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Triorganogermanes as non-toxic Reagents in Radical Reactions

By

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A Dotoral Thesis

Submitted in partial fulfilment of the requirements
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Abstract

Triorganogermanes as non-toxic Reagents in Radical Reactions

Sussie L. Krintel

Ph.D. 2002

Tributyltin hydride (TBTH) has proven to be an extremely useful synthetic reagent which has been widely used for generating free radicals, is largely responsible for the large increase in the use of free radicals in organic synthesis and is the reagent of choice for many researchers. However, the tin residues are highly toxic and difficult to separate from reaction mixtures which precludes the use of tributyltin hydride in the pharmaceutical industry. In this project, triorganogermanium compounds have been investigated as possible alternatives to tin based radical mediators.

We have shown that tributylgermanium hydride (TBGH) can replace TBTH in most types of radical reactions. We have successfully used TBGH for the abstraction of I, Br, Cl (in activated α-chloroamides), SePh, NO_2, Barton esters and thiocarbonyl-imidazolides. Alkyl, vinyl and aryl radicals have been generated from the respective iodo- and bromo-precursors and acyl radicals from acyl phenylselanides. Cyclisation onto alkenes and heteroarenes have proved successful. All the performed reactions were carried out under the same conditions with TBTH. In general, TBGH is slower but higher ratios of cyclisation to reduction are observed as compared to TBTH.

A new germanium based radical mediator was developed which was found to exhibit excellent reactivity in the radical reactions tested. The facile synthesis of this reagent enables a variety of triorganogermanium compounds to be synthesised and tested as radical mediators.

Studies of a solid supported approach to germanium mediated radical reactions were initiated and the results obtained were very promising, although some optimising of reaction conditions would be beneficial.

Acknowledgements

I would like to express my gratitude to Russ for being a solid rock in the turbulent world of radical chemistry. Many are the times where I on the edge of tears have gone to his office only to come out with a big smile on my face and with new-found motivation to continue my research. Many thanks to Mark for welcoming me to GSK and for useful discussions, suggestions and support.

I am grateful to all the members of F009 and F402 for ensuring that going to work was more than just another day in the office. Where would I be without the joyful company of Emma Mann (who guided me safely through my first year in Loughborough), Will Barton and Ben Buckley (on a rainy day, it was always possible to induce them into discussions of who has the biggest column...), Véronique Serre, Anthony Fletcher, Serge Reignier, Graeme Potts, Rehana Karim, Cara Johnson and Martin Cloonan.

Many thanks to the technical staff at Loughborough University, especially Dr. Tim Smith, Dr. Mark Edgar, John Spray, Alastair Daley, Andy Kowalski, Diane Dowson, Dave Wilson and John Kershaw.

Thanks to Loughborough University and GlaxoSmithKline for the funding and equipment provided for my research.

Most of all, all my love and thanks to Véronique, Tim and Sylvain for proving to me the value of true friendship in a tough world. May our lives forever be entwined...

Abbreviations

addn.	Addition
ACCN	Azobiscyclohexanecarbonitrile
AIBN	Azobisisobutyronitrile
AMBN	Azobismethylbutyronitrile
Ar	Aromatic
Bn	Benzyl
bs	Broad singlet
Bz	Benzoyl
Cp	Cyclopentadiene
d	Doublet
DCM	Dichloromethane
DMAP	*N*-Dimethylamino pyridine
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
GC	Gas chromatography
El	Electrophil(ic)
Et	Ethyl
eq.	Equivalent(s)
h	Hour(s)
HMPA	Hexamethylphosphoramide
Hz	Hertz
IR	Infrared
J	Coupling constant
LAH	Lithium aluminium hydride
Lit.	Literature
M	Molar
m	Multiplet
Me	Methyl
MHz	Megahertz
min	Minute(s)
mm	Milimeter (Hg)

mp	Melting point
MS	Mass spectroscopy
Ms	Mesyl
n.d.	Not determined
NMR	Nuclear magnetic resonance
Nuc	Nucleophil(ic)
PAHs	Polyaromatic hydrocarbons
Ph	Phenyl
ppm	Parts per million
Pr	Propyl
PRC	Polarity reversal catalysis
t	Triplet
TBGH	Tributylgermanium hydride
TBTH	Tributyltin hydride
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Tetramethylsilyl
TPGBr	Triphenylgermanium bromide
TPGH	Triphenylgermanium hydride
TPTH	Triphenyltin hydride
Ts	*p*-Toluenesulfonate
TTMSS	Tris(trimethylsilyl)silane
UV	Ultraviolet
V-70	Azobis(4-methoxy-2,4-dimethyl)valeronitrile

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Chapter 1. Introduction

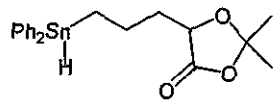
1.1 General introduction

Radical reactions have now stopped being a mere curiosity in organic chemistry and have become the method of choice in a variety of organic syntheses. This is especially due to the mild reaction conditions employed and the great tolerance toward a variety of functional groups in the molecule. Trialkyltin hydrides, especially tributyltin hydride (TBTH), have often been the chosen reagents and their efficiency as radical mediators is indisputable. Unfortunately, some problems are related to their use in organic chemistry. Tin compounds have been shown to be toxic (LD_{50} for TBTH is 127 mg per kg in rats)[1] and this combined with the fact that tin residues often are difficult to remove from crude reaction mixtures, results in tin mediated reactions being of very limited use in the pharmaceutical industry. Therefore, minimisation or removal of the problems associated with the use of trialkyltin hydrides has become a research area of great importance.[2]

An obvious way of doing so is to use the toxic trialkyltin hydride in a catalytic manner and then add a reducing reagent in stoichiometric amount. This approach has been employed widely with a variety of radical precursors with good results.[3] The very fast reduction of R_3SnX (X = halogen) formed *in situ* in many radical reactions can also be used as a simple way of removing tin residues. If stoichiometric use of R_3SnH is mandatory in a given radical reaction, treatment of the crude reaction mixture with a reducing reagent (e.g. $NaBH_3CN$) will often give R_3SnH by reduction of the tin by-products formed in reaction. R_3SnH are very nonpolar compounds and can in most cases quite easily be separated from reaction products by chromatography.[4] It is possible at the same time to take advantage of the excellent reactivity of tin hydrides and ease the purification of the reaction mixture, by employing fluorous tin reagents, as demonstrated by Curran *et al.*[5] The reactivity of these compounds are similar to those of "normal" tin hydrides but since the low-boiling perfluorinated fluids are immiscible in both water and many organic solvent, removal of tin residues can be done by simple extraction into perfluorinated solvent (e.g. perfluoromethylcyclo-hexane or perfluorohexane).

In the same line of work, Clive *et al.* [6] have published the use of the tin hydride **1** shown in **Figure 1**. Stannane **1** has been employed in different radical reactions leading to isolation of the products in high yields. The advantage of **1** is that after reaction, tin containing by-products are easily removed by mild hydrolysis (LiOH-water-THF or TsOH-water-THF) which converts them into base soluble compounds.

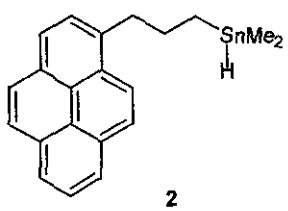
Figure 1. Triorganotin hydride **1** employed by Clive.



1

Gastaldi and Stien, who have taken advantage from the fact that polyaromatic hydrocarbons (PAHs) adsorb on charcoal, have presented another "modified" tin hydride.[7] They developed dimethyl-3-pyrenypropyl tin hydride **2** (**Figure 2**) and have found it to be very efficient in radical reactions. After reaction, the adsorption of the pyrene core on charcoal can be monitored by UV and the solids removed by filtration, allowing isolation of the reaction product.

Figure 2. Dimethyl-3-pyrenypropyl tin hydride **2** employed by Gastaldi and Stien.



2

Solid phase chemistry has opened up other methods for handling the problems concerning the use of tin hydrides in radical chemistry. Generally speaking, the difficulties in removing tin residues from reaction mixtures can be dealt with in two ways using solid phase approaches since either the tin reagent[8] or the radical precursor[9] can be attached to a resin. In both cases, purification of the reaction product(s) will largely be carried out by filtration.

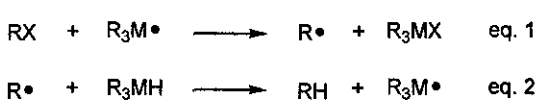
So far this introduction has only dealt with minimising the problems associated with the use of tin hydrides as radical mediators. Still, another way of overcoming these

problems would be to remove the cause of them, *i.e.* to use alternatives to triorganotin hydrides.

1.2 Alternatives to triorganotin hydrides

A large amount of research has been devoted to finding radical mediators that will be lacking the toxicity and purification problems connected with the use of triorganotin hydrides, but which will display similar reactivity. Some proposed alternatives include indium metal (radical addition to conjugated alkenes only),[10] gallium hydride,[11] alkylmercury halides,[12] and dimanganese decacarbonyl.[13] Hypophosphorous acid has been reported to show good reactivity in a variety of radical reactions and the reagent has the great advantage that it can be employed in aqueous media.[14,15] All these reagents have shown promising results when used as radical mediators but some of the more widely used alternatives still remain to be mentioned. The efficiency of tin hydrides as radical mediators is caused by (a) organotin radicals generate carbon centred radicals from many functional groups, and (b) tributyltin hydride traps radicals with sufficient rate and regenerates the tin radicals, *i.e.* eq. 2 (**Scheme 1**, M = Sn) is sufficiently fast to keep the chain reaction going. For hydrides derived from other elements to be even considered as candidates to "the throne of tin" both eq. 1 and 2 (**Scheme 1**) must be efficient radical processes.

Scheme 1. Schematic presentation of radical reactions.



From the position in the periodic table of elements, silicon and germanium derived compounds are expected to display reactivities similar to the reactivity of their tin analogues. From kinetic studies, rate constants for reactions with alkyl radicals (*i.e.* eq. 2, **Scheme 1**) have been determined for a number of hydrogen donors. Some of these values are shown in **Table 1**[16] for reactions with primary radicals only, and it can be seen that Et_3SiH (and to some extent, Ph_3SiH) reacts with radicals so slowly that chain propagation will be inefficient. Therefore, these reagents would not be good substitutes for tin hydrides, but tris(trimethylsilyl)silane (TTMSS) and

tributylgermanium hydride (TBGH) [and obviously TBTH and triphenyltin hydride (TPTH)] would, judged from this criteria.

Table 1. Rate constants for H-donation to primary radicals.

Donor	Radical	Rate constant ($M^{-1}s^{-1}$)[a]
Et_3SiH	RCH_2•	$k_{25} = 7.0 \times 10^2$
Ph_3SiH	RCH_2•	$k_{50} = 3.0 \times 10^4$
$(Me_3Si)_3SiH$	RCH_2•	$k_{25} = 3.8 \times 10^5$
Bu_3GeH	RCH_2•	$k_{25} = 1.0 \times 10^5$
Bu_3SnH	RCH_2•	$k_{25} = 2.4 \times 10^6$
Ph_3SnH	RCH_2•	k_{25} = ca. 5.0×10^6

[a]Reactions temperatrue (°C) as subscript

For TTMSS and TBGH to be considered as possible alternatives to TBTH, these reagents have to be capable of generating radicals from different functional groups, *i.e.* eq. 1, **Scheme 1**, has to be an efficient process. Most frequently, halides are used as radical precursors, and the rate constants for the formation of tertiary radicals from *t*-BuBr are shown in **Table 2.**[17] From these data it is clear that TTMSS will abstract bromide at approximately the same rate as will TBTH, whereas the generation of $(CH_3)_3C$• by TBGH is a slightly slower reaction. The reaction is still sufficiently fast, though, to be able to mediate the radical chain reaction.

Table 2. Rate constant for Br-abstraction by R_3MH.

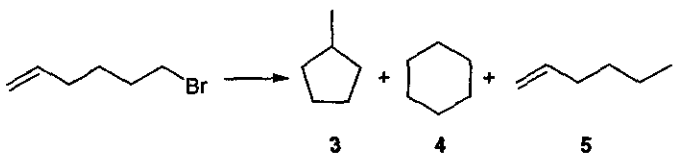
Halide	R_3MH	Rate constant ($M^{-1}s^{-1}$)[a]
$(CH_3)_3Br$	TBTH	$k_{25} = 1.4 \times 10^8$
$(CH_3)_3Br$	TBGH	$k_{27} = (8.6 \pm 1.0) \times 10^7$
$(CH_3)_3Br$	TTMSS	$k_{20} = 1.1 \times 10^8$

[a]Reactions temperatrue (°C) as subscript

No kinetic data can be found for the reaction of triphenylgermanium hydride (TPGH), but it is reasonable to believe that this compound will be more reactive than TBGH, and the reactivity is probably similar to that of TBTH.

TTMSS was first reported by Gilman *et al.*[18] in 1965, but is was not until 20 years later that Chatgilialoglu and co-workers[19] saw its real potential as a radical mediator. Since then, it has become the most successful tin hydride substitute to date. It has been employed in both reductions and radical cyclisation reactions, and in the latter, selectivity towards cyclisation is often observed (**Scheme 2**).[17]

Scheme 2. Radical cyclisation of 6-bromohex-1-ene.



Reagents and conditions: TTMSS (1 eq.), AIBN, 70 °C [**3** (93 %), **4** (2 %) and **5** (4 %)] or TBTH (1 eq.), AIBN, 70°C [**3** (83 %), **4** (1 %) and **5** (15 %)].

In the reaction of hexenyl bromide with TTMSS and TBTH respectively, it was found that reaction with the former gave a 24:1 ratio of cyclic:reduced product whereas the ratio in the tin mediated reaction was only 6:1.[19] This change in reactivity is easily explained by the lower H-donor ability of TTMSS compared to TBTH and is a good example of the reactivity of TTMSS.

1.3 Triorganogermanium compounds in radical reactions

One of the major problems with tin reagents is, as mentioned earlier, that they are toxic. Organogermanium compounds have been shown to display much less toxicity than both the corresponding organotin- and silicon analogues. The toxicity of butylchlorogermanes $Bu_{4-n}GeCl_n$ administered *i.p.* grows with increasing number of chlorine atoms in the molecule (1280, 96, 50 mg kg^{-1} for mice and 1970, 100, 48 mg kg^{-1} for rats).[20] Results provided to us by Professor Oshima of Kyoto University indicate an initial LD_{50} for tri-2-furanylgermane of 0.5-2.0 g per kg in rats, hence very low acute toxicity.

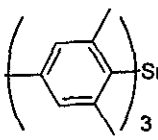
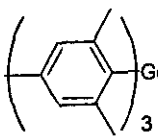
From the kinetic data, triorganogermanes should react sufficiently fast with both halides and radicals to initiate and propagate radical chain reactions, and evidence reported in the literature proves that this is in fact the case. In the following examples, precedence for the use of triorganogermanium compounds in radical chemistry will be discussed according to reaction type.

1.3.1 Radical reduction of organic halides

Hershberger *et al.* initiated in the mid 1980's an investigation of the reactivity of germanium derived radical mediators and compared this reactivity with the tin analogues. Some of their results of reductions of iodoundecane are shown in **Table 3**.[21]

Table 3. Comparison of reactivity in reduction of iodoundecane.

n-$C_{11}H_{23}I$ ⟶ n-$C_{11}H_{24}$

	R_3MH	% n-$C_{11}H_{24}$	% n-$C_{11}H_{23}I$ (GC-yield)
1.	Bu_3SnH	98	4
	Bu_3GeH	70	20
2.	Ph_3SnH	93	5
	Ph_3GeH	98	5
3.		93	11
		<1	97

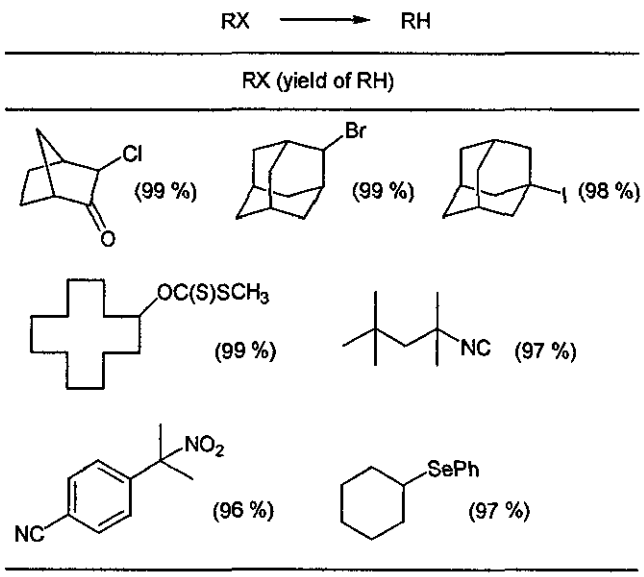
Reagents and conditions: R_3MH (1 eq.), AIBN, benzene, 80 °C, 8 h.

They found that reactions promoted by TBGH appear to be slower than the TBTH mediated reaction, as seen by the amount of starting material recovered after 8 h reflux. This may be a consequence of the lower ability of TBGH to carry the chain reaction and the problem may be overcome by introduction of several charges of AIBN. Both the TPTH and TPGH mediated reactions are complete after 8 h. Apparently steric hindrance in the hydride is more important for the

triorganogermanium hydride than for the triorganotin hydride as can be seen from entry 3 (**Table 3**). The authors have unfortunately not given any explanation, but it could be a point worth noticing if considering using triorganogermanium hydride instead of triorganotin hydride.

Inspired by the success of TTMSS, Chatgilialoglu and co-workers developed the corresponding tris(trimethylsilyl)germane and tested the compound in the reduction of a variety of organic compounds (**Table 4**).[22] Tris(trimethylsilyl)germane proved to be a very effective reducing agent in reactions of halides, thiono esters (Barton-McCombie reaction), isocyanides and nitro and phenylselanide derivatives, where up to quantitative yields in all reactions were observed by GC analysis.

Table 4. Reductions by tris(trimethylsilyl)germane.



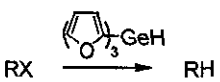
Reagents and conditions: RX (0.2 M), $(CH_3Si)_3GeH$ (0.4 M), AIBN (10 mol %), toluene, 82 °C, 20-60 min.

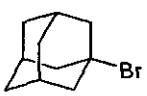
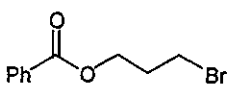
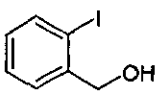
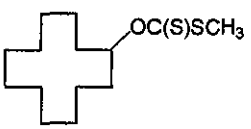
The authors quantified the observed reactivity by utilising the 5-hexenyl cyclisation as a radical clock and measured the rate constant for H-abstraction from $(CH_3Si)_3GeH$ as $k_{25} = 3.1 \times 10^6\ M^{-1}s^{-1}$, making this reagent slightly more reactive than TBTH in radical reductions.

Among the people investigating triorganogermanium hydrides as alternatives to triorganotin hydrides, Oshima *et al.* have been some of the more conspicuous

pioneers. They have tested various germanium based radical mediators in different radical reactions and have found that TPGH is efficient in Et_3B-initiated radical reduction of organic halides. More recently, Oshima *et al.* have developed tri-2-furanylgermane, which was also shown to reduce organic halides when initiated by triethylborane. The advantage of triethylborane is that, unlike reactions initiated by AIBN or other azo-based initiators, reactions can be performed at room temperature leading to very mild reaction conditions. The results obtained by Oshima *et al.* (**Table 5**)[23] showed that (primary and secondary) halides are reduced in high yield and also that the Barton-McCombie reaction (**Table 5**, entry 7) proceeded at room temperature. Comparison of the yields of the latter reaction with the results obtained by Chatgilialoglu and co-workers (**Table 4**) suggests that tris(trimethylsilyl)germane may be superior to tri-2-furanylgermane in these reactions.

Table 5. Reductions using tri-2-furanylgermane.



Entry	RX	time/h	yield/%
1	n-$C_{12}H_{25}I$	1	99
2	n-$C_{12}H_{25}Br$	2	99
3	n-$C_{10}H_{21}CH(Br)CH_3$	6	99
4		2.5	83
5		2	99
6		1.5	93[a]
7		1	80

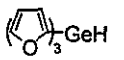
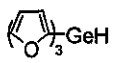
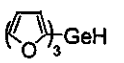
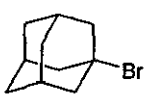
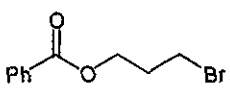
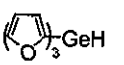
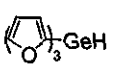
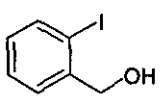
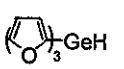
Reagents and conditions: RX (0.1 M), tri-2-furanylgermane (0.12 M), Et_3B (hexane solution, 10 mol %), THF, ambient temperature. [a]1.5 eq. of tri-2-furanylgermane used.

By using $NaBH_4$ as co-reducing reagent, Oshima *et al.*[23] examined catalytic reductions with tri-2-furanylgermane, TPGH and TBGH. The results (**Table 6**) proved that even

tertiary halides could be reduced in good yield but also that the tested alkyl chloride was recovered almost unchanged (entry 5, **Table 6**). Ester and THP functionalities (**Table 6**, entries 8 and 9 respectively) could survive under these mild conditions and the amount of catalyst could be reduced to 2 mol % without any significant decrease in yield (entries 1 and 2, **Table 6**).

Table 6. Catalytic reductions using R_3GeH.

RX $\xrightarrow{R'_3GeH}$ RH

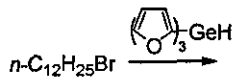
Entry	RX	R'_3GeH	time/h	yield/%
1	*n*-$C_{12}H_{25}I$		4	98
2	*n*-$C_{12}H_{25}I$		12	96[a]
3	*n*-$C_{12}H_{25}I$	Ph_3GeH	4	98
4	*n*-$C_{12}H_{25}I$	*n*-Bu_3GeH	6	89
5	*n*-$C_{12}H_{25}Cl$		24	5[b]
6	*n*-$C_{10}H_{21}CH(Br)CH_3$	Ph_3GeH	5	89
7		Ph_3GeH	10	73
8			4	90
9	$I(CH_2)_6OTHP$		1	97
10			7[c]	77

Reagents and conditions: R^1X (0.1 M), R^2_3GeH (0.01 M), $NaBH_4$ (0.2 M), Et_3B (hexane solution, 20 mol %), THF, ambient temperature. [a]Tri-2-furanylgermane (2 mol %) was employed. [b]Starting material (95 %) was recovered. [c]AIBN (0.2 M) was used instead of Et_3B and $NaBH_4$ (0.4 M) was employed. This reaction was performed at reflux in THF.

The research group of Oshima has also been investigating radical reactions in aqueous media and among the reactions tested, reduction of halides by tri-2-furanylgermane proved quite promising. By varying the solvent in the reduction of 1-bromododecane, it was found that water was superior to the more commonly used benzene and hexane (**Table 7**).[23] These results were interesting because the solubility of tri-2-furanylgermane turned out to be quite poor in water. Using water as a solvent, dodecane was obtained in 87 % yield after 20 min (entry 4, **Table 7**), whereas the

reaction performed in hexane (entry 3, **Table 7**) was far from complete after this time. Interestingly, without any solvent (entry 5, **Table 7**) dodecane was formed in 81 % yield.

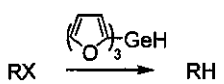
Table 7. Reduction of 1-bromododecane in various solvents.

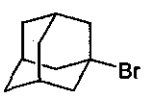


Entry	Solvent	yield/%	n-$C_{12}H_{25}Br$
1	THF	90	5
2	benzene	74	19
3	hexane	44	51
4[a]	H_2O	87	6
5	neat	81	9

Reagents and conditions: n-$C_{12}H_{25}Br$ (0.1 M), tri-2-furanylgermane (0.12 M), Et_3B (hexane solution, 20 mol %) in solvent, ambient temperature, 20 min. [a]A methanol solution of Et_3B (20 mol %) was used.

Table 8. Reduction of organic halides in water.



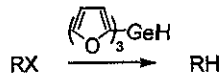
Entry	RX	time/min	yield/%
1	n-$C_{12}H_{25}I$	5	85
2	n-$C_{12}H_{25}Br$	25	89
3[a]	n-$C_{12}H_{25}Br$	25	80
4	n-$C_{10}H_{21}CH(Br)CH_3$	15	83
5		20	92

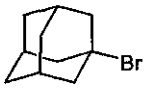
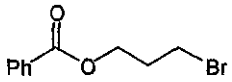
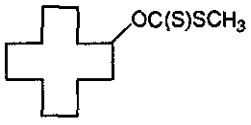
Reagents and conditions: RX (0.1 M), tri-2-furanylgermane (0.12 M), Et_3B (methanol solution, 20 mol %) in water, ambient temperature. [a]TPGH used instead of tri-2-furanylgermane.

The research group then investigated the reduction of several organic halides in water (**Table 8**) and again, high yields of the reduced hydrocarbons were obtained.[23] It should also be noted that TPGH was found efficient as a radical reductant in water (**Table 8**, entry 3) although tri-2-furanylgermane seems more reactive.

When water is used as a solvent, a solution of Et_3B in methanol or ethanol has to be employed and the question was whether the alcohol could have an effect on the outcome of the reductions. To eliminate this possibility, Oshima *et al* attempted the preparation of an aqueous solution of Et_3B but the attempt was fruitless. Instead they performed radical reductions initiated by V-70 (2,2'-azobis(4-methoxy-2,4-dimethyl)valeronitrile), a water soluble azo-initiator. V-70 is not active at room temperature, and therefore these reactions were performed at 80 °C. The reactions, some of which shown in **Table 9**, gave good to excellent yields regardless of solubility of the radical precursor in water and thereby proved the lack of effect caused by alcohol in the earlier performed reactions.

Table 9. V-70 initiated reduction of organic halides.



Entry	RX	time/min	yield/%
1	n-$C_{12}H_{25}I$	30	80
2	n-$C_{12}H_{25}Br$	30	83
3	n-$C_{10}H_{21}CH(Br)CH_3$	20	82
4		60	92
5		60	99
6	$I(CH_2)_3OTHP$	15	88
7		30	63

Reagents and conditions: RX (0.1 M), tri-2-furanylgermane (0.12 M), V-70 (10 mol %) in water, 80 °C.

Reactions employing solid supported organogermanium compounds have not been extensively investigated. In fact, to the best of our knowledge, only one publication can be found on this topic.[24] Mochida *et al.* have employed three different polystyrene-bound organogermanium hydrides (**Figure 3**) in the reduction of octane halides and obtained reasonable yields (**Table 10**).

Figure 3. Solid-supported organogermanium hydrides.

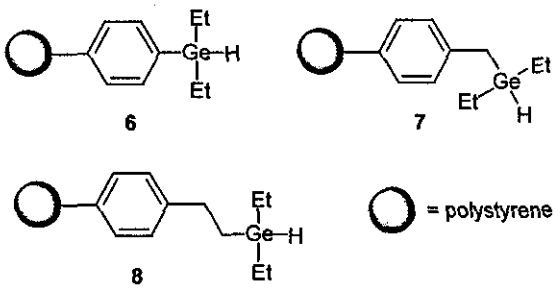


Table 10. Reduction of octane halides by solid-supported organogermanium hydrides.

$CH_3(CH_2)_6CH_2X \xrightarrow{GeH} CH_3(CH_2)_6CH_3$

Entry	X	GeH[a]	yield
1	I	6	54 %
2	Br		17 %
3	Cl		10 %
4	I	7	45 %
5	Br		20 %
6	Cl		trace
7	I	8	60 %
8	Br		60 %
9	Cl		34 %

Reagents and conditions: Reactions initiated by DTBP and heated at 135 °C for 20 h. GC-yields reported. [a]Numbers refer to the germanium hydrides in **Figure 3**.

From the table it can be seen that the polymer in which the germanium atom is separated from the aromatic linkage by an ethyl group (**8, Figure 3**) is the most effective hydrogen donor of the three. This is probably due to less steric crowding around the GeH moiety. It can also be seen from the table that the reactivity of the halides falls in the order I > Br > Cl. Both these trends are also observed when applying to the reduction on halobenzenes (**Table 11**). After use, the polymer could be regenerated by treatment with LAH and the authors found that the extent of regeneration by this method several times was 90 %. This, combined by the ease of purification of reduction products (filtration), makes this reduction method very efficient from a ecological and economical point of view. It is a wonder that more research has not been performed in this area.

Table 11. Reduction of halo benzenes by solid-supported organogermanium hydrides.

PhX $\xrightarrow{GeH}$ PhH

Entry	X	*GeH*[a]	yield
1	I	6	38 %
2	Br		13 %
3	Cl		0 %
4	I	7	44 %
5	Br		trace
6	Cl		0 %
7	I	8	55 %
8	Br		45 %
9	Cl		trace

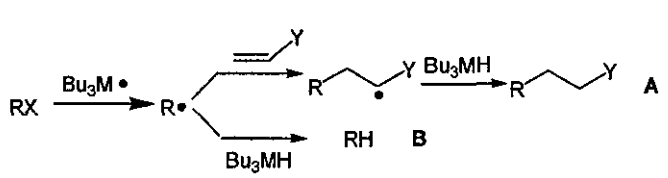
Reagents and conditions: Reactions initiated by DTBP and heated at 135 °C for 20 h. GC-yields reported. [a]Numbers refer to the germanium hydrides in **Figure 3.**

From the reactions discussed throughout this section, trialkylgermanium hydrides appear to be efficient radical mediators in reduction reactions but also other types of radical reactions have been performed using these triorganotin alternatives. Among these reactions are reductive alkylation of olefins.

1.3.2. Reductive alkylation of olefins

Hershberger *et al.* have investigated the reductive alkylation of active olefins mediated by TBGH and compared the reactivity with that of TBTH. The schematic presentation of this process is shown in **Scheme 3.**

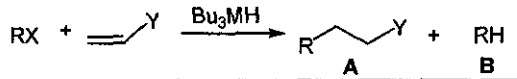
Scheme 3. Schematic presentation of the reductive alkylation of olefins.

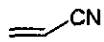
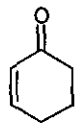


The reaction can give rise to two products, the addition product **A** and the product arising from direct reduction of the initially formed alkyl radical, **B**. Due to the lower H-donor ability of TBGH, and hence slower reaction rate of the competing formation

of **B**, TBGH should theoretically be superior to TBTH in reactions of this type. This is also the conclusion the authors draw after the series of reactions shown in **Table 12.**[25]

Table 12. Comparison of TBTH and TBGH in reductive alkylations.

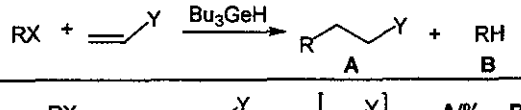


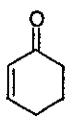
Entry	RX		M	solvent	A/%[a]	B/%[a]
1	*n*-$C_{11}H_{23}I$		Ge	CH_3CN	71	11
2	*n*-$C_{11}H_{23}I$		Ge	C_6H_6	63	14
3	*n*-$C_{11}H_{23}I$		Sn	C_6H_6	40	47
4	$PhCH_2I$		Ge	C_6H_6	76	--[b]
5	$PhCH_2I$		Sn	C_6H_6	33	--[b]
6	*n*-$C_{11}H_{23}I$		Ge	CH_3CN	21	60
7	*n*-$C_{11}H_{23}I$		Sn	C_6H_6	5	95
8	*c*-$C_6H_{11}I$		Ge	CH_3CN	31	--[b]
9	*c*-$C_6H_{11}I$		Sn	C_6H_6	7	--[b]

Reagents and conditions: RX (0.1 M), olefin (0.15 M), Bu_3MH (0.1 M), AIBN (0.02 M) in solvent, reflux, 6-12 h. [a]Yields determined by GC analysis. [b]Yields not determined.

From the data, it can be seen that TBGH generally gives very good yields of addition products, in all cases higher than the corresponding tin-mediated reactions. The addition of alkyl radicals to acrylonitrile are generally high yielding, whereas the addition to 2-cyclohexen-1-one are apparently more sluggish reactions, giving poor yields of addition products. An interesting point worth noticing in this series of reactions is that TBGH–induced reactions proceed well in benzene but the yields of the addition adducts are generally improved by performing the reaction in acetonitrile, whereas the reactions mediated by TBTH were all performed in benzene. Unfortunately, the authors do not comment on whether the use of acetonitrile has been tested and found to decrease the yields of addition product in reactions induced by TBTH.

Table 13. Effect of olefin concentration in reductive alkylations.



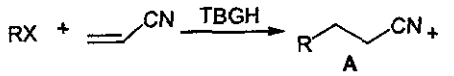
Entry	RX		$\left[\right]_0$	A/%	B/%
1	*n*-$C_{11}H_{23}I$		0.10 M	69	12
2	*n*-$C_{11}H_{23}I$		0.15 M	71	11
3	*n*-$C_{11}H_{23}I$		1.00 M	14[a]	1
4	*c*-$C_6H_{11}I$		0.15 M	79	<5
5	*c*-$C_6H_{11}I$		0.40 M	42	<5
6	$PhCH_2I$		0.10 M	61	4
7	$PhCH_2I$		0.15 M	76	2
8	*n*-$C_{11}H_{23}I$		0.15 M	21	60
9	*n*-$C_{11}H_{23}I$		1.00 M	68	<5

Reagents and conditions: RX (0.1 M), olefin, Bu_3MH (0.1 M), AIBN (0.01 M), CH_3CN, reflux, 8 h. Yields determined by GC-analysis. [a]Hydrogermylation product formed in 46 % yield.

Generally when performing tin hydride induced reductive alkylation reactions, a large excess of olefin has to be employed in order to optimise the yield of addition product. This is partly evident from the low yields of addition products in the reactions shown in **Table 12**, where 1.5 eq. of the olefin was employed in all cases, leading to low yields in the reactions promoted by TBTH. Because of the low H-donor ability of TBGH, high olefin concentration will not be necessary in reactions promoted by this reagent, a conclusion found by Hershberger *et al.* based on the reaction series shown in **Table 13**.[21] In reactions using acrylonitrile as the radical acceptor, a metal hydride:alkyl halide:olefin concentration ratio of 1:1:1 (**Table 13**, entries 1 and 6) or 1:1:1.5 (**Table 13**, entries 2, 4 and 7) is preferable to conditions employing the olefin in high concentration (**Table 13**, entries 3 and 5). At high olefin concentrations, the yields of addition products are lowered by competitive formation of hydrogermylation product. The situation is altered when the radical acceptor is 2-cyclohexen-1-one. As mentioned, the reaction is more sluggish than reaction with a terminal olefin, and it is found that the yield of addition product is increased by the use of high alkene concentration (**Table 13**, entries 8 and 9). Only at high olefin concentrations will the

alkyl addition be favoured to simple reduction, and even at high alkene concentrations, the hydrogermylation product is not observed.

Table 14. Effect of the leaving groups in reductive alkylations.



Entry	RX	A/%	B/%
1	*n*-$C_{11}H_{23}I$	71	11
2	*n*-$C_{11}H_{23}Br^{a}$	11	11
3	*n*-$C_{11}H_{23}Cl^{b}$	<5	<5
4	*n*-$C_{11}H_{23}SPh^{b}$	<5	<5
5	*n*-$C_{11}H_{23}SePh^{b}$	<5	<5

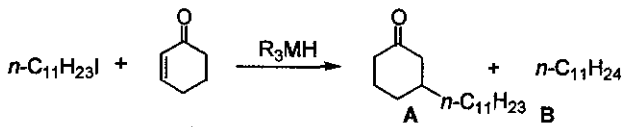
Reagents and conditions: RX (0.1 M), olefin (0.15 M), Bu_3MH (0.1 M), AIBN (0.01 M), CH_3CN, reflux, 8 h. Yields determined by GC analysis. [a]Hydrogermylation product formed in 51 % yield. [b]Hydrogermylation product major.

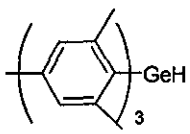
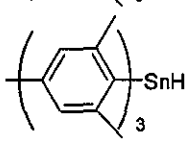
The same authors have been investigating the effect of leaving groups in TBGH-induced reductive additions to olefins.[21] The results are shown in **Table 14** and it can be seen that in cases of less reactive leaving groups (chloro, phenylthio and phenylseleno) no addition to acrylonitrile was observed. Instead the major product observed in these cases was the product of hydrogermylation, 3-(tributylgermyl)propanenitrile. This reaction is even the major reaction pathway in the reaction between 1-bromoundecane and acrylonitrile (**Table 14**, entry 2) meaning that only iodo precursors are sufficiently reactive towards germyl radicals to afford good yields of addition product with acrylonitrile.

As the case in radical reduction of alkyl halides, Hershberger *et al.* have also investigated the ability of different germanium hydrides to induce reductive alkylation of 2-cyclohexen-1-one and compared to the corresponding tin based reagents (**Table 15**).[21] The results show that there is no significant difference in reactivity between TBTH, trimesityltin hydride, TPTH and trieneopentyltin hydride (**Table 15**, entries 2, 4, 6 and 8 respectively), indicating that steric and electronic effects of the radical mediator do not greatly influence the outcome of the addition reactions. The same trend was roughly observed in the reactions promoted by the germanium hydrides but

still leaving TBGH as the most efficient radical mediators tested in this series. As observed earlier, reactions employing germanium hydrides (except the unreactive trimesitylgermanium hydride) generally give higher yields of the addition products, but also the direct reduction products are observed in high yields.

Table 15. Comparison of reactivity in alkyl addition to 2-cyclohexen-1-one.



Entry	R_3MH	A/%	B/%	n-$C_{11}H_{23}I$/%
1	Bu_3GeH	21	60	25
2	Bu_3SnH	5	95	<2
3		<2	<2	100
4		6	80	16
5	Ph_3GeH	13	83	3
6	Ph_3SnH	<2	88	10
7	$(c\text{-}C_6H_{11})_3GeH$	16	37	57
8	$((CH_3)_3CCH_2)_3SnH$	3	88	8

[a]*Reagents and conditions*: RX (0.1 M), olefin (0.15 M), R_3MH (0.1 M), AIBN (0.01 M), CH_3CN for M = Ge and benzene for M = Sn, reflux, 8 h. Yields determined by GC analysis.

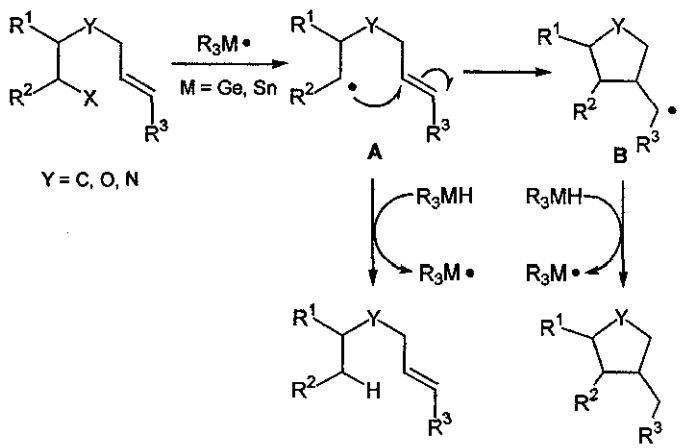
The conclusion on the large amount of intermolecular reductive alkylations performed by tin and germanium hydrides presented by this group must be that trialkylgermanium hydrides are only of any real use as tin hydride alternatives in reactions involving precious olefins, *i.e.* where the olefin can not be employed in large excess.

The reactions discussed in this paragraph have all been intermolecular reactions, but a widely used intramolecular version of this reaction is the radical cyclisation reaction.

1.3.3. Radical cyclisation reactions

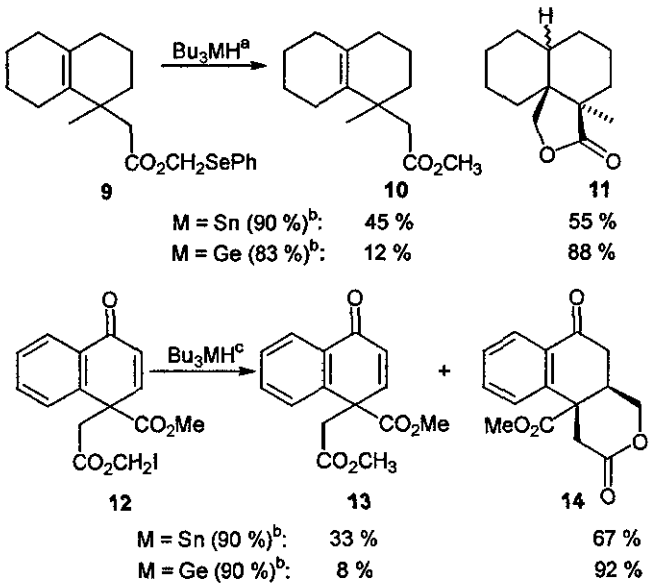
The mechanism of radical cyclisation is shown in **Scheme 4** and as in the intermolecular reaction, the initial step is the formation of radical **A**. This radical can now either be reduced directly or add to a C-C multiple bond positioned in a suitable position. The formed cyclic radical **B** is then reduced, leading to the cyclic product. As evident from the addition reactions, reactions promoted by trialkylgermanium hydrides could be expected to give a higher ratio of cyclic to reduced product than trialkyltin hydrides. This is due to the lower H-donor ability of the former allowing more time for the slower cyclisation reaction to occur.

Scheme 4. Schematic presentation of the radical cyclisation reaction.



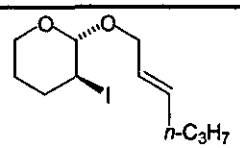
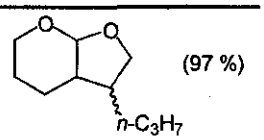
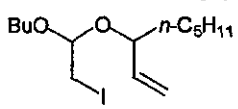
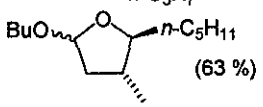
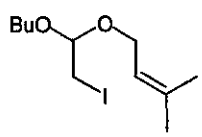
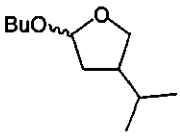
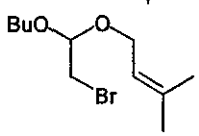
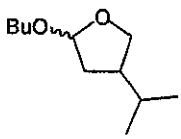
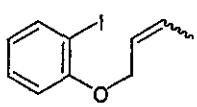
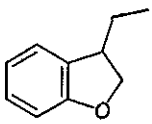
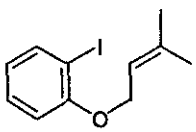
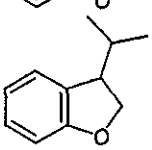
In **Scheme 2**, it was shown that the TTMSS-induced reaction gave higher ratios of cyclic product compared to TBTH and Beckwith and Pigou have shown the same to be true for TBGH induced reactions.[26] In the formation of lactones by radical cyclisation, TBGH was found to improve the yields of cyclic products (two examples shown in **Scheme 5**), even if the combined yields of the TBGH promoted reactions in general were slightly lower than the combined yields of the corresponding reactions mediated by TBTH. All the cyclisations proceed in the *exo*-mode and only *cis*-fused products are formed in agreement with the discussions published by Beckwith.[27]

Scheme 5. Formation of lactones by radical cyclisation reactions.



Reagents and conditions: [a]TBTH (1.4 eq.) or TBGH (1.3 eq.), benzene or *t*-butylbenzene, 80 °C. [b]Combined yield. [c]TBTH (1.0 eq.) or TBGH (1.0 eq.), benzene or *t*-butylbenzene, 80 °C.

Table 16. Radical cyclisations with tri-2-furanylgermane.

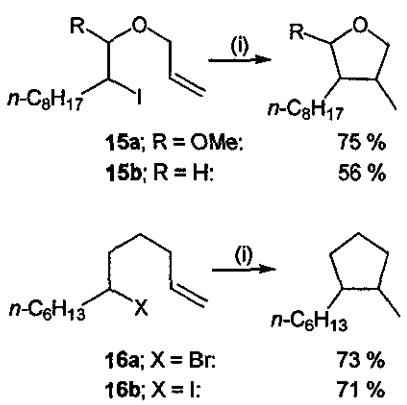
Entry	substrate	time/min	product (yield)
1		15	 (97 %)
2		90	 (63 %)
3		30	 (quant.)
4		90	 (18 %)
5		120	 (89 %)
6		90	 (88 %)

Reagents and conditions: Substrate (0.1 M), tri-2-furanylgermane (0.12 M), Et_3B (hexane solution, 20 mol %), THF, ambient temperature.

Oshima *et al.* have been employing tri-2-furanylgermane in Et_3B-initiated radical cyclisation reactions of alkyl and aryl halides.[23] The results are shown in **Table 16** and as can be seen, this reagent promotes fast and very high yielding reactions. Again it should be noted that the use of triethylborane as initiator enables the reactions to occur under very mild reaction conditions.

The cyclisation reaction could also be performed by catalytic use of tri-2-furanylgermane, but the authors found TPGH more suitable for use in a catalytic manner. For instance, use of TPGH in the radical cyclisation of allyl β-iodoalkyl ether **15b** provided the cyclic product in 56 % yield in contrast to the same reaction promoted by tri-2-furanylgermane which only gave the cyclic product in 20 % yield (**Scheme 6**).

Scheme 6. Radical cyclisation using catalytic R_3GeH.



Reagents and conditions: (i) Substrate (0.1 M), TPGH (0.01 M), $NaBH_4$ (0.2 M), Et_3B (hexane solution, 20 mol %), THF, ambient temperature.

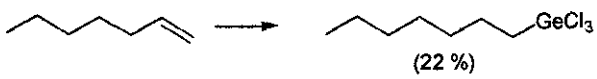
The reactions presented in this paragraph have shown that germanium-derived reagents give high yields in radical cyclisation reactions, and that the ratio of cyclic to reduced product often can be improved by changing the mediator from a tin- to a germanium-based one.

1.3.4. Hydrogermylation of C-C multiple bonds

As mentioned in section 1.3.2, hydrogermylation can be a competing reaction in the reductive alkylation of olefins, but the hydrogermylation reaction is interesting in its

own respect. In fact, already in 1954, the reaction between trichlorogermane and an olefin was published in the literature.[28] The reaction, shown in **Scheme 7**, was designed in order to investigate whether the Ge-H bond of Cl_3GeH would act like the Si-H bond of Cl_3SiH, previously shown to add to C=C double bonds by a radical mechanism.[29]

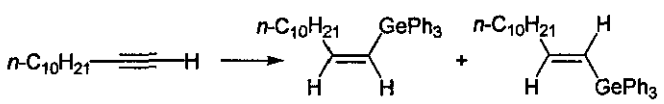
Scheme 7. Hydrogermylation by Cl_3GeH.



Reagents and conditions: Cl_3GeH (0.1 mol), 1-hexene (0.22 mol), benzyl peroxide (0.003 mol), reflux under pressure for 35 h.

As expected, the Ge-H bond of Cl_3GeH did react like the corresponding Si-H bond and the hydrogermylation product was obtained in 22 % yield. The exact position of addition of Cl_3GeH was not determined, but the authors argue that the Ge-centred radical adds to the terminal end of 1-hexene, due to the formation of the more stable, internal radical.

Table 17. Hydrogermylation of 1-dodecyne.

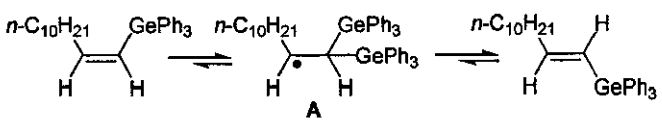


Entry	temp./°C	time/h	yield/%	*(Z)/(E)*
1	-78[a]	3	76	>20/1
2	-20[b]	2	78	2/1
3	25[b]	2	77	1/9
4	60[b]	2	99	<1/20
5	0(THF)[b]	2	84	8/1
6	0[c]	2	80	10/1

Reagents and conditions: [a]Acetylene (1.1 mmol), TPGH (1.0 mmol), Et_3B (1.0 mmol), toluene. [b]Acetylene (1.0 mmol), TPGH (1.1 mmol), Et_3B (1.0 mmol), benzene unless otherwise stated. [c]Acetylene (1.0 mmol), TPGH (1.1 mmol), Et_3B (1.0 mmol), benzene and MeOH.

Generally, hydrogermylations are not highly stereoselective reactions, but Oshima and co-workers have found that Et_3B initiated hydrogermylation reactions occur with good control of regio- and stereoselectivity.[30,31] By varying the conditions of the reaction between 1-dodecyne and TPGH, it was possible to control the stereochemistry of the product (**Table 17**). When the reaction was performed at –78 °C with a small excess of 1-dodecyne (entry 1, **Table 17**), the (*Z*)-isomer was the major product, whereas the (*E*)-isomer was formed predominantly in reactions at 60 °C employing 1.1 eq. of TPGH (entry 4, **Table 17**). The authors assumed that the reason for this selectivity was the fact that the *trans* addition, *i.e.* (*Z*), product is the kinetically controlled product and that it would isomerise into the (*E*)-product under thermodynamic conditions. This was proved by a reaction with (*Z*)-1-triphenylgermyl-1-dodecene, which, when treated with a catalytic amount of TPGH and Et_3B, isomerised completely to the (*E*)-isomer by the mechanism shown in **Scheme 8.**

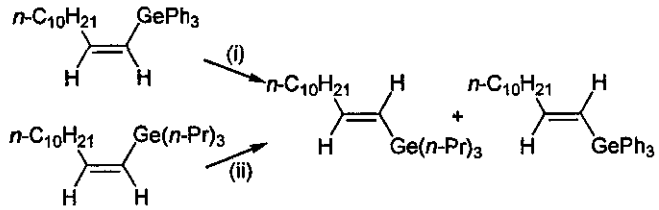
Scheme 8. Isomerisation of (*Z*)-1-triphenylgermyl-1-dodecene.



Reagents and conditions: (*Z*)-1-triphenylgermyl-1-dodecene (1.0 mmol), TPGH (0.1 mmol), Et_3B (hexane solution, 0.1 mmol), benzene, 60 °C, 4 h, (*E*)-1-triphenylgermyl-1-dodecene (88 %) exclusively.

The authors suggest that the germyl radical attacks the double bond at the position substituted by the triphenylgermyl group leading to intermediate **A**.[31] Free rotation of the C-C bond followed by elimination of $Ph_3Ge\bullet$ leads to the thermodynamic equilibrium. This mechanism has been proposed earlier[32] and an experiment by Oshima and co-workers supported this view where treatment of (*Z*)-triphenylgermyl-1-dodecene with *n*-Pr_3GeH and Et_3B gave a 2:5 mixture of (*E*)-tripropylgermyl-1-dodecene and (*E*)-triphenylgermyl-1-dodecene (**Scheme 9**).[31] The same product distribution was obtained when treating (*Z*)-tripropylgermyl-1-dodecene with TPGH and Et_3B.

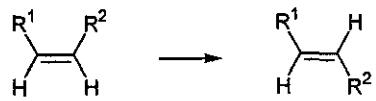
Scheme 9. Mechanism investigation.



Reagents and conditions: (i) (*Z*)-triphenylgermyl-1-dodecene (1.0 mmol), *n*-Pr_3GeH (1.0 mmol), Et_3B (hexane solution, 0.1 mmol), 60 °C, 4 h gave the products in 88 % combined yield. (ii) (*Z*)-tripropylgermyl-1-dodecene (1.0 mmol), TPGH (1.0 mmol), Et_3B (1.0 mmol), 60 °C, 4 h gave the products in 88 % combined yield.

Oshima *et al.* used this concept to isomerise various olefins by treatment with TPGH and Et_3B. Some of their results are shown in **Table 18**[31] and as can be seen, all the (*Z*)-olefins were successfully equilibrated to their (*E*) counterpart in these high yielding reactions.

Table 18. Isomerisation of olefins.



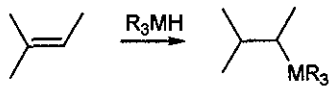
Entry	R^1	R^2	substrate (*Z*)/(*E*)	time/h	yield	product (*Z*)/(*E*)
1	*n*-C_5H_{11}	*n*-C_5H_{11}	>20/1	10	90	15/85
2	*t*-Bu	*n*-C_8H_{17}	>20/1	10	91	0/100
3	*n*-C_6H_{13}	Ph	100/0	5	96	0/100
4	Ph	Ph	>20/1	2	81	<1/20
5	*n*-C_6H_{13}	$SiPhMe_2$	>20/1	10	84	<1/20
6	*n*-$C_{10}H_{21}$	$GePh_3$	10/1	4	88	<1/20
7	$HO(CH_2)_2$	$GePh_3$	>20/1	10	70	<1/20

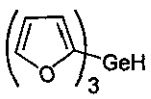
Reagents and conditions: Olefin (1.0 mmol), TPGH (0.1 mmol), Et_3B (hexane solution, 0.1 mmol), benzene, 60 °C, 10 h.

All these reactions have been performed employing TPGH or (*n*-$Pr)_3GeH$ as reagent, but Oshima *et al.* have since found tri-2-furanylgermane superior to these reagents in simple hydrogermylation reactions.[33,34] When treating 2-methyl-2-butene with

different germanes, TBTH and TTMSS, tri-2-furanylgermane was proven to afford to best yield of the desired product (**Table 19**).

Table 19. Hydrometalation of trisubstituted alkene.



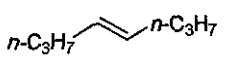
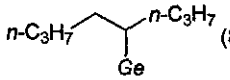
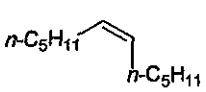
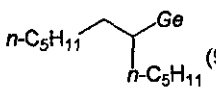
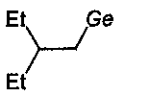
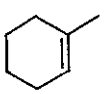
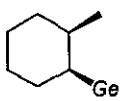
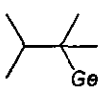
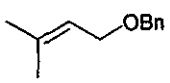
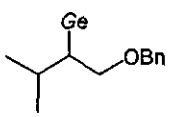
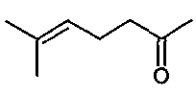
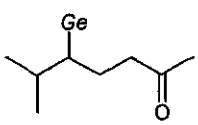
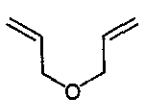
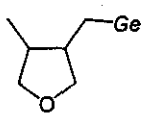
Entry	R_3MH	yield
1		90 %
2	TPGH	11 %
3	$(n\text{-}C_6H_{13})_3GeH$	0 %
4	TBTH	0 %
5	TTMSS	0 %

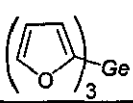
Reagents and conditions: Tri-2-furanylgermane (1.0 mmol), alkene (2.0 mmol), Et_3B (1.0 M solution in hexane, 0.1 mmol). Reactions performed neat at 0 °C.

Treatment of various alkenes with tri-2-furanylgermane in the presence of Et_3B gave the corresponding adducts in good yields. (**Table 20**). Tri-2-furanylgermane adds very easily to both internal and terminal alkenes, regardless of whether these are di-, tri- or tetrasubstituted. Several solvents were investigated in the addition reaction, but it was found that the best results were obtained without any other solvent present than the small amount of hexane from the Et_3B solution. In the addition to 1-methylcyclohexene, only the *cis*-isomer was obtained (entry 4, **Table 20**). It is interesting to note that even under concentrated conditions, diallyl ether was converted in high yield into the tetrahydrofuran derivative by a sequential addition-cyclisation process in preference to simple reduction (entry 8, **Table 20**). The reasons why tri-2-furanylgemane is so successful in the addition to alkenes is not clear, but the authors argue that the addition of the tri-2-furanylgermyl radical to alkenes may be less reversible than the analogous reactions of other trialkyl- or triarylgermyl radicals, *i.e.* that $D(R^1{}_3Ge\text{-}R^2)$ is greater for R^1 = 2-furanyl than for R^1 = Ph or Bu. Also mentioned as a reason is that the hydrogen atom transfer from tri-2-furanylgermane to the initially formed C-centred radical is faster than from the other trialkylgermanes, *i.e.* tri-2-furanylgemane is a better hydrogen donor than the other germanes tested. Both these

theories are supported by investigations of the reactivity of tris(trimethylsilyl)germane in hydrogermylation reactions published by Chatgilialoglu *et al.*[35]

Table 20. Addition of tri-2-furanylgermane to alkenes.

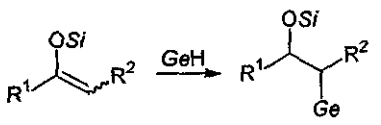
Entry	substrate	product (yield)
1		 (82 %)
2		 (90 %)
3		 (quant.)
4		 (85 %)
5		 (84 %)
6		 (85 %)
7		 (88 %)
8		 (95 %)

Ge = 

Reagents and conditions: Tri-2-furanylgermane (1.0 mmol), alkene (2.0 mmol), Et_3B (1.0 M solution in hexane, 0.1 mmol). Reactions performed neat at 0 °C.

Tri-2-furanylgermane also adds successfully to silyl ethers yielding β-siloxygermanes with high regioselectivity as shown in **Table 21.**[31] As seen in the addition of tri-2-furanylgermane to 1-methylcyclohexene, the addition to the trimethylsilyl enol ether derived from cyclohexanone produced only the *cis*-isomer (entry 2, **Table 21**). All reactions but one proceed in high yields, but the reaction with the *t*-butyldimethylsilyl enol ether was very sluggish and the addition product was only obtained in 26 % yield (entry 5, **Table 21**).

Table 21. Addition of tri-2-furanylgermane to silyl enol ethers.

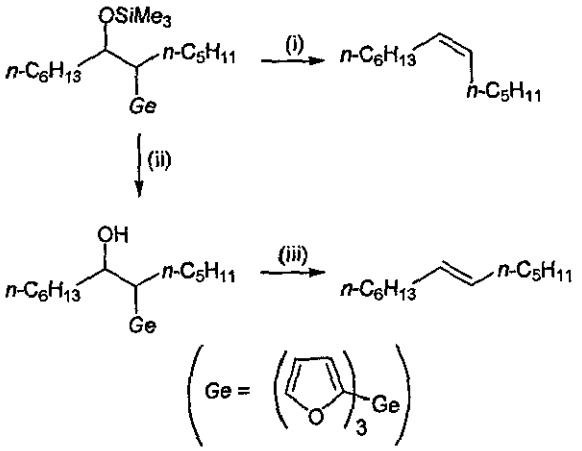


Entry	R^1	R^2	*Si*	yield
1	n-C_6H_{13}	n-C_5H_{11}	$SiMe_3$	69 %
2	—$(CH_2)_4$—		$SiMe_3$	95 %[a]
3	n-$C_{10}H_{21}$	H	$SiMe_3$	98 %
4	H	n-$C_{11}H_{23}$	$SiMe_3$	95 %
5	n-C_6H_{13}	n-C_5H_{11}	Si-t-BuMe_2	26 %

Reagents and conditions: Tri-2-furanylgermane (1.0 mmol), silyl enol ether (2.0 mmol), Et_3B (1.0 M solution in hexane, 0.1 mmol). Reactions were performed neat at ambient temperature. [a]Only the *cis*-product was obtained.

The authors then showed that either acid or base catalysis facilitated elimination of the β-siloxygermanes to alkenes (**Scheme 10**), hence providing a new and mild method of converting ketones into alkenes.

Scheme 10. Stereospecific 1,2-elimination of β-siloxygermanes.

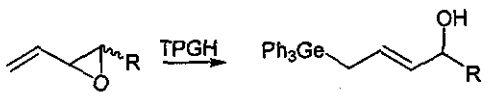


Reagents and conditions: (i) Substrate (0.5 mmol), TMSOTf (0.06 mmol), DCM, ambient temperature, 20 min. Quantitative yield, (*Z*)/(*E*); 95/5. (ii) Substrate (0.5 mmol), K_2CO_3 (1.0 mmol), methanol, ambient temperature, 30 min. (iii) Substrate from step (ii), KH (0.5 mmol), 18-crown-6 (cat.), HMPA, 80 °C, 2 h. 76 % yield, (*Z*)/(*E*); <1/99.

Oshima *et al.* have also investigated the addition of germyl centred radicals to vinyloxiranes.[36] Some of their results are shown in **Table 22**, and it is interesting to

note from entry 3 that in contrast to the ionic ring opening, the carbonyl functionality is not affected by this radical approach.

Table 22. Radical addition of triphenylgermyl radicals to vinyloxiranes.

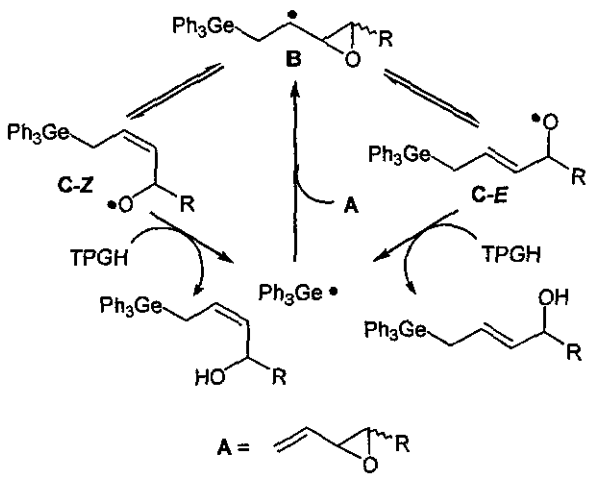


Entry	R	Yield/%
1	*H*	84 (*E*/*Z* = 79/21)
2	CH_2CH_2Ph	73
3	$(CH_2)_7COCH_3$	78

Reagents and conditions: Vinyloxirane (1.0 mmol), TPGH (0.5 mmol), Et_3B (1.0 M solution in hexane, 1.0 mmol), hexane (3 cm^3), ambient temperature, 4 h.

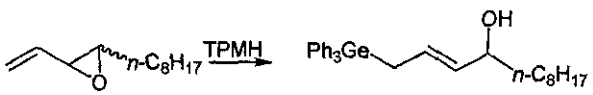
The fact that the reaction produces a majority of (*E*)-olefins can be explained by the proposed mechanism for the chain reaction (**Scheme 11**).[36] Addition of triphenylgermyl radical to vinyloxirane forms radical **B**, which is then transformed into oxygen centred radicals **C-*Z*** or **C-*E***. Because of steric hindrance surrounding the oxygen atom in **C-*Z***, radical **C-*E*** is more rapidly trapped by TPGH, hence giving the (*E*)-isomer as a the major product and regenerating triphenylgermyl radical.

Scheme 11. Mechanism of the addition to vinyloxiranes.



When treating 3,4-epoxy-1-dodecene with TPGH (1.1 eq) the addition product was obtained as the (*E*) isomer only. Increasing the concentration of the reaction, the (*E*)- and (*Z*)-allylic alcohols were formed as a 86/14 mixture (**Table 23**) because of radicals **C-*Z*** and **C-*E*** (**Scheme 11**) being trapped by TPGH before reaching the equilibrium. Interestingly, substituting TPGH with TPTH furnished a 89/11 mixture of (*E*)- and (Z)-isomers (**Table 23**), reflecting that TPTH is a better hydrogen-donor than TPGH, leading to facile interception of the oxygen-centred radicals, hence again interfering with the equilibrium.

Table 23. Influence of concentration.

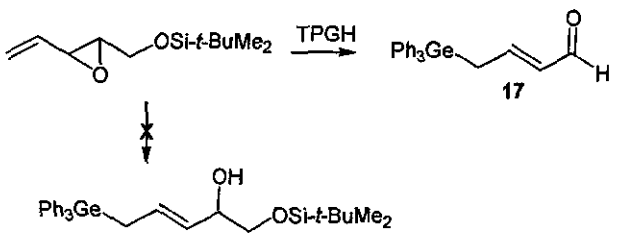


Entry	M	yield/%
1	Ge[a]	96 ((*E*)-isomer only)
2	Ge[b]	84 (*E*/*Z* = 86/14)
3	Sn[c]	(*E*/*Z* = 89/11)[d]

Reagents and conditions: [a]Vinyloxirane (1.0 mmol), TPGH (0.5 mmol), Et_3B (1.0 M solution in hexane, 1.0 mmol), hexane (3 cm^3), ambient temperature, 4 h. [b]Vinyloxirane (1.0 mmol), TPGH (0.5 mmol), Et_3B (1.0 M solution in hexane, 1.0 mmol), benzene (0.5 cm^3), ambient temperature, 4 h. [c]Vinyloxirane (1.0 mmol), TPTH (0.5 mmol), Et_3B (1.0 M solution in hexane, 1.0 mmol), hexane (3 cm^3), ambient temperature, 4 h. [d]Yield not determined.

When Oshima *et al.* tried to expand the scope of the addition of TPGH to vinyloxiranes to include addition to (2,3-epoxy-4-pentenyloxy)trialkylsilanes, it was found that instead of the expected allylic alcohol, an α,β-unsaturated aldehyde **17** was obtained in 44 % yield (**Scheme 12**).[37]

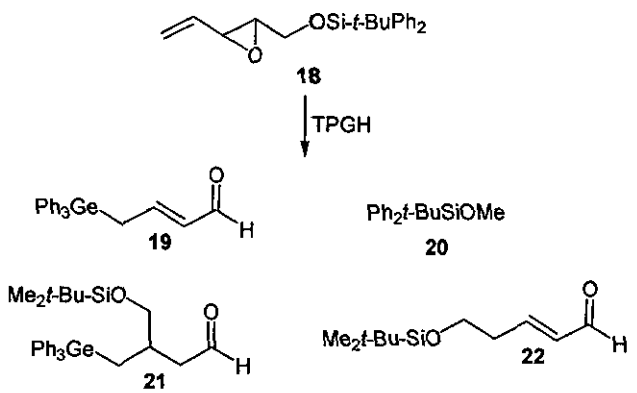
Scheme 12. Addition to (2,3-epoxy-4-pentenyloxy)trialkylsilane.



Reagents and conditions: (2,3-Epoxy-4-pentenyloxy)trialkylsilane (0.45 mmol), TPGH (0.3 mmol), Et_3B (1.0 M solution in hexane, 1.0 mmol), hexane (3 cm^3), ambient temperature, 9 h.

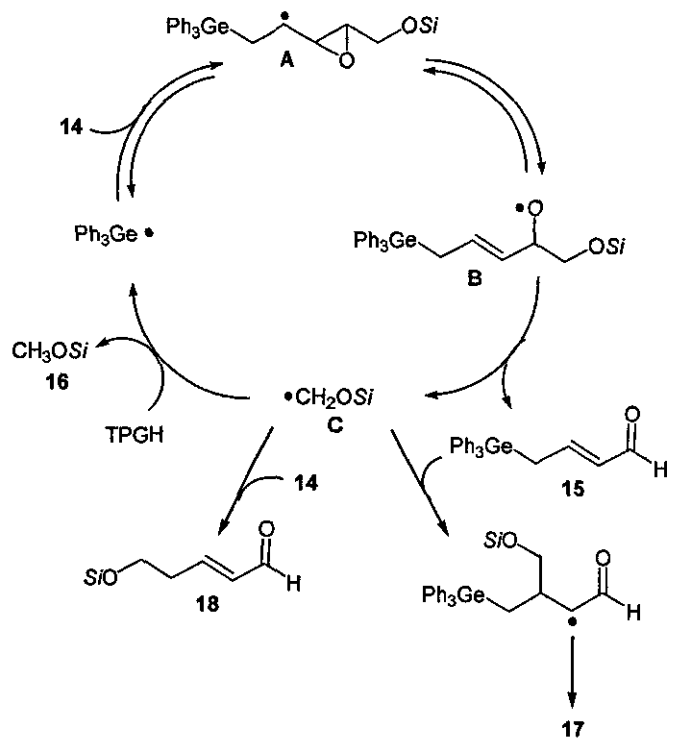
In order to investigate the mechanism of the formation of the aldehyde, *t*-butyldiphenyl(2,3-epoxy-4-pentenyloxy)silane **18** was reacted with TPGH, this time employing AIBN as initiator. Careful analysis of the reaction mixture revealed the product distribution shown in **Scheme 13**. The formation of aldehydes **21** and **22** indicates that the siloxymethyl radical may exist as a crucial intermediate.

Scheme 13. Product distribution in the reaction of silane **18**.



Reagents and conditions: *t*-Butyldiphenyl(2,3-epoxy-4-pentenyloxy)silane (0.45 mmol), TPGH (0.3 mmol), AIBN, benzene, reflux. **19** (0.18 mmol), **20** (0.10 mmol), **21** (0.05 mmol) and **22** (0.07 mmol).

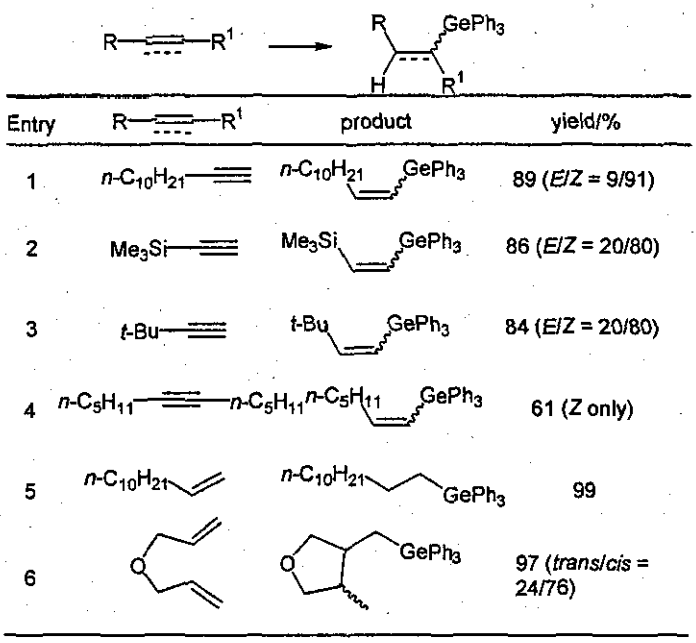
Scheme 14. Proposed mechanism of the addition to silane **18**



These results led to the following proposed mechanism (**Scheme 14**). Addition of triphenylgermyl radical to the C-C double bond creates radical **A**, followed by ring opening to radical **B**. β-Scission of the alkoxy radical generates aldehyde **19** and radical **C**, which abstracts hydrogen from TPGH to form **20** and $Ph_3Ge\bullet$ and thereby continues the radical chain. Products **21** and **22** are produced when radical reacts with **19** and **18** respectively.

Most of the reactions published by Oshima *et al.* in this area have employed Et_3B as the radical initiator. They have shown, though, that the reactions also can proceed utilising tributylmanganate (II) as initiator.[38] Some representative results are shown in **Table 24**, and as can be seen, employing a catalytic amount of manganate produced good to excellent yields of addition adducts. In the case of addition to diallyl ether, the corresponding cyclised product was obtained (entry 6, **Table 24**).

Table 24. *n*-Bu_3MnLi-mediated radical addition of TPGH to acetylene or alkene.

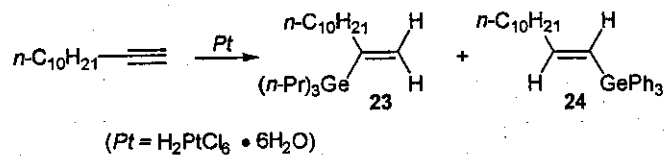


Reagents and conditions: Acetylene or alkene (1.0 mmol), TPGH (1.5 mmol), tributylmanganate(II) (derived from *n*-BuLi and $MnCl_2$, 0.1 mmol), ambient temperature, 11 h.

As is evident from the reactions mentioned in this section, Oshima and co-workers are responsible for the vast majority of the research performed in the area of addition of germyl centred radicals to C-C multiple bonds. The research group has, along with others, published other hydrogermylation reactions, not specifically interesting in this

context, since these Pt- and Pd-catalysed reactions do not proceed *via* a radical pathway, e.g. **Scheme 15**.[39]

Scheme 15. Non-radical hydrogermylation reaction.



Reagents and conditions: 1-Dodecyne (1.0 mmol), TPGH (1.0 mmol), *Pt* (0.15 mol %), 100 °C, 30 min, **23/24** = 25/75, 99 % combined yield.

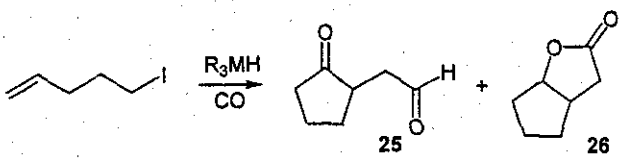
Some of the most frequently used radical reactions have been discussed in this introduction, and as should be evident, trialkylgermanium hydrides show good reactivity in the vast majority of reaction types. In most cases, yields and product distribution mimic the results obtained by the use of triorganotin hydrides. In the following section, examples of other radical reactions employing triorganogermanium hydrides will be given.

1.3.5. Miscellaneous radical reactions promoted by R_3GeH

In most types of reactions, TBTH- and TBGH-mediated radical transformations give rise to identical products, even if the distribution of these may vary. When Ryu and co-workers investigated the double carbonylation of pent-4-enyl iodide they found that two different products were formed, depending on radical mediator employed in the reaction. The TBTH mediated system gave the keto aldehyde **25** whereas TBGH afforded the bicyclic γ-lactone **26**. (**Table 25**).[40] The same two adducts were formed when the reaction conditions were applied on other pent-4-enyl iodides, and in all cases, TBTH-mediated reactions gave rise to very little formation of the bicyclic γ-lactone or none at all. The explanation of the observed difference in reactivity of the two radical mediators lies, again, in TBTH being a better hydrogen-donor than TBGH. When reacting pent-4-enyl iodide with either TBGH or TBTH in the presence of CO, radical **A** is initially formed (**Scheme 16**). Subsequent 5-*exo* cyclisation gives primary radical **B** which can isomerise to the secondary radical **C**. This does not happen since because of the high CO concentration, **B** is trapped by a second molecule of CO,

hence acyl radical **D** is formed, in preference to isomerisation to **C**. A good hydrogen-donor such as TBTH will trap **D** to form **25**, but in the presence of a poorer hydrogen-donor, formation of radical **E** may compete with the intermolecular hydrogen transfer. Formation of **E** may occur by either a 5-*endo* cyclisation (path a, **Scheme 16**) or by iodine atom transfer followed by cyclisation (path b, **Scheme 16**) as discussed by the authors. Finally, hydrogen abstraction from the mediator gives the final product **26**.

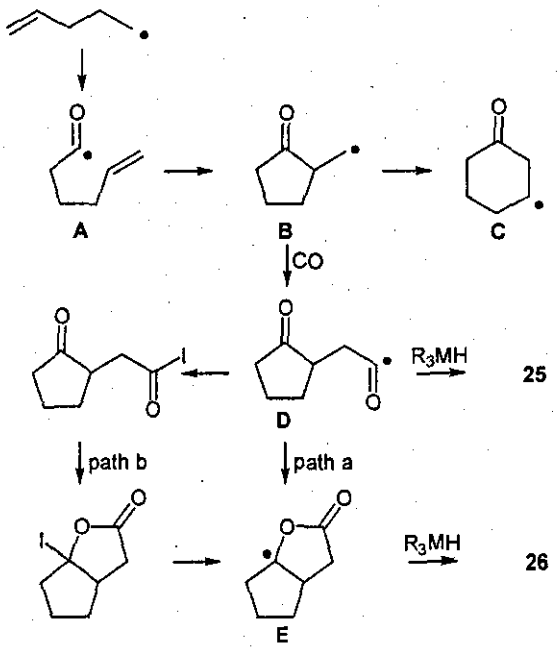
Table 25. Double carbonylation reaction.



Entry	R_3MH	25 / %	26 / %
1	TBTH[a]	44	0
2	TBGH[b]	6	27
3	TTMSS[c]	12	19

Reagents and conditions: [a]Pent-4-enyl iodide (0.01 M), TBTH (1.2 eq.), AIBN, CO (90 atm), benzene, 80 °C, 3 h. [b]Pent-4-enyl iodide (0.02-0.06 M), TBGH (1.5 eq.), AIBN, CO (90 atm), benzene, 70-100 °C, 5 h. [c]Pent-4-enyl iodide (0.01 M), TTMSS (1.1 eq.), AIBN, CO (90 atm), benzene, 80 °C, 5 h.

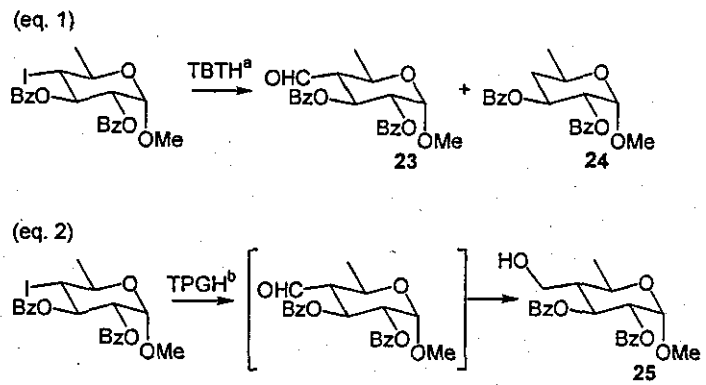
Scheme 16. Mechanism of the formation of products **25** and **26**.



It is interesting to note that when employing TTMSS, **26** was the major product, but **25** was formed in a higher amount than in the reaction promoted by TBGH (**Table 25**, entry 3). This correlates nicely with the mechanism and with the rate constants in **Table 2**, where TTMSS is situated between TBTH and TBGH as far as hydrogen atom donation is concerned (k_{25} = 3.8 × 10^5, k_{25} = 2.4 × 10^6 and k_{25} = 1.0 × 10^5 $M^{-1}s^{-1}$, respectively).

Radical carbonylation reactions can also be performed employing a catalytic amount of triorganogermanium hydride. This has been elegantly illustrated by Gupta and Kahne in their attempt to introduce a hydroxymethyl (or formyl) functionality into a carbohydrate moiety.[41] When a 4,6-di-deoxy-4-iodo glucose derivative was treated with TBTH in the presence of CO, only 5 % of the desired 4-formyl derivative **27** was obtained (**Scheme 17**, eq. 1). The major product was the 4,6-di-deoxy sugar **28**, originating from the initially formed secondary radical abstracting a hydrogen atom from TBTH before trapping CO. When the same reaction was mediated by a catalytic amount of TPGH along with a co-reductant, CO was trapped and the resulting formyl derivative reduced *in situ* to afford the desired 4-hydroxymethyl derivative **29** in reasonable yield (**Scheme 17**, eq. 2)

Scheme 17. Intermolecular CO trapping by sugar-derived, secondary radical.

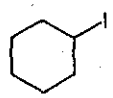
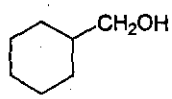
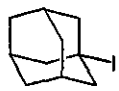
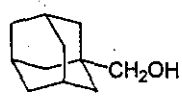


Reagents and conditions: [a]TBTH (2 eq), AIBN, CO (1200 psi), benzene, 105 °C, 8 h, **27** (5 %) and **28** (yield not reported). [b]TPGH (0.1 eq), $NaBH_3CN$ (2.9 eq), AIBN, CO (1400 psi), benzene/THF (50/1), 105 °C, 12 h, **29** (37 %).

Testing the reaction with some standard alkyl iodides showed the method's validity as an efficient way of introducing hydroxymethyl groups, especially in substrates where the initially formed radical has some stability, 3° > 2° > 1°, as is evident from **Table**

26. Unfortunately, the authors did not perform the reaction under catalytic TBTH conditions, and it is therefore difficult to establish whether the nice results obtained are due to the use of trialkylgermanium hydride, or simply due to the low concentration of radical mediator in the reaction mixture.

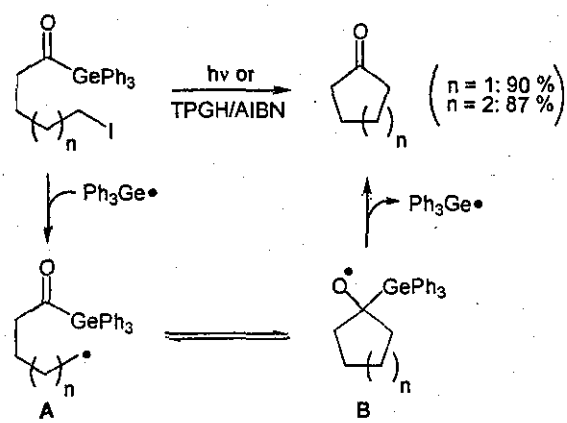
Table 26. Formation of hydroxymethyl functionality by intermolecular CO trapping.

Entry	substrate	product	yield
1	$CH_3(CH_2)_9I$	$CH_3(CH_2)_9CH_2OH$	59 %
2			62 %
3			75 %

Reagents and conditions: TPGH (0.1 eq), $NaBH_3CN$ (2.9 eq), AIBN, CO (1400 psi), benzene/THF (50/1), 105 °C, 12 h.

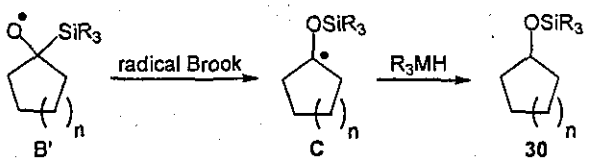
Curran *et al.* have investigated acylgermanes and found them to be very good radical acceptors. The rates of cyclisation are dependent on the substituents on germanium, ring size and radical substituent effects.[42] The mechanism of the intramolecular radical addition to acylgermanes is outlined in **Scheme 18** along with some of the results obtained.[43] Initiation in the usual manner gave primary radical **A**, which cyclises reversibly onto the acyl group, forming oxygen-centred radical **B**. Elimination of $Ph_3Ge\bullet$ enables the radical chain reaction to continue and produces the cyclic ketones in high yields.

Scheme 18. Acylgermanes as radical acceptor.



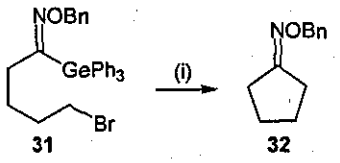
Interestingly, acylsilanes have also been shown to be good radical accceptors, yet they do not react like the acylgermanes. Instead of eliminating $R_3Si\bullet$, the silicon analogue of radical **B**, **B'** (**Scheme 19**) undergoes a "radical Brook"-rearrangement to give radical **C**, which then abstracts a hydrogen atom from the radical mediator, leading to the observed product **30**.[44] This difference in reactivity is presumably due to the slightly stronger O-Si bond compared to the corresponding O-Ge bond ($D(Me_3M\text{-}OEt)$ = 111 and 107 kcal mol^{-1} for M = Si and Ge respectively),[45] hence Si has a higher affinity towards oxygen than Ge.

Scheme 19. Radical Brook rearrangement in addition to acylsilanes.



As simple acylgermanes, acylgermane oxime ethers and hydrazones have also proven to be efficient radical acceptors following the same mechanism as detailed in **Scheme 18**.[46] When irradiating acylgermane oxime ether **31** (**Scheme 20**) in benzene for 90 min at ambient temperature, cyclopentanone *O*-benzyl oxime ether **32** was isolated in 95 % yield.

Scheme 20. Radical cyclisation of acylgermane oxime ether **31**.

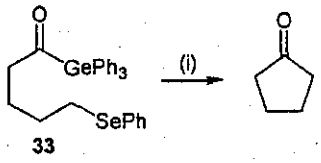


Reagents and conditions: (i) **31**, benzene, irradiated (254 nm) at ambient temperature, 90 min, **32** (95 %).

When employing the same conditions with PhSe-containing analogues, only unreacted radical precursors were isolated from the crude reaction mixture. It was assumed that both the C=N and the PhSe-C bond resist photolytic cleavage, since PhSe bearing acylgermane **33** (**Scheme 21**) cyclised in quantitative yield on irradiation.[42] To obtain cyclised adducts from the PhSe-substituted acylgermane oxime ethers, 10 mol % of

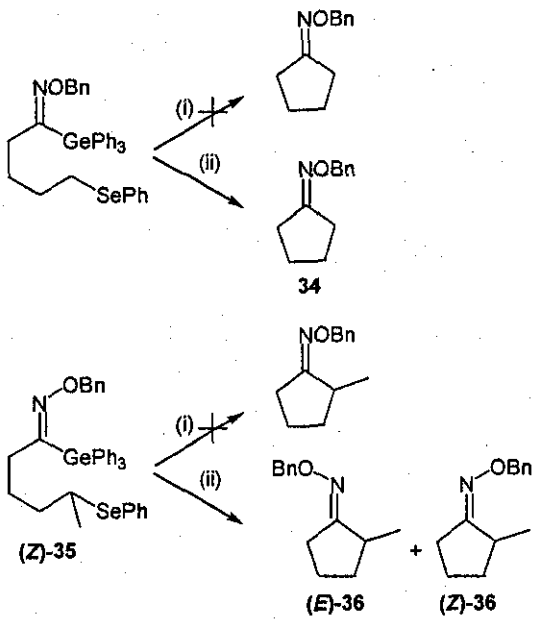
hexamethyl-ditin was added to initiate the photolytic reactions. That change in reaction conditions gave rise to the formation of the cyclised products in high yields (**Scheme 22**).[42]

Scheme 21. Radical cyclisation of PhSe-acylgermane precursor.



Reagents and conditions: (i) **33**, benzene irradiated (254 nm) at ambient temperature, 90 min, cyclopentanone (100 %).

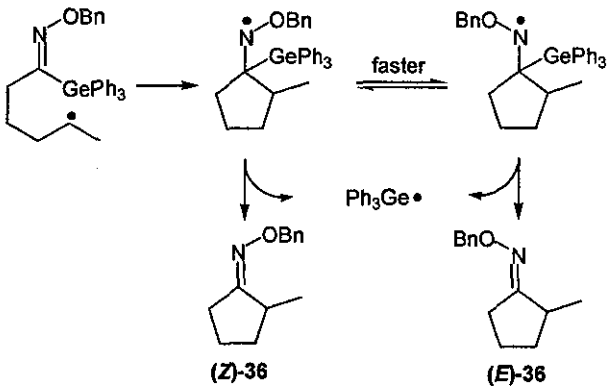
Scheme 22. Radical cyclisation of PhSe-bearing acylgermanes oxime ethers.



Reagents and conditions: (i) Precursor, benzene, irradiated (254 nm) at ambient temperature, 90 min. (ii) Precursor, Me_6Sn_2 (10 mol %), C_6D_6, irradiated (254 nm) at ambient temperature, 90 min, **34** (95 %) or **36** (66 % combined yield) respectively.

It is interesting to note that in the reaction of (*Z*)-oxime ether **35**, the cyclisation proceeds with predominant inversion leading to formation of the (*E*)-isomer of cyclopentanone *O*-benzyl oxime ether **36** as the major product (**Scheme 22**). This suggests that bond rotation of the initially formed radical is a faster process than elimination of $Ph_3Ge\bullet$ (**Scheme 23**).

Scheme 23. Rationale for the predominant isomerisation of precursor.



This introduction has focused on the ability of triorganogermanium hydrides to induce radical reaction. Organogermanium compounds are also, as mentioned in section 1.3.4, participants in reactions of a more ionic character. These reaction types include Barbier reactions under microwave irradiation,[47] formation of germanium-cumulenes by insertion of carbenes,[48] Stille-type couplings[49] and base catalysed additions of tri-2-furanylgermane to aldehydes and α,β-unsaturated carbonyl compounds.[50] All these reactions are in their own respect good examples of the reactivity of organogermanium compounds, but not very interesting in the context of this thesis. What is interesting, on the other hand, is the very promising reactivity triorganogermanium hydrides and halides have in radical reactions, judged from the reactions discussed in this introduction. It should be apparent that the "low" hydrogen-donor ability of triorganogermanium hydrides facilitate slower radical processes, *e.g.* radical cyclisations, to occur at the expense of simple reductions, often observed as a competing process in reactions promoted by triorganotin hydrides. This difference in reactivity means that reactions mediated by triorganogermanium hydrides often give higher yields of cyclic products, or in some cases different products, than in reactions induced by triorganotin hydrides.

Some of the reported studies in the introduction were published at the same time as or after our own studies but are included for a full description of other work.

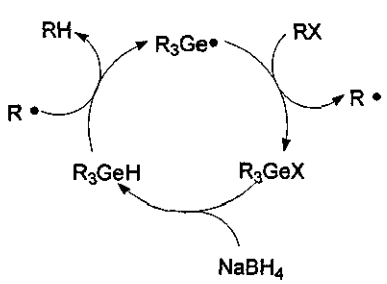
Chapter 2. Results and discussion

The aim of the research underlying this thesis is to investigate whether triorganogermanium compounds are able to become serious alternatives to triorganotin hydrides as radical mediators. From the introduction it is clear that triorganogermanium hydrides are indeed able to promote the radical reactions but a representative range of radical precursors have not been tested with these triorganotin substitutes. Therefore, this thesis will cover a variety of radical precursors employed in suitable types of radical reactions. Moreover, the difference in reactivity of the tin- and germanium-based mediators may be an area which could be emphasised further than is reported in the literature. For this purpose, all reactions have been performed employing both groups of reagents. The discussion is divided according to type of radical precursor, starting out with the synthesis of relevant triorganogermanium compounds.

2.1 Synthesis of triorganogermanium compounds

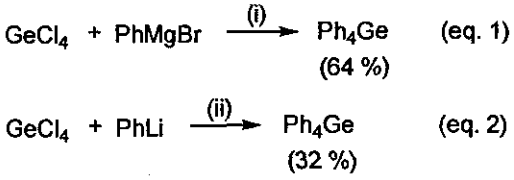
To represent the group of triorganogermanium compounds, triphenylgermanium bromide (TPGBr), TPGH and TBGH were chosen. TPGH and TBGH were chosen because they are the most frequently used in the literature and TPGBr because it would be interesting to investigate whether this reagent could be used as a catalytic radical mediator. Looking at the catalytic cycle of $R_3Ge\bullet$ in a given radical reaction (here exemplified by a radical reduction), it can be seen that it is possible to enter the cycle at two stages, with the hydride and with the halide (**Scheme 24**).

Scheme 24. Catalytic cycle for R_3GeH.



Entering the cycle with the triorganogermanium halide, the initial step is reduction by the co-reductant (*e.g.* $NaBH_4$) employed in stoichiometric amount to form triorganogermanium hydride, which is responsible for mediation of the radical reaction. Since TPGBr was considered more stable than TPGH, it was assumed more easy to handle this reagent as a catalytic reductant. TPGBr and TPGH can both be formed from tetraphenylgermane, which in turn is produced from $GeCl_4$ by either a Grignard reaction[51] or by reaction with phenyllithium[52] in accordance with literature procedures (**Scheme 25**).

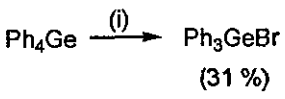
Scheme 25. Synthesis of tetraphenylgermane.



Reagents and conditions: (i) Toluene, reflux, 2 h. (ii) Toluene, ambient temperature, 3.5 h.

In the Grignard reaction (eq. 1, **Scheme 25**), tetrachlorogermane in toluene is added to a solution of benzylmagnesium bromide in diethyl ether and it turns out that it is very important quickly to remove the diethyl ether by distillation. If the ether is not replaced with toluene, the major product of the reaction is not tetraphenylgermane, but instead hexaphenyldigermane. It has not been determined why the formation of the Ge-Ge bond is favoured in ether and not in toluene. The synthesis was performed with the Grignard reagent in excess and it was found that 10 equivalents of the reagent gave the best result (64 %). Alternatively, treatment of $GeCl_4$ with phenyllithium afforded Ph_4Ge in poor yield (eq. 2, **Scheme 25**). With Ph_4Ge secured, treatment with bromine gave TPGBr (**Scheme 26**).[53]

Scheme 26. Synthesis of TPGBr.

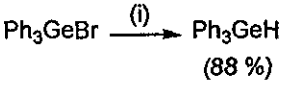


Reagents and conditions: Br_2 (1.5 eq.), PhCl, reflux, 45 min.

The reaction was easily performed by refluxing a mixture of tetraphenylgermane and bromine in chlorobenzene, but the yield (31 %) was not impressive. In the literature,[53] this reaction is done with dibromoethane as solvent and the reported yields are much higher (up to 82 %). The (apparently) strong influence of the solvent on the reaction yield indicates that dibromoethane may act as an extra bromine source. In this work, the use of dibromoethane was avoided because of the toxicity of this solvent, and chlorobenzene was chosen as a solvent because of the similarities in the boiling points of the two solvents. In order to compensate for the bromine donated by dibromoethane, the reaction was repeated using 3 equivalents of Br_2 and reacted at room temperature overnight, but this reaction did not give TPGBr. The actual product of the reaction was not determined.

In order to employ TPGBr in a catalytic manner, it was necessary to establish efficient reduction conditions. For this purpose, the reduction of TPGBr to TPGH was attempted several times under different conditions. The best yield of TPGH was obtained by refluxing a solution of TPGBr and sodium borohydride in *t*-BuOH for 30 min, which afforded TPGH in 88 % yield (**Scheme 27**).

Scheme 27. Reduction of TPGBr.



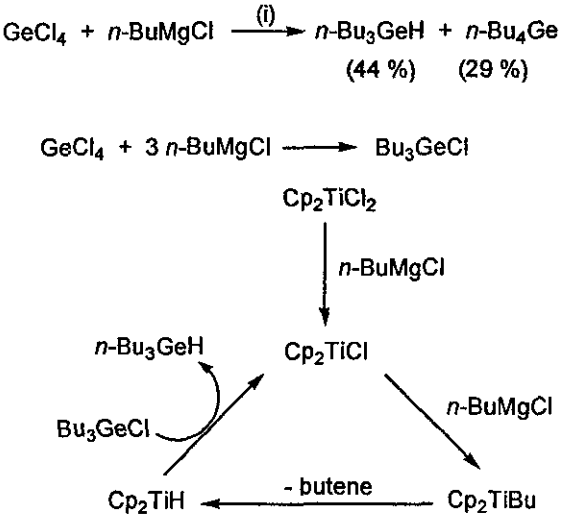
Reagents and conditions: $NaBH_4$ (15 eq.), *t*-BuOH, reflux, 30 min.

Attempts to perform the reaction at lower temperature produced only trace amounts of TPGH. It was therefore concluded that any use of TPGH or TPGBr in a catalytic manner had to be carried out at elevated temperature.

Colacot has published a synthesis of TBGH involving a Cp_2TiCl_2-catalysed Grignard reaction.[54] The reaction and proposed mechanism is shown in **Scheme 28.** The yields of the reaction varied quite significantly each time it has been performed, with the yield of TBGH ranging from 23 % to 53 %. The reason for this variation can partly be down to inconsistency in quality of the commercially supplied *n*-BuMgBr. After reaction, the two products are separated by "kugel-rohr" distillation, and because TBGH and tetrabutylgermanium have very similar boiling points (123 °C/20 mm Hg

and 170 °C/20 mm Hg respectively),[54] the distillation normally had to be repeated. This extensive distillation process may be an additional reason for the inconsistency of yields obtained. A nice and quite unexpected feature about TBGH is that it turned out to be relatively stable, at least when kept in freezer under a nitrogen atmosphere. The stability has been proven by ^{1}H-NMR spectroscopy by simply obtaining spectra of the same sample with regular intervals. The stability is remarkable when compared to the stability of TBTH where slow and steady decomposition of reagent is a common problem. This does not seem to be a problem in the germanium case. A solution of TBTH in $CDCl_3$ was shown by ^{1}H-NMR spectroscopy to be largely decomposed within 24 h. However, a $CDCl_3$ solution of TBGH remained stable over several weeks.

Scheme 28. Synthesis of TBGH.



Reagents and conditions: (i) *n*-BuMgBr (2 M solution in Et_2O, 5 eq.), Cp_2TiCl_2 (~ 8 mol %), reflux, 18 h.

The mechanism proposed by Colacot employs 5 equivalents of *n*-BuMgCl and a catalytic amount of Cp_2TiCl_2, the role of the latter believed to be as follows; Cp_2TiCl_2 is being reduced to $Cp_2Ti(III)Cl$ followed by substitution of the chloride atom, giving $Cp_2Ti(III)Bu$, which eliminates butene to afford Ti(III)H, responsible for reduction of the initially formed Bu_3GeCl.

If TBGH was to be used in a catalytic manner, it is necessary to establish the reaction conditions, under which the reduction from the tributylgermanium halide is most facile. For this purpose, a tributylgermanium halide was needed. This could be

accomplished by a redistribution reaction between tetrabutylgermanium and tin(IV)chloride. Bulten and Drenth[55] have found that this reaction proceeds smoothly at high temperature (eq. 1, **Scheme 33**). The authors also found that in the reaction of tetraethylgermanium, employment of $MeNO_2$ as solvent prevented the need for immense heating of the reaction mixture (eq. 2 and 3, **Scheme 29**).

Scheme 29. Redistribution reaction between Bu_4Ge and $SnCl_4$.

$$Bu_4Ge + SnCl_4 \xrightarrow[210\ ^{\circ}C]{(i)} Bu_3GeCl + BuSnCl_3 \quad \text{(100 \% conversion)} \qquad \text{(eq. 1)}$$

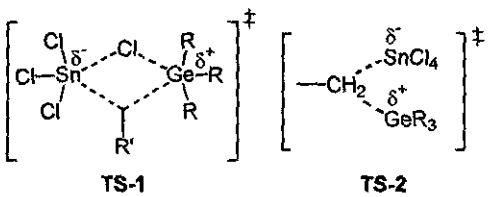
$$Et_4Ge + SnCl_4 \xrightarrow[150\ ^{\circ}C]{(i)} Et_3GeCl + EtSnCl_3 \quad \text{(100 \% conversion)} \qquad \text{(eq. 2)}$$

$$Et_4Ge + SnCl_4 \xrightarrow[50\ ^{\circ}C]{(ii)} Et_3GeCl + EtSnCl_3 \quad \text{(100 \% conversion)} \qquad \text{(eq. 3)}$$

Reagents and conditions: (i) Equimolar amounts of reagents, performed in Carius tubes at the indicated temperature for 1-2 h. (ii) Equimolar amounts of reagents (0.56 M each) in $MeNO_2$, performed in Carius tubes at 50 °C for 45 min.

The reason for the enhanced reactivity by addition of a polar solvent is believed to be that in presence of $MeNO_2$, there is a larger charge separation in transition-state compared to when the reaction is performed neat, *i.e.* the interaction Ge-Cl is of minor importance. The reaction then proceeds *via* a S_E2 (open) rather than by a S_E2 (cyclic) mechanism, represented by transition-states **TS-2** and **TS-1** respectively (**Figure 4**).

Figure 4. Transition-states in the redistribution reaction between Bu_4Ge and $SnCl_4$.



TS-1 **TS-2**

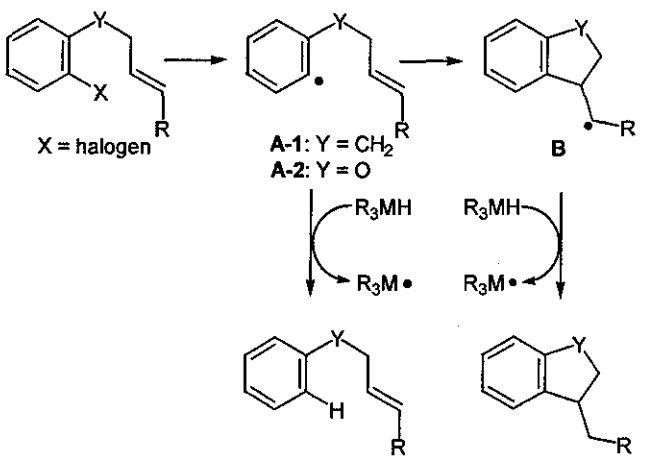
In the work presented in this thesis, formation of Bu_3GeCl was attempted by this approach, but unfortunately, the result was inconclusive. The problem lies in the fact that the two products of a successful reaction (Bu_3GeCl and $BuSnCl_3$) have similar boiling points (126-131 °C/13 mm Hg and 96-104 °C/12 mm Hg respectively).[56] The products could probably have been separated by careful, fractional distillation, but this

was not done on the very small reaction scale employed in this attempt. Further investigations were not performed and therefore only a few reactions have been performed employing TBGH in a catalytic manner and if so, by using a "trial and error-approach". Most of the radical reactions employing TBGH as radical mediator have been carried out using the reagent in stoichiometric amounts.

2.2 Radical reactions with aromatic precursors

Radical cyclisation of aromatic halo precursors are often employed as test-reactions when investigating radical mediators ability to promote various reactions. As seen earlier, two criteria must be fulfilled in order for the reagent to be effective. Firstly, the mediator must be able to break the relatively strong halogen-aryl bond, hence form radical **A** (**Scheme 30**). Secondly, the mediator should be capable of donating a hydrogen atom to radical **B** formed by cyclisation. The rate constant of bromine abstraction from C_6H_5Br by $Bu_3Ge\bullet$ at ambient temperature has been measured by Lusztyk *et al.* and the value ($<1.0 \times 10^5$ $M^{-1}s^{-1}$)[17] indicates that the reaction may be rather slow. With the corresponding rate of abstraction of halogen by a tin centred radical presumably higher, a faster reaction is expected in reactions promoted by this type of radical mediator.

Scheme 30. Schematic representation of radical cyclisation of aromatic precursor.

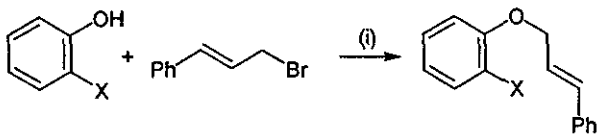


The direct reduction of radical **A** must be considered as a possible competing reaction pathway, even if the cyclisations of aryl radicals are very fast processes. Ingold,

among others, has measured the rate constants of the 5-*exo* cyclisation (k_c) of **A-1** (Y = CH_2, R = H) and **A-2** (Y = O, R = H) at 30 °C as being 4.0×10^8 s^{-1} and 6.3×10^9 s^{-1} respectively.[57] The same group have also established the rate constants of the reaction of aryl radicals with TBTH and TBGH (k_H) and found these values as being 5.9×10^8 M^{-1} s^{-1} and 2.6×10^8 M^{-1} s^{-1} respectively at 30 °C, proving that hydrogen transfer from TBTH or TBGH to radical **A** is indeed likely to happen, especially in reactions with radicals of type **A-1**. With $k_H^{Sn}/k_H^{Ge} = 2$, it is hoped that reactions promoted by germanium based mediators will increase the ratio of cyclic to reduced product, providing that the employed triorganogermane will be able to reduce radical **B** and hence continue the radical chain for different R-groups. From the results of Oshima (see Introduction) we know that the radical cyclisation of aromatic precursors leading to radicals of type **A-1** (R = H or Me) proceed smoothly in the presence of tri-2-furanylgermane. In this section, our attempts to cyclise other aromatic precursors by reaction with TBGH and triphenylgermanium compounds will be discussed.

1-Bromo-2-[(3-phenylprop-2-enyl)oxy]benzene **33** and 1-iodo-2-[(3-phenylprop-2-enyl)oxy]benzene **34** were synthesised according to **Scheme 31.** Heating a mixture of cinnamyl bromide with 2-bromophenol or 2-iodophenol in the presence of base afforded **33** and **34** respectively in reasonable yield.

Scheme 31. Synthesis of 1-bromo- and 1-iodo-2-[(3-phenylprop-2-enyl)oxy]benzene.

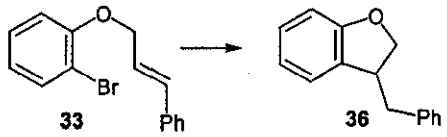


X = Br: **33** (81 %)
X = I: **34** (70 %)
X = H: **35** (21 %)

Reagents and conditions: (i) K_2CO_3, acetone, reflux, 17 h.

In a radical reaction of **33** or **34**, direct reduction of the initially formed aryl radical will form (3-phenylprop-2-enyl)oxybenzene **35**. To be able to identify the presence of **35** in crude reaction mixtures by spectroscopic methods, **35** was synthesised applying the same method. Radical cyclisation of **33** was performed numerous times employing different reaction conditions and some of the results are shown in **Table 27.**

Table 27. Radical cyclisation of **33**.



Entry	Radical mediator	Reaction conditions	Product
1	Bu_3SnCl (0.1 eq.)	$NaBH_4$, AIBN, *t*-BuOH, reflux, 4 h	**36** (77 %)[a]
2	TPGBr (0.1 eq.)	$NaBH_4$, AIBN, *t*-BuOH, reflux, 11 h	**33** (n.d.)[b]
3	TPGH (0.1 eq.)	$NaBH_4$, AIBN, *t*-BuOH, reflux, 20 h	**33** (n.d.)[b]
4	TPGBr (0.1 eq.)	$NaBH_4$, Et_3B, THF, ambient temperature, 21 h	**33** (n.d.)[b,c]
5	TBTH (2 eq.)	AMBN, C_6H_{12}, reflux, 3 h	**36** (52 %)[a]
6	TBGH (1.8 eq.)	AMBN, C_6H_{12}, reflux, 3 h	**36** (7 %)[a]

[a]Determined by the use of an internal standard in ^{1}H-NMR spectroscopy. [b]n.d. = not determined.
[c]Additional product present.

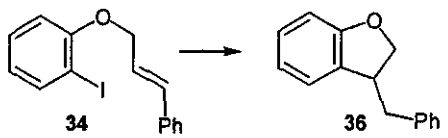
The reactions promoted by catalytic or stoichiometric amounts of tributyltin chloride or TBTH (**Table 27**, entries 1 and 5 respectively) gave the desired cyclic product 3-benzyl-2,3-dihydrobenzofuran **36** in various yields and speak for themselves. The reactions promoted by triorganogermanium hydride or bromide, however, are more troublesome. Entry 2 (**Table 27**) shows that after refluxing **33** with 0.1 eq. of TPGBr in the presence of AIBN for 11 h no formation of **35** or **36** was observed by ^{1}H-NMR spectroscopy. From the tributyltin chloride mediated reaction it was known that cyclisation of **33** was indeed possible and that the AIBN and the sodium borohydride were reactive. The *in situ* reduction of TPGBr to TPGH is known to occur under the conditions applied (see **Scheme 27**) so the lack of cyclisation could not be caused by inefficient reduction of the radical mediator. Entering the catalytic cycle with TPGH did not give any difference in the outcome of the reaction as can be seen from entry 3 (**Table 27**). In order to explain this lack of reactivity, we questioned whether AIBN

was able to generate the triphenylgermyl radical at all, but from the work of Hershberger *et al.*[21] this seemed an unlikely answer since they were employing AIBN as a radical initiator in TPGH promoted reductions of alkyl halides. To confirm whether or not inefficient initiation by AIBN was causing the lack of reaction, the conditions used by Oshima and co-workers[23] were adopted. They used triethylborane to initiate the radical cyclisation of an aromatic iodo compound, but applying their conditions (Et_3B, $NaBH_4$, THF, ambient temperature) on **33** did not improve the outcome of the reaction (**Table 27**, entry 4). After 21 h unreacted **33** could be detected by ^{1}H-NMR spectroscopy along with a small amount of a different compound. The spectral data of this compound did not correspond with either **33** or **35** and the identification of this compound was not pursued. When changing the radical mediator to TBGH a small amount of the desired product was obtained as seen in entry 6 (**Table 27**). The results of radical cyclisation of **33** were not very encouraging, but it was hoped that the lack of cyclisation in the reactions promoted by germanium based radical mediators was an unsuccessful homolytic cleavage of the aryl-Br bond in **33**. It was therefore hoped that radical cyclisation of iodo analogue **34** would prove more facile due to the weaker aryl-I bond. As can be seen from **Table 28**, this was not the case. As in the radical cyclisation of **33**, mediation by tin based reagents gave rise to the cyclic product **36** in moderate to excellent yields (entries 1, 3, 5 and 7, **Table 28**). Employing identical conditions, in reactions promoted by germanium compounds, **36** was not formed to any great extent. In fact, **36** was only observed in very low yield by adding TBGH slowly to a refluxing solution of **34** (entry 6, **Table 28**).

It is interesting to note that in none of the cyclisation reactions of **33** or **34**, the reduced product **35** is observed by ^{1}H-NMR spectroscopy of the crude reaction mixtures. This lack of reduction was observed even if the total amount of radical mediator was added early in the reaction, hence the concentration of R_3MH was high throughout reaction time. With reference to the rate constants for hydrogen-atom transfer from the mediators discussed early in this section, some formation of **35** was expected at least when the mediator was not added slowly by syringe-pump technique. From this it can be concluded that the 5-*exo* cyclisations of these cinnamyl ethers are too fast reactions for the bimolecular hydrogen transfer to compete. When this is the case, then why do the germanium based mediators fail to facilitate the cyclic product? The answer to this question lies in the final reduction of the formed cyclic radical. The rate constant for

the hydrogen transfer from TBTH to a benzylic radical, that is the reaction shown in **Scheme 32**, is 3.6×10^4 M^{-1} s^{-1} at ambient temperature.[16] The corresponding rate constant for hydrogen transfer for TBGH is unknown, but can be estimated by comparison of known rate constants. The rate constants for hydrogen abstraction by primary alkyl radicals from TBTH and TBGH at 80 °C is 1.5×10^7 M^{-1} s^{-1} and 3.8×10^5 M^{-1} s^{-1} respectively, *i.e. ca* 40 times faster for TBTH than for TBGH. If this correlation is valid, k_H for reaction between a benzyl radical and TBGH will be in the order of 9×10^2 M^{-1} s^{-1}; in other words, so slow that reduction will not occur. If reduction is not accomplished, Ge-centred radicals will not be formed, *i.e.* the chain reaction is inhibited.

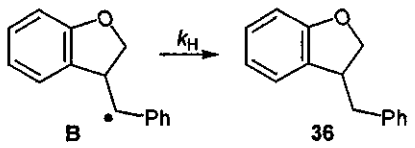
Table 28. Radical cyclisation of **34**.



Entry	Radical mediator	Reaction conditions	Product(s)
1	Bu_3SnCl (0.1 eq.)	$NaBH_4$, AIBN, *t*-BuOH, reflux, 2 h	**36** (59 %)[a]
2	TPGBr (0.1 eq.)	$NaBH_4$, AIBN, *t*-BuOH, reflux, 28 h	**34** (n.d.)[b]
3	TBTH (1.8 eq.)	AMBN, C_6H_{12}, reflux, 3 h	**36** (92 %)[a]
4	TBGH (1.3 eq.)	AMBN, C_6H_{12}, reflux, 3 h	**34** (79 %)
5	TBTH (2.2 eq.)	AMBN, $CH_3CN/PhCH_3$, syringe-pump addn., reflux, 3 h	**36** (52 %)[a]
6	TBGH (1.8 eq.)	AMBN, $CH_3CN/PhCH_3$, syringe-pump addn., reflux, 3 h	**36** (4 %)[a]
7	TBTH (2.0 eq.)	Et_3B, THF, ambient temperature, 21 h	**36** (64 %)[a]
8	TBGH (1.3 eq.)	Et_3B, C_6H_{12}, ambient temperature, 21 h	**34** (90 %)

[a]Determined by the use of an internal standard in ^{1}H-NMR spectroscopy. [b]n.d. = not determined.

Scheme 32. Reduction of benzylic radical **B.**



B 36

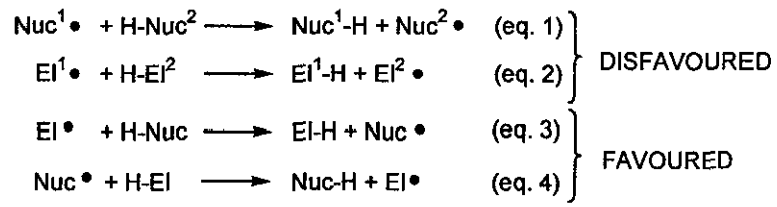
$PhCH_2\bullet$: $k_H^{TBTH} = 3.6 \times 10^4\ M^{-1}\ s^{-1}$ at 25 °C

$RCH_2\bullet$: $k_H^{TBTH} = 1.5 \times 10^7\ M^{-1}\ s^{-1}$ at 80 °C

$k_H^{TBGH} = 3.8 \times 10^5\ M^{-1}\ s^{-1}$ at 80 °C

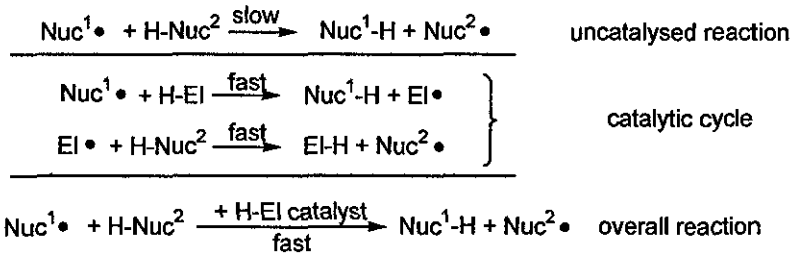
In order to overcome the problem with reduction of the very stable, hence fairly unreactive, benzylic radical, attention was paid to work by Roberts focusing on the use of 'polarity-reversal catalysis' (PRC) in radical reactions. [58] The background for this concept is outlined in **Scheme 33.**

Scheme 33. Background of PRC.



Nuc = nucleophilic, El = electrophilic

Scheme 34. Principle of PRC.

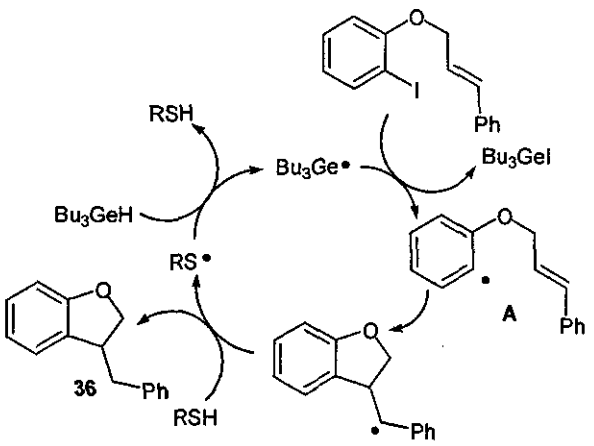


When reacting a nucleophilic radical (Nuc •) with the hydride of another nucleophilic radical (eq. 1, **Scheme 33**), or an electrophilic radical (El •) with the hydride of another electrophilic radical (eq. 2, **Scheme 33**), these reactions are strongly disfavoured. The reaction between an electrophilic radical with the hydride of an nucleophilic radical (eq. 3, **Scheme 33**), or vice versa (eq. 4, **Scheme 33**), are favoured

reactions. When dealing with a nucleophilic radical, it can therefore be of advantage to use a hydride of an electrophilic radical as catalyst in accordance with **Scheme 34.**

By using a reactive catalyst, one slow reaction step is substituted by a cycle of two fast reaction steps which both benefit from favourable polar effects, facilitating the overall reaction to proceed. Even if benzylic radicals are not considered particularly nucleophilic, the principle behind PRC can be used to overcome the problems associated with the slow hydrogen atom abstraction by these. By using a catalytic amount of a good hydrogen donor such as a thiol in the cyclisation reactions of **33** and **34**, continuous generating of Ge-centred radicals, responsible for generation of radical **A**, should be secured (**Scheme 35**).

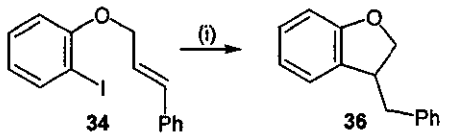
Scheme 35. Catalytic cycle for the use of PRC.



The rate constant for the hydrogen transfer from PhSH to benzylic radicals is k_H^{PhSH} = 3.1×10^5 M^{-1} s^{-1} at 25 °C,[16] *i.e. ca* 10 times higher than k_H^{TBTH}. Since TBTH is known to induce cyclisation, PhSH should be a sufficiently good hydrogen donor to act as a catalyst in cyclisations of this type. It has not been possible to find the rate constant for hydrogen abstraction from TBGH by a sulfur-centred radical but this reaction is assumed to be fast.

Repetition of the TBGH-induced cyclisation of **34** in the presence of PhSH (10 mol %), facilitated the formation of **36** in good isolated yield (**Scheme 36**), indicating that the lack of cyclic product observed earlier indeed was caused by inhibition of the radical chain reaction.

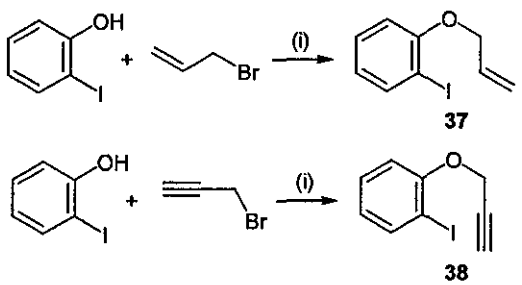
Scheme 36. Radical cyclisation of **34**, catalysed by PhSH.



Reagents and conditions: (i) TBGH (1 eq.), PhSH (0.1 eq.), ACCN, cyclohexane, reflux, 9 h, **36** (75 %).

If the aromatic radical precursor instead of a cinnamyl ether has a propenyl ether or a propynyl ether linkage, the resulting cyclic radical, now a primary methyl or methylene radical, will not be strongly stabilised and reduction by both TBTH and TBGH should be accomplished without a catalyst present. For this purpose, 2-iodo-1-(prop-2-enyloxy)benzene **37** and 2-iodo-1-(prop-2-ynyloxy)benzene **38** were synthesised (**Scheme 37**).

Scheme 37. Synthesis of **37** and **38**.



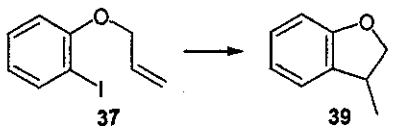
Reagents and conditions: (i) K_2CO_3, acetone, reflux for 4 or 5 h, **37** (93 %), **38** (94 %).

Treatment of 2-iodophenol with allyl bromide or propargyl bromide in the presence of base afforded **37** and **38** respectively in good yields.

Radical cyclisation of **37** under different reaction conditions showed that excellent yields of the desired cyclic product 3-methyl-2,3-dihydrobenzofuran **39** could be obtained in the absence or presence of PhSH (entries 3 and 4, **Table 29**), hence further indicating that the cyclisation of derivatives **33** and **34** was inhibited by an inefficient chain propagation. In the cyclisation of **37**, TBTH- and TBGH-induced reactions gave equally good yields of cyclic product, except for one reaction. The reaction shown in entry 2 (**Table 29**) produced, along with **39**, an additional product, identified by NMR and mass spectroscopy as 3-iodomethyl-2,3-dihydrobenzofuran **40**. The formation of this compound is probably due to impurities in the TBGH employed, since an

insufficient amount of TBGH may promote the abstraction of iodine from **37** (or Bu_3GeI) by the cyclic radical **A** (**Scheme 38**).

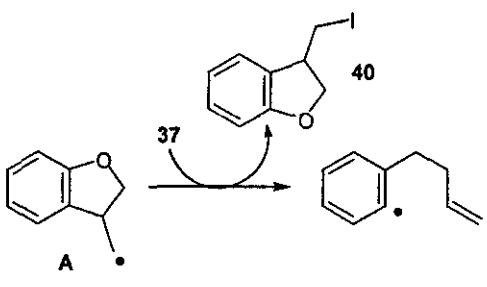
Table 29. Radical cyclisation of **37**.



Entry	Radical mediator	Reaction conditions	Product(s)
1	TBTH (1.2 eq.)	ACCN, $PhCH_3$, reflux, 2 h	**39** (86 %)
2	TBGH (1.2 eq.)	ACCN, $PhCH_3$, reflux, 6 h	**39** (22 %)[a] **40** (28 %)[a]
3	TBGH (1.2 eq.)	AIBN, PhSH (0.1 eq.), $PhCH_3$, reflux, 2 h	**39** (85 %)
4	TBGH (1.2 eq.)	ACCN, $PhCH_3$, reflux, 3 h	**39** (91 %)
5	TBGH (0.1 eq.)	$NaBH_4$, *t*-BuOH/$PhCH_3$, AIBN, reflux, 2 h	**37** (83 %)
6	TBGH (0.1 eq.)	$NaBH_4$, *t*-BuOH/$PhCH_3$, AIBN, reflux, 6 h	**39** (44 %) **37** (37 %)

[a]Determined by the use of an internal standard in ^{1}H-NMR spectroscopy.

Scheme 38. Formation of iodomethyl derivative **40**.

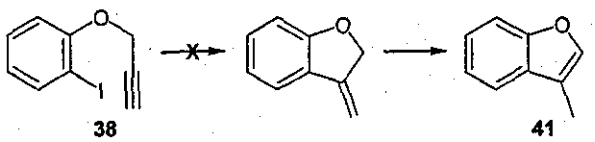


The hypothesis of impure TBGH was confirmed by repeating the reaction after careful distillation of TBGH. This reaction (entry 4, **Table 29**) gave **39** as the sole product. Catalytic use of TBGH in the cyclisation of **37** could be performed (entry 6, **Table**

29), but this is a noticeably slower process than when employing TBGH in stoichiometric amounts as can be seen by comparison of entries 4 and 5. The reaction conditions were not optimised.

Although the radical cyclisation of **37** was very successful when employing TBGH, the cyclisation of **38** proved more troublesome. In fact, several attempts to obtain cyclic product 3-methyl-benzofuran **41** failed (**Scheme 39**). Complex mixtures of products were obtained and the reaction was dismissed.

Scheme 39. Attempted radical cyclisation of **38**.



Reagents and conditions: TBTH (1.5 eq.) or TBGH (1.2 eq.), ACCN, toluene, reflux, 4 h.

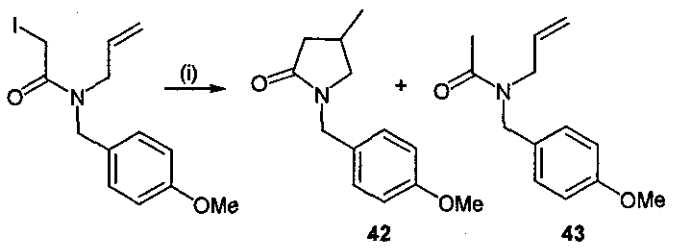
Conclusion of section 2.2

Radical cyclisation reactions of aromatic precursors was initially chosen as test-reactions in the investigation of the reactivity of triorganogermanium compounds because it was envisaged that these poorer hydrogen donors would induce formation of cyclic products in preference to products arising from simple reduction reactions. To our surprise, reduction products were not observed in any of the radical reactions and a conclusion on the selectivity of the reaction could not be drawn. The difference in hydrogen donation was found to have another consequence. In radical cyclisation of 1-bromo- and 1-iodo-2-[(3-phenylprop-2-enyl)oxy]benzene (**33** and **34** respectively), a very stable benzylic radical is formed and it turned out that the hydrogen abstraction from triorganogermanes by this radical was very slow and radical reaction was inhibited. To overcome this problem, PhSH was used in catalytic amount to secure chain propagation in reactions promoted by germanium based radical mediators. With this change in reaction conditions, TBGH showed reactivity similar to the stannanes employed.

2.3 Radical reactions with amide precursors

Amide precursors have been used by Parsons *et al.*[13] in radical cyclisation reactions using dimanganese decacarbonyl as radical mediator (**Scheme 40**). The mediator facilitates the formation of both the desired cyclic product 1-(4-methoxybenzyl)-4-methylpyrrolidin-2-one **42** and the reduced uncyclised product *N*-allyl-*N*-(4-methoxybenzyl)acetamide **43**, arising from direct reduction of the initially formed amide radical. Therefore, the amide was assessed as being a suitable system to use in the investigation of whether triorganogermanes will induce a selectivity towards cyclisation in the reaction.

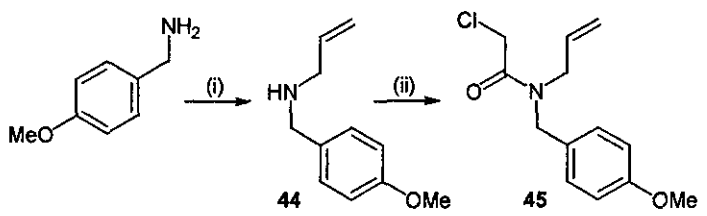
Scheme 40. Radical cyclisation performed by Parsons *et al.*



Reagents and conditions: $Mn_2(CO)_{10}$ (0.1 eq.), propan-2-ol / DCM, irradiation, **42** (54 %), **43** (8 %).

Parsons and co-workers were performing their reactions with *N*-allyl-2-iodo-*N*-(4-methoxybenzyl)acetamide but since the radical centre resulting from halogen abstraction is stabilised by the amide moiety and the C-Cl bond weakened, even the chloro compound should be sufficiently reactive to act as a radical precursor. The synthesis of *N*-allyl-2-chloro-*N*-(4-methoxybenzyl)acetamide **45** is outlined in **Scheme 41**.

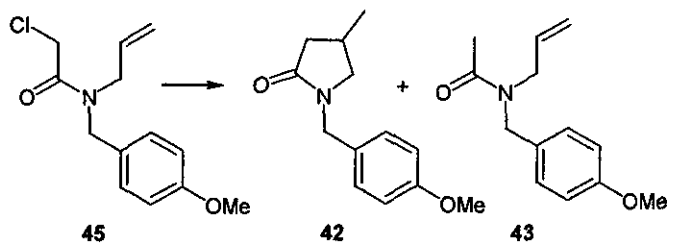
Scheme 41. Synthesis of *N*-allyl-2-chloro-*N*-(4-methoxybenzyl)acetamide **45**.



Reagents and conditions: (i) Allyl bromide, K_2CO_3, acetonitrile, ambient temperature, 17 h. (ii) Chloroacetyl chloride, K_2CO_3, diethyl ether, ambient temperature, 17 h, **45** (57 % in two steps).

N,N-Dialkylation of 4-methoxybenzylamine with allylbromide and chloroacetyl chloride afforded **45** in reasonable overall yield.

Table 30. Radical cyclisation of **45**.



45 **42** **43**

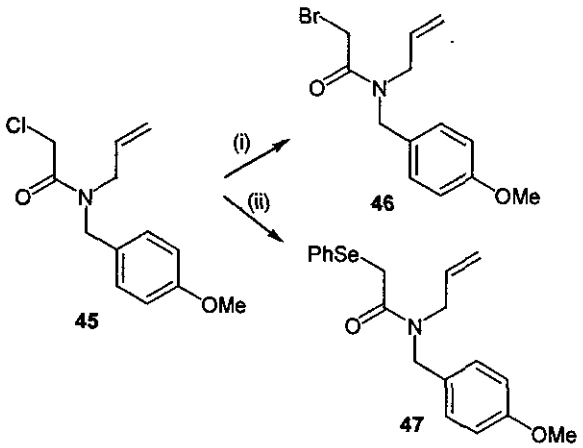
Entry	Radical mediator	Reaction conditions	Product(s)	Ratio **42/43**
1	TBTH (1.5 eq.)	AMBN, C_6H_{12}, reflux, 1 h	**42** (47 %) **43** (23 %)	~ 2
2	TBGH (1.5 eq.)	AMBN, C_6H_{12}, reflux, 4 h	**42** (34 %) **43** (13 %)[a]	2.6
3	TBGH (1.5 eq.)	AMBN, C_6H_{12}, reflux, 8 h	**42** (42 %) **43** (17 %)[b]	2.5
4	TBGH (1.5 eq.)	AMBN, C_6H_{12}, reflux, 12 h	**42** (48 %) **43** (23 %)[c]	2.1

[a]Unreacted **45** (25 %) was recovered. [b]Unreacted **45** (23 %) was recovered. [c]Unreacted **45** (22 %) was recovered.

Radical cyclisation of *N*-allyl-2-chloro-*N*-(4-methoxybenzyl)acetamide revealed that both TBTH and TBGH are able to induce cyclisation but also that reactions promoted by the latter were more sluggish (**Table 30**). Even after refluxing **45** for 12 h in the presence of TBGH and AMBN, unreacted starting material could be recovered in 22 % yield. Increasing the reaction time even further can be troublesome due to the need of repeated addition of AMBN to secure continuously radical chain initiation. At 85 °C $t_{½}^{AMBN} \approx t_{½}^{AIBN} = \sim 60$ min,[59] meaning that the initiator has to be added with regular intervals. These radical cyclisations were encouraging since reactions promoted by TBGH gave a higher ratio of cyclic product to reduced product than the corresponding Sn-mediated reaction (**42/43**, **Table 30**), a selectivity we expected to observe in reactions mediated by the poorer hydrogen donor TBGH.

To investigate the effect of leaving groups in the cyclisation of amide precursors, **45** was reacted with sodium bromide and phenylselanide ($PhSe^-$) to give *N*-allyl-2-bromo-*N*-(4-methoxybenzyl)acetamide **46** and *N*-allyl-*N*-(4-methoxybenzyl)-2-phenylselanyl-acetamide **47** respectively (**Scheme 42**).

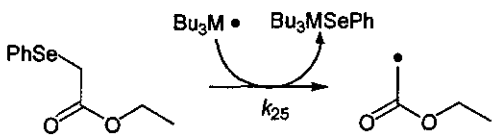
Scheme 42. Synthesis of amides **46** and **47**.



Reagents and conditions: (i) NaBr (3.5 eq.), acetone, reflux, 18 h, **46** (74 %). (ii) $NaBH_4$, PhSeSePh (0.5 eq.), ethanol, ambient temperature, 17 h, **47** (85 %).

The bromide and phenylselanide were chosen as leaving groups partly because of their easy preparation from **45**, partly because reaction with Ge-based mediators should proceed with relative ease. In fact, kinetic studies have shown the rate constant for the reaction of a phenylselanyl ester with $Bu_3Ge\bullet$ and $Bu_3Sn\bullet$ as being 9.2×10^8 $M^{-1}s^{-1}$ and 1.2×10^8 $M^{-1}s^{-1}$ respectively at 25 °C (**Scheme 43**),[60] indicating a more facile reaction with the former.

Scheme 43. Reaction of phenylselanyl derivative.

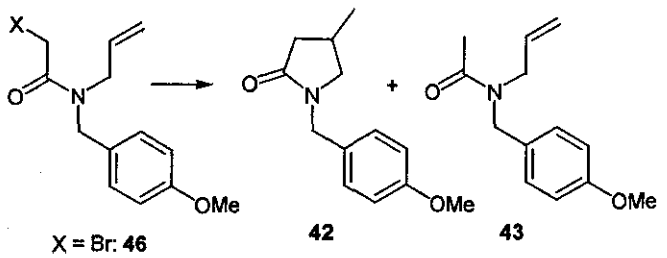


$k_{25}^{M=Ge} = 9.2 \times 10^8\ M^{-1}s^{-1}$

$k_{25}^{M=Sn} = 1.2 \times 10^8\ M^{-1}s^{-1}$

When radical cyclisation reactions were performed with **46** and **47** the trends observed in reactions with the chloride **45** were more pronounced (**Table 31**). The cyclisation of bromide **46** mediated by TBTH was complete after 30 min, affording cyclic product **42** and reduced product **43** as roughly a 1:1 mixture (entry 1, **Table 31**). The identical reaction performed by TBGH had not gone to completion after 5.5 h, but gave a ratio of **42/43** = 8 (entry 2, **Table 31**). The cyclisation of phenylselanide **47** gave ratios of **42/43** = 0.8 and **42/43** = 3.5 for TBTH and TBGH respectively (entries 3 and 5, **Table 31**). Refluxing for 5 h in the presence of TBGH and AMBN secured complete consumption of phenylselanyl amide **47** and a better ratio of cyclised to reduced products (entry 5, **Table 31**).

Table 31. Radical cyclisation of **46** and **47**.



42 **43**

X = Br: **46**
X = PhSe: **47**

Entry	X	Radical mediator	Reaction conditions	Product(s)	Ratio **42/43**
1	Br	TBTH (1.4 eq.)	AMBN, C_6H_{12}, reflux, 30 min	**42** (39 %) **43** (33 %)	1.2
2	Br	TBGH (1.1 eq.)	AMBN, C_6H_{12}, reflux, 5.5 h	**42** (64 %) **43** (8 %)[a]	8
3	PhSe	TBTH (1.7 eq.)	AMBN, C_6H_{12}, reflux, 3 h	**42** (29 %) **43** (38 %)	0.8
4	PhSe	TBGH (1.0 eq.)	AMBN, C_6H_{12}, reflux, 3 h	**42** (18 %) **43** (8 %)[b]	2.3
5	PhSe	TBGH (1.5 eq.)	AMBN, C_6H_{12}, reflux, 5 h	**42** (67 %) **43** (19 %)	3.5

[a]Unreacted **46** (12 %) was recovered. [b]Unreacted **47** (48 %) was recovered.

It is possible that the apparently sluggish TBGH-mediated cyclisation of **45**, **46** and **47** is not a consequence of an inefficient radical reaction but a mere question of amounts

of TBGH. Therefore, it is possible that these cyclisation reactions could all have been driven to completion by employing a larger excess of the mediator. In most cases, only a slight excess of TBGH was employed under the assumption of completely pure material.

Conclusion of section 2.3

Radical reactions with amide precursors have been shown to proceed with good selectivity towards cyclisation when promoted by TBGH. This selectivity is most pronounced in the cyclisation of bromo amide **46**, where the ratio of cyclic to reduced product is as high as 8 when cyclisation is mediated by TBGH and only 1.2 when promoted by TBTH. The reason for this enhanced selectivity is the lower hydrogen donor ability of TBGH compared to TBTH, enabling the slower cyclisation reaction to occur in preference to reduction of the initially formed amide radical. Reactions promoted by TBGH have proven to be slower processes than the TBTH-mediated reactions, presumably due to less rapid reduction of the final radical formed by cyclisation.

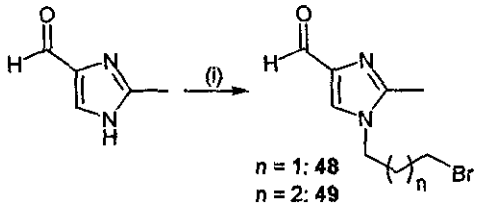
2.4 Radical reactions with heterocyclic precursors

Reactions involving heteroarenes have been an area of interest in recent years due to their presence in various natural products and/or compounds of biological interest. Radical reactions can be advantageous in this context due to mild reaction conditions and therefore great tolerance towards a variety of functional groups. Our research group has contributed largely to the research, especially with radical cyclisations onto imidazoles, pyrroles and pyrazoles and has found that radical reactions promoted by triorganotin hydrides facilitate the formation of desired cyclic products in high yields. For this reason, it was obvious to investigate whether triorganogermanium compounds would be as efficient radical mediators in reactions with these precursors.

2.4.1 Radical reactions with imidazole precursors

N-Alkylation of 2-methyl imidazole-4-carbaldehyde in accordance with literature precedence afforded 1-(3-bromopropyl)-2-methyl-1*H*-imidazole-4-carbaldehyde **48** and 1-(4-bromobutyl)-2-methyl-1*H*-imidazole-4-carbaldehyde **49** (**Scheme 44**).[61]

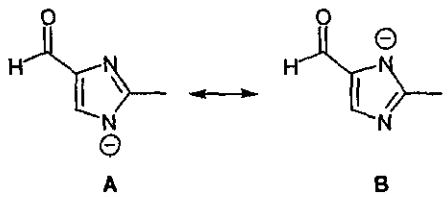
Scheme 44. Synthesis of imidazole derivatives **48** and **49**.



Reagents and conditions: (i) NaH (1.5 eq.), 1,3-dibromopropane (5 eq.) or 1,4-dibromobutane (5 eq.), THF, reflux, 2 h, **48** (53 %), **49** (72 %).

The anion of 2-methyl-imidazole-4-carbaldehyde is ambident and nucleophilic attack can theoretically occur *via* both of the canonical forms **A** and **B** in **Scheme 45.** In the syntheses of **48** and **49**, only products arising from canonical form **A** were observed. This regio-selectivity can be explained by influence of the electron withdrawing aldehyde functionality present in the molecule. The nucleophilicity of **B** is more affected by the aldehyde group than **A**, hence alkylation occur *via* this canonical form. Steric hindrance surrounding the anion in **B** would also explain some regio-selectivity of the nucleophilic attack.

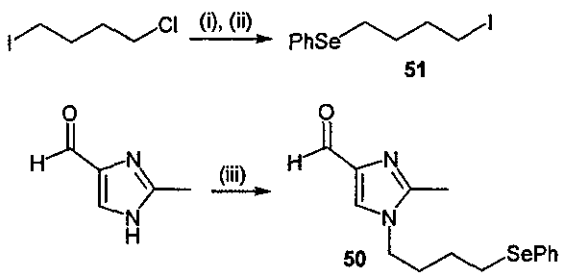
Scheme 45. Canonical forms of imidazole anion.



Along with **48** and **49**, a phenylselanyl derivative of 2-methyl-imidazole-4-carbaldehyde **50** was also synthesised in order to investigate the effect of the leaving group in radical reactions. To synthesise **50**, 1-iodo-4-phenylselanylbutane **51** was required. Reaction of 1-bromo-4-chlorobutane with PhSeSePh and $NaBH_4$ gave 1-

chloro-4-phenylselanylbutane, which upon treatment with NaI in a Finkelstein halogen exchange reaction afforded **51** in 63 % yield.

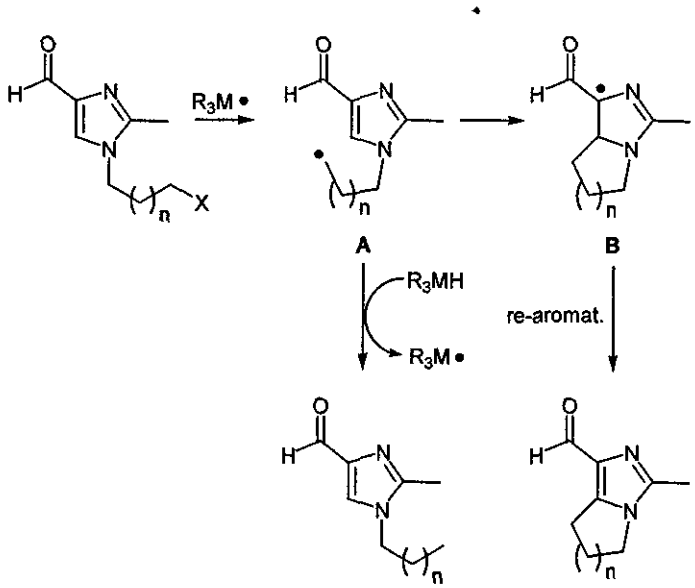
Scheme 46. Synthesis of imidazole derivative **50**.



Reagents and conditions: (i) PhSeSePh (0.5 eq.), $NaBH_4$ (1.1 eq.), ethanol, ambient temperature, 18 h. (ii) NaI, acetone, reflux, 17 h, **51** (63 % in two steps). (iii) NaH (1.5 eq.), **51** (1.2 eq.), THF, reflux, 5 h, **50** (27 %).

N-Alkylation of 2-methyl-imidazole-4-carbaldehyde gave the desired phenylselanyl derivative **50** (**Scheme 46**). The poor yield of **50** (27 %) is probably due to decomposition of the relatively unstable iodo compound **51**. The yield was not optimised.

Scheme 47. Mechanism of radical cyclisation of imidazole derivatives.

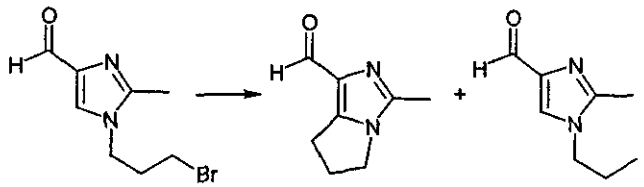


As mentioned, radical cyclisation of imidazole precursors have been performed successfully within the research group. The mechanism of the reaction is outlined in **Scheme 47**. Bromine (or PhSe) abstraction by the employed radical mediator gives

alkyl radical **A**, which can be reduced directly to give the reduced product or cyclise in an *exo* manner to give an very stable aryl radical **B** which upon re-aromatisation produces the desired cyclic product.

When radical cyclisation of 1-(3-bromopropyl)-2-methyl-1*H*-imidazole-4-carbaldehyde **48** was performed under various reaction conditions, the results were far from encouraging. The best results obtained are shown in **Table 32.** All attempts to optimise reaction conditions, *i.e.* improve the outcome of this cyclisation reaction, proved fruitless. The lack of cyclisation of the alkyl radical can possibly be explained by ring strain in the 5,5 ring system formed by 5-*exo* cyclisation, but this does not explain why reduction of the radical is not observed to a greater extent. It is possible that the yields of 3-methyl-6,7-dihydro-5*H*-pyrrolo[1,2-*c*]imidazole-1-carbaldehyde **52** and 2-methyl-1-propyl-1*H*-imidazole-4-carbaldehyde **53** could have been improved by increasing the reaction temperature. Attempts to perform the reaction in toluene were quite unsuccessful because of low solubility of the radical precursor in this solvent. Instead of exploring this further, the attention was turned to radical cyclisation of **49** and **50.** In these cases, the product of cyclisation would be a 5,6 ring system free of ring strain and hence hopefully more prone to cyclise.

Table 32. Radical cyclisation of **48.**



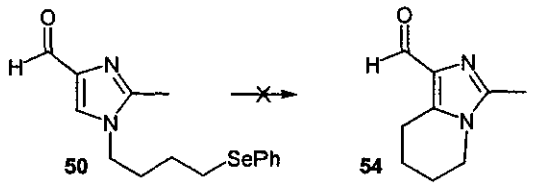
48 **52** **53**

Entry	Radical mediator	Reaction conditions	Product(s)[a]
1	TBTH (1.9 eq.)	AMBN, CH_3CN, reflux, 3 h	**52** (14 %) **53** (7 %)[b]
2	TBGH (1.1 eq.)	AMBN, CH_3CN, reflux, 3 h	**52** (10 %) **53** (7 %)[c]

[a]All yields determined by the use of an internal standard in ^{1}H-NMR spectroscopy. [b]Unreacted **48** (68 %) was recovered. [c]Unreacted **48** (42 %) was recovered.

The radical cyclisation of phenylselanyl derivative **50** was only attempted once with TBTH and once with TBGH since these reactions did not seem worth optimising. In both cases only unreacted **50** was observed by ^{1}H-NMR spectroscopy (**Table 33**).

Table 33. Attempted radical cyclisation of **50**.



Entry	Radical mediator	Reaction conditions	Product[a]
1	TBTH (1.6 eq.)	AMBN, CH_3CN/ $PhCH_3$, syringe-pump addn., reflux, 3 h	**50** (84 %)
2	TBGH (1.2 eq.)	AMBN, CH_3CN/ $PhCH_3$, syringe-pump addn., reflux, 3 h	**50** (80 %)

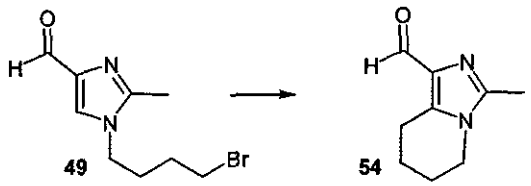
[a]Yields determined by the use of an internal standard in ^{1}H-NMR spectroscopy.

We have not determined why the cyclisation of the phenylselanyl derivative was so unsuccessful. Both mediators should be able to cleave the Se-C bond and when the alkyl radical is formed, cyclisation should occur quite readily, as observed within the Bowman research group.[61]

That the PhSe functional group might partly be the cause of the lack of radical reaction with **50** was indicated by the results obtained in radical cyclisation reactions with the bromo-analogue **49** (**Table 34**). The results mostly speak for themselves and a now quite familiar pattern is observed. TBGH is not as efficient a radical mediator as TBTH, giving much lower yields of cyclic product 3-methyl-5,6,7,8-tetrahydro-imidazo[1,5-*a*]pyridine-1-carbaldehyde **54**. The tin mediated reactions give very variable yields and the solvent of choice seems very important. This is most evident when comparing entries 2 *vs.* 4 and entries 7 *vs.* 9, where a solvent change from cyclohexane to toluene increases the yield of cyclic product **54** dramatically. Entry 4 is very interesting in its own respect, since this reaction is performed without syringe-pump addition of TBTH. This reaction gave **54** in 62 % and no product arising from reduction which nicely illustrates the ease of cyclisation of the precursor. The

reactions mediated by TBGH follows the pattern of the tin mediated reactions but the yields are much lower.

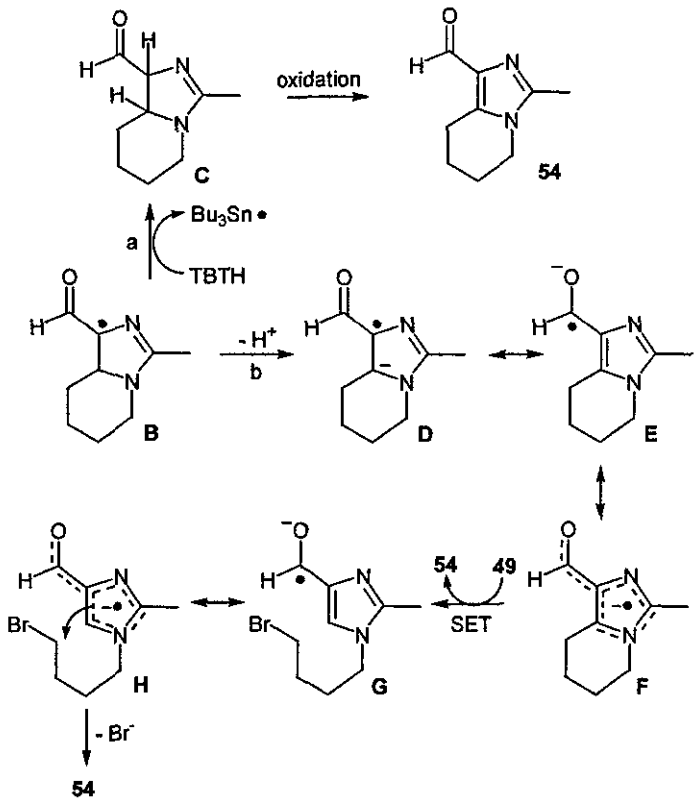
Table 34. Radical cyclisation of **49**.



Entry	Radical mediator	Reaction conditions	Product(s)[a]
1	Bu_3SnCl (1.2 eq.)	Et_3B, THF, ambient temperature, 7 h	**49** (36 %) **54** (12 %)
2	TBTH (1.2 eq.)	AMBN, C_6H_{12}, reflux, 3 h	**49** (58 %) **54** (28 %)
3	TBGH (1.5 eq.)	AMBN, C_6H_{12}, reflux, 3 h	**49** (74 %) **54** (9 %)
4	TBTH (1.2 eq.)	AMBN, CH_3CN, reflux, 3 h	**49** (29 %) **54** (62 %)
5	TBGH (1.5 eq.)	AMBN, CH_3CN, reflux, 3 h	**49** (69 %) **54** (21 %)
6	TBTH (1.5 eq.)	AMBN, $CH_3CH_2CH_2CN$, reflux, 3 h	**49** (21 %) **54** (21 %)
7	TBTH (2.0 eq.)	AIBMe, CH_3CN/ C_6H_{12}, syringe-pump addn., reflux, 5 h	**49** (49 %) **54** (26 %)
8	TBTH (2.0 eq.)	AMBN, CH_3CN/ $PhCH_3$, syringe-pump addn., reflux, 3 h	**49** (n.d.)[b] **54** (30 %)
9	TBTH (2.0 eq.)	AIBMe, CH_3CN/ $PhCH_3$, syringe-pump addn., reflux, 3 h	**49** (n.d.)[b] **54** (77 %)
10	TBGH (2.0 eq.)	AIBMe, CH_3CN/ $PhCH_3$, syringe-pump addn., reflux, 3 h	**49** (26 %) **54** (10 %)

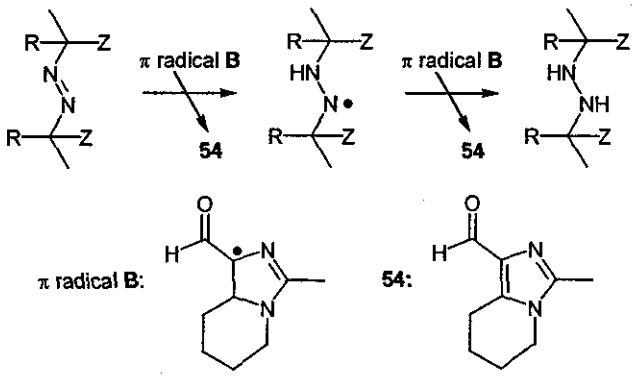
[a]All yields determined by the use of an internal standard in ^{1}H-NMR spectroscopy. [b]n.d. = not determined.

Scheme 48. Possible mechanisms of the re-aromatising of radical **B**.



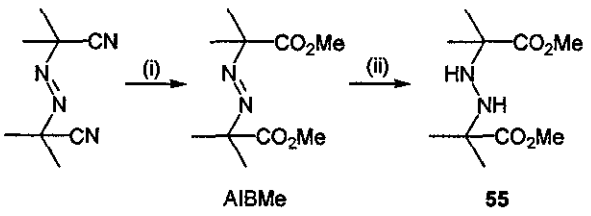
The reaction of 1-(4-bromobutyl)-2-methyl-1*H*-imidazole-4-carbaldehyde **49** with TBTH has been repeated numerous times, partly to make a comparison with the germanium mediated reactions, but also in order to investigate the mechanism of the re-aromatisation of the cyclic radical **B** (**Scheme 47** and **Scheme 48**). The route to this radical is without much discussion, but there has been some debate concerning the re-aromatising of radical **B** to product **54**. One possibility could be the formation of the dihydroimidazole **C** (route a, **Scheme 48**) by H-abstraction by radical **B** from TBTH followed by air-oxidation in work-up of the reaction mixture. Two factors rule out this possibility; radical **B** is too stable (and hence too unreactive) to react with TBTH and this research group have carefully examined crude reaction mixtures and never found any trace of the dihydroimidazole.[61] In the same line of work, the group originally proposed a anion radical mechanism[62] (route b, **Scheme 48**) but later reactions revealed that this proposal is not probable.[63] Instead, it seems likely that the radical initiator could play a more active role in the mechanism than just being an initiator. It has been shown that in order to obtain the cyclic product in high yield, an excess of initiator must be added to the mixture.[63] So the question is now whether the initiator is responsible for the re-aromatisation by the pathway shown in **Scheme 49**.

Scheme 49. Possible cause of the re-aromatising of radical **B**.



If the initiator is responsible for the oxidation of the stable π-radical, the hydrazine derivative of this initiator must be formed in the reaction. The reduced forms of AIBN and AMBN are quite unstable which can explain the absence of these products in crude radical reaction mixtures. To investigate this, the methyl ester analogue of AIBN (AIBMe) and the reduction product of this compound 2-[*N*-(1-methoxycarbonyl-1-methylethyl)hydrazino]-2-methyl-propionic acid methyl ester **55** were synthesised (**Scheme 50**). This initiator was chosen because the methyl ester functional groups were assumed to enhance the stability of the compound. In the reduction of AIBMe the addition of $CuSO_4$ turned out to be very important, since the Cu^{II} oxidises the hydrazine to the reactive NH=NH,[64] which then is responsible for the reduction of AIBMe.

Scheme 50. Synthesis of AIBMe and its reduced form **55**.

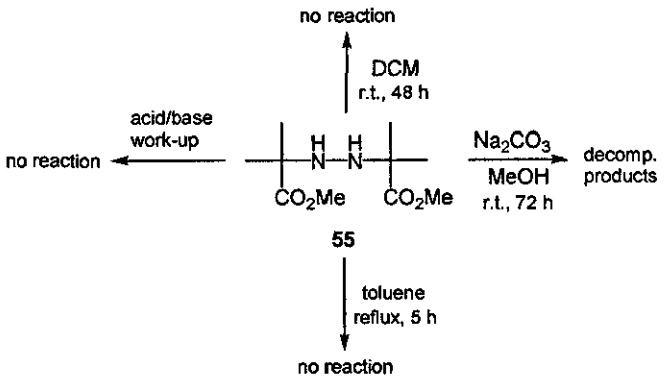


Reagents and conditions: (i) HCl (g), methanol, 0 °C, 18 h, AIBMe (91 %) (ii) Hydrazine hydrate (4.8 eq.), $CuSO_4$ (0.1 eq.), methanol, ambient temperature, 17 h, **55** (21 %).

If AIBMe is responsible for the re-aromatisation, **55** should be formed in the reaction. When the cyclisation reaction was carried out using AIBMe as radical initiator (entries 7, 9 and 10, **Table 34**) no **55** was observed by ^{1}H-NMR spectroscopy. A possibility

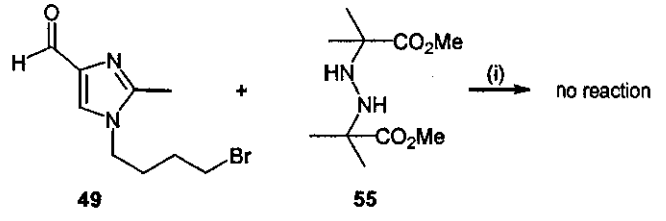
could be instability of **55** under the reaction conditions but this was ruled out by a series of experiments in accordance with **Scheme 51**.

Scheme 51: "Stability-check" of **55**.



The hydrazine **55** was stable towards air-oxidation in DCM over 48 h, towards refluxing in toluene for 5 h and towards the acid/base extraction used as work-up procedure in the radical reactions. Only in a basic solution of MeOH was decomposition observed. The last question to be answered with respect to the stability of **55**, was whether the compound is stable under the exact radical reaction conditions, *i.e.* in the presence of both radical precursor and radical mediator. Since no radical initiator was present, no cyclisation should occur and the possibility of **55** being oxidised back to AIBMe under these conditions, hopefully ruled out. When this "blank" reaction with no radical initiator was performed the result was a bit surprising **(Scheme 52)**.

Scheme 52. "Blank" radical reaction of **49**.

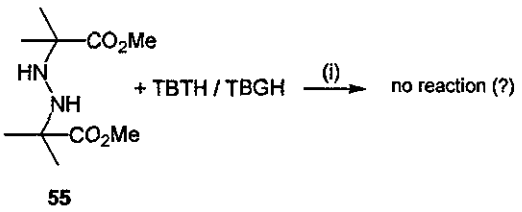


Reagents and conditions: (i) TBTH (2.0 eq.), CH_3CN, toluene, reflux, 3 h. **49** (88 %).

After reaction, **55** was detected in only 2 % yield by the use of internal standard in ^{1}H-NMR spectroscopy of the crude reaction mixture and after work-up only in an amount

corresponding to a yield of 0.8 %. The radical precursor **49** on the other hand was recovered in 88 % yield. A logical thought was thereafter to react **55** with TBTH and TBGH. The results of these reactions were far from conclusive (**Scheme 53**).

Scheme 53. Reactions of **55** with TBTH and TBGH.



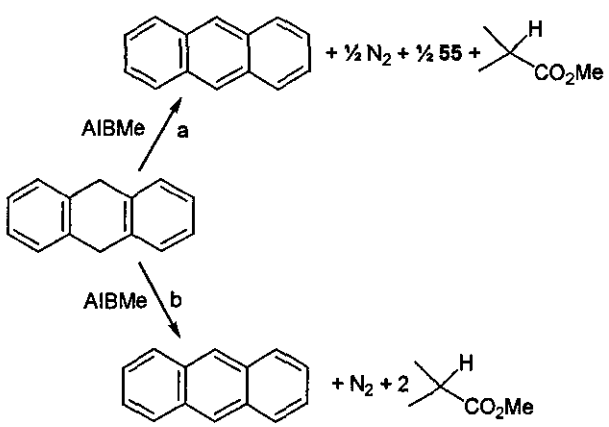
55

Reagents and conditions: (i) **55**, TBTH (2.5 eq.) or TBGH (2.2 eq.), toluene, reflux, 3 h.

It was not possible to isolate **55** in quantitative yield in either of the two reactions, but this can be the effect of working with very small quantities. In the tin reaction no product apart from unreacted **55** can be seen by GC-MS, whereas in the reaction promoted by TBGH other minor products could be detected. These products were not identified.

The question in this mechanistic study is whether AIBMe, or other initiators, are able to oxidise π-aromatic radicals. In order to answer this question by other means, 9,10-dihydroanthracene was reacted with AIBMe (**Scheme 54**). AIBMe should be able to oxidise 9,10-dihydroanthracene to anthracene and by measuring the amounts of **55** and/or N_2 formed in the reaction, it should in theory be possible to determine which of the routes indicated in **Scheme 54** the reaction had taken.

Scheme 54. Oxidation of 9,10-dihydroanthracene.



If route a is valid, **55** should be observed meaning that AIBMe is the oxidant, whereas the detection of the formation of 1 eq. of N_2 would indicate that AIBMe only acts as an initiator in this reaction, hence route b is followed. Unfortunately this reaction was fruitless since no anthracene was formed in the reaction probably because of low oxidising ability of AIBMe. Whether a suitable sensitiser could be employed in the reaction and thereby facilitate the formation of anthracene was not determined. However, these reactions made it clear that the investigation of the mechanism is not as straight forward as believed. It was decided not to pursue this further.

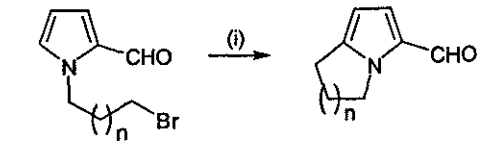
Conclusion of section 2.4.1

Radical cyclisations of imidazole precursors have been shown to be inefficient processes when cyclisation gives rise to 5,5-ring systems in which there is a certain ring strain. These precursors only form the cyclic product in low yields when treated with either TBTH or TBGH. In the formation of 5,6-ring systems, ring strain is not a problem, but when reacting the phenylselanyl derivative under radical conditions, no formation of the desired cyclic product is observed, regardless of mediator employed. Only when reacting 1-(4-bromobutyl)-2-methyl-1*H*-imidazole-4-carbaldehyde **49** good to excellent yields of cyclic product were determined by ^{1}H-NMR spectroscopy. TBTH gives rise to much higher yields than TBGH, but since the mechanism of re-aromatisation of the π-arene radical is unclear, attempts have not been made to optimise reaction conditions of the use of this germanium based radical mediator. If reduction of the π-arene radical by the mediator is crucial, it is possible that employment of a better hydrogen atom donor could be beneficial, but as it is, this remains unknown.

2.4.2 Radical reactions with pyrrole derivatives

Radical reactions of pyrrole derivatives have successfully been performed within the Bowman group.[61] Employing TBTH as radical mediator, pyrrole derivatives **56**, **57** and **58** were cyclised in moderate to good yields (**Scheme 55**). In none of the reactions was the corresponding reduced product observed, indicating the efficiency in the radical addition to the electron deficient C-C double bond.

Scheme 55.



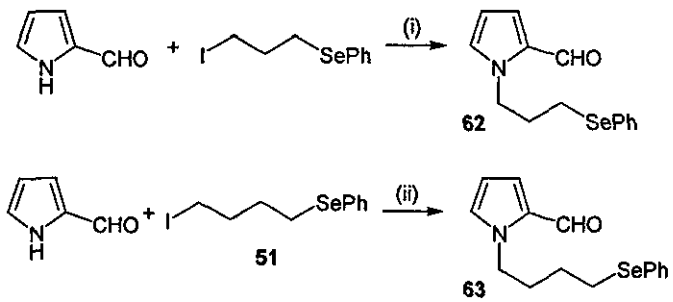
n = 1: **56**
n = 2: **57**
n = 3: **58**

n = 1: **59** (28 %)
n = 2: **60** (55 %)
n = 3: **61** (40 %)

Reagents and conditions: TBTH (1.5 eq.) and AIBN (0.25 eq.) in toluene added by syringe-pump, 5 h.

To investigate the ability of TBGH to induce cyclisation of precursors of this type, 1-(3-phenylselanylpropyl)-1*H*-pyrrole-2-carbaldehyde **62** and 1-(4-phenylselanylbutyl)-1*H*-pyrrole-2-carbaldehyde **63** were synthesised according to **Scheme 56**. Heating the anion of pyrrole-2-carbaldehyde in the presence of either 1-iodo-3-phenylselanylpropane or 1-iodo-4-phenylselanylbutane **51** afforded the *N*-alkylated products **62** and **63** respectively.

Scheme 56. Synthesis of pyrrole derivatives **62** and **63**.

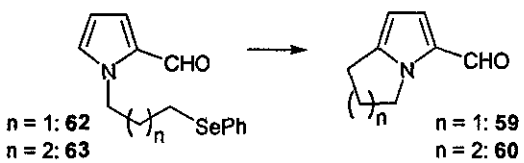


Reagents and conditions: (i) NaH (1.2 eq.), 1-iodo-3-phenylselanylpropane (2.0 eq.), THF, reflux, 150 min, **62** (75 %). (ii) NaH (1.2 eq.), **51** (2.3 eq.), THF, 50 °C, 17 h, **63** (70 %).

Despite the lack of success in the TBGH-mediated radical cyclisation of the phenylselanyl imidazole derivative **50**, it was hoped that the pyrrole analogue would yield better cyclisation in the presence of TBGH. As can be seen in **Table 35** this was not the case. The reaction of 1-(3-phenylselanylpropyl)-1*H*-pyrrole-2-carbaldehyde **62** with TBTH proceeded well and the cyclic product 6,7-dihydro-5*H*-pyrrolizine-3-carbaldehyde **59** was isolated in 49 % yield (entry 1, **Table 35**). Employing identical reaction conditions with TBGH as radical mediator did not give rise to formation of any **59**, in which case only unreacted **62** could be observed by ^{1}H-NMR spectroscopy of the crude reaction mixture (entry 2, **Table 35**). Both these reactions were performed

adding the mediator by syringe-pump, hence the concentration of TBTH or TBGH is kept low throughout the reaction time and no formation of any reduced product was detected. Changing the reaction conditions slightly so that the total amount of TBGH was added initially gave rise to a small amount of cyclic product **59** which was observed by ^{1}H-NMR spectroscopy (entry 3, **Table 35**). This very low yield was not determined and the product not isolated. The radical cyclisation of 1-(4-phenylselanylbutyl)-1*H*-pyrrole-2-carbaldehyde **63** was only successfully performed with TBTH as a comparison (entry 4, **Table 35**). The low yield of cyclic product 5,6,7,8-tetrahydro-indolizine-3-carbaldehyde **60** in reactions promoted by TBGH did not inspire any further investigation of this reaction. Interestingly, AIBMe initiated the reaction and ^{1}H-NMR spectroscopy of the crude reaction mixture showed signals corresponding to the reduced form of this compound, **55**. This could be an indication of AIBMe actually being responsible for the re-aromatisation of the π-arene radical formed by cyclisation. Even if this result contradicts the results obtained in the radical reactions of imidazole precursors, this was not pursued any further.

Table 35. Radical cyclisation of pyrrole derivatives **62** and **63**.



Entry	n	Radical mediator	Reaction conditions	Product(s)
1	1	TBTH (1.6 eq.)	AIBN, $PhCH_3$, syringe-pump addn., reflux, 5 h	**59** (49 %)
2	1	TBGH (1.2 eq.)	AIBN, $PhCH_3$, syringe-pump addn., reflux, 5 h	**62** (n.d.)[a]
3	1	TBGH (4.3 eq.)	AIBN, $PhCH_3$, reflux, 5.5 h	**62** (n.d.)[a] **59** (n.d.)[a]
4	2	TBTH (1.9 eq.)	AIBMe, $CH_3CN/PhCH_3$, syringe-pump addn., reflux, 3 h	**60** (29 %)[b]

[a]n.d.: Not determined. [b]Determined by the use of an internal standard in ^{1}H-NMR spectroscopy.

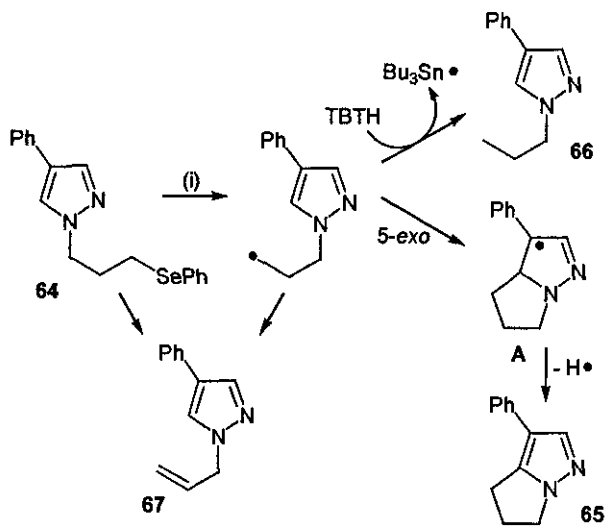
Conclusion of section 2.4.2

The radical cyclisations of the pyrrole derivatives did not proceed as well employing TBGH as mediator compared to the use of TBTH. Whether the lack of reactivity of TBGH in these reactions is caused by the same problems associated with the radical cyclisation of the imidazole derivatives has not been determined.

2.4.3 Radical reactions with pyrazole derivatives

Like the imidazole and pyrrole precursors, pyrazole derivatives have been employed in radical reactions within the Bowman group. By reacting 4-phenyl-1-(3-phenylselanyl-propyl)-1*H*-pyrazole **64** with TBTH, the first radical approach to withasomnine **65**, a alternative medicine remedy and a claimed aphrodisiac, was accomplished (**Scheme 57**).[65]

Scheme 57. Synthesis of withasomnine **65** by radical cyclisation.

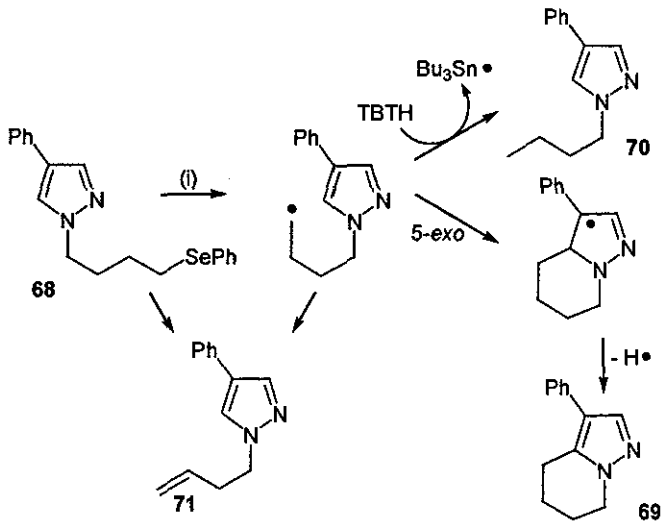


Reagents and conditions: TBTH (1.3 eq.) and ACCN (2.0 eq.) in toluene added by syringe-pump, 5 h, **65** (38 %), **66** (17 %) and **67** (trace).

Along with withasomnine, the reduced product **66** and the elimination product **67** were also formed in the reaction. The mechanism of this radical reaction is similar to the oxidative radical cyclisation of the imidazole and pyrrole precursors, but differs from those on one significant point. With the imidazole and pyrazole derivatives, the initially formed alkyl radical adds to a electron deficient C-C double bond, whereas in

the addition to the pyrazole ring the C-C double bond is quite electron rich due to the electron donating phenyl substituent. Hence the stabilising effect of the phenyl group on radical **A** (**Scheme 57**) is of greater importance than electronic factors in this addition.

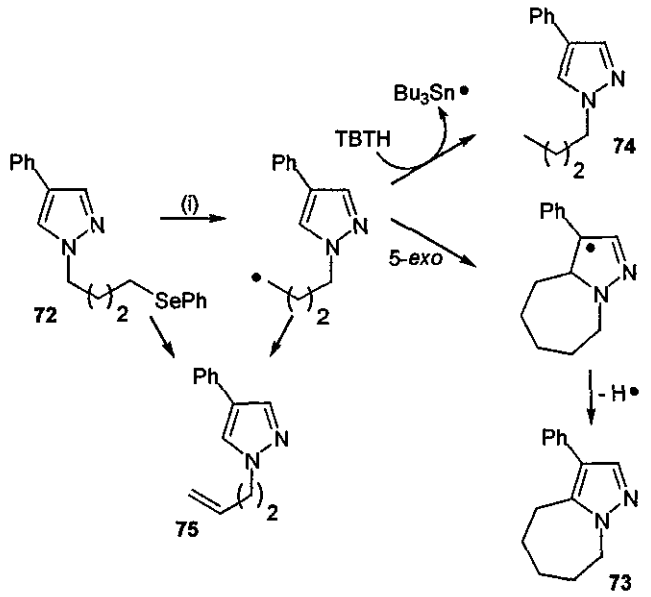
Scheme 58. Radical cyclisation of phenylpyrazole **68.**



Reagents and conditions: TBTH (1.3 eq.) and ACCN (2.0 eq.) in toluene added by syringe-pump, 5 h, **69** (63 %) and **70** (trace).

Employing identical reaction conditions, 4-phenyl-1-(4-phenylselanyl-butyl)-1*H*-pyrazole **68** was converted into the bicyclic pyrazole derivative 3-phenyl-4,5,6,7-tetrahydro-pyrazolo[1,5-a]pyridine **69** in high yield (63 %). This reaction also afforded the reduced product 1-butyl-4-phenyl-1*H*-pyrazole **70** in trace amount, but in this case no formation of the elimination product 1-but-3-enyl-4-phenyl-1*H*-pyrazole **71** was observed (**Scheme 58**).[65] The high yield of **69** in the radical cyclisation of **68** illustrates the ease of formation of the 5,6 bicyclic ring system, whereas the formation of a 5,7 bicyclic ring system is less successful as seen in the radical cyclisation of 4-phenyl-1-(5-phenylselanyl-pentyl)-1*H*-pyrazole **72** which upon treatment with TBTH produced the reduced product 1-pentyl-4-phenyl-1*H*-pyrazole **74** as the major product (**Scheme 59**).[65]

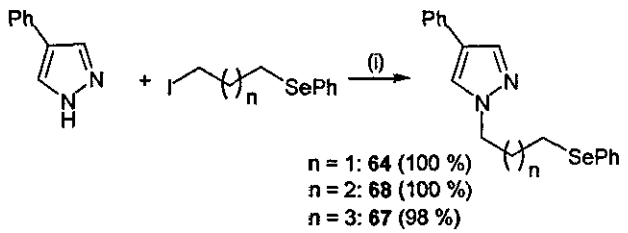
Scheme 59. Radical cyclisation of phenylpyrazole **72**.



Reagents and conditions: TBTH (1.3 eq.) and ACCN (2.0 eq.) in toluene added by syringe-pump, 5 h, **73** (37 %) and **74** (48 %).

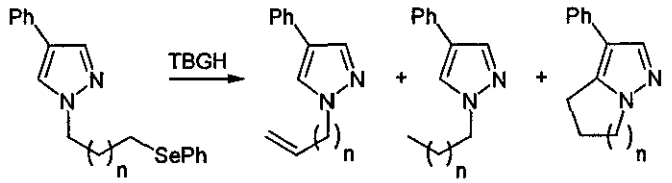
We sought to investigate whether the reactivity of TBTH observed with these heteroarenes could be mimicked by TBGH. Therefore, 4-phenyl-1-(3-phenylselanyl-propyl)-1*H*-pyrazole **64**, 4-phenyl-1-(4-phenylselanylbutyl)-1*H*-pyrazole **68** and 4-phenyl-1-(5-phenylselanylpentyl)-1*H*-pyrazole **72** were included in this investigation. The syntheses of these compounds are shown in **Scheme 60**.[66] Reacting the anion of 4-phenylpyrazole with 1-iodo-3-(phenylselanyl)propane, 1-iodo-4-(phenylselanyl)-butane and 1-iodo-5-(phenylselanyl)pentane afforded **64**, **68** and **72** respectively in quantitative yields.

Scheme 60. Syntheses of pyrazole derivatives **64**, **68** and **72**.



Reagents and conditions: 1-Iodo-3-phenylselanylpropyl, 1-iodo-4-phenylselanylbutyl or 1-iodo-5-phenylselanylpentyl (2.0 eq.), KOH, DMF, ambient temperature, 17 h.

Table 36. Radical cyclisation of phenylpyrazole precursors.



n = 1: **64**
n = 2: **68**
n = 3: **72**

n = 1: **67**
n = 2: **71**
n = 3: **75**

n = 1: **66**
n = 2: **70**
n = 3: **74**

n = 1: **65**
n = 2: **69**
n = 3: **73**

Entry	n	Radical mediator	Reaction conditions	Product(s)
1	1	TBGH (1.1 eq.)	ACCN[a], $PhCH_3$, syringe-pump addn., reflux, 6 h	**66** (19 %)[b] **67** (7 %)
2	1	TBGH (1.1 eq.)	ACCN[c], $PhCH_3$, syringe-pump addn., reflux, 6 h	**67** (30 %)[d]
3	1	TBGH (2.4 eq.)	Et_3B, C_6H_{12}, ambient temperature, 26 h	**66** (66 %)
4	2	TBGH (1.1 eq.)	ACCN[a], $PhCH_3$, syringe-pump addn., reflux, 10 h	**71** (4 %)[e]
5	2	TBGH (1.2 eq.)	ACCN[c], $PhCH_3$, syringe-pump addn., reflux, 10 h	**71** (16 %)[f]
6	2	TBGH (2.6 eq.)	Et_3B, C_6H_{12}, ambient temperature, 34 h	**69** (44 %.) **71** (4 %)
7	3	TBTH (1.1 eq.)	ACCN[a], $PhCH_3$, syringe-pump addn., reflux, 10 h	**75** (62 %)

[a]ACCN added simultaneously with TBGH in syringe-pump. [b]Unreacted **64** (47 %). [c]ACCN added independently every 45 min. [d]Unreacted **64** (70 %). [e]Unreacted **68** (77 %). [f]Unreacted **68** (52 %).

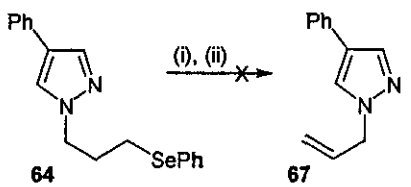
When employing these phenylpyrazole derivatives in TBGH-promoted radical cyclisation reactions, a mixed bag of results were obtained (**Table 36**). Performing the radical cyclisation of **64** under identical reaction conditions as employed by William Barton,[65] reduced product **66** and elimination product **67** were formed in low yields (19 % and 7 % respectively, entry 1, **Table 36**). Adding the initiator independently every 45 min altered the product distribution and only **67** and unreacted **64** were observed by ^{1}H-NMR spectroscopy (entry 2, **Table 36**). By changing the reaction conditions to Et_3B-initiated reaction at ambient temperature, the formation of

elimination product **67** could be suppressed and reduced product **66** was isolated as the sole product in 66 % yield (entry 3, **Table 36**).

A similar reaction pattern was observed in the radical cyclisation of phenylpyrazole **68** where reactions at elevated temperature afforded only elimination product **71** in low yields (entries 4 and 5, **Table 36**). Performing the reaction at ambient temperature using Et_3B as radical initiator gave rise to the formation of cyclic product **69** in 44 % yield (entry 6, **Table 36**). The radical cyclisation reaction of phenylpyrazole **72** on the other hand only formed the elimination product 1-pent-4-enyl-4-phenyl-1*H*-pyrazole **75** when treated with TBGH and ACCN in refluxing toluene (entry 7, **Table 36**).

The formation of the elimination products in these radical reactions has been the centre of some debate within the research group since the mechanism by which these products are formed is not obvious. From the results obtained in this work and in work performed by colleagues in the Bowman group, it is clear that the presence of a heteroatom in a suitable position is required for the elimination to occur. The elimination products have not been noted in radical reactions of precursors in which the (phenylselanyl)alkyl chain is attached to a arene without a second N-atom. If the heteroatom is participating in the elimination of PhSeH, this is very likely to inhibit radical reaction, since PhSeH is a very good hydrogen donor, which would react with any intermediate radical and inhibit the chain reaction. The data in **Table 36** indicate that the elimination process may be of thermal origin since it occurs predominantly at elevated temperature. Test reactions showed that heating **64** in toluene in the presence or absence of TBGH did not lead to any formation of **67** and the idea that the process could be purely thermal was dismissed (**Scheme 61**).

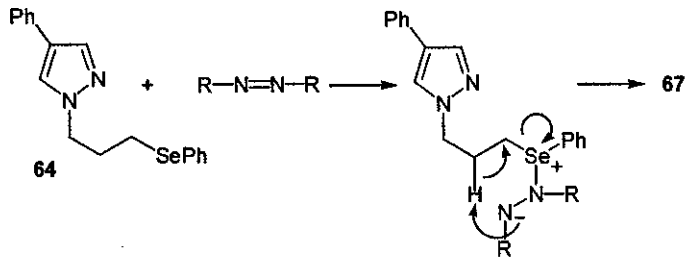
Scheme 61. 'Blank reaction' of **64**.



Reagents and conditions: (i) Toluene, reflux, 16 h. (ii) TBGH (1.6 eq.), toluene, reflux, 18 h.

Another idea was that the azo initiator could play a crucial role in the elimination reaction by attack of the selanide followed by intramolecular hydrogen abstraction and elimination in accordance with **Scheme 62.** To test this hypothesis, **64** was treated with DIAD in refluxing toluene but this reaction also failed to give any elimination product and the mechanistic study was terminated.

Scheme 62. Possible elimination mechanism.



Conclusion of section 2.4.3

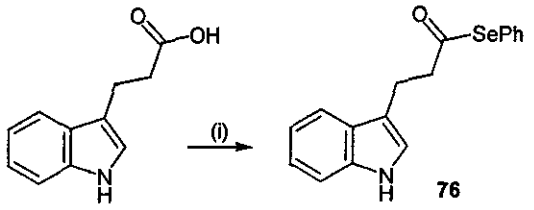
Radical cyclisation of phenylpyrazole precursors has proven to be more efficient reactions when promoted by TBTH than when TBGH is employed as radical mediator. By performing the reactions at ambient temperature, reasonable yields of products arising from radical reactions can be obtained. At elevated temperature, the major products with all precursors are formed by elimination. The nature of the reaction pathway leading to these elimination products has not been investigated fully.

2.4.4 Radical reactions with indole precursors

For use in other research projects, 3-(1*H*-indol-3-yl)selenopropionic acid Se-phenyl ester **76** was synthesised within the Bowman group (**Scheme 63**).[67]

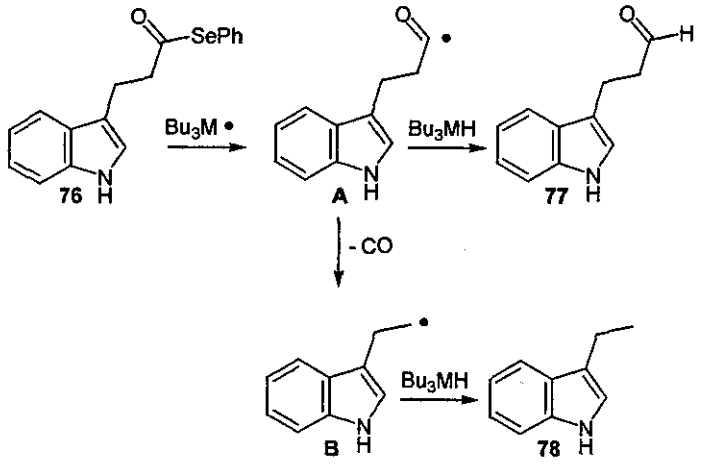
Reacting this indole derivative under radical conditions would be interesting to include in the investigation of the reactivity of triorganogermanium hydrides since this could be different from the reactivity of the corresponding tin based mediators. Once again, the lower hydrogen donor ability of the former could lead to a change in product distribution in radical reactions promoted by the two classes of reagents. The radical pathways are shown in **Scheme 64.**

Scheme 63. Synthesis of **76.**



Reagents and conditions: (i) Bu_3P, (1.5 eq.), PhSeSePh (1.5 eq.), DMF, ambient temperature, 4 h, **76** (98 %).

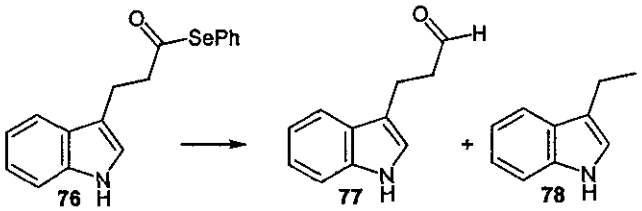
Scheme 64. Mechanism of the radical reaction of **76.**



Radical **A** is formed by homolytic Se-C bond cleavage and can either be trapped by hydrogen abstraction to give aldehyde 3-(1*H*-indol-3-yl)propionaldehyde **77** or eliminate CO to form radical **B**, which upon hydrogen abstraction gives the decarbonylated product 3-ethyl-1*H*-indole **78**. Since TBTH is a better hydrogen donor than TBGH, is was believed that some aldehyde **77** would be formed in the TBTH mediated radical reaction of **76**, whereas reaction with TBGH would only give rise to the formation of **78**. When the radical reactions of **76** were performed, both TBTH and TBGH both gave the decarbonylated product **78** as the major reaction product (**Table 37**). The TBGH mediated reaction gave **78** in 63 % yield (entry 2, **Table 37**) and the same product was obtained in 48 % yield when the reaction was mediated by TBTH (entry 1, **Table 37**). Along with **78**, other products could be detected by ^{1}H-NMR spectroscopy of the crude Sn-promoted reaction mixture. An aldehyde peak was visible at 9.7 ppm in an amount corresponding to 9 % yield as determined by the use of internal standard in ^{1}H-NMR spectroscopy. Unfortunately, attempted isolation of

this and other by-products failed and these could not be identified. It would be plausible, though, that the formation of aldehyde **77** could be observed to a minor extent in reactions promoted by the relatively good hydrogen donor TBTH.

Table 37. Radical reaction of indole derivative **76.**



Entry	Radical mediator	Reaction conditions	Product(s)[a]
1	TBTH (1.1 eq.)	AIBN, $PhCH_3$, reflux, 2 h	**78** (48 %) **77** (9 %)[b]
2	TBGH (1.1 eq.)	AIBN, $PhCH_3$, reflux, 2 h	**78** (63 %)

[a]Yields determined by the use of an internal standard in ^{1}H-NMR spectroscopy. [b]Product not characterised.

Conclusion of section 2.4

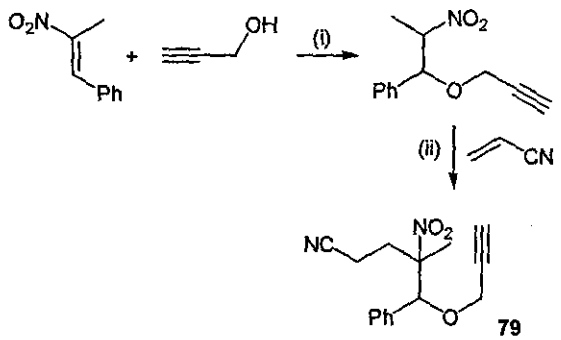
The conclusion of the radical reactions of heterocyclic precursors discussed in this section must be that triorganogermanes do not appear able to substitute tin based radical mediators for this purpose. Reactions employing triorganogermanes are generally slower processes than that of the corresponding reactions promoted by the tin counterparts and any enhanced selectivity towards cyclisation has not been observed. It is possible that the reaction conditions in some cases could be optimised once the full mechanism of the oxidative cyclisation has been clarified.

2.5 Radical reactions with alkyl precursors

From the introduction it is known that triorganogermanes are able to induce radical reactions with alkyl precursors. To test this ability further and to investigate the capacity of triorganogermanes to react with leaving groups other than halides and selenides, 3-nitro-3-methyl-4-phenyl-4-(prop-2-ynyloxo)butyl cyanide **79** was

synthesised in accordance with literature procedure (**Scheme 65**).[68] Base catalysed Michael addition of propargyl alcohol to *trans*-β-methyl-β-nitrostyrene, followed by alkylation with acrylonitrile afforded nitro precursor **79** as a mixture of diastereoisomers in moderate overall yield.

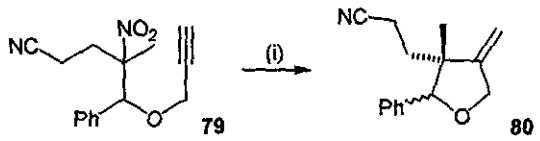
Scheme 65. Synthesis of nitro precursor **79**.



Reagents and conditions: (i) NaH (1.1 eq.), THF, ambient temperature, 18 h. (ii) NaH (1.2 eq.), acrylonitrile (1.2 eq.), THF, ambient temperature, 90 min, **79** (43 %).

TBTH-induced radical cyclisation of **79** has been performed by Ono *et al.* who obtained the cyclic product 3-(3-methyl-4-methylene-2-phenyl-tetrahydro-furan-3-yl) propionitrile **80** in good yield (**Scheme 66**).[68]

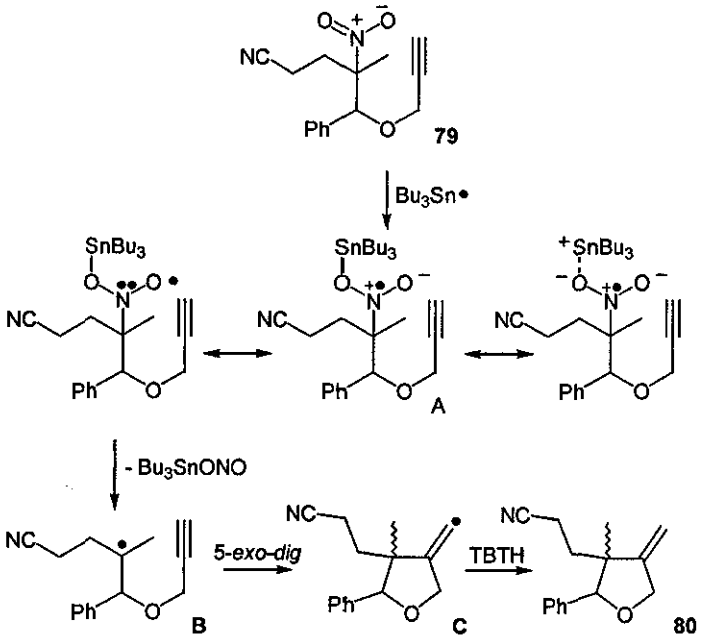
Scheme 66. Radical cyclisation of nitro precursor **79**.



Reagents and conditions: (i) TBTH (1.3 eq.), AIBN, benzene, reflux, 2 h, **80** (79 %).

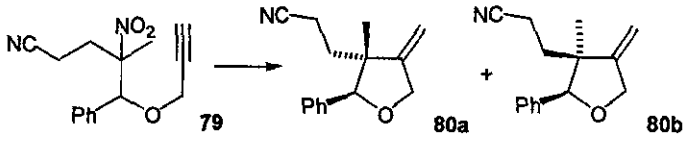
The mechanism of this radical cyclisation is slightly different from the other radical cyclisation reactions presented previously, since the initial step is addition of the tin centred radical to oxygen giving the nitroxyl **A**,[69] followed by elimination to give alkyl radical **B** (**Scheme 67**) which then cyclises in a 5-*exo*-*dig* manner yielding the cyclic methylene radical **C**. Hydrogen abstraction from TBTH affords the desired product **80**.

Scheme 67. Mechanism of radical cyclisation of **79**.



Since this radical cyclisation would be an efficient way of testing the affinity of germanium centred radicals towards oxygen, the reaction was reproduced employing both TBTH and TBGH as radical mediators. Some of the results obtained are shown in **Table 38**. Reacting **79** with TBTH afforded **80** as a mixture of diastereoisomers in reasonable combined yield (entry 1, **Table 38**). The assignment of stereochemistry was determined by careful nOe experiments. Repeating the reaction employing TBGH as radical mediator gave a much lower yield of the two products, but large amounts of unreacted **79** were observed by ^{1}H-NMR spectroscopy of the crude reaction mixtures. Attempts to increase reaction temperature also failed to improve yields (entries 2 and 3, **Table 38**). We believe that unsuccessful chain propagation could be the reason for the sluggishness of the cyclisation, but attempts to overcome this problem by employing both initiator and mediator in large excess failed (entry 4, **Table 38**). It is interesting to note that the major diastereoisomer formed in the cyclisation reaction is dependant of radical mediator used. The tin-promoted reaction gives roughly a 1:1 mixture of products with the formation of **80a**, Me and Ph being *syn*, being slightly dominant, whereas the isomer in which the Me and Ph groups are *anti* to each other is formed as the major product in all reactions mediated by TBGH. The α-chiral centre induces the diastereoselectivity observed in these radical cyclisations.

Table 38. Radical cyclisation of **79**.

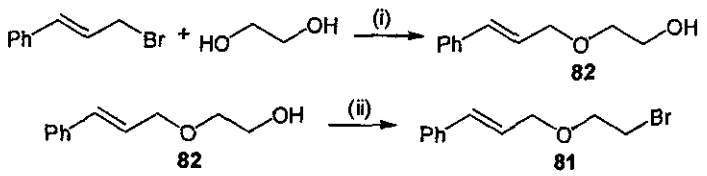


Entry	Radical mediator	Reaction conditions	Product(s)[a]
1	TBTH (1.3 eq.)	AIBN, CH_3CN, reflux, 3 h	**80a** (21 %) **80b** (18 %)[b]
2	TBGH (1.3 eq.)	AIBN, CH_3CN, reflux, 3 h	**80a** (5 %) **80b** (15 %)[c]
3	TBGH (1.3 eq.)	AIBN, $PhCH_3$, reflux, 5 h	**80a** (3 %) **80b** (17 %)[d]
4	TBGH (1.8 eq.)	AIBN (2.4 eq.), CH_3CN, reflux, 5 h	**80** (15 %)[e]

[a]Yields determined by the use of an internal standard in ^{1}H-NMR spectroscopy. [b]Unreacted **79** (9 %). [c]Unreacted **79** (51 %). [d]Unreacted **79** (53 %). [e]Mixture of diastereoisomers, unreacted **79** (51 %).

Another class of alkyl precursors employed in this investigation was unsaturated ethers. Here only the synthesis and radical cyclisation of 3-[(2-bromoethyl)oxy]-prop-2-enyl-benzene **81** will be discussed. This precursor was synthesised in two steps from cinnamyl bromide in accordance with **Scheme 68**.

Scheme 68. Synthesis of alkyl precursor **81**.

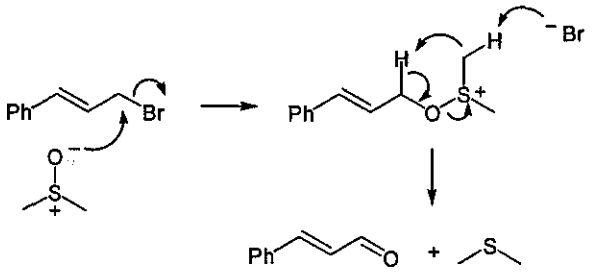


Reagents and conditions: (i) KOH (2.0 eq.), DMSO or DMF, ambient temperature, 1 h, **82** (35 %) in DMSO or **82** (87 %) in DMF. (ii) Ph_3P (1.6 eq.), CBr_4 (1.6 eq.), CH_3CN, ambient temperature, 45 min, **81** (100 %).

The yield of the first step, formation of 2-(3-phenylprop-2-enyloxy)ethanol **82**, turned out to be significantly influenced by the choice of solvent. Performing the reaction in DMSO only gave rise to the formation of **82** in 35 % yield, whereas repeating the reaction in DMF afforded **82** in a rewarding 87 % yield. The low yield when

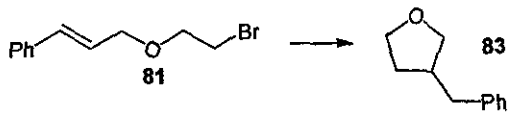
employing DMSO was explained by two factors. Water could have been present in the solvent causing hydrolysis of cinnamyl bromide to give cinnamyl alcohol, which was indeed isolated in 26 % yield. Also isolated was cinnamaldehyde which in turn can have been formed by a Kornblum reaction with the DMSO solvent (**Scheme 69**), a reaction not possible to occur when employing DMF as solvent. With **82** secured, treatment with Ph_3P and CBr_4 gave the desired precursor **81**.

Scheme 69. Kornblum reaction with DMSO.



The radical reaction of **81** has been attempted numerous times, each time with very discouraging results. In most cases, no formation of the desired tetrahydrofuranyl derivative could not be detected either by ^{1}H-NMR spectroscopy or careful GS-MS analysis of the crude reaction mixtures. Not until the idea of PRC (**Scheme 35**, section 2.2) occurred to us was the formation of 3-benzyl-tetrahydrofuran **83** by radical cyclisation successful. As seen in the radical cyclisation of the aromatic precursors derived from cinnamyl bromide, the cyclic radical formed in the radical cyclisation of **81** is a very stable benzylic radical, incapable of hydrogen abstraction from either TBTH or TBGH. Therefore, it was hoped that the addition of the good hydrogen donor PhSH in catalytic amount could have a positive effect on the outcome of the radical reaction. As can be seen in **Table 39**, this change in reaction conditions facilitated the formation of **83**, albeit in very low yields. It is believed that the low yields partly are a consequence of **83** being quite volatile,[70] hence the product was evaporated along with the cyclohexane employed as solvent in these reactions. This theory was being supported by the fact that no unreacted starting material **81** was isolated in either reaction.

Table 39. Radical cyclisation of **81**.



Entry	Radical mediator	Reaction conditions	Product(s)[a]
1	TBTH (1.2 eq.)	AMBN, PhSH (0.1 eq), C_6H_{12}, reflux, 5 h	**83** (11 %)[b]
2	TBGH (1.2 eq.)	AMBN, PhSH (0.1 eq), C_6H_{12}, reflux, 5 h	**83** (10 %)[b]

[a]Yields determined by the use of an internal standard in ^{1}H-NMR spectroscopy.

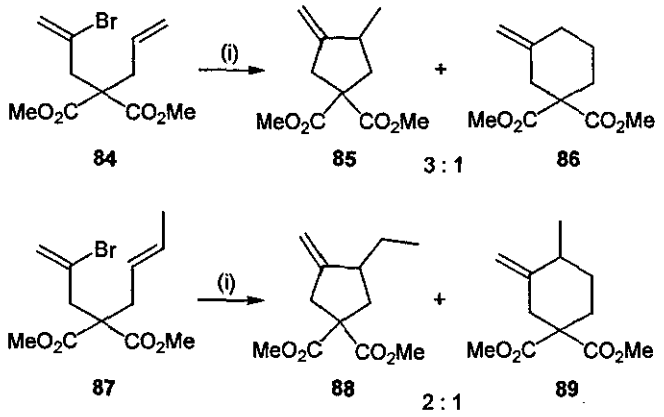
Conclusion of section 2.5

Both TBTH and TBGH have proven rather poor as radical mediators in the radical reactions of the alkyl precursors discussed in this section, but with TBTH being slightly more efficient. In the radical reactions of nitro compounds, TBGH-promoted reactions could not be driven to completion and large amounts of unreacted starting material were obtained. Radical cyclisation of the unsaturated ether **81** failed unless a more effective hydrogen donor was added in a catalytic amount. Even this adjustment of reaction conditions only led to the formation of the desired tetrahydrofuranyl derivative in low yields. It is possible that this reaction could be optimised by employing a more volatile solvent and less harsh reaction conditions.

2.6 Radical reactions with vinylic precursors

Since their introduction by Stork and Baine in 1982,[71] vinyl radical cyclisations have become quite popular in organic synthesis. They found that when treating substituted malonic esters with TBTH, good to excellent yields of cyclised products were obtained. In most cases mixtures of constitutional isomers were obtained (**Scheme 70**).

Scheme 70. Radical cyclisation presented by Stork and Baine.



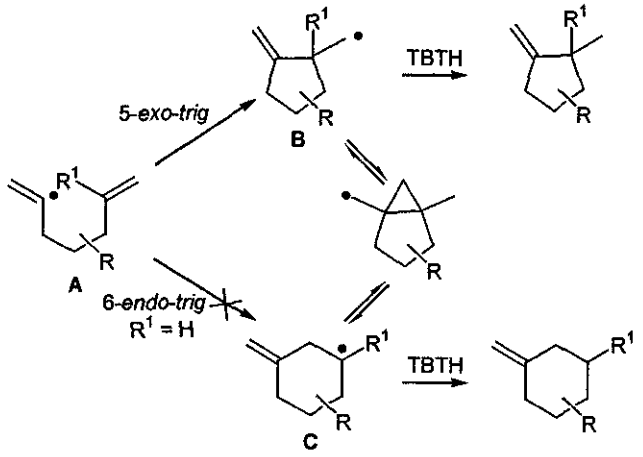
Reagents and conditions: TBTH (0.02 M), combined yields 75 – 95 %.

In both the cases shown in **Scheme 70,** the formation of the 5-membered cyclic products (**85** and **88**) were dominant. The 6-membered cyclic products (**86** and **89**) were also observed in relatively large amounts. It could be tempting to explain the formation of **86** and **89** as being the results of 6-*endo-trig* cyclisations. Exact rate constants for the 5-*exo-trig* and 6-*endo-trig* cyclisations of vinylic precursors have not been found, but comparison of rates with other precursors give a qualitative idea of the relative rate constants for the two cyclisation reactions. Beckwith and Schiesser have reviewed the rates of cyclisation of various alkyl radical precursors and found k_{25}^{exo}:k_{25}^{endo} as being roughly 98:2,[72] hence it is assumed unlikely for the *6-endo-trig* cyclisation of **84** and **87** to occur. Instead the formation of the formal *6-endo* product can be explained by the mechanism shown in **Scheme 71**. Homolytic Br-C bond cleavage leads to vinylic radical **A**, which then cyclises in a 5-*exo-trig* mode giving 5-membered cyclic methylene radical **B**. **B** can now either be reduced to the 5-membered product or rearrange to give the more stable 6-membered methyl radical **C** which is trapped by hydrogen abstraction from TBTH to form the 6-membered product.

If a 5-membered product is desired in a given reaction, high concentration of TBTH must be retained throughout reaction in order to trap radical **B** (**Scheme 71**) before rearrangement.[73] Alternatively, it has been shown that addition of PhSeSePh increases the relative amount of the 5-membered product formed.[74] The role of PhSeSePh is identical to that of PhSH described earlier, *i.e.* reaction between PhSeSePh and TBTH

gives PhSeH, a good hydrogen donor, which traps the initially formed cyclic radical more readily than TBTH alone.

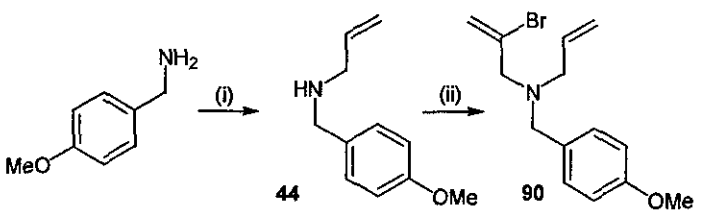
Scheme 71. Mechanism of radical cyclisation of vinylic precursors.



Because of the difference in hydrogen donor ability, it was believed that TBTH and TBGH would give rise to different product distributions in radical cyclisations of vinyl precursors, in that TBTH promoted reactions primarily should give 5-membered cyclic products, whereas the 6-membered products should be formed as the major products in reactions mediated by TBGH.

Initially, allyl-(2-bromoallyl)-4-(methoxybenzyl)amine **90** was assessed suitable for this purpose and it was synthesised in accordance with **Scheme 72.** Subsequent *N*-dialkylation of 4-methoxybenzylamine by allyl bromide and 2,3-dibromopropene afforded **90** in low overall yield.

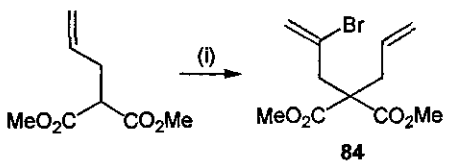
Scheme 72. Synthesis of vinylic precursor **90.**



Reagents and conditions: (i) K_2CO_3 (3.0 eq.), allyl bromide, CH_3CN, ambient temperature, 18 h. (ii) K_2CO_3, 2,3-dibromopropene, acetone, ambient temperature, 19 h, **90** (19 % in two steps).

Reaction of **90** under radical conditions did not give rise to the formation of cyclic products; instead complex mixtures of unidentified products were obtained. Even when improvement of chain propagation and reactivity was attempted by addition of PhSH, the yield did not improve. In all reactions, loss of the methoxy group seemed to be occurring. Initially it was believed that the functionality was being cleaved by reaction with the slightly acidic silica gel used as stationary phase in column chromatography, but repetition of reactions, followed by purification using neutral alumina revealed that this was not the case. The cause of the de-methoxylation was not investigated further. Instead we decided to focus on 2-allyl-2-(2-bromoallyl)malonic acid dimethyl ester **84**, employed by Stork and Baine.[71] The synthesis of **84** is outlined in **Scheme 73**.

Scheme 73. Synthesis of vinyl precursor **84**.

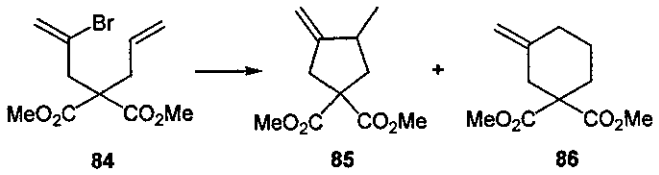


Reagents and conditions: (i) NaOMe (1.1 eq.), 2,3-dibromopropene, methanol, ambient temperature, 20 h, **84** (54 %).

When **84** was subjected to radical conditions, varied yields of cyclic products 3-methyl-4-methylene-cyclopentane-1,1-dicarboxylic acid dimethyl ester **85** and 3-methylene-cyclohexane-1,1-dicarboxylic acid dimethyl ester **86** were obtained (**Table 40**). Reaction of **84** with TBTH afforded a roughly 2:1 mixture of **85** to **86** in an 88 % combined yield (entry 1, **Table 40**). Performing the reaction under identical reaction conditions but employing TBGH as radical mediator lowered the combined yield of the two products considerably (entry 2, **Table 40**). In this case, along with **85** and **86**, products arising from hydrogermylation of the final products (**91** and **92**, **Figure 5**) were also present. Unfortunately, these products could not be isolated and their presence were only indicated by ^{1}H-NMR spectroscopy and confirmed by GC-MS analysis and their yields were not determined. The yields of **85** and **86** in reactions promoted by TBGH could be improved by the addition of 10 molar % of PhSH, once again taking advantage of the good hydrogen donor ability of this electrophilic reagent (entry 3, **Table 40**). In this case, formation of the 6-membered cyclic product **86** could

almost entirely be suppressed by trapping the 5-membered cyclic radical prior to rearrangement.

Table 40. Radical cyclisation of malonate derivative **84**.

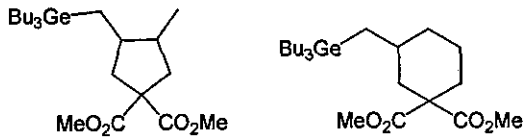


84 **85** **86**

Entry	Radical mediator	Reaction conditions	Product(s)
1	TBTH (1.1 eq.)	AMBN, $PhCH_3$, reflux, 4 h	**85**:**86**; 2:1.1 (88 %)[a]
2	TBGH (1.1 eq.)	AMBN, $PhCH_3$, reflux, 4 h	**85** (11 %)[b,c] **86** (4 %)[b]
3	TBGH (1.2 eq.)	AMBN, PhSH (0.1 eq), $PhCH_3$, reflux, 5 h	**85** (33 %)[b,d] **86** (5 %)[b]

[a]Combined yield. [b]Yields determined by the use of an internal standard in ^{1}H-NMR spectroscopy. [c]**91** and **92** also present in undetermined yields. [d]Unreacted **84** (13 %).

Figure 5. Products **91** and **92** arising from hydrogermylation.



91 **92**

Conclusion of section 2.6

Switching between radical mediators in the cyclisation of the vinylic precursors did not give the anticipated control of constitutional isomers predicted from the difference in rate of hydrogen donation. Radical cyclisation of amine derivative **90** was unsuccessful, regardless of mediator employed presumably due to decomposition of precursor. The malonate derivative **84** gave mixtures of products, with the formation of the 5-membered product **85** being predominant in reactions with both TBTH and TBGH. However, the relatively large amounts of hydrogermylation products obscured

the actual 5-*exo*:6-*endo* ratio. Addition of PhSH increased the relative amount of **85**, but it was not possible to completely suppress the formation of **86**.

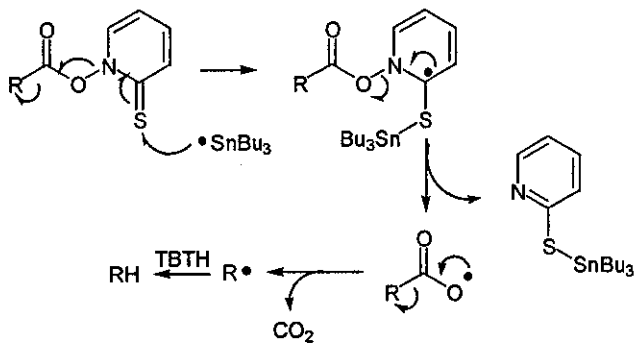
2.7 Radical reactions with Barton esters

Decarboxylations[75] and deoxygenations[76] *via* Barton esters are some of the most widely used radical transformations in organic synthesis. Because of the mild reaction conditions employed, removal of carboxylic or hydroxy groups can be selectively carried out in the presence of other functional groups. As with other radical reactions, TBTH has been employed almost exclusively as the radical mediator in transformations of this kind. In the following sections, radical decarboxylations and deoxygenations performed by trialkylgermanes will be discussed.

2.7.1 Radical decarboxylations

Radical decarboxylations of carboxylic acids can be accomplished by initial formation of Barton esters. The mechanism of the radical decarboxylation is shown in **Scheme 74**. The tin-centred radical attacks the S-atom of the thiopyridone moiety to yield a stable π-radical, subsequent *β*-scission and elimination of CO_2 gives the carbon-centred radical, which upon hydrogen abstraction from TBTH affords the reduced product, RH.

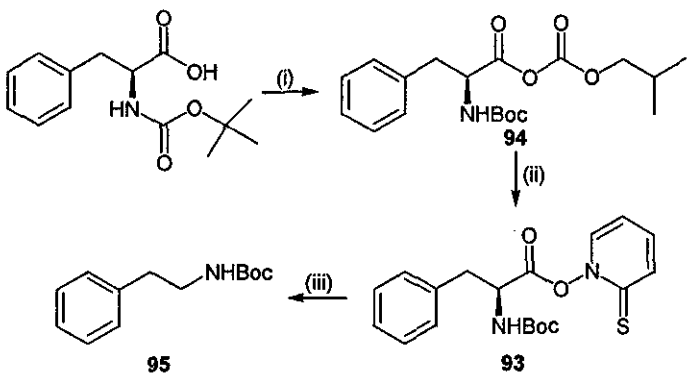
Scheme 74. Mechanism of radical decarboxylation of Barton esters.



In this work, esters derived from *N*-Boc-L-phenylalanine and adamatane-carbonyl chloride have been transformed into *N*-hydroxy-2-thiopyridone esters and reacted under radical conditions. Since these esters are very light sensitive, we considered that

it would be more efficient to generate the precursors *in situ*. The synthesis of Barton ester 2-*N*-Boc-3-phenyl-propionic acid 2-thioxo-2*H*-pyridin-1-yl ester **93** derived from *N*-Boc-L-phenylalanine and subsequent radical decarboxylation was carried out in accordance with the literature procedure (**Scheme 75**).[75]

Scheme 75. Formation and radical decarboxylation of Barton ester **93**.



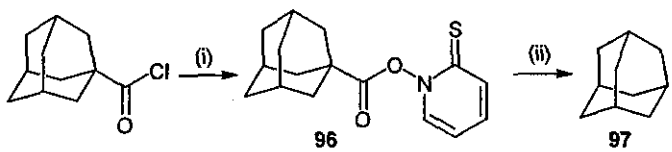
Reagents and conditions: (i) *N*-Methylmorpholine (1.0 eq.), isobutyl chloroformate (1.0 eq.), THF, -15 °C, 10 min. (ii) *N*-Hydroxy-2-thiopyridone (1.2 eq.), Et_3N (1.2 eq.), THF, -15 °C, 1 h. (iii) TBTH (2.0 eq.) or TBGH (2.0 eq.), AIBN, toluene, reflux, 1 h.

Reacting *N*-Boc-L-phenylalanine with isobutyl chloroformate and *N*-methyl-morpholine should afford the mixed anhydride **94**, which upon treatment with *N*-hydroxy-2-thiopyridone transforms to ester **93**. The formation of esters of this type can quite easily be monitored by the appearance of bright yellow spots on TLC. When this reaction was presumed complete by TLC, the solvent was removed by evaporation and the residue re-dissolved in toluene and divided between two reaction flasks. To one flask was added TBTH and to the other TBGH and the radical reactions carried out in accordance with the procedure described in the experimental section. Unfortunately, neither of the reactions afforded phenethylamine **95** and attempts to secure formation of the mixed anhydride **94** and Barton ester **93** prior to radical reaction proved fruitless. If formation of the mixed anhydride **94** is not accomplished, **93** will not be produced, hence reaction with TBTH or TBGH is pointless. Instead of investigating why this crucial intermediate product was not formed, we decided to start the reaction sequence with a carboxylic acid chloride.

Treatment of adamatane-carbonyl chloride with *N*-hydroxy-2-thiopyridone in the presence of DMAP gave Barton ester adamantane-1-carboxylic acid 2-thioxo-2*H*-

pyridin-1-yl ester **96**, which upon reaction with TBTH or TBGH afforded adamatane **97** (**Scheme 76**). The reaction promoted by TBTH gave a rewarding 81 % yield of **97**, whereas adamantane was formed in only 33 % yield when treated with TBGH. It is possible that this lower yield is not entirely down to lower affinity of germanium centred radicals towards S-atoms, but can also partly be caused by less successful formation of the Barton ester. In contrast to the attempted formation of the Barton ester of phenylalanine, this initial reaction was carried out separately for the two radical mediators.

Scheme 76. Formation and radical decarboxylation of adamatane Barton ester **96.**



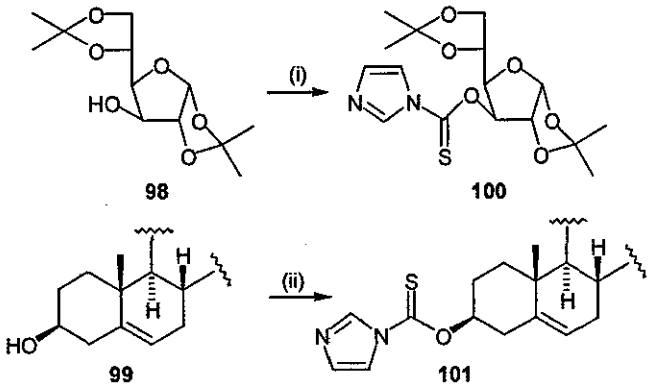
Reagents and conditions: (i) DMAP (1.0 eq.), *N*-hydroxy-2-thiopyridone (1.2 eq.), toluene, reflux, 15 min. (ii) TBTH (3.0 eq.) or TBGH (3.0 eq.), toluene, reflux, 1 h, **97** [81 % (TBTH), 33 % (TBGH)].

The possibility that the lower yield in the TBGH-promoted reaction of **96** is due to lower affinity of germanium centred radicals towards S-atoms was disproved when deoxygenations of secondary alcohols were performed.

2.7.2 Radical deoxygenations

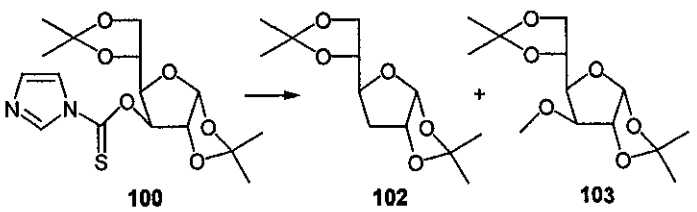
Both primary[77] and secondary[78] alcohols can easily be deoxygenated by Barton-McCombie reactions *via* Barton-type esters. In this work, only thiocarbonyl-imidazolides have been employed as leaving groups due to their ease of preparation and stability towards light. Tin-promoted reductions of these compounds are well known in the literature[78] and the reactions normally proceed in high yields. To investigate whether triorganogermanes could mimic the excellent reactivity of tin-based radical mediators, the thiocarbonyl-imidazolide esters of a glucose derivative and of cholesterol were synthesised (**Scheme 77**). Reaction of 1,2:5,6-di-*O*-isopropylidine-α-D-glucofuranose **98** and cholesterol **99** with thiocarbonyl diimidazole in the presence of catalytic amounts of DMAP gave the thiocarbonyl derivatives **100** and **101** respectively in high yields.

Scheme 77. Synthesis of thiocarbonyl-imidazolides **100** and **101.**



Reagents and conditions: (i) Thiocarbonyl diimidazole (2.0 eq.), DMAP (3 molar %), CH_3CN, reflux, 150 min, **100** (100 %). (ii) Thiocarbonyl diimidazole (2.0 eq.), DMAP (0.2 eq.), CH_3CN, reflux, 3 h, **101** (84 %).

Table 41. Radical deoxygenation of glucose derivative **100.**

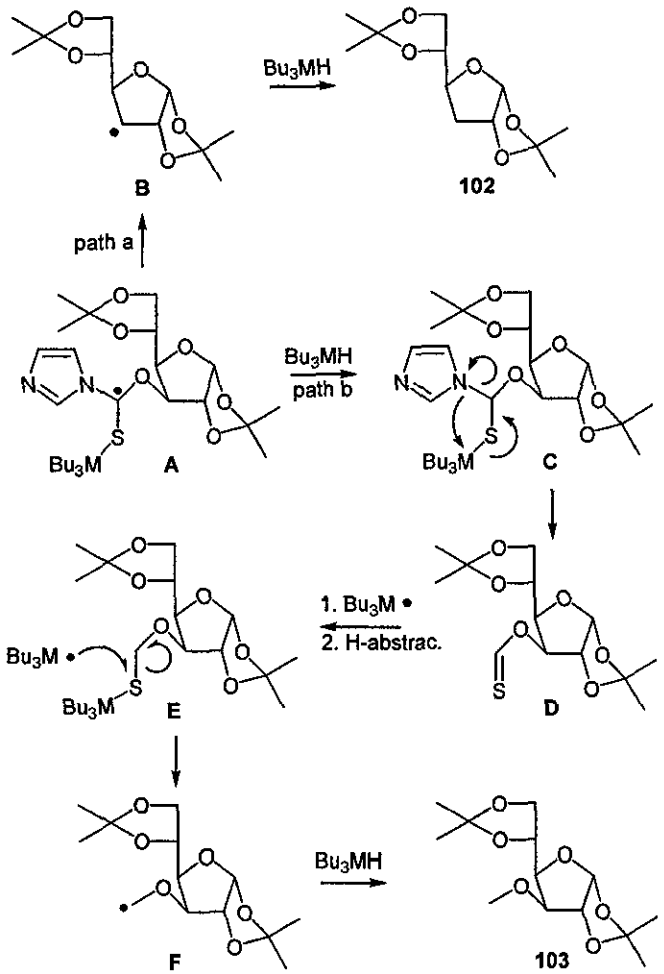


Entry	Radical mediator	Reaction conditions[a]	Product(s)
1	TBTH (8.0 eq.)	$PhCH_3$, reflux, 90 min	**102** (29 %)[b] **103** (28 %)[b]
2	TBGH (5.4 eq.)	$PhCH_3$, reflux, 90 min	**102** (87 %)

[a]**100** added to the mediator ("inverse addition"). [b]Yields determined by the use of an internal standard in ^{1}H-NMR spectroscopy.

When the glucose derivative **100** was treated with TBTH and TBGH, remarkably different results were observed in the two reactions (**Table 41**). Whereas the TBGH-promoted radical reaction afforded the fully reduced product 3-deoxy-1,2:5,6-di-*O*-isopropylidine-α-D-glucofuranose **102** in high yield (entry 2, **Table 41**), reaction with TBTH gave rise to the formation of a 1:1 mixture of **102** and the 3-methoxy compound **103** (entry 1, **Table 41**).

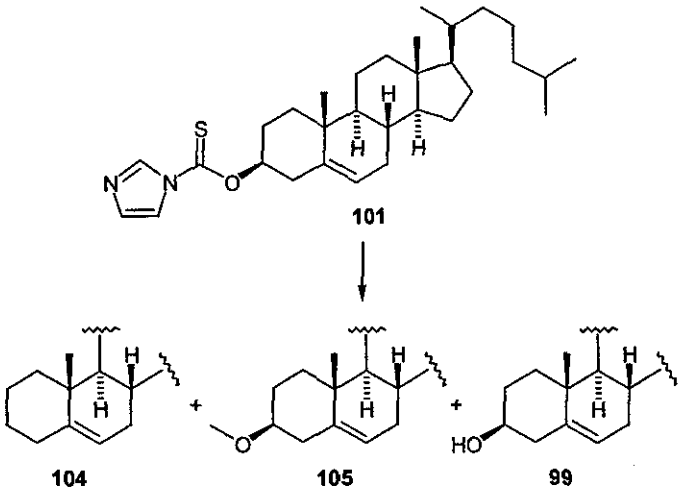
Scheme 78. Mechanism of the formation of the methoxy product **103**.[79]



The formation of **103** in reaction with TBTH can once again be explained by the difference in hydrogen donation of the two radical mediators. The initial step in the mechanism of the deoxygenation is the formation of radical **A** (**Scheme 78**) by attack of stannyl-or germyl-centred radical on the S-atom. Ideally, **A** should undergo β-scission yielding radical **B**, which upon reaction with the radical mediator gives the fully reduced product **102** (path a, **Scheme 78**). However, in the presence of a good hydrogen donor, competing reduction of radical **A** can occur (path b, **Scheme 78**), forming the thio compound **C**, which eliminates Im-MBu_3 to give the thio aldehyde **D**. Another addition-reduction sequence gives the thio acetal **E**, which upon elimination of $(Bu_3M)_2S$ forms the methoxy radical **F**. Finally, hydrogen abstraction gives methoxy product **103**. Apparently, this sequence of additions, reductions and eliminations processes exclusively occurs in the presence of the better hydrogen donor TBTH, whereas in reactions promoted by TBGH, β-scission is the preferred reaction

pathway. It is interesting to note that in both reactions, the precursor **100** is added to the mediator ("inverse addition") and even under these concentrated conditions, the TBGH-induced reaction did not give rise to any formation of **103**.

Table 42. Radical deoxygenation of cholesteryl derivative **101**.



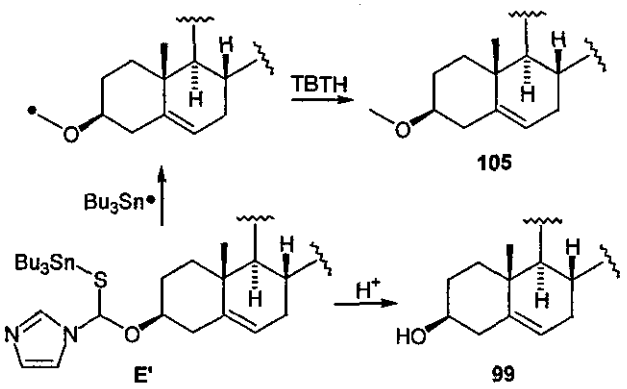
Entry	Radical mediator	Reaction conditions	Product(s)
1	TBTH (2.0 eq.)	ACCN, $PhCH_3$, reflux, 3 h[a]	**104** (54 %)
2	TBGH (2.0 eq.)	ACCN, $PhCH_3$, reflux, 3 h[a]	**104** (60 %)
3	TBTH (2.0 eq.)	ACCN, $PhCH_3$, reflux, 3 h[b]	**104** (5 %), **99** (51 %) and **105** (11 %)[c]
4	TBGH (2.0 eq.)	ACCN, $PhCH_3$, reflux, 3 h[b]	**104** (67 %)

[a]**101** added to the mediator ("inverse addition"). [b]The mediator was added to **101** ("normal addition"). [c]Yields determined by the use of an internal standard in ^{1}H-NMR spectroscopy.

The difference in reactivity of TBTH and TBGH was also apparent when reacting cholesteryl derivative **101** under radical conditions (**Table 42**). Using the same addition mode as in the radical deoxygenation of **100**, reaction of the cholesteryl derivative **101** with TBTH and TBGH afforded the fully reduced product cholest-5-ene **104** in good isolated yields (entries 1 and 2, **Table 42**). Changing the reaction conditions slightly so that the mediator was added to **101** turned out to have a significant impact on the outcome of the TBTH-mediated reaction. Whereas reaction

with TBGH was not altered by this change and afforded **104** in good yield (entry 4, **Table 42**), the TBTH-promoted reaction gave cholesterol **99** as the major product (entry 3, **Table 42**) along with small amounts of cholest-5-ene **104** and the methoxy derivative **105**. The formation of **99** follows the mechanism outlined in **Scheme 78** until the formation of thio acetal **E'** (**Scheme 79**) which is hydrolysed to give cholesterol **99** on work-up.

Scheme 79. Mechanism of the formation of **99** and **105**.



It is odd that the order of addition has such an impact on yields in tin-mediated reactions, but is a phenomenon well presented in the literature.[78]

Conclusion of section 2.7

The radical decarboxylation and deoxygenation reactions of Barton-type esters have proven to proceed with varied success when promoted with TBTH and TBGH. TBTH appears to be a more efficient reagent in radical decarboxylation reactions, whereas TBGH is superior in radical deoxygenations. The enhanced reactivity of TBGH in reactions of the latter type is due to the lower hydrogen donor ability of TBGH compared to TBTH, resulting in exclusive formation of fully reduced products. TBTH-induced reactions often give by-products arising from premature hydrogen-atom donation in significant amounts.

2.8 Triorganogermanes as reagents in solid phase organic synthesis

As mentioned in the introduction, solid phase approaches to radical chemistry can be dealt with in two different ways since either the radical precursor or the radical mediator can be attached to a polymer backbone. Both methods have been investigated within the Bowman research group and will be discussed in the following section.

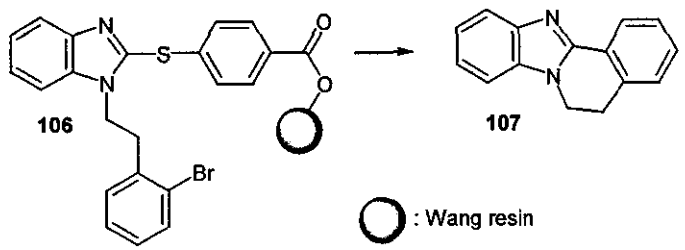
The advantages of solid phase chemistry are well known and include easier purification of crude reaction mixtures. The ease of purification is one of the reasons why the solid supported approach to tin-mediated radical chemistry has become popular, but may also be one of the reasons why the germanium analogues have not drawn much attention. Generally speaking, reactions promoted by triorganogermanes are more easy to purify due to enhanced stability of the germanium compounds employed and generated during reaction. Purification of these reactions is mostly carried out by simple chromatography with a minimum of the "streaking" problems, associated with many tin-based reagents. On the other hand, the possibility of regeneration of resin bound reagents could be a inducement to employ this type of germanium reagent since it would minimise the extra cost involved when using germanium- rather than tin- based radical mediators.

As part of her Ph. D. project in the Bowman group, Rehana Karim has been investigating radical reactions of resin bound benzimidazole precursors as a method of synthesising polycyclic heteroarenes. A variety of radical mediators and reaction conditions were employed in this research and some of the results obtained are shown in **Table 43**. Of the reagents tested as radical mediators in these reactions, TBGH was the most successful, inducing the formation of 5,6-dihydro-benzo[4,5]imidazo[2,1-*a*]isoquinoline **107** in 71 % yield (entry 2, **Table 43**).

The mechanism of this radical cyclisation (illustrated in **Scheme 80** with TBGH as mediator) differs from the other radical cyclisation reactions discussed previously in this chapter in that no hydrogen transfer from the mediator is required for successful formation of the desired tetracyclic product **107**. Instead the chain propagation is secured by reaction between S-centred radical **A** (**Scheme 80**) and the mediator. From the discussion of the use of PhSH as a "polarity transfer catalysts" in section 2.1, this

process is known to be favourable, which may be a reason for the efficiency of TBGH in the radical cyclisation of benzimidazole **106**.

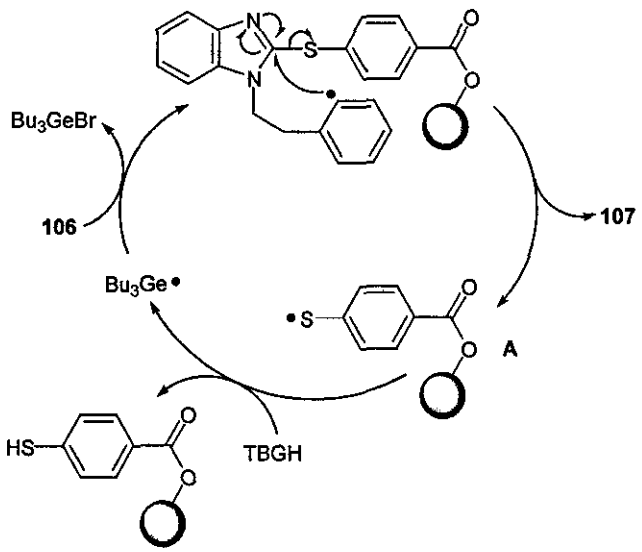
Table 43. Radical cyclisations of Wang tethered benzimidazole precursor **106**.[80]



Entry	Radical mediator	Reaction conditions	Product(s)[a]
1	TBTH	AIBN, $PhCH_3$, syringe-pump addition, reflux	**107** (44 %)
2	TBGH	AIBN, $PhCH_3$, reflux	**107** (71 %)
3	TTMSS	Et_3B, $PhCH_3$, ambient temperature	**107** (29 %)

[a]Yields determined by the use of an internal standard in ^{1}H-NMR spectroscopy.

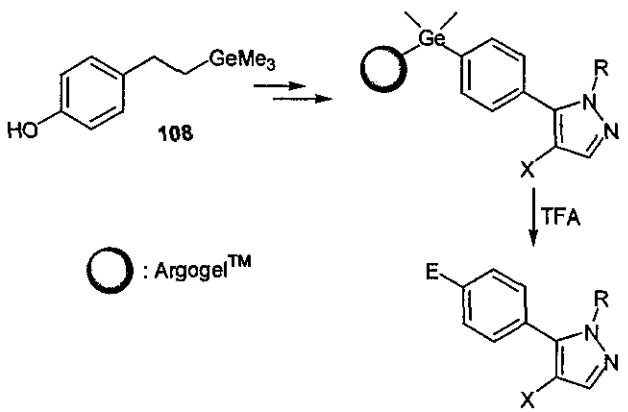
Scheme 80. Mechanism of the radical cyclisation of **106**.



As mentioned in the introduction, only very little research on the use of solid supported triorganogermanes have been presented in the literature. Owing to the advantages of resin bound reagents in general and the novelty of solid supported triorganogermanes as radical mediators, it was decided to investigate this area.

Spivey *et al.* have been employing germanium compounds as "trace-less" linkers in the synthesis of a pyrazole library (**Scheme 81**).[81] Modification of 4-(2-trimethylgermylethyl)phenol **108** afforded Argogel™-linked products **A** which upon cleavage with TFA gave the free pyrazole derivatives in high purity. 4-(2-Trimethyl-germylethyl)phenol **108** seemed suitable as a starting point for the development of a new germanium based radical mediator.

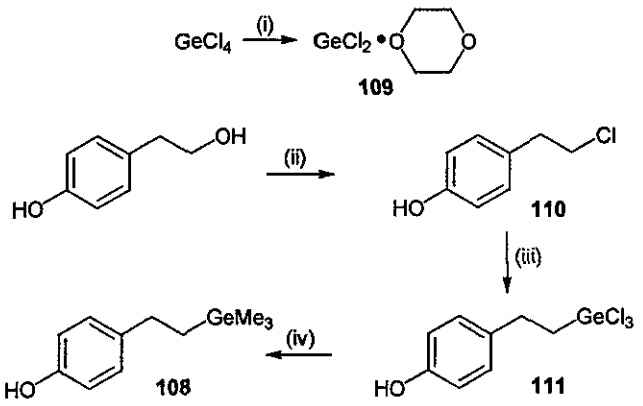
Scheme 81. Use of a germanium linker by Spivey *et al.*



2.8.1 Synthesis of new germanium-based radical mediators

Starting from the most available source of germanium, $GeCl_4$, **108** could be synthesised by the sequence of reactions detailed in **Scheme 82.** By treating $GeCl_4$ with tetramethyldisiloxane in refluxing dioxane, the dichlorogermylene-1,4-dioxane complex **109** was obtained as a stable white crystalline product in high yield. Insertion of this germylene into the C-Cl bond of 4-(2-chloroethyl)phenol **110**, synthesised from 4-hydroxyphenethyl, afforded 4-(2-trichlorogermylethyl)phenol **111** in quantitative yield. Finally, Grignard reaction with methylmagnesium bromide secured the formation of **108.**

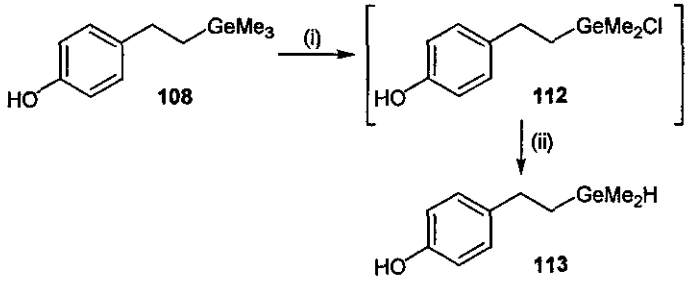
Scheme 82. Synthesis of 4-(2-trimethylgermylethyl)phenol **106.**



Reagents and conditions: (i) Tetramethyldisiloxane (1.0 eq.), 1,4-dioxane, reflux, 3 h, **109** (80 %). (ii) Conc. HCl (aq.), 110 °C, 18 h, **110** (100 %). (iii) **109**, 140 °C, 18 h, **111** (100 %). (iv) MeMgBr (6.0 eq.), toluene, reflux, 17 h, **108** (94 %).

Since it was desired to test this compound as a radical reagent, the germanium hydride was needed and this was accomplished by synthesising 4-(2-dimethylgermylethyl)-phenol **113** from **108** in two steps (**Scheme 83**).

Scheme 83. Synthesis of 4-(2-dimethylgermylethyl)phenol **113.**

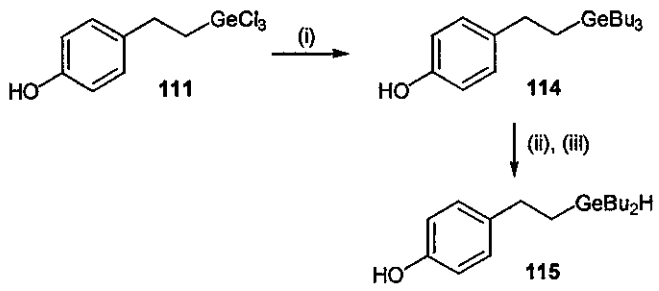


Reagents and conditions: (i) $SnCl_4$ (1.0 eq.), $MeNO_2$, 50 °C, 18 h, **112** not isolated. (ii) $NaBH_4$ (2.0 eq.), methanol, ambient temperature, 7 h, **113** (67 % in two steps).

Following the procedure of Bulten and Drenth,[55] discussed in section 2.1, 4-(2-chlorodimethylgermylethyl)phenol **112** was produced by treatment of **108** with tin(IV)chloride in nitromethane. Due to troublesome purification, best results were obtained when crude **112** was subjected to reduction by sodium borohydride, in this case yielding 4-(2-dimethylgermylethyl)phenol **113** in 67 % yield. The reaction steps leading to **113** are all simple reactions and the use of a Grignard reaction provides an easy method of synthesising a variety of triorganogermanes, the only limiting factor being the availability of Grignard reagents. As an example, 4-(2-

dibutylgermylethyl)phenol **115** was synthesised by Richard Jones, under the supervision of Prof. W. R. Bowman and S. L. Krintel as part of his final year undergraduate project (**Scheme 84**).

Scheme 84. Synthesis of 4-(2-dibutylgermylethyl)phenol **115**.

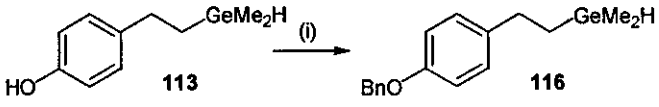


Reagents and conditions: (i) *n*-BuMgBr (6.0 eq.), toluene, reflux, 17 h, **114** (59 %). (ii) $SnCl_4$ (1.1 eq.), $MeNO_2$, 50 °C, 18 h, product not isolated. (iii) $NaBH_4$ (3.0 eq.), methanol, ambient temperature, 5 h, **115** (19 % in two steps).

We intended to study whether radical reactions employing **115** would provide some information on how steric effects surrounding the germanium atom would affect the reactivity of the triorganogermane. Unfortunately, only one radical reaction was performed as part of the project and the result obtained was very inconclusive.

In order to mimic the steric effect that attachment to solid support would have on the triorganogermane, **113** was benzylated by the conventional method, affording 4-(2-dimethylgermylethyl)phenyl benzyl ether **116** (**Scheme 85**).

Scheme 85. Synthesis of 4-(2-dimethylgermylethyl)phenyl benzyl ether **116**.



Reagents and conditions: (i) NaH (1.7 eq.), BnBr (1.5 eq.), THF, reflux, 3 h, **116** (87 %).

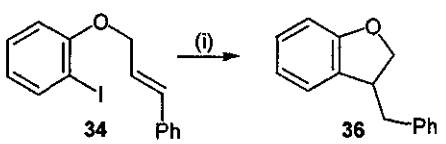
The benzylation reaction proceeded smoothly but it turned out to very difficult to separate **116** from unreacted benzyl bromide by column chromatography. Therefore, an alternative purification procedure was employed. By re-dissolving the crude reaction mixture in THF and adding diethylamine, the resulting diethylbenzylamine could easily be separated by chromatography, giving the pure **116** in high yield.

2.8.2 Radical reactions employing triorganogermanes 113 and 116

Before functionalising the triorganogermanes further, we tested whether **113** and **116** were able to induce radical reactions. In order to compare the obtained results, only precursors previously employed in radical reactions promoted by TBGH were included in this study.

When reacting 1-iodo-2-[(3-phenylprop-2-enyl)oxy]benzene **34** with germane **113**, a rather surprisingly high yield of 3-benzyl-2,3-dihydrobenzofuran **36** was detected by ^{1}H-NMR spectroscopy (**Scheme 86**). Obviously, the yield (22 %) is not as high as when the reaction was performed using TBTH as radical mediator (up to 92 %) but is still surprising since TBGH was unable to form **36** because of low reducing power towards the very stable benzylic radical formed by cyclisation. Only when PhSH was added as a "polarity transfer catalyst", the cyclic product **36** was formed in the presence of TBGH. The result in **Scheme 86** indicates that the new triorganogermane **113** exhibits better hydrogen donor ability than TBGH, a factor that may be crucial for other radical reactions. We believe that this effect is largely steric, *i.e.* two methyl groups are smaller than two butyl groups.

Scheme 86. Radical cyclisation of aromatic precursor **34.**

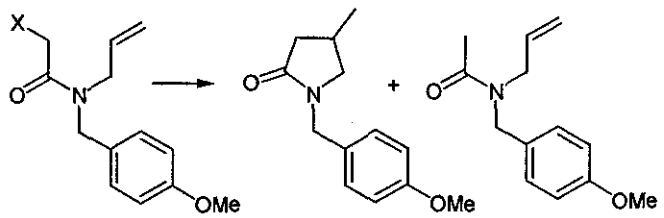


Reagents and conditions: (i) **113** (1.2 eq.), ACCN, toluene, reflux, 5.5 h, **36** (22 % by ^{1}H-NMR spectroscopy).

Similarly promising results were obtained when triorganogermanes **113** and **116** were employed in the radical cyclisation of amide precursors (**Table 44**). When the chloro amide **45** was treated with the germane **113**, the cyclic product 1-(4-methoxybenzyl)-4-methyl-pyrrolidin-2-one **42** was isolated in 47 % yield (entry 1, **Table 44**) along with unreacted **45** (18 %) and a small amount of reduced product *N*-allyl-*N*-(4-methoxybenzyl)acetamide **43**. An identical yield of **42** was obtained when employing germane **116** (entry 2, **Table 44**) and comparing these results with those detected when employing TBGH (section 2.3 and entry 5, **Table 44**) reveals that **113** and **116**

are at least as efficient radical mediators as TBGH in reactions of this type. The yields of cyclic product **42** are in all cases similar, but the reduced product **43** is formed to a lesser extent when employing **113** or **116**. These results, combined with the result in **Scheme 86**, places the hydrogen donor abilities of **113** and **116** between those of TBGH and TBTH. Due to this conclusion, the result in entry 3 (**Table 44**) was rather confusing. When reacting bromo amide **46** with a catalytic amount of **116** in the presence of $NaBH_4$, cyclic product **42** was only obtained in 18 % yield with the major product being reduced product **43**. However, repetition of the reaction in the absence of **116** revealed that a simple reduction of **45** by $NaBH_4$ occurred, producing **43** in similar yield.

Table 44. Radical cyclisation of amide precursors **45** and **46**.



X = Cl: **45**
X = Br: **46**

42 **43**

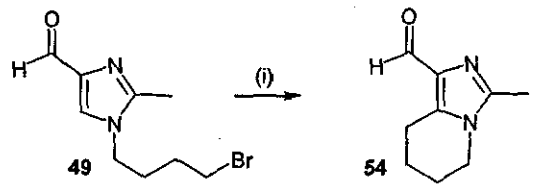
Entry	X	Radical mediator	Reaction conditions	Product(s)
1	Cl	**113** (1.2 eq.)	ACCN, $PhCH_3$, reflux, 8 h	**42** (47 %) **43** (n.d.)[a]
2	Cl	**116** (1.1 eq.)	ACCN, $PhCH_3$, reflux, 8 h	**42** (47 %) **43** (3 %)
3	Br	**116** (0.3 eq.)	ACCN, $NaBH_4$, $PhCH_3$, reflux, 7 h	**42** (18 %) **43** (50 %)
4[b]	Cl	TBTH (1.5 eq.)	AMBN, C_6H_{12}, reflux, 1 h	**42** (47 %) **43** (23 %)
5[b]	Cl	TBGH (1.5 eq.)	AMBN, C_6H_{12}, reflux, 12 h	**42** (48 %) **43** (23 %)

[a]n.d. = not determined. [b]Data from **Table 30**.

In section 2.4, radical cyclisation of 1-(4-bromobutyl)-2-methyl-1*H*-imidazole-4-carbaldehyde **49** mediated by TBGH was found to be a sluggish reaction, only forming

3-methyl-5,6,7,8-tetrahydro-imidazo[1,5-*a*]pyridine-1-carbaldehyde **54** in very low yields (up to 21 %). Repeating the reaction in the presence of **113** produced **54** in a slightly better yield (**Scheme 87**).

Scheme 87. Radical cyclisation of imidazole precursor **49**.

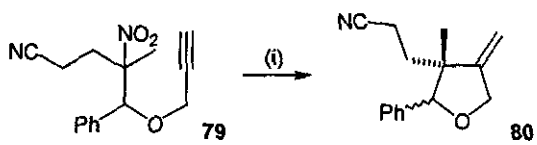


Reagents and conditions: **113** (1.1 eq.), ACCN, toluene, reflux, 4 h, **54** (25 %).

As concluded in section 2.4, optimisation of the reaction conditions could be beneficial in germane-induced reactions but is difficult as long as the mechanism has not been fully elucidated.

As the last radical cyclisation tested with triorganogermane **113**, 3-nitro-3-methyl-4-phenyl-4-(prop-2-ynyloxo)butyl cyanide **79** represented the group of alkyl precursors. When reacting **79** with **113** in refluxing acetonitrile, 3-(3-methyl-4-methylene-2-phenyl-tetrahydrofuran-3-yl)propionitrile **80** as a mixture of diastereoisomers was detected in low yield by the use of internal standard in ^{1}H-NMR spectroscopy (**Scheme 88**).

Scheme 88. Radical cyclisation of nitro precursor **79**.



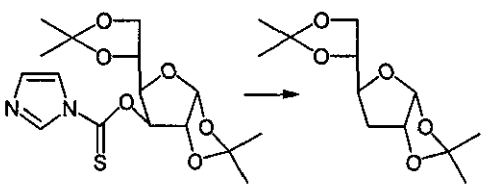
Reagents and conditions: **113** (1.2 eq.), AIBN, CH_3CN, reflux, 5 h, **80** (10 %) and **79** (44 %).

It is unclear why the until now very promising radical mediator **113** fails to generate cyclic product **80** to a greater extent. The germane **113** has proven to be a good hydrogen donor why insufficiently reduction of the cyclic methylene radical, hence in-continuous radical chain propagation, is unlikely to be the cause of failure. Other, unidentified, products were present in the crude reaction mixture and it is possible that

additional radical processes are taking place, competing with the desired pathway. It is possible for hydrogermylation of the cyclic product **80** to occur, but products arising from this competing reaction has not been observed in any radical reaction with 3-nitro-3-methyl-4-phenyl-4-(prop-2-ynyloxo)butyl cyanide **79**, hence this theory can not be confirmed. Either way, both TBGH and TBTH were more efficient reagents in the cyclisation of **79**.

TBGH has been shown to promote radical deoxygenations in high yields (section 2.7.2) and because of the proven ability to induce radical reactions, **113** and **116** were expected to at least mimic the good reactivity of TBGH in reactions of this type. This expectation was fully met when reacting 1,2:5,6-di-*O*-isopropylidine-3-*O*-thio-carbonylimidazole-α-D-glucofuranose **100** with triorganogermanes **113** and **116** (**Table 45**). Both mediators afforded 3-deoxy-1,2:5,6-di-*O*-isopropylidine-α-D-glucofuranose **102** in near quantitative yields, hence proving more efficient than TBGH and, more significantly, TBTH. The reaction promoted by **116** proved slightly slower though, and reflux for 8 h was needed for the reaction to be complete.

Table 45. Radical deoxygenation of thiocarbonyl-imidazolide **100**.



100 **102**

Entry	Radical mediator	Reaction conditions	Product
1	**113** (3.0 eq.)	ACCN, $PhCH_3$, reflux, 2 h	**102** (94 %)
2	**116** (3.0 eq.)	ACCN, $PhCH_3$, reflux, 8 h	**102** (91 %)

Conclusion of section 2.8.2

The results obtained by triorganogermane **113** were all but one very promising regarding the ability to induce radical reactions of various types of precursors. Moreover, the reactivity of this new triorganogermanium hydride did not seem to be

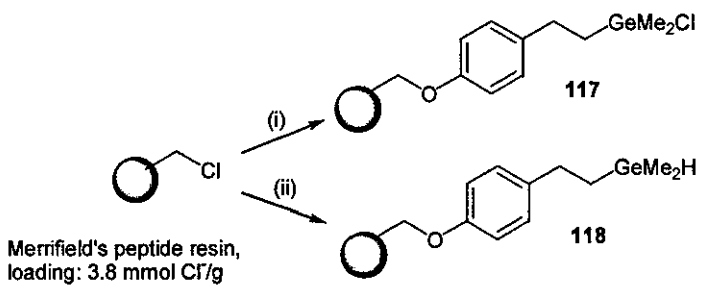
significantly decreased by increasing the steric bulk as seen by the reactions promoted by benzylated derivative **116**. Therefore, attention was drawn to the solid supported analogues.

2.8.3 Synthesis of solid supported, Ge-based radical mediators

Two different resins were used in this investigation, Merrifield peptide resin and Quadragel™, both with a polystyrene backbone. Merrifield peptide resin was chosen partly because of the availability of resins with different loadings which was assumed to be beneficial, considering the cost of germanium, and partly because the beads were expected to be less likely to break during reaction. Quadragel™ is a polystyrene backbone attached to tetraethyleneglycol and the reason for choosing Quadragel™ was of more practical character, since the side chains make the resin gel-like allowing NMR spectroscopy by traditional methods, hence facilitating ease in the characterisation of the functionalised resin.

In the benzylation of germane **113**, modification of the hydroxy group was carried out by simple deprotonation by treatment with NaH followed by addition of BnBr. By applying the same approach, 4-(2-chlorodimethylgermylethyl)phenyl ether resin **117** and 4-(2-dimethylgermylethyl)phenyl ether resin **118** were produced from the Merrifield peptide resin (**Scheme 89**).

Scheme 89. Synthesis of functionalised resins **117** and **118**.



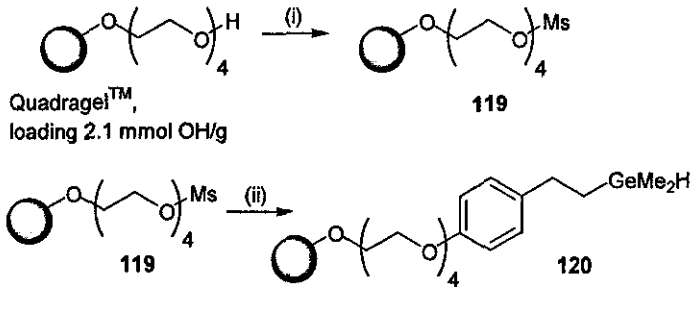
Reagents and conditions: (i) **112** (5.0 eq.), NaH (7.5 eq.), THF, ambient temperature, 114 h, **117** (1.02 mmol GeCl/g, 27 %). (ii) **113** (5.0 eq.), NaH (7.2 eq.), THF, reflux, 17 h, **118** (1.04 mmol GeCl/g, 27 %).

Proof of the incorporation of the germaium moeity onto the resin was obtained by IR spectroscopy and the loadings of the functionalised resins **117** and **118** (1.02 mmol

and 1.04 mmol Ge/g, respectively) were established by mass difference. This is not a very accurate method, but elemental analysis as a mean of determination would be fruitless with these compounds due to the absence of heteroatoms. Instead, we attempted to cleave the germanium moiety from the resin by treatment of **118** with TFA, but unfortunately no cleaved product was observed by this method.

A suitable leaving group was needed on Quadragel™ in order to functionalise this resin by nucleophilic displacement. Mesylation of Quadragel™ afforded **119**, which upon treatment with the phenoxide of **113** gave 4-(2-dimethylgermylethyl)phenyl ether resin **120** in quantitative yield (**Scheme 90**).

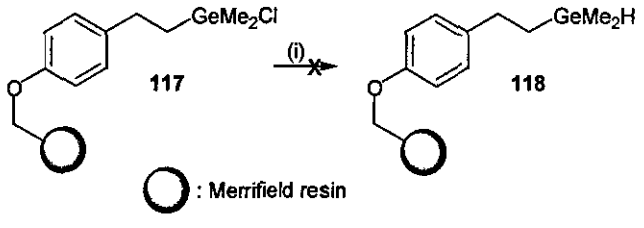
Scheme 90. Synthesis of functionalised resin **120.**



Reagents and conditions: (i) MsCl (5.0 eq.), pyridine, ambient temperature, 2 h, **119** (2.1 mmol Ms/g, 100 %). (ii) **113** (2.0 eq.), NaH (2.0 eq.) and KI (2.0 eq.), DMF, 60 °C, 24 h, **120** (2.1 mmol GeH/g, 100 %).

The main reason for the synthesis of the chlorogermyl resin **117** was that the ease of reduction could be investigated. Catalytic use and/or regeneration of the solid supported reagents would be ideal but even a large excess of $NaBH_4$ failed to reduce **117** to **118** (**Scheme 91**), hence the optimum reduction conditions could not be established.

Scheme 91. Attempted reduction of chlorogermyl resin **117.**



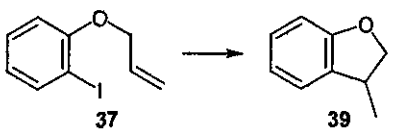
Reagents and conditions: $NaBH_4$ (11.0 eq.), THF/MeOH, ambient temperature, 135 h.

Due to failure in reduction of these solid supported triorganogermanium compounds, none of the radical reactions in the following section were performed using catalytic amounts of the radical reagent and the possibility of repeated use of regenerated reagent was not investigated.

2.8.4 Radical reactions employing resin bound, Ge-based mediators

Radical cyclisation of 2-iodo-1-(prop-2-enyloxy)benzene **37** was discussed in section 2.2 and was found to proceed well in the presence of TBGH. When the reaction was promoted by **120**, optimisation of reaction conditions by trial and error eventually resulted in the formation of cyclic product 3-methyl-2,3-dihydrobenzofuran **39** (**Table 46**).

Table 46. Radical cyclisation of aromatic precursor **37**.



37 **39**

Entry	Radical mediator	Reaction conditions	Product
1	**120** (3.0 eq.)	AIBN, $PhCH_3$, 85 °C, 4 h	**37** (n.d.)[a]
2	**120** (3.5 eq.)	AIBN, $PhCH_3$, 95-110 °C, 20 h	**39** (26 %)[b]
3	**120** (3.6 eq.)	AIBN, $PhCH_3$, reflux, 16 h	**39** (78 %)

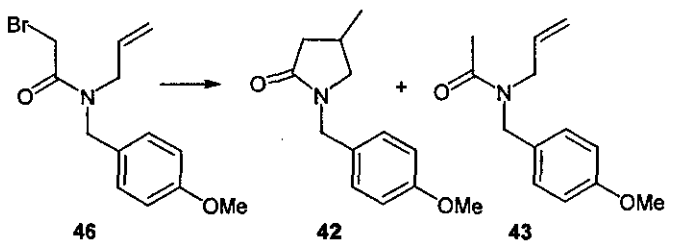
[a]n.d. = not determined. [b]Yield determined by the use of an internal standard in ^{1}H-NMR spectroscopy.

Initially, one of the major concerns was to prevent the relatively sensitive resin beads from breaking. It was assumed to be the case if the reaction mixture was stirred by conventional methods. By rotating the reaction mixture, the beads should remain intact but it was difficult to ensure a sufficiently high reaction temperature for the radical reaction to proceed. By rotating at 85 °C only unreacted **37** was observed by ^{1}H-NMR spectroscopy of the filtrate (entry 1, **Table 46**), whereas increasing the temperature

slightly enabled the formation of cyclic product **39** in moderate yield (entry 2, **Table 46**). Only when risking breaking the resin beads by refluxing the mixture with very gentle magnetic stirring was **39** formed in good isolated yield (entry 3, **Table 46**). The yield is not quite as impressive as the yield obtained with TBGH (91 %) but it is probable that the solid supported synthesis of **39** could be optimised even further, hence improving the yield of this reaction.

Earlier in this section, triorganogermanes **113** and **116** were found to be highly efficient as radical mediators in the cyclisation of amide precursors. When the reaction with the amide **46** was repeated in the presence of solid supported germanium reagents **118** and **120**, these reagents also proved their ability to promote radical cyclisation. Reaction of *N*-allyl-2-bromo-*N*-(4-methoxybenzyl)acetamide **46** with **118** or **120** afforded cyclic product **42** in moderate to good yields (**Table 47**).

Table 47. Radical cyclisation of bromo amide **46**.



46 **42** **43**

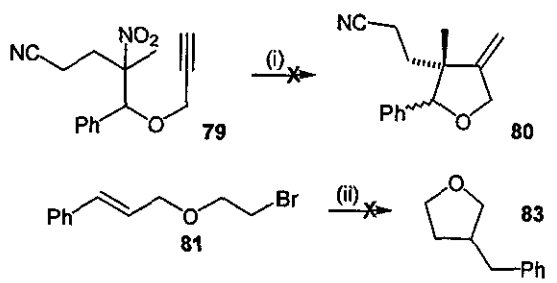
Entry	Radical mediator	Reaction conditions	Product
1	**118** (0.5 eq.)	ACCN, $PhCH_3$, reflux, 9 h	**42** (30 %)[a]
2	**118** (0.5 eq.)	ACCN, $PhCH_3$, reflux, 24 h	**42** (35 %)[a]
3	**120** (2.5 eq.)	AIBN, $PhCH_3$, 85 °C, 17 h	**46** (n.d.)[b]
4	**120** (2.6 eq.)	AIBN, $PhCH_3$, reflux, 19 h	**42** (57 %)[c]

[a]Yields calculated with respect to **118**. [b]n.d. = not determined. [c]Yield determined by the use of an internal standard ^{1}H-NMR spectroscopy.

Due to incorrect calculations, the reactions promoted by the germane linked to the Merrifield resin **118** were performed employing only 0.5 eq. of the solid supported reagent, hence the yields in entries 1 and 2 (**Table 47**) are calculated with respect to the amount of resin employed. With this in mind, the isolated yields are reasonable. However, the need for optimisation of these reaction conditions is apparent. In both reactions were large amounts of unreacted starting material **46** recovered and also the reduced product **43** was observed in small amounts. In the reactions promoted by the Quadragel-based mediator, reflux of the reaction mixture was again crucial for the radical process to proceed (entries 3 and 4, **Table 47**).

The radical cyclisations of alkyl precursors were not as successful as expected when promoted by triorganogermanes and it was therefore no great surprise that resin bound germane **120** failed to produce any cyclic products in reaction with 3-nitro-3-methyl-4-phenyl-4-(prop-2-ynyloxo)butyl cyanide **79** and 3-[(2-bromoethyl)oxy]-prop-2-enyl-benzene **81** (**Scheme 92**). In both reactions, only unreacted starting materials were detected by ^{1}H-NMR spectroscopy of the crude reaction mixture. It is possible though, that increasing the reaction temperature in the reaction of **81**, could have improved the outcome of the reaction.

Scheme 92. Attempted radical cyclisation of alkyl precursors **79** and **81**.

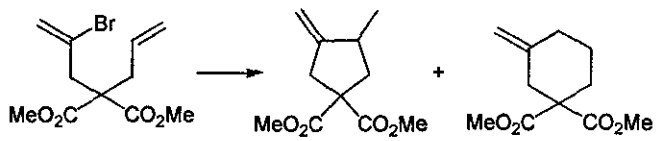


Reagents and conditions: (i) **120** (2.6 eq.), AIBN, toluene, reflux, 16 h. (ii) **120** (3.1 eq.), PhSH (0.1 eq.), ACCN, toluene, 90 °C 16 h.

The last radical cyclisation reactions performed with solid supported germanium reagents were with vinylic precursor, 2-allyl-2-(2-bromoallyl)malonic acid dimethyl ester **84**. When this reaction was performed utilising TBTH, **85** and **86** were obtained as a 2:1 mixture in 88 % combined yield. By adding PhSH as a hydrogen donor, the corresponding TBGH-mediated reaction afforded **85** and **86** as a 6.6:1 mixture in a combined 38 % yield, whereas the reaction in the absence of PhSH gave a poor 15 %

combined yield with the product ratio being roughly 3:1 in favour of **85** (section 2.6). With 4-(2-dimethylgermylethyl)phenol **113**, being a better hydrogen donor than TBGH, it was hoped that the resin bound analogue would increase the combined yield of cyclic products and maybe have an effect on the product distribution. As is evident from **Table 48**, this was partly the case. Treatment of **84** with **120** in the absence of PhSH gave a moderate yield of products in a 1.4:1 mixture in favour of **85** (entry 1, **Table 48**). This was quite surprising since this result indicates that **120** is actually a poorer hydrogen donor than TBGH, hence contradicting the results obtained with the free 4-(2-dimethylgermylethyl)phenol **113** in the radical cyclisation of aromatic precursor **34** earlier in this section. In contrast to the reaction promoted by TBGH in the presence of PhSH, the combined use of PhSH and **120** gave the 5-membered product **85** as the sole product in moderate yield (entry 2, **Table 48**). Hence in this case completely trapping of the 5-membered cyclic radical prior to rearrangement was accomplished by PhSH. In both reactions are the combined yields of cyclic product(s) and unreacted starting material **84** quite low. It is possible that this is a consequence of hydrogermylation as seen in the solution phase reactions with precursor **84**. The products arising from hydrogermylation will remain resin bound, hence will not appear as products in the crude reaction mixtures after filtration. Unfortunately, IR spectroscopy of the resin after reaction did not reveal further information on this matter.

Table 48. Radical cyclisation of malonate derivative **84**.



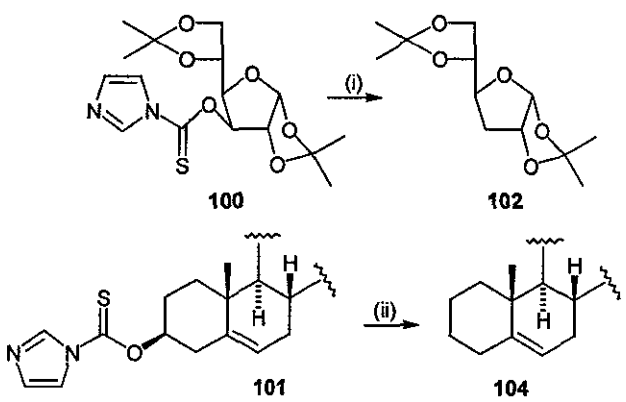
84 **85** **86**

Entry	Radical mediator	Reaction conditions	Product(s)[a]
1	**120** (4.0 eq.)	AIBN, $PhCH_3$, reflux, 19 h	**85** (19 %)[b] **86** (14 %)
2	**120** (4.0 eq.)	AIBN, PhSH (0.1 eq.), $PhCH_3$, reflux, 4 h	**85** (30 %)

[a]Yields determined by the use of an internal standard in ^{1}H-NMR spectroscopy. [b]Unreacted **84** (25 %).

As far as radical deoxygenations are concerned, germanium based mediators have proven to be superior to their tin based analogues, as seen in the reactions promoted by TBGH, 4-(2-dimethylgermylethyl)phenol **113** and 4-(2-dimethylgermylethyl)phenyl benzyl ether **116**. As the final radical investigation with the solid supported germanium reagents, deoxygenations of the glucose derivative **100** and the cholesteryl derivative **101** were reacted with the resin bound mediators **118** and **120**, respectively (**Scheme 93**). The radical deoxygenation of imidazole precursor **100** was performed employing only 1.3 eq. of **118**, but still the fully reduced product **102** was isolated in 36 % yield. This is a noticeably lower yield than previously obtained in reactions mediated by germanium-based reagents, but it is reasonable to believe that the yield could be much improved by employing a larger excess of the radical reagent. The radical deoxygenation of cholesteryl derivative **101** on the other hand, afforded the highest yield of the fully reduced product **104** seen in the investigation of this precursor. It was rewarding to note that no other products were formed in either of these reactions, hence even if the hydrogen donor ability of the resin bound germanes is higher than that of TBGH, hydrogen donation to initially formed radicals does not compete with the desired β-scission.

Scheme 93. Radical deoxygenations employing solid supported Ge-reagents.



Reagents and conditions: (i) **118** (1.3 eq.), ACCN, toluene, reflux, 7 h, **102** (36 %). (ii) **120** (4.4 eq.), ACCN, toluene, reflux, 17 h, **104** (68 %).

Conclusion of section 2.8

The preliminary studies of a solid supported approach to germanium hydride induced radical chemistry have proven quite successful. Employing TBGH in the radical

cyclisation of resin bound radical precursors produced the corresponding polycyclic product in high yield. Due to the mechanism of this process, unreacted starting material and any reduced product will remain bound to the resin whilst the cyclic product will be in solution. This means that separation of the product from germanium residues is still needed but due to relatively stability of germanium product, this is normally not a great problem.

Employing a recently published reaction sequence, a new germanium-based radical mediator was synthesised and tested in radical reactions. The mediator was found to be highly effective in radical reactions and especially in radical deoxygenations where it was superior to both TBTH and TBGH. The good reactivity observed can possibly be explained by a greater hydrogen donor ability compared to TBGH, hence chain propagation is more efficient. Attachment of this mediator to resins was easily achieved by nucleophilic displacement and the resulting solid supported reagents were shown to display good reactivity in radical reactions. Virtually all of the reactions tested gave moderate to good yields of the desired products and it is believed that optimisation of reaction conditions will improve these yields significantly.

2.9 Conclusion

The use of triorganogermanium compounds as mediators of radical reactions has been shown to exhibit both advantages and certain disadvantages in comparison with the widely used radical mediator, TBTH (tributyltin hydride).

Reactions promoted by triorganogermanium compounds have proven to be slower processes as predicted from the kinetic data available. The slower reaction is due to the stronger Ge-H bond when compared to the Sn-H bond, hence inefficient chain propagation is often observed. We have shown in one example that this problem can be overcome by the addition of a "polarity reversal catalyst" and further investigation of this method of enhancing the reactivity of triorganogermanium compounds could be very beneficial.

The stability of TBGH (tributylgermanium hydride) is significantly greater than the stability of TBTH, a fact that balances the extra cost associated with the use of germanium-centred radical mediators. The enhanced stability also eases the

purification of crude reaction mixtures. In reactions with triorganotin compounds, column chromatography is often troublesome due to decomposition of tin by-products on the column. These "streaking" problems are very rarely experienced in purification of reactions promoted by triorganogermanium compounds.

The stronger Ge-H bond as compared to the corresponding Sn-H bond, and hence lower hydrogen-donor ability has been shown to be of value in certain radical reactions. In some radical cyclisation reactions, higher ratios of cyclic to reduced products have been obtained. This is due to the bimolecular hydrogen abstraction from R_3GeH being less favourable than the intramolecular radical cyclisation. Triorganogermanium hydrides have been found to be superior to TBTH in radical deoxygenations where products arising from premature hydrogen donation are often observed in tin-mediated reactions.

The investigation of the use of solid supported germanium reagents has only been preliminary but the results have been encouraging. A new germanium based radical mediator has been developed which has shown good reactivity as a radical mediator. When this reagent was attached onto a resin, reasonable results were obtained. However, reaction conditions have to be optimised and a more broad variety of radical precursors must be tested in the investigation for this approach to radical chemistry to be of common use. Development of new solid supported reagents as well as catalytic use of these are other examples of studies which could be of great interest.

The studies leading to this thesis was the initial investigation of the possibility of triorganogermanium compounds to be alternatives to the corresponding tin based reagents. Along with the areas already mentioned, optimising of existing methods of synthesising the germanium compounds and development of new germanium based radical mediators would be needed in order for "the throne of tin" to be under any serious threat.

Chapter 3. Experimentals

3.1 General experimentals

IR spectra were determined using a Perkin Elmer FT-IR Paragon 1000 spectrometer as thin films unless otherwise stated. Wave numbers of selected peaks are given in cm^{-1}. ^{1}H NMR spectra were measured using a Bruker AC 250 spectrometer or a Bruker DPX 400 MHz spectrometer. *J* values are given in Hz. ^{13}C NMR spectra were measured using a Bruker DPX 400 MHz spectrometer at 100.6 MHz unless otherwise stated. NMR spectra were recorded using tetramethylsilane (TMS) as the internal reference in $CDCl_3$ unless otherwise stated. Mass spectra were recorded using a Kratos MS 80 instrument. The GC-MS used was the Fisons GC 8000 series (AS 800). When reporting MS or GC-MS of germanium compounds, only the strongest peaks corresponding to the major isotope of Ge is recorded. Elemental analysis was carried out on a Perkin Elmer 2400 CHN Elemental Analyser. Melting points were measured using an Electrothermal 9100 melting point machine, and are uncorrected.

TLC using silica gel as the absorbent was carried out with aluminium backed plates with silica gel (Merck Kiesel 60 F_{254}) and TLC using alumina as the absorbent was carried out with aluminium backed plates coated with aluminium oxide (Merck 15, type T). Column chromatography was carried out using silica gel unless otherwise stated with Merck Kiesel 60 H silica. Column chromatography using alumina was carried out with Aldrich aluminium oxide (Merck 60 PF_{254}, type E).

All of the alkylation and radical reactions were carried out using dry glassware and under an atmosphere of nitrogen. Anhydrous acetonitrile, THF, toluene and cyclohexane were obtained commercially and were used as obtained. Sodium hydride was obtained as 60 % dispersion in mineral oil.

Light petroleum refers to the fraction, bp 40-60 °C. Light petroleum and EtOAc were distilled from calcium chloride, dichloromethane (DCM) and toluene were distilled from calcium hydride. Analytical grade diethyl ether and acetone were obtained commercially.

3.2 Experimentals for Chapter 2.1

Tetraphenylgermanium

$$GeCl_4 \longrightarrow Ph_4Ge$$

Method A:[51]

Bromobenzene (15.7 g, 100 mmol) was added dropwise to a mixture of magnesium (2.43 g, 100 mmol) and iodine (one crystal) in anhydrous diethyl ether (50 cm^3) until reaction started. The remaining bromobenzene was added at such rate as to maintain gentle reflux. After the addition was complete, the mixture was refluxed for another hour. After cooling to room temperature, a solution of tetrachlorogermane (2.14 g, 10 mmol) in anhydrous toluene (25 cm^3) was added and the diethyl ether immediately replaced by toluene through distillation. The mixture was refluxed for two more hours and the excess phenylmagnesium bromide destroyed by addition of 1 M aqueous hydrochloric acid. The mixture was then heated, filtered and the toluene layer separated while still hot. The toluene solution was cooled, giving a creamy white solid, which was recrystallised from toluene to give tetraphenylgermanium as colourless needles (2.28 g, 64 %); mp: 235-236 °C (lit.[51] 235.7 °C); (Found: C, 75.52; H, 5.19, $C_{24}H_{20}Ge$ requires C, 75.66; H, 5.29); ν_{max} (KBr)/cm^{-1} 1428, 1089, 741, 736 and 698; δ_H 7.33-7.44 (12 H, m, Ph) and 7.49-7.54 (8 H, m, Ph); δ_C 128.28, 129.12 and 135.42; *m/z* 382 (M^{+1}, 1 %), 305 (53), 228 (85), 151 (100) and 77 (62).

Method B:[52]

Phenyllithium (1.8 M solution in hexane, 11.5 cm^3, 20.70 mmol) was added dropwise to a solution of tetrachlorogermane (1.00 g, 4.66 mmol) in anhydrous toluene (4 cm^3) at 0 °C and the resulting milky white mixture was stirred for 3.5 h at ambient temperature. The mixture was poured into water and extracted with EtOAc. The combined organic layers were dried ($MgSO_4$) and evaporated to dryness to give a pale yellow solid, which was recrystallised from toluene to give tetraphenylgermanium as colourless needles (0.57 g, 1.50 mmol, 32 %).

Triphenylgermanium bromide[53]

$$Ph_4Ge \longrightarrow Ph_3GeBr$$

Bromine (0.62 g, 3.89 mmol) was added dropwise to a refluxing solution of tetraphenylgermane (1.00 g, 2.62 mmol) in chlorobenzene (7 cm^3) and the mixture was refluxed for 45 min. The solvent and unreacted bromine were removed by concentration of the mixture *in vacuo* to give a orange semi-solid, which was recrystallised from methanol to give triphenylgermanium bromide as small colourless crystals (0.31 g, 31 %); mp: 136-137 °C (lit.[53] 138 °C); ν_{max} (KBr)/cm^{-1} 3059, 1483, 1433, 1090, 735 and 691; δ_H 7.43-7.48 (9 H, m, Ph) and 7.61-7.65 (6 H, m, Ph); δ_C 128.62, 130.45, 134.23 and 134.66; *m/z* 384 (M^+, 1 %), 305 (70), 226 (8), 151 (65), 77 (82) and 51 (100).

Triphenylgermanium hydride[53]

$$Ph_3GeBr \longrightarrow Ph_3GeH$$

Sodium borohydride (0.044 g, 1.17 mmol) was added to a solution of triphenylgermanium bromide (0.030 g, 0.078 mmol) in anhydrous *t*-BuOH (10 cm^3) and the mixture was refluxed for 30 min. The mixture was poured into water and extracted with diethyl ether. The organic layer was washed with water, dried ($MgSO_4$) and evaporated to dryness to give triphenylgermanium hydride as an white solid (0.021 g, 0.069 mmol, 88 %); mp 40-41 °C (lit.[53] 41 °C); δ_H 5.73 (1 H, s, GeH) and 7.15-7.72 (15 H, m, Ph); δ_C 127.36, 131.02, 134.59 and 135.98; *m/z* 306 (M^+, 100 %), 228 (33) and 151 (19).

Tributylgermanium hydride and tetrabutylgermanium[54]

$$GeCl_4 \longrightarrow Bu_3GeH + Bu_4Ge$$

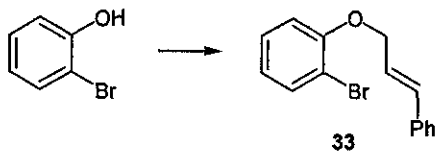
Tetrachlorogermanium (8.75 g, 40.8 mmol) and butylmagnesium chloride (2 M solution in diethyl ether, 100 cm^3) were successively added dropwise to a solution of Cp_2TiCl_2 (0.76 g, 3.1 mmol) in freshly distilled diethyl ether (200 cm^3) at –78 °C over 45 min. The mixture was allowed to warm up to room temperature over 45 min during

which period a colour change from milky red to milky green was observed and thereafter refluxed for 15 h. After cooling 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 ($MgSO_4$) and evaporated to dryness to give a residue which was filtered through celite to remove a red solid. Distillation under reduced pressure gave two products; TBGH (5.25 g, 21.5 mmol, 53 %) and Bu_4Ge (4.30 g, 14.3 mmol, 35 %) as colourless liquids.[54] TBGH: 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, sep, *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).

3.3 Experimentals for Chapter 2.2

3.3.1 Synthesis of aromatic precursors

1-Bromo-2-[(3-phenylprop-2-enyl)oxy]benzene 33[82]

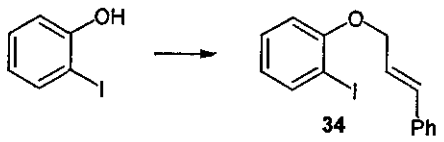


33

A mixture of 2-bromophenol (1.00 g, 5.78 mmol), cinnamyl bromide (1.14 g, 5.78 mmol), potassium carbonate (0.80 g, 5.79 mmol) in acetone (4 cm^3) was refluxed for 17 h. The mixture was then poured into water and extracted with diethyl ether. The combined organic layers were washed with aqueous NaOH solution and with aqueous NaCl solution, dried ($MgSO_4$) and evaporated to dryness to give a yellow oil, which was purified by column chromatography (light petroleum:DCM; 7:1) to give 1-bromo-2-[(3-phenylprop-2-enyl)oxy]benzene **33** as a colourless oil (1.35 g, 4.65 mmol, 81 %); (Found: 288.0155, $C_{15}H_{13}{}^{79}BrO$ requires: 288.0150); ν_{max} (DCM)/cm^{-1} 3059,

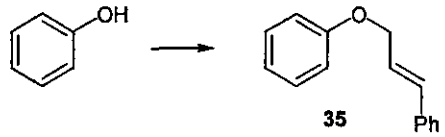
3025, 1585, 1573, 1478, 1442, 1277, 1244, 1030, 965, 745 and 692; δ_H 4.76 (2 H, dd, *J* 5.6, 1.5, 1-H), 6.41 (1 H, dt, *J* 16.0, 5.6, 2-H) 6.78 (1 H, dd, *J* 16.0, 1.5, 3-H), 6.81-6.96 (2 H, m, Ph), 7.15-7.45 (6 H, m, Ph) and 7.55 (1 H, dd, *J* 7.9, 1.6, Ph); δ_C 69.8 (1-C), 112.5 (Ar 1-C), 114.0 (Ar 3-C), 122.1 (Ar 5-C), 124.0 (2-C), 126.7 (Ph 2,6-C), 128.0 (Ph 4-C), 128.4 (3-C), 128.6 (Ph 3,5-C), 133.1 (Ar 4-C), 133.5 (Ar 6-C), 136.4 (Ph 1-C) and 155.0 (Ar 2-C); *m/z* 290 (M^+, $C_{15}H_{13}{}^{81}BrO$, 3 %), 288 (M^+, $C_{15}H_{13}{}^{79}BrO$, 3 %), 145 (6), 143 (6), 117 (100), 115 (76), 91 (41), 86 (26), 84 (40), 77 (11), 63 (7) and 49 (44).

1-Iodo-2[(3-phenylprop-2-enyl)oxy]benzene 34



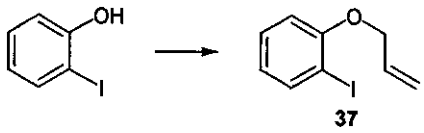
A mixture of cinnamyl bromide (4.48 g, 22.7 mmol), iodophenol (5.0 g, 22.7 mmol) and potassium carbonate (3.14 g, 22.7 mmol) in acetone (16 cm^3) was refluxed for 17 h, and thereafter cooled to room temperature. The mixture was poured into water and extracted with diethyl ether. The combined organic layers were washed with aqueous NaOH solution and with aqueous NaCl solution, dried ($MgSO_4$) and evaporated to dryness to give a yellow oil, which was purified by column chromatography (light petroleum:DCM; 8:1) to give 1-iodo-2[(3-phenylprop-2-enyl)oxy]benzene **34** as a white solid (5.35 g, 15.91 mmol, 70 %) which melts at room temperature; (Found: 336.0012, $C_{15}H_{13}IO$ requires: 336.0011); ν_{max} (DCM)/cm^{-1} 3058, 3023, 1586, 1571, 1476, 1442, 1276, 1245, 1031, 966, 745 and 692; δ_H 4.77 (2 H, dd, *J* 5.4, 1.6, 1-H), 6.41 (1 H, dt, *J* 16.0, 5.4, 2-H) 6.72 (1 H, dt, *J* 7.8, 1.6, Ph), 6.82 (1 H, d, *J* 16.0, 3-H), 6.87 (1 H, dd, *J* 8.3, 1.4, Ph), 7.24-7.44 (6 H, m, Ph) and 7.79 (1 H, dd, *J* 7.8, 1.6, Ph); δ_C 70.16 (1-C), 87.3 (Ar 1-C), 113.2 (Ar 3-C), 123.2 (Ar 5-C), 124.4 (2-C), 127.0 (Ph 2,6-C), 128.3 (3-C), 129.0 (Ph 3,5-C), 129.9 (Ph 4-C), 133.3 (Ar 4-C), 136.9 (Ph 1-C), 140.0 (Ar 6-C) and 157.7 (Ar 2-C); *m/z* 336 (15 %), 253 (5), 219 (10), 191 (10), 117 (100), 115 (100), 91 (55) and 64 (20).

(3-Phenylprop-2-enyl)oxy-benzene 35[83]



A mixture of phenol (0.49 g, 5.15 mmol), cinnamyl bromide (1.05 g, 5.31 mmol), potassium carbonate (0.73 g, 5.31 mmol) in acetone (5 cm^3) was refluxed for 17 h. The mixture was then poured into water and extracted with diethyl ether. The combined organic layers were washed with aqueous NaOH solution and with saturated aqueous NaCl solution, dried ($MgSO_4$) and evaporated to dryness to give a yellow oil, which was purified by column chromatography (light petroleum:DCM; 7:1) to give 2-[(3-phenylprop-2-enyl)oxy]benzene **35** as a white solid (0.225 g, 1.07 mmol, 21 %); mp 66-67 °C (Lit.[83] 65-66 °C); δ_H 4.70 (2 H, dd, *J* 5.7, 1.4, 1-H), 6.42 (1 H, dt, *J* 16.0, 5.7, 2-H), 6.73 (1 H, d, *J* 16.0, 3-H), 6.84-6.99 (3 H, m, Ph) and 7.07-7.42 (7 H, m, Ph); δ_C 68.6 (1-C), 114.8 (Ar 2,6-C), 120.9 (Ar 4-C), 124.5 (3-C), 126.0 (2-C), 126.6 (Ph 2,6-C), 127.8 (Ph 4-C), 128.6 (Ph 3,5-C), 129.5 (Ar 3,5-C), 133.0 (Ph 1-C) and 158.6 (Ar 1-C), *m/z* 210 (M^+, 8 %), 165 (10), 115 (48), 103 (27), 91 (46), 78 (85), 77 (86), 65 (65), 63 (44), 51 (64) and 39 (100).

2-Iodo-1-(prop-2-enyloxy)benzene 37[84]



Allylbromide (1.1 g, 9.1 mmol) was added to a mixture of 2-iodophenyl (2.0 g, 9.1 mmol) and potassium carbonate (1.3 g, 9.1 mmol) in acetone (8 cm^3) and the resulting solution refluxed for 4 h. After cooling to room temperature, water was added to the mixture and extracted into diethyl ether. The organic layer was washed with aqueous sodium hydroxide and brine, dried ($MgSO_4$) and evaporated to dryness to give 2-iodo-1-(prop-2-enyloxy)benzene **37** as an colourless oil (2.2 g, 8.5 mmol, 93 %), which did not need further purification; (Found: 259.9698, C_9H_9IO requires 259.9698); ν_{max} /cm^{-1} 3062, 3016, 2986, 2918, 2863, 1579, 1473, 1441, 1419, 1275, 1247, 1229, 1123, 1048, 1017 and 748; δ_H (400 MHz) 4.48 (2 H, bs, 3-H), 5.25 (1 H, d, *J* 10.8, 1_A-H),

5.48 (1 H, d, *J* 17.2, 1_B-H), 5.98 (1 H, m, 2-H), 6.67 (2 H, m, Ar 4,6-H), 7.21 (1 H, m, Ar 5-H) and 7.73 (1H, m, Ar 3-H); δ_C 70.06 (3-C), 87.25 (Ar 2-C), 112.87 (1-C), 118.05 (Ar 6-C), 123.18 (Ar 4-C), 129.94 (Ar 5-C), 133.07 (2-C), 139.96 (Ar 3-C) and 157.53 (Ar 1-C); *m/z* 260 (M^+, 100 %), 220 (21), 191 (20), 133 (44), 119 (13), 105 (59), 92 (49), 77 (18), 63 (43) and 41 (77).

2-Iodo-1-(prop-2-ynyloxy)benzene 38

38

Propargylbromide (80 % in toluene, 1.35 g, 9.1 mmol) was added to a solution of 2-iodophenyl (2.0 g, 9.1 mmol) and potassium carbonate (1.3 g, 9.1 mmol) in acetone (8 cm^3) and the resulting solution refluxed for 5 h. After cooling to room temperature, water was added to the mixture and extracted into diethyl ether. The organic layer was washed with aqueous sodium hydroxide and brine, dried ($MgSO_4$) and evaporated to dryness to give a yellow oil. Column chromatography (light petroleum: EtOAc; 8:1) gave 2-iodo-1-(prop-2-ynyloxy)benzene **38** as a colourless oil (2.2 g, 8.5 mmol, 94 %); (Found: 257.9542, C_9H_7IO requires 257.9542); ν_{max} (DCM)/cm^{-1} 3290, 1581, 1470, 1447, 1372, 1277, 1225, 1050, 1018 and 645; δ_H (400 MHz) 2.51 (1 H, bs, 1-H), 4.71 (2 H, bs, 3-H), 6.71 (1 H, bs, Ar 6-H), 6.94 (1 H, bs, Ar 4-H), 7.26 (1 H, bs, Ar 5-H) and 7.74 (1H, m, Ar 3-H); δ_C 57.39 (3-C), 76.72 (1-C), 78.57 (2-C), 87.11 (Ar 2-C), 113.52 (Ar 6-C), 123.94 (Ar 4-C), 129.52 (Ar 5-C), 139.81 (Ar 3-C) and 156.69 (Ar 1-C); *m/z* 258 (M^+, 53 %), 219 (17), 191 (21), 131 (100), 103 (40), 92 (53), 77 (26) and 63 (38).

3.3.2 Radical cyclisation of aromatic precursors

General cyclisation procedure:

The radical mediator [and PhSH (10 %) if employed in reaction] was added dropwise to a mixture of the radical precursor in anhydrous solvent at room temperature. The mixture was heated to reflux and the radical initiator was added, followed by refluxing for the time indicated under each reaction. If the reaction time is more than 3 h, another small amount of the initiator was added after this period of time. Cooling to room temperature and evaporation of the mixture to dryness gave in most cases oils which were purified by column chromatography.

General procedure when using catalytic amounts of the radical mediator:

The radical mediator was added dropwise to a solution of the radical precursor in *t*-BuOH at room temperature, followed by addition of sodium borohydride. The mixture was heated to reflux and AIBN was added, followed by refluxing for the time indicated under each reaction, during which time AIBN was added every hour. After cooling to room temperature the mixture was poured into water and extracted with diethyl ether. The organic layer was washed with water (× 7) to remove *t*-BuOH, dried over $MgSO_4$ and evaporated to dryness.

General procedure when using triethylborane as radical initiator:

The radical mediator and triethylborane (1.0 M solution in THF) was added dropwise to a solution of the radical precursor in anhydrous solvent at room temperature. If the use of radical mediator was in a catalytic manner, sodium borohydride was also added at this stage. The mixture was stirred at room temperature for the time indicated under each reaction, poured into water and extracted with DCM. The organic layer was dried ($MgSO_4$) and evaporated to dryness.

General procedure when using syringe-pump addition of the radical mediator:

Using syringe-pump technique, the radical mediator in anhydrous solvent was added to a refluxing mixture of the radical precursor in anhydrous solvent over the period of time indicated under each reaction. The initiator was added initially and thereafter every 40 min. Cooling to room temperature and evaporation of the mixture to dryness gave the crude reaction mixtures.

Radical cyclisation of 1-bromo-2-[(3-phenylprop-2-enyl)oxy]-benzene 33

Table 27, entry 1:

Following the general procedure when using catalytic amounts of the radical mediator, 1-bromo-2-[(3-phenylprop-2-enyl)oxy]-benzene **33** (0.2 g, 0.7 mmol) in *t*-BuOH (50 cm^3) was reacted with tributyltin chloride (22.5 mg, 0.07 mmol) and sodium borohydride (39.0 mg, 1.0 mmol) for 4 h. The yield of 3-benzyl-2,3-dihydro-benzofuran **36** (77 %) was determined by ^{1}H-NMR spectroscopy using 1,4-dinitrobenzene as the internal standard.[85] δ_H 2.80 (1 H, dd, *J* 13.8 and 8.9, C*H*$_2$Ph), 3.03 (1 H, dd, *J* 13.8 and 6.4, C*H*$_2$Ph) 3.71 (1 H, m, C*H*CH$_2$Ph), 4.24 (1 H, dd, *J* 8.9 and 6.0, OC*H*$_2$), 4.48 (1 H, dd, *J* 8.9 and 8.9, OC*H*$_2$), 6.79 (2 H, m, Ar 4,6-C), 6.94 (1 H, d, *J* 7.8, Ar 5-C), 7.06-7.32 (6 H, m, Ph and Ar 3-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).

Table 27, entry 2:

Following the general procedure when using catalytic amounts of the radical mediator, 1-bromo-2-[(3-phenylprop-2-enyl)oxy]benzene **33** (0.2 g, 0.7 mmol) in *t*-BuOH (50 cm^3) was reacted with triphenylgermanium bromide (27 mg, 0.07 mmol) and sodium borohydride (39.0 g, 1.0 mmol) for 11 h. The resulting oil was identified by ^{1}H-NMR spectroscopy as unreacted starting material **33**. The amount of recovered **33** was not determined.

Table 27, entry 3:

Following the general procedure when using catalytic amounts of the radical mediator, 1-bromo-2-[(3-phenylprop-2-enyl)oxy]benzene **33** (0.2 g, 0.7 mmol) in *t*-BuOH (50 cm^3) was reacted with triphenylgermanium hydride (21 mg, 0.07 mmol) and sodium borohydride (39.0 mg, 1.0 mmol) for 4 h, followed by reflux overnight. The resulting

oil was identified by ^{1}H-NMR spectroscopy as unreacted starting material **33**. The amount of recovered **33** was not determined.

Table 27, entry 4:

Following the general procedure when using triethylborane as radical initiator, 1-bromo-2-[(3-phenylprop-2-enyl)oxy]benzene **33** (0.2 g, 0.7 mmol) in THF (7 cm^3) was reacted with triphenylgermanium bromide (27 mg, 0.07 mmol), sodium borohydride (52.0 mg, 1.4 mmol) and triethylborane (1.0 M solution, 0.14 ml, 0.14 mmol) for 21 h. The resulting oil was identified by ^{1}H-NMR spectroscopy as unreacted starting material **33** along with a trace amount of another compound. The amount of recovered **33** was not determined.

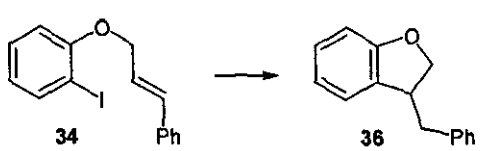
Table 27, entry 5:

Following the general cyclisation procedure, 1-bromo-2-[(3-phenylprop-2-enyl)oxy]-benzene **33** (0.1 g, 0.3 mmol) in cyclohexane (35 cm^3) was reacted with TBTH (0.18 g, 0.6 mmol) and AMBN for 3 h. The yield of 3-benzyl-2,3-dihydro-benzofuran **36** (52 %) was determined by ^{1}H-NMR spectroscopy using 1,4-dinitrobenzene as the internal standard.

Table 27, entry 6:

Following the general cyclisation procedure, 1-bromo-2-[(3-phenylprop-2-enyl)oxy]-benzene **33** (0.13 g, 0.4 mmol) in cyclohexane (40 cm^3) was reacted with TBGH (0.16 g, 0.7 mmol) and AMBN for 3 h. The yields of 3-benzyl-2,3-dihydro-benzofuran **36** (7 %) and unreacted starting material **33** (83 %) were determined by ^{1}H-NMR spectroscopy using 1,4-dinitrobenzene as the internal standard.

Radical cyclisation of 1-iodo-2-[(3-phenylprop-2-enyl)oxy]benzene 34



34 36

Table 28, entry 1:

Following the general procedure when using catalytic amounts of the radical mediator, 1-iodo-2-[(3-phenylprop-2-enyl)oxy]benzene **34** (0.2 g, 0.6 mmol) in *t*-BuOH (50 cm^3) was reacted with tributyltin chloride (22.0 mg, 0.06 mmol) and sodium

borohydride (34.0 mg, 0.9 mmol) for 2 h. The yield of 3-benzyl-2,3-dihydrobenzofuran **36** (83 %) was determined by ^{1}H-NMR spectroscopy with 1,4-dinitrobenzene as the internal standard. Column chromatography (light petroleum:EtOAc; 30:1) gave 3-benzyl-2,3-dihydrobenzofuran **36** as a colourless oil (0.07 g, 0.35 mmol, 59 %). The spectral data were as above.

Table 28, entry 2:

Following the general procedure when using catalytic amounts of the radical mediator, 1-iodo-2-[(3-phenylprop-2-enyl)oxy]benzene **34** (0.2 g, 0.6 mmol) in *t*-BuOH (50 cm^3) was reacted with TBGBr (23.0 mg, 0.06 mmol) and sodium borohydride (34 mg, 0.9 mmol) for 28 h. AIBN was added every hour for the first 8 and the last 4 h. The resulting oil was identified by ^{1}H-NMR spectroscopy as unreacted starting material **34**. The amount of recovered **34** was not determined.

Table 28, entry 3:

Following the general cyclisation procedure, 1-iodo-2-[(3-phenylprop-2-enyl)oxy]-benzene **34** (0.15 g, 0.4 mmol) in cyclohexane (35 cm^3) was reacted with TBTH (0.19 g, 0.7 mmol) and AMBN for 3 h. The yield of 3-benzyl-2,3-dihydrobenzofuran **36** (92 %) was determined by ^{1}H-NMR spectroscopy using 1,4-dinitrobenzene as the internal standard.

Table 28, entry 4:

Following the general cyclisation procedure, 1-iodo-2-[(3-phenylprop-2-enyl)oxy]-benzene **34** (0.11 g, 0.3 mmol) in cyclohexane (35 cm^3) was reacted with TBGH (0.09 g, 0.4 mmol) and AMBN for 3 h. The yield of recovered starting material **34** (79 %) was determined by ^{1}H-NMR spectroscopy using 1,4-dinitrobenzene as the internal standard.

Table 28, entry 5:

Following the general procedure when using syringe-pump addition of the radical mediator, 1-iodo-2-[(3-phenylprop-2-enyl)oxy]benzene **34** (0.11 g, 0.3 mmol) in acetonitrile (30 cm^3) was reacted with TBTH (0.19 g, 0.7 mmol) in toluene (10 cm^3) and AMBN for 3 h. The yield of 3-benzyl-2,3-dihydrobenzofuran **36** (48 %) was determined by ^{1}H-NMR spectroscopy using 1,4-dinitrobenzene as the internal standard.

Table 28, entry 6:

Following the general procedure when using syringe-pump addition of the radical mediator, 1-iodo-2-[(3-phenylprop-2-enyl)oxy]benzene **34** (0.12 g, 0.4 mmol) in acetonitrile (30 cm^3) was reacted with TBGH (0.09 g, 0.4 mmol) in toluene (10 cm^3) and AMBN for 3 h. The yields of 3-benzyl-2,3-dihydrobenzofuran **36** (4 %) and unreacted starting material **34** (36 %) were determined by ^{1}H-NMR spectroscopy using 1,4-dinitrobenzene as the internal standard.

Table 28, entry 7:

Following the general procedure when using triethylborane as radical initiator, 1-iodo-2-[(3-phenylprop-2-enyl)oxy]benzene **34** (0.1 g, 0.30 mmol) in THF (30 cm^3) was reacted with TBTH (0.17 g, 0.60 mmol) and Et_3B (1.0 M in THF, 1.2 mmol) for 3 h. Column chromatography (light petroleum:DCM; 8:1) gave 3-benzyl-2,3-dihydrobenzofuran **36** in 64 % yield as determined by the use of 1,4-dinitrobenzene in ^{1}H-NMR spectroscopy.

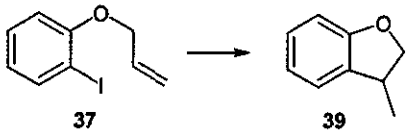
Table 28, entry 8:

TBGH (47.0 mg, 0.19 mmol) and Et_3B (1.0 M in THF, 0.28 mmol) were added successively and dropwise to a solution of 1-iodo-2-[(3-phenylprop-2-enyl)oxy]-benzene **34** (50.0 mg, 0.15 mmol) in anhydrous cyclohexane (25 cm^3). The mixture was exposed to air *via* a needle and stirred for 8 h. TLC showed the presence of starting material **34** and further TBGH (47.0 mg, 0.19 mmol) and Et_3B (1.0 M in THF, 0.28 mmol) were added. After 18 h stirring at ambient temperature, **34** was still present and yet more TBGH (47.0 mg, 0.19 mmol) and Et_3B (1.0 M in THF, 0.28 mmol) were added and the mixture stirred for 8 h. Evaporation of solvent followed by column chromatography (light petroleum:DCM; 8:1) gave only unreacted **34** (45.0 mg, 0.13 mmol, 90 %).

In the presence of TBGH and PhSH:

Following the general cyclisation procedure, 1-iodo-2-[(3-phenylprop-2-enyl)oxy]-benzene **34** (0.1 g, 0.4 mmol) in anhydrous cyclohexane (35 cm^3) was reacted with TBGH (0.1 g, 0.4 mmol), PhSH (4 mg, 0.04 mmol) and ACCN (0.2 g, 0.4 mmol in total) for 9 h. Column chromatography (light petroleum:DCM; 10:1 $\rightarrow$ 5:1) gave 3-benzyl-2,3-dihydrobenzofuran **36** (56 mg, 0.27 mmol, 75 %) as an colourless oil.

Radical cyclisation of 2-iodo-1-(prop-2-enyloxy)benzene 37



37 39

Table 29, entry 1:

Following the general cyclisation procedure, 2-iodo-1-(prop-2-enyloxy)benzene **37** (0.11 g, 0.42 mmol) in toluene (40 cm^3) was reacted with TBTH (0.15 g, 0.5 mmol) and ACCN (0.11 g, 0.45 mmol) for 2 h giving 3-methyl-2,3-dihydrobenzofuran **39** (57.7 mg, 0.43 mmol, 86 %) as a colourless oil.[86] δ_H 1.33 (3 H, d, *J* 6.9, Me), 3.47-3.62 (1 H, m, C*H*Me), 4.07 (1 H, dd, *J* 7.8, 8.8, C*H*O), 4.68 (1 H, dd, *J* 8.8, 8.8, C*H*O), 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 (62.5 MHz) 20.01 (Me), 37.16 (*C*HMe), 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).

Table 29, entry 2:

Following the general cyclisation procedure, 2-iodo-1-(prop-2-enyloxy)benzene **37** (0.11 g, 0.42 mmol) in toluene (40 cm^3) was reacted with TBGH (0.12 g, 0.5 mmol) and ACCN (0.19 g, 0.78 mmol) for 6 h giving a mixture of 3-methyl-2,3-dihydrobenzofuran **39** and 3-iodomethyl-2,3-dihydrobenzofuran **40**. The yields of the two compounds (22 % and 28 % respectively) were determined by the use of 1,4-dimethoxybenzene as the internal standard in ^{1}H-NMR spectroscopy. **40**:[86] δ_H 3.19 (1 H, t, *J* 9.8, C*H*I), 3.44 (1 H, dd, *J* 4.4 and 10.0, C*H*I), 3.77-3.88 (1 H, m, C*H*CH_2I), 4.32 (1 H, dd, *J* 5.3 and 9.3, C*H*O), 4.63 (1 H, dd, *J* 8.6 and 8.6, C*H*O), 6.78-6.89 (2 H, m, Ar 4,6-H) and 7.10-7.24 (2 H, m, Ar 3,5-H); δ_C 8.94 (*C*H_2I), 44.84 (*C*HCH_2I), 77.67 (OCH_2), 110.26 (Ar 6-C), 120.68 (Ar 4-C), 124.34 (Ar 5-C), 128.77 (Ar 2-C), 129.36 (Ar 3-C) and 160.19 (Ar 1-C); *m/z* 260 (M^+ 44 %), 141 (67), 127 (100) and 91 (55).

Table 29, entry 3:

Following the general cyclisation procedure, 2-iodo-1-(prop-2-enyloxy)benzene **37** (0.17 g, 0.65 mmol) in toluene (45 cm^3) was reacted with TBGH (0.19 g, 0.78 mmol),

PhSH (7.2 mg, 0.06 mmol) and AIBN (30.0 mg, 0.18 mmol) for 2 h giving 3-methyl-2,3-dihydro-benzofuran **39** (74.1 mg, 0.55 mmol, 85 %) as a colourless oil.

Table 29, entry 4:

Following the general cyclisation procedure, 2-iodo-1-(prop-2-enyloxy)benzene **37** (96.0 mg, 0.37 mmol) in toluene (38 cm^3) was reacted with TBGH (0.11 g, 0.44 mmol) and AIBN (35.0 mg, 0.2 mmol) for 2 h giving 3-methyl-2,3-dihydrobenzofuran **39** (45.1 mg, 0.34 mmol, 91 %) as a colourless oil.

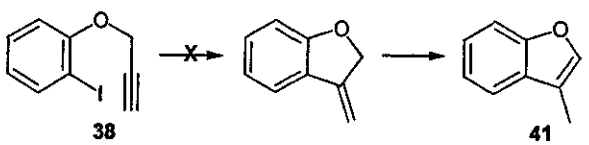
Table 29, entry 5:

Following the general procedure when using catalytic amounts of the radical mediator, 2-iodo-1-(prop-2-enyloxy)benzene **37** (94.0 mg, 0.36 mmol) in toluene (22 cm^3) and *t*-BuOH (1 cm^3) was reacted with TBGH (9.4 mg, 0.04 mmol) and sodium borohydride (29.0 mg, 0.77 mmol) for 2 h. ^{1}H-NMR spectroscopy revealed the presence of starting material **37** in 83 % yield.

Table 29, entry 6:

As above, but with increased reaction time (6 h), gave a mixture of unreacted starting material **37** (37 %) and 3-methyl-2,3-dihydrobenzofuran **39** (44 %) as determined by the use of 1,4-dimethoxybenzene as the internal standard in ^{1}H-NMR spectroscopy.

Attempted radical cyclisation of 2-iodo-1-(prop-2-ynyloxy)benzene 38



38 **41**

Employing TBTH:

Following the general cyclisation procedure, 2-iodo-1-(prop-2-ynyloxy)benzene **38** (0.11 g, 0.43 mmol) in anhydrous toluene (40 cm^3) was reacted with TBTH (0.19 g, 0.65 mmol) and ACCN (0.14 g, 0.56 mmol in total) for 4 h. ^{1}H-NMR spectroscopy of the crude reaction mixture revealed signs of cyclic product, but column chromatography (light petroleum:DCM; 8:1) did not give any wanted product. Instead, a complex mixture of products was obtained. These were not identified.

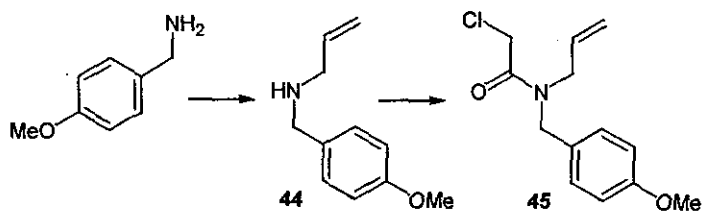
Employing TBGH:

Following the general cyclisation procedure, 2-iodo-1-(prop-2-ynyloxy)benzene **38** (0.11 g, 0.43 mmol) in anhydrous toluene (40 cm^3) was reacted with TBGH (0.13 g, 0.52 mmol) and ACCN (0.18 g, 0.74 mmol in total) for 4 h. ^{1}H-NMR spectroscopy of the crude reaction mixture did not reveal any signs of cyclic products, and column chromatography (light petroleum:DCM; 8:1) did not give any products of interest.

3.4 Experimentals for Chapter 2.3

3.4.1 Synthesis of amide precursors

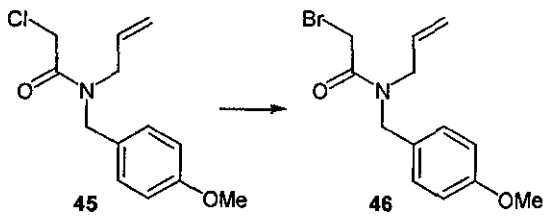
N-Allyl-2-chloro-N-(4-methoxybenzyl)acetamide 45



Potassium carbonate (23.0 g, 0.168 mol) was added to a solution of 4-methoxybenzylamine (7.88 g, 57.4 mmol) in acetonitrile (230 cm^3) at 0 °C followed by dropwise addition of a solution of allyl bromide (5.79 g, 47.8 mmol) in acetonitrile (46 cm^3). The resulting mixture was stirred at ambient temperature for 17 h, filtered and evaporated to dryness. The resulting oil was dissolved in acetone (230 cm^3), potassium carbonate (31.0 g, 0.225 mol) was added at 0 °C, followed by dropwise addition of a solution of chloroacetyl chloride (9.78 g, 86.6 mmol) in diethyl ether (46 cm^3). The mixture was stirred at ambient temperature for 17 h, filtered and evaporated to dryness. Column chromatography (light petroleum:EtOAc; 4:1) gave *N*-allyl-2-chloro-*N*-(4-methoxybenzyl)acetamide **45** as a pale yellow oil (6.92 g, 27.3 mmol, 57 %); (Found: 253.0871, $C_{13}H_{16}ClNO_2$ requires: 253.0870); ν_{max} /cm^{-1} 2935, 2836, 1735, 1655, 1612, 1513,1459 and 739; mixture of conformers: δ_H 3.79 and 3.81 (2 H, 2 × s, CH_2Cl), 3.87 and 3.99 (2 H, 2 × d, *J* 5.8, $NCH_2CH{=}CH_2$), 4.10 (3 H, s, OMe), 4.52 and 4.54 (2 H, 2 × s, NCH_2Ar), 5.10-5.29 (2 H, m, $CH{=}CH_2$), 5.69-5.84 (1 H, m, $CH{=}CH_2$), 6.85 and 6.89 (2 H, 2 × d, *J* 8.7, Ar 3,5-H) and 7.11 and 7.18 (2 H, 2 × d, *J* 8.8, Ar 2,6-H); δ_C 41.73 (CH_2Br), 48.51 ($NCH_2CH{=}CH_2$), 49.52 and 50.40 (NCH_2Ar),

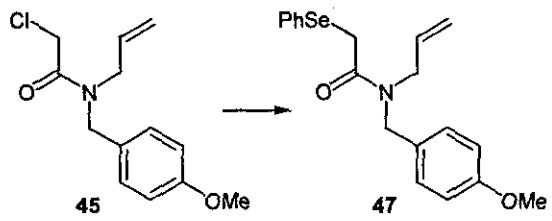
55.70 (OMe), 114.44 and 114.81 (Ar 3,5-C), 117.80 and 118.33 ($CH=CH_2$), 128.16 (Ar 1-C), 129.11 and 129.99 (Ar 2,6-C), 132.46 and 132.82 ($CH=CH_2$), 159.52 and 159.71 (Ar 4-C) and 167.07 and 167.25 (C=O); *m/z* 253 (10 %), 212 (75), 176 (20), 161 (18), 136 (40), 121 (100), 115 (20) and 91 (20).

_N_-Allyl-2-bromo-_N_-(4-methoxybenzyl)acetamide 46



Sodium bromide (0.94 g, 9.2 mmol) was added to a solution of *N*-allyl-2-chloro-*N*-(4-methoxybenzyl)acetamide **45** (0.66 g, 2.6 mmol) in freshly distilled acetone (9 cm^3) and the mixture refluxed overnight. After cooling to room temperature, acetone was added and the mixture filtered. Addition of diethyl ether, filtration and evaporation of the mixture to dryness gave *N*-allyl-2-bromo-*N*-(4-methoxybenzyl)acetamide **46** (0.57 g, 1.9 mmol, 74 %) as a pale yellow oil which did not require further purification; (Found: M^{+1}, 298.0437, $C_{13}H_{17}BrNO_2^+$ requires: 298.0443); ν_{max} /cm^{-1} 2940, 2836, 1651, 1612, 1513, 1455 and 738; mixture of conformers: δ_H 3.78 and 3.81 (3 H, 2 × s, OMe), 3.87 (2 H, s, CH_2Br), 3.88 and 3.98 (2 H, 2 × d, *J* 5.8, $NCH_2CH=CH_2$), 4.53 (2 H, s, NCH_2Ar), 5.18 (2 H, m, $CH=CH_2$), 5.76 (1 H, m, $CH=CH_2$), 6.86 (2 H, m, Ar 3,5-H) and 7.11 and 7.17 (2 H, 2 × d, *J* 8.6, Ar 2,6-H); δ_C 26.4 (CH_2Br), 48.1 ($NCH_2CH=CH_2$), 49.6 and 50.6 (NCH_2Ar), 55.3 and 55.4 (OMe), 114.1 and 114.4 (Ar 3,5-C), 117.4 and 117.8 ($CH=CH_2$), 128.8 (Ar 1-C), 129.5 and 129.6 (Ar 2,6-C), 132.4 and 132.5 ($CH=CH_2$), 159.1 and 159.3 (Ar 4-C) and 167.0 and 167.2 (C=O); *m/z* 255 (7 %), 253 (10), 214 (20), 212 (60), 136 (65), 121 (100), 91 (20) and 77 (50).

_N_-Allyl -_N_-(4-methoxybenzyl)-2-phenylselanyl-acetamide 47



Sodium borohydride (0.08 g, 2.2 mmol) was at 0 °C added to a solution of diphenyl diselenide (0.31 g, 1.0 mmol) in absolute ethanol (180 cm^3) and stirred at room temperature for 10 min before a solution of *N*-allyl-2-chloro-*N*-(4-methoxybenzyl)acetamide **45** (0.5 g, 2.0 mmol) in absolute ethanol (31 cm^3) was added dropwise. The mixture was stirred overnight and evaporated to dryness. The resulting oil was added to an aqueous solution of hydrochloric acid (2M) and extracted into DCM. The combined organic layer was washed with a saturated aqueous solution of $NaHCO_3$ in water and with a saturated aqueous solution of sodium chloride, dried ($MgSO_4$) and evaporated to dryness to give *N*-allyl-2-phenylselanyl-*N*-(4-methoxybenzyl)acetamide **47** (0.63 g, 1.7 mmol, 85 %) as a yellow oil which did not require further purification; (Found: M^+, 375.0748, $C_{19}H_{21}BrNO_2Se$ requires: 375.0738); ν_{max} (DCM)/cm^{-1} 3054, 3001, 2954, 2930, 2834, 1650, 1636, 1621, 1512, 1458, 1440, 1414. 1247, 1175 and 739; mixture of conformers: δ_H 3.71 (2 H, s, CH_2SePh), 3.79 (3 H, s, OMe), 3.97 and 3.77 (2 H, 2 × d, *J* 5.8, $NCH_2CH{=}CH_2$), 4.51 and 4.40 (2 H, 2 × s, NCH_2Ar), 5.71 (1 H, m, $CH{=}CH_2$), 5.15 (2 H, m, $CH{=}CH_2$), 6.85 (2 H, m, Ar 3,5-H), 7.15 and 7.06 (2 H, 2 × d, *J* 8.6, Ar 2,6-H), 7.26 (3 H, m, Ph 3,4,5-H) and 7.59 (2H, m, Ph 2,6-H); δ_C 28.3 (CH_2SePh), 48.0 ($NCH_2CH{=}CH_2$), 50.4 and 49.6 (NCH_2Ar), 55.3 and 55.2 (OMe), 114.3 and 114.0 (Ar 3,5-C), 117.6 and 117.0 ($CH{=}CH_2$), 127.4 and 127.7 (Ph 2,6-C), 127.8 (Ph 4-C), 128.9 (Ar 1-C), 129.3 and 129.2 (Ph 3,5-C), 129.6 and 129.5 (Ar 2,6-C), 132.64 (Ph 1-C), 133.7 and 133.6 ($CH{=}CH_2$), 159.2 and 159.0 (Ar 4-C) and 169.9 and 169.7 (C=O); *m/z* 375 (M^+, 5 %), 314 (5), 218 (100), 176 (25), 157 (30), 136 (80), 121 (100), 105 (15), 91 (100), 77 (96), 65 (32), 55 (100) and 41 (43).

3.4.2 Radical cyclisation of amide precursors

General cyclisation procedure:

The radical mediator was added dropwise to a mixture of the radical precursor in anhydrous cyclohexane (~ 0.014 M) at room temperature. The mixture was heated to reflux and AMBN was added, followed by refluxing for the time indicated under each reaction. If the reaction time was more than 3 h, another small amount of AMBN was added after this period of time. Cooling to room temperature and evaporation of the mixture to dryness gave in most cases oils which were purified by column chromatography.

Radical cyclisation of *N*-allyl-2-chloro-*N*-(4-methoxybenzyl)acetamide 45

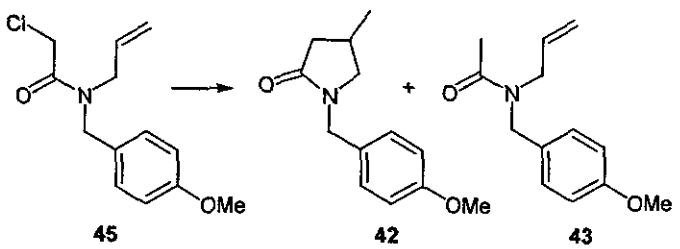


Table 30, entry 1:

Following the general cyclisation procedure, *N*-allyl-2-chloro-*N*-(4-methoxybenzyl)-acetamide **45** (0.16 g, 0.6 mmol) was reacted with TBTH (0.26 g, 0.9 mmol) for 1 h. Column chromatography (light petroleum:EtOAc; 1:1) gave 1-(4-methoxybenzyl)-4-methylpyrrolidin-2-one **42** (65.1 mg, 0.3 mmol, 47 %) along with *N*-allyl-*N*-(methoxy-benzyl)acetamide **43** (36.4 mg, 0.2 mmol, 26 %). Both products were isolated as oils.[13] **42**: δ_H 1.06 (3 H, d, *J* 7.0, Me), 2.06 (1 H, dd, *J* 16.2 and 7.0, 3-H), 2.28-2.48 (1 H, m, 4-H), 2.60 (1 H, dd, *J* 16.2 and 8.3, 3-H), 2.80 (1 H, dd, *J* 9.6 and 5.8, 5-H), 3.34 (1 H, dd, *J* 9.6 and 7.9, 5-H), 3.79 (3 H, s, OMe), 4.37 (2 H, s, NCH_2Ph), 6.85 (2 H, d, *J* 8.6, Ar 3,5-H), and 7.16 (2 H, d, *J* 8.6, Ar 2,6-H); δ_C 20.10 (Me), 26.60 (4-C), 39.80 (3-C), 46.15 (5-C), 54.08 (NCH_2Ph), 55.57 (OMe), 114.32 (Ar 3,5-C), 129.21 (Ar 1-C), 129.76 (Ar 2,6-C), 159.12 (Ar 4-C) and 175.29 (2-C); *m/z* 219 (M^+, 100 %), 176 (35), 146 (32), 121 (91), 91 (28), 78 (47), 77 (44), 55 (32), 42 (82) and 41 (93). **43**, mixture of rotamers: δ_H 2.13 and 2.16 (3 H, 2 × s, C(O)Me), 3.79 (3 H, s, OMe), 3.80 and 3.98 (2 H, 2 × d, *J* 6.0, NCH_2CHMe), 4.44 and 4.52 (2 H, 2 × s, NCH_2Ar), 5.06-5.24 (2 H, m, CH=CH_2), 5.65-5.85 (1 H, m, C*H*=CH_2), 6.84 and 6.89 (2 H, 2 × d, *J* 8.7, Ar 3,5-

H), and.7.10 and 7.18 (2 H, 2 × d, *J* 8.7, Ar 2,6-H); δ_C 21.84 and 22.05 (C(O)Me), 47.91 (NCH_2CHMe), 50.05 and 50.78 (NCH_2Ar), 55.65 (OMe), 114.68 (Ar 3,5-C), 117.14 and 117.81 ($CH=CH_2$), 128.04 (Ar 1-C), 130.02 (Ar 2,6-C), 132.91 and 133.43 ($CH=CH_2$), 159.34 (Ar 4-C) and 171.26 (*C*=O); *m/z* 219 (M^+, 18 %), 178 (32), 136 (76), 121 (39), 91 (13), 78 (21), 77 (19), 55 (32) and 43 (100).

Table 30, entry 2:

Following the general cyclisation procedure, *N*-allyl-2-chloro-*N*-(4-methoxybenzyl)-acetamide **45** (0.15 g, 0.6 mmol) was reacted with TBGH (0.22 g, 0.9 mmol) for 4 h. Column chromatography (light petroleum:EtOAc; 4:1→1:1) gave 1-(4-methoxybenzyl)-4-methylpyrrolidin-2-one **42** (43.8 mg, 0.2 mmol, 34 %) along with *N*-allyl-*N*-(methoxy-benzyl)acetamide **43** (17.0 mg, 0.08 mmol, 13 %) and unreacted starting material **45** (37.3 mg, 0.15 mmol, 25 %).

Table 30, entry 3:

As above, but with increased reaction time (8 h) and addition of AMBN every 2 h. The product distribution was as follows: 1-(4-Methoxybenzyl)-4-methylpyrrolidin-2-one **42** (42 %), *N*-allyl-*N*-(methoxybenzyl)acetamide **43** (17 %) and unreacted starting material **45** (23 %).

Table 30, entry 4:

As above. Further increment of reaction time (12 h) and addition of AMBN every 1 h, gave the following product distribution: 1-(4-Methoxybenzyl)-4-methylpyrrolidin-2-one **42** (48 %), *N*-allyl-*N*-(methoxybenzyl)acetamide **43** (23 %) and unreacted starting material **45** (22 %).

Radical cyclisation of *N*-allyl-2-bromo-*N*-(4-methoxybenzyl)acetamide 46

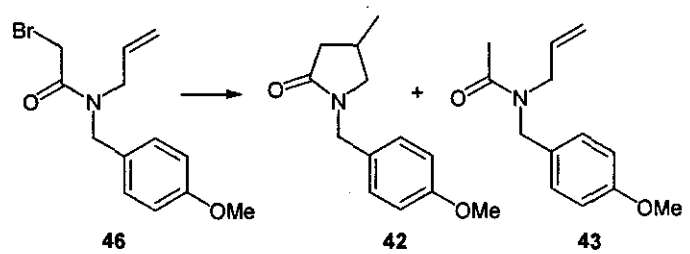


Table 31, entry 1:

Following the general cyclisation procedure *N*-allyl-2-bromo-*N*-(4-methoxybenzyl)-acetamide **46** (0.21 g, 0.7 mmol) was reacted with TBTH (0.30g, 1.0 mmol) for 30 min. Column chromatography (light petroleum:EtOAc; 1:1) gave 1-(4-methoxybenzyl)-4-methylpyrrolidin-2-one **42** (59.1 mg, 0.3 mmol, 39 %) along with *N*-allyl-*N*-(methoxybenzyl)acetamide **43** (50.0 mg, 0.2 mmol, 33 %). The spectral data were as above.

Table 31, entry 2:

Following the general cyclisation procedure, *N*-allyl-2-bromo-*N*-(4-methoxybenzyl)-acetamide **46** (0.21 g, 0.7 mmol) was reacted with TBGH (0.20 g, 0.8 mmol) for 5.5 h. Column chromatography (light petroleum:EtOAc; 4:1→1:1) gave 1-(4-methoxybenzyl)-4-methylpyrrolidin-2-one **42** (96.7 mg, 0.44 mmol, 64 %) along with *N*-allyl-*N*-(methoxybenzyl)acetamide **43** (12.0 mg, 0.06 mmol, 8 %) and unreacted starting material **46** (24.0 mg, 0.08 mmol, 12 %).

Radical cyclisation of *N*-allyl-*N*-(4-methoxybenzyl)-2-phenylselanyl-acetamide 47

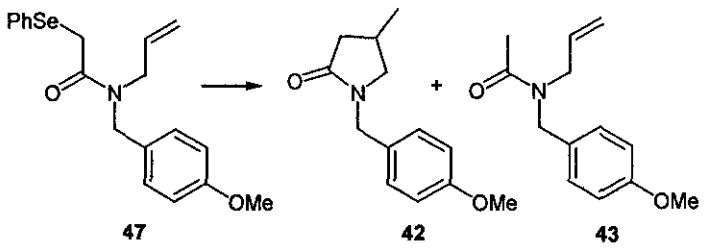


Table 31, entry 3:

Following the general cyclisation procedure, *N*-allyl-*N*-(4-methoxybenzyl)-2-phenyl-selanylacetamide **47** (0.12 g, 0.3 mmol) was reacted with TBTH (0.14 g, 0.5 mmol) for 3 h. Column chromatography (light petroleum:EtOAc; 1:1) gave 1-(4-

methoxybenzyl)-4-methylpyrrolidin-2-one **42** (19.9 mg, 0.1 mmol, 29 %) along with *N*-allyl-*N*-(4-methoxybenzyl)acetamide **43** (26.5 mg, 0.1 mmol, 38 %).

Table 31, entry 4:

Following the general cyclisation procedure, *N*-allyl-*N*-(4-methoxybenzyl)-2-phenylselanylacetamide **47** (0.11 g, 0.3 mmol) was reacted with TBGH (0.08 g, 0.3 mmol) for 3 h. Column chromatography (light petroleum:EtOAc; 4:1→1:1) gave 1-(4-methoxybenzyl)-4-methylpyrrolidin-2-one **42** (11.4 mg, 0.05 mmol, 18 %) along with *N*-allyl-*N*-(4-methoxybenzyl)acetamide **43** (5.0 mg, 0.02 mmol, 8 %) and unreacted starting material **47** (50.3 mg, 0.13 mmol, 48 %).

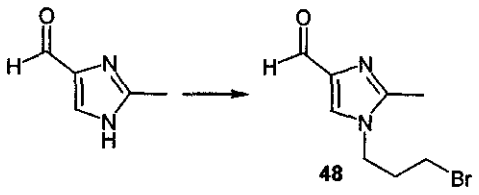
Table 31, entry 5:

Following the general cyclisation procedure, *N*-allyl-*N*-(4-methoxy-benzyl)-2-phenylselanylacetamide **47** (0.09 g, 0.2 mmol) was reacted with TBGH (0.07 g, 0.3 mmol) for 5 h. Column chromatography (light petroleum:EtOAc; 4:1→1:1) gave 1-(4-methoxybenzyl)-4-methylpyrrolidin-2-one **42** (35.2 mg, 0.2 mmol, 67 %) along with *N*-allyl-*N*-(4-methoxybenzyl)acetamide **43** (10.1 mg, 0.06 mmol, 19 %).

3.5 Experimentals for Chapter 2.4

3.5.1 Synthesis of heterocyclic precursors

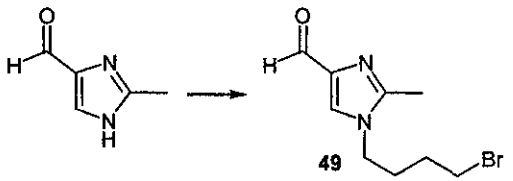
1-(3-Bromopropyl)-2-methyl-1*H*-imidazole-4-carbaldehyde 48



2-Methyl-imidazole-4-carbaldehyde (0.52 g, 4.7 mmol) was added to a mixture of sodium hydride (0.27 g, 6.8 mmol) in anhydrous THF (100 cm^3) and stirred at ambient temperature for 30 min. 1,3-Dibromopropane (2.31 ml, 22.7 mmol) was added and the resulting mixture refluxed for 2 h. After cooling to room temperature the mixture was filtered through celite and evaporated to dryness. Aqueous hydrochloric acid was added and the mixture washed with light petroleum. The aqueous layer was

neutralised by addition of $NaHCO_3$, basified to pH 14 with dilute NaOH solution and extracted into DCM. The organic layer was dried ($MgSO_4$) and evaporated to dryness to give 1-(3-bromopropyl)-2-methyl-1*H*-imidazole-4-carbaldehyde **48** as a yellow oil, which did not require further purification (0.58 g, 2.5 mmol, 53 %). (Found: M^+, 230.0050, $C_8H_{11}N_2O^{79}Br$ requires 230.0054); ν_{max} /cm^{-1} 2929, 2847 and 1681; δ_H 2.22-2.35 (2 H, m, 2-H), 2.48 (3 H, s, Me), 3.37 (2 H, t, *J* 5.8, 3-H), 4.13 (2 H, t, *J* 5.8, 1-H), 7.60 (1 H, s, Im 5-H) and 9.80 (1 H, s, CHO); δ_C 13.1 (Me), 28.8 (2-C), 32.5 (3-C), 44.3 (1-C), 125.5 (Im 5-C), 141.1 (Im 2-C), 147.3 (Im 4-C) and 185.4 (CHO); *m/z* 232 (M^+, ^{81}Br, 13 %), 231 (M^{+1}, ^{79}Br, 4), 230 (M^+, ^{79}Br, 12), 211 (4), 186 (4), 165 (10), 152 (14), 137 (21), 109 (9), 97 (14), 83 (16), 71 (21), 57 (28) and 41 (100).

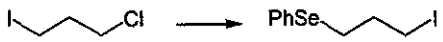
1-(4-Bromobutyl)-2-methyl-1*H*-imidazole-4-carbaldehyde 49



49

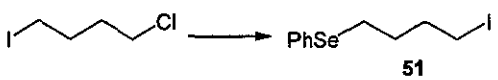
2-Methyl-imidazole-4-carbaldehyde (0.98 g, 8.9 mmol) was added to a mixture of sodium hydride (0.62 g, 15.4 mmol) in anhydrous THF (100 cm^3) and stirred at ambient temperature for 30 min. This mixture was added dropwise to a solution of 1,4-dibromobutane (5.31 ml, 44.6 mmol) in anhydrous THF (25 cm^3) and the resulting mixture refluxed for 2 h. After cooling to room temperature, the mixture was filtered through celite and evaporated to dryness. Aqueous hydrochloric acid was added and washed with light petroleum. The aqueous layer was neutralised by addition of $NaHCO_3$, basified to pH 14 and extracted into DCM. The organic layer was dried ($MgSO_4$) and evaporated to dryness to give 1-(4-bromobutyl)-2-methyl-1*H*-imidazole-4-carbaldehyde **49** as a yellow oil, which did not require further purification (1.59 g, 6.4 mmol, 72 %). (Found: 244.0211, $C_9H_{13}N_2O^{79}Br$ requires 244.0211); ν_{max} /cm^{-1} 2955, 2816, 2755, 1681 and 635; δ_H 1.75-1.97 (4 H, m, 2,3-H), 2.37 (3 H, s, Me), 3.37 (2 H, t, *J* 5.8, 4-H), 3.91 (2 H, t, *J* 5.8, 1-H), 7.51 (1 H, s, Im 5-H) and 9.70 (1 H, s, CHO); δ_C 13.16 (Me), 28.95 (3-C), 29.28 (2-C), 32.27 (4-C), 45.99 (1-C), 125.65 (Im 5-C), 140.50 (Im 2-C), 146.83 (Im 4-C) and 185.49 (CHO); *m/z* 246 (M^+, ^{81}Br, 20 %), 244 (M^+, ^{79}Br, 20 %), 165 (100), 152 (94), 137 (76), 123 (60), 109 (34), 95 (17), 83 (29), 68 (22), 55 (43) and 41 (30).

1-Iodo-3-(phenylselanyl)propane



Sodium borohydride (1.37 g, 36.2 mmol) was added to a mixture of diphenyldiselanide (5.00 g, 16.0 mmol) in absolute ethanol (500 cm^3) at 0 °C. After stirring at ambient temperature for 0.5 h, 1-bromo-3-chloropropane (6.57 g, 32.6 mmol) was added dropwise and the resulting mixture stirred for 17 h. The solvent was evaporated and the residue dissolved in aqueous hydrochloric acid (2 M) and extracted into diethyl ether. The organic layer was washed with saturated aqueous solutions of $NaHCO_3$ and brine, dried ($MgSO_4$) and evaporated to dryness to give 1-chloro-3-(phenylselanyl)propane as a colourless oil (7.57 g, 32.5 mmol, 100 %). TLC and ^1H spectroscopy indicated a pure product. 1-Chloro-3-(phenylselanyl)propane (7.57 g, 32.5 mmol) was dissolved in acetone (500 cm^3), sodium iodide (45 g, 0.3 mol) was added and the mixture was refluxed for 17 h. After cooling to room temperature, the solids were removed by filtration and the volatiles removed by evaporation. The residue was triturated with diethyl ether, filtered and evaporated to dryness to give 1-iodo-3-(phenylselanyl)propane as a yellow oil (7.91 g, 24.3 mmol, 74 %). (Found: M^+, 325.9067, $C_9H_{11}{}^{80}SeI$ requires 325.9071); ν_{max} /cm^{-1} 3051, 2977, 2927, 1577, 1477, 1438, 1265, 1203, 736, 705 and 671; δ_H 2.05-2.20 (2 H, m, 3-H), 2.93 (2 H, t, *J* 6.9, 1-H), 3.28 (2 H, t, *J* 6.7, 3-H), 7.24-7.30 (3 H, m, Ar 3,4,5-H) and 7.50-7.53 (2 H, m, Ar 2,6-H); δ_C (62.5 MHz) 6.51 (2-C), 28.48 (3-C), 33.59 (1-C), 127.47 (Ar 4-C), 129.49 (Ar 3,5-C), 129.60 (Ar 1-C) and 133.26 (Ar 2,6-C); *m/z* 329 (M^{+1}, ^{82}Se, 1 %), 328 (M^+, ^{82}Se, 10), 327 (M^{+1}, ^{80}Se, 7), 326 (M^+, ^{80}Se, 57), 325 (28), 324 (27), 323 (10), 321 (11), 284 (21), 199 (94), 171 (32), 157 (100), 117 (9), 91 (63), 77 (71), 65 (17), 51 (42) and 41 (56).

1-Iodo-4-(phenylselanyl)butane 51

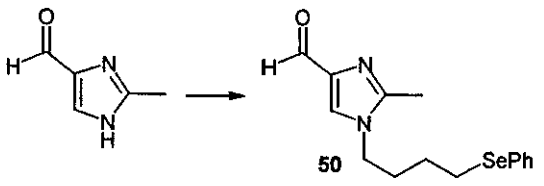


51

Sodium borohydride (1.37 g, 36.2 mmol) was added to a mixture of diphenyl diselanide (5.02 g, 16.0 mmol) in absolute ethanol (500 cm^3) at 0 °C. After stirring at ambient temperature for 0.5 h, 1-bromo-4-chlorobutane (5.50 g, 32.1 mmol) was added dropwise and the resulting mixture stirred for 17 h. The solvent was evaporated

to dryness and the residue dissolved in aqueous hydrochloric acid (2 M) and extracted into diethyl ether. The organic layer was washed with saturated aqueous solutions of $NaHCO_3$ and brine, dried ($MgSO_4$) and evaporated to dryness to give 1-chloro-4-(phenylselanyl)butane as a colourless oil (7.95 g, 32.1 mmol, 100 %). TLC and ^1H spectroscopy indicated a pure product. 1-Chloro-4-(phenylselanyl)butane (2.00 g, 8.1 mmol) was dissolved in acetone (134 cm^3), sodium iodide (17 g, 0.1 mol) was added and the mixture was refluxed for 17 h. After cooling to room temperature, the solids were removed by filtration and the volatiles removed by evaporation. The residue was triturated with diethyl ether, filtered and evaporated to dryness to give 1-iodo-4-(phenylselanyl)butane **51** as a yellow oil (1.73 g, 5.1 mmol, 63 %). (Found: M+, 339.9228, $C_{10}H_{13}{}^{80}SeI$ requires 339.9228); ν_{max} /cm^{-1} 2360, 908 and 765; δ_H (400 MHz) 1.70-1.78 (2 H, m, 3-H), 1.84-1.91 (2 H, m, 2-H), 2.84 (2 H, t, *J* 7.2, 4-H), 3.10 (2 H, t, *J* 7.0, 1-H), 7.15-7.22 (3 H, m, Ar 3,4,5-H) and 7.38-7.44 (2 H, m, Ar 2,6-H); δ_C 26.52 (4-C), 30.76 (3-C), 33.19 (2-C), 33.78 (1-C), 126.92 (Ar 4-C), 129.08 (Ar 3,5-C), 129.95 (Ar 1-C) and 132.68 (Ar 2,6-C); *m/z* 213 (M^+, 100 %), 184 (15), 171 (31), 157 (13), 91 (53), 77 (69) and 55 (93).

1-(4-Phenylselanylbutyl)-2-methyl-1*H*-imidazole-4-carbaldehyde 50

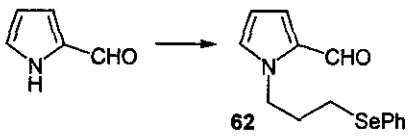


50

2-Methyl-imidazole-4-carbaldehyde (1.00 g, 9.1 mmol) was added to a mixture of sodium hydride (0.55 g, 13.6 mmol) in anhydrous THF (100 cm^3) and stirred at ambient temperature for 30 min. 1-Iodo-4-(phenylselanyl)butane **51** (3.71 g, 10.9 mmol) was added and the resulting mixture refluxed for 5 h. After cooling to room temperature the mixture was evaporated to dryness to give a yellow oil. Column chromatography (DCM:MeOH; 99:1→ DCM:MeOH; 90:1) gave 1-(4-phenylselanylbutyl)-2-methyl-1*H*-imidazole-4-carbaldehyde **50** as a pale yellow oil (0.79 g, 2.5 mmol, 27 %). (Found: 322.0587, $C_{15}H_{18}N_2OSe$ requires 322.0584); ν_{max} /cm^{-1} 2936, 2251, 1680, 1578, 1547, 1477, 1437, 1418, 1374, 1162, 1022, 999, 732, 691 and 649; δ_H 1.65-1.98 (4 H, m, 2,3-H), 2.40 (3 H. s, Me), 2.90 (2 H, t, *J* 6.9, 4-H), 3.87 (2 H, t, *J* 6.9, 1-H), 7.24-7.27 (3 H, m, Ph 2,4,6-H), 7.45-7.49 (3 H, m, Im 5-H

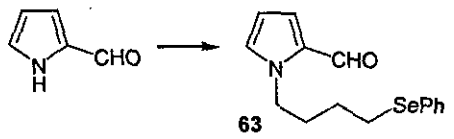
and Ph 3,5-H) and 9.77 (1 H, s, CHO); δ_C 13.1 (Me), 26.7 (4-C), 27.0 (2-C), 30.1 (3-C), 46.2 (1-C), 125.6 (Im 5-C), 127.3 (Ph 1-C), 129.2 (Ph 3,5-C), 133.0 (Ph 2,6-C), 140.4 (Im 2-C), 146.8 (Im 4-C) and 185.5 (CHO); *m/z* 326 (M^{+4}, 3), 325 (M^{+3}, 4), 324 (M^{+2}, 20), 323 (M^{+1}, 9), 322 (M^+, 55), 248 (4), 213 (16), 183 (3), 165 (48), 157 (23), 137 (100), 113 (12), 111 (8), 95 (17), 77 (16), 68 (7), 55 (21) and 41 (7).

1-(3-Phenylselanylpropyl)-1*H*-pyrrole-2-carbaldehyde 62



Pyrrole-2-carbaldehyde (1.00 g, 10.5 mmol) was added to a suspension of sodium hydride (0.50 g, 12.5 mmol) in anhydrous THF (90 cm^3) and the mixture stirred at ambient temperature for 0.5 h. 1-Iodo-3-(phenylselanyl)propane (6.70 g, 20.6 mmol) in anhydrous THF (10 cm^3) was added dropwise and the mixture heated at reflux for 17 h. After cooling to room temperature and evaporation to dryness, the resulting brown oil was purified by column chromatography (light petroleum:DCM; 15:85) to give 1-(3-phenylselanylpropyl)-1*H*-pyrrole-2-carbaldehyde **62** as a pale yellow oil (2.30 g, 7.9 mmol, 75 %). (Found: M^+, 293.0324, $C_{14}H_{15}NO^{80}Se$ requires 293.0319); ν_{max} /cm^{-1} 2944, 2804, 1666, 1652, 1576, 1526, 761 and 738; δ_H 2.10-2.21 (2 H, m, 2-H), 2.83 (2 H, t, *J* 7.2, 3-H), 4.43 (2 H, t, *J* 6.7, 1-H), 6.22 (1 H, dd, *J* 3.9, 2.8, pyrrole 4-H), 6.93-6.96 (2 H, m, pyrrole 3,5-H), 7.24-7.32 (3 H, m, Ph 3,4,5-H), 7.45-7.50 (2 H, m, Ph 2,6-H) and 9.53 (1 H, s, CHO); δ_C 24.46 (2-C), 29.89 (3-C), 48.80 (1-C), 110.18 (pyrrole 4-C), 125.47 (pyrrole 3-C), 127.67 (Ph 4-C), 129.58 (Ph 2,6-C), 130.07 (Ph 1-C), 131.65 (pyrrole 2-C), 132.32 (pyrrole 5-C), 133.09 (Ph 3,5-C) and 179.63 (CHO), *m/z* 293 (M^+, 31), 263 (15), 236 (3), 212 (10), 180 (21), 165 (25), 136 (100), 108 (90), 91 (27), 80 (70), 67 (18), 57 (22), 53 (42) and 41 (43).

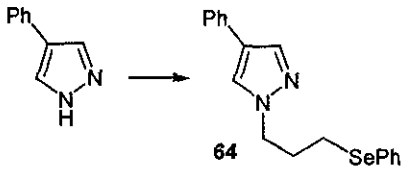
1-(4-Phenylselanylbutyl)-1*H*-pyrrole-2-carbaldehyde 63



63

Pyrrole-2-carbaldehyde (0.5 g, 5.3 mmol) was added to a suspension of sodium hydride (0.25 g, 6.3 mmol) in anhydrous THF (40 cm^3) and the mixture stirred at ambient temperature for 0.5 h. 1-Iodo-4-(phenylselanyl)butane (4.07 g, 12.0 mmol) in anhydrous THF (10 cm^3) was added dropwise and the mixture heated at 50 °C for 17 h. After cooling to room temperature and evaporation to dryness, the resulting brown oil was purified by column chromatography (light petroleum:DCM; 15:85) to give 1-(4-phenylselanylbutyl)-1*H*-pyrrole-2-carbaldehyde **63** as a pale yellow oil (1.13 g, 3.7 mmol, 70 %). (Found: M^+, 307.0476, $C_{15}H_{17}NO^{80}Se$ requires 307.0475); ν_{max} /cm^{-1} 2935, 1662, 1578, 1525, 765 and 737; δ_H 1.64-1.73 (2 H, m, 3-H), 1.82-1.94 (2 H, m, 2-H), 2.88 (2 H, t, *J* 7.2, 4-H), 4.29 (2 H, t, *J* 7.0, 1-H), 6.20 (1 H, dd, *J* 4.2, 2.5, pyrrole 4-H), 6.94 (2 H, m, pyrrole 3,5-H), 7.23-7.27 (3 H, m, Ph 3,4,5-H), 7.44-7.48 (2 H, m, Ph 2,6-H) and 9.51 (1 H, s, CHO); δ_C 27.28 (3-C), 27.59 (2-C), 31.27 (4-C), 48.42 (1-C), 109.76 (pyrrole 4-C), 124.94 (pyrrole 3-C), 126.87 (Ph 2,6-C), 129.07 (Ph 4-C), 131.22 (Ph 1-C), 132.68 (pyrrole 5-C), 132.70 (pyrrole 2-C), 132.80 (Ph 3,5-C) and 179.36 (CHO), *m/z* 226 (16 %), 157 (22), 151 (23), 149 (45), 132 (17), 122 (65), 121 (50), 108 (90), 94 (34) and 93 (21).

4-Phenyl-1-(3-phenylselanylpropyl)-1*H*-pyrazole 64[66]

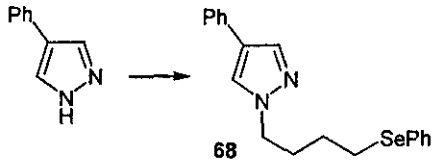


64

4-Phenyl-pyrazole (0.15 g, 1.0 mmol) was added to a stirred suspension of crushed potassium hydroxide (0.17 g, 3.0 mmol) in DMF (15 cm^3) and stirring was continued for 30 min. 1-Iodo-3-(phenylselenyl)propane (0.65 g, 2.0 mmol) was added slowly to the stirred suspension and the mixture was stirred overnight. The crude reaction mixture was partitioned between water and EtOAc and the aqueous layer separated and extracted with EtOAc. The combined organic extracts were washed twice with

water and twice with brine, dried and evaporated to dryness. The crude off-white oily solid was purified by column chromatography (light petroleum:EtOAc; 5:1) to yield 4-phenyl-1-(3-phenylselanylpropyl)-1*H*-pyrazole **64** (0.34 g, 100%) as a white solid; mp 48-50 °C; (Found: $(M+H)^+$, 343.0717. $C_{18}H_{19}N_2Se$ requires 343.0713); ν_{max} (KBr) /cm^{-1} 1607, 760 and 693; δ_H 2.23-2.37 (2 H, m, 2-H), 2.91 (2 H, t, *J* 7.1, 3-H), 4.31 (2 H, t, *J* 6.5, 1-H), 7.24-7.32 (4 H, m, Ph), 7.37-7.52 (6 H, m, Ph), 7.53 (1 H, s, pyrazole 3-H) and 7.77 (1 H, s, pyrazole 5-H); δ_C 24.36 (2-C), 30.42 (3-C), 51.31 (1-C), 122.88 (pyrazole 4-C), 125.48 (Ph 2,6-C), 125.72 (pyrazole 3-C), 126.36 (Ph 4-C), 127.14 (Se-Ph 4-C), 128.83 (phenyl 3,5-C), 129.19 (Se-Ph 3,5-C), 129.54 (Se-Ph 1-C), 132.54 (Ph 1-C), 132.85 (Se-Ph 2,6-C) and 136.95 (pyrazole 5-C); *m/z* 343 ($(M+H)^+$, 29%) and 187 (100).

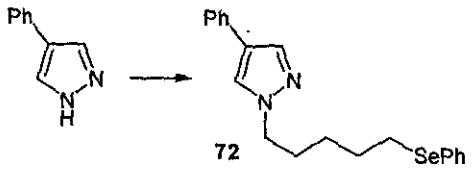
4-Phenyl-1-(4-phenylselanylbutyl)-1*H*-pyrazole 68[66]



68

4-Phenyl-pyrazole (37 mg, 0.26 mmol) was added to a stirred suspension of crushed potassium hydroxide (44 mg, 0.78 mmol) in DMF (5 cm^3) and stirring was continued for 30 min. 1-Iodo-4-(phenylselanyl)butane (175 mg, 0.52 mmol) was added slowly to the stirred suspension and the mixture was stirred overnight. The crude reaction mixture was partitioned between water and EtOAc and the aqueous layer was separated and extracted with EtOAc. The combined organic extracts were washed twice with water and twice with brine, dried and evaporated to dryness. The crude off-white oily solid was purified by column chromatography (light petroleum: EtOAc; 5:1) to yield 4-phenyl-1-(3-phenylselanylpropyl)-1*H*-pyrazole **68** (0.34 g, 100 %) as a white solid; mp 44-45 °C; ν_{max} (KBr)/cm^{-1} 1607, 760 and 692; δ_H (400 MHz) 1.69-1.76 (2 H, m, 3-H), 1.99-2.07 (2 H, m, 2-H), 2.91 (2 H, t, *J* 7.2, 4-H), 4.14 (2 H, t, *J* 6.9, 1-H), 7.21-7.23 (4 H, m, Ph), 7.30-7.37 (2 H, m, Ph), 7.45-7.47 (4 H, m, Ph), 7.57 (1 H, s, pyrazole 3-H) and 7.75 (1 H, s, pyrazole 5-H); δ_C 27.10-27.19 (2,3-C), 30.32 (4-C), 51.76 (1-C), 122.97 (pyrazole 4-C), 125.51 (Ph 2,6-C), 125.88 (pyrazole 3-C), 126.34 (Ph 4-C), 126.93 (Se-Ph 4-C), 128.84 (Ph 3,5-C), 129.07 (Se-Ph 3,5-C), 129.98 (Se-Ph 1-C), 132.66 (Ph 1-C), 132.77 (Se-Ph 2,6-C) and 136.70 (pyrazole 5-C).

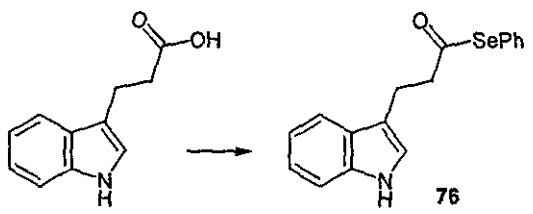
4-Phenyl-1-(5-phenylselanylpentyl)-1*H*-pyrazole 72[66]



72

4-Phenyl-pyrazole (0.30 g, 2.1 mmol) was added to a stirred suspension of crushed potassium hydroxide (0.35 g, 6.3 mmol) in DMF (25 cm^3) and stirring was continued for 30 min. 1-Iodo-5-(phenylselanyl)pentane (0.88 g, 2.5 mmol) was added slowly to the stirred suspension and the mixture stirred overnight. The crude reaction mixture was partitioned between water and EtOAc and the aqueous layer separated and extracted with EtOAc. The combined organic extracts were washed twice with water and twice with brine, dried and evaporated to dryness. The crude off-white oily solid was purified by column chromatography (light petroleum: EtOAc; 5:1) to yield 4-phenyl-1-(5-phenylselenylpentyl)-1*H*-pyrazole **72** (0.76 g, 98%) as a white solid; mp 36-37 °C; (Found: M^+, 370.0943. $C_{20}H_{22}N_2Se$ requires 370.0948); ν_{max} (KBr)/cm^{-1} 1607, 760, 736, 693 and 666; δ_H (400 MHz) 1.16-1.26 (2 H, m, 3-H), 1.66-1.75 (2 H, m, 4-H), 1.83-1.90 (2 H, m, 2-H), 2.86 (2 H, t, *J* 7.6, 5-H), 4.07 (2 H, t, *J* 7.0, 1-H), 7.18-7.25 (4 H, m, Ph), 7.31-7.36 (2 H, m, Ph), 7.42-7.48 (4 H, m, Ph), 7.55 (1 H, s, pyrazole 3-H) and 7.76 (1 H, s, pyrazole 5-H); δ_C 26.75 (3-C), 27.53 (4-C), 29.65 (2-C), 29.84 (5-C), 52.16 (1-C), 122.70 (pyrazole 4-C), 125.48 (Ph 2,6-C), 125.96 (pyrazole 3-C), 126.31 (Ph 4-C), 126.78 (Se-Ph 4-C), 128.86 (Ph 3,5-C), 129.05 (Se-Ph 3,5-C), 130.15 (Se-Ph 1-C), 132.56 (Ph 1-C), 132.70 (Se-Ph 2,6-C) and 136.62 (pyrazole 5-C); *m/z* 370 (M^+, 6%), 213 (100), 157 (100), 157 (100), 145 (29) and 103 (23).

3-(1*H*-Indol-3-yl)propionic acid Se-phenyl ester 76[67]



76

Tri-*n*-butylphosphine (4.79 cm^3, 19.22 mmol) was added dropwise to a solution of 3-(1*H*-indol-3-yl)-propionic acid (2.42 g, 12.81 mmol) and diphenyl diselanide (6.00 g,

19.22 mmol) in anhydrous DCM (30 cm^3) at 0 °C, and the resulting mixture stirred at ambient temperature for 4 h. The reaction was added to water, extracted into DCM, dried ($MgSO_4$), filtered though a pad of celite and evaporated to dryness. Column chromatography (light petroleum:Et_2O; 1:0 → 3:1) gave 3-(1*H*-indol-3-yl)-selenopropionic acid Se-phenyl ester **76** as a yellow oil (4.13 g, 12.58 mmol, 98 %). (Found: 329.0319, $C_{17}H_{15}SeNO$ requires 329.0319); ν_{max} /cm^{-1} 3419, 3055, 2908, 2580, 1882, 1717, 1619, 1577, 1476, 1459, 1438, 1339, 1020, 738, and 689; δ_H (400 MHz) 3.04-3.08 (2 H, m, 2-H), 3.11-3.15 (2 H, m, 3-H), 6.88 (1 H, d, *J* 2.4, Ar 2-H), 7.11 (1 H, m, Ar 6-H), 7.17 (1 H, m, Ar 7-H), 7.27 (1 H, d, *J* 7.2, Ar 5-H), 7.33-7.35 (3 H, m, Ph 2,4,6-H), 7.46-7.49 (2 H, Ph 3,5-C), 7.54 (1 H, d, *J* 8.0, Ar 8-H) and 7.89 (1 H, bs, NH); δ_C 21.44 (2-C), 48.33 (3-C), 111.75 (Ar 8-C), 114.35 (Ar 3-C), 119.04 (Ar 7-C), 119.86 (Ar 5-C), 122.27 (Ar 6-C), 122.56 (Ar 2-C), 126.92 (Ar 4-C), 127.46 (Ph 1-C), 129.36 (Ph 4-C), 129.84 (Ph 3,5-C), 136.28 (Ph 2,6-C), 136.71 (Ar 9-C) and 200.87 (C=O); *m/z* 329 (M^+, 36 %), 314 (10), 172 (100), 157 (43), 144 (100), 130 (100), 115 (61), 103 (26), 89 (24), 77 (75), 63 (14) and 51 (29).

3.5.2 Radical cyclisation of heterocyclic precursors

3.5.2.1 Radical cyclisation of imidazole precursors

General cyclisation procedure:

The radical mediator was added dropwise to a mixture of the radical precursor in anhydrous solvent at room temperature. The mixture was heated to reflux and initiator was added, followed by refluxing for the time indicated under each reaction. If the reaction time was longer than 3 h, another small amount of initiator was added after this period of time. Cooling to room temperature and evaporation of the mixture to dryness gave oils which were added aqueous hydrochloric acid and washed with light petroleum. The aqueous layer was neutralised by addition of $NaHCO_3$ and basified to pH 14 and extracted into DCM. The organic layer was dried ($MgSO_4$) and evaporated to dryness to give the products as pale yellow oils.

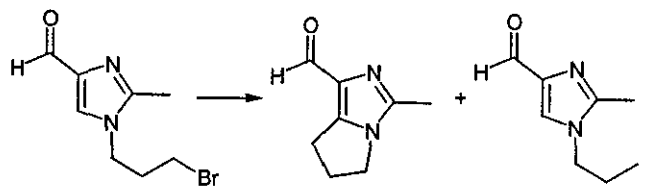
General procedure when using triethylborane as radical initiator:

The radical mediator and triethylborane (1.0 M solution in THF) were added dropwise to a solution of the radical precursor in anhydrous solvent at room temperature. The mixture was stirred at room temperature for the time indicated under each reaction, poured into water and extracted with DCM. The organic layer was dried ($MgSO_4$) and evaporated to dryness to give oils which were added aqueous hydrochloric acid and washed with light petroleum. The aqueous layer was neutralised by addition of $NaHCO_3$ and basified to pH 14 and extracted into DCM. The organic layer was dried ($MgSO_4$) and evaporated to dryness to give the products as pale yellow oils.

General procedure when using syringe-pump addition of the radical mediator:

Using syringe-pump technique, the radical mediator in anhydrous solvent was added to a refluxing mixture of the radical precursor in anhydrous solvent over the period of time indicated under each reaction. The initiator was added initially and thereafter every 40 min. After cooling to room temperature and evaporation to dryness, aqueous hydrochloric acid was added and washed with light petroleum. The aqueous layer was neutralised by addition of $NaHCO_3$ and basified to pH 14 and extracted into DCM. The organic layer was dried ($MgSO_4$) and evaporated to dryness to give the products as pale yellow oils.

Radical cyclisation of 1-(3-bromopropyl)-2-methyl-1*H*-imidazole-4-carbaldehyde 48



48 **52** **53**

Table 32, entry 1:

Following the general cyclisation procedure, 1-(3-bromopropyl)-2-methyl-1*H*-imidazole-4-carbaldehyde **48** (0.16 g, 0.7 mmol) in acetonitrile (50 cm^3) was reacted with TBTH (0.38 g, 1.3 mmol) and AMBN (excess) for 3 h. AMBN was added every hour. The yields of 3-methyl-6,7-dihydro-5*H*-pyrrolo[1,2-*c*]-imidazole-1-carbaldehyde **52** (14 %), 2-methyl-1-propyl-1*H*-imidazole-4-carbaldehyde **53** (7 %) and unreacted starting material **48** (68 %) were determined by ^{1}H-NMR spectroscopy using 1,4-

dinitrobenzene as internal standard. **52**:[87] δ_H 2.41 (3 H, s, Me), 2.69-2.77 (2 H, m, 6-H), 3.10 (2 H, t, *J* 7.5, 7-H), 3.92 (2 H, t, *J* 7.2, 5-H) and 9.76 (1 H, s, CHO); δ_C 13.49 (Me), 24.10 (6-C), 29.32 (7-C), 44.40 (5-C), 132.31 (3-C), 141.48 (1-C), 145.63 (8-C) and 186.02 (CHO); *m/z* 152 (M^{+2}, 8 %), 151 (M^{+1}, 11), 150 (M^+, 100 %), 149 (67), 135 (2), 123 (4), 122 (18), 121 (17), 109 (6), 108 (3), 95 (5), 94 (3), 92 (5) and 91 (39). **53**:[87] δ_H 0.97 (3 H, t, *J* 6.3, 3-H), 1.74-1.88 (2 H, m, 2-H), 2.43 (3 H, s, Me), 3.87 (2 H, t, *J* 7.2, 1-H), 7.55 (1 H, s, Im 5-H) and 9.79 (1 H, s, CHO); δ_C (62.5 MHz) 10.90 (3-C), 13.00 (Me), 23.62 (2-C), 48.28 (1-C), 125.66 (Im 5-C), 140.00 (Im 2-C), 146.92 (Im 4-C) and 185.45 (CHO); *m/z* 153 (M^{+1}, 10 %), 152 (M^+, 100), 151 (27), 138 (16), 137 (33), 124 (17), 123 (33), 109 (25), 95 (10) and 82 (14).

Table 32, entry 2:

Following the general cyclisation procedure, 1-(3-bromopropyl)-2-methyl-1*H*-imidazole-4-carbaldehyde **48** (0.20 g, 0.9 mmol) in acetonitrile (60 cm^3) was reacted with TBGH (0.26 g, 1.0 mmol) and AMBN (excess) for 3 h. The yields of 3-methyl-6,7-dihydro-5*H*-pyrrolo[1,2-*c*]imidazole-1-carbaldehyde **52** (10 %), 2-methyl-1-propyl-1*H*-imidazole-4-carbaldehyde **53** (7 %) and unreacted starting material **48** (42 %) were determined by ^{1}H-NMR spectroscopy using 1,4-dinitrobenzene as the internal standard.

Attempted radical cyclisation of 1-(4-phenylselanylbutyl)-2-methyl-1*H*-imidazole-4-carbaldehyde 50

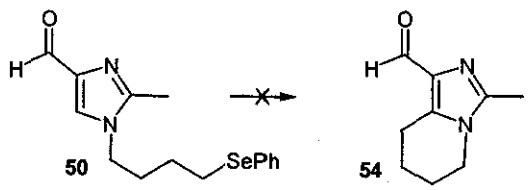


Table 33, entry 1:

Following the general procedure when using syringe-pump addition of the radical mediator, 1-(4-phenylselanylbutyl)-2-methyl-1*H*-imidazole-4-carbaldehyde **50** (0.21 g, 0.7 mmol) in acetonitrile (50 cm^3) was reacted with TBGH (0.19 g, 0.8 mmol) in toluene (50 cm^3) and AMBN (excess) for 3 h to give unreacted starting material **50** (0.17 g, 0.5 mmol, 80 %).

Table 33, entry 2:

Following the general procedure when using syringe-pump addition of the radical mediator, 1-(4-phenylselanylbutyl)-2-methyl-1*H*-imidazole-4-carbaldehyde **50** (0.16 g, 0.5 mmol) in acetonitrile (35 cm^3) was reacted with TBTH (0.22 g, 0.8 mmol) in toluene and AMBN (excess) for 3 h and to give unreacted starting material **50** (0.14 g, 0.4 mmol, 84 %).

Radical cyclisation of 1-(4-bromobutyl)-2-methyl-1*H*-imidazole-4-carbaldehyde 49

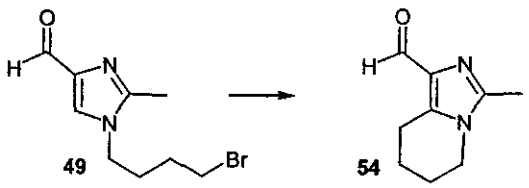


Table 34, entry 1:

Following the general procedure when using triethylborane as radical initiator, 1-(4-bromobutyl)-2-methyl-1*H*-imidazole-4-carbaldehyde **49** (94.0 mg, 0.41 mmol) in THF (5 cm^3) was reacted with tributyltin chloride (0.16 g, 0.5 mmol) and triethylborane (1 M, 0.1 mmol) for 7 h. The yields of 3-methyl-5,6,7,8-tetrahydro-imidazo[1,5-*a*]pyridine-1-carbaldehyde **54** (12 %) and unreacted starting material **49** (36 %) were determined by ^{1}H-NMR spectroscopy using 1,4-dinitrobenzene as the internal standard.[87] δ_H 1.78-1.92 (2 H, m, 7-H), 1.94-2.08 (2 H, m, 6-H), 2.37 (3 H, s, Me), 3.09 (2 H, t, *J* 6.3, 8-H), 3.85 (2 H, t, *J* 6.3, 5-H) and 9.85 (1 H, s, CHO); δ_C 13.16 (Me), 19.38 (7-C), 22.52 (6-C), 22.88 (8-C), 43.15 (5-C), 135.48 (3-C), 137.58 (1-C), 145.06 (9-C) and 186.76 (CHO); *m/z* 164 (100 %), 163 (94), 152 (21), 135 (20), 123 (13), 109 (11) and 97 (26).

Table 34, entries 2 + 4:

Following the general procedure 2, 1-(4-bromobutyl)-2-methyl-1*H*-imidazole-4-carbaldehyde **49** (0.12 g, 0.5 mmol) in cyclohexane (35 cm^3) was reacted with TBTH (0.18 g, 0.6 mmol) and AMBN (excess) for 3 h. The yields of 3-methyl-5,6,7,8-tetrahydro-imidazo[1,5-*a*]pyridine-1-carbaldehyde **54** (28 %) and unreacted starting material **49** (58 %) were determined by ^{1}H-NMR spectroscopy using 1,4-dinitrobenzene as the internal standard.

In an identical reaction but with CH_3CN as solvent the product distribution was as follows: 3-Methyl-5,6,7,8-tetrahydro-imidazo[1,5-*a*]pyridine-1-carbaldehyde **54** (62 %) and unreacted starting material **49** (29 %).

Table 34, entries 3 + 5:

Following the general cyclisation procedure, 1-(4-bromobutyl)-2-methyl-1*H*-imidazole-4-carbaldehyde **49** (0.11 g, 0.4 mmol) in cyclohexane (30 cm^3) was reacted with TBGH (0.16 g, 0.6 mmol) and AMBN (excess) for 3 h. The yields of 3-methyl-5,6,7,8-tetrahydro-imidazo[1,5-*a*]pyridine-1-carbaldehyde **54** (9 %) and unreacted starting material **49** (74 %) were determined by ^{1}H-NMR spectroscopy using 1,4-dinitrobenzene as the internal standard.

In an identical reaction but with CH_3CN as solvent the product distribution was as follows: 3-Methyl-5,6,7,8-tetrahydro-imidazo[1,5-*a*]pyridine-1-carbaldehyde **54** (21 %) and unreacted starting material **49** (69 %).

Table 34, entry 6:

Following the general cyclisation procedure, 1-(4-bromobutyl)-2-methyl-1*H*-imidazole-4-carbaldehyde **49** (0.09 g, 0.4 mmol) in butyronitrile (30 cm^3) was reacted with TBTH (0.18 g, 0.6 mmol) in butyronitrile and AMBN (excess) for 12 h. AMBM was added every hour. The yields of 3-methyl-5,6,7,8-tetrahydro-imidazo[1,5-*a*]pyridine-1-carbaldehyde **54** (21 %) and unreacted starting material **49** (21 %) were determined by ^{1}H-NMR spectroscopy using 1,4-dinitrobenzene as the internal standard.

Table 34, entry 7:

Following general procedure when using syringe-pump addition of the radical mediator, 1-(4-bromobutyl)-2-methyl-1*H*-imidazole-4-carbaldehyde **49** (0.20 g, 0.8 mmol) in acetonitrile (70 cm^3) was reacted with TBTH (0.47 g, 1.6 mmol) in cyclohexane (50 cm^3) and AIBMe (0.24 g, 1.1 mmol in total) for 5 h. AIBMe was added every 30 min. The yields of 3-methyl-5,6,7,8-tetrahydro-imidazo[1,5-*a*]pyridine-1-carbaldehyde **54** (26 %) and unreacted starting material **49** (49 %) were determined by ^{1}H-NMR spectroscopy using 1,4-dinitrobenzene as the internal standard.

Table 34, entry 8:

Following general procedure when using syringe-pump addition of the radical mediator, 1-(4-bromobutyl)-2-methyl-1*H*-imidazole-4-carbaldehyde **49** (0.2 g, 0.8 mmol) in acetonitrile (70 cm^3) was reacted with TBTH (0.48 g, 1.6 mmol) in toluene (50 cm^3) and AMBN (0.31 g, 1.6 mmol) for 3 h. The yield of 3-methyl-5,6,7,8-tetrahydro-imidazo[1,5-*a*]pyridine-1-carbaldehyde **54** (30 %) was determined by ^{1}H-NMR spectroscopy using 1,4-dinitrobenzene as the internal standard.

Table 34, entry 9:

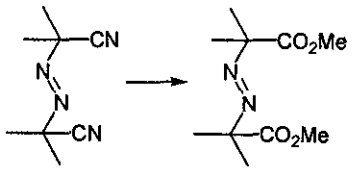
Following general procedure when using syringe-pump addition of the radical mediator, 1-(4-bromobutyl)-2-methyl-1*H*-imidazole-4-carbaldehyde **49** (0.19 g, 0.8 mmol) in acetonitrile (70 cm^3) was reacted with TBTH (0.49 g, 1.6 mmol) in toluene (50 cm^3) and AIBMe (0.37 g, 1.6 mmol) for 3 h. The yield of 3-methyl-5,6,7,8-tetrahydro-imidazo[1,5-*a*]pyridine-1-carbaldehyde **54** (77 %) was determined by ^{1}H-NMR spectroscopy using 1,4-dinitrobenzene as the internal standard.

Table 34, entry 10:

Following general procedure when using syringe-pump addition of the radical mediator, 1-(4-bromobutyl)-2-methyl-1*H*-imidazole-4-carbaldehyde **49** (0.19 g, 0.8 mmol) in acetonitrile (70 cm^3) was reacted with TBGH (0.39 g, 1.6 mmol) in toluene (50 cm^3) and AIBMe (0.37 g, 1.6 mmol) for 3 h. The yields of 3-methyl-5,6,7,8-tetrahydro-imidazo[1,5-*a*]pyridine-1-carbaldehyde **54** (12 %) and unreacted starting material **49** (26 %) were determined by ^{1}H-NMR spectroscopy using 1,4-dinitrobenzene as the internal standard.

Experimental for the mechanistic investigation

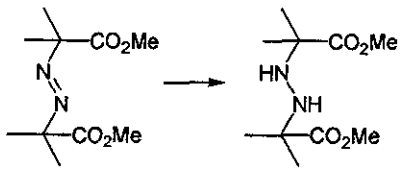
Synthesis of AIBMe[65]



AIBMe

HCl gas was bubbled through a stirred suspension of AIBN (10.0 g, 60.9 mmol) in methanol (150 cm^3) at –20 °C. After 45 min, the HCl source was removed and the mixture stirred at 0 °C overnight, cooled to –78 °C and the white solid collected by suction when cold. The solid was added to ice/water, extracted into DCM, dried ($MgSO_4$) and evaporated to dryness to give AIBMe (12.73 g, 55.3 mmol, 91 %) as a colourless oil which crystallised on cooling. (Found: M + H 231.1345, $C_{10}H_{19}N_2O_4$ requires 231.1345); ν_{max} (DCM)/cm^{-1} 2992, 1738, 1468, 1365, 1288, 1152, 857 and 562; δ_H 1.39 (12 H, s, Me) and 3.66 (6 H, s, OMe); δ_C 23.02 (Me), 52.51 (OMe), 75.43 (CMe_2), and 173.94 (CO_2Me); *m/z* (FAB) 231 (M + H, 100 %), 216 (90), 171 (20) and 101 (90).

Synthesis of 2-[*N*-(1-methoxycarbonyl-1-methylethyl)hydrazino]-2-methyl-propionic acid methyl ester 55[65]

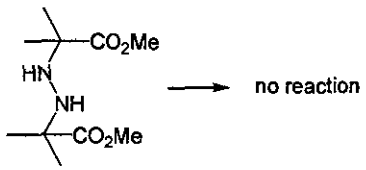


AIBMe **55**

A solution of hydrazine hydrate (0.31 g, 6.2 mmol) in methanol (12 cm^3) was added dropwise to a solution of AIBMe (0.30 g, 1.3 mmol) in methanol (25 cm^3) followed by addition of a solution of copper(II)sulfate (0.01 g, 0.06 mmol) in methanol (1 cm^3). The mixture was stirred overnight, filtered and evaporated to dryness. The residue was partitioned between aqueous hydrochloric acid (1 M) and EtOAc and the organic layer further extracted with hydrochloric acid. The combined aqueous phases were washed with EtOAc, neutralised with $NaHCO_3$ and aqueous NaOH was added to pH 14.

Extraction into EtOAc, drying ($MgSO_4$) and evaporation to dryness gave 2-[*N*-(1-methoxycarbonyl-1-methylethyl)hydrazino]-2-methyl-propionic acid methyl ester **55** as a pale brown oil (64.8 mg, 0.3 mmol, 21 %). (Found: M^+ 232.1423, $C_{10}H_{20}N_2O_4$ requires 232.1423); ν_{max} /cm^{-1} 3435 and 1728; δ_H 3.71 (6 H, s, OMe) and 1.23 (12 H, s, Me); δ_C 23.91 (Me), 51.91 (OMe), 61.33 (CMe_2) and 177.62 (CO_2Me); *m/z* 232 (M^+, 17 %), 113 (65) and 102 (100).

Stability-check of 55



55

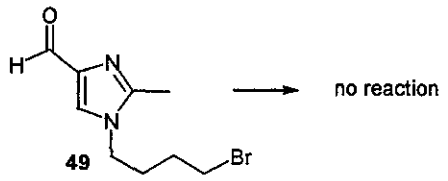
A stirred solution of 2-[*N*-(1-methoxycarbonyl-1-methylethyl)hydrazino]-2-methyl-propionic acid methyl ester **55** (65 mg) in DCM (25 cm^3) was left for 2 days and evaporated to dryness. Unreacted **55** was recovered (58 mg, 90 %).

A stirred solution of 2-[*N*-(1-methoxycarbonyl-1-methylethyl)hydrazino]-2-methyl-propionic acid methyl ester **55** (15 mg) in toluene (20 cm^3) was refluxed for 5 h and evaporated to dryness. Unreacted **55** was recovered (14 mg, 93 %).

The residue was dissolved in aqueous hydrochloric acid (1 M) and washed with light petroleum. The aqueous phase was neutralised with $NaHCO_3$ and aqueous NaOH was added to pH 14. Extraction into DCM, drying ($MgSO_4$) and evaporation to dryness gave unreacted **55** (13 mg, 93 %).

A stirred solution of 2-[*N*-(1-methoxycarbonyl-1-methylethyl)hydrazino]-2-methyl-propionic acid methyl ester **55** (58 mg, 0.25 mmol) in methanol (20 cm^3) was added Na_2CO_3 (18 mg, 0.2 mmol), left for 2 days and evaporated to dryness. The ^{1}H-NMR spectra revealed a mixture of unreacted **55**, a small amount of AIBMe and an unknown decomposition product.

"Blank" radical cyclisation reaction using 55



49

TBTH (0.12 g, 0.4 mmol) in anhydrous toluene (10 cm^3) was added by syringe-pump to a refluxing mixture of 1-(4-bromobutyl)-2-methyl-1*H*-imidazole-4-carbaldehyde **49** (50 mg, 0.2 mmol) and **55** (40 mg, 0.2 mmol) in anhydrous CH_3CN (18 cm^3) over 3 h. Cooling to room temperature and evaporation of solvent gave the crude reaction mixture in which no cyclic product could be observed by ^{1}H-NMR spectroscopy. 2-[*N*-(1-Methoxycarbonyl-1-methylethyl)hydrazino]-2-methyl-propionic acid methyl ester **55** could be detected by the use of 1,4-dinitrobenzene as the internal standard in yield corresponding to 2 %. Aqueous hydrochloric acid (2 M) was added and the solution washed with light petroleum. The aqueous layer was neutralised by addition of $NaHCO_3$ and basified to pH 14 by addition of aqueous NaOH (2 M) and extracted into DCM. The organic layer was dried ($MgSO_4$) and evaporated to dryness to give a pale yellow oil. By the use of 1,4-dinitrobenzene as the internal standard in ^{1}H-NMR spectroscopy the yields of recovered radical precursor **49** and 2-[*N*-(1-methoxycarbonyl-1-methylethyl)hydrazino]-2-methyl-propionic acid methyl ester **55** were determined as 88 % and 0.8 % respectively.

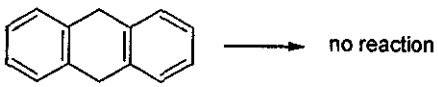
Reaction between 55 and TBGH

A solution of 2-[*N*-(1-methoxycarbonyl-1-methylethyl)hydrazino]-2-methyl-propionic acid methyl ester **55** (70 mg, 0.3 mmol) and TBGH (0.16 g, 0.67 mmol) in anhydrous toluene (20 cm^3) was heated at reflux for 3 h, cooled to room temperature and evaporated to dryness. Aqueous hydrochloric acid (2 M) was added and the solution washed with light petroleum. The aqueous layer was neutralised by addition of $NaHCO_3$ and basified to pH 14 by addition of aqueous NaOH (2 M) and extracted into DCM. The organic layer was dried ($MgSO_4$) and evaporated to dryness to give a pale yellow oil (47 mg). The products of the reaction were not identified.

Reaction between 55 and TBTH

A solution of 2-[*N*-(1-methoxycarbonyl-1-methylethyl)hydrazino]-2-methyl-propionic acid methyl ester **55** (70 mg, 0.3 mmol) and TBTH (0.22 g, 0.74 mmol) in anhydrous toluene (20 cm^3) was heated at reflux for 3 h, cooled to room temperature and evaporated to dryness. Aqueous hydrochloric acid (2 M) was added and the solution washed with light petroleum. The aqueous layer was neutralised by addition of $NaHCO_3$ and basified to pH 14 by addition of aqueous NaOH (2 M) and extracted into DCM. The organic layer was dried ($MgSO_4$) and evaporated to dryness to give a pale yellow oil identified by GC-MS as 2-[*N*-(1-methoxycarbonyl-1-methyl-ethyl)hydrazino]-2-methyl-propionic acid methyl ester **55** (42 mg, 0.2 mmol, 60 %).

Measurement of nitrogen formation; oxidation of 9,10-dihydroanthracene



A solution of 9,10-dihydroanthracene (0.18 g, 1.0 mmol) and AIBMe (0.23 g, 1.0 mmol) in *t*-BuOH (20 cm^3) was connected to the burette and heated at 100 °C for 3 h. After cooling to room temperature, the burette was levelled and the difference in volume determined as 20.3 cm^3, corresponding to 0.84 mmol of N_2 (84 % of expected amount). Evaporation of the solvent gave 0.45 g of crude reaction mixture, including some *t*-BuOH. Using *p* -dinitrobenzene as the internal standard, ^{1}H-NMR spectroscopy showed the presence of unreacted 9,10-dihydroanthracene (37 %) as indicated by singlet at 3.97 ppm.

3.5.2.2 Radical cyclisation of pyrrole derivatives

General cyclisation procedure:

The radical mediator was added dropwise to a mixture of the radical precursor in anhydrous solvent at room temperature. The mixture was heated to reflux and initiator was added, followed by refluxing for the time indicated under each reaction. If the reaction time was longer than 3 h, another small amount of initiator was added after this period of time. Cooling to room temperature and evaporation of the mixture to dryness gave oils which in most cases were purified by column chromatography.

General procedure when using syringe-pump addition of the radical mediator:

Using syringe-pump technique, the radical mediator in anhydrous solvent was added to a refluxing mixture of the radical precursor in anhydrous solvent over the period of time indicated under each reaction. The initiator was added initially and thereafter every 40 min. Cooling to room temperature and evaporation of the mixture to dryness gave oils which in most cases were purified by column chromatography.

Radical cyclisation of 1-(3-phenylselanylpropyl)-1*H*-pyrrole-2-carbaldehyde 62

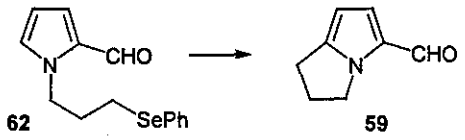


Table 35, entry 1:

Following the general procedure when using syringe-pump addition of the radical mediator, 1-(3-phenylselanylpropyl)-1*H*-2-pyrrole-2-carbaldehyde **62** (0.27 g, 0.93 mmol) in toluene (70 cm^3) was reacted with TBTH (0.45 g, 1.5 mmol) in toluene and AIBN (0.22 g, 1.3 mmol) for 5 h. Column chromatography (light petroleum:EtOAc: 95:5→85:15) gave a mixture of 6,7-dihydro-5*H*-pyrrolizine-3-carbaldehyde **59** and AIBN. Yet another column (light petroleum:EtOAc: 4:1) gave 6,7-dihydro-5*H*-pyrrolizine-3-carbaldehyde **59** (61.1 mg, 0.45 mmol, 49 %) as a colourless oil.[61] δ_H 2.48-2.60 (2 H, m, 6-H), 2.82 (2 H, t, *J* 7.5, 5-H), 4.26 (2 H, t, *J* 7.2, 7-H), 5.98 (1 H, d, *J* 3.7, 2-H), 6.94 (1 H, d, *J* 3.9, 1-H) and 9.40 (1 H, s, CHO); δ_C 24.43 (6-C), 27.54 (7-C), 47.79 (5-C), 103.50 (2-C), 128.68 (8-C), 132.21 (1-C), 133.75 (3-C) and 178.49 (CHO); *m/z* 135 (M^+, 100 %), 120 (17), 106 (55), 79 (51) and 65 (6).

Table 35, entry 2:

Following the general procedure when using syringe-pump addition of the radical mediator, 1-(3-phenylselanylpropyl)-1*H*-pyrrole-2-carbaldehyde **62** (0.31 g, 1.1 mmol) in toluene (70 cm^3) was reacted with TBGH (0.33 g, 1.3 mmol) in toluene and AIBN (0.22 g, 1.3 mmol) for 5 h. ^{1}H-NMR spectroscopy showed only unreacted starting material **62**.

Table 35, entry 3:

Following the general cyclisation procedure, 1-(3-phenylselanylpropyl)-1*H*-pyrrole-2-carbaldehyde **62** (0.10 g, 0.3 mmol) in toluene (50 cm^3) was reacted with TBGH (0.33 g, 1.3 mmol) for 5.5 h. A small amount of AIBN (0.22 g, 1.3 mmol added in total) was added every 30 minutes. Analysis using TLC and ^{1}H-NMR spectroscopy showed unreacted starting material **62**, but also traces of 6,7-dihydro-5*H*-pyrrolizine-3-carbaldehyde **59**.

Radical cyclisation of 1-(4-phenylselanylbutyl)-1*H*-pyrrole-2-carbaldehyde 63

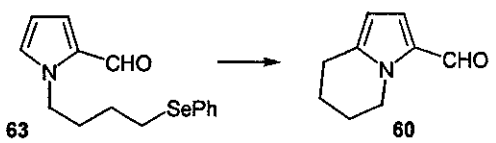


Table 35, entry 4:

Following the general procedure when using syringe-pump addition of the radical mediator, 1-(4-phenylselanylbutyl)-1*H*-pyrrole-2-carbaldehyde **63** (0.30 g, 1.0 mmol) in acetonitrile (70 cm^3) was reacted with TBTH (0.56 g, 1.9 mmol) in toluene and AIBMe (0.30 g, 1.3 mmol) for 5 h. A small amount of AIBMe in toluene was added every hour. After cooling to room temperature and evaporation to dryness, EtOAc and potassium fluoride were successively added and the resulting mixture vigorously stirred for two hours. The organic layer was separated, dried ($MgSO_4$) and evaporated to dryness. Column chromatography (light petroleum:EtOAc: 95:5→85:15) gave 5,6,7,8-tetrahydro-indolizine-3-carbaldehyde **60**[61] (42 mg, 0.28 mmol, 29 %) along with a mixture of AIBMe and **55**. The yield of 5,6,7,8-tetrahydro-indolizine-3-carbaldehyde **60** was determined by the use of 1,4-dinitrobenzene as the internal standard in ^{1}H-NMR spectroscopy. δ_H 1.85-1.71 (2 H, m, 6-H), 1.97-1.89 (2 H, m, 7-H), 2.75 (2 H, t, *J* 6.2, 8-H), 4.28 (2 H, t, *J* 6.0, 5-H), 5.98 (1 H, dd, *J* 4.2, 0.7, 2-H), 6.78 (1 H, d, *J* 4.2, 1-H), and.9.32 (1 H, s, CHO); δ_C 19.77 (7-C), 22.92 (6-C), 23.75 (8-C), 45.60 (5-C), 107.93 (2-C), 124.01 (9-C), 131.13 (1-C), 133.40 (3-C) and.178.17 (CHO); *m/z* 149 (M^+, 100 %), 134 (18), 120 (52), 108 (34), 93 (24), 80 (10) and 65 (12).

3.5.2.3 Radical cyclisation of pyrazole derivatives

Radical cyclisation of 4-phenyl-1-(3-phenylselanylpropyl)-1*H*-pyrazole 64

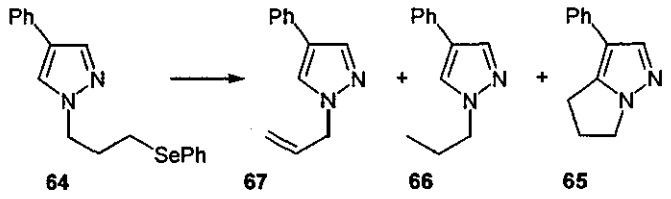


Table 36, entry 1:

General cyclisation procedure:

A solution of TBGH (85 mg, 0.3 mmol) and ACCN (0.2 g, 0.6 mmol) in anhydrous toluene (50 cm^3) was added by syringe pump to a refluxing solution of 4-phenyl-1-(3-phenylselanylpropyl)-1*H*-pyrazole **64** (0.1 g, 0.3 mmol) in anhydrous toluene (200 cm^3) was over 6 h. The reaction mixture was refluxed for further 30 min after complete addition, cooled to room temperature and evaporated to dryness. Column chromatography (light petroleum:EtOAc; 5:1) gave a mixture of unreacted starting material **64** (47 %), 4-phenyl-1-propyl-1*H*-pyrazole **66** (19 %) and 1-allyl-4-phenyl-1*H*-pyrazole **67** (7 %). All yields were determined by the use of 1,4-dimethoxybenzene as the internal standard in ^{1}H-NMR spectroscopy. **66**:[65] (Found: M^+, 186.1154. $C_{12}H_{14}N_2$ requires 186.1157); ν_{max} /cm^{-1} 3131; δ_H 0.95 (3 H, t, *J* 7.4, Me), 1.89-1.98 (2 H, m, 2-H), 4.11 (2 H, t, *J* 7.2, 1-H), 7.19-7.25 (1 H, m, Ph 4-H), 7.34-7.38 (2 H, m, Ph 3,5-H), 7.47-7.49 (2 H, m, Ph 2,6-H), 7.63 (1 H, s, pyrazole 3-H) and 7.78 (1 H, s, pyrazole 5-H); δ_C 11.14 (3-C), 23.71 (2-C), 54.03 (1-C), 122.65 (pyrazole 4-C), 125.44 (Ph 2,6-C), 125.89 (pyrazole 3-C), 126.23 (Ph 4-C), 128.79 (Ph 3,5-C), 132.75 (Ph 1-C) and 136.54 (pyrazole 5-C); *m/z* 186 (M^+, 87 %), 157 (100) and 144 (64). **67**: δ_H 4.66-4.75 (2 H, m, 1-H), 5.20-5.29 (2 H, m, CH=CH_2), 5.95-6.11 (1 H, m, C*H*=CH_2), 7.51-7.17 (5 H, m, Ph), 7.62 (1 H, s, pyrazole 3-H) and 7.79 (1 H, s, pyrazole 5-H); *m/z* 184 (M^+, 44 %), 183 (55), 157 (19), 156 (16), 143 (22), 102 (18), 89 (27), 77 (10), 63 (31), 41 (66) and 39 (100).

Table 36, entry 2:

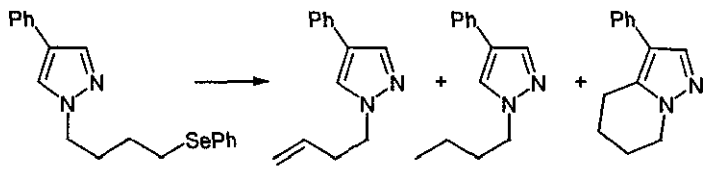
Repeating the reaction but adding ACCN every 45 min gave unreacted starting material **64** (70 %) and 1-allyl-4-phenyl-1*H*-pyrazole **67** (30 %). Both yields were

determined by the use of 1,4-dimethoxybenzene as internal standard in ^{1}H-NMR spectroscopy.

Table 36, entry 3:

TBGH (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-(3-phenylselanylpropyl)-1*H*-pyrazole **64** (0.05 g, 0.15 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 TBGH (43 mg, 0.18 mmol) and Et_3B (1.0 M in hexane, 0.28 mmol) were added and the mixture stirred for further 18 h. Evaporation to dryness followed by column chromatography (light petroleum:EtOAc: 10:1 → 2:1) gave 4-phenyl-1-propyl-1*H*-pyrazole **66** (17.8 mg, 0.1 mmol, 66 %) as an colourless oil.

Radical cyclisation of 4-phenyl-1-(4-phenylselanylbutyl)-1*H*-pyrazole 68



68 **71** **70** **69**

Table 36, entry 4:

Following the general cyclisation procedure, 4-phenyl-1-(4-phenylselanylbutyl)-1*H*-pyrazole **68** (0.1 g, 0.3 mmol) was reacted with TBGH (83 mg, 0.3 mmol) for 10 h to give unreacted starting material **68** (77 %) and 1-but-3-enyl-4-phenyl-1*H*-pyrazole **71** (4 %). Both yields were determined by the use of 1,4-dimethoxybenzene as the internal standard in ^{1}H-NMR spectroscopy. **71**: δ_H 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=C*H*$_2$), 5.70-5.87 (1 H, m, C*H*=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).

Table 36, entry 5:

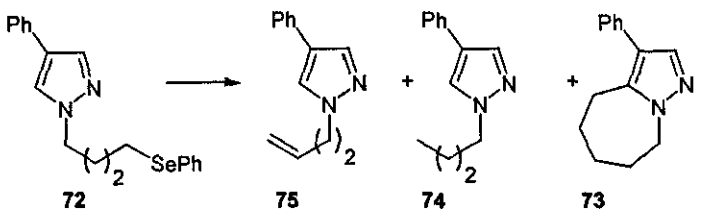
Repeating the reaction but adding ACCN every 45 min gave unreacted starting material **68** (52 %) and 1-but-3-enyl-4-phenyl-1*H*-pyrazole **71** (16 %). Both yields

were determined by the use of 1,4-dimethoxybenzene as the internal standard in ^{1}H-NMR spectroscopy.

Table 36, *entry 6*:

TBGH (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 **68** (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 TBGH (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 TBGH (43 mg, 0.18 mmol) and Et_3B (1.0 M in hexane, 0.28 mmol) were added yet again. The mixture was then stirred for further 8 h. Evaporation to dryness followed by column chromatography (light petroleum:EtOAc: 10:1 → 2:1) gave 3-phenyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine **69** (44 %), unreacted starting material **68** (7 %) and 1-but-3-enyl-4-phenyl-1*H*-pyrazole **71** (4 %). All yields were determined by the use of 1,4-dimethoxybenzene as the internal standard in ^{1}H-NMR spectroscopy. **69**:[65] (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 %).

Radical cyclisation of 4-phenyl-1-(5-phenylselanylpentyl)-1*H*-pyrazole 72



72 **75** **74** **73**

Table 36, entry 7:

Following the general cyclisation procedure, 4-phenyl-1-(5-phenylselanylpentyl)-1*H*-pyrazole **72** (0.1 g, 0.3 mmol) was reacted with TBGH (79 mg, 0.3 mmol) for 10 h to give 1-pent-4-enyl-4-phenyl-1*H*-pyrazole **75** in 62 % yield. Due to by-products, the yield was determined by the use of 1,4-dimethoxybenzene as the internal standard in

^{1}H-NMR spectroscopy. δ_H 1.47-1.85 (4 H, m, H-2 and 3), 4.16 (2 H, t, *J* 6.7, H-1), 5.01-5.08 (2 H, m, CH=C*H*$_2$), 5.72-5.88 (1 H, m, C*H*=CH$_2$), 7.19-7.38 (3 H, m, Ar H-3, 4, and 5), 7.46-7.49 (2 H, m, Ar H-2,6), 7.64 (1 H, s, pyrazole 3-H) and 7.80 (1 H, s, pyrazole 5-H); *m/z* 212 (M^+, 5 %), 211 (10), 157 (32), 144 (15), 130 (12), 102 (27), 89 (29), 77 (16), 67 (25), 53 (25), 41 (80) and 39 (100).

"Blank" reaction of 4-phenyl-1-(4-phenylselanylpropyl)-1*H*-pyrazole 64

A solution of 4-phenyl-1-(4-phenylselanylpropyl)-1*H*-pyrazole **64** (16.0 mg, 0.05 mmol) in anhydrous toluene (35 cm^3) was refluxed for 16 h, cooled to ambient temperature and evaporated to dryness. ^{1}H-NMR spectroscopy revealed that no reaction had occurred. The oil was re-dissolved in anhydrous toluene (35 cm^3), added TBGH (19 mg, 0.08 mmol) and refluxed for 18 h. ^{1}H-NMR spectroscopy after cooling and evaporation of solvent showed only signals corresponding to the pyrazole precursor **64**.

3.5.2.4 Radical decarbonylation of 3-(1H-indol-3-yl)propionic acid Se-phenyl ester

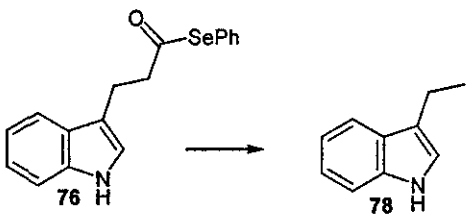


Table 37, entry 1:

TBTH (0.12 g, 0.41 mmol) was added to a solution of 3-(1*H*-indol-3-yl)-seleno-propionic acid Se-phenyl ester **76** (0.12 g, 0.37 mmol) in anhydrous toluene (40 cm^3) and the mixture heated to reflux. AIBN (0.12 g, 0.73 mmol in total) was added initially and then in small portions every 45 min. After refluxing for 2 h, the mixture was cooled to ambient temperature and evaporated to dryness. Use of 1,4-dimethoxybenzene as the internal standard in ^{1}H-NMR spectroscopy revealed the formation of decarbonylated product 3-ethyl-1*H*-indole **78** in 47 % yield. Column chromatography (light petroleum:EtOAc; 10:1 → 3:1) gave the decarbonylated product **78** as a colourless oil (14.0 mg, 0.10 mmol, 27 %) along with other, unidentified products. (Found: 145.0890, $C_{10}H_{11}N$ requires 145.0892); ν_{max}

(DCM)/cm^{-1} 3414, 3056, 2963, 2829, 1702, 1682, 1604, 1455, 1421, 1339, 1223, 1093 and 741; δ_H 1.33 (3 H, t, *J* 7.5, CH_3), 2.79 (2 H, q, *J* 7.5, CH_2), 6.94 (1 H, m, Ar 2-H), 7.07-7.22 (2 H, m, Ar 6,7-H), 7.33 (1 H, d, *J* 7.6, Ar 8-H), 7.61 (1 H, d, *J* 7.6, Ar 5-H) and 7.84 (1 H, bs, NH); δ_C 14.44 (CH_3), 17.29 (CH_2), 111.01 (Ar 8-C), 118.80 (Ar 3-C), 118.93 (Ar 7-C), 119.03 (Ar 5-C), 120.41 (Ar 6-C), 121.86 (Ar 2-C), 130.20 (Ar 4-C) and 136.37 (Ar 9-C); *m/z* 145 (78 %), 130 (100) and 77 (21).

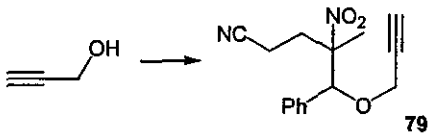
Table 37, entry 2:

Reacting 3-(1*H*-Indol-3-yl)-selenopropionic acid Se-phenyl ester **76** (0.12 g, 0.37 mmol) in anhydrous toluene (30 cm^3) with TBGH (94.9 mg, 0.39 mmol) and ACCN (0.15 g, 0.91 mmol in total) in accordance with the procedure detailed above gave 3-ethyl-1*H*-indole **78** in 63 % yield as determined by the use of an internal standard in ^{1}H-NMR spectroscopy.

3.6 Experimentals for Chapter 2.5

3.6.1 Synthesis of alkyl precursors

3-Nitro-3-methyl-4-phenyl-4-(prop-2-ynyloxy)butyl cyanide 79[88]



79

Propargyl alcohol (0.8 g, 13.5 mmol) was added dropwise to a suspension of sodium hydride (0.5 g, 13.5 mmol) in anhydrous THF (10 cm^3) at 0 °C and the mixture stirred for 15 min at 0°C followed by addition of *trans*-*β*-methyl-*β*-nitrostyrene (2.0 g, 12.3 mmol). The mixture was stirred at ambient temperature overnight, poured into a ice/water mixture and neutralised with H_2NOH•HCl. Extraction into DCM and washing of the organic fractions with water, followed by drying ($MgSO_4$) and evaporation of solvent gave the crude product. Purification by column chromatography (light petroleum:EtOAc; 4:1) to give 2-nitro-1-phenylpropyl prop-2-ynyl ether as a mixture of diastereoisomers. NaH (0.2 g, 5.5 mmol) was added to a solution of 2-nitro-1-phenylpropyl prop-2-ynyl ether (1.0 g, 4.6 mmol) in anhydrous THF (10 cm^3) at 0 °C and the suspension stirred at 0 °C for 20 min. Acrylonitrile (0.3

g, 5.5 mmol) was added dropwise and the resulting mixture stirred at room temperature for 90 min. Methanol and water were added and the solution extracted into DCM, dried ($MgSO_4$) and evaporated to dryness to give the crude product as an yellow oil. Column chromatography (light petroleum:EtOAc; 4:1) gave 3-nitro-3-methyl-4-phenyl-4-(prop-2-ynyloxy)butyl cyanide **79** as a mixture of diastereoisomers (0.5 g, 1.9 mmol, 43 %). (Found: M + H, 273.1234, $C_{15}H_{17}N_2O_3$ requires 273.1239); δ_H 1.47 and 1.63 (3 H, s, Me), 2.21-2.79 (5 H, m, CH_2CH_2CN and C≡C*H*), 3.88-3.93 (1 H, m, $OCH_2C{\equiv}CH$), 4.18 and 4.22 (1 H, dd, *J* 2.3 and 15.9, $OCH_2C{\equiv}CH$), 5.14 and 5.18 (1 H, s, C*H*Ph) and 7.18-7.44 (5 H, m, Ph); δ_C 13.02 (CH_2CN), 19.65 (Me), 30.8 (CH_2CH_2CN), 56.81 ($OCH_2C{\equiv}CH$), 76.18 (*C*HPh), 78.44 (CNO_2), 83.91 (C≡*C*H), 93.02 (*C*≡CH), 119.31 (*C*N), 128.67 (Ph 3,5-C), 129.21 (Ph 2,6-C), 129.90 (Ph 4-C) and 133.86 (Ph 1-C); *m/z* (FAB) 273 (M + H, 14 %), 226 (95), 217 (20), 171 (20), 145 (90), 137 (100) and 105 (65).

2-(3-Phenylprop-2-enyloxy)ethanol 82[89]

82

Method A:

Ethylene glycol (0.125 g, 2.0 mmol) and cinnamyl bromide (0.2 g, 1.0 mmol) were successively added at room temperature to a mixture of potassium hydroxide (0.11 g, 2.0 mmol) in anhydrous DMSO (5 cm^3) and the mixture was stirred at room temperature for 1 h. The mixture was poured into water and extracted with DCM. The aqueous phase was acidified with aqueous 2 M HCl and extracted with DCM. The combined organic layers were washed with water, dried ($MgSO_4$) and evaporated to dryness to give a yellow oil. Column chromatography (light petroleum:EtOAc; 3:2) gave 2-(3-phenylprop-2-enyloxy)ethanol **82** as a colourless oil (0.06 g, 0.4 mmol, 35 %) along with cinnamyl alcohol (0.04 g, 0.3 mmol, 26 %) and cinnamyl aldehyde (the yield was not determined). ν_{max} /cm^{-1} 3416, 3026, 2929, 2864, 1495, 1449 and 1116; δ_H 2.54 (1 H, bs, OH) 3.59 (2 H, m, CH_2OH) 3.76 (2 H, m, CH_2CH_2OH), 4.18 (2 H, dd, *J* 6.1, 1.4, $CH{=}CHCH_2$), 6.28 (1 H, dt, *J* 15.9, 6.1, $CH{=}CHCH_2$), 6.60 (1 H, d, *J* 15.9, $CH{=}CHCH_2$), and 7.20-7.40 (5 H, m, Ph); δ_C 61.67 (CH_2OH), 71.35 ($CH{=}CHCH_2$), 71.72 (CH_2CH_2OH), 125.63 ($CH{=}CHCH_2$), 125.70 (Ph 2,6-C), 127.76

(*C*H=CHCH$_2$), 128.41 (Ph 3,5-C), 134.63 (Ph 4-C) and 136.53 (Ph 1-C); *m/z* 178 (2 %), 177 (3), 133 (50), 117 (90), 115 (100), 105 (72), 100 (60), 91 (85) and 73 (82).

Method B:[89]

Ethylene glycol (0.06 g, 0.1 mmol) and cinnamyl bromide (0.1 g, 0.5 mmol) were successively added at room temperature to a mixture of sodium hydride (0.04 g, 1.1 mmol) in anhydrous DMF (3 cm^3) and the mixture was stirred at room temperature for 1 h. The mixture was poured into water and extracted with DCM. The organic layers were washed with water (× 6) to remove DMF, dried ($MgSO_4$) and evaporated to dryness to give a yellow oil. Column chromatography (light petroleum:EtOAc; 3:2) gave the isolated 2-(3-phenylprop-2-enyloxy)ethanol **82** as a colourless oil (0.08 g, 0.4 mmol, 87 %).

3-[(2-Bromoethyl)oxy]-prop-1-enylbenzene 81

Triphenylphosphine (0.21 g, 0.8 mmol) and carbon tetrabromide (0.27 g, 0.8 mmol) in anhydrous CH_3CN (6 cm^3) was added to a solution of 2-(3-phenylprop-2-enyloxy)ethanol **82** (0.1 g, 0.5 mmol) at 0 °C and the mixture was stirred at room temperature in 45 min. Evaporation of the solvent followed by column chromatography (light petroleum:EtOAc; 15:1) gave 3-[(2-bromoethyl)oxy]-prop-1-enylbenzene **81** as a pale yellow oil (0.13 g, 0.5 mmol, 100 %); (Found: C, 54.60; H, 5.20, $C_{11}H_{13}BrO$ requires: C, 54.79; H, 5.43); ν_{max} /cm^{-1} 3026, 2851, 1715, 1494, 1449, 1359 and 1116; δ_H 3.48 (2 H, dd, *J* 6.1, 6.1, C*H*$_2$Br), 3.79 (2 H, dd, *J* = 6.1, 6.1, C*H*$_2$CH$_2$Br), 4.20 (2 H, dd, *J* 6.0, 1.4, CH=CHC*H*$_2$), 6.27 (1 H, dt, *J* 16.0, 6.0, CH=C*H*CH$_2$), 6.61 (1 H, d, *J* 16.0, C*H*=CHCH$_2$), and 7.23-7.41 (5 H, m, Ph); δ_C 31.11 (*C*H$_2$Br), 70.40 (CH=CH*C*H$_2$) 72.06 (*C*H$_2$CH$_2$Br), 126.06 (CH=*C*HCH$_2$), 127.23 (Ph 2,6-C), 128.28 (*C*H=CHCH$_2$), 129.40 (Ph 3,5-C), 129.44 (Ph 4-C) and 136.99 (Ph 1-C); *m/z* 242 (23 %), 240 (23), 161 (3), 143 (7), 133 (70), 117 (55), 115 (65), 105 (100), 91 (48) and 77 (67).

3.6.2 Radical cyclisation of alkyl precursors

Radical cyclisation of 3-nitro-3-methyl-4-phenyl-4-(prop-2-ynyloxy)butyl cyanide 79

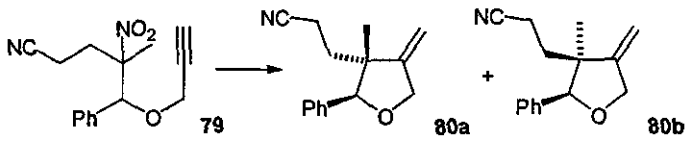


Table 38, entry 1:

General procedure:

TBTH (0.13 g, 0.4 mmol) was added dropwise to a solution of 3-nitro-3-methyl-4-phenyl-4-(prop-2-ynyloxy)butyl cyanide **79** (90 mg, 0.3 mmol) in anhydrous acetonitrile (2 cm^3) and the mixture heated at reflux for 3 h. AIBN (40 mg, 0.2 mmol in total) was added initially and then in portions every hour. After cooling to room temperature, the solution was evaporated to dryness and the crude reaction mixture purified by column chromatography (light petroleum:EtOAc; 10:1) to give 3-(3-methyl-4-methylene-2-phenyl-tetrahydro-furan-3-yl)propionitrile **80** as two diastereoisomers (18 % (**80b**) and 21 % (**80a**) respectively) and unreacted starting material (9 %). Due to by-products, the yields were determined by the use of 1,4-dimethoxybenzene as the internal standard in ^{1}H-NMR spectroscopy. **80a**:[88] δ_H (400 MHz) 0.64 (3 H, s, Me), 1.88 (2 H, m, $NCCH_2CH_2$), 2.38 (2 H, dd, *J* 7.6 and 8.4, $NCCH_2$), 4.40 (1 H, dt, *J* 2.4 and 13.6, OCH_2), 4.62-4.66 (2 H, m, PhCH and OCH_2), 4.80 (1 H, t, *J* 2.4, C=CH), 5.05 (1 H, t, *J* 2.0, C=CH) and 7.16-7.29 (5 H, m, Ph); δ_C 12.99 ($NCCH_2$), 22.79 (Me), 33.42 ($NCCH_2CH_2$), 48.85 (CCH_3), 71.43 ($C=CH_2$), 87.50 (PhC), 105.40 ($C=CH_2$), 120.33 (CN), 126.99 (Ph C-2,5), 128.61 (Ph C-4), 128.69 (Ph C-2,6), 138.92 (Ph C-1) and 153.45 ($C=CH_2$); *m/z* 227 (5 %), 128 (8), 120 (12), 107 (100), 79 (85), 53 (30) and 41 (35). **80b**:[88] δ_H (400 MHz) 1.11 (3 H, s, Me), 1.88 (2 H, m, $NCCH_2CH_2$), 2.38 (2 H, dd, *J* 7.6 and 8.4, $NCCH_2$), 4.39 (1 H, dt, *J* 2.4 and 13.6, OCH_2), 4.90 (1 H, s, PhCH), 4.59 (1 H, dt, *J* 2.0 and 13.6, OCH_2), 4.84 (1 H, t, *J* 2.4, C=CH), 5.05 (1 H, t, *J* 2.0, C=CH) and 7.25-7.30 (5 H, m, Ph); δ_C 12.63 ($NCCH_2$), 23.78 (Me), 30.03 ($NCCH_2CH_2$), 48.37 (CCH_3), 70.34 ($=CH_2$), 89.86 (PhC), 106.42 ($C=CH_2$), 120.61 (CN), 126.65 (Ph C-2,5), 128.86 (Ph C-4), 128.97 (Ph

C-2,6), 137.02 (Ph C-1) and 153.39 (C=CH_2); *m/z* 227 (5 %), 128 (8), 120 (12), 107 (100), 79 (85), 53 (30) and 41 (35).

Table 38, entry 2:

Following the general procedure, 3-nitro-3-methyl-4-phenyl-4-(prop-2-ynyloxy)butyl cyanide **79** (90 mg, 0.3 mmol) was reacted with TBGH (0.10 g, 0.4 mmol) to give the two diastereoisomeric products (15 % (**80b**) and 5 % (**80a**) respectively) and unreacted starting material **79** (51 %). Due to by-products, the yields were determined by the use of 1,4-dimethoxybenzene as the internal standard in ^{1}H-NMR spectroscopy.

Table 38, entry 3:

Following the general procedure, 3-nitro-3-methyl-4-phenyl-4-(prop-2-ynyloxy)butyl cyanide **79** (0.1 g, 0.3 mmol) in toluene (2 cm^3) was reacted with TBGH (0.14 g, 0.4 mmol) for 5 h to give the two diastereoisomeric products (17 % (**80b**) and 3 % (**80a**) respectively) and unreacted starting material **79** (53 %). Due to by-products, the yields were determined by the use of 1,4-dimethoxybenzene as the internal standard in ^{1}H-NMR spectroscopy.

Table 38, entry 4:

Following the general procedure, 3-nitro-3-methyl-4-phenyl-4-(prop-2-ynyloxy)butyl cyanide **79** (0.1 g, 0.3 mmol) in acetonitrile (2 cm^3) was reacted with TBGH (0.14 g, 0.55 mmol) and AIBN (0.12 g, 0.73 mmol) for 5 h to give 3-(3-methyl-4-methylene-2-phenyl-tetrahydro-furan-3-yl)propionitrile **80** as a mixture of diastereoisomers (15 % in total) and unreacted starting material (51 %). Due to by-products, the yields were determined by the use of 1,4-dimethoxybenzene as the internal standard in ^{1}H-NMR spectroscopy.

Radical cyclisation of 3-[(2-bromoethyl)oxy]-prop-1-enylbenzene 81

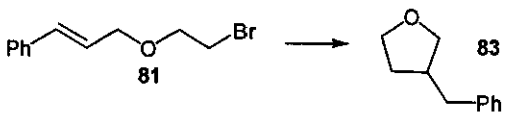


Table 39, entry 1:

TBTH (0.28 g, 0.95 mmol) and PhSH (8.7 mg, 0.08 mmol) were added successively and dropwise to a solution of 3-[(2-bromoethyl)oxy]-prop-1-enylbenzene **81** (0.19 g,

0.79 mmol) in anhydrous cyclohexane (50 cm^3) and the mixture heated at reflux for 5 h. AMBN (0.15 g, 0.78 mmol) was added initially and then in portions every hour. After cooling to room temperature, the solution was evaporated to dryness and the crude residue purified by column chromatography (light petroleum:EtOAc; 1:0 → 15:1) to give 11 % of 3-benzyl-tetrahydrofuran **83**.[90] Due to interfering signals, the yield was determined by the use of 1,4-dimethoxybenzene as the internal standard in ^{1}H-NMR spectroscopy. δ_H 1.56-1.65 (1 H, m, 4-H), 1.93-2.03 (1 H, m, 4-H), 2.46-2.57 (1 H, m, 3-H), 2.68-2.71 (2 H, m, C*H*$_2$Ph), 3.47 (1 H, dd, *J* 8.3 and 6.7, 2-H), 3.72-3-96 (3 H, m, 2,5-H) and 7.16-7.30 (5 H, m, Ph); δ_C 32.39 (4-C), 39.39 (*C*H$_2$Ph), 41.43 (3-C), 67.98 (5-C), 73.45 (2-C), 126.01 (Ph 4-C), 128.57 (Ph 3,5-C), 128.95 (Ph 2,6-C) and 140.05 (Ph 1-C); *m/z* 162 (M^+, 22 %), 144 (12), 117 (20), 115 (14), 92 (97) and 91 (100).

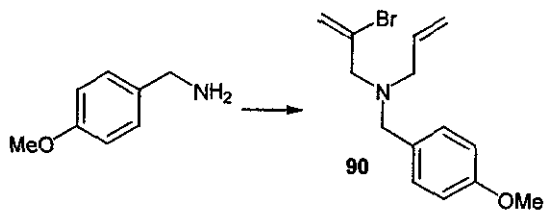
Table 39, entry 2:

Employing the procedure detailed above, 3-[(2-bromoethyl)oxy]-prop-1-enylbenzene **81** (0.12 g, 0.50 mmol) was reacted with TBGH (0.15 g, 0.60 mmol) to give 3-benzyl-tetrahydrofuran **83** in 10 % yield as determined by the use of 1,4-dimethoxybenzene as the internal standard in ^{1}H-NMR spectroscopy.

3.7 Experimentals for Chapter 2.6

3.7.1 Synthesis of vinylic precursors

Allyl-(2-bromoallyl)-(4-methoxybenzyl)amine 90

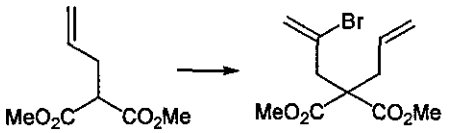


90

A solution of allyl bromide (4.1 g, 33.5 mmol) in acetonitrile (20 cm^3) was added dropwise to a mixture of 4-methoxybenzylamine (5.0 g, 36.5 mmol) and potassium carbonate (14.7 g, 0.11 mol) in acetonitrile (150 cm^3) at 0 °C. The mixture was stirred at ambient temperature overnight, filtered and evaporated to dryness. The resulting oil

was dissolved in acetone (130 cm^3) and cooled to 0 °C. Potassium carbonate (20.0 g, 0.15 mol) and a solution of 2,3-dibromopropene (80 %, 15.5 g, 60.6 mmol) in acetone (20 cm^3) were added and the mixture stirred at ambient temperature overnight. Filtration and evaporation to dryness afforded a yellow oil, which was purified by column chromatography (light petroleum;DCM; 10:1 → 5:1) to give allyl-(2-bromo-allyl)-(4-methoxybenzyl)amine **90** as a colourless oil (2.04 g, 6.9 mmol, 19 %). (Found: 295.0575, $C_{14}H_{18}BrNO$ requires 295.0572); ν_{max} /cm^{-1} 3001, 2931, 2833, 2360, 2342, 1629, 1612, 1585, 1511 1464, 1440, 1419, 1370, 1301, 1249, 1171, 1103, 1037, 988, 922, 895 and 815; δ_H 3.10 (2 H, d, *J* 6.3, $NCH_2CH{=}CH_2$), 3.25 (2 H, s, $NCH_2CBr{=}CH_2$), 3.57 (2 H, s, NCH_2Ar), 3.79 (3 H, s, OMe), 5.13-5.25 (2 H, m, $CH{=}CH_2$), 5.57 (1 H, s, $CBr{=}CH_2$), 5.78-5.92 (2 H, m, $CBr{=}CH_2$, $CH{=}CH_2$,), 6.85 (2 H, d, *J* 8.6, Ar 3,5-H) and 7.27 (2 H, d, *J* 8.6, Ar 2,6-H); δ_C 55.64 (OMe), 56.23 ($NCH_2CH{=}CH_2$), 57.05 (NCH_2Ar), 61.62 ($NCH_2CBr{=}CH_2$), 114.02 (Ar 3,5-C), 118.08 ($CBr{=}CH_2$), 118.47 ($NCH_2CH{=}CH_2$), 130.29 (Ar 2,6-C), 131.25 ($CBr{=}CH_2$), 132.67 (Ar 1-C), 135.75 ($NCH_2CH{=}CH_2$) and 159.06 (Ar 4-C); *m/z* 297 (M^+, $C_{14}H_{18}{}^{81}BrNO$, 22 %), 295 (M^+, $C_{14}H_{18}{}^{79}BrNO$, 22 %), 216 (18), 190 (39), 122 (57), 121 (100), 91 (18), 78 (30), 77 (27) and 41 (17).

2-Allyl-2-(2-bromoallyl)malonic acid dimethyl ester 84



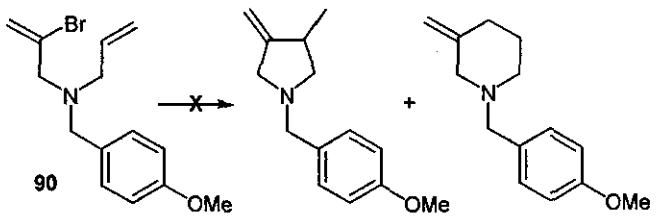
84

A solution of sodium (0.50 g, 21.5 mmol) in MeOH (10 ml) was added dropwise to a solution of dimethyl allylmalonate (3.0 g, 17.42 mmol) in MeOH (40 cm^3) and the mixture stirred for 10 min. 2,3-Dibromopropene (4.20 g, 21.0 mmol) was added dropwise and the resulting mixture stirred at ambient temperature for 20 h. The reaction was quenched by water and extracted into DCM. Drying ($MgSO_4$) and evaporation to dryness gave the crude product, which was purified by column chromatography (light petroleum:EtOAc; 6:1) to give 2-allyl-2-(2-bromo-allyl)malonic acid dimethyl ester (2.73 g, 9.4 mmol, 54 %) as a colourless oil; (Found: $(M\text{-}H)^+$, 289.0080, $C_{11}H_{14}{}^{79}BrO_4$ requires 289.0026), δ_H (400 MHz) 2.77 (2 H, d, *J* 7.6, $CH_2CH{=}CH_2$), 3.15 (2 H, s, $CH_2C(Br){=}CH_2$), 3.74 (6 H, s, Me), 5.11-5.15 (2 H,

m, $CH_2CH{=}CH_2$) and 5.60-5.69 (3 H, m, $CH_2CH{=}CH_2$ and $CH_2C(Br){=}CH_2$); δ_C 36.16 ($CH_2CH{=}CH_2$), 43.12 ($CH_2C(Br){=}CH_2$), 52.68 (Me), 57.04 (C_q), 119.67 ($CH_2C(Br){=}CH_2$), 122.21 ($CH_2CH{=}CH_2$), 127.00 ($CH_2C(Br){=}CH_2$), 132.05 ($CH_2CH{=}CH_2$) and 170.54 (C=O); m/z 291 (M^+, ^{81}Br, 6 %), 289 (M^+, ^{79}Br, 7 %), 271 (6), 269 (7), 211 (100), 199 (8), 171 (7), 151 (42), 139 (25), 91 (68), 77 (26), 59 (37) and 41 (23).

3.7.2 Radical cyclisation of vinylic precursors

Attempted radical cyclisation of allyl-(2-bromoallyl)-(4-methoxybenzyl)amine 90



Employing TBTH as radical mediator:

TBTH (0.24 g, 0.84 mmol) was added to a solution of allyl-(2-bromoallyl)-(4-methoxybenzyl)amine **90** (0.11 g, 0.37 mmol) in anhydrous toluene (30 cm^3) and the mixture heated to reflux. ACCN (0.1 g, 0.41 mmol in total) was added initially and then in small portions every 45 min. After refluxing for 2 h, the mixture was cooled to ambient temperature and evaporated to dryness. ^{1}H-NMR of the crude reaction mixture revealed signs of cyclic product, but column chromatography (light petroleum:DCM; 5:1) on silica appeared to cleave off the PMB group and only led to a complex mixture of products. Repetition of the reaction followed by chromatography on neutral alumina did not improve the outcome the reaction.

Employing TBGH as radical mediator:

Allyl-(2-bromoallyl)-(4-methoxybenzyl)amine **90** (0.11 g, 0.37 mmol) in anhydrous toluene (30 cm^3) was reacted with TBGH (0.11 g, 0.44 mmol) and ACCN (0.1 g, 0.41 mmol in total) in accordance with the procedure detailed above, with the same conclusion as in the TBTH promoted reaction. Repetition of the reaction followed by chromatography on neutral alumina did not improve the outcome the reaction.

Employing TBGH as radical mediator in the presence of PhSH:

Applying the same procedure as detailed above, the same lack of cyclic products was detected.

Radical cyclisation of 2-allyl-2-(2-bromoallyl)malonic acid dimethyl ester 84

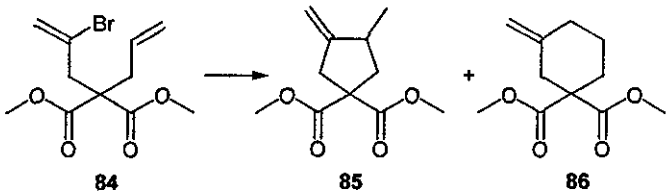


Table 40, entry 1:

General procedure:

TBTH (0.10 g, 0.35 mmol) was added to a solution of 2-allyl-2-(2-bromoallyl)malonic acid dimethyl ester **84** (92.0 mg, 0.32 mmol) in anhydrous toluene (18 cm^3) and the mixture heated to reflux. AMBN (30.0 mg, 0.16 mmol in total) was added initially and then in small portions every 45 min. After refluxing for 4 h, the mixture was cooled to ambient temperature and evaporated to dryness. Column chromatography (light petroleum:EtOAc; 19:1) gave a mixture of isomere products 3-methyl-4-methylene-cyclopentane-1,1-dicarboxylic acid dimethyl ester **85** and 3-methylene-cyclohexane-1,1-dicarboxylic acid dimethyl ester **86** (**85**:**86**; 2:1.1, 58.7 mg, 0.28 mmol, 88 % in total).[91] **85**: δ_H 1.11 (3 H, d, *J* 6.0, Me), 1.76-1.80 (2 H, m, 2-H), 2.55-2.59 (1 H, m, 3-H), 2.92-297 (1 H, m, 5-H), 3.04-3.08 (1 H, m, 5-H), 3.72 (3 H, s, CO_2Me), 3.73 (3 H, s, CO_2Me), 4.81 (1 H, s, C=C*H*) and 4.91 (1 H, s, C=C*H*); δ_C 18.33 (Me), 37.65 (3-C), 40.97 (2-C), 42.61 (5-C), 53.12 (CO_2*Me*), 53.17 (CO_2*Me*), 58.51 (1-C), 105.98 (=*C*H_2), 144.42 (4-C), 172.71 (C=O) and 172.84 (C=O); *m/z* 212 (M^+, 3 %), 181 (8), 180 (6), 153 (9), 152 (78), 121 (17), 93 (100), 91 (26) and 77 (23). **86**: δ_H 1.63-1.76 (2 H, m, 5-H), 2.04-2.14 (4 H, m, 4,6-H), 2.68 (2 H, s, 2-C), 3.72 (3 H, s, CO_2Me) and 4.74 (2 H, s, C=CH_2); δ_C 24.57 (5-C), 31.55 (4-C), 34.25 (6-C), 40.05 (2-C), 52.93 (CO_2*Me*), 57.13 (1-C), 111.06 (C=*C*H_2), 153.53 (3-C) and 172.03 (C=O); *m/z* 212 (M^+, 6 %), 181 (4), 180 (10), 153 (15), 152 (80), 121 (21), 93 (100), 91 (34) and 77 (21).

Table 40, entry 2:

Following the general procedure, 2-allyl-2-(2-bromoallyl)malonic acid dimethyl ester **84** (0.11 g, 0.36 mmol) was reacted with TBGH (0.10 g, 0.4 mmol) to give a mixture of 3-methyl-4-methylene-cyclopentane-1,1-dicarboxylic acid dimethyl ester **85** and 3-methylene-cyclohexane-1,1-dicarboxylic acid dimethyl ester **86** in 11 % and 4 % yields respectively along with undetermined amounts of the corresponding addition products **91** and **92** as determined by the use of 1,4-dimethoxybenzene as the internal standard in ^{1}H-NMR spectroscopy. **91** and **92**: *m/z* 456 (M^+, 10 %), 399 (29), 245 (36), 189 (100), 133 (63), 131 (62), 91 (53), 55 (32) and 41 (27).

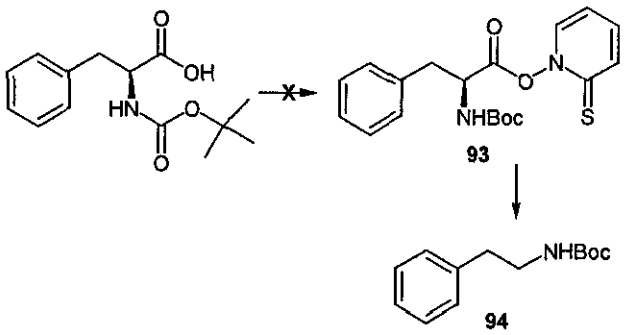
Table 40, entry 3:

Following the general procedure, 2-allyl-2-(2-bromoallyl)malonic acid dimethyl ester (0.10 g, 0.34 mmol) was reacted with TBGH (0.13 g, 0.52 mmol), AMBN (60.0 mg, 0.37 mmol) and PhSH (3.8 mg, 0.03 mmol) for 5 h. The yields of 3-methyl-4-methylene-cyclopentane-1,1-dicarboxylic acid dimethyl ester **85** (33 %), 3-methylene-cyclohexane-1,1-dicarboxylic acid dimethyl ester **86** (5 %) and unreacted starting material **84** (13 %) were determined by the use of 1,4-dimethoxybenzene as the internal standard in ^{1}H-NMR spectroscopy.

3.8 Experimentals for Chapter 2.7

3.8.1 Formation and decarboxylations of Barton-esters

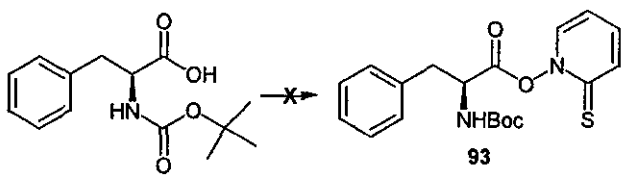
Attempted formation and radical decarboxylation of the Barton ester 93[75]



N-Methylmorpholine (0.10 g, 1.0 mmol) and isobutyl chloroformate (0.14 g, 1.0 mmol) were added to a mixture of *N*-Boc-L-phenylalanine (0.27 g, 1.0 mmol) in

anhydrous THF (5 cm^3) at –15 °C and the reaction shielded from light with aluminum foil. After stirring for 10 min at this temperature, a solution of triethylamine (0.12 g, 1.2 mmol) and *N*-hydroxy-2-thiopyridone (0.15 g, 1.2 mmol) in anhydrous THF (3 cm^3) was added. While keeping the temperature at –15 °C, the mixture was stirred for 1 h. Still under aluminum foil protection, the precipitate was removed by filtration, washed with cold, anhydrous THF and the combined organic phases were evaporated to give a yellow-green oil. The crude material was dissolved in anhydrous toluene (20 cm^3) and divided between two flasks. To one flask, TBTH (0.29 g, 1.0 mmol) was added and TBGH (0.25 g, 1.0 mmol) to the other. Both radical reactions, continuously under aluminum foil protection, were heated to reflux, added AIBN (15.0 mg, 0.09 mmol in each case) and refluxed for 1 h. After cooling to ambient temperature and evaporation to dryness, diethyl ether was added and the organic layer washed with aqueous, saturated $NaHCO_3$, H_2O, aqueous HCl, H_2O and finally with brine, before drying ($MgSO_4$) and evaporation to dryness. ^{1}H-NMR spectroscopy showed in both cases a complex mixture of products, which was also the case after column chromatography. The products were not identified.

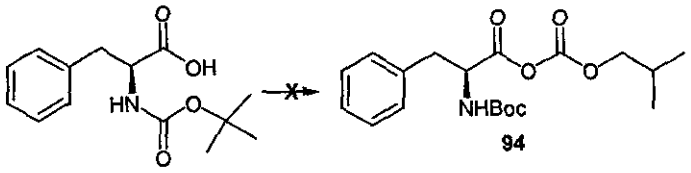
Attempted formation of the Barton Ester 93[75]



93

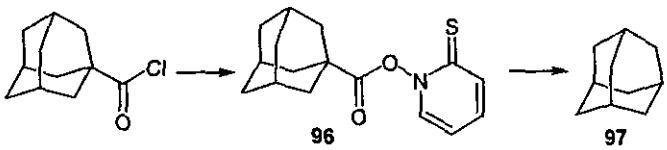
N-Methylmorpholine (0.10 g, 1.0 mmol) and isobutyl chloroformate (0.14 g, 1.0 mmol) were added to a mixture of *N*-Boc-L-phenylalanine (0.27 g, 1.0 mmol) in anhydrous THF (5 cm^3) at –15 °C and the reaction shielded from light with aluminum foil. After stirring for 10 min at this temperature, a solution of triethylamine (0.12 g, 1.2 mmol) and *N*-hydroxy-2-thiopyridone (0.15 g, 1.2 mmol) in anhydrous THF (3 cm^3) was added. While keeping the temperature at –15 °C, the mixture was stirred for 2 h. Still under aluminum foil protection, the precipitate was removed by filtration, washed with cold anhydrous THF and the combined organic phases were evaporated to dryness to give a yellow-green oil. TLC showed two yellow spots but after column chromatography (light petroleum:EtOAc; 1:1) was the outcome of the reaction very complex. The products were not identified.

Attempted formation of the mixed anhydride 94[75]



Et_3N (0.19 g, 1.89 mmol) was added to a solution of *N*-Boc-L-phenylalanine (0.5 g, 1.88 mmol) in anhydrous THF (5 cm^3) and the mixture cooled to 0 °C at which temperature isobutyl chloroformate (0.26 g, 1.89 mmol) was added dropwise. A white precipitate was observed almost immediately and the mixture stirred at 0 °C for 3 h. The precipitate was removed by filtration and the filtrate evaporated to dryness. The ^{1}H-NMR spectrum of the crude reaction mixture did not show any signals corresponding to the desired mixed anhydride and the mixture was not purified.

Formation and radical decarboxylation of Barton ester 96[75]



Employing TBTH as radical mediator:

DMAP (60.0 mg, 0.5 mmol) was added to a solution of *N*-hydroxy-2-thiopyridone (76 mg, 0.6 mmol) in anhydrous toluene (5 cm^3) and the mixture heated to reflux. A solution of adamatane-carbonyl chloride (0.10 g, 0.5 mmol) in anhydrous toluene (2.5 cm^3) was added dropwise and the resulting mixture stirred at reflux for 15 min before adding TBTH (0.44 g, 1.5 mmol) and AIBN (15 mg, 0.09 mmol) followed by heating at reflux for 1 h. The reaction mixture was cooled to 80 °C and, after addition of carbontetrachloride (10 cm^3), stirred at this temperature for 1 h, cooled to ambient temperature and evaporated to dryness. Potassium fluoride (5 cm^3) and a solution of iodine (few crystals) in DCM (5 cm^3) were added and the mixture stirred at ambient temperature for 18 h. The white precipitate was removed by filtration and washed with DCM. The aqueous layer was separated and extracted into DCM. The combined organic phases were washed with aqueous sodium thiosulfate, water and brine, dried ($MgSO_4$) and evaporated to dryness to give a yellow semi-solid. Careful

recrystallisation from EtOH gave adamatane **97** (55.2 mg, 0.41 mmol, 81 %) as a white solid. All data are identical to those of commercial material.

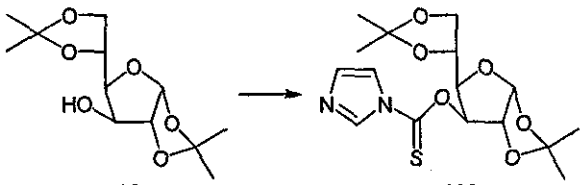
Employing TBGH as radical mediator:

Employing the amounts and method detailed above, adamatane-carbonyl chloride (0.10 g, 0.5 mmol) was reacted with TBGH (0.37 g, 1.5 mmol) to give adamatane **97** (22.3 mg, 0.16 mmol, 33 %) as a white solid.

3.8.2 Formation and radical reactions of thiocarbonyl derivatives

3.8.2.1 Synthesis of thiocarbonyl imidazolides precursors

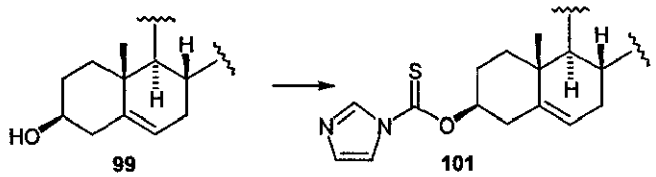
1,2:5,6-Di-*O*-isopropylidene-3-*O*-thiocarbonylimidazole-α-D-glucofuranose 100[92]



98 100

Thiocarbonyl diimidazole (1.40 g, 7.7 mmol) and DMAP (0.02 g, 0.1 mmol) were added to a solution of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (1.00 g, 3.8 mmol) in acetonitrile (30 cm^3) and the mixture refluxed for 150 min. Cooling to room temperature and evaporating the mixture to dryness gave 1,2:5,6-di-*O*-isopropylidene-3-*O*-thiocarbonylimidazole-α-D-glucofuranose **100** as a pale yellow gummy oil (1.44 g, 3.8 mmol, 100 %) which did not need further purification. δ_H 1.29 (3 H, s, Me), 1.35 (3 H, s, Me), 1.42 (3 H, s, Me), 1.59 (3 H, s, Me), 4.07-4.15 (2 H, m, 5,6_b-H), 4.31 (2 H, m, 4,6_a-H), 4.77 (1 H, d, *J* 3.8, 2-H), 5.84 (1 H, d, *J* 2.1, 3-H), 5.96 (1 H, d, *J* 3.8, 1-H), 7.06 (1 H, s, Im 5-H), 7.62 (1 H, s, Im 4-H) and 8.32 (1 H, s, Im 2-H); δ_C 25.1 (Me); 26.2 (Me) 26.6 (Me), 26.9 (Me), 67.6 (6-C), 72.4 (4-C), 79.8 (3-C), 82.7 (5-C), 84.5 (2-C), 105.5 (1-C), 109.9 (C_q), 112.8 (C_q), 117.9 (Im 5-C), 131.2 (Im 4-C), 136.8 (Im 2-C) and 182.45 (C=S); *m/z* 371 (M^++1, 2 %), 355 (10), 303 (10), 244 (10), 211 (10), 111 (15), 101 (90), 68 (70), 59 (35) and 43 (100).

Cholesteryl-1-thiocarbonylimidazole 101[78]

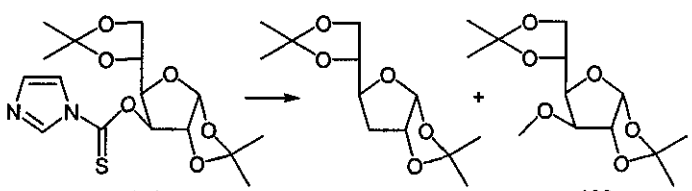


99 101

Thiocarbonyl diimidazole (1.98 g, 11.1 mmol) and a catalytic amount of DMAP (20 mol %) were added to a stirred solution of cholesterol **99** (2.0 g, 5.2 mmol) in acetonitrile (40 cm^3) and the mixture heated at reflux for 23 h. Cooling to room temperature, evaporation of solvent and recrystallisation from Et_2O gave the cholesterol derivative **101** as a white powder (2.16 g, 4.3 mmol, 84 %).[78] (Found: C, 75.20; H, 9.70, N, 5.55. $C_{31}H_{48}ON_2S$ requires: C, 74.95; H, 9.74, N, 5.64) δ_H 0.69 (3 H, s, Me), 0.86-2.11 (38 H, m), 2.56 (2 H, m, H_B), 5.34 (1 H, m, H_C), 5.46 (1 H, bd, *J* 4.9, H_A), 7.03 (1 H, s, Im 2-H), 7.64 (1 H, s, Im 4-H) and 8.34 (1 H, s, Im 5-H); δ_C 12.26 (CH or CH_3), 19.12 (CH or CH_3), 19.72 (CH or CH_3), 21.44 (CH_2), 22.97 (CH or CH_3), 23.23 (CH or CH_3), 24.22 (CH_2), 24.67 (CH_2), 27.44 (CH_2), 28.41 (CH or CH_3), 28.68 (CH_2), 32.21 (CH_2), 32.31 (CH or CH_3), 36.17 (CH or CH_3), 36.57 (CH_2), 37.00 (CH_2), 37.13 (CH_2), 37.60 (C_q), 39.90 (CH_2), 40.07 (CH_2), 42.69 (C_q), 50.34 (CH or CH_3), 56.50 (CH or CH_3), 57.03 (CH or CH_3), 84.01 (*C*HOR), 118.27 (C=*C*H), 124.25 (Im 4-C), 131.01 (Im 5-H), 137.14 (Im 4-H), 138.90 (*C*=CH) and 183.68 (C=S).

3.8.2.2 Radical deoxygenation of thiocarbonyl imidazolides

Radical deoxygenation of 1,2:5,6-di-*O*-isopropylidene-3-*O*-thiocarbonylimidazole-α-D-glucofuranose 100



100 102 103

Table 41, entry 1:

1,2:5,6-di-*O*-isopropylidene-3-*O*-thiocarbonylimidazole-α-D-glucofuranose **100** (0.15 g, 0.4 mmol) in anhydrous toluene (5 cm^3) was added dropwise to a refluxing solution

of TBTH (0.94 g, 3.2 mmol) in anhydrous toluene (5 cm^3) and the mixture was refluxed for 90 min. Cooling to room temperature and evaporation to dryness followed by column chromatography (light petroleum:EtOAc; 3:1) gave 3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose **102** and 1,2:5,6-di-*O*-isopropylidene-3-*O*-methyl-α-D-glucofuranose **103** in 29 and 28 % yield respectively as determined by the use of 1,4-dinitrobenzene as the internal standard in ^{1}H-NMR spectroscopy. **102**:[78,93] δ_H 1.27 (3 H, s, Me), 1.31 (3 H, s, Me), 1.37 (3 H, s, Me), 1.46 (3 H, s, Me), 1.66-1.77 (1 H, m, 3-H), 2.14 (1 H, dd, *J* 13.0 and 3.5, 3-H), 3.73-3.81 (1 H, m, 5-H), 4.02-4.15 (3 H, m, 4,6-H), 4.71 (1 H, dd, *J* 3.7 and 3.7, 2-H) and 5.76 (1 H, d, *J* 3.7, 1-H); δ_C 25.5 (Me), 26.3 (Me), 26.8 (Me), 27.1 (Me), 35.6 (3-C), 67.5 (6-C), 77.1 (2-C), 79.0 (5-C), 80.8 (4-C), 106.0 (1-C), 109.9 (C_q), and 111.6 (C_q); *m/z* 245 (2 %), 229 (60), 171 (8), 143 (60), 111 (65), 101 (48), 85 (70), 83 (50), 59 (75), 54 (90) and 43 (100). **103**:[94] δ_H 1.29 (3 H, s, Me), 1.33 (3 H, s, Me), 1.40 (3 H, s, Me), 1.48 (3 H, s, Me), 3.42 (3 H, s, OMe), 3.74 (1 H, d, *J* 3.0, 3-H), 3.97 (1 H, dd, *J* 8.80 and 5.78, 6-H), 4.02-4.18 (2 H, m, 4,6-H), 4.27 (1 H, dt, *J* 7.88 and 5.78, 5-H), 4.54 (1 H, d, *J* 3.9, 2-H) and.5.83 (1 H, d, *J* 3.7, 1-H); δ_C 25.27 (Me), 26.63 (Me), 26.88 (Me), 26.99 (Me), 58.19 (OMe), 66.97 (4-C), 72.45 (6-C), 80.89 (3-C), 81.50 (5-C), 83.56 (2-C), 105,16 (C_q), 109.22 (1-C) and 111.59 (C_q).

Table 41, entry 2:

1,2:5,6-Di-*O*-isopropylidene-3-*O*-thiocarbonylimidazole-α-D-glucofuranose **100** (0.19 g, 0.5 mmol) in anhydrous toluene (5 cm^3) was added dropwise to a refluxing solution of TBGH (0.66 g, 2.7 mmol) in anhydrous toluene (5 cm^3) and the mixture was refluxed for 90 min. Cooling to room temperature and evaporation to dryness followed by column chromatography (light petroleum:EtOAc; 3:1) gave 3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose **102** as a pale yellow oil (0.11 g, 0.4 mmol, 87 %).

Radical deoxygenation of cholesteryl 1-thiocarbonylimidazole

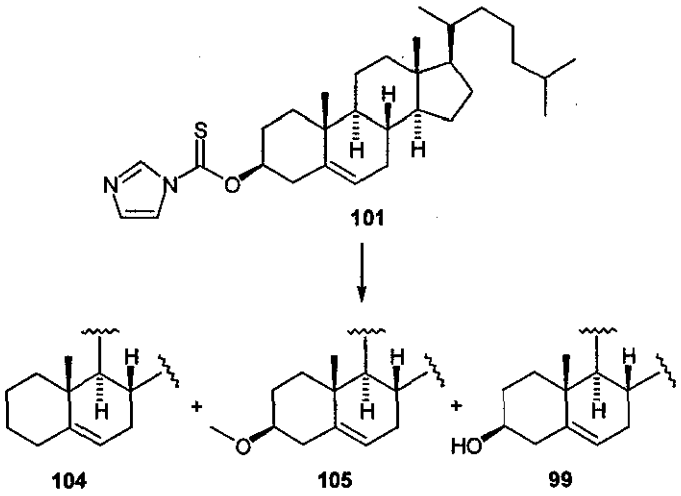


Table 42, entry 1:

A solution of cholesteryl-1-thiocarbonylimidazole **101** (0.1 g, 0.2 mmol) in anhydrous toluene (5 cm^3) was added dropwise to a refluxing solution of TBTH (0.2 g, 0.4 mmol) in anhydrous toluene (4 cm^3) and the mixture refluxed for 3 h. ACCN (0.12 g, 0.5 mmol in total) was added initially and then every 45 min. Cooling to room temperature, evaporation of solvent, column chromatography (light petroleum on alumina), followed by recrystallisation from EtOH gave cholest-5-ene **104** as a white solid (40 mg, 0.1 mmol, 54 %); mp 87-89 °C (lit.[92] 88-89 °C); (Found: C: 87.56, H: 12.48, $C_{27}H_{46}$ requires C: 87.49, H: 12.51); δ_H (400 MHz) 0.68 (3 H, s, Me), 0.86 (3 H, d, *J* 6.8, Me), 0.87 (3 H, d, *J* 6.4, Me), 0.92 (3 H, d, *J* 6.4, Me), 1.00 (3 H, s, Me), 0.98-2.02 (29 H, m), 2.23 (2 H, m, H_B) and 5.27 (1 H, t, *J* 2.0, C=C*H*); δ_C 11.89 (CH or CH_3), 18.74 (CH or CH_3), 19.48 (CH or CH_3), 20.79 (CH_2), 22.58 (CH or CH_3), 22.59 (CH_2), 22.83 (CH or CH_3), 23.86 (CH_2), 24.30 (CH_2), 28.03 (CH or CH_3), 28.09 (CH_2), 28.27 (CH_2), 31.87 (CH or CH_3), 31.91 (CH_2), 32.92 (CH_2), 35.82 (CH or CH_3), 36.23 (CH_2), 37.56 (C_q), 39.55 (CH_2), 39.90 (CH_2), 42.33 (C_q), 50.63 (CH or CH_3), 56.20 (CH or CH_3), 56.91 (CH or CH_3), 118.99 (C=CH) and 143.74 (*C*=CH).

Table 42, entry 2:

Following the procedure described above, cholesteryl-1-thiocarbonylimidazole **101** (0.1 g, 0.2 mmol) was reacted with TBGH (0.1 g, 0.4 mmol) to give cholest-5-ene **104** as a white solid (45 mg, 0.1 mmol, 60 %).

Table 42, entry 3:

TBGH (0.1 g, 0.4 mmol) was added dropwise to a refluxing solution of cholesteryl-1-thiocarbonylimidazole **101** (0.1 g, 0.2 mmol) in anhydrous toluene (9 cm^3) and the mixture refluxed for 3 h. ACCN (0.123 g, 0.5 mmol in total) was added initially and then every 45 min. Cooling to room temperature, evaporation of solvent, column chromatography (light petroleum on alumina), followed by recrystallisation from EtOH gave cholest-5-ene **104** as a white solid (50 mg, 0.14 mmol, 67 %).

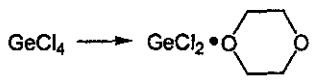
Table 42, entry 4:

Following the procedure described above, cholesteryl-1-thiocarbonylimidazole (0.1 g, 0.2 mmol) was reacted with TBTH (0.2 g, 0.4 mmol) to give cholest-5-ene **104** (5 %), cholesterol **99** (51 %) and the OMe product **105** (11 %). Due to unsuccessful purification of these products, the yields are determined by the use of 1,4-dimethoxybenzene as the internal standard in ^{1}H-NMR spectroscopy. **99**: All spectral data were identical to those of commercial material. **105**:[95] δ_H 0.65 (3 H, s, Me), 0.86 (3 H, d, *J* 6.8, Me), 0.87 (3 H, d, *J* 6.4, Me), 0.92 (3 H, d, *J* 6.4, Me), 1.00 (3 H, s, Me), 0.98-2.02 (29 H, m), 2.23 (2 H, m, H_B), 3.06 (1 H, m, C*H*OMe), 3.35 (3 H, s, OMe) and 5.35 (1 H, d, *J* 5.0, C=C*H*); δ_C 11.86 (CH or CH_3), 18.72 (CH or CH_3), 19.38 (CH or CH_3), 21.07 (CH_2), 22.60 (CH or CH_3), 22.83 (CH or CH_3), 23.91 (CH_2), 24.29 (CH_2), 28.02 (CH or CH_3), 28.13 (CH_2), 28.24 (CH_2), 31.88 (CH or CH_3), 31.93 (CH_2), 35.83 (CH or CH_3), 36.79 (CH_2), 37.17 (C_q), 37.24 (CH_2), 38.76 (CH_2), 39.51 (CH_2), 39.78 (CH_2), 42.32 (C_q), 50.14 (CH or CH_3), 56.14 (OMe), 56.21 (CH or CH_3), 56.78 (CH or CH_3), 80.35 (*C*HOMe), 121.60 (C=*C*H) and 140.88.

3.9 Experimentals for Chapter 2.8

3.9.1 Synthesis of 4-(2-dimethylgermylethyl)phenol and derivatives

Dichlorogermylene/1,4-dioxane complex 109[81]



109

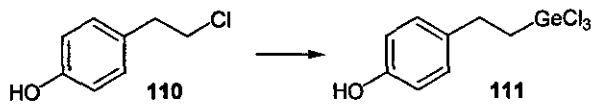
A solution of germanium tetrachloride (25.0 g, 0.12 mol) and tetramethyldisiloxane (15.66 g, 0.12 mol) in anhydrous 1,4-dioxane (53 cm^3) was heated at reflux for 3 h and allowed to cool to room temperature overnight. After further cooling to 0 °C the white precipitate was collected by vacuum filtration and washed with cold dichloromethane to give the dichlorogermylene/1,4-dioxane complex **109** as a white powder (21.6 g, 93.3 mmol, 80%); mp 178-181 °C (decomp.) (lit.[81] 179-182 °C). ν_{max} (KBr) /cm^{-1} 1450, 1350, 1290, 1252, 1105, 1060, 1040, 870, 850 and 610.

4-(2-Chloroethyl)phenol 110[81]

110

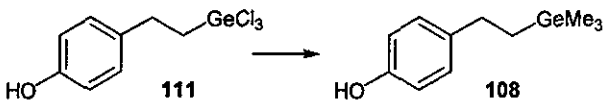
A mixture of 4-hydroxyphenethyl alcohol (25.0 g, 0.18 mol) and concentrated hydrochloric acid (150 cm^3) was heated at 110 °C for 18 h. After cooling to ambient temperature, the mixture was poured into water and extracted with diethyl ether. The organic layer was dried ($MgSO_4$) and evaporated to dryness to give 4-(2-chloroethyl)phenol **110** as a pale yellow oil (28.7 g, 0.18 mol, 100 %). δ_H (400 MHz) 2.99 (2 H, t, *J* 7.6, 1-H), 3.67 (2 H, t, *J* 7.2, 2-H), 4.74 (1 H, bs, OH), 6.78 (2 H, *J* 8.7, Ar 3,5-H) and 7.09 (2 H, d, *J* 8.7, Ar 2,6-H); δ_C 38.69 (1-C), 45.81 (2-C), 115.94 (Ar 3,5-C), 130.54 (Ar 2,6-C), 130.93 (Ar 1-C) and 154.6 (Ar 1-C); *m/z* 156 (M^+, 24 %), 107 (100), 91 (17), 77 (33) and 49 (48).

4-(2-Trichlorogermylethyl)phenol 111[81]



A mixture of the dichlorogermylene/1,4-dioxane complex **109** (23.5 g, 0.10 mol) and 4-(2-chloroethyl)phenol **110** (15.9 g, 0.1 mol) was heated at 140 °C for 18 h. After cooling to ambient temperature, the solution was poured into DCM and this mixture added dropwise to water. The resulting yellow precipitate was collected by filtration, washed successively with DCM (to remove traces of starting material) and water (to remove water-soluble monomeric germanium oxide impurities resulting from hydrolysis of any excess dichlorogermylene complex) and dried by suction. The white powder was dissolved in concentrated hydrochloric acid and extracted into DCM. The organic layer was dried ($MgSO_4$) and evaporated to dryness to give 4-(2-trichlorogermylethyl)phenol **111** as a colourless (slightly white) oil (31.0 g, 0.1 mol, 100%). ν_{max} /cm^{-1} 3338, 2446, 1175 and 829; δ_H (400 MHz) 2.31 (2 H, t, *J* 7.6, 1-H), 2.93-2.98 (2 H, m, 2-H), 6.79 (2 H, *J* 8.7, Ar 3,5-H) and 7.09 (2 H, d, *J* 9.0, Ar 2,6-H); δ_C 28.58 (1-C), 34.62 (2-C), 116.23 (Ar 2,6-C), 129.83 (Ar 3,5-C), 132.17 (Ar 4-C) and 154.44 (Ar 1-C).

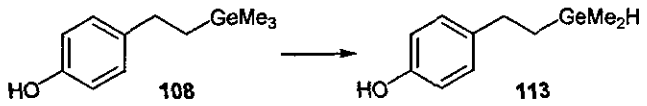
4-(2-Trimethylgermylethyl)phenol 108[81]



Methylmagnesium bromide (3.0 M in diethyl ether, 0.60 mol) was added dropwise to a solution of 4-(2-trichlorogermylethyl)phenol **111** (30.0 g, 0.10 mol) in anhydrous toluene (120 cm^3) at 0 °C and the resulting mixture refluxed for 17 h. After cooling to ambient temperature, aqueous hydrochloric acid (1 M) was carefully added to the "semi-solid" obtained, which was then extracted into diethyl ether. The organic layer was dried ($MgSO_4$) and evaporated to dryness to give a brown oil, which was purified by column chromatography (light petroleum:EtOAc; 9:1) to give 4-(2-trimethylgermylethyl)phenol **108** as a pale yellow oil (22.5 g, 94.2 mmol, 94 %); mp 47-49 °C (lit.[81] 47-48 °C); δ_H (400 MHz) 0.09 (9 H, s, Me), 0.98-1.04 (2 H, m, 1-H), 2.58-2.64 (2 H, m, 2-H), 4.63 (1 H, bs, OH), 6.74 (2 H, *J* 8.8, Ar 3,5-H) and.7.06 (2 H,

d, *J* 9.0, Ar 2,6-H); δ_C –2.40 (Me), 18.72 (1-C), 30.36 (2-C), 115.76 (Ar 2,6-C), 128.46 (Ar 3,5-C), 137.28 (Ar 4-C) and 153.26 (Ar 1-C);

4-(2-Dimethylgermylethyl)phenol 113



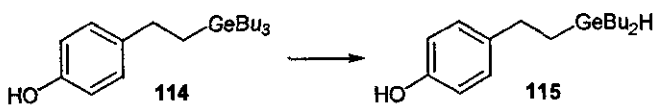
Tin(IV)chloride (6.75 g, 27.0 mmol) was added dropwise to a solution of 4-(2-trimethylgermylethyl)phenol **108** (6.20 g, 26.0 mmol) in nitromethane (55 cm^3), and the mixture stirred at 50 °C overnight. The mixture was cooled to room temperature and evaporated to dryness. The resulting black oil was dissolved in methanol (125 cm^3). Sodium borohydride (1.00 g, 26.5 mmol) was added and the mixture stirred for 3 h. Addition of water and methanol, extraction into DCM, drying ($MgSO_4$) and evaporation to dryness gave a mixture of the product, 4-(2-chlorodimethyl-germylethyl)phenol **113** and unreacted 4-(2-trimethylgermylethyl)phenol **108**. The mixture was dissolved in methanol (125 cm^3) and $NaBH_4$ (1.00 g, 26.4 mmol) added and stirred for 4 h. Work-up as detailed above, followed by column chromatography (light petroleum:EtOAc, 93:7) to remove the unreacted **108**, gave 4-(2-dimethylgermylethyl)phenol **113** as a colourless oil (3.92 g, 17.4 mmol, 67 %). (Found: $(M\text{-}H)^+$, 225.0335, $C_{10}H_{15}GeO$ requires 225.0337); ν_{max} /cm^{-1} 3331, 2924, 2021, 1612, 1599, 1510, 1364, 1236, 1173 and 833; δ_H (400 MHz) 0.26 (9 H, s, Me), 1.16-1.21 (2 H, m, 1-H), 2.70-2.74 (2 H, m, 2-H), 3.90 (1 H, nonet, *J* 3.4, Ge-H), 6.05 (1 H, bs, OH), 6.82 (2 H, *J* 8.8, Ar 3,5-H) and 7.11 (2 H, d, *J* 8.8, Ar 2,6-H); δ_C –4.31 (Me), 17.45 (1-C), 31.90 (2-C), 116.06 (Ar 2,6-C), 129.81 (Ar 3,5-C), 137.64 (Ar 4-C) and 154.19 (Ar 1-C); *m/z* 225 (M^+, 100 %), 197 (43), 165 (16) and 104 (52).

4-(2-Tributylgermylethyl)phenol 114

n-Butylmagnesium bromide (8.0 g, 49.9 mmol) was added dropwise to a solution of 4-(2-trichlorogermylethyl)phenol **111** (2.50 g, 8.3 mmol) in anhydrous toluene (10 cm^3) at 0 °C and the resulting mixture was refluxed for 17 h. After cooling to ambient

temperature, aqueous hydrochloric acid (1.0 M) was carefully added to the 'semi-solid' obtained, this was then extracted into diethyl ether. The organic layer was dried ($MgSO_4$) and evaporated to dryness to give a brown oil, which was purified by column chromatography (light petroleum:EtOAc; 9:1) to give 4-(2-tributylgermylethyl)phenol **114** as a pale yellow oil (1.79 g, 4.9 mmol, 59 %). (Found: 366.1977, $C_{20}H_{36}GeO$ requires 366.1978); δ_H (400 MHz) 0.70-0.74 (6 H, q, *J* 15.9, Bu 1-H), 0.87-0.90 (9 H, m, Bu 4-H), 0.98-1.03 (2 H, m, 2-H), 1.30-1.34 (12 H, m, Bu 2,3-H), 2.57-2.61 (2 H, m, 1-H), 4.76 (1 H, bs, OH), 6.75 (2 H, d, *J* 8.3, Ar 3,5-H) and 7.07 (2 H, d, *J* 8.3, Ar 2,6-H); δ_C 12.46 (Bu 1-C), 13.67 (Bu 4-C), 15.03 (1-C), 26.77 (Bu 3-C), 27.50 (Bu 2-C), 30.50 (2-C), 115.09 (Ar 3,5-C), 128.82 (Ar 2,6-C), 137.89 (Ar 4-C) and 153.35 (Ar 1-C); m/z 366 (M^+, <1 %), 309 (100), 253 (33), 189 (100), 167 (20), 133 (85), 121 (21), 107 (38), 89 (21), 77 (16) and 55 (42).

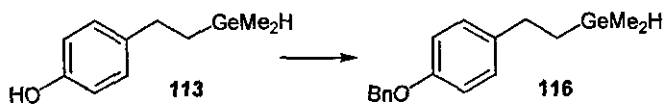
4-(2-Dibutylgermylethyl)phenol 115



Tin(IV)chloride (2.0 g, 4.4 mmol) was added dropwise to a solution of 4-(2-tributylgermylethyl)phenol **114** (1.79 g, 4.89 mmol) in nitromethane (16 cm^3), and the mixture stirred at 50 °C overnight. The mixture was cooled to ambient temperature and evaporated to dryness. The resulting oil was dissolved in methanol (25 cm^3) and sodium borohydride (0.56 g, 14.7 mmol) was added and the mixture stirred for 5 h. Addition of water and methanol, extraction into DCM, drying ($MgSO_4$) and evaporation to dryness followed by chromatography (light petroleum:EtOAc, 20:1) gave 4-(2-dibutylgermylethyl)phenol **115** as a pale brown oil (0.21 g, 0.69 mmol, 14 %). (Found: 310.1351, $C_{16}H_{28}GeO$ requires 310.1352); ν_{max} (DCM)/cm^{-1} 3328, 2956, 2925, 2869, 2852, 2004, 1612, 1512, 1454, 1234, 1172 and 725; δ_H (400 MHz) 0.78-0.83 (4 H, m, Bu 1-H), 0.87-0.90 (6 H, Bu 4-H), 1.09-1.12 (2 H, m, 2-H), 1.31-1.41 (8 H, m, Bu 2,3-H), 2.64-2.68 (2 H, m, 1-H), 3.71-3.74 (1 H, m, Ge-*H*), 5.44 (1 H, bs, OH), 6.75 (2 H, d, *J* 8.3, Ar 3,5-H), 7.07 (2 H, d, *J* 8.3, Ar 2,6-H); δ_C 11.83 (Bu 1-C), 13.77 (Bu 4-C), 14.25 (1-C), 25.99 (Bu 3-C), 28.45 (Bu 2-C), 31.55 (2-C), 115.10 (Ar 3,5-C), 128.93 (Ar 2,6-C), 137.18 (Ar 4-C) and 153.47 (Ar 1-C); *m/z* 310 (M^+, 6 %),

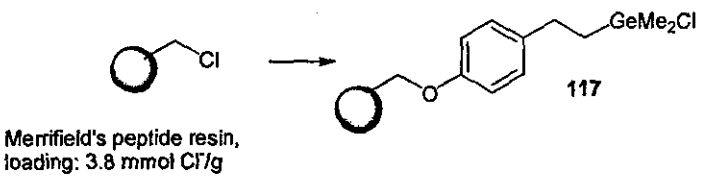
253 (100), 197 (65), 167 (29), 133 (45), 121 (41), 107 (40), 91 (24), 77 (28) and 55 (43).

4-(2-Dimethylgermylethyl)phenyl benzyl ether 116



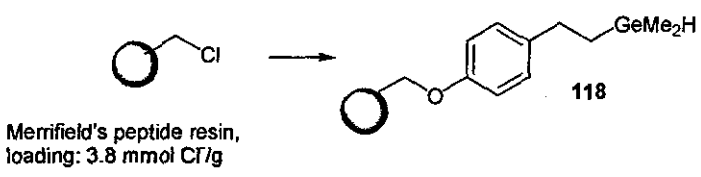
Sodium hydride (60 % in mineral oil, 0.41 g, 10.3 mmol) was added to a solution of 4-(2-dimethylgermylethyl)phenol **113** (1.34 g, 6.0 mmol) in anhydrous THF (50 cm^3) and the slurry stirred for 30 min. Benzyl bromide (1.58 g, 9.2 mmol) was added dropwise and the mixture refluxed for 3 h. After cooling to room temperature any excess NaH was destroyed by careful addition of MeOH, EtOH and H_2O. The mixture was added to water and extracted into diethyl ether, dried ($MgSO_4$) and evaporated to dryness. Column chromatography (light petroleum:EtOAc; 98:2) did not separate the desired product **116** from the excess benzyl bromide used. An alternative purification method was used in which the mixture was dissolved in anhydrous THF (50 cm^3) and diethylamine (0.71 g, 9.7 mmol) added and stirred for 3 h followed by reflux for 90 min. After cooling to room temperature aqueous HCl (1 M) was added and the mixture extracted into DCM, dried ($MgSO_4$) and evaporated to dryness to give 4-(2-dimethylgermylethyl)phenyl benzyl ether **116** as a pale yellow oil (1.65 g, 5.2 mmol, 87 %); (Found: $(M-H)^+$, 315.0811, $C_{17}H_{21}GeO$ requires 315.0808); ν_{max} /cm^{-1} 2860, 2019, 1610, 1454, 1380, 1298, 1174, 1026 and 783; δ_H (400 MHz) 0.04 (9 H, s, Me), 0.96-1.00 (2 H, m, 1-H), 2.51-2.55 (2 H, m, 2-H), 3.69 (1 H, nonet, *J* 3.4, Ge-H), 4.88 (2 H, s, C*H*$_2$Ph), 6.75 (2 H, *J* 8.8, Ar 3,5-H), 6.96 (2 H, d, *J* 8.8, Ar 2,6-H) and 7.16-7.29 (5 H, m, Ph); δ_C –5.85 (Me), 15.89 (1-C), 30.37 (2-C), 69.34 (*C*H$_2$Ph), 113.92 (Ar 2,6-C), 126.91 (Ph 2,6-C), 127.18 (Ph 4-C), 127.67 (Ar 3,5-C), 128.07 (Ph 3,5-C), 136.27 (Ar 4-C), 136.57 (Ph 1-C) and 156.20 (Ar 1-C); *m/z* 315 (M^+, 72 %), 211 (20), 177 (25), 149 (100) and 111 (24).

4-(2-Chlorodimethylgermylethyl)phenyl ether Merrifield resin 117



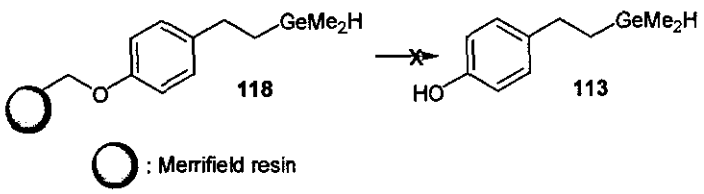
Sodium hydride (60 % in mineral oil, 0.57 g, 14.2 mmol) was added to a solution of 4-(2-chlorodimethylgermylethyl)phenol **112** (2.47 g, 9.5 mmol) in anhydrous THF (20 cm^3). The mixture was stirred for 45 min before adding it dropwise to a stirred slurry of Merrifield's peptide resin (3.8 mmol Cl^-/g, 0.50 g, 1.9 mmol) in anhydrous THF (5 cm^3). The resulting mixture was stirred at room temperature for 114 h. DCM was added to the reaction mixture and MeOH carefully added to destroy any excess NaH. The solid was collected by filtration, washed several times with DCM and H_2O and oven dried to obtain the polymer **117** as pale brown beads (0.59 g, equivalent to a loading of 1.02 mmol GeCl/g). (Found: C: 66.07 %, H: 5.65 %); ν_{max} (KBr) 2898, 2707, 1962, 1882, 1812, 1707, 1605 and 1501.

4-(2-Dimethylgermylethyl)phenyl ether Merrifield resin 118



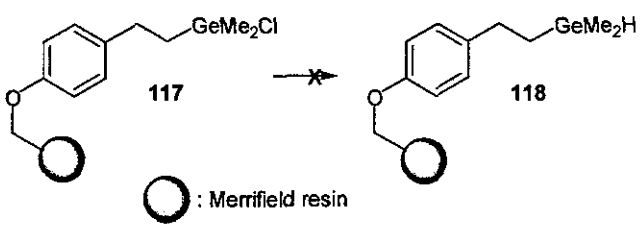
Sodium hydride (60 % in mineral oil, 0.55 g, 13.7 mmol) was added to a solution of 4-(2-dimethylgermylethyl)phenol **113** (2.15 g, 9.6 mmol) in anhydrous THF (20 cm^3). The mixture was stirred for 45 min before adding it dropwise to a stirred slurry of Merrifield's peptide resin (3.8 mmol Cl^-/g, 0.50 g, 1.9 mmol) in anhydrous THF (10 cm^3). The resulting mixture was refluxed for 17 h. DCM was added to the reaction mixture and MeOH carefully added to destroy any excess NaH. The solid was collected by filtration, washed several times with DCM and H_2O and oven dried to obtain the polymer **118** as pale brown beads (0.59 g, equivalent to a loading of 1.04 mmol GeH/g). (Found: C: 69.98 %, H: 6.50 %); ν_{max} (KBr)/cm^{-1} 3856, 2985, 2030, 1705, 1535, 1497 and 1353.

Attempted cleavage of 4-(2-dimethylgermylethyl)phenyl ether Merrifield resin



A slurry of 4-(2-dimethylgermylethyl)phenyl ether resin **118** (0.10 g, 0.1 mmol) in trifluoroacetic acid (1 cm^3) and DCM (4 cm^3) was stirred for 135 h. The resin was filtered of and washed several times with DCM and H_2O. The organic layer was dried ($MgSO_4$) and evaporated to dryness. ^{1}H-NMR spectroscopy of the crude showed no signs of cleaved product.

Attempted reduction of 4-(2-chlorodimethylgermylethyl)phenyl ether resin



Sodium borohydride (0.16 g, 4.2 mmol) was added to a stirred slurry of 4-(2-chlorodimethylgermylethyl)phenyl ether resin **117** (0.37 g, 0.38 mmol) in THF (10 cm^3) and MeOH (2 cm^3) and the mixture stirred for 135 h. DCM was added the reaction mixture and MeOH carefully added to destroy any excess $NaBH_4$. The solid was collected by filtration and washed several times with DCM and H_2O to obtain the polymer as pale brown beads (0.27 g). From mass balance and from IR spectroscopy it was concluded that no reduction had occurred.

Quadragel^{TM} mesylate 119

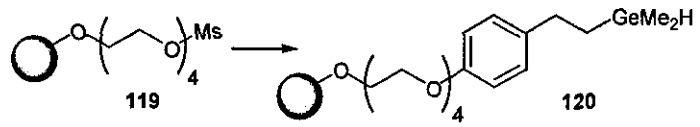
Quadragel^{TM},
loading 2.1 mmol OH/g

119

Quadragel^{TM} (9.74 g, 20.8 mmol) was swollen in pyridine (200 cm^3) and cooled to 0 °C. Mesyl chloride (11.54 g, 0.10 mol) was added over 5 min and the suspension was rotated at ambient temperature. The reaction was quenched with aqueous THF after 2

h and the resin removed by filtration and washed with aqueous THF, THF and methanol. The resin was dried *in vacuo* overnight to yield an off-white polymer **119** (11.25 g, equivalent to a loading of 2.2 mmol Ms/g). ν_{max} (KBr)/cm^{-1} 2925, 2853, 1609, 1353, 1174 and 1109; δ_H 1.36-2.05 (b, PS-C*H*$_n$), 3.04 (3 H, s, b, SO_2Me), 3.66-4.02 (b, OC*H*$_2$), 4.35 (2 H, b, C*H*$_2$OMs) and 6.56-7.04 (b, Ph-H); δ_C 37.55 (SO_2Me), 39.43-44.32 (Ph-*C*H$_n$), 67.18 (*C*H$_2$OMs), 68.87-70.48 (O*C*H$_2$), 113.91 (phenyl 2,6-C) and 125.53-127.92 (phenyl *C*H).

Quadragel^{TM}-germane 120



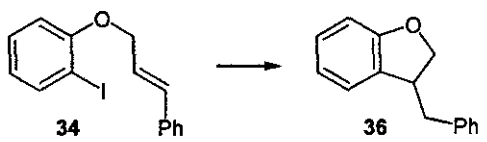
119 120

Quadragel^{TM},
loading 2.1 mmol Ms/g

Quadragel mesylate **119** (5.0 g, ~11 mmol) was swollen in DMF (70 cm^3). 4-(2-dimethylgermylethyl)phenol **113** (5.02 g, 22.3 mmol), sodium hydride (0.90 g, 22.4 mmol) and potassium iodide (3.72 g, 22.4 mmol) were added and the suspension rotated at 60 °C for 24 h. The reaction was cooled to ambient temperature, quenched with aqueous THF and the resin removed by filtration and washed with aqueous THF, THF and methanol. The resin was dried *in vacuo* overnight to yield an dark brown polymer **120** (6.97 g, equivalent to a loading of 2.2 mmol GeH/g). ν_{max} (KBr)/cm^{-1} 3379, 2929, 2028, 1658, 1606, 1196 and 1056; δ_H 0.17-0.36 (b, Me and 1-C), 1.31-1.54 (b, PS-C*H*$_n$), 2.48 (s, b, 2-C), 3.42-4.20 (b, OC*H*$_2$C*H*$_2$O), and 6.56-7.04 (b, Ph-H and Ar-H); δ_C –4.69 (Me), 16.69 (1-C), 31.46 (2-C), 39.98-44.83 (Ph-*C*H$_n$), 67.85 (*C*H$_2$O), 70.20-71.03 (O*C*H$_2$), 114.90 (Ph 2,6-C and Ar 2,6-H), 125.98-127.92 (Ph *C*H), 129.14 (Ar 3,5-C), 137.25 (Ar 4-C) and 157.24 (Ar 1-C).

3.9.2 Radical reactions employing 4-(2-dimethylgermylethyl)phenol and derivatives

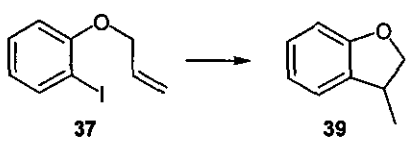
Radical cyclisation of 1-iodo-2-[(3-phenylprop-2-enyl)oxy]benzene 34



34 36

4-(Dimethylgermylethyl)phenol **113** (0.16 g, 0.7 mmol) in toluene (2 cm^3) was added dropwise to a solution of 1-iodo-2-[(3-phenylprop-2-enyl)oxy]benzene **34** (0.2 g, 0.6 mmol) in toluene (45 cm^3). The mixture was heated at reflux for 5.5 h. ACCN (0.15 g, 0.6 mmol in total) was added initially and then every 45 min. Cooling to room temperature and evaporation of the mixture to dryness gave an pale yellow oil. The yields of 3-benzyl-2,3-dihydro-benzofuran **36** (22 %) and unreacted starting material **34** (38 %) was determined by ^{1}H-NMR spectroscopy using 1,4-dinitrobenzene as the internal standard. All spectral data were identical to those of authentic material.

Radical cyclisation of 2-iodo-1-(prop-2-enyloxy)benzene 37



37 39

Table 46, entry 1:

Quadragel^{TM}-germane **120** (0.31 g, 0.68 mmol) was allowed to swell in anhydrous toluene (15 cm^3) before 2-iodo-1-(prop-2-enyloxy)benzene **37** (60.0 mg, 0.23 mmol) in anhydrous toluene (5 cm^3) and AIBN (63.0 mg, 0.38 mmol) were added. The mixture was rotated at 85 °C for 4 h with a further portion of AIBN (63.0 mg, 0.38 mmol) added after 3 h. After cooling to ambient temperature, the resin was removed by filtration and washed with DCM several times. Evaporation of the filtrate gave a pale yellow oil, which was identified as starting material by ^{1}H-NMR spectroscopy.

Table 46, entry 2:

Quadragel^{TM}-germane **120** (0.30 g, 0.66 mmol) was allowed to swell in anhydrous toluene (5 cm^3) before 2-iodo-1-(prop-2-enyloxy)benzene **37** (50.0 mg, 0.19 mmol) in anhydrous toluene (1 cm^3) and AIBN (65.0 mg, 0.39 mmol) were added. The mixture

was rotated at 95 °C for 2 h. A further portion of AIBN (50.0 mg, 0.30 mmol) was added and the oil bath temperature increased to 105 °C and the mixture rotated for 18 h. After cooling to ambient temperature, the resin was removed by filtration and washed with DCM several times. Evaporation of the filtrate gave a pale yellow oil, which was identified as a mixture of 3-methyl-2,3-dihydro-benzofuran **39** (26 %) and unreacted starting material **37** (28 %) by ^{1}H-NMR spectroscopy. Both yields are determined by the use of 1,4-dimethoxybenzene as the internal standard. All spectral data were identical to those of authentic material.

Table 46, entry 3:

Quadragel^{TM}-germane **120** (0.34 g, 0.75 mmol) was allowed to swell in anhydrous toluene (12 cm^3) before 2-iodo-1-(prop-2-enyloxy)benzene (54.0 mg, 0.21 mmol) and AIBN (0.12 g, 0.73 mmol) were added and the mixture was refluxed for 16 h. After cooling to ambient temperature, the resin was removed by filtration and washed with DCM several times. Evaporation of the filtrate gave the crude cyclic product as a yellow oil. The yield of 3-methyl-2,3-dihydro-benzofuran **39** (78 %) was determined by the use of 1,4-dimethoxybenzene as the internal standard in ^{1}H-NMR spectroscopy.

Radical cyclisation of amide precursors 45 and 46

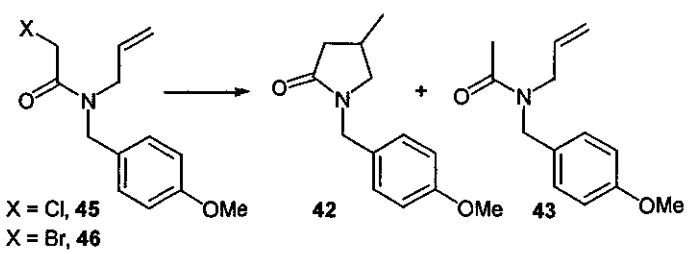


Table 44, entry 1:

4-(2-Dimethylgermylethyl)phenol **113** (0.14 g, 0.6 mmol) was added to a solution of *N*-allyl-2-chloro-*N*-(4-methoxybenzyl)acetamide **45** (0.13 g, 0.5 mmol) in anhydrous toluene (40 cm^3) and the mixture heated at reflux for 8 h, during which ACCN (0.08 g, 0.3 mmol in total) was added every hour. Cooled to room temperature and evaporated to dryness. Column chromatography (light petroleum:EtOAc; 4:1 → 1:1) gave 1-(4-methoxybenzyl)-4-methylpyrrolidin-2-one as a colourless oil **42** (0.05 g, 0.2 mmol, 47 %) along with unreacted starting material **45** (0.02 g, 0.1 mmol, 18 %) and a small

amount of *N*-allyl-*N*-(4-methoxybenzyl)acetamide **43**. All spectral data were identical to those of authentic materials.

Table 44, entry 2:

4-(2-Dimethylgermylethyl)phenyl benzyl ether **116** (0.17 g, 0.5 mmol) was added to a solution of *N*-allyl-2-chloro-*N*-(4-methoxybenzyl)acetamide **45** (0.12 g, 0.45 mmol) in anhydrous toluene (30 cm^3) and the mixture heated at reflux for 8 h, during which time ACCN (0.14 g, 0.6 mmol in total) was added every 45 min. The reaction was cooled to room temperature and evaporated to dryness. Column chromatography (light petroleum:EtOAc; 4:1 → 1:1) gave 1-(4-methoxybenzyl)-4-methylpyrrolidin-2-one **42** as a colourless oil (0.05 g, 0.2 mmol, 47 %) along with unreacted starting material **45** and *N*-allyl-*N*-(4-methoxybenzyl)acetamide **43** (2.5 mg, 0.01 mmol, 3 %).

Table 44, entry 3:

Sodium borohydride (0.05 g, 1.2 mmol) was added to a solution of *N*-allyl-2-bromo-*N*-(4-methoxybenzyl)acetamide **46** (0.23 g, 0.7 mmol) and 4-(2-dimethylgermyl-ethyl)phenyl benzyl ether **116** (0.05 g, 0.2 mmol) in anhydrous toluene (40 cm^3) and methanol (5 cm^3) and the mixture heated at reflux for 7 h, during which time ACCN (0.27 g, 1.1 mmol in total) was added every 45 min. The mixture was cooled to room temperature and evaporated to dryness. Column chromatography of the residue (light petroleum:EtOAc; 4:1 → 1:1) gave 1-(4-methoxybenzyl)-4-methylpyrrolidin-2-one **42** (0.03 g, 0.1 mmol, 18 %) along with *N*-allyl-*N*-(4-methoxybenzyl)acetamide **43** (0.09 g, 0.4 mmol, 50 %).

Table 47, entry 1:

4-(2-Dimethylgermylethyl)phenyl ether Merrifield resin **118** (0.19 g, 0.2 mmol) was added to a solution of *N*-allyl-2-bromo-*N*-(4-methoxybenzyl)acetamide **46** (0.11 g, 0.4 mmol) in anhydrous toluene (20 cm^3) and the mixture heated at reflux for 9 h, during which time ACCN (0.23 g, 1.0 mmol in total) was added every 45 min. The reaction was cooled to room temperature, filtered and evaporated to dryness. Column chromatography of the residue (light petroleum:EtOAc; 4:1 → 1:1) gave 1-(4-methoxybenzyl)-4-methyl-pyrrolidin-2-one **42** as a colourless oil (0.014 g, 0.06 mmol, 30 % with respect to resin) along with unreacted starting material **46** (0.08 g, 0.3 mmol, 66 %).

Table 47, entry 2:

As above, but refluxing over 24 h and using syringe-pump technique to ensure continuously addition of ACCN (0.21 g, 0.9 mmol) the products were 1-(4-methoxy-benzyl)-4-methylpyrrolidin-2-one **42** (14.7 mg, 0.07 mmol, 35 % with respect to resin) and unreacted starting material **46** (0.06 g, 0.2 mmol, 53%).

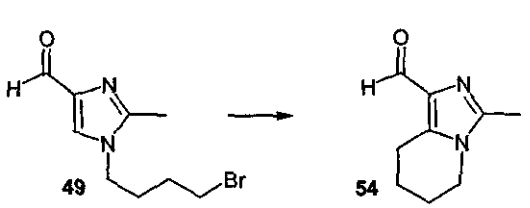
Table 47, entry 3:

Quadragel^{TM}-germane **120** (0.32 g, 0.70 mmol) was allowed to swell in anhydrous toluene (10 cm^3) before *N*-allyl-2-bromo-*N*-(4-methoxybenzyl)acetamide **46** (90.0 mg, 0.30 mmol) in anhydrous toluene (2 cm^3) and AIBN (0.13 g, 0.67 mmol) were added and the mixture rotated at 85 °C for 17 h. After cooling to ambient temperature, the resin was removed by filtration and washed with DCM several times. Evaporation of the filtrate gave a yellow oil, which was identified as unreacted starting material **46** by ^{1}H-NMR spectroscopy.

Table 47, entry 4:

Quadragel^{TM}-germane **120** (0.35 g, 0.77 mmol) was allowed to swell in anhydrous toluene (10 cm^3) before *N*-allyl-2-bromo-*N*-(4-methoxybenzyl)acetamide **46** (90.0 mg, 0.30 mmol) and AIBN (0.26 g, 1.58 mmol) were added and the mixture was refluxed for 19 h. After cooling to ambient temperature, the resin was removed by filtration and washed with DCM several times. Evaporation of the filtrate gave the crude 1-(4-methoxybenzyl)-4-methylpyrrolidin-2-one **42** as a yellow oil. The yield (57 %) was determined by the use of 1,4-dimethoxybenzene as the internal standard in ^{1}H-NMR spectroscopy.

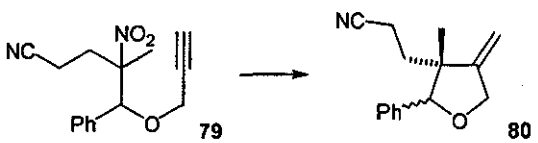
Radical cyclisation of 1-(4-bromobutyl)-2-methyl-1H-imidazole-4-carbaldehyde 49



4-(2-Dimethylgermylethyl)phenol **113** (0.12 g, 0.5 mmol) was added dropwise to a solution of 1-(4-bromobutyl)-2-methyl-1*H*-imidazole-4-carbaldehyde **49** (0.11 g, 0.45 mmol) in anhydrous toluene (60 cm^3) and the mixture was heated at reflux for 4 h,

during which ACCN (0.13 g, 0.5 mmol in total) was added every 45 min. After cooling to ambient temperature, the mixture was poured into water and aqueous NaOH (2 M) was added to pH 14. The basic layer was extracted with DCM and the resulting organic phase dried ($MgSO_4$) and evaporated to dryness The yields of 3-methyl-5,6,7,8-tetrahydro-imidazo[1,5-a]pyridine-1-carbaldehyde **54** (25 %) and unreacted starting material **49** (18 %) were determined by ^{1}H-NMR spectroscopy using 1,4-dinitrobenzene as the internal standard. All data were identical to those of authentic materials.

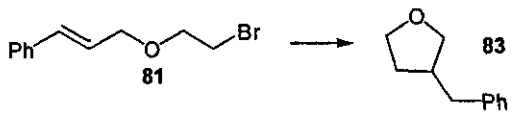
Radical cyclisation of 3-nitro-3-methyl-4-phenyl-4-(prop-2-ynyloxy)butyl cyanide 79



4-(2-Dimethylgermylethyl)phenol **113** (0.11 g, 0.49 mmol) was added dropwise to a solution of 3-nitro-3-methyl-4-phenyl-4-(prop-2-ynyloxy)butyl cyanide **79** (0.11 g, 0.4 mmol) in anhydrous acetonitrile (2.5 cm^3) and the mixture heated at reflux for 5 h. AIBN (excess) was added initially and then in portions every hour. After cooling to room temperature, the solvent was evaporated and the crude reaction mixture purified by column chromatography (light petroleum:EtOAc; 10:1) to give 3-(3-methyl-4-methylene-2-phenyl-tetrahydro-furan-3-yl)propionitrile **80** as two diastereoisomeric products (10 % in total) and unreacted starting material **79** (27 %). Due to by-products, the yields were determined by the use of 1,4-dimethoxybenzene as the internal standard in ^{1}H-NMR spectroscopy. All data were identical to those of authentic materials.

Quadragel^{TM}-germane **120** (0.34 g, 0.75 mmol) was allowed to swell in anhydrous acetonitrile (2 cm^3) before 3-nitro-3-methyl-4-phenyl-4-(prop-2-ynyloxy)butyl cyanide **79** (80.0 mg, 0.29 mmol) and AIBN (0.24 g, 1.2 mmol) were added and the mixture was refluxed for 16 h. After cooling to ambient temperature, the resin was removed by filtration and washed with DCM several times. Evaporation of the filtrate gave a yellow oil which was identified by ^{1}H-NMR spectroscopy as unreacted starting material **79**.

Radical cyclisation of 3-[(2-bromoethyl)oxy]-prop-1-enylbenzene 81



Quadragel™-germane **120** (0.35 g, 0.77 mmol) was allowed to swell in anhydrous toluene (10 cm^3) before 3-[(2-bromoethyl)oxy]-prop-1-enylbenzene **81** (60.0 mg, 0.25 mmol), PhSH (3.8 mg, 0.03 mmol) and ACCN (90 mg, 0.47 mmol) were added and the mixture was heated at 90 °C for 16 h. After cooling to ambient temperature, the resin was removed by filtration and washed with DCM several times. A crude sample was taken out for GC-MS analysis at this stage and it showed that no cyclic product **83** was present in the crude reaction mixture.

Radical cyclisation of 2-allyl-2-(2-bromoallyl)malonic acid dimethyl ester 84

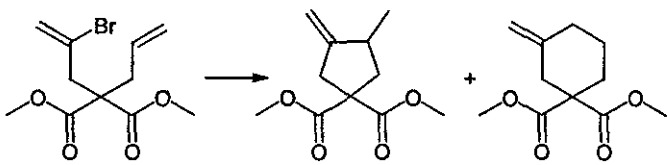


Table 48, entry 1:

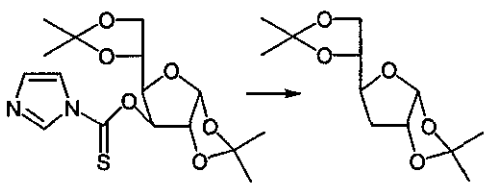
Quadragel™-germane **120** (0.36 g, 0.79 mmol) was allowed to swell in anhydrous toluene (12 cm^3) before 2-allyl-2-(2-bromoallyl)malonic acid dimethyl ester **84** (57.0 mg, 0.20 mmol) and AIBN (0.12 g, 0.73 mmol) were added and the mixture was refluxed for 19 h. After cooling to ambient temperature, the resin was removed by filtration and washed with DCM several times. Evaporation of the filtrate gave the crude product as a yellow oil. The yields of 3-methyl-4-methylene-cyclopentane-1,1-dicarboxylic acid dimethyl ester **85** (19 %) and 3-methylene-cyclohexane-1,1-dicarboxylic acid dimethyl ester **86** (14 %) and unreacted starting material **84** (25 %) were determined by the use of 1,4-dimethoxybenzene as the internal standard in ^{1}H-NMR spectroscopy. All spectral data were identical to those of authentic material.

Table 48, entry 2:

Quadragel™-germane **120** (0.36 g, 0.79 mmol) was allowed to swell in anhydrous toluene (10 cm^3) before 2-allyl-2-(2-bromoallyl)malonic acid dimethyl ester **84** (70.0 mg, 0.24 mmol), PhSH (3.8 mg, 0.03 mmol) and AIBN (0.12 g, 0.73 mmol) were

added and the mixture was refluxed for 19 h. After cooling to ambient temperature, the resin was removed by filtration and washed with DCM several times. Evaporation of the filtrate gave the crude product as a yellow oil. The yield of 3-methyl-4-methylene-cyclopentane-1,1-dicarboxylic acid dimethyl ester **85** (30 %) was determined by the use of 1,4-dimethoxybenzene as the internal standard in ^{1}H-NMR spectroscopy.

Radical deoxygenation of 1,2:5,6-di-*O*-isopropylidene-3-*O*-thiocarbonylimidazole-α-D-glucofuranose 100



100 **102**

Table 45; entry 1:

A solution of 4-(2-dimethylgermylethyl)phenol **113** (0.19 g, 0.9 mmol) in anhydrous toluene (3 cm^3) was added dropwise to a refluxing solution of thiocarbonylimidazole derivative **100** (0.10 g, 0.3 mmol) in anhydrous toluene (3 cm^3) followed by addition of ACCN (0.03 g, 0.1 mmol). The mixture was refluxed for 2 h, cooled to room temperature and evaporated to dryness. Column chromatography of the residue (light petroleum:EtOAc; 4:1 → 1:1) gave 3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose **102** as a colourless oil (0.06 g, 0.3 mmol, 94 %). All data were identical to those of authentic material.

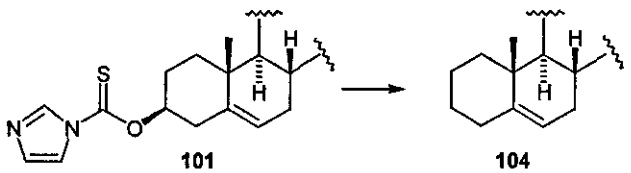
Table 45; entry 2:

A solution of 4-(2-dimethylgermylethyl)phenyl benzyl ether **116** (0.30 g, 1.0 mmol) in anhydrous toluene (3 cm^3) was added dropwise to a refluxing solution of thiocarbonylimidazole derivative **100** (0.13 g, 0.3 mmol) in anhydrous toluene (3 cm^3) and the mixture heated at reflux for 8 h, during which ACCN (0.10 g, 0.4 mmol in total) was added every 45 min. Cooled to room temperature and evaporated to dryness. Column chromatography (light petroleum:EtOAc; 4:1 → 1:1) gave 3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose **102** as a colourless oil (0.08 g, 0.3 mmol, 91 %).

Employing 4-(2-dimethylgermylethyl)phenyl ether Merrifield resin **118**:

4-(2-Dimethylgermylethyl)phenyl ether Merrifield resin **118** (0.40 g, 0.4 mmol) was added to a solution of thiocarbonylimidazole derivative **100** (0.12 g, 0.3 mmol) in anhydrous toluene (6 cm^3) and the mixture heated at reflux for 7 h, during which ACCN (0.13 g, 0.5 mmol in total) was added every 40 min. Cooled to room temperature, filtered and evaporated to dryness. Column chromatography (light petroleum:EtOAc; 4:1 → 1:1) gave 3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose **102** as a colourless oil (28 mg, 0.1 mmol, 36 %).

Radical deoxygenation of cholesteryl-1-thiocarbonylimidazole 101



101 **104**

Quadragel^{TM}-germane **120** (0.40 g, 0.88 mmol) was allowed to swell in anhydrous toluene (10 cm^3) before cholesteryl-1-thiocarbonylimidazole **101** (0.10 g, 0.20 mmol) and ACCN (80.0 mg, 0.40 mmol) were added and the mixture was refluxed for 17 h. After cooling to ambient temperature, the resin was removed by filtration and washed with DCM several times. Evaporation of the filtrate gave pale yellow semi-solid, which contained 70 % of the reduced product as determined by the use of 1,4-dimethoxybenzene as internal standard in ^{1}H-NMR spectroscopy. Crystallisation from EtOH gave 5-cholestene **104** as a white solid (51.0 mg, 0.14 mmol, 68 %). All spectral data were identical to those of authentic material.

References

[1] K. Oshima, *EUCHEM Organic Free Radical Conference*, University of York, July **2002**.

[2] Excellent reviews in this area have been published; (a) P. A. Baguley and J. C. Walton, *Angew. Chem. Int. Ed.*, **1998**, *37*, 3072. (b) A. Struder and S. Amrein, *Synthesis*, **2002**, 835. (c) A. Parsons, *Chem. in Britain*, Feb. **2002**, 42.

[3] For examples see (a) E. J. Corey and J. W. Suggs, *J. Org. Chem.*, **1975**, *40*, 2554. (b) D. S. Hays and G. C. Fu, *J. Org. Chem.*, **1998**, *63*, 2796.

[4] D. Crich and S. Sun, *J. Org. Chem.*, **1996**, *61*, 7200.

[5] (a) D. P. Curran and S. Hadida, *J. Am. Chem. Soc.*, **1996**, *118*, 2531. (b) I. Ruy, T. Niguma, S. Minakata, M. Komatsu, S. Hadida and D. P. Curran, *Tetrahedron Lett.*, **1997**, *38*, 7883. (c) S. Hadida, M. S. Super, E. J. Beckman and D. P. Curran, *J. Am. Chem. Soc.*, **1997**, *119*, 7406. (d) D. P. Curran, S. Hadida, S.-Y. Kim and Z. Luo, *J. Am. Chem. Soc.*, **1999**, *121*, 6607.

[6] D. L. J. Clive and J. Wang, *J. Org. Chem.*, **2002**, *67*, 1192.

[7] S. Gestaldi and D. Stien, *Tetrahedron Lett.*, **2002**, *43*, 4309.

[8] (a) Y. Ueno, K. Chino, M. Watanabe, O. Moriya and M. Okawara, *J. Am. Chem. Soc.*, **1982**, *104*, 5564. (b) U. Gerigk, M. Gerlach, W. P. Neuman, R. Vieler and V. Weintritt, *Synlett*, **1990**, 448. (c) M. Gerlach, F. Jördens, H. Kuhn, W. P. Neuman and M. Peterseim, *J. Org. Chem.*, **1991**, *56*, 5971. (d) G. Ruel, N. K. The, G. Dumartin, B. Delmond and M. Pereyre, *J. Organomet. Chem.*, **1993**, C18. (e) G. Dumartin, M. Pourcel, B. Delmond, O. Donard and M. Pereyre, *Tetrahedron Lett.*, **1998**, *39*, 4663. (f) E. J. Enholm and J. P. Schulte II, *Org. Letters*, **1999**, *1*, 1275.

[9] In radical reactions mediated by R_3SnH: (a) M. P. Sibi and S. V. Chandramouli, *Tetrahedron Lett.*, **1997**, *38*, 8929. (b) A. Routledge, C. Abell and S. Balasubramanian, *Synlett*, **1997**, 61. (c) A. Ganesan in "Radicals in Organic Synthesis", eds., P. Renaud and M. P. Sibi, Wiley-VCH, Weinheim, **2001**, vol. 2, 80-91.

[10] D. O. Jang and D. H. Cho, *Synlett*, **2002**, 631.

[11] S. Mikami, K. Fujita, T. Nakamura, H. Yorimitsu, H. Shinokubo, S. Matsubara and K. Oshima, *Org. Letters*, **2001**, *3*, 1853.

[12] G. A. Russel, P. Chen, B. H. Kim and R. Rajaratnam, *J. Am. Chem. Soc.*, **1997**, *119*, 8795.

[13] B. C. Gilbert, W. Kalz, C. I. Lindsay, P. T. McGrail, A. F. Parsons and D. T. E. Whittaker, *J. Chem. Soc., Perkin Trans. 1*, **2000**, 1187.

[14] (a) H. Yorimitsu, H. Shinokubo and K. Oshima, *Chem. Letters*, **2000**, 104 and references cited therein. (b) Y. Kita, H. Nambu, N. G. Ramesh, G. Anilkumar and M. Matsugi, *Org. Letters*, **2001**, *3*, 1157. (c) H. Yorimitsu, H. Shinokubo and K. Oshima, *Bull. Chem. Soc. Jpn.*, **2001**, *74*, 225.

[15] H. Yorimitsu, H. Shinokubo and K. Oshima, *Synlett*, **2002**, 674 and references cited therein.

[16] (a) M. Newcomb, *Tetrahedron*, **1993**, *49*, 1151 and references cited therein. (b) J. Lysztyk, B. Maillard, D. A. Lindsay and K. U. Ingold, *J. Am. Chem. Soc.*, **1983**, *105*, 3578.

[17] (a) K. U. Ingold, J. Lusztyk and J. C. Scaiano, *J. Am. Chem. Soc.*, **1984**, *106*, 343. (b) C. Chatgilialoglu, *Acc. Chem. Res.*, **1992**, *25*, 188.

[18] H. Gilman, W. H. Atwell, P. K. Sen and C. L. Smith, *J. Organomet. Chem.*, **1965**, *4*, 163.

[19] (a) A. Alberti, C. Chatgilialoglu, G. F. Pedulli and P. Zanirato, *J. Am. Chem. Soc.*, **1986**, *108*, 4993. (b) C. Chatgilialoglu, D. Griller and M. Lesage, *J. Org. Chem.*, **1988**, *53*, 3641. (c) B. Giese, B. Kopping and C. Chatgilialoglu, *Tetrahedron Lett.*, **1989**, *30*, 681.

[20] E. Lukevics and L. M. Ignatovich in *The Chemistry of Organic Germanium, Tin and Lead compounds*, eds. S. Patai and Z. Rappoport, Wiley, **1995**, Chapter 17.

[21] P. Pike, S. Hershberger and J. Hershberger, *Tetrahedron*, **1988**, *44*, 6295.

[22] C. Chatgilialoglu and M. Ballestri, *Organometallics*, **1995**, *14*, 5017.

[23] (a) T. Nakamura, H. Yorimitsu, H. Shinokubo and K. Oshima, *Synlett*, **1999**, 1415. (b) T. Nakamura, H. Yorimitsu, H. Shinokubo, S. Matsubara and K. Oshima, *Bull. Chem. Soc. Jpn.*, **2001**, *74*, 747.

[24] K. Mochida, H. Sugimoto and Y. Yokoyama, *Polyhedron*, **1997**, *16*, 1767.

[25] P. Pike, S. Hershberger and J. Hershberger, *Tetrahedron Lett.*, **1985**, *26*, 6289.

[26] A. L. J. Beckwith and P. E. Pigou, *J. Chem. Soc., Chem. Commun.*, **1986**, 85.

[27] (a) A. L. J. Beckwith, *Tetrahedron*, **1981**, *37*, 3073. (b) A. L. J. Beckwith, C. J. Easton and A. K. Serelis, *J. Chem. Soc., Chem. Commun.*, **1980**, 482.

[28] A. K. Fisher, R. C. West and E. G. Rochow, *J. Am. Chem. Soc.*, **1954**, *76*, 5878.

[29] M. S. Kharasch, E. V. Jensen and W. H. Urry, *Science*, **1945**, *102*, 128.

[30] Y. Ichinose, K. Nozaki, K. Wakamatsu, K. Oshima and K. Utimoto, *Tetrahedron Lett.*, **1987**, *28*, 3709.

[31] K. Nozaki, Y. Ichinose, K. Wakamatsu, K. Oshima, and K. Utimoto, *Bull. Chem. Soc. Jpn.*, **1990**, *63*, 2268.

[32] R. J. P. Corriu and J. J. E. Moreau, *J. Organomet. Chem.*, **1972**, *40*, 73.

[33] S. Tanaka, T. Nakamura, H. Yorimitsu, H. Shinokubo and K. Oshima, *Org. Lett.*, **2000**, *2*, 1911.

[34] T. Nakamura, S. Tanaka, H. Yorimitsu, H. Shinokubo and K. Oshima, *C. R. Acad. Sci. Paris, Chimie*, **2001**, *4*, 461.

[35] S. Bernardoni, M. Lucarini, G. F. Pedulli, L. Valgimigli, V. Gevorgyan and C. Chatgilialoglu, *J. Org. Chem.*, **1997**, *62*, 8009.

[36] S. Tanaka, T. Nakamura, H. Yorimitsu, H. Shionkubo, S. Matsubara and K. Oshima, *Synlett*, **2001**, 1278.

[37] S. Tanaka, T. Nakamura, H. Yorimitsu and K. Oshima, *Synlett*, **2002**, 569.

[38] H. Kinoshita, H. Kakiya and K. Oshima, *Bull. Chem. Soc. Jpn.*, **2000**, *73*, 2159.

[39] (a) H. Oda, Y. Morizawa, K. Oshima and H. Nozaki, *Tetrahedron Lett.*, **1984**, *25*, 3221. (b) N. Chatani, N. Horiuchi and T. Hanafusa, *J. Org. Chem.*, **1990**, *55*, 3393. (c) K. Mochida, C. Hodota, H. Yamashita and M. Tanaka, *Chem. Letters*, **1992**, 1635. (d) H. Kinoshita, T. Nakamura, H. Kakiay, H. Shinokubo, S. Matsubara and K. Oshima, *Org. Letters*, **2001**, 3, 2521. (e) T. Nakano, K. Ono, Y. Senda and T. Migita, *J. Organomet. Chem.*, **2001**, 313. (f) H. Kinoshita, H. Shinokubo and K. Oshima, *J. Am. Chem. Soc.*, **2002**, *124*, 4220.

[40] S. Tsunoi, I. Ryu, S. Yamasaki, H. Fukushima, M. Tanaka, M. Komatsu and N. Sonoda, *J. Am. Chem. Soc.*, **1996**, *118*, 10670.

[41] V. Gupta and D. Kahne, *Tetrahedron Lett.*, **1993**, *34*, 591.

[42] D. P. Curran, U. Diederichsen and M. Palovich, *J. Am. Chem. Soc.*, **1997**, *119*, 4798.

[43] D. P. Curran and M. Palovich, *Synlett*, **1992**, 631.

[44] (a) Y.-M. Tsai and S.-Y. Chang, *J. Chem. Soc., Chem. Commun.*, **1995**, 981. (b) C.-H. Huang, S.-Y. Chang, N.-S. Wang and Y.-M. Tsai, *J. Org. Chem.*, **2001**, *66*, 8983.

[45] R. A. Jackson, *J. Organomet. Chem.*, **1979**, 17.

[46] U. Iserloh and D. P. Curran, *J. Org. Chem.*, **1998**, *63*, 4711.

[47] F. David-Quillot, S. Lunot, D. Marsacq and A. Duchéne, *Tetrahedron Lett.*, **2000**, *41*, 4905.

[48] P. J. Stang and M. R. White, *J. Am. Chem. Soc.*, **1981**, *103*, 5429.

[49] M. Kosugi, T. Tanji, Y. Tanaka, A. Yoshida, K. Fugami, M. Kameyama and T. Migita, *J. Organomet. Chem.*, **1996**, 255.

[50] T. Nakamura, H. Yorimitsu, H. Shinokubo and K. Oshima, *Tetrahedron*, **2001**, *57*, 9827.

[51] O. H. Johnson, W. H. Nebergall and D. M. Harris, *Inorganic Syntheses*, **1957**, *5*, 70.

[52] T. Nakamura, H. Yorimitsu, H. Shinokubo and K. Oshima, *Synlett*, **1999**, 1415.

[53] O. H. Johnson, W. H. Nebergall and D. M. Harris, *Inorganic Syntheses* **1957**, *5*, 76.

[54] T. J. Colacot, *J. Organomet. Chem.*, **1999**, 378.

[55] E. J. Bulten and W. Drenth, *J. Organomet. Chem.*, **1973**, 179.

[56] J. G. A. Luijten and F. Rijkens, *Recueil*, **1964**, *83*, 857.

[57] L. J. Johnston, J. Lusztyk, D. D. M. Wayner, A. N. Abeywickreyma, A. L. J. Beckwith, J. C. Scaiano and K. U. Ingold, *J. Am. Chem. Soc.*, **1985**, *107*, 4594.

[58] B. P. Roberts, *Chem. Soc. Rev.*, **1999**, *28*, 25.

[59] W. B. Motherwell and D. Crich, *Free Radical Chain Reactions in Organic Synthesis*, Acedemic Press, London, **1991**, page 12.

[60] A. L. J. Beckwith and P. E. Pigou, *Aust. J. Chem.*, **1986**, *39*, 1151.

[61] F. Aldabbagh, W. R. Bowman, E. Mann and A. M. Z. Slavin, *Tetrahedron*, **1999**, *55*, 8111.

[62] W. R. Bowman, E. Mann and J. Parr, *J. Chem. Soc., Perkin Trans. I*, **2000**, 2991.

[63] A. L. J. Beckwith, W. R. Bowman, E. Mann, J. Parr and J. H. D. Storey, unpublished work.

[64] E. J. Corey, W. L. Mock and D. J. Pasto, *Tetrahedron Lett.*, **1961**, 347.

[65] W. R. S. Barton, Ph. D. thesis, Loughborough University, 2002.

[66] Synthesised by W. R. S. Barton.

[67] Synthesised by A. J. Fletcher.

[68] N. Ono, H. Miyake, A. Kamimura, I. Hamamoto, R. Tamura and A. Kaji, *Tetrahedron*, **1985**, *41*, 4013.

[69] W. R. Bowman, D. Crosby and P. J. Westlake, *J. Chem. Soc., Perkin Trans 2*, **1991**, 73.

[70] S. A. Ahmad-Junan, A. J. Walkington and D. A. Whiting, *J. Chem. Soc., Perkin Trans. I*, **1992**, 2313.

[71] G. Stork and N. H. Baine, *J. Am. Chem. Soc.*, **1982**, *104*, 2321.

[72] A. L. J. Beckwith and C. H. Schiesser, *Tetrahedron*, **1985**, *41*, 3925.

[73] (a) G. Stork and R. Mook, Jr., *Tetrahedron Lett.*, **1986**, *27*, 4529. (b) A. M. Gómez, M. D. Company, C. Uriel, S. Valverde and J. C. López, *Tetrahedron Lett.*, **2002**, *43*, 4997.

[74] (a) D. Crich, J.-T. Hwang, S. Gastaldi, F. Recupero and D. J. Wink, *J. Org. Chem.*, **1999**, *64*, 2877. (b) D. Crich, J.-T. Hwang and H. Liu, *Tetrahedron Lett.*, **1996**, *37*, 3105.

[75] (a) D. H. R. Barton, Y. Hervé, P. Potier and J. Thierry, *J. Chem. Soc., Chem. Commun.*, **1984**, 1298. (b) D. H. R. Barton, Y. Hervé, P. Potier and J. Thierry, *Tetrahedron*, **1988**, *44*, 5479 and references cited therein.

[76] *E.g.* S. L. Krintel, J. Jiménez-Barbero and T. Skrydstrup, *Tetrahedron Lett.*, **1999**, *40*, 7565.

[77] D. H. R. Barton, W. B. Motherwell and A. Strange, *J. Chem. Soc., Chem. Commun.*, **1981**, 743.

[78] D. H. R. Barton and S. W. McCombie, *J. Chem. Soc., Perkin Trans. I*, **1975**, 1574.

[79] (a) W. R. Bowman, D. S. Brown, C. A. Burns, B. A. Marples and N. A. Zaidi, *Tetrahedron*, **1992**, *48*, 6883. (b) C. S. Bensasson, J. Cornforth, M.-H. Du and J. R. Hansen, *J. Chem. Soc., Chem. Commun.*, **1997**, 1509.

[80] Reactions performed by Rehana Karim.

[81] A. C. Spivey, C. M. Diaper, H. Adams and A. J. Rudge, *J. Org. Chem.*, **2000**, *65*, 5253.

[82] C. J. Moody, K. J. Doyle, M. C. Elliott and T. J. Mowlem, *J. Chem. Soc., Perkin Trans. 1*, **1997**, 2413.

[83] E. Keinan, M. Sahai, Z. Roth, A. Nudelman and J. Herzig, *J. Org. Chem.*, **1985**, *50*, 3558.

[84] M. Uchiyama, M. Kanuda, O. Mishima and N. Yokoyama, *J. Am. Chem. Soc.*, **1998**, *20*, 4945.

[85] C. Gervais, D. Anker, G. Carret and H. Pacheco, *Tetrahedron*, **1979**, *35*, 745.

[86] H. Bhandal, V. F. Patel, G. Pattenden and J. J. Russel, *J. Chem. Soc., Perkin Trans. 1*, **1990**, 2691.

[87] E. Mann, Ph. D. thesis, Loughborough University, 2001.

[88] N. Ono, H. Miyake, A. Kamimura, I. Hamamoto, R. Tamura and A. Kaji, *Tetrahedron*, **1985**, *41*, 4023.

[89] M. Kizil and J. A. Murphy, *Tetrahedron*, **1997**, *53*, 16847.

[90] a) S. A. Ahmad-Junan, A. J. Walkington and D. A. Whiting, *J. Chem. Soc., Perkin Trans. 1*, **1992**, 2313. b) M. Yato, K. Homma and A. Ishida, *Tetrahedron*, **2001**, *57*, 5353.

[91] S. Ozaki, I. Horiguchi, H. Matsushita and H. Ohmori, *Tetrahedron Lett.*, **1994**, *35*, 725.

[92] H. Hagiwara, S. Ohtsubo and M. Kato, *Tetrahedron*, **1997**, *53*, 2415.

[93] S. J. Cole, J. N. Kirwan, B. P. Roberts and C. R. Willis, *J. Chem. Soc., Perkin Trans. 1*, **1991**, 103.

[94] H.-S. Dang, B. P. Roberts and D. A. Tocher, *J. Chem. Soc., Perkin Trans. 1*, **2001**, 2452.

[95] K. N. Scott and T. H. Mareci, *Can. J. Chem.*, **1979**, *57*, 27.