Taming the free radical shrew – learning to control homolytic reactions at higher heteroatoms

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Free radical chemistry has come a long way in a relatively short period of time. Armed with mechanistic and rate constant data, the synthetic practitioner can now apply free radical chemistry to the synthesis of many different classes of target molecule with confidence. This Feature Article highlights progress made in the understanding and application of free radical reactions at main group higher heteroatoms and demonstrates how this knowledge can be used to construct interesting higher heterocycles, many of which exhibit biological activity, through the use of intramolecular homolytic substitution chemistry.

Introduction

Free radical chemistry has come a long way since the work of Moses Gomberg.[1] In defiance of, and perhaps catalysed by, Gomberg wishing to "reserve the field" for himself, free radical chemistry has undertaken a remarkable journey in a relatively short time. Initially reserved for the manufacture of polymeric materials, serious radical chemistry lay dormant for decades, waiting for its moment to "come out and play" with its older, traditionally-based, ionic sibling and rival. In earlier days, like a troublesome child, free radical chemistry was often to blame for reactions "going wrong", or whenever intractable tars were produced.[2]

Free radicals are receiving unprecedented attention these days, especially in unlikely places such as media advertising with companies extolling the virtues of products that contain antioxidants. With slogans like "reduce the visible signs of ageing"[3] and "radicals are bad",[4] who can blame the unflattering image that free radicals appear to have inherited. In a further example, Snapple's "Tea for Life" webpage informs the potential consumer that free radicals, apart from being "as evil as they sound", are also "on your body's most wanted list".[5]

Misinformation is also unhelpful. For example, the term "free radical" seems to mean different things to different people. To the uninformed, the term seems to only involve reactive, destructive, arguably "evil" oxygen species.[4] Likewise, many reactive oxygen species in biological systems have been confused by those with little knowledge of molecular structure and function, with free radicals, regardless of whether or not they contain any unpaired spin.

On the other hand, many workers have put this previously troublesome adolescent to good use. The literature now boasts a plethora of elegant syntheses, performed in high yield, with high regiocontrol and with excellent stereocontrol.[6] The significant contributions of predecessors and colleagues that led to this maturing of the discipline are too numerous to mention.† What is important to emphasize is the significant role that quality rate constant and mechanistic data play in the design of synthetic procedures involving free radicals.[2] Indeed, without the decades of meticulous work carried out in global partnership from the 1960s through to the late eighties and today, this Feature Article would probably end here. This practitioner is indebted to those who contributed early on to the harnessing of what are ostensibly reactive intermediates, so that we can participate without fear in the free radical chemistry playground.

This article focuses on free radical chemistry involving higher heteroatoms. Intramolecular homolytic substitution chemistry is one of the more recent additions to the chemist's

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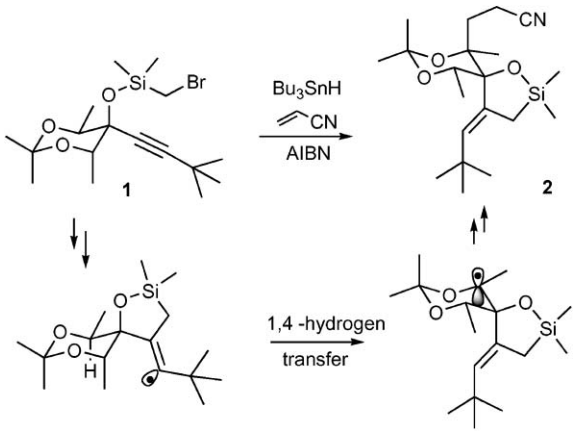
† Contributions from workers such as Barton, Beckwith, Chatgilialoglu, Crich, Curran, Davies, Fischer, Giese, Ingold, Kim, Lusztyk, Newcomb, Peduli, Roberts, Ryu, Scaiano, Walling and Zard, as well as others, are responsible for the excellent state of health that free radical chemistry now finds itself in.



Scheme 1

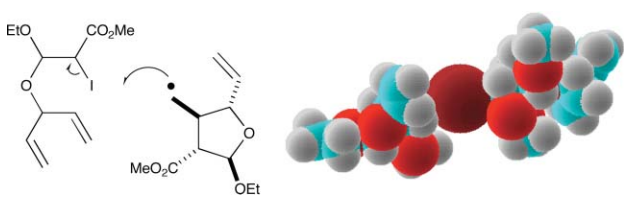
heterocycle-forming synthetic armoury.[7,8] There are no real shrews in this story, just reactive intermediates that have been misunderstood and, more recently, tamed.

It is ten years since I contributed to a review on homolytic substitution chemistry.[8] While this article is not intended to be a comprehensive review, it will focus on progress made over the last decade with particular emphasis on our journey of discovery in the research laboratories at the University of Melbourne.

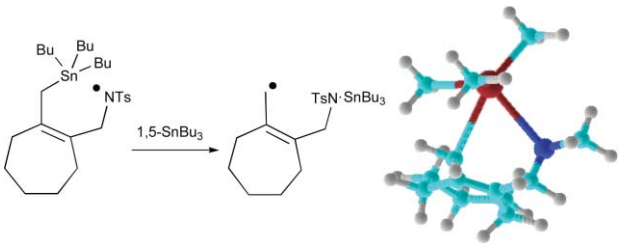
Discussion

This story begins in Europe, in the laboratories of Malacria. Trawling through numerous examples of stunning free radical mediated synthetic transformations from these laboratories, one cannot help stumbling across the transformation of bromomethyldimethylsilyl ether (**1**) into silacycle (**2**) by the action of tributyltin hydride under standard radical reaction conditions.[9] One of the key steps in this process is a 1,4-hydrogen transfer (intramolecular homolytic substitution reaction at hydrogen), a rearrangement that requires a significantly non-linear arrangement of attacking and leaving groups (Scheme 1). This example is included here simply to highlight the fact that intramolecular H-transfer processes are feasible; indeed there are numerous examples in the literature.

When asked some years ago whether or not I was aware of any similar intramolecular transfers involving halogen, I had to confess that I did not.[10] Indeed, to the best of my knowledge there are no examples of any intramolecular free radical transfers involving chlorine, bromine or iodine, only one involving sulfur[11] and none involving selenium or tellurium. However, numerous intermolecular examples exist, including some from the laboratories of Renaud.[12] The transformation



Scheme 2



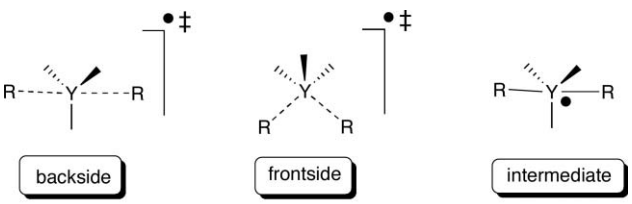
Scheme 3

depicted in Scheme 2 almost certainly involves a collinear arrangement of attacking and leaving radicals, and when space-filling models are used, one can begin to understand how anything other than a collinear arrangement might be very difficult to achieve.

If one accepts this pseudo-steric argument, then how is it that trialkylsilyl, germyl and stannyl groups undergo rapid and efficient intramolecular translocations? An example from the laboratories of Kim is shown in Scheme 3.[13]

This quandary prompted us to investigate the mechanistic requirements of homolytic substitution reactions involving main-group heteroatoms. The information that we gained not only helped us to understand this chemistry better, it also provided necessary information for the design and construction of higher heterocycles by free radical means.

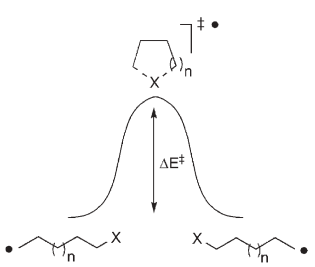
It is generally agreed that three mechanisms exist for homolytic substitution at higher heteroatoms.[8] These include a backside mechanism similar to S_N2, leading to Walden inversion as well as a frontside mechanism that would result in retention of configuration at asymmetric silicon, germanium or tin. The third possibility involves a hypervalent intermediate that may or may not pseudo-rotate prior to dissociation, possibly resulting in racemization in chiral systems. We felt that computational chemistry, as well as some prudent mechanistic experiments, would shed light on the fundamental reasons for the observed trends that are summarized in Scheme 4.[14]



$R^{\bullet} + X{-}L \rightarrow R{-}X + L^{\bullet}$

X	inter-molecular	intra-molecular
H	✔	✔
SiR_3	✔	✔
GeR_3	✔	✔
SnR_3	✔	✔
SR	✔	✘
SeR	✔	✘
TeR	✔	✘
Cl	✔	✘
Br	✔	✘
I	✔	✘

Scheme 4



n	ΔE‡ (kJ mol^{-1}) Cl	Br	I
2	191.0	-	-
3	170.9	149.2	136.0
4 (C_s)	163.5	137.9	120.0
4 (C_2)	198.4	175.6	-

MP2/DZP

Scheme 5

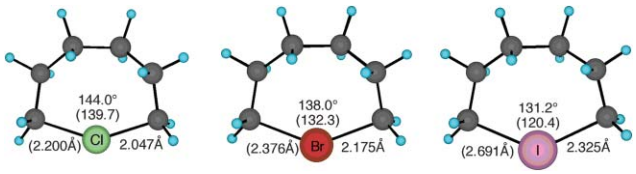
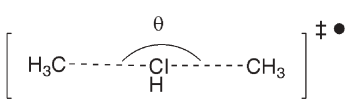


Fig. 1 MP2/DZP calculated transition states for 1,6-halogen transfer reactions in 6-halo-1-hexyl radicals.

Initial computational investigations into intramolecular halogen transfers are highlighted in Scheme 5, with selected transition states displayed in Fig. 1.[15]

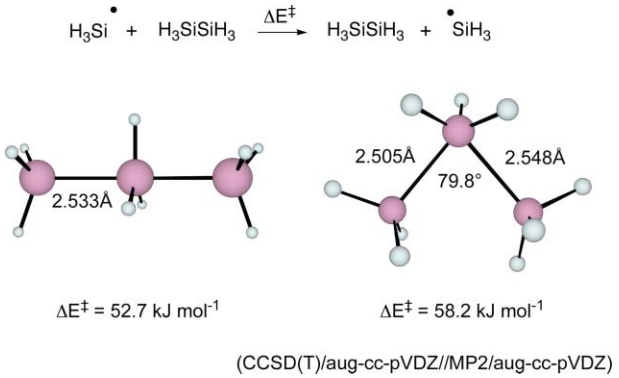
The data provided in Scheme 5 clearly indicate that, consistent with the lack of any reported examples, intramolecular 1,4-, 1,5- and 1,6-homolytic translocations of chlorine, bromine and iodine have prohibitively high energy barriers. The smallest MP2/DZP calculated $\Delta E^{\ddagger}$, determined for the 1,6-transfer of iodine through a C_s-symmetric transition state, at about 120 kJ mol^{-1}, is calculated to be some 70 kJ mol^{-1} higher than that for the analogous intermolecular reaction at the same level of theory.[8] This difference is almost certainly associated with the geometry of the transition state, and deviations from collinearity during attack at the halogen atom must be significant enough to impart substantial strain in the transition structures displayed in Fig. 1.

In order to test this hypothesis, Wild determined the angular dependence of the MP2/DZP calculated transition state (**3**) for the attack of methyl radical at the chlorine atom in chloromethane, and showed that there is a continual rise in energy as the attack angle (θ) is reduced from the ideal collinear arrangement (180°) to maximum at 90°, at which point the transition state has suffered an increase of some 112 kJ mol^{-1}.[15] While there was a 3.4 kJ mol^{-1} decrease in energy in progressing to 80°, no saddle point for frontside attack was located. It is clear from this study that homolytic substitution at halogen has a strong preference for backside attack in which the attacking and leaving radicals adopt a collinear arrangement.



3

In contrast to this, computational studies have revealed that homolytic substitution by numerous free radicals at the Si, Ge and Sn atoms in organosilanes, germanes and stannanes can proceed *via* both frontside and backside mechanisms, and that depending on geometrical requirements, either or both

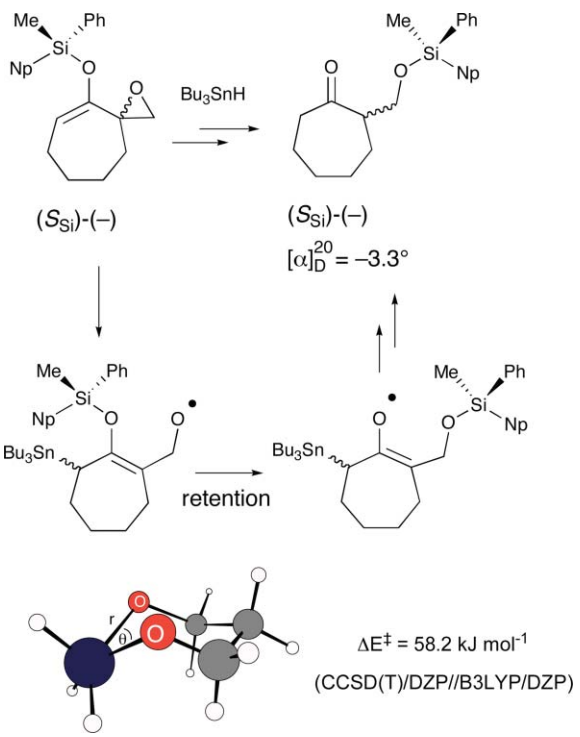


Scheme 6

mechanisms may operate.[13,16,17] For example, the degenerate reaction of silyl radical with disilane is calculated to have energy barriers of 52.7 and 58.2 kJ mol^{-1} for the frontside and backside pathways respectively (Scheme 6).[17] Similar results have been obtained for other related systems.

These computational studies have been nicely complemented in our laboratories by Horvat who showed that intramolecular homolytic substitution at a chiral silicon atom proceeds with retention of configuration and through a frontside attack mechanism (Scheme 7).[18] It is interesting to note that Chatgilialoglu reported the free radical degradation of poly(phenylsilane), a process that most likely involves intramolecular attack of silyl radicals at tetravalent silicon.[19]

So what then of translocations involving chalcogen? Computational studies suggest that group transfer processes involving homolytic substitution at sulfur and selenium proceed through a backside mechanism and, as was observed



Scheme 7

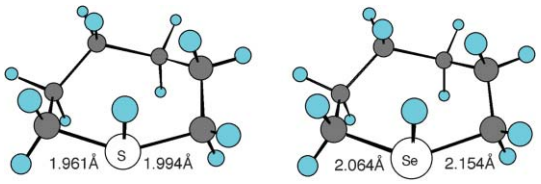


Fig. 2 MP2/DZP calculated transition states for homolytic 1,6-transfers of sulfur and selenium groups in 6-chalcogenyl-1-hexyl radicals.

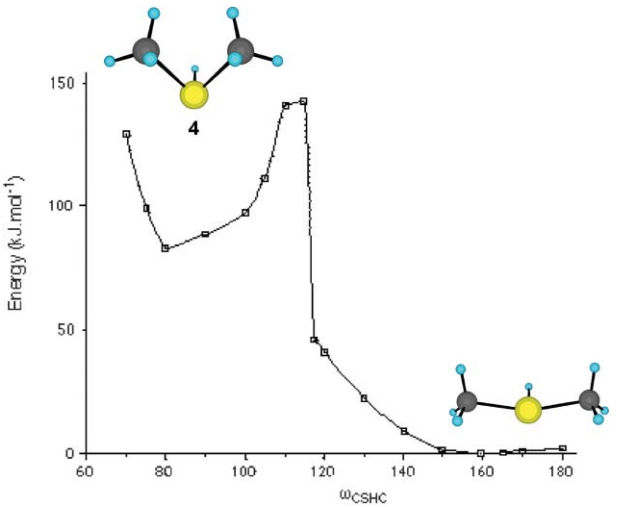
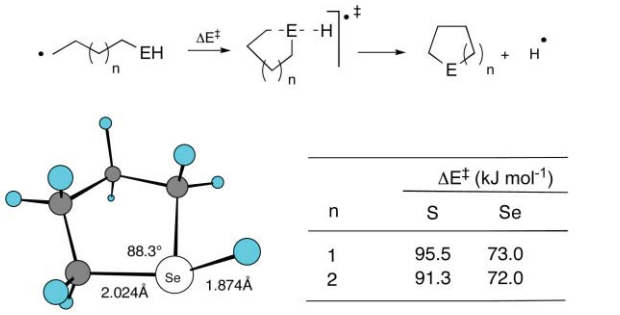


Fig. 3 MP2/DZP calculated dependence of the energy of the transition attack angle (ω_{CSHC}) in the reaction of methyl radical at the sulfur atom in methanethiol with expulsion of methyl radical.

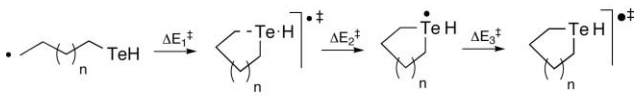
for the halogens, have prohibitively high energy barriers. MP2/DZP energy barriers lie in the 90–140 kJ mol^{-1} range for 1,5-, 1,6- and 1,7-chalcogen transfer, depending on the heteroatom undergoing substitution, and the length of the alkyl chain.[20] Examples of transition states are displayed in Fig. 2.

In an attempt to locate a frontside transition state for chalcogen transfer, we once again took a simple transition state, namely that for attack of methyl radical at the sulfur atom in methanethiol, and determined the effect of deviation of attack angle on transition state energy. The results are summarized in Fig. 3.[20] In agreement with previous calculations,[21] the ideal attack angle (ω) is found to be about 160°, a value that can be rationalized in terms of orbital interactions in the transition state.[21] As the angle is decreased, the energy rises sharply until a maximum is reached at about 120°, at which point the energy has risen by almost 150 kJ mol^{-1}. At smaller angles (ω), a considerable decrease in energy is observed until an angle of about 80° is achieved. The similarity of this structure (**4**) to that of the frontside transition state depicted in Scheme 6 led us to (momentarily) conclude that a frontside transition state for homolytic substitution at chalcogen had been located. However, frequency analysis revealed two imaginary frequencies. All attempts to optimize this structure led to its collapse to the transition state for ring-closure, with expulsion of hydrogen atom.

So here we observe a fundamental difference between chalcogen and halogen: the second substituent on chalcogen



n	ΔE‡ (kJ mol^{-1}) S	Se
1	95.5	73.0
2	91.3	72.0



n	(kJ mol^{-1}) ΔE_1	ΔE_2	ΔE_3
1	24.4	1.3	25.3
2	33.8	2.8	19.5

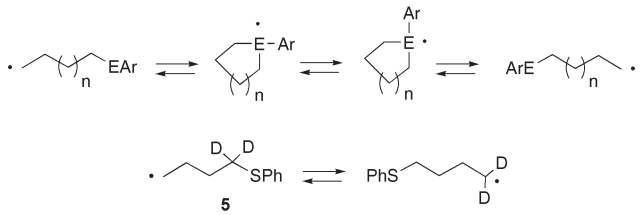
Scheme 8

can act as a leaving group and attempts to "force" a frontside attack will lead to another, preferred, backside attack trajectory for loss of the other ligand.

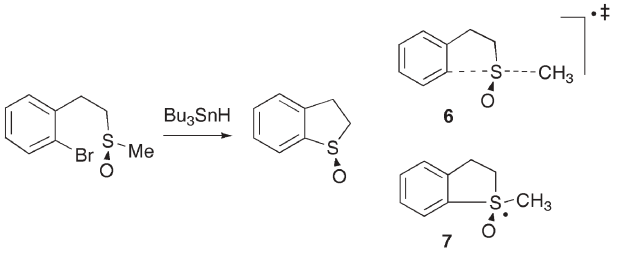
However, the story becomes a little more complicated in that reactions involving tellurium mostly involve hypervalent intermediates.[20] Scheme 8 contrasts the differences between the reaction pathways for homolytic sulfur, selenium and tellurium ring-closure chemistry.[20] The examples provided lie on the same potential energy surfaces as the translocation examples discussed above. Despite this, it is clear that ring-closure with expulsion of hydrogen atom (an unlikely leaving group), with MP2/DZP calculated energy barriers in the range 50–96 kJ mol^{-1}, depending on the heteroatom involved, is preferred to the analogous translocation reaction by about 40 kJ mol^{-1} in each case.[20]

Given these computational data, one might begin to imagine ways of engineering systems that would result in translocation of chalcogen-containing groups. With a stabilizing group present on the heteroatom (*e.g.* aryl), it is almost certain that the energy barriers for translocation chemistry would be reduced. In addition, hypervalent intermediates, if they are formed, would benefit from this substituent and would therefore become longer-lived. If this substituent were also a poor leaving group (*e.g.* aryl), one might reasonably expect that the ring-closure pathway would be virtually impossible. We therefore postulate that homolytic translocation *via* hypervalent intermediates might be possible for systems disposed to forming intermediates, namely for those involving tellurium (Scheme 9).[14] It is interesting to note that we reported some years ago that labelled 4-(phenylthio)-1-butyl radicals (**5**) undergo (pseudo) degenerate rearrangement that involves homolytic transfer of the stabilized sulfur moiety, and almost certainly through a [9–S–3] intermediate (Scheme 9).[11]

Ring-forming, intramolecular homolytic substitution chemistry at sulfur had been reported on a few occasions prior to



Scheme 9



Scheme 10

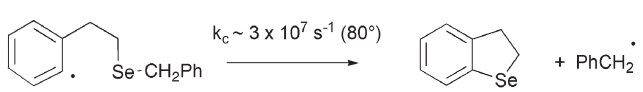
this practitioner entering the field[22–24] and more recently.[25] Indeed, Beckwith and Boate reported twenty years ago that these reactions proceed with inversion of configuration at stereogenic sulfur, necessitating the involvement of a backside attack transition state (**6**) similar to that involved in S_N2 chemistry, or a hypervalent intermediate (**7**) that is too short-lived to undergo pseudo-rotation prior to dissociation (Scheme 10).[24]

Encouraged by this history, we began to explore the formation of selenium and, later, tellurium containing ring-systems through the use of intramolecular homolytic substitution chemistry. When we began our foray into this area, these were unknown chemical reactions.

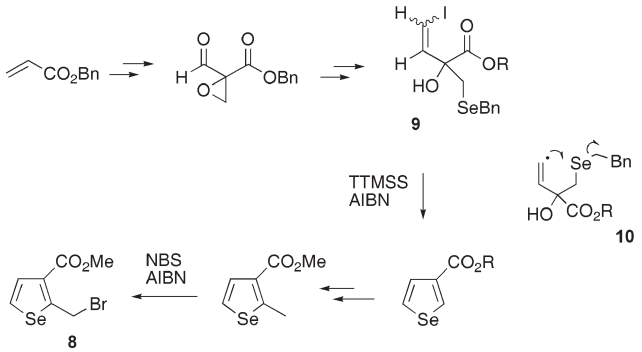
As previously mentioned, rate-constant data are critical when designing synthetic chemistry based on free radical reactions. While the literature abounded with data for intramolecular homolytic addition reactions, there were only limited data available for radical cyclization reactions involving homolytic substitution at sulfur,[8] and, of course, none for selenium or tellurium. One of our first tasks, therefore, was to get a good estimate for ring-closure at selenium, which we achieved through competitive kinetics (Scheme 11).

Not only did the experiment depicted in Scheme 11 demonstrate the feasibility of ring-closure at selenium, it also showed that the substitution reaction was fast, with an approximate rate constant (k_c) of 3×10^7 s^{-1} at 80°.[26] Indeed, this value is some 2–4 orders of magnitude faster than those for similar reactions involving sulfur and explains why no competitive intramolecular benzylic hydrogen abstraction was observed in this system.[23]

Intramolecular homolytic substitution chemistry has allowed us, at the University of Melbourne, to prepare many



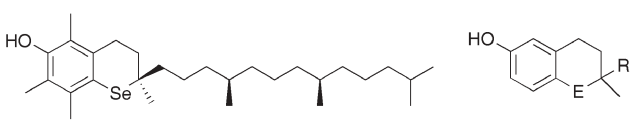
Scheme 11



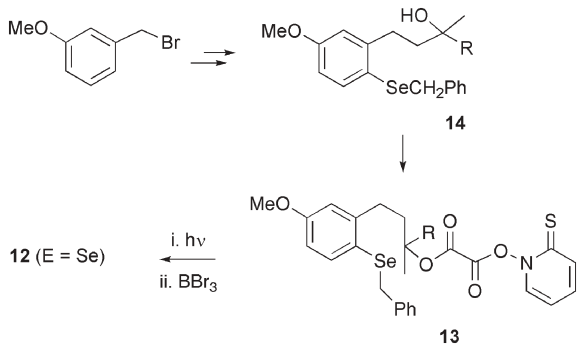
Scheme 12

interesting compounds, some of which are of biological relevance. A very recent example based on our "first generation chemistry" includes the preparation of methyl 2-(bromomethyl)selenophene-3-carboxylate (**8**), a key intermediate in the preparation of a class of important selenium-containing bioactive molecules.[27] Scheme 12 depicts an abbreviated synthesis of **8**, in which one of the key steps involves treatment of iodide (**9**) with tris(trimethylsilyl)silane to afford (after concomitant dehydration) the selenophene-3-carboxylate, presumably *via* cyclization of the vinyl radical (**10**).

With significant recent global interest in antioxidants, we became involved in a research programme aimed at the preparation of novel molecules that combine the beneficial antioxidant effects of organoselenium and organotellurium compounds[28] with the more traditional phenolic type molecules. As such, we became interested in structures such as α-selenotocopherol (**11**) and related compounds (**12**). While we were able to prepare the model compound **12** (E = Se) through intramolecular homolytic substitution chemistry (Scheme 13),[29] it was several years later that α-selenotocopherol (**11**) itself was prepared in an analogous fashion by Engman and coworkers, who were able to overcome the significant difficulties we encountered in fully functionalizing the aromatic ring, presumably due to steric factors.[30] Interestingly, **11** proved to be slightly less effective as an antioxidant than α-tocopherol (Vitamin E) itself.[30] It is interesting to note that the key ring-closing step in Scheme 13 involves the photochemical decomposition of the pyridinethiooxycarbonyl oxalate ester (**13**) (PTOC ester, Barton ester) derived from tertiary alcohol (**14**) as originally described by Barton and Crich.[31]



Some years earlier, we demonstrated that Ebselen (**15**), a non-steroidal antiinflammatory compound, as well as analogues, could be prepared through the use of intramolecular homolytic substitution chemistry involving amidyl radicals (Scheme 14).[32] While radicals (**16**) derived from PTOC imidate esters were effective for most compounds of interest, Ebselen itself could not be prepared in this manner. Instead, amidyl radical (**17**), generated through peroxyl radical mediated



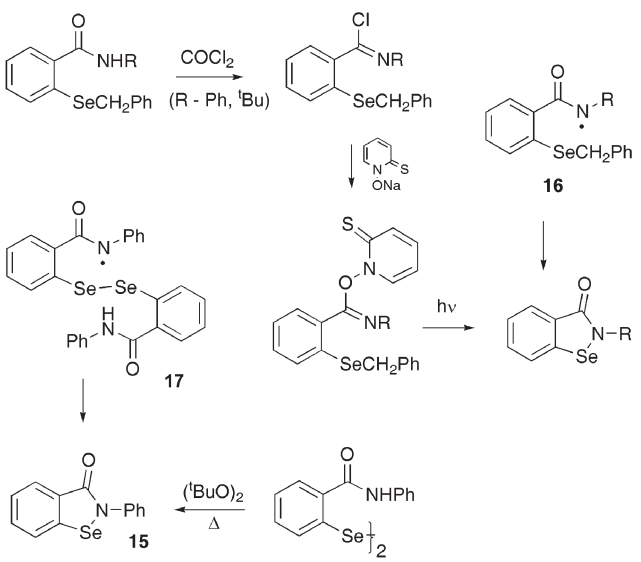
Scheme 13

hydrogen abstraction chemistry, was used to prepare the target pharmaceutical hopeful.[32]

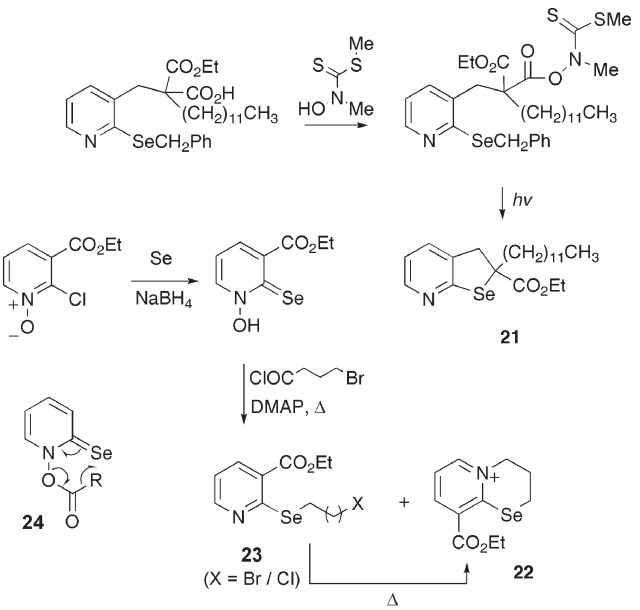
One of the significant drawbacks associated with Ebselen is its lack of water solubility and therefore oral bioavailability.[33] With this in mind, we set about preparing analogues of Ebselen and related antiinflammatory compounds with improved solubility properties. Fenner was able to successfully prepare 2,3-dihydroselenolo[2,3-*b*]pyridines (**21**) (Scheme 15) through photolysis of a thiohydroximate ester.[34] This transformation utilises Kim's modification[35] of Barton's PTOC chemistry and, in our hands, has always produced superior outcomes.

The water-soluble 2-carboethoxy-3,4-dihydro-2*H*-1-seleno-4a-azonianaphthalenium salt (**22**) could be prepared by spontaneous ionic ring-closure of mixed halides (**23**),[34] themselves prepared through the use of a rarely-used rearrangement (**24**).[36] It is believed that this rearrangement involves a (pericyclic) homolytic cage mechanism.[36]

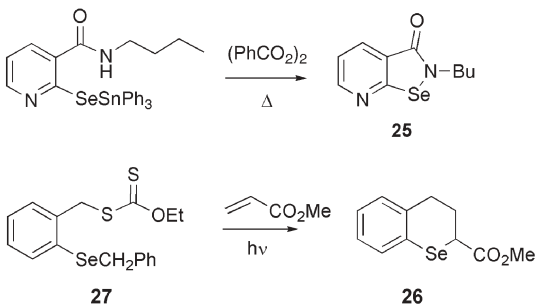
In related work, Staples utilised amidyl radical cyclization chemistry to prepare pyridine-fused Ebselen analogues (**25**),[37] and also provided a new twist to the elegant xanthate chemistry pioneered by Zard in the preparation of dihydrobenzoselenanes (**26**) (Scheme 16).[38] We believe that the transformation of xanthate (**27**) into **26** by photolysis in the



Scheme 14



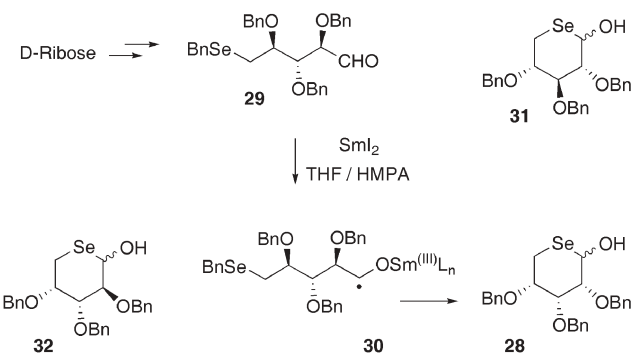
Scheme 15



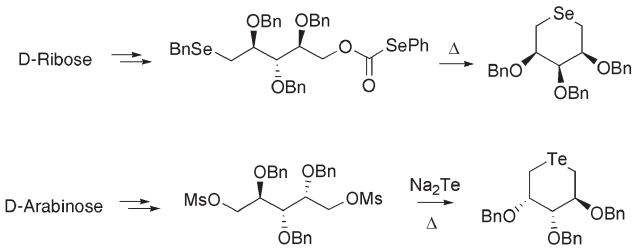
Scheme 16

presence of methyl acrylate represents the first example of a tandem intermolecular homolytic addition/intramolecular homolytic substitution process. It is interesting to note that **25** is effective at quenching ozone produced during experiments designed to induce amyloid formation in low density lipoprotein (LDL).[39]

Our exploration of water-soluble selenium-containing antioxidant systems includes the preparation of carbohydrate analogues such as those depicted in Scheme 17. For example,



Scheme 17



Scheme 18

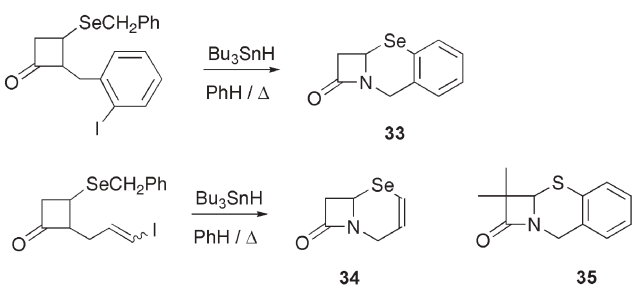
Zheng demonstrated that 2,3,4-tri-*O*-benzyl-5-deoxy-5-seleno-D-ribopyranose (**28**) could be prepared by treatment of aldehyde (**29**), itself derived from ribose, with samarium(II) iodide.[40] Presumably this transformation involves ring-closure of radical (**30**). In similar fashion, selenosugars (**31**, **32**) were prepared from xylose and arabinose respectively.[40]

It should be noted here that Nguyen was able to prepare deoxy seleno- and tellurosugars through the use of ionic chemistry. Some examples are shown in Scheme 18.[40,41]

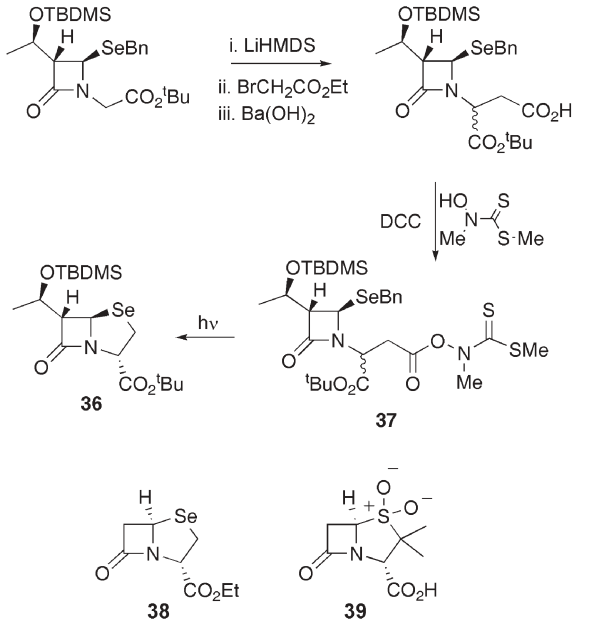
Homolytic substitution chemistry afforded us a novel opportunity to prepare selenium analogues of penam and cephem type antibiotic analogues and related compounds. To that end, Martin showed that 2,2a-dihydro-1*H*,8*H*-azeto[2,1-*b*][1,3]benzoselenazin-1-one (**33**) and 5-selena-1-azabicyclo[4.2.0]oct-3-en-8-one (**34**) could be efficiently prepared through homolytic substitution chemistry under standard conditions (Scheme 19).[42] This chemistry is analogous to that reported by Beckwith and Boate for the preparation of penicillin analogue (**35**).[23]

Carland expanded this chemistry to include the synthesis of the aza-7-oxo-4-selenabicyclo[3.2.0]heptane (**36**), once again through the use of a Kim thiohydroxamate ester (**37**).[42] In similar fashion, the selenium analogue (**38**) of the β-lactamase inhibitor, Sulbactam (**39**) was also prepared (Scheme 20).[42]

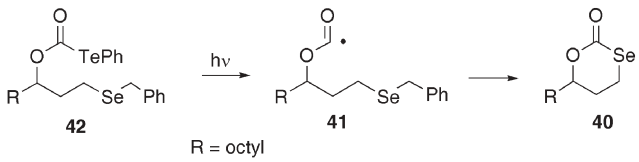
So far this article has focused on our synthetic endeavours toward selenium-containing heterocycles. Earlier on, brief mention was made of tellurium-containing heterocycles and it is now time to explore this chemistry. This tale begins with Lucas' preparation of previously unknown cyclic selenocarbonates (*e.g.* **40**) through oxyacyl radical mediated homolytic substitution chemistry.[43,44] On this occasion, radical (**41**) was conveniently generated from telluroformate (**42**) (Scheme 21) through chemistry inspired by the acyl radical work described by Crich.[45] It is interesting to compare the reactivities (and stabilities) of telluroformates with telluroesters (**43**) such as



Scheme 19

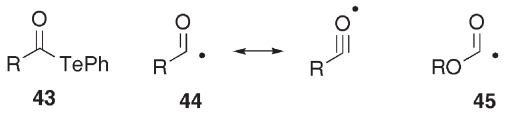


Scheme 20



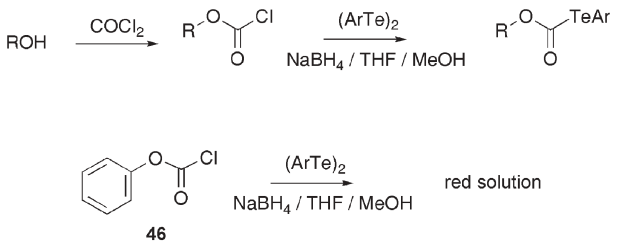
Scheme 21

those used by Crich to generate his acyl radicals. In our hands, telluroformates proved to be significantly more stable than telluroesters and could be handled under white light without precautions. In contrast, telluroesters require shielding from background light, especially during chromatography. This difference is attributed to the increased stability of the acyl radical (**44**) over the oxyacyl (**45**) due to resonance and this stabilization has been calculated by Skidmore to be worth 40–45 kJ mol^{-1}.[46]

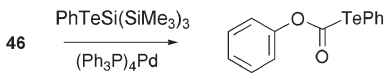


Telluroformates represent our first foray into organotellurium chemistry and this chemistry provided many riches for our research endeavours, but only after some initial hurdles were overcome. It should be noted here that, unlike ^{77}Se, ^{125}Te is well-behaved in NMR spectroscopy and, accordingly, we found ^{125}Te NMR spectroscopy to be a powerful analytical tool for use during our synthetic endeavours.[47]

Telluroformates are typically prepared from chloroformates as depicted in Scheme 22.[44] While the required telluroformates were obtained in excellent yields on most occasions, problems associated with adventitious oxygen and some classes of aromatic substrate, for example in the reaction of phenyl chloroformate (**46**), are major drawbacks.[48]



Scheme 22



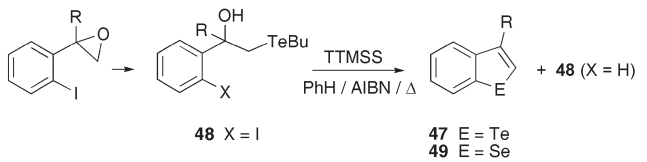
Scheme 23

It is interesting to note that diphenyl ditelluride is a deep red colour. Upon reduction with sodium borohydride, the solution becomes colourless. Adventitious oxygen results in rapid reformation of the red colouration and significantly diminished yields. Addition of a number of aromatic substrates, including **46**, also results in rapid reformation of PhTeTePh.[28] While the mechanism of this transformation is not clear to us, we have speculated that rapid electron transfer occurs with these substrates resulting in oxidation of the phenyltellurolate ion to the phenyltellanyl radical which undergoes rapid dimerization.[28]

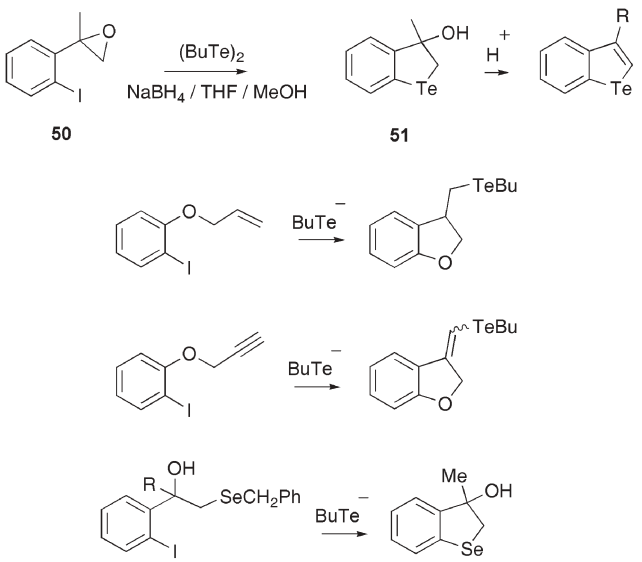
To overcome this synthetic bottleneck, Skidmore developed palladium-mediated chemistry that afforded telluroformates and telluroesters, as well as their selenium analogues, in excellent yield, an example of which is given in Scheme 23.[49]

Of course, there is another twist to this story, and this twist has its origin in rate constant data. Rate studies, as well as computational data, suggest that the rates of homolytic substitution at the halogen and chalcogen in a given row of the periodic table are very similar.[8] For example, the rate constants for attack of primary alkyl radical at a tellurium or iodine centre in a series of substituted ethyl acetates has been determined to be about 2×10^7 $M^{-1}s^{-1}$ at 50°.[50] What precursors are we then to choose for the preparation of tellurium-containing rings such as **47**? It is very likely that the use of iodides such as **48** will lead to a mixture of products (**47**, **48** X = H) at best (Scheme 24). Without recourse to a satisfactory solution, we chose to nevertheless explore chemistry analogous to that which we published previously for the preparation of benzoselenophenes (**49**).[26]

Imagine our surprise when Laws treated oxirane (**50**) with sodium butyltellurolate ($BuTe^-$) and retrieved none of the expected telluride (**48**), but rather obtained 2,3-dihydro-3-hydroxy-3-methylbenzo[*b*]tellurophene (**51**) in 62% yield (Scheme 25).[51] How does one begin to write a plausible



Scheme 24



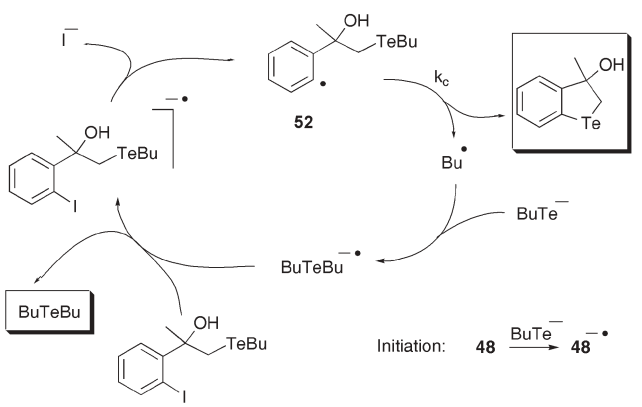
Scheme 25

mechanism for a seemingly impossible transformation? The reader might like to consider the other transformations depicted in Scheme 25 during their mechanistic ponderings.[51]

What is clear from this outcome is twofold: never underestimate serendipity and: intramolecular homolytic substitution chemistry at a tellurium centre is possible. We just needed to think "outside the box" in order to make it possible. When we considered the information provided by the data presented in Schemes 22 and 25, a tandem alkyltelluride-mediated $S_{RN}1$/S_Hi mechanism seemed consistent with all of the available information (Scheme 26).[28]

This work also allowed us to determine for the first time a rate constant (k_c, Scheme 26) for intramolecular homolytic substitution by an aryl radical at tellurium with expulsion of butyl radical; radical (**52**) was determined to ring close with a rate constant of about 5×10^8 s^{-1} at 25°.[28] This value is to be compared with 3×10^7 s^{-1} at 80° for a similar reaction at selenium (Scheme 11)[26] and is consistent with expectation based on intermolecular chemistry, allowing for differences in leaving group.[8]

Having discovered a new method for the generation of aryl radicals from aryl iodides, one that is arguably "greener" than

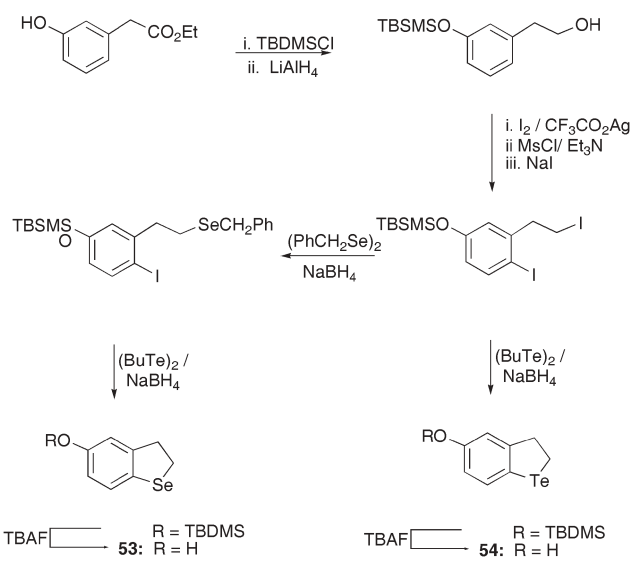


Scheme 26

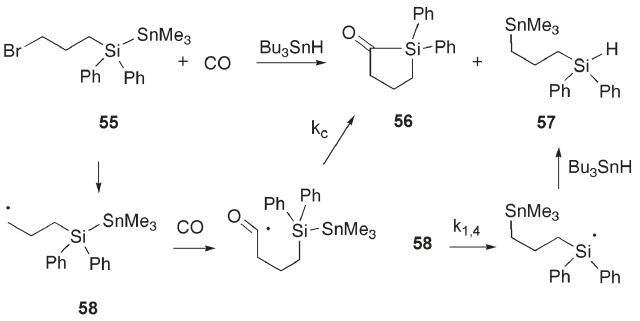
standard stannane mediated chemistry because the tellurium byproducts behave discretely on chromatography, it became apparent to us that this chemistry could be used to make tellurium containing heterocycles that may be potent antioxidants. It should be noted at this point that selenium is a well recognized essential trace element in man, with doses of around 55–70 μg required to maintain a healthy diet in humans.[52] Selenocysteine is now regarded as the twenty-first essential amino acid.[53] Tellurium, at least at this point in time, would appear to have no natural biological function in mammals.[54]

In collaboration with Engman, we prepared both selenium- and tellurium-containing antioxidants (**53**, **54**) as depicted in Scheme 27.[28] While the selenium analogue (**53**) was found to be essentially devoid of any glutathione peroxidase activity, the dihydrobenzotellurophene (**54**) showed excellent activity and an ''outstanding ability to protect liver microsomes'' subjected to stimulated lipid peroxidation by Fe(II)/ADP/ascorbate, with an IC_{50} value of 0.13 μM.[55]

As this story is nearing its conclusion, it is probably appropriate to make some comment regarding intramolecular homolytic substitution chemistry involving silicon, germanium and tin. We have already seen that Si, Ge and Sn appear to be ''promiscuous'',[7] having no real preference for frontside or backside attack, being free to react in the manner dictated by their environment. Despite the (recent) availability of this mechanistic information, to the best of my knowledge, no rate constant data exist for any intramolecular homolytic substitution reaction involving translocation of a Si, Ge or Sn containing group. Driven largely by curiosity surrounding acyl radicals, radicals that have recently been shown to masquerade as electrophiles,[56] this story briefly visits Japan and Europe through the work of Studer, Ryu, Matsubara and others, with my association largely restricted to computational chemistry. Scheme 28 summarizes the outcome of the reaction of bromide (**55**) with carbon monoxide in the presence of tributyltin hydride, a reaction that produces both the silacycle (**56**) through an S_Hi process, and the stannasilane (**57**) through



Scheme 27



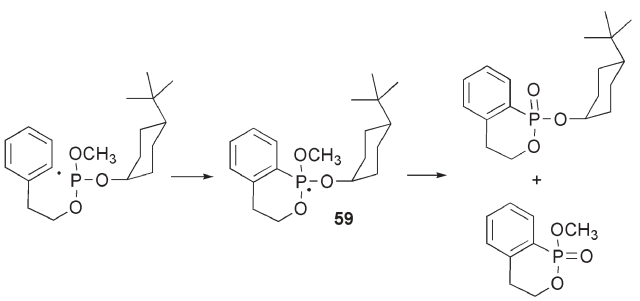
Scheme 28

a homolytic 1,4-translocation of the trimethylstannyl group in radical (**58**).[57] The 1,4-translocation reaction involving **58** has been determined to proceed with a rate constant ($k_{1,4}$) of 9.3 × 10^4 s^{-1} at 80°, and an approximate Arrhenius expression:

$$\log k_{1,5} = 11.8 - 46/2.3RT, \text{ where } R = 8.314 \text{ kJ mol}^{-1} \text{ K}^{-1}.$$

The experimentally determined activation energy (46 kJ mol^{-1}) is in excellent agreement with values calculated at several levels of theory that lie in the 46–60 kJ mol^{-1} range.[57] These rate data are to be compared with those determined previously by Studer who reported rate constants of 10^4–10^6 s^{-1} (80°) for homolytic cyclization at silicon.[58]

This story is not complete without a brief comment on free radical reactions involving phosphorus, arsenic and antimony. It is well established that free radical attack at the phosphorus atom in a variety of phosphorus-containing compounds results in the formation of stable, hypervalent, phosphoranyl radicals that are trigonal bipyramidal in structure.[7,8] Several reviews have been written on this topic and the interested reader is referred to these.[59] While we contributed to the understanding of this chemistry through computational techniques some time ago,[60] there have been no reports of this chemistry being used to prepare phosphorus heterocycles. However, if appropriately substituted, these intermediates (*e.g.* **59**) can undergo β-scission, with the overall process resulting in substitution through an addition/β-scission mechanism. An example that employs this chemistry at phosphorus for the preparation of phosphorus heterocycles comes from the laboratories of Koreeda and is shown in Scheme 29.[61] There would appear to be no examples of this chemistry being used for the preparation of arsenic or antimony containing rings.



Scheme 29

Conclusions

Work in our laboratories at the University of Melbourne, as well as in other places around the world, has led to a more complete understanding of the intimate details surrounding the mechanism of free radical homolytic substitution chemistry that was available to us only a short time ago. We now believe that we understand the mechanistic requirements for free radical attack at several higher heteroatoms that include the halogens, chalcogens, as well as silicon, germanium and tin. Never underestimating serendipity, we appear to also have evolved over the past decade or so to a better understanding of the thermodynamic and kinetic requirements of several of these processes. We are now at the point of being able to use this information for the design of new free radical reactions and the preparation of higher heterocycles of biological significance. Who knows where this chemistry will lead to in the future? Will you join us and play?

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The support of the Australian Research Council over the years, and more recently through the Centres of Excellence programme is gratefully acknowledged. Generous allocation of computing resources from several sources including the University of Melbourne, Osaka Prefecture University, Ormond Supercomputing Facility and the Victorian Institute for Chemical Sciences is appreciated. Finally, without my coworkers who include students, postdocs and other colleagues, there would be nothing to write about. Thank you all.

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