from the amide, are scarce. Naito has shown that intermolecular addition can be achieved in these cases by activating the oxime ether with a Lewis acid (Scheme 122).[268] Utilising an excess of reagents permitted highly diastereoselective

(>95% de) addition of various alkyl radicals to oxime ethers **403**. Interestingly, good selectivity required the presence of both the α-substituent and the camphor auxiliary. Removal of the chiral auxiliary led to addition in 83% de, whilst removal of the α-substituent (**403**; R=H) had an even more dramatic effect with almost complete loss of selectivity (5% de). The huge excess of reagents is not attractive, yet the potential shown by the diastereoselective radical reactions of unactivated oxime ethers promises to broaden the utility of imine derivatives as radical acceptors.



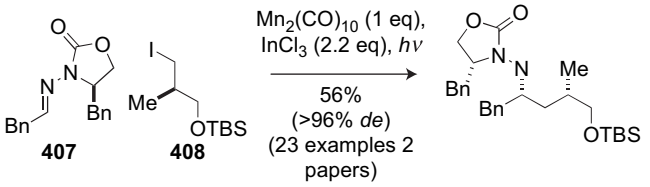
Scheme 122.

As the previous examples have shown, additions to the C=N bond are not without their limitations; invariably, the C=N bond is activated by an electron-withdrawing substituent and primary carbon radicals are rarely viable reagents, limiting these methodologies to the synthesis of β-branched amino acids. A potential solution to many of these shortcomings is the reaction of 1,3-dioxolanyl radicals with *N*-acyl aldohydrazones under chiral auxiliary control.[269] In an ingenious 'one-pot' reaction, a variety of aldehydes **404**, including alkyl, aromatic and electron-rich aldehydes, were transformed into *N*-acyl hydrazones by condensation with (*S*)-3-amino-4-benzyl-1,3-oxazolan-2-one **405** in 1,3-dioxolane; irradiation of the reaction mixture with UV light in the presence benzophenone and indium(III) chloride initiated radical addition to give **406** in excellent yield and with good diastereoselectivity (Scheme 123). The indium(III) chloride has a remarkable effect on the reaction, reducing the reaction time considerably and improving the diastereoselectivity markedly, suggesting that chelation between indium and the *N*-acyl hydrazone is important. An analogous methodology has been developed for the addition of ethers and acetals to aryl sulfinimines.[270] This chemistry relies on α-C–H activation by dimethylzinc, as described above (see Scheme 115) and occurs with up to 82% ee after oxidation of the sulfoxide to a sulfone.



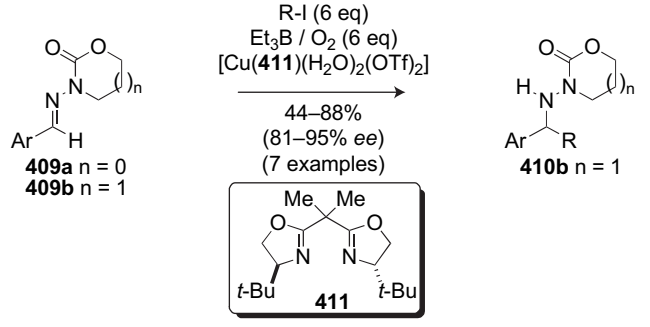
Scheme 123.

One potential solution to the perennial problem of the addition of unstable primary alkyl radicals to C=N bonds is the use of dimanganese decacarbonyl [$Mn_2(CO)_{10}$] under photolysis conditions; this reagent is more practicable than tin hydride reagents, as it is a relatively stable solid that reacts to give by-products that are readily removed from the reaction medium. Friestad has shown that manganese-mediated addition of alkyl radicals to chiral hydrazones occurs with excellent yields and diastereoselectivity.[271] The reaction tolerates a range of primary and secondary iodides as radical precursors, but fails to furnish any product with allyl, benzyl or *tert*-butyl bromides. The structure of the radical acceptor appears to be unimportant, and even α-branched alkyl imino compounds react in good yields. The advantages of this methodology are the mild, non-basic conditions that allow a wide range of functional groups to be tolerated. Thus, functionalised halides such as **408** can be used in highly selective additions to **407**, allowing the convenient preparation of precursors for γ-substituted γ-amino acids (Scheme 124).[272] Currently, the greatest disadvantage with this methodology is that the reaction is either a non-chain process or has a short chain length, and therefore 1–2 equiv of $Mn_2(CO)_{10}$ are required.



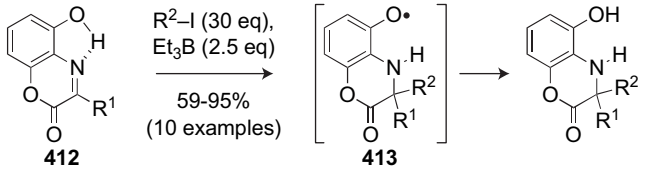
Scheme 124.

Catalytic enantioselective radical additions to C=N bonds are now being developed; one of the most attractive is the addition of alkyl radicals to achiral *N*-acyl hydrazones utilising sub-stoichiometric chiral Lewis acids.[273] Interestingly, this paper suggests that no addition occurs in the absence of the Lewis acid, which is in contrast to Alonso's results (see Scheme 123).[269] The nature of the achiral auxiliary is important, and the oxazolidinone-derived *N*-acyl hydrazone **409a** proved ineffectual, but the valerolactam derivative **409b** was more profitable (Scheme 125). Reaction under tin-free conditions in the presence of bis(oxazoline) **411** and copper(II) triflate gave **410** in good yields and enantioselectivity. With a reduced loading of the Lewis acid (10 mol %), the yield was maintained, but the selectivity was lost (95 vs 46% ee). Whilst the selectivity is disappointing, this is the first evidence of catalyst turnover with enantioselective Lewis acid-controlled radical additions to C=N bonds and bodes well for future research.



Scheme 125.

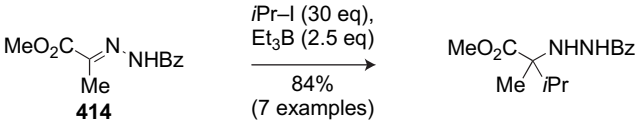
Invariably, studies on intermolecular radical additions to C=N bonds involve aldimines; the challenge of addition to ketimine derivatives remains unresolved. These limitations are slowing being addressed and a protocol for the addition of alkyl radicals to *N*-aryl ketimines in aqueous media has been developed (Scheme 126).[274,275] Key to the success of this methodology is the *ortho*-hydroxyl group on the aryl ring of **412**; only substrates with this phenol functionality give the desired products in meaningful yields.



Scheme 126.

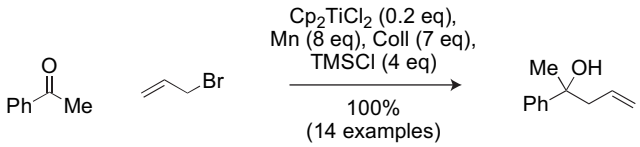
Intramolecular hydrogen bonding is believed to stabilise the imine in aqueous media and provide Lewis-acidic activation. Its reactivity is comparable to an imine with a strong electron-withdrawing substituent such as an *N*-sulfonyl imine. Additionally, the intermediate aminyl radical would be stabilised by both a [1,4]-hydrogen shift and delocalisation of the radical around the aryl ring **413**. Ethyl, secondary and tertiary radicals add smoothly to the imine in the presence of triethylborane. The latter reagent acts as both the initiator and aids chain propagation by trapping the intermediate radical with concomitant release of a new ethyl radical. Not only is this the first time intermolecular radical additions to ketimine derivatives have been reported, but also the use of aqueous, 'tin-free' conditions makes it an attractive procedure for the preparation of nitrogenous compounds. Attempts to convert this transformation into an enantioselective process have met with mixed results; the desired product is formed along with a compound arising from the addition of a second alkyl radical *meta* to the hydroxyl functionality.[275] Intriguingly, the enantiomeric excess of the latter compound was considerably higher than that of the desired product (80 vs 23% ee).

Other ketimino radical acceptors have been investigated, including *N*-benzoyl hydrazones, oxime ethers and diphenyl hydrazones.[276] The optimum acceptor appears to be the *N*-benzoyl hydrazone with the others giving poor yields. Although good yields were obtained for the addition of secondary and tertiary radicals to the pyruvic acid derivative **414**, the necessity for a large excess of alkyl halide is far from ideal (Scheme 127). A promising result is that these reactions could also be performed in an aqueous medium with equal or improved yields to those observed under standard anhydrous conditions.



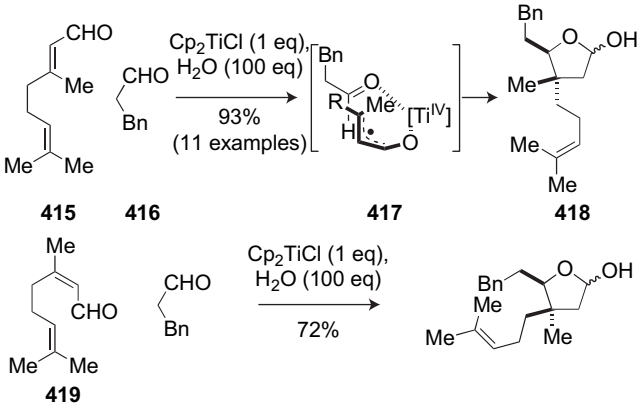
Scheme 127.

Radical additions to aldehydes and ketones are problematic, due to the propensity of the intermediate alkoxy radicals to undergo the reverse, fragmentation process. Compounds that are both oxo- and radico-philic can temper this competing reaction. Titanocene(III) reagents offer great potential in this area (see Section 2.7.1) and have been employed in the allylation of aldehydes. This operationally simple methodology proceeds under Barbier-like conditions with a solution of the titanocene(III) reagent being added dropwise to the reaction mixture.[277] The allylation is highly chemoselective for aldehydes even in the presence of ketones. Highly regioselective crotylation can also be achieved, furnishing the γ-regioisomer almost exclusively along with traces of the product of pinacol couplings. The isolation of the latter suggests the reaction is radical in nature and not ionic. Intriguingly, *p*-nitrobenzaldehyde is inert under these reaction conditions and it is tempting to speculate that ketyl radicals are involved although the catalytic variant developed by Oltra and Cuerva appears to rule out this possibility. The catalytic system utilises the conditions of Cuerva (see Section 2.7.1), Cp_2TiCl_2 (0.2 equiv)/Mn (8 equiv)/Me_3SiCl (4 equiv)/collidine (7 equiv), and permits a range of activated halides including allyl, propargyl and benzyl bromides to add to both aldehydes and ketones (Scheme 128).[278] Ring opening of cyclopropyl phenyl ketone does not occur under these reaction conditions, implying that the ketyl radical is not formed, although, as the reaction in Scheme 22 indicates, not ruling out the possibility of ketyl radical involvement. Attempts to develop an enantioselective variant of this procedure have met with limited success; utilising chiral titanium complex **188** (see Scheme 51), an enantiomeric excess of just 20% was observed. This is an excellent preliminary result and it is anticipated that better-designed titanium complexes will result in higher enantiomeric excesses.



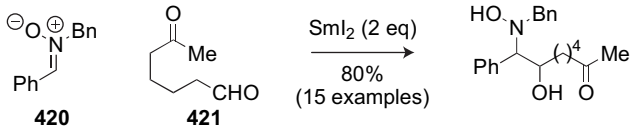
Scheme 128.

An interesting coupling of aldehydes, such as **416**, and conjugated alkenals, such as **415**, to form γ-lactols **418** has recently been reported (Scheme 129).[279] At first glance, this reaction appears to be a simple example of umpolung-like chemistry, with a titanium-ketyl radical undergoing 1,4-addition to an α,β-unsaturated aldehyde, but the reaction is more complex and potentially more valuable. It is believed that the reverse process occurs and the titanium(III) reduces the *alkenal*, furnishing a titanoxy-allyl-type radical that then participates in a pseudo intramolecular coupling to the aldehyde **417**. Radical addition to the carbonyl group is irreversible, due to reduction of the resulting alkoxy radical and trapping of the alkoxide by the metal centre. Water is essential to prevent pinacol-like coupling reactions; low-valent titanium species are believed to exist as dimers that encourage the homo-coupling of two ketyl radicals (see Section 2.7.1; Fig. 3); the addition of water breaks up the dimer and gives two mono-titanium aqua complexes. The reaction shows a high degree of stereoselectivity, with the geometry of the alkenal (**415** vs **419**) controlling the relative stereochemistry of C-4 and C-5, although it is not clear if this is due to rapid reaction or restricted rotation. The reaction shows great potential for the future with one example of a catalytic variant being reported along with one attempt at an enantioselective coupling (33% ee) utilising dichloro[(*R*,*R*)-ethylenebis(4,5,6,7-tetrahydro-1-indenyl)]titanium(IV) as pre-catalyst. It is interesting to compare this methodology to the work of Skrydstrup illustrated in Schemes 58 and 59.[170]



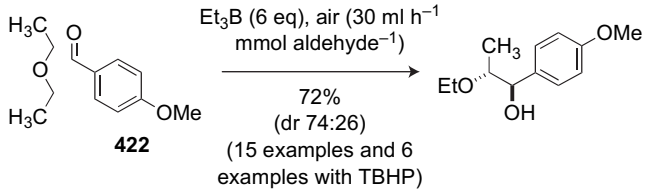
Scheme 129.

Samarium(II) iodide can also act as a radical trap (see Section 2.7.4) and, thus, permits irreversible addition to aldehydes and ketones; reduction of nitrone **420** to a ketyl-like radical is followed by chemoselective addition to the aldehyde of **421** (Scheme 130).[280] The methodology appears to be remarkably powerful, with no limitations in the structure of either substrate being observed. The reaction shows excellent chemoselectivity for aldehydes versus ketones. It is thought that the high oxophilicity of the samarium encourages the desired coupling by coordinating to both the nitrone oxygen and the incoming carbonyl moiety.



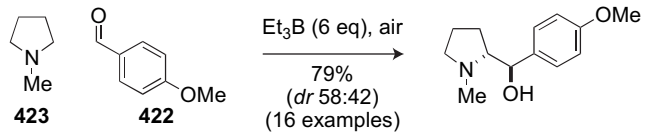
Scheme 130.

Radicals derived from C–H activation have also been used in additions to carbonyls; hydroxyalkylation of ethers can be achieved by treating an aldehyde **422** with excess of ether, normally the solvent, and an excess of triethylborane under a constant flow of air (Scheme 131).[281] Fragmentation of the resulting alkoxy radical does not occur, due to the triethylborane, which acts as a Lewis acid, radical initiator and radical trap. The reaction proceeds with both aliphatic and aromatic aldehydes to give predominantly the *anti*-products. A range of ethers can be used in the reaction including tetrahydrofuran, diethyl ether and the acetal, 1,3-dioxolane. Symmetric ethers devoid of regiochemical issues give better results than non-symmetric substrates. The reaction can also be performed with *tert*-butyl hydrogen peroxide (TBHP) as the radical initiator; both the yield and diastereoselectivity are identical to reactions carried out with air as the initiator.[282]



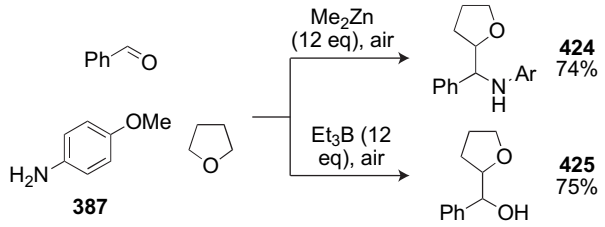
Scheme 131.

The α-C–H position of amines is readily activated, as shown by the radical reactivity of tertiary amides, ureas and amines. Radical hydroxyalkylation can be achieved with triethylborane acting as a radical initiator and oxy radical scavenger (Scheme 132).[283] One problem with tertiary amines such as **423** is the possible complication of regioisomers, depending upon which hydrogen is abstracted; fortunately, CH_2 alkylation is preferential to CH_3 alkylation, as the resulting radical is stabilised by hyperconjugation and because it results in the release of ring strain.



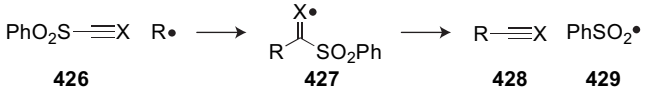
Scheme 132.

Fascinating chemoselectivity can be achieved in a related reaction; the product distribution of the three-component coupling reaction of benzaldehyde, an aryl amine **387** and tetrahydrofuran was found to be highly dependent upon the initiator used.[284] Employing triethylborane and air gave the product of hydroxyalkylation **425** (Scheme 133) as the major product. Yet, if dimethylzinc and air were used, then the amine **424** was the sole product of the reaction. It is unclear whether this selectivity is the result of the dimethylzinc accelerating the formation of the imine prior to radical addition or due to a different reactivity profile of the imine, formed in an equilibration reaction with the aldehyde, with the different initiators. Triethylborane does promote radical addition to the imine, but at a slower rate than the zinc reagent. Dimethylzinc can mediate the addition of ethereal radicals to aldehydes, but at a considerably retarded rate and at the β-position of the tetrahydrofuran ring.[285]

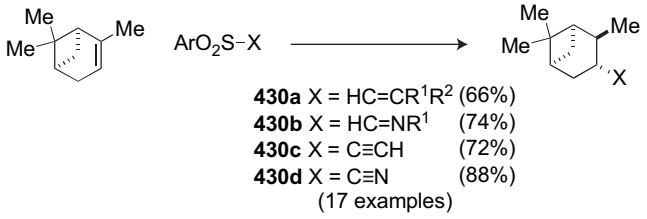


Scheme 133.

Sulfones are attractive reagents for radical couplings to multiple bond acceptors and they have been fundamental in developing a general process for the hydroalkenylation (**430a**), hydromethanimination (**430b**), hydroalkynylation (**430c**) and hydrocyanation (**430d**) of alkenes.[180] The process relies on radical addition to the carbon of a multiple bond bearing the arylsulfone (**426**; Scheme 134). β-Elimination of radical **427** not only regenerates the multiple bond found in the product (**428**), but also expels a sulfonyl radical **429** that can act as the radical chain carrier and thus propagate the process. This general approach works efficiently with primary, secondary and tertiary radicals derived from organoboranes. This wide reactivity profile compares favourably with palladium-mediated alternatives such as the Suzuki and Sonogashira reactions, which are frequently problematic with alkyl (sp^3) boronic esters. In particular, it should be noted there are no palladium-catalysed cross couplings between alkylboranes and alkynyl derivatives, to give **430c**, or with nitriles, to give **430d** (Scheme 135). The generality of this methodology, combined with the use of cheap, readily available, non-toxic reagents, make it an extremely attractive strategy for the formation of C–C bonds.



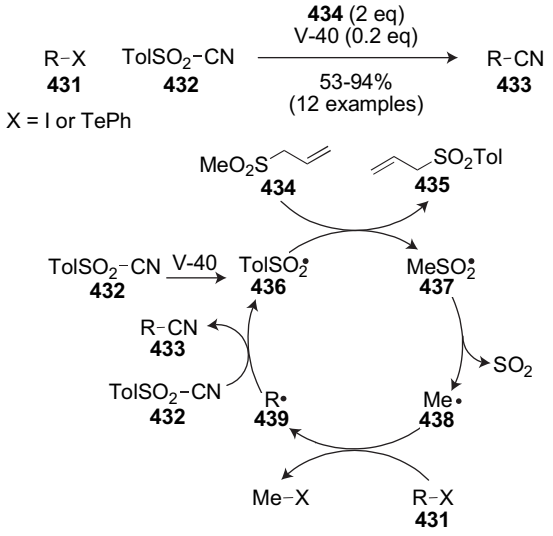
Scheme 134.



Scheme 135.

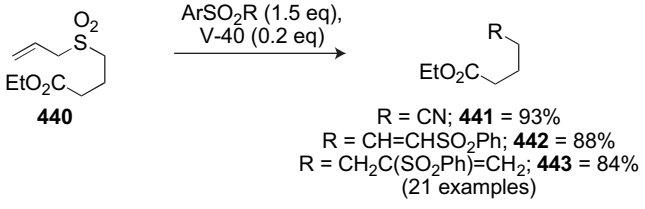
The methodology described above is a natural progression of Kim's tin-free, radical-based method for the cyanation of alkyl iodides and tellurides **431** (Scheme 136).[286] The reaction employs methyl allyl sulfone **434** as a source of methyl radicals that facilitate an iodine-atom-transfer step for the generation of alkyl radicals. The reaction is initiated by homolysis of toluenesulfonyl cyanide **432** in the presence of the initiator, 1,1-azobis(cyclohexanecarbonitrile) (V-40), a thermally more stable analogue of AIBN, to give the toluenesulfonyl radical **436**. This interacts with **434** to generate first **437**, which undergoes thermal decomposition to the methyl radical **438**. Potentially, the methylsulfonyl radical **437** could react with either **434** or **435** prior to decomposition; fortunately, neither process is detrimental. Addition to **434** is degenerate, whilst addition to **435** regenerates **436**. The methyl radical **438** is necessary to instigate the atom transfer with **431** to give the desired alkyl radical **439**. Finally, this reacts with **432** to give product **433** and propagate the chain reaction. The reaction

gives moderate-to-good yields for benzylic, secondary and tertiary iodides, but is ineffectual with primary iodides; the problem is competitive addition of the methyl radical **438** to **432** to give acetonitrile, due to an inefficient iodine-atom-transfer step. Fortunately, phenyltelluride-group transfer from primary alkyltellurides to the methyl radical is considerably faster than the corresponding iodine transfer and permits the reaction to proceed in excellent yields.



Scheme 136.

The inefficiency of iodine-atom transfer from primary halides has been a limitation in a number of radical methodologies. Whilst the use of tellurides clearly overcomes such limitations, other radical precursors have also been investigated. Alkyl allyl sulfones, such as **440**, appear to be excellent radical precursors for a variety of C–C bond-forming reactions.[287] This methodology has permitted the cyanation **441**, alkenylation **442**, allylation **443**, and tandem radical reactions to be performed (Scheme 137). The success of the alkyl allyl sulfones as radical precursors in these reactions can be attributed to the fate of the alkyl sulfone radical (analogous to **437**; Scheme 136). As with the allyl methyl sulfone methodology, most non-productive pathways are either degenerate or reversible and so the desired reaction ultimately occurs in good yield.

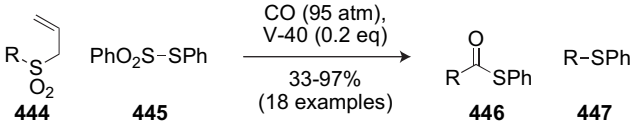


Scheme 137.

The addition of radicals to C=X bonds offers a rapid and efficient route to highly functionalised molecules. An initial problem due to the reversibility of many of these addition processes is steadily being overcome by the use of radical traps that hamper fragmentation. The low basicity of radicals means that many of these transformations are more general and versatile than their ionic counterparts.

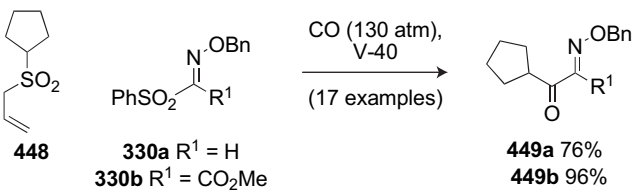
3.1.7. *Radical carbonylations*

Radical carbonylation reactions are a valuable alternative to the more traditional transition-metal mediated carbonylation reactions and offer a practical route to acyl radicals. By employing common alkyl radical precursors and 'inserting' carbon dioxide, carbonylation reactions avoid the difficulties associated with many acyl radical precursors and partially suppress competitive radical decarbonylation. The reactions of acyl radicals formed in such a manner, which include atom- and group-transfer reactions, as well as both inter- and intra-molecular additions, radical cascades and radical translocations, have been summarised in a review.[35] Care must be taken with radical carbonylations to minimise side reactions; the correct chain carrier is required to curtail premature reduction and, depending upon the stability of the initial radical, decarbonylation can still be an issue.[288a,b] Sulfone radical precursors have been employed in an elegant synthesis of thiol esters under metal-free conditions.[289] Treatment of a variety of alkyl allyl sulfones **444** under the optimum conditions furnishes the thiol esters **446** in good yields (Scheme 138). Homolysis of phenyl benzenethiosulfonate **445** generates a phenylsulfonyl radical that reacts with the allyl moiety to give a secondary radical, which disproportionates to phenyl allyl sulfone and an alkylsulfonyl radical. The latter undergoes thermal desulfonylation to furnish the required alkyl radical that reacts with carbon monoxide to yield the acyl radical. Finally, trapping of the acyl radical by **445** yields the product **446** and regenerates the chain carrier. Primary alkyl radicals give excellent yields in this transformation, but both secondary and tertiary alkyl radicals result in significant quantities of sulfide **447**, due to more favourable decarbonylation; benzylic sulfones fail to give any product. Performing the reactions under a high pressure of carbon monoxide with a low concentration of starting material reduces the formation of **447**. The process can be incorporated into quite remarkable multi-component coupling reactions.



Scheme 138.

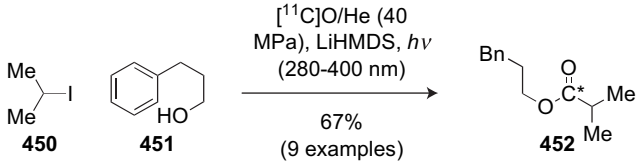
Analogous chemistry has been developed for the synthesis of acylated oxime ethers **449a**,**b**. A range of allyl sulfones, such as **448**, undergo a three-component coupling reaction with carbon monoxide and phenylsulfonyl oxime ether derivatives such as **330a**,**b** to give **449a**,**b** (Scheme 139).[290] Primary halides invariably furnish the desired carbonylated product, but secondary halides are more problematic; the stability of secondary radicals means that the carbonylation step is inefficient and direct addition to the oxime ether becomes a competitive side reaction. This can be overcome by increasing the pressure of carbon monoxide or by the use of oxime ether **330b**; it appears that **330b** is more reactive towards acyl radicals than **330a** and, thus, traps the carbonylated intermediate more effectively. Even with **330b**, benzylic radicals fail to give the desired product. As with the previous reaction, this methodology can be incorporated into sequential radical processes involving cyclisations and multiple carbonylations.



Scheme 139.

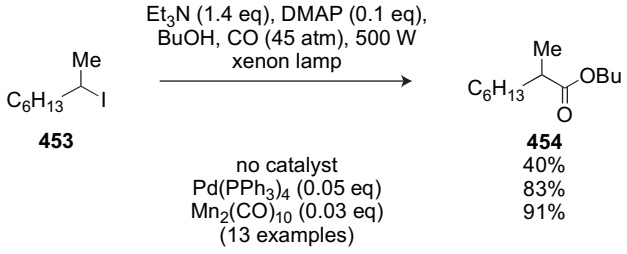
Radical carbonylation has recently been applied to the synthesis of *carbonyl*-^{11}C-labelled esters **452**.[291] The synthesis of such compounds is taxing, due to the short half-life of ^{11}C ($t_{1/2}$=20.3 min),

which means that the syntheses must utilise simple starting materials, be rapid and not involve tedious purification procedures if useful quantities of material are to be isolated; radical carbonylation fulfils all of these criteria and is simply achieved by the photolysis of an alkyl iodide **450** in the desired alcohol **451** with base under an atmosphere of [^{11}C]O (Scheme 140). A strong, soluble base is essential, as it permits the formation of a small quantity of alkoxide that drives the equilibrium in favour of product formation. Alternatively, it was found that running the reactions in the presence of ketones that show either high efficiency for singlet–triplet intersystem crossing or good hydrogen-atom abstraction properties had a highly beneficial effect and negated the need for base. Such chemistry permits the necessarily rapid synthesis of these short-lived labeled compounds and shows a number of advantages over the more common metal-based preparations.[292]



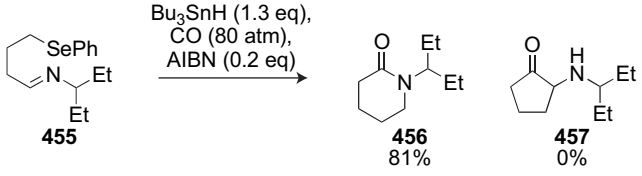
Scheme 140.

Atom transfer radical carbonylation is an efficient method for the preparation of a range of carbonyl-containing compounds. Generally, the ease of atom transfer governs the efficiency of the reaction, with tertiary halides giving superior results to primary halides. This limitation can be somewhat mitigated by effecting the reaction under palladium(0) or dimanganese decacarbonyl/irradiation conditions.[293] A comparison of the efficiency of the conversion of a secondary iodide **453** into an ester **454** under the different reaction conditions, i.e., no metal catalyst, palladium(0) catalysis and dimanganese decacarbonyl catalysis, is shown in Scheme 141. Whilst the carbonylation of secondary iodides occurs in the absence of a metal, as indicated by the formation of **454** (40%), the reaction is greatly accelerated by both metals. This methodology was applied to the synthesis of a number of natural products including a precursor of hinokinin and dihydrocapsaicin.



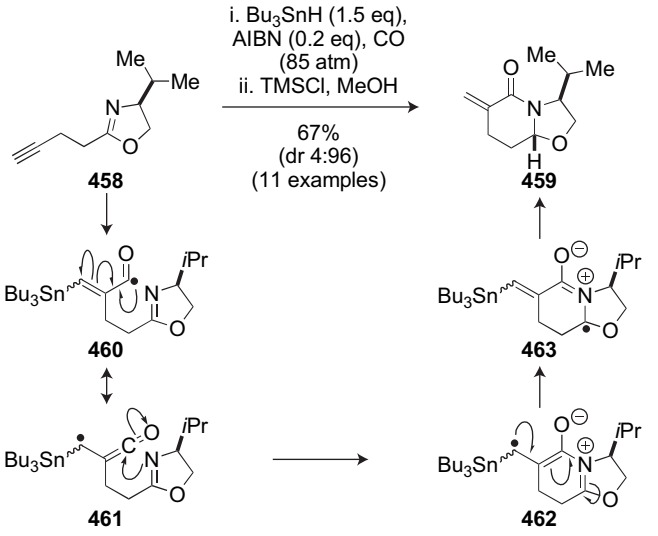
Scheme 141.

Trapping the acyl radical formed during carbonylation by an intramolecular ionic process negates decarbonylation and leads to increased yields of the insertion product (Scheme 142). One strategy involves cyclisation on to an imine such as **455** and proceeds with excellent regioselectivity for attack at the N-terminus of the imine (**456** vs **457**).[294a,b,295] The selectivity has been ascribed to 'polarity matching' of the two functional groups; effectively, the nitrogen lone pair of the imine attacks the electrophilic carbon of the acyl radical. This is demonstrated in the cyclisation of **455** by a 6-*endo* process in favour of the 5-*exo* cyclisation that would normally be expected to predominate.



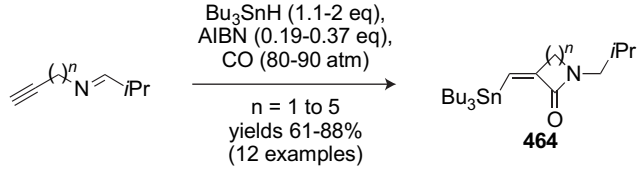
Scheme 142.

Alkenyl radicals, generated by the addition of a stannyl radical to an alkyne, such as **458**, undergo a similar reaction sequence; carbonylation is followed by highly regioselective *N*-philic cyclisation to give **459** (Scheme 143).[295] Again, the regioselectivity is best understood by invoking an ionic cyclisation and not a radical cyclisation of **460** on to the imine. Nucleophilic addition of the internal imine group to the α-ketenyl radical, **461**, which is simply a resonance form of **460**, gives the zwitterionic intermediate **462**. Hydrogen abstraction by resonance form **463** then propagates the chain reaction. Thus, carbonylation occurs via a radical process, whilst the cyclisation is probably ionic in nature. The high stereoselectivity displayed in Scheme 143 for the formation of **459** looks promising, but is misleading; the radical cyclisation occurs with almost no selectivity (dr 42:58) and the impressive value is due to epimerisation during the acidic protodestannylation step.



Scheme 143.

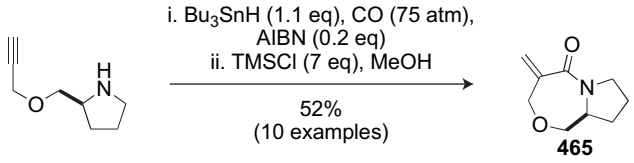
The influence of polarity on the mode of radical cyclisation permits an unusually general method for the synthesis of small- and medium-ring lactams **464**; 4-, 5-, 6-, 7- and 8-membered rings can all be prepared with complete selectivity for the *N*-philic mode of attack (Scheme 144).[296] The cyclisation is highly stereoselective, favouring the formation of the *Z*-alkenylstannane. Presumably, coordination between the tin moiety and the carbonyl oxygen prior to equilibration of the various allyl radical resonance forms leads to this geometry. The stereoselectivity can be reversed by altering the hydrogen donor; both tris(trimethylsilyl)silane (TTMSS) and hexanethiol form predominantly the *E*-alkene adduct, with the former generally giving the greater selectivity. With these two reagents, the stereoselectivity is believed to be controlled exclusively by steric factors.[297] The concept of 'polarity matching' may have



Scheme 144.

important applications in other radical cyclisations and it will be interesting to see if it increases the generality of other processes.

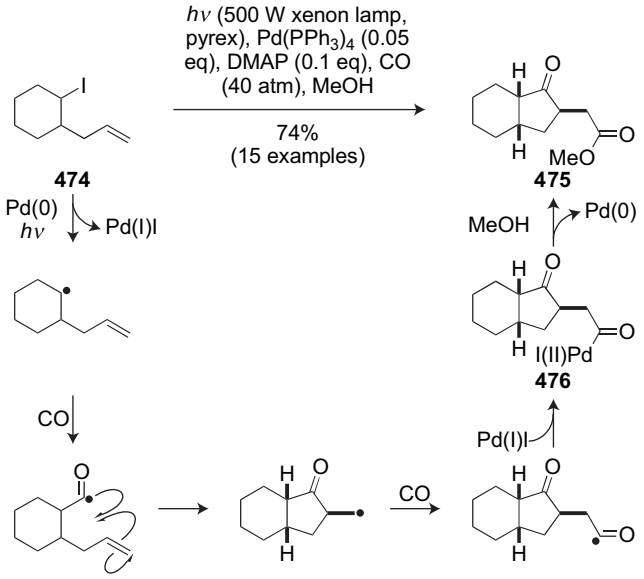
As the mechanism in Scheme 143 suggests, the imine moiety is not an essential element of the reaction as the cyclisation step is a simple ionic addition. Consequently, other nucleophiles, such as amines, can be incorporated into the reaction, permitting the synthesis of lactams such as **465** (Scheme 145).[298] The reaction proceeds in moderate yields to give a mixture of the alkenylstannane and the protodestannylated product **465**. The former product is readily converted into the latter by treatment with trimethylsilyl chloride and methanol. A variety of ring sizes can be efficiently synthesised, ranging from five- to eight-membered rings. The methodology is successful for the three-component intermolecular coupling of an alkyne, carbon monoxide and primary or secondary amines to furnish α-methylene amides. An attractive feature of this coupling protocol is that the reaction can be performed with just 20 mol % of tributyltin hydride.[299]



Scheme 145.

An example of radical carbonylation that truly demonstrates the remarkable ability of radical chemistry to rapidly increase molecular complexity is the synthesis of pyrrolidine **469** by a one-pot, *four*-component coupling (Scheme 146).[300] The success of such processes was determined by carefully balancing the electronics of each component; initially, the alkyl radical **470** formed from **466** adds to carbon monoxide to form a nucleophilic acyl radical **471** (bonds formed in this reaction are marked in bold.). This radical preferentially adds to electron-deficient alkenes, such as acryontrile **467**, to give an electrophilic radical **472** that adds to the electron-rich tin enolate **468** to give **473**. Fragmentation of **473** then results in the formation of the product **469** and a tin radical to propagate the chain. The use of tin enolate **468** as the chain-transfer reagent is vital; use of tin hydride led to premature reduction, normally at the acyl radical (**471**) stage. This reaction involves the formation of four new C–C bonds with remarkable chemoselectivity and highlights the ambiphilic nature of radicals. A similar strategy has been employed in the synthesis of 3-substituted cyclohexanones.[301]

It is possible to achieve multiple radical carbonylations under palladium-mediated conditions.[302] Alkenyl iodide **474** can be converted into the cyclopentanone **475** in good yield via the formation of four new bonds, i.e., three C–C bonds and a C–O bond (Scheme 147). No reaction is observed under exclusively radical or ionic conditions and the transformation requires a combination of the two. It is thought that the final ionic termination step is incapable of



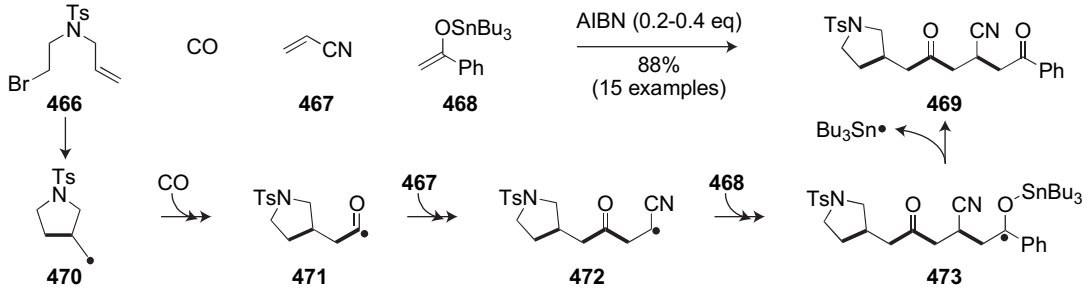
Scheme 147.

shifting five equilibration steps, namely homolysis, carbonylation, cyclisation, carbonylation and iodine-atom transfer, to completion unless both radical and metal-promoted reaction pathways are operating. Whilst substituting diethylamine for methanol does indeed permit the formation of amides, the transformation gives a mixture of triply carbonylated, α,δ-diketo amides, and doubly carbonylated products. The reaction proceeds by palladium-mediated radical cyclisation and carbonylation before forming an acyl-palladium species **476** that undergoes reductive elimination to give the ester. It will be interesting to see if this methodology can be combined with the new transition-metal-mediated radical couplings described in Section 2.7.5 to allow novel rapid routes to complex molecules.

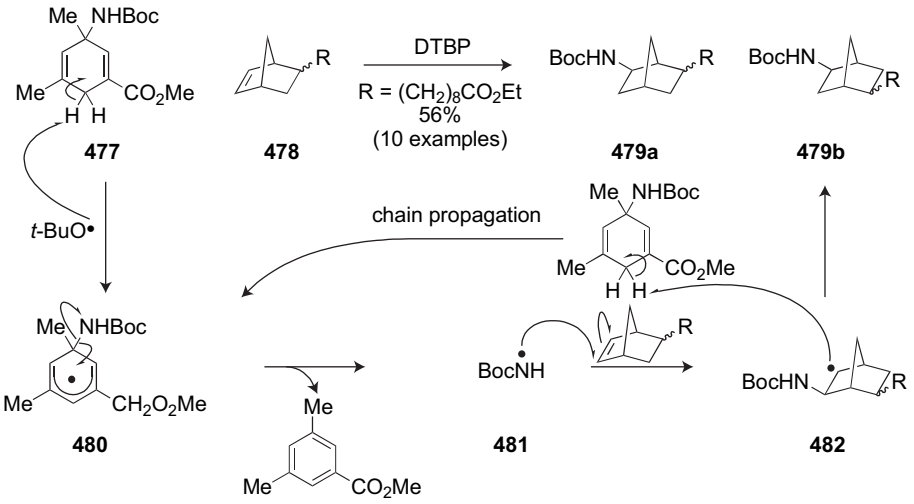
Radical carbonylations overcome many of the limitations observed in the chemistry of acyl radicals and can even be employed in systems prone to decarbonylation. Furthermore, the functional-group tolerance displayed by radical reactions allows carbonylation to be incorporated into cascade processes and multi-component couplings that permit the rapid assembly of complex molecules. They offer an attractive alternative to transition-metal-mediated carbonylations.

3.1.8. *Coupling reactions forming C–X bonds*

Hydroamination of alkenes is one of the most atom-economical methods for the preparation of amines. Considerable effort has been expended in the study of transition-metal-mediated reactions, but these are frequently limited to activated systems or require expensive and unstable metal complexes. Radical chemistry offers an attractive alternative through the addition of *N*-centred



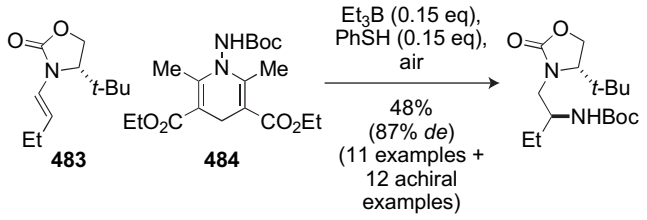
Scheme 146.



Scheme 148.

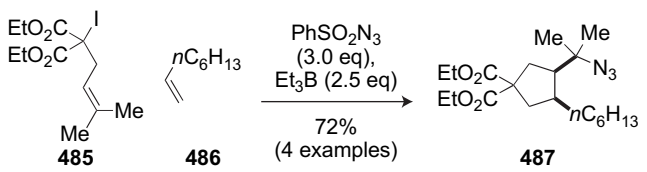
radicals to alkenes; unfortunately, there are still a number of complications, due to the instability of many *N*-radical precursors and the difficulties associated with their preparation. Zard has recently reviewed the chemistry of *N*-centred radicals.[42] The ideal methodology would involve the homolytic fission of an N–H bond prior to addition; unfortunately, whilst the addition of *N*-centred radicals to alkenes is an established reaction, the subsequent hydrogen transfer from the N–H moiety to the *C*-centred radical, a process required for chain propagation, is inefficient. In order to overcome this problem the hydrogen atom has been replaced in a variety of precursors; traditionally, amino halides such as *tert*-butyl *N*,*N*-dibromocarbamate[303] have been employed, but dienes such as **477** are more promising.[304] The precursor **477** is readily prepared via a Diels–Alder reaction and is relatively stable; its activity is based on the concept of the aromatisation of 1,4-cyclohexadienes developed by Studer and Walton (see Section 2.10.1). The radical reaction is initiated by abstraction of a hydrogen from **477** with di-*tert*-butyl peroxide (DTBP) to give the radical **480** (Scheme 148). Aromatisation of the latter proceeds with expulsion of the desired *N*-centred radical **481**, which then undergoes addition to the alkene **478** to generate the alkyl radical **482**. Alkyl radical **482** propagates the chain by interacting with **477** to regenerate **480** and give the regioisomeric products **479a** and **479b**. The methodology works for a variety of alkenes and delivers the amination products as versatile Boc-protected amines. The electrophilic nature of the carbamoyl radical means that addition occurs efficiently with simple alkenes, but fails with electron-deficient alkenes. Electron-rich alkenes undergo polymerisation under the standard reaction conditions, but this shortcoming can be circumvented by the addition of a PRC, such as methyl thioglycolate (see Section 2.5). This methodology represents one of the first examples of a transition-metal-free transfer hydroamination and provides a potentially valuable, tin-free, stable reagent for the generation of *N*-radicals.

Recently, this methodology has been improved with the advent of **484** as a nitrogen source.[305] *N*-Aminated Hantzch ester **484** is easier to prepare and permits the hydroamination of both electron-rich and electron-poor alkenes. The reactions must be performed in the presence of a PRC in order to facilitate the problematic hydrogen-transfer step, but they occur at room temperature or below, an improvement over **477**, which requires the reactions to be conducted at 140 °C. The use of lower reaction temperatures has permitted the first stereoselective intermolecular radical hydroamination to be studied. Addition to enecarbamates **483** derived from Evans's oxazolidinones occurs with high diastereoselectivity (Scheme 149). This methodology delivers anti-Markovnikov products that are complementary to those normally obtained from metal-catalysed reactions. Furthermore, the amines are protected, making them easy to isolate. It is anticipated that this, and analogous, methodology will see considerable use in the future.



Scheme 149.

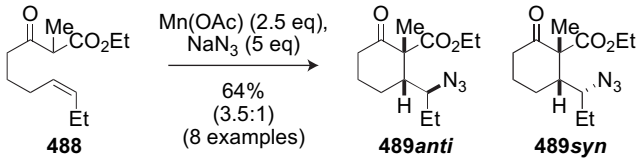
C–N bonds can also be formed by the addition of *C*-centred radicals to nitrogen-based radical acceptors. Renaud has developed a versatile strategy for the carboazidation of alkenes employing benzenesulfonyl azide as the source of nitrogen (Scheme 150). The early development of this methodology has been summarised in an excellent account.[306] The reaction involves atom or group transfer from an alkyl halide or xanthate to an alkene followed by addition of the second alkyl radical to benzenesulfonyl azide to give the desired product. Initially, the methodology relied on the use of hexamethylditin as the chain carrier and required an excess of the alkene, but, by replacing the tin reagent with triethylborane/oxygen, a far more practical procedure was developed.[307] The reactions can now be performed in water at room temperature in the open air with no recourse to inert atmosphere techniques; they proceed more rapidly and need only one equivalent of alkene. Scheme 150 shows a multi-component coupling sequence that involves intermolecular addition of **485** to alkene **486** followed by cyclisation and, finally, addition of the resulting tertiary radical to the azide to



Scheme 150.

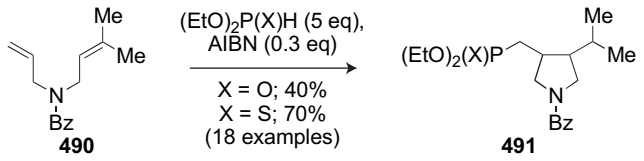
give **487**. The only drawback at present is that an excess of triethylborane must be employed, as the reaction is not a chain process, but, considering the ease of the methodology, it is anticipated that it will see considerable use in the future. The original tin-based methodology has been utilised in the total synthesis of a number of alkaloids including lepadiformine.[308] This synthesis employed pyridinesulfonyl azide instead of benzensulfonyl azide to facilitate purification and, thus, allow the use of a large excess of the azide source.[309] A diastereoselective variant was employed during the synthesis of the hyacinthacine A_1.[310]

Azides are suitable radical acceptors for manganese(III)-mediated oxidative couplings as shown in Scheme 151.[311] The starting materials must be 1,3-dicarbonyl compounds to ensure that the substrate **488** is oxidised in preference to the azide anion; if the latter occurs, simple diazidation of the alkene is observed. A range of primary, secondary and tertiary azides can be prepared via direct addition of the initial radical to the azide or as part of a tandem cyclisation–addition sequence that gives carbocycles such as **489**.



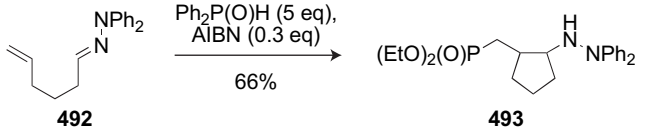
Scheme 151.

Not unsurprisingly, phosphorus-centred radicals, like *N*-centred radicals, undergo coupling reactions with alkenes, thus permitting the formation of organophosphorus compounds. A review of the use of phosphorus-centred radicals was published in 2005[14] and the addition of phosphinylidene-containing compounds to unactivated unsaturated hydrocarbons was surveyed in 2008.[39] The radical Pudovik reaction, or the addition of *P*-centred radicals to multiple bonds, is currently undergoing rejuvenation; such reactions offer a rapid route into highly functionalised organic molecules with all the inherent advantages of radical chemistry. At the forefront of this revival is the finding that dienes such as **490** react with diethyl phosphite in the presence of a radical initiator to give the cyclic phosphonates **491** in good yields (Scheme 152).[312] The reaction can be initiated by either AIBN at 80 °C or triethylborane/oxygen at room temperature and is thought to proceed via the formation of a phosphonyl radical that adds to the least-hindered alkene prior to cyclisation. Reduction by diethyl phosphite gives **491** and propagates the chain. The reaction shows few limitations, forming various sizes of carbocycle and cyclic amines and ethers. Whilst convenient, diethyl phosphite is not the optimum phosphorus hydride; both diphenylphosphine oxide and diethyl thiophosphite give better results, with the latter reagent being particularly effective. All phosphorus reagents display a slower hydrogen transfer than the analogous tin reagents, rendering the need for slow addition via a syringe pump unnecessary. A disadvantage is that the reactions often proceed with a low chain length and therefore require an excess of reagents. Diethyl thiophosphite is a better hydrogen donor, and as a result, only 1.5 equiv are required instead of 5.0 equiv for the other reagents. Additionally, it gives far better yields for the cyclisation of prenyl derivatives, highlighting its greater reducing power.



Scheme 152.

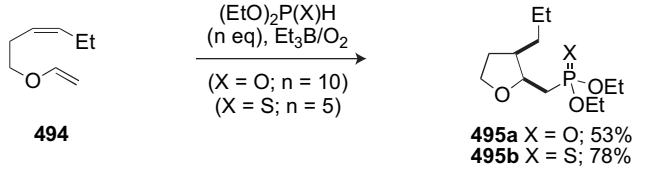
Hydrazone **492** fails to cyclise in the presence of diethyl phosphite and requires the enhanced reactivity of diphenylphosphine oxide before it undergoes productive cyclisation to give the hydrazine **493** (Scheme 153). A similar reactivity profile is observed with alkynes; the thiophosphite adds to give predominantly *Z*-alkenes, yet diethyl phosphite fails to undergo any addition.[313]



Scheme 153.

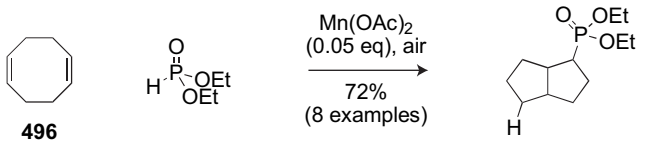
A more detailed study of the various phosphorus reagents found that P=S compounds were more reactive than their P=O counterparts and that phenyl substituents were preferable to ethoxy groups. The reactivity of these reagents mirrored the theoretical bond dissociation energies of the P–H bond calculated by density functional theory (DFT); those compounds with the weakest P–H bond react faster with alkenes.[314] Diphenylphosphine sulfide adds to a variety of mono- and di-substituted alkenes as well as permitting addition to electron-deficient alkenes, a process that is normally quite challenging to electrophilic *P*-centred radicals.[315]

The electrophilic nature of *P*-centred radicals has facilitated the development of methodology for the synthesis of phosphonylated cyclic ethers, compounds that show a remarkable similarity to a range of biologically important β-alkoxy phosphonates. Simple intermolecular addition to a range of enol ethers such as tri-*O*-acetyl-D-glucal occurs in good yields when an excess of both the phosphite and the initiator are used.[316] More interesting, is the combined intermolecular–intramolecular radical addition sequence reaction of enol ether **494** with diethyl thiophosphite that gives **495a** with high diastereoselectivity (Scheme 154). Intriguingly, the thiophosphite gives the higher yields for the synthesis of tetrahydrofurans (78 vs 53% for the synthesis of **495b**), compared to the phosphite, but only the latter reagent furnishes tetrahydropyrans. This unexpected result might arise due to the increased reactivity of the thiophosphite allowing non-chemoselective addition to either alkene and, thus, increasing the chance of side reactions.



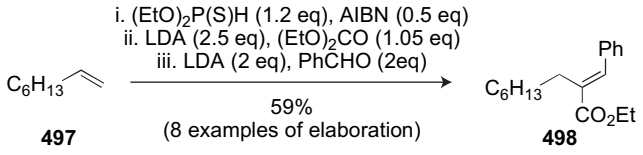
Scheme 154.[90]

Manganese(III) has been employed to generate *P*-centred radicals; just 0.05 equiv of manganese(II) acetate under an atmosphere of air is required to permit the hydrophosphorylation of alkenes such as **496** in good yields (Scheme 155).[317] It is assumed that the oxygen oxidises the manganese(II) to the active manganese(III) species under these reaction conditions. Phosphorylation of both internal and terminal alkenes is possible although the former suffer from poor regioselectivity.



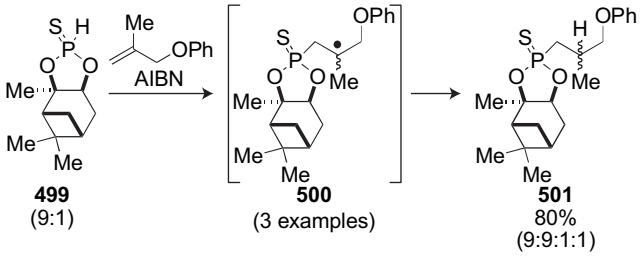
Scheme 155.

One of the chief advantages of phosphorus-based reagents over their tin-containing counterparts is the utility of the phosphorus moiety for further manipulation. Both non-stabilised phosphonates and phosphonothioates readily undergo Horner–Wadsworth–Emmons-type alkene formation in good yields.[318] Ketones tend to give higher yields than aldehydes and both sets of substrates preferentially form the *E*-isomer. The thiophosphite derivatives can be utilised in a clean one-pot radical addition–elaboration–alkenylation sequence that is ably demonstrated by the formation of the trisubstituted alkene **498** from terminal alkene **497** (Scheme 156); radical addition is followed by ionic acylation and, finally, Horner–Wadsworth–Emmons-type alkenation. The tandem addition of a *P*-centred radical followed by cyclisation has been employed in the synthesis of the core of the quinuclidines.[319]



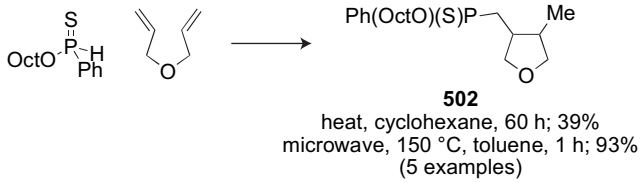
Scheme 156.

Chiral phosphorus reagents have been developed in an attempt to achieve either diastereo- or enantioselective radical reactions. Thiophosphite **499** is readily prepared as a mixture of diastereoisomers differing at the phosphorus atom. Radical addition to alkenes or alkynes occurs with retention of configuration at the phosphorus.[313] For example, when a 9:1 mixture of thiophosphites is reacted with ethynylbenzene, a 9:1 mixture of diastereoisomeric *Z*-alkenes is formed in 90% yield. Unfortunately, addition to prochiral alkenes is less successful (Scheme 157); whilst retention of the phosphorus configuration is still observed, hydrogen abstraction by **500** is non-selective and **501** is formed as a mixture of diastereoisomers. It is highly likely that this limitation is a result of the shape of the chiral scaffold and that the careful design of a new phosphorus hydride will overcome these disappointing results (see Section 2.12).



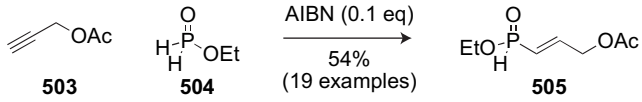
Scheme 157.

Phosphorus-based radical methodology lends itself well to 'green' chemistry; it is possible to initiate the reactions without recourse to a radical initiator simply by heating. Whilst the use of conventional heating results in the formation of the product, it is too slow to be of practical value (39% of **502** after 60 h; Scheme 158). Alternatively, microwave heating results in a more rapid reaction (93% of **502** after 1 h).[314] Amongst the many advantages that radicals display, compared to ionic systems, is their impunity to water. The main stumbling point to exploiting this is the limited solubility of most organic compounds in water. One compromise is the addition of diphenylphosphine oxide to a range of unactivated alkenes, which can be achieved in methanol with triethylborane initiation.[320] More promising is the use of dibutylphosphine oxide, which is both an efficient radical hydrogen donor and is soluble in water.[321] Simple addition–cyclisation sequences can be achieved with dibutylphosphine oxide in pure water with 4,4′-azobis(4-cyanovaleric acid) (V-501) as the water-soluble initiator. Use of a less-soluble phosphine oxide results in a dramatic decrease in yield or requires the use of a catalytic amount of surfactant, such as cetyltrimethylammonium bromide (CTAB). Obviously, with the current desire for more environmentally benign transformations, the ability to carry out such reactions in pure water is an important advance.



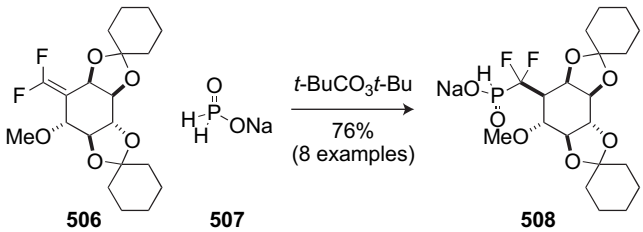
Scheme 158.

Phosphorus species with two P–H bonds can also be employed in radical reactions. Ethyl phosphinate **504** readily adds to both alkenes and alkynes.[322] Interestingly, only the mono addition product was isolated, even though these compounds have the potential to add to 2 equiv of alkene/alkyne. Hydrophosphinylation of terminal alkyne **503** highlights the value of this methodology as this alkyne does not participate in nickel- or palladium-catalysed hydrophophinylation, yet, under these mild radical conditions, a good yield of **505** is achieved (Scheme 159).



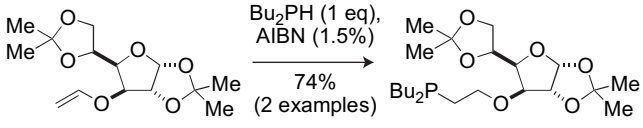
Scheme 159.

The electrophilic nature of *P*-centred radicals often restricts them to reactions with electron-rich alkenes and this is one of the limiting factors in the study of α,α-difluorinated organophosphorus compounds, which are potentially valuable isosteres of natural phosphates. It appears that the sodium salt of hypophosphorus acid **507** offers a solution to this problem and is sufficiently nucleophilic to add to highly electron-poor alkenes.[323] Neither diethyl phosphite nor diethyl thiophosphite react with the electron-deficient alkene **506**, yet **507** underwent clean addition to give **508** in high yield (Scheme 160). The reason for this unique reactivity is unclear at present, but the involvement of a tautomeric phosphorus(III) species has been ruled out.



Scheme 160.

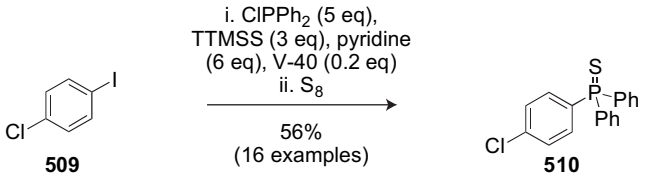
Simple phosphines undergo radical addition to electron-rich alkenes upon treatment with the radical initiator (Scheme 161).[324] Unfortunately, there are no direct comparisons between these



Scheme 161.

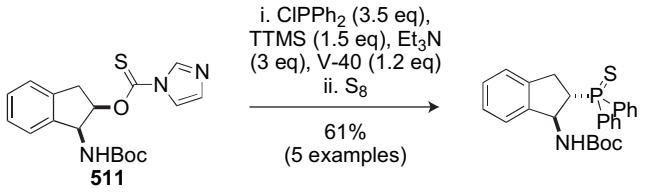
reactions and other phosphorus species and so it is difficult to comment on the utility of this reaction. Suffice to say that the use of phosphorus(III) is invariably less practical than the use of phosphorus(V) reagents, due to the propensity of the former to undergo oxidation.

Organophosphines are important molecules employed in catalysis and advanced materials. Conventional ionic phosphination reactions normally require highly basic or forceful conditions. Radical-mediated phosphination of aryl iodides and/or alkylimidazole-1-carbothioates offers a mild method for the formation of these valuable substrates.[325] The overall transformation is very simple and is exemplified by the examples in Schemes 162 and 163. Treatment of an aryl iodide **509** with a chlorophosphine, TTMSS as the chain carrier and 1,1′-azobis(cyclohexane-1-carbonitrile) (V-40) in the presence of pyridine affords the arylphosphines **510** in moderate-to-excellent yields. A variety of both electron-withdrawing and electron-donating groups are tolerated on the aryl ring including chlorides and bromides. Sterically demanding substrates such as mesityl iodide are also phosphinated in good yield. Both diphenyl- and dicyclohexyl-chlorophosphines readily react, but the more demanding chlorodi(*tert*-butyl)phosphine gave a poor yield (<11%).



Scheme 162.

Imidazole-1-carbothioates were found to be the optimum precursors for the phosphination of primary and secondary alkyl radicals such as **511** (Scheme 163). Tertiary alkyl radicals were poor substrates for the phosphination reaction. The proposed mechanism for this transformation is complex with two concurrent radical processes taking place. The first forms a bisphosphine via the radical reduction of the chlorophosphine followed by base-mediated reaction of the resultant phosphine with remaining chlorophosphine. The bisphosphine then enters the second radical reaction where it traps either the aryl or alkyl radical.



Scheme 163.

The use of phosphorus radicals as both chain propagators and reagents for the hydrophosphinylation of alkenes and alkynes is an extremely valuable addition to the chemist's arsenal. These compounds and the strategies devised around their use offer a number of pronounced advantages over the more traditional tin reagents; phosphorus reagents are non-toxic, easily removed from the reaction mixture, are cheap, can be employed in aqueous media, react under mild conditions and, in many cases, allow the addition of useful functionality into a compound. The ease by which these reagents can be modified means that their reactivity can be readily tuned and, potentially, chirality can be incorporated. It is anticipated that considerably more use of phosphorus reagents will be seen in the future radical methodology.

4. Conclusions

No longer a mere curiosity, the chemistry of radicals now attracts considerable attention, due to its versatility and attractive properties. With the shift in emphasis away from tin-based protocols, the last obstacle to the widespread acceptance of radical chemistry is being removed. The 'green' credentials of radical transformations means that they will undoubtedly play an important role in synthetic chemistry in the coming years. As Section 2 reveals, many alternatives to tin-based reagents are being developed to accommodate this newfound interest; particularly attractive is the use of transition-metal catalysts for the generation of alkyl radicals. The use of iron nanoparticles along with cobalt and nickel complexes will undoubtedly open up new vistas in radical chemistry, but other reagents also deserve a more comprehensive study; thiols show much promise, especially in the area of polarity-reversal catalysts, and this should/could have major implications for enantioselective radical transformations. Phosphorus-based hydride sources also display potential, not only due to the importance of phosphorus-containing compounds, but also as environmentally benign replacements for tin hydrides. Aside from the new reagents, the establishment of new radical methodology continues apace as chemists lose their fear of radicals; methodologies based on the use of xanthates or employing the persistent radical effect offer plenty of scope for developing mild, yet powerful, new routes to complex molecules. Whilst the former has been exploited reasonably widely, the latter chemistry still requires more thorough research, but offers great rewards for those who master it. Two areas clearly display exciting opportunities; direct C–H activation and catalytic enantioselective radical additions. Direct C–H activation is especially important, as it allows the functionalisation of non-activated molecules and the use of radical chemistry without the need to synthesise special radical precursors; the chemistry depicted in Schemes 54, 55, 85, 86, 115, 119, 123, 131 and 132 shows that both these concepts can be achieved and that radical chemistry rivals metal catalysis as a means of performing these important transformations. Enantioselective radical reactions have been intensively studied over the last ten years and, whilst many important advances have been made, it is far from a mature area. The chemistry of MacMillan and Sibi, combining enamine catalysis and radical chemistry, undoubtedly shows one new avenue that will be pursued in the coming years, but one can also imagine the use of chiral Brønsted acids playing an important role in new organocatalytic radical reactions. Polarity-reversal catalysts have also shown potential in this arena, yet they have not received the attention they deserve. One should not overlook the possibilities engendered by the use of transition-metal catalysts in radical chemistry; such compounds are a good pedigree in non-radical enantioselective catalysis and it seems probable that this will be extended to radical reactions.

It is hoped that this review has highlighted the possibilities radical chemistry presents and will encourage the greater use of this chemistry in synthesis. Part two of this review will concentrate on radical cyclisations and rearrangements and can be found in a subsequent issue of *Tetrahedron*.

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Biographical sketch

Gareth J. Rowlands was born and raised in Horsham, West Sussex, UK. He obtained his first degree from Imperial College, London and stayed there to complete his PhD under the supervision of Donald Craig. In 1996 he joined Prof. Steven V. Ley's group at Cambridge University as a Royal Commission for the Exhibition of 1851 Research Fellow. After three years, he moved to Brighton to take up a lectureship in organic chemistry at the University of Sussex. Seven years and a few grey hairs later, he moved to New Zealand where he is currently enjoying life as a senior lecturer at Massey University. He loves chemistry a little too much to be healthy and, when forced to narrow his interests, he professes to be intrigued by enantioselective catalysis, organocatalysis, radicals and, of course, the chemistry of [2.2]paracyclophane. Dr. Rowlands has been interested in science since his first encounter with Dr. Egon Spengler, and whilst chemistry may not be so esoteric, it is often equally enigmatic.