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Tributylgermanium hydride as a replacement for tributyltin hydride in radical reactions †

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Tributylgermanium hydride (Bu_3GeH) can be used as an alternative to tributyltin hydride (Bu_3SnH) as a radical generating reagent with a wide range of radical substrates. Tributylgermanium hydride has several practical advantages over tributyltin hydride, *e.g.* low toxicity, good stability and much easier work-up of reactions. The reagent can be easily prepared in good yield and stored indefinitely. Suitable substrates include iodides, bromides, activated chlorides, phenyl selenides, *tert*-nitroalkanes, thiocarbonylimidazolides and Barton esters. Alkyl, vinyl and aryl radicals can be generated in radical reactions including reduction and cyclisation processes. Common radical initiators such as ACCN and triethylborane can be used. The slower rate of hydrogen abstraction by carbon-centred radicals from Bu_3GeH as compared to Bu_3SnH facilitates improved cyclisation yields. Polarity reversal catalysis (PRC) with phenylthiol can be used in reactions which generate stable radical intermediates which will not abstract hydrogen from Bu_3GeH.

Introduction

Tributyltin hydride has proved to be an excellent radical generating reagent and has been central to the development of modern synthetic radical chemistry. However, there are three major problems with the use of Bu_3SnH and other triorganotin hydrides. Firstly, the toxicity of these compounds rules out their extensive use in pharmaceutical synthesis. Secondly, removal of tributyltin residues from reaction mixtures is fraught with problems. Thirdly, Bu_3SnH is not very stable and decomposes steadily even if carefully stored. The reagent is best bought in fresh or distilled prior to use. With these problems, great difficulty has been encountered in removing organotin residues in pharmaceutical preparations to below the 100 ppm level which is required to avoid toxicity in human consumption. This toxicity problem has almost completely precluded its use by the pharmaceutical industry and hence precluded a wide range of very useful radical reactions in pharmaceutical synthesis.

The search for superior alternatives to Bu_3SnH has been a central goal for free-radical chemists in recent years. A replacement reagent needs to overcome all three problems while at the same time exhibiting a similar range of reactivity and ease of use. In addition, the cost of purchase or synthesis of the new reagent needs to be comparable. In this paper we report our investigation of the use of Bu_3GeH to replace Bu_3SnH as a reagent of standard use. Although use of Bu_3GeH as a radical generating reagent is not novel, wide ranging studies to demonstrate its potential and applicability have been generally lacking.

Several very useful reviews have fully detailed the search for alternatives to Bu_3SnH.[1,2] Alternatives can be generally grouped into several main categories which include:

1. Use of triorganotin hydrides with procedures to minimise the amount of tin residues. The use of catalytic amounts of the stable Bu_3SnCl with another hydride, *e.g.* sodium borohydride, to generate and regenerate Bu_3SnH *in situ* has proved useful and should always be considered if borohydride sensitive groups are not present. Similarly, a number of extractable triorganotin hydrides have been developed.[1–4] Triorganotin hydrides have also been attached to solid phase resins[3,5] or in reverse, the reagents have been attached to solid phase resins and the tin residues washed away.[5] Another development is the application of fluorous triorganotin hydrides using fluorous phase separation techniques.[3,6]

2. Use of other group XIV hydrides. Silanes,[1–3] in particular, tris(trimethylsilyl)silane [$(TMS)_3SiH$ or TTMSS] and polymethylhydrosiloxanes[7] have been extensively developed. Polarity reversal catalysis (PRC) developed by Roberts has allowed triorganosilanes with strong Si–H bonds, *e.g.* Et_3SiH, to be used in conjunction with thiols.[8]

3. New radical generating reagents. An increasing number of new reagents are being reported, *e.g.* silylated cyclohexadienes,[9] gallium hydride ($HGaCl_2$),[10] indium(III) chloride and sodium borohydride[11] and hypophosphorous acid (H_3PO_2) and 1-ethylpiperidine hypophosphite (EPHP).[12] Samarium diiodide has gained popularity as a reductive route to generating radicals but is weakly radioactive which precludes its use as a non-toxic alternative to Bu_3SnH.[13] Manganese triacetate provides a useful oxidative route to generating radicals but is limited to β-dicarbonyl compounds.[14]

4. Precursors which regenerate radicals, *e.g.* xanthates[15] and Barton esters,[16] and the use of atom transfer reactions.[17]

In our studies, we chose Bu_3GeH, a group XIV analogue of Bu_3SnH which is chemically most similar. Potentially, this allows for a similar range of radical reactions and appeared to be the most obvious candidate for development. For the same reasons of similarity to Bu_3SnH, TTMSS has been developed and has proved popular although costly.[3] Surprisingly, although the potential of Bu_3GeH has been known for a considerable time,[18] there are few reports of its use in synthetic studies.[19] The most useful synthetic protocol has been the triphenylgermanium hydride mediated radical carbonylation/cyclisation reactions.[20] Most importantly, reports in the literature[21] indicate that organogermanium compounds are not toxic. However, full toxicology studies on Bu_3GeH or Bu_3GeX compounds are required to fully elucidate this factor. Therefore, the germanium compounds are excellent replacements for toxic triorganotin hydrides.

† Electronic supplementary information (ESI) available: full experimental details and data. See http://www.rsc.org/suppdata/ob/b3/b310520b/

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Prior to our study, tris(trimethylsilyl)germanium hydride $(TMS)_3GeH$, an analogue of TTMSS, was developed to overcome the slow rate of hydrogen abstraction from Bu_3GeH.[22] This reagent behaves similarly to Bu_3SnH with a slightly faster rate of hydrogen abstraction, *i.e.* the rate of abstraction of hydrogen by primary radicals = 3.1×10^6 M^{-1} s^{-1} at 25 °C. The difficulty of synthesis of the reagent has probably precluded its application more widely. Shortly after our studies were initiated, several key papers were published by Oshima and co-workers showing the utility of triorganogermanium compounds in radical reactions.[23–25] Most of these studies report the use of tri-(2-furyl)germanium hydride. These studies also include the triethylborane (Et_3B)-induced radical hydrogermylation of alkynes, alkenes and silyl enol ethers using tri-(2-furyl)germanium hydride[25] and the tri-(2-furyl)germanium hydride mediated hydrogermylation of alkynes and dienes in water using Pd(0) catalysis.[26]

As for much of radical chemistry, excellent kinetic studies have predated the synthetic application, and this is the also the case for Bu_3GeH. Considerable kinetic information has been reported for Bu_3GeH.[2,27,28] The rates of bromine abstraction in S_H2 reactions is similar for both Bu_3SnH and Bu_3GeH, *e.g.* rates of Br-abstraction from CH_2=$CH(CH_2)_4Br$ at 25 °C by: $Bu_3Ge^{\bullet}$ (4.6×10^7 M^{-1} s^{-1}); $Bu_3Sn^{\bullet}$ (5.0×10^7 M^{-1} s^{-1})[27] and the rates of Br-abstraction from $(CH_3)_3CBr$ at 25 °C by: $Bu_3Ge^{\bullet}$ (8.6×10^7 M^{-1} s^{-1}); $Bu_3Sn^{\bullet}$ (1.4×10^8 M^{-1} s^{-1}). However, the rate of H-abstraction by primary alkyl radicals from Bu_3GeH is 24 times slower than from Bu_3SnH, *e.g.* rate of H-abstraction by primary radicals ($RCH_2^{\bullet}$) at 25 °C from: Bu_3GeH (1.0×10^5 M^{-1} s^{-1}); Bu_3SnH (2.4×10^6 M^{-1} s^{-1}).[27] The rate of H-abstraction from Bu_3GeH by more reactive radicals is faster as expected, *e.g.* Me_2C=$CH^{\bullet}$ (3.5×10^7 M^{-1} s^{-1} at 27 °C). Although rates of radical reactions using tri-(2-furyl)germanium hydride have not been reported,[23–25] the rates of H-abstraction are likely to be slightly faster than for Bu_3GeH by comparison with Bu_3SnH and Ph_3SnH. This reagent is also relatively easy to prepare and therefore further study is required to determine whether tri-(2-furyl)germanium hydride or Bu_3GeH is the more useful radical reagent.

Results and discussion

There are no reports in the literature on the other two criteria, *i.e.* ease of removal from reaction products and stability of triorganogermanium hydrides. Our studies were aimed at determining whether Bu_3GeH could replace Bu_3SnH as the general radical reagent. To this end we studied the synthesis and cost, stability, ease of work-up and the range of reactivity of Bu_3GeH.

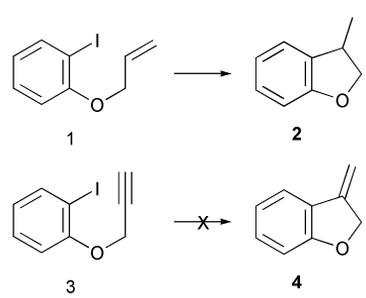
Our first target was to determine a facile synthesis of a suitable triorganogermanium reagent. We initially investigated the synthesis of triphenylgermanium hydride on the basis that the rate of abstraction of hydrogen would be usefully placed in between that of Bu_3GeH and Bu_3SnH. Tetraphenylgermane was synthesised in good yield by the reaction between germanium(IV) chloride and phenylmagnesium bromide[29] or phenyllithium.[30] The tetraphenylgermane was converted to triphenylgermanium bromide with bromine in 1,2-dibromethane[31] which in turn was converted to triphenylgermanium hydride by reduction with sodium borohydride. However, we discovered that the triphenylgermanium bromide and hydride were largely insoluble in the common solvents used for radical reactions and we abandoned this route.

We adapted a published synthesis of Bu_3GeH involving a Cp_2TiCl_2-catalysed (8 mol%) Grignard reaction between germanium tetrachloride and butylmagnesium chloride.[32] This route uses the cheapest source of germanium, germanium tetrachloride. Only one reaction is required which is time saving and also cuts costs, whereas other procedures use two reactions, one to add the butyl groups and another to reduce the resulting tributylgermanium chloride to the hydride. The mechanism proposed[32] is as follows: Cp_2TiCl_2 is reduced to Cp_2Ti(III)Cl followed by substitution of the chloride atom giving Cp_2Ti(III)-Bu which eliminates butene to afford Cp_2Ti(III)H, which is responsible for the reduction of the initially formed Bu_3GeCl. The yields were variable but commonly at *ca.* 50%. The main difficulty was the requirement for careful distillation using a 'Kugelrohr' apparatus because Bu_3GeH and tetrabutylgermanium have similar boiling points (123 °C/20 mmHg and 170 °C/20 mmHg respectively). The distillation normally had to be repeated.

We were most pleased to discover the excellent stability of Bu_3GeH. Bu_3GeH was indefinitely stable when stored in a freezer under a nitrogen atmosphere. As a test of solvent stability we followed the decomposition of Bu_3GeH and Bu_3SnH in $CDCl_3$ solutions (in NMR tubes) using ^1H NMR spectroscopy. The Bu_3SnH was shown to largely decompose within 24 h whereas the Bu_3GeH remained stable over several weeks with the spectrum unaltered. Bu_3GeH can be prepared on a large scale by this route and stored indefinitely for later use. Thus, the prohibitive cost of purchasing Bu_3GeH at present is not justified and can be easily synthesised in the laboratory for *ca.* 5–7 times the price of the purchase of Bu_3SnH. Part of this excess cost is offset by the superior stability and lack of wastage, whereas poor stability, considerable wastage and general frustration are common with the use of Bu_3SnH.

We tested the use of Bu_3GeH as a radical mediator on a representative range of radical precursors which included the generation of aliphatic, vinyl and aryl radicals, cyclisation and reduction reactions and reactions with a range of radical-abstractable groups.

Bromo- and iodo-arenes were first studied in a classic radical cyclisation reaction. The rate of H-abstraction from Bu_3GeH by aryl radicals is fast (2.6×10^8 M^{-1} s^{-1} at 29 °C)[27] but the rate of bromine abstraction from bromobenzene by $Bu_3Ge^{\bullet}$ radicals at ambient temperature is relatively slow ($<1.0 \times 10^5$ M^{-1} s^{-1})[33] which indicated that the reaction may be slow. Therefore, iodoarenes were first studied (see Scheme 1, Table 1). Cyclisation of 2-iodo-1-(prop-2-enyloxy)benzene **1** gave similar yields of 3-methyl-2,3-dihydrobenzofuran using Bu_3GeH and Bu_3SnH with the former reaction being slightly slower. The catalytic use of Bu_3GeH with sodium borohydride to reduce the tributylgermanium iodide back to the hydride was less effective but needs further study. The use of catalytic phenylthiol for polarity reversal catalysis (PRC) was unnecessary.[34] Cyclisation of the alkyne **3** using Bu_3GeH did not result in the expected cyclic product **4** (or the tautomer, 3-methylbenzofuran) but gave an intractable mixture which suggested that $Bu_3Ge^{\bullet}$ radicals had added to the double bond. The slow addition of $Bu_3Ge^{\bullet}$ radicals to alkenes is a known disadvantage, especially if stable radicals result from the addition.[35]



Scheme 1

The radical cyclisation reactions of 1-iodo-2-[(3-phenylprop-2-enyl)oxy]benzene **5a** and 1-bromo-2-[(3-phenylprop-2-enyl)-oxy]benzene **5b** were also investigated (Scheme 2 and Table 2). The rate of bromine abstraction from bromobenzene by $Bu_3Ge^{\bullet}$ radicals at ambient temperature is relatively slow

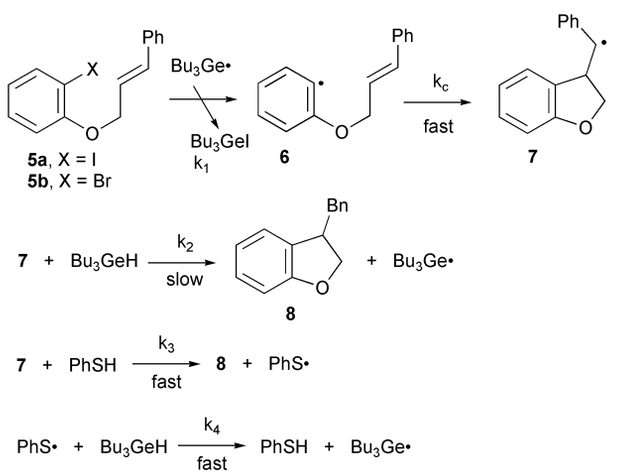
Table 1 Cyclisation of 2-iodo-1-(prop-2-enyloxy)benzene **1**

	Reaction conditions	yields
Bu_3SnH (1.2 equiv.)	ACCN, toluene, reflux, 2 h	**2** (86%)
Bu_3GeH (1.2 equiv.)	ACCN, toluene, reflux, 3 h	**2** (91%)
Bu_3GeH (0.1 equiv.)	AIBN, *t*-BuOH–toluene, reflux, $NaBH_4$, 2 h; 6 h	**1** (83%), **2** (0%); **1** (37%), **2** (44%)
Bu_3GeH (1.2 equiv.)	AIBN, toluene, reflux, 2 h, PhSH (0.1 equiv.),	**2** (85%)

Table 2 Radical cyclisation of 1-iodo- and 1-bromo2-[(3-phenylprop-2-enyl)oxy]benzene (**5a** and **5b** respectively)

Reaction conditions	Radical precursor	Yield **8** (%)
Bu_3SnCl (0.1 equiv.), $NaBH_4$, AIBN, *t*-BuOH, reflux, 4 h	**5a**	59
	5b	77
Bu_3SnH (2 equiv.),AMBN,[a] cyclohexane, reflux, 3 h	**5a**	92
	5b	52
Bu_3GeH (1.3 equiv.),AMBN, cyclohexane, reflux, 3 h	**5a**	0
Bu_3GeH (1.0 equiv.), PhSH (0.1 equiv.) ACCN, cyclohexane, reflux, 9 h	**5a**	75
Bu_3GeH (1.8 equiv.),AMBN, cyclohexane, reflux, 3 h	**5b**	7
Bu_3SnH (2.2 equiv.), syringe-pump addition AMBN, MeCN/ toluene, reflux, 3 h	**5a**	52
Bu_3GeH (1.8 equiv.), syringe-pump addition AMBN, MeCN/ toluene, reflux, 3 h	**5a**	4
Bu_3SnH (2 equiv.), Et_3B, THF, 25 °C, 21 h	**5a**	64
Bu_3GeH (1.3 equiv.), Et_3B, cyclohexane, 25 °C, 21 h	**5a**	0

[a] AMBN = **a**zobis**m**ethyliso**b**utyro**n**itrile or by IUPAC nomenclature, 2-(1-cyano-1-methyl-propylazo)-2-methyl-butyronitrile.



Scheme 2 Polarity reversal catalysis (PRC) with Bu_3GeH using PhSH.

($<1.0 \times 10^5$ M^{-1} s^{-1})[33] but will be faster at higher temperatures and the rate of abstraction of iodine (k_1) will be faster again. The rate of cyclisation of the intermediate aryl radical from **1** has been measured as 6.3×10^9 s^{-1} at 30 °C[36] and, therefore, the rate of cyclisation (k_C) of the aryl radical **6** will be considerably faster. Although the rates of H-abstraction by aryl radicals from Bu_3SnH and Bu_3GeH are fast (5.9×10^8 M^{-1} s^{-1} and 2.6×10^8 M^{-1} s^{-1} respectively at 30 °C)[27,36] the rate of cyclisation should be considerably faster and reduction to uncyclised [(3-phenylprop-2-enyl)oxy]benzene is unlikely. The rates are favourable and good cyclisation reactions were expected. We were initially perplexed when the cyclisations using Bu_3SnH gave good yields of the cyclised product **8** with largely unaltered starting material **5a** or **5b** whereas the yields with Bu_3GeH were extremely low (Table 2). Various different reaction conditions and initiators failed to improve the yields.

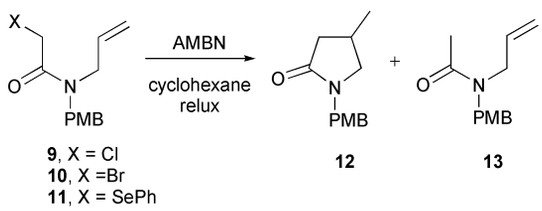
We suggest that the poor reactions with Bu_3GeH are due to the slow rate of H-abstraction (k_2) by the intermediate benzyl radical **7** from Bu_3GeH. While this rate has not been measured, the rate of H-abstraction from Bu_3SnH by benzyl radicals has been measured (3.6×10^4 M^{-1} s^{-1} at 25 °C). The rate is fast enough to allow chain propagation. However, the rate of H-abstraction from Bu_3GeH is likely to be some 20–30 times slower, *i.e.* too slow to facilitate propagation and hence the chain reaction is inhibited. This example illustrates that the slow rate of H-abstraction from Bu_3GeH can be a disadvantage compared to Bu_3SnH. In order to overcome the problem of reduction of the very stable, hence unreactive, benzylic radical intermediate **7**, we applied the 'polarity-reversal catalysis' (PRC) technique developed by Roberts[34] with excellent success. The yield of cyclisation to **8** increased to 75% (Table 2). The benzyl radical intermediate **7**, which we suggest is nucleophilic, reacts relatively rapidly (k_3) with the electrophilic source of hydrogen (PhSH). The rate of reaction between benzyl radicals and PhSH is 3.1×10^5 M^{-1} s^{-1} at 25 °C.[27,28] The rate of H-abstraction from nucleophilic Bu_3GeH by electrophilic phenylthiyl radicals (k_4) is unknown but is predicted to be similar to the rate of H-abstraction by electrophilic *tert*-butoxyl radicals (9.2×10^7 M^{-1} s^{-1} at 27 °C).[28] Therefore, one very slow rate (k_2) is replaced by two relatively fast rates (k_3 and k_4) using the favourable polarity of the radical intermediates. This is the first example of the use of PRC with triorganogermanium hydrides and provides a route around the problems of slow H-abstraction by radical intermediates from Bu_3GeH.

Since we started our studies, Oshima and co-workers have reported the abstraction of iodine from iodo arenes using tri-(2-furyl)-germanium hydride.[24]

We used the amides **9**–**11**[37] to study the efficacy of Bu_3GeH with different radical-abstractable groups, *i.e.* Cl, Br, PhSe (Table 3). Iodine is predicted to react faster than bromine. The reactions were carried out with the Bu_3GeH or Bu_3SnH added at the beginning of the reaction so that the relative amounts of cyclised 1-(4-methoxybenzyl)-4-methylpyrrolidin-2-one **12** and the reduced uncyclised product *N*-allyl-*N*-(4-methoxybenzyl)-acetamide **13** could be measured. Slow addition of Bu_3GeH or Bu_3SnH with the use of a syringe pump would give largely cyclised products. The C–Cl bond in the precursors **9**, alpha to the amide moiety, is weakened and is therefore sufficiently reactive to act as a radical precursor. The rates of reaction of the initial step should be similar for Bu_3GeH and Bu_3SnH. In fact, the rate of abstraction for phenylselanyl with $Bu_3Ge^{\bullet}$ (9.2×10^8 M^{-1} s^{-1} at 25 °C) is slightly faster than that for $Bu_3Sn^{\bullet}$ (1.2×10^8 M^{-1} s^{-1} at 25 °C).[38] The major difference in reactivity will be the rate of H-abstraction by the intermediate radicals and hence Bu_3GeH should favour cyclisation over reduction to **13**. This selectivity was in fact observed (Table 3) for all three radical leaving groups and was most marked for bromine, *i.e. ca.* seven times more selective based on recovered **10**. As expected, the Bu_3GeH reactions were slower.

Table 3 Comparison between Bu_3SnH and Bu_3GeH for Cl, Br and SePh radical leaving groups

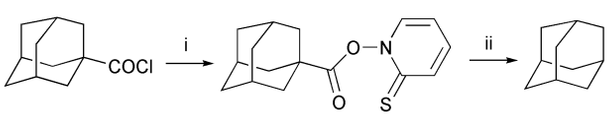
Reaction conditions	Radical precursor	Products (Yields)
Bu_3SnH (1.5 equiv.),1 h	**9**	**9** (0%), **12** (47%), **13** (23%)
Bu_3GeH (1.5 equiv.), 4 h	**9**	**9** (25%), **12** (34%), **13** (13%)
Bu_3GeH (1.5 equiv.), 8 h	**9**	**9** (23%), **12** (42%), **13** (17%)
Bu_3GeH (1.5 equiv.),12 h	**9**	**9** (22%), **12** (48%), **13** (23%)
Bu_3SnH (1.4 equiv.), 30 min	**10**	**10** (0%), **12** (39%), **13** (33%)
Bu_3GeH (1.1 equiv.), 5.5 h	**10**	**10** (12%), **12** (64%), **13** (8%)
Bu_3SnH (1.7 equiv.), 3 h	**11**	**11** (0%), **12** (29%), **13** (38%)
Bu_3GeH (1.1 equiv.), 3 h	**11**	**11** (48%), **12** (18%), **13** (8%)
Bu_3GeH (1.1 equiv.), 5 h	**11**	**11** (0%), **12** (67%), **13** (19%)



9, X = Cl
10, X =Br
11, X = SePh

12 **13**

Bu_3GeH was tested on widely used synthetic reactions using thiocarbonyl reagents, *i.e.* decarboxylation using Barton esters and deoxygenation using the Barton–McCombie reaction.[39] The $Bu_3Ge^{\bullet}$ radical adds successfully to the sulfur of the thiocarbonyl group and facilitates the breakdown of the resulting radical intermediates as reported for $Bu_3Sn^{\bullet}$ radicals. The use of Bu_3GeH was tested on the Barton ester of adamantane-1-carboxylic acid. The ester was prepared *in situ* from the acid chloride and reacted directly with Bu_3GeH and Bu_3SnH (Scheme 3). The one pot reaction is the normal method but does not indicate the yield of each step. The reaction with Bu_3GeH gave a 33% yield of adamantane whereas the reaction with Bu_3SnH under the same conditions yielded 81%. Although the reaction was not repeated it indicates that Bu_3GeH reacts successfully with Barton esters in decarboxylation reactions.



Scheme 3 *Reagents and conditions*: i. DMAP (1.0 equiv.), *N*-hydroxy-2-thiopyridone (1.2 equiv.), toluene, reflux, 15 min; ii. Bu_3GeH (3.0 equiv.), toluene, reflux, 1 h, adamantane (33%).

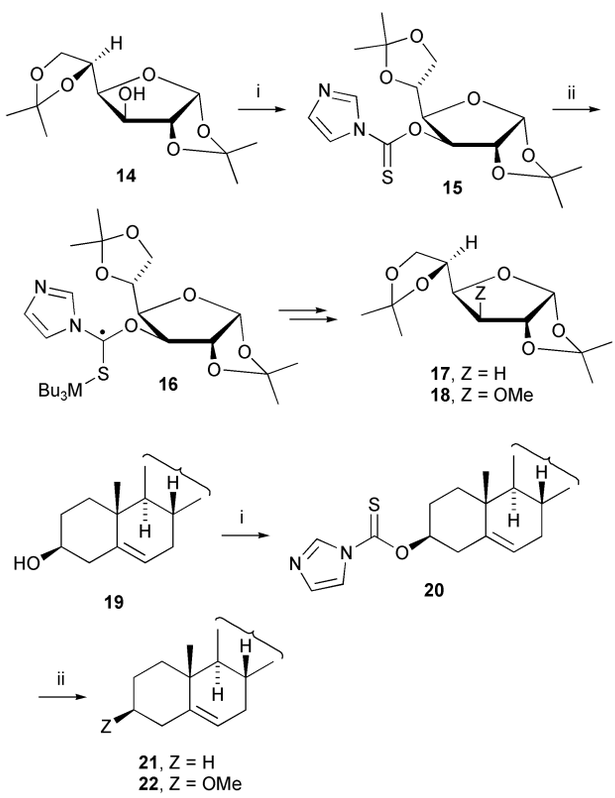
Both primary and secondary alcohols can be easily deoxygenated using Barton–McCombie reactions of thiocarbonylimidazolides.[39] Bu_3SnH-promoted reduction of these compounds is well known in the literature and the reactions normally proceed in high yields. In order to investigate whether Bu_3GeH could mimic the excellent reactivity of Bu_3SnH, the thiocarbonylimidazolide esters of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose **15** and cholesterol **20** were synthesised and reacted with Bu_3GeH and Bu_3SnH for comparison (Scheme 4, Table 4). The glucose ester **15** was added to Bu_3GeH or Bu_3SnH in the reaction mixture to ensure a high concentration of the radical mediator. When the concentration of Bu_3SnH is relatively high, thiocarbonylimidazolides can be reduced to the corresponding methoxy compounds.[40] The faster H-abstraction from Bu_3SnH facilitates interception of the initial intermediate radical **16** by reduction and eventually yields the methoxy analogue **18** (28%) as well as the expected deoxygenated product **17** (29%). The H-abstraction is slower from Bu_3GeH to the intermediate **16**, which has time to fragment (β-scission), finally yielding **17** (87%). None of the methoxy derivative **18** was formed indicating that no reduction of **16** took place.

The radical deoxygenation of the cholesterol thiocarbonylimidazolide **20** using Bu_3GeH also gave a good yield of cholestane **21** when either **20** was added to Bu_3GeH (60%) or when Bu_3GeH was added to **20** (67%) in the reaction. Unexpectedly,

Table 4 Reactions of Bu_3GeH and Bu_3SnH with thiocarbonyl reagents

Reaction conditions	Product(s) (Yields)
15, Bu_3SnH (8.0 equiv.), 90 min [a]	**17** (29%), **18** (28%)
15, Bu_3GeH (5.4 equiv.), 90 min [a]	**17** (87%), **18** (0%)
19, Bu_3SnH (2.0 equiv.), 3 h [a]	**19** (0%), **21** (54%), **22** (0%)
19, Bu_3GeH (2.4 equiv.), 3 h [a]	**19** (0%), **21** (60%), **22** (0%)
19, Bu_3SnH (2.0 equiv.), 3 h [b]	**19** (51%), **21** (5%), **22** (11%)
19, Bu_3GeH (2.0 equiv.), 3 h [b]	**19** (0%), **21** (67%), **22** (0%)

[a] **15** or **19** was added to Bu_3SnH or Bu_3GeH. [b] Bu_3SnH or Bu_3GeH was added to **19**.



14 **15** **16**

17, Z = H
18, Z = OMe

19 **20**

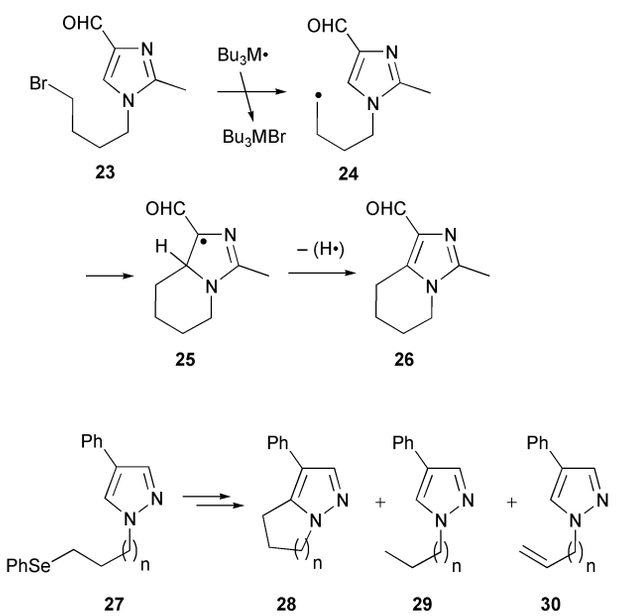
21, Z = H
22, Z = OMe

Scheme 4 *Reagents and conditions*: i. thiocarbonyldiimidazole (2.0 equiv.), DMAP (0.2 equiv.), CH_3CN, reflux, 150 min (**15**, 100%; **20**, 84%); ii. toluene, reflux, ACCN, Bu_3MH (see Table 4).

the Bu_3SnH results were more confusing; when **20** was added to Bu_3SnH a good yield of the deoxygenated product **21** was obtained (54%), but when Bu_3SnH was added to **20** in the reaction, a mixture of **19**, **21** and **22** were obtained. Both **19** and **22** result from Bu_3SnH interception of the intermediate radical by fast H-abstraction from Bu_3SnH. By comparison with literature studies,[40] the cholesterol **19** results from hydrolysis of the reduced radical intermediate, not hydrolysis of the imidazolide **20**. In summary, Bu_3GeH gives more reliable results than Bu_3SnH under various reaction conditions in the two Barton–McCombie reactions investigated. Reduction of a

thioxanthate has also been reported using reduction with tri-(2-furyl)germanium hydride.[24]

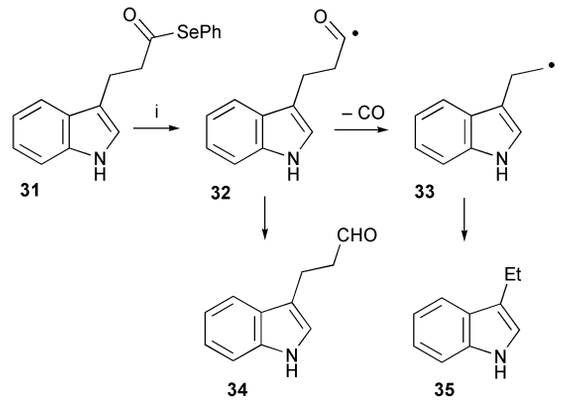
Cyclisation onto azoles was investigated in order to ascertain whether Bu_3GeH would give better cyclisation results than Bu_3SnH (Scheme 5). We chose two examples from our previous studies, imidazole **23**[41] and pyrazoles **27**.[42] The slower rate of H-abstraction from Bu_3GeH (as compared to Bu_3SnH) by the intermediate **24** should favour cyclisation to the π-radical **25** over reduction. The mechanism involves an oxidative step in rearomatisation which is uncertain but H-abstraction by radicals resulting from breakdown of the initiator is most likely.[42] The reaction of the imidazole **23** was slower for Bu_3GeH than Bu_3SnH as expected and neither gave any uncyclised reduced products [Bu_3SnH (1.2 equiv.), AMBN, MeCN, reflux, 3 h, unaltered **23** (29%) and **26** (62%); Bu_3GeH (1.5 equiv.), AMBN, MeCN, reflux, 3 h, unaltered **23** (69%) and **26** (21%)]. Higher temperatures using refluxing toluene gave similar yields with no major improvement whereas use of cyclohexane as the solvent gave lower yields. The 'oxidative' step appears to proceed with both radical reagents which supports the proposition that this step is independent of the radical reagent.[42]



Scheme 5 Radical cyclisation onto azoles.

Cyclisation of the pyrazole **27** had proved problematic with Bu_3SnH and successful results were only obtained using tris(trimethylsilyl)silane and triethylborane (Et_3B) and low temperatures.[42] At higher temperatures considerable amounts of the alkenes **30** (n = 1, 2) had been formed by an unknown mechanism. Reaction of **27** (n = 1) in refluxing toluene gave only the alkene **30** (n = 1, 30%) [Bu_3GeH (1.1 equiv.), ACCN, 6 h] whereas reaction in cyclohexane at room temperature gave only the uncyclised reduced compound **29** (n = 1, 66%) [Bu_3GeH (2.4 equiv.), Et_3B, 26 h]. Even with the slow rate of H-abstraction from Bu_3GeH the intermediate alkyl radical is reduced faster than cyclisation takes place, thereby providing no advantage over Bu_3SnH.[42] The six-membered ring cyclisation is more favourable for both reagents due to less ring strain during cyclisation onto the azole. Reaction of **27** (n = 2) gave a reasonable yield of the cyclised pyrazole **28** (44%) [Bu_3GeH (2.4 equiv.), Et_3B, cyclohexane, room temperature, 34 h] with only traces of the alkene **30** (n = 2, 4%). When the reaction was repeated in refluxing toluene only the alkene **30** (n = 2, 16%) was obtained with unaltered **27** (n = 2, 52%). The results using Bu_3GeH are similar to and give no advantage over Bu_3SnH.

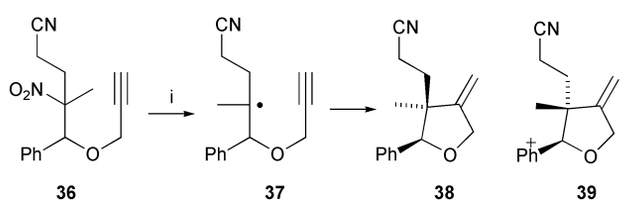
$Bu_3Ge^{\bullet}$ was shown to abstract the PhSe moiety from acyl selanides, *e.g.* **31**, to generate acyl radicals (Scheme 6). The



Scheme 6 *Reagents and conditions*: i. Bu_3SnH (1.1 equiv.), AIBN, toluene, reflux, 2 h, (**34**, 9%; **35**, 48%); Bu_3GeH (1.1 equiv.), ACCN, toluene, reflux, 1 h (**34**, 0%; **35**, 63%).

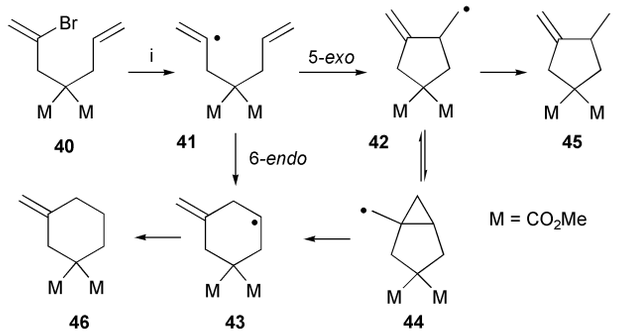
intermediate acyl radical loses carbon monoxide to yield the indol-3-ylethyl radical **33** which is reduced. The rate of decarbonylation is slow (*ca.* 2×10^2 M^{-1} s^{-1} at 80 °C to yield primary alkyl radicals[43]) and therefore Bu_3SnH is able to intercept some of the acyl radical **32** prior to decarbonylation. However, the slower rate of H-abstraction from Bu_3GeH by **32** allows full decarbonylation to **33** and a good yield of 3-ethylindole. Acyl selanides can be synthesised in high yield from the carboxylic acids and the radical reaction is facile and, therefore, the protocol provides a good alternative route to that of Barton esters for the decarboxylation of carboxylic acids.

Bu_3SnH-mediated radical cyclisation using nitro precursors have been developed by Ono and co-workers. The $Bu_3Sn^{\bullet}$ radicals add to the oxygen of the nitro group yielding an intermediate nitroxyl which breaks down to yield an intermediate alkyl radical **37**. The mechanism is fully discussed in the literature.[44] We chose a suitable example, 3-nitro-3-methyl-4-phenyl-4-(prop-2-ynyloxy)butyl cyanide **36**,[45] but obtained poor results with both Bu_3SnH and Bu_3GeH (Scheme 7). Both diastereomers of the cyclised product **38** and **39** were obtained. The Bu_3GeH reactions were disappointing with large amounts of unaltered starting material. Longer reaction times with a larger excess of Bu_3GeH did not enhance the yields. It is interesting to note that the diastereoselectivity in the cyclisation reaction is dependant on the radical mediator used. The Bu_3SnH-mediated reaction gave *ca.* a 1 : 1 mixture of diastereomers whereas the Bu_3GeH-mediated reactions gave a majority of the diastereomer with the two large groups in a *syn* position.



Scheme 7 *Reagents and conditions*: i. Bu_3SnH (1.3 equiv.), AIBN, MeCN, reflux, 3 h (**38**, 21%; **39**, 18%); Bu_3GeH (1.3 equiv.), AIBN, reflux: MeCN, 3 h, (**38**, 8%; **39**, 15%; **36**, 51%) and toluene, 5 h, (**38**, 3%; **39**, 17%; **36**, 53%).

Vinyl radicals were also generated using Bu_3GeH from the vinyl bromide **40** which has been the subject of several studies[46] (Scheme 8). The vinyl radical **41** cyclises by both 5-*exo* and 6-*endo* modes.[46] The 5-*exo* radical intermediate **42** is also able to rearrange *via* **44** to the 6-*endo* radical **43**. We hoped that use of Bu_3GeH would allow more time for the rearrangement to take place, thereby increasing the amount of 6-*endo* product relative to the use of Bu_3SnH. The Bu_3SnH reaction gave an 88% yield of cyclised products as reported in the literature. However, Bu_3GeH gave a very disappointing yield (15%). The



Scheme 8 *Reagents and conditions*: i. AMBN, toluene, reflux, 4 h: Bu_3SnH (1.1 equiv.), (**45**, 57%; **46**, 31%) and Bu_3GeH (1.1 equiv.), (**45**,11%; **46**, 4%); Bu_3GeH (1.1 equiv.), PhSH (0.1. equiv.), AMBN, toluene, reflux, 5 h, (**45**, 33%; **46**, 5%).

starting material was largely consumed indicating that the radicals had been formed. Analysis of the crude reaction mixture by ^{1}H NMR spectroscopy and GCMS showed that the major products resulted from $Bu_3Ge^{\bullet}$ radical addition to the alkene group of the cyclised products **45** and **46**. These addition products were not separable and were not further characterised. These disappointing results indicate a limitation of the use of Bu_3GeH. We also used the PRC protocol with a catalytic amount of PhSH. As expected, this procedure speeded up the reaction and therefore facilitated a higher yield of the 5-*exo* product (33%).

Experimental

Commercial dry solvents were used in all reactions except for light petroleum and ethyl acetate which were distilled from $CaCl_2$ and dichloromethane (DCM) which was distilled over phosphorus pentoxide. Light petroleum refers to the bp 40–60 °C fraction. Sodium hydride was obtained as a 60% dispersion in oil and was washed with light petroleum. Mps were determined on an Electrothermal 9100 melting point apparatus and are uncorrected. Elemental analyses were determined on a Perkin Elmer 2400 CHN Elemental Analyser in conjunction with a Perkin Elmer AD-4 Autobalance. IR spectra were recorded on a Perkin-Elmer Paragon 1000 FT-IR spectrophotometer on NaCl plates. ^{1}H (250 MHz) and ^{13}C (62.5 MHz) NMR spectra were recorded on a Bruker AC-250 spectrometer as solutions of $CDCl_3$ with tetramethylsilane (TMS) as the internal standard for ^{1}H NMR spectra and deuteriochloroform the standard for ^{13}C NMR spectra unless otherwise specified. Chemical shifts are given in parts per million (ppm) and *J* values in hertz (Hz). Mass spectra were recorded on a JEOL SX102 mass spectrometer or carried out by the EPSRC Mass Spectrometry Service at the University of Wales, Swansea. GC-MS was carried out on a Fisons 8000 series GC-MS apparatus using a 15 m × 0.25 mm DB-5 column and an electron impact low resolution mass spectrometer. TLC using silica gel as absorbent was carried out with aluminium backed plates coated with silica gel (Merck Kieselgel 60 F254). Silica gel (Merck Kieselgel 60 H silica) was used for column chromatography unless otherwise specified.

1,2:5,6-Di-*O*-isopropylidene-3-*O*-thiocarbonylimidazole-α-D-glucofuranose **15**,[47] the thiocarbonylimidazolide of cholesterol **20**,[48] 1-(3-bromobutyl)-2-methyl-1*H*-imidazole-4-carbaldehyde **23**,[41] 4-phenyl-1-(3-phenylselanylpropyl)-1*H*-pyrazole **27** (n = 1),[42] 4-phenyl-1-(4-phenylselanylbutyl)-1*H*-pyrazole **27** (n = 2)[42] and 3-nitro-3-methyl-4-phenyl-4-(prop-2-ynyloxy)-butyl cyanide **36**[44] were synthesised using literature procedures.

Tributylgermanium hydride[32]

Tetrachlorogermanium (8.75 g, 40.8 mmol) and butylmagnesium chloride (2 M solution in diethyl ether, 100 cm^3) were successively added dropwise to a solution of Cp_2TiCl_2 (0.76 g, 3.1 mmol) in freshly distilled diethyl ether (200 cm^3) at −78 °C over 45 min. The mixture was allowed to warm to room temperature over 45 min during which period a colour change from milky red to milky green was observed and thereafter refluxed for 15 h. The reaction mixture was cooled to 0 °C, aqueous hydrochloric acid (2 M, 100 cm^3) was added over 1 h and a colour change to red was observed. The organic layer was separated and the aqueous phase was extracted with diethyl ether. The combined organic layer was dried and evaporated to dryness to yield a residue which was filtered through Celite to remove a red solid. Distillation under reduced pressure gave two products; Bu_3GeH (5.25 g, 21.5 mmol, 53%) and tetrabutylgermanium (4.30 g, 14.3 mmol, 35%) as colourless liquids.[32] Bu_3GeH: ν_{max}/cm^{-1} 2957, 2927, 2870, 2853, 2006 and 1460; δ_H 0.82–0.92 (15 H, m, 1, 4-H), 1.34–1.43 (12 H, m, 2, 3-H) and 3.68 (1 H, septet, *J* 2.8, GeH); δ_C 11.92 (3-C), 13.80 (4-C), 26.19 (2-C) and 28.75 (1-C); *m*/*z* 245 (23%), 217 (21), 189 (23), 161 (100), 133 (47) and 105 (41). Bu_4Ge: ν_{max}/cm^{-1} 2956, 2922, 2870, 2853 and 1460, δ_H 0.69–0.72 (8 H, m, 1-H), 0.86–0.94 (12 H, m, 4-H) and 1.31–1.44 (16 H, m, 2, 3-H); δ_C 12.52 (3-C), 13.80 (4-C), 26.70 (2-C) and 27.56 (1-C). This data is identical to published data.[32]

General procedure for radical reactions

A solution of Bu_3GeH or Bu_3SnH was added dropwise to a mixture of the radical precursor in anhydrous solvent at room temperature under an atmosphere of nitrogen. The mixture was heated to reflux and the radical initiator was added, followed by heating under reflux for the time indicated for each reaction. A portion of the radical initiator was added every 40 min. The reaction mixture was cooled to room temperature and evaporated to dryness. The residues were analysed by ^{1}H NMR spectroscopy and TLC and by GCMS when required. The crude residues were purified by column chromatography.

Polarity reversal catalysis (PRC) with the addition of phenylthiol. Phenylthiol (0.1 equiv.) was added along with Bu_3GeH or Bu_3SnH at the beginning of the reaction.

Catalytic amounts of the radical mediator. Bu_3GeH or Bu_3SnH was added dropwise to the solution of the radical precursor in *t*-BuOH at room temperature, followed by addition of sodium borohydride (2 equiv.). The mixture was heated to reflux and AIBN was added, followed by heating under reflux for the time indicated. More AIBN was added every hour upto a total of 0.2 equivalents. After cooling to room temperature the mixture was poured into water and extracted with diethyl ether. The organic layer was washed with water to remove *t*-BuOH, dried and evaporated to dryness.

Triethylborane as the radical initiator. Bu_3GeH or Bu_3SnH and triethylborane (1.0 M solution in THF) were added dropwise to a solution of the radical precursor in anhydrous solvent at room temperature. If the radical mediator was used in a catalytic manner, sodium borohydride was also added at this stage. The mixture was stirred at room temperature for the time indicated. Air was allowed to infuse into the reaction through an open syringe needle in a septum covering one of the necks of the reaction flask.

Syringe-pump addition of the radical mediator. A solution of Bu_3GeH or Bu_3SnH in anhydrous solvent was added by syringe pump to a refluxing mixture of the radical precursor in anhydrous solvent over the period of time indicated under each reaction. The radical initiator was added initially and every 40 min.

Representative procedures are detailed below and the rest of the procedures are reported in the supplementary data. †

Cyclisation of 2-iodo-1-(prop-2-enyloxy)benzene 1

A solution of Bu_3GeH (0.11 g, 0.44 mmol), 2-iodo-1-(prop-2-enyloxy)benzene **1** (96.0 mg, 0.37 mmol) and AIBN (35.0 mg, 0.2 mmol) in toluene (38 cm^3) was heated under reflux for 2 h. Purification gave 3-methyl-2,3-dihydrobenzofuran **2** (45.1 mg, 0.34 mmol, 91%) as a colourless oil. δ_H 1.33 (3 H, d, *J* 6.9, Me), 3.47–3.62 (1 H, m, CHMe), 4.07 (1 H, dd, *J* 7.8, 8.8, CH_AH_BO), 4.68 (1 H, dd, *J* 8.8, 8.8, CH_AH_BO), 6.77–6.89 (2 H, m, Ar 4,6-H) and 7.08–7.17 (2 H, m, Ar 3,5-H); δ_C 20.01 (Me), 37.16 (CHMe), 79.10 (OCH_2), 110.09 (Ar 6-C), 121.05 (Ar 4-C), 124.41 (Ar 5-C), 128.61 (Ar 3-C), 132.87 (Ar 2-C) and 160.29 (Ar 1-C); *m*/*z* 134 (84%), 119 (95) and 91 (100). Spectroscopic data agreed with those in the literature.[49] Other reactions of 2-iodo-1-(prop-2-enyloxy)benzene **1** are reported in Table 1.

Radical cyclisation of 1-iodo-2-[(3-phenylprop-2-enyl)oxy]-benzene 5a using PRC

1-Iodo-2-[(3-phenylprop-2-enyl)oxy]benzene **5a** (100 mg, 0.4 mmol) in anhydrous cyclohexane (35 cm^3), Bu_3GeH (0.1 g, 0.4 mmol), phenylthiol (4 mg, 0.04 mmol) and ACCN (0.2 g, 0.4 mmol in total) were reacted for 9 h using the general procedure for radical reactions. Column chromatography of the resulting mixture using light petroleum and DCM as eluants gave 3-benzyl-2,3-dihydrobenzofuran **8** (56 mg, 0.27 mmol, 75%) as a colourless oil. δ_H 2.80 (1 H, dd, *J* 13.8 and 8.9, CH_2Ph), 3.03 (1 H, dd, *J* 13.8 and 6.4, CH_2Ph), 3.71 (1 H, m, 3-H), 4.24 (1 H, dd, *J* 8.9, 6.0, 2-H), 4.48 (1 H, dd, *J* 8.9 and 8.9, 2-H), 6.79 (2 H, m, 5,7-H), 6.94 (1 H, d, *J* 7.8, 4-H), 7.06–7.32 (6 H, m, Ph and 6-H); δ_C 29.91 (3-C), 39.99 (2-C), 42.37 (1-C), 108.57 (Ar 6-C), 119.25 (Ar 4-C), 123.51 (Ph 4-C), 125.42 (Ar 5-C), 127.22 (Ar 3-C), 127.32 (Ph 2,6-C), 127.52 (Ph 3,5-C), 129.24 (Ar 2-C), 138.13 (Ph 1-C) and 158.89 (Ar 1-C); *m*/*z* 109 (65%), 108 (54), 81 (40), 79 (33), 53 (39) and 41 (100). Spectroscopic data agreed with those in the literature.[50] Other reactions of 1-iodo-2-[(3-phenylprop-2-enyl)oxy]benzene **5a** and those of 1-bromo-2-[(3-phenylprop-2-enyl)oxy]benzene **5b** are reported in Table 2.

Cyclisation of 4-phenyl-1-(4-phenylselanylbutyl)-1*H*-pyrazole 27 (*n* = 2)

Bu_3GeH (43 mg, 0.18 mmol) and Et_3B (1.0 M in hexane, 0.28 mmol) were added dropwise to a solution of 4-phenyl-1-(4-phenylselanylbutyl)-1*H*-pyrazole **27** (*n* = 2) (0.05 g, 0.14 mmol) in anhydrous cyclohexane (25 cm^3). The flask was fitted with a rubber septum and exposed to air *via* a needle while stirring at ambient temperature for 8 h. Further Bu_3GeH (43 mg, 0.18 mmol) and Et_3B (1.0 M in hexane, 0.28 mmol) were added and the mixture stirred for a further 18 h after which period Bu_3GeH (43 mg, 0.18 mmol) and Et_3B (1.0 M in hexane, 0.28 mmol) were again added. The mixture was stirred for a further 8 h. Evaporation to dryness followed by column chromatography using mixtures of light petroleum and EtOAc as eluant gave 3-phenyl-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridine **28** (*n* = 2) (44%), unreacted starting material **27** (*n* = 2) (7%) and 1-but-3-enyl-4-phenyl-1*H*-pyrazole **30** (*n* = 2) (4%). All yields were initially determined with the use of 1,4-dimethoxybenzene as the internal standard in ^1H NMR spectroscopy. **28** (*n* = 2):[42] (Found: M^+, 199.1233. $C_{13}H_{14}N_2$ requires 199.1235); ν_{max}/cm^{-1} 1602, 764 and 699; δ_H 1.84–1.90 (2 H, m, 5-H), 2.04–2.12 (2 H, m, 6-H), 2.95 (2 H, t, *J* 6.2, 4-H), 4.20 (2 H, t, *J* 7.0, 7-H), 7.20–7.28 (1 H, m, Ph 4-H), 7.34–7.41 (4 H, m, Ph 2,3,5,6-H) and 7.43 (1 H, s, 2-H); δ_C 20.55 (5-C), 23.12 (6-C), 23.15 (4-C), 48.18 (7-H), 118.49 (3-C), 125.75 (Ph 4-C), 126.76 (Ph 2,6-C), 128.61 (Ph 3,5-C), 133.67 (Ph 1-C), 135.79 (2-C) and 137.25 (9-C); *m*/*z* 199 (M^+, 100%). **30** (*n* = 2): 2.61–2.69 (2 H, m, 2-H), 4.21 (2 H, t, *J* 7.0, 1-H), 5.06–5.13 (2 H, m, CH=CH_2), 5.70–5.87 (1 H, m, CH=CH_2), 7.26–7.38 (3 H, m, Ph 3,4,5-H), 7.46–7.49 (2 H, m, Ph 2,6-H), 7.61 (1 H, s, pyrazole 3-H) and 7.77 (1 H, s, pyrazole 5-H); *m*/*z* 198 (M^+, 42%), 197 (46), 170 (28), 157 (100), 144 (53), 130 (27) 103 (33), 89 (21), 77 (23) and 39 (38).

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