

NOVEL RADICAL REACTIONS INVOLVING SULFUR-CONTAINING COMPOUNDS

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in Partial Fulfilment of the Requirements
for the Degree of
Doctor of Philosophy

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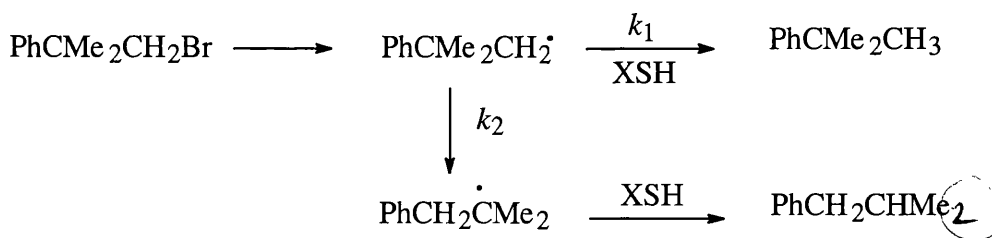
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ABSTRACT

1. Thiol-catalysed Radical-chain Reduction of Organic halides by Hexabutylditin in the Presence of Malonic acid

Thiol-catalyzed radical-chain reduction using hexabutylditin and malonic acid has been developed and found to be effective for the reduction of organic halides. Thiols effectively catalyse the radical-chain reduction in conjunction with malonic acid. The reduction of tertiary α -haloesters with silanes in the presence of thiols was found to be inefficient because of steric congestion and unfavourable polar effects.

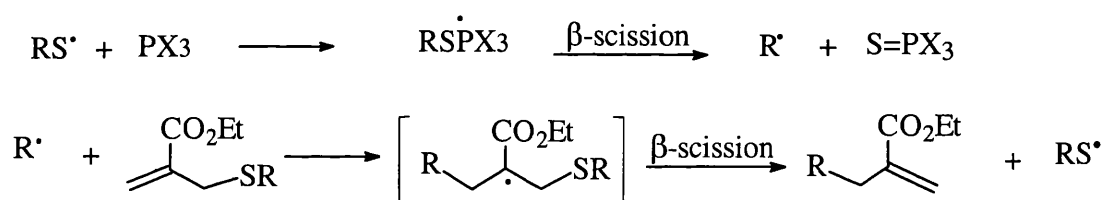
The thiol-catalysed reduction of alkyl halides with hexabutylditin together with malonic acid proved to be an effective replacement for tributyltin hydride and the reduction of primary, secondary and tertiary alkyl halides and of 1-bromoacetophenone was successfully accomplished in excellent yields. Radicals generated from ethyl 2-bromohexanoate, 4-bromobenzyl bromide, methyl 2-bromobenzoate and methyl 2-iodobenzoate abstract hydrogen-atoms relatively slowly from thiols, because such radicals are either electrophilic or stabilised. However, the reduction of these halides could be carried out successfully under optimised conditions.



Study of the neophyl rearrangement showed that the concentration of the thiol can be controlled so as to promote the formation of the rearranged product (isobutylbenzene) without the need to work under conditions of high dilution.

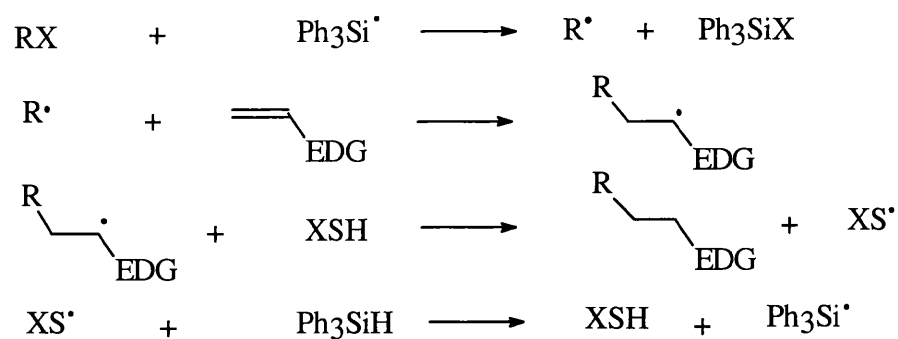
2. Radical-chain Desulfurization of 2-(Alkylthiomethyl) Acrylates with Triphenylphosphine: a New Route to 2-Alkylacrylates.

A study of radical-chain desulfurization of 2-(alkylthiomethyl)acrylates with triphenylphosphine has been carried out. Carbon-carbon bond-forming reactions using allylic sulfides mediated by phosphites or phosphines were based on the ready β -scission of alkylthiophosphoranyl radical adducts to produce the alkyl radical. The radical reactions of simple allylic sulfides, without electron-withdrawing ester substituents, in the presence of phosphorus(III) compounds gave poor yields. However, 2-methylene-3-alkylthiopropoate esters react with triphenylphosphine in refluxing octane, in the presence of initiator, to give 2-methylenealkanoates in moderate yields, together with triphenylphosphine sulfide. Success in this case is related to polar effects, because nucleophilic alkyl radicals add easily to electron-deficient alkenes bearing an electron-withdrawing group.



3. Radical-chain Reductive Alkylation of Electron-rich Alkenes: Carbon-carbon Bond Formation using Silanes in the Presence of Thiols as Polarity-reversal Catalysts.

Radical-chain reductive alkylation of electron-rich alkenes with electrophilic radicals has been carried out. The use of triorganosilanes in the presence of thiols as polarity-reversal catalyst can serve as an effective replacement for trialkyltin hydride. The S-H group of a thiol provides an electron-deficient hydrogen, which favours hydrogen atom transfer to nucleophilic alkyl radicals, while polar effects discriminate against the abstraction of hydrogen from thiols by electrophilic radicals. The thiol-catalyzed reductive alkylation of



unsubstituted terminal electron-rich alkenes by α -halogenoesters in the presence of triphenylsilane under free-radical conditions gave good yields of carboxyalkylated products. Under the same conditions, the radical-chain addition to prochiral alkenes of the type $\text{H}_2\text{C}=\text{CR}^1\text{R}^2$, catalysed by small amounts of homochiral thiols, afforded optically-active adducts in moderate enantiomeric purity.

ACKNOWLEDGEMENTS

First of all, I would like to thank my supervisor, Dr Brian Roberts, for all his support, advice and help in obtaining financial support.

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Finally, I thank my family for all their support during my studies at UCL.

I would like to dedicate this thesis to my Mother.

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SECTION A: INTRODUCTION

RADICAL CHEMISTRY OF ORGANOSULFUR COMPOUNDS

CHAPTER 1

FORMATION AND PROPERTIES OF IMPORTANT TYPES OF SULFUR RADICALS

Sulfur compounds are ubiquitous on the Earth and are especially important in biological processes. The important types of sulfur radicals are thiyl radicals (RS^\bullet), sulfinyl radicals ($\text{RS}^\bullet\text{O}$) and sulfonyl radicals ($\text{RS}^\bullet\text{O}_2$). Thiyl radicals are the most common and important in this family. Mono- and di-oxygenated sulfinyl and sulfonyl radicals are hypervalent species.

1.1. Thiyl Radicals

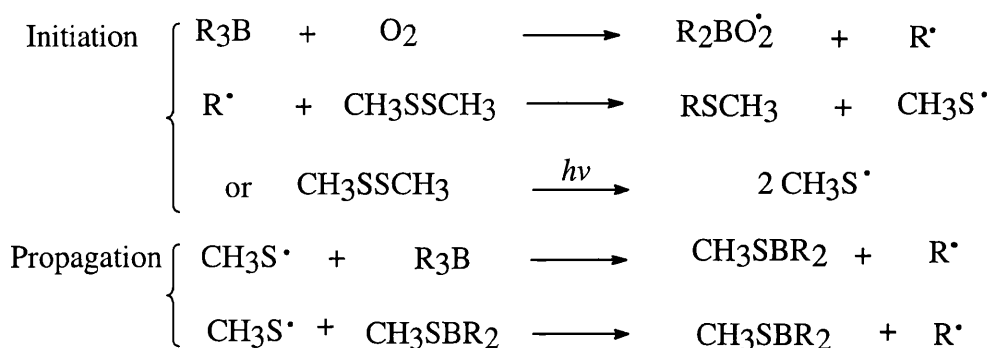
Since thiols have relatively weak S-H bonds (366 kJ mol^{-1}) compared to C-H bonds (*ca.* 410 kJ mol^{-1}), the thiyl radical **1** can be produced by reaction of a thiol with an alkyl radical [eqn. (1.1.1)].¹



Another common route to generate thiyl radicals is by radical displacement reactions on disulfides.² Although most disulfides do not undergo thermal homolytic dissociation, they do undergo photolytic dissociation quite readily [eqn. (1.1.2)].

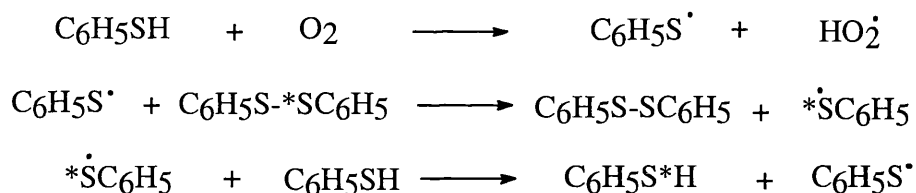


Also, thiyl radicals are involved in the reactions of trialkylboranes with disulfides, initiated by oxygen or ultraviolet light. This chain reaction provides a convenient route to alkyl- and aryl-sulfides (**Scheme 1.1.1**).³



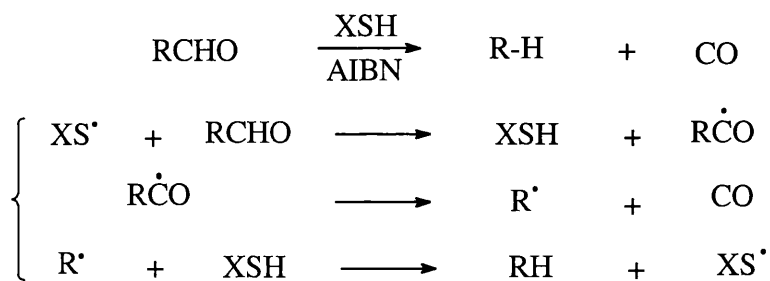
Scheme 1.1.1

Fava *et al.* have shown that thiyl radicals can be generated from the reaction between a thiol and oxygen, which can be used as the initiation step for the exchange reaction between a disulfide and the corresponding thiol (**Scheme 1.1.2**).⁴



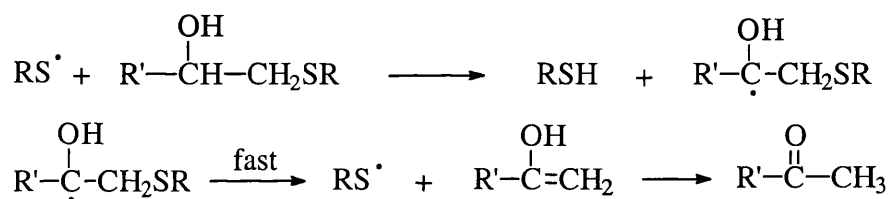
Scheme 1.1.2

Although hydrogen-atom abstraction is a common reaction of an alkoxy radical, the corresponding reaction of a thiyl radical is relatively slow. Hydrogen-atom abstraction by a thiyl radical can be observed in the presence of a good hydrogen-atom donor to suppress the reverse reaction. For example, hydrogen-atom abstraction by a thiyl radical is involved in the thiol-catalysed decarbonylation of an aldehyde. After the resulting acyl radical loses carbon monoxide, the alkyl radical produced abstracts a hydrogen-atom from the thiol and generates a thiyl radical which abstracts the aldehydic hydrogen-atom to give rise to a chain process (**Scheme 1.1.3**).⁵



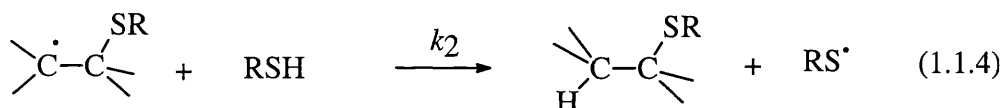
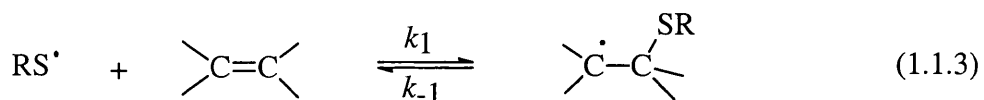
Scheme 1.1.3

Similarly, Huyser and Kellogg have demonstrated that hydrogen-atom abstraction by thiyl radicals takes place in the radical-chain reaction of β -hydroxysulfides with thiols to give ketones (**Scheme 1.1.4**).⁶

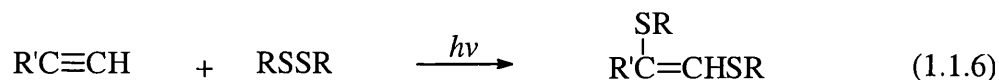
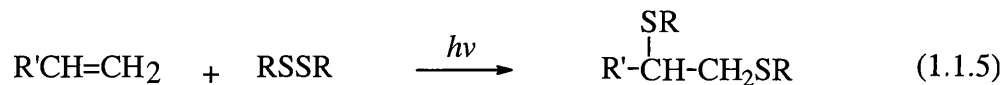


Scheme 1.1.4

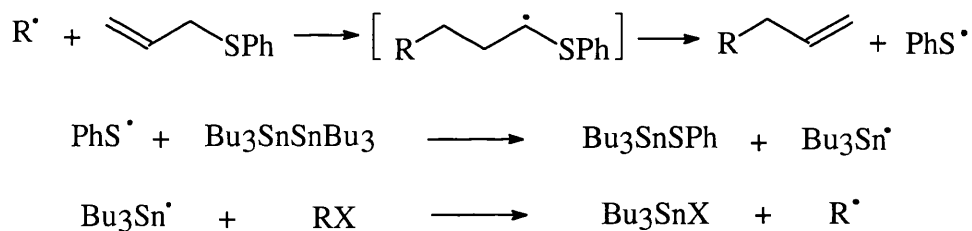
Hydrogen-atom abstraction by thiyl radicals takes place in the addition of a thiol to a carbon-carbon double bond.⁷ The reversibility of the addition of a thiyl radical to an olefin plays an important role in the overall thiol-olefin addition reaction. The exothermic addition step (1.1.3) is reversible and the values of k_{-1} can be large compared to k_1 and k_2 . Step (1.1.4) is also exothermic because the dissociation energy (BDE) of a C-H bond is generally greater than that of an S-H bond, which explains the ready addition of thiols to alkenes without telomer formation [eqns. (1.1.3) and (1.1.4)].



The photochemical reactions of terminal olefins with disulfides gave very poor yields. However, the reaction of disulfides with terminal acetylenes gave good yields, because the addition of a thiyl radical to the alkyne is much less reversible than its addition to an olefin [eqns. (1.1.5) and (1.1.6)].⁸

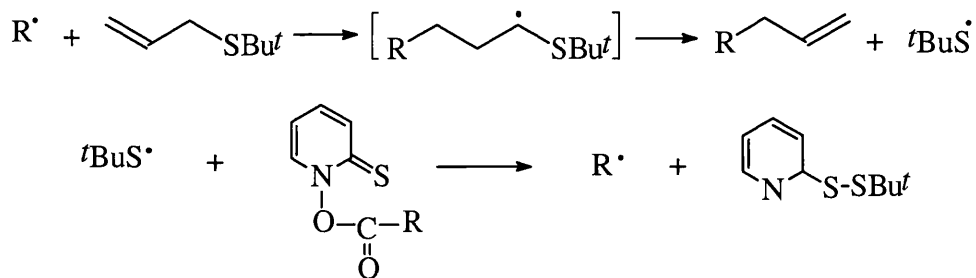


The addition of a radical to a terminal double bond in an alkyl allyl sulfide generates an alkylthiyl radical, because alkyl radicals with β -C-S bonds undergo β -scission readily. Keck and co-workers have shown that the phenylthiyl radical carry the chain reaction of allyl phenyl sulfide with hexabutylditin and an alkyl halide. The generated tributyltin radical reacts with alkyl halide to generate the starting radical R' which reacts with the allyl sulfide to give the allylation product of R' (**Scheme 1.1.5**).⁹



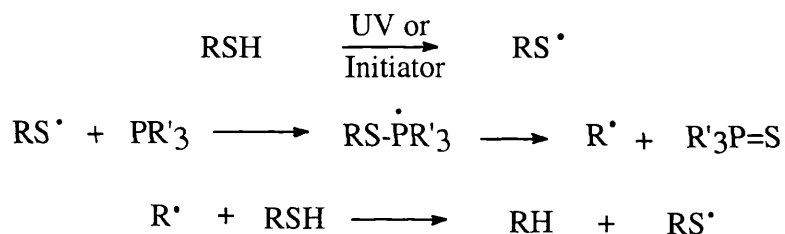
Scheme 1.1.5

Similarly, Barton and Crich have reported that allylation products can be obtained from the reaction of allyl *tert*-butyl sulfide with the esters of *N*-hydroxy-2-thiopyridone. The reaction involves trapping of the *tert*-butylthiyl radical which is generated from β -scission of the adduct radical (**Scheme 1.1.6**).¹⁰



Scheme 1.1.6

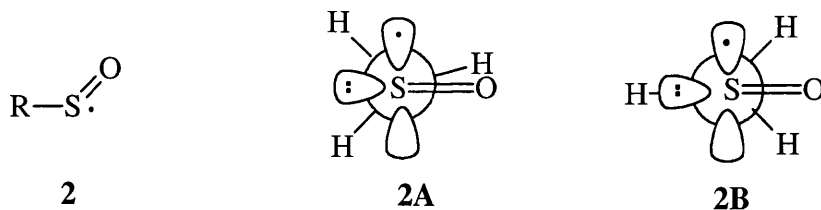
Although alkanethiols do not react with phosphorus(III) compounds under ionic conditions, they are quantitatively converted into alkanes under the influence of ultraviolet light or in the presence of an initiator. Walling and his co-workers have shown that alkylthiyl radicals react with trialkyl phosphites to undergo desulfurisation *via* β -scission of an intermediate phosphoranyl radical to give the corresponding alkyl radicals (**Scheme 1.1.7**).¹¹



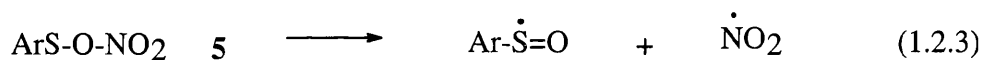
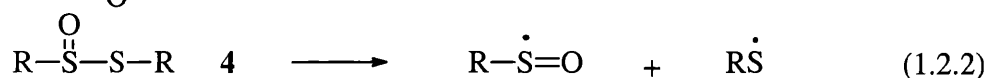
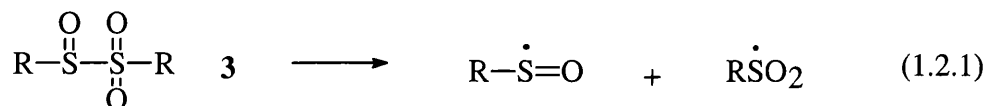
Scheme 1.1.7

1.2. Sulfinyl Radicals

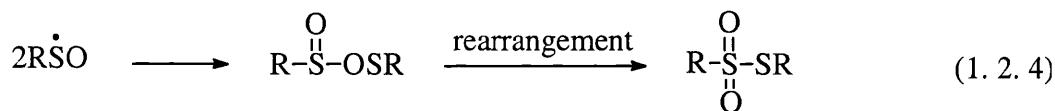
Sulfinyl radicals have the general structure **2**, and are formal analogues of peroxy (ROO^\bullet) and perthiyl radicals (RSS^\bullet). At low temperature (88 K) the methanesulfinyl radical has a fixed conformation in which one β -C-H bond lies in the nodal plane of sulfur 3p orbital, but it was not possible to distinguish between the two possible conformations **2A** and **2B**.¹²



Sulfinyl radicals can be generated by thermal homolytic dissociation of either sulfinyl sulfones **3**¹³ or thiosulfonates **4**¹⁴ and of arylsulfonyl nitrates **5**¹⁵ [eqns. (1.2.1)-(1.2.3)].

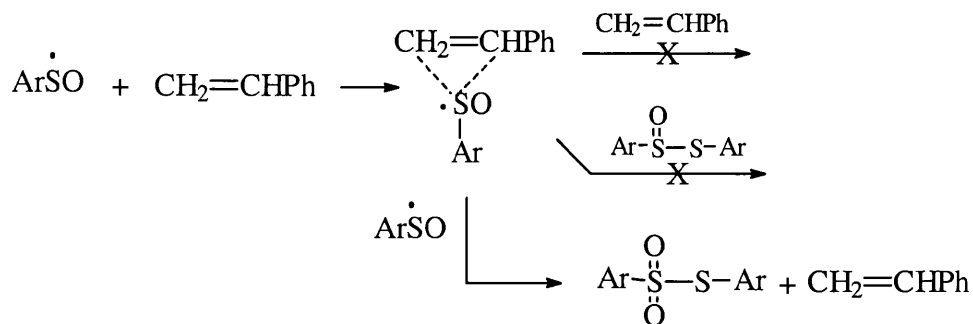


The characteristic reaction of sulfinyl radicals is bimolecular self-reaction. Combination of two sulfinyl radicals leads to a thiosulfonate (RSO_2SR) as a final product. The mechanism has been suggested that a head-to-tail combination of two sulfinyl radicals gives *O,S*-sulfonylsulfinate, which then rearranges to give thiosulfonate [eqn. (1.2.4)].¹⁶



Early studies have indicated that sulfinyl radicals do not add to an olefinic double bond. The attempted addition of sulfinyl radicals across the double bond gives only thiosulfonate by combination of two sulfinyl radicals followed by rearrangement

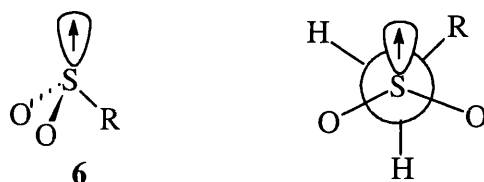
(Scheme 1.2.1).^{14(a)}



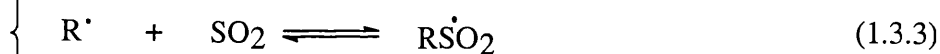
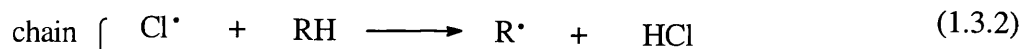
Scheme 1.2.1

1.3. Sulfonyl Radicals

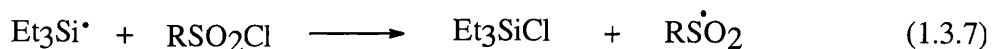
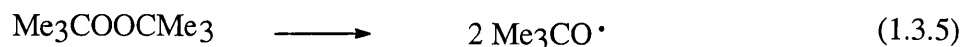
Sulfonyl radicals have a pyramidal structure **6** and the degree of pyramidalization increases as the electronegativity of the substituent in X-SO₂ increases. The most stable conformation is the staggered structure.



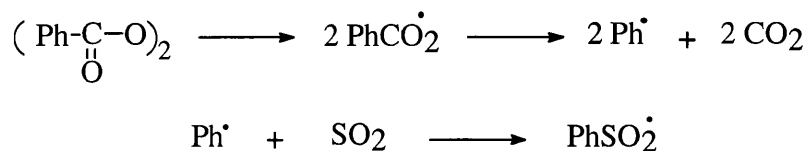
An important method for obtaining sulfonyl radicals is the reversible addition of an alkyl or an aryl radical to sulfur dioxide. The reaction is involved as an intermediate step in the formation of alkylsulfonyl chlorides from alkanes, sulfur dioxide and chlorine [eqns (1.3.1)-(1.3.4)].¹⁷



A common way to generate sulfonyl radicals is the photolysis of solutions containing di-*t*-butyl peroxide, triethylsilane and the corresponding sulfonyl chloride [eqns. (1.3.5) - (1.3.7)].¹⁸

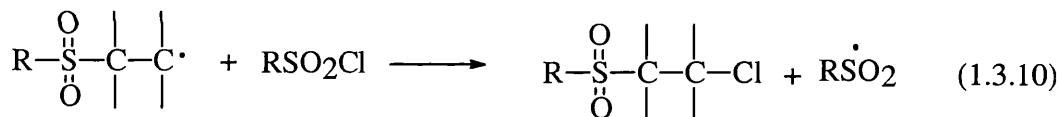
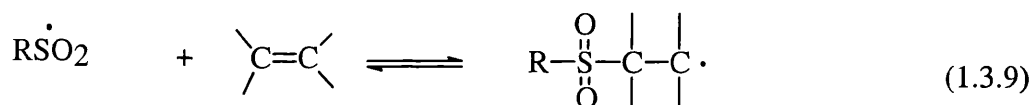
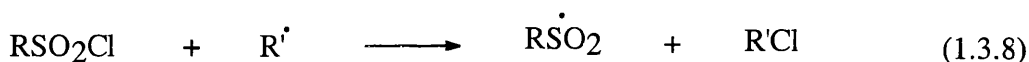


Squire and Waters have demonstrated that phenylsulfonyl radicals can be formed by decomposition of benzoyl peroxide during passage of sulfur dioxide through a solution (Scheme 1.3.1).¹⁹

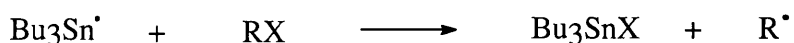
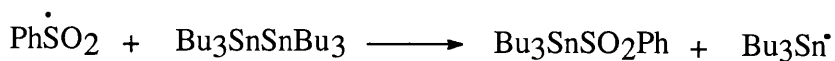
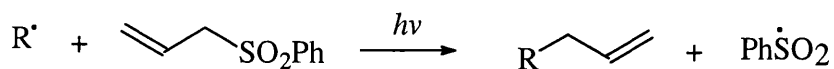


Scheme 1.3.1

Also, sulfonyl radicals can be generated from sulfonyl halides by the abstraction of halide by alkyl or aryl radicals [eqn. (1.3.8)].²⁰ This reaction is involved in the addition of a sulfonyl halide across a carbon-carbon double bond [eqns. (1.3.8) and (1.3.10)].²¹ The addition of a sulfonyl radical to an olefin is usually a reversible reaction.

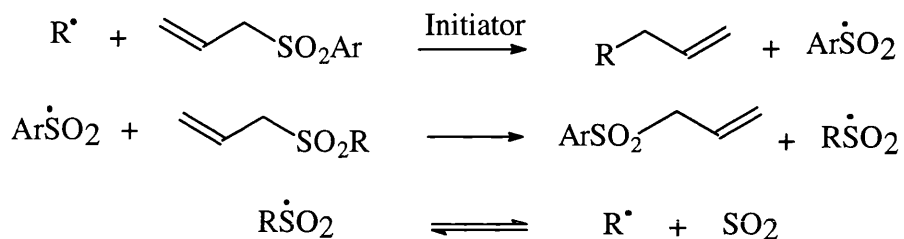


Allylic sulfones can be used for C-allylation reaction in the presence of hexabutylditin under photolytic conditions. The sulfonyl radical generated by β -scission of the adduct radical is trapped by hexabutylditin and the generated tributyltin radical carries the radical-chain reaction (Scheme 1.3.2).²²



Scheme 1.3.2

Finally, French workers have shown that an allylation reaction can be brought about by alkyl allyl sulfone with excess of allyl aryl sulfone as second chain-carrying reagent. Allyl aryl sulfones do not undergo α -scission and prevent the reaction of allylation adducts with alkyl radicals to give polymerisation. The extrusion of sulfur dioxide from the alkyl sulfonyl radical generates an alkyl radical which carries the radical-chain reaction (**Scheme 1.3.3**).²³



Scheme 1.3.3

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CHAPTER 2

POLAR EFFECTS IN HYDROGEN-ATOM ABSTRACTION REACTIONS

In recent years, radical chemistry has been applied with success to many problems in organic synthesis and the recently published monographs on radical chemistry have led to an increase in interest in the use of these intermediates in the organic synthesis.¹

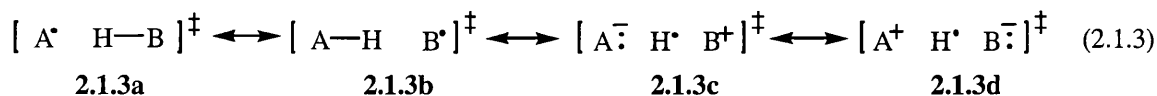
In addition to the overall enthalpy change that accompanies a radical reaction, polar, steric and stereoelectronic factors are important in determining the rate of the process.² We have argued that polar effects on radical reactions can be exploited to develop new radical-chain reactions.

2.1. The Concept of Polar Effects in Hydrogen-Atom Abstraction Reactions

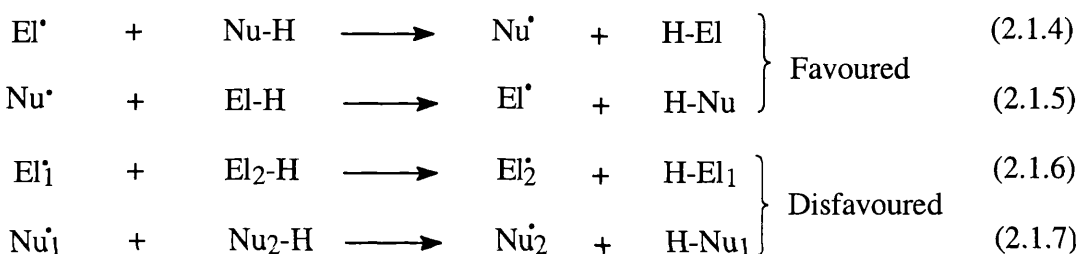
Polar effects relate to the concept of polarity in the transition state. Within the context of the reactions of electrically-neutral free radicals, the term "polar effect" is used to describe the influence on the activation energy of any charge transfer which may occur on proceeding from the reactant to the transition state. Tedder has emphasised the importance of polarity as "*In thermoneutral reactions the rate of atom transfer is very dependent on the degree of polarity in the transition state (Rule 3).*"^{2(a)} However, if there is no simple relationship between the activation energy and the heat of reaction.



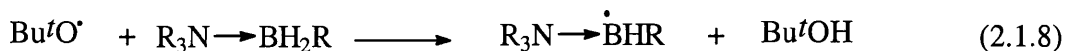
Free radical substitution reactions can involve two atom transfer steps [eqn. (2.1.1) and (2.1.2)]. The substitution of X for B is determined by the hydrogen-atom abstraction step. The transition state for the hydrogen-atom transfer reaction shown in eqn. (2.1.1) may be represented in valence-bond terms as a hybrid of the structures (2.1.3a)-(2.1.3d) and, within a series of reactions for which the overall enthalpy change is similar, the activation energies would be expected to decrease as the contributions from the charge-separated structures (2.1.3c) and (2.1.3d) increase.³ If the structure (2.1.3c) is more important than



(2.1.3d), the radical A[·] may be described as *electrophilic* and B[·] is said to be *nucleophilic*, while if structure (2.1.3b) is the more important, A[·] is nucleophilic and B[·] is electrophilic. For such a series of reactions, the activation energy is predicted to decrease as the electronegativity difference between A[·] and B[·] increases. If El[·] and Nu[·] represent electrophilic and nucleophilic radicals, respectively, the hydrogen-atom abstraction reactions (2.1.4) and (2.1.5) should be favoured because of polar effects, while reactions (2.1.6) and (2.1.7) will not.



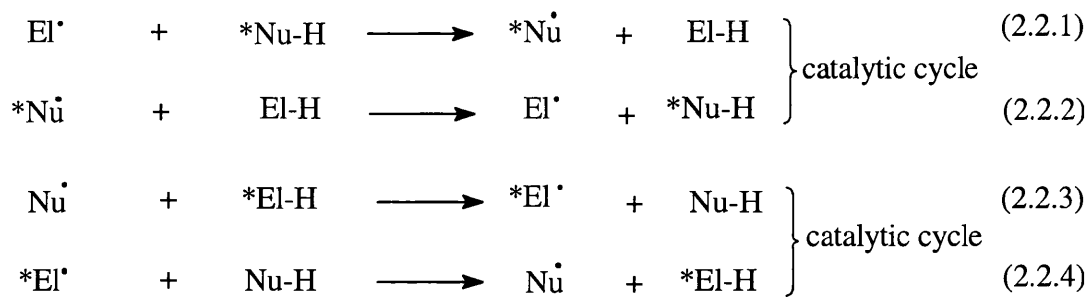
Although radical philicity is clearly a *relative* attribute,⁴ a radical that has a high ionisation energy (IE) and a high electron affinity (EA) will usually exhibit electrophilicity, while a low IE and EA will usually confer nucleophilic properties. In general, radicals that have a high Mulliken electronegativity [(IE + EA)/2] will be electrophilic and those with a low electronegativity will be nucleophilic.⁵ Amine-alkylboryl radicals (R₃N→ \dot{B} HR) are isoelectronic with secondary alkyl radicals (R₃C- \dot{C} HR) and are very readily generated by hydrogen-atom transfer to *tert*-butoxyl radicals from the corresponding amine-alkylborane complex [eqn. (2.1.8)].⁶ Alkoxy radicals are thus electrophilic, while amine-boryl radicals have particularly low ionisation energies (6.39 eV has been calculated for H₃N→ \dot{B} HMe)⁴ and are very nucleophilic, accounting for the high rate of reaction (2.1.8) which is an



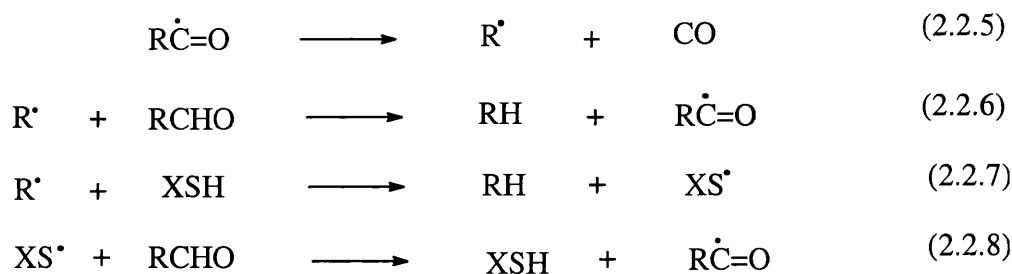
example of the general type shown in eqn. (2.1.4); for reaction (2.1.8), the charge-separated structure $[\text{Bu}^t\text{O}^- \text{H}^+ \text{RHB} \leftarrow \text{NR}_3]$ (cf. 2.1.3c) is an important contributor to the transition state. The cyanomethyl radical derived from acetonitrile is electrophilic and these results can be understood in terms of polar effects, since reactions (2.1.9) and (2.1.10) constitute examples of the general processes shown in eqns. (2.1.5) and (2.1.6), respectively. Consistent with these observations, the *overall* abstraction of hydrogen from acetonitrile by the electrophilic alkoxyl radical is promoted by a small amount of amine-alkylborane, through the sequence of rapid reactions (2.1.8) and (2.1.9) which replace the relatively-inefficient single step (2.1.10).⁷ The polarity of the radical that abstracts hydrogen from the acetonitrile is thereby reversed (from an electrophilic alkoxyl radical to a nucleophilic amine-boryl radical) thus facilitating the overall transfer of hydrogen and, for this reason, the process is referred to as *polarity-reversal catalysis*.^{6,7}

2.2. Polarity Reversal Catalysis in Hydrogen-Atom Abstraction Reactions

Polarity reversal catalysis is a process in which the slow single step is replaced by two fast, consecutive steps. The principle underlying polarity-reversal catalysis of hydrogen-atom transfer is generalised in [eqns. (2.2.1)-(2.2.4)]. The lack of stabilising charge-transfer in the transition state for the direct abstraction shown in [eqn. (2.1.6)] is overcome by including an *hydridic* catalyst H^*Nu , when the single-step process is replaced by a cycle of two hydrogen-atom transfer reactions both of which benefit from favourable polar effects. Similarly, the slow direct abstraction reaction (2.1.7) is promoted by a *protic* catalyst H^*El .⁴

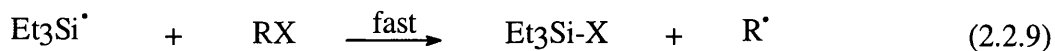


The concept of polarity reversal catalysis (PRC) is based on the exploitation of polar factors. Barrett and Waters reported that thiols catalyse the radical-chain decarbonylation of aldehydes [eqns. (2.2.5) and (2.2.6)].⁸ *In the discussion following this page, Mayo suggested an explanation for the catalysis based on the polar effects. Mayo pointed out that the chain-propagating abstraction of hydrogen from an aldehyde by an alkyl radical [eqn. (2.2.6)] does not benefit from polar effects in the transition state, because both the alkyl radical and the acyl radical are nucleophilic. Mayo proposed that the catalysis of the overall hydrogen transfer reaction (2.2.6), through the cycle of reactions (2.2.7) and (2.2.8), could be understood because the thiyl radical is electrophilic. The thiol is acting as a protic polarity-reversal catalyst for reaction (2.2.6) and this catalytic cycle can be used with advantage in several types of radical-chain reaction.*

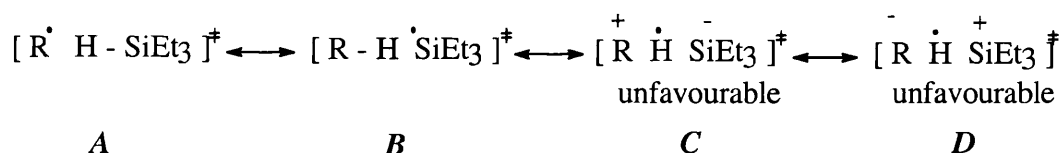


Tributyltin hydride is pre-eminent amongst reagents for the homolytic reductive removal of functional group from an organic compound. However, for practical and ecological reasons it would be desirable to use mild silanes in place of trialkyltin hydrides. However, hydrogen-atom donating ability of organosilanes is relatively poor and does not support chain reactions easily, because the Si-H bond is relatively strong [BDE of Et₃Si-H and (Me₃Si)₃Si-H are 398 and 351 kJ mol⁻¹]⁹ compared with the Sn-H bond (308 kJ mol⁻¹

in Bu_3SnH).⁹ As a consequence, reductions using simple silanes are not generally viable under mild conditions. Although reaction in [eqn. (2.2.10)] is usually exothermic, it does

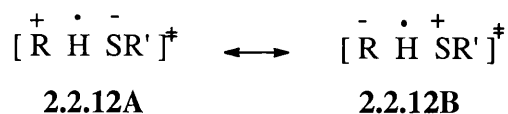


not benefit from favourable polar effects because both the alkyl radical and the silyl radical are nucleophilic. Considering the low electronegativity of silicon, a silane provides an electron-rich hydrogen-atom. Thus, the transition state for the reaction between the silane and the alkyl radical in equation (2.2.10) is not favoured by polar factors, because neither *C* nor *D* contribute appreciably to the transition state for hydrogen-atom abstraction by nucleophilic alkyl radicals (**Scheme 2. 2. 1**).

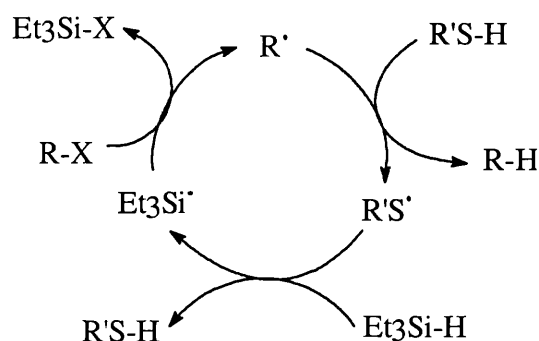


Scheme 2. 2. 1

If a nucleophilic alkyl radical reacts with a silane in the presence of the thiol, the overall reaction will become favourable from the point of polar effect, because electron-rich alkyl radicals easily abstract electron-deficient hydrogen-atoms from thiols to generate electrophilic thiyl radicals which easily abstract electron-rich hydrogen-atoms from the silanes [eqns. (2.2.11) and (2.2.12)].



Another advantage of the thiol-mediated reduction of alkyl halides using silanes is that the S-H bond ($\text{MeS-H } 365 \text{ kJ mol}^{-1}$) is weaker than the Si-H bond ($\text{Et}_3\text{Si-H } 398 \text{ kJ mol}^{-1}$). Thus, the overall chain propagation sequence for the reduction of alkyl halides with organosilanes in the presence of thiols is summarised in **Scheme 2.2.2**. In the propagation sequence, the alkyl radical abstracts a hydrogen-atom from the thiol to yield the reduction product and a thiyl radical, that goes on to abstract the hydrogen-atom from the silane to regenerate the thiol and give the silyl radical. The silyl radical abstracts a halogen atom from the alkyl halide to produce the silyl halide and regenerate the starting alkyl radical.

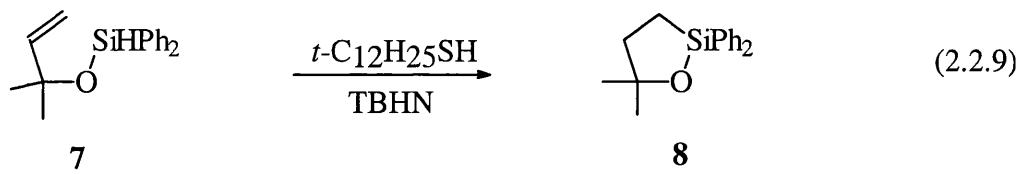


Scheme 2.2.2

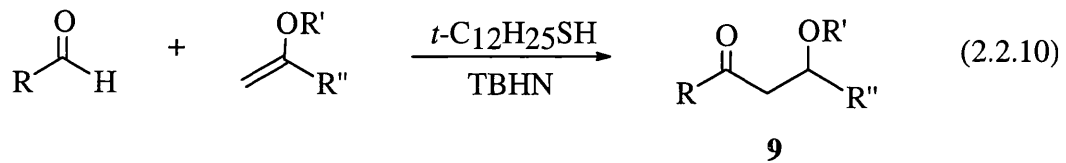
The use of thiols as polarity-reversal catalysts have been developed by the Roberts' group. They have shown that the reduction of alkyl halides or sulfides using organosilanes in the presence of a catalytic amount of thiol give excellent yields.¹⁰

The deoxygenation of primary and secondary alcohol by their xanthate esters, which is known as the Barton-McCombie reaction using tributyltin hydride,¹¹ was carried out using triethylsilane in the presence of *tert*-dodecanthiol as polarity reversal catalyst give excellent yields.¹²

Hydrosilylation reactions of alkenes using a silane-thiol couple have been found effective for the inter- and intra-molecular reaction.¹³ The radical cyclisation of diphenyl (1,1-dimethyl-2-propenyloxy)silane **7** in the presence of thiol catalyst afforded 95 % yield of **8**.



Thiols catalyse the radical-chain addition of primary aliphatic aldehydes to terminal alkenes to give ketonic adducts **9** in moderate to good yields.¹³



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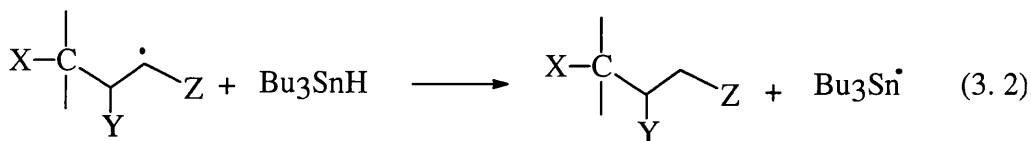
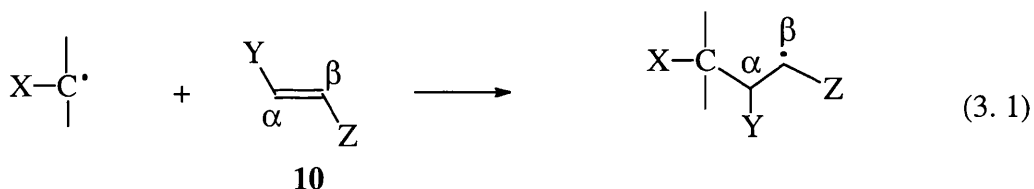
CHAPTER 3

POLAR EFFECTS ON RADICAL ADDITION REACTIONS

Free radical addition is a two step process involving an addition step followed by atom transfer. The addition of a carbon radical to a carbon-carbon double bond is exothermic, since a π -bond is broken ($226 - 247 \text{ kJ mol}^{-1}$) and a carbon-carbon single bond (368 kJ mol^{-1}) is formed. If the stability of the attacking radical increases, the reaction may become reversible, since the reaction becomes less exothermic.¹

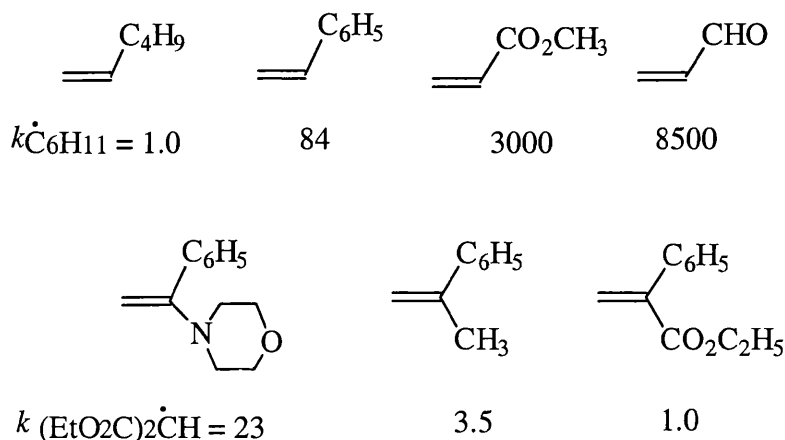
A number of factors have been thought to play an important role in determining the rate of radical addition to alkenes. Although polar effects cannot be completely separated from the strength of the bond formed (enthalpic effects), polar effects in the transition state are certainly very important, as are steric effects and all influence the energy state of the transition state.² Polar effects due to substituents on alkenes can have a major effect on the overall rate of addition of radicals to olefins by lowering the activation energy. For example, the addition of nucleophilic alkyl radicals to alkenes can be accelerated by a factor of 10^3 or 10^4 by the introduction of an electron-withdrawing substituent on alkenes.³

The rate constant for addition (k_a) is important in the design of radical chains for bimolecular addition reactions [eqn. (3.1) - (3.2)].³ The factors affecting the magnitude of k_a are polar and steric effects of the alkene substituents (Y and Z) which control reactivity and selectivity. Giese and his co-workers have reviewed the effect of substituents on the rate of addition of radicals to alkenes.²



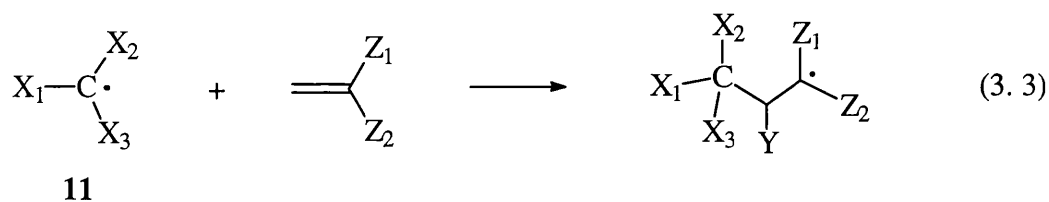
The β -substituents (Z) on alkenes **10** exert mainly polar effects. Thus, electron-withdrawing substituents lower the energy of alkene and accelerate the addition of a nucleophilic alkyl radicals. On the contrary, the addition of electrophilic radicals is

accelerated by electron-donating substituents on alkenes. For example, the rate of addition of the cyclohexyl radical to acrolein increases by 8500 compared with the corresponding reaction of 1-hexene at 20 °C (Scheme 3.1).



Scheme 3.1

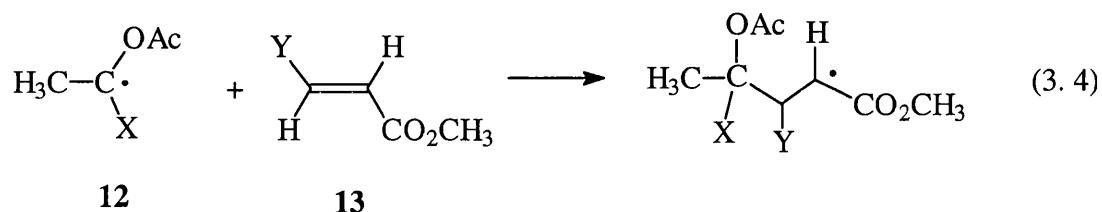
The α -substituents (Y) on alkenes **10** exert both steric and polar effects. Compared to the substituents (Z), the steric effect of substituents (Y) are very large. Thus, non-activating α -substituents (Y) retard the rate of addition of radicals by steric hindrance. Electron-withdrawing α -substituents (Y) exert smaller polar effect than those of β -substituents and only slightly accelerate the rate.



Substituents at the incipient radical centre exert polar effects on the rate of addition to alkenes [eqn. (3.3)]. Roberts *et al.* and Minisci *et al.*⁴ have observed that alkyl groups substituted on radical **11** increase the reactivity in addition reaction with the electron-deficient alkenes. For example, diethyl vinylphosphate [$Z_1 = \text{H}$, $Z_2 = \text{PO}(\text{OEt})_2$] reacts 24 times faster with the *tert*-butyl radical ($X_1 = X_2 = X_3 = \text{CH}_3$) than with the methyl radical ($X_1 = X_2 = X_3 = \text{H}$). Thus, the polar effects which increase the nucleophilicity of radical **11**

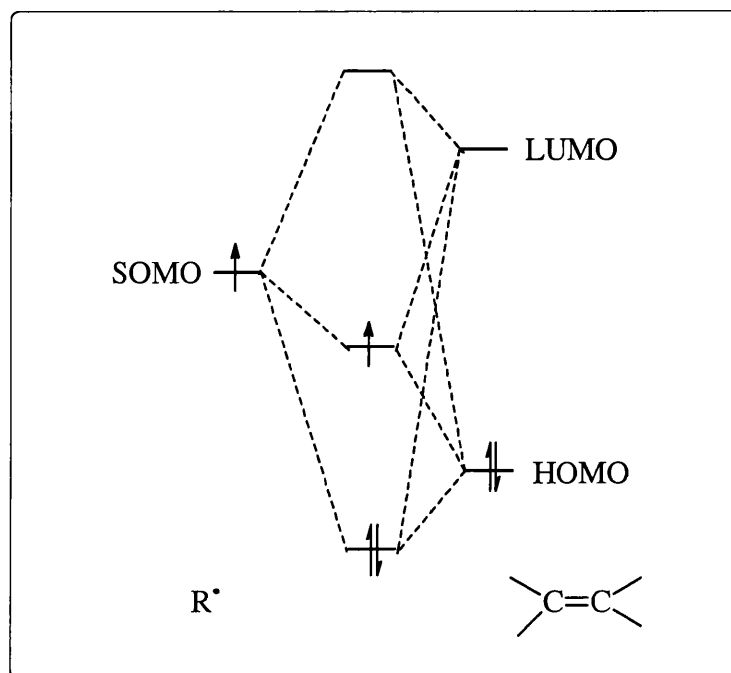
s is more important than the substituent effect on the stability of the radicals. Although radical stabilizing substituents have relatively little effect, the mesomeric-stabilizing phenyl group reduces the rate of addition. On the contrary, electron-withdrawing groups such as X = CN or X = OAc on radical **11** decrease the rate of addition to acrylonitrile.^{2(a)}

Substituents on the radical exert reactivity and selectivity on the attacking radical [eqn. (3.4)]. For example, when methyl substituent (X = CH₃) on radical **12** is replaced by a tertiary butyl, the rate of addition to fumaric ester (Y = CO₂CH₃) **13** decreases by a factor of 260. Also, substituents on alkene **13** have a large steric effect for the rate of addition. For example, when the substituent (X) on the radical **12** is *tert*-butyl, the rate of the addition to acrylic ester (Y = H) **13** is 13 times faster than to fumaric ester (Y = CO₂CH₃) **13** [eqn. (3.4)].



An interpretation of polar effects in radical addition reactions is provided by Frontier Molecular Orbital Theory.⁵ Orbital interactions between SOMO of a radical and HOMO and LUMO of an alkene can explain the polar effect, as shown in (Scheme 3.2).

When the reactants approach one another, the smaller the energy difference between the frontier orbitals, the larger the stabilizing effect. For example, when the radical raises the SOMO energy by nucleophilic alkyl substituents and the alkene lower the LUMO energy by electron withdrawing substituents, SOMO-LUMO interaction becomes dominant by decreasing the energy difference and increases the addition rate. On the contrary, when the radical has a lower SOMO energy because of electron-withdrawing substituents and the alkene has a high-energy HOMO energy because of electron donating substituents, the SOMO-HOMO interaction becomes dominant. The radical becomes electrophilic and the alkene becomes electrophilic.



Scheme 3.2. Interaction between the SOMO of free-radical and the HOMO and LUMO of an alkene.

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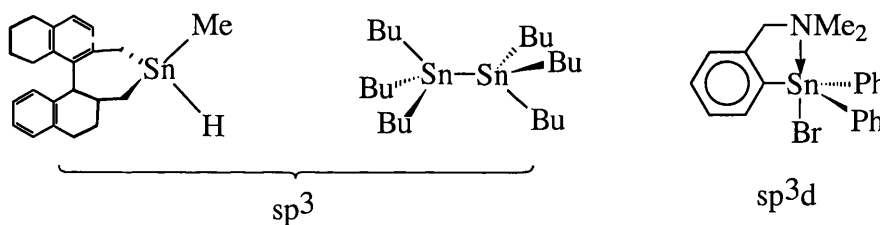
SECTION B

THIOL-CATALYZED RADICAL-CHAIN REDUCTION OF ORGANIC HALIDES BY HEXABUTYLDITIN IN THE PRESENCE OF MALONIC ACID

CHAPTER 4

INTRODUCTION

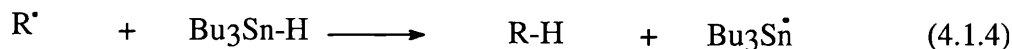
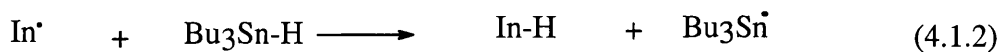
The application of organotin compounds is growing in modern synthetic methodology. The Sn-C bonds of an organotin compound are considered to be covalent (sp^3), but easily polarisable. When organotin compounds bear electronegative substituents, their Lewis acidity increases and coordination with electron-rich sites in substituents can lead to sp^3d or sp^3d^2 penta- or hexa-coordination. Organotin compounds show little ionisation in aqueous solution and most are poorly soluble in water. Organotin compounds have long bonds which are associated with low bond dissociation energies that facilitate homolytic reactions.¹



4.1. Reduction of Organic Halides with Organotin Compounds

Radical reactions using organotin hydrides have permeated the whole area of organic chemistry.² Halogen abstraction from an organic halide by the tributyltin radical and the trapping of the resulting carbon-centred radical by tributyltin hydride are basic to the use of tin hydrides. Organic halides can be reduced in the presence of a variety of functional groups such as alkene, alkyne, phenyl ether, epoxide, alcohol, ketone and ester.

The reduction of an organic halide by tributyltin hydride involves a radical-chain reaction [eqns. (4.1.1) - (4.1.4)] which is usually initiated by thermal decomposition of azobis(isobutyronitrile) (AIBN). Other radical sources of peroxides, ultraviolet light and simple heating can be used for initiation.



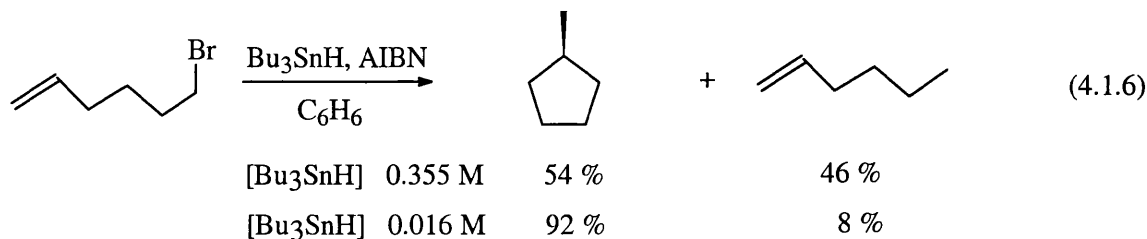
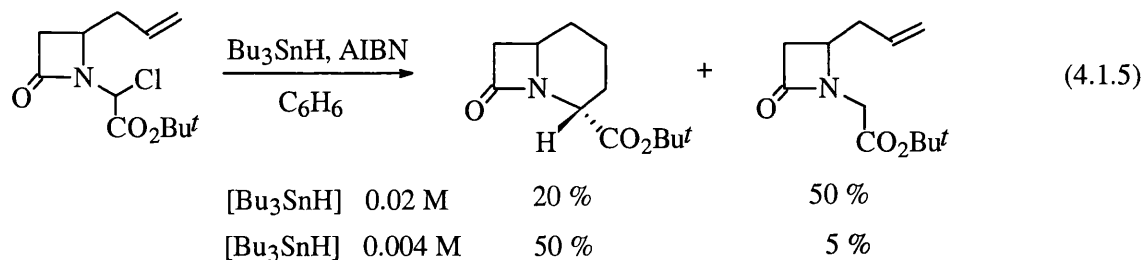
The organotin radical can abstract chlorine, bromine and iodine atoms from saturated or olefinic carbon atoms, but fluorine cannot be abstracted, because the carbon-fluorine bond is extremely strong.³

The rate of halogen abstraction from carbon increases with stabilisation of the anionic character of the carbon in transition state. The rate constant k for halogen-atom abstraction by the tributyltin radical depends on the kind of halogen: k is $\sim 10^2$ for chlorine, $\sim 10^7$ for bromine and $\sim 10^9 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ for iodine at room temperature. Also, the rate depends on the kind of substrates; the order of reactivity is tertiary halide > secondary halide > primary halide.⁴

Hydrogen-atom transfer from tributyltin hydride to alkyl radicals occurs with rate constants of 10^5 - $10^6 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ at room temperature. These rates do not depend much on the substituents at the radical centre.⁵ Simple alkyl radicals react with tributyltin hydride with rate constants on the order of $2 \times 10^6 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$. Tributyltin hydride is used in many areas of organic synthesis such as dehalogenation, deoxygenation or inter- and intra-molecular carbon-carbon bond-forming reactions.

However, such reactions of tributyltin hydride often have drawbacks. First, the Sn-H bond is relatively weak (310 kJ mol^{-1}) and hydrogen-atom transfer from tributyltin hydride to carbon-centred radical occurs very rapidly. However, if the desired product is from the trapping of a rearranged product, it may be necessary to keep low concentrations of tributyltin hydride (often by using syringe pump techniques) to ensure a good yield of the rearranged product [*e.g.* eqns. (4.1.5) and (4.1.6)].⁶

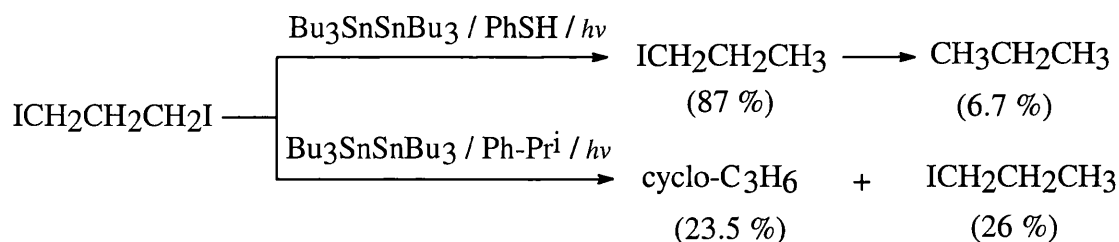
Another drawback is that tributyltin hydride and its derivatives are toxic as well as difficult to eliminate from the reaction product.



4.2. Reduction of Organic Halides with Organoditins

Since the use of tributyltin hydride has the limitation due to its high hydrogen-atom donating ability, organoditin reagents are often convenient substitutes for tin hydrides.⁸ The organotin radical can be generated from the organoditin by initiators or by ultraviolet light.

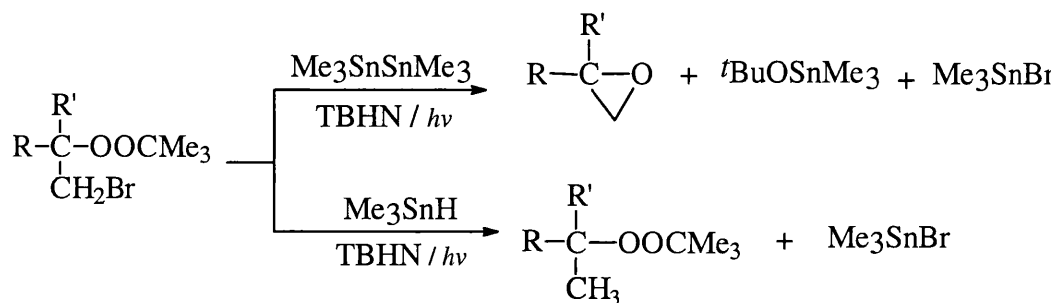
Kuivila and Pian have reported that organoditins sometimes have an advantage over tin hydride methods.^{8(a)} For example, 3-iodopropyl radicals were converted to cyclopropane by intramolecular homolytic substitution with isopropylbenzene as a less efficient hydrogen-atom donor solvent, or to 1-iodopropane by hydrogen-atom abstraction from the more efficient hydrogen-atom donor, thiophenol (**Scheme 4.2.1**).



Scheme 4.2.1

Bloodworth *et al.* have detected the formation of β -peroxyalkyl radicals and oxiranes when a mixture of β -bromoperoxides and hexamethylditin in benzene was

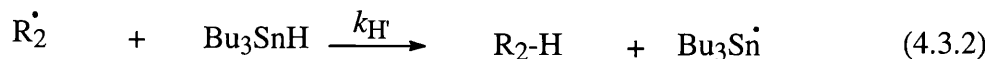
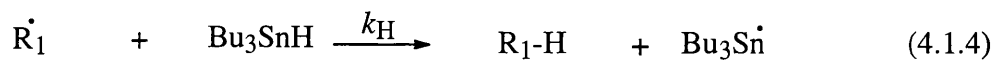
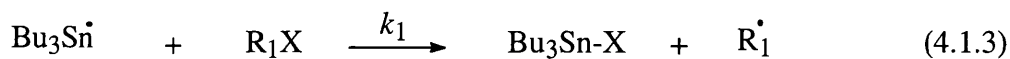
irradiated. However, when trimethyltin hydride was used, the reduction of the β -peroxyalkyl radical competes with oxirane formation (**Scheme 4.2.2**).^{8(c)}



Scheme 4.2.2

4.3. Free-Radical Rearrangements

Hydrogen-atom abstraction by a carbon-centred radical from tributyltin hydride is rapid and gives a simple reduction product, as shown in [eqn. (4.1.4)]. However, in some instances, the radical can rearrange before abstracting a hydrogen-atom from the tin hydride, and a competition occurs between rearrangement and hydrogen-atom abstraction, as shown in [eqns. (4.3.1) and (4.3.2)].⁹ Rather than the simple reduction product, trapping of a rearranged product is often desired. As mentioned previously, the high rate of reduction can then become a disadvantage because of the trapping of $\text{R}_1\cdot$ prior to its rearrangement.



When the radical $\text{R}_1\cdot$ rearranges with a rate constant k_{R} to give the radical $\text{R}_2\cdot$ in competition with reduction with a rate constant k_{H} to give $\text{R}_1\text{-H}$, the actual composition of

hydrocarbon mixtures depends on the concentration of Bu_3SnH and on the rate constant k_r and k_H . From analysis of the products and the known value of k_H , the isomerisation rate constant k_r can be computed (**Scheme 4.3.1**).¹⁰ By adopting the steady-state approximation, the rate of appearance of each radical is equal to the rate of its disappearance [eqns. (4.3.3) and (4.3.4)].

$$-\frac{d[\dot{\text{R}}_1]}{dt} = k_1 [\text{Bu}_3\dot{\text{Sn}}] [\text{R}_1\text{X}] - k_H [\dot{\text{R}}_1] [\text{Bu}_3\text{SnH}] = 0 \quad (4.3.3)$$

$$\frac{d[\dot{\text{R}}_2]}{dt} = k_R [\dot{\text{R}}_1] - k_H [\dot{\text{R}}_2] [\text{Bu}_3\text{SnH}] = 0 \quad (4.3.4)$$

Hence, the rates of formation of R_1H and R_2H are as given in [eqns. (4.3.5) and (4.3.6)].

$$\frac{d[\text{R}_1\text{H}]}{dt} = k_H [\dot{\text{R}}_1] [\text{Bu}_3\text{SnH}] = k_1 [\text{R}_1\text{X}] [\text{Bu}_3\dot{\text{Sn}}] \quad (4.3.5)$$

$$\frac{d[\text{R}_2\text{H}]}{dt} = k_H [\dot{\text{R}}_2] [\text{Bu}_3\text{SnH}] = k_R [\dot{\text{R}}_1] \quad (4.3.6)$$

Finally, we have [eqn.(4.3.7)].

$$\frac{d[\text{R}_1\text{H}]}{d[\text{R}_2\text{H}]} = \frac{k_H [\dot{\text{R}}_1] [\text{Bu}_3\text{SnH}]}{k_R [\dot{\text{R}}_1]} = \frac{k_H [\text{Bu}_3\text{SnH}]}{k_R} \quad (4.3.7)$$

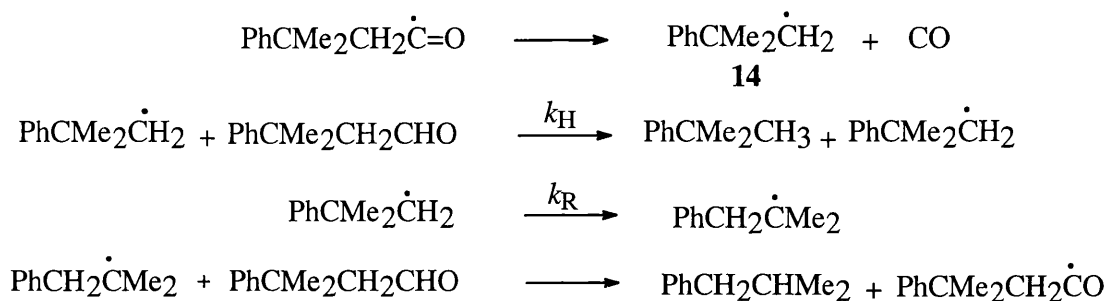
Provided that the tributyltin hydride is the only source of hydrogen-atoms and its concentration does not change significantly during reaction, then [eqn. (4.3.7)] can be integrated to obtain the expression shown in [eqn. (4.3.8)].¹¹

$$\frac{k_H}{k_R} = \frac{1}{[\text{Bu}_3\text{SnH}]} \cdot \frac{[\text{R}_1\text{-H}]}{[\text{R}_2\text{-H}]} \quad (4.3.8)$$

From a synthetic point of view, control of concentration in the hydrogen-atom donor can drive the reaction towards $\text{R}_1\text{-H}$ or $\text{R}_2\text{-H}$. Rate constants for reductions of alkyl halides by Bu_3SnH have also been measured using laser flash photolysis methods.⁵ Simple alkyl radicals react with tributyltin hydride with rate constants of *ca.* $2 \times 10^6 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ at room temperature.

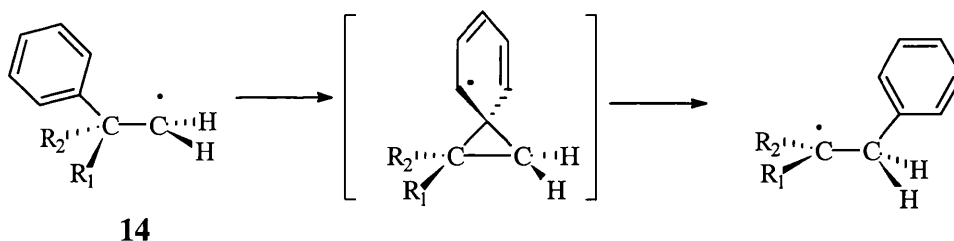
The 1,2-aryl migrations, the prototype of which is the neophyl radical (**14**) rearrangement, have been well-documented.¹³ The neophyl rearrangement has been

studied in the thermal decomposition of *tert*-butyl 3-methyl-3-phenylperbutyrate¹⁴ and the free-radical decarbonylation of 3-methyl-3-phenylbutyraldehyde¹⁵. For example, Winstein and Seubold have found that decarbonylation of β -phenylisovaleraldehyde initiated by *tert*-butyl peroxide gave a 1:1 mixture of *tert*-butyl- and isobutyl-benzenes (**Scheme 4.3.2**).¹⁵



Scheme 4.3.2

The neophyl rearrangement observed in this reaction takes place through the intramolecular formation of a cyclohexadienyl radical, followed by its ring opening. The driving force for the rearrangement is the formation of a tertiary radical from a primary radical (**Scheme 4.3.3**). The rate constant for rearrangement of the neophyl radical **14** has been well established and used as a "radical clock" to measure the rate constants for abstraction by **14** from various hydrogen-atom donors.^{11, 13}



Scheme 4.3.3

The aims of this part of the project are summarised below.

- (1) To investigate and optimise reaction condition for the reduction of α -haloesters using triorganosilanes in the presence of thiol catalysts.
- (2) To investigate and optimise reaction conditions for the reduction of racemic organic halides with a hexabutyldistannane in the presence of thiol catalysts.
- (3) To investigate the rearrangement of the neophyl radical generated in systems containing hexabutyldistannane and a thiol catalyst.

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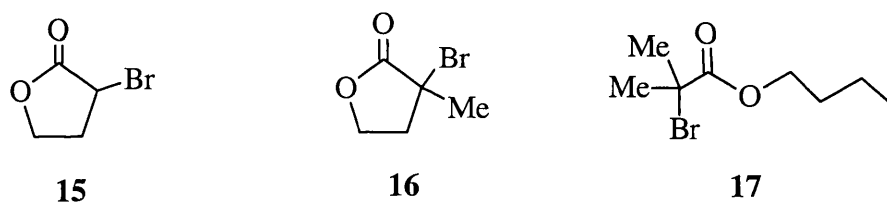
CHAPTER 5

RESULTS AND DISCUSSION

5.1 Reduction of α -Bromoesters Using Silanes in the Presence of Thiols

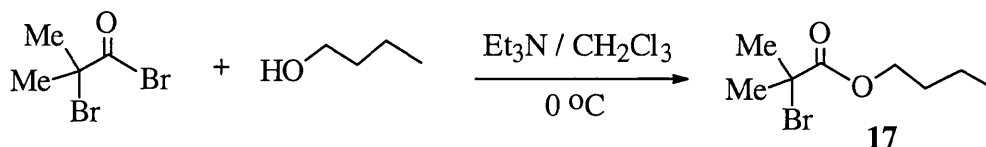
The reduction of alkyl halides, dialkyl sulfides and xanthates using silanes in the presence of a catalytic amount of thiols has been carried out by Roberts and co-workers.¹ Reduction proceeds by a radical chain mechanism and the thiol mediates hydrogen-atom transfer from the relatively strong Si-H bond of silanes to alkyl radicals.

Since radicals generated from *tert*- α -haloesters can be prochiral and have been used in several synthetic applications,² the development of methodology for the reduction of these compounds is of value. To check for the reduction of *tert*- α -haloesters using a silane in the presence of a thiol, α -bromo- γ -butyrolactone (**15**), α -bromo- α -methyl- γ -butyrolactone (**16**) and butyl 2-bromo-2-methyl propanoate (**17**) were chosen as substrates



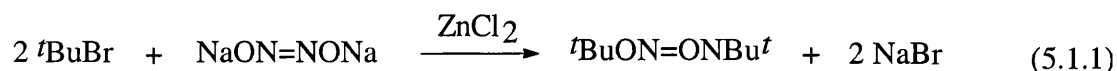
Scheme 5.1.1

(Scheme 5.1.1). The α -Bromo- γ -butyrolactones **15** and **16** are commercially available from Aldrich. Butyl 2-bromo-2-methyl propanoate **17** was easily prepared by esterification of 2-bromo-2-methylpropionyl bromide with butan-1-ol in the presence of triethylamine to give the product as a colourless oil in 70 % yield (Scheme 5.1.2).

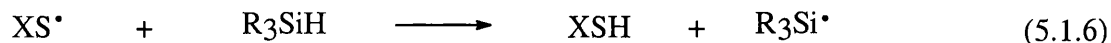
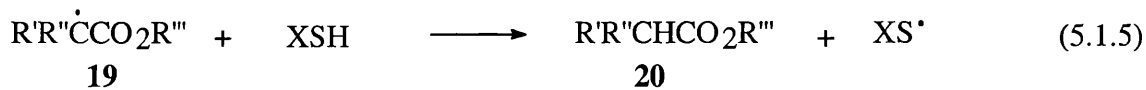
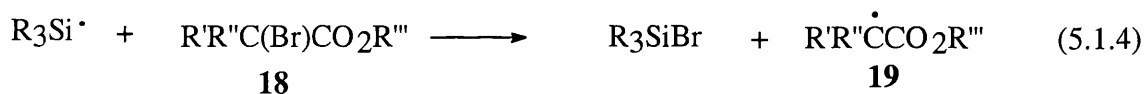
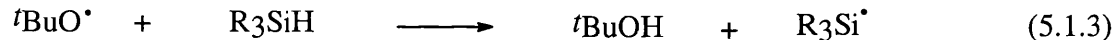


Scheme 5.1.2

Radical chain reactions were initiated by thermal decomposition of di-*tert*-butyl hyponitrite (TBHN) which generates *tert*-butoxyl radicals at relatively low temperature ($t_{1/2} = 55$ min. at 60 °C). TBHN was prepared, following the procedure described by Mendenhall,³ by reaction of sodium hyponitrite with *tert*-butyl bromide in the presence of zinc chloride [eqn. (5.1.1)].

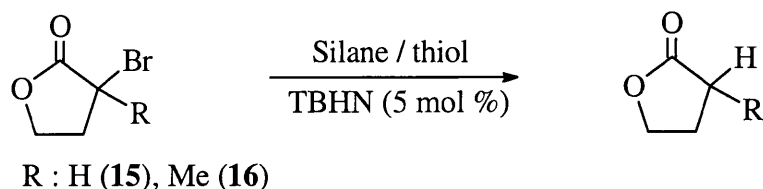


Chain propagation proceeds as follows: the *tert*-butoxyl radical abstracts a hydrogen-atom of the silane to generate a silyl radical which abstracts a bromine-atom from the α -bromoester **18**. The resulting α -alkoxycarbonylalkyl radical **19** then abstracts a hydrogen-atom from the thiol to give the reduction product **20** and the thiyl radical. The thiyl radical abstracts the hydrogen-atom from the silane to produce the silyl radical [eqns. (5.1.2)-(5.1.6)].



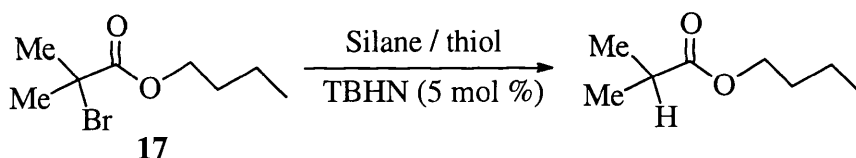
Typically, under the stream of argon, a mixture of α -bromo- γ -butyrolactone (**15**, 1.5 mmol), triethylsilane (3 mmol), TBHN (5 mol % based on bromide) and *tert*-dodecanethiol (5 mol %) in hexane (5 cm³) was heated at 60 °C for 1 hour. After cooling the reaction mixture, the crude product was analysed by gas chromatography using an OV-101-packed column with temperature programming from 80 to 200 °C. The hydrocarbon products of interest were identified by comparison of their retention times with those of authentic materials. GLC analysis showed that 95 % of α -bromo- γ -

butyrolactone (**15**) was converted into γ -butyrolactone. However, when the reaction was repeated with



Scheme 5. 1. 3

α -bromo- α -methyl- γ -butyrolactone (**16**) under otherwise identical condition, no reduction product was detected by GLC analysis. The reduction of the butyl 2-bromo-2-methylpropanoate (**17**) was also investigated (**Scheme 5.1.4**) and the results of the reaction with the variation of silanes and thiol catalysts are summarised in **Table 5.1.1**.



Scheme 5. 1. 4

The results in **Table 5.1.1** indicate that the reduction of the *sec*- α -bromolactone **15** occurred efficiently with triethylsilane in the presence of thiols (entry 1). However, under the same conditions, the reduction of the *tert*- α -bromolactone **16** did not occur with a range of silanes. Diphenylmethylsilane, dimethylphenylsilane, triphenylsilane and diphenylsilane all failed to bring about efficient reduction (entries 2-6). However, there was a tendency for yields to increase as the amount of thiol catalyst was increased (entries 7-8). The reduction of the *tert*- α -bromoester **17** showed similar results (entries 9-12). Encouragingly, when diphenylsilane was used in the presence of thiol catalyst, the *tert*- α -bromoester **17** was completely reduced (entry 13). However, in the absence of the thiol the reduction of **17** with diphenylsilane still gave 72 % yield of the reduction product (entry 14).

Halogen abstraction by the silyl radical is faster than that by the tributyltin radical under comparable conditions [eqn. (5.1.4)], because the Si-Br bond (BDE of Me₃Si-Br 427 kJ mol⁻¹) is stronger than the Sn-Br bond (BDE 347 kJ mol⁻¹).⁵ Hence, the rate determining step in the silane reductions is probably hydrogen-atom transfer from the thiol or the silane to the α -alkoxycarbonylalkyl radical **19**.

Table 5.1.1 Reduction of α -bromoesters using silanes in the presence of thiols and TBHN (5 mol %) at 60 °C for 1h^a

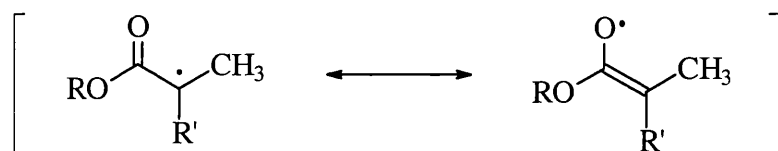
Entry	Bromide	Silane (equiv.)	Thiol (equiv.)	conversion yield (%) ^b
1	15	Et ₃ SiH (2)	<i>tert</i> -C ₁₂ H ₂₅ SH (5)	95
2	16	Et ₃ SiH (2)	<i>tert</i> -C ₁₂ H ₂₅ SH (5)	0
3	16	Ph ₂ MeSiH (1.5)	<i>tert</i> -C ₁₂ H ₂₅ SH (5)	0
4	16	Ph ₃ SiH (1.5)	<i>tert</i> -C ₁₂ H ₂₅ SH (5)	0
5	16	Ph ₂ SiH ₂ (1.5)	<i>n</i> -C ₁₂ H ₂₅ SH (5)	5
6	16	Ph ₂ SiH ₂ (1.5)	MeO ₂ CCH ₂ SH (5)	2
7	16	Et ₃ SiH (2)	<i>tert</i> -C ₁₂ H ₂₅ SH (10)	9
8	16	Et ₃ SiH (2)	MeO ₂ CCH ₂ SH (10)	17
9	17	Et ₃ SiH (2)	<i>n</i> -C ₁₂ H ₂₅ SH (5)	3
10	17	PhMe ₂ SiH (2)	<i>n</i> -C ₁₂ H ₂₅ SH (5)	0
11	17	Ph ₂ MeSiH (2)	<i>n</i> -C ₁₂ H ₂₅ SH (5)	1
12	17	Ph ₃ SiH (2)	<i>n</i> -C ₁₂ H ₂₅ SH (5)	2
13	17	Ph ₂ SiH ₂ (2)	<i>n</i> -C ₁₂ H ₂₅ SH (5)	100
14	17	Ph ₂ SiH ₂ (2)	-	72

a. Reaction condition : A mixture of the α -bromoester (1.5 mmol), silane (3 mmol), thiol (5 mol % based on the substrate) and TBHN (5 mol %) in hexane (5 cm³) was heated to reflux at 60 °C for 1 h .

b. Conversion yield of the reduction product determined by GLC: $100 \times [\text{RH}]_{\text{Area}} / \{[\text{RH}]_{\text{Area}} + [\text{RBr}]_{\text{Area}}\}$

The secondary radical $\text{RO}_2\dot{\text{C}}\text{CHR}^1$ has an electron-withdrawing alkoxy-carbonyl group and an electron-donating alkyl group attached at the radical centre. The α -C-H bond in an ester is also weakened because of conjugative delocalisation of the unpaired electron onto the carbonyl group (**Scheme 5.1.5**). However, this type of radical evidently abstracts hydrogen from the thiol sufficiently rapidly to maintain the chain. The radical $\text{RO}_2\dot{\text{C}}\text{CHR}^1$ can probably be classed as ‘‘ambiphilic’’,⁵ such that its philicity is determined by the reagent with which it is required to react.

The *tert*- α -alkoxy-carbonylalkyl radical **19** should be more nucleophilic than the *sec*- α -alkoxy-carbonylalkyl radical and thus polar effects should favour its abstraction of hydrogen from the thiol. However, **19** is more sterically hindered and also the C-H bond formed where it abstracts hydrogen is relatively weak and it apparently abstracts hydrogen from the thiol too slowly to maintain the chain. With Ph_2SiH_2 as a reducing agent, it appears that this silane can function as the hydrogen transfer agent in the absence of thiol. In Ph_2SiH_2 there are two Si-H bonds per molecule and these are probably weaker than in triorganosilanes. It is also possible that polar effects increase the rate of abstraction from this silane by the ambiphilic α -carbonylalkyl radical, with $[\text{Ph}_2\text{HSi}^+ \text{H}^- \text{CR}^1\text{R}^2\text{CO}_2\text{R}]$ (entry 14).

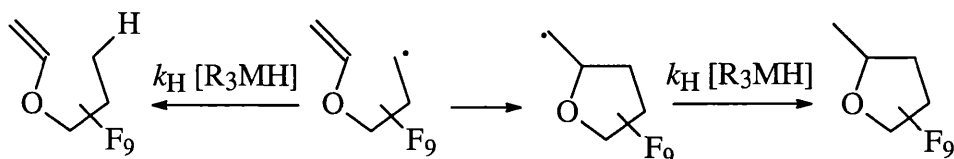


Scheme 5.1.5. Resonance structures of α - alkoxy-carbonylalkyl radicals **19**

Guindon *et al.* have shown that *tert*- α -haloesters of the type $\text{R}^1\text{R}^2\text{C}(\text{Hal})\text{CO}_2\text{R}$ are effectively reduced by tributyltin hydride which donates hydridic hydrogen-atom to ambiphilic *tert*- α -alkoxy-carbonylalkyl radicals.^{2(b)} The rate constants for abstraction of hydrogen-atom from tributyltin hydride and from silanes by electrophilic perfluoro-*n*-alkyl radicals at room temperature are listed in **Table 5.1.2**.⁴ Evidently the rate of

abstraction increases significantly as the strength of the M-H bond decreases, as expected, suggesting that Ph_2SiH_2 will be a more effective hydrogen-atom donor than Et_3SiH .

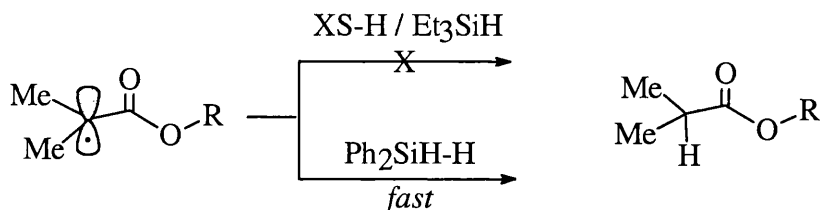
Table 5.1.2. The rate constants for abstraction of hydrogen-atom from tributyltin hydride and silanes by electrophilic perfluoroalkyl radicals



H-transfer agent	$n\text{-Bu}_3\text{SnH}$	$(\text{TMS})_3\text{SiH}$	$(\text{TMS})_2\text{MeSiH}$	Et_3SiH
$k_H (10^6 \text{ M}^{-1} \text{ s}^{-1})^a$	203	51	16.3	0.75
BDE ($\text{R}_3\text{M-H}$) ^b	310	351		398

a. Data from Ref. 4 (a). b. Data from 4 (b) and 4 (c). *Note:* Although the Si-H bond dissociation energy in Ph_2SiH_2 has not been reported, we may estimate that it will be significantly less than that in Et_3SiH (398 kJ mol^{-1}), because it is known that the value of BDH (Si-H) decreases with increasing number of Si-phenyl groups and as the number of hydrogen atoms attached to silicon increases.

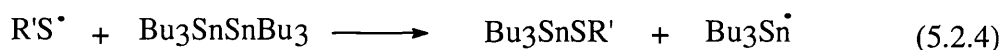
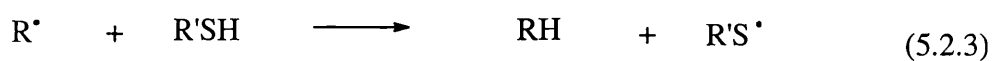
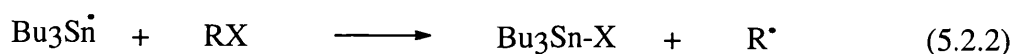
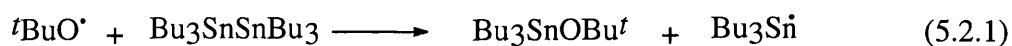
The results summarised in **Scheme 5.1.6** can then be rationalised in the following way. With the $\text{RSH}/\text{Et}_3\text{SiH}$ couple neither the thiol nor the silane donates a hydrogen-atom effectively to the ambiphilic and stabilised *tert*-radical $[\text{C}^\cdot\text{R}^1\text{R}^2\text{CO}_2\text{R}]$. However, with Ph_2SiH_2 in the absence of thiol the abstraction is effective, because the Si-H bond is weaker than that in Et_3SiH . In the presence of thiol, the reduction by Ph_2SiH_2 is also successful, presumably because it is still the silane that donates a hydrogen atom to the enolate radical. The thiol in this case is probably a passive by-stander.



Scheme 5.1.6

5.2. Reduction of Organic Halides Using Hexabutylditin and Malonic Acid in the Presence of Thiol Catalyst

The above problems for the reduction of electrophilic radicals in the use of silanes in the presence of thiols led us to consider the use of organotin radicals, generated from hexabutylditin. The tributyltin radical can be easily generated from hexabutylditin. For example, in the presence of TBHN, hexabutylditin reacts with *tert*-butoxyl radicals to generate tributyltin radicals, which in turn can react with alkyl halides to produce tributyltin halides and alkyl radicals. By choosing a suitable co-reactant, the reaction can be controlled toward the desired product. In the presence of an efficient hydrogen-atom donor, such as a thiol, alkyl radicals abstract the hydrogen-atom to give the reduction product and the thiyl radical which reacts with hexabutylditin to regenerate the tributyltin radical and support a radical chain sequence, as shown in [eqns. (5.2.1) - (5.2.4)].



Preliminary experiments were conducted to check the possibility of the reduction of simple alkyl halides using hexabutylditin in the presence of various thiols as hydrogen atom donors. 1-Bromododecane **21** was chosen as a substrate. Typically, TBHN (5 mol % based on alkyl halide) was added to a solution of 1-bromododecane (5 mmol), hexabutylditin (5 mmol) and *tert*-dodecanethiol (5 mmol) in hexane (4 ml). The reaction mixture was heated to reflux at 70 °C for an hour. After cooling the reaction mixture, this was analysed by gas chromatography without prior work-up. The hydrocarbon product of interest was identified by comparison of its retention time with authentic material. The results are summarised in **Table 5.2.1**.

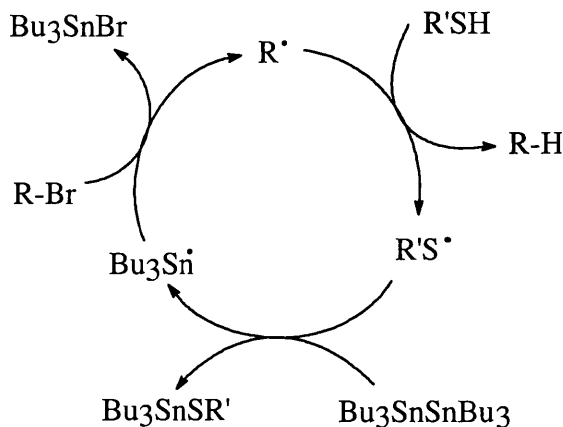
The reduction of 1-bromododecane (**21**) using hexabutylditin gave high yields in the presence of stoichiometric amounts of thiol as hydrogen-atom donor; *e.g.* 1-dodecanethiol, 1-butanethiol, thiophenol, methyl thioglycolate and *tert*-dodecanethiol worked well. Among them 1-dodecanethiol gave the best results, but adamantanethiol was found to be an inefficient hydrogen-atom donor. Also, it was found that use of excess hexabutylditin (1.20 equiv.) and thiol (1.20 equiv.) was required to convert the bromide **21** completely into dodecane (entries 7-8). This was probably due to the low purity of hexabutylditin, which can be oxidised in the presence of oxygen and water to give bis(tributyltin) oxide ($\text{Bu}_3\text{SnOSnBu}_3$) and tributyltin hydroxide (Bu_3SnOH). The reaction was found to be insensitive to the solvent (entries 7 and 8). The overall chain propagation sequence can be represented in (**Scheme 5.2.1**).

The method summarised in **Scheme 5.2.1** was applied to the reduction of α -bromolactones **15** and **16**. When the α -bromolactones were reacted with hexabutylditin (1.2 equiv.) and 1-dodecanethiol (1.2 equiv.) under the usual conditions, no products were detected by gas chromatographic analysis. Probably, α -bromolactones **15** and **16** or their reduction products underwent ring-opening reactions, as evidenced by the disappearance of **15** and **16** without the appearance of reduction product [eqn. (5.2.5)].

Table 5.2.1. Reduction of 1-bromododecane (**21**) using hexabutylditin and thiols^a

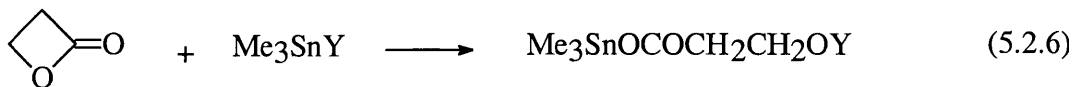
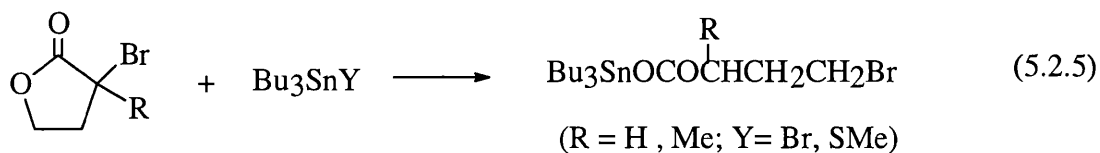
Entry	$\text{Bu}_3\text{SnSnBu}_3$ (equiv.)	Thiol (mol %)	Conversion Yield (%) ^b
1	1.0	<i>tert</i> - $\text{C}_{12}\text{H}_{25}\text{SH}$ (100)	87
2	1.0	1-Butanethiol (100)	93
3	1.0	Benzenethiol (100)	90
4	1.0	$\text{MeO}_2\text{CCH}_2\text{SH}$ (100)	81
5	1.0	Adamantanethiol (100)	59
6	1.0	$1\text{-C}_{12}\text{H}_{25}\text{SH}$ (100)	96
7	1.2	$1\text{-C}_{12}\text{H}_{25}\text{SH}$ (120)	100
8	1.2	$1\text{-C}_{12}\text{H}_{25}\text{SH}$ (120)	100 ^c

a. Reaction condition : A mixture of 1-bromododecane (5 mmol), hexabutylditin (5 mmol), thiol (5 mmol) and TBHN (5 mol %) in hexane (2 cm³) was heated to reflux at 70 °C for 1 h. b. Percent of reduction product determined by GLC: $100 \times [\text{RH}]_{\text{Area}} / \{[\text{RH}]_{\text{Area}} + [\text{RBr}]_{\text{Area}}\}$. c. Dioxane was used as solvent.



Scheme 5.2.1

Itoh *et al.* have reported that β -propiolactone undergoes a ring-opening reaction with trimethyltin bromide or trimethyltin methylsulfide, due to strong affinity of tin for oxygen. These authors explained ring-opening reaction by involving the soft acid-base concept where tributyltin is as soft acid to attack the sp³ oxygen atom and bromine is a soft base to attack the O-CH₂ carbon [eqn. (5.2.6)].⁶ Similarly, the ring opening of α -bromolactones can be explained.



The use of a stoichiometric amount of thiol raises a practical problem due to the stench of these compounds. Attempts were made to develop a method in which the thiol

can be a catalyst. The method should recycle the thiol from the tributyltin mercaptide which is generated by the reaction of a thiyl radical and hexabutyltin. We thus sought a co-reagent that would react with the trialkyltin mercaptide *in situ* to regenerate the thiol.

Although trialkyltin mercaptides are known to be relatively stable compounds and do not react with water, there has been a report that the tin-sulphur bond can be cleaved by reagents such as phosphorus trichloride and bromine to produce trialkyltin halides.^{7(a)} Also, carboxylic acids, especially malonic acid, have been used for the destannanylation of relatively inert Sn-OR and Sn-NR₂ bonds, as illustrated in [eqn. (5.2.7)].^{7(b)} There has

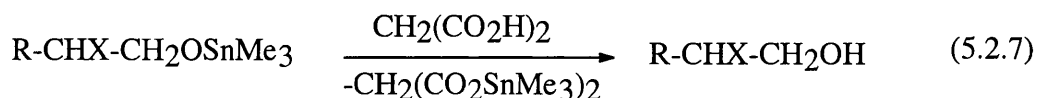


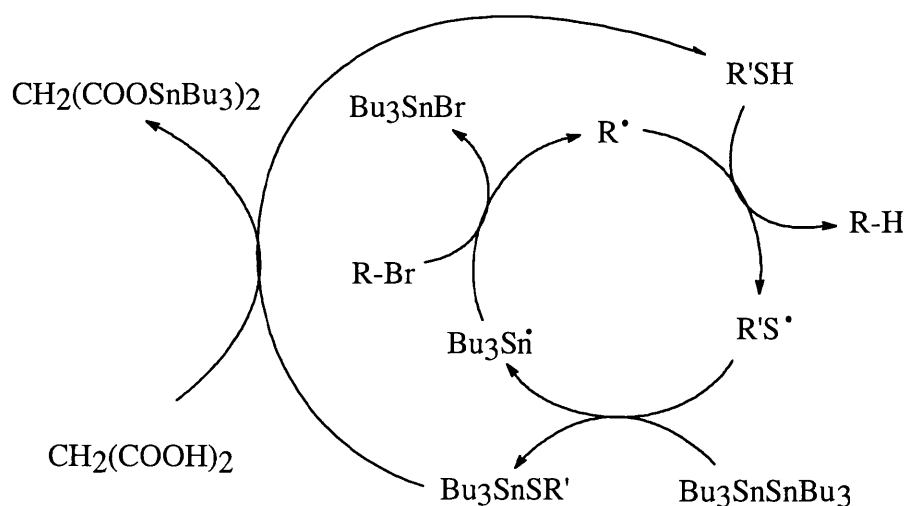
Table 5.2.2. Reduction of 1-bromododecane **21** using hexabutyltin and carboxylic acids in the presence of TBHN (5 mol %) and thiol (5mol %)^a

Entry	Bu ₃ SnSnBu ₃ (equiv.)	Thiol (5 mol %)	Carboxylic acid (equiv.)	Conversion Yield (%) ^b
1	1.2	1-C ₁₂ H ₂₅ SH	Acetic acid (1.2)	83
2	1.2	1-C ₁₂ H ₂₅ SH	Trifluoroacetic acid (1.2)	86
3	1.2	1-C ₁₂ H ₂₅ SH	<i>p</i> -Toluenesulfonic acid (1.2)	83
4	1.2	1-C ₁₂ H ₂₅ SH	Oxalic acid (1.2)	71
5	1.2	1-C ₁₂ H ₂₅ SH	Methylmalonic acid (0.6)	54
6	1.2	1-C ₁₂ H ₂₅ SH	Glutaric acid (1.2)	69
7	1.2	1-C ₁₂ H ₂₅ SH	Pentan-2,4-dione (1.2)	5
8	1.2	1-C ₁₂ H ₂₅ SH	Malonic acid (0.6)	94
9	1.2	-	Malonic acid (0.6)	8
10	1.2	Benzenethiol	Malonic acid (0.6)	74
11	1.3	Benzenethiol	Malonic acid (1.2)	100

a. Condition: a reaction mixture of 1-bromododecane (5 mmol), thiol (5 mol %), TBHN (5 mol%) and specified above in dioxane (2 cm³) was heated at 70 °C for 1 h. b. Percent of reduction product determined by GLC: $100 \times [\text{RH}]_{\text{Area}} / \{[\text{RH}]_{\text{Area}} + [\text{RBr}]_{\text{Area}}\}$.

been a report that a mixture of trialkyltin esters and mercaptans exists in equilibrium with trialkyltin mercaptides and carboxylic acid, as shown in [eqn. (5.2.8)].⁸ Thus, if the carboxylic acid is introduced into the reaction in [eqn. (5.2.4)] as a co-reagent, it could regenerate the thiol from the trialkyltin mercaptide (Bu₃SnSR') [eqn. (5.2.8)]. Acetic acid, trifluoroacetic acid, *p*-toluenesulfonic acid, oxalic acid, malonic acid, methylmalonic acid and glutaric acid, among others, were examined to find the effective co-reagent, as summarised in (Table 5.2.2).

Although most of carboxylic acids were found to be effective, malonic acid gave the good results (entry 8). However, pentan-2,4-dione did not donate hydrogen-atoms at all (entry 7). The use of benzenethiol as a catalyst gave a somewhat lower yield of dodecane than the use of 1-dodecanethiol (entries 8 and 10), but use of excess malonic acid with benzenethiol was found to complete the reduction of **21** (entry 11). In the absence of the thiol, only a low yield was obtained (entry 9), which indicates that a catalytic amount of the thiol sufficiently supports the radical chain reduction of alkyl halides using hexabutyltin and carboxylic acids through the equilibrium shown in eqn. (5.2.8). Therefore, the propagation cycle for the thiol-catalysed reduction can be completed by adding equation (5.2.8) to equations (5.2.1)-(5.2.4), and the overall propagation sequence in Scheme 5.2.1 can be replaced by the Scheme 5.2.2.



Scheme 5.2.2

The use of TBHN as an initiator has practical problems, because it is not commercially available and the yield of TBHN is sometimes not reproducible. Therefore, commercially available azobis(isobutyronitrile) (AIBN, $t_{1/2} = 1$ h at 85 °C), and 1,1-di-*tert*-butylperoxycyclohexane (DTBC, $t_{1/2} = 1$ h at 115 °C) would be better from a practical point of view.

Based on results in **Table 5.2.2**, reduction of 1-bromododecane was carried out to investigate initiation by AIBN and DTBC in the presence of thiols and the results are summarised in (**Table 5.2.3**). The reduction was dependent on the kind of the thiol. *tert*-Dodecanethiol gave a relatively low yield of dodecane compared with the other thiols (entry 1). 1-Dodecanethiol and benzenethiol gave higher yields than methyl thioglycolate

Table 5.2.3. The reduction of 1-bromododecane (**21**) by hexabutylditin (1.1 equiv.) and malonic acid (1.2 equiv.) in the presence of catalytic amounts of thiol and AIBN or DTBC^a

Entry	Thiol (mol %)	Initiator (5 mol %)	Solvent	Malonic acid (1.2 equiv.)	Yield (%) ^b
1	<i>tert</i> -C ₁₂ H ₂₅ SH (5)	AIBN	Dimethoxyethane	Malonic acid	34
2	MeO ₂ CCH ₂ SH (5)	AIBN	Dimethoxyethane	Malonic acid	74
3	1-C ₁₂ H ₂₅ SH (5)	AIBN	Dimethoxyethane	Malonic acid	81
4	1-C ₁₂ H ₂₅ SH (5)	AIBN	Benzene	Malonic acid	89
5	Benzenethiol (5)	AIBN	Dimethoxyethane	Malonic acid	84
6	Benzenethiol (5)	-	Dimethoxyethane	Malonic acid	2
7	-	AIBN	Dimethoxyethane	Malonic acid	1
8	Benzenethiol (5)	AIBN	Dimethoxyethane	-	4
9	Benzenethiol (100)	AIBN	Dimethoxyethane	-	82
10	Benzenethiol (5)	AIBN	Benzene	Malonic acid	93
11	Benzenethiol (5)	DTBC	Toluene	Malonic acid	90

a. Conditions: a mixture of 1-bromododecane (1.0 mmol), hexabutylditin (1.1 mmol), malonic acid (1.2 mmol), the thiol (5 mol %), AIBN (5 mol %) in the solvent (4 cm³) with decane as an internal standard was heated at at 80 °C for 3 h. b. Determined by GLC using decane as internal standard.

and *tert*-dodecanethiol (entries 3 and 5). The use of stoichiometric amounts of the thiol without carboxylic acid gave yields of dodecane, which are similar to those obtained using a catalytic amount of the thiol in the presence carboxylic acid (entries 5 and 9).

Although malonic acid is only sparingly soluble in benzene, use of 1,2-dimethoxyethane as solvent (in which the acid is very soluble) had little effect (entries 3 and 4). Furthermore, when benzenethiol was used, the reaction in benzene gave a better yield of dodecane than the reaction in dimethoxyethane. In the absence of thiol, of initiator or of malonic acid, the reduction gave negligible yields (entries 6-8). Therefore,

Table 5.2.4. Reduction of butyl 2-bromo-2-methyl propanoate (**17**) using hexabutylditin (1.3 equiv.) and malonic acid (1.2 equiv.) in the presence of thiol catalyst^a

Entry	Thiol (mol %)	Initiator (mol %)	Condition	Conversion Yield (%) ^b
1	n-C ₁₂ H ₂₅ SH (5)	TBHN (5)	70 °C / 1 h	9
2	<i>tert</i> -C ₁₂ H ₂₅ SH(5)	TBHN (5)	70 °C / 1 h	5
3	MeO ₂ CCH ₂ SH(5)	TBHN (5)	60 °C / 1 h	4
4	Benzenethiol (5)	TBHN (5)	70 °C / 1 h	8
5	-	TBHN (5)	70 °C / 1 h	3
6	Benzenethiol (10)	TBHN (5)	70 °C / 1 h	33
7	Benzenethiol (50)	TBHN (5)	70 °C / 1 h	73
8	Benzenethiol (100)	TBHN (5)	70 °C / 1 h	95
9	Benzenethiol (10)	AIBN (10)	80 °C / 1 h	10
10	Benzenethiol (50)	AIBN (10)	80 °C / 1 h	62
11	Benzenethiol (10)	AIBN (10)	UV ^c / 1 h	14
12	Benzenethiol (10)	AIBN (10)	80 °C / 1 h	2 ^d

a. Condition: A reaction mixture of butyl 2-bromo-2-methylpropanoate (5 mmol), hexabutylditin (1.3 equiv.), malonic acid (1.2 equiv.) in dioxane (1 cm³) in the presence of thiol and initiator was heated. b.

Percent of reduction product determined by GLC: $100 \times [\text{RH}]_{\text{Area}} / \{[\text{RH}]_{\text{Area}} + [\text{RBr}]_{\text{Area}}\}$. c. The reaction mixture in a quartz flask was immersed in a water cooling bath at 12-14 °C, and irradiated with light from a 160 W medium-pressure mercury discharge lamp at a distance of *ca.* 5 cm. d. Without malonic acid.

the combination of the thiol, initiator and malonic acid is required to support the efficient radical-chain propagation.

Since the reduction of *tert*- α -bromoesters using silanes in the presence of thiol catalysts was found to be a slow reaction (**Table 5.1.1**), it was important to attempt the reduction of butyl 2-bromo-2-methylpropanoate (**17**) using hexabutylditin and malonic acid in the presence of the thiol.

Typically, under a stream of argon, a mixture of the *tert*- α -bromoester **17** (0.25 mmol), hexabutylditin (1.3 equiv.) and malonic acid (1.2 equiv.) in the presence of the 1-dodecanethiol (5 mol %) and TBHN (5 mol %) in dioxane (1 cm³) was heated at 70 °C for 1 h. Gas chromatographic analysis showed that the *tert*- α -bromoester **17** was converted into butyl 2-methylpropanoate in 9 % yield (entry 1). The use of other thiols and initiators gave similarly low yields and the results are summarised in **Table 5.2.4**. In the absence of the thiol or malonic acid only trace amount of the product was detected (entries 5 and 12). When the amount of thiophenol was increased, yields had a tendency to increase. With a molar equivalent of thiophenol, the reduction of the *tert*- α -bromoester **17** was achieved 95 % yield (entries 6-8). It appears that this high concentration of the thiol was required in order to trap effectively the *tert*- α -alkoxycarbonylalkyl radical **19**. Wayner has achieved the reduction of *tert*- α -alkoxycarbonylalkyl radicals generated from α -*tert*-bromoesters of the type $\text{Me}_2\text{C}(\text{Br})\text{CO}_2\text{R}'$ with 1,2,2,6,6-pentamethylpiperidine (BDE of $\text{R}_2\text{NCH}_2\text{-H}$ is 356-377 kJ mol⁻¹) in the presence of excess amounts of thiols to overcome the high steric demand of hydrogen-atom transfer from 1,2,2,6,6-pentamethylpiperidine.^{2(a)}

The scope of the thiol-catalysed radical reduction of organic halides using hexabutylditin and malonic acid was investigated by examining reaction of 1-iodododecane (**22**), 2-bromoadamantane (**23**), 1-bromoadamantane (**24**), 1-bromoacetophenone (**25**), ethyl 2-bromohexanoate (**26**), *p*-bromobenzyl bromide (**27**), methyl 2-bromobenzoate (**28**), and methyl 2-iodobenzoate (**29**). These substrates and their authentic reduction products for the comparison of gas chromatographic analysis are commercially available

from Aldrich. Ethyl hexanoate, which is the reduction product of ethyl 2-bromohexanoate **27**, was prepared from hexanoic acid.

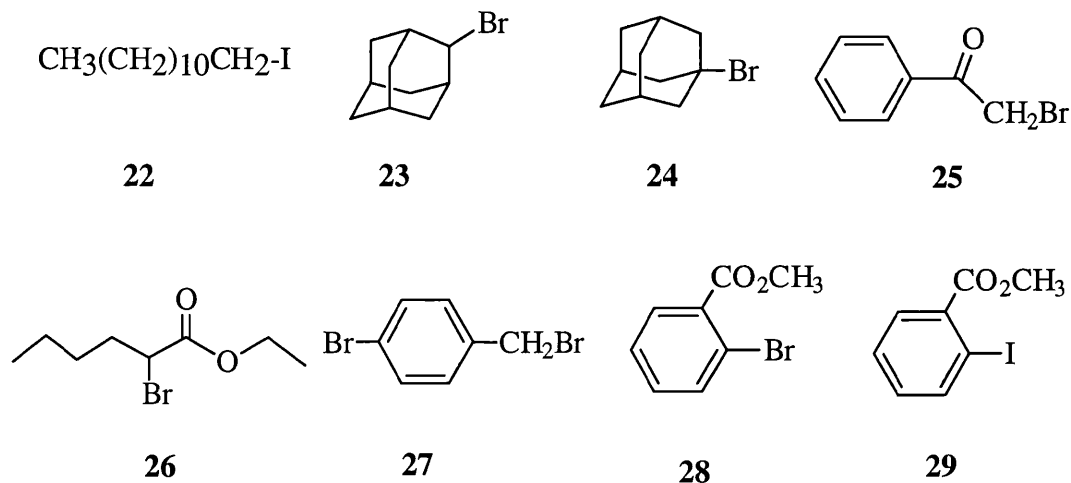


Table 5.2.5. Reduction of primary, secondary and tertiary alkyl halides by hexabutyliditin and malonic acid in the presence of thiol catalysts^a

Entry	R-Hal	Thiol (5 mol %)	Initiator (5 mol %)	Solvent	Condition (°C / h)	Yield (%) ^b
1	22	<i>tert</i> -C ₁₂ H ₂₅ SH (5)	TBHN	Dioxane	70 °C / 1h	95
2	22	Benzenethiol (5)	AIBN	Benzene	reflux / 1h	95
3	23	<i>tert</i> -C ₁₂ H ₂₅ SH (5)	TBHN	Dioxane	70 °C / 1h	93
4	23	1-C ₁₂ H ₂₅ SH (5)	AIBN	Benzene	reflux / 1h	90
5	23	Benzenethiol (5)	AIBN	Benzene	reflux / 1h	97
6	24	<i>tert</i> -C ₁₂ H ₂₅ SH (5)	TBHN	Dioxane	70 °C / 1h	95
7	24	1-C ₁₂ H ₂₅ SH (5)	AIBN	Benzene	reflux / 1h	90

a. Condition: a mixture of the substrate (1.0 mmol), hexabutyliditin (1.1 mmol), malonic acid (1.2 mmol), the thiol and the initiator (5 mol %) was heated. b. Determined by GLC using decane as an internal standard.

The reductive dehalogenations of primary, secondary and bridgehead tertiary alkyl halides gave excellent yields (**Table 5.2.5**). With TBHN or AIBN as initiator, 1-

iodododecane (**22**) was reduced to give dodecane in 95 % yields (entries 1 and 2). Also, the reductions of 2-bromoadamantane (**23**) and of the bridgehead tertiary 1-bromoadmantane (**24**) were successful to give over 90 % yields (entries 3-7). Yields from the reduction of the primary, secondary and tertiary alkyl halides are high, because hydrogen-atom transfer from thiols to nucleophilic alkyl radicals is very rapid.

Table 5.2.6. Reduction of organic halides by hexabutylditin and malonic acid in the presence of thiol catalyst^a

Entry	R-Hal	Thiol (5 mol %)	Initiator (5 mol %)	Solvent	Condition (°C / h)	Yield (%) ^b
1	25	n-C ₁₂ H ₂₅ SH (5)	TBHN	Dioxane	70 °C / 1h	83
2	25	Benzenethiol (5)	AIBN	Benzene	reflux / 1h	99
3	25	Benzenethiol (5)	-	Benzene	reflux / 1h	0.4
4	26	<i>tert</i> -C ₁₂ H ₂₅ SH (5)	TBHN	Dioxane	70 °C / 1h	27
5	26	n-C ₁₂ H ₂₅ SH (5)	TBHN	Dioxane	70 °C / 1h	59
6	26	Benzenethiol (5)	TBHN	Dioxane	70 °C / 1h	64
7	26	Benzenethiol (5)	AIBN	Benzene	reflux / 3h	86
8	27	Benzenethiol (5)	TBHN	Dioxane	70 °C / 1h	46
9	27	Benzenethiol (5)	AIBN	Benzene	reflux / 3h	67
10	27	Benzenethiol (10)	AIBN	Benzene	reflux / 3h	95
11	28	Benzenethiol (10)	AIBN	DME ^c	reflux / 3h	51
12	29	Benzenethiol (5)	AIBN	DME	reflux / 3h	30
13	29	Benzenethiol (10)	AIBN	DME	reflux / 3h	85

a. Condition: a mixture of substrate (1.0 mmol), hexabutylditin (1.1 mmol), malonic acid (1.2 mmol), thiol and initiator (5 mol %) was heated. b. Determined by GLC using decane as internal standard. c. Dimethoxyethane.

The reduction of the primary α -bromoketone, 1-bromoacetophenone (**25**), was fast and quantitative within 1 h (Table 5.2.6, entries 1 and 2). The carbonyl group in the

substrate did not interfere with the dehalogenative reduction of the α -bromoester **25**. The reaction was proved to proceed by a radical chain mechanism, because in the absence of AIBN no acetophenone was formed (entries 16 -18).

Under the same conditions, the reduction of the *sec*- α -bromoester **26** was carried out. When reactions were performed with thiols and TBHN at 70 °C for 1h under the usual conditions, the reactivity of thiols as catalysts appeared to be in the order of benzenethiol > *tert*-dodecanethiol > 1-dodecanethiol (Table 5.2.6, entries 4-6). However, the rate of reduction of the *sec*- α -bromoester **26** was lower than that of the primary α -bromoester **25**. For example, a mixture of the *sec*- α -bromoester **26** (1 mmol), hexabutylditin (1.1 mmol), malonic acid (1.2 mmol), decane (internal standard), benzenethiol (5 mol %) and AIBN (5 mol %) was heated in refluxing benzene. The reaction mixture was analysed after 1 h, 2 h, and 3 h to give 35 %, 57 % and 86 % yields of reduction product, respectively (entry 7).

Also, the reduction of *p*-bromobenzyl bromide (**27**) was slow. When a mixture of the bromide **27** with hexabutylditin and malonic acid in the presence of benzenethiol (5 mol %) and AIBN was heated in refluxing benzene for 3 h, gas chromatographic analysis showed 67 % of *p*-bromotoluene (entry 9). However, when a slight excess of benzenethiol (10 mol %) was used under otherwise identical conditions, the yield of the reduction product reached 95 %. In this reaction, the bromine atom attached directly to the benzene ring was not affected.

The reduction of aromatic halides was carried out in 1,2-dimethoxyethane (DME). The reduction of methyl 2-bromobenzoate (**28**) gave a lower yield than obtained from methyl 2-iodobenzoate, because the C-Hal bond strength in bromobenzene (BDE of Ph-Br is 339 kJ mol⁻¹) is greater than that in iodobenzene (BDE of Ph-I is 272 kJ mol⁻¹). When a slight excess of thiol (10 mol %) was used, methyl 2-bromobenzoate (**28**) and methyl 2-iodobenzoate (**29**) gave 51 and 85 % yields of methyl benzoate, respectively.

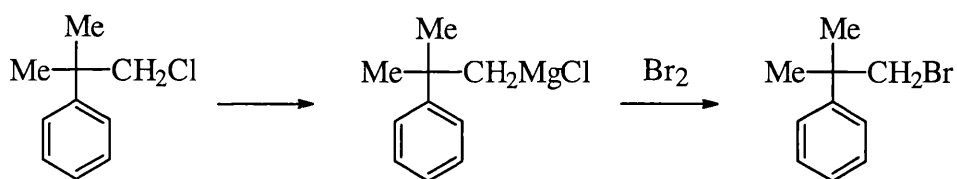
In conclusion, the radical-based reduction of primary, secondary and tertiary alkyl halides or 1-bromoacetophenone by hexabutylditin and malonic acid in the presence of catalytic amounts of a thiol was successfully accomplished with excellent yields. Radicals generated from ethyl 2-bromohexanoate, 4-bromobenzyl bromide, methyl 2-bromobenzoate and methyl 2-iodobenzoate abstract hydrogen-atoms relatively slowly from thiols, because radicals derived from those compounds are either electrophilic or stabilised. However, the reduction of these substrates using hexabutylditin, malonic acid

and a catalytic amount of thiol could be controlled to give good yields by optimising the reaction conditions. When radicals generated from tertiary α -haloesters were intermediates, yields of reduction products tend to increase with the amount of thiol present and good yields could be obtained when an equimolar amount of thiol was present. The usefulness of this reaction system lies in its potential for controlling the reaction rate by thiol concentration. The use of suitable hydrogen-atom donating thiols could be used to circumvent the need for slow addition of tributyltin hydride or the use of large volumes of solvent.

5.3. Thiol-Catalysed Radical Rearrangement of Neophyl Bromide.

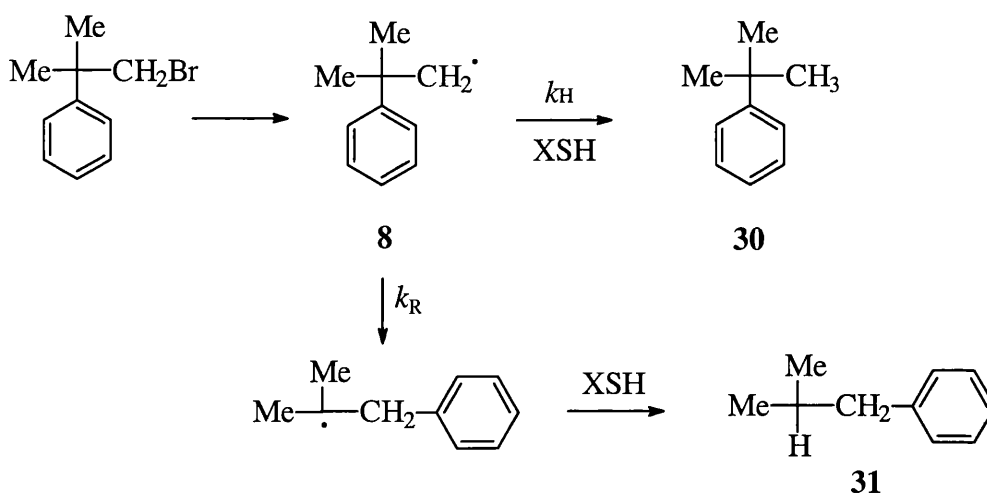
Radical rearrangement provides a method for examining the radical-molecule reaction kinetics.¹⁰ The neophyl rearrangement was applied to the reduction using hexabutylditin and malonic acid catalysed by thiol and this rearrangement produces *tert*-butylbenzene (**30**) and isobutylbenzene (**31**).

Neophyl bromide was prepared following the procedure described by Fainberg and Winstein.⁹ To a filtered solution of the neophyl Grignard reagent in diethyl ether, prepared from neophyl chloride, was added bromine below 5 °C. Fractional distillation gave 74 % of neophyl bromide (**Scheme 5.3.1**).



Scheme 5.3.1

The reduction of neophyl bromide was studied using 1,1-di-*tert*-butylperoxycyclohexane and AIBN as initiators. The reaction mixture was analysed by gas chromatography using an OV-101-packed column with temperature programming from 80 to 200 °C. *tert*-Butylbenzene **30** and isobutylbenzene **31** were identified by comparison of their retention times with those of the authentic materials and yields were determined using an internal standard.



Scheme 5.3.2

Initial studies were carried out with AIBN in refluxing benzene solvent. Typically, a mixture of neophyl bromide (1 mmol), hexabutyltin (1.1 mmol), malonic acid (1.2 mmol), TBHN (5 mol % based on neophyl bromide), dodecane (internal standard) and thiol (5 mol %, 0.0125 mol dm⁻³) in benzene (4 cm³) was placed on a pre-heated oil bath (85 °C) and stirred for 3 h. After cooling to room temperature, gas chromatographic analysis of the mixture showed that *tert*-butylbenzene **30** and isobutylbenzene **31** were produced in a total yield of 92.4 %; the value of [30]/[31] was 7.4. However, when the reaction was repeated with a lower concentration of the thiol (5 mol %, 0.005 mol dm⁻³), by adding more solvent (10 cm³) under otherwise identical conditions, the value of [30]/[31] was reduced to 4.6 (entries 1 and 2 in **Table 5.3.1**). Further experiments were carried out, varying the nature of the thiol and its concentration. The use of 1,1-di-*tert*-butylperoxycyclohexane as an initiator was also investigated. The results are summarised in **Table 5.3.1**.

The ratio of *tert*-butylbenzene : isobutylbenzene [30]/[31] was relatively high with a high concentration of the thiol, but was decreased by lowering the thiol concentration (entries 1 and 2). Also, the hydrogen-donating ability of the thiol had a major effect on the total yield. For example, benzenethiol (an effective hydrogen-atom donor) gave a high yield even under dilute conditions, but methyl thioglycolate (MTG) showed lower yields

of products (entries 1-4). When the concentration of thiol was very low, the total yield became lowered, but the yield of the rearranged product increased (entries 3-5).

Table 5.3.1. Reduction of neophyl bromide by hexabutylditin and malonic acid in the presence of thiols^a

Entry	Thiol (mol %)	Molarity of thiol (mol dm ⁻³) ^b	Initiator (5 mol %)	Solvent (Reflux)	Yield (%) ^c 30 : 31	Ratio (30/31)
1	PhSH (5)	(0.0125) ^d	AIBN	Benzene	81 : 11	7.4
2	PhSH (5)	(0.005) ^e	AIBN	Benzene	74 : 16	4.6
3	MTG (5)	(0.0125) ^d	AIBN	Benzene	38 : 3	12.7
4	MTG (2)	(0.002) ^e	AIBN	Benzene	25 : 11	2.3
5	NDT (5)	(0.0125) ^d	AIBN	Benzene	79 : 13	6.1
6	NDT (5)	(0.005) ^e	AIBN	Benzene	62 : 15	4.1
7	PhSH (2)	(0.002) ^e	DTBC	Toluene	59 : 39	1.5
8	PhSH (1)	(0.001) ^e	DTBC ^f	Toluene	38 : 54	0.7
9	PhSH (0.5)	(0.0005) ^e	DTBC ^f	Toluene	15 : 53	0.3
10	MTG (2)	(0.002) ^e	DTBC	Toluene	58 : 33	1.8
11	MTG (0.5)	(0.0005) ^e	DTBC	Toluene	14 : 27	0.5
12	TDT (2)	(0.002) ^e	DTBC	Toluene	34 : 17	0.73
13	TDT (0.5)	(0.0005) ^e	DTBC	Toluene	2 : 6	0.32
14	Bu ₃ SnH	(0.01) ^g	DTBC	Toluene	49 : 47	1.1

a. A mixture of neophyl bromide (1 mmol), malonic acid (1.2 mmol), initiator (5 mol %), the thiol and hexabutylditin (1.3 mmol) was reacted in refluxing solvent for 3h. b. Initial quantities present; these amounts of thiols were added to the solution. c. Determined by gas chromatography using dodecane as internal standard. d. 4 cm³ of benzene was used. e. 10 cm³ of benzene was used. f. 1,1-Di-*tert*-butylperoxycyclohexane (DTBC, 5 mol %) was added at the start of the reaction and after 1h another portion of DTBC (5 mol %) was added. g. A mixture of neophyl bromide (0.5 mmol), Bu₃SnH (0.68 mmol) and DTBC (5 mol%) in toluene (68 cm³) was heated to reflux for 4h.

The neophyl rearrangement is relatively slow. Even at a relatively high temperature in a large volume of refluxing toluene (68 cm³), reduction of neophyl bromide (0.5 mmol) with *tributyltin hydride* (0.68 mmol, 0.01 mol dm⁻³) in the presence of 1,1-di-*tert*-butylperoxycyclohexane (5 mol % based on bromide), gave slightly more *tert*-butylbenzene (49 %) than isobutyl benzene (47 %) (entry 14). However the reduction of neophyl bromide by hexabutylditin and malonic acid in the presence of benzenethiol (1 mol %) afforded higher yields of rearranged product under conditions of *much higher reagent concentration*. For example, reduction of neophyl bromide (1mmol) by hexabutylditin and malonic acid in refluxing toluene (10 cm³), in the presence of 1,1-di-*tert*-butylperoxycyclohexane (5 mol %) and benzenethiol (1 mol %) gave *tert*-butylbenzene (38 %) and isobutylbenzene (54 %) (entry 8). This shows the advantage of using the ditin-thiol couple as a replacement for the tin hydride.

Newcomb has abandoned the determination of rate constants for hydrogen-atom abstraction using the thiol-silane system based on Roberts' work, because in kinetic studies with unsaturated species the thiol is partially consumed by addition to alkene.¹⁰ However, if the possible addition to C=C bonds is excluded by using the neophyl rearrangement as a radical clock, it was thought possible to measure the rate constants for hydrogen-atom abstraction from thiols using eqn. (5.3.1). Using the data obtained in refluxing toluene (b.p. 111 °C) for benzenethiol in **Table 5.3.1**, the value of [30]/[31] was plotted against [PhSH] added initially (see **Figure 5.3.1**). The slope of the graph is k_H/k_R and a value of $7 \times 10^2 \text{ dm}^3 \text{ mol}^{-1}$ was obtained for this ratio. Franz *et al.* have studied the neophyl rearrangement in detail and the rate constant k_R is $6.7 \times 10^4 \text{ s}^{-1}$ at 111 °C,¹¹ which leads to a value for k_H of *ca.* $5 \times 10^7 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ at this temperature. Apparent rate constants for hydrogen-atom abstraction from other thiols obtained using the data in **Table 5.3.1** are also summarised in **Table 5.3.2**.

$$\frac{[\text{PhCMe}_3]}{[\text{PhCH}_2\text{CHMe}_2]} = \frac{[\mathbf{30}]}{[\mathbf{31}]} = [\text{PhS-H}] \cdot \frac{k_H^{\text{RSH}}}{k_R} \quad (5.3.1)$$

The rate constant for abstraction of hydrogen from benzenethiol by a primary alkyl radical has been determined to be *ca.* $2.6 \times 10^8 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ at 111 °C¹² Although the errors involved must be quite large, these results indicate that not all of the thiol added

initially is present throughout the reaction and that the majority of it is present as the tin mercaptide[eqn. (5.2.8)]. In fact, the results imply that only about 18% of the benzenethiol

Table 5.3.2. Apparent rate constants for hydrogen-atom abstraction from thiols determined in the reduction of neophyl bromide using hexabutylditin and malonic acid in the presence of thiol catalysts

Entry	Initiator	Temperature (°C)	Thiol	Apparent rate constant k_H^{RSH} (dm ³ mol ⁻¹ s ⁻¹)
1	AIBN	80	MTG	2 x 10 ⁶
2	AIBN	80	NDT	1 x 10 ⁶
3	DTBC	111	Benzenethiol	5 x 10 ⁷
4	DTBC	111	MTG	6 x 10 ⁶
5	DTBC	111	TDT	3 x 10 ⁶

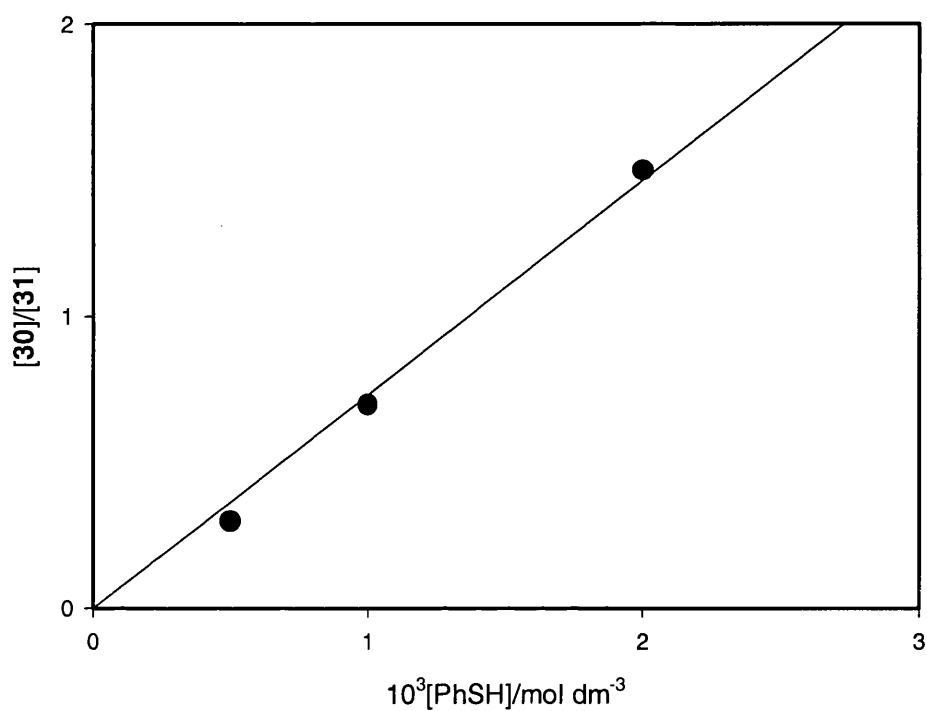


Figure 5.3.1. Variation of [30] / [31] as a function of initial benzenethiol concentration at 111 °C

added initially is present on average during the reaction. Thus, because of the variable and unknown amounts of thiol present during the reactions, the ditiol/thiol/malonic acid system cannot be used to measure the rate constants for hydrogen-atom abstraction from the thiol.

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CHAPTER 6

EXPERIMENTAL

6.1. General Procedures

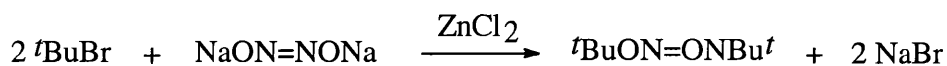
NMR spectra were recorded using a Varian VXR-400 instrument (400 MHz for ^1H). The solvent was CDCl_3 and chemical shifts are reported in ppm relative to the residual protons in the solvent (δ_{H} 7.24).

Gas chromatographic analysis was performed using a Pye-Unicam Series 304 gas chromatography, equipped with a flame-ionisation detector and a Hewlett-Packard model 3392A integrator. A glass column (3 m x 4 mm bore) packed with 10 % OV-101 on chromosorb WHP 80-100 mesh was used; the carrier gas was nitrogen and the detector response was calibrated using mixtures of authentic compounds with an internal standard.

All reactions were performed under the atmosphere of argon using dry solvents. Substrates for reduction were purchased from Aldrich and were used as received. Ethyl hexanoate was prepared as the authentic reduction product of ethyl 2-bromohexanoate. Triethylsilane, dimethylphenylsilane, diphenylsilane triphenylsilane and diphenylmethylsilane were used as received. Hexabutylditin was handled under the stream of argon and stored under argon in a fridge. Thiols were used as received and carboxylic acids were available in the laboratory. AIBN (Merck-BDH) was used as received, di-*tert*-butyl hyponitrite was prepared following the procedure described by Mendenhall,¹ and 1,1-di-*tert*-butylperoxycyclohexane (DTBC) was a gift from Peroxide-Chemie Ltd. and was used as the 50 % w/w solution in white mineral oil, as provided. Solvents such as benzene, hexane, dioxane, 1,2-dimethoxyethane and toluene (all HPLC grade) were purchased from Aldrich and used as received.

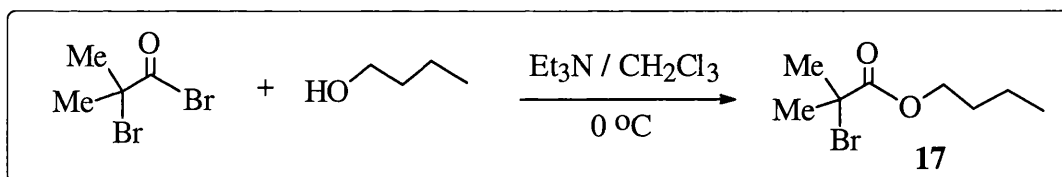
6.2. Preparation of Initiator and Substrates

1. Preparation of di-*tert*-butyl hyponitrite (TBHN)¹



Under a stream of dry argon, sodium hyponitrite (2.12 g, 20 mmol) was added to a mixture of excess 2-bromo-2-methylpropane (16 cm³, 0.14 mol) and zinc chloride (2.40 g, 0.018 mol) in dry diethyl ether (20 cm³) at 0 °C. The mixture was stirred for 30 min at 0 °C, stored in a freezer at 4 °C overnight and then filtered to remove the solid. The filtrate was washed with ice water (2 x 20 cm³) and dried over MgSO₄. After the removal of the solvent by rotatory evaporation at room temperature, the residual solid was recrystallized from methanol in a freezer (-20 °C) to give 2.0 g of white solid (56 %). ¹H NMR spectrum showed single sharp peak at 1.36 ppm.

2. Preparation of butyl 2-bromo-2-methyl propanoate (**17**)



A mixture of triethylamine (3.1 cm³, 22 mmol) and 1-butanol (2.1 cm³, 22 mmol) in dry dichloromethane (20 cm³) in a flask was placed in an ice-bath and 2-bromoisobutyryl bromide (2.5 cm³, 20 mmol) in dry dichloromethane (10 cm³) was added slowly at a rate such that the temperature of the mixture did not exceed 10 °C. The reaction mixture was stirred for an hour at 4 °C, allowed warm to room temperature, stirred for 6 hours and then poured into brine. The reaction mixture was washed with saturated brine. The organic

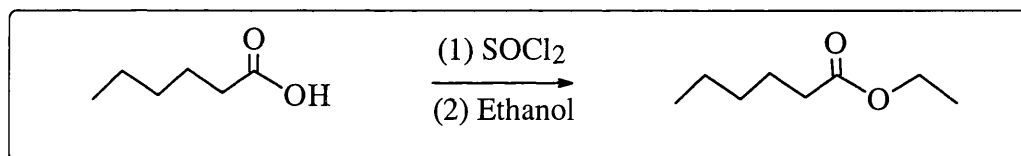
layer was washed with brine and dried over MgSO_4 . After evaporation using a rotary evaporator, the residual oil was distilled under reduced pressure to give 3.15 g of colourless oil (71 %).

B.p. $23\text{ }^\circ\text{C}/0.01\text{ Torr}$.

δ_{H} : 0.75 (t, 3H, CH_3), 1.24 (m, 2H, $\text{OCH}_2\text{CH}_2\text{CH}_2$), 1.50 (m, 2H, $\text{OCH}_2\text{CH}_2\text{CH}_2$), 1.72 (s, 6H, 2 CH_3), 4.00 (t, 2H, OCH_2).

δ_{C} : 13.68, 19.05, 30.39, 30.76, 55.97, 65.86, 171.74.

3. Preparation of ethyl hexanoate (17)



A mixture of hexanoic acid (6.3 cm^3 , 5 mmol) and thionyl chloride (7.3 cm^3 , 10 mmol) was heated under reflux at $60\text{ }^\circ\text{C}$ (oil bath) until gas evolution ceased. The excess of thionyl chloride was removed by distillation using a rotary evaporator. The residue was diluted with dichloromethane (20 cm^3), cooled to $0\text{ }^\circ\text{C}$, ethanol (10 cm^3) was added slowly and the mixture was stirred for 3 h at room temperature. The mixture was poured into water, washed with saturated brine, dried over MgSO_4 , evaporated solvent using a rotary evaporator and purified by short-path silica-gel column chromatography to give a colourless oil 4.3 g (60 %).

δ_{H} : 0.95 (3H, t, CH_3), 1.25 (3H, t, CH_3), 1.31 (4H, m, $\text{COCH}_2\text{CH}_2\text{CH}_2$), 1.63 (2H, m, CH_2CH_2), 4.11 (2H, q, OCH_2).

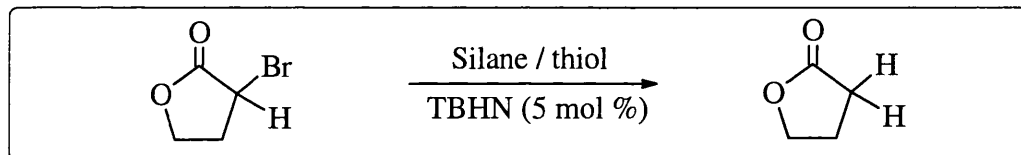
6.3. Reduction of α -Haloesters with Silanes and Catalytic Amount of Thiols

Reagents and solvent were introduced by weight and volume, respectively, into a dry, argon filled round bottomed 2-necked flask equipped with a magnetic bar and a

condeneor with argon flowing downwards through it. The flask was immersed in a pre-heated (bath temperature 70 °C for initiation of TBHN) and the contents was stirred under reflux under the slow stream of argon. The mixture was allowed to cool to room temperature and analysed by GLC without prior work-up.

Typically, to a mixture of α -bromoester (1.5 mmol), silane (3 mmol), and thiol (5 mol %) in dry hexane (3 cm³), TBHN (5 mol %) was added. The reaction flask was placed in a pre-heated oil bath (70 °C) and was stirred under argon for 1 h. The reaction mixture was allowed to cool to room temperature and analysed by GLC.

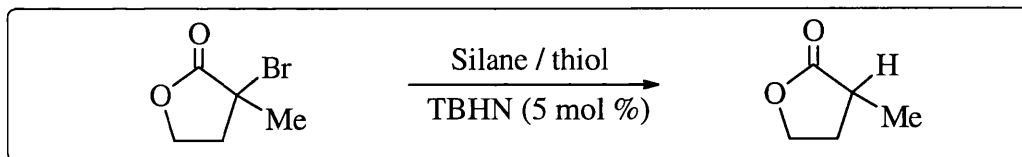
1. γ -Butyrolactone from α -bromo- γ -butyrolactone



Under a slow stream of argon a mixture of α -bromo- γ -butyrolactone (0.25 cm³, 3.0 mmol), triethylsilane (0.96 cm³), *tert*-dodecanethiol (35 μ l, 0.075 mmol) and TBHN (19 mg, 0.075 mmol) in dry hexane (3 cm³) was placed in a pre-heated oil bath at 70 °C and stirred for 2 hours. The reaction mixture was cooled to room temperature and gas chromatographic analysis showed γ -butyrolactone was present in 95 % yield. The reaction mixture was evaporated to give a crude product which was diluted with diethyl ether (20 cm³), washed with brine (2 x 20 cm³) and dried over MgSO₄. The solvent was evaporated and the residue was analysed by ¹H NMR spectroscopy to show a 89:11 mixture of γ -butyrolactone and α -bromo- γ -butyrolactone.

δ_{H} for γ -butyrolactone: 2.23-2.29 (m, 2H, CH₂CH₂CH₂), 2.47 (t, 2H, CH₂C=O), 4.34 (t, 2H, OCH₂).

2. α -Methyl- γ -butyrolactone from α -bromo- α -methyl- γ -butyrolactone



To a mixture of α -bromo- α -methyl- γ -butyrolactone (0.17 cm³, 1.5 mmol), triethylsilane (0.48 cm³, 3.0 mmol) and *tert*-dodecanethiol (0.018 cm³, 5 mol %) in dry hexane (1 cm³), was added TBHN (1.9 mg, 5 mol %) under a stream of argon. The reaction mixture was placed in a pre-heated oil bath at 70 °C and stirred under argon for 2 hr. The reaction mixture was cooled to room temperature and analysed by GLC without prior work-up. The results are reported in **Table 5.1.1**.

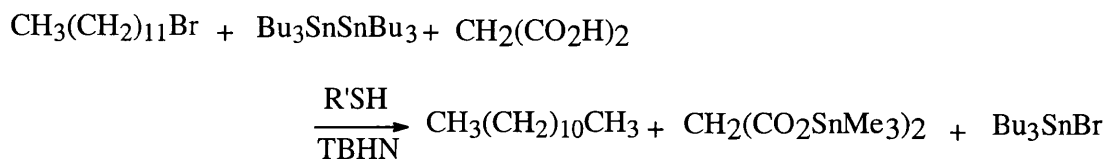
6.4. General Procedure for the Reduction of Alkyl bromides by Hexabutylditin and an Equimolar Amount of Thiols



To mixture of alkyl bromide (0.25 mmol), hexabutylditin (0.25 mmol) and thiol (0.25 mmol) in dry hexane (1 cm³), was added TBHN (5 mol % based on alkyl bromide). The flask containing the reaction mixture was placed in a pre-heated oil bath at 70 °C and was stirred under argon for 1h. The mixture was allowed to cool to room temperature and analysed by GLC without prior work-up.

In a representative run, to a mixture of 1-bromododecane (60 μ l, 0.25 mmol), hexabutylditin (126 μ l, 0.25 mmol), and 1-dodecanethiol (60 μ l, 0.25 mmol) in dry hexane (1 cm³), TBHN (3 mg, 5 mol %) was added under a slow stream of argon. The reaction mixture was stirred under argon at 70 °C for 2 h and allowed to cool to room temperature. Gas chromatographic analysis showed 96 % conversion to dodecane. The results are reported in **Table 5. 2. 1**.

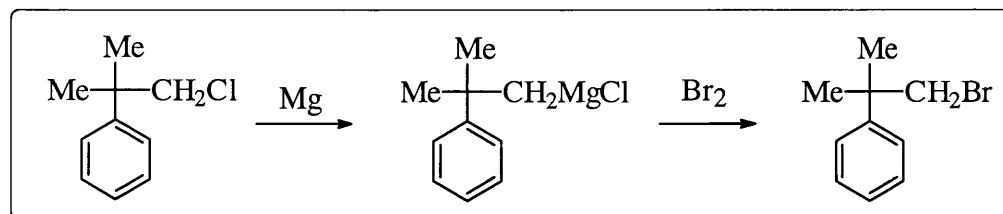
6.5. General Procedure for the Radical Reduction of Alkyl bromides by Hexabutylditin, Carboxylic Acids and Catalytic Amount of Thiols



To a mixture of alkyl bromide (0.25 mmol), hexabutylditin (0.32 mmol), malonic acid (0.33 mmol), thiol (5 mol %) and decane as internal standard in dry hexane (1 cm³), TBHN (5 mol % based on the alkyl bromide) was added. The reaction flask was placed in a pre-heated oil bath and stirred under argon at 70 °C for 1 h. The mixture was allowed to cool to room temperature and analysed by GLC. The results are reported in **Table 5. 2. 2**

In a representative run, to a mixture of 2-bromoacetophenone (50.2 mg, 0.25 mmol), hexabutylditin (143 μl, 0.25 mmol), malonic acid (31.2 mg, 1.2 equiv.), 1-dodecanethiol (3 μl, 5 mol %) and decane (15.6 μl, 0.11 mmol) as internal standard in dry hexane (1 cm³), TBHN (3 mg, 5 mol %) was added. The reaction mixture was stirred under argon at 70 °C for 2 h. Gas chromatographic analysis showed 83 % conversion to acetophenone. The results are reported in **Table 5.2.3**.

6.6..Preparation of Neophyl Bromide²



To a stirred solution of magnesium turnings (5 g, 0.21 g atom) in dry diethyl ether (50 cm³) and 1,2-dibromoethane to activate the reaction, neophyl chloride (30 g, 0.18 mol) in

dry diethyl ether (50 cm³) was added slowly. After the addition of neophyl chloride, the mixture heated to reflux for 2 h to complete the reaction. After cooling the mixture to room temperature, it was filtered under a stream of nitrogen to remove the unreacted magnesium. To the neophyl Grignard reagent in ether, was slowly added (for 1 h) bromine (30 g) diluted in dry diethyl ether (50 cm³) so as to keep the temperature below 5 °C. The mixture was stirred a further 1 h at room temperature. The ether layer was washed with aqueous sodium sulphite (50 cm³ x 2), with aqueous sodium bicarbonate (50 cm³ x 2) and dried over anhydrous potassium carbonate. After removal of the solvent by evaporation, the residue oil was purified by fractional distillation to give 74 % of neophyl bromide

Bp. 47-49 °C / 0.03 Torr. (lit.² 85-86 °C / 0.004 Torr.)

δ_{H} : 1.50 (s, 6H, 2 CH₃), 3.60 (s, 2H, CH₂Br), 7.28-7.48 (m, 5H, Ph)

δ_{C} : 27.28, 39.12, 46.97, 125.87, 126.58, 128.39, 146.01.

m/z (EI) : 214 (M⁺2, 3%), 212 (M⁺, 3%), 119 (100 %, M⁺-CH₂Br).

6.7 Neophyl Rearrangement

To a mixture of neophyl bromide (1 mmol), malonic acid (1.2 mmol), dodecane (internal standard) and AIBN (5 mol %) in benzene (10 cm³), was added benzenethiol (5 mol %) and hexabutylditin (1.3 mmol). The reaction mixture was placed to a pre-heated oil bath at 80 °C, stirred for 3 h and allowed to cool at room temperature. Gas chromatographic analysis without prior work up showed that a 74.4: 16.1 mixture of *tert*-butylbenzene and isobutylbenzene was produced. The experiment with 1,1-di-*tert*-butylperoxycyclohexane (DTBC) as initiator was carried out in refluxing toluene solvent, the results are summarised in **Table 5.3.1**.

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SECTION C

RADICAL-CHAIN DESULFURISATION OF

2-(ALKYLTHIOMETHYL)ACRYLATES WITH TRIPHENYLPHOSPHINE:

NEW ROUTE TO 2-ALKYLACRYLATES

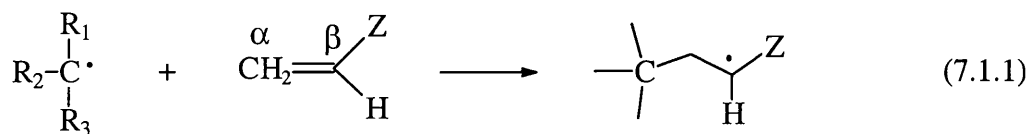
CHAPTER 7

INTRODUCTION

7.1. Radical Addition and Fragmentation Reactions

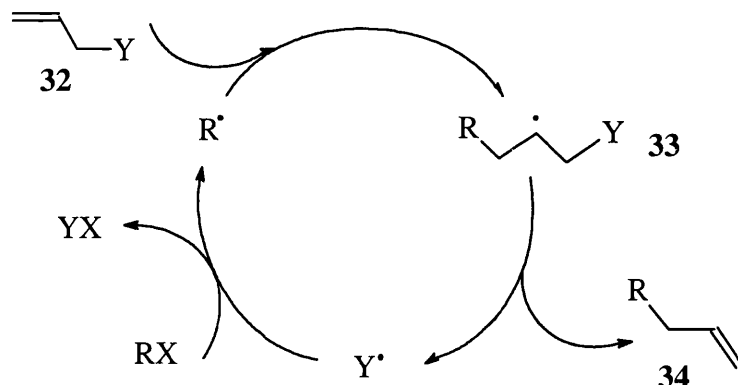
In radical addition reactions, the rate depends on the substituent on the alkene and the substituent on the radical.¹ The substituent on the β -carbon of the alkene mainly exerts a polar effect towards the attacking radical. When the substituent on the alkene is electron-attracting group, reactivity of a nucleophilic radical increases because of a favourable polar effect.

The substituent on the radical also exerts a polar effect on the addition to the alkene. When the radical has one or two electron-donating substituents, nucleophilicity increases reactivity towards electrophilic alkenes [eqn. (7.1.1)]. For example, a secondary alkyl radical reacts with acrylonitrile 7.3 times faster than the primary alkyl radical.



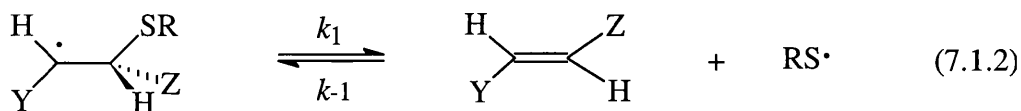
Fragmentation is the reverse of addition. This process commonly occurs when the chain transfer agent (*e.g.* $\text{Bu}_3\text{Sn}\cdot$) is eliminated from the adduct radical leading to allylic or vinylic substitution. Fragmentation processes are often endothermic and are favoured

by raising the temperature. The main driving force is the entropy increase upon fragmentation involving a bond β to the radical centre. The overall propagation sequence of radical fragmentation, often called allylation, is represented in **Scheme 7.1.1**, in which the adduct radical is transformed into the non-radical product by β -bond cleavage of the chain transfer agent.



Scheme 7.1.1

Radicals such as $\text{Br}\cdot$, $\text{RS}\cdot$, $\text{R}_3\text{Sn}\cdot$ and $\text{RSO}_2\cdot$ can add to the double bond, but these reactions are reversible because bonds formed are weak (BDEs of C-Br and C-SR are $\sim 293 \text{ kJ mol}^{-1}$, and C-SnR₃ and C-SO₂R are $\sim 251 \text{ kJ mol}^{-1}$).² It is noteworthy that β -thio-substituted radicals easily undergo elimination of thiyl radicals to afford alkenes, because the exothermic addition is reversible at normal temperature [eqn. (7.1.2)].

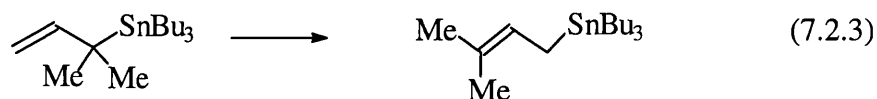
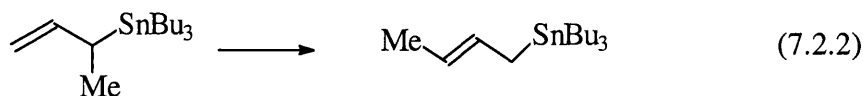


Radical allylation reactions such as the “allyltin method” and the “vinyltin method”, which results in vinylation, involve such fragmentation reactions.³

7.2. The Allyltin Method

Keck and co-workers have shown that allyl stannanes can be used for allylation of organic halides.⁴ The propagation sequence involves the fragmentation of an adduct radical to produce a β -tributyltin radical and the allylated product **34**. Halide abstraction by the tributyltin radical provides the alkyl radical which adds to allyltributylstannane **32** to produce the β -tributyltin adduct radical **33** (see **Scheme 7.1.1**, when Y is Bu_3Sn).

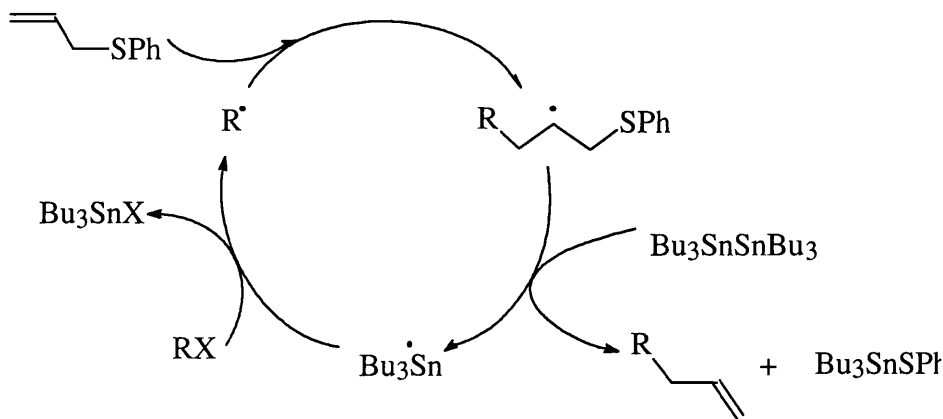
The advantage of the allyltin method is that tributyltin hydride is not involved in the reaction. Thus, intermediate radicals are not intercepted by tributyltin hydride, and low concentrations are not required as in the tributyltin hydride method. The disadvantage is that the method is limited to only allyl- and methallyl-stannanes. In the case of a crotylstannane, an allylic hydrogen abstraction occurs to generate an unreactive species, because addition to the internal double bond is slow as a result of steric hindrance [eqn. (7.2.1)]. Also, if methyl substituents are present at C-3 of the allylstannane, this rapidly rearranges to the more stable isomer, as shown in [eqns. (7.2.2) and (7.2.3)].



7.3. β -Carbon-Sulfur Bond Cleavage Method

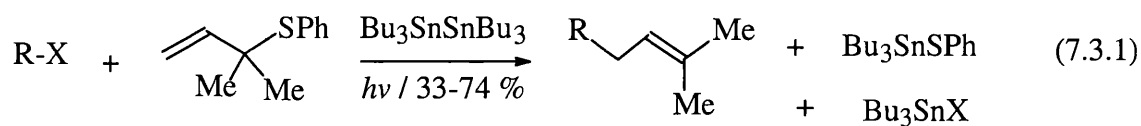
An alkyl radical with a β -carbon-sulfur bond also undergoes a rapid β -scission reaction. To overcome the limitations of allyltin method, Keck and Byers have reported a

method in which the allyltin is replaced by an allylic phenyl sulfide in the presence of hexabutylditin as shown in (Scheme 7.3.1).⁵ In the propagation sequence, after addition of the alkyl radical to the allyl sulfide, fragmentation produces the phenylthiyl radical. Addition of the phenylthiyl radical to hexabutylditin generates the tributyltin radical.



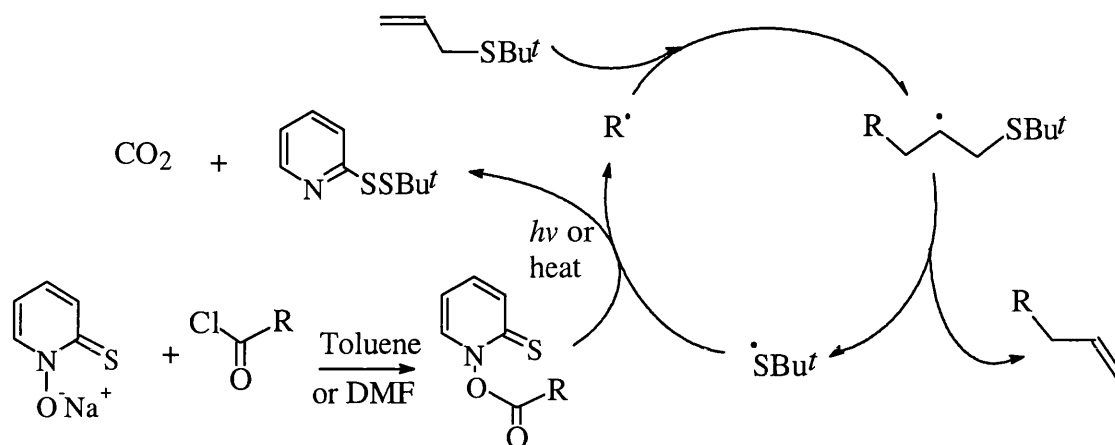
Scheme 7.3.1

For example, irradiation of 3-methyl-3-phenylthiobut-1-ene and an alkyl halide in the presence of hexabutylditin gave a moderate yield of the allylic substituted product without formation of the rearranged product [eqn. (7.3.1)].



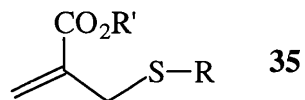
Barton and Crich have reported that carbon radicals, generated from the esters of *N*-hydroxy-2-thiopyridone, react with allyl *tert*-butyl sulfides to give allylic substituted products.⁶ This one-pot reaction was carried out by adding the acid chloride to the sodium salt of the *O*-acylthiohydroxamic acid in the presence of the allyl *tert*-butyl sulfide in boiling chlorobenzene. In the reaction sequence, the alkyl radical attacks the allyl *tert*-butylsulfide to give the adduct radical, which undergoes rapid β -scission to give the

allylated product and the *tert*-butylthiyl radical. The *tert*-butylthiyl radical attacks the *O*-acylthiohydroxamate to regenerate the alkyl radical (Scheme 7.3.2).

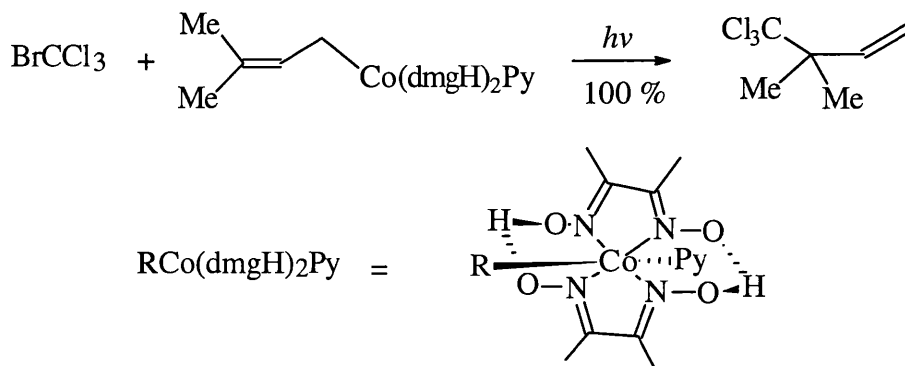


Scheme 7.3.2

It was found that the allylation using the thiohydroxamate ester was promoted when an electron-withdrawing group was present at the β -carbon of the allyl thioether **35** and yields are higher than in the above addition procedure ranging from 50 to 75 %.⁶



7.4. The Carbon-Cobalt Bond Cleavage Method

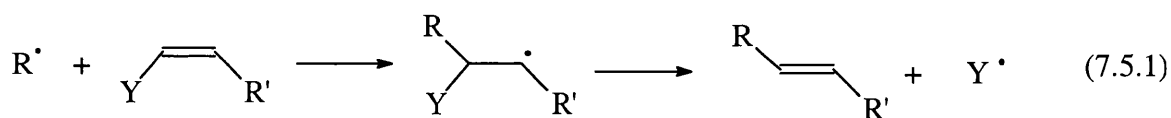


Scheme 7.4.1

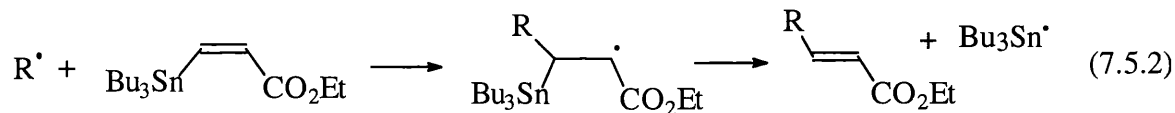
Another radical chain allylation method is the carbon-cobalt bond cleavage method, which benefits from the rapid cleavage of Co-C bond. Allyl cobaloximes have been used with electrophilic radicals in this context and the cobaloxime process can be used with crotyl and substituted allylic systems, as shown in (Scheme 7.4.1).⁷

7.5. The Vinyltin Method

When an alkyl radical reacts with an alkene to produce an adduct radical which has a weak β -bond (C-Y), fragmentation occurs *via* an addition-elimination sequence. A comprehensive survey of the vinyltin method has been carried out by the Russell group, as shown in [eqn. (7.5.1)].⁸

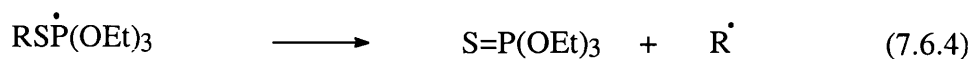
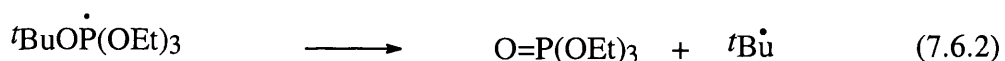


The vinyltin method is similar to the allyltin method, but here the alkyl radical is required to attack a tin-substituted olefin in order to give the product *via* a β -elimination. Thus, Baldwin has reported that the reaction of nucleophilic alkyl radicals with activated β -stannyl acrylates affords β -alkyl acrylates in good yields [eqn. (7.5.2)].⁹

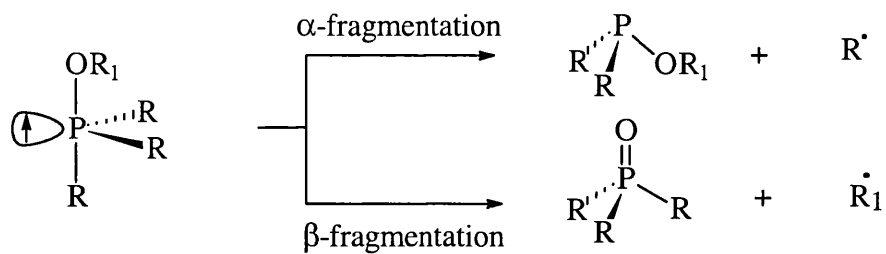


7.6. Desulfurisation by Trivalent Phosphorus Compounds

The radical reactions of trivalent phosphorus molecules have been well reviewed.¹⁰ The unoccupied d-orbital of phosphorus(III) molecules facilitates reaction with the radical by allowing the valence shell expansion *via* oxidative addition. For example, the reaction of a phosphorus(III) compound with an alkoxy radical or a thiyl radical easily gives a phosphoranyl radical, since P-O and P-S bonds are relatively strong [BDE of P-O bond is 352 kJ mol⁻¹ in P(OEt)₃ and the P-S bond is 218 kJ mol⁻¹, estimated from P₄S₄] [eqns. (7.6.1) and (7.6.3)].¹²



Walling and co-workers have shown that such phosphoranyl radicals can provide an alkyl radical through fragmentation, as shown in [eqns. (7.6.2) and (7.6.4)], with driving force provided by the formation of very strong P=O and P=S bonds.¹¹ In general, fragmentation of a phosphoranyl radical can occur by an α -scission or β -scission reaction (**Scheme 7.6.1**). For example, the reaction of the *tert*-butoxyl radical with a trialkyl phosphite or triphenylphosphine gives mainly the β -scission product [BDEs of C-O bond is 381 kJ mol⁻¹ and P-O bond is 347 kJ mol⁻¹ for P(OCH₃)₃ respectively], but in the reaction



Scheme 7.6.1

of the *tert*-butoxyl radical with tributylphosphine the product consists of 80 % $\text{Bu}_2\text{POBu}^\cdot$ and 20 % $\text{Bu}_3\text{P}=\text{O}$ [BDE of P-C is 322 kJ mol^{-1} for $\text{P}(\text{C}_6\text{H}_5)_3$] indicating that α -scission is predominant.¹³

References to Chapter 7

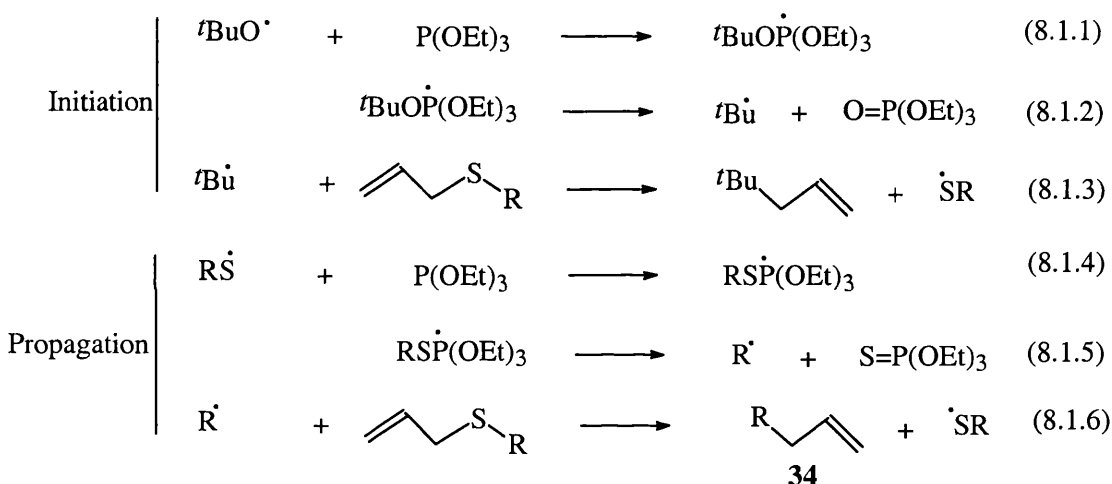
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CHAPTER 8

RESULTS AND DISCUSSION

8.1. Addition of Alkyl Radicals to Alkyl Allyl Sulfides

Radical reactions of allyl alkyl sulfides in the presence of phosphorus(III) compounds was examined first as a potential carbon-carbon bond forming reaction. When allyl alkyl sulfides are allowed to react with phosphorus(III) compounds under radical conditions, the reaction would be expected to proceed to give allylated products **34** via a radical chain sequence [eqns. (8.1.1)-(8.1.6)].



Initial reactions were carried out with allyl hexyl sulfide **36** and triethyl phosphite in the presence of di-*tert*-butyl hyponitrite (TBHN, $t_{1/2} = 60$ °C, 55 min). Typically, a mixture of allyl hexyl sulfide **36** (0.25 mmol), triethyl phosphite (0.25 mmol), TBHN (5 mol % based on sulfide) and decane (internal standard) in hexane (1.0 cm³) was heated at 60 °C for 2 h. The reaction mixture was allowed to cool and then was analysed by gas chromatography. The analysis showed 5 % of 1-nonene was formed, but the majority of the allyl hexyl sulfide and triethyl phosphite remained unreacted. A further investigation of the reaction by varying conditions, initiators and phosphorus(III) compounds was performed and the results are summarised in **Table 8.1.1**.

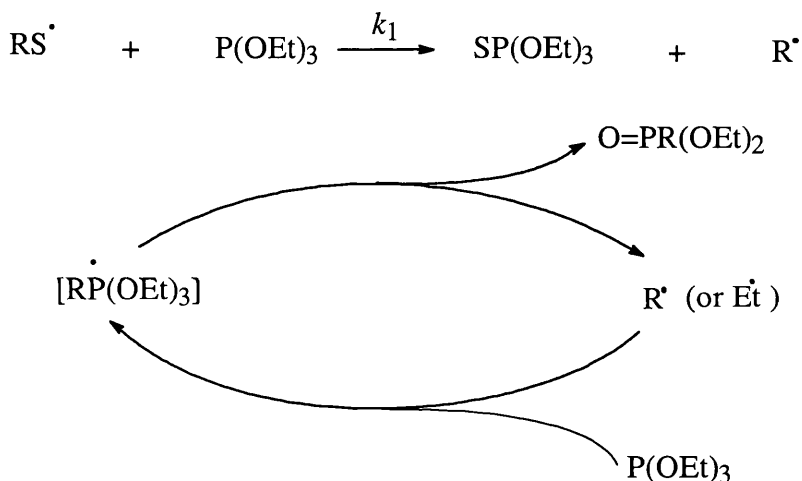
Reactions of allyl hexyl sulfide with an excess of triethyl phosphite did not raise yields (entries 1-3). Also, it was found that the reaction was insensitive to solvent effects (entries 4-6). Variation of initiators and initiating conditions has no effect (entries 8-11). Changing the phosphorus(III) compound, *e.g.* triethyl phosphite, tris(*p*-fluorophenyl)phosphine and triphenylphosphine did not raise the yield of 1-nonene (entries 12-14). However, in the absence of triethyl phosphite the reaction did not occur (entry 7).

Table 8.1.1. Radical reactions of allyl hexyl sulfide with phosphorous (III) compounds

Entry	PX ₃ (equiv.)	Initiator (mol %)	Solvent	Condition (°C / h)	Yield (%) ^a
1	P(OEt) ₃ (1.0)	TBHN (5)	Hexane	60 / 2	5
2	P(OEt) ₃ (2.0)	TBHN (5)	Hexane	60 / 2	5
3	P(OEt) ₃ (10.0)	TBHN (5)	Hexane	60 / 2	4
4	P(OEt) ₃ (1.1)	TBHN (5)	Dioxane	60 / 3	5
5	P(OEt) ₃ (1.1)	TBHN (5)	Benzene	60 / 2	4
6	P(OEt) ₃ (1.1)	TBHN (5)	-	60 / 2	6
7	-	TBHN (5)	Benzene	70 / 3	-
8	P(OEt) ₃ (1.1)	TBHN (10)	Benzene	60 / 2	6
9	P(OEt) ₃ (1.1)	AIBN (10)	Benzene	82 / 2	4
10	P(OEt) ₃ (1.1)	DBPC (10) ^b	Decane	100 / 2	3
11	P(OEt) ₃ (1.1)	DTBP (10) ^c	Decane	130 / 2	2
12	PEt ₃ (1.2)	TBHN (5)	Benzene	70 / 2	3
13	P(<i>p</i> -F-C ₆ H ₄) ₃ (1.2)	TBHN (5)	Benzene	70 / 2	4
14	PPh ₃ (1.2)	TBHN (13)	Benzene	70 / 2	8

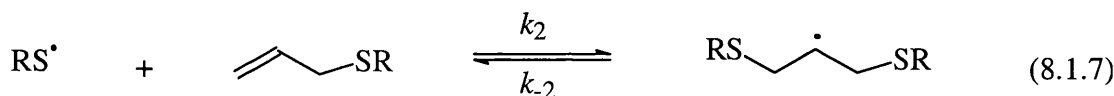
a. Yields were determined by gas chromatography using decane as internal standard. b. 1,1-di-*tert*-butylperoxycyclohexane. c. di-*tert*-butyl peroxide.

When the reaction in entry 1 was monitored using gas chromatography, nonene was formed in 0.5 %, 4 %, 5 %, and 6 % yields after 0.5 h, 1 h, 2 h, and 3 h, respectively. Although the majority of the allyl hexyl sulfide was still present after 3 h, triethyl phosphite was consumed to a far greater extent: 1.4 %, 33 % and 76 % after 0.5 h, 1 h and 3 h, to give two strong peaks in the chromatogram, probably due to $\text{SP}(\text{OEt})_3$ and $\text{OPEt}(\text{OEt})_2$, in the ratio of 4:1. However, in the reactions with triphenylphosphine the peaks of by-products did not increase after 2 h. Those results suggest that the alkyl radical generated from the phosphoranyl radical $\text{RSP}'(\text{OEt})_3$ mainly reacts with triethyl phosphite *via* a radical chain to generate $\text{SP}(\text{OEt})_3$ and $\text{OPEt}(\text{OEt})_2$, as shown in (Scheme 8.1.1).



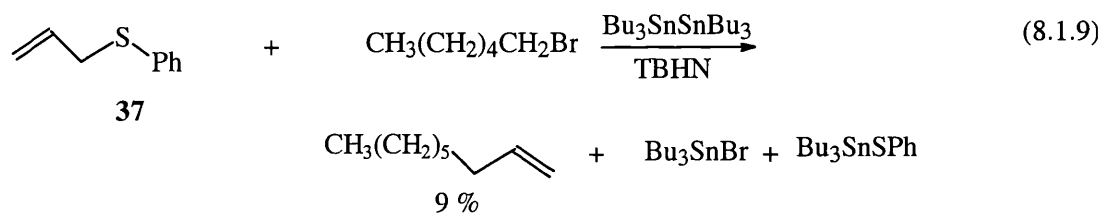
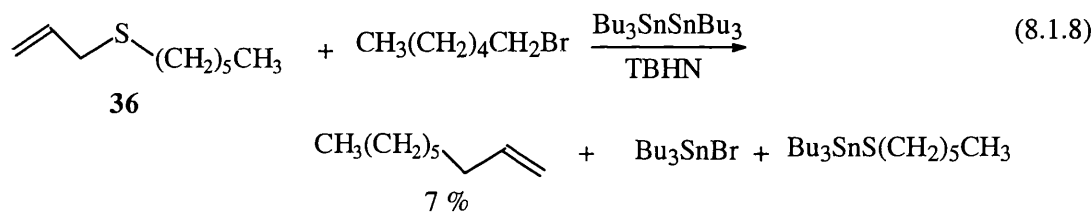
Scheme 8.1.1

Walling and Pearson have reported that the reaction of alkenes, thiols and triethyl phosphite in the presence of AIBN gave dialkyl sulfides.² In this report the rate constant for the formation of the phosphoranyl radical (k_1) was estimated to be as $8 \times 10^8 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$, using the known rate constant for the addition of the thiyl radical to the alkene ($k_2 = 2.5 \times 10^8 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$), assuming that the reversibility of reaction (8.1.7) can be neglected.



However, the similar values of k_1 and k_2 suggest that there would be a competition between the addition of the thiyl radical to the allyl alkyl sulfide and to the trivalent phosphorus compound to give the phosphoranyl radical.

Two independent experiments were carried out to check the reactivity of allyl sulfides by modifying Keck's procedure, in which the allyl phenyl sulfide and an alkyl halide were allowed to react with hexabutylditin, initiated by UV irradiation for 13 h to afford the allylated product.³ First, allyl hexyl sulfide **36** was allowed to react with hexabutylditin (1.3 equiv. based on sulfide), 1-bromohexane (1.0 equiv.) and TBHN (5 mol %) in benzene solution at 70 °C for 3 hours. Gas chromatographic analysis showed 7 % of 1-nonene was formed [eqn. (8.1.8)]. Under the same conditions, the



reaction of allyl phenyl sulfide **37** was carried out and gave a 9 % yield [eqn. (8.1.9)]. These results are consistent with Barton and Crich's results concerning the reaction of esters of *N*-hydroxy-2-thiopyridone with allylic sulfides (see **Scheme 7.3.2**).⁴ Therefore, it is clear that the addition of the alkyl radical to the double bond in an alkyl or aryl allyl sulfide is relatively slow. Because it is already known that the β -elimination of the thiyl radical is rapid,⁵ the slow addition of the nucleophilic alkyl radical to the electron-rich alkene is probably the result of an unfavourable polar effect.

8.2. Carbon-Carbon Bond Forming Reactions Using β -Ethoxycarbonyl Allylic Sulfides

Clearly in order to improve the yield, it is necessary to activate the alkene by introducing an electron-withdrawing group on the C=C bond. The activating substituent (Y) was provided by the ester group present at the 2-position in the allylic moiety. The function of the β -alkoxycarbonyl group is to lower the LUMO energy of the alkene to facilitate interaction with the SOMO of the nucleophilic alkyl radical (Figure 8.2.1).

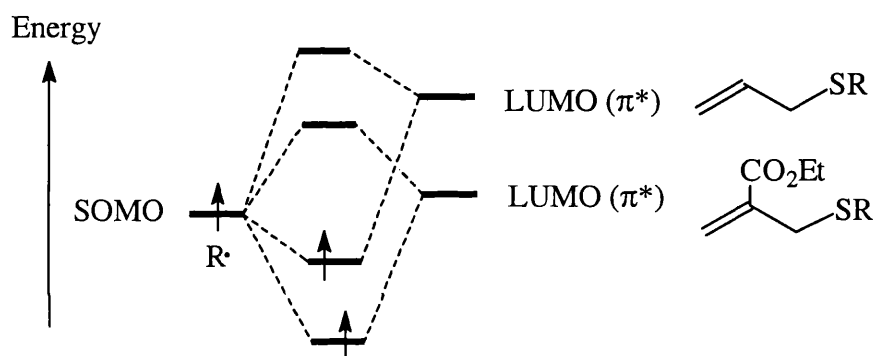
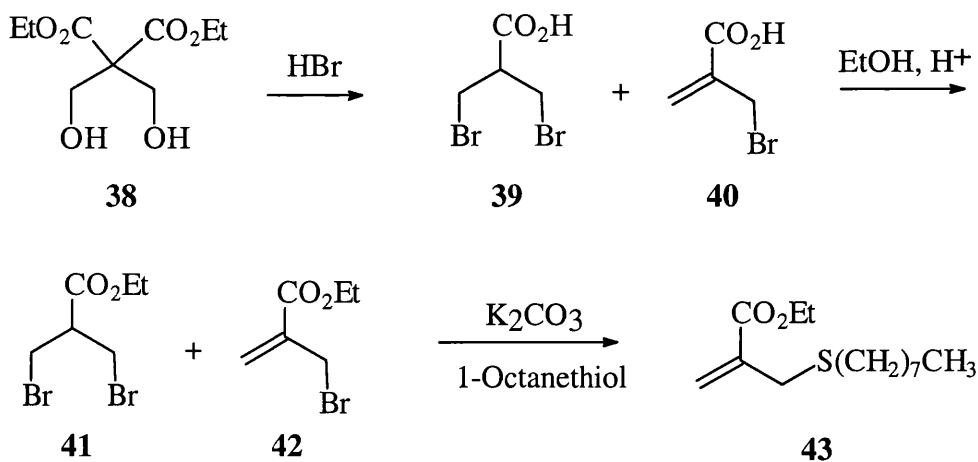


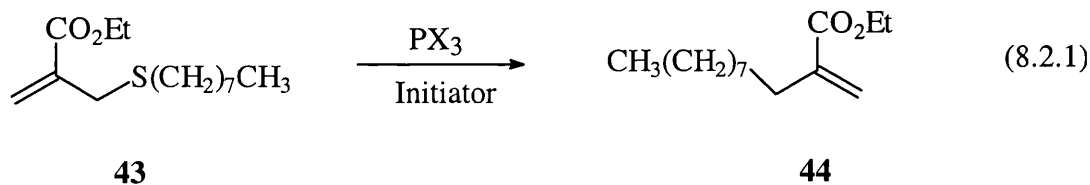
Figure 8.2.1. Frontier molecular orbital interactions for addition of a nucleophilic alkyl radical to an allylic sulfide

The acrylate **43** was prepared in three steps following a literature method.⁶ Hydrobromination of diethyl bis(hydroxymethyl)malonate (**38**) gave a 1:2 mixture of β,β' -dibromoisobutyric acid (**39**) and α -bromomethylacrylic acid (**40**) which were esterified with ethanol. The resulting mixture of ethyl β,β' -dibromoisobutyrate (**41**) and ethyl α -bromomethyl acrylate (**42**) was allowed to react with 1-octanethiol and potassium carbonate in ethanol to afford ethyl 2-methylene-3-octylthiopropionate (**43**) in 78 % yield, as shown in (Scheme 8.2.1).



Scheme 8.2.1

Radical reactions of acrylates **43** with phosphorus(III) compounds such as triethyl phosphite, triphenylphosphine and trimethyl phosphite were examined in the presence of initiators such as di-*tert*-butyl hyponitrite, 1,1-di-*tert*-butylperoxy-cyclohexane (DTBC, $t_{1/2} = 1$ h, 115 °C), and di-*tert*-butyl peroxide (DTBP, $t_{1/2} = 1$ h, 150 °C) [eqn. (8.2.1)].



Typically, a mixture of the acrylate **43** (3.0 mmol), triethyl phosphite (3.3 mmol) and TBHN (0.15 mmol) in benzene (1.5 cm³) was heated under a stream of argon at 60 °C for 3 h. After cooling the reaction mixture, the solvent was evaporated and the residue was distilled using a Kügelrohr apparatus (50 °C, 0.02 Torr) to remove the unreacted triethyl phosphite and the triethyl thiophosphate. The residue was purified by silica gel column to afford 32 % of 2-ethoxycarbonyl-1-nonene (**44**). When triphenylphosphine was used, the reaction mixture was filtered to remove the solid Ph₃P=S and then purified by silica gel column chromatography.

Table 8.2.1. Radical reactions of ethyl 2-methylene-3-octylthiopropionate with the phosphorus (III) compounds

Entry	PX ₃ (III) (equiv.)	Initiator (mol %)	Solvent	Condition (°C / h)	Yield of 44 (%) ^a
1	P(OEt) ₃ (1.2)	TBHN (5)	Benzene	63 / 2	32
2	P(OEt) ₃ (1.2)	DBPC (27) ^b	Octane	115 / 2	20
3	P(OEt) ₃ (1.2)	DTBP (5) ^c	Chlorobenzene	115 / 7	25
4	PPh ₃ (1.2)	TBHN (5)	Benzene	63 / 1	17
5	PPh ₃ (1.2)	DBPC (27)	Octane	115 / 2	50 ^d
6	PPh ₃ (1.2)	DTBP (5)	Chlorobenzene	130 / 7	25
7	P(OMe) ₃ (1.2)	DBPC (27)	Octane	100 / 3	30
8	P(OMe) ₃ (1.2)	DBPC (27) ^e	Dioxane	100 / 3	23
9	P(OMe) ₃ (1.2)	DBPC (27)	-	100 / 3	23

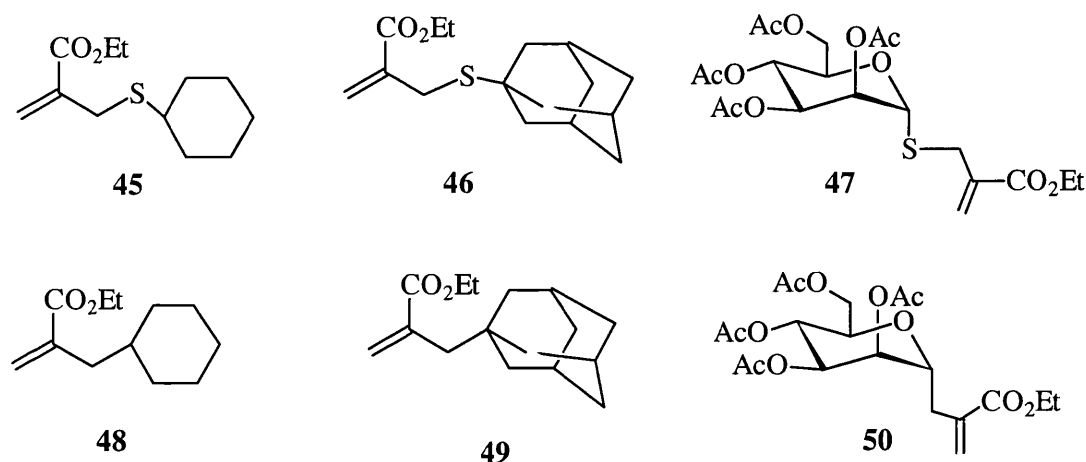
a. Isolated yield by column chromatography. b. 1,1-Di-*tert*-butylperoxycyclohexane as a 50 % w/w solution in mineral oil. c. Di-*tert*-butyl peroxide. d. Kügelrohr distillation (125 °C / 0.03 Torr).

e. Initiator in 1 cm³ of dioxane was added using syringe pump at 100 °C for 1.5 h and stirred additional 1.5 h.

Variation of initiators and initiating conditions gave a variety of results, as summarised in **Table 8.2.1**. When reactions with the allyl sulfide **43** and triethyl phosphite were carried out, initiation using TBHN gave better results than others (entry 1). However, when the reaction with triphenylphosphine was performed, initiation using DTBC in refluxing octane at 115 °C gave the best yield (entry 5). It is noteworthy that the reaction with triphenylphosphine and AIBN in benzene at 80 °C gave only polymeric material.

To explore the scope of the allylation reaction, secondary and tertiary acrylates **45-46** (**Scheme 8.2.2**) were prepared following the procedure as depicted in (**Scheme 8.2.1**). A mixture β,β'-dibromoisobutyrate **41** containing α-bromomethyl acrylate **42** and potassium carbonate in ethanol was allowed to react with cyclohexanethiol to afford ethyl 2-methylene-3-cyclohexylthiopropionate (**45**) in 62 % yield. Under the

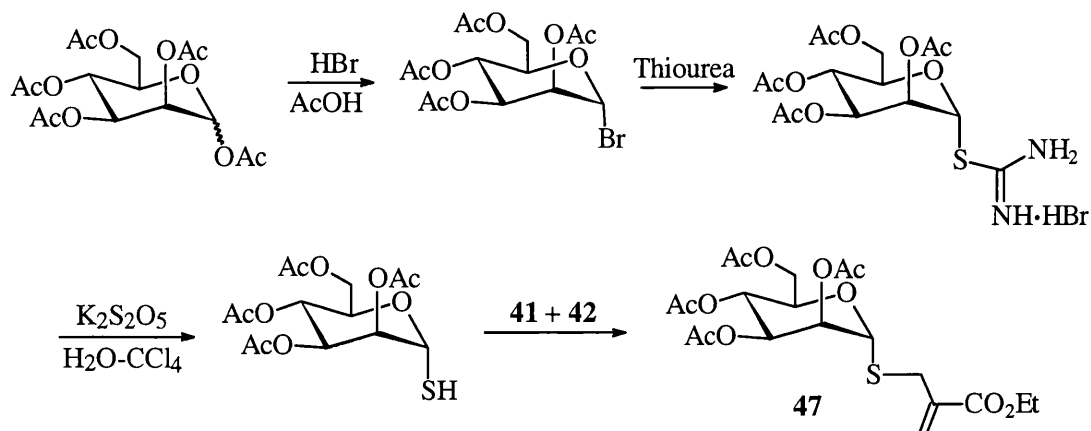
same condition, the reaction of adamantanethiol with **41** gave ethyl 2-methylene-3-adamantylthiopropionate **46** in 72 % yield.



Scheme 8.2.2

The intermolecular radical allylation of 1- or 6-bromosugars using allylstannanes has been investigated in the groups of Giese and of Keck.⁷ Also, to avoid the use of allylstannane, methods using allylic sulfides were developed by the groups of Keck and Barton.^{4,8} Therefore, the application of our present method to the sugar moiety is of value.

1-Thio- α -D-mannopyranose tetraacetate was prepared following the procedure described in the literature.⁹ Acetylation of D-mannose with acetic anhydride in the presence of pyridine gave the penta-O-acetyl-D-mannose, which was brominated by hydrobromic acid in acetic acid. The resulting α -D-mannosyl bromide was allowed to react with thiourea to give the α -D-mannosyl-thiopseudouronium salt which was treated with potassium metabisulfite to afford mainly 1-thio- α -D-mannopyranose, together with 1-thio- β -D-mannopyranose as a by-product. The α -D-thioacrylate **47**, which has a characteristic doublet at 5.16 ppm in the ¹H NMR spectrum was obtained in 44 % yield from the reaction of **41** and **42** with 1-thio- α -D-mannopyranose tetraacetate and potassium carbonate by stirring for 15 h at room temperature (**Scheme 8.2.3**).



Scheme 8.2.3

Table 8.2.2. The radical desulfurization of ethyl 2-methylene-3-cyclohexylthiopropanate **45** with trivalent phosphorus compounds to give **48**.

Entry	PX ₃ (III) (equiv.)	Initiator (mol %)	Solvent	Condition (°C / h)	Yield of 48 (%) ^a
1	PPh ₃ (1.1)	DTBP (2)	Chlorobenzene	130 / 2.5	26
2	PPh ₃ (1.1)	DTBP (5)	Chlorobenzene	130 / 2.5	42
3	PPh ₃ (1.1)	DTBP (10)	Chlorobenzene	130 / 7	23
4	PPh ₃ (1.1)	DTBP (40)	Chlorobenzene	130 / 7	28
5	PPh ₃ (1.1)	DBPC (5)	Octane	130 / 3	47
6	PPh ₃ (1.1)	DBPC (5) ^b	Octane	115 / 3	57
7	P(OEt) ₃ (1.1)	DTBP (10)	Chlorobenzene	130 / 3	polymer
8	P(OMe) ₃ (1.1)	DTBP (10)	Chlorobenzene	130 / 3	polymer
9	P(OCH ₂ CF ₃) ₃ (1.1)	DTBP (10)	Chlorobenzene	130 / 3	polymer

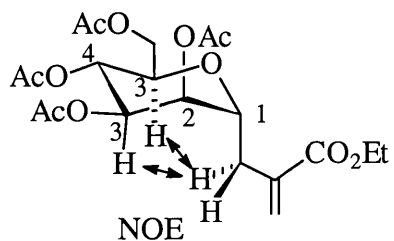
a. Isolated yield by column chromatography. b. The initiator was added in three equal portions of *ca.* 3 mol %, one present initially and the others after 1 and 2 h.

The reaction of the thioacrylate **45** with triphenylphosphine in chlorobenzene was carried out in the presence of di-*tert*-butyl peroxide (5 mol %) at 130 °C to afford a 42 % yield of **48**, as shown in **Table 8.2.2**. However, the use of di-*tert*-butyl peroxide

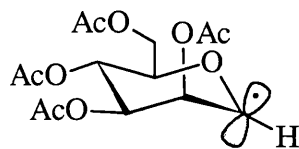
at high temperature produced polymeric material and which lowered the yield. This problem became severe when the amount of initiator was increased and for the long reaction times (entries 3 and 4). Also, the use of triethyl phosphite and di-*tert*-butyl peroxide at 130 °C for 2 h gave only polymeric material which was indicated by the appearance of strong multiplets at δ 1.3 and 3.7 and disappearance of the starting material in ^1H NMR spectrum of the mixture (entries 7-9). The use triphenylphosphine (1.1 equiv.) in the presence of 1,1-di-*tert*-butylperoxycyclohexane (DBPC, 5 mol %) in octane at 115 °C was found to minimize the formation of polymeric material (entry 5). More elaborate control by adding 1,1-di-*tert*-butylperoxycyclohexane in three equal portion of *ca.* 3 mol % (based on the starting thioacrylate **45**) increased the yield of the product **48** to 57 %. One portion was present at initially and the others were added after 1 and 2 h; the total reaction time was 3h.

The reactions of the tertiary thioacrylate **46** with triphenylphosphine in octane solvent, adding three equal portions of di-*tert*-butyl peroxycyclohexane (3 x 3 mol %) at 115 °C for 3h gave 71 % of the acrylate **49**. When di-*tert*-butyl peroxide was used as initiator at 130 °C for 6 h, the yield reached 80 %. Obviously, the tertiary radical generated from **46** has greater reactivity towards the alkene and exerts a stronger polar effect on the addition to the electron-deficient alkene than primary or secondary alkyl radicals.

Similarly, by adding three equal portions of di-*tert*-butylperoxycyclohexane, the reaction of the α -mannosyl thioacrylate **47** with triphenylphosphine at 115 °C for 3 h gave 52 % of the acrylate **50**. Reaction of the α -mannosyl thioacrylate **47** gave exclusively the α -anomer **50**, which has a characteristic single peak in the ^1H NMR spectrum at δ 6.29. None of the β -anomer was detected by ^1H NMR. The exclusive formation of the α -anomer **50**, as a consequence of attack of the thioacrylate **47** at the axial face of the intermediate radical **51**, would be expected on both stereoelectronic and steric grounds.¹⁰ The stereochemistry of α -mannosyl acrylate **50** was confirmed by NOE experiments, in which strong enhancements of the absorptions from the axial protons attached to C-3 and C-5 were observed during irradiation of the less-shielded allylic proton (δ 2.77) (**Scheme 8.2.4**).



50



51

Scheme 8.2.4

Polymerisation of the product acrylate could take place towards the end of the reaction when the concentration of the 2-methylene-3-alkylthiopropanoates is low and this seems to be the main factor limiting the yield of the product in this reaction.

References to Chapter 8

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CHAPTER 9

EXPERIMENTAL

9.1. General Procedures

Gas chromatographic analysis was performed using a Pye-Unicam 204 chromatograph equipped with a flame-ionization detector and Hewlett-Packard model 3392A integrator. A glass column (2 m x 4 mm bore) packed with 10 % OV-101 on Chromosorb WHP 80-100 mesh was used with nitrogen carrier gas. The detector response was calibrated using mixtures of authentic compounds and internal standard.

NMR spectra were recorded using a Varian VXR-400 (400 MHz for ^1H) or a Bruker AC-300 (300 MHz for ^1H) instrument. The solvent was CDCl_3 and chemical shifts are reported relative to the residual protons in the solvent (δ_{H} 7.24); coupling constants are quoted in Hz. All NMR data reported were recorded using the Varian VXR-400 instrument.

Infrared (IR) spectra were recorded with a Perkin-Elmer 1600 series FT-IR spectrometer and major peaks are reported in units of cm^{-1} . Mass spectra were obtained from a VG 7070H or VG ZAB-2F spectrometer using electron impact ionisation (EI, 70 eV) by the Mass Spectrometry Service at the Chemistry Department, UCL. Elemental analyses were performed by the UCL Microanalytical Service.

Flash column chromatography was carried out using Merck Kieselgel 60 (230-400 mesh). Thin-layer chromatography (TLC) was carried out using Kieselgel 60 F_{254} pre-coated aluminium plates. Visualisation of TLC plates was made by ultraviolet light (254 nm) or by immersion in a 10 % w/v solution of phosphomolybdic acid in methanol, followed by heating the plate with a hot blower.

All manipulations and reactions of air-sensitive compounds were carried out under an atmosphere of dry argon using dry solvents.

Hexane, benzene and 1,4-dioxane (HPLC grade) were purchased from Aldrich and were used without further purification. Petroleum refers to light petroleum (bp 40-60 °C).

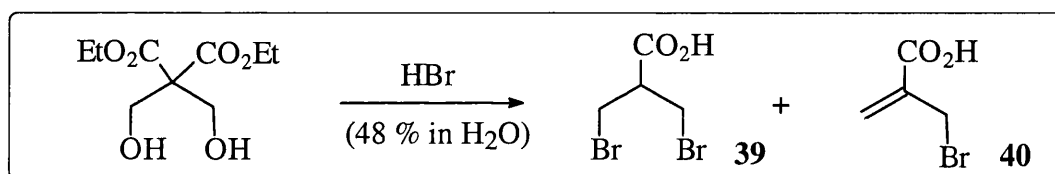
Di-*tert*-butyl hyponitrite (TBHN, $t_{1/2}$ = ca. 55 min) was prepared by the reaction of sodium hyponitrite with *tert*-butyl bromide in the presence of zinc chloride, following the method described by Mendenhall.¹ Azobis(isobutyronitrile) (AIBN) and di-*tert*-butyl

peroxide (DTBP) were used as received. 1,1-Di-*tert*-butylperoxycyclohexane (DBPC) was obtained from Peroxid-Chemie Ltd., as a 50 % w/w solution in mineral oil. Allyl hexyl sulfide and allyl phenyl sulfide were purchased from Lancaster Synthesis Ltd., and were used without purification. 1-Octanethiol and cyclohexanethiol were purchased from Aldrich, and adamantanethiol was available in the lab.

9.2. Preparation of Ethyl 2-methylene-3-alkylthiopropionate

1. Preparation of ethyl 2-methylene-3-octylthiopropionate (**43**)²

(a) β,β' -Dibromoisobutyric acid (**39**) and α -(bromomethyl)acrylic acid (**40**)

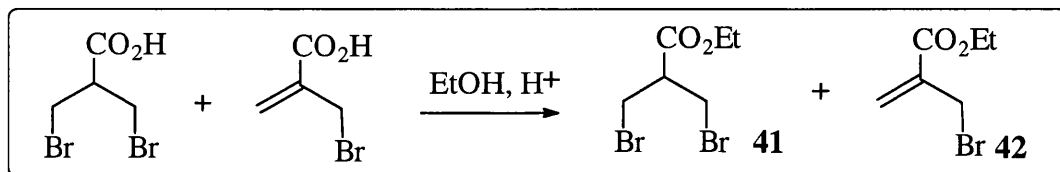


A mixture of diethyl bis(hydroxymethyl)malonate (44 g, 0.2 mol) and 48 % hydrobromic acid in H₂O (335 cm³, 15 equiv.) was placed in a flask that was equipped with a distillation head. The reaction mixture was heated until ethyl bromide was evolved and distillation was continued for 2 hours to remove all the ethyl bromide. The remaining material was heated under reflux for a further 8 hours (bath temp. 140~150 °C), and then allowed to chill in an ice bath for an hour. The white crystals produced were removed by filtration, and the filtrate was extracted with methylene chloride (3 x 50 cm³). The crystals were combined with organic extract, washed with brine, dried over MgSO₄, and evaporated to afford a white solid (35.9 g). The ¹H NMR spectrum showed that the solid was a 1:2 mixture of α -(bromomethyl)acrylic acid (**40**) and β,β' -dibromoisobutyric acid (**39**), and the mixture was used for the next reaction without further purification. (In the literature report,² only β,β' -dibromoisobutyric acid was obtained, mp: 100-102 °C, IR 1697 cm⁻¹).

δ_{H} (CDCl₃) for β,β' -dibromoisobutyric acid (**39**); 3.25 (1H, m, CH), 3.70~3.85 (4H, m, 2CH₂Br), 10.6 (1H, s, COOH).

δ_{H} (CDCl₃) for α -(bromomethyl)acrylic acid (**40**); 4.28 (2H, s, CH₂Br), 6.11 (1H, s, C=C-H), 6.50 (1H, s, C=C-H), 12.5 (1H, s, CO₂H).

(b) β,β' -Dibromoisobutyric acid (**41**) and α -(bromomethyl)acrylic acid (**42**)



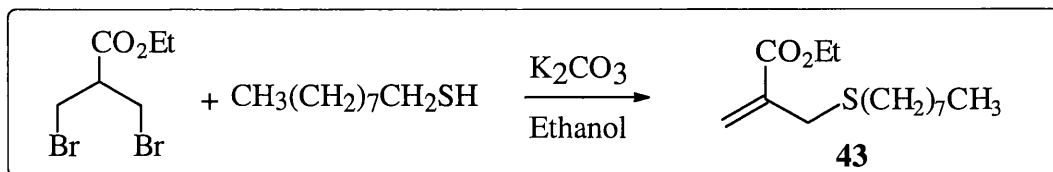
To the mixture of α -(bromomethyl)acrylic acid and β,β' -dibromoisobutyric acid (35.9 g), ethanol (100 cm³) and dry benzene (100 cm³), was added concentrated sulfuric acid (1 cm³). The reaction mixture was heated under reflux for 3 days until the reaction was completed (monitoring by TLC), and was then allowed to cool to room temperature. The mixture was diluted with diethyl ether (100 cm³), washed with water (2 x 100 cm³) and 5% aqueous sodium bicarbonate (100 cm³), dried over MgSO₄ and evaporated under reduced pressure. The resulting oil was distilled under reduced pressure to afford 30.7 g of colourless oil. ¹H NMR analysis showed that the oil was a 2 : 3 mixture of ethyl α -bromomethylacrylate (**42**) and ethyl β,β' -dibromoisobutyrate (**41**), and the mixture was used for the next reaction without prior purification.

Bp 57-60 °C / 0.02 Torr. (lit.² ethyl α -bromomethylacrylate (**42**) 59-65 °C / 3.9 mm, and β,β' -dibromoisobutyrate (**41**) 84-86 °C / 2.5 mm)

δ_{H} (CDCl₃) for ethyl β,β' -dibromoisobutyrate (**41**); 1.29 (3H, t, OCH₂CH₃), 3.18 (1H, m, CH), 3.65-3.80 (4H, m, 2CH₂Br), 4.25 (2H, q, OCH₂CH₃).

δ_{H} (CDCl₃) for ethyl α -(bromomethyl)acrylate (**42**); 1.29 (3H, t, OCH₂CH₃), 4.15 (2H, s, CH₂Br), 4.23 (2H, q, OCH₂CH₃), 5.90 (1H, s, C=C-H), 6.30 (1H, s, C=C-H).

(c) Preparation of ethyl 2-methylene-3-octylthiopropionate (**43**)



1-Octanethiol (11.0 ml, 63 mmol) was added to a mixture of ethyl β,β' -dibromoisobutyrate (**41**) and ethyl α -(bromomethyl)acrylate (**42**) (17.36 g, *ca.* 63 mmol) and potassium carbonate (8.75 g, 63 mmol) in absolute ethanol (50 ml). The reaction mixture was stirred at 63 °C (bath temp.) for 15 hours, cooled and the solid material was removed by filtration. The filtrate was distilled at atmospheric pressure to remove the ethanol and the residue was distilled under the reduced pressure to give 11.31 g of colourless oil (70 %).

Bp. 104-106 °C / 0.03 Torr.

Found: C, 64.94; H, 10.19. $\text{C}_{14}\text{H}_{26}\text{O}_2\text{S}$ requires C, 65.07; H, 10.15 %.

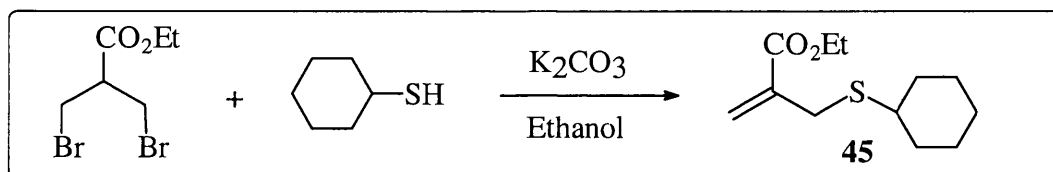
δ_{H} (CDCl_3): 0.88 (3H, t, J 6.8, CH_3), 1.15-1.40 (13H, m, 5CH_2 , CH_3), 2.45 (2H, t, J 7.6, SCH_2), 3.37 (2H, s, CH_2SC), 4.22 (2H, q, J 7.6, OCH_2), 5.63 (1H, s, C=C-H), 6.20 (1H, s, C=C-H).

δ_{C} : 14.2, 14.2, 22.7, 29.0, 29.2, 29.3, 31.6, 31.9, 32.8, 61.0, 125.5, 137.3.

m/z (EI): 258 (20, M^+), 213 (15, $[\text{M}-\text{CH}_3\text{CH}_2\text{O}]^+$), 184 (12, $[\text{M}-\text{COOCH}_2\text{CH}_3]^+$), 145 (47, $[\text{M}-(\text{CH}_2)_7\text{CH}_3]^+$), 114 (52, $[\text{M}-\text{S}(\text{CH}_2)_8]^+$), 69 (100).

IR (cm^{-1} , liq.film): 1722 (C=O), 1631 (C=C stretching), 1189 (C-O stretching).

2. Preparation of ethyl 2-methylene-3-octylthiopropionate (**45**)²



Clear oil. 62 %.

Bp. 71 °C / 0.03 Torr.

Found: C, 63.34; H, 8.76. C₁₂H₂₀O₂S requires.: C, 63.12; H, 8.83%

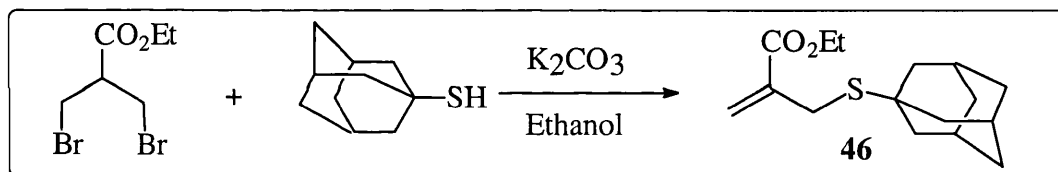
δ_{H} (CDCl₃): 1.30 (3H, t, *J* 7.1, CH₃), 1.24-1.33(6H, m, 3CH₂), 1.76 (2H, m, CH₂), 1.95 (2H, m, CH₂), 2.59 (1H, m), 3.42 (2H, s, SCH₂), 4.24 (2H, q, *J* 7.2, OCH₂), 5.69 (1H, d, C=C-H cis to carboxy), 6.20 (1H, d, C=C-H trans to carboxy).

δ_{C} : 14.2(CH₃), 25.9 (C-3), 26.1, 30.9 (CH₂), 33.4 (3CH), 43.2 (S-C-3CH₂), 61.0 (OCH₂), 125.6 (vinyl), 137.8 (C-2), 166.4 (C=O).

MS(EI) *m/z*: 230 (20, M⁺+ 2), 229(M⁺+1,12), 115 (88), 100(33), 81(33).

IR (cm⁻¹, liq. film): 1720 (C=O), 1631(C=C), 1189 (C-O).

3. Preparation of ethyl 2-methylene-3-adamantylthiopropionate (**46**)



This compound was prepared by stirring the reaction mixture for 15 h at room temperature to afford the product as a viscous oil. Yield 89 %, bp. 135-138 °C / 0.02 Torr.

Found: C, 68.3; H, 8.7, C₁₆H₂₄O₂S requires C, 68.5; H, 8.6 %.

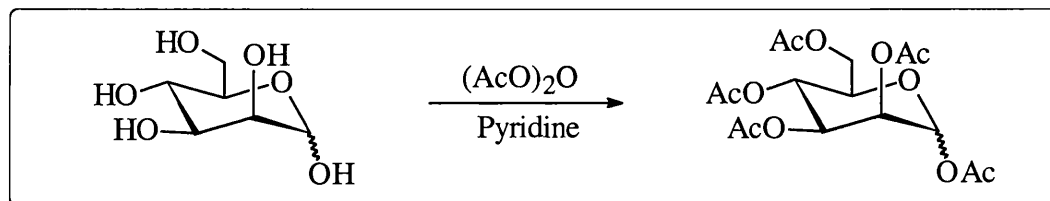
δ_{H} (CDCl₃): 1.30 (3H, t, *J* 7.2, CH₃), 1.67 (6H, m, equatorial H on 6CH₂), 1.87 (6H, m, axial H on 6CH₂), 2.03 (3H, s, 3 CH), 3.43 (2H, s, SCH₂), 4.22 (2H, q, *J* 7.2, OCH₂), 5.81 (1H, s, C=C-H cis to carboxy), 6.22 (1H, s, C=C-H trans to carboxy).

δ_{C} : 14.2 (CH₃), 26.7 (C-3), 29.7, 36.3 (CH₂), 43.4 (3CH), 45.1 (S-C-3CH₂), 60.9 (OCH₂), 126.4 (vinyl), 138.3 (C-2), 166.4 (C=O).

MS (EI) *m/z*: 280 (48, M⁺), 135 (100), 107 (23), 93 (59), 79 (65).

4. Preparation of ethyl 2-methylene-3-(2',3',4',6'-tetra-*O*-acetyl- α -D-mannopyranosyl)thio propanoate (47)

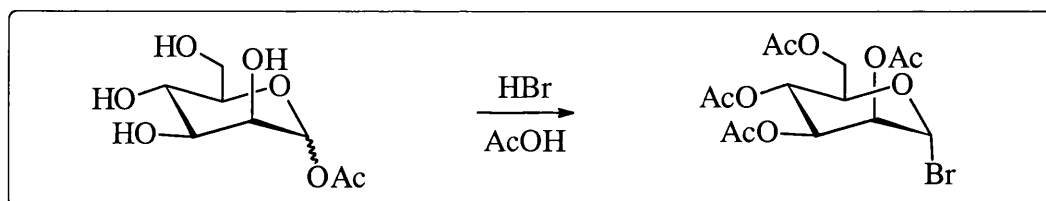
(a) Penta-*O*-acetyl- α -D-mannose³



A mixture of D-mannose (10.4 g, 5.6 mmol), pyridine (40 cm³) and acetic anhydride (35.7 g, 350 mmol) was stirred for 4 h at room temperature and allowed to stand overnight. The reaction mixture was concentrated in *vacuo*, and then co-evaporated with toluene (3 x 30 cm³) to remove the excess of pyridine. The residue was diluted with diethyl ether (70 cm³), washed with water (40 cm³) and brine (40 cm³), dried over MgSO₄ and evaporated under reduced pressure. The crude material (21.18 g) was used for the next reaction without further purification.

δ_{H} (CDCl₃): δ 2.00 (3H, s, Ac), 2.05 (3H, s, Ac), 2.09 (3H, s, Ac), 2.15 (3H, s, Ac), 2.17 (3H, s, Ac), 4.01-4.12 (2H, m, H₅, H₆^A), 4.27 (1H, s, dd, *J* 12.4, 4.9, H₆^B), 5.23-5.32 (3H, m, H₂, H₃, H₄), 6.09 (1H, s, H₁).

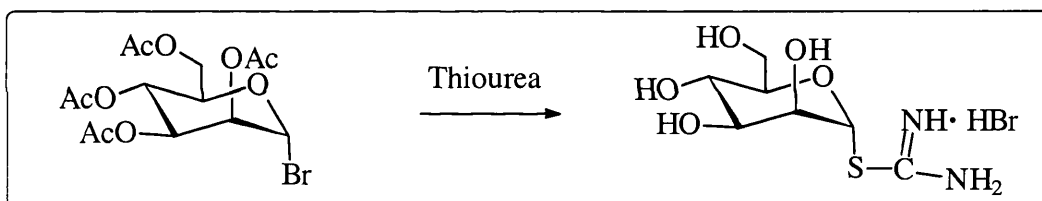
(b) 2,3,4,6-Tetra-*O*-acetyl- α -D-mannosyl bromide



To a stirred solution of penta-*O*-acetyl- α -D-mannose (21 g, 50 mmol) in dry methylene chloride (50 cm³) at 0 °C was added dropwise HBr (30 %, 62 cm³) in acetic acid. The reaction mixture was stirred for 3 h at room temperature and kept in a fridge at 4 °C overnight. The mixture was diluted with dichloromethane (150 cm³), washed successively with ice water (5 x 200 cm³), 5 % aqueous NaHCO₃ (100 cm³), and brine (100 cm³). After drying over MgSO₄, the solvent was evaporated under reduced pressure to afford a white solid (21.3 g, 96 %) which was taken to the next step without prior purification.

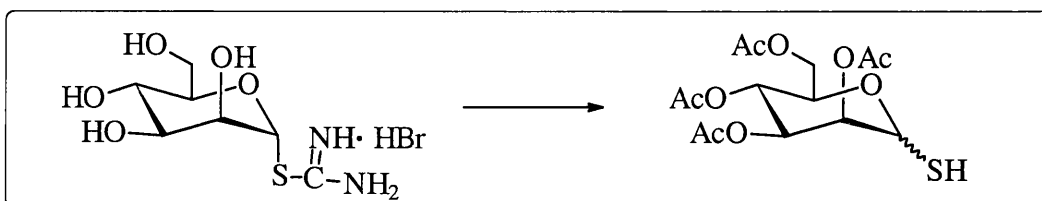
δ_{H} (CDCl₃): 2.00 (3H, s, Ac), 2.06 (3H, s, Ac), 2.10 (3H, s, Ac), 2.17 (3H, s, Ac), 4.14 (1H, d, *J* 12.4, H₆^A), 4.23 (1H, m, H₄), 4.32 (1H, dd, *J* 12.4 and 4.8, H₆^B), 5.37 (1H, t, *J* 10, H₅), 5.43 (1H, d, *J* 8, H₂), 5.71 (1H, dd, *J* 10 and 3.2, H₃), 6.30 (1H, s, H₁).

(c) 2-*S*-(2,3,4,6-Tetra-*O*-acetyl- α -D-mannopyranosyl)-2-pseudouronium bromide.



A stirred solution of 2,3,4,6-tetra-*O*-acetyl- α -D-mannosyl bromide (21.3 g, 52 mmol) and thiourea (5.9 g, 78 mmol) in dry acetone (30 cm³) was heated under reflux for 2 h. After cooling to room temperature, the solvent was evaporated under reduced pressure to give a pale yellow syrup which was taken to the next step without any further purification.

(d) 2,3,4,6-Tetra-*O*-acetyl-1-thio- α -D-mannopyranose



A solution of the HBr salt (25.3 g, 52 mmol) and potassium metabisulfite (11.6 g, 52 mmol) in CCl_4 (50 cm^3) and water (40 cm^3) was stirred and heated under reflux for 30 min. The mixture was cooled to room temperature, washed successively with water (40 cm^3), brine (40 cm^3) and dried over MgSO_4 . The solvent was removed under reduced pressure and the residue was purified by flash-column chromatography [petroleum spirit-diethyl ether (2:1) followed by (1:1)] to afford the product as a colourless oil (g), which was diluted in ethanol. At this stage, a colourless oil, which does not dissolve in ethanol, is apparently polymeric material present. The ethanol solution was decanted from the polymer into another flask, and left to stand in fridge at 4 °C for 3 days before the solid was removed by filtration and was confirmed as β -anomer by its ^1H NMR spectrum. The filtrate was collected and the solvent was removed to give a colourless syrup containing a 5:2 mixture of α -anomer and β -anomer, as shown by the ^1H NMR spectrum.

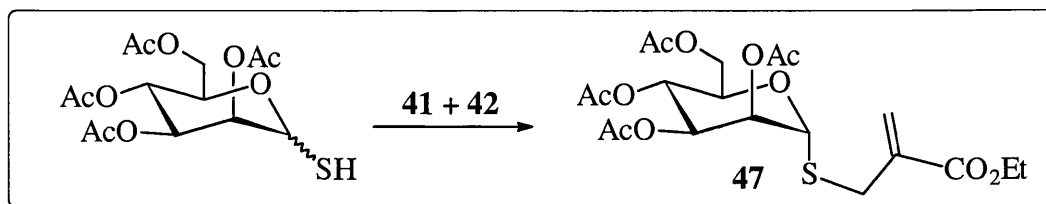
Found C, 46.44; H, 5.54, $\text{C}_{14}\text{H}_{20}\text{O}_9\text{S}$ requires C, 46.15; H, 5.33 %

δ_{H} (CDCl_3) for the β -anomer: 1.99 (3H, s, Ac), 2.05 (3H, s, Ac), 2.10 (3H, s, Ac), 2.24 (3H, s, Ac), 2.57 (1H, d, J 6.4, SH), 3.71 (1H, ddd, J 10, 6.0 and 2.4, H_c), 4.13 (1H, dd, J 12.4 and 2.4, H_c^{A}), 4.25 (1H, dd, J 12.4 and 5.6 H_c^{B}), 4.89 (1H, dd, J 6 and 1.2, H_4), 5.08 (1H, 2d, J 3.4, 10.2, H_2), 5.23 (1H, dd, J 10 and 10, H_3), 5.44 (1H, dd, J 1.0, 3.4, H_1)

^1H NMR spectrum of α -anomer appears 2.4 Hz lower field than β -anomer which is confirmed by a 5:2 mixture of α - and β -anomer spectrum, and the H-1 proton of α -anomer appears singlet at δ 5.30.

δ_{C} : 20.66, 20.73, 20.79, 20.93, 62.16, 66.07, 68.54, 69.65, 71.86, 76.76, 169.65, 169.88, 169.93, 170.66.

(e) Preparation of ethyl 2-methylene-3-(2',3',4',6'-tetra-*O*-acetyl-D-mannopyranosyl)thio propanoate (**47**).



A mixture of ethyl β , β' -dibromoisobutyrate (3.0 g, 11mmol), 2,3,4,6-tetra-*O*-acetyl-1-thio-D-mannopyranose (3.0 g, 8 mmol, a 5:2 mixture of α - and β -anomer), K_2CO_3 (2.5 g, 18 mmol) in ethanol (20 cm³) was stirred overnight at room temperature for 15 h. After the precipitate was filtered off, the mixture was diluted with water (50 cm³), extracted using diethyl ether (3 x 20 cm³), dried over $MgSO_4$ and the solvent removed under the reduced pressure. The residue was purified by flash column chromatography (eluent: CH_2Cl_2 : petroleum spirit : diethyl ether = 2:2:1) to give 2.32 g of viscous oil (44 %).

Found: C, 50.62; H, 5.95; S, 6.53. $C_{20}H_{28}O_{11}S$ requires C, 50.41; H, 5.92; S, 6.73 %

δ_H ($CDCl_3$): 1.30 (3H, t, J 7.2, OCH_2CH_3), 1.96 (3H, s, OAc), 2.03(3H, s, OAc), 2.09 (3H, s, OAc), 2.14 (3H, s, OAc), 3.39 (1H, d, J 14, $CH_2^A S$), 3.50 (1H, d, J 14, $CH_2^B S$), 4.09 (1H, m), 4.22 (2H, m), 4.32 (2H, m), 5.16 (1H, s, H_1), 5.29 (2H, m), 5.70 (1H, s, $C=CH^A$), 6.24 (1H, s, $C=CH^B$).

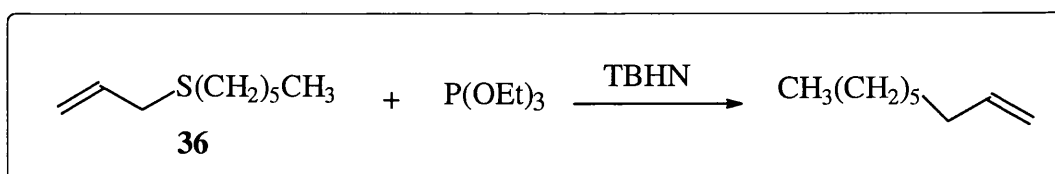
δ_C : 14.18, 20.63, 20.72, 20.77, 20.93, 30.90, 61.23, 62.33, 66.21, 69.02, 69.66, 70.62, 81.13, 127.19, 135.65, 165.55, 169.70, 169.75, 169.86, 170.61.

MS (EI) m/z : 331 [M^+ -ethylthioacrylate (145), 40 %], 169 (83 %), 109 (45 %), 43 (100 %).

IR (cm⁻¹, liq. film): 1748 (C=O), 1630 (C=C), 1226 (C-O).

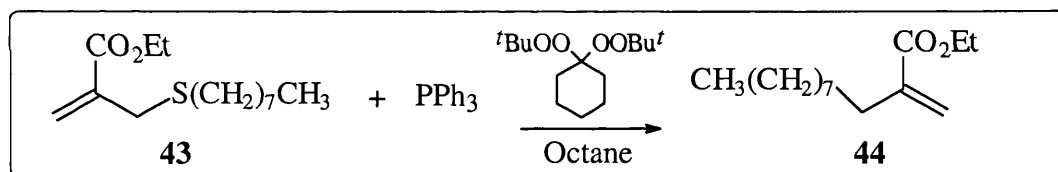
9.3. Radical-Chain Desulfurisation of Alkylthio Acrylates

1. General procedure for the preparation of 1-nonene from allyl hexyl sulfide (**36**).



To a mixture of allyl hexyl sulfide (39.6 mg, 0.25 mmol), triethyl phosphite (48 μl , 0.25 mmol) and decane (internal standard) in hexane (1 cm^3), TBHN (32 mg, 5 mol % based on sulfide) was added under a slow stream of argon. The reaction mixture was stirred at 60 $^\circ\text{C}$ for 2 hours, cooled to room temperature. Gas chromatographic analysis showed that 1-nonene was produced in 5 % yield.

2. 2-Ethoxycarbonyl-1-nonene (**44**) from ethyl 2-methylene-3-octylthiopropanate (**43**).



To a mixture of ethyl 2-methylene-3-octylthiopropanate (0.62g, 2.4 mmol) and triphenylphosphine (0.63 g, 2.4 mmol) in octane (2.5 cm^3), 1,1-di-*tert*-butylperoxy-cyclohexane (DBPC, 0.24 ml, 27 mol %, 50 % w/w in mineral oil) was added. The mixture was stirred at 115 $^\circ\text{C}$ for 2 hours, cooled and petroleum-spirit (10 cm^3) was added to solidify the triphenylphosphine sulfide. After filtering off this solid, the filtrate was collected and the solvent was removed under reduced pressure. The residue was purified by K \ddot{u} gelrohr distillation (125 $^\circ\text{C}$ / 0.03 Torr) to give 0.27 g of colourless oil (51 %).

Found: C, 74.23; H, 11.66. $\text{C}_{14}\text{H}_{26}\text{O}_2$ requires: C, 74.27; H, 11.58 %.

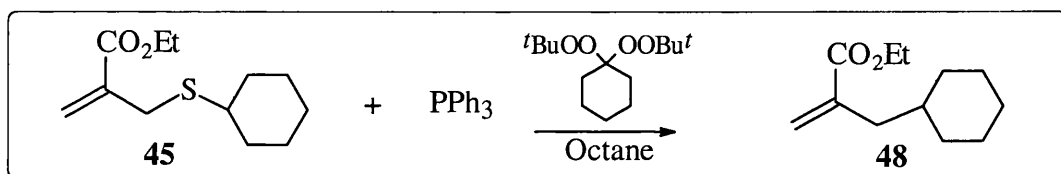
δ_{H} (CDCl_3): δ 0.88 (3H, t, J 6.8, CH_3), 1.26-1.32 (15H, m, 6CH_2 , CH_3), 1.45 (2H, m, $\text{CH}_2\text{CH}_2(\text{CH}_2)\text{CH}_3$), 2.29 (2H, t, J 7.6, OCH_2CH_3), 4.20 (2H, q, J 6.8, CH_2), 5.50 (1H, s, C=C-H), 6.10 (1H, s, C=C-H).

δ_c : 14.2, 22.7, 28.4, 29.1, 29.2, 29.3, 29.4, 29.5, 31.8, 31.9, 60.5, 124.1, 141.1, 167.4.

m/z (EI): 226 (6, M^+), 181 (18, $[M-CH_3CH_2O]^+$), 155 (15, $[M-COOCH_2CH_3]^+$), 141 (10, $[M-(CH_2)_7CH_3]^+$), 115 (100, $[M-S(CH_2)_8]^+$), 102 (88), 95 (23), 87 (48), 69 (46), 55 (42), 43 (38), 29 (17).

IR (cm^{-1} , liq. film) : 1720 (C=O), 1632 (C=C), 1178 (C-O).

3. Ethyl 2-methylene-3-cyclohexylpropanoate (**48**) from ethyl 2-methylene-3-cyclohexylthiopropionate (**45**).⁴



To a mixture of ethyl 2-methylene-3-cyclohexylthiopropionate (0.50 g, 2.2 mmol) and triphenylphosphine (0.60 g, 2.3 mmol) in octane (2.0 cm^3), 1,1-di-*tert*-butylperoxy cyclohexane (DBPC, 41 μ l, 5 mol %) was added. The mixture was stirred at 130 °C for 3 hours, cooled, petroleum-spirit (10 cm^3) was added and the solid filtered off. The filtrate was collected and the solvent was removed under reduced pressure. The product was purified by column chromatography (petroleum spirit-diethyl ether (10:1) to give the product 47 % as a clear oil. Under the same conditions, when 1,1-di-*tert*-butylperoxy-cyclohexane was added in three equal portions of *ca.* 3 mol %, one present initially and the others after 1 and 2 h, for 3 h at 115 °C; the isolated yield was raised to 57 %.

Found: C, 73.72; H, 10.39. requires: C, 73.43; H, 10.27 %.

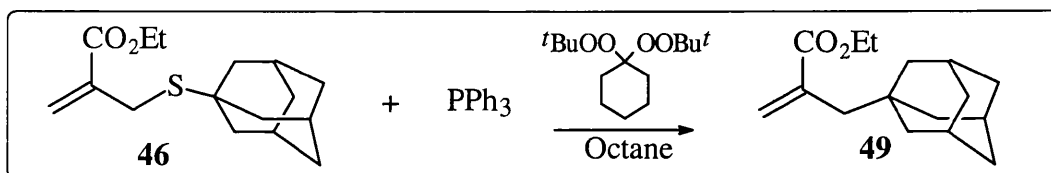
δ_H ($CDCl_3$): δ 0.88 (2H, m, axial H), 1.20(2H, m, eq. H), 1.29 (3H, t, J 7.1, CH_3), 1.43 (1H,m), 1.67 (6H,m), 2.18 (2H, d, J 7.0, SCH_2), 4.19 (2H, d, J 7.0, OCH_2), 5.46 (1H, d, C=C-H cis to carboxy), 6.10 (1H, d, C=C-H trans to carboxy).

δ_c : 14.24(CH_3), 26.27 (C-3), 26.55, 33.097(CH_2), 36.68 (3CH), 39.94 (S-C-3 CH_2), 60.55 (OCH_2), 125.50 (vinyl), 139.50 (C-2),167.50 (C=O).

MS (EI) m/z : 197 (7, $M^+ + 1$), 196 (M^+ , 14), 114 (100), 86(65), 83(25).

IR (cm⁻¹, liq. film) : 1719, 1629, 1178 1157.

4. Ethyl 2-methylene-3-adamantylpropanoate (**49**) from ethyl 2-methylene-3-adamantylthiopropanoate (**46**).



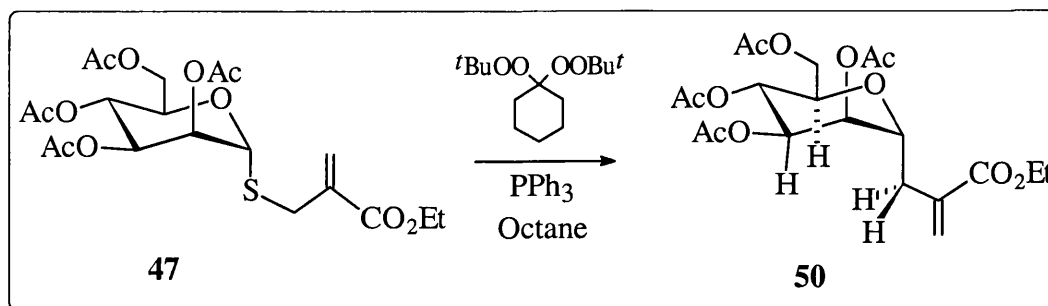
To a mixture of ethyl 2-methylene-3-(1-adamantylthio)propanoate (0.70g, 2.5 mmol), triphenylphosphine (0.72 g, 2.75 mmol) in octane (5 cm³), 1,1-di-*tert*-butylperoxy-cyclohexane (43 μ l, 0.08 mmol in 50% w/w in mineral oil) was added. The mixture was stirred at 130 °C for 3 hours under a stream of argon. A further portion of peroxide (0.08 mmol) was added after 1 h, and another was added after 2 h. The mixture was allowed to cool and petroleum spirit (b.p. 40-60 °C, 5 cm³) was added to solidify the triphenylphosphine sulfide which was removed by filtration. The solvent was removed from the filtrate using a rotary evaporator, and the residue was purified by flash chromatography (petroleum spirit:diethyl ether 10:1) to give 0.44 g of a colourless oil (75 %). Under the same conditions, when di-*tert*-butyl peroxide was added in three equal portions of *ca.* 3 mol %, one present initially and the others after 1 and 2 h, after heating for 3 h at 115 °C in chlorobenzene, the isolated yield was 80 %.

(Barton⁴ separated this compound by K \ddot{u} gelrohr distillation b.p. 150 °C / 3 Torr).

δ_{H} (CDCl₃): 1.30 (3H, t, *J* 7.8, CH₃), 1.44 (6H, br, *J* 2.3, H^{eq} on 6CH₂), 1.63 (6H, m, H^{eq} on 6CH₂), 1.92 (3H, s, 3 CH), 2.15 (2H, s, SCH₂), 4.18, (2H, s, *J* 7.8, OCH₂), 5.40 (1H, d, *cis* C=C-H), 6.17 (1H, d, *J* 2.0, *trans* C=C-H).

δ_{C} : 14.2 (CH₃), 28.7 (C-3), 37.0 (CH₂), 42.1 (3CH), 45.5 (S-C-3CH₂), 60.6 (OCH₂), 126.9 (vinyl), 137.6 (C-2), 168.3 (C=O).

5. Ethyl 2-methylene-3-(2',3',4',6'-tetra-*O*-acetyl-D-mannopyranosyl)propanoate (**50**) from ethyl 2-methylene-3-(2',3',4',6'-tetra-*O*-acetyl-D-mannopyranosyl)thiopropoate (**47**).



This reaction was carried out by adding 1,1-di-*tert*-butylperoxycyclohexane in three equal portions of *ca.* 3 mol % using octane solvent; total heating time was for 3 h at 115 °C. After purification using flash column chromatography, the product was obtained as a viscous oil in 52 % yield.

Found 54.28, H, 6.49. C₂₀H₂₈O₁₁ requires C, 54.06, H, 6.35 %

δ_{H} (CDCl₃): 1.29(3H, t, *J* 7.1, OCH₂CH₃), 2.01 (3H, s, Ac), 2.05 (3H, s, Ac), 2.06 (3H, s, Ac), 2.11 (3H, s, Ac), 2.63 (1H, dd, *J* 14.6 and 4.5, allylic-H^A), 2.77 (1H, dd, *J* 14.6 and 9.8, allylic-H^B), 3.95 (1H, m, H-5), 4.03 (1H, dd, *J* 12.1 and 2.8, H-6^A), 4.20 (2H, q, *J* 7.1), 4.21 (1H, m, H1), 4.29(1H, dd, *J* 12.1 and 6.1, H-6^B), 5.20 (2H, m, H-2, 4), 5.27 (1H, dd, *J* 9.0 and 3.2, H-3), 5.71 (1H, d, *J* 1.0), 6.29 (1H, d, *J* 1.0), (the assignments were made on the basis of by ¹H-¹H decoupling experiments).

δ_{C} : 14.2, 20.7(1), 20.7(2), 20.8, 20.9, 31.5, 61.0, 66.8, 68.7, 70.2, 70.4, 73.8, 121.8, 135.8, 166.3, 169.9, 170.0, 170.2, 170.6.

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1. G. D. Mendenhall, *Tetrahedron Lett.*, **24**, 451 (1985).
2. A. F. Ferris, *J. Org. Chem.*, **20**, 780 (1955).
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4. D. H. R. Barton and D. Crich, *J. Chem. Soc. Perkin Trans. 1*, 1618 (1986).

SECTION D

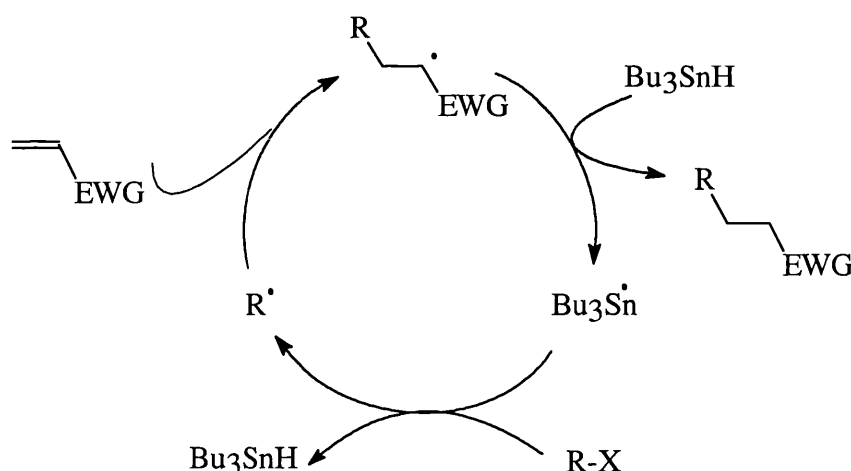
RADICAL-CHAIN REDUCTIVE ALKYLATION OF ELECTRON-RICH ALKENES: CARBON-CARBON BOND FORMATION MEDIATED BY SILANES IN THE PRESENCE OF THIOLS AS POLARITY-REVERSAL CATALYSTS.

CHAPTER 10

INTRODUCTION

10.1. Radical Addition Reactions Using Tributyltin Hydride

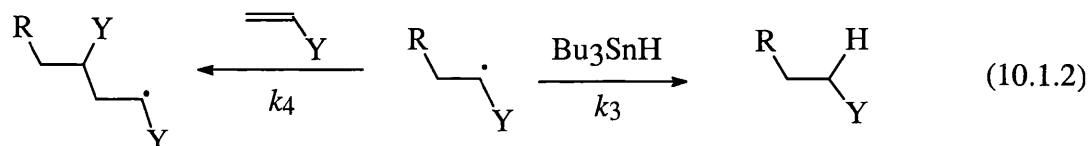
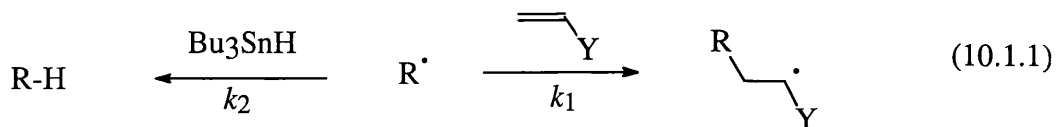
Addition of carbon-centred radicals to alkenes is an important synthetic method for the C-C bond formation. The reductive addition of an alkyl halide to an alkene mediated by tributyltin hydride has been called the tin-method.¹ The propagation sequence involves the alkyl radical attacking the alkene followed by hydrogen-atom abstraction by the adduct radical from tributyltin hydride to yield the product and the chain-carrying tributyltin radical. The tributyltin radical abstracts the halogen from the alkyl halide to generate the alkyl radical and continues the radical-chain reaction (**Scheme 10.1.1**).¹



Scheme 10.1.1

There is a competition between radical reactions during the formation of the product, as shown in [eqn. (10.1.1) and (10.1.2)]. To avoid the competition each radical must have a selectivity toward the desired reaction. For example, the alkyl radical must

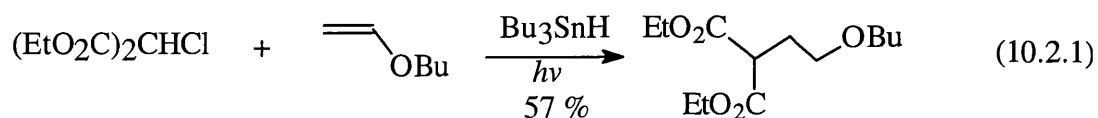
react faster with the alkene to give the adduct radical rather than with tributyltin hydride to give reduction product. Also, the adduct radical must react faster with tributyltin hydride to give the addition product than with the alkene. Substituents on the alkene are important in



controlling this competition by virtue of polar effects on the addition reaction between the alkene and the radical. Hence, in reductive alkylation by the tin hydride method, alkenes generally need electron-withdrawing substituents to react with the nucleophilic alkyl radicals generated from alkyl bromides or iodides.²

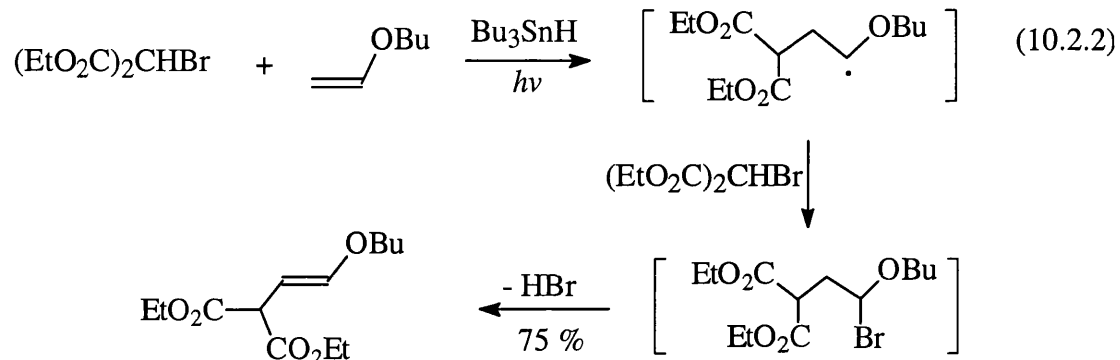
10.2. Electrophilic Radical Addition Reactions

Polar effects facilitate the addition of electrophilic radicals to electron-rich alkenes. There are some examples of the successful use of electrophilic α -alkoxycarbonylalkyl radicals to add to electron-rich alkenes using tributyltin hydride. Giese has reported that the addition reaction between diethyl chloromalonate and an enol ether can be mediated by tin hydride to afford the addition product [eqn. (10.2.1)].³ However, the reaction of diethyl

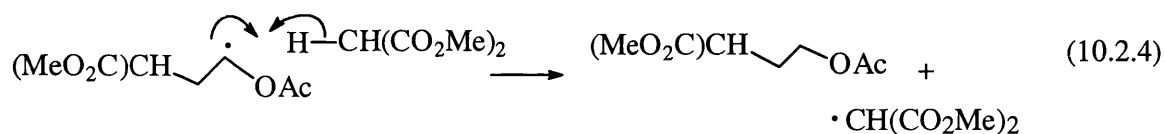


bromomalonate with the enol ether gives a different product, because the nucleophilic adduct radical abstracts bromine atom from the bromomalonate rather than the electron-

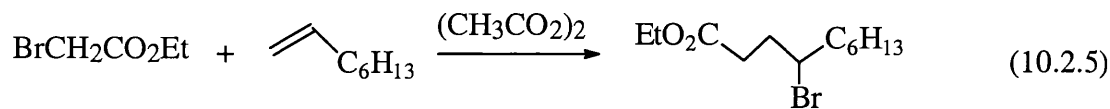
rich hydrogen atom from tributyltin hydride. The elimination of HBr from the adduct gives the substituted vinyl ether [eqn. (10.2.2)].



Hydrogen-atom transfer reactions can be used to mediate these addition reactions. For example, the weak α -C-H bonds of dimethyl malonate can be functionalized by addition to vinyl acetate. When a mixture of vinyl acetate (1 equiv.) and di-*tert*-butyl peroxide (0.2 equiv.) is added slowly to dimethyl malonate (10 equiv.) at 150 °C, the adduct was obtained in 65 % yield [eqns. (10.2.3)].⁴



Kharasch has reported that halogen-atom transfer can also mediate such reaction. When diacetyl peroxide was added slowly to a mixture of excess ethyl bromoacetate and 1-octene at 90 °C, ethyl 4-bromodecanoate was obtained in 75 % yield [eqn. (10.2.5)].⁵



10.3. Alternative Hydrogen-Atom Donors for the Radical Chain Methods.

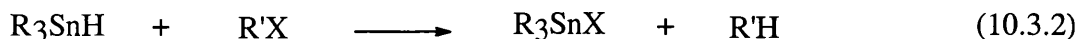
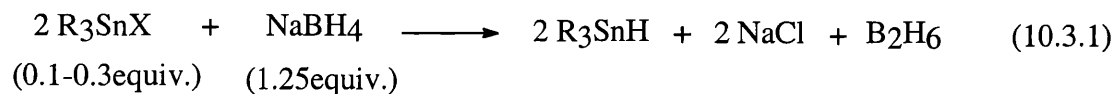
Radical reactions based on the tin hydride methods permeate synthetic radical chemistry. However, reactions based on tin hydride methods have several drawbacks. First, some triorganotin compounds are highly toxic and create a disposal problem. In the series of $R_n\text{SnX}_{4-n}$, $R_3\text{SnX}$ has the highest biological activity and maximum mammalian toxicity occurs with $R = \text{Me}$ or Et . Toxicities decrease for Bu or Ph and a minimum activity is

Table 10.3.1. Toxicity of triorganotin compounds.⁶

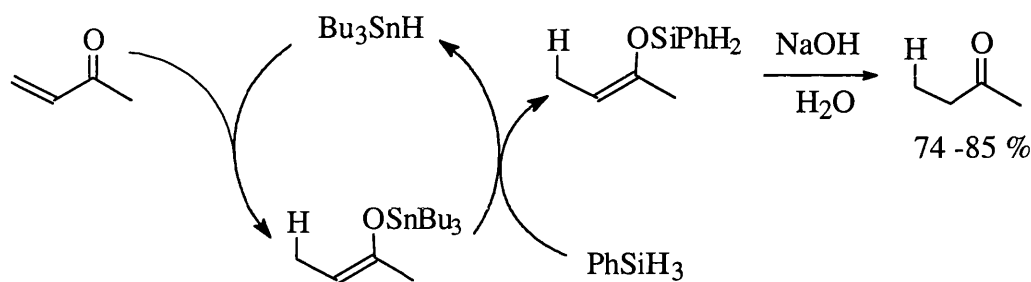
Compound	Me_3SnCl	Et_3SnCl	Bu_3SnCl	$(\text{Bu}_3\text{Sn})_2\text{O}$	Oct_3SnCl
LD_{50} (mg Kg^{-1})	9-20	10	123-349	148-234	>4000

observed for the octyl group (**Table 10.3.1**).⁶ Second, the desired products are frequently contaminated by trace amounts of organotin compounds, which cause difficulties in utilising these for drug syntheses. Also, in large scale reactions the work-up procedure and product isolation are difficult. Third, the purity of commercial Bu_3SnH varies because of slow oxidation by air and other oxidants, forming bis(tributyltin) oxide and insoluble dibutyltin oxide. Thus, careful purification is needed for precise work. Fourth, the reactive tin hydride acts as an effective radical scavenger, which often requires the slow addition of the tin hydride to keep concentrations low in the reaction mixture.

Therefore, the use of a stoichiometric quantity of tributyltin hydride with alkyl halides has been replaced by non-tin-based alternatives or by organotin-catalyzed processes supported by other hydrogen-atom donors.⁷ For example, Corey *et al.* have reported that the reduction of organic halides with catalytic amounts of tin hydrides can be carried in the presence of excess NaBH_4 . In this process, organotin hydride is regenerated by the reaction of the organotin halide and NaBH_4 in ethanol (which traps the resulting diborane) [eqn. (10.3.1)-(10.3.2)].⁸



David *et al.* have reported that conjugate reduction of enones can be successfully accomplished with phenylsilane in the presence of a catalytic amount of Bu_3SnH via the radical chain process shown (Scheme 10.3.1).⁹



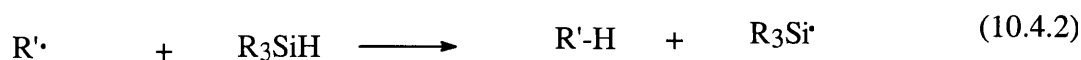
Scheme 10.3.1

Substantial effort has been devoted to the development of alternatives to tin hydrides such as the use of tris(trimethylsilyl)silane¹⁰ and trialkylgermanes.¹¹ However, there is a tendency to avoid the use of germanium hydrides because their high cost.

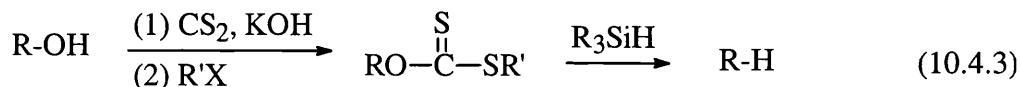
10.4. Radical Reactions Using Silanes

Organosilanes such as $(\text{Me}_3\text{Si})_3\text{SiH}$ have been studied in detail as hydrogen atom donors and as an alternative to trialkyltin hydrides by Chatgililoglu.¹⁰ Radical chain reactions involving silyl radicals generated from this and other complex silanes result in reductions of organohalides, hydrosilylation of alkenes and C-C bond formation of alkenes in the presence of suitable alkyl radicals.

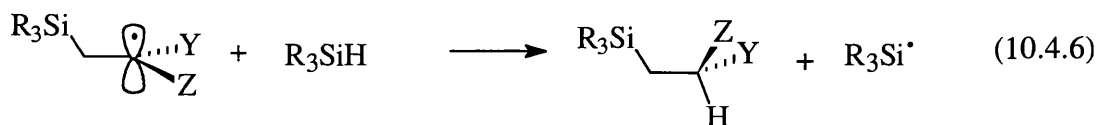
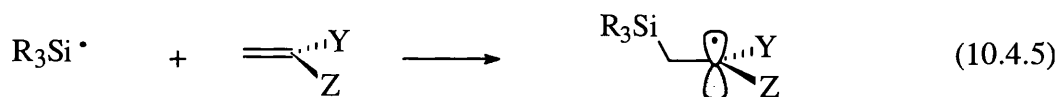
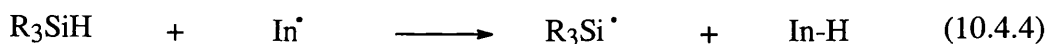
A two-step propagation sequences is involved in these radical-chain reductions: removal of halides or pseudohalides by the silyl radical followed by reduction using $(\text{Me}_3\text{Si})_3\text{SiH}$, $(\text{Me}_3\text{Si})_2\text{SiHMe}$ or $(\text{RS})_3\text{SiH}$, as shown in [eqns. (10.4.1) and (10.4.2)].



Silanes can be used for deoxygenation of an alcohol *via* thionoesters, the tin analogue of which is the Barton-McCombie reaction [eqn. (10.4.3)].¹²



Hydrosilylation can proceed by a radical-chain mechanism, as shown in [eqns. (10.4.4)-(10.4.6)]. The addition of the silyl radical to C-C double bond is irreversible, because the relatively high strength of the Si-C bond (394 kJ mol⁻¹ in case of Me₄Si).¹³ Hydrosilylation with (Me₃Si)₃SiH or (Me₃Si)₂SiHMe gave good yields with high regioselectivity (anti-Markovnikov), as shown in [eqn. (10.4.6)].



However, alkyl- or aryl-substituted silanes are inefficient in giving similar products, due to their poor hydrogen-atom donating properties. Difficulties in carrying out the free-radical addition of trialkylsilanes to alkene C=C bonds are partly due to telomerization competing with the radical transfer step.

Jackson and El-Durini have reported that this difficulty can be overcome by the use of a large excess of trialkylsilane, initiated by di-*tert*-butyl peroxide, under high temperature conditions (110-170 °C) as described in [eqns. (10.4.7)-(10.4.9)].¹⁴

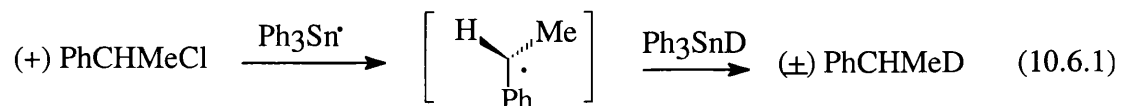


10.5. Radical Addition Reactions using Alkyl- or Phenyl-substituted Silanes in the Presence of Thiols.

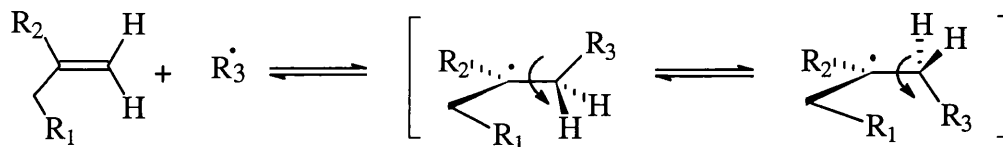
Alkyl radicals have little tendency to abstract electron-rich hydrogen-atom from R_3SiH (R: alkyl or phenyl) due to the high Si-H bond strength and unfavourable polar effects. Radical-chain reactions using silanes in the presence of thiols as polarity-reversal catalysts has been developed by Roberts' group, as discussed in **Chapter 2**. Hydrogen-atom transfer and halogen atom abstraction reactions by the silane-thiol couple are fast enough to propagate the radical-chain reaction.

10.6. Stereochemistry of Intermolecular Free-Radical Reactions

In a planar or near planar carbon-centred radical $\text{X}_3\text{C}^\bullet$, the unpaired electron occupies a π -orbital which allows attack from two faces. For example, the reduction of optically active 1-chloro-1-phenylethane by triphenyltin deuteride yields racemic 1-deutero-phenylethane [eqn. (10.6.1)].¹⁵

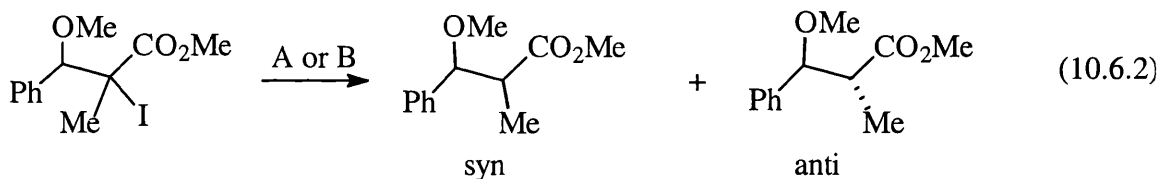


Addition to prochiral alkenes can give adduct radicals which go on to react with high diastereoselectivity, provided the substituents are such as to cause pronounced conformational preferences (**Scheme 10.6.1**).



Scheme 10.6.1

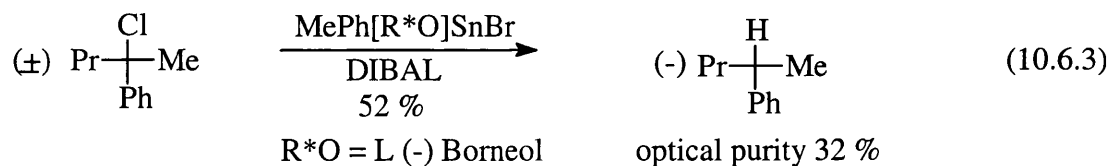
There have been some significant recent advances in the development of stereoselective processes which make use of chiral auxiliaries and 1,2-asymmetric induction the reactions of α -carbonylalkyl radicals. For example, Guindon has demonstrated that stereoselective chelation-controlled reduction of α -iodoesters can work effectively in the presence of Lewis acid giving up to 99:1 diastereoselectivity ratios [eqn. (10.6.2)].¹⁶



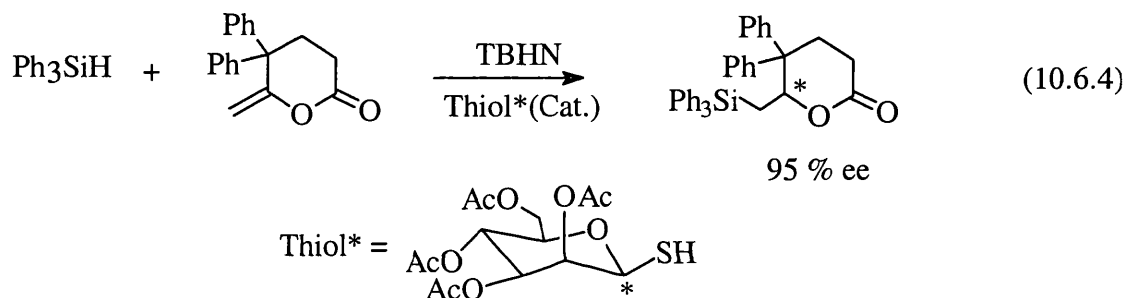
A= Bu_3SnH (2 equiv.), AIBN, -78°C , Syn : Anti = 1 : 25 (86 %)

B= Bu_3SnH (2 equiv.), AIBN, MgI_2 , -78°C , Syn : Anti = 25 : 1 (78 %)

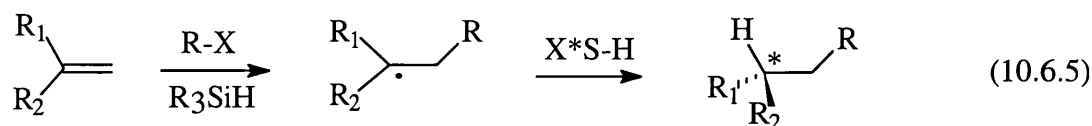
When the hydrogen-atom donor is a homochiral compound, enantiomeric excesses could in principle be obtained by differentiating the approach of the homochiral hydrogen-atom donor to one enantiotopic face of a prochiral radical. However, when optically active organotin hydrides were used as hydrogen-atom donors, only poor to moderate enantiomeric excess have been observed. [*e.g.* eqn. (10.6.3)].¹⁷



High enantioselectivities are possible when a cyclic radical reacts from a preferred conformation. Recently, Roberts, *et al.* have shown that radical-chain hydrosilylation in the presence of catalytic amount of optically active thiol can give relatively high enantiomeric excesses [eqn. (10.6.4)].¹⁸



We reasoned that the possibility exists for enantioselective reductive alkylation, mediated by silanes, in the presence of optically active thiol catalysts. Therefore, the first aim of this part of the project was to establish the radical-chain reductive addition of electrophilic radical precursors to electron-rich alkenes, mediated silanes in the presence of thiols. The second aim was to achieve enantioselective reductive alkylation of prochiral alkenes, using silanes in the presence of optically active thiol catalysts [eqn. (10.6.5)].



References to Chapter 10

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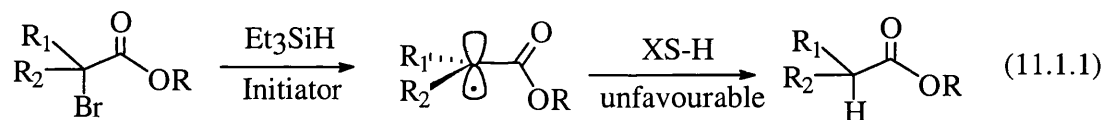
CHAPTER 11

RESULTS AND DISCUSSION

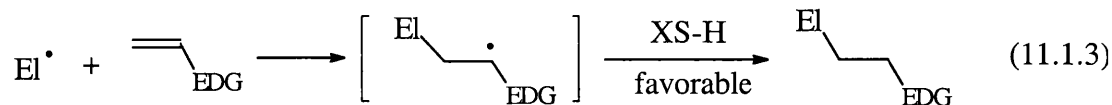
11.1. The Use of Thiols as Polarity-Reversal Catalysts

Radical-chain reactions mediated by silanes in the presence of thiols as a polarity reversal catalyst have been studied by Roberts' group.¹ Propagation steps include the abstraction of a halogen atom from the alkyl halide by a silyl radical followed by the reduction of the generated alkyl radical by the thiol catalyst. The thiyl radical generated in this reaction goes on to abstract a hydrogen atom from the silane to regenerate the silyl radical and continue the chain reaction. Excellent yields have been reported for the reduction of alkyl halides and xanthates.²

The S-H group of a thiol provides an electron-deficient hydrogen-atom, which favours transfer to nucleophilic alkyl radicals. On the contrary, polar effects will discriminate against the abstraction of hydrogen-atoms from thiols by electrophilic radicals, which was evidenced by the reaction of α -bromoesters with the silane-thiol couple, as discussed in Chapter 5 [eqn. (11.1.1)].



Therefore, the classical nucleophilic radical addition to an electron-deficient alkene would not be favoured as a step in reductive alkylation mediated by silane in the presence of thiol catalyst, because the adduct radical is electrophilic [eqn. (11.1.2)]. However, addition of an electrophilic radical to an alkene substituted by an electron-donating group generates a nucleophilic adduct radical, for which polar effects are favourable for abstraction of hydrogen from the thiol [eqn. (11.1.3)]. Therefore, reductive alkylation of electron-rich alkenes, mediated by the silane-thiol couple, could be a new method for C-C bond formation when the alkyl halide provides an electrophilic alkyl radical.

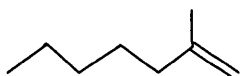


11.2. Preparation of Electron-Rich Alkenes

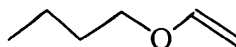
Acyclic electron-rich alkenes **52-57** were chosen for radical addition reactions. Alkenes **52-55** were commercially available and purchased from Aldrich. Alkenes **56-57** were available in the laboratory. The cyclic electron-rich alkenes **58-60** were also investigated. The alkene **58** is commercially available and was purchased from Aldrich; the alkene **59** was available in our laboratory.



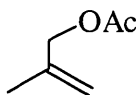
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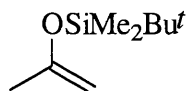
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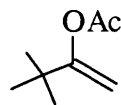
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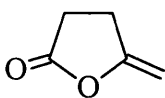
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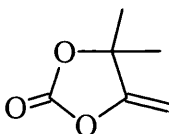
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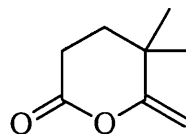
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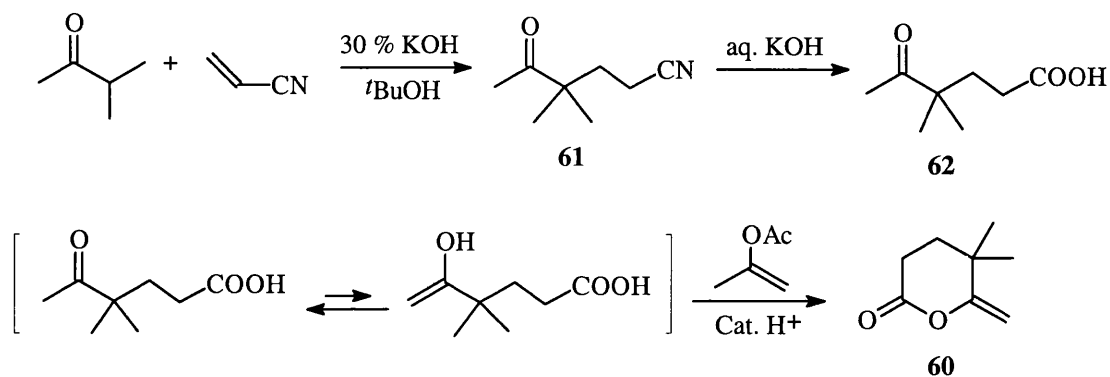
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60

Methylenelactone **60** was prepared following the procedure described by Shusherina *et al.*³ Base-catalysed Michael addition of isopropyl methyl ketone to acrylonitrile gave the keto-nitrile **61**, which was hydrolysed to afford the keto-acid **62** in quantitative yield. The formation of the methylenelactone **60** by dehydration using acetyl

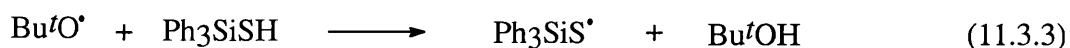
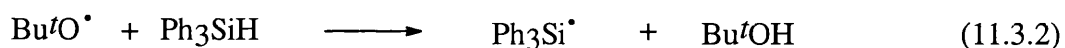
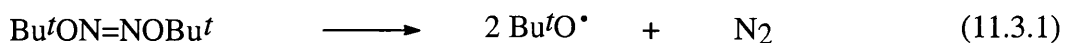
chloride described by Shusherina was found to be less reproducible than when using isopropenyl acetate, because hydrolysis of the methylenelactone **60** to the keto-acid **62** by acid generated from acetyl chloride occurred during the reaction or work-up procedure. The method using isopropenyl acetate gave a good yield (60 %) with good reproducibility (Scheme 11.2.1).



Scheme 11.2.1

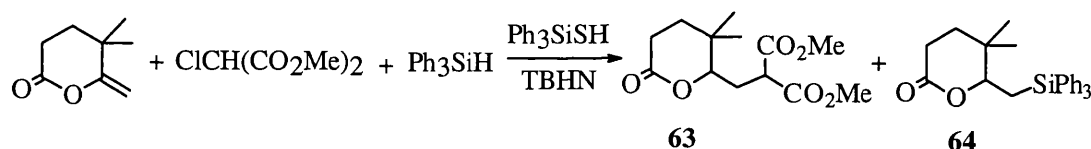
11.3. Malonyl Radical Addition to 5,5-Dimethyl-6-methylenetetrahydropyran-2-one with Silanes in the Presence of Triphenylsilanethiol as Polarity-Reversal Catalyst

Initial reactions were carried out using the methylenelactone **60** as an electron-rich alkene and dimethyl chloromalonate as an electrophilic radical precursor. Triphenylsilanethiol was used as polarity reversal catalyst to promote the radical-chain propagation with triphenylsilane. The reactions were initiated by catalytic amounts of *tert*-butyl hyponitrite (TBHN). The *tert*-butoxyl radical rapidly abstracts the hydrogen-atom



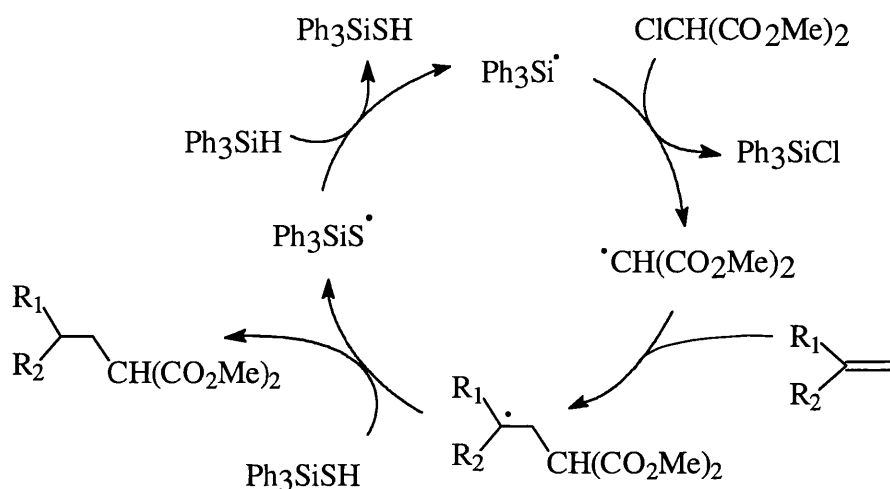
from the silane or triphenylsilanethiol to initiate the radical-chain reaction, as shown in [eqn. (11.3.1-11.3.3)].

Typically, a mixture of the methylenelactone **60** (2.50 mmol), dimethyl chloromalonate (3.25 mmol), triphenylsilane (3.25 mmol) and TBHN (0.125 mmol) in benzene (4 cm³) was stirred at 60 °C for 2 h. After removal of solvent using rotatory evaporator, ¹H NMR spectroscopic analysis of the crude mixture showed that no adduct was formed. When the reaction was repeated in the presence of triphenylsilanethiol (TPST, 0.125 mmol) under the same conditions, ¹H NMR spectroscopic analysis showed a 5:1 mixture of the carboxyalkylated adduct **63** and the silylated adduct **64**. The mixture was diluted with diethyl ether and washed with 5 % aqueous sodium bicarbonate and then with saturated brine. The organic layer was dried over MgSO₄ and the solvent was removed using rotary evaporator. The residue was purified by flash-column chromatography to afford 0.44 g (65 %) of the adduct **63** and 0.1 g (10 %) of the adduct **64**. The reaction is described in **Scheme 11.3.1**.



Scheme 11.3.1

In the absence of thiol the reaction did not occur. In the presence of triphenylsilanethiol, the thiol efficiently supported the reductive carboxyalkylation of the electron-rich alkene mediated by the electrophilic malonyl radical. The principle of polarity-reversal catalysis, in this case triphenylsilanethiol as catalyst, was applied to promote the abstraction of electron-rich hydrogen from the silane.⁴ The overall radical-chain mechanism of the thiol-catalysed reductive carboxyalkylation proceeds through the propagation sequence illustrated in **Scheme 11.3.2**.



Scheme 11.3.2

To establish the scope of these addition reaction of the alkene **60**, experiments were repeated with chloromalonate and bromomalonate and results are summarised in **Table 11.1.1**. The malonyl radical generated from chloromalonate was added readily to the alkene **60** to afford a moderate yield of **63** (entries 1 and 2). In the absence of initiator or thiol the reaction did not occur (entries 3 and 4).

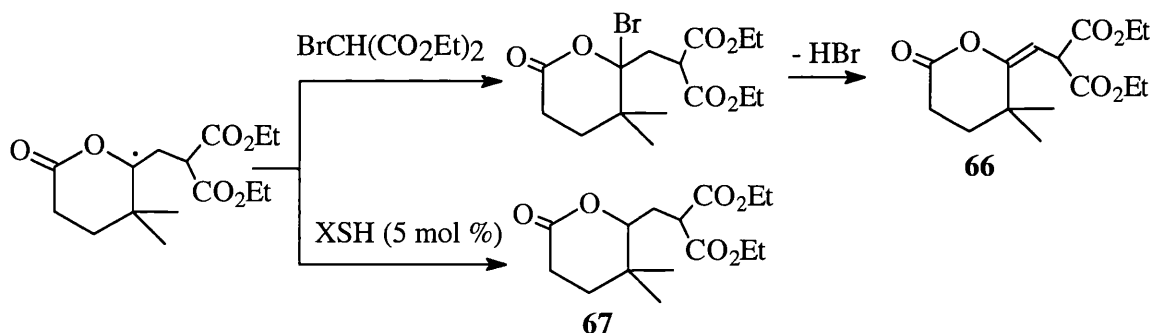
However, the reactions of the alkene **60** with bromomalonates gave very poor results (entries 6-8). Even though bromomalonates were expected to be reactive electrophilic-radical precursors, ¹H NMR spectroscopic analysis of the crude reaction mixture showed that reactions of bromomalonate with the alkene **60** produced only a trace amount of the carboxyalkylated product **67**, together with the keto-acid **62** as the major product.

Giese has reported that the radical addition of bromomalonates to electron-rich alkenes, using the tin hydride method gave the substitution product **66** by elimination of HBr.⁵ However, in this reaction using the silane-thiol couple the substitution product **66** could not be detected. Therefore, the reaction was probably terminated at an initial stage caused by HBr generated from the reaction to form a Giese type substitution product, followed by acid-catalysed ring opening of **60** [**Scheme 11.3.3**].

Table 11.1.1. Electrophilic carboxyalkylation of 5,5-dimethyl-6-methylenetetrahydropyran-2-one

Entry	R-Hal (1.3 equiv.)	Condition ^a	product	Yield (%) ^b
1	ClCH(CO ₂ Me) ₂	A	63	65
2	ClCH(CO ₂ Me) ₂	B	63	63
3	ClCH(CO ₂ Me) ₂	A ^c	63	-
4	ClCH(CO ₂ Me) ₂	A ^d	63	-
5	ClCH(CO ₂ Et) ₂	A	65	62
6	BrCH(CO ₂ Et) ₂	A	65	5
7	BrCH(CO ₂ Me) ₂	B	63	trace
8	BrCMe(CO ₂ Me) ₂	A	63	trace

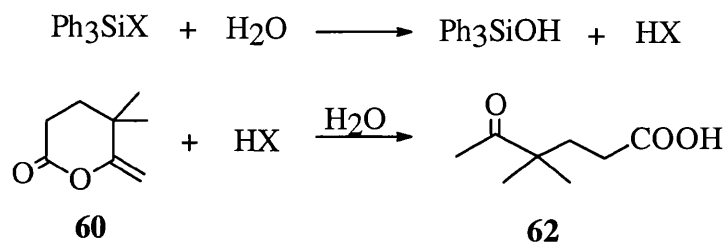
a. *Condition A*: Methylene lactone (2.5 mmol), TBHN (5 mol), triphenylsilanethiol (5 mol) and triphenylsilane (1.3 equiv.) in benzene (4 ml) were stirred at 60 °C for 2 h. *Condition B*: the same as *condition A* except di-lauroyl peroxide (5 mol %) and methyl thioglycolate (5 mol %) in benzene were used at 80 °C for 2 h. b. Isolated yields. c. No thiol was added. d. No initiator was used.



Scheme 11.3.3

The triphenylsilyl halide generated by these reactions is water sensitive and readily reacts with moisture to produce Ph₃SiOH and the hydrogen halide (BDEs for Me₃Si-Br, Me₃Si-Cl and Me₃Si-OH are 427, 490 and 557 kJ mol⁻¹, respectively).⁶ Consequently, ¹H NMR spectroscopic analysis of crude reaction mixtures often showed considerable

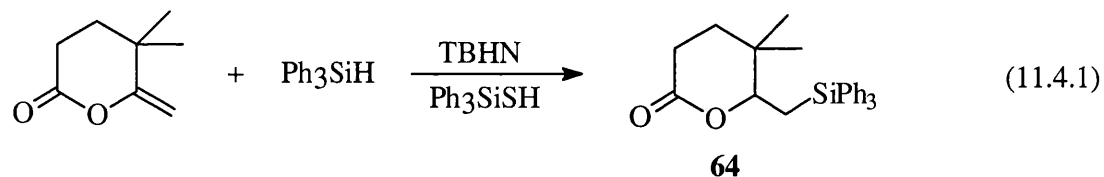
amounts of keto-acid **62**, which is thought to be formed by acid-catalysed hydrolytic ring opening reaction of the methylenelactone **60** (Scheme 11.3.4). However, the ring-opened acid from the carboxyalkylated product or the hydrosilylated product was not detected.



Scheme 11.3.4

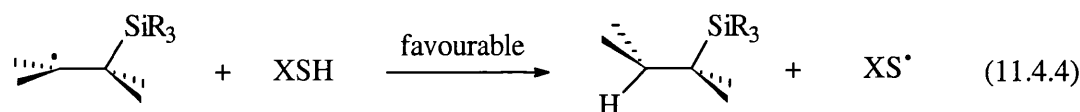
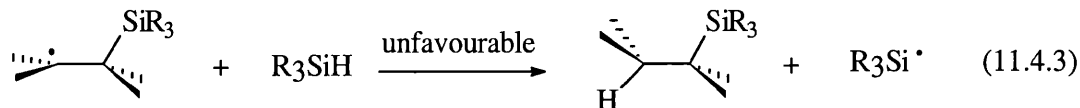
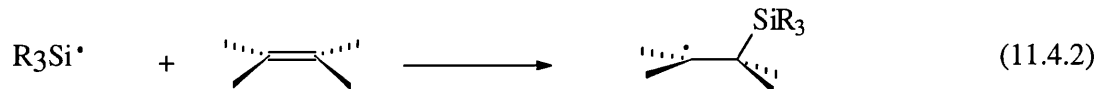
11.4. Competition Between Carboxyalkylation and Hydrosilylation by Silanes in the Presence of Thiols

The radical-chain hydrosilylation of alkenes catalysed by thiols has been studied by Roberts' group.⁴ In the present work, there is a competition between reductive carboxyalkylation and hydrosilylation in the presence of the silane-thiol couple, because the conditions differ only in the presence or absence of the electrophilic radical precursor. To examine the competition between the radical-chain hydrosilylation [eqn. (11.4.1)] and carboxyalkylation a series of experiments was carried out.

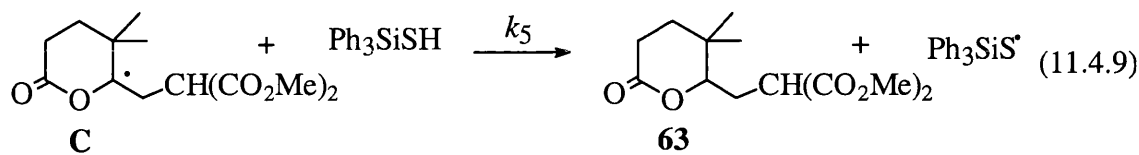
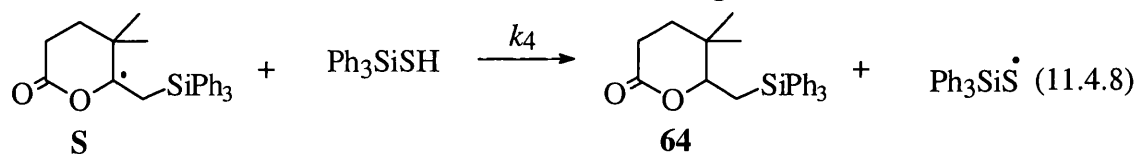
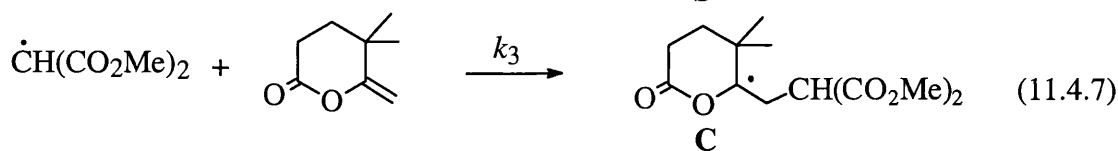
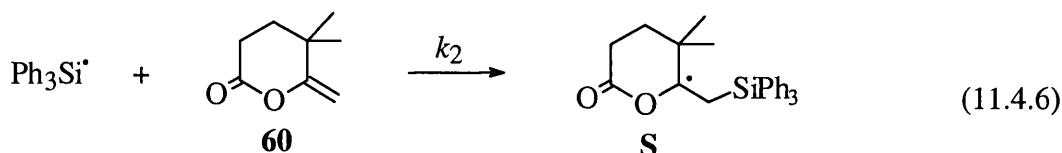
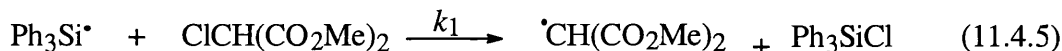


A mixture of the methylenelactone **60** (2.50 mmol) and triphenylsilane (3.25 mmol) in hexane (4 cm³) in the presence of triphenylsilanethiol (0.125 mmol) and TBHN (0.125 mmol) was stirred at 60 °C for 2.5 h. After cooling, the mixture was purified using flash column chromatography to afford the hydrosilylated adduct **64** in 84% yield [eqn. (11.4.1)]. However, in the presence of dimethyl chloromalonate under otherwise identical

conditions, the carboxyalkylated adduct **63** and the hydrosilylated adduct **64** were isolated in 65 and 10 %, respectively.



The radical-chain addition of the silyl radical to C-C double bond is a very fast process. The rate constants for the addition of triethylsilyl radicals to alkenes were reported to be 4.6×10^8 , 4.8×10^6 and $1.4 \times 10^6 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ for methyl acrylate, 1-hexene and furan, respectively at 27 °C.⁷ The addition rate of the silyl radical has a tendency to decrease with increasing electron-richness of the alkene. Hydrosilylation reactions are irreversible with simple silanes, but the yields are very poor with trialkylsilanes.⁸ Silanes are poor hydrogen-atom donors toward adduct radicals and can not propagate radical-chain reactions, as shown in [eqns.(11.4.2) and (11.4.3)]. However, in the presence of a thiol as polarity reversal catalyst, reactions proceed efficiently [eqn. (11.4.4)].⁴



When the electrophilic radical precursor is present, carboxyalkylation competes with hydrosilylation, because the triphenylsilyl radical and the malonyl radical are present simultaneously in the reaction mixture and react with the methylenelactone **60**, as shown in [eqns. (11.4.6) and (11.4.7)].

The competition between hydrosilylation and carboxyalkylation can be expressed kinetically in the following way. Assuming that the only fate of the malonyl radical is addition to **60** to give the adduct radical **C** [eqn. (11.4.7)] and that all of **S** and **C** go on to give **63** and **64** by reaction with thiol [eqns. (11.4.8) and (11.4.9)], then the following equation may be derived.

$$\frac{d[\mathbf{63}]}{dt} = k_1 [\text{Ph}_3\text{Si}^\bullet] [\text{ClCH}(\text{CO}_2\text{Me})_2] \quad (11.4.10)$$

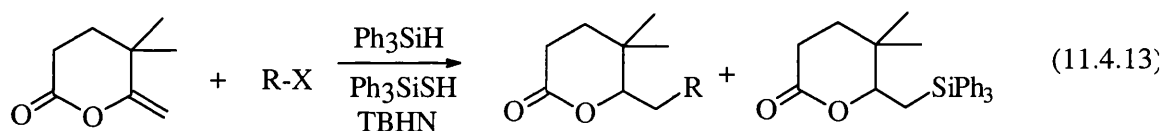
$$\frac{d[\mathbf{64}]}{dt} = k_2 [\text{Ph}_3\text{Si}^\bullet][\mathbf{60}] \quad (11.4.11)$$

Combining these equations we obtain eqn. (11.4.12).

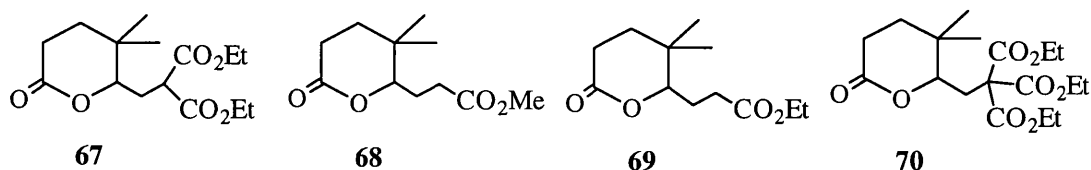
$$\frac{d[\mathbf{63}]}{d[\mathbf{64}]} = \frac{k_1 [\text{ClCH}(\text{CO}_2\text{Me})_2]}{k_2 [\mathbf{60}]} \quad (11.4.12)$$

Hence, in order to maximise the yield of **63** relative to **64** it is necessary to keep the concentration of the chloromalonate high relative to that of the methylenelactone **60**. At this level of approximation, the ratio [**63**]:[**64**] does not depend on the concentration of triphenylsilane, nor on the concentration of the thiol catalyst.

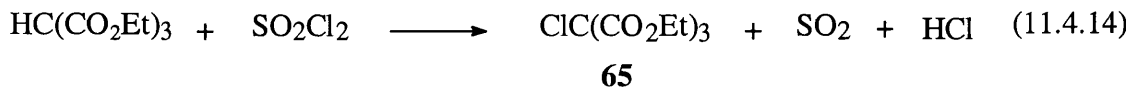
The triphenylsilyl radical is involved in a competition between halogen atom abstraction and addition to the alkene. Although kinetic data for halogen abstraction is scarce, some rate constants (*cf.* k_1) for halogen atom abstraction by triphenylsilyl radicals are known. Those for abstraction from *tert*-butyl chloride, CH_2Cl_2 and 1-bromopentane are 2.5×10^6 , 7.1×10^6 and $5.4 \times 10^9 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ at 25 °C.⁷ Thus, the rates of halogen abstraction from many alkyl halides by triphenylsilyl radicals need to be sufficiently faster than those for addition of triphenylsilyl radicals to electron-rich alkenes to suppress the formation of the hydrosilylated adduct **64**. Hence, it is best to use reactive alkyl halides for a successful reaction.



Reactions of the methylenelactone **60** with methyl chloroacetate, methyl bromoacetate, ethyl bromoacetate and triethyl chloromethanetricarboxylate **65** were carried out under a variety of conditions [eqn. (11.4.13)] and the results are summarised in **Table 11.4.1**.



Triethyl chloromethanetricarboxylate **65** was prepared by chlorination of triethyl methanetricarboxylate in refluxing sulfuryl chloride at 80 °C for 6 h, followed by distillation twice to afford pure product in 94 % yield [eqn. (11.4.14)].⁹



A one-pot reaction of the methylenelactone **60** with methyl chloroacetate gave a 21:79 mixture of the carboxyalkylated product **68** and the hydrosilylated product **64** (entry 1). Methyl chloroacetate was found to be least reactive for carboxyalkylation among the α -haloesters and favoured hydrosilylation, because Cl-C bonds are strong and abstraction of a chlorine atom by the triphenylsilyl radical is slow. When the reaction was repeated, increasing the amount of methyl chloroacetate or by the slow addition of triphenylsilane using syringe pump to reduce the concentration of the triphenylsilyl radical, the yield of the carboxyalkylated product **68** was raised (entries 2 and 3).

Reactions of the methylenelactone **60** with the bromoacetates were found to be efficient in producing carboxyalkylated products **68** and **69** (entries 4-6). Bromine-atom abstraction by the triphenylsilyl radical is rapid. Reaction of the electron-rich alkene is faster with the electrophilic α -alkoxycarbonylalkyl radical than with the nucleophilic triphenylsilyl radical. However, a control reaction in which the amount of methyl bromoacetate was increased showed a reverse effect and the yield of the carboxyalkylated product **68** (entry 5) was reduced, probably due to the ring opening reaction by HBr formed from excess of methyl bromoacetate.

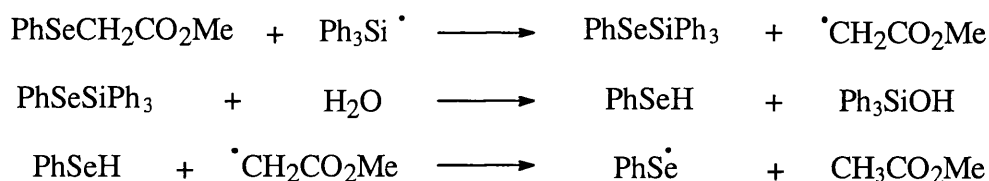
Table 11.4.1. Carboxyalkylation of the methylenelactone **60** with the electrophilic radical with triphenylsilane in the presence of thiol.

Entry	RX (equiv.)	Condition ^a	Ratio (Product : 64) ^b	Product	Yield (%) ^c
1	ClCH ₂ CO ₂ Me (1.3)	A ^d	21 : 79	68	18 (75)
2	ClCH ₂ CO ₂ Me (2.6)	A	46 : 54	68	37 (40)
3	ClCH ₂ CO ₂ Me (1.3)	B	50 : 50	68	39 (45)
4	BrCH ₂ CO ₂ Me (1.5)	A	97 : 3	68	87
5	BrCH ₂ CO ₂ Me (2.6)	A	100 : 0	68	70
6	BrCH ₂ CO ₂ Et (1.3)	A	100 : 0	69	73
7	ClCH(CO ₂ Me) ₂ (1.3)	A	79 : 21	63	65 (10)

8	ClCH(CO ₂ Me) ₂ (2.6)	<i>A</i>	82 : 18	63	63
9	ClCH(CO ₂ Me) ₂ (1.3)	<i>B</i>	80 : 20	63	61
10	ClCH(CO ₂ Me) ₂ (1.3)	<i>C</i>	84 : 16	63	67 (13)
11	ClC(CO ₂ Et) ₃ (1.3)	<i>A</i>	78 : 22	70	57 (19)
12	ClC(CO ₂ Et) ₃ (2.6)	<i>A</i>	91 : 9	70	45

a. Condition *A*: Ph₃SiH (1.3 equiv.), TBHN (5 mol % based on alkene), Ph₃SiSH in benzene were heated at 60 °C for 2 h. Condition *B*: the same as *A*, except Ph₃SiH (1.3eq.) and TBHN (5 mol %) was added using syringe pump for 1 h. Condition *C*: the same as *A*, except Ph₃SiH (1.3eq.) was added four equal portions every 25 min and then stirred 1 h. b. Based on ¹H NMR analysis before purification. c. isolated yield. the yields in brackets are the yields of isolated **64**. d. The reaction in hexane.

Although the reaction of methylenelactone **60** with methyl phenylselenylacetate and triphenylsilane on occasion gave a high yield (87 %) of the carboxyalkylated product **68** without formation of the silylated product **64**, this reaction was not reproducible. Although the reason for this is not clear, there was a suggestion that PhSeH generated from the reaction of moisture sensitive triphenylsilylselenide could be the cause, because the highly reactive benzeneselenol consumes radicals and inhibits the radical-chain reaction (**Scheme 11.4.1**). Byers and Lane have reported that sunlamp photolysis of diethyl (2-phenylseleno)propanedioate with a variety of electron-rich olefins yielded addition products. However, the reaction by thermal initiation with catalytic amounts of AIBN did proceed much more slowly than in the photochemically-initiated reactions.¹⁰



Scheme 11.4.1

The reaction of methylenelactone **60** with dimethyl chloromalonate produces a 4:1 mixtures of the carboxyalkylated adduct **63** and the hydrosilylated adduct **64** (entries 7-9).

However, increasing the amount of dimethyl chloromalonate did not much improve the yield of the carboxyalkylated product **63**.

The steric effect is important in the reaction of triethyl chloromethanetricarboxylate **65**. The tris(ethoxycarbonyl)methyl radical should be much more electrophilic than the malonyl radical, but the yield from the reaction with the chloromethanetricarboxylate is slightly lower than that from the chloromalonate (entries 11 and 12). This is probably because the addition to the C=C bond is sterically hindered and also the unpaired electron in tris(ethoxycarbonyl)methyl radical is more delocalised than in the malonyl radical. The rates of addition of the malonyl radical and the tris(ethoxycarbonyl)methyl radical to ethene have been studied by Diart and Roberts and the rate constant are 7.3×10^3 and $1.4 \times 10^3 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ at 221 K.¹¹ Although increasing the amount of **65** raised the yield of the carboxyalkylated product **70**, the ring opening reaction of the methylenelactone **60** occurred and a major side product was the keto-acid **62**.

The reaction of diethyl 2-chloro-2-methylmalonate, which was easily prepared by the reaction of diethyl methylmalonate and sulfuryl chloride,⁹ was also attempted. However, only a trace amount of product was detected by ¹H NMR analysis of the reaction mixture and no adduct was isolated. The low reactivity of diethyl chloromethylmalonate toward the methylenelactone **60** is probably due to the sterically hindered, and stabilised nature of $\text{MeC}(\text{CO}_2\text{Et})_2$.

Therefore, the trend in the reactivity of α -haloesters towards reductive alkylation of electron-rich alkenes are the order of bromoacetate > chloromalonate \geq triethyl chloromethanetricarboxylate > diethyl 2-chloro-2-methylmalonate. These reactivities are explainable as a combination of halogen-carbon bond strength effects, polar effects and steric effects.

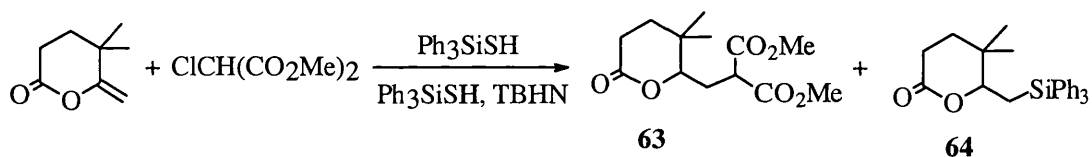
11.5. Solvent Effects and Silane Effects

The solvent effect on the electrophilic radical addition reactions of the methylenelactone **60** was investigated. The results in **Table 11.5.1** show that there is no significant solvent effect amongst hexane, benzene and dioxane. The slightly different yields in hexane might be due to the reduced solubility of reagents; triphenylsilane and the

methylenelactone **60** have good solubility in hexane, but dimethyl chloromalonate has less soluble. Thus, the triphenylsilyl radical would have more chance to react with the methylenelactone **60** in hexane rather than abstract the chlorine atom from less miscible dimethyl chloromalonate.

The effect of changing the silane was also investigated. The reactions of the methylenelactone **60** with PhMe_2SiH and Ph_2MeSiH gave low yields of the carboxyalkylated product **63** (entries 4 and 5). It is known that phenyl substituents on silicon have a smaller effect on the Si-H bond strength than on the C-H bond strength in corresponding carbon analogues. This is because of the larger size of silicon compared with carbon and because of the pyramidal nature of the silyl radical. Rate constants for abstraction of hydrogen by alkyl radicals decrease in the order of $\text{Ph}_3\text{SiH} > \text{Ph}_2\text{MeSiH} > \text{PhMe}_2\text{SiH} > \text{Me}_3\text{SiH}$.^{7(b)} Therefore, it is clear that the hydrogen-atom donating abilities of silanes towards thiyl radicals have significant effects on these carboxyalkylation reactions.

Table 11.5.1 Solvent effects and silane variation in the addition of electrophilic radicals to alkenes

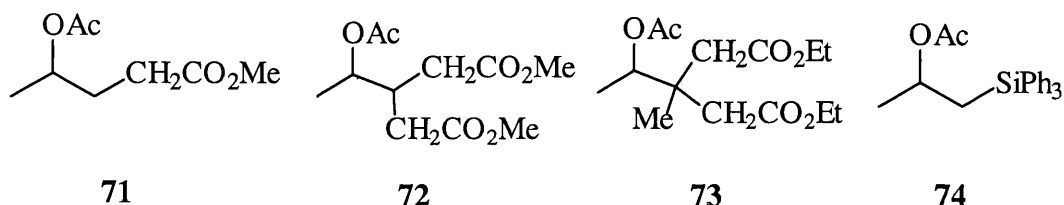


Entry	Halide (equiv.)	Silane (equiv.)	Solvent	Thiol	Ratio ^a (63 : 64)	Yield ^b of 63 (%)
1	1.3	Ph_3SiH (1.3)	Hexane	PTST	73 : 27	58
2	1.3	Ph_3SiH (1.3)	Dioxane	PTST	80 : 20	63
3	1.3	Ph_3SiH (1.3)	Benzene	PTST	81 : 19	65
4	1.3	PhMe_2SiH (1.3)	Benzene	PTST	84 : 16	26
5	1.3	Ph_2MeSiH (1.3)	Benzene	PTST	83 : 17	22

a. The ratios determined by ¹H NMR spectroscopic analysis of crude reaction mixture. b. Isolated yield of carboxyalkylated product **63**.

11.6. Further Reductive Carboxyalkylation Reactions

To examine the scope of the reaction, the radical-chain addition of electrophilic radicals to the acyclic alkenes **52-57** and to the cyclic alkenes **58** and **59** were investigated.



Initial reactions were carried out with isopropenyl acetate **52** and available electrophilic radical precursors. Di-*tert*-butyl hyponitrite (TBHN) and dilauroyl peroxide (DLP) were chosen as initiators. Triphenylsilanethiol (TPST) and methyl thioglycolate (MTG) were selected as polarity-reversal catalysts; results of the reaction are summarised in **Table 11.6.1**.

When a mixture of isopropenyl acetate (2.50 mmol), triphenylsilane (3.25 mmol), dimethyl chloromalonate (3.75 mmol) and TBHN (0.125 mmol) was heated under nitrogen for 2 h, ¹H NMR spectroscopic analysis of the reaction mixture showed less than 1 % of the adduct **72** was formed (entry 7). However, when the reaction was repeated in the presence of methyl thioglycolate (MTG, 5 mol% based on alkene), 78 % of the adduct **72** was isolated (entry 5). Similarly, 88% of the adduct **72** was isolated when triphenylsilanethiol (TPST) was used (entry 6). When the reactions were repeated with methyl bromoacetate in the presence of either TPST or MTG, 72 and 75 % yields of the

Table 11.6.1 The electrophilic radical addition to isopropenyl acetate

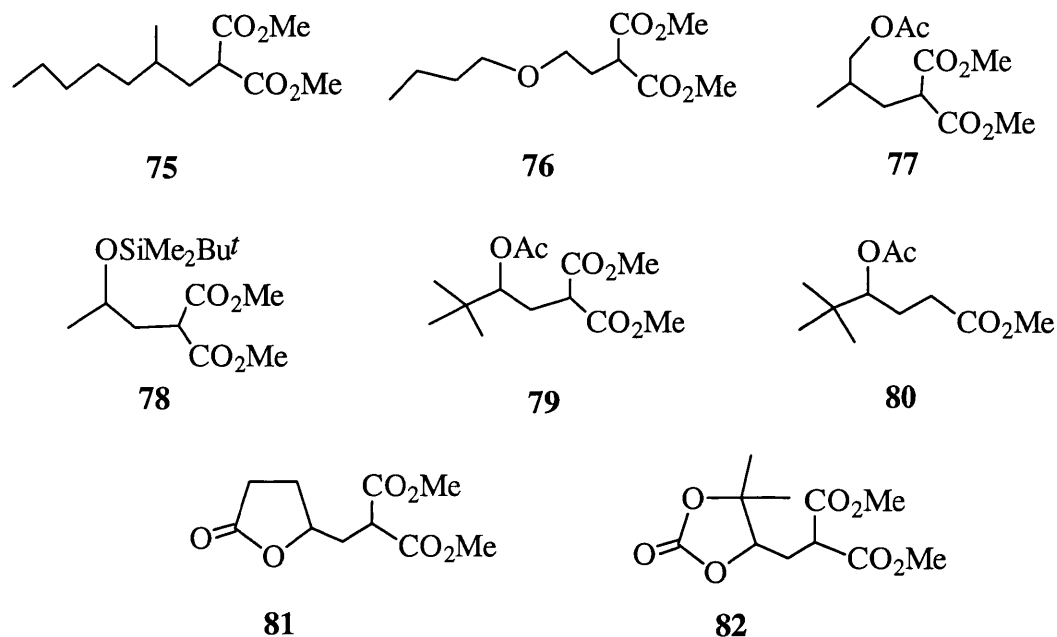
Entry	R-Hal (1.3 equiv.)	Thiol (5 mol%)	Initiator (5 mol%)	Solvent	Product	Yield ^a (%)
1	ClCH ₂ CO ₂ Me	TPST ^b	TBHN ^c	Dioxane	71	40 (50) ^d
2	BrCH ₂ CO ₂ Me	TPST	TBHN	Dioxane	71	72

3	BrCH ₂ CO ₂ Me	MTG ^e	TBHN	Dioxane	71	75
4	BrCH ₂ CO ₂ Me	MTG	DLP ^f	Benzene	71	76
5	ClCH(CO ₂ Me) ₂	MTG	TBHN	Dioxane	72	78
6	ClCH(CO ₂ Me) ₂	TPST	TBHN	Dioxane	72	88
7	ClCH(CO ₂ Me) ₂	-	TBHN	Dioxane	72	-
8	BrCMe(CO ₂ Et) ₂	TPST	TBHN	Benzene	73	78
9	BrCMe(CO ₂ Et) ₂	TPST	DLP	Benzene	73	73
10	BrCMe(CO ₂ Et) ₂	MTG	DLP	Benzene	73	70
11	ClCMe(CO ₂ Et) ₂	TPST	DLP	Benzene	73	76
12	ClCMe(CO ₂ Et) ₂	MTG	DLP	Benzene	73	82
13	-	TPST	DLP	Benzene	74	(99)

a. Isolated yield. b. Triphenylsilanethiol. c. When di-*tert*-butyl hyponitrite was used, the reaction mixture was heated at 60 °C for 2 h. d. The yield in brackets is of the hydrosilylated product **74**. e. Methyl thioglycolate. f. When dilauroyl peroxide was used, the reaction mixture was heated at 80 °C for 2 h.

adduct **71** were obtained (entries 2-3). Also, with dilauroyl peroxide initiator (5 mol %) and MTG (5 mol %) at 80 °C, a similar yield of product was obtained (entry 4). However, when the reactions with methyl chloroacetate was repeated under the same conditions, 40% of the carboxyalkylated adduct **71** and 50% of the hydrosilylated adduct **74** were isolated (entry 1). Evidently, the triphenylsilyl radical adds competitively to the double bond at about the same rate as it abstracts halogen from methyl chloroacetate.

Unlike the reactions of the methylenelactone **60**, the reactions of isopropenyl acetate **52** with diethyl 2-bromo-2-methylmalonate were successful. A good yield of the adduct **73** was obtained from the reductive alkylation of isopropenyl acetate with diethyl 2-bromo-2-methylmalonate and 2-chloro-2-methylmalonate in the presence of a thiol catalyst such as MTG or TPST (entries 8-12). Without electrophilic radical precursor, only hydrosilylation adduct **74** was obtained in 99 % yield (entry 13).



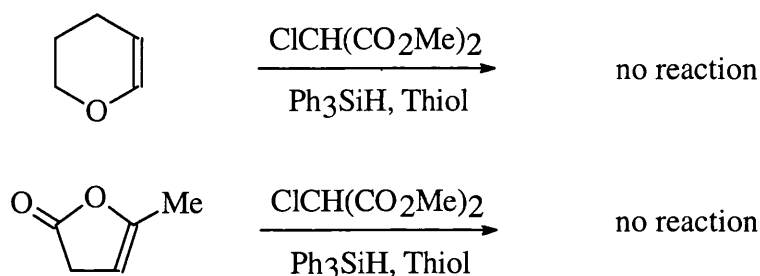
Similarly, addition reactions with electron-rich alkenes **53-59** were carried out to obtain adducts **75-82** and the results are summarised in **Table 11.6.2**. The reaction of 2-methyl-1-heptene (**53**) and dimethyl chloromalonate with triphenylsilane in the presence of triphenylsilanethiol gave a 60% yield (entry 1). Electron-rich alkenes such as butyl vinyl ether (**54**), 2-(acetoxymethyl)propene (**55**), 2-(*tert*-butyldimethylsiloxy)propene (**56**) and 3,3-dimethyl-2-acetoxybutene (**57**) react readily with dimethyl chloromalonate and gave good yields of adducts (entries 2-7). The alkene **55** which has an activating group remote from C=C double bond gave 77 % yield of the adduct **77** (entry 3). Addition to the cyclic terminal alkene **58** gave **81** in 76 % yield (entry 7), but the reaction of the sterically congested alkene **59** afforded a slightly lower yield **82** (entry 8).

Table 11.6.2 Reductive alkylation of electron-rich terminal alkenes with organic halides in the presence of triphenylsilane and catalysed by triphenylsilanethiol

Entry	Alkene	R-Hal (1.3 equiv.)	Initiator (5 mol %)	Thiol (5 mol %)	Adduct	Yield (%) ^a
1	53	ClCH(CO ₂ Me) ₂	TBHN	TPST	75	60
2	54	ClCH(CO ₂ Me) ₂	TBHN	TPST	76	78
3	55	ClCH(CO ₂ Me) ₂	TBHN	TPST	77	70

4	56	$\text{ClCH}(\text{CO}_2\text{Me})_2$	TBHN	TPST	78	85
5	57	$\text{ClCH}(\text{CO}_2\text{Me})_2$	TBHN	TPST	79	86
6	57	$\text{BrCH}_2\text{CO}_2\text{Me}$	TBHN	TPST	80	75
7	58	$\text{ClCH}(\text{CO}_2\text{Me})_2$	TBHN	TPST	81	76
8	59	$\text{ClCH}(\text{CO}_2\text{Me})_2$	TBHN	TPST	82	67

a. Isolated yields.

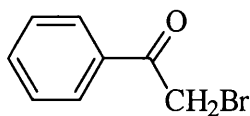


Scheme 11.6.1

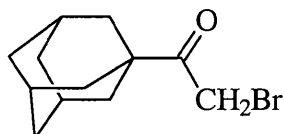
Although the reductive carboxyalkylation of terminal alkenes afforded good yields of the adducts, reactions with 1,2-disubstituted alkenes were sluggish. For example, the reactions of 3,4-dihydro-2*H*-pyran and of α -angelicalactone with the malonyl radical generated from dimethyl chloromalonate in the presence of triphenylsilane and triphenylsilanethiol gave no adducts. (**Scheme 11.6.1**).

11.7. Reductive Addition of α -Haloketones to Electron-Rich Alkenes

To extend the scope of the radical-chain addition to electron-rich alkenes, 2-bromoacetophenone (**83**) and adamantyl bromomethyl ketone (**84**) were investigated as electrophilic radical precursors. The ketone **83** was purchased from Adrich as a yellow solid and was purified by recrystallisation from petroleum-diethyl ether (10:1) to give a white solid. The ketone **84** was used as received.



83

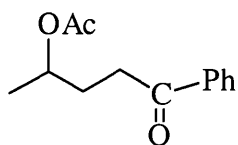


84

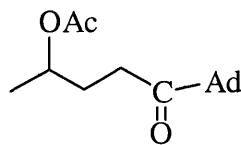
To a mixture of isopropenyl acetate (2.50 mmol), 2-bromoacetophenone (3.13 mmol), triphenylsilane (3.13 mmol), and dilauroyl peroxide (0.25 mmol) in benzene (4 cm³) was added methyl thioglycolate (0.13 mmol). The reaction mixture was heated at 80 °C for 2h, cooled to room temperature, the solvent was evaporated and the residue was purified by silica gel column chromatography to afford the adduct **85** in 54 % yield, together with acetophenone 56 % (based on 2-bromoacetophenone). In the reaction with the ketone **83**, no silylated product **74** was detected. Also, the reaction of isopropenyl acetate with the ketone **84** gave the adduct **86** in 58 % yield.

Under the same conditions, reactions of alkenes **57**, **59** and **60** with the ketone **83** were carried out. The reaction the alkene **59** with the ketone **83** gave the adduct **88** in 22% yield and acetophenone in 10 % yield (based on 2-bromoacetophenone). Also, the reaction with the alkene **57** gave the adduct **87** in 34 % yield, and the alkene **60** gave the adduct **89** in 21% yield.

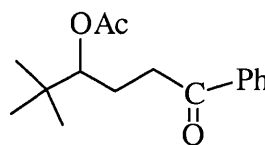
It is noteworthy that the reaction of alkenes and 2-bromoacetophenone with triphenylsilane in the presence of thiol produced the reduction product in addition to the carboxyalkylated products. The silylated adduct was not detected. Evidently, bromine atom abstraction from the ketone **83** and **84** by the triphenylsilyl radical is so rapid that competitive addition of the silyl radical to the alkene does not take place.



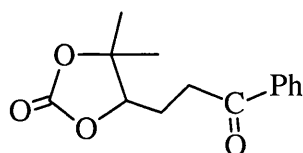
85



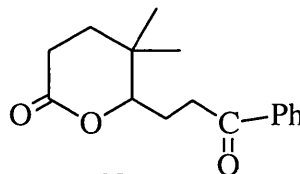
86



87

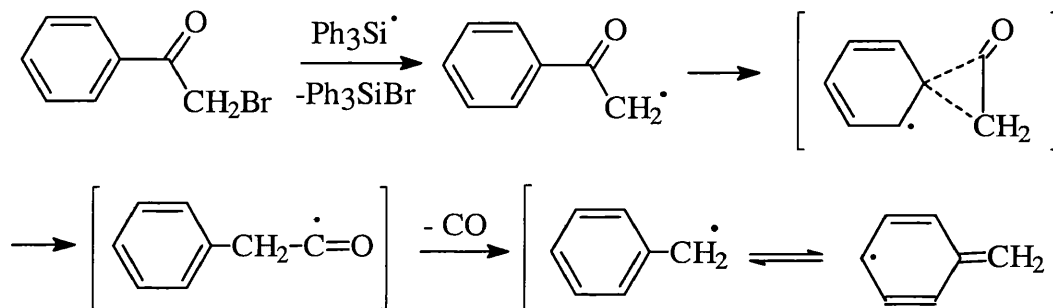


88



89

The reaction of electron-rich alkenes with 2-bromoacetophenone gave relatively low yields. There was a suggestion that the radical generated from 2-bromo acetophenone would possibly rearrange to generate a stabilised benzyl radical, which might be the cause of the low yield of the addition product (**Scheme 11.7.1**).

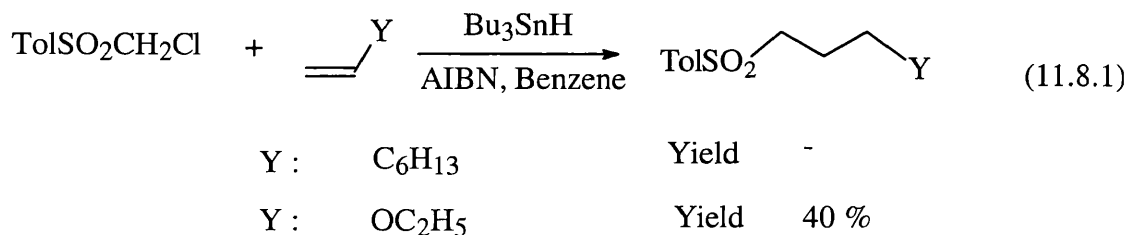


Scheme 11.7.1

11.8. Addition of Sulfonylated Carbon-Centred Radicals to Electron-Rich Alkenes

It was expected that phenylsulfonylmethyl radicals would be highly reactive electrophilic radicals, since ESR studies of these species showed that they are not stabilised by the sulfur function.¹³

The radical addition reactions of sulfonylated carbon-centred radicals have been studied by Renaud.¹⁴ The reactions 1-octene with chloromethyl *p*-tolyl sulfone in the presence of tributyltin hydride and AIBN in refluxing benzene gave no product. However, when the reaction was repeated with ethyl vinyl ether, a 40 % yield of the addition adduct was obtained.



Radical addition reactions of α -iodoalkyl phenyl sulfones to alkenes have been performed by Masnyk.¹⁵ The reaction of iodomethyl phenyl sulfone with 1-hexene in the

		(5 mol%)	(5 mol%)			90 : 91 : 74
1	Ph ₃ SiH	DLP	TPST	Benzene	80 / 2	35 : 10 : ND
2	Ph ₃ SiH	DLP	MTG	Benzene	80 / 2	39 : NI : ND
3	Ph ₃ SiH	DLP ^c	MTG ^c	Benzene	80 / 2	45 : 10 : ND
4	Ph ₃ SiH ^d	DLP	MTG ^d	Benzene	80 / 2	44 : 7 : ND
5	Ph ₃ SiH	DLP	MTG	Benzene	80 / 2	40 ^e : NI : ND
6	Ph ₃ SiH	DLP	-	Benzene	80 / 2	-
7	Ph ₃ SiH	TBHN ^f	MTG	n-Hexane	60 / 2	9 : 69 : ND
8	TTMSS	DLP	MTG	Benzene	80 / 2	12 : 71 : ND
9	Ph ₃ SiH	DTCP	MTG	n-Octane	113 / 2	35 : 65 : ND
10	Et ₃ SiH	DTCP	MTG	Dioxane	100 / 2	29 : 46 : ND

a. 1.30 Equivalent of the silane was used. b. Isolated yield, NI means not isolated, ND means not detected by ¹H NMR of crude reaction mixture. c. A mixture of MTG and DLP in benzene was added through syringe pump for 1 h. d. A mixture of MTG and Ph₃SiH in benzene was added through syringe pump for 1 h to the reaction mixture where MTG is initially present. e. Excess amount of isopropenyl acetate (2.0 equiv.) used, and the yield is based on bromomethyl phenyl sulfone. f. Additional TBHN (5 mol %) was added after 1h.

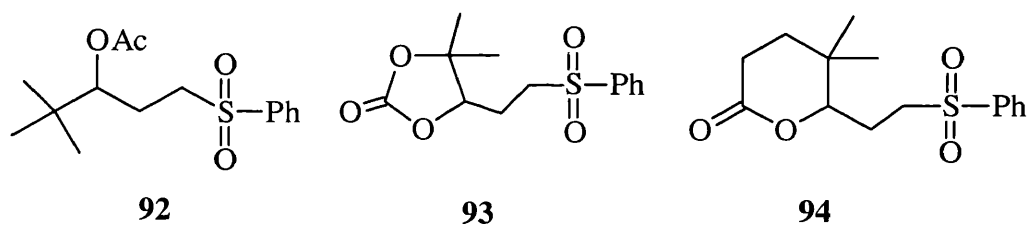
Chlorine-atom abstraction from chloromethyl phenyl sulfone by the triphenylsilyl radical is slow, making the hydrosilylation reaction dominant. On the contrary, in the reaction of bromomethyl phenyl sulfone, bromine-atom abstraction is rapid enough to give the adduct **90** without the formation of the hydrosilylated product. However, the addition of the sulfonylated methyl radical competes with its reduction to give PhSO₂Me, although evidently the rate of addition is faster than that of reduction.

Although the use of triphenylsilanethiol and methyl thioglycolate as catalysts gave similar results (entries 1 and 2), in the absence of the thiol reaction did not occur (entry 6). Reactions carried out by slow addition of MTG with DLP or MTG with triphenylsilane raised yields of the addition adduct **90** up to 45% and lowered the reduction adduct **91** (entries 3-4). Use of excess isopropenyl acetate (2 equiv.) had no effect (entry 5).

When the reaction was repeated with TBHN (5 mol %) as initiator at 60 °C and additional TBHN (5 mol %) was added after 1h, 9 % of the addition adduct **90** and 69 % of the reduction adduct **91** were isolated (entry 7).

The reaction using tris(trimethylsilyl)silane (TTMSS) in place of Ph_3SiH in the absence of the thiol gave mainly the reduction adduct **91** and the addition adduct **90** as minor product (entries 8). Although most reactions of isopropenyl acetate and bromomethyl phenyl sulfone did not go completion under the conditions summarised in **Table 11.8.1**, ^1H NMR spectroscopic analysis showed that with TTMSS the bromomethyl phenyl sulfone was completely consumed.

When the reaction using 1,1-di-*tert*-butylperoxycyclohexane (DTCP) as initiator was carried out at 113 °C for 2 h, 35 % of the addition adduct **90** and 65% of the reduction adduct **91** were isolated (entry 9). When the reaction was repeated with triethylsilane and DTCP under the same conditions, lower yields of products **90** and **91** were obtained (entry 10).



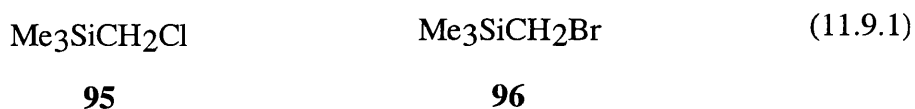
The reaction of the alkene **57** and bromomethyl phenyl sulfone with triphenylsilane in the presence of methyl thioglycolate gave the adduct **92** in 48 % yield and the reduction product **91** in 29 % yield. Under the same conditions, reaction of the alkene **59** gave the adduct **93** in 48 % yield and the reduction product **91** in 18 % yield. Also, the reaction with the alkene **60** gave 58 % of the adduct **94**.

11.9. Radical Addition Reactions of Miscellaneous α -Halo Compounds to the Electron-rich Alkenes Using Silanes in the Presence of Thiols

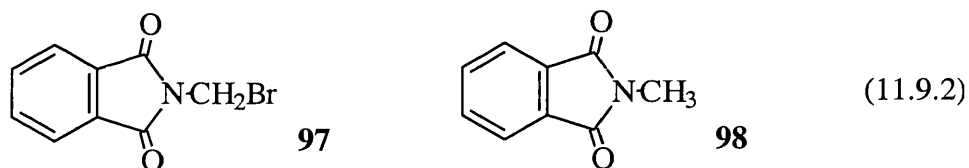
To further extend the scope of the reaction, possible electrophilic radical precursors **95-101** were investigated for the reductive addition to electron-rich alkenes using silane in the presence of the thiol.

When the reaction of chloromethyltrimethylsilane (**95**) and the methylenelactone **60** with triphenylsilane in the presence of TPST (5 mol %) and TBHN (5 mol %) was carried out at 60 °C for 2 h, only the hydrosilylated product **64** was isolated in 89 % yield.

When the reaction was repeated with isopropenyl acetate using DLP (5 mol %) at 80 °C under otherwise similar conditions, again only the hydrosilylated product **74** was isolated in 80 % yield. Probably, the C-Cl bond is too strong to support the formation of the trimethylsilylmethyl radical, and the triphenylsilyl radical reacts with the alkene to give the hydrosilylated product. However, when the reaction was repeated with bromomethyltrimethylsilane (**96**), only a trace amount of the hydrosilylated product **74** was detected by ¹H NMR analysis of the reaction mixture. The trimethylsilylmethyl radical is probably insufficient electrophilic to add rapidly to the alkene. Therefore, the trimethylsilylmethyl radical could be reduced to tetramethylsilane which would be lost by evaporation.



N-Bromomethylphthalimide (**97**) was examined as an electrophilic radical precursor. When the addition reaction of isopropenyl acetate and the halide **97** (1.5 equiv.) was performed, ¹H NMR spectroscopic analysis of reaction mixture showed a 14:9 mixture of **97** and **98** without any other products. Apparently, this is a case of nucleophilic radical reduction by silane-thiol couple.



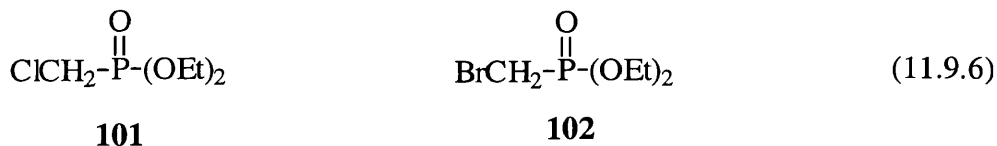
The reaction of bromomethylacetamide (**99**) and isopropenyl acetate with triphenylsilane in the presence of DLP and triphenylsilanethiol in dioxane was also attempted. However, only the hydrosilylated product **74** was detected by ¹H NMR spectroscopic analysis of the reaction mixture. Purification of the reaction mixture by column chromatography gave 36 % of the hydrosilylated product **74**.



When the reaction of 1-bromo-2,2-dimethoxypropane (**100**) and isopropenyl acetate under otherwise identical conditions was attempted, ¹H NMR spectroscopic analysis of reaction mixture showed no products were formed. Baldwin and co-workers have used



1-bromo-2,2-diethoxyethane in C-C bond formation with the sterically hindered and electron-deficient vinylstannane [eqn. (11.9.5)]. Comparing Baldwin's reaction, the compound **100** is the precursor of the nucleophilic radical. Probably, the compound **100** could be reduced to give low boiling product and pumped away during the work-up.



It was thought that an α -phosphonylalkyl radical should be rather electrophilic due to the electron-withdrawing effect of the diethoxyphosphonyl group. There has been a report that the addition reaction of α -phosphonylalkyl radicals derived from α -halophosphonates, adds to electron-rich and -deficient alkenes in the presence of tributyltin hydride to give a mixture of adduct and diethyl methylphosphonate as reduction product.¹⁶

When the reaction of dimethyl chloromethylphosphate (**101**) and isopropenyl acetate with triphenylsilane in the presence of triphenylsilanethiol and DLP was attempted, the ¹H NMR spectrum of the reaction mixture showed a 15:1 mixture of the hydrosilylation adduct and diethyl methylphosphonate, but no adduct was detected. Also,

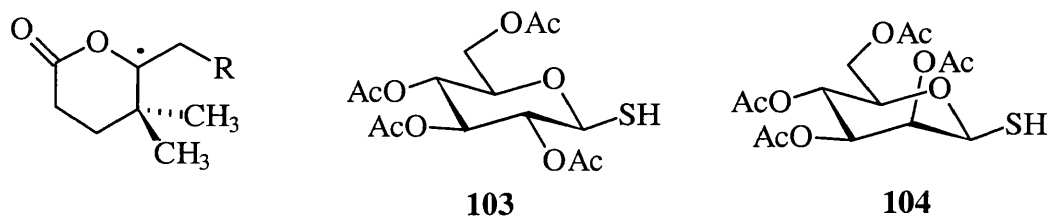
When the reaction was repeated with dimethyl bromomethylphosphate (**33**), only trace amounts of diethyl methylphosphonate as a reduction product were detected in the ^1H NMR spectrum.

11.10. Catalytic Transfer of Chirality to the Electron-Rich Alkenes by Silanes in the Presence of Chiral-Thiols

When the α -alkoxycarbonylalkyl radical attacks the double bond of the methylenelactone **60**, the resulting radical is prochiral. A difference in the rate of hydrogen-atom transfer from a homochiral thiol to the *Re* and *Si* faces of a prochiral carbon-centered radical will be enantioselective.

The practical hydrogen-atom donor in our system is the thiol as a polarity-reversal catalyst. Therefore, for the study of enantioselective hydrogen-atom transfer the homochiral thiol catalysts, 2,3,4,6-tetra-*O*-acetyl-1-thio- β -D-glucopyranose (**103**) and 2,3,4,6-tetra-*O*-acetyl-1-thio- β -D-mannopyranose (**104**) were selected. The thiol **103** was purchased from Aldrich. The thiol **104** was prepared following the procedure described in the literature;¹⁷ the α -mannosethiol was prepared from the corresponding α -mannosyl bromide and thiourea to give mainly the α -mannosylthiopseudouronium salt. Hydrolysis of this salt gave the crude thiol which was taken up by ethanol and crystallised in the freezer to give the β -mannosethiol **104** as a white solid. The majority of the α -mannosethiol was contained in the mother liquor.

Methylenelactone **60** was used as a prochiral substrate and methyl bromoacetate, dimethyl chloromalonate and triethyl chloromethanetricarboxylate were used as electrophilic radical precursors.



As shown in **Table 11.10.1**, reductive carboxyalkylation of the methylenelactone **60** with the bromoacetate and triphenylsilane in the presence of carbohydrate-derived

thiols **103** and **104** gave adducts **68** and **69** in good chemical yields, but with low optical purities. Although the chemical yields using the chiral thiols **103** and **104** were similar to those of reactions with triphenylsilanethiol and methyl thioglycolate, enantiomeric excesses of adducts **68** and **69** did not vary with the nature of chiral thiol (**103** or **104**) or with any changes in initiation conditions (entries 1-3).

When the reaction was repeated using dialkyl chloromalonate in place of the bromoacetate, the enantiomeric excesses of **63** and **67** increased up to 28 % (entries 4-7).

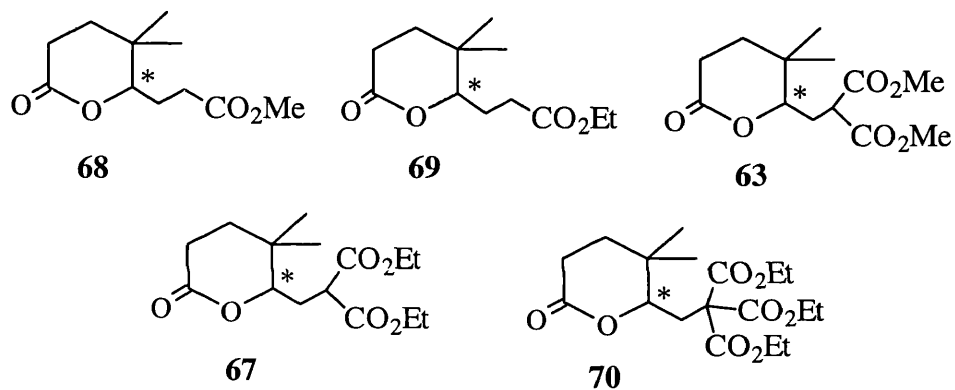
When the reactions of the methylenelactone **60** were repeated with triethyl chloromethanetricarboxylate, chemical yields were generally low but the ee of the product **70** varied greatly depending on the nature of thiols. With the β -glucosethiol **103** as catalyst, an ee of 46 % was achieved as determined by 400 MHz ^1H NMR using $\text{Eu}(\text{hfc})_3$ as shift reagent. When the reaction was repeated, the ee of 47 % was determined using 500 MHz ^1H NMR using $\text{Eu}(\text{hfc})_3$ as shift reagent. However, when the β -mannosethiol **104** was used as a catalyst, the product **70** showed the highest ee of 72 % (entries 8 and 9). Repetition of the reaction with β -mannosethiol **104** gave an ee of 71 % as determined by 500 MHz ^1H NMR using $\text{Eu}(\text{hfc})_3$ as shift reagent. The resulting product **70** was recrystallised from hexane to give material of 100 % enantiomeric excess, $[\alpha]_D^{22} = -31.4$ (c 0.025, CHCl_3). The absence of the (+)-enantiomer was confirmed by adding a small amount of racemic **70** to the NMR tube containing the homochiral product and $\text{Eu}(\text{hfc})_3$, and re-recording the 500 MHz ^1H NMR spectrum.

Table 11.10.1 Enantioselective carboxyalkylation of the methylenelactone **60** using optically active thiol catalysts

Entry	R-Hal (1.3 equiv.)	Thiol ^a	Method	Product	Yield ^b (%)	Product ee (%) ^c	$[\alpha]_D^{20\pm 2}$ (CHCl_3)
1	$\text{BrCH}_2\text{CO}_2\text{Me}$	103	A ^d	68	72	19 ^e	-
2	$\text{BrCH}_2\text{CO}_2\text{Me}$	104	A	68	65	19 ^e	-
3	$\text{BrCH}_2\text{CO}_2\text{Et}$	103	B ^e	69	85	20 ^e	-19.3 (c, 1.57)
4	$\text{ClCH}(\text{CO}_2\text{Me})_2$	103	B	63	62	28 ^e	-14.6 (c, 0.95)
5	$\text{ClCH}(\text{CO}_2\text{Me})_2$	103	A	63	63	24 ^f	-

6	ClCH(CO ₂ Me) ₂	104	A	63	64	27 ^f	-14.5 (c, 3.05)
7	ClCH(CO ₂ Et) ₂	103	B	67	59	24 ^c	-16.8 (c, 2.10)
8	ClC(CO ₂ Et) ₃	103	B	70	47	46 ^c	
9	ClC(CO ₂ Et) ₃	104	B	70	54	71 ^c	-24.7 (c, 1.72)

a. 5 mol% based on the methylenelactone **60**. b. Isolated yield. c. The ee was determined by ¹H NMR analysis using a homochiral shift reagent [Eu(hfc)₃]. d. *Condition A*: A mixture of the methylenelactone **60** (2.5 mmol), α-haloester (3.25 mmol), triphenylsilane (3.25 mmol), TBHN (5 mol%) in benzene was heated at 60 °C for 2 h. e. *Condition B*: the same as *condition A* except DLP (5 mol%) was used as initiator at 80 °C. f. Determined by chiral-stationary-phase HPLC analysis using Daicel Chemical Industries Chiral-OD column, detector 233 nm, 1 % isopropanol, 1 ml/min, retention time 47 and 55, the enantiomer present in excess was eluted second.



References to Chapter 11

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CHAPTER 12

EXPERIMENTAL

12.1. General Procedures

NMR spectra were recorded using a Varian VXR-400 (400 MHz for ^1H) or a Bruker AC-300 (300 MHz for ^1H) instruments. The solvent was CDCl_3 and chemical shifts are reported relative to the residual protons in the solvent (δ_{H} 7.24); coupling constants are quoted in Hz. All NMR data reported were obtained using the Varian VXR-400 instrument. The Bruker AC-300 instrument was mainly used to check the extent of the reaction by recording the NMR spectrum of the crude reaction mixture.

Enantiomeric excess (ee) was determined by chiral-stationary-phase HPLC analysis (Chiralcel-OD column, eluent: hexane-isopropyl alcohol 99:1) or by ^1H NMR analysis using a homochiral shift reagent $[\text{Eu}(\text{hfc})_3]$. Optical rotations were measured on an AA Series Polaar 2000 Polarimeter (Optical Activity Ltd.), using a 1 dm path length cell, and are given in units of $10^{-1} \text{deg cm}^2 \text{g}^{-1}$.

Infrared (IR) spectra were recorded with a Perkin-Elmer Model 1600 series FT-IR spectrophotometer as liquid films, Nujol mulls or KBr pellets and major peaks are reported in units of cm^{-1} . Mass spectra were obtained using a VG 7070H or VG ZAB-2F spectrometer in conjunction with electron impact ionisation (EI, 70 eV) or atmospheric pressure chemical ionisation (APCI) by the Mass Spectrometry Service in the Chemistry Department at UCL. Elemental analyses were performed by the Microanalytical Service at UCL. Melting points were determined using a Büchi Model 510 melting point apparatus in capillary tubes or a Reichert hot-stage apparatus and were not corrected.

Column chromatography and TLC were carried out using Merck Kieselgel 60 (230-400 mesh) and Kieselgel 60 F₂₅₄ aluminium-backed pre-coated plates, respectively. Visualisation of the TLC plates was made by ultraviolet light (254 nm) and with iodine stain. All manipulations and reactions of air-sensitive compounds were carried out under an atmosphere of dry nitrogen.

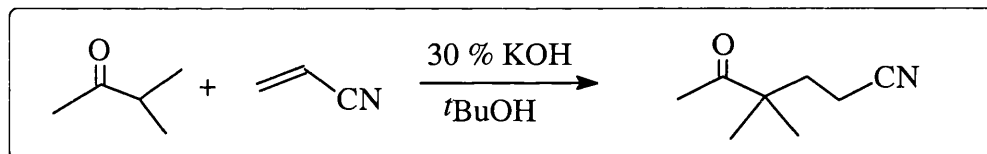
12.2. Materials

Hexane, benzene, 1,4-dioxane and chloroform (all HPLC grade) were purchased from the Aldrich Co. and used without further purification. Petroleum refers to light petroleum (b.p. 40-60 °C). Triphenylsilane and other silanes and the thiols (triphenylsilanethiol, methyl thioglycolate and 2,3,4,6-tetra-*O*-acetyl-1-thio- β -D-glucopyranose) were also obtained from Aldrich and were used as received. 2,3,4,6-Tetra-*O*-acetyl-1-thio- β -D-mannopyranose was prepared following the procedure described in the literature.¹ Di-*tert*-butyl hyponitrite (TBHN, $t_{1/2}$ = ca. 55 min at 60 °C) was prepared by the reaction of sodium hyponitrite with *tert*-butyl bromide in the presence of zinc chloride, using the method described by Mendenhall.² Dilauroyl peroxide (DLP) and azobis (isobutyronitrile) (AIBN) were used as received.

Bromomethyl phenyl sulfone was purchased from Aldrich and purified by passage through a short column of silica gel (eluent; diethyl ether-petroleum 2 :1), to remove the brown colour, and was then recrystallized from diethyl ether-petroleum (1:2) to give a white solid (m.p. 50-51 °C, lit.³ 51-52°C).

12.3. Preparation of 5,5-dimethyl-6-methylenetetrahydropyran-2-one (60)

(a). Preparation of 4,4-dimethyl-5-oxohexanenitrile (61)²



To a stirred solution of methyl isopropyl ketone (26.7 cm³, 0.25 mol), 2-methyl-2-propanol (2.30 g, 0.03 mol) and 30 % KOH (w/w) in methanol (5.5 cm³), acrylonitrile (15.9 g, 0.30 mol) was added dropwise at a rate such that the temperature of the mixture did not exceed 40 °C. The reaction mixture was stirred for 4 h and then left to stand overnight at room temperature. The reaction mixture was poured into a separatory funnel containing a mixture of brine (100 cm³) and diethyl ether (100 cm³). The organic layer was washed with brine (3 x 50 cm³) and dried over anhydrous MgSO₄. After removal of

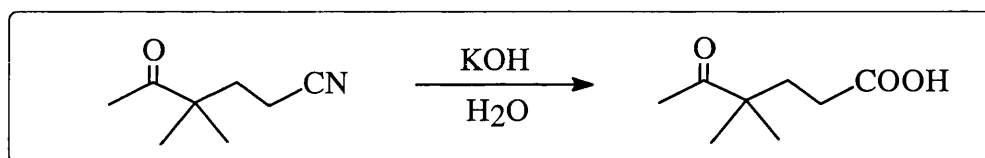
the solvent using a rotatory evaporator, the residue was distilled under reduced pressure to afford a colourless oil (33.4 g, 96 %).

Bp 70 °C / 0.2 Torr (lit.² b.p. 126-127 °C / 15.0 Torr)

δ_{H} (CDCl₃): 1.16 (6H, s, CMe₂), 1.87 (2H, m, CH₂CMe₂), 2.12 (3H, s, CH₃C=O), 2.25 (2H, m, CH₂CN).

δ_{C} : 12.9, 23.8, 24.1, 25.0, 34.4, 46.8, 167.6.

(b). Preparation of 4,4-dimethyl-5-oxohexanoic acid (**62**)²

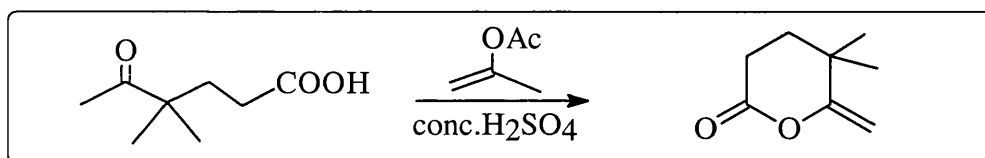


A mixture of 4,4-dimethyl-5-oxohexanenitrile (**61**) (33.4 g, 0.24 mol) and potassium hydroxide (35.2 g, 0.63 mol) dissolved in water (150 cm³) was heated under reflux for 2.5 h. The reaction mixture was allowed to cool and extracted with diethyl ether (2 x 50 cm³) to remove unwanted organic material. The aqueous layer was treated with 2M HCl until the solution became acidic (pH 1-3), and the oil layer formed was extracted with diethyl ether (3 x 50 cm³). The organic phase was dried over anhydrous MgSO₄ and the solvent was removed using rotatory evaporator to afford a pale yellow oil which solidified on standing (33.4 g, 88 %). The NMR spectrum showed that the product was pure enough to use for the next step without further purification (lit.⁴ m.p. 46-47 °C)

δ_{H} (CDCl₃): 1.13 (6H, s, CMe₂), 1.85 (2H, m, CH₂CMe₂), 2.15 (3H, s, CH₃C=O), 2.25 (2H, m, CH₂CO₂), 12.3 (1H, br, COOH)

δ_{C} : 24.0, 24.9, 29.6, 33.7, 46.9, 145.1, 167.6 (C=O), 179.3 (COOH).

(c). Preparation of 5,5-dimethyl-6-methylenetetrahydropyran-2-one (**60**)³



A mixture of 4,4-dimethyl-5-oxohexanoic acid (**62**) (33.4 g, 0.21 mol), isopropenyl acetate (63.5 g, 0.63 mol) and conc. H₂SO₄ (3 drops) was placed in a flask which was equipped for distillation. The reaction mixture was heated in an oil bath (100 °C) such that slow distillation occurred at *ca.* 58 °C (mainly acetone) for 2.5 h. After removal of this low boiling material, the reaction mixture was distilled under reduced pressure to afford colourless liquid (b.p. 94 °C / 0.05 Torr) which was redistilled to afford pure methylenelactone (17.7 g, 60 %).

B.p. 60-62 °C / 0.05 Torr. (lit.³ b.p. 95-96 °C / 10 Torr)

Found: C, 68.25; H, 8.65. C₈H₁₂O₂ requires C, 68.55; H, 8.63 %.

δ_H (CDCl₃): 1.02 (6H, s, CMe₂), 1.68 (2H, t, *J* 7.2, CH₂CMe₂), 2.64 (2H, t, *J* 7.2, CH₂C=O), 4.35 (1H, d, *J* 2.0, vinyl CH), 4.63 (1H, d, *J* 2.0, vinyl CH).

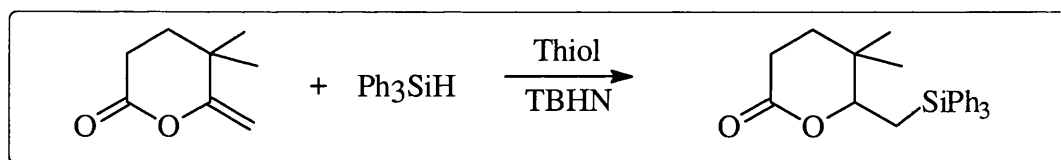
δ_C: 26.4, 27.7, 31.8, 32.5, 92.0, 163.5, 168.4.

m/z (EI): 141 (M+1, 100), 97 (30), 70 (30), 55 (48), 43 (98).

IR (cm⁻¹, liq. film): 1761.5 (C=O), 1652.1 (C=C), 1168 (C-O).

12.4 Electrophilic Radical Addition Reactions of Electron-rich Alkenes in the Presence of Silanes and Thiols.

1. 6-Triphenylsilylmethyl-5,5-dimethyltetrahydropyran-2-one (**64**)⁵



[Method 1] A mixture of the methylenelactone **60** (0.36 g, 2.56 mmol), triphenylsilane (0.85 g, 3.25 mmol), triphenylsilanethiol (0.036 g, 0.125 mmol), TBHN (0.022 g, 0.125 mmol) and hexane (4 cm³) was placed in a 2-neck flask which was equipped with a condenser and stoppered side-arm. A nitrogen gas bubbler was fitted over the condenser and nitrogen gas was briefly flushed through side arm in the flask. Under a slow stream of nitrogen, the reaction mixture was placed in a pre-heated oil bath (60 °C). The reaction

mixture was stirred for 2.5 h at 60 °C and then allowed to cool. to room temperature. After removal of the solvent using a rotatory evaporator, the residue was purified by flash column chromatography [TLC; R_f 0.5, petroleum : ethyl acetate = 4:1 eluent] to afford the hydrosilylated product as a white solid (0.86 g, 84 %).

M.p. 112.4 °C

Found: C, 77.70; H, 7.04. $C_{26}H_{28}O_2Si$ requires C, 77.96; H, 7.05 %.

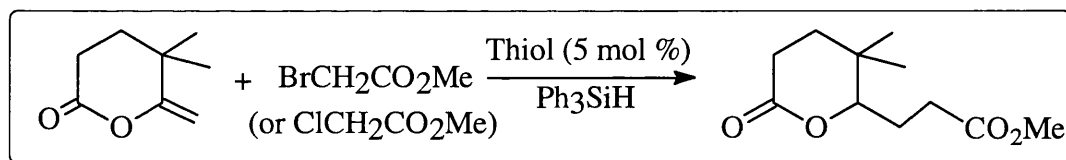
δ_H (CDCl₃): 0.92 (3H, s, CMe^A), 1.00 (3H, s, CMe^B), 1.58 (3H, m, SiCH^A and CH₂), 1.79 (1H, dd, J 15.0 and 11.5, SiCH^B), 2.40 (2H, m, CH₂C=O), 4.11 (1H, dd, J 11.5 and 2.4, O-CH), 7.38 (9H, m, C₆H₅), 7.59 (6H, m, C₆H₅).

δ_C : 14.9, 19.2, 26.5, 27.3, 33.0, 33.9, 84.6, 127.8, 129.5, 134.4, 135.8, 170.9.

m/z (EI): 400 (M^+ , 1), 323 ($M^+ - C_6H_5^+$, 100), 259 (Ph_3Si^+ , 85), 199 (81).

[Method 2] The same reaction was repeated except that 2,3,4,6-tetra-*O*-acetyl-1-thio- β -D-glucopyranose was used as catalyst instead of triphenylsilanethiol to afford optically active product (88 %). A 51 % ee was measured using a Chiralcel-OD column with detector at 254 nm (eluent: 1% isopropyl alcohol in *n*-hexane, t_R 11.8 and 13.3 with a flow rate 1.0 cm³ min⁻¹).

2. 5,5-Dimethyl-6-[2-(methoxycarbonyl)ethyl]tetrahydropyran-2-one (**68**)



[Method 1] A mixture of the methylenelactone **60** (0.35 g, 2.50 mmol), methyl bromoacetate (0.36 cm³, 3.75 mmol), triphenylsilane (0.85 g, 3.25 mmol), triphenylsilanethiol (36 mg, 0.125 mmol), TBHN (22 mg, 0.125 mmol) and benzene (4 cm³) was placed in a 2-necked flask which was equipped with condenser and side-arm. A nitrogen gas bubbler was fitted over the condenser and nitrogen gas was briefly flushed over through side-arm in the flask. Under a slow stream of nitrogen, the reaction mixture was placed in a pre-heated oil bath (60 °C). The reaction mixture was stirred for 2 h at 60

°C and then allowed to cool. After removal of the solvent using a rotatory evaporator, the residue was diluted with diethyl ether and washed with 5 % aqueous NaHCO₃ and then with saturated brine. The organic layer was dried over MgSO₄ and the solvent was removed using rotatory evaporator. The residue was purified by flash column chromatography [TLC; R_f 0.3, petroleum : ethyl acetate = 4 : 1 eluent] to afford a clear oil (0.47 g, 87 %).

Found: C, 61.57; H, 8.41. C₁₁H₁₈O₄ requires C, 61.66; H, 8.47 %.

δ_H (CDCl₃): 0.94 (3H, s, CMe^A), 1.01 (3H, s, CMe^B), 1.57-1.64 (1H, dddd, *J* 0.8, 1.6, 5.2 and 6.8, OCHCH^A), 1.66-1.77 (2H, m, 4-CH₂), 1.90-1.98 (1H, dddd, *J* 0.8, 1.2, 2.0, 2.8, 8.0, OCHCH^B), 2.42-2.65 (4H, m, 3-CH₂, CH₂COO), 3.65 (3H, d, *J* 0.8, OCH₃), 3.97-4.00 (1H, dd, *J* 1.6 and 11.2, 6-CH).

δ_C : 19.4, 25.2, 26.4, 27.4, 30.0, 32.0, 34.4, 51.6, 86.4, 171.3, 173.7.

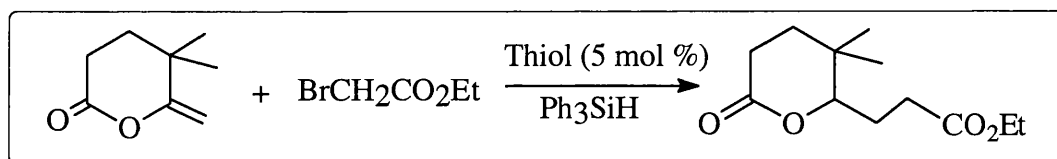
m/z (EI): 214 (M⁺, 0.8), 199 (M⁺-CH₃, 5), 183 (M⁺-OCH₃, 8), 70 (CH₂=CHCO₂, 100), 56 (CO₂CH₃ + H⁺, 86).

IR (cm⁻¹, liq. film) : 1736.5 (C=O), 1440, 1352, 1167.5 (C-O), 1056 (C-O).

[Method 2] The same reaction as described in Method 1 was repeated, except that 2,3,4,6-tetra-*O*-acetyl-1-thio-β-*D*-glucopyranose (5 mol % based on the methylenelactone **60**) was used instead of triphenylsilanethiol (5 mol %) to afford the optically active product **68** (72 % of yield). An ee of 19 % was determined by ¹H NMR using Eu(hfc)₃ as homochiral shift reagent. When the reaction was repeated with 2,3,4,6-tetra-*O*-acetyl-1-thio-β-*D*-mannopyranose (5 mol %), the carboxyalkylated product **68** showed an ee of 19 % and 65 % yield.

[Method 3] When the reaction described in Method 1 was repeated with methyl chloroacetate (1.3 equiv. based on the methylenelactone **60**) instead of methyl bromoacetate, 18 % of the carboxyalkylated product **68** and 75 % of the hydrosilylated product **64** were obtained. However, when the reaction was repeated with 2.6 equiv. of methyl chloroacetate, 37 % of the carboxyalkylated **68** product and 40 % of the hydrosilylated product **64** were obtained.

3. 5,5-Dimethyl-6-[2-(ethoxycarbonyl)ethyl]tetrahydropyran-2-one (**69**)



[Method 1] A mixture of the methylenelactone **60** (0.36 g, 2.57 mmol), methyl bromoacetate (0.36 cm³, 3.75 mmol), triphenylsilane (0.85 g, 3.25 mmol), triphenylsilanethiol (36 mg, 0.125 mmol), TBHN (22 mg, 0.125 mmol) and benzene (4 cm³) was placed in a 2-neck flask which was equipped with condenser and side-arm. Under a slow stream of nitrogen, the reaction mixture was placed in a pre-heated oil bath (60 °C). The mixture was stirred for 2 h at 60 °C, and then allowed to cool to room temperature. After the usual work up, the crude product was purified by flash column chromatography to afford a clear oil (0.43 g, 73 %).

Found: C, 63.10; H, 8.99. C₁₂H₂₀O₄ requires C, 63.12; H, 8.84 %.

δ_{H} (CDCl₃): 0.94 (3H, s, CMe^A), 1.01 (3H, s, CMe^B), 1.22 (3H, t, OCH₂CH₃), 1.59-1.78 (3H, m, 4-CH₂, OCHCH^A), 1.92-2.00 (1H, m, OCHCH^B), 2.43-2.66 (4H, m, 3-CH₂, and CH₂CO₂), 3.97 (1H, dd, *J* 1.6 and 11.2, 6-CH), 4.09 (2H, q, OCH₂CH₃). The analysis was confirmed by ¹H-¹H decoupling experiments.

δ_{C} : 14.2, 19.4, 25.2, 26.4, 27.4, 30.3, 32.0, 34.4, 60.5, 86.5, 171.4, 173.3.

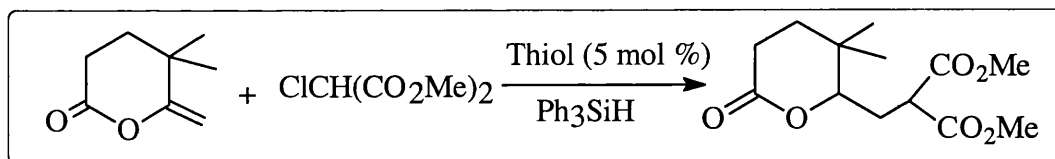
m/z (EI): 229 (M⁺+1, 29), 183 (M⁺-OCH₂CH₃, 21), 165 (100), 155 (M⁺-CO₂Et, 4 %).

IR (cm⁻¹, liq. film): 1733.4 (C=O), 1469.9 (C=C), 1371.7, 1349.0, 1055.6

[Method 2] The reaction of the methylenelactone **60** and ethyl bromoacetate with triphenylsilane in the presence of 2,3,4,6-tetra-*O*-acetyl-1-thio- β -D-glucopyranose (5 mol % based on the methylenelactone **60**) and DLP in refluxing benzene (bath 85 °C) for 2 h afforded a clear oil (85 % yield). An ee of 20 % was determined by ¹H NMR using Eu(hfc)₃ as chiral shift reagent.

$[\alpha]_{\text{D}}^{22} = -19.3$ (*c* 1.57, CHCl₃)

4. 5,5-Dimethyl-6-[2,2-di(methoxycarbonyl)ethyl]tetrahydropyran-2-one (**63**)



[Method 1] Under a slow stream of nitrogen, a mixture of the methylenelactone **60** (0.35 g, 2.50 mmol), dimethyl chloromalonate (0.36 cm³, 3.75 mmol), triphenylsilane (0.85 g, 3.25 mmol), triphenylsilanethiol (36 mg, 0.125 mmol), and TBHN (22 mg, 0.125 mmol) in benzene (4 cm³) was stirred for 2 h at 60 °C. After the usual work up, the residue was purified by flash column chromatography to afford the carboxyalkylated product **63** (0.44 g, 65 %) as a clear oil and the hydrosilylated product **64** as a by-product (0.1 g, 10 %). The visualisation of the TLC plate was made using ultraviolet light (254 nm) and with iodine stain [*R_f* 0.1 of the adduct **63** and 0.5 of the adduct **64** (diethyl ether-petroleum 1 : 2 eluent)].

Found: C, 56.98; H, 7.49. C₁₃H₂₀O₆ requires C, 57.33; H, 7.40 %.

δ_{H} (CDCl₃): 0.96 (3H, s, CMe^A), 1.02 (3H, s, CMe^B), 1.57-1.74 (2H, m, 4-CH₂), 1.94-2.07 (1H, m, OCHCH^A), 2.21-2.28 (1H, m, OCHCH^B), 2.50-2.54 (2H, m, 3-CH₂), 3.73 (6H, s, 2OCH₃), 4.00 (1H, dd, *J* 1.6, 11.2, 6-CH). The analysis was confirmed by ¹H-¹H NMR decoupling experiments

δ_{C} : 19.3, 26.2, 27.3, 29.6, 31.9, 34.3, 47.8, 52.7, 52.8, 84.6, 169.4, 169.7, 170.7.

m/z (EI): 273 (M⁺+1, 3), 272 (M, 1), 70 (100 %).

IR (cm⁻¹, liq. film) : 1779(C=O), 1736.6, 1437.8, 1350, 1259.7, 1162 (C-O).

[Method 2] When the reaction was repeated without triphenylsilanethiol catalyst, the ¹H NMR spectrum (300 MHz) of the residue, which was taken after the usual work up, showed no carboxyalkylated product **63**. However, when the reaction was repeated in the presence of a catalytic amount triphenylsilanethiol (5 mol%) with either hexane or dioxane as solvent, 58 % and 63 % yields of the carboxyalkylated product **63** were isolated.

[Method 3] When the reaction of Method 1 was repeated with the variation of silane to dimethylphenylsilane (1.30 equiv.) or diphenylmethylsilane (1.30 equiv.) under otherwise

identical conditions, the carboxyalkylated product **63** were isolated 26 and 22 % yields, respectively.

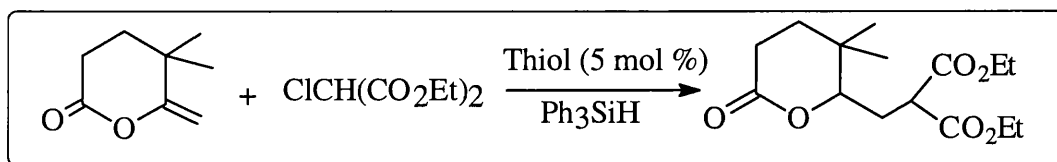
[Method 4] When the reaction of Method 1 was repeated, but with the addition of triphenylsilane in four equal portions (total 1.30 equiv. based on the methylenelactone **60**), the carboxyalkylated product **63** was isolated in 67 % yield. When the reaction was repeated with the addition of triphenylsilane (1.30 equiv. dissolved in benzene 4 cm³) and TBHN (5 mol %), using a motor-driven syringe pump, during 1 h and additional 1 h stirring, the yield of the carboxyalkylated product **63** was 61 %.

[Method 5] The reaction of Method 1 was repeated using 2,3,4,6-tetra-*O*-acetyl-1-thio- β -D-glucopyranose (5 mol %) instead of triphenylsilanethiol to afford the optically active product **63** (63 % yield) and 24 % ee was determined by chiral-stationary-phase HPLC analysis (Chiralcel-OD column, eluent: hexane-isopropyl alcohol 98:2). When the reaction with 2,3,4,6-tetra-*O*-acetyl-1-thio- β -D-glucopyranose (5 mol %) repeated, an ee of 28 % was determined by ¹H NMR using homochiral shift reagent Eu(hfc)₃ and $[\alpha]_{\text{D}}^{22} = -14.6$ (c: 0.945).

When the reaction with 2,3,4,6-tetra-*O*-acetyl-1-thio- β -D-mannopyranose was repeated, 64 % of the carboxyalkylated product **63** was obtained and an ee of 27 % was determined by chiral-stationary-phase HPLC analysis (Chiralcel-OD column). The optical rotation $[\alpha]_{\text{D}}^{22}$ was -14.6 (c: 2.1, CHCl₃).

[Method 6] Under the same conditions as for Method 1, except that 2,3,4,6-tetra-*O*-acetyl-1-thio- β -D-glucopyranose (5 mol %) and DLP (5 mol %) in benzene were used into a reaction temperature of under reflux for 2 h (bath 85 °C), 62 % of the carboxyalkylated product **63** was obtained. This showed an ee of 28 % ee [Eu(hfc)₃ shift reagent] $[\alpha]_{\text{D}}^{22} = -14.6$ (c 0.945, CHCl₃).

5. 5,5-Dimethyl-6-[2,2-di(ethoxycarbonyl)ethyl]tetrahydropyran-2-one (**67**)



[Method 1] A mixture of the methylenelactone **60** (0.36 g, 2.56 mmol), diethyl chloromalonate (1.23 cm³, 3.25 mmol) triphenylsilane (0.85 g, 3.25 mmol), TBHN (0.022 g, 0.125 mmol) and triphenylsilanethiol (0.036 g, 0.125 mmol) in benzene (4 cm³) was placed in a 2-necked flask which was equipped with condenser and side-arm. Under a slow stream of nitrogen, the reaction mixture was placed in a pre-heated oil bath (60 °C). The mixture was stirred for 2 h and then allowed to cool to room temperature. After the usual work-up, the residue was purified by flash-column chromatography [TLC; R_f 0.25, petroleum : ethyl acetate = 4:1 eluent] to afford the product **67** as a clear oil (0.47 g, 62 %).

Found: C, 60.31; H, 7.89. C₁₅H₂₄O₆ requires C, 59.98; H, 8.05 %.

δ_{H} (CDCl₃): 0.96 (3H, s, CMe^A), 1.03 (3H, s, CMe^B), 1.25 (6H, 2t, 2OCH₂CH₃), 1.57-1.74 (2H, m, 4-CH₂), 1.92-1.99 (1H, ddd, *J* 14.4, 11.2 and 4, OCHCH^A), 2.20-2.27 (1H, ddd, *J* 14.4, 10.8 and 1.6, OCHCH^B), 2.50-2.54 (2H, m, 3-CH₂), 3.71-3.75 (1H, dd, *J* 10.8, and 4, CHCO₂), 4.00-4.03 (1H, dd, *J* 11.2 and 1.6, 6-CH), 4.15-4.23 (4H, m, 2 OCH₂CH₃).

The analysis was confirmed by ¹H-¹H NMR decoupling experiments.

δ_{C} : 13.98, 14.02, 19.2, 26.2, 27.3, 29.4, 31.9, 34.3, 48.1, 61.5, 61.6, 84.6, 169.0, 169.3, 170.9.

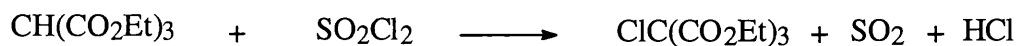
m/z (EI): 301 (M⁺+1, 87), 199 (M⁺ - CO₂CH₂CH₃ - CH₂CH₃ - H, 14.5), 29 (CH₂CH₃, 100).

IR (liq. film) : 1731.4, 1469.9, 1370.2, 1338.9, 1164.9, 1046.5.

[Method 2] When the same reaction was repeated with 2,3,4,6-tetra-*O*-acetyl-1-thio- β -D-glucopyranose and DLP as initiator (both 5 mol % based on the methylenelactone **60**) under reflux (bath 85 °C) for 2 h, the yield was 59 % and an ee of 24 % was determined by ¹H NMR using Eu(hfc)₃. The optical rotation [α]_D²² was -16.8 (c: 2.1, CHCl₃).

[Method 3] When the reaction Method 1 was repeated with diethyl bromomalonate, less than 10 % of product was detected by ^1H NMR analysis of the reaction mixture. After the usual work up, the reaction mixture was separated to afford 5 % of the carboxyalkylated product **67** and 3 % of the hydrosilylated product **64**.

6. Preparation of triethyl chloromethanetricarboxylate (**65**)⁶



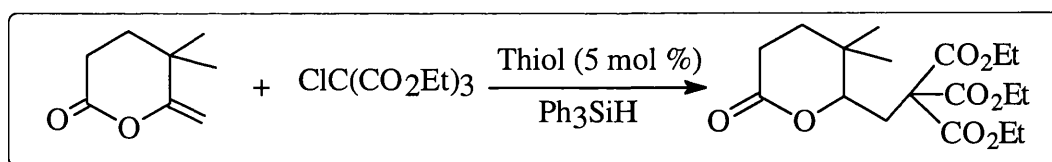
A mixture of triethyl methanetricarboxylate (12.0 g, 51.7 mmol) and sulfuryl chloride (7.0 cm³, 87.4 mmol) was heated under reflux in an oil bath at 80 °C 6 h. ^1H NMR analysis of the reaction mixture showed that the reaction was completed. Excess sulfuryl chloride was removed by distillation and the residue was distilled under reduced pressure to afford 13.8 g of product (84-86 °C / 0.02 Torr) as a colourless oil, which was redistilled to give pure product.

Bp. 97-99 °C / 0.01 Torr (lit.⁶ 145-147 °C / 0.015 Torr)

δ_{H} (CDCl₃): 1.35 (9H, t, 3 CH₃), 4.32 (6H, q, 3 CH₂).

δ_{C} : 13.75, 63.87, 69.43, 163.26 (C=O).

7. 5,5-dimethyl-6-[2,2,2-tri(ethoxycarbonyl)ethyl]tetrahydropyran-2-one (**70**)



[Method 1] A mixture of the methylenelactone **60** (0.35 g, 2.5 mmol), triethyl chloromethanetricarboxylate (0.87 g, 3.25 mmol), triphenylsilane (0.85 g, 3.25 mmol), TBHN (20 mg, 0.125 mmol) and triphenylsilanethiol (36 mg, 0.125 mmol) in benzene (4 cm³) was placed in a 2-necked flask which was equipped with a condenser and a side-arm. Under a slow stream of nitrogen, the reaction mixture was placed in a pre-heated oil bath

(60 °C). The mixture was stirred for 2 h and then allowed to cool room temperature. After the usual work-up, the residue was purified by flash-column chromatography [TLC; R_f 0.25, petroleum : diethyl ether = 1:1 eluent] to afford the product **70** as clear oil (0.53 g, 57 %).

Found: C, 58.20; H, 7.64, $C_{15}H_{24}O_6$. requires C, 58.05; H, 7.58 %.

δ_H ($CDCl_3$): 0.96 (3H, s, CMe^A), 1.06 (3H, s, CMe^B), 1.26 (6H, 2t, $2OCH_2CH_3$), 1.56-1.65 (1H, ddd, J 13.6, 7.2 and 5.6, $4-CH^A$), 1.68-1.75 (1H, m, $4-CH^B$), 2.15 (1H, dd, J 12.8 and 0.8, $OCHCH^A$), 2.24-2.30 (1H, dd, J 14.8 and 10, $OCHCH^B$), 2.46-2.57 (2H, m, $3-CH_2$), 4.26 (6H, q, J 7.2, OCH_2CH_3), 4.54-4.57 (1H, dd, J 10 and 1.6, 6-CH). The analysis was confirmed by 1H - 1H NMR decoupling experiments.

δ_C : 13.9, 19.7, 26.3, 27.3, 32.3, 34.3, 34.3, 62.3, 62.9, 82.4, 166.5, 170.3.

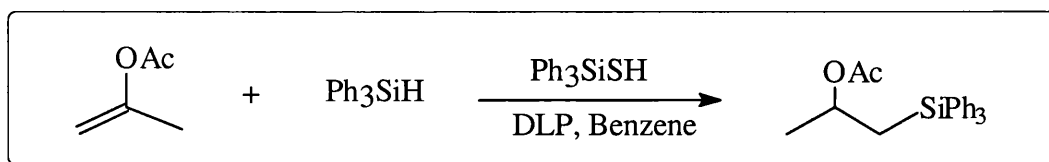
m/z (EI): 373 ($M^+ + 1$, 5), 372 (M^+ , 1), 327 ($M^+ - COOH$, 30), 29 (100)

IR (liq. film) : 1740.2, 1469.4, 1368, 1221, 1075

[Method 2] When the reaction of Method 1 was repeated with 2,3,4,6-tetra-*O*-acetyl-1-thio- β -D-glucopyranose (5 mol % based on the methylenelactone **60**) instead of triphenylsilanethiol in the presence of DLP under reflux for 2 h, 56 % yield was obtained and an ee of 46 % was determined by 1H NMR using the homochiral shift reagent $Eu(hfc)_3$.

[Method 3] When the reaction of Method 2 was repeated with 2,3,4,6-tetra-*O*-acetyl-1-thio- β -D-mannopyranose (5 mol %) in the presence of DLP under reflux for 2 h, a 54 % yield was obtained as an oil which solidified on standing at 5 °C. An ee of 72 % was determined by 1H NMR using the homochiral shift reagent $Eu(hfc)_3$; $[\alpha]_D^{26} = -24.7$ (c: 1.715, $CHCl_3$). The resulting solid was recrystallised from hexane to afford a colourless product which was analysed by 1H NMR using the homochiral shift reagent $Eu(hfc)_3$ to show an ee of 100 %. $[\alpha]_D^{22} = -31.4$ (c: 0.025, $CHCl_3$.) When this reaction was repeated under the same condition, 48 % of the product **70** was obtained and the ee of 71 % was determined by 1H NMR using the homochiral shift reagent $Eu(hfc)_3$.

8. Preparation of 2-acetoxy 3-triphenylsilylpropane (**74**)



A mixture of isopropenyl acetate (0.27 g, 2.73 mmol), triphenylsilane (0.85 g, 3.25 mmol), triphenylsilanethiol (37 mg, 0.125 mmol) and dry benzene (5 cm³) was placed in a 2-necked flask which was equipped with a condenser. A nitrogen gas bubbler was fitted over the condenser and nitrogen gas was briefly flushed out through side arm of the flask. The reaction mixture was placed in a pre-heated oil bath (85 °C) and DLP (0.01 g, 0.125 mmol) was added under the stream of nitrogen. The reaction mixture was stirred for 2 h, and then allowed to cool to room temperature. After removal of solvent using a rotatory evaporator, the residue was purified by flash-column chromatography [TLC; R_f 0.47, diethyl ether: petroleum = 1 : 4 eluent] to afford the product **74** as a white solid (0.96, 99.4 %).

M.p. 61-62 °C

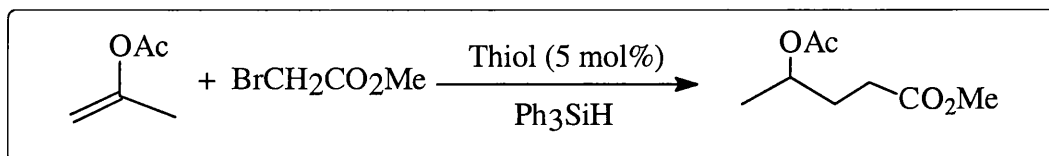
Found: C, 76.72; H, 6.67. C₂₃H₂₄O₂Si requires C, 76.62; H, 6.71 %.

δ_H (CDCl₃): 1.21 (3H, d, *J* 6, CH₃), 1.69 (3H, s, COCH₃), 1.72 (1H, dd, *J* 14.8 and 6, SiCH^A), 1.97 (1H, dd, *J* 14.8 and 8, SiCH^B), 5.18 (1H, m, CH-O), 7.36 (9H, m), 7.55 (6H, m).

δ_C: 20.9, 21.8, 23.4, 69.1, 127.8, 129.4, 134.5, 135.6, 170.2.

MS (EI) *m/z*: 259 (Ph₃Si, 44), 241 (M⁺ - Ph - COCH₃ + H, 100), 199 (37).

9. Preparation of methyl 4-acetoxypentanoate (**71**)



[Method 1] A solution in dry dioxane (4 cm³) containing isopropenyl acetate (0.250 g, 2.50 mmol), triphenylsilanethiol (0.846 g, 3.25 mmol), methyl bromoacetate (0.510 g, 2.56 mmol), TBHN (22 mg, 0.125 mmol) and triphenylsilanethiol (37 mg, 0.125 mmol) was stirred and heated at 60 °C under an atmosphere of dry argon for 2h. The solvent was removed by evaporation under reduced pressure, the residue was dissolved in diethyl ether (10 cm³) and the solution was washed with 5 % aqueous sodium hydrogen carbonate, then with saturated brine and the dried over MgSO₄. After evaporation of the ether, petroleum (5 cm³) was added and the slurry was filtered to remove most of the triphenylsilanol, which was washed on the sinter with a little petroleum. After evaporation of the solvent from the filtrate, the residue was purified by flash-chromatography (eluent: petroleum-diethyl ether 95:5 to 5:1) to give the adduct as a clear oil (0.31 g, 72 %).

Found: C, 55.40; H, 8.00. C₈H₁₄O₄ requires C, 55.16; H, 8.10 %.

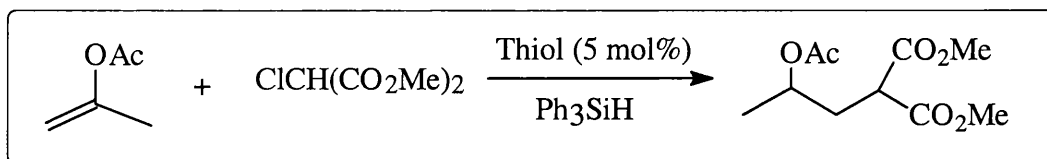
δ_H (CDCl₃): 1.20 (3H, dd, *J* 6.4 and 0.8, CH₃), 1.87 (2H, m, CH₂CH₂CO₂), 2.00 (3H, d, *J* 0.8, OAc), 2.33 (2H, m, CH₂CO₂), 3.66 (3H, s, CO₂Me), 4.90 (1H, m, OCH).

δ_C : 19.8, 21.2, 30.1, 30.8, 51.6, 69.9, 170.6, 173.4.

IR (cm⁻¹, liq. film): 1738, 1439, 1375, 1245, 1077.

[Method 2] When the reaction of Method 1 was repeated with methyl thioglycolate (MTG, 5 mol % based on isopropenyl acetate) instead of triphenylsilanethiol, a 75 % yield of the adduct **71** was obtained. Also, repetition of the reaction using triphenylsilanethiol (5 mol %) and DLP (10 mol %) as initiator in benzene at 80 °C for 2 h gave 76 % of adduct.

10. Preparation of dimethyl (2-acetoxypropyl)malonate (**72**)



[Method 1] A mixture of isopropenyl acetate (0.25 g, 2.50 mmol), dimethyl chloromalonate (0.53 g, 3.10 mmol), triphenylsilane (0.85 g, 3.25 mmol), TBHN (32 mg, 0.13 mmol), methyl thioglycolate (11.4 μl, 0.125 mmol) and dioxane (4 cm³) was placed

in a 2-necked flask which was equipped with a condenser. A nitrogen gas bubbler was fitted over the condenser and nitrogen gas was briefly flushed out through side arm of the flask. The reaction mixture was placed in a pre-heated oil bath (60 °C) and stirred under an atmosphere of argon for 2 h, and then allowed to cool to room temperature. The solvent was removed by evaporation under reduced pressure, the residue was dissolved in diethyl ether (10 cm³) and the solution was washed with 5 % aqueous sodium hydrogen carbonate, then with saturated brine and the dried (MgSO₄). After removal of solvent using rotatory evaporator, petroleum (5 cm³) was added to the residue and the slurry was filtered to remove most of the triphenylsilanol, which was washed on the sinter with a little petroleum. After evaporation of the solvent from the filtrate, the residue was purified by flash-chromatography (eluent: petroleum-diethyl ether 95:5 to 5:1) to give the adduct as a clear oil (0.45 g, 78 %).

Found: C, 51.84; H, 6.78. C₁₀H₁₆O₆ requires C, 51.72; H, 6.94 %

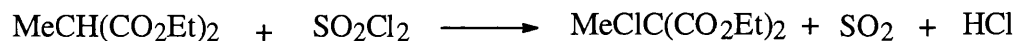
δ_{H} (CDCl₃): 1.26 (3H, dd, *J* 6.6, 1.2, CH₃), 2.01 (3H, d, *J* 1.2, COCH₃), 2.18 (2H, m, CH₂), 3.47 (1H, dd, *J* 8.4 and 6.0, CHCO₂), 3.75 (6H, 2S, 2CO₂Me), 4.90 (1H, m, OCH).

δ_{C} : 20.2, 21.3, 34.8, 48.5, 52.7, 52.8, 68.7, 169.3, 169.5, 170.5.

IR (cm⁻¹, liq.film): 1739.5, 1438.5, 1373.5, 1337.2, 1243.5, 1156.9, 1064.

[Method 2] When the reaction of Method 1 was repeated using triphenylsilanethiol (5 mol %) and TBHN (5 mol %) in dioxane at 60 °C, an 88 % yield of the carboxyalkylated product **72** was obtained. The same reaction in benzene gave a 87 % yield.

11. Preparation of diethyl 2-chloro-2-methylmalonate.⁶



A mixture of diethyl methylmalonate (8.70 g, 50 mmol) and sulfuryl chloride (6.0 cm³, 75 mmol) was heated under reflux in oil bath (100 °C) for 4. The reaction was shown to have gone to completion checked by taking ¹H NMR spectrum. Excess amount of sulfuryl chloride was removed by rotatory evaporation and the residue was distilled under reduced

pressure to give 10.0 g of product, which was redistilled to afford the pure product as a clear oil (8.8 g, 85 %).

Bp. 40-44 °C / 0.02 Torr

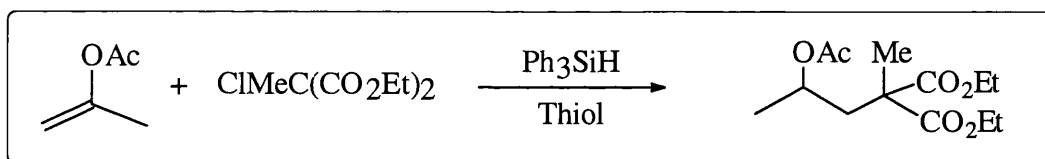
δ_{H} (CDCl₃): 1.28 (6H, t, CH₃), 1.90 (3H, s, CH₃), 4.28 (4H, q, 2OCH₂)

δ_{C} : 13.76, 25.54, 62.89, 167.24

IR (liq. film): 1741

MS (APCI) *m/z*: 209 (M⁺+1, 8), 173 (M⁺-Cl, 21), 159 (95, M⁺- Cl - CH₃), 145 (M⁺-Cl - CH₂CH₃, 100), 131 (79), 127 (56),

12. Preparation of diethyl (2-acetoxypropyl)methylmalonate (73)



[Method 1] A solution in dry dioxane (4 cm³) containing isopropenyl acetate (0.25 g, 2.50 mmol), triphenylsilane (0.85 g, 3.25 mmol), diethyl 2-bromo-2-methylmalonate (0.79 g, 3.13 mmol), TBHN (32 mg, 0.125 mmol) and triphenylsilanethiol (37 mg, 0.125 mmol) was stirred and heated at 60 °C under an atmosphere of dry nitrogen for 2h. The solvent was removed by evaporation under reduced pressure, the residue was dissolved in diethyl ether (10 cm³) and the solution was washed with 5 % aqueous sodium hydrogen carbonate, then with saturated brine and the dried (MgSO₄). After evaporation of the ether, petroleum (5 cm³) was added and the slurry was filtered to remove most of the triphenylsilanol, which was washed on the sinter with a little petroleum. After evaporation of the solvent from the filtrate, the residue was purified by flash-chromatography (eluent: petroleum-diethyl ether 95:5 to 5:1) to give the adduct as a clear oil (0.52 g, 78%).

Found: C, 57.21; H, 8.27. C₁₃H₂₂O₆ requires C, 56.92; H, 8.08 %.

δ_{H} (CDCl₃): 1.21-1.27 (9H, m, 2CO₂CH₂CH₃, 1-CH₃), 1.39 (3H, s, CH₃), 1.94 (3H, s, OAc), 2.09 (1H, dd, *J* 15.0 and 3.0, CH^A), 2.32 (1H, dd, *J* 10.4 and 15.0 CH^B), 4.17 (4H, m, 2OCH₂CH₃), 5.02 (1H, m, OCH)

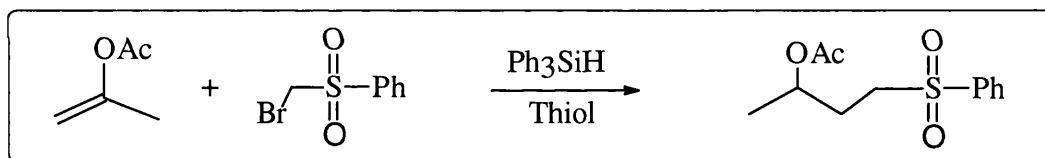
δ_{C} : 14.0, 19.5, 21.0, 21.1, 40.7, 52.0, 61.1, 61.5, 67.4, 170.3, 171.8, 172.2

MS (EI) m/z : 276 ($M^{+}+1$, 45), 275 (M^{+} , 2), 199 (100),

IR (cm^{-1} , liq. film): 1734.9, 1455, 1375.7, 1296.6, 1243, 1159, 1117, 1071, 1022

[Method 2] A mixture of isopropenyl acetate (0.25 g, 2.50 mmol), diethyl chloromethylmalonate (0.78 g, 3.70 mmol), DLP (80 mg, 0.13 mmol), triphenylsilanethiol (36.5 mg, 0.125 mmol) and triphenylsilane (0.85 g, 3.25 mmol) in dry benzene (5 cm^3) was placed in a 2-necked flask. Under the stream of nitrogen, the reaction mixture was placed in a pre-heated oil bath ($85 \text{ }^{\circ}\text{C}$) and stirred for 2 h. After the usual work up, the residue was purified by flash-column chromatography to afford the product as a clear oil (0.53, 76 %). When the reaction was repeated with TBHN (32 mg, 0.125 mmol) and methyl thioglycolate ($11.4 \mu\text{l}$, 0.125 mmol) as catalyst at $60 \text{ }^{\circ}\text{C}$ for 2 h, a 82 % (0.57 g) of the carboxyalkylated product was obtained.

13. Preparation of 3-acetoxybutyl phenyl sulfone (**90**).



[Method 1] A mixture of isopropenyl acetate (0.22 g, 2.15 mmol), bromomethyl phenyl sulfone (0.59 g, 2.50 mmol), DLP (80 mg, 0.20 mmol), triphenylsilanethiol (29 mg, 0.10 mmol) and triphenylsilane (0.85 g, 3.25 mmol) in dry benzene (5 cm^3) was placed in a 2-necked flask which was equipped with a condenser. The reaction mixture was placed in a pre-heated oil bath ($85 \text{ }^{\circ}\text{C}$), stirred and heated under an atmosphere of nitrogen for 2 h. After removal of solvent using rotary evaporator, the residue was purified by flash-column chromatography [TLC; R_f 0.18, petroleum : ethyl acetate = 4 : 1 eluent] to afford the product as a clear oil (0.19 g, 35 %) and methyl phenyl sulfone as a white solid (0.03g, 10 %).

Found: C, 56.18; H, 6.47; S 12.26. $\text{C}_{12}\text{H}_{16}\text{O}_4\text{S}$ requires C, 56.23; H, 6.29; S 12.51 %.

δ_{H} (CDCl_3): 1.21 (3H, dd, J 6.0 and 0.8, CH_3), 1.98 (2H, m, CH_2), 2.00 (3H, d, J 0.8, COCH_3), 3.13 (2H, m, CH_2SO_2), 4.92 (1H, m, $\underline{\text{CHOAc}}$), 7.59 (2H, t, J 8, meta H), 7.91 (1H, t, J 8, para H), 7.93 (2H, dd, J 8, ortho H).

δ_{C} : 19.9, 21.2, 28.8, 52.8, 68.8, 128.1, 129.4, 133.9, 138.9, 170.2.

m/z (EI): 256 (M^+ , 2), 255 (M^+-1 , 5), 213 ($-\text{COCH}_2$, 13), 115 ($\text{M}^+-\text{C}_6\text{H}_5\text{SO}_2$, 30), 77 (C_6H_5^+ , 27), 54 (80), 41 (100).

IR (cm^{-1} , liq. film): 1735.6 (C=O), 1447 (phenyl), 1374, 1307(SO_2), 1243, 1148(SO_2), 1087.5

Methyl phenyl sulfone (PhSO_2CH_3)

δ_{H} (CDCl_3): 3.10 (3H, m, CH_3), 7.59 (2H, t, J 8, meta H), 7.91 (1H, t, J 8, para H), 7.93 (2H, dd, J 8, ortho H)

δ_{C} : 44.4, 127.8, 129.3, 133.6, 140.5

MS (EI) m/z : 156 (M^+ , 35), 141 (M^+-CH_3 , 40), 77 (C_6H_5^+ , 100).

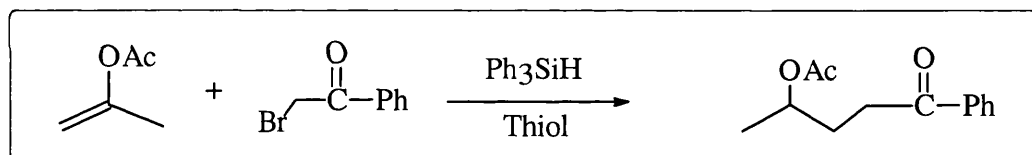
[Method 2] A mixture of isopropenyl acetate (0.21 g, 2.13 mmol), bromomethyl phenyl sulfone (0.59 g, 2.50 mmol), triphenylsilane (0.85 g, 3.25 mmol) and dry benzene (4 cm^3) was placed in a 2-necked flask which was equipped with a condenser. A nitrogen gas bubbler was fitted over the condenser and nitrogen gas was briefly flushed out through the side arm of the flask. After the reaction mixture was placed in a pre-heated oil bath (85 $^{\circ}\text{C}$), a mixture of methyl thioglycolate (9.2 μl , 0.13 mmol) and DLP (0.08 g, 0.10 mmol) in benzene (4 ml) was added during 2 h from a syringe attached to a motor-driven pump. After the addition was completed, the reaction mixture was stirred for an additional 1 h. After usual work up, purification by flash-column chromatography afforded the adduct as a clear oil (0.24 g, 45 %) and methyl phenyl sulfone as a white solid (0.04 g, 12 %).

[Method 3] A mixture of isopropenyl acetate (0.21 g, 2.13 mmol), bromomethyl phenyl sulfone (0.59 g, 2.50 mmol), tris(trimethylsilyl)silane (0.80 cm^3 , 3.25 mmol), methyl thioglycolate (9.2 μl , 0.13 mmol) and DLP (0.08 g, 0.10 mmol) in dry benzene (8.0 cm^3) was placed in a 2-neck flask which was equipped with condenser. A nitrogen gas bubbler was fitted over the condenser and nitrogen gas was briefly flushed out through the side

arm. The reaction mixture was placed in a pre-heated oil bath (85 °C) and stirred for 2 h. After usual work up and purification, the adduct was obtained as a clear oil (0.09 g, 12 %) and methyl phenyl sulfone as a white solid (0.28 g, 71 %).

[Method 4] The reaction of Method 1 was repeated with chloromethyl phenyl sulfone. Under an atmosphere of nitrogen, a mixture of isopropenyl acetate (0.27 g, 2.60 mmol), chloromethyl phenyl sulfone (0.59 g, 2.50 mmol), DLP (50 mg, 0.05 mmol), triphenylsilanethiol (29 mg, 0.10 mmol) and triphenylsilane (0.85 g, 3.25 mmol) in dry benzene (5 cm³) was placed in a pre-heated oil bath (85 °C) and stirred and heated for 2 h. After removal of solvent using rotatory evaporator, the residue was purified by flash-column chromatography to give only 2-acetoxy-3-triphenylsilyl propane **74** as a white solid (0.74g, 78 %).

14. Preparation of 3-acetoxy butyl phenyl ketone (**85**)



A mixture of isopropenyl acetate (0.251 g, 2.46 mmol), bromomethyl phenyl ketone (0.622 g, 3.25 mmol), DLP (100 mg, 0.25 mmol), methyl thioglycolate (11.4 μl, 0.125 mmol) and triphenylsilane (0.85 g, 3.25 mmol) in dry benzene (8 cm³) was placed in a 2-necked flask which was equipped with a condenser. The reaction mixture was placed in a pre-heated oil bath (85 °C) and stirred and heated under an atmosphere of nitrogen for 2 h. After the usual work up treatment with aqueous sodium bicarbonate, the crude product was purified by flash-column chromatography [TLC; R_f 0.18, eluent; petroleum : ethyl acetate = 4 : 1] to afford the adduct as a pale yellow oil (0.30 g, 54 %).

Found: C, 70.63; H, 7.32. C₁₃H₁₆O₃ requires C, 70.89; H, 7.32 %.

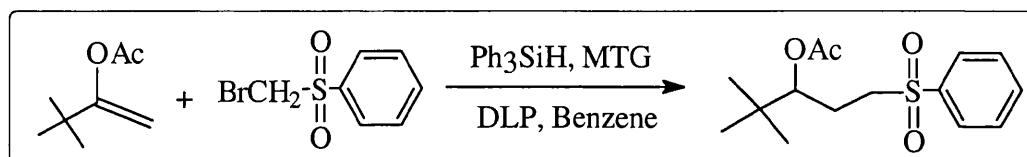
δ_H (CDCl₃): 1.28 (3H, dd, *J* 6.0 and 0.8, CH₃), 2.00 (3H, d, *J* 0.8, OAc), 2.01 (2H, m, CH₂CH₂C=O), 3.02 (2H, dd, *J* 14.0 and 7.2, CH₂CO), 5.00 (1H, m, OCH), 7.46 (2H, t, *J* 8.0, meta H), 7.56 (1H, t, *J* 8.0, para H), 7.95 (2H, dd, *J* 8.0, ortho H).

δ_c : 20.2, 21.4, 30.2, 34.5, 70.5, 128.0, 128.6, 133.1, 136.8, 170.8, 199.3

MS (EI) m/z : 177 (M^+ - $\text{CH}_3\text{C}=\text{O}$, 30), 160 (M^+ - $\text{CH}_3\text{CO}_2\text{H}$, 13.4), 120 (30.6), 105 ($\text{C}_6\text{H}_5^+\text{C}=\text{O}$, 100), 77 (C_6H_5^+ , 52.6), 43 ($\text{CH}_3\text{C}=\text{O}$, 43.4)

IR (cm^{-1} , liq.film): 1733.5, 1686.4, 1449, 1374, 1247

15. Preparation of 3-acetoxy-4,4-dimethylpentyl phenyl sulfone (**92**)



A mixture of 3,3-dimethyl-2-acetoxybut-1-ene (0.362 g, 2.57 mmol), bromomethyl phenyl sulfone (0.767 g, 3.25 mmol), DLP (100 mg, 0.25 mmol), methyl thioglycolate (11.4 μl , 0.125 mmol) and triphenylsilane (0.85 g, 3.25 mmol) in dry benzene (8 cm^3) was placed in a 2-neck flask. The reaction mixture was placed in a pre-heated oil bath (85 $^\circ\text{C}$) and stirred and heated under an atmosphere of nitrogen for 2 h. After the usual work up, the crude product was purified by flash-column chromatography [TLC; R_f 0.19, eluent; petroleum : diethyl ether = 2 : 1] to afford the adduct as a pale yellow oil (0.37 g, 48 %), along with methyl phenyl sulfone as a white solid (0.12 g, 29 %)

Found: C, 60.10; H, 7.54; S, 10.74. $\text{C}_{15}\text{H}_{22}\text{O}_4\text{S}$ requires C, 60.38; H, 7.43; S, 10.46 %.

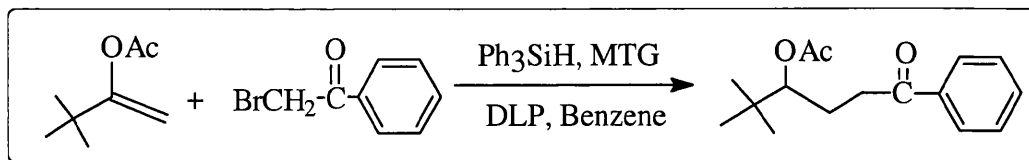
δ_H (CDCl_3): 0.87 (9H, d, J 0.8, 3CH_3), 2.03 (3H, d, J 0.8, OAc), 2.01 (2H, m, CH_2), 3.02 (2H, m, SO_2CH_2), 4.66 (1H, dd, J 8.4 and 1.6, OCH), 7.58 (2H, t, J 1.2, meta H), 7.56 (1H, t, J 1.2, para H), 7.95 (2H, dd, J 1.2, ortho H)

δ_c : 20.9, 22.8, 25.8, 34.8, 53.9, 79.0, 128, 129.4, 133.9, 139.1, 171.1

MS (EI) m/z : 299 (M^+ + 1, 0.8), 255 (M^+ - $\text{CH}_3\text{C}=\text{O}$, 2), 157 (M^+ - $\text{C}_6\text{H}_5\text{SO}_4^+$, 2.5), 199 (28.5), 143 (34.4), 97 (30.7), 77 (C_6H_5^+ , 24.6), 43 ($\text{CH}_3\text{C}=\text{O}$, 100)

IR (cm^{-1} , liq.film): 1732.6 (C=O), 1476 (C_6H_5), 1445 (C_6H_5), 1372 (SO_2), 1241 (C-O), 1148 (SO_2), 1082, 1022.

16. Preparation of 3-acetoxy-4,4-dimethylpentyl phenyl ketone (**87**)



A mixture of 3,3-dimethyl-2-acetoxybut-1-ene (0.363 g, 2.55 mmol), 2-bromoacetophenone (0.694 g, 3.25 mmol), DLP (100 mg, 0.25 mmol), methyl thioglycolate (11.4 μ l, 0.125 mmol) and triphenylsilane (0.85 g, 3.25 mmol) in dry benzene (8 cm³) was placed in a 2-neck flask. The reaction mixture was placed in a pre-heated oil bath (85 °C), and stirred and heated under an atmosphere of nitrogen for 2 h. After the usual work up, the crude product was purified by flash-column chromatography [TLC; R_f 0.33, eluent; petroleum : diethyl ether = 5 : 1] to afford the adduct as a pale colourless oil (0.23 g, 34 %) which solidified on standing. The reduction product, acetophenone, was detected by ¹H NMR spectroscopic analysis of the reaction mixture but was not isolated.

M.p. 53-54 °C

Found: C, 73.35; H, 8.52. C₁₆H₂₂O₃ requires C, 73.25; H, 8.45 %.

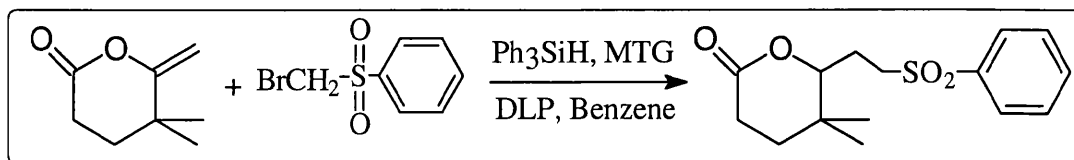
δ_{H} (CDCl₃): 0.93 (9H, s, 3 CH₃), 1.89 (1H, m, [^]CH₂C=O), 2.07 (3H, s, OAc), 2.09 (1H, m, [^]CH₂C=O), 2.95 (2H, m, CH₂), 4.81 (1H, dd, *J* 11.2 and 1.6, O-CH), 7.45 (2H, t, *J* 8, meta H), 7.56 (1H, t, *J* 1.2, para H), 7.95 (2H, dd, *J* 7.6, 1.2, ortho H)

δ_{C} : 21.1, 24.2, 25.9, 34.8, 35.6, 80.5, 128.0, 128.1, 133.1, 136.9, 171.3, 199.6.

MS (EI) *m/z*: 219 ((M⁺ - COCH₃), 8), 105 (C₆H₅CO⁺, 100), 77 (C₆H₅⁺, 56).

IR (KBr): 1729.8, 1676.7, 1439.1, 1368.5, 1249.1, 1047.6, 1023.

17. Preparation of 6-(2-phenylsulfonyl)ethyl-5,5-dimethyl tetrahydropyran-2-one (**94**)



A mixture of the methylenelactone **60** (0.354 g, 2.52 mmol), bromomethyl phenyl sulfone (0.77 g, 3.25 mmol), DLP (100 mg, 0.25 mmol), methyl thioglycolate (11.4 μ l, 0.125

mmol) and triphenylsilane (0.85 g, 3.25 mmol) in dry benzene (8.0 cm³) was placed in a 2-necked flask. The reaction mixture was placed in a pre-heated oil bath (85 °C) and stirred and heated under an atmosphere of nitrogen for 2 h. After the usual work up, the crude product was purified by flash-column chromatography [TLC; *R_f* 0.33, eluent; petroleum : diethyl ether = 5 : 1] to afford the adduct as a colourless oil which later solidified on standing (0.43 g, 58 %).

M.p. 127-128 °C

Found C, 60.78; H, 6.72; S, 10.50 C₁₅H₂₀O₄S requires C, 60.79; H, 6.80; S, 10.82

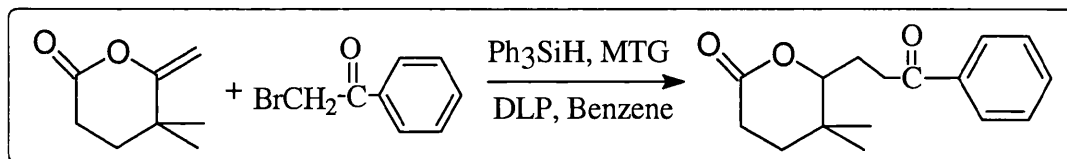
δ_{H} : 0.93 (3 H, s, Me^A), 1.01 (3 H, s, Me^B), 1.61 (1 H, m, 4-CH^A), 1.70 (1 H, m, 4-CH^B), 1.91 (1 H, m, OCHCH^A), 2.15 (1 H, m, OCHCH^B), 2.51 (2H, 3-CH₂), 3.14 (1 H, ddd, J 14.0, 9.8 and 5.6, CH^ASO₂), 3.41 (1 H, ddd, J 14.0, 9.8 and 5.2, CH^BSO₂), 4.07 (1 H, dd, J 11.2 and 2.0, 6-H), 7.58 (2 H, m, Ph), 7.67 (1 H, m, Ph), 7.91 (2 H, m, Ph). The analysis was confirmed by ¹H-¹H NMR decoupling experiments.

δ_{C} : 19.0, 23.2, 26.3, 27.3, 32.0, 34.3, 52.9, 85.3, 127.9, 129.4, 133.9, 139.1, 170.8.

MS (EI) *m/z*: 296 (M⁺, 3), 240 (37), 199 (31), 143 (67), 125 (22), 98 (62), 77 (C₆H₅⁺, 52), 70 (C₆H₅⁺, 100), 56 (76).

IR (KBr): 1736 (C=O), 1584 (Ph), 1470 (Ph), 1446 (Ph), 1306 (SO₂), 1148 (C-O), 1086 (SO₂), 1047 (C-O).

18. Preparation of -6-(benzoyl-ethyl)-5,5-dimethyl-tetrahydropyran-2-one (89)



A mixture of methylenelactone (0.36 g, 2.55 mmol), bromomethyl phenyl ketone (0.69 g, 3.25 mmol), DLP (0.10 g, 0.25 mmol), methyl thioglycolate (11.4 μ l, 0.125 mmol) and triphenylsilane (0.85 g, 3.25 mmol) in dry benzene (8 cm³) was placed in a 2-necked flask. The reaction mixture was placed in a pre-heated oil bath (85 °C) and stirred and heated under an atmosphere for 2 h. After the usual work up, the crude product was

purified by flash-column chromatography [TLC; R_f 0.5, eluent; petroleum : diethyl ether : dichloromethane = 2 : 1 : 2] to afford the adduct as a colourless oil (0.14 g, 21 %).

Found: C, 73.61; H, 7.89. $C_{16}H_{20}O_3$ requires C, 73.82; H, 7.74 %.

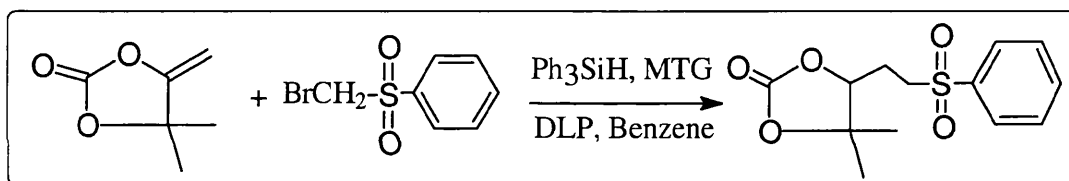
δ_H ($CDCl_3$): 0.97 (3H, s, CMe^A), 1.06 (3H, s, CMe^B), 1.58-1.64 (1H, ddd, J 6.8, 5.6 and 1.6, H_7), 1.66-1.83 (2H, m, H_3 and H_4), 2.14 (1H, ddq, J 1.6, 8.8 and 10.4, H_6), 2.52 (2H, m, $CH_2C=O$), 3.13 (1H, dt, J 7.6), 3.29 (1H, 2dd, J 7.6 and 4.8), 4.04 (1H, dd, J 1.6 and 11.2, H_5), 7.42 (2H, m, meta H), 7.53 (1H, m, para H), 7.94 (2H, m, ortho H)

δ_C : 19.4, 24.2, 26.5, 27.4, 32.1, 34.5, 34.6, 86.9, 128.0, 128.6, 133.2, 136.8, 171.7, 199.6.

MS (EI) m/z : 260 (M^+ , 32), 141 (34), 120 (93), 105 ($C_6H_5^+C=O$, 100), 84 (51), 77 ($C_6H_5^+$, 85).

IR (cm^{-1} , liq. film): 1732 (C=O), 1682 (Ph), 1598 (Ph), 1050 (C-O).

19. Preparation of 4,4-dimethyl-5-(2-phenylsulphonyl-ethyl)-1,3-dioxolan-2-one(93)



A mixture of 4,4-dimethyl-1,3-dioxolan-2-one (0.32 g, 2.51 mmol), bromomethyl-phenyl sulfone (0.77 g, 3.25 mmol), DLP (0.10 g, 0.25 mmol), methyl thioglycolate (11.4 μ l, 0.125 mmol) and triphenylsilane (0.85 g, 3.25 mmol) in dry benzene (8 cm^3) was placed in a 2-necked flask. The reaction mixture was placed in a pre-heated oil bath (85 $^{\circ}C$) and stirred and heated under an atmosphere of nitrogen for 2 h. After the usual work up, the crude product was purified by flash-column chromatography [TLC; R_f 0.19, eluent; petroleum : diethyl ether = 2 : 1] to afford the adduct as a pale yellow oil (0.34 g, 48 %), and along with methyl phenyl sulfone as a white solid (0.09 g, 18 %)

Found: C, 55.18; H, 5.64; S, 11.25. $C_{13}H_{16}O_5S$ requires C, 54.92; H, 5.67, S, 11.28 %.

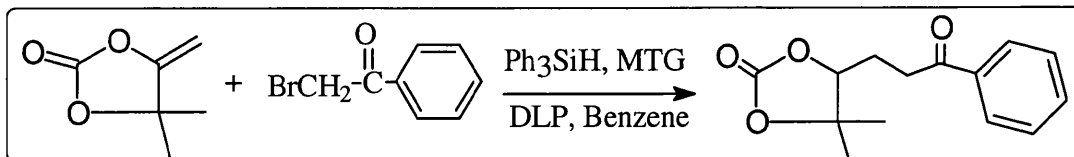
δ_H ($CDCl_3$): 1.32 (3H, s, CMe^A), 1.44 (3H, s, CMe^B), 1.99-2.07 (2H, m, SO_2CH_2), 3.11-3.20 (1H, m, ACH_2), 3.22-3.31 (1H, m, BCH_2), 4.35 (1H, dd, J 2.8 and 10.8, O-CH), 7.53-7.87 (5H, m, C_6H_5).

δ_C : 21.2, 23.0, 26.2, 52.6, 82.9, 84.0, 127.9, 129.6, 134.3, 138.7, 153.3.

MS (EI) m/z : 285 ($M^+ + 1$, 3 %), 141 ($M^+ - \text{PhSO}_4 + 2\text{H}^+$, 44 %), 98 ($M^+ - \text{PhSO}_4 - \text{CO}_2$, 100 %), 77 (C_6H_5^+ , 100 %).

IR (cm^{-1} , liq. film): 1790 (C=O), 1447.6 (Ph), 1308, 1279, 1147.4.

20. Preparation of 4,4-dimethyl-5-(2-benzoyl-ethyl)-1,3-dioxolan-2-one (**88**)



A mixture of 4,4-dimethyl-1,3-dioxolan-2-one (0.32 g, 2.51 mmol), bromomethyl phenyl ketone (0.69 g, 3.25 mmol), DLP (0.10 g, 0.25 mmol), methyl thioglycolate (11.4 μl , 0.125 mmol) and triphenylsilane (0.85 g, 3.25 mmol) in dry benzene (8 cm^3) was placed in a 2-necked flask. The reaction mixture was placed in a pre-heated oil bath (85 $^\circ\text{C}$) and stirred and heated under an atmosphere of nitrogen for 2 h. After the usual work up, the crude product was purified by flash-column chromatography [TLC; R_f 0.15, eluent; petroleum : diethyl ether = 2 : 1] to afford the adduct as a pale yellow oil (0.14 g, 22 %) which solidified on standing.

M.p. 99-100 $^\circ\text{C}$.

Found: C, 67.91; H, 6.51. $\text{C}_{14}\text{H}_{16}\text{O}_4$ requires C, 67.73; H, 6.50 %.

δ_{H} (CDCl_3): 1.44 (3H, s, CMe^{A}), 1.55 (3H, s, CMe^{B}), 1.92-2.02 (1H, m, $^{\text{A}}\text{CH}_2$), 2.11-2.19 (1H, dddd, J 2.4, 5.2 and 7.6, $^{\text{B}}\text{CH}_2$), 3.15-3.31 (2H, m, $\text{CH}_2\text{C}=\text{O}$), 4.39 (1H, dd, J 2.4 and 11.2, O-CH), 7.47-7.98 (5H, m, C_6H_5).

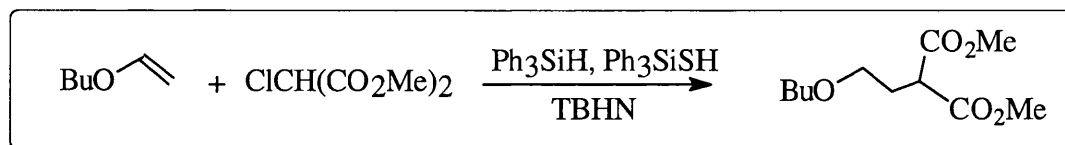
δ_{C} : 21.3, 23.6, 26.1, 34.3, 84.2, 84.5, 128.0, 128.8, 133.6, 136.4, 154.0, 198.4.

MS (EI) m/z : 204 ($M^+ - \text{CO}_2$, 3), 120 (54), 105 ($\text{C}_6\text{H}_5\text{CO}^+$, 100), 77 (C_6H_5^+ , 56).

IR (cm^{-1} , liq. film): 1783 (C=O), 1685 (Ph), 1355, 1280, 1097 (measured before solidification)

The following compounds were prepared by thiol-catalysed reductive carboxyalkylation of alkenes, using the same general procedure of dimethyl (2-acetoxypropyl)malonate (**72**).

21. Dimethyl (2-butoxymethyl)malonate (76)



Clear oil, yield 78 %

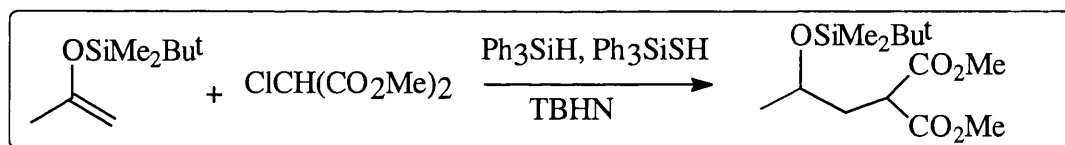
Found: C, 56.72; H, 8.79. C₁₁H₂₀O₅ requires C, 56.88; H, 8.68 %.

δ_{H} : 0.89 (3 H, t, *J* 7.3, Me), 1.43 (2 H, m, CH₂), 1.50 (2 H, m, CH₂), 2.16 (2 H, m, CH₂), 3.36 (2 H, t, *J* 6.5, CH₂), 3.43 (2 H, t, *J* 6.0, CH₂), 3.56 (1 H, t, *J* 7.3, CH), 3.72 (6 H, s, 2 OMe).

δ_{C} : 13.9, 19.2, 29.0, 31.7, 48.8, 52.5, 53.9, 67.7, 70.7, 169.8.

IR (cm⁻¹, liq. film): 1736, 1437, 1160.

22. Dimethyl [(2-*tert*-butyldimethylsiloxy)propyl]malonate (78)



Clear oil, yield 85 %

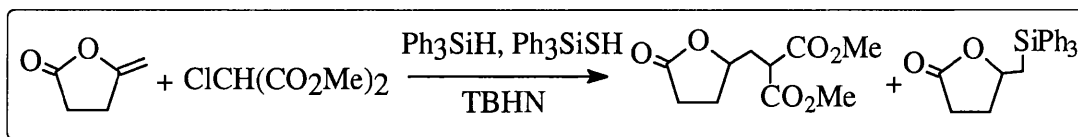
Found: C, 55.4; H, 9.4. C₁₃H₂₂O₆ requires C, 55.23; H, 9.27 %.

δ_{H} : 0.01 (3 H, s, SiMe), 0.04 (3 H, s, SiMe), 0.87 (9 H, s, Bu^t), 1.15 (3 H, d, *J* 6.1, Me), 1.93 (1 H, ddd, *J* 13.8, 8.9 and 4.8, CH₂^A), 2.07 (1 H, ddd, *J* 13.8, 9.6 and 3.7, CH₂^B), 3.62 (1 H, dd, *J* 9.6 and 4.8, CH), 3.73 (3 H, s, OMe), 3.74 (3 H, s, OMe), 3.83 (1 H, m, OCH).

δ_{C} : -5.1, -4.3, 19.0, 23.9, 25.8, 38.3, 48.2, 52.4, 52.6, 66.0, 170.0, 170.3.

IR (cm⁻¹, liq. film): 1739, 1438, 1342, 1253, 1152.

23. 5-[2,2-di(methoxycarbonyl)ethyl]tetrahydrofuran-2-one (**81**)



Clear oil, yield 76 %

Found: C, 52.24; H, 6.22. C₁₃H₂₂O₆ requires C, 52.17; H, 6.13 %.

δ_{H} : 1.90 (1 H, m), 2.15 (1 H, ddd, *J* 15.1, 9.7 and 5.3), 2.23 (2 H, m), 2.53 (2H, m, CH₂-ring), 3.66 (1 H, dd, *J* 9.4 and 5.3, CH), 3.73 (3 H, s, OMe), 3.75 (3 H, s, OMe), 4.52 (1 H, m, OCH).

δ_{C} : 27.9, 28.4, 34.7, 48.2, 52.8, 77.8, 169.1, 173.3.

IR (cm⁻¹, liq. film): 1735, 1740, 1438, 1180.

5-(Triphenylsilylmethyl)tetrahydrofuran-2-one

M.p. 96-98 °C, yield 11 %

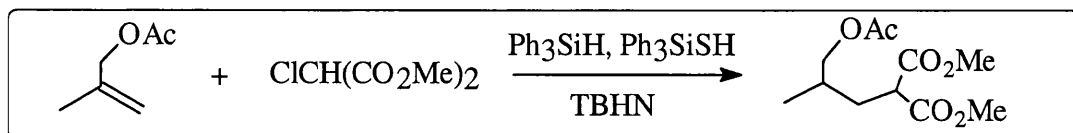
Found: C, 76.51; H, 6.57. C₁₃H₂₂O₆ requires C, 76.26; H, 6.40 %.

δ_{H} : 1.65 (1 H, m, CH₂^A-ring), 1.80 (1 H, dd, *J* 14.4 and 9.5, CH^ASi), 1.97 (1 H, m, CH₂^B-ring), 2.23 (1 H, dd, *J* 14.4 and 5.0, CH^BSi), 2.40 (2 H, m, CH₂), 4.72 (1 H, m, OCH), 7.3-7.6 (15 H, m).

δ_{C} : 21.5, 29.5, 30.8, 79.5, 128.1, 129.9, 133.7, 135.6, 176.8.,

IR (cm⁻¹, Nujol mull): 1736, 1460, 1377, 1167.

24. Dimethyl [2-(acetoxymethyl)propyl]malonate (**77**)



Clear oil, yield 63 %.

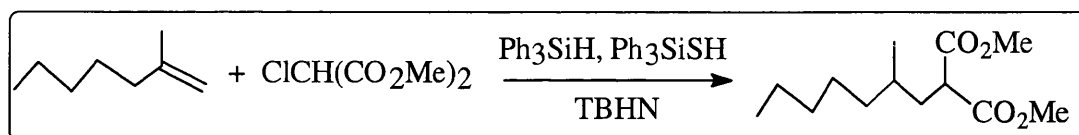
Found: C, 53.72; H, 7.39. C₁₁H₁₈O₆ requires C, 53.65; H, 7.39 %

δ_{H} : 0.95 (3 H, d J 6.4, Me), 1.79 (2 H, m, CH₂), 2.04 (1 H, m, CH), 2.05 (3 H, s, Ac), 3.50 (1 H, dd, J 8.4 and 6.8, CH), 3.73 (6H, s, OMe), 3.91 (2 H, ddd, J 13.7, 11.0 and 5.5, OCH₂).

δ_{C} : 16.5, 20.8, 30.6, 32.6, 49.4, 52.6, 68.6, 169.6, 169.8, 171.0.

IR (cm⁻¹, liq. film): 1738, 1439, 1369, 1242, 1157..

25. Dimethyl (2-methylheptyl)malonate (75)



Clear oil, yield 60 %.

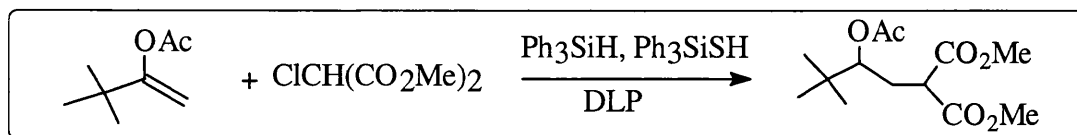
Found: C, 64.75; H, 10.03. C₁₃H₂₄O₄ requires C, 64.91; H, 9.90 %.

δ_{H} : 0.87 (3 H, t, J 7.0, Me), 0.88 (3 H, d, J 6.5), 1.0-1.5 (9 H, 4 CH₂ and CH), 1.67 (1 H, ddd, J 14.5, 7.9 and 6.6, H^A-3), 1.96 (1 H, ddd, J 14.5, 8.6 and 5.5, H^B-3), 3.47 (1 H, dd, J 8.6 and 6.6, CH), 3.73 (3 H, s, OMe), 3.73 (3 H, s, OMe).

δ_{C} : 14.1, 19.2, 22.6, 26.3, 30.8, 32.0, 35.9, 36.6, 49.8, 52.41 and 52.46 (OMe), 170.1, 170.2.

IR (cm⁻¹, liq. film): 1739, 1437, 1331, 1247, 1200, 1154.

26. Dimethyl (2-acetoxy-3,3-dimethylbutyl)malonate (79)



Clear oil, yield 72 %

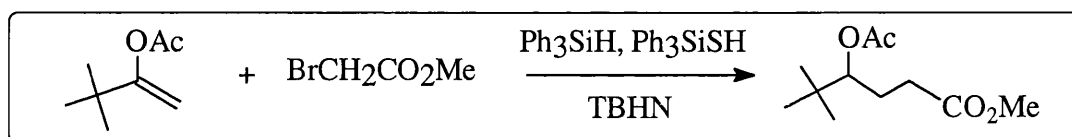
Found: C, 56.87; H, 8.00. C₁₃H₂₂O₆ requires C, 56.92; H, 8.08 %.

δ_{H} : 0.90 (9 H, s, Bu^l), 1.98 (1 H, ddd, J 14.4, 11.1 and 4.8, CH₂^A), 2.05, 3 H, s, Ac), 2.28 (1 H, ddd, J 14.4, 9.9 and 2.0, CH₂^B), 3.72 (3 H, s, OMe), 3.74 (3 H, s, OMe), 4.73 (1 H, dd, J 11.1 and 2.0, CH).

δ_{C} : 20.8, 25.7, 29.2, 34.7, 48.7, 52.7, 78.2, 169.8, 171.0.

IR (cm⁻¹, liq. film): 1738, 1437, 1372, 1243, 1155.

27 Methyl 4-acetoxy-5,5-dimethylhexanoate (**80**)



Clear oil, yield 75 %

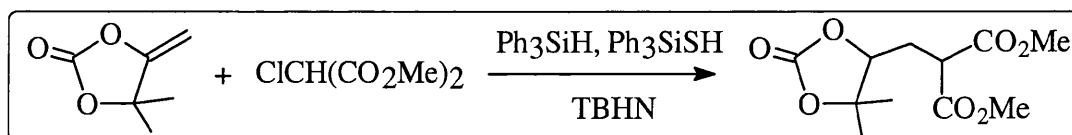
Found: C, 61.14; H, 9.21. $\text{C}_{11}\text{H}_{20}\text{O}_4$ requires C, 61.09; H, 9.32 %.

δ_{H} : 0.91 (9 H, s, Bu^l), 1.75 (1 H, m, CH₂^A), 1.95 (1 H, m, CH₂^B), 2.06 (3 H, s, Ac), 2.28 (2 H, t, J 7.9, CH₂), 3.68 (3 H, s, OMe), 4.72 (1 H, dd, J 11.0 and 2.2, CH).

δ_{C} : 20.9, 24.9, 25.9, 31.0, 34.6 (t-C), 51.6, 79.9, 171.1, 173.7.

IR (cm⁻¹, liq. film): 1739, 1435, 1371, 1242, 1167.

28. 5-[(2,2-dimethoxycarbonyl)ethyl]-4,4-dimethyl-1,3-dioxolan-2-one (**82**)



Clear oil, yield 40 %

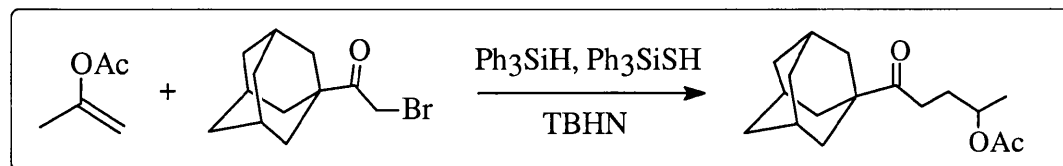
Found: C, 50.92; H, 6.31. $\text{C}_{11}\text{H}_{16}\text{O}_7$ requires C, 50.77; H, 6.20 %.

δ_{H} : 1.40 (3 H, s, Me), 1.50 (3 H, s, Me), 2.17 (2 H, M CH₂), 3.64 (1 H, dd, J 9.5 and 4.9, CH), 3.76 (3 H, s, OMe), 3.77 (3 H, s, OMe), 4.30 (1 H, dd, J 10.5 and 3.0, OCH).

δ_{C} : 21.1, 26.0, 28.7, 52.9, 53.0, 82.3, 83.8, 153.3, 168.7, 168.8.

IR (cm⁻¹, liq. film): 1789, 1737, 1439, 1346, 1277.

29. 3-(Acetoxy)butyl 1-adamantyl ketone



Viscous oil, yield 58 %

Found: C, 73.59 ; H, 9.32. $\text{C}_{17}\text{H}_{26}\text{O}_3$ requires C, 73.35 ; H, 9.41 %.

δ_{H} : 1.21 (3 H, d, J 6.3, Me), 1.69-1.90 (17 H, complex Ad and CH_2), 2.02 (3 H, s, Ac),
2.47 (2 H, m, OCCH_2), 4.87 (1 H, m, CHOAc).

δ_{C} : 20.1, 21.4, 27.9, 29.7, 31.9, 36.5, 38.3, 46.3, 70.5, 170.7, 214.6.

IR (cm^{-1} , liq. film): 1736, 1694, 1451, 1373, 1244.

References to Chapter 12

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