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Thiols, thioethers, and related compounds as sources of C-centred radicals

Cite this: *Chem. Soc. Rev.*, 2013, **42**, 7900

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Received 21st April 2013

DOI: 10.1039/c3cs60143a

www.rsc.org/csr

Due to their stability, availability and reactivity, sulfides are particularly attractive sources of carbon-centered radicals. However, their reactivity in homolytic substitution processes is strongly reduced when compared with the corresponding selenides or halides. Despite this, sulfur-containing compounds can be engineered so that they become effective agents in radical chain reactions. A detailed description of the reactivity of organo-sulfur compounds is reported here with the aim of providing clear guidance on the scope and limitation of their use as radical precursors in chain reactions.

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Dr Fabrice Dénès was born in Paris (France) in 1975. He completed his undergraduate and postgraduate studies at the University Pierre et Marie Curie (Paris, France) and received his PhD in 2002 under the supervision of Prof. J.-F. Normant and Dr F. Chemla. He then joined Prof. P. Renaud at the University of Bern (Switzerland) as a postdoctoral associate. In 2005, he moved to the University of Nantes (France) where he was appointed assistant professor in



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radicals were “incapable of an independent existence”, is now well and truly behind us.¹ Over the past 25 years radical chain reactions have changed organic chemistry, having progressed from mere curiosities to key methodologies for organic synthesis. They are particularly suitable for the formation of carbon–carbon and carbon–heteroatom bonds through the addition of carbon-centered radicals to unsaturated systems. Both intra- and intermolecular processes have been developed but other reactions that include interesting rearrangements are also of synthetic importance^{2,3}

A radical chain process usually involves a radical precursor, one or more (frequently two) radical traps that typically include an alkene and a trialkylstannane reagent such as tributyltin hydride, as well as a radical initiator that is usually present in sub-stoichiometric quantities. Over the past few decades, significant effort has been dedicated to the investigation of the reactivity of radical traps, and the literature now abounds with kinetic data for both inter- and intra-molecular homolytic addition chemistry.¹ In addition, driven by the toxicity of tin-containing compounds, there has been considerable interest in the development of tin-free replacements for commonly used tin-containing traps that include Bu₃SnH.^{4,5}

In contrast, the reactivities of radical precursors have been less intensively investigated, and this is probably due to the fact that simple carbon-centered radicals can be prepared readily from the corresponding halides (mostly bromides and iodides) *via* homolytic substitution.⁶ Despite their general utility, halides cannot be used for the generation of all types of radicals. For example, some functionalized bromides and iodides, such as 1-bromo/iodo-1-alkoxyalkanes, are highly electrophilic and unstable, as a consequence they are not suitable for the generation of the corresponding radicals under mild conditions. This problem can be solved in many cases by employing the corresponding selenide, and phenylselenide radical precursors have become more commonly used.^{7,8} Unfortunately, organoselenium



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reagents do not represent a viable solution except for small scale research applications, mainly because of price and toxicity at high doses.⁹ In addition, contamination of phenylselenide precursors with trace amounts of diphenyldiselenide can often lead to unexpected outcomes because of the propensity of the diselenide to form benzeneselenol *in situ*.¹⁰

Alkylsulfides, on the other hand, are generally more stable than the corresponding selenides as well as being less toxic and cheaper to make. This makes them particularly attractive sources of carbon-centered radicals. However, their reactivity in homolytic substitution processes is strongly reduced when compared with the corresponding selenides or halides. Despite this, sulfur-containing compounds can be engineered so that they become effective agents in radical chain reactions.

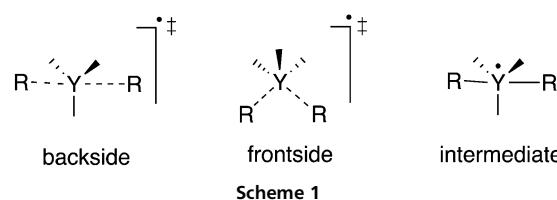
We present in this review article a detailed description of the reactivity of organo-sulfur compounds with the aim of providing clear guidance on the scope and limitation of their use. This, in turn, should greatly facilitate, through planning, their use as radical precursors in chain reactions.

1.2 The mechanism of homolytic substitution chemistry at sulfur

While intermolecular homolytic substitution chemistry has distinct similarities to its ionic (nucleophilic substitution) cousin, there are also differences that the practitioner needs to be aware of before incorporating this chemistry into a synthetic sequence.

Bimolecular homolytic substitution ($S_{\text{H}}2$) is a concerted process, similar to $S_{\text{N}}2$, during which a bond is formed with the attacking radical with simultaneous cleavage of the bond to the leaving radical. This process can occur either in an intra- or intermolecular fashion, however in the intramolecular case the reaction is no longer bimolecular and is better referred to as " $S_{\text{Hi}}1$ "; this review will discuss these two pathways (inter *versus* intra) separately.¹¹

It is generally agreed that homolytic substitution at a higher heteroatom can occur *via* three different mechanisms. The first two are concerted mechanisms in which the substitution process proceeds either *via* a backside or frontside trajectory. The backside process is similar to its S_N2 cousin and results in Walden inversion and inversion of stereochemistry when the atom undergoing substitution is stereogenic, while the front-side process leads to retention of stereochemistry (Scheme 1).¹¹ A third possibility involves a stepwise mechanism leading to the formation of a hypervalent intermediate which, depending on its lifetime, may or may not undergo pseudorotation (and stereochemical scrambling) prior to dissociation (Scheme 1). Apart from homolytic substitution at the pnictogens for which



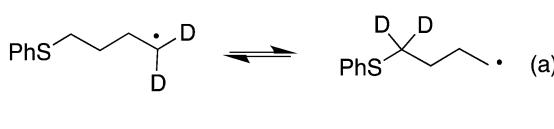
Scheme 1

there are numerous examples involving intermediates, and tellurium for which homolytic substitution is often calculated to proceed through intermediates, there is little evidence for the involvement of intermediates in homolytic substitution chemistry involving other main-group heteroatoms including the halogens and chalcogens.¹¹ It should also be noted that S_H chemistry is rare for first-row elements, including carbon, and this is largely due to a mismatch in orbital overlap; this represents the main point of departure between the nucleophilic and homolytic substitution processes, with the former often preferring the smaller first-row elements.¹¹ Another difference between S_N and S_H processes is that solvation plays a less important role in the latter since neutral radical species are less likely to lead to charged or significantly polar transition states. In the case of sulfides, to the best of our knowledge, there exist two examples of chemistry that support the existence of [9-S-3] hypervalent structures. The SH₃ radical has been detected by mass spectrometry and was shown to have a lifetime of 0.2–2.8 μs indicating that it must correspond to a local minimum on its potential energy surface.^{12,13} The experimental detection of the SH₃ radical provided a challenge for computational chemistry which was only able to reproduce the nature of the SH₃ potential energy surface when a pseudopotential basis set was employed, highlighting the need for caution and the careful benchmarking of methods when modeling homolytic substitution.¹⁴

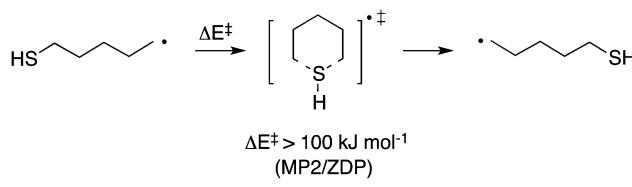
The other experimental result implicating a [9-S-3] hypervalent structure involved the rearrangement of the 4-(phenylthio)-(1,1-D₂)butyl radical to the isomeric 4-(phenylthio)(4,4-D₂)butyl radical (Scheme 2, eqn (a)).¹⁵ This transformation can only occur through a process involving a hypervalent intermediate, which is long-lived enough to undergo pseudorotation prior to dissociation (Scheme 2, eqn (b)).

The alternative frontside mechanism is extremely unlikely; calculations predict energy barriers in excess of 100 kJ mol⁻¹ for the 1,5-translocation of the SH group in the 6-thiahexyl radical, and the absence of a frontside transition state during the degenerate S_{H2} process involving the methyl radical and methanethiol (Scheme 3).¹⁶

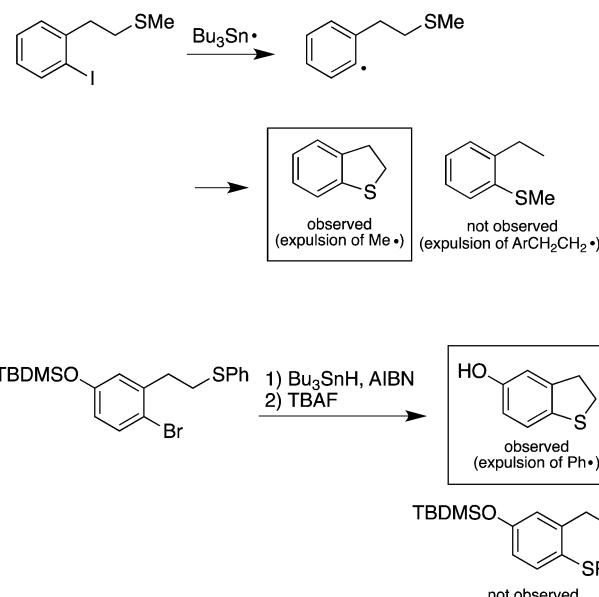
Further strong evidence that supports the concerted backside mechanism for homolytic substitution reactions involving sulfides is provided in Scheme 4.^{17,18} Both examples reveal that the observed reaction products result from the expulsion of the less stable leaving group, presumably because when constrained to the backside trajectory, it is geometrically impossible for the attacking aryl radical to expel the more favourable ligand on sulfur.



Scheme 2

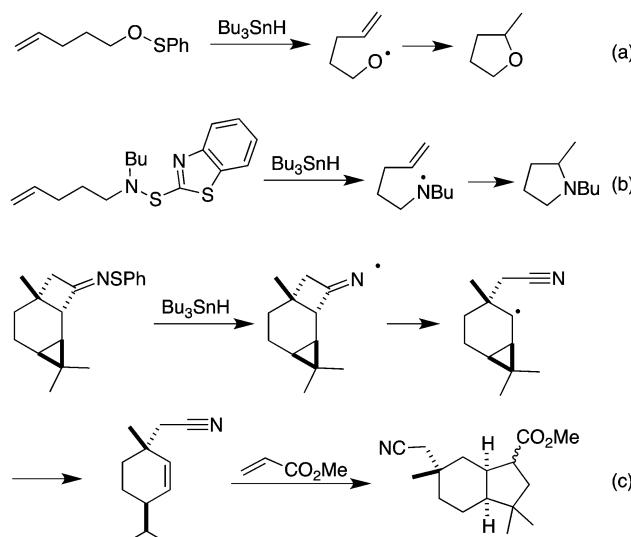
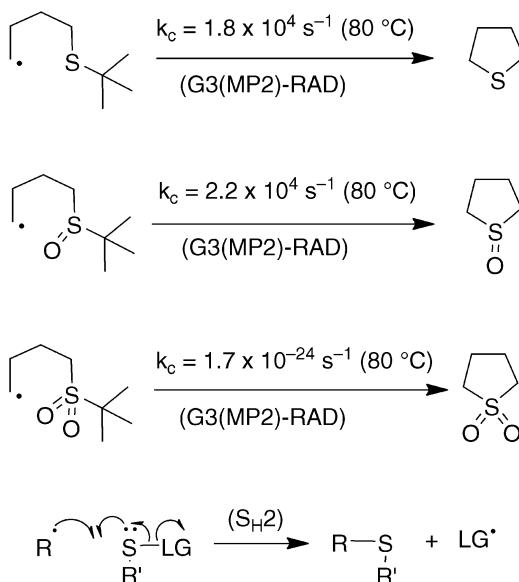


Scheme 3



Scheme 4

Kinetic studies also support a concerted mechanism for the reaction of the phenyl radical with disulfides.^{19–22} In the case of disulfides, Krenske and Houk were able to locate transition states for both frontside and backside mechanisms using density functional theory, however the backside mechanism was favoured in each case.²³ For example, the reaction of the methyl radical with dimethyldisulfide with expulsion of the methylthiyl radical was calculated to proceed with an energy barrier of 19.7 kJ mol⁻¹ (B3LYP/6-31G(d)) and a favoured attack angle that is close to collinear (160°). In comparison, the analogous frontside transition state (83° attack angle) was calculated to require an additional 56 kJ mol⁻¹ at the same level of theory.²³ Very recently, high-level calculations have revealed an important difference between S_{H2} and S_{N2} processes. In an attempt to understand the lack of homolytic substitution chemistry at the sulfur atom of sulfones,²⁴ Schiesser showed that the lone-pairs of electrons on the sulfur atom undergoing substitution are crucial to the substitution reaction and that in the absence of these electrons (as in sulfones) S_{H2} chemistry at sulfur proceeds “ridiculously slowly”²⁵ (Scheme 5). Natural bond orbital analyses on the transition states involved in this chemistry revealed that for sulfides and sulfoxides the LP_S → SOMO interaction is by far the dominant interaction, accounting for over 85% of the transition state electronic energy.²⁵ This study also concluded that carbon-centred radicals are *electrophilic* in their reactions at sulfide and sulfoxide sulfur,

**Scheme 6**

a consequence of the considerable lone-pair assistance afforded by the heteroatom.²⁵ As a consequence of this study, an alternative mechanistic rationale was proposed for S_2H_2 at sulfur (Scheme 5). It seems reasonable to suggest that a similar mechanism might operate for non-carbon-centred radical attack at sulfur that may include chain-carrying radicals such as tributyltin.

Homolytic substitution by radical generating reagents such as tributyltin radicals at alkyl- and aryl-sulfides has proven useful for generating C-centred radicals,²⁶ as well as alkoxy,²⁷ aminyl,^{28–33} iminyl radicals,^{34,35} and more recently phosphorus-centered³⁶ radicals. The radical produced in this manner can either undergo hydrogen atom abstraction from the reagent (*e.g.* stannane) in a reductive desulfurization process, or be trapped intra- or inter-molecularly. Some examples involving cyclizations of alkoxy²⁷ (eqn (a)) and aminyl³³ (eqn (b)) radicals as well as a cascade process involving an initial iminyl radical^{35,37} (eqn (c)) are provided in Scheme 6.

While sulfides offer an opportunity to generate a wide variety of radical types, this review will limit discussion to reactions that afford synthetically useful carbon-centred radicals. However, before we venture into the wealth of opportunities available to the synthetic practitioner, an understanding of chemoselectivity principles and fundamental kinetics is necessary in order to maximize opportunities.

1.3 Chemoselectivity principles

Like other free radical chemistry of synthetic importance, kinetic data are crucial for our ability to construct conditions conducive to the required outcome. The following section provides some examples of the available opportunities that flow from an appreciation of basic kinetics.

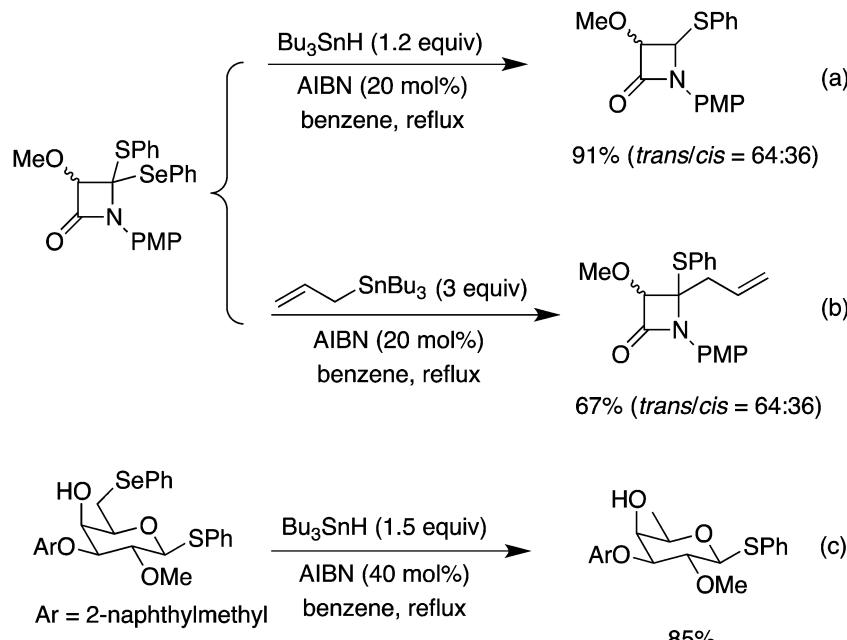
Table 1 lists rate constants ($25\text{ }^\circ\text{C}$) for the reactions of sulfides, selenides and halides with chain carrying tributylgermyl and stanny radicals.^{38–40} Inspection of Table 1 reveals a spread of

Table 1 Rate constants for reactions of tributylgermyl and stanny radicals with selected halides, sulfides and selenides

Radical	Substrate	Temp ($^\circ\text{C}$)	$k (\text{M}^{-1} \text{s}^{-1})$	Ref.
$\text{Bu}_3\text{Ge}^\bullet$	$\text{PhSCH}_2\text{CO}_2\text{Et}$	25	8.5×10^5	38
$\text{Bu}_3\text{Ge}^\bullet$	PhSCH_2OBu	25	1.6×10^4	38
$\text{Bu}_3\text{Ge}^\bullet$	$\text{PhSCH}_2\text{OC(O)Pr}$	25	4.5×10^3	38
$\text{Bu}_3\text{Ge}^\bullet$	$\text{PhSeCH}_2\text{CO}_2\text{Et}$	25	9.2×10^8	38
$\text{Bu}_3\text{Ge}^\bullet$	$\text{ClCH}_2\text{CO}_2\text{Et}$	25	1.8×10^6	38
$\text{Bu}_3\text{Ge}^\bullet$	$\text{PhSeCH}_2\text{OBu}$	25	2.3×10^7	38
$\text{Bu}_3\text{Ge}^\bullet$	$\text{Br}(\text{CH}_2)_5\text{CH}_3$	25	4.6×10^7	38
$\text{Bu}_3\text{Sn}^\bullet$	$\text{PhSCH}_2\text{CO}_2\text{Et}$	25	2.0×10^5	39
$\text{Bu}_3\text{Sn}^\bullet$	$\text{PhSeCH}_2\text{CO}_2\text{Et}$	25	1.0×10^8	39
$\text{Bu}_3\text{Sn}^\bullet$	$\text{ClCH}_2\text{CO}_2\text{Et}$	25	1.0×10^6	39
$\text{Bu}_3\text{Sn}^\bullet$	PhSCH_2OBu	25	1.0×10^3	39
$\text{Bu}_3\text{Sn}^\bullet$	$\text{PhSeCH}_2\text{OBu}$	25	6.0×10^6	39
$\text{Bu}_3\text{Sn}^\bullet$	$\text{Br}(\text{CH}_2)_5\text{CH}_3$	25	1.9×10^7	40
$\text{Bu}_3\text{Sn}^\bullet$	$\text{Cl}(\text{CH}_2)_5\text{CH}_3$	25	7.0×10^3	39

rate constants that spans approximately three orders of magnitude for any given reagent, with thioethers often at the lower end of reactivity. It is not surprising therefore that selective removal of a variety of functional groups can be achieved in the presence of a thioether. For example, generation of the PhS-substituted radical from 4-phenylselanyl-4-phenylsulfanylazetidinone can be readily achieved (Scheme 7, eqn (a) and (b)).^{41,42} In eqn (a), reductive deselanylation affords the β -lactam in excellent yield, while eqn (b) depicts selective allylation even though the reaction was carried out in the presence of an excess of the allyltin species. The phenylselanyl moiety does not require special activation in order to be removed chemoselectively, as illustrated by the selective deselanylation of the carbohydrate derivative in eqn (c) (Scheme 7).⁴² These outcomes are a direct consequence of the (at least) three orders of magnitude reactivity difference between PhS and PhSe in their reaction with $\text{Bu}_3\text{Sn}^\bullet$.

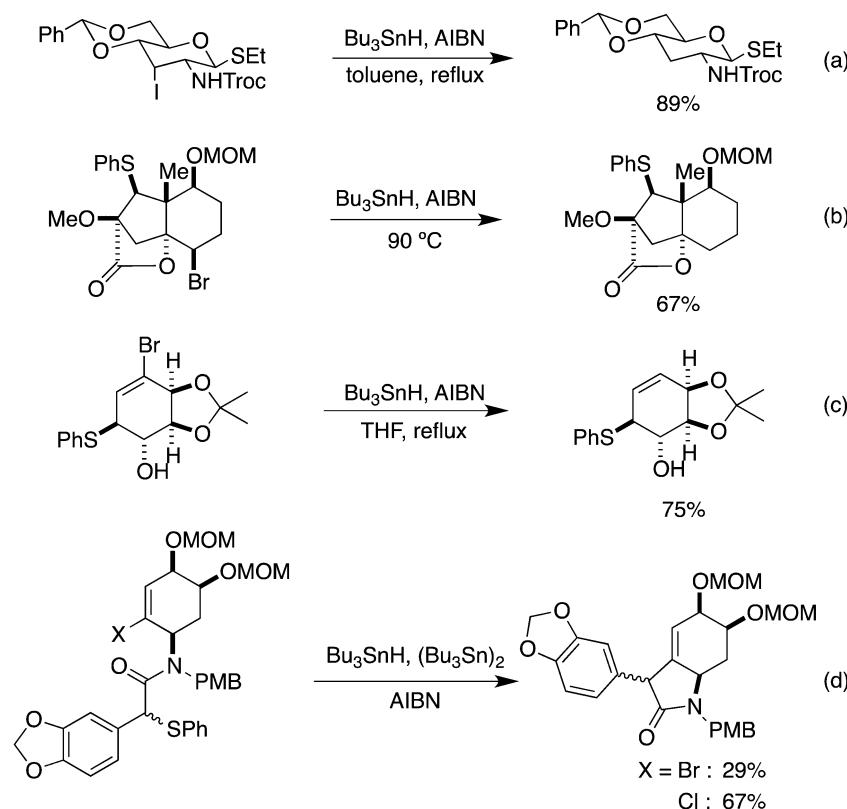
The data provided in Table 1 also suggest that debromination and deiodination should be possible in the presence of thioether moieties, and this is indeed the case (Scheme 8). For example, even a hemithioacetal is compatible under deiodination conditions



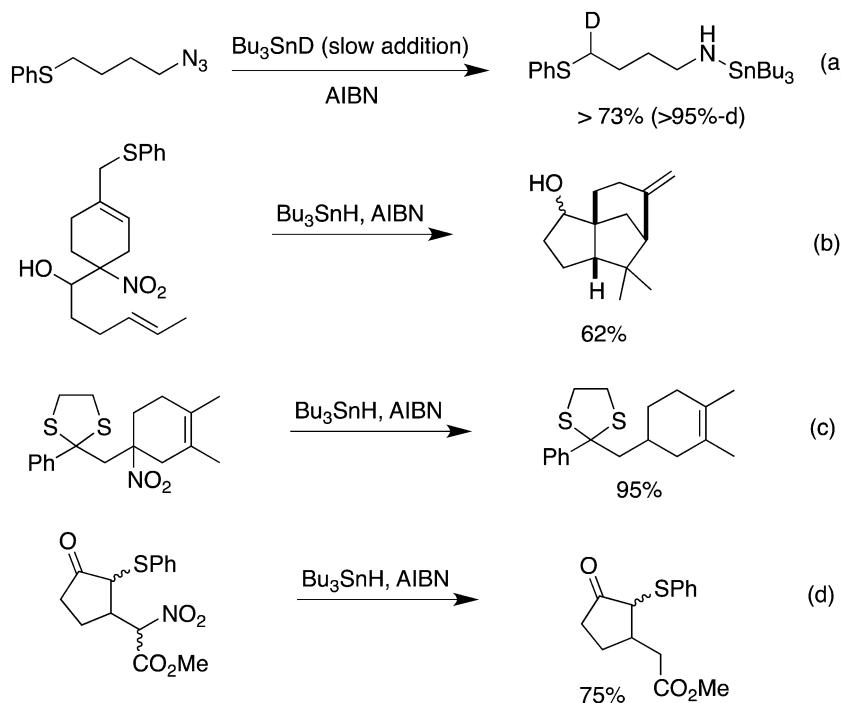
Scheme 7

(Scheme 8, eqn (a)).⁴³ The best conditions for this transformation involve the slow addition of Bu₃SnH (1.3 equivalent) to a refluxing solution of precursor and AIBN in toluene. Careful control of the reaction allowed the competing partial dechlorination

of the 2,2,2-trichloroethoxycarbonyl (Troc) protecting group to be limited. Similarly, selective debromination can be achieved in the presence of sulfides as illustrated by alkyl- and alkenyl bromides (Scheme 8, eqn (b) and (c)).^{44,45} In eqn (b), the authors mention that



Scheme 8



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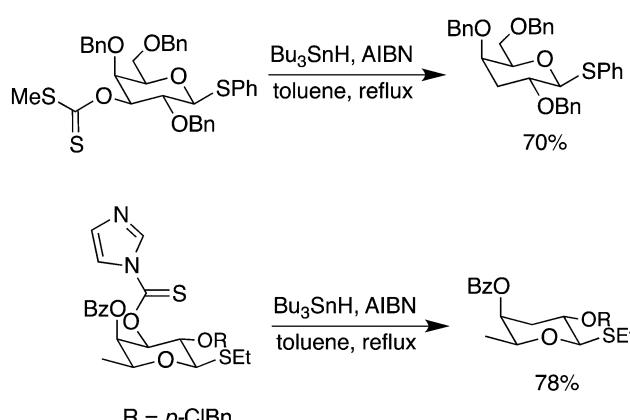
reductive desulfurization is observed if reaction times longer than 5 min are used.⁴⁵ The dehalogenation of a vinyl bromide (Scheme 8, eqn (c)) is easily achieved with Bu_3SnH in refluxing THF. In this case however, the sulfur atom might be sterically less accessible due to the particular fused-bicyclic structure of the starting material. As expected based on the data in Table 1, dechlorination is more difficult to achieve in the presence of a thioether functionality and reductive desulfurization may often compete. One can take advantage of this lower reactivity of chlorine to remove selectively a sulfanyl moiety, especially when the latter is located adjacent to a carbonyl group, as illustrated in eqn (d) (Scheme 8).⁴⁶ For dehalogenation to be successful, the authors used a mixture of Bu_3SnH and $(\text{Bu}_3\text{Sn})_2$ in the presence of AIBN to generate the carbon-centered radical that undergoes addition onto the alkenyl halide ($\text{X} = \text{Br}, \text{Cl}$). Subsequent β -fragmentation affords the unsaturated product. In this case, the best results were obtained with $\text{X} = \text{Cl}$ since desulfurization can compete favorably with dechlorination of the alkenyl moiety.

Azides,⁴⁷ nitriles⁴⁸ and nitro groups^{49,50} can be reduced in the presence of a phenylsulfanyl group, as illustrated in Scheme 9. The success of the reaction depicted in eqn (b) lies in the selective formation of a tertiary alkyl radical, which undergoes two consecutive 5-*exo*-trig cyclizations. β -Fragmentation in the final step to eject a phenylthiyl radical affords the desired *exo*-methylene system. Reductive denitration of tertiary nitro derivatives can be carried out in the presence of dithioketals as illustrated by the reduction depicted in eqn (c).⁴⁹ Activated secondary nitro groups can also be removed cleanly, even in the presence of an α -keto phenylsulfanyl group (Scheme 9, eqn (d)).⁵¹

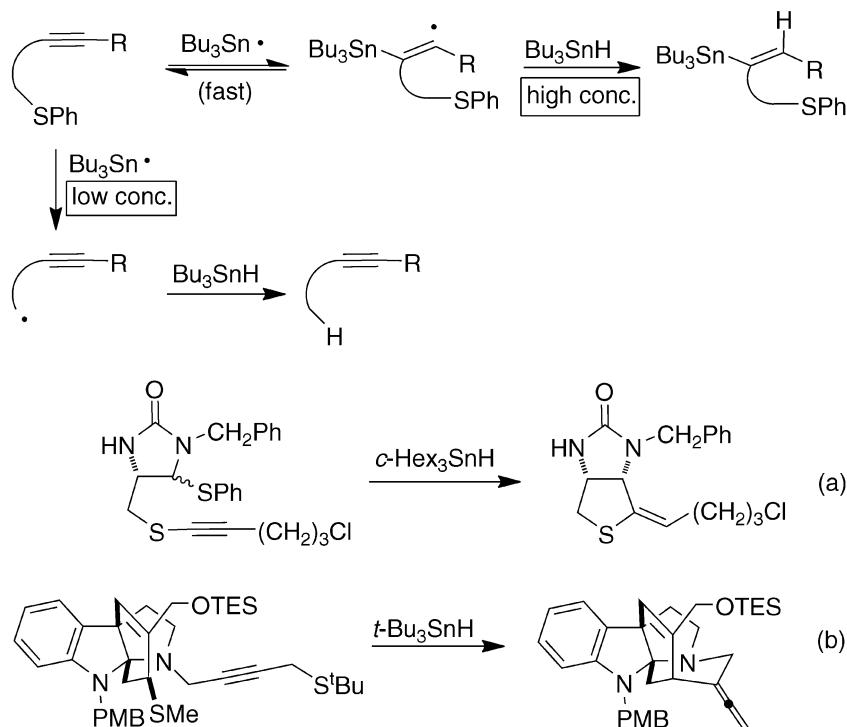
Xanthates and thiocarbonylimidazoles are also able to be selectively reacted in the presence of a thioether moiety.

Two examples of relevance to carbohydrate chemistry are depicted in Scheme 10.^{52,53}

Alkene and alkyne motifs are also compatible with the thioether radical precursors. Indeed, hydrostannylation does usually not compete with the reduction of the sulfanyl group. This is a consequence of the reversibility of the homolytic addition process involving stannyl radicals at either unsaturated moiety.^{54–56} High concentrations of stannane or polarity-reversal catalysis⁵⁷ is often required to effect free radical hydrostannylation, especially with bulky stannanes.^{58,59} When low concentrations of tin hydride are used, the alkenyl radical arising from the addition of the tin-centered radical onto the alkyne (or alkene) cannot be trapped fast enough to compete with β -fragmentation to regenerate the carbon–carbon multiple bond, effectively increasing the likelihood of stannyl radical attack at sulfur (Scheme 11).



concept:



Scheme 11

When problems are encountered, these can usually be overcome through the use of more hindered tin hydrides to prevent addition to the alkene or alkyne as illustrated in Scheme 11, eqn (a) and (b).^{60,61}

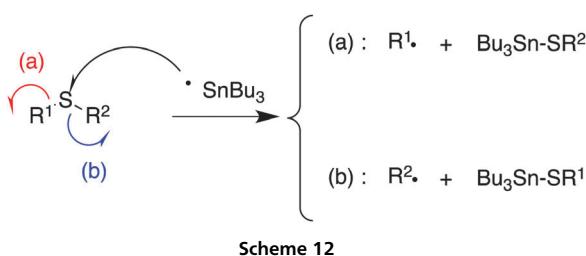
1.4 Regioselectivity: choice of leaving group

Under normal circumstances, the stannyl radical used in the chemistry described above has the choice of ejecting one of two different leaving groups (or both) during its homolytic attack at the sulfur atom in an unsymmetrical thioether (Scheme 12). Typically, the synthetic practitioner requires a regioselective outcome and designs the radical precursor in order to strongly favor the desired outcome. Aryl substituents (*e.g.* PhS) are particularly useful in that regard.²⁶ However, for completeness, it is desirable to briefly examine regioselectivity principles that arise when the leaving groups are more similar.

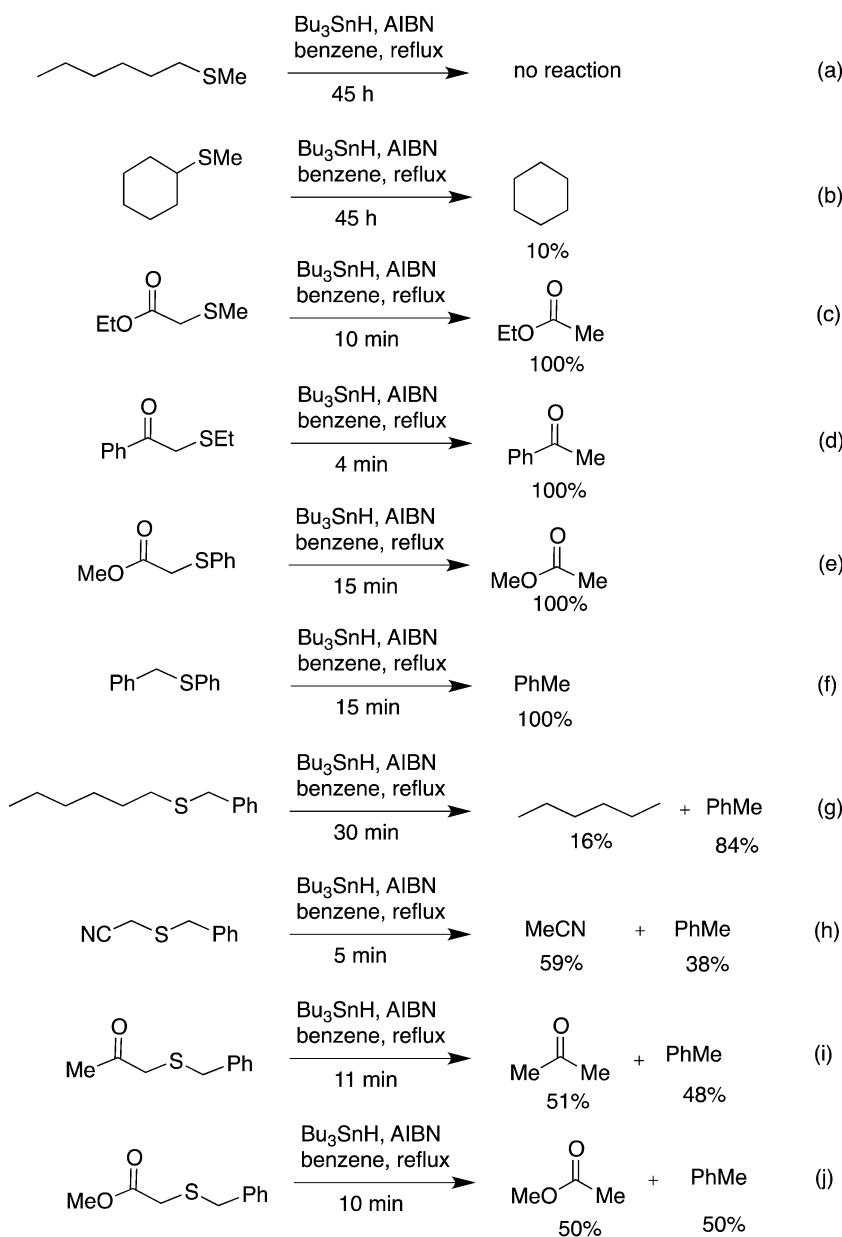
The scope and limitations of the use of tributyltin or triphenyltin hydride for the selective reduction of unsymmetrical sulfides have been extensively studied.²⁶ Dialkylsulfides generally react

poorly with stannanes. On the other hand, the reduction of benzylmethylsulfide with Bu₃SnH produces toluene and methyl tributyltin sulfide in excellent yield. The reduction of benzyl sulfides substituted with longer alkyl chains is more complex and is probably due to a less regioselective homolytic cleavage for the C–S bond. Phenylsulfides exhibit greater reactivity towards tributyltin hydride relative to the corresponding methylsulfide. The reduction of α -alkylthio- or α -(arylthio)carbonyl compounds proceeds efficiently by treatment with 1 equivalent of tributyltin hydride using AIBN initiation in refluxing benzene.²⁶

The examples depicted in Scheme 13 provide guidance in relation to relative reactivity and regioselectivity for reactions involving tributyltin hydride with unsymmetrical sulfides.²⁶ When unactivated sulfides are used, it is often difficult to drive the reaction to completion, even after prolonged heating. Sometimes slow addition techniques can overcome this problem,⁶² which is primarily due to the low rate constant for the S_{H2} reaction between the tributyltin radical and the thioether; approximately $10^2 \text{ M}^{-1} \text{ s}^{-1}$ (80°) for 1-(phenylthio)-nonane based on the data of Beckwith and Pigou.³⁹ These low rate constants make it difficult to maintain radical chain processes in which other key steps are significantly faster.⁶² The first two examples in Scheme 13 (eqn (a) and (b)) reveal how difficult it is to remove an unactivated thioether moiety; even after 45 h at reflux in benzene, tributyltin hydride is only able to promote a 10% conversion of methylthiocyclohexane to cyclohexane, while methylthiohexane is completely unreacted under identical conditions. The remaining examples



Scheme 12



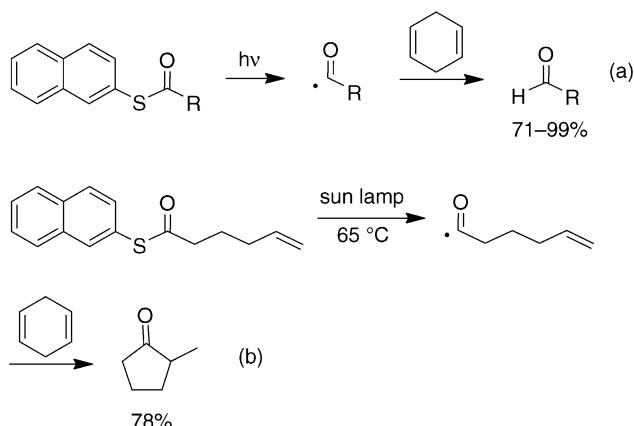
In Scheme 13 depict the chemistry of activated sulfides. When there is a clear reactivity difference, stannane reduction affords exclusively the product arising from the expulsion of the better leaving group (eqn (c)–(f)) in good conversion and in synthetically acceptable periods of time. Eqn (g)–(j) depict systems in which the reactivities of the two competing $S_{H2}2$ processes are similar to cause concern; even hexylbenzylsulfide produces small quantities of hexane (eqn (g)), while the problem becomes more serious for the remaining examples in Scheme 13 (eqn (h)–(j)).

1.5 Cascade and non-chain processes

Most of the chemistry to this point has involved chain reactions that predominantly involve tin reagents as chain carriers.

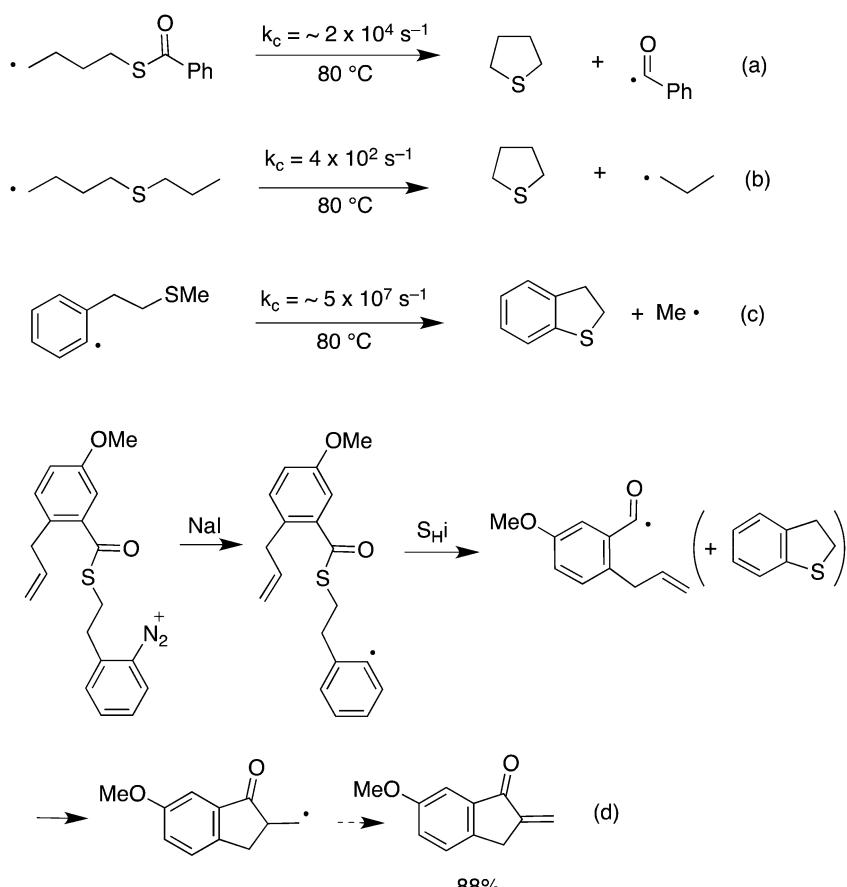
It is also important to note that there are examples of synthetically useful carbon-centred radicals produced from sulfides in non-chain methods that are also tin-free. The examples provided below make use of the photochemical properties of appropriately constructed sulfides, as well as the more favourable kinetics associated with intramolecular homolytic substitution reactions.

2-Naphthyl thioesters readily generate acyl radicals upon photolysis (Scheme 14, eqn (a)); hydrogen atom transfer from cyclohexadiene affords the corresponding aldehyde in good-to-excellent yield.⁶³ When a radical trap is suitably positioned in the alkyl chain, photolysis (sun lamp, 65 °C) affords a cyclic ketone as illustrated by the preparation of 2-methylcyclopentanone (Scheme 14, eqn (b)).⁶³ It should be noted that cyclohexanone (19%) and 5-hexenal (3%) are also produced in this reaction.



Since the pioneering work of Kampmeier and co-workers in the late 1970s, intramolecular homolytic substitution (S_{Hi}) at sulfur has also developed into synthetically useful methodology for the generation of carbon- and heteroatom-centred radicals, with emphasis on convenient tin-free methods that have emerged over the past fifteen years.⁶⁴ S_{Hi} processes have the advantage of favourable entropy terms that lead to more favourable rate constants when compared with their bimolecular

counterparts, especially when aryl radicals are involved.⁶⁵ For example, the knowledge that the 4-(benzylthio)butyl radical ring-closes with expulsion of the benzoyl radical with an approximate rate constant of $2 \times 10^4 \text{ s}^{-1}$ at 80°C (Scheme 15, eqn (a)),⁶⁶ some two orders of magnitude faster than that for the corresponding reaction with expulsion of a primary alkyl radical (Scheme 15, eqn (b)),⁶⁷ together with the knowledge that a similar aryl radical cyclizes with a rate constant of $\sim 5 \times 10^7 \text{ s}^{-1}$ with expulsion of the methyl radical (Scheme 15, eqn (c)),⁶⁸ allowed Crich to creatively exploit S_{Hi} chemistry and to demonstrate that a variety of radicals can be generated under tin-free conditions.⁶⁹ In a key example, treatment of a diazonium salt with iodide results in formation of a cyclic α -methyleneketone in 88% yield (Scheme 15, eqn (d)). Presumably the aryl radical undergoes facile S_{Hi} at sulfur to afford the desired acyl radical (and dihydrobenzothiophene byproduct) that then cyclizes onto the alkene to eventually give the enone in good yield (Scheme 15, eqn (d)).⁶⁹ One might argue on the basis of the rate constant data provided above that in this process the aryl radical would ring-close with a rate constant in excess of 10^8 s^{-1} , extremely favourable for the required synthetic outcome. This procedure represents an efficient method for the tin-free generation of acyl radicals that cannot normally be directly generated from acyl halides.



2 Thioethers

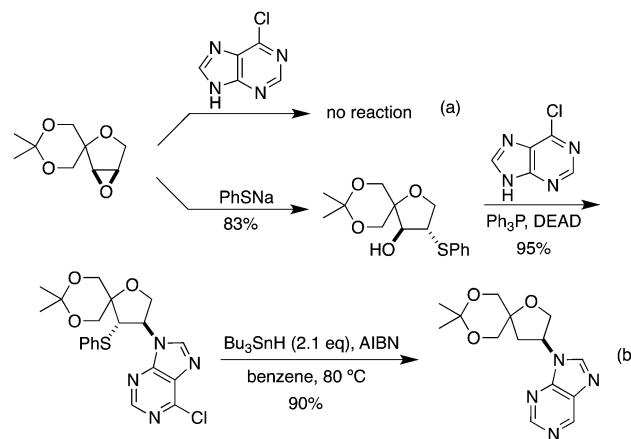
2.1 Generation of non-stabilized carbon-centred radicals

2.1.1 Reductive desulfurization and other intermolecular reactions

2.1.1.1 Tin hydride mediated intermolecular substitution. As shown in the introduction (Section 1), only aryl alkyl sulfides are reactive and selective enough to produce alkyl radicals efficiently *via* S_{H2} chemistry with triorganotin radicals. The reductive removal of arylthio groups *via* radical processes represents a mild and efficient alternative to the desulfurization with RANEY® nickel. This reaction is important in carbohydrate chemistry due to the rich chemistry of sulfur derivatives. For instance, phenylsulfanyl substituents are used as directing groups to control the introduction of nucleophiles *via* formation of intermediate episulfoniums.⁷⁰ The phenylsulfanyl moiety may then be removed either by RANEY® nickel treatment or by using a reductive desulfurization with tin hydride. In their total synthesis of apoptolidin A, Koert and co-workers reported the stereoselective formation of the β -isomer of a disaccharide thanks to the formation of an intermediate episulfonium (Scheme 16).⁷¹ After conversion of the tosylate into the corresponding iodide, reductive desulfurization-deiodination was achieved by treatment with Bu_3SnH and AIBN.

Other applications of this strategy can be found in the nucleoside series,⁷² as well as in the preparation of nucleoside analogues such as racemic isonucleosides (Scheme 17, eqn (b)).⁷³ Direct ring-opening of the furan epoxide with 6-chloropurine was not successful (Scheme 17, eqn (a)). However, the use of the more nucleophilic thiolate allowed the introduction of the sulfide that led to the formation of an episulfonium ion under Mitsunobu's conditions. Ring-opening of this highly reactive intermediate by 6-chloropurine was achieved in high yield. Final removal of the phenylsulfanyl moiety, with concomitant cleavage of the carbon–chlorine bond, took place in high yield upon treatment with Bu_3SnH in the presence of AIBN.⁷³

Similarly, glycosylation of *N*-acetylneuraminic acid was achieved in a highly stereoselective manner by using a phenylthio substituent as a stereodirecting group.⁷⁴ The reductive desulfurization took place efficiently on these oligosaccharides (Scheme 18).

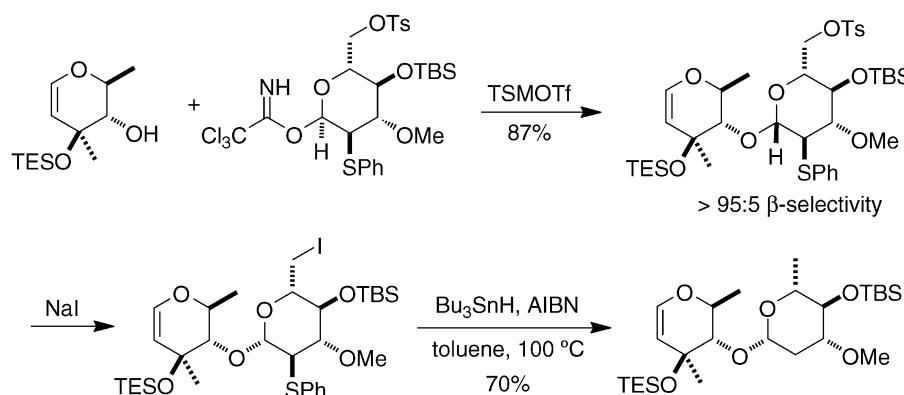


Scheme 17

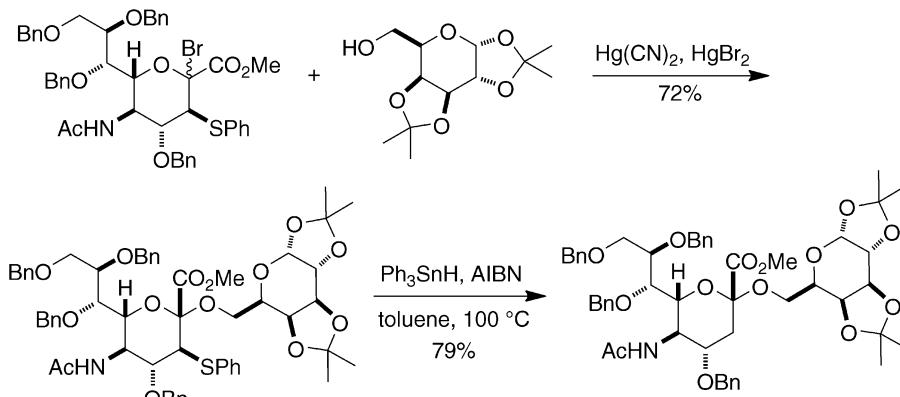
The preparation of 4-hydroxy-2-cyclohexenone and *trans*-cyclohex-2-ene-1,4-diol, two chiral building blocks used for the preparation of carba-sugars, also relies on the desulfurization of a phenyl sulfide *via* a non-stabilized polyfunctionalized cyclohexen-4-yl radical.⁷⁵

2.1.1.2 Tin hydride mediated intramolecular homolytic substitution. The moderate predisposition of alkyl sulfides toward intermolecular homolytic substitution is an important limitation to the use of sulfides as precursors for the generation of non-stabilized alkyl radicals. Therefore, indirect approaches have been developed where the slow intermolecular homolytic substitution (Scheme 19, eqn (1)) is replaced by two efficient steps, *i.e.* the rapid reaction of an aryl iodide with a stannyl radical (Scheme 19, eqn (2)) followed by an intramolecular homolytic substitution involving an aryl radical (Scheme 19, eqn (3)).

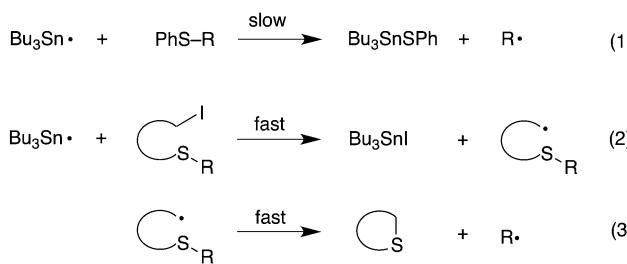
Maruoka reported an efficient method to generate alkyl radicals from alkyl *o*-iodobiphenyl sulfides (Scheme 20).⁷⁶ For instance, the generation of primary alkyl radicals that fail by the direct intermolecular procedure proves to be easy to achieve and can be carried out at $-78\text{ }^\circ\text{C}$. Interestingly, the *o*-iodobiphenylthio moiety reacts with the tin radical at a rate comparable to alkyl iodides and much faster than alkyl bromides.



Scheme 16



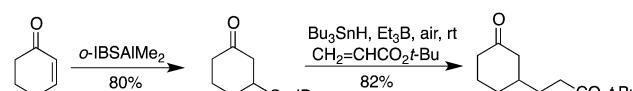
Scheme 18



Scheme 19

This high reactivity is attributed to the formation of the very stable dibenzothiophene and to the intrinsic reactivity of the iodobiphenyl relative to a simple iodoarene.

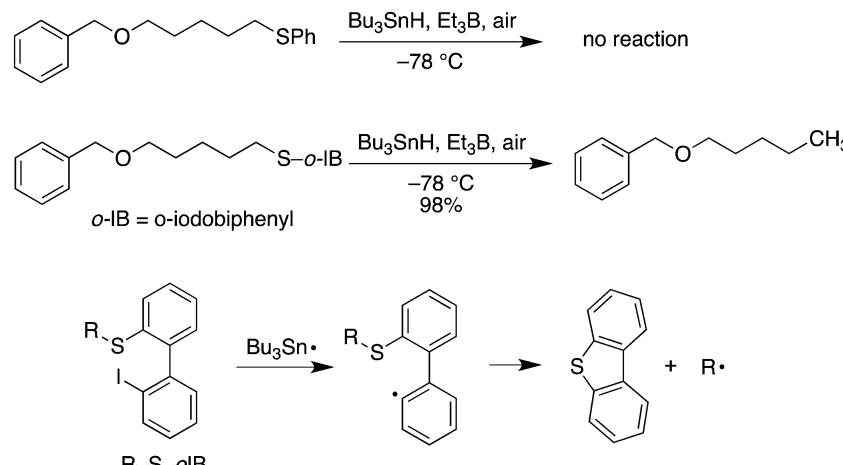
One of the very attractive aspects of this chemistry is the fact that the *o*-iodobiphenylthio moiety can be easily introduced into various substrates, allowing for convenient access to a wide range of carbon-centred radicals. For instance, treatment of cyclohexenone with the dimethylaluminium thiolate afforded the 3-sulfanylated cyclohexanone that was used for the generation of a homoenolyl radical (Scheme 21). Addition to *tert*-butyl acrylate



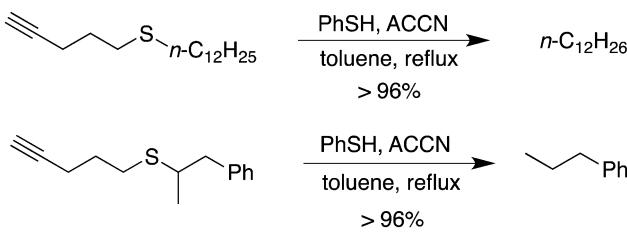
Scheme 21

afforded the product of conjugate addition (a 1,6-dicarbonyl compound) in good yield.

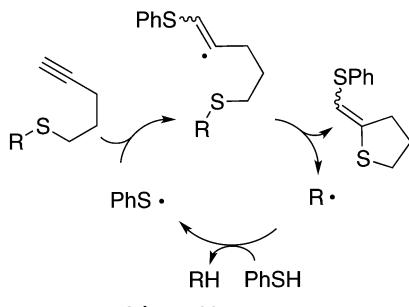
2.1.1.3 Tin-free mediated intramolecular homolytic substitution. By using an intramolecular homolytic substitution, Minozzi, Nanni, Spagnolo and coworkers generated alkyl radicals efficiently from alkyl 4-pentynyl sulfides under tin-free conditions (Scheme 22).⁷⁷ This tin-free process is based upon the generation of a reactive alkenyl radical by addition of the phenylthiyl radical onto terminal alkynes. Intramolecular homolytic substitution at the sulfur atom affords the desired alkyl radical and 2-(phenylthiomethylene)thiophene. Optimized reaction conditions require the use of slow addition techniques in order to minimize the competing hydrogen abstraction from the thiol prior to the desired homolytic



Scheme 20



ACCN = 1,1'-azobis(cyanocyclohexane)

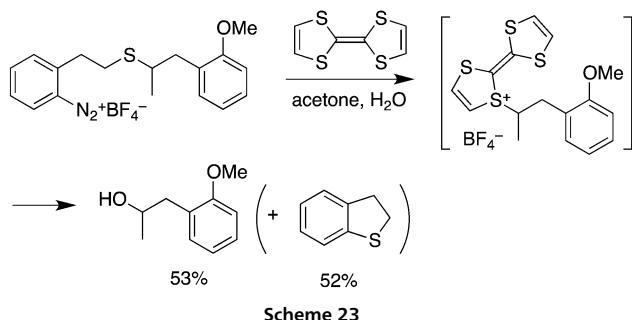


Scheme 22

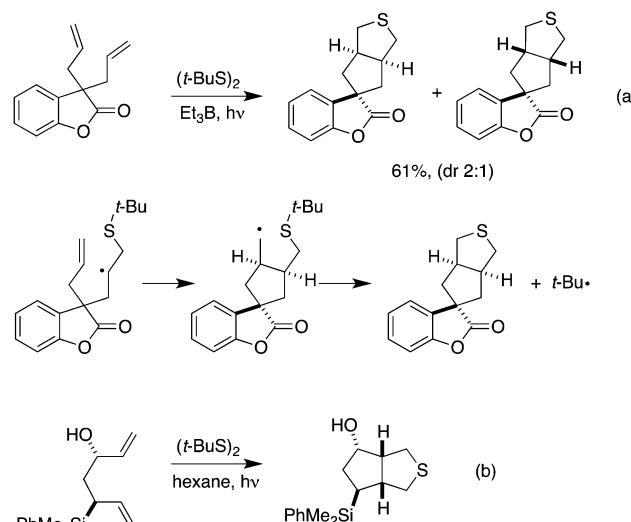
substitution at the sulfur atom. A variety of carbon-centred radicals could be generated using this approach, including stabilized carbon-centred radicals and acyl radicals (*vide infra*).

Murphy reported an alternative tin-free procedure based on an intramolecular homolytic substitution involving an aryl radical generated by single electron reduction from tetrathiofulvalene (TTF) to a diazonium salt.⁷⁸ The reaction is not a chain process and the final radical is oxidatively trapped to form a *S*-alkyltetrathiafulvalenium tetrafluoroborate salt. When the TTF salt is linked to a secondary carbon atom, it can undergo hydrolysis to afford the corresponding alcohol (Scheme 23).⁷⁸

Harrowen took advantage of homolytic substitution at sulfur to prepare tetrahydrothiophene derivatives by treating 1,6-dienes with di(*tert*-butyl)disulfide and triethylborane. In this reaction, a *tert*-butyl radical is generated during the intramolecular homolytic substitution and is presumably propagating the chain process (Scheme 24, eqn (a)).⁷⁹ Landais and co-workers reported the formation of a tetrahydrothiophene derivative by the closely related cyclization of 3-silahepta-1,6-dienes. As previously observed with these substrates, the presence of the silyl group allows to control the diastereoselectivity of the cyclization process (Scheme 24, eqn (b)).⁸⁰



Scheme 23



Scheme 24

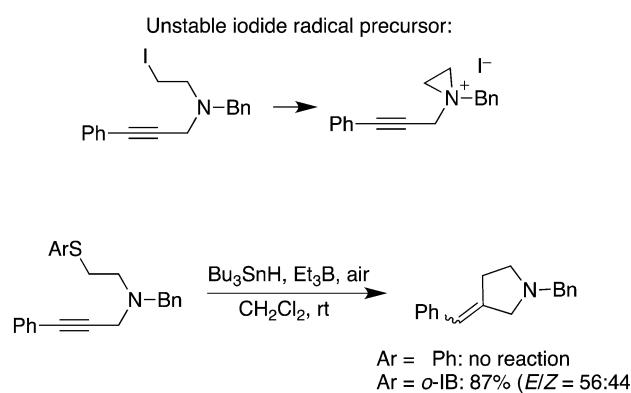
2.1.2 Cyclizations and other rearrangements. Maruoka reported the cyclization of non-stabilized alkyl radicals generated from the corresponding *o*-iodobiphenylthio derivative.⁷⁶ A propargylic amine that did not allow the preparation of a stable iodide radical precursor could be cleanly cyclized by use of the *ortho*-iodobiphenylsulfide (Scheme 25). Under the same reaction conditions, the corresponding phenylsulfides are recovered unchanged.

Chrich reported a β -(acycloxy)alkyl radical rearrangement (Surzur-Tanner rearrangement) starting from a 2-(*o*-bromophenyl)-ethyl sulfide (Scheme 26).⁸¹ The radical generation process is similar to Maruoka's method and affords 1,2-dihydrobenzothiophene as a side product.

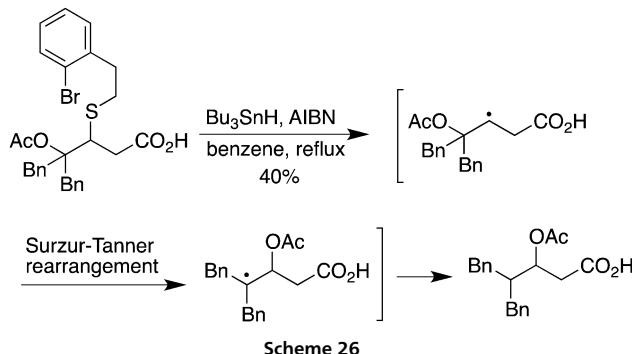
The thiophenol-mediated intramolecular homolytic substitution at the sulfur atom developed by Minozzi, Nanni and Spagnolo also allows the cyclization of non-stabilized carbon-centred radicals (Scheme 27).⁷⁷

2.2 Generation of *gem*-difluoroalkyl radicals

2.2.1 Reductive desulfurization. Pohmakotr and co-workers reported the addition of PhSCF₂SiMe₃ onto cyclic imides.⁸²



Scheme 25



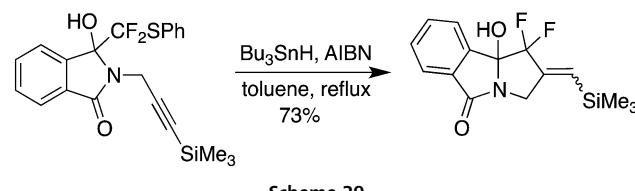
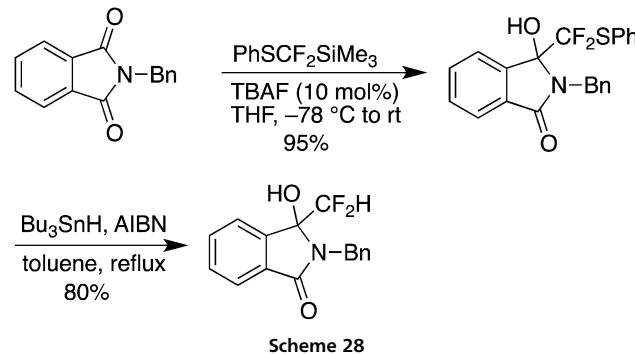
The addition was carried out in the presence of a catalytic amount of anhydrous tetrabutylammonium fluoride (TBAF), or alternatively tetrabutylammonium triphenyldifluorosilicate (TBAT) in dry THF. The use of Bu_3SnH and AIBN in refluxing toluene promoted reductive desulfurization of the resulting adduct (Scheme 28).

2.2.2 Cyclization reactions. In the case of *N*-allyl-, *N*-propargyl-, and *N*-homoallyl derivatives, intramolecular trapping of the *gem*-difluoroalkyl radical intermediate leads to 1-azabicyclic compounds in moderate to good yields (Scheme 29).

2.3 Generation of benzylic radicals

Benzylic sulfides are very good and stable radical precursors, which have been used in tin hydride mediated reactions. During the early developments of the radical decarboxylation process, Barton reported the generation of carboxyl radicals through a radical fragmentation reaction (Scheme 30). Homolytic substitution at sulfur produces the desired benzylic radical that fragments rapidly to generate a carboxyl radical, which undergoes decarboxylation to eventually deliver an alkyl radical.⁸³ The chain reaction is completed by hydrogen abstraction from Bu_3SnH . In this case, the fragmentation process is favoured by the formation of phenanthrene, an aromatic side product.

Sano and co-workers reported an elegant approach to the erythrinane skeleton based upon the formation of the C-ring of the tetrahydroisoquinoline moiety *via* a Pummerer-type cyclization, followed by a reductive desulfurization (Scheme 31).^{84,85} The Pummerer-type cyclization takes place in high yield and the reductive desulfurization product is efficiently obtained by using an excess of Bu_3SnH . Other functional groups, including mesylate and the carbonyl moieties, remain unchanged at the end of the reaction. Desmaële reported a closely related approach to the erythrina skeleton using a Pummerer-type cyclization.⁸⁶ The reductive desulfurization of the intermediate

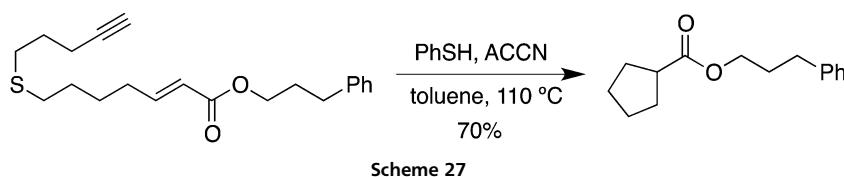


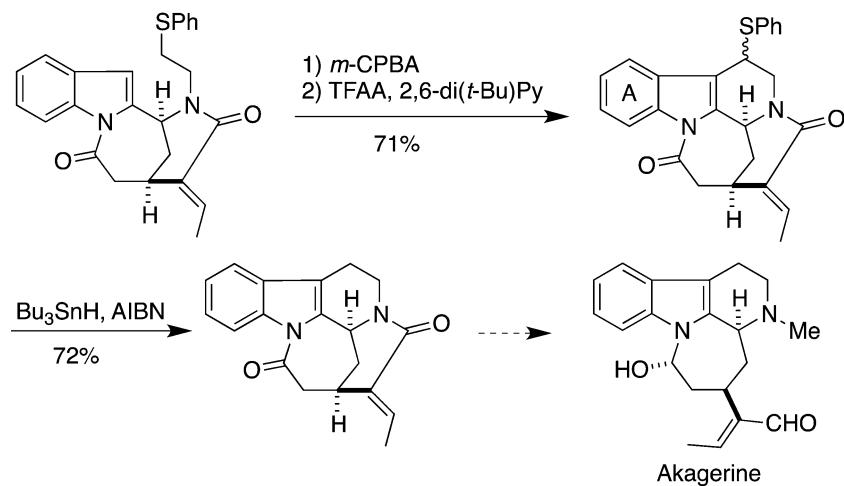
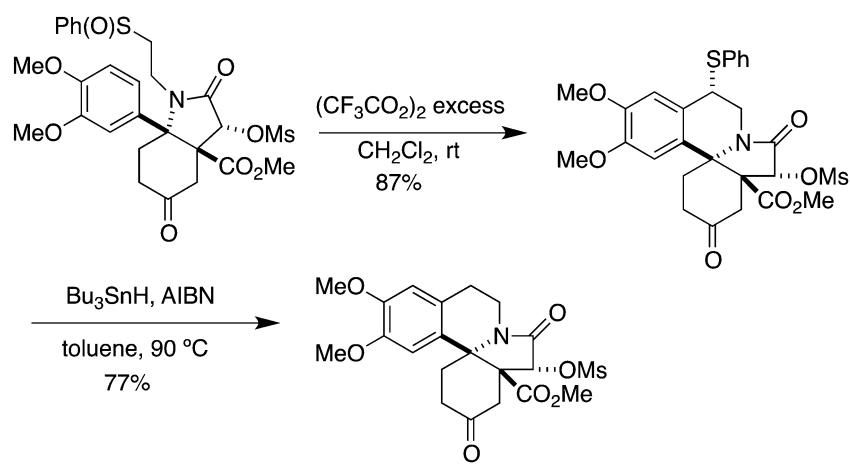
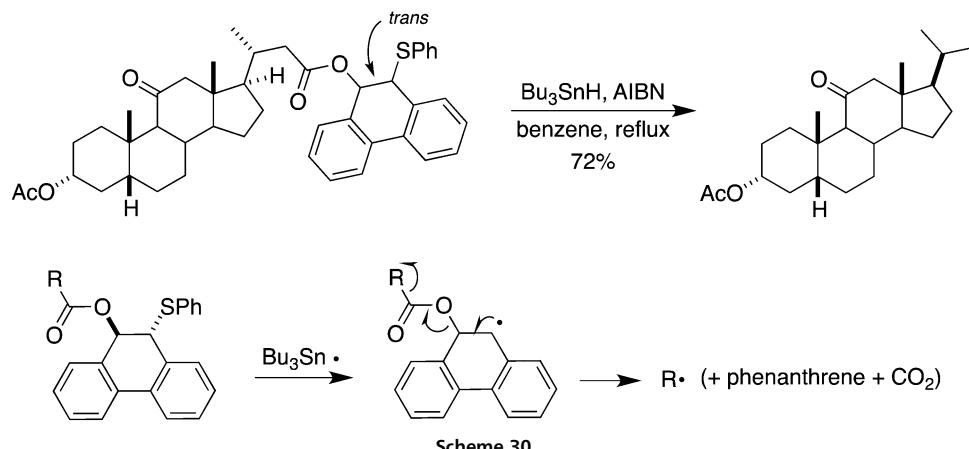
thioether is achieved in good yield using the tin hydride method, whereas RANEY® nickel fails.

Tributyltin hydride mediated reductive desulfurization is also successful in the indole alkaloid series. Amat and Bosch reported a Pummerer-type cyclization/reductive desulfurization to access the indoloquinolizidine skeleton of corynantheidine.⁸⁷ Bonjoch and Bosch used the same approach for the C-ring formation of the alkaloid akagerine (Scheme 32).⁸⁸

2.4 Generation of allylic radicals

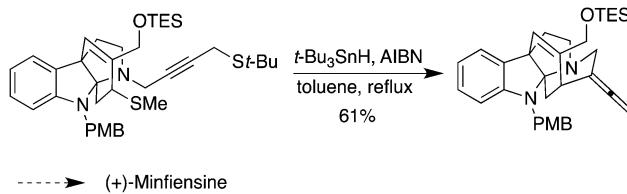
The use of allylic sulfides as a source of allyl radicals is also well documented since the early work of Gutierrez (see Section 1).²⁶ However, their use is more delicate than the corresponding benzylic sulfides due to a possible competition between S_H and S_H' processes. The undesired S_H' leading to the formation of allylstannanes can be minimized (in most cases suppressed) by using allylic systems that are substituted at the γ -position. Using methyl sulfides instead of the classical phenyl sulfides also proved to favor the S_H reaction over the S_H' since the thiy radical formed during the S_H' with allylic methyl sulfide is not stabilized by delocalization. A nice example of radical desulfurization–cyclization sequence involving the formation of an allyl radical has been reported by McMillan in the total synthesis of minfiensine.⁶¹ The final piperidine ring was installed using a cascade reaction involving homolytic substitution at the sulfur atom of an allylic methyl sulfide, followed by





6-*exo*-dig cyclization onto a propargylic sulfide moiety and final β -fragmentation of the resulting alkanyl radical to produce an allene (Scheme 33). Interestingly, in this process, the use of the

prototypical Bu_3SnH did not afford the desired allene. The use of the bulky $t\text{-Bu}_3\text{SnH}$ prevents the addition of the tin-centred radical onto the propargylic and/or allylic sulfide moiety.



Scheme 33



Scheme 35

2.5 Generation of enoyl radicals and related species

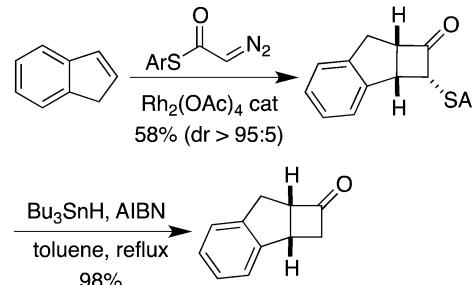
Sulfides are extensively utilized for the generation of enoyl radicals from α -alkylthio- or α -arylthio carbonyl compounds. The enoyl radicals thus formed can either abstract a hydrogen atom from tributyltin hydride (reductive desulfurization), react with a radical trap or be involved in cyclization processes.

2.5.1 Reductive desulfurization and other intermolecular reactions. Homolytic substitution at sulfides adjacent to carbonyl groups generates enoyl radicals that can abstract hydrogen atoms from suitable sources (desulfurization). Stereoselective desulfurization reactions involving cyclic and acyclic enoyl radicals have been reported.

Natsugari and co-workers employed radical desulfurization to access the 5,6-*cis* skeleton of carbapenem antibiotic C-10393.⁸⁹ The reaction was carried out with Bu_3SnH or Ph_3SnH under thermal or photolytic initiation. Under optimized reaction conditions (2 equivalents of Ph_3SnH , 20 mol% of AIBN, in refluxing acetone), the desulfurized compound was obtained in 96% yield as an 87:13 mixture of diastereoisomers (Scheme 34).

Highly diastereoselective reductive desulfurizations have been reported in the azetidin-2-one series. For instance, Bari described a stereoselective desulfurization of allylated azetidin-2-ones using Bu_3SnH and AIBN in refluxing toluene (Scheme 35).⁹⁰ When the same compounds are subjected to desulfurization with RANEY® nickel, the reductive cleavage of the carbon–sulfur bond also occurs with a high level of diastereoselectivity. In this case however, the desulfurization is accompanied by the reduction of the carbon–carbon double bond.

Thio-substituted ketenes can be generated from α -diazo thiol esters *via* a rhodium-catalyzed rearrangement. These ketenes react easily with a variety of ketenophiles to provide

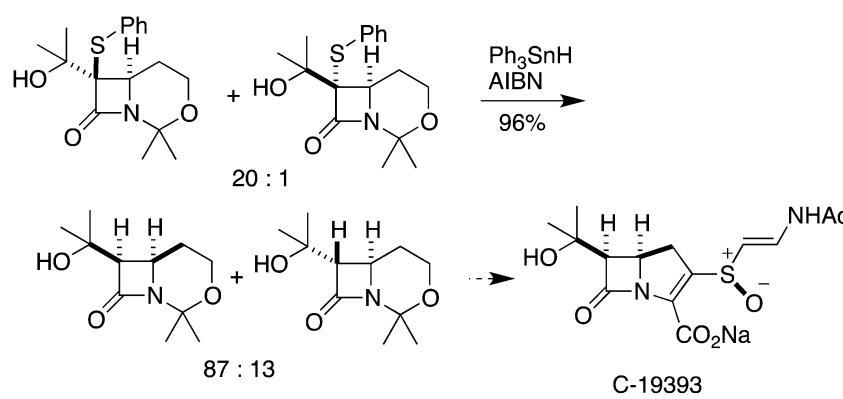


Scheme 36

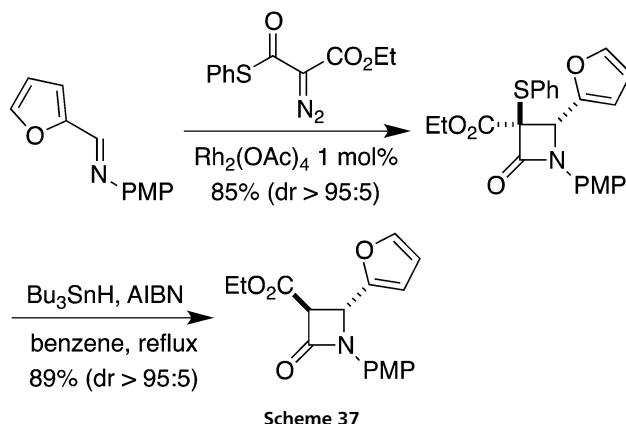
α -thiocyclobutanones, cyclobutenones, and β -lactams.⁹¹ Reductive desulfurization of these cycloadducts takes place under mild conditions and in excellent yields (*e.g.* Scheme 36). This sequence represents a useful alternative to the dichloroketene-based methodology for the synthesis of four-membered carbocycles and heterocycles.

A versatile method for the synthesis of 3-alkoxycarbonyl β -lactam derivatives *via* ketene-imine cycloaddition reactions of ethoxycarbonyl(phenylthio)ketene with various imines and subsequent desulfurization reaction was reported by Xu (Scheme 37).⁹² The desulfurization reaction affords the more stable *trans* isomer presumably *via* an epimerization process.

Posner reported the synthesis of unsaturated, bridged, bicyclic lactones from 3-(*p*-tolylthio)-2-pyrone. This electron rich thiolated pyrone underwent inverse electron demand Diels–Alder cycloaddition with electrophilic dienophiles such as α -methylenevalerolactone. The bicyclic lactone product was converted into a spiro derivative by methanolysis. Final radical desulfurization followed by base catalyzed double bond isomerization gave an α,β -unsaturated spiroester (Scheme 38).⁹³



Scheme 34



The stereoselective synthesis of carbasugars related to the gabosine family was achieved from a monoketalized thiolated *p*-benzoquinone (Scheme 39).⁹⁴ A highly stereoselective desulfurization in the presence of Bu_3SnH under AIBN initiation gave the protected epigabosine O in 83% yield.

In the early 1980s, Evans developed an efficient approach to achieve highly diastereoselective aldolization reactions based upon the use of boron enolates of chiral *N*-acyl oxazolidinones.⁹⁵ Excellent levels of diastereoselectivities are obtained in most cases except for *N*-acetyl oxazolidinones, which leads to a nearly 1:1 mixture of diastereoisomers. The use of *N*-2-methylthioacetyl-oxazolidinone solves this problem. High levels of stereoinduction are obtained and desulfurization gives the desired acetate aldol

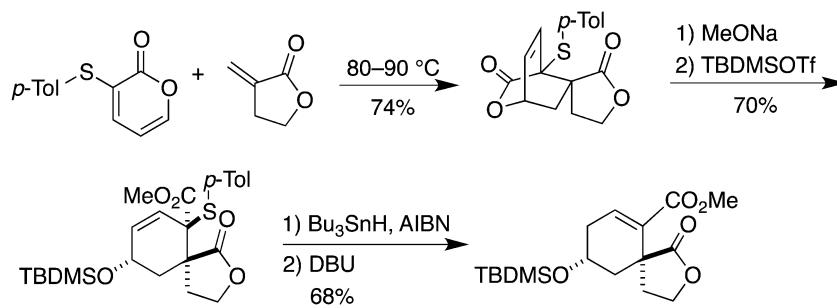
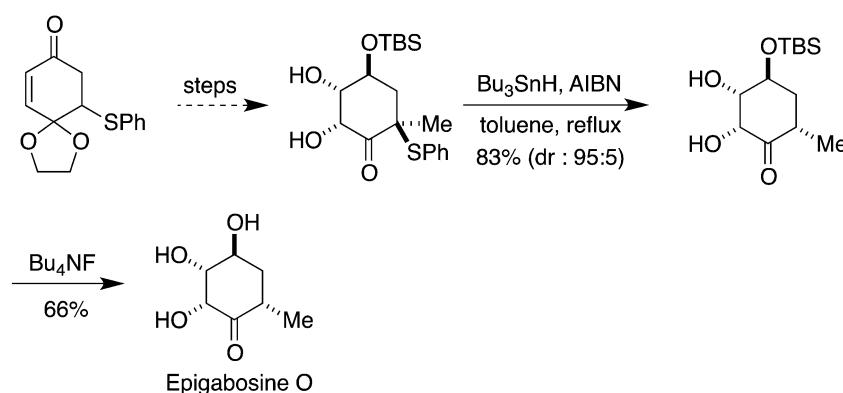
products in high enantiomeric purity. In his early work, Evans used RANEY® nickel to achieve the reductive cleavage. Later on, tin hydride mediated desulfurization was used and gave good results in complex molecules.⁹⁶ This approach is illustrated in Scheme 40 with the total synthesis of xestodecalactones B and C reported by She and Pan.⁹⁷

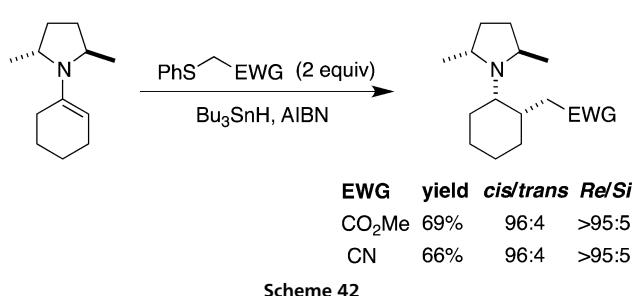
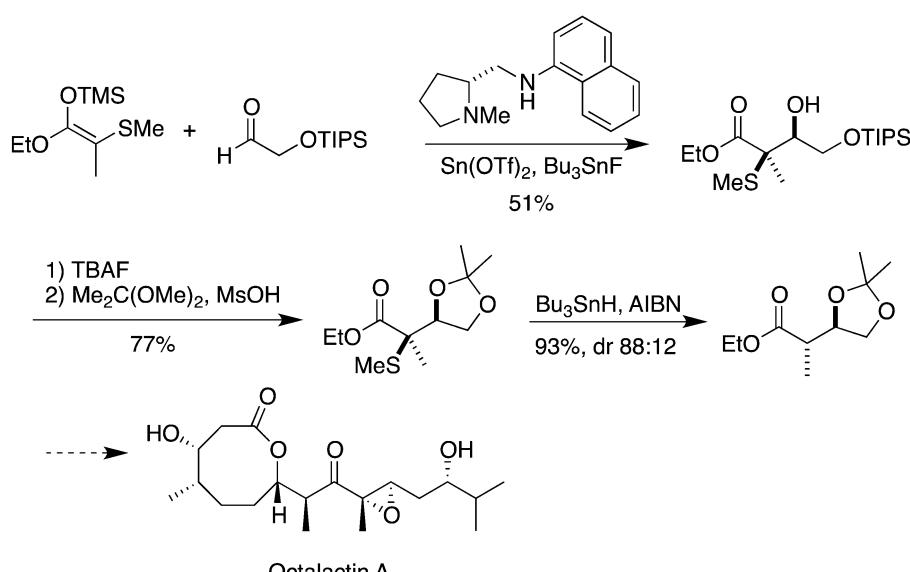
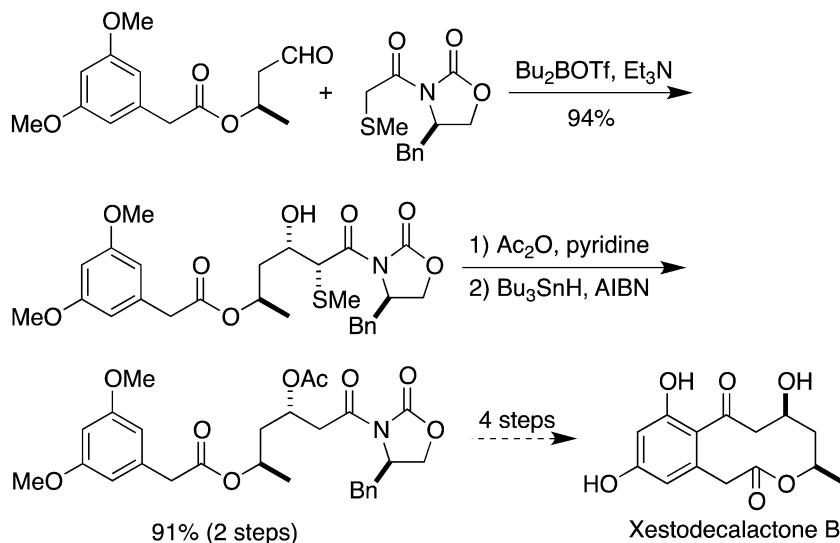
Stereoselective desulfurizations have also been reported in the aldol series. For instance, Shiina and co-workers accomplished the total synthesis of octalactin A, a macrolactone isolated from the marine bacterium *Streptomyces* sp., via an asymmetric aldol reaction.⁹⁸ Desulfurization was performed with Bu_3SnH and AIBN in refluxing benzene. The hydrogen atom abstraction from the tin hydride occurs with good stereocontrol (Scheme 41).

Intermolecular trapping of enoyl radicals generated from sulfides is possible but not very well documented. Renaud and co-workers reported the radical addition of ester and nitrile substituted radicals to enamines. For this chemistry, the use of the corresponding bromide or iodide is not possible due to fast competitive ionic enamine alkylation. Following previous reports,⁹⁹ high levels of diastereoselectivity are obtained with enamines derived from cyclohexanones and related substrates (Scheme 42).^{100–102}

Minozzi, Nanni and Spagnolo used their tin-free thiophenol-mediated intramolecular homolytic substitution at the sulfur atom to add the acetate enoyl radical to a vinyl ether (Scheme 43).⁷⁷

2.5.2 Sulfides as radical precursors for cyclizations. Enoyl radicals generated from α -thiolated carbonyl compounds under

**Scheme 38****Scheme 39**

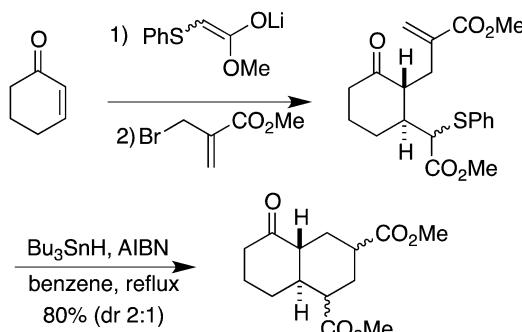
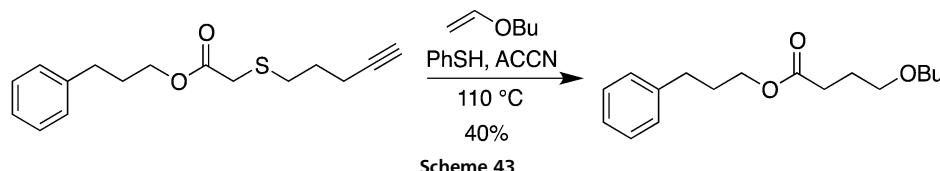


tin hydride conditions are used for cyclization processes. Posner prepared fused bicyclic systems from cyclic α,β -unsaturated ketones by tandem conjugate addition of the enolate derived from α -methyl phenylthioacetate followed by allylation of the

resulting enolate.¹⁰³ Upon treatment with Bu_3SnH and AIBN, cyclization of the α -phenylthioester group afforded the fused bicyclic system *via* a 6-*endo* radical cyclization (Scheme 44).

Ikeda and Ishibashi reported a formal synthesis of pancratine utilizing a $(Me_3Si)_3SiH$ mediated desulfurization–cyclization sequence (Scheme 45).¹⁰⁴ In the synthesis of the cyclization precursor, they took advantage of the rich chemistry of organo-sulfur derivatives by running a Friedel–Crafts alkylation between 1,2-methylenedioxybenzene and ethyl 2-chloro-2-(phenylthio)-acetate. After conversion of the ester to an allylic amide, the α -1-aryl-1-phenylthioacetamide was treated with $(TMS)_3SiH$ and AIBN to afford the cyclized product in 84% yield.

Kamimura has investigated the regioselectivity of the conjugate addition of thiols to unsymmetrical fumaric acid derivatives. In the absence of base, the mixed ester/amide of fumaric



acid reacted with thiols to afford the α -phenylthioester that cyclized upon treatment with Bu_3SnH *via* a 6-*exo*-trig pathway to deliver the piperidinone product (Scheme 46, eqn (a)). Under alkaline conditions, the conjugate addition afforded the α -phenylthioamide and, after radical cyclization, the pyrrolidinone resulting from a 5-*exo*-trig cyclization was formed selectively (Scheme 46, eqn (b)).¹⁰⁵

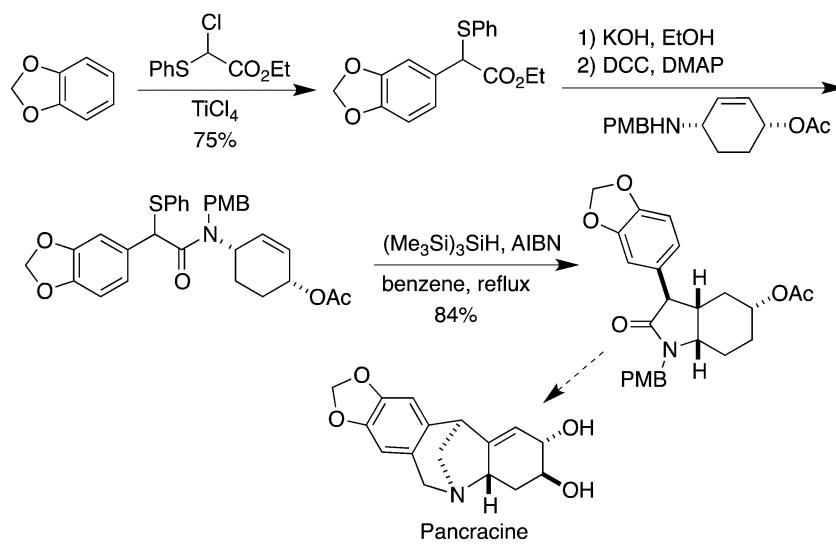
Minozzi, Nanni and Spagnolo applied their thiophenol mediated reaction for the synthesis of γ -lactones (Scheme 47) and γ -lactams *via* the intramolecular trapping of the electrophilic radical generated in the $\text{S}_{\text{H}}2$ reaction.⁷⁷ This reaction is particularly interesting since the formation of such lactones *via* tin hydride mediated radical cyclization of the corresponding haloesters is not efficient and afforded mainly uncyclized products.^{106,107}

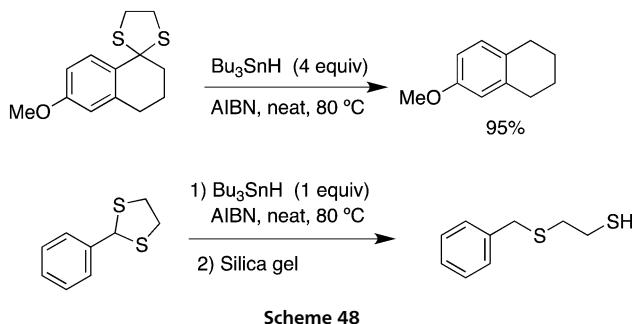
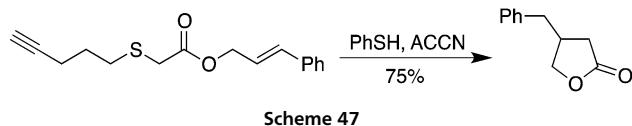
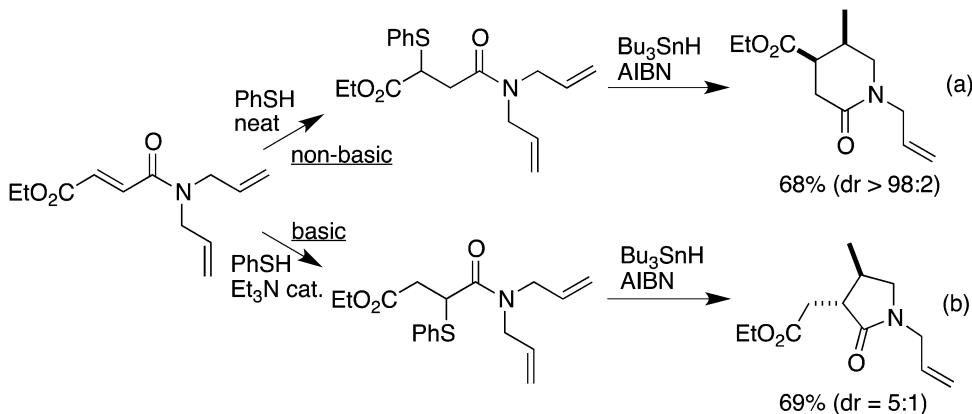
3 Dithioacetals and ketals

3.1 Reductive bis-desulfurization

A two step procedure for the deoxygenation of aldehydes and ketones has been developed by McIntosh and Gutierrez. The aldehydes or ketones are converted into the corresponding dithioacetals or dithioketals, respectively, and then desulfurized in the presence of an excess of Bu_3SnH and AIBN at 80 °C, under neat conditions or in solution in benzene (Scheme 48, eqn (a)).^{108,109} The homolytic cleavage of the first carbon–sulfur bond is highly regioselective, as demonstrated by the reaction carried out with only one equivalent of tin hydride, which led exclusively to the formation of a thioether (Scheme 48, eqn (b)). The cleavage of the second carbon–sulfur bond is more difficult and its regioselectivity ($\text{C}-\text{S}-\text{C}$ *versus* $\text{C}-\text{S}-\text{Sn}$) depends on the structure of the precursors. Therefore, full desulfurization of dithioacetals requires generally more than two equivalents of Bu_3SnH .¹¹⁰

The method complements nicely the classical deoxygenation methods such as the Wolff–Kischner and Clemmensen reactions as well as the RANEY® nickel mediated desulfurization. For instance, Hoppe and co-workers completed their synthesis of (–)-metachromin A thanks to a tin hydride-mediated reductive desulfurization of a key dithiane (Scheme 49). In this particular example, desulfurization with RANEY® nickel led to reduction and isomerization of the carbon–carbon double bonds, Birch conditions gave either mono-desulfurization at –78 °C or reduction of the aromatic ring at higher temperature and preparation of the hydrazone led to degradation.¹¹¹





The Kuck group reported clean desulfurization of the *cis,cis,cis,trans*-[5.5.5.6]fenestrane dithioketal under radical conditions. Epimerization of the skeleton into the all-*cis* diastereoisomer occurred during all attempts at removing the carbonyl group using either Wolff-Kishner or RANEY® nickel conditions (Scheme 50).¹¹²

The reductive desulfurization of dithioketals gives good results for the preparation of 1*H,1H*-perfluoroalkylated aromatic compounds from the corresponding ketones, while Clemmensen reduction is unsuccessful.¹¹³ The use of deuterated tin hydride to introduce two geminal deuterium atoms in the molecule represents an attractive feature of the radical desulfurization.^{114–116} The formation of dithioketals followed

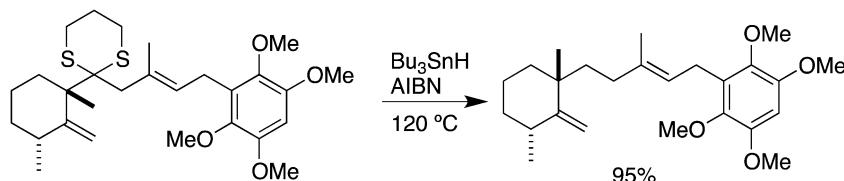
by desulfurization under radical conditions has found many applications in total synthesis as a mild procedure to remove a carbonyl group. In their formal total synthesis of (+)-aphanorphine, Zhai and co-workers used this method to reduce an arylketone (Scheme 51).¹¹⁷

Padwa and co-workers prepared the azatricyclic skeleton of an advanced halichlorine intermediate *via* a similar reductive desulfurization process (Scheme 52).¹¹⁸ Interestingly, neither epimerization of the α -methyl lactam nor reduction of the carbon–carbon double bond was observed.

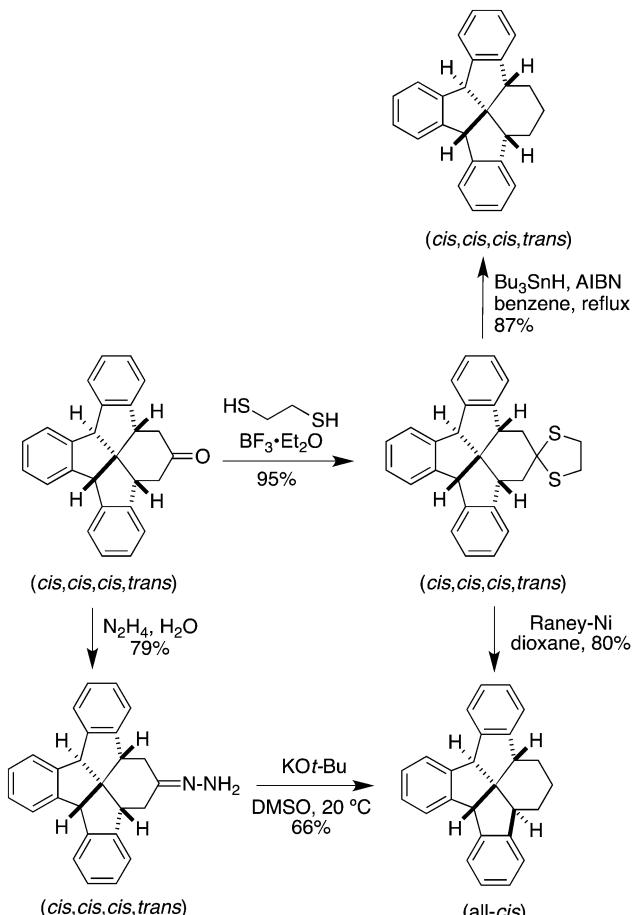
Dithioacetal or dithioketal moieties are often used to create new carbon–carbon bonds *via* metallation and alkylation. For instance Mäkelä and co-workers prepared the *trans*- α,β -dibenzyl- γ -butyrolactone skeleton of the mammalian lignan enterolactone using a conjugate addition of the metallated benzyl dithioacetal onto butenolide followed by benzylation of the resulting enolate. Complete desulfurization of the dithioacetal adducts was achieved using either RANEY® nickel in refluxing ethanol or an excess of Bu₃SnH in toluene. Under the tin hydride conditions, neither debenzylation nor hydrogenation of the alkenyl moiety was observed (Scheme 53).¹¹⁹

Kiyooka and coworkers developed an asymmetric aldol reaction using a dithiolane silyl nucleophile and a chiral oxazaborolidinone as a chiral inductor. The use of a dithiolane ensures a better stereocontrol of the aldol reaction than the corresponding non-substituted silyl ketene acetal (Scheme 54).¹²⁰

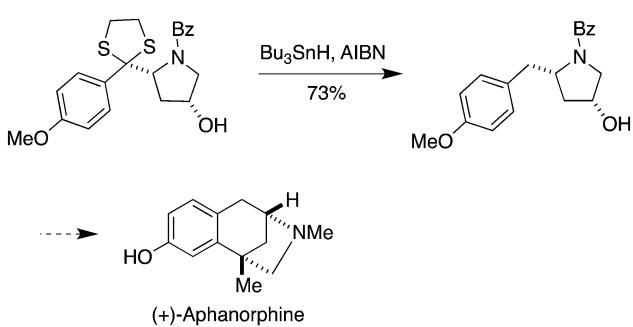
Reductive desulfurization of dithioacetals and dithioketals derived from enals and enones is reported. In these cases, allylic radicals are formed, and these can be trapped by the tin hydride leading to carbon–carbon double bond regioisomers. Nevertheless, examples of regioselective trapping have been



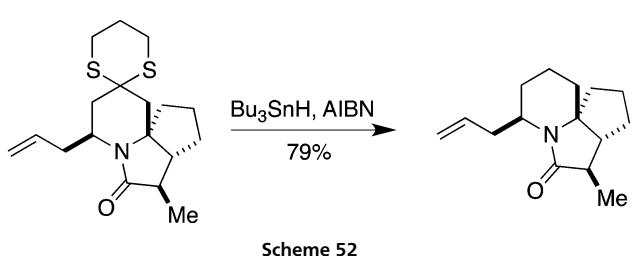
Scheme 49



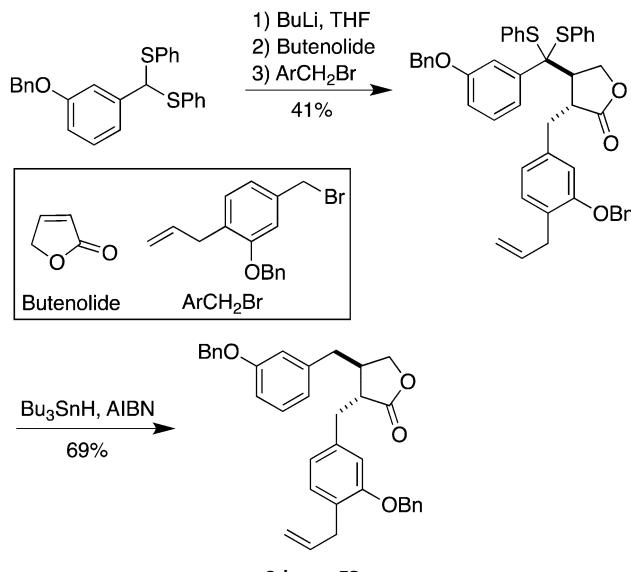
Scheme 50



Scheme 51



Scheme 52



Scheme 53

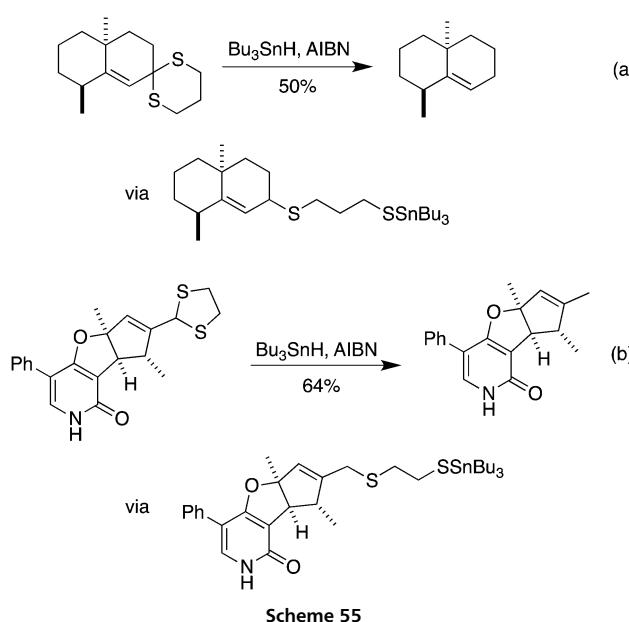
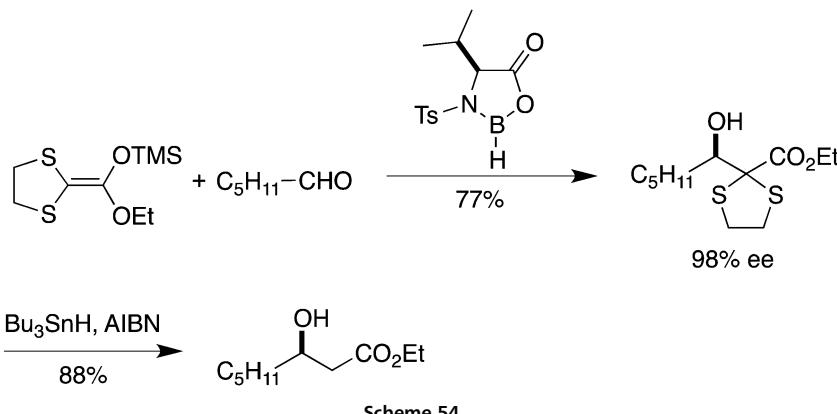
geosmin synthase in streptomycetes, Schulz and co-workers utilized such a reductive desulfurization. The intermediate allylic radical abstracts a hydrogen atom from tin hydride at the less hindered position (Scheme 55, eqn (a)).¹²¹ Similarly, Omura, Nagamitsu and co-workers completed the total synthesis of citridone A using a tin hydride-mediated desulfurization of a dithioacetal. Here again, steric hindrance might account for the regioselectivity observed by the authors during the desulfurization (Scheme 55, eqn (b)).¹²² This regioselective reductive desulfurization implies two consecutive regioselective hydrogen atom abstraction from the tin hydride. The cleavage of the first carbon–sulfur bond generates an intermediate allylsulfide that can be further reduced by tin hydride.

Tris(trimethylsilyl)silane is usually not suitable for complete desulfurization reaction (*vide infra*). With this reagent, the reaction stops after mono-desulfurization¹²³ and cleavage of the second carbon–sulfur bond is not observed (for an exception, see example 2, Scheme 45). However, complete desulfurizations were reported in the polysilacycloalkane series. Shimizu and coworkers examined without success various reaction conditions to achieve complete desulfurization, including RANEY® nickel and lithium-primary amine. However, high yields were only reached using a large excess (typically 8 equivalents) of $(Me_3Si)_3SiH$ or $(i-PrS)_3SiH$ and AIBN as a radical initiator (Scheme 56). The reaction with tin hydride also gave good results with slightly shorter reaction times.^{124,125}

3.2 Reductive mono-desulfurization

Controlled mono-desulfurization can be achieved either with tris(trimethylsilyl)silane or with tin hydride (see Scheme 48). For instance, tris(trimethylsilyl)silane cleaves 1,3-dithiolanes or 1,3-dithianes efficiently.¹²³ Even in the presence of an excess of silane, the reaction stops at the monodesulfurization step leading to clean formation of thioethers (Scheme 57).

disclosed. In their synthesis of 8,10-dimethyl-1(9)-octalin, a bicyclic compound identified as a metabolite formed by



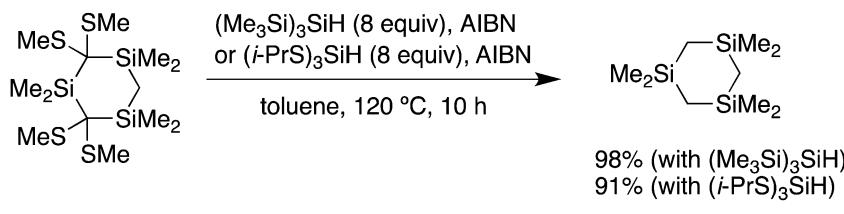
Ikeda and co-workers reported the preparation of β -lactams by radical cyclization of *N*-[2,2-bis(phenylthio)ethenyl]- α -bromo-alkanamides. In order to minimize direct hydrogen abstraction from the non-cyclized radical, a solution of Bu_3SnH and AIBN was slowly added to the precursor. The resulting dithioketal derivative could then undergo complete or partial tin hydride-mediated desulfurization^{126,127} depending on the reaction conditions. This method was employed to prepare the β -lactam skeletons of (+)-PS-5, a carbapenem antibiotic (Scheme 58), and (+)-thienamycin.^{127–129}

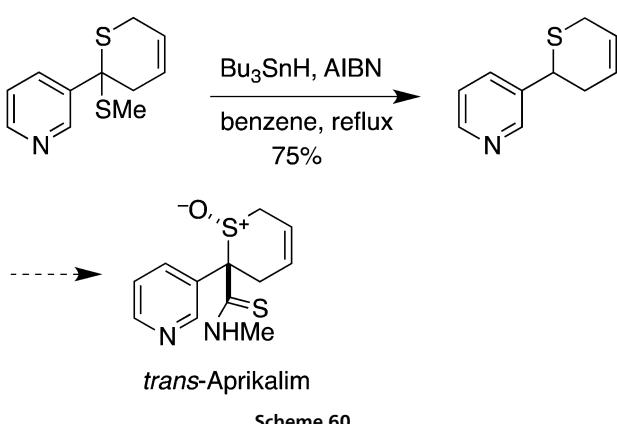
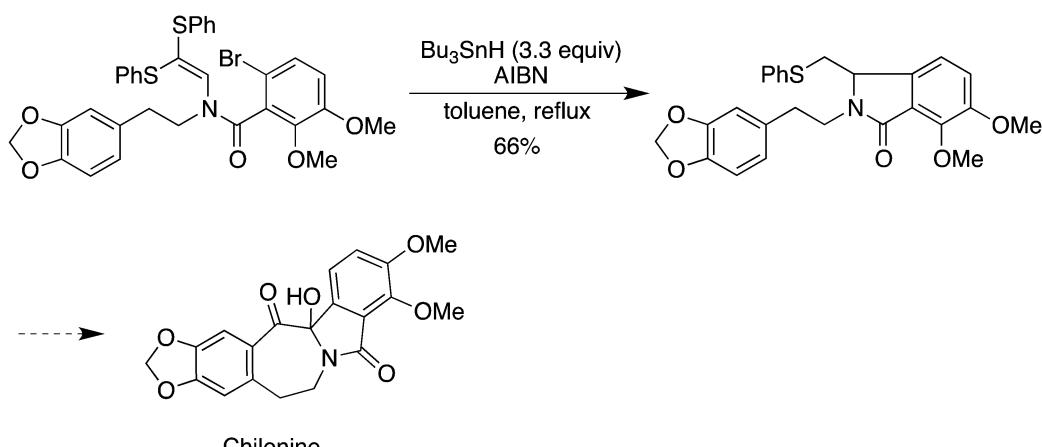
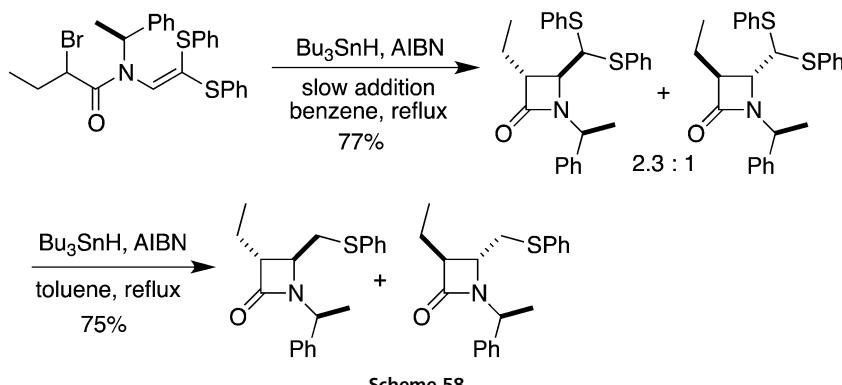
Similarly, the cyclization of a bis-phenylthiolated *N*-(*o*-bromophenyl)enamine proceeded selectively in a 5-*exo*-trig mode. Addition of Bu_3SnH and AIBN in refluxing toluene afforded the mono-desulfurized cyclized product in 66% yield.¹³⁰ The remaining phenylthio moiety was oxidized to the corresponding sulfoxide, which was subjected to a Pummerer-type cyclization to form the 7-membered ring of chilinenine, a member of the isoindolobenzazepine alkaloid family (Scheme 59). This *gem*-disulfur-directed 5-*exo*-trig radical cyclization strategy with subsequent mono-desulfurization of the cyclized product was also successfully applied to the total synthesis of mappicine ketone, a close analogue of camptothecin.¹³¹

Dihydro-thiapyrans undergo selective mono-desulfurization in the presence of Bu_3SnH and AIBN to deliver thiopyrans.¹³² An advanced intermediate for the synthesis of aprikalin,¹³³ a member of the potassium channel activator class of molecules, was prepared by this strategy (Scheme 60).

3.3 Cyclization reactions

Intermolecular addition of 1-alkylthio substituted radicals generated from dithioacetals to alkenes is not well documented. Fallis and Yadav reported a tin-mediated 5-*exo*-trig cyclization strongly suggesting that these types of intramolecular additions are possible.¹³⁴ Homolytic cleavage competes favorably with the





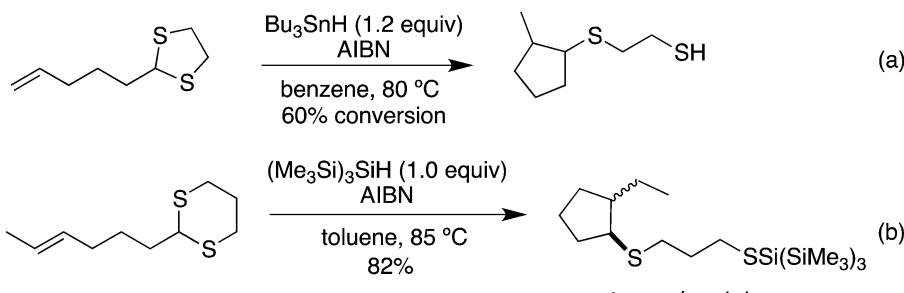
addition of the tin-centered radical onto the alkene moiety (Scheme 61, eqn (a)). Intramolecular trapping of the carbon-centred radical intermediate to form a 5-membered ring was also achieved in high yield by using $(\text{SiMe}_3)_3\text{SiH}$, a selective reagent for mono-desulfurization (*vide supra*) (Scheme 61, eqn (b)).¹²³ This approach is limited to internal alkenes since terminal alkenes afford mainly hydrosilylation products.

Similar results were obtained by Tsai and co-workers using diphenyldithioacetals. α -Sulfanyl radicals generated from diphenyldithioacetals give in general better yields than those

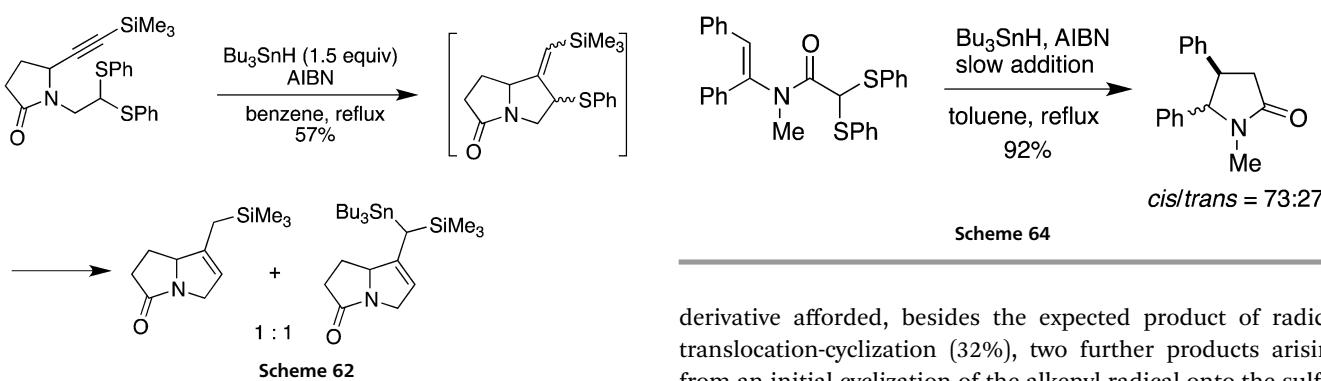
obtained from α -chloro- α -sulfanyl precursors. The best results are obtained with substrates presenting an electron-poor olefin.^{135,136} Cyclization onto an alkynyl silane was used to form the bicyclic skeleton of pyrrolizidine alkaloids (Scheme 62). In this process, the intermediate sulfide undergoes desulfurization due to its allylic character. However, the competitive formation of an allylstannane *via* allylic homolytic substitution is also observed.¹³⁷

The radical cyclization of thioacetals onto activated alkenes was also reported in the β -lactam series starting from dipropylthioacetal¹³⁸ (Scheme 63, eqn (a)) as well as cyclic dithioacetal.^{139,140} Similarly, ethylthio substituted alkyl radicals generated from dithioacetals underwent cyclization onto oxime ethers affording aminocyclopentane derivatives (Scheme 63, eqn (b)).¹⁴¹ In this case, the use of standard conditions led only to the recovery of the starting material and a large excess of Bu_3SnH together with 2.5 equivalents of AIBN had to be employed in order to obtain the cyclized product in high yield. No desulfurization of the final compound was observed under these conditions.

Examples of cyclization onto enamides in a 5-*endo* mode were reported (Scheme 64). A slow addition of Bu_3SnH and AIBN was used in order to limit the hydrogen atom abstraction from the tin hydride by the stabilized radical intermediate prior to cyclization. The presence of a carbamoyl substituent favors the formation of the fully desulfurized product. In this series,



Scheme 61



dithioacetals gave better results than the corresponding gem-dichloro precursors.^{142,143}

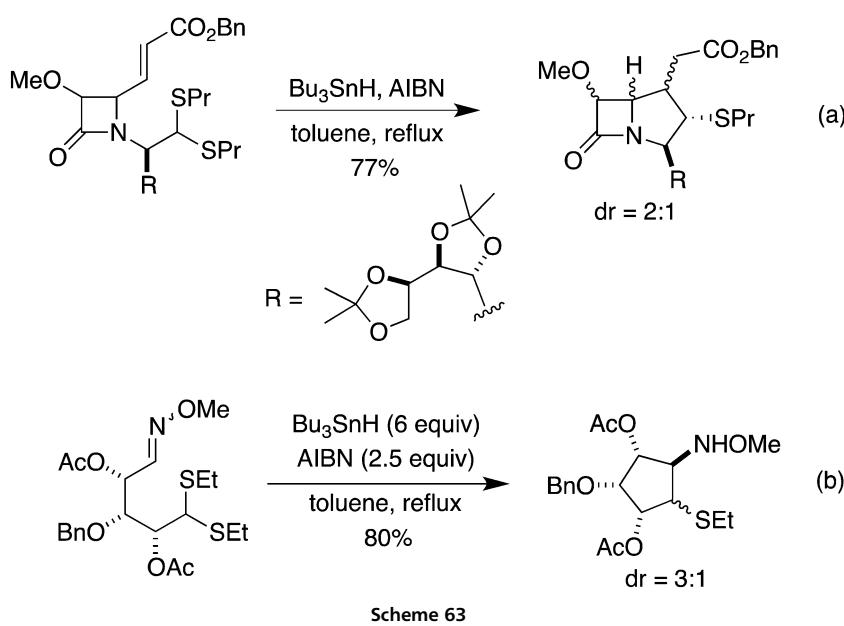
3.4 Homolytic substitution involving alkenyl radicals

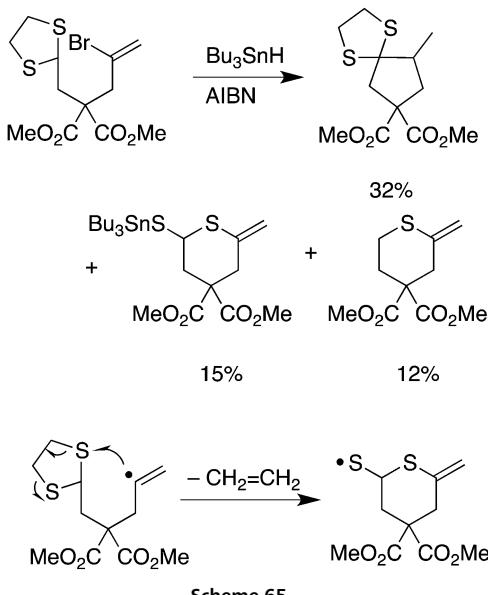
In the course of their studies on 1,5-hydrogen transfer involving dithioacetals, Curran and coworkers observed unexpected products resulting from intramolecular homolytic substitution at a sulfur atom.¹⁴⁴ The reaction conducted on a 1,3-dithiolane

derivative afforded, besides the expected product of radical translocation-cyclization (32%), two further products arising from an initial cyclization of the alkenyl radical onto the sulfur atom of the dithiolane (Scheme 65).

4 O,S-Acetals

Radical desulfurization of hemithioketals represents an efficient approach for the generation of α -alkoxy radicals. The latter can either be reduced by H-abstraction from a hydrogen donor, or can engage in carbon–carbon bond forming processes. This method has been extensively applied in the total





Scheme 65

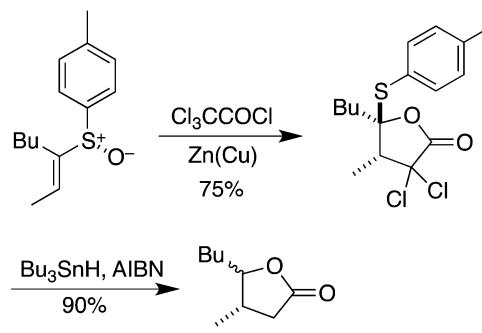
syntheses of complex polycyclic ethers such as brevetoxin A and B, ciguatoxin, gambierol, and gymnocyn A.

4.1 Reductive desulfurization

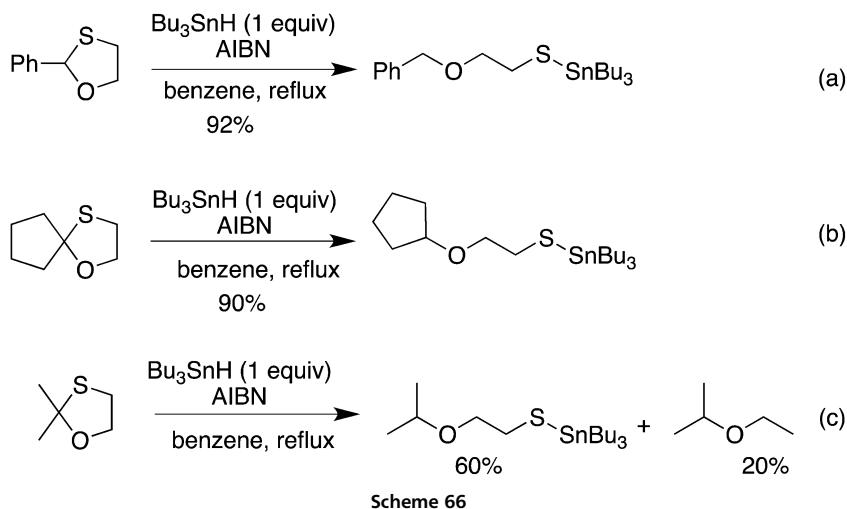
Gutierrez and co-workers studied the reductive desulfurization of oxathiolanes with Bu_3SnH and AIBN (Scheme 66). The 1,2-oxathiolanes were easily prepared by condensation of aldehydes and ketones with mercaptoethanol. In contrast to the related 1,3-dithiane and 1,3-dithiolane, for which the selective cleavage of one of the two carbon–sulfur bonds is achieved without any over-reduction, the efficiency of the cleavage of the carbon–sulfur bond in the corresponding 1,2-oxathiolanes is substrate-dependent. Indeed, the expected β -alkoxyethyl tributyltin sulfide obtained by reductive desulfurization is often contaminated by various amounts of the corresponding desulfurized alkyl ethyl ether (Scheme 66, eqn (c)). Surprisingly, the reaction conducted in the presence of two equivalents of

Bu_3SnH gave only poor yield of the desulfurized ether. Destannylation of the β -alkoxyethyl tributyltin sulfides could be achieved on silica gel.¹¹⁰

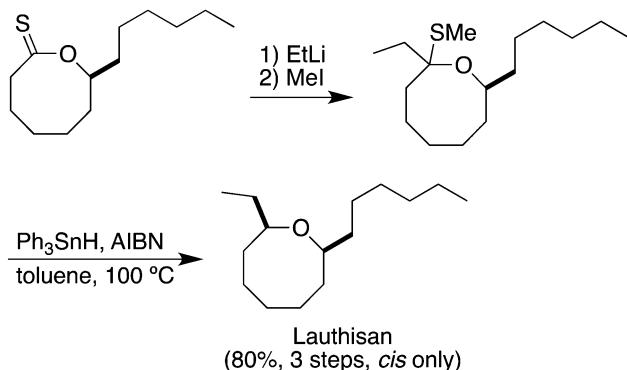
Marino and co-workers developed an elegant approach to γ -arylthiobutyrolactones based upon a highly stereoselective [3,3] sigmatropic rearrangement involving the adduct formed between dichloroketene and a vinylsulfoxide.¹⁴⁵ The use of an optically pure vinylsulfoxide allows rapid access to optically enriched γ -arylthiobutyrolactones.^{146–148} This methodology was employed for the total synthesis of optically pure natural products^{149,150} and intermediates.^{151–153} Selective removal of the chlorine atoms was achieved with aluminium amalgam and zinc–copper couple without cleavage of the arylthio group. Treatment of the chlorinated lactones with freshly prepared RANEY® nickel afforded the dechlorinated and desulfurized γ -butyrolactones.^{146,151} Dechlorination–desulfurization could be achieved by using an excess of Bu_3SnH in toluene and AIBN as a radical initiator (Scheme 67). Selective dechlorination using Bu_3SnH and AIBN without desulfurization was also reported.¹⁵⁰ By controlling the *E/Z* stereochemistry of the starting enantiomerically pure alkylsulfoxide, Kosugi, Uda, and co-workers have prepared both enantiomers of β -alkyl- γ -butyrolactones.¹⁵²



Scheme 67



Scheme 66



Scheme 68

Nicolaou and co-workers reported a three-step sequence to convert macrolactones into the corresponding cyclic ethers. The former are easily available using standard procedures for macro-lactonization, whereas the formation of macrocyclic ethers is more challenging. Nucleophilic addition of organometallic reagents onto macrocyclic thionolactones, followed by electrophilic trapping of the resulting thiolate anions with methyl iodide, gives mixed thioketals that can be easily desulfurized. The success of the reaction lies in the thermal stability of the tetrahedral intermediate obtained by nucleophilic addition onto the thionolactone. Under the same reaction conditions, the corresponding macrolactones generally undergo a ring-opening process due to the high reactivity of the tetrahedral intermediate.¹⁵⁴ The reaction is quite general, leading to medium and large-ring ethers in good overall yields. Interestingly, the reductive desulfurization with an excess of Bu_3SnH or Ph_3SnH and AIBN in refluxing toluene is highly *cis* diastereoselective in eight-membered ring systems (Scheme 68). The preparation of 14-membered macrocyclic ethers using the same strategy is not stereoselective.¹⁵⁵

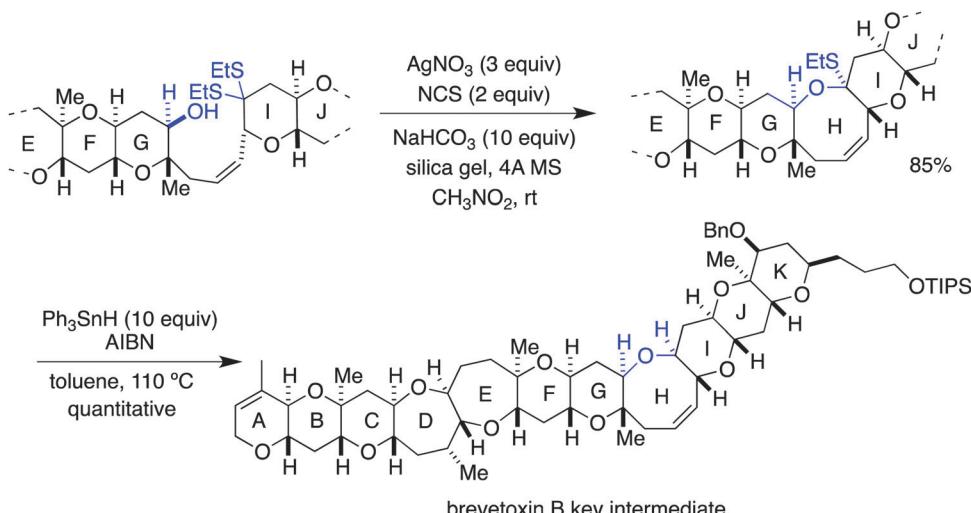
The 8-membered ring cyclic ether skeleton is found in naturally occurring polycyclic ethers such as brevetoxin A and B.

Due to several factors that disfavor the cyclization, including entropy and transannular interactions, few methods are available for the formation of these medium-ring systems. Nicolaou and co-workers reported an efficient approach to the oxocene and oxocane ring systems based upon the cyclization of hydroxy dithioketals.¹⁵⁶ In the presence of a Lewis acid, hydroxy dithioketals led to the corresponding cyclic hemithioketals, either *via* a sulfonium ion intermediate or *via* a preassociative mechanism.¹⁵⁷ The choice of the reaction conditions proved to be crucial for the success of the cyclization and good results were obtained with silver salts in the presence of a base with or without *N*-chlorosuccinimide. Homolytic cleavage of the carbon-sulfur bond was best achieved in the presence of an excess of Ph_3SnH and AIBN in refluxing toluene. Reductive desulfurization using Bu_3SnH or the more hindered *t*- Bu_3SnH was also disclosed. This method was successfully applied in several approaches to brevetoxin B (Scheme 69)^{158,159} and ciguatoxin.¹⁶⁰ However, it was inefficient in the approach to brevetoxin A (*vide infra*).¹⁶¹

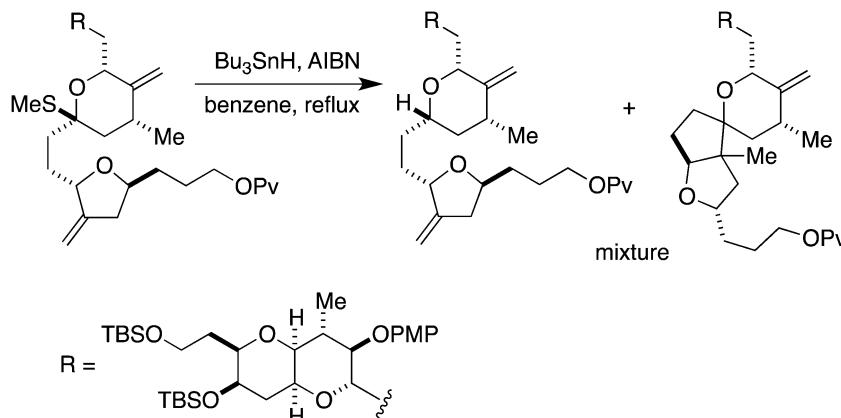
This method was also used for the formation of tetrahydro-pyran rings in polycyclic ethers as illustrated by Sasaki's and Rainer's efforts towards the synthesis of ciguatoxins^{162,163} and gamberiol.^{164–166} In the total synthesis of gymnocin A, four of the fourteen cyclic ether moieties present in the molecule were built according to this method.^{167–169}

With substrates containing unsaturations, rearranged products arising from a competing cyclization process are occasionally observed. These side-reactions are illustrated in Scheme 70 with the preparation of the C14–C38 segment of halichondrins reported by Kishi and co-workers.¹⁷⁰ Treatment of the cyclic hemithioketal with Bu_3SnH and AIBN led to a mixture of the desired desulfurized product contaminated by a substantial amount of a spirocyclic compound resulting from a 5-*exo*-trig cyclization onto the *exo*-methylene moiety.

In the total synthesis of brevetoxin A, Nicolaou and co-workers observed a rearrangement of the polyether skeleton during the desulfurization process. A 1,2-alkenyl shift involving



Scheme 69



Scheme 70

formation of a transient cyclopropylmethyl radical takes place (Scheme 71).¹⁶¹

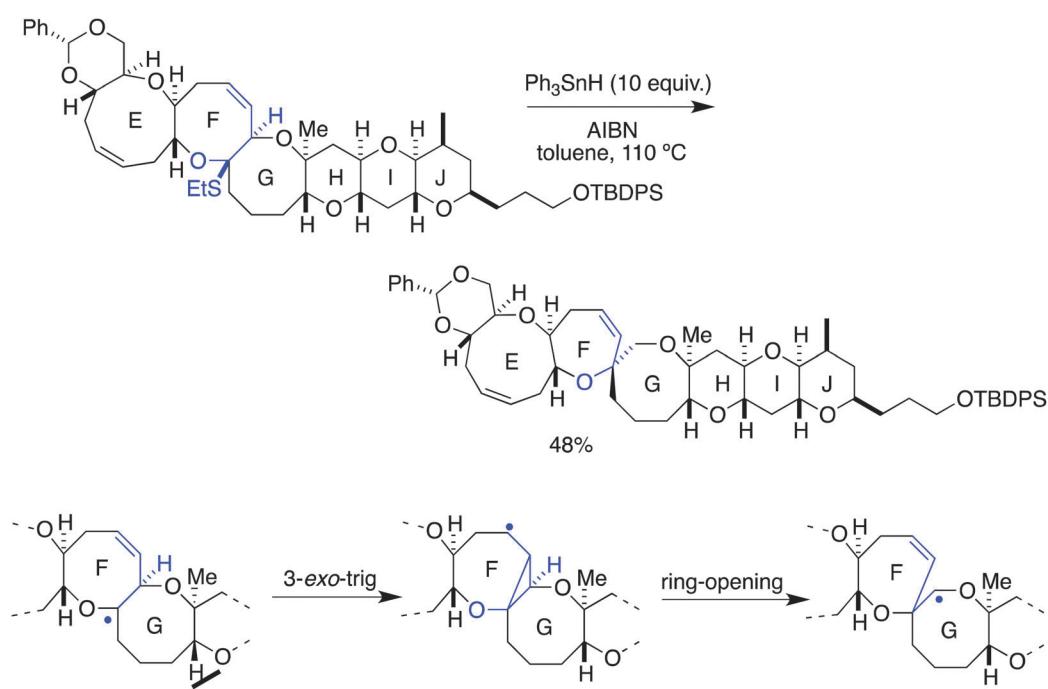
Although the aforementioned cyclization and rearrangement examples were undesired, the intramolecular trapping of the α -alkoxy radicals generated from *O,S*-acetals and ketals allows effective formation of 5- and 6-membered rings. A selection of examples will be briefly discussed in the following section.

4.2 Cyclization reactions and intermolecular trapping

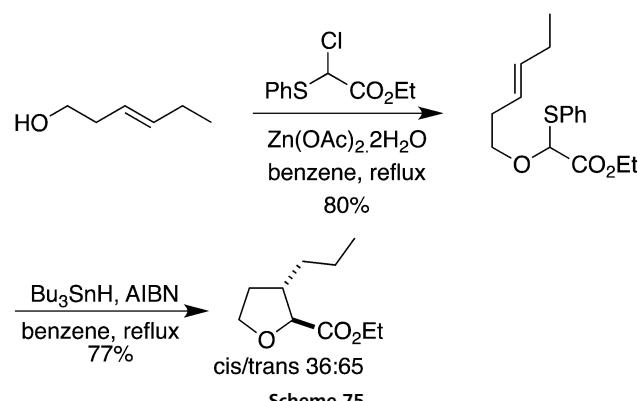
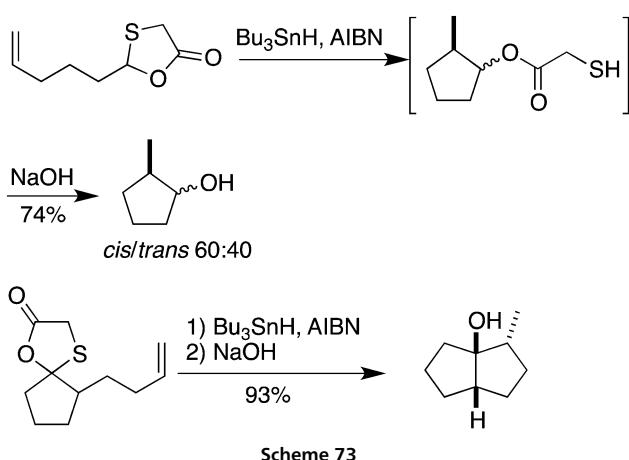
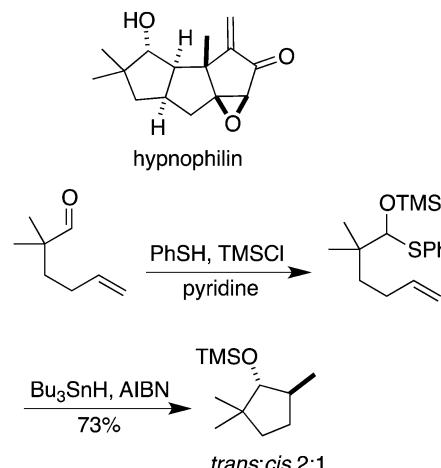
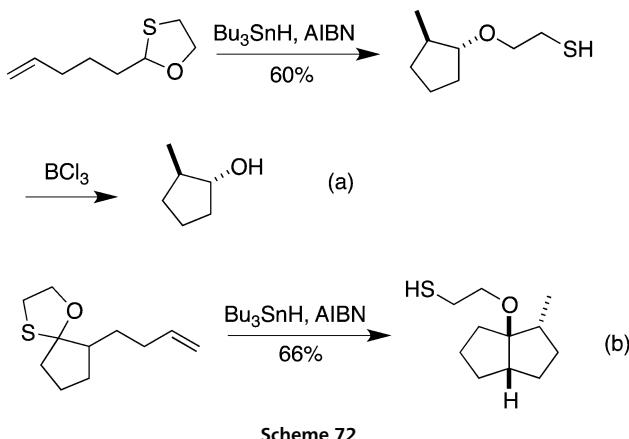
The cyclization of hemithioketals and hemithioacetals was investigated by Fallis and Yadav.¹³⁴ The hemithioacetal derived from hex-5-enal cyclized in good yield in the presence of Bu_3SnH and AIBN in refluxing benzene. Interestingly, the product was formed as a single diastereoisomer and, after cleavage of the ether with BCl_3 , *trans*-2-methylcyclopentanol

was obtained (Scheme 72, eqn (a)). Similarly, a fused-bicyclic compound was prepared in 66% yield *via* cyclization of a 1,3-dithiolane (Scheme 72, eqn (b)).

The cleavage of the ether side chain with BCl_3 is sluggish with hindered systems, thus hampering the access to cyclopentanols using this approach. To address this issue, the same authors investigated the generation of α -acyloxyl radicals from the related 1,3-oxathiolan-5-ones.^{171,172} The precursors were easily prepared from aldehydes and ketones and β -mercaptopropanoic acid. The cyclization of 1,3-oxathiolan-5-ones possessing an alkenyl side chain was achieved by slow addition of Bu_3SnH and AIBN. Treatment of the cyclized product with NaOH liberated the free alcohol. Monocyclic as well as fused- and bridged-bicyclic cyclopentanols and cyclohexanols were prepared by this procedure (Scheme 73). In contrast to the cyclization of related 1,3-oxathiolanes, which led to *trans* cyclopentanols, moderate stereocontrol



Scheme 71



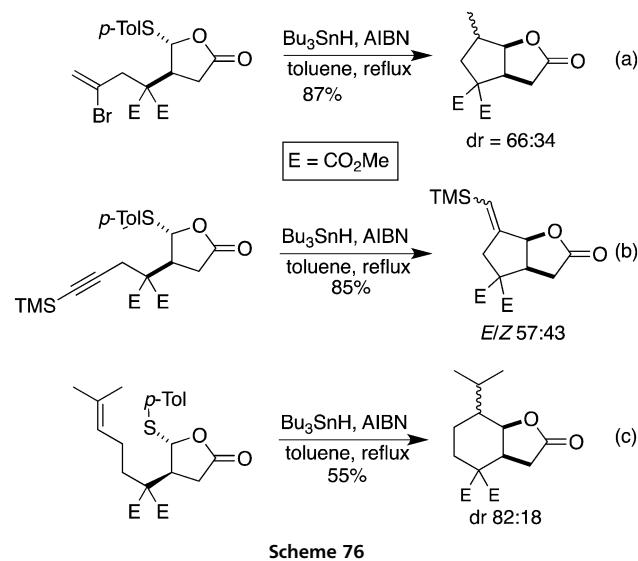
in favour of the *cis* isomer was observed in the 1,3-oxathiolan-5-one series.

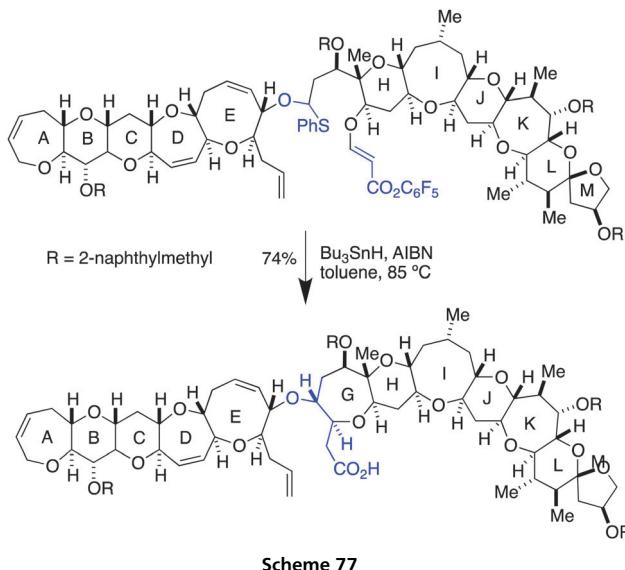
For their synthesis of the linear triquinane hypnophilin, Curran and co-workers investigated the use of hemithioacetals to generate α -alkoxy radicals. ¹⁷³ The cyclization reaction was tested on a model substrate easily prepared from the corresponding aldehyde. The cyclization with Bu_3SnH afforded the silylated cyclopentanol in 73% (Scheme 74) whereas direct reductive cyclization of the aldehyde precursors using Li/NH_3 or SmI_2 in THF led to significant amounts of the uncyclized alcohol. However, the desired hemithioacetal precursor required for the total synthesis of hypnophilin could not be prepared.

According to Speckamp, oxacyclic esters are efficiently prepared from simple acyclic alcohols by condensation with 2-chloro-2-(phenylthio)acetic acid ethyl ester followed by a radical desulfurization–cyclization sequence. ¹⁷⁴ Tetrahydrofurans (Scheme 75), fused-bicyclic tetrahydrofurans as well as tetrahydropyrans were prepared following this method.

Following their reports on the preparation of γ -arylsulfanylbutyrolactones from vinylsulfoxides and dichloroketene, Marino and co-workers prepared enantiomerically enriched γ -arylsulfanylbutyrolactones having a pendant alkenyl- or alkynyl side chain. Desulfurization was achieved in the presence of a slight excess

of Bu_3SnH and AIBN in refluxing toluene. The resulting α -acyloxy radicals cyclized to form 5- and 6-membered rings in moderate to high yields (Scheme 76, eqn (a)–(c)). ¹⁴⁸ In the



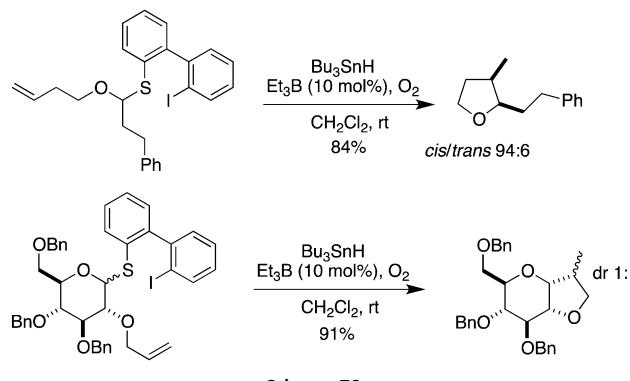
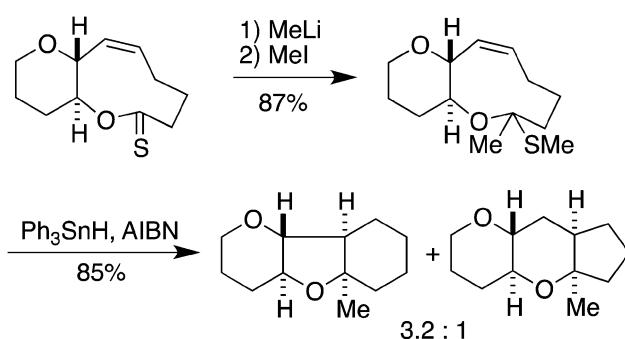


first example (Scheme 76, eqn (a)), the formation of the saturated product indicates that debromination occurred prior to homolytic substitution at sulfur.

Cyclization of α -alkoxy radicals generated from hemithioketals has also been employed in complex molecules. For instance, Hirama and co-workers employed a 7-*exo*-trig cyclization to form the 7-membered ring G of ciguatoxin.¹⁷⁵ The α -alkoxyl radical was generated from the corresponding acyclic hemithioketal with Bu_3SnH in toluene. The presence of the electron-withdrawing group on the radical trap on ring H is crucial in order to favour the desired 7-*exo* cyclization over a 6-*exo* cyclization onto the unactivated alkanyl side chain present on ring E (Scheme 77). Under the optimized reaction conditions, the desired 7-membered ring carboxylic acid was isolated in 74% yield accompanied by 7% of the 6-*exo* cyclization product.

Nicolaou and co-workers reported transannular cyclizations for the formation of tricyclic systems from bicyclic thionolactones.¹⁵⁴ Treatment of the thionolactone with MeLi followed by electrophilic trapping with methyl iodide afforded a mixed thioketal that, upon treatment with Ph_3SnH and AIBN, cyclized to give a 3.2:1 mixture of isomers in good yield (Scheme 78).

Maruoka and co-workers used their *o*-iodobiphenylthio group (see Section 2, Schemes 20 and 21) for the generation

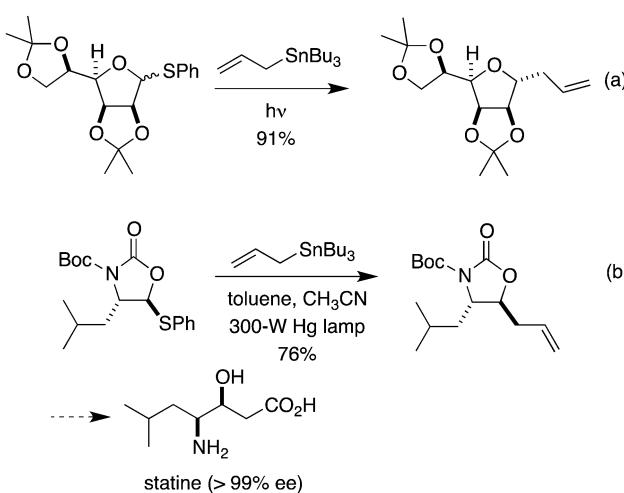


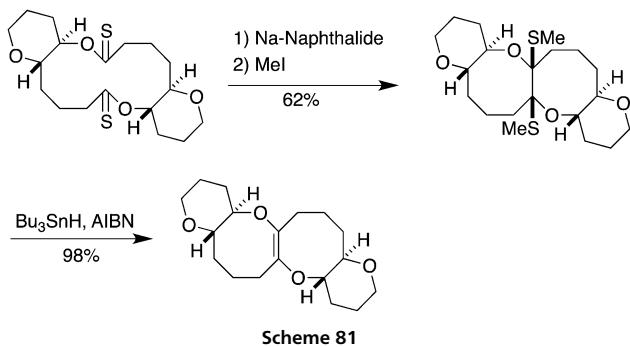
of α -alkoxyl radicals under mild conditions.⁷⁶ Under $\text{Et}_3\text{B}/\text{O}_2$ initiation conditions, cyclizations leading to tetrahydrofurans were performed at room temperature in high yields with moderate to high levels of diastereoselectivity (Scheme 79).

Although not well documented, the intermolecular trapping of α -alkoxy radicals is possible. During their studies on the radical cyclization of oxathiolanones (Scheme 73), Yadav and Fallis reported intermolecular allylation with allyltributyltin and methallyltributyltin. Under their reaction conditions, intermolecular trapping of the α -acyloxy radical with the allyltin reagent competes favourably with the cyclization reaction.^{171,172} Keck and co-workers stressed the advantages of hemithioketals in terms of ease of preparation and stability compared to the corresponding α -haloethers in allylation reactions at the anomeric centre of glycosides (Scheme 80, eqn (a)).¹⁷⁶ Under modified Keck' allylation conditions, Kano and co-workers were able to access optically pure 1,2-amino alcohols from 5-(phenylthio)oxazolidin-2-ones derived from (*S*)-amino acids (Scheme 80, eqn (b)).¹⁷⁷

4.3 Fragmentation reactions

α -Alkoxy β -alkylthio radicals undergo β -fragmentation reactions, thus leading to the corresponding enol ethers. Based on this idea, Nicolaou and co-workers developed a simple





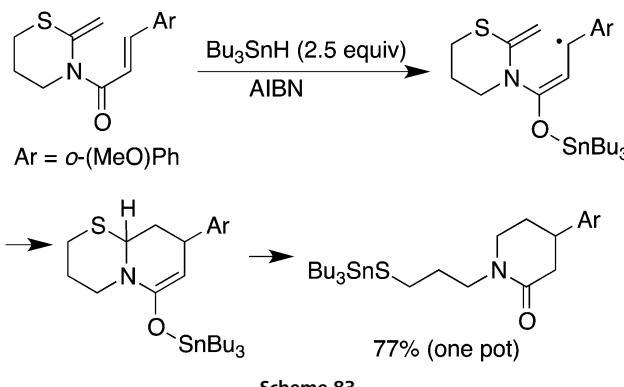
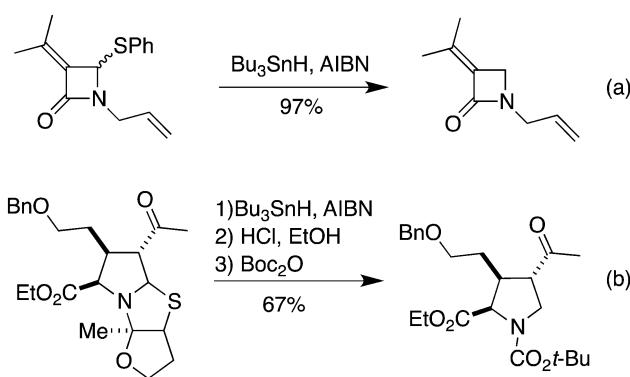
method to access *cis*-fused oxobicyclic systems from macrodithionolactones (Scheme 81).^{178,179}

5 N,S-Acetals

N,S-Acetals represent stable precursors for 1-amino- and amido-substituted carbon-centred radicals.¹⁸⁰ The precursors can be conveniently prepared from the corresponding *N,O*-acetals in the presence of a Lewis acid and a thiol or under Mitsunobu conditions. Intramolecular Pummerer reactions also allow the formation of *N,S*-acetals with simultaneous creation of a new carbon–nitrogen bond.^{38–39,181,182}

5.1 Reductive desulfurization

α -Acylamino radicals are generated by treatment of phenylthio or alkylthio lactams with Bu_3SnH in the presence of AIBN (Scheme 82, eqn (a)).^{50,183–185} Kraus and co-workers reported an approach to α -allokainic acid based upon a diastereoselective 1,3-cycloaddition, followed by the reductive cleavage of the carbon–sulfur bond (Scheme 82, eqn (b)).¹⁸⁵ This reaction sequence highlights the efficiency of radical desulfurization since neither RANEY® nickel nor Li/NH₃ gave satisfactory results. Monn and Valli applied a similar approach for the synthesis of kainic acid.¹⁸⁶ The reaction conditions are compatible with various functionalities, including enol ethers, which are reduced when RANEY® nickel is used,¹⁸⁷ and acyclic-sugar purine nucleosides, which are prone to undergo sugar-base cleavage under most standard desulfurization conditions.¹⁸⁸

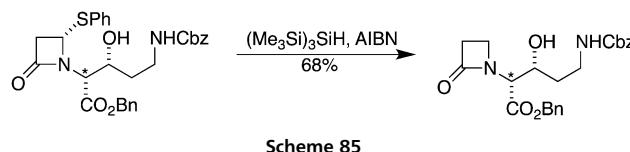
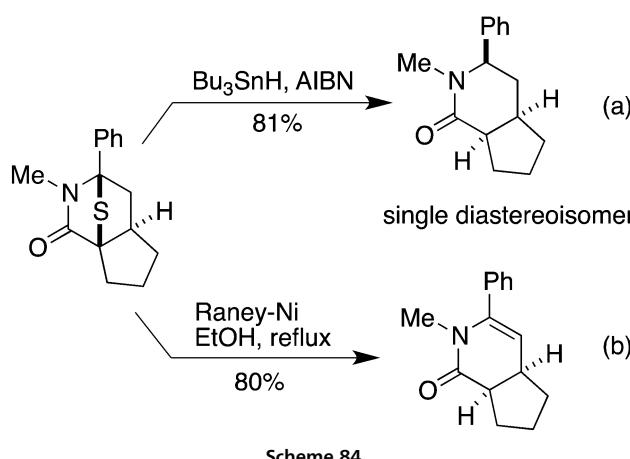


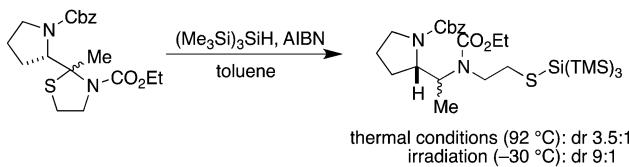
A sequential process involving 6-*endo* cyclization of an allylic radical generated by addition of a stannyl radical to an unsaturated amide followed by a desulfurization gave a δ -valerolactam in good yield (Scheme 83).¹⁸⁹

Reductive desulfurization of *N,S*-acetals using Bu_3SnH advantageously replaced RANEY® nickel when the latter promoted concomitant dehydrogenation leading to unsaturated products.^{190,191} The following examples reported by Padwa and co-workers highlight the complementarity of the two approaches (Scheme 84, eqn (a) and (b)).¹⁹¹ The complete diastereoselectivity of the tin hydride process is remarkable (Scheme 84, eqn (a)).

Reductive desulfurization of *N,S*-acetals under tin-free conditions is also possible by using tris(trimethylsilyl)silane. An approach to ¹⁴C-labelled proclavaminic acid is depicted in Scheme 85.¹⁹²

The tris(trimethylsilyl)silane-mediated reductive desulfurization of *N,S*-acetals and *N,S*-ketals can be achieved in high yields in toluene under thermal¹⁹³ or photochemical initiation (300 nm





Scheme 86

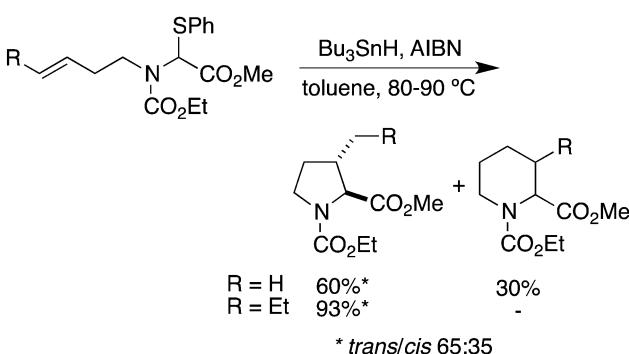
in a Rayonet reactor).¹⁹⁴ Under photochemical conditions, the desulfurization can be conducted at low temperature, thus allowing the diastereoselectivity of the hydrogen atom abstraction from the silane to be enhanced to synthetically useful levels, as illustrated by the challenging examples reported by Arya and Lesage in the acyclic series (Scheme 86).¹⁹⁴ However, the presence of terminal alkenes is not compatible with the use of tris(trimethylsilyl)silane since hydrosilylation is faster than the desired desulfurization.¹⁹⁵

5.2 Cyclization reactions

α -Aminoalkyl and α -amidoalkyl radicals are frequently used for cyclization reactions. Since this topic was reviewed in 1996¹⁸⁰ and 2004,¹⁹⁶ the following section will be limited to selected examples that give a brief overview of the synthetic potential of *N,S*-acetals for the construction of nitrogen-containing heterocycles.

Hiemstra, Speckamp and co-workers have extensively investigated the reactivity of acyclic α -amidoalkyl radicals generated from the corresponding *N,S*-acetals in the presence of Bu_3SnH and AIBN. Pyrrolidinones, piperidinones, as well as indolizidinones were prepared from precursors having an alkenyl side chain. The regioselectivity of the cyclization step is strongly influenced by the substitution at the alkenyl moiety and by the structure of the precursor (cyclic *versus* acyclic). Both 5-*exo*-trig and 6-*endo*-trig cyclizations are observed with terminal alkenes. The regioselectivity can be driven to the exclusive formation of the 5-membered ring by using 1,2-disubstituted alkenes (Scheme 87).^{197,198} Alkynes are good radical traps under these reaction conditions whereas nitriles fail to react.

Similarly, cyclic α -acylamino radicals cyclize onto olefins, alkynes, and allenes to give indolizidinones and pyrrolizidinones (Scheme 88).^{199–201} The success of the cyclization of α -acylamino radicals onto alkynes in a 5-*exo* mode is highly



Scheme 87

dependent on the substitution at the alkyne moiety, the best results being obtained with sterically demanding groups such as trimethylsilyl and *tert*-butyl. In all cases, non-cyclized desulfurization products are isolated, even under high dilution of tin hydride (Scheme 88, eqn (b)).^{202,203} Interestingly, 6-*exo* cyclizations are more efficient (Scheme 88, eqn (c)). Padwa showed that *N*-benzyl and *N*-sulfonyl analogues fail to cyclize in a 5-*exo*-trig mode and gave only moderate yields in 6-*exo*-trig cyclizations.^{204,205}

Keck and co-workers prepared a pyrrolizidinone in moderate yield under photochemical activation of an allylstannane-containing substrate (Scheme 89).²⁰⁶ In this case, ionic cyclizations involving an *N*-acyliminium ion proved to be more efficient.

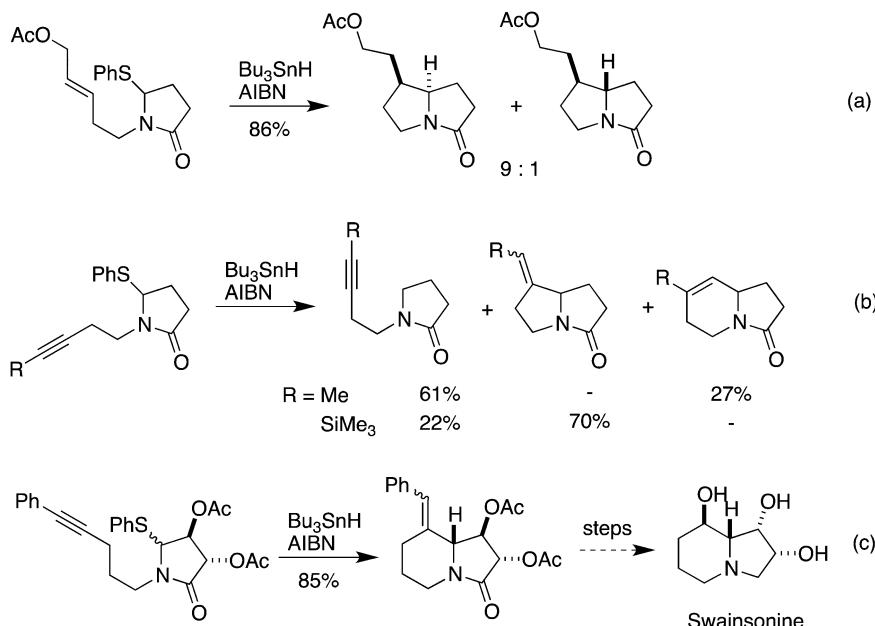
Corey and co-workers reported an enantioselective synthesis of (+)-biotine. A radical 5-*exo*-dig cyclization was employed to install the fused-bicyclic skeleton (Scheme 90).⁶⁰ The use of $(c\text{-}C_6H_{11})_3SnH$ instead of Bu_3SnH effectively minimized competing side-reactions resulting from the addition of trialkyltin radicals to the alkyne moiety. Other precursors for the radical cyclization (*e.g.* the phenylselenide or dithiobenzoate analogues) were less efficient due to their thermal instability.

Bridged-bicyclic skeletons can be prepared *via* cyclization of α -acylamino radicals, as illustrated by the formal total synthesis of epibatidine reported by Clive (Scheme 91).²⁰⁷

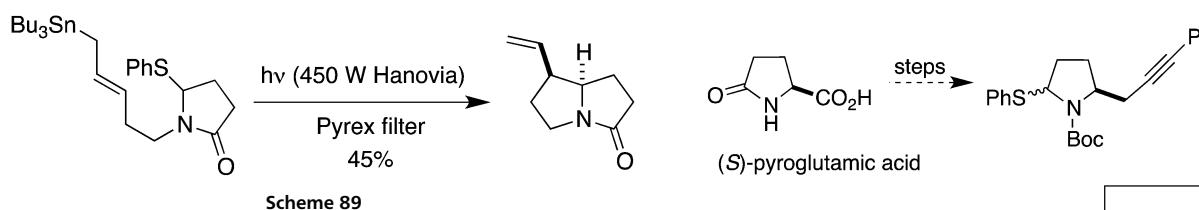
6-*Endo*-cyclizations are also described in the β -lactam series. For instance, Kametani and co-workers reported the preparation of carbacephams from 4-phenylthioazetidinones *via* a regioselective 6-*endo*-trig cyclization process (Scheme 92, eqn (a)).²⁰⁸ Similarly, an α -acylamino radical derived from *N*-phenylthiomethyl β -lactams was reported to cyclize *via* a 7-*endo* mode to give the corresponding fused-bicyclic β -lactam in moderate yield (Scheme 92, eqn (b)).^{209,210} Due to the azetidinone ring, unfavourable strain in the transition state disfavours the 6-membered ring relative to the 7-membered ring.²¹¹ In contrast to the acyclic substrates reported by Hiemstra and Speckamp, the cyclization onto an alkynyl side chain is more difficult in the azetidin-2-one series.²⁰⁸

Cyclizations of *N,S*-acetals with tris(trimethylsilyl)silane were investigated by Arya. With non-terminal alkenes, the competing hydrosilylation could be minimized and high yields were obtained from thiazolidine derivatives using AIBN as an initiator under either thermal¹⁹⁵ or photochemical conditions.¹⁹⁴ After purification, the silicon–sulfur bond was cleaved in the presence of tetrabutylammonium fluoride and the resulting thiolate anion engaged in a carbon–sulfur bond formation (Scheme 93).¹⁹⁵ Samarium(II) iodide allows desulfurization of *N,S*-acetals followed by intermolecular trapping of the α -amidoalkyl radical intermediate.²¹² However, this process does not involve homolytic substitution at the sulfur, and therefore, it lies beyond the scope of this review.

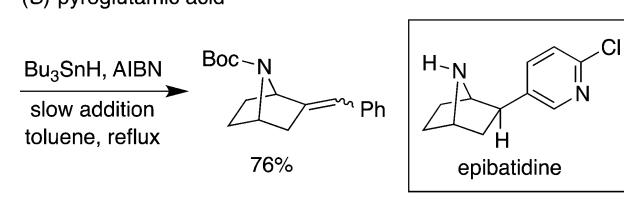
Additions of 1-amidoalkyl radicals onto electron-deficient alkenes are favored by polarity matching and enthalpic effects. Successful examples of cyclization involving 1-amidoalkyl radicals generated from *N,S*-acetals onto vinylphosphonates have been reported by Shibuya.²¹³ Hart and co-workers reported a spectacular example of cyclization onto an electron deficient



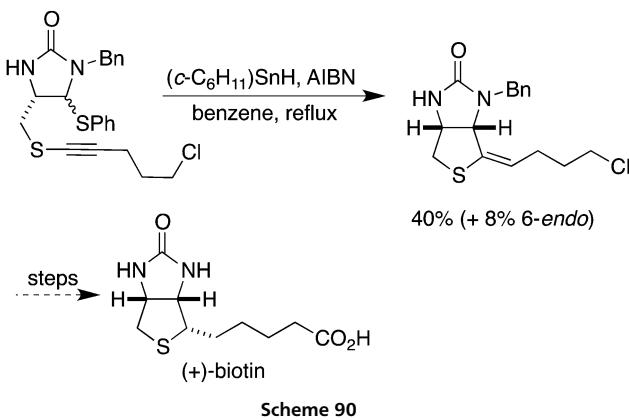
Scheme 88



Scheme 89



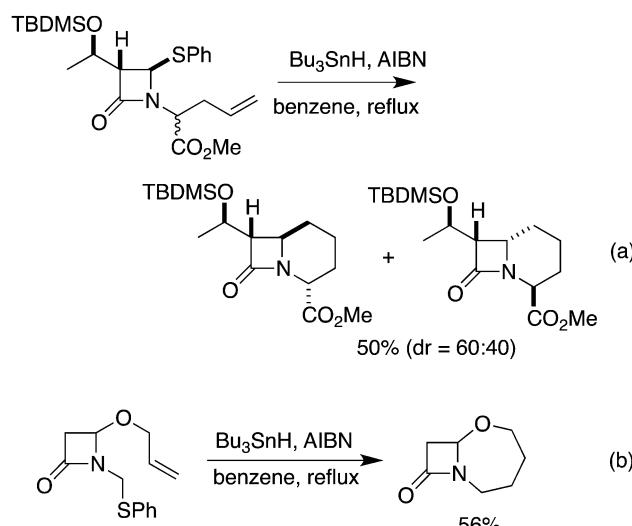
Scheme 91



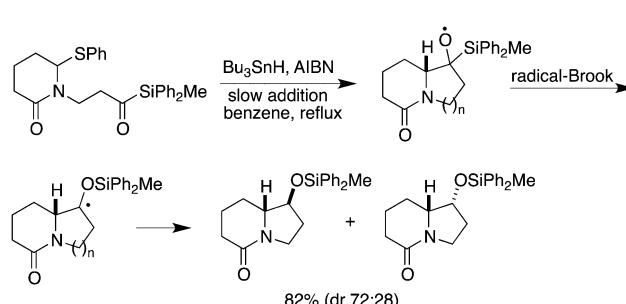
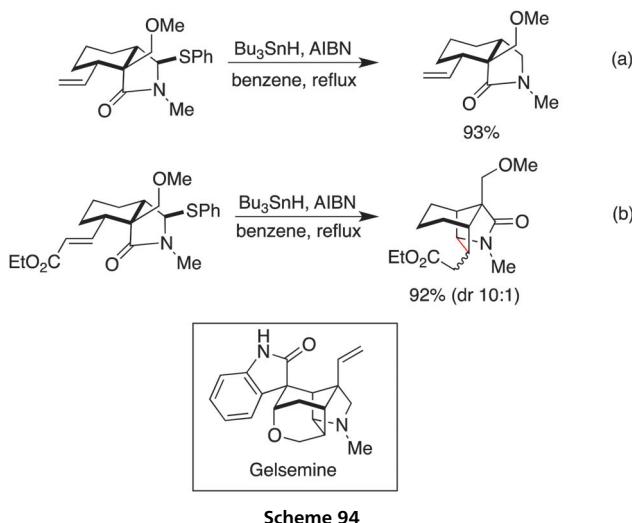
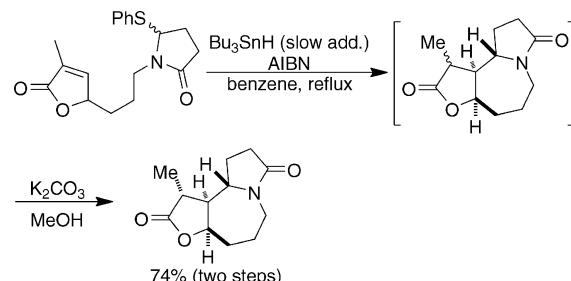
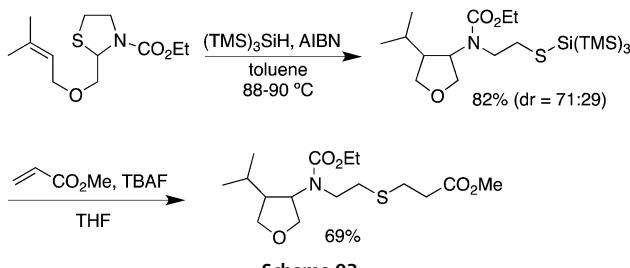
Scheme 90

alkene in their synthesis of gelsemine. On a model substrate, cyclization onto a non-activated alkene afforded exclusively the product of reductive desulfurization (Scheme 94, eqn (a)). The desired cyclization product was obtained in high yields when the alkene was activated by an ester group (Scheme 94, eqn (b)).²¹⁴ The total synthesis of gelsemine takes advantage of this observation and was completed *via* an efficient 5-*exo*-trig radical cyclization.^{215,216}

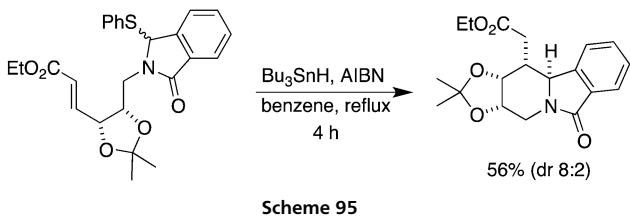
The presence of an electron-withdrawing group at the olefin terminus allowed a clean 6-*exo*-cyclization affording a



Scheme 92



sulfur is followed by addition onto the acylsilane. The resulting oxygen-centred radical undergoes radical-Brook rearrangement to give the α -silyloxy radical that abstracts a hydrogen atom preferentially from the less hindered face of the bicyclic system.



tetrahydropyrido[2,1-*a*]isoindolone without formation of the non-cyclized desulfurized product (Scheme 95).^{217–219} In this case, a relatively high concentration of tin hydride was tolerated (slow addition over only 10 minutes).

Khim and Schultz reported the synthesis of (–)-9,10-bis-*epi*-stemoamide based upon a 7-*exo*-trig radical cyclization. The cyclization was achieved in refluxing benzene using a slow addition of Bu_3SnH and AIBN over 24 h and gave the tricyclic skeleton as a mixture of epimers at C-10. Epimerization with K_2CO_3 in MeOH gave (–)-9,10-bis-*epi*-stemoamide in 74% over the two steps (Scheme 96).²²⁰ The same key step was used by Cossy and co-workers to prepare racemic 9,10-bis-*epi*-stemoamide, albeit in much lower yield.^{221,222}

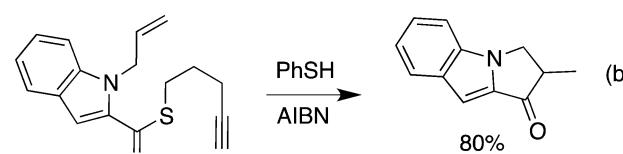
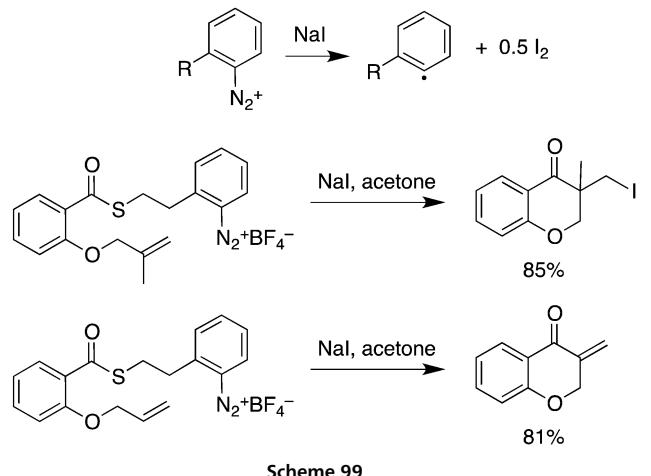
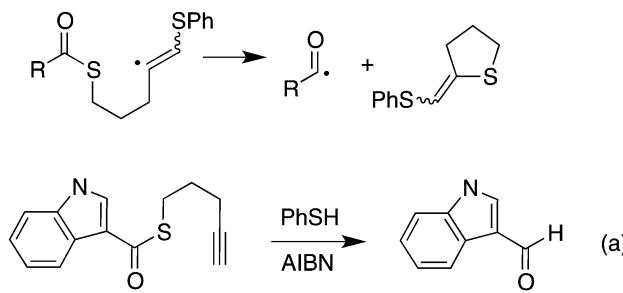
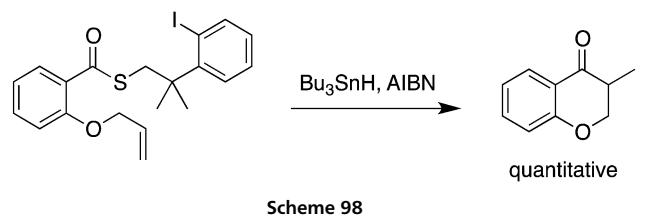
Tsai and co-workers reported an elegant approach to pyrrolizidinones, indolizidinones and quinolizidinones based upon the intramolecular addition of α -acylamino radicals onto acylsilanes (Scheme 97).²²³ Polyhydroxylated alkaloids were also prepared by this method.²²⁴ The homolytic substitution at

6 Thioesters

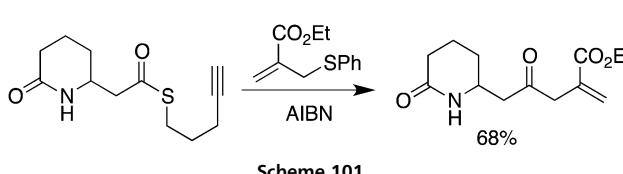
The formation of acyl radicals from simple thioesters *via* intermolecular homolytic substitution is inefficient. Selenoesters give more satisfactory results but are handicapped by the toxicity of organoselenium derivatives.²²⁵ As mentioned in the introduction (Section 1) and in analogy to thioether derivatives (Section 2), intramolecular homolytic substitution at the sulfur atom of thioesters takes place efficiently and useful preparative reactions are reported.⁶⁴ Depending on the nature of the substrates, the acyl radicals can either abstract a hydrogen atom to give the corresponding aldehydes, engage in carbon–carbon bond forming processes, or undergo an α -fragmentation leading to alkyl radicals.²²⁶

6.1 Acyl radicals

Crich and co-workers developed a method for the generation of acyl radicals from thioesters *via* an intramolecular homolytic substitution involving aryl radicals (Scheme 98). The thioesters are easily prepared by esterification of the corresponding carboxylic acid with the thiol. The *gem*-dimethyl substituents are present to favor the intramolecular homolytic substitution, thus limiting the competing direct hydrogen atom abstraction from the tin or silicon hydride. Generation of the corresponding aryl radical is carried out with Bu_3SnH or $(Me_3Si)_3SiH$ in the presence of AIBN and affords the cyclized products in good to high yields.²²⁶



Scheme 100



Scheme 100

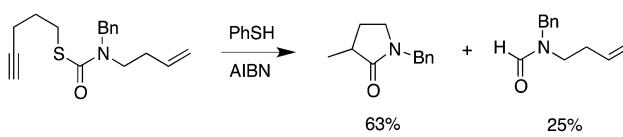
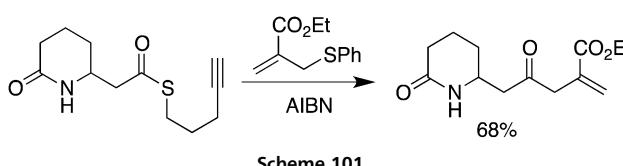
Treatment of diazonium salts with NaI in acetone offers an elegant tin free alternative for the generation of aryl radicals. After intramolecular homolytic substitution at sulfur, the acyl radical cyclizes and trapping of the cyclized radical with the iodine formed during the reduction of the diazonium salt affords the final product (Scheme 99). When a hydrogen atom is present at the α -position, elimination of HI leads to the isolation of the methylenechromanone.⁶⁹ Other reducing agents such as thiols and copper(I) salts can also be used.

Spagnolo and coworkers developed an alternative strategy for the generation of acyl radicals.^{227,228} In their approach, *S*-pent-4-yn-1-yl thioesters are treated with thiophenol and AIBN to furnish aldehydes resulting from direct hydrogen atom abstraction (Scheme 100, eqn. (a)) or products resulting from the cyclization of the intermediate acyl radicals followed by hydrogen atom abstraction (Scheme 100, eqn (b)).

This protocol is effective for cyclization onto alkenes but less efficient with azides. Crich and co-workers prepared γ - and δ -lactones via formation of acyl radicals using Spagnolo's precursors, followed by intermolecular allylation with an allylsulfide (Scheme 101). The thiyl radical generated via β -fragmentation during the last step of the allylation process propagates the radical chain, thus allowing allylation of acyl radicals to be carried out under tin-free conditions.²²⁹

Spagnolo and coworkers extended this approach to the generation of carbamoyl radicals. They prepared pyrrolidinones (Scheme 102) and azetidinones via 5-*exo* and 4-*exo* cyclization of *N*-benzylcarbamoyl radicals.²³⁰

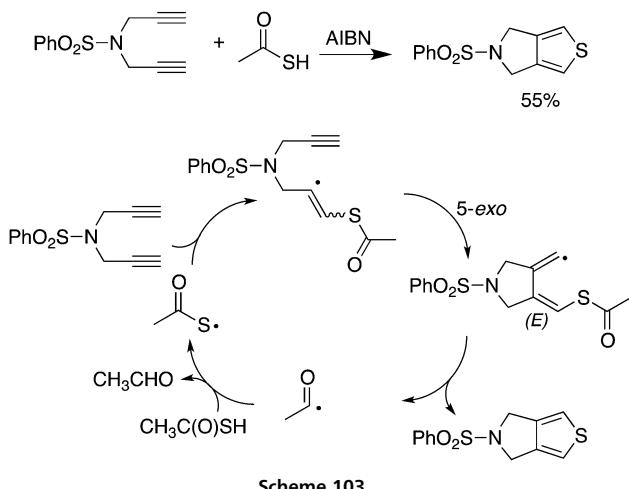
The formation of acyl radicals via homolytic substitution at sulfur can be used to prepare thiophene derivatives.



Padwa and co-workers reported that radical addition of thioacetic acid onto a bis-propargylic sulfonamide led to a pyrrolothiophene via a radical cascade involving addition of the sulfur-centred radical onto the carbon–carbon triple bond followed by a 5-*exo* cyclization. Finally, the resulting alketyl radical undergoes a homolytic substitution at the sulfur atom with simultaneous elimination of an acyl radical (Scheme 103).²⁰⁴ Only the *E*-isomer of the cyclized radical is suitable for the homolytic substitution. This might explain the moderate yield obtained in this transformation. The role of the acyl radical is to sustain the chain process and acetaldehyde is formed as a byproduct.

6.2 α -Ketenyl radicals

Starting from α,β -unsaturated thioesters, it is possible to generate acyl radicals that are in equilibrium with α -ketenyl radicals. Starting from 2-(*o*-iodophenyl)ethyl thioester, Pattenden prepared diquinane skeletons²³¹ and reported a formal synthesis of racemic modhephene involving a tandem transannulation-cyclization sequence to form the 3,3,3-propellane skeleton (Scheme 104).^{231,232}



This is illustrated by the preparation of a nor-triterpene derivative from the corresponding thioester (Scheme 105).²²⁶

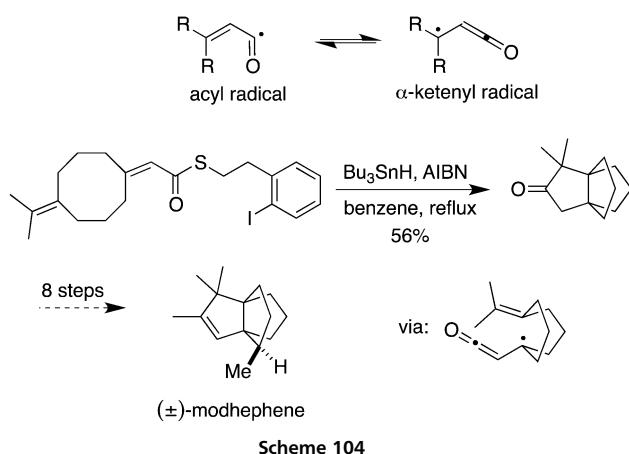
This process is of particular interest in the sugar series. For instance, Crich and co-workers used this approach to prepare selectively β -mannosides (Scheme 106).²³³

An elegant approach for the preparation of 6-deoxy sugars via the fragmentation of benzylidene acetals was also developed (Scheme 107).²³⁴ Similar regioselectivities were observed by Roberts in the thiol-catalyzed opening of bicyclic benzylidene acetals.²³⁵

7 Thiiranes and 1,2-dithietanes

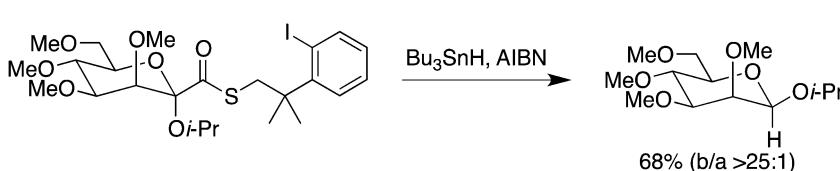
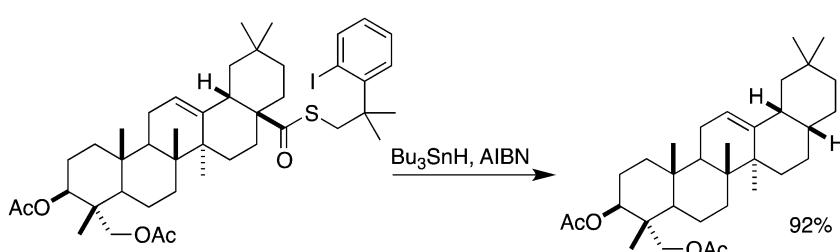
The reactivity of strained thioethers such as thiiranes and 1,2-dithietanes under radical conditions has received only moderate attention. Thiiranes undergo desulfurization to give alkenes under various conditions, including methods using alkyl iodides,²³⁶ trivalent phosphorus compounds,^{237,238} alkyl lithiums,²³⁹ and P_2I_4 .²⁴⁰ Extrusion of the sulfur atom by thermolysis is also feasible.²³⁸ The use of zinc in acetic acid, lithium in ethylamine and RANEY® nickel has also been reported, although in these cases partial or complete reduction into the corresponding alkanes has been observed.²⁴⁰ On the other hand, thiiranes readily undergo desulfurization to give olefins in high yield upon reaction with Bu_3SnH and AIBN.²⁴⁰ High yields are generally obtained from mono-, di-, tri-, and tetraalkyl-substituted thiiranes,^{240,241} as well as with α -alkoxythiiranes and thiiranes having an alkenyl or alkynyl side chain (Scheme 108).²⁴¹ Surprisingly, the reaction is not general in scope since no reaction has been observed with some thiiranes possessing electron-withdrawing groups.²⁴¹ The desulfurization with Bu_3SnH appeared to be non-stereospecific, *cis*-disubstituted thiiranes leading preferentially to the *E*-olefins (Scheme 108, eqn (c)).²⁴¹

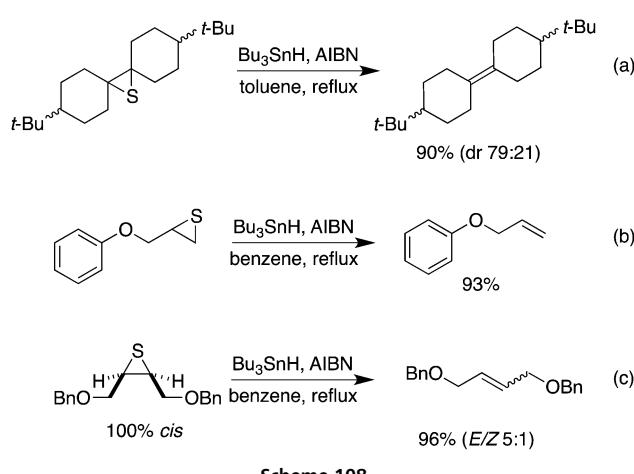
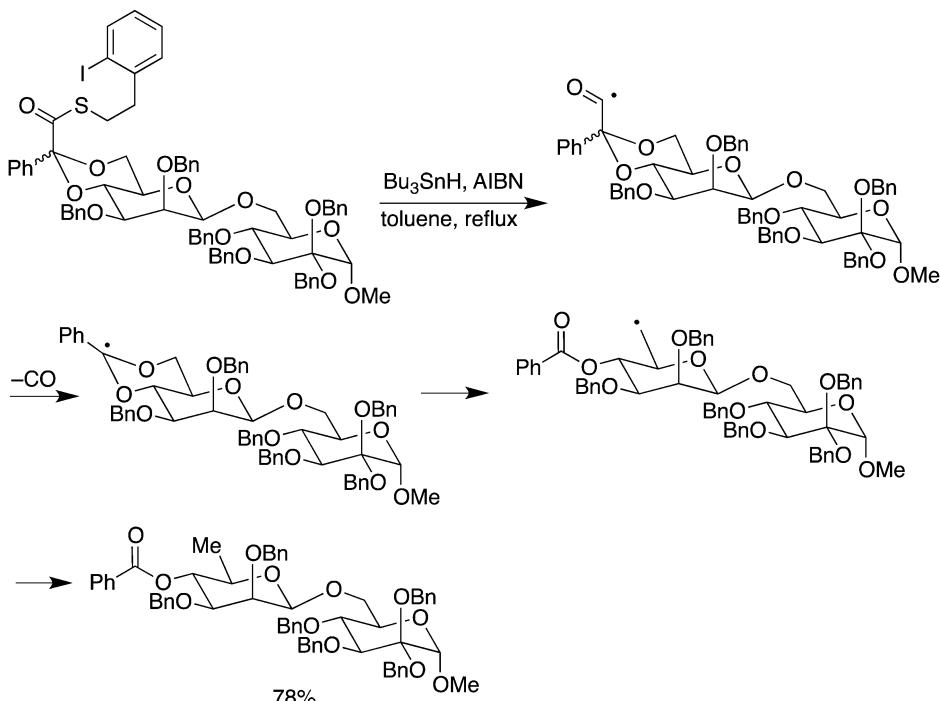
From a mechanistic point of view, the desulfurization of thiiranes is closely related to the desulfurization of simple thioethers. The attack of the tin-centred radical onto the sulfur atom induces



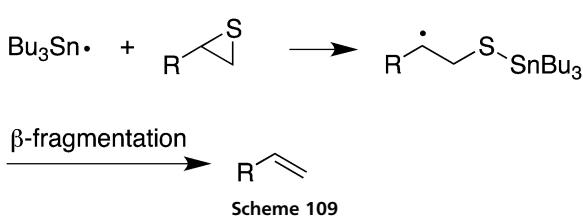
6.3 Alkyl radicals

Acy radical s derived from α -branched carboxylic acids can decarbonylate to generate secondary and tertiary alkyl radicals.²²⁵

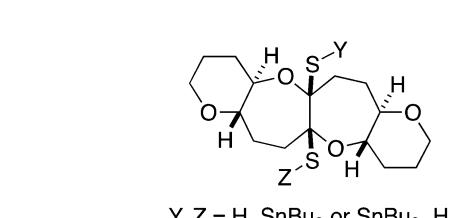
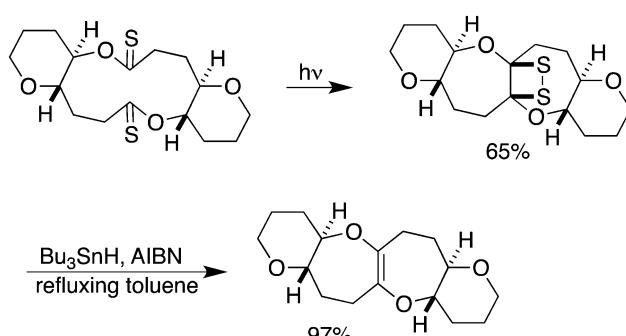




the ring opening of the thiirane, leading to a β -thioalkyl radical which undergoes β -fragmentation with expulsion of a thiy radical to give the olefin (Scheme 109). All attempts to trap the β -thioalkyl radical intermediate in an intra- or intermolecular fashion have been unsuccessful, even when a slow addition of the thiirane to a refluxing solution of Bu_3SnH in



benzene was used. The absence of reactivity of the related epoxides and episulfoxides under these reaction conditions demonstrates that the success of this process lies not only in the ring strain, but also in the high affinity of the tin atom for the sulfur atom of thioethers. Competition experiments between a thiirane and benzyl 4-pentenyl sulfide demonstrated that the ring strain has a beneficial effect on the rate of the homolytic substitution since no desulfurization of the benzyl alkyl thioether was observed.²⁴¹



Although 1,2-dithietanes are unstable, Nicolaou and co-workers were able to prepare a 1,2-dithiethane by irradiation of a dithiolactone. Desulfurization with Bu_3SnH and AIBN in refluxing toluene afforded the alkene in high yield (Scheme 110).²³⁸ The intervention of a tin-centred radical was not rigorously demonstrated since the extrusion of the sulfur atom could also be achieved by simple thermolysis, albeit at a higher temperature. A plausible mechanism for the alkene formation could involve the formation of an intermediate 2-((tributylstannyll)thio)-alkanethiol that undergoes a homolytic substitution followed by a β -fragmentation process.

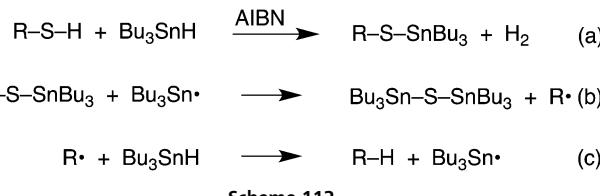
8 Thiols

8.1 Reductive desulfurization of alkanethiols

Thiols are scarcely used as precursors of C-centred radicals since they usually act in a different way in radical processes by transferring rapidly a hydrogen atom to alkyl radicals. Alkanethiols can be reduced by tin hydrides into the corresponding alkanes.^{242–244} Vedejs and Powell showed that primary and secondary mercaptans are desulfurized in good to high yields by using Bu_3SnH and AIBN (Scheme 111, eqn (a)), whereas reduction of the corresponding methylsulfides was less efficient.²⁴³ The authors applied this reaction in the final step of their total synthesis of phoracantholide I, a 10-membered ring macrolactone (Scheme 111, eqn (b)).

No detailed mechanistic investigation is available for this reaction, however, based on experimental observations of Pang and Becker,²⁴² one can assume that the first step of the reaction is the formation of stannyl alkyl sulfide and hydrogen (Scheme 112, eqn (a)). This first step is supported by the isolation of methyl tributylstannyl sulfide upon treatment of methanethiol with Ph_3SnH in the presence of AIBN. No reaction is observed in the absence of a radical initiator indicating that this first step occurs presumably *via* a radical pathway. Once the alkyl tributylstannyl sulfide is formed, it can react like normal sulfide (see Section 2) in the reduction process *via* homolytic substitution at sulfur according to the chain process described in eqn (b) and (c) (Scheme 112).

Only rare examples of tin-free radical desulfurization of mercaptans have been reported. Roberts and co-workers showed that desulfurization of β -glucose thiol was efficiently



Scheme 112

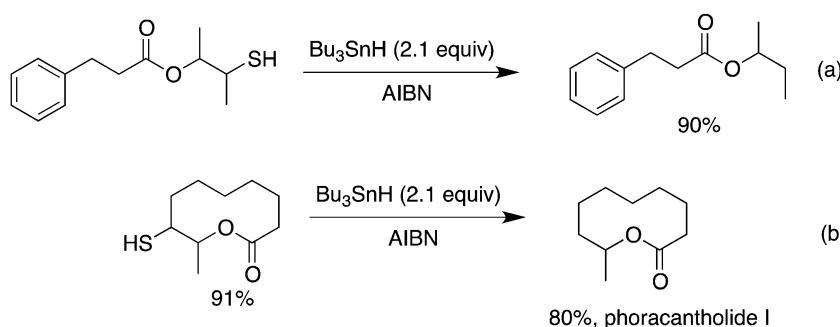
achieved in the presence of triphenylsilane and a stoichiometric amount of di-*tert*-butylhyponitrite as a radical initiator (Scheme 113).^{245,246}

Under these reaction conditions, hydrogen atom abstraction from the thiol by the oxygen-centred radical generated by thermal decomposition of di-*tert*-butylhyponitrite leads to a thiyl radical (Scheme 114, initiation), which abstracts the hydrogen atom from the silane to form the corresponding silyl radical according to the principle of “Polar Reversal Catalysis” (Scheme 114, eqn (a)).²⁴⁷ The latter attacks the thiol at the sulfur atom (homolytic substitution), affording the alkyl radical (Scheme 114, eqn (b)) that abstracts the hydrogen atom from the thiol (Scheme 114, eqn (c)), thus liberating a thiyl radical that propagates the chain. Robert showed that this desulfurization reaction does usually not compete with the hydrosilylation of alkenes.^{245,248,249}

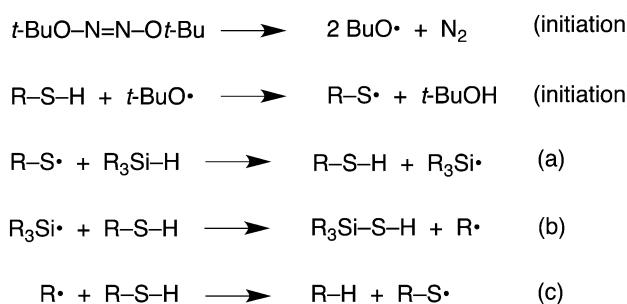
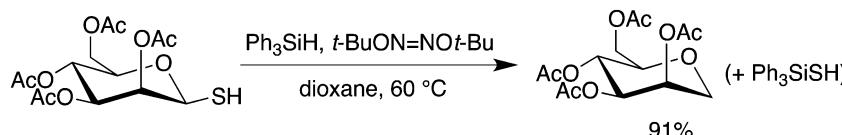
Other radical mediated desulfurizations of alkenes involving reaction with trialkylphosphites have been reported but do not involve any homolytic substitution step but rather addition of a thiyl radical to the phosphorus atom followed by β -fragmentation of the alkyl radical.²⁵⁰

9 Miscellaneous: O,O,S-, N,O,S-, O,S,S-, P,S,S-orthoesters

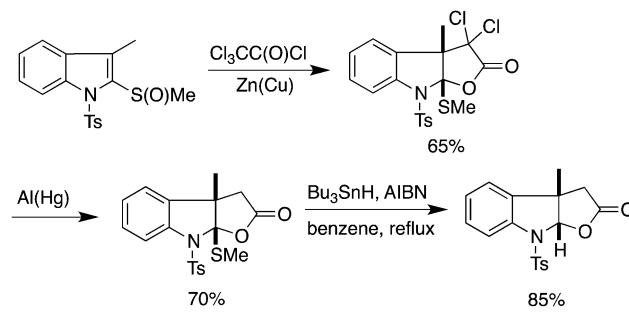
Reductive desulfurization is used in carbohydrate chemistry for the diastereoselective preparation of β -glycosides.²⁵¹ The hemithio *ortho* esters are easily prepared by treating the corresponding thionolactones with an alcohol in the presence of methyl iodide and 2,6-di-*tert*-butyl-4-methylpyridine as a base. Homolytic cleavage of the carbon–sulfur bond is achieved by treatment with Bu_3SnH and AIBN under photolytic or thermal conditions (Scheme 115). Hydrogen-atom abstraction from tin hydride occurs preferentially from the axial position delivering



Scheme 111



Scheme 114

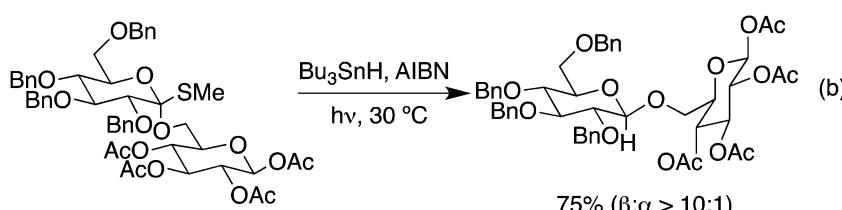
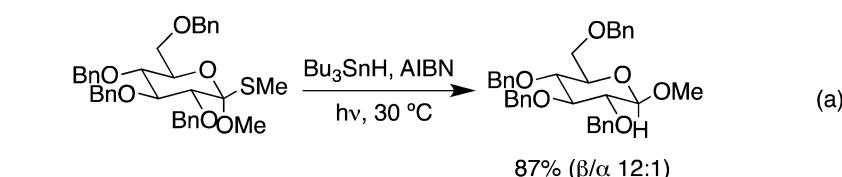
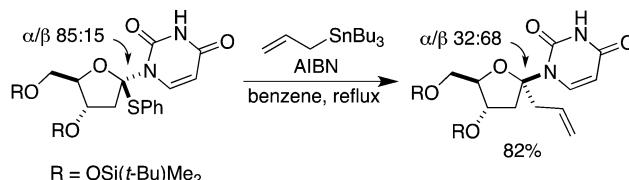


β -glycosides with β/α selectivities $>6:1$ under photolytic initiation at 30°C (Scheme 115, eqn (a)). The same procedure allows the preparation of β -linked disaccharides in high yields and high diastereoselectivities (Scheme 115, eqn (b)).

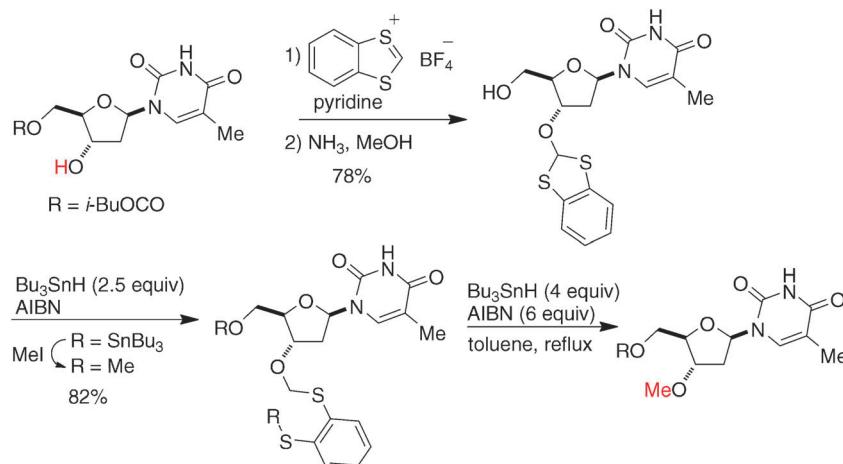
Marino's method to access the γ -butyrolactone skeleton from vinylsulfoxides and dichloroketene (Section 4, Scheme 67) was successfully extended to include vinylsulfoxides derived from indole.²⁵² The [3,3]-sigmatropic rearrangement between 2-(methylsulfinyl)-*N*-(methylsulfonyl)indole and dichloroketene gave a bicyclic indoline in 65% yield. Dechlorination with aluminium amalgam followed by reductive desulfurization in the presence of 2 equivalents of Bu_3SnH and AIBN in refluxing benzene afforded the desired lactone (Scheme 116). This strategy was used for the total synthesis of (–)-physostigmine. In this case, the size of the substituent on the sulfur atom proved crucial for both the chemical yields and the stereo-selectivity. The best results in terms of chirality transfer during the sigmatropic rearrangement were obtained with the isopropylsulfoxide.²⁵³

Tanaka reported the use of 1'-*C*-phenylthio-2'-deoxynucleosides as anomeric radical precursors.²⁵⁴ Radical allylation with allyl(tributyl)tin or allyl(triphenyl)tin gave the products in good yields (Scheme 117). Intermolecular trapping with electron-poor alkenes such as acrylonitrile or methyl acrylate in the presence of Bu_3SnH required optimized reaction conditions in order to limit the undesired addition of the intermediate radical onto the purine base.

Sekine and co-workers developed an approach to selectively methylate a primary or secondary hydroxyl group of nucleosides without affecting the purine base (Scheme 118).^{255,256} The approach consists in introducing a benzodithiol-2-yl (BDT)



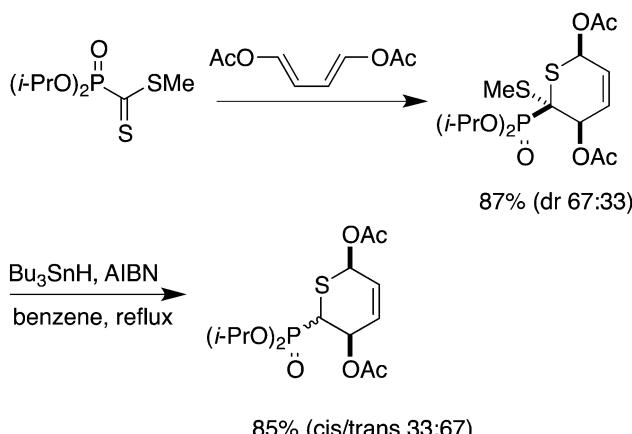
Scheme 115



Scheme 118

group followed by converting it into a methyl group using two consecutive reductive desulfurizations. While the ring-opening of the BDT-protected alcohol was achieved by using 2.5 equivalents of Bu_3SnH , the cleavage of the second carbon–sulfur bond is more difficult due to steric hindrance caused by the introduction of the tributyltin moiety. Nevertheless, after conversion into the corresponding *S*-methyl derivative, the second reductive desulfurization could be achieved with a large excess of both Bu_3SnH and AIBN. Interestingly, this fastidious approach proved successful in cases where direct desulfurization with RANEY® nickel gave unsatisfactory results.

The Masson group reported the preparation of (3,6-dihydro-2-methylsulfanyl-2*H*-thiopyran)phosphonate derivatives using a [4+2] cycloaddition between a diene and a phosphonodithioformate. Following the work of Balczewski on the mono-desulfurization of phosphonodithioacetals,²⁵⁷ selective reductive mono-desulfurization could be achieved in the presence of Bu_3SnH and AIBN in refluxing benzene. The more stable radical was formed exclusively and no opening of the thiopyran ring was observed (Scheme 119).^{258–260}



Scheme 119

10 Conclusions

Homolytic substitution at sulfur can be engineered to become a very efficient method for the generation of variously substituted carbon-centred radicals. Stabilized radicals are produced in a straightforward manner using intermolecular bimolecular homolytic substitutions ($S_{\text{H}2}$). Non-stabilized alkyl radicals and acyl radicals are, on the other hand, better generated by using intramolecular homolytic substitutions (S_{Hi}). Easily available aryl and alkenyl radicals can be transformed into sophisticated alkyl radicals. The main advantages of using sulfides are the stability of the radical precursors under a variety of conditions, the ease of preparation of sulfides and related compounds based on the very rich chemistry of sulfur derivatives and, finally, the low toxicity associated with sulfides and related moieties.

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