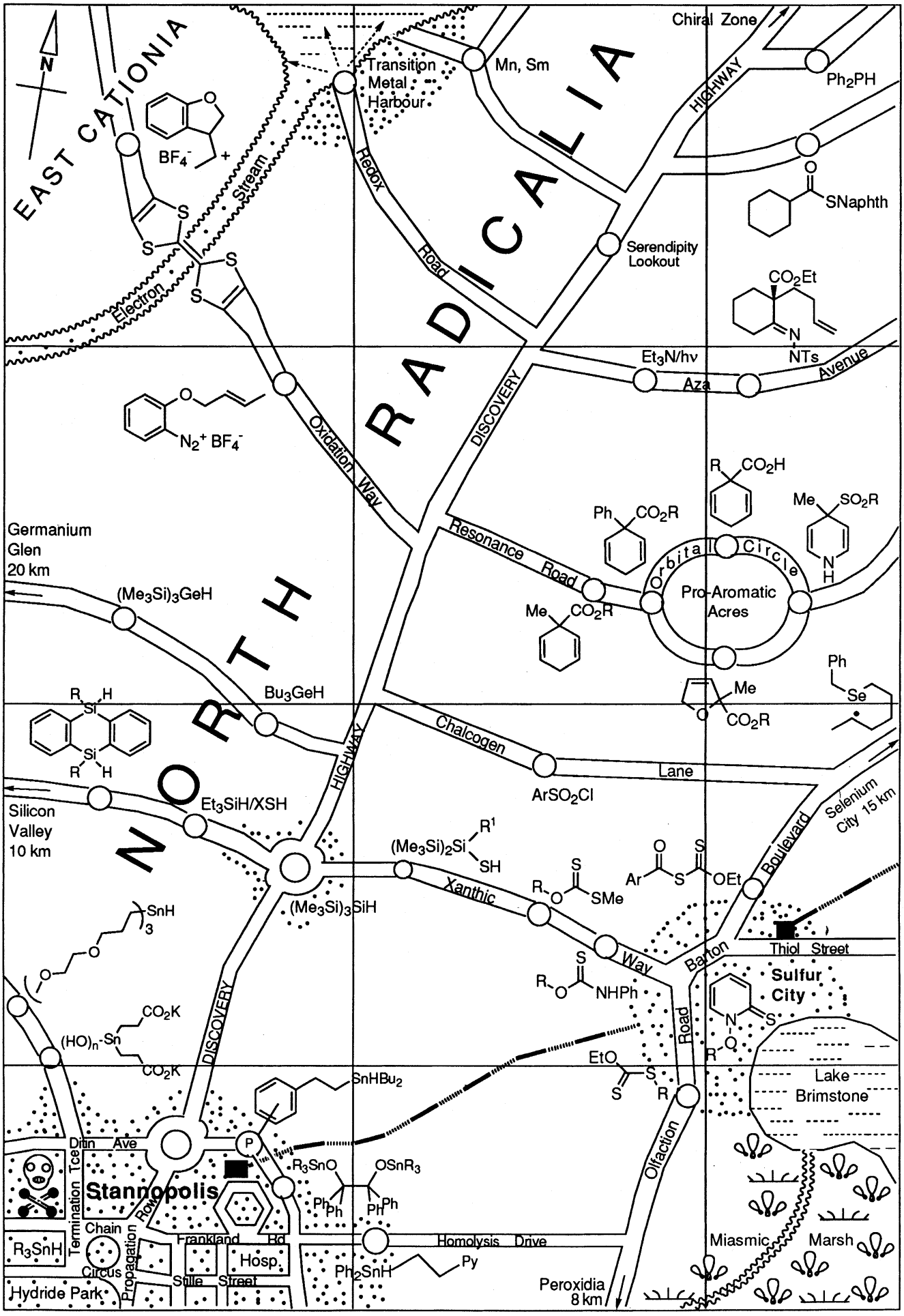


Flight from the Tyranny of Tin: The Quest for Practical Radical Sources Free from Metal Encumbrances

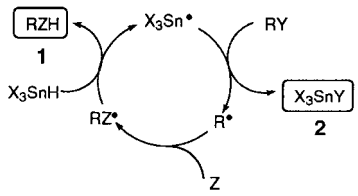
Paul A. Baguley and John C. Walton*

The versatility, predictability, and functional-group tolerance of free radical methodology has led to the gradual emergence of homolytic disconnections, which are steadily taking their place alongside more familiar ionic disconnections in the armory of synthetic chemistry. Currently, organotin reagents dominate the area and are the almost automatic choice for radical ring closures, ring expansions, cascade reactions, and the like. Organotin residues are notoriously difficult to remove from desired end products, and this, coupled with the fact that many organotin compounds are neurotoxins, makes techniques using tin inappropriate for syntheses of drugs, medicines, and other formulations intended for human consumption. Objections to tin apply with diminished but still significant force to other metals. These constraints have triggered quests for methods of nullifying the impact of tin, for new metal-free ways of generating free radicals, for new chain processes, for mediating efficient syntheses, and for all-organic single electron transfer agents. This review draws together the principal innovations in a fast-moving but scattered enterprise. Individual methods based around redesigned tin reagents, organosilyl substitutes, thiocarbonyl and related sulfur reagents, cyclohexadienes, tetrathiafulvalenes, and others are illustrated with synthetic examples. Brief descriptions of the strengths and weaknesses of individual reagents are supplied to enable dissatisfied synthetic chemists to make a rationally directed escape into tin-free comfort zones (such as that depicted in the frontispiece on the opposite page).

Keywords: radicals · silicon · synthetic methods · thiocarbonyl compounds · tin

1. Introduction

The burgeoning use of homolytic methodology in the field of organic synthesis owes much to the superlative flexibility of organotin reagents, which enables them to flourish with an exceptionally wide range of substrates and reaction conditions. Ever since the original discovery of radical generation by organotin hydrides (X_3SnH),[1] a spiral of applications has wound inexorably upward. At present tin reagents dominate free radical chemistry, and their influence is reaching continually deeper into the mainstream of synthetic science.[2] They have proved particularly serviceable for the substitution of hydrogen in place of halogen, hydroxyl, amino, nitro, thiol, selenide, carboxylate, and other functional groups.[3] Organotin hydrides also mediate radical additions to alkenes and alkynes (Z, Scheme 1) in reductive carbon–carbon bond formations,[4–6] although premature hydrogen transfer to the prior radical can be a problem. Allylstannanes have found considerable use as reagents for allylations,[6] as have propynylstannanes in the corresponding production of allenes.[7] Organotin-mediated one-carbon ring expansions of alicyclic, polycyclic, and heterocyclic β-keto esters take place in high yields for a variety of ring sizes.[8, 9]



Scheme 1. The basic organotin hydride mediated reaction chain.

Most importantly, however, tin-based methods exercise an autocratic influence in the domain of radical ring closures. A plethora of such annulations pervades the recent literature. Unsaturated alkyl, aryl, vinyl, acyl, aminyl, alkoxyl, and other heteroradicals propagate their cycles on chain gangs cease-

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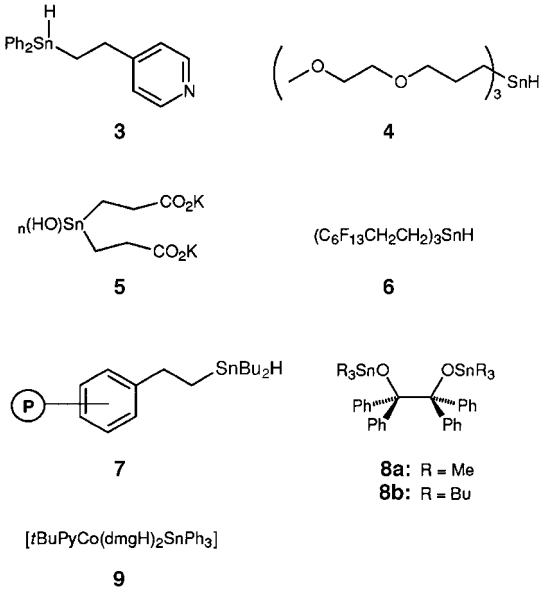
lessly disciplined by the vigilant agents of tin.[10–12] Five-membered rings with many different embellishments are a speciality, but larger rings, intricate polycycles, and a wide range of exotic heterocycles have all been hammered out on the anvils of tin. So pervasive is the method that even key steps in natural product syntheses have come to depend on organotin reagents.[13, 14] For example, the synthesis of (±)-morphine by Parker et al. incorporated a tin hydride mediated bicyclization of an aryl radical,[15] and the synthesis of prostaglandin $F_{2\alpha}$ by Stork et al. included an *exo*-cyclization of a cyclopentenyloxyalkyl iodide brought about by tin hydride generated in situ.[16] Also, Curran et al. have carried out several notable tin hydride assisted preparations of triquinane natural products, including silphiperfolene.[17] Cascade sequences are some of the most exquisite examples of the synthetic art, and organotin hydride promoted representatives are at the cutting edge.[18] Spectacular archetypes include the construction of a tetracyclic homosteroid by means of a quadruple *endo*-cyclization cascade starting from a tetraene selenoester[19] and the degradative triple β-scission cascades of bromomethylcubanes[20] and basketanes.[21]

The success of tin reagents has given them such prestige and notoriety that they practically monopolize the market place for homolytic synthetic and kinetic applications. It is small wonder that this dominance has been referred to as the "tyranny of tin". The tin hegemony has been established at no small price, and the main burdens under which the vassals of tin groan are the hazardous handling and disposal of toxic garbage (**2**) and the penchant of tin for prematurely zapping hydrogen onto immature structures. Medicines, drugs, and food additives contaminated with tin are unsafe for human consumption, hence there is an urgent need for new metal-free reagents to unlock the chemical doorway, liberate the vassals, and free-up radical methodology for use in the food and medicines industries. A great deal of attention has been directed recently to radical generation with reagents based on compounds of mercury, cobalt, manganese, or samarium, and some fascinating transformations have been achieved. However, these metals suffer toxic effects of their own and contamination by them of food or pharmaceuticals cannot be contemplated. This review focuses therefore on the search for metal-free methods of generating radicals, of propagating chain reactions, and of mediating alternative homolytic processes.

2. Viewing the Tyrant's New Clothes

A not inconsiderable enterprise of the tin federation has been the design and production of alternative tin compounds that will facilitate or minimize the disposal of tin garbage. Pyridylstannane **3**, prepared from 4-vinylpyridine, affords products in yields comparable to those obtained with tributyltin hydride.[22] The advantage of this reagent is that the organotin halide by-products have R_f values of approximately zero for elution with ethyl acetate/hexane, and this enables products to be isolated relatively easily (Scheme 2).



Scheme 2. New organotin reagents for homolytic transformations.

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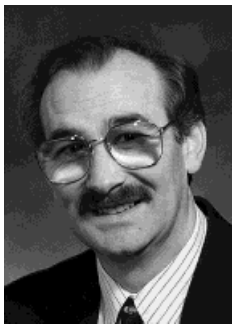
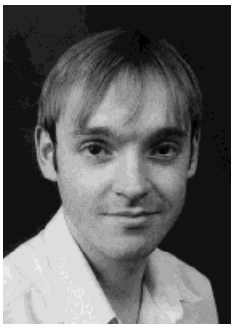


J. C. Walton



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Paul Baguley was born in Warrington, UK, in 1973, and studied chemistry at the University of Glasgow, graduating in 1994. He subsequently joined Professor Walton's group in St. Andrews, where his Ph.D. research was largely concerned with designing and testing alternative free radical sources. He was recently appointed as a Senior Scientist with Oxford Asymmetry International.

Converse techniques generate tin residues that are extremely nonpolar and elute before the product. One such method depends on treatment of the product mixture with an excess of sodium cyanoborohydride in *tert*-butyl alcohol, such that after completion the reaction mixture contains the desired product and regenerated organotin hydride.[23] Column chromatography allows separation of the product from the organotin hydride, which elutes from the column first and can be reused. An alternative chromatographic workup involves dilution of the reaction mixture with undried diethyl ether and addition of a slight excess of diazabicycloundecene (DBU) followed by dropwise addition of an ethereal solution of iodine until the iodine color just persists. The solution is filtered through a short column of silica gel with diethyl ether as eluent. Tin hydroxides and distannoxanes, together with DBU hydrohalides and excess DBU remain at the top of the column, and the product elutes virtually free of tin.[24]

The water-soluble tin hydride **4**[25] and hydroxide **5**[26] enable reductions and cyclizations to be carried out in environmentally friendly aqueous solutions. The polarity of **4** facilitates product isolation, though its synthesis is rather lengthy. Reagent **5** is heated with the substrate, $NaBH_4$, and the water-soluble initiator 4,4′-azobis(4-cyanovaleric acid) (ACVA) in a dilute aqueous alkali solution. The $NaBH_4$ reduces **5** to the corresponding hydride, which is utilized in situ to generate the corresponding tin radical.

A modest means of separating out tin compounds relies on the immiscibility of hexane and acetonitrile, and the extraction of organotin species into the hexane layer and of the organic product into the acetonitrile layer; however, this is limited by the partitioning of some organic products between both solvents.[27] An evolution of this approach employs fluorous reagent **6**, which can be prepared in a three-step synthesis.[28] Reactions are carried out in trifluoromethylbenzene, which is then evaporated and replaced by dichloromethane/perfluorocyclohexane. The fluorous tin by-products remain in the fluorocarbon layer, thus facilitating the clean isolation of the desired organic product. The method was also extended to the catalytic use of **6**, with sodium cyanoborohydride as reducing agent.

Polymer-supported tin hydrides are probably the most effective for isolating a desired organic compound free from tin by-products.[29–31] As the polymers are insoluble in the reaction solvent, an organic product can be isolated simply by filtering off the polymeric tin halides, which can usually be recycled to hydrides for further use. Polymers of type **7** have been reported to be of general use for reductions of halides and for ring closures,[29] although their preparation is not a trivial task.[29, 32]

The problem of premature reduction of intermediate radicals, which is so prevalent with tin hydrides, may be avoided by use of distannanes or by resort to other tin-based precursors. Use of bis(trimethylstannyl)benzopinacolate (**8a**) as a thermal source of trimethylstannyl radicals was advocated some time ago.[33] Recently, it has been demonstrated that alkyl radicals generated from halides and selenides, by use of **8a**, add to the carbon–nitrogen double bond of *O*-benzylformaldoxime.[34] Owing to the expense and toxicity of trimethylstannyl derivatives, the alternative tributyl reagent **8b**, which can be prepared in almost quantitative yield from benzopinacol and tributylstannyldimethylamine, has also been endorsed.[35] A disadvantage of these methods, however, is the troublesome removal of both tin residues and benzophenone.

Photolysis of (triphenyltin)cobaloxime **9** yields a triphenyltin radical which propagates cyclizations. An advantage is that the intermediate Co^{II} radical can oxidize the cyclized radical to yield an olefin.[36] Although some benefits may accrue from the use of these novel tin reagents, the fundamental problem of tin toxicity remains a constant menace. A significant number of radical chemists have therefore sought refuge with more clement relatives of tyrant tin.

3. Checking Silicon and Germanium: Sibling Imitators of the Tyrant

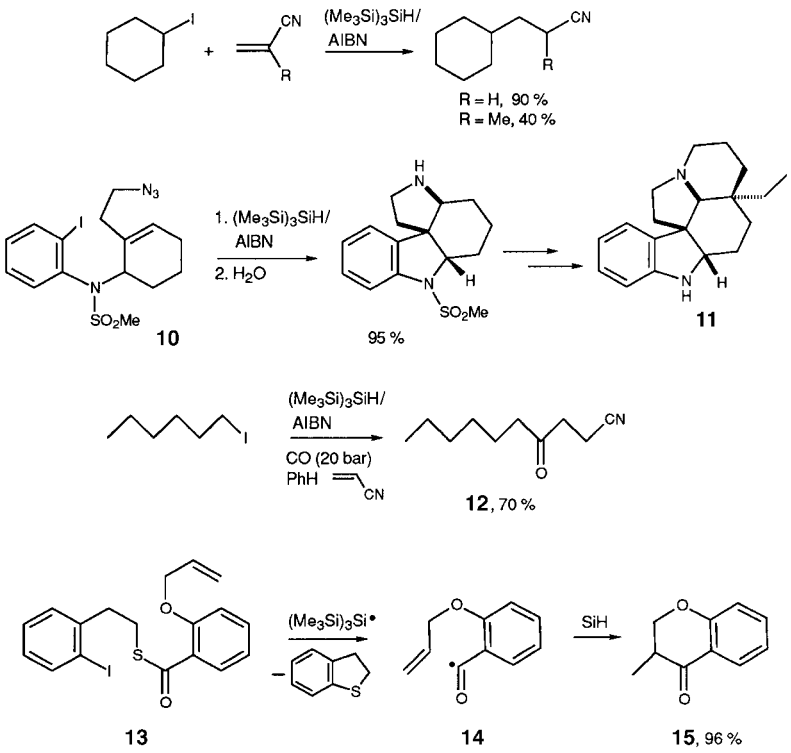
The silicon–hydrogen bond in simple triorganosilanes is too strong for ready hydrogen transfer, and therefore chain processes are difficult to maintain. Although triethylsilane[37–39] and diphenylsilane[40] have been advocated as alternatives to organotin hydrides, the range of amenable substrates is limited and the reaction temperature is often undesirably high (120–140 °C); it is unlikely that either will be a popular reagent. A shrewd remedy for this problem is to include a catalytic amount of an alkanethiol, such as *tert*-dodecanethiol (XSH), with the triethylsilane in the reaction mixture.[41] Nucleophilic alkyl radicals abstract hydrogen from thiols much more readily than from electron-rich trialkylsilanes, but the resulting electrophilic thiyl radicals abstract hydrogen from the silane more readily than the alkyl radicals. Thus, the thiol is regenerated along with the chain-carrying silyl radical, and yields of RH exceed 90%. This procedure, termed polarity-reversal catalysis, is also effective for hydrosilylation of alkenes using triethylsilane:[42]

$$R^{\cdot} + XSH \rightarrow RH + XS^{\cdot}$$

$$XS^{\cdot} + Et_3SiH \rightarrow XSH + Et_3Si^{\cdot}$$

$$Et_3Si^{\cdot} + RY \rightarrow R^{\cdot} + Et_3SiY$$

The most successful and widely used replacement for tin hydride is undoubtedly tris(trimethylsilyl)silane.[43, 44] Not only does this reagent pose little toxic threat, but it also produces fewer by-products of direct reduction because its Si–H bond is about 5 kcal mol^{-1} stronger than the Sn–H bond of tributyltin hydride. This has often enabled radical procedures to be accomplished with a stoichiometric amount of the silane in the initial reaction mixture, instead of the tedious slow-addition, high-dilution technique frequently essential with tin hydrides. Examples of intermolecular radical additions to acrylonitrile (R = H) and methacrylonitrile (R = CH_3),[44] an intramolecular double ring closure of an unsaturated aryl iodide **10**[45] in the synthesis of aspidospermidine (**11**), and an intermolecular tandem carbonylation–addition sequence yielding 3-oxonitrile **12**,[46] all mediated by $(Me_3Si)_3SiH$, are shown in Scheme 3. The aryl radical



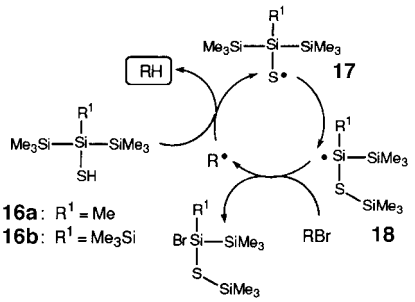
Scheme 3. Typical applications of tris(trimethylsilyl)silane.

obtained on treatment of thiol ester **13** with $(Me_3Si)_3SiH$ underwent an intramolecular homolytic substitution reaction (S_Hi) at sulfur to form dihydrobenzothiophene with displacement of acyl radical **14**, which underwent ring closure to yield cyclic ketone **15** after the final hydrogen-transfer step.

Variants of this reaction were also reported.[47] Alkylated heteroaromatic units have been prepared by use of $(Me_3Si)_3SiH$ (or $(Me_3Si)_4Si$) with an alkyl halide and a protonated quinoline or similar heterocycle.[48] $(Me_3Si)_4Si$ has also been used in place of $Me_3SnSnMe_3$ to mediate an efficient synthesis of the anticancer drug camptothecin.[49] The radical cascade reaction involved an intermolecular addition of an amidovinyl radical to phenylisonitrile to afford an imidoyl radical which underwent two intramolecular cyclizations. Similar routes were used to synthesize a range of derivatives.

$(Me_3Si)_3SiH$ is certainly a versatile reagent that can be used to accomplish a range of useful transformations. Its most serious drawback is the propensity of the $(Me_3Si)_3Si^{\bullet}$ radical to add to multiple bonds. In fact $(Me_3Si)_3SiH$ is an efficient reagent for hydrosilylating alkenes and alkynes.[50] Other disadvantages are the cost and the need to handle under argon; thus far it has barely dented the dominance of tin. One solution to the problem of high cost is to use the reagent in catalytic quantities, together with sodium borohydride to regenerate the reagent from the silicon–halogen by-products.[51] Good yields can be obtained with simple substrates, but this procedure undermines a general benefit of homolytic methodology, namely freedom from the need for protecting groups.

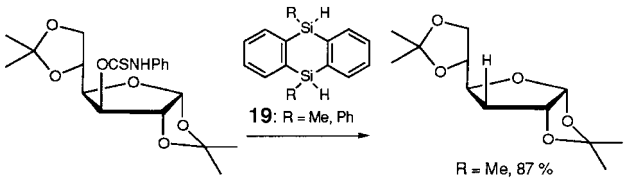
Several other silanes have emerged as challengers to the authority of tin. The electronegativity of sulfur, and the possibility of 3p–3p overlap between silicon and sulfur atoms, was expected to reduce the Si–H bond strength of tri(alkylthio)silanes below that of Et_3SiH. In some simple experiments with bromides, iodides, isocyanides, xanthate esters, and phenyl selenides, nearly quantitative yields of reduced products were obtained with $(Me_3Si)_3SiH$.[52] Heptamethyltrisilane-2-thiol[53] (**16a**) and tris(trimethylsilyl)silane-2-thiol[54] (**16b**) possess thiol groups which readily donate hydrogen atoms to C-centered radicals to afford thiyl radicals **17** (Scheme 4). These reagents then take advantage of the rapid



Scheme 4. Mode of action of trimethylsilylsilanethiols.

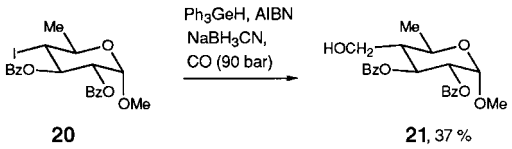
1,2-migration of a Me_3Si group from silicon to sulfur in **17**, thus unmasking silyl radical **18**. This selectively abstracts halogens, and hence reduction of a variety of organic halides is facilitated.

The synthetic range of (trimethylsilyl)silanethiol reagents is limited due to their thermal instability and the fast rate of hydrogen transfer by the thiol, which is approximately an order of magnitude greater than that of tributyltin hydride. Recently, 9,10-dihydro-9,10-disilaanthracenes **19** were shown to be effective for the reduction of alkyl halides and for the deoxygenation of alcohols, via *O*-thiocarbonyl derivatives, under mild conditions (Scheme 5).[55, 56] The ease of their preparation,[57] coupled with the good yields, are indicators of an auspicious future for these reagents.



Scheme 5. Use of 9,10-dihydro-9,10-disilaanthracenes for deoxygenation of alcohols.

Tributylgermanium hydride has a relatively strong Ge–H bond, and therefore direct substrate reduction is usually not significant.[58, 59] The advantage over tin hydrides that this bestows has been the basis of the rare applications of germanium hydrides. Thus, addition of C-centered radicals to alkenes can proceed with essentially equimolar amounts of the halide and alkene. The preparation of monosaccharide **21**, which was required for a mechanistic study of the complex natural product calicheamicin, exemplifies the use of germanium hydrides.[60] Attempts to replace the iodine atom of **20** (Scheme 6) with a hydroxymethyl substituent using ionic



Scheme 6. Use of triphenylgermanium hydride in a reductive carbonylation.

reagents were thwarted by elimination reactions. Attention was therefore turned towards generating the corresponding alkyl radical under an atmosphere of CO. The tin hydride method gave only the product of direct reduction, but use of catalytic quantities of Ph_3GeH with $NaBH_3CN$ resulted in the isolation of 37% of monosaccharide **21**. An additional advantage with the catalytic method was the in situ reduction of the carbonyl functionality to the hydroxyl group.

Simpler iodides, such as adamantyl iodide, underwent the same reaction in yields exceeding 60%.[60] However, the lower reactivity of Ge-centered radicals usually restricts reductions to iodides. Furthermore, tributylgermanium hydride is more prone to add to alkenes than its tin counterpart and is significantly more expensive.

Tris(trimethylsilyl)germane, $(Me_3Si)_3GeH$, reduces a variety of functional groups in high yields.[61] However, the rate of hydrogen abstraction from $(Me_3Si)_3GeH$ by a primary alkyl radical, measured with the hex-5-enyl radical clock, was found to be even faster than from tributyltin hydride,[61] and this will limit the reagent's usefulness.

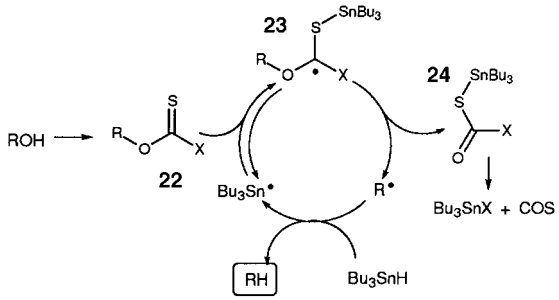
Highlights of the synthetic advantages of silicon and germanium reagents have been presented in this section. Many organic chemists have been beguiled into trying one or more of these reagents only to be disappointed by their cost, handling problems, and limited range of applicability and have returned to the thralldom of tin consoling themselves with the thought "better the devil you know".

4. Seeking Sanctuary in Sulfur's Odorous Realm

In the search for a complete break with harmful metal habits, the homolytic susceptibilities of numerous sulfur compounds have been explored. Promising results cluster around molecules containing the thiocarbonyl moiety.

4.1. On the Horns of the Thiocarbonyl Dilemma: To Collaborate or Not To Collaborate with Tin

The Barton–McCombie reaction of organotin hydrides with thiocarbonyl compounds **22** has been widely used as a means of generating radicals from primary and secondary alcohols and as a mild method for deoxygenating them.[62, 63] The reaction probably proceeds by reversible addition of the stannyl radical to the thiocarbonyl sulfur atom to generate C-centered radical **23**. This species undergoes β-scission to afford the corresponding carbonyl compound **24** and an alkyl radical, which abstracts hydrogen from the organotin hydride (Scheme 7).[64] The original procedure employed xanthates (**22**, X = SMe), thiobenzoates (**22**, X = Ph), or thiocarbonyl



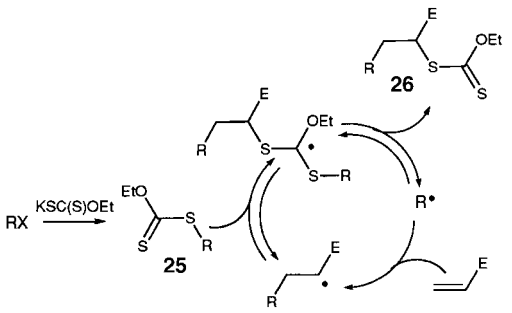
Scheme 7. Chain propagation of the Barton–McCombie deoxygenation of alcohols.

imidazoles (**22**, X = imidazole), but several other derivatives, notably thionocarbonates (**22**, X = OPh or OMe), are also satisfactory. Suitable procedures for the preparation of individual thiocarbonyls and applications of the method in the areas of steroids, carbohydrates, terpenoids, and nucleosides have been conveniently collated.[66]

The conspicuous catch with this procedure is the reappearance of obnoxious organotin hydride. Possible means of avoiding this are being sought. For example, *N*-phenylthioxocarbamates (**22**, X = NHPh) may be prepared in good yields by the reaction of the appropriate alcohol with phenyl isothiocyanate in the presence of sodium hydride.[67] Deoxygenations of alkanols, as well as sugars, proceed in yields of over 80% with these substrates, when $(Me_3Si)_3SiH$/AIBN is deployed in place of tin. Several phosphorus derivatives, including hypophosphorus acid and di-*n*-butylphosphane oxide, also function well as hydrogen donors. For example, *S*-methyl dithiocarbonates of tertiary and secondary alcohols were deoxygenated in high yields by use of the phosphane oxide in boiling dioxane; primary alcohols needed higher temperatures.[68] Methods that cut tin involvement to catalytic quantities have also been devised.[69, 70] A catalytic amount of $(Bu_3Sn)_2O$ may be combined with a stoichiometric amount of polymethylhydrosiloxane, TMSO{Si(HO)(Me)}$_n$TMS, as reducing agent. Thus, the organotin oxide is reduced in situ to tributyltin hydride, which induces the deoxygenation process. However, the reaction has to be performed in *n*-butyl alcohol to allow efficient reduction of the tin by-products. The advantages of this method include the use of very cheap reagents, diminished contamination problems, and the isolation of products in similar yields to the stoichiometric method.

4.2. Eluding Metal Overtures with the Aid of Xanthates

Dithiocarbonates (xanthates) and related compounds have been studied with particular thoroughness.[65] Following addition of a radical, ethoxyxanthates such as **25** (or the corresponding methoxy derivatives) do not fragment in the Barton–McCombie mode, but undergo C–S bond scission to generate R$^\cdot$ and a new xanthate **26**. Radical R$^\cdot$ can add to an alkene or, if unsaturated, cyclize before continuing the chain by addition to more starting xanthate **25** (Scheme 8). The additions of C-centered radicals to the xanthates are reversible, but by judicious choice of initial xanthates and reaction



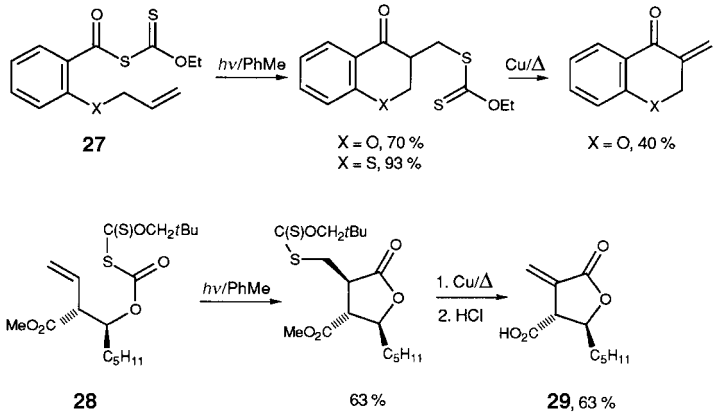
Scheme 8. Chain propagation steps for addition to alkenes of radicals generated from *O*-ethyl dithiocarbonates (xanthates).

conditions, good yields (> 60 %) of a wide variety of product xanthates **26** can be obtained.

Xanthates of type **25** are easily made by nucleophilic displacement from alkyl halides, tosylates, methylsulfonates, etc. by potassium *O*-ethyl xanthate, which is itself prepared from KOEt and CS_2 in ethanol. The chain reaction is initiated with catalytic quantities of peroxide and hence provides a metal-free route of considerable generality for homolytic inter-[71] and intramolecular syntheses[72, 73] which implement C–C bond formations and supply rings with various substitution patterns. The xanthate functionality can sometimes be removed by reduction with dilauroyl peroxide in propan-2-ol, or by treatment with DBU, or by heating with Cu powder.

The corresponding *S*-acyl xanthates (e.g. **27**) were convenient precursors of acyl radicals and were found to be useful reagents for additions and cyclizations.[65] Xanthic anhydrides ROC(S)SC(S)OR, derived from primary and secondary alcohols, extruded alkoxythiocarbonyl radicals on photolysis and hence, by rapid loss of COS, afforded R$^{\bullet}$.[74] More importantly, *S*-alkoxycarbonyl xanthates of the type ROC(O)SC(S)OCH$_2$*t*Bu functioned very satisfactorily as radical sources through loss of CO_2 from the intermediate alkoxycarbonyl radicals, and were thus transformed into ordinary xanthates (Scheme 9).[75]

The finding that appropriately unsaturated alkoxycarbonyl radicals (e.g. **28**) underwent ring closure before CO_2 loss was of special synthetic significance, because it supplied an auspicious route to lactones such as (±)-cinnamolide and the antibacterial agent (±)-methylenolactocin (**29**).[76, 77] Other members of the xanthate family such as thiocarbazones[78] and iminodithiocarbonates[79] were found to be good precursors for nitrogen-centered radicals, but catalytic or stoichiometric amounts of tin compounds were required for efficient chain propagation.

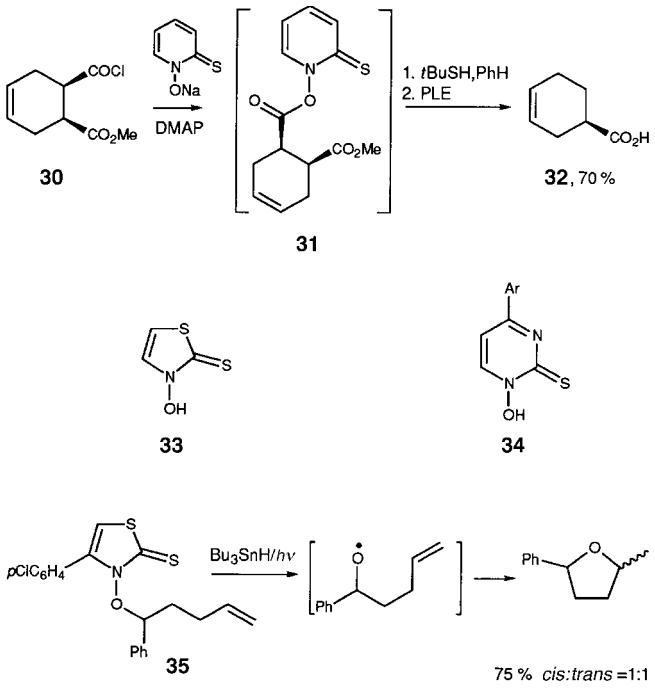


Scheme 9. Homolytic transformations of *S*-acyl xanthates and *S*-alkoxycarbonyl xanthates.

4.3. Weighing Thiohydroxamic Esters: Supple Partners for Tin and Sulfur

The now classic "Barton esters"—that is, *O*-acyl derivatives of the thionohydroxamic acid *N*-hydroxypyridine-2-thione, for example, **31**—have been widely applied for the mild decarboxylation of carboxylic acids.[3, 80] They may be used in concert with an organotin hydride, but the latter can often be replaced by a thiol (usually 2-methylpropane-2-thiol) with little if any loss of efficiency and easier removal of the resultant *tert*-butyl pyridyl disulfide by-product. The success of this methodology is due to the susceptibility of the thione functionality to addition of tin- and sulfur-centered radicals,[81] the weakness of the N–O bond, and the use of aromatization as a favorable thermodynamic driving force.

Since the introduction of Barton esters, numerous applications of this radical-based methodology have been reported, for example 1) the conversion of carboxylic acids into thiols,[82] cyanides[83] and isothiocyanides,[83] 2) the homologation of carboxylic acids either by two carbon atoms to yield amides[84] and α-keto acids[85] or by one carbon atom to give aldehydes,[86] and 3) the generation of oxygen-centered radicals.[87] The method is particularly popular for reductive decarboxylations. For example, (*R*)-3-cyclohexenecarboxylic acid (**32**) was required as the starting point for the synthesis of the natural product FK506 (Scheme 10).[88] Acid chloride **30**



Scheme 10. Examples of Barton esters and alternative thiohydroxamic esters as well as their synthetic applications. PLE = pig liver esterase.

was converted into the corresponding thiohydroxamic ester **31**, which underwent smooth decarboxylation with 2-methylpropane-2-thiol in benzene to give the required product after enzymic hydrolysis.

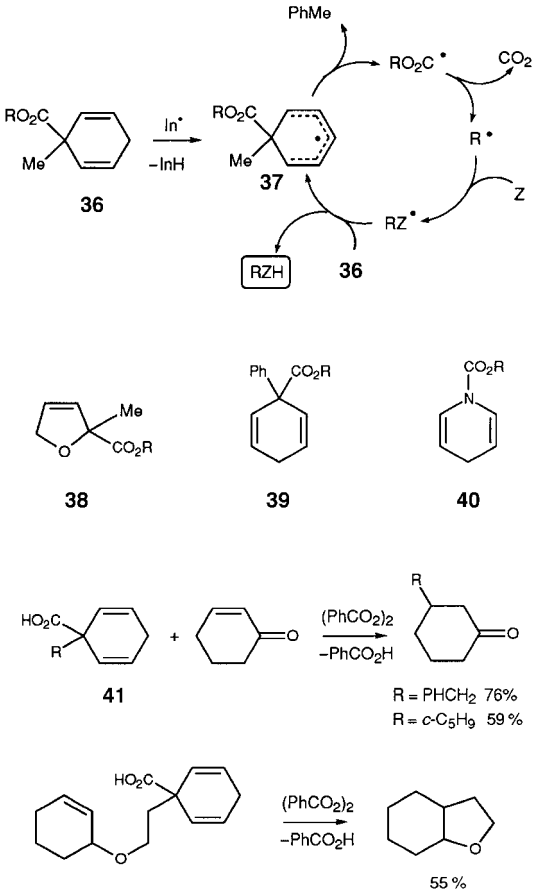
A range of alternative *N*-thiohydroxamic esters has been examined,[3, 89] including *O*-acyl derivatives of *N*-hydroxythiazole-2(3*H*)-thione (**33**) and *N*-hydroxy-2(1*H*)-pyrimidine-2-thione (**34**).[90] *N*-Alkoxy derivatives of 4-(*p*-chlorophenyl)-thiazole-2(3*H*)-thiones **35** yield alkoxyl radicals which, if appropriately functionalized, undergo ring closure to afford tetrahydrofuran derivatives in good yields.[91] Most of these alternatives need more vigorous conditions for use, or require organotin partners, so that the original type of esters **31** are generally best.

Although most of the sulfur-based reagents reach optimum performance in symbiotic relationships with organotin compounds, several practical metal-free systems have been discovered. The chief inconvenience of this chemistry lies in the fetid reek that accompanies the use of thiols and many other sulfur compounds. This miasma, which envelops products and personnel alike, evokes dire social and environmental repercussions.

5. Renouncing the Tin – Halogen – Chalcogen Carousel in Favor of "Proaromatic" Compounds

A potential means of avoiding tin depends on arranging hydrogen abstraction from a suitable reagent as the first stage of chain propagation, rather than halogen or chalcogen displacement. Because C-centered radicals are comparatively unselective in hydrogen abstractions, consequent problems with regioselectivity have inhibited design of suitable multipurpose reagents. However, several series of "proaromatic" esters deliver the required regioselectivity by means of allylic activation, simultaneously taking advantage of rearomatization as the driving force for generation of the desired radical.[92] 1-Methylcyclohexa-2,5-diene-1-carboxylic acid, which is easily made by Birch reduction and methylation of benzoic acid, acted as a prototype reagent and furnished a range of esters **36**. Their general mode of chain operation, for addition of the alcohol-derived radicals to alkenes (*Z*), is shown in Scheme 11; bromination/deoxygenation occurred in analogous fashion in the presence of excess NBS.[93] Good to moderate yields of adducts (or bromides) were obtained from **36** and the analogous 2-methyl-2,5-dihydrofuroic esters **38**, derived from secondary, tertiary, or benzylic alcohols.

Advantages of these reagents included the innocuous and volatile by-products, the success with use of metal-free initiators such as dibenzoyl peroxide and *tert*-butyl perbenzoate, and the comparatively slow rate of hydrogen donation by **36**, which repressed direct reduction of R·. However, the chains were short, so that comparatively large amounts of initiators had to be used. In addition, some β-scission of the intermediate cyclohexadienyl radicals **37** took place in the unwanted mode to generate Me· and yield aromatic esters $PhCO_2R$ as by-products. To evade this problem esters of 1-phenylcyclohexa-2,5-diene-1-carboxylic acid (**39**) and *N*-alkoxycarbonyl derivatives (**40**) of 1,4-dihydropyridine, both



Scheme 11. Use of 1-alkylcyclohexa-2,5-diene-1-carboxylic acids and esters and related compounds as proaromatic radical precursors.

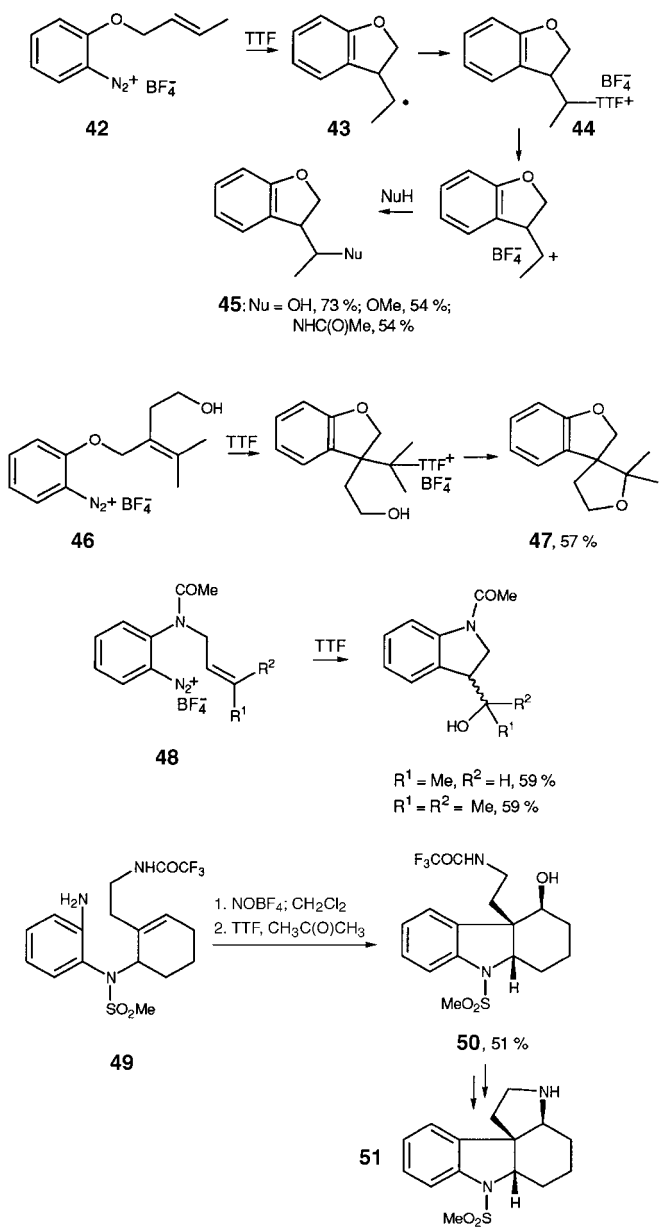
of which have only one viable fragmentation mode for the corresponding delocalized radicals, are currently under study.

Lateral thinking prompted the idea that 1-alkylcyclohexa-2,5-diene-1-carboxylic acids **41** could function in a similar way.[94] In this case fragmentation of the intermediate cyclohexadienyl radical yields mainly the desired radical together with benzoic acid, which is easily removed by an alkaline extraction. Examples of inter- and intramolecular additions are shown in Scheme 11. There was no problem with premature hydrogen donation, but loss of the hydroxyformyl radical, $\cdot CO_2H$, led to production of alkyl arenes RPh as by-products, particularly for primary radicals.

6. Metal Mimics: Crossing the Tetrathiafulvalene Bridge from Radicals to Cations

Production of aryl radicals by treatment of aryldiazonium salts with Cu^I has been in sporadic use ever since radicals were first recognized as reactive intermediates in solution. In a novel breakthrough, the metal is superseded as the electron donor by the all-organic tetrathiafulvalene (TTF).[95, 96] Treatment of aryldiazonium tetrafluoroborates **42** with TTF in acetone led to the formation of dihydrobenzofurans **45** in very respectable yields. Initial single electron transfer and nitrogen expulsion was followed by 5-*exo*-cyclization of the aryl radical to afford intermediate radical **43** plus the TTF radical cation,

which coupled together to produce the tetrathiafulvalenium salt **44**. Substitution of TTF in **44** occurred by S_N1 loss of the TTF group followed by trapping of the intermediate carbocation by an external nucleophile (Scheme 12).



Scheme 12. Stereocontrolled synthesis of polycycles by treatment of diazonium salts with TTF. Nu = nucleophile, DCM = CH_2Cl_2.

Suitably designed carbocations could be efficiently trapped by internal nucleophiles, thus opening new routes to a range of polycycles.[97] For example, diazonium salt **46** was prepared and allowed to react with TTF in situ to yield spirocyclic compound **47**. Similarly, functionalized indolines were synthesized by treating diazonium tetrafluoroborates such as **48** with TTF in moist acetone.[98] *N*-Benzoyl protection was not effective because competing cyclization onto the benzoyl group resulted in formation of a complex mixture of products. The method has also been successfully applied to the synthesis of the tetracycle **51**, which is a common subunit in alkaloid natural products such as aspidospermidine, strychnine, and vinblastine.[99, 100] One route involved preparation of aromatic amine **49**, which was diazotized and allowed to react with TTF in situ to afford hexahydrocarbazole **50** in a stereoselective manner, that is, with complete control of the stereochemistry at the three new stereocenters. Alcohol **50** was oxidized to the corresponding ketone, which on deprotection spontaneously gave the cyclic imine; this was reduced to **51** with excellent stereoselectivity.

The TTF-mediated radical-polar crossover methodology enables cascade sequences of radical and ionic reactions to be marshalled most effectively in the complete absence of metals. Attractive features of these reactions include the use of TTF in catalytic amounts and the ability to mediate cyclizations under mild conditions. The success of TTF as a reagent is due to its ability to act as an effective electron donor and its aptitude to trap radicals at a sufficiently slow rate to allow the aryl radical to cyclize before capture. Some control over the termination point of a cascade can be exercised by choosing functionalized diazadithiafulvalenes, because the rate of coupling of the radical with the fulvalene radical cation is sensitive to the steric environment around sulfur.[101] Currently the major limitation is the requirement for arenediazonium salts as starting materials.

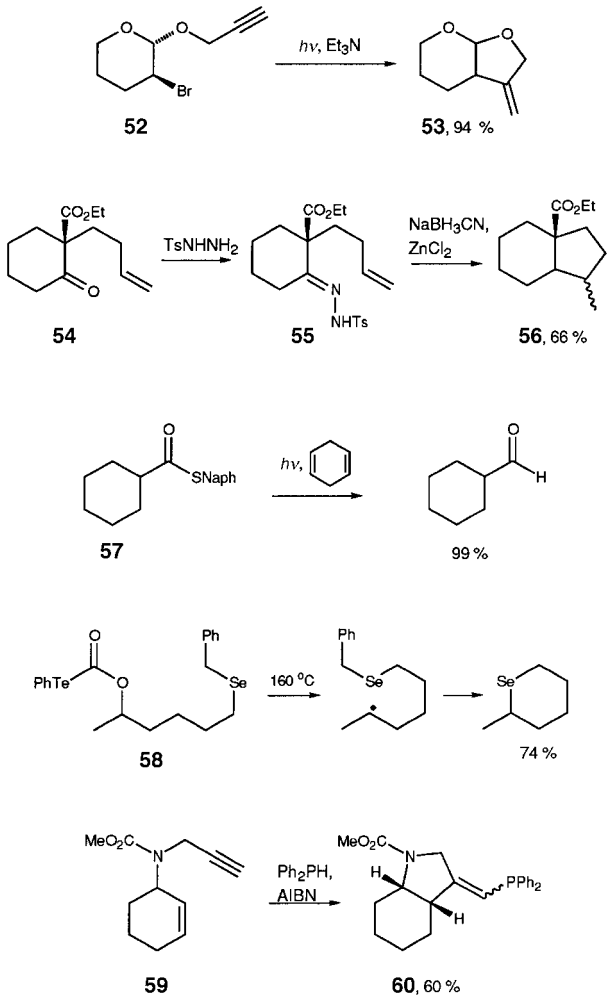
7. Assorted Allies on the March Away from Tin

Several new metal-free systems for generating radicals and managing homolytic sequences have been discovered recently. Alkyl bromides and iodides yield C-centered radicals simply on irradiation in the presence of an excess of triethylamine.[102] That this procedure was suitable for ring closures was demonstrated by the isolation of bicyclic ether **53** in almost quantitative yield on subjecting the bromotetrahydropyran derivative **52** to this operation (Scheme 13).

Reduction of tosyl hydrazone **55**, with $NaBH_3CN$ in the presence of $ZnCl_2$, yielded bicyclic ester **56** as a 3.5:1 mixture of diasteroisomers by a radical cyclization.[103] Thus, the ketone functional group in compound **54** could be regarded, in this reaction, as a synthetic equivalent to an alkyl radical. 2-Naphthyl thioesters have been introduced as new sources of acyl radicals.[104] For example, when a solution of thioester **57** in benzene was irradiated in the presence of the hydrogen donor cyclohexa-1,4-diene, cyclohexanal was formed in essentially quantitative yield.

Several tellurium compounds have been tested as sources of alkyl radicals in homolytic sequences. Aryltelluraformates (e.g. **58**), prepared by reaction of the corresponding chloroformates with diaryldditellurides and $NaBH_4$, generated alkyl radicals under thermal and photochemical conditions.[105] Thermolysis of **58** generated a C-centered radical, after decarboxylation, which cyclized by an intramolecular substitution reaction to yield 2-methylselenacyclohexane, which was isolated as the dibromide.

The P–H bond in diphenylphosphane is weak enough to sustain a radical chain process. For example, addition of $^{\bullet}PPh_2$ radicals to the alkyne group of unsaturated ester **59**, followed by ring closure, led to aza-bicycle **60** in 66% yield.[106] The scope, range of viability, and advantages of these processes have still to be properly mapped out.



Scheme 13. Synthetic applications of miscellaneous homolytic methods. Ts = tosyl = *p*-toluenesulfonyl, Naph = 2-naphthyl.

8. Summary and Outlook

The flight from tin is still proceeding at a rapid pace. None of the reagents developed so far has the flexibility or range of applicability possessed by organotin hydrides. However, selection from a range of positive measures for the avoidance of metal reagents and tin contamination is now a real option. Tris(trimethylsilyl)silane is usually a satisfactory replacement for stannanes in cyclizations and cascade reactions employing organohalide precursors. It is less successful with other precursors and in intermolecular reactions where silyl radical addition can compete. For those indifferent to odor, Barton ester/thiol methodology succeeds with a good range of carboxylic acid precursors. Likewise, xanthates show great promise for intra- and intermolecular transformations of alcohols. One of the most important challenges confronting homolytic chemistry in the next few years is the development of general protocols for control of stereochemistry. Proaromatic compounds based on cyclohexadienes are well adapted for inclusion of chiral substituents designed to promote chiral hydrogen transfer. The use of TTF, and related metal mimics, induces crossover from radical to cationic chemistry at an appropriate junction point. In this way, the well-established stereocontrol in radical bicyclizations may be successfully combined with proven ionic stereochemical know-how.

If none of these options are suitable, catalytic quantities of a tin reagent can be employed in conjunction with a reducing agent such as $NaBH_4$. This detracts from a general benefit of radical chemistry, namely tolerance of functional groups, because carbonyl and other moieties may be simultaneously reduced. Alternatively, contact with tin can be minimized by working with polymeric or water-soluble tin reagents.

Recent research has therefore opened up many promising avenues, and there is good hope that a large section of homolytic chemistry may eventually escape from the thraldom of tin.

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