Novel Routes to Benzofurans using Titanium-Alkylidene Chemistry

A Thesis submitted in part fulfilment of the requirements of the degree of Doctor of Philosophy

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Dedicated to my family

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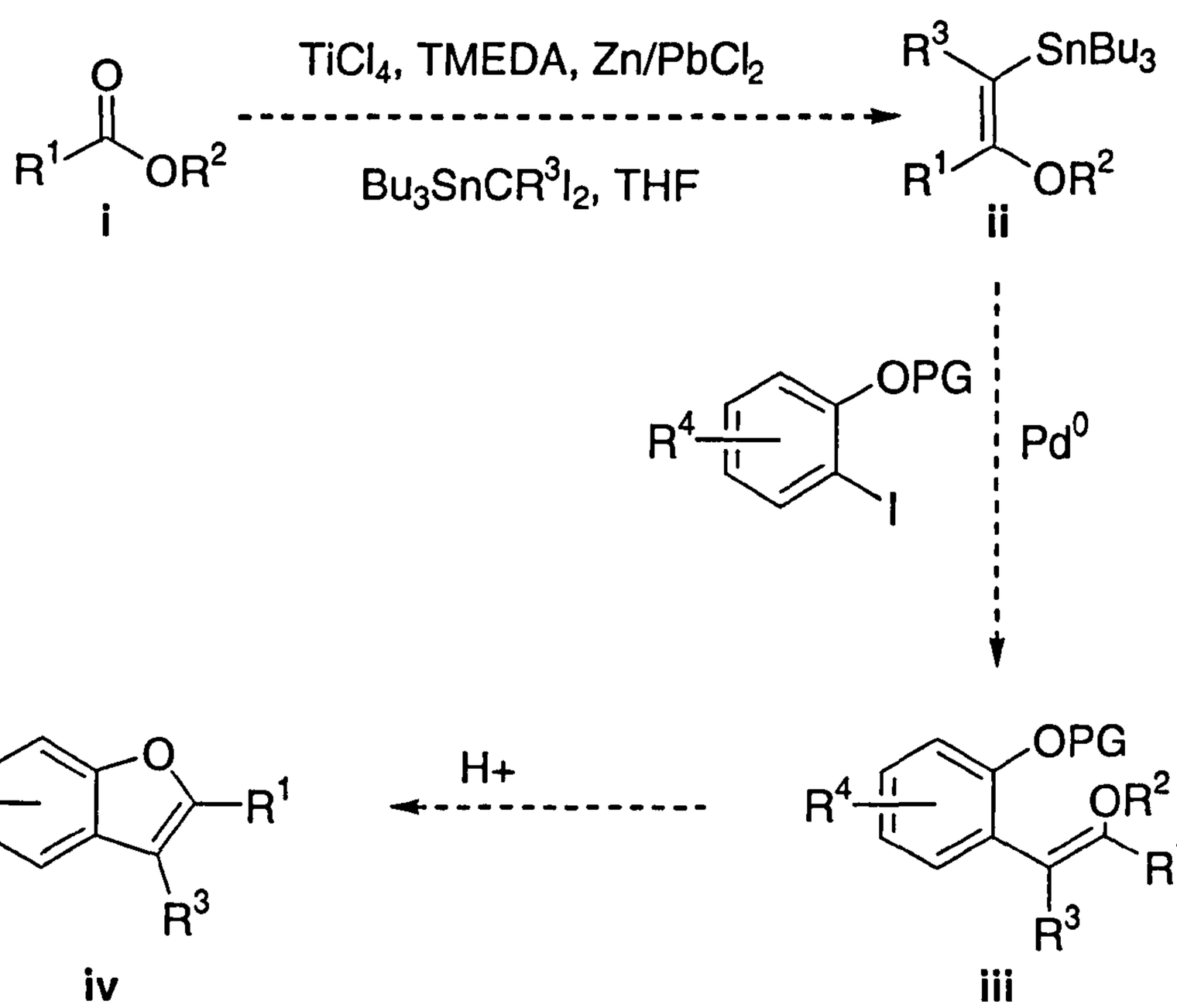
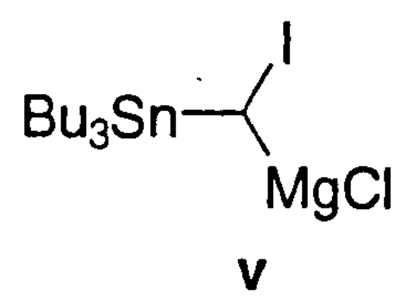
Summary

We have investigated two routes to functionalised benzofurans using titanium alkylidene chemistry.

The first route looked at the alkylidenation of esters **i** to give β-alkoxyvinylstannanes **ii**. A cross-coupling reaction would have given enol ether products **iii**, followed by an acid-induced cyclisation to give the desired benzofurans **iv**.

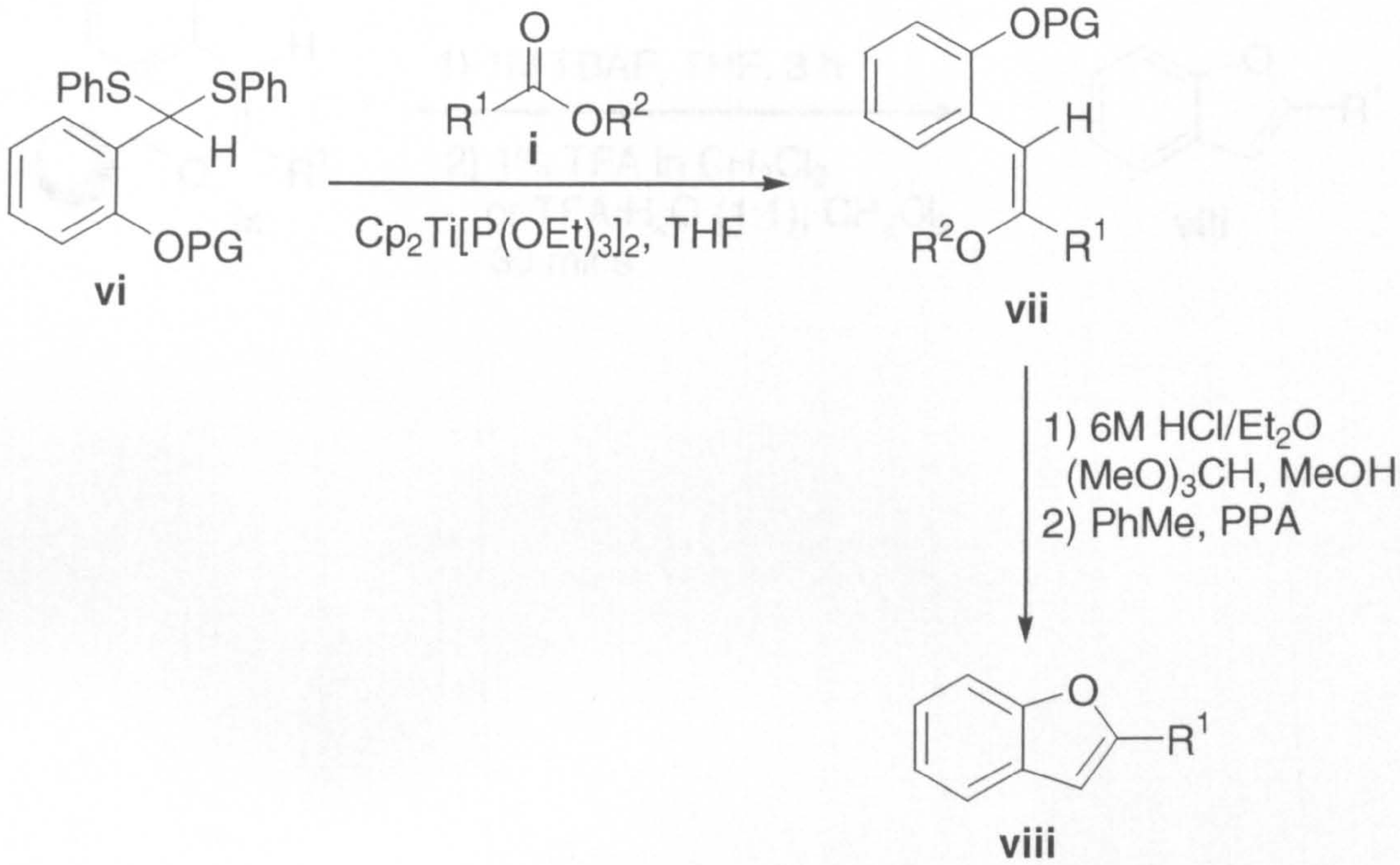


This approach was not successful, but during the course of investigating the route, we formed the novel dimetallic reagent **v**, the properties of which we examined.

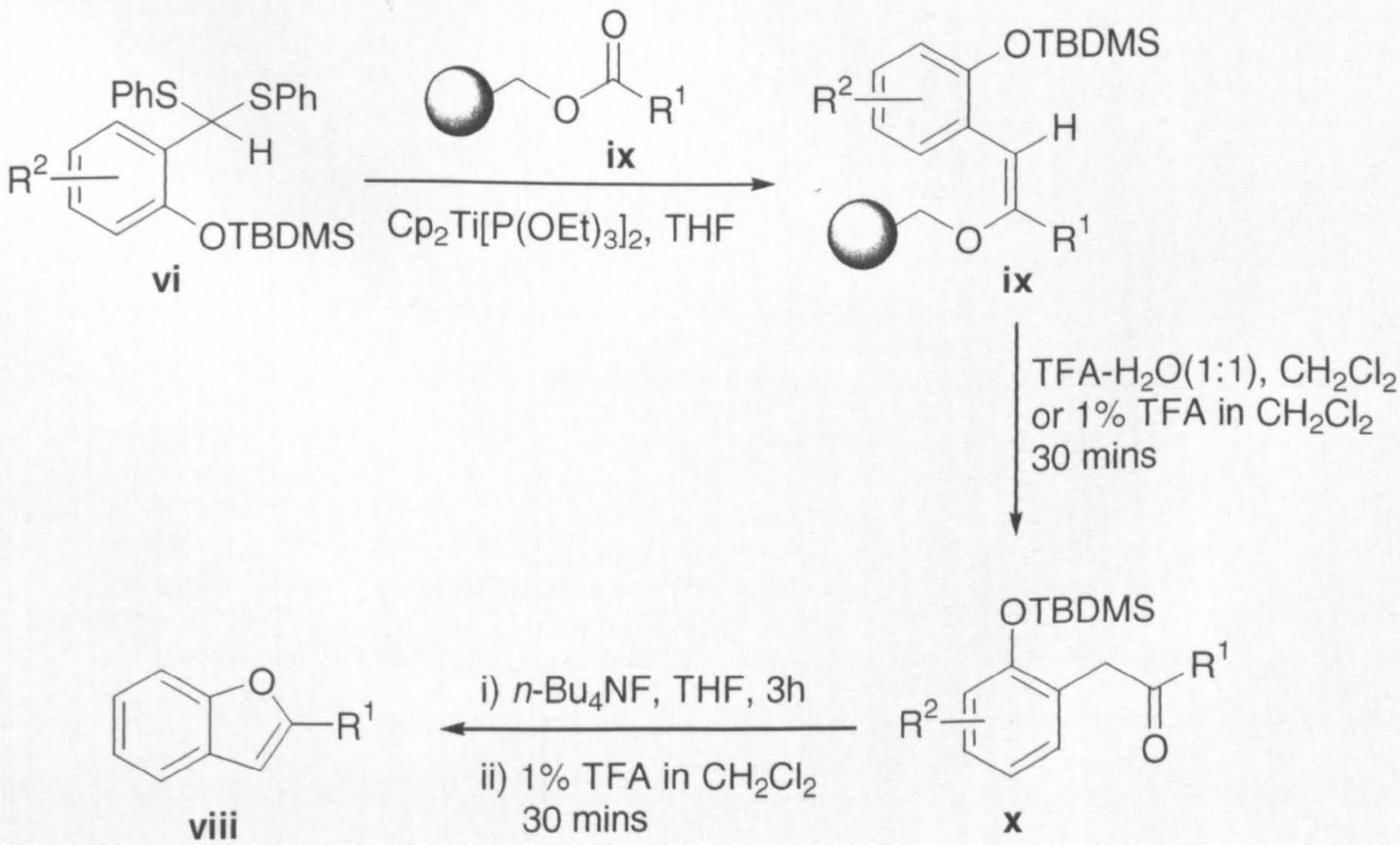


v

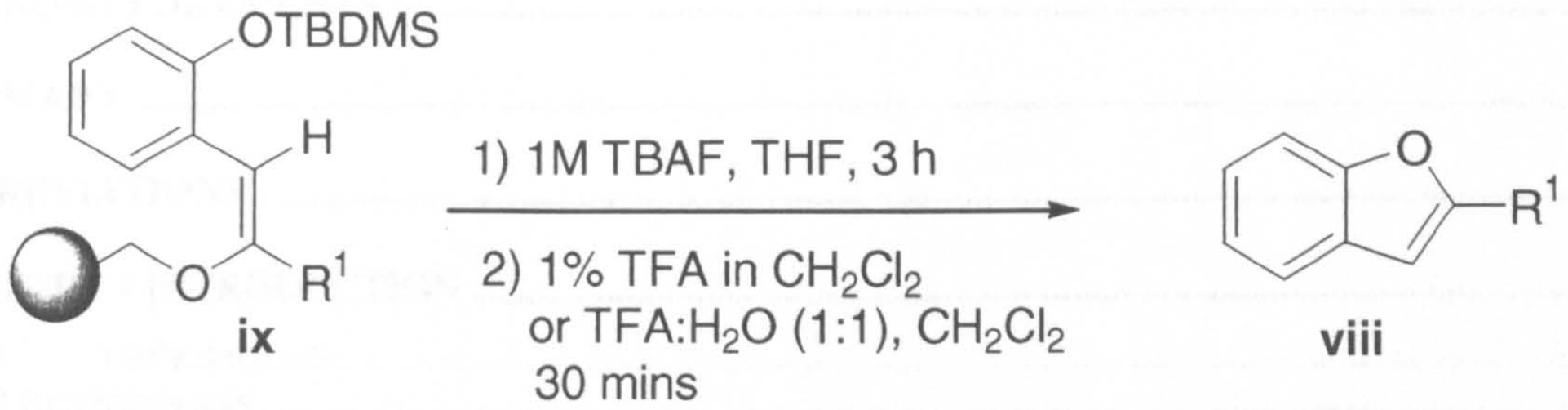
We looked at a second route that involved the use of thioacetals **vi**. Alkylidenation of esters **i** were carried out followed in one case by cyclisation of the enol ethers **vii** formed, giving benzofuran **viii** (R^1 = Ph).



We also successfully carried out the second route on solid phase, where Wang and Merrifield resin-bound esters **ix** were alkylidenated. This was the first reported incidence of Takeda-style alkylidenations on solid phase. Cleavage of the resin-bound enol ethers was achieved using mild acidic conditions. This gave ketone products **x**. In one case ketone **x** was converted into benzofuran **viii** (R^1 = CH_2CH_2Ph) by deprotection followed by acid treatment.



Finally, we carried out an alternative direct cleavage to a range of benzofurans **viii**, by deprotecting the resin-bound enol ether **ix** and then cleaving with mild acid as before.



Contents

Abbreviations

Å	angstrom	HWE	Horner/Wadsworth/Emmons
Ac	acetyl	LDA	lithium diisoproylamine
aq.	aqueous	m	multiplet (NMR spectroscopy)
b.p.	boiling point	M	molarity
brd	broad doublet (NMR spectroscopy)	MHz	megaHertz
bs	broad singlet (NMR spectroscopy)	MOM	methoxymethyl
°C	degrees centigrade	min(s)	minute(s)
Cp	cyclopentadienyl ligand	m.p.	melting point
CI	chemical ionisation	ms	molecular sieves
cm	centimetre	*N*-IS	*N*-iodosuccinimide
d	doublet (NMR spectroscopy)	NMR	nuclear magnetic resonance
DABCO	1,4-diazabicyclo[2.2.2.]octane	PPA	polyphosphoric acid
DCC	1,3-dicyclohexylcarbodiimide	q	quartet (NMR spectroscopy)
DCM	dichloromethane	r.t.	room temperature
DEPT	distorsionless enhancement through polarisation transfer	SPS	solid phase synthesis
DIC	1,3-diisopropylcarbodiimide	t	triplet (NMR spectroscopy)
DMAP	4-dimethylaminopyridine	TBAF	tetrabutylammonium fluoride
DMF	*N*,*N*-dimethylformamide	TBDMS	*tert*-butyldimethylsilyl
EI	electron impact	TFA	trifluoroacetic acid
eq	equivalent	THF	tetrahydrofuran
DEAD	Diethyl azodicarboxylate	TMEDA	*N*, *N*, *N'*, *N'*-tetramethylethylenediamine
FAB	fast atom bombardment	TMG	*N*, *N*, *N'*, *N'*-tetramethylguanidine
h	hour(s)	TMS	trimethylsilyl
IR	infrared	TPS	triphenyl silyl

Chapter 1 Introduction

1.1 Background

At the beginning of this project I wished to -

- produce a novel route to functionalised benzo[*b*]furans, the route should be general, simple and have the possibility of building up functionality round the ring.

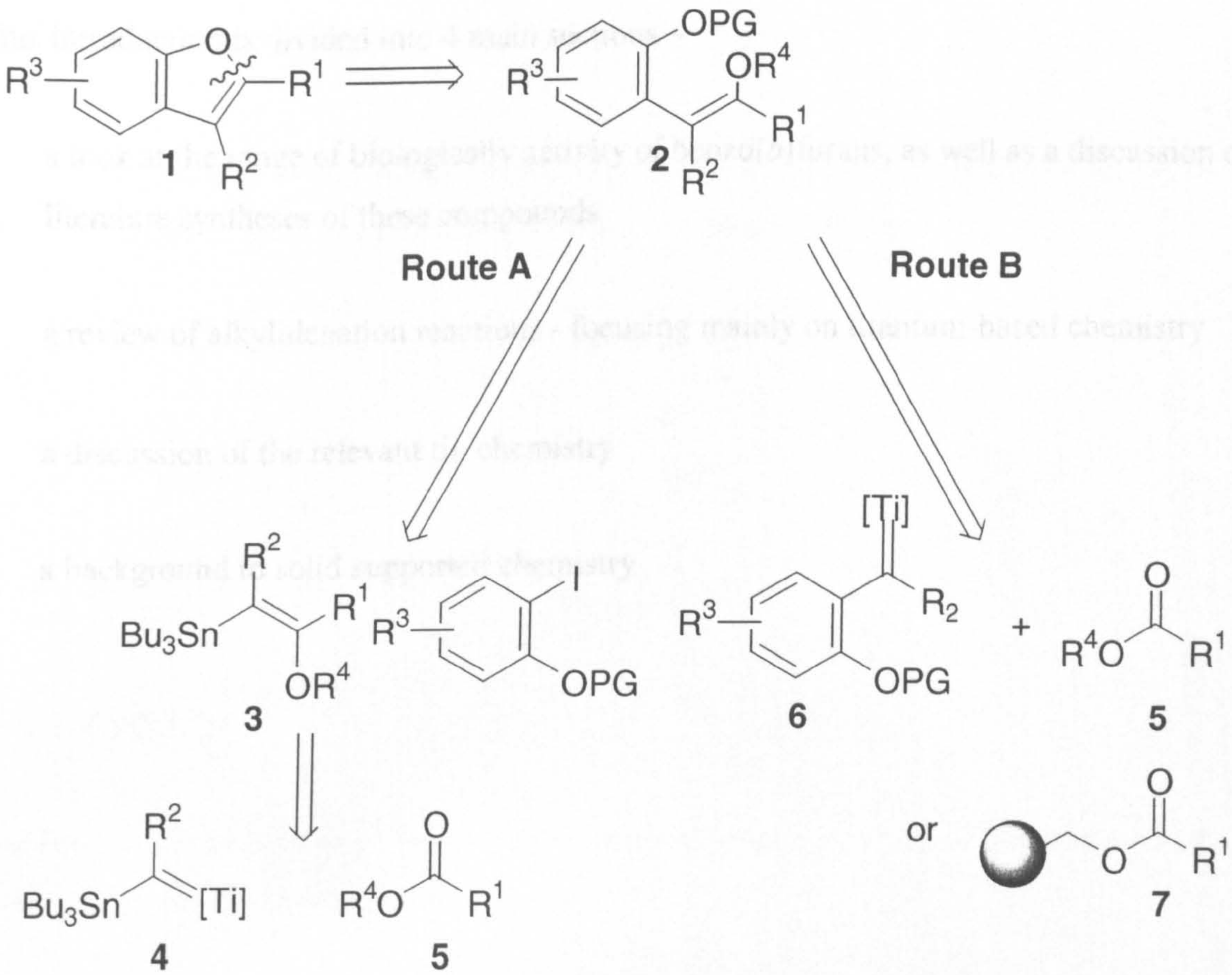
- use titanium-based alkylidenation chemistry as part of the route. Our group has experience using this type of chemistry [1, 2] and so we are aware of the power of this class of reactions. The formation of novel titanium-alkylidene reagents would be a major part of the route to benzofurans and would exploit this type of chemistry in a new way.

- develop a route that could be adapted to form other heterocycles.

As the project moved on I also wished to -

- show how the route was amenable to conversion to solid phase synthesis (SPS). Both the pharmaceutical and agrochemical industries are keen to develop routes where a large number of functionalised compounds, particularly heterocyclic compounds, can be synthesised quickly and easily and our route should fulfil this requirement.

With these aims in mind the two routes shown below were attempted. Both routes involved the synthesis of 2-substituted benzofurans **1** *via* the enol ether intermediates **2**, which are formed using titanium-based alkylidenation reactions. The second route is amenable to conversion from solution to solid phase (Scheme 1).



Scheme 1

Route A extends the methodology of Takai.[3] It was proposed that the novel tin-containing alkylidene reagent **4** could be reacted with a range of esters **5** to give a series of alkenyltins **3**. A subsequent cross-coupling/acid induced cyclisation strategy[4] would give the desired benzofurans **1**.

Route B is based on the work of Takeda[5] and employs the novel titanium reagent **6**. Alkylidenation of esters and subsequent cyclisation of the enol ethers **2** would yield the benzofuran products **1**. **Route B** could also be carried out on solid phase using resin-bound esters **7**.

This introduction is divided into 4 main sections –

- a look at the range of biologically activity of benzo[*b*]furans, as well as a discussion of literature syntheses of these compounds

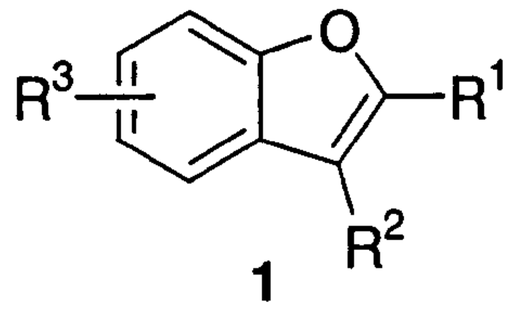
- a review of alkylidenation reactions - focusing mainly on titanium-based chemistry

- a discussion of the relevant tin chemistry

- a background to solid supported chemistry

1.2 Benzofurans

This section looks at the range of activity of benzo[*b*]furans (hereafter referred to as benzofurans) **1** (Figure 1) and a number of approaches to their synthesis.



1

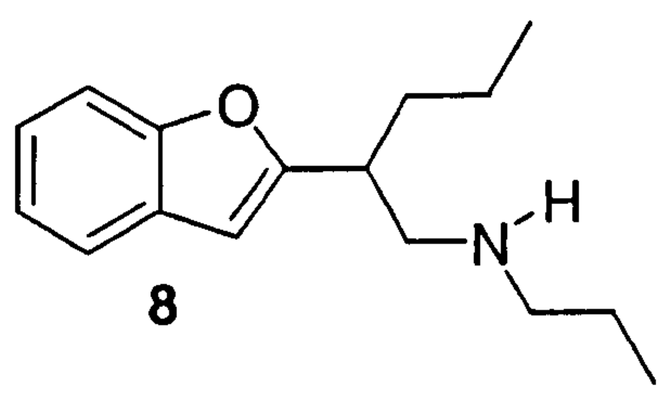
Figure 1

1.2.1 Activity

The benzofuran nucleus is a common one in natural products and its substituted derivatives have a wide range of biological activities.

1.2.1.1 Pharmacological

Certain benzofurans have been shown to be active within the brain. BPAP **8** (Figure 2) selectively enhances the release of catecholamine and serotonin in the brains of rats.[6] Benzofuran-2-carboxamide **9** has related activity, acting as a 5-HT_{2C} serotonin receptor antagonist (Figure 2).[7]



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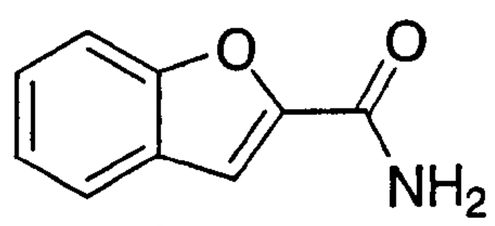
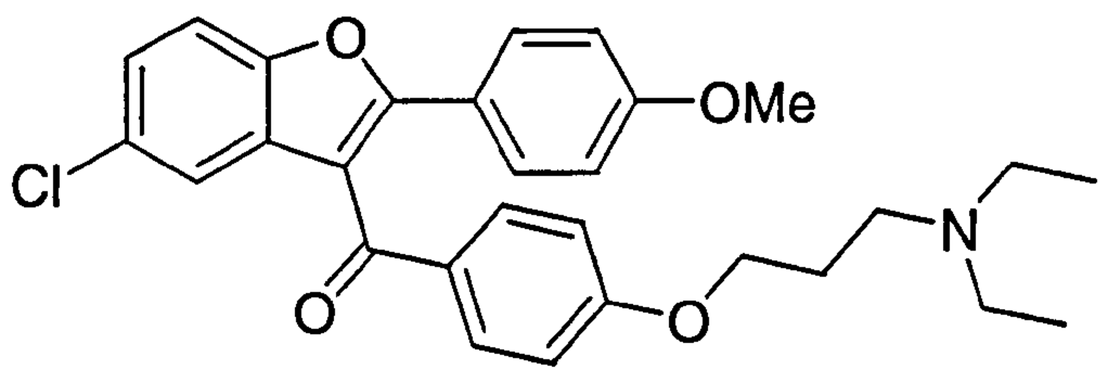


9

Figure 2

Other benzofurans have shown potential as anti-Alzheimer's drugs. Alzheimer's disease is thought to be related to the deposition of β-amyloid peptide in the brain and SKF-74652 **10** (Figure 3) inhibits the fibril formation of this particular peptide.[8]

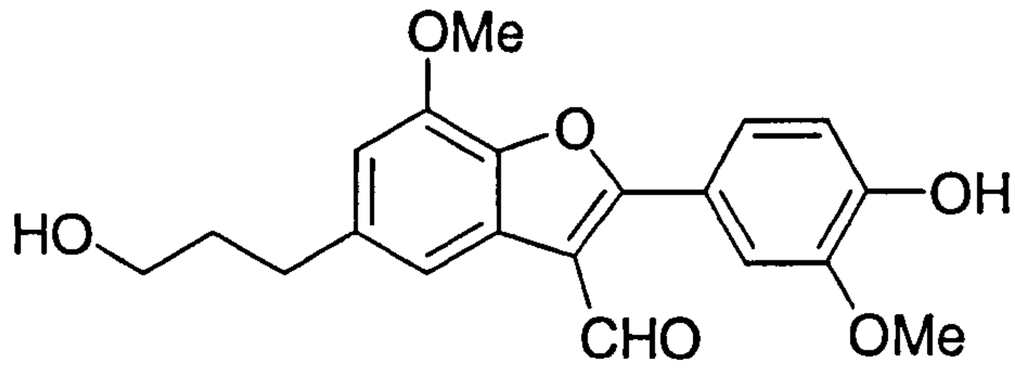


10

SKF-74652

Figure 3

Other medical conditions have been treated with benzofurans. For example aldehyde **11** has been used to treat coronary heart disease,[9] while machicendiol **12** shows cytostatic activity against human leukaemia HL60 cells and is part of a plant extract that has been used in the treatment of asthma, rheumatism and ulcers.[10] GR 117289 **13** acts as an angiotensin II receptor antagonist and therefore has potential as a treatment for hypertension and congestive heart failure (Figure 4).[11]



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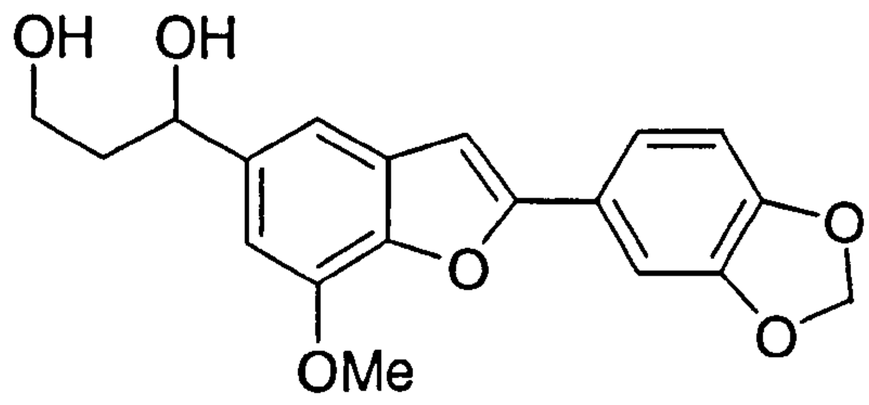

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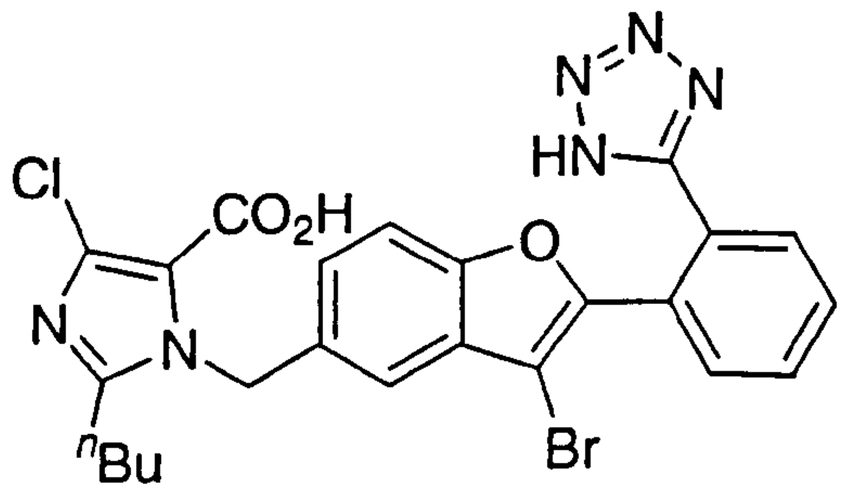

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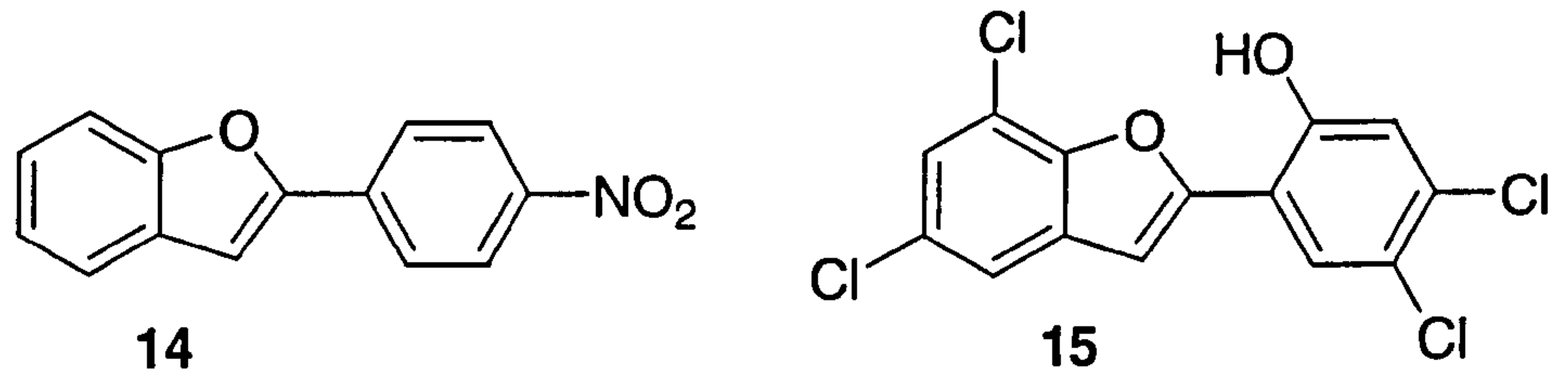
Figure 4

1.2.1.2 Antibacterial

A number of substituted benzofurans act as antibiotics e.g. 2-arylbenzofuran **14** shows high activity against *Strophylococci*, *Pyocyaneae* and *E. Coli* bacterium,[12] while 2-arylbenzofuran **15** shows bacterial and bacteriostatic activity against *Staphylococcus aureus* (Figure 5).[12]

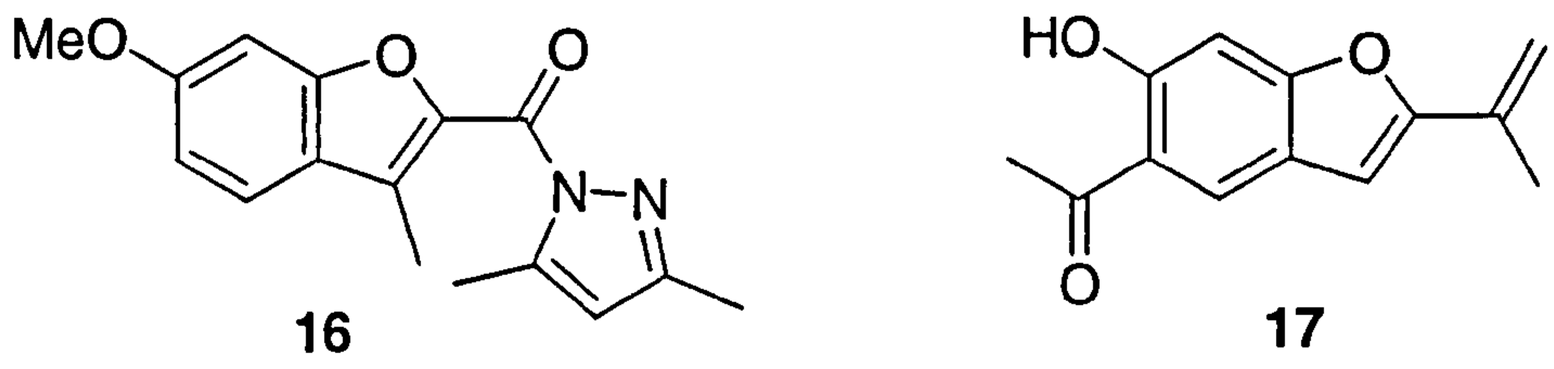


14 **15**

Figure 5

1.2.1.3 Pesticides

Benzofurans have also been used as pesticides - e.g. benzofuran **16** is active against the sweet potato weevil *Cylas formicarius elgantus* (a destructive pest of the sweet potato plant),[13] while Euparin **17** acts as a growth inhibitor against the larvae of *Tenebrio molitor* – a yellow mealworm (Figure 6).[14]



16 **17**

Euparin

Figure 6

1.2.1.4 Other Activity

Benzofurans have also found use in industry - e.g. carboxylic acid **18** has been used as a brightening agent in textiles, wool, paper and nylon (Figure 7).[12]

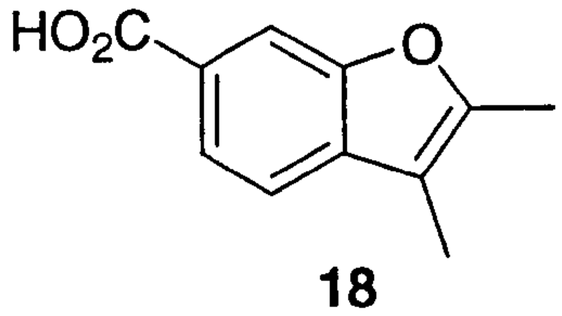


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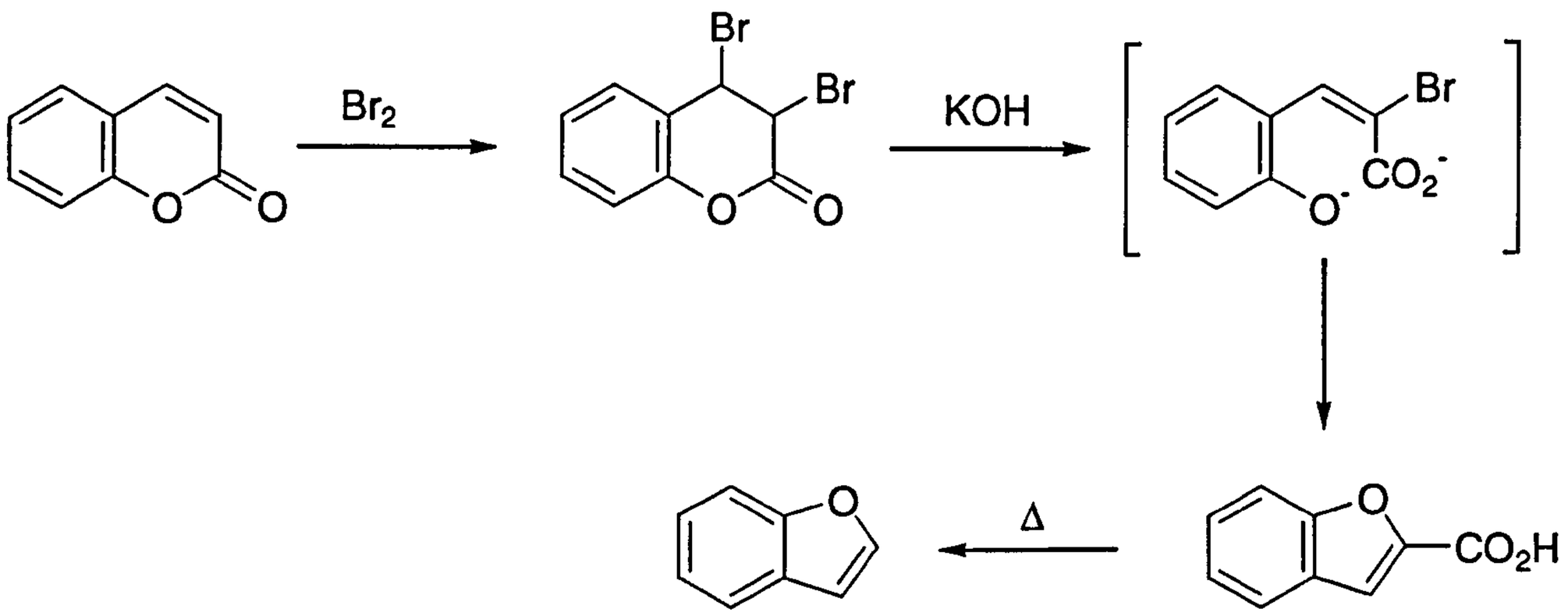
Figure 7

1.2.2 Synthesis

This section looks at some of the important syntheses of benzofurans involving both solution and solid phase chemistry. In the examples given particular attention is paid to those involving 2-substituted benzofurans.

1.2.2.1 Solution phase syntheses

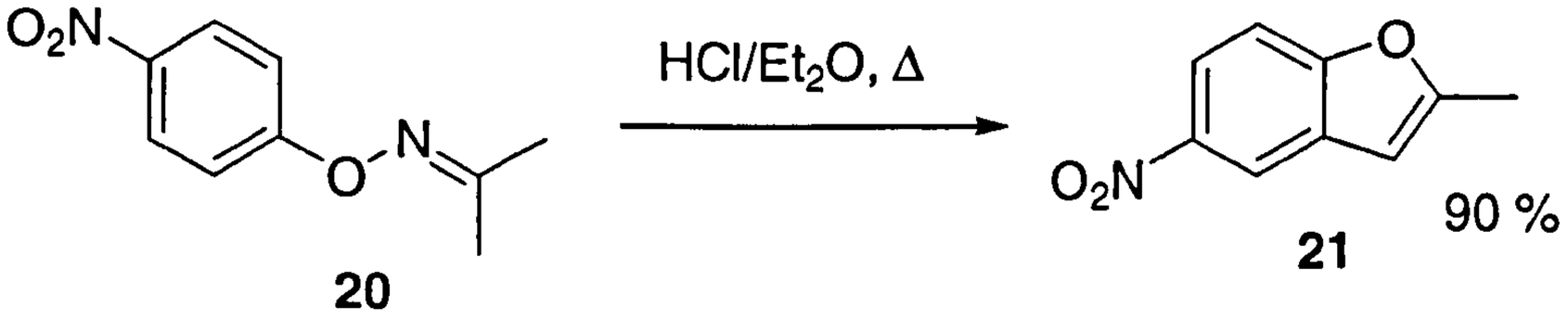
Benzofuran **19** itself was first synthesised by Perkin who formed it *via* a coumarin ring contraction reaction (Scheme 2).[12]



19

Scheme 2

The classic Fisher indole synthesis has been extended to encompass the synthesis of benzofurans, as shown here by Mooradian.[15] In his synthesis, benzofuran **21** was formed from its corresponding nitro-substituted oxime **20** (Scheme 3). A limitation in this reaction is that an electron-withdrawing group must be present *ortho* or *para* to the oxygen on the oxime so as to prevent formation of unwanted oxime products.[15]

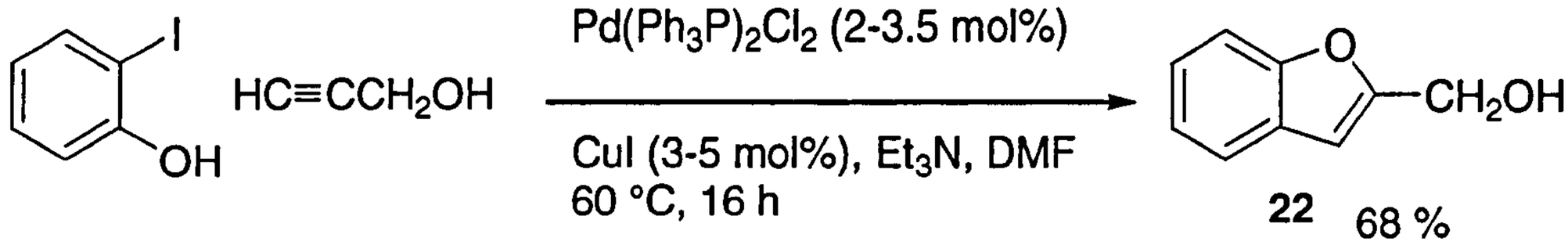


20 **21**

Scheme 3

A common way of synthesising substituted benzofurans is *via* the reaction of a phenol with an alkyne.

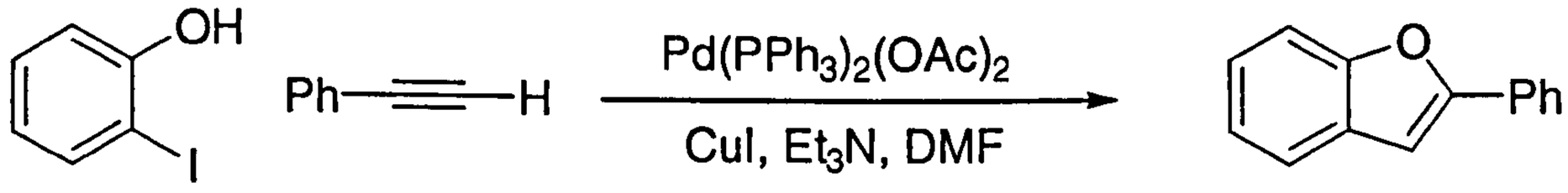
Kundu and co-workers developed such a procedure for their synthesis of benzofuran derivatives such as **22** (Scheme 4).[16]



22 68 %

Scheme 4

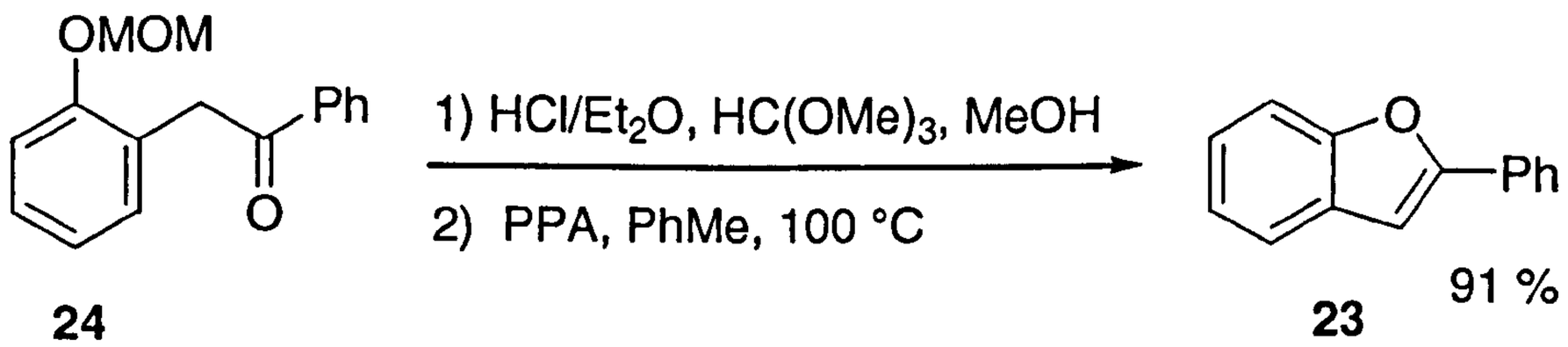
Arcadi and co-workers[17] used a similar approach in their synthesis of 2-phenylbenzo[*b*]furan **23**. As above, Sonogashira coupling conditions gave the product as a single regioisomer (Scheme 5).



23 80 %

Scheme 5

The cyclodehydration of aryloxyaldehydes or ketones is a popular method of benzofuran synthesis. The most common dehydrating agents used for this purpose are polyphosphoric acid (PPA) and sulfuric acid. Kato and Miyaura employed this method in their synthesis of 2-phenylbenzo[*b*]furan **23**.[18] 2-(2'-Methoxymethyl)phenylacetophenone **24** was treated with HCl in methanol in the presence of trimethylorthoformate. Subsequent treatment with PPA in toluene at 100 °C yielded the desired product (Scheme 6).



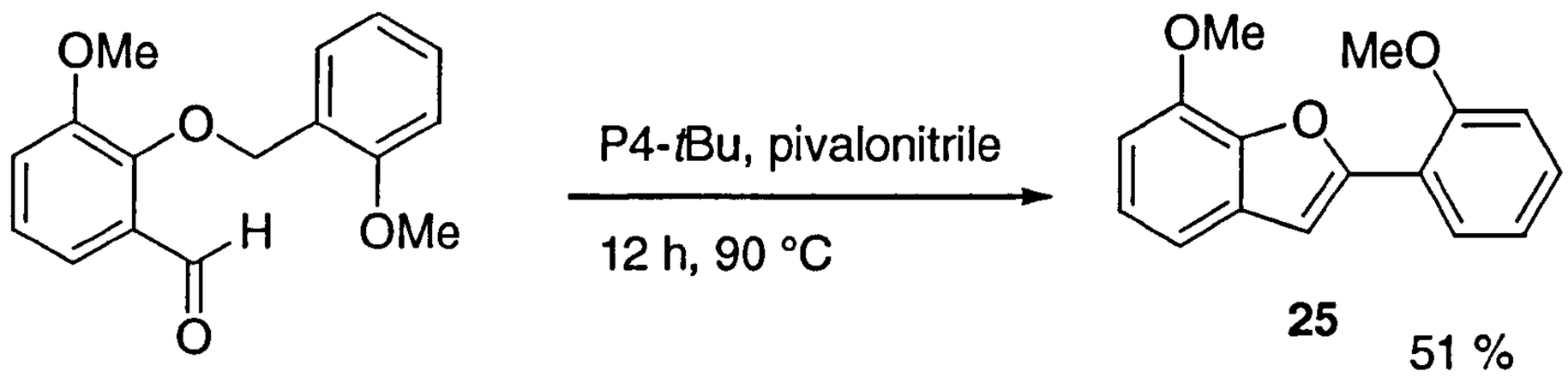
24

91 %

23

Scheme 6

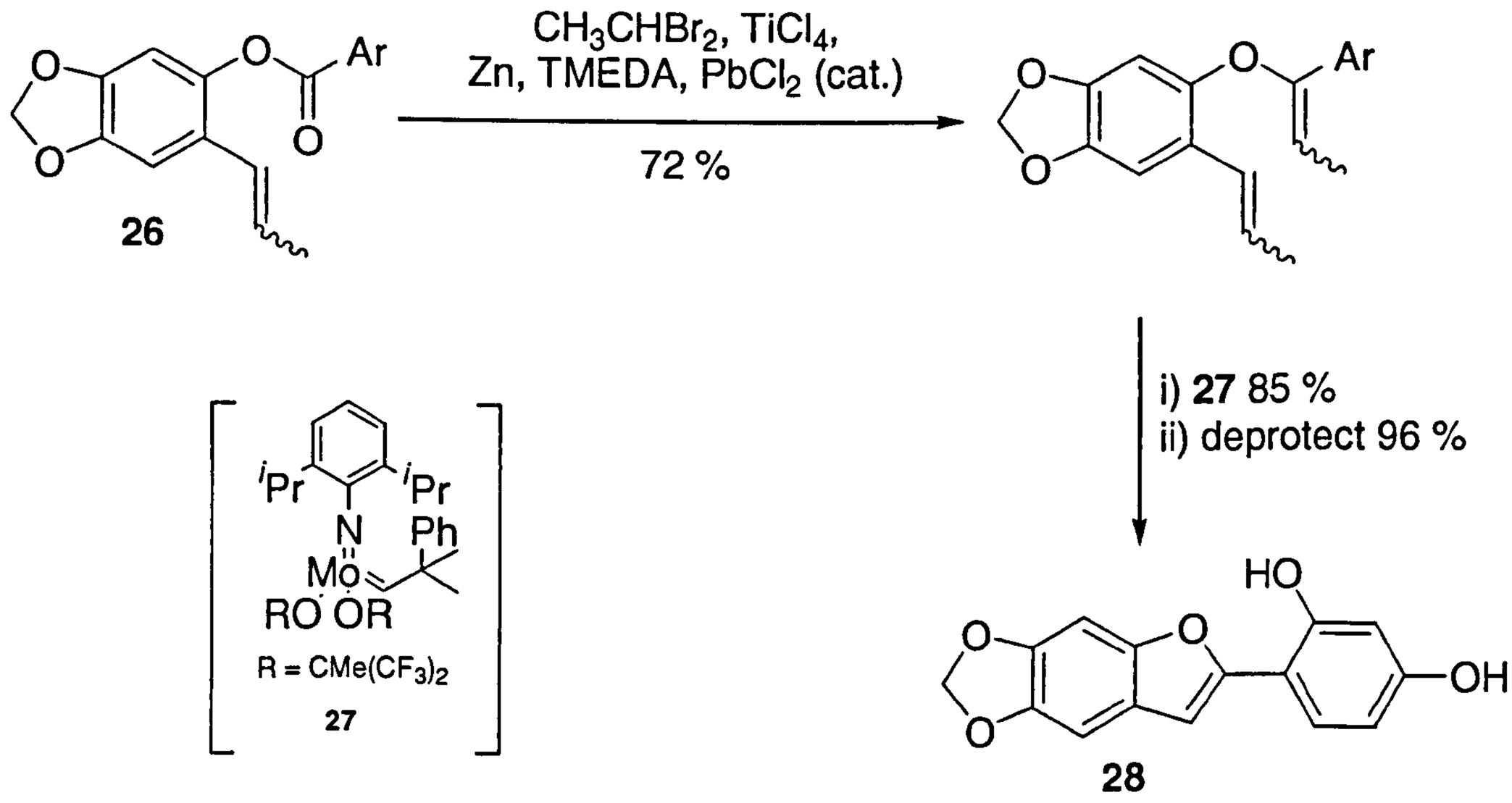
More recently, Kraus and co-workers synthesised 2-arylbenzofurans such as **25** *via* the base-mediated cyclisation of *ortho*-substituted benzaldehydes.[19] By using a non-ionic phosphorus 'superbase', benzaldehydes containing methoxy-substituents could be effectively cyclised (Scheme 7).



P4-*t*Bu = *t*Bu=P[N=P(NMe$_2$)$_3$]$_3$

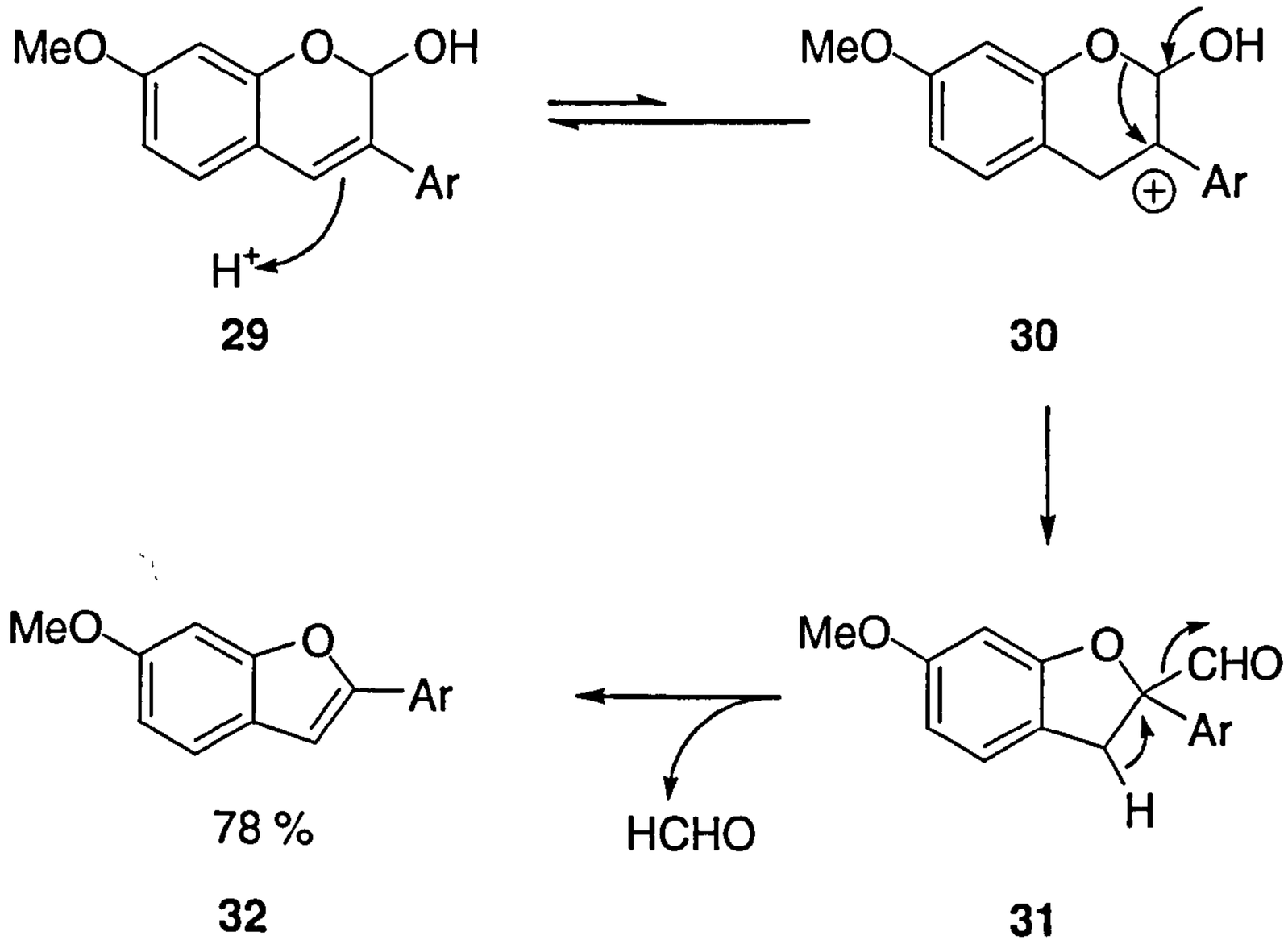
Scheme 7

Grubbs and co-workers showed that ring closing metathesis can be used as part of an approach to substituted benzofurans.[20] Alkylidenation of ester **26** using Takai's procedure (see section 1.3.4 of this chapter) followed by ring closing metathesis catalysed by molybdenum complex **27** gave phytoalexin **28** in 59 % overall yield from the ester (Scheme 8).



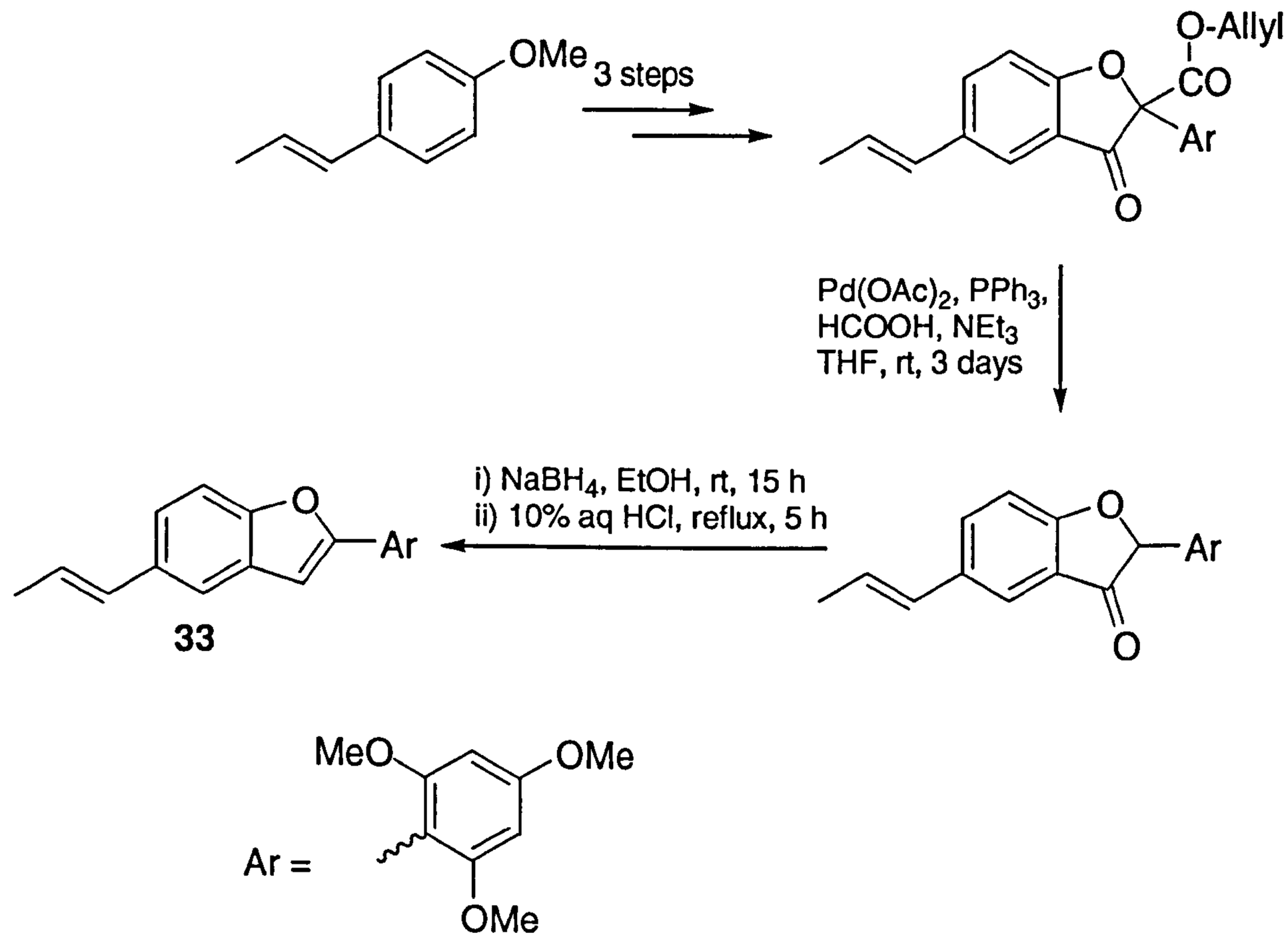
Scheme 8

Substituted benzofurans have also been synthesised *via* rearrangement reactions. This is exemplified by Kinoshita's synthesis of 2-arylbenzofuran[21] **32**. Treatment of **29** with acid formed a cation **30** which spontaneously contracted to give the benzofuran **32** *via* the dihydrobenzofuran intermediate **31** (Scheme 9).



Scheme 9

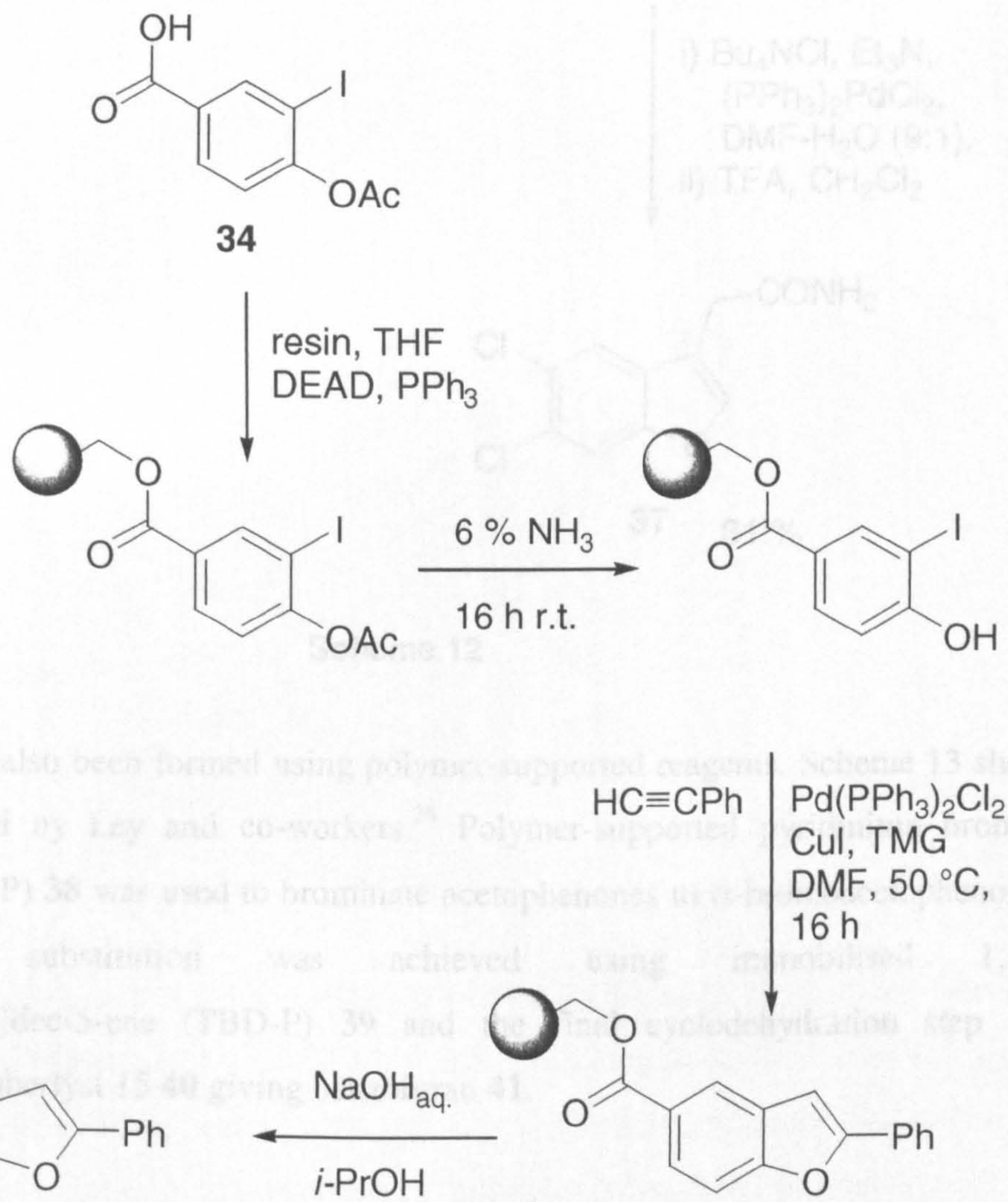
2-Aryl benzofurans have been synthesised via the reduction and dehydration of 2-arylbenzofuranones. Donnelly and co-workers used this approach in their synthesis of the naturally occurring nor-neolignan **33**, which is effective against diarrhoea and mild fevers (Scheme 10).[22]



Scheme 10

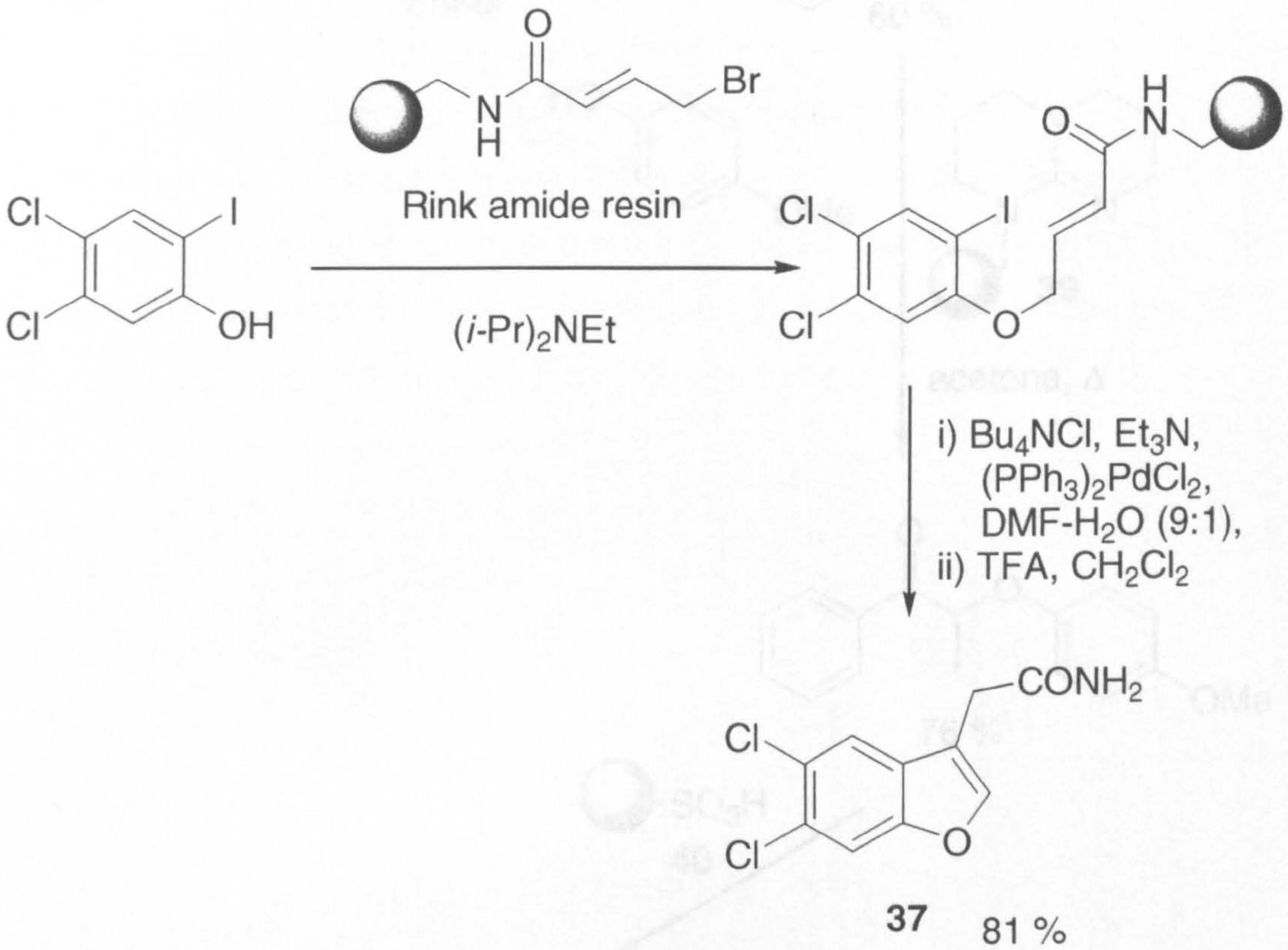
1.2.2.2 Solid Phase Synthesis

As in many other areas of synthetic organic chemistry, many recent syntheses of benzofurans have been carried out using solid phase synthesis (SPS). In their syntheses of benzofurans, Fancelli and co-workers used an approach similar to that of Kundu and Arcadi described previously. An arylcarboxylic acid containing an iodo-functionality **34** was coupled to TentaGel™ hydroxy resin. Palladium chemistry was employed as before to attach an alkyne and form the resin-bound benzofuran **35**, which was cleaved under basic conditions to give the carboxylic acid **36**. (Scheme 11).[23]



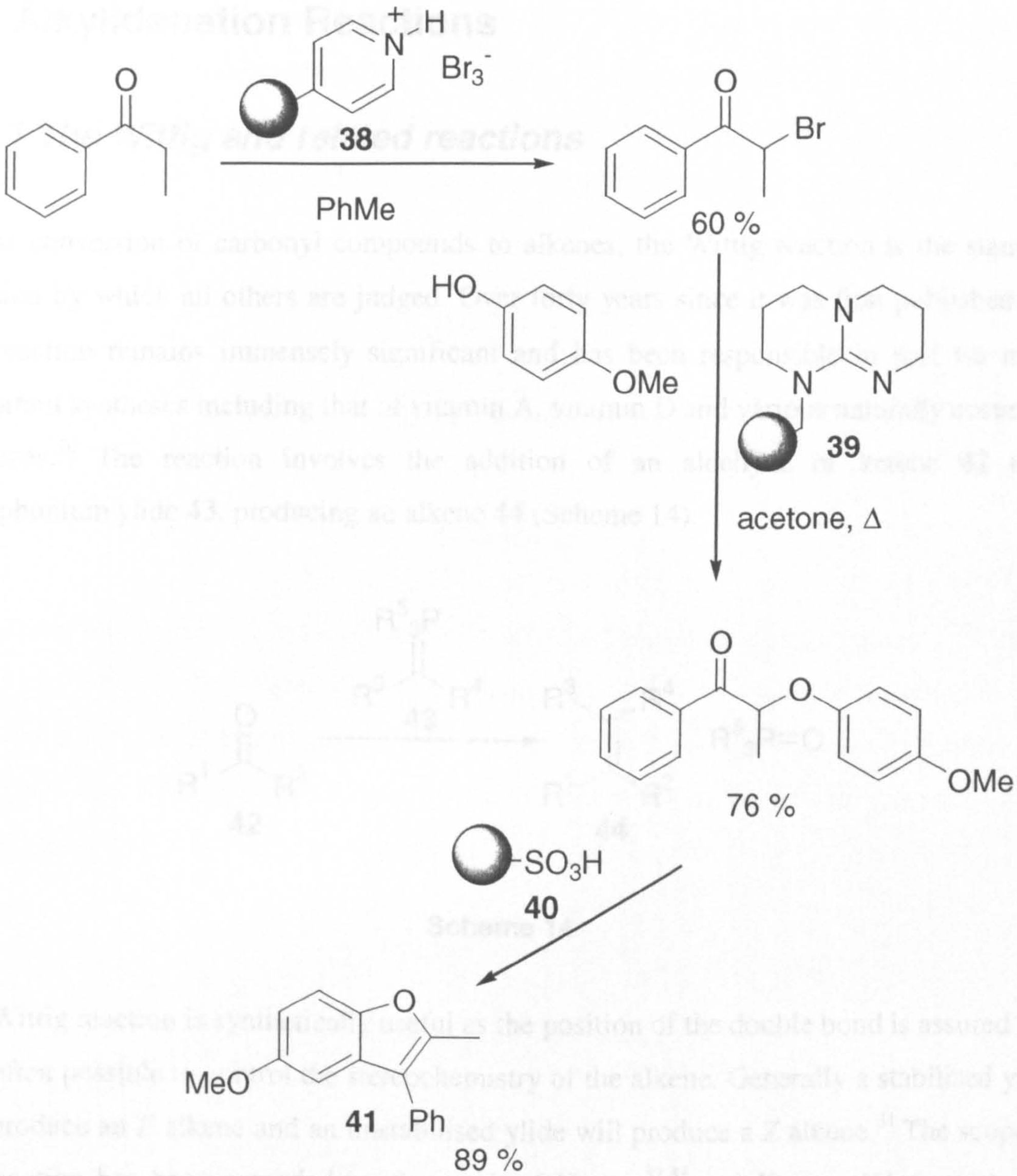
Scheme 11

Zhang and Maryanoff have also adopted palladium chemistry in their SPS benzofuran synthesis. They adapted a palladium-mediated, intramolecular Heck-type reaction to the solid phase and used it to form amide-functionalised benzofurans (e.g. **37**, Scheme 12).[24]



Scheme 12

Benzofurans have also been formed using polymer-supported reagents. Scheme 13 shows the approach used by Ley and co-workers.[25] Polymer-supported pyridinium bromide perbromide (PSPBP) **38** was used to brominate acetophenones to α-bromoacetophenones. Bromine-phenol substitution was achieved using immobilised 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD-P) **39** and the final cyclodehydration step was achieved using Amberlyst 15 **40** giving benzofuran **41**.



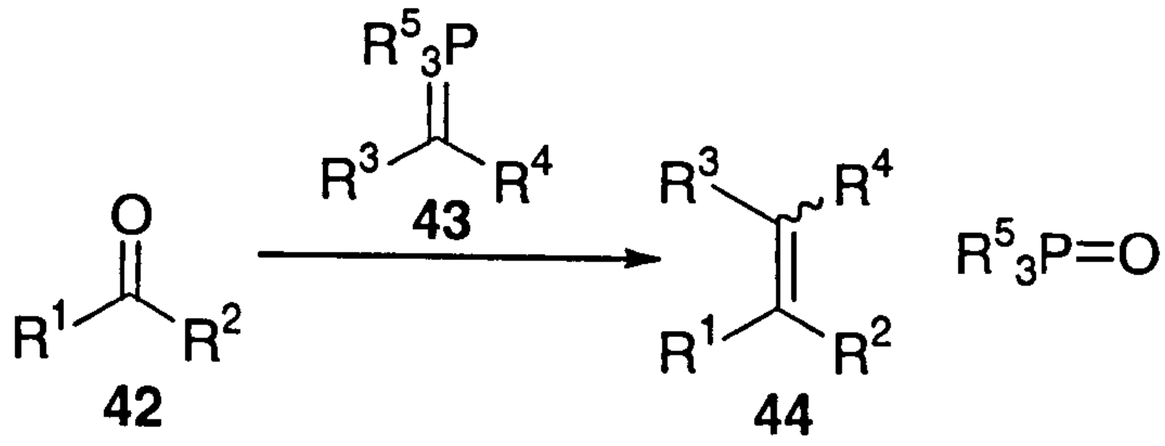
Scheme 13

The use of SPS has become increasingly important in heterocycle synthesis and new approaches are always required. 'Traceless' synthesis – where no sign of resin-attachment is evident in the final product (such as the carboxyl and amide functionalities seen in the products of Scheme 11 and 12) is particularly desirable. More detail on this type of SPS chemistry appears at the end of this chapter (section 1.5.2.5), while a discussion on my own synthesis of benzofurans on solid phase appears in Chapter 4.

1.3 Alkylidenation Reactions

1.3.1 The Wittig and related reactions

In the conversion of carbonyl compounds to alkenes, the Wittig reaction is the standard reaction by which all others are judged. Over forty years since it was first published,[26-29] the reaction remains immensely significant and has been responsible in part for many important syntheses including that of vitamin A, vitamin D and various naturally occurring polyenes.[30] The reaction involves the addition of an aldehyde or ketone **42** to a phosphonium ylide **43**, producing an alkene **44** (Scheme 14).



Scheme 14

The Wittig reaction is synthetically useful as the position of the double bond is assured and it is often possible to control the stereochemistry of the alkene. Generally a stabilised ylide will produce an *E* alkene and an unstabilised ylide will produce a *Z* alkene.[31] The scope of the reaction has been extended by the work of Horner[32,33] and Horner, Wadsworth and Emmons[34-36] (HWE) who used the anions of phosphine oxide **45** and diethyl phosphonate **46** respectively to generate alkenes (Figure 8). The main advantage of the HWE reaction lies in the solubility of the reaction by-products in water. Also the reaction has proven to be effective with hindered ketones that are unreactive in the classical Wittig reaction.[37]

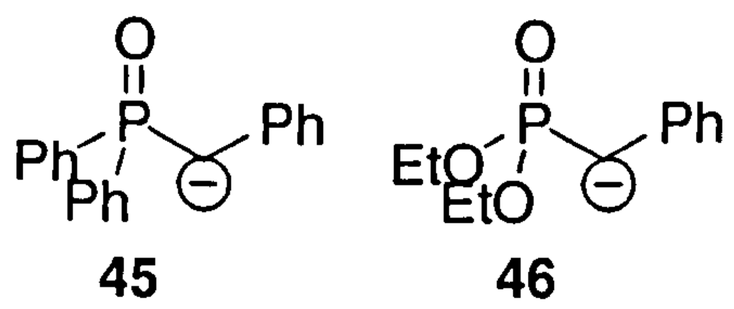
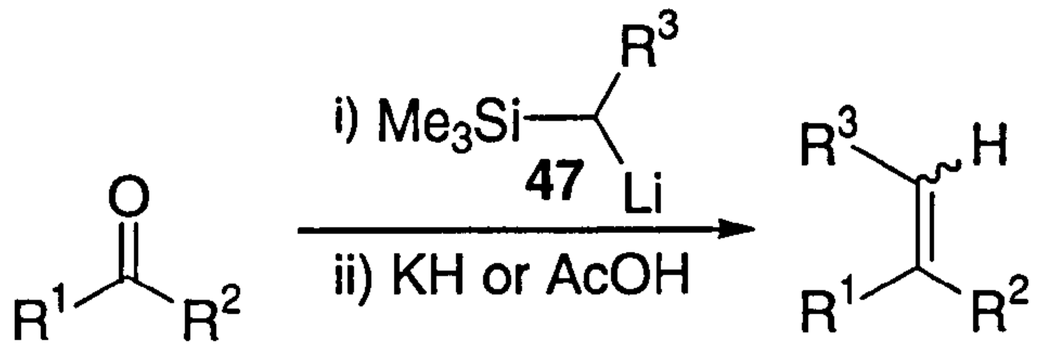


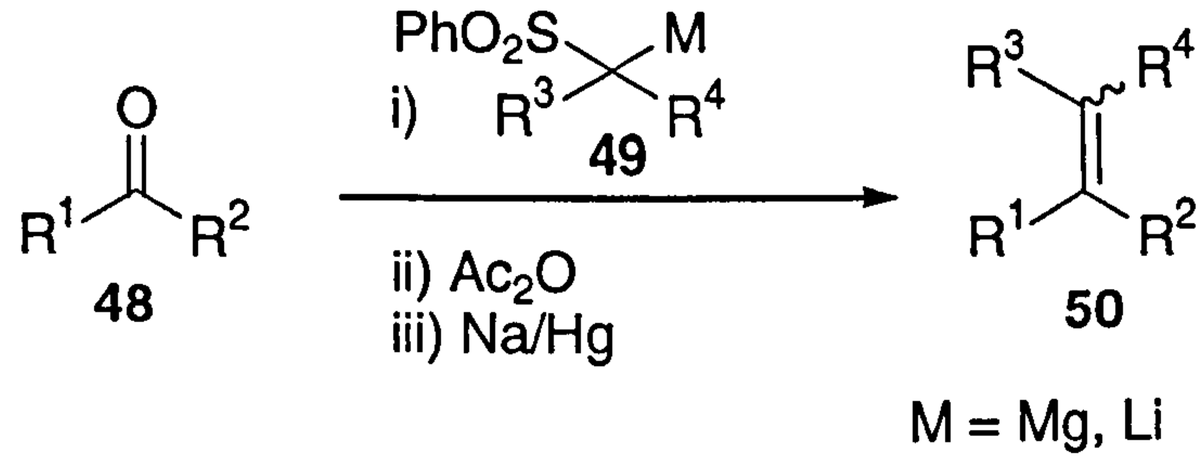
Figure 8

Alternatives to the Wittig reaction have included reactions that utilise silicon reagents **47** (Peterson)[38,39] and sulfur reagents **49** (Julia).[40,41] The Peterson olefination (Scheme 15) has the advantage that the by-product (hexamethyldisiloxane) is volatile and thus easier to remove than the phosphine oxides produced in the Wittig reaction.



Scheme 15

Marc Julia introduced the use of sulfur-stabilised carbanions in alkylidenations.[40,41] In this reaction a sulfone derivative **49** is metallated and added to a carbonyl compound **48**, followed by functionalisation and reductive elimination to give the alkene **50** (Scheme 16). Kocienski and Lythgoe later demonstrated the *trans*-selectivity of the process.[42] More recently a one-pot procedure was introduced by Sylvestre Julia.[43]

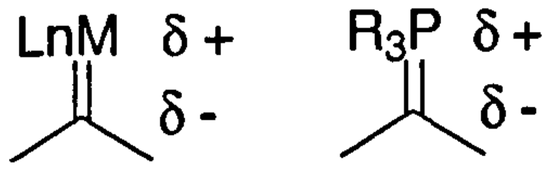


Scheme 16

The main disadvantage of the Wittig and related reactions lies in their inability to convert carboxylic acid derivatives into alkenes.[44] A second problem is that due to the basic medium of the Wittig and Julia reactions, reactions on easily enolisable carbonyls can lead to the formation of unwanted side products.[37] The problem of converting base-sensitive ketones and higher oxidation state carbonyls into alkenes has been addressed through the use of transition metal alkylidene chemistry. Titanium alkylidenes have proved particularly useful and this class of reagents is discussed in the next section.

1.3.2 Titanium-based reagents

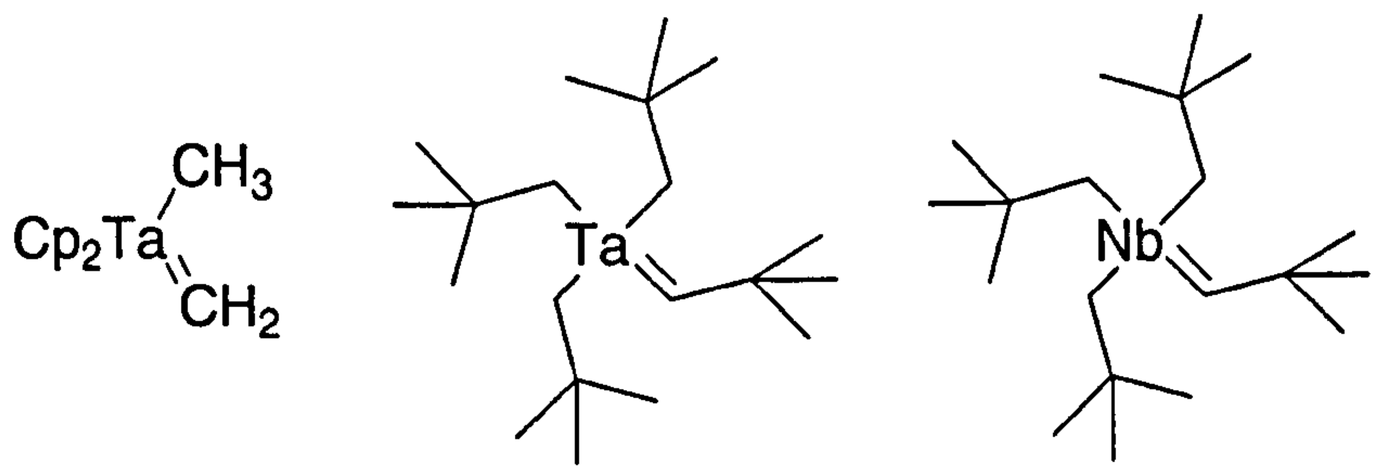
In the mid to late 1970s Schrock published complexes with the general formula $R_2C{=}MLn$ **51** (Figure 9).[45,46]



51 **52**

Figure 9

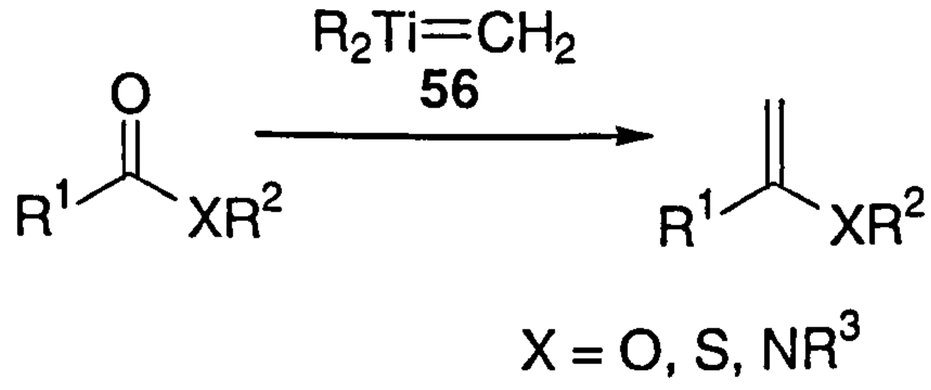
These 'Schrock-type carbenes' are high valent carbene complexes of early transition metals and act as structural analogues to Wittig's phosphonium ylides **52** (e.g. **53 - 55**, Figure 10).



53 **54** **55**

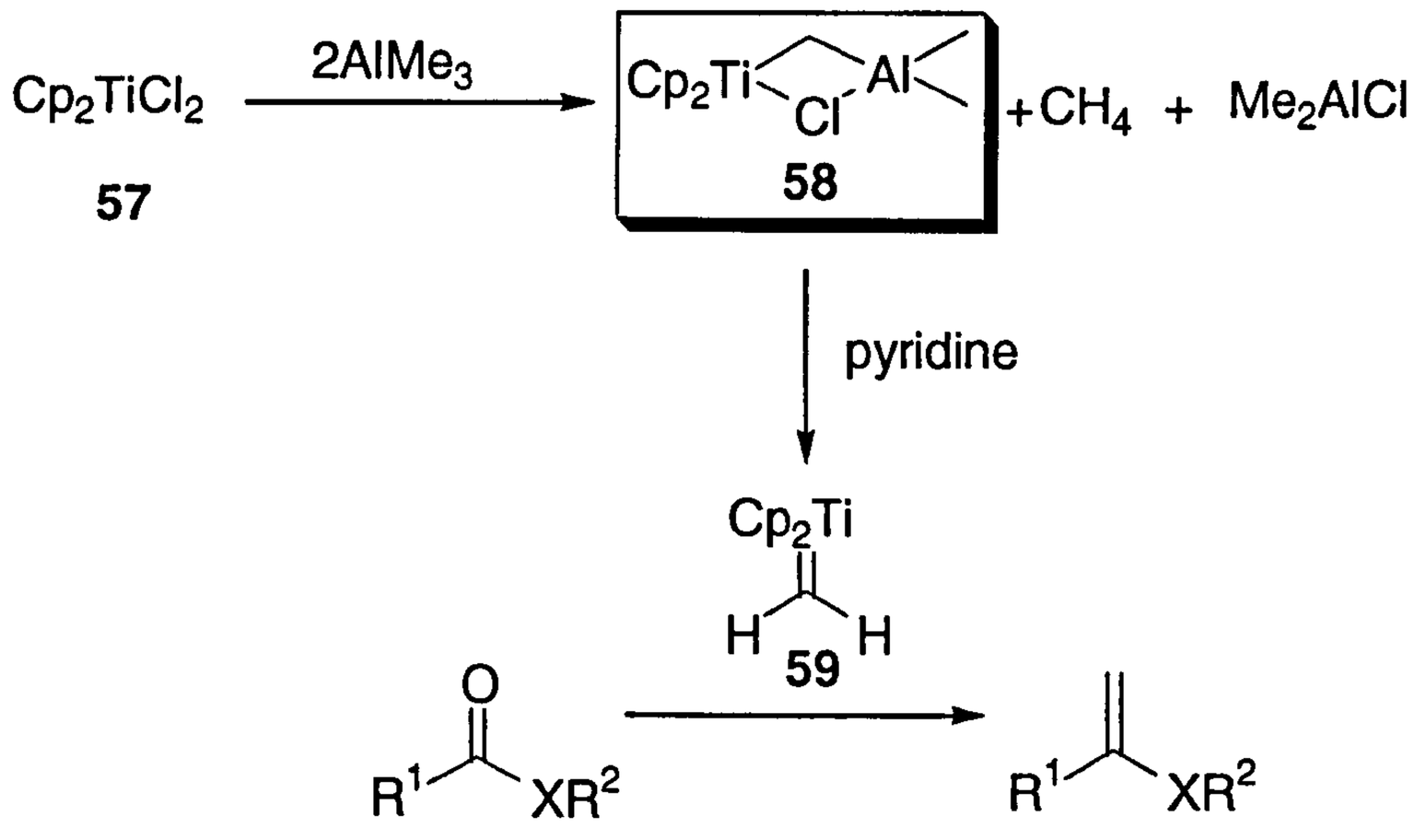
Figure 10

Since Schrock's discovery, a number of related titanium-complexes have appeared in the literature.[47] Like Schrock's original complexes, these titanium complexes **56** have an ylide-like character, being nucleophilic at the carbon atom. However, when used in alkylidenation reactions, the reaction conditions are neutral or slightly Lewis acidic, and therefore reactions can be carried out on base sensitive ketones and aldehydes as well as carboxylic acid derivatives (Scheme 17).



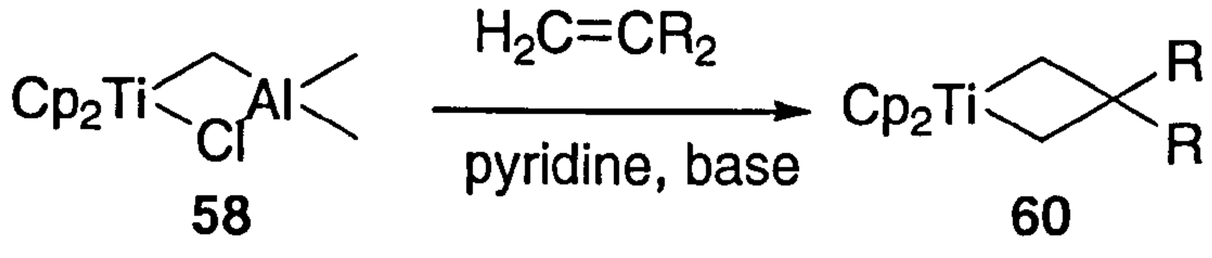
Scheme 17

The first person to exploit this new type of chemistry to any effect was Tebbe, who in 1978 reported the preparation of a titanium complex **58** from titanocene dichloride **57** and two equivalents of trimethylaluminium (Scheme 18).[48] This reagent was shown to be able to methylenate a wide range of carbonyl compounds and mechanistic work suggested the reactive species was $Cp_2Ti{=}CH_2$ **59**.[37] The aluminium atom was thought to stabilise the alkylidene reagent and also to direct the abstraction of hydrogen from methyl rather than Cp groups.[37] The Tebbe reagent has since been widely used in synthesis, e.g. Nicolaou used it as part of his synthesis of Zaragozic acid.[49]



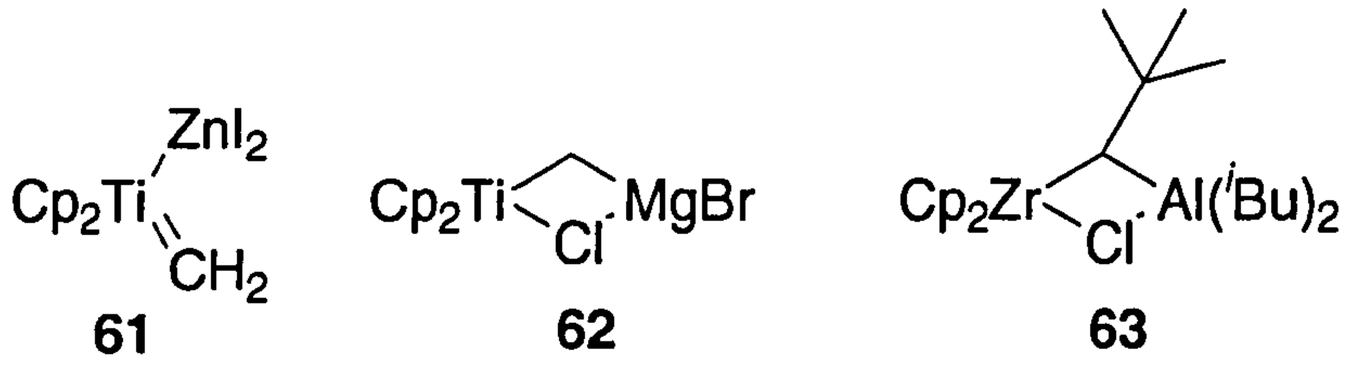
Scheme 18

Grubbs later formed the related metallocycle complexes **60** by treating the Tebbe reagent **58** with an alkene in the presence of base (Scheme 19).[47] Metallocycles **60** are also precursors to Schrock carbenes.



Scheme 19

Other alternatives to the Tebbe reagent in the form of $Cp_2TiCH_2ZnI_2$ **61** and $Cp_2Ti(Cl)CH_2MgBr$ **62** have been used by Eisch[50] and Bickelhaupt[51,52] while Schwartz[53,54] has developed a zirconium analogue **63** (Figure 11).



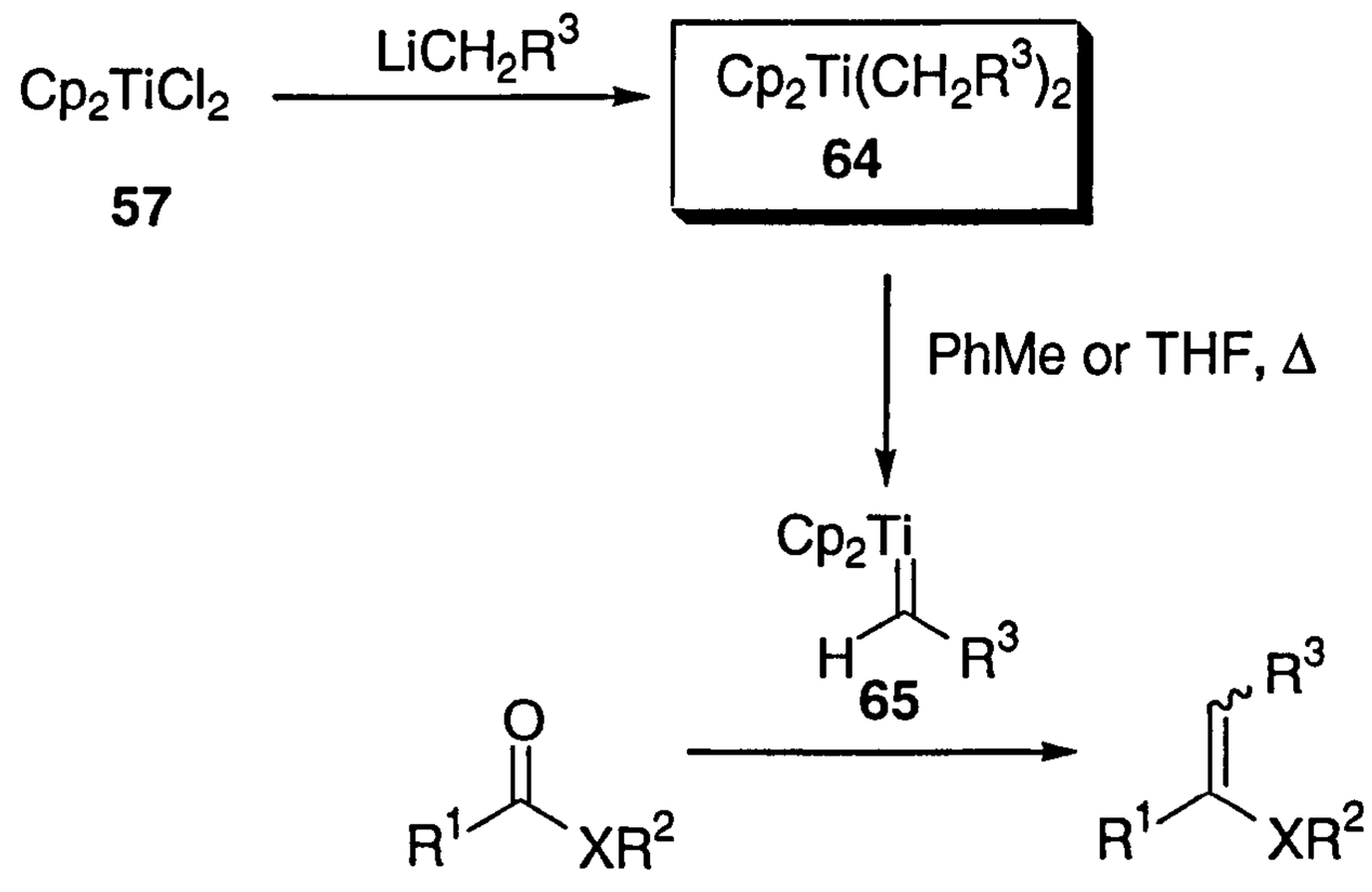
61 **62** **63**

Figure 11

All of these reagents have some shortcomings. In addition to the problems with using the pyrophoric trimethylaluminium in its formation,[50] the Tebbe complex is very sensitive to air and moisture,[44] and hence special techniques are required to prepare the compound. (The reagent can be bought as a 0.5 M solution in toluene, but at £70.20 for 25 cm^3, it remains rather expensive). Grubbs reagents are more stable and can be handled in air for short periods of time.[47] In both reactions transfer to the carbonyl group is limited to methylene.[55] Although Schrock's and Schwartz's complexes can transfer R groups to the carbonyl, these generally have to be bulky moieties such as neopentyl.[45,46,53,54] Moreover, there is very poor stereocontrol in the reactions involving Schrock complexes and along with the modified Eisch and Bickelhaupt reagents, they have not as yet found great use in organic synthesis.[37]

1.3.3 The Petasis alkylidenation

The Petasis alkylidenation (Scheme 20) avoids many of the problems associated with the Tebbe and Schrock reagents.[56] The titanium complexes **64** used are easily prepared from titanocene dichloride (Cp_2TiCl_2 **57**). They are briefly stable to air and water and can be stored as THF or toluene solutions in the freezer for long periods of time.[56]

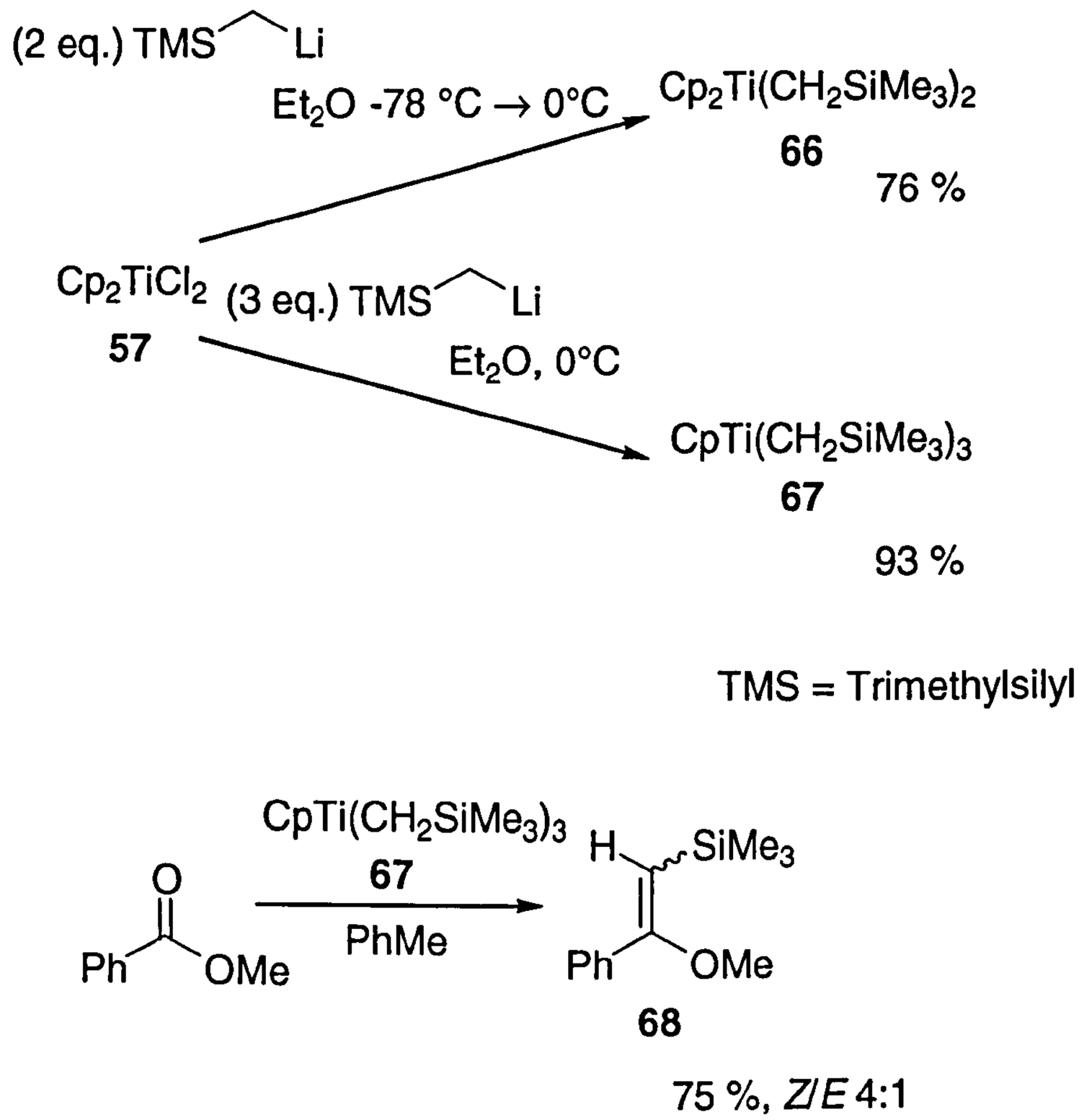


Scheme 20

The reaction employs titanocene derived compounds $Cp_2Ti(CH_2R^3)_2$ **64**, where R^3 =H or aryl. Alkylidenations can be carried out on a number of compounds including aldehydes, ketones, esters, lactones, thioesters, silyl esters, amides and carbonates.[57] The complexes cannot contain R^3 groups that have a β-hydrogen atom, due to the occurrence of facile β-hydride elimination reactions.[58, 59]

The mechanism of the reaction is not yet fully understood, but appears to involve a metal-alkylidene complex $Cp_2Ti{=}CHR$ **65** as the reactive species.[56]

Petasis has used the related compounds *bis*(trimethylsilylmethyl)titanocene **66** and *tris*(trimethylsilylmethyl)titanocene **67** to produce β-heterosubstituted alkenylsilanes such as **68** (Scheme 21).[60-62]



Scheme 21

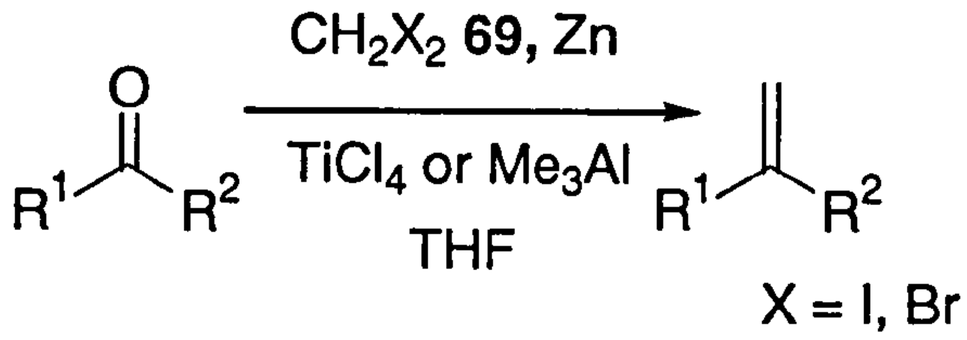
Although Petasis was the first to use this class of silicon compounds as alkylidenating agents, they have been known in the literature for some time.[63-65]

Analogues of the Petasis reagent described above have been used in the allenation of carbonyl compounds[66] and in the ring opening metathesis polymerisation (ROMP) of norbornene.[67]

1.3.4 The Takai alkylidenation and related reactions

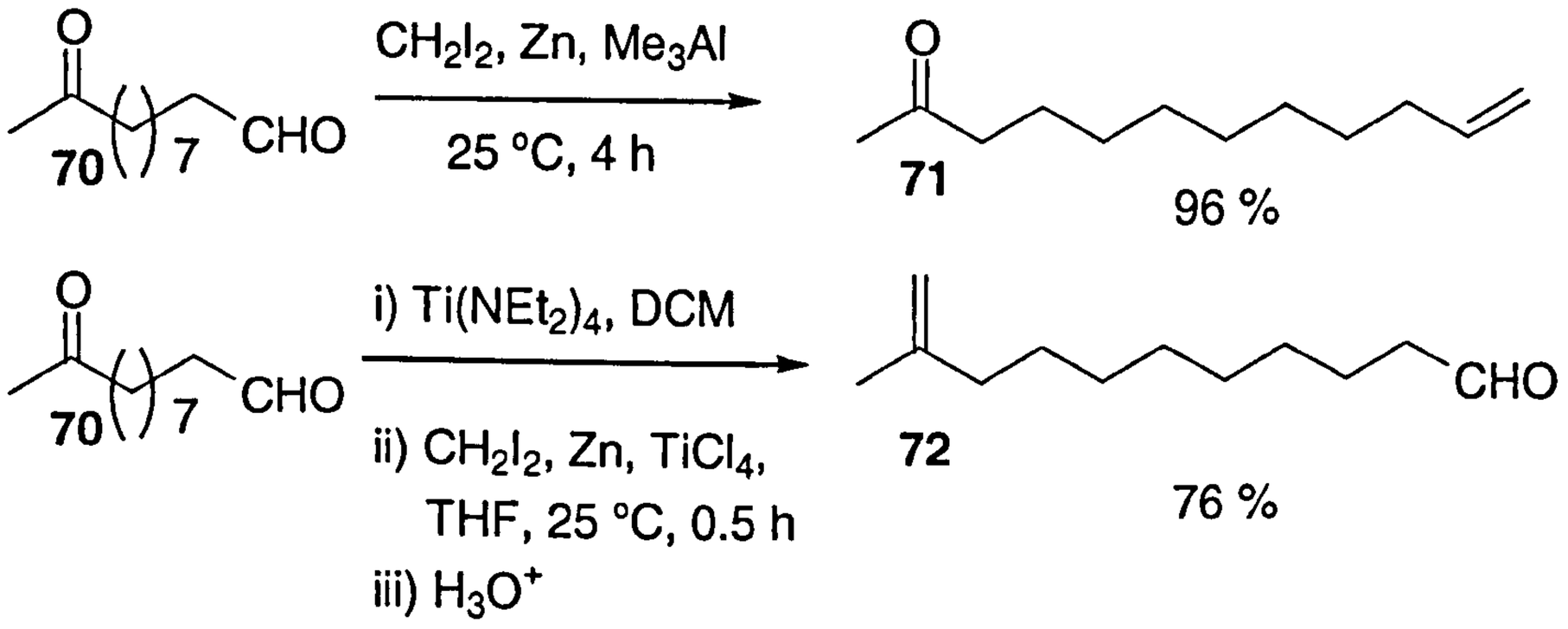
1.3.4.1 Introduction

Takai's work is based on a 1978 paper by his co-worker Oshima[68] which showed that enolisable ketones and aldehydes could be effectively methylenated using a 1,1-dihalomethane **69** in the presence of zinc and a Lewis acid such as trimethylaluminium or titanium tetrachloride (Scheme 22). Lombardo[69] later described a method of synthesising a $CH_2Br_2/Zn/TiCl_4$ reagent that could be stored in the freezer.



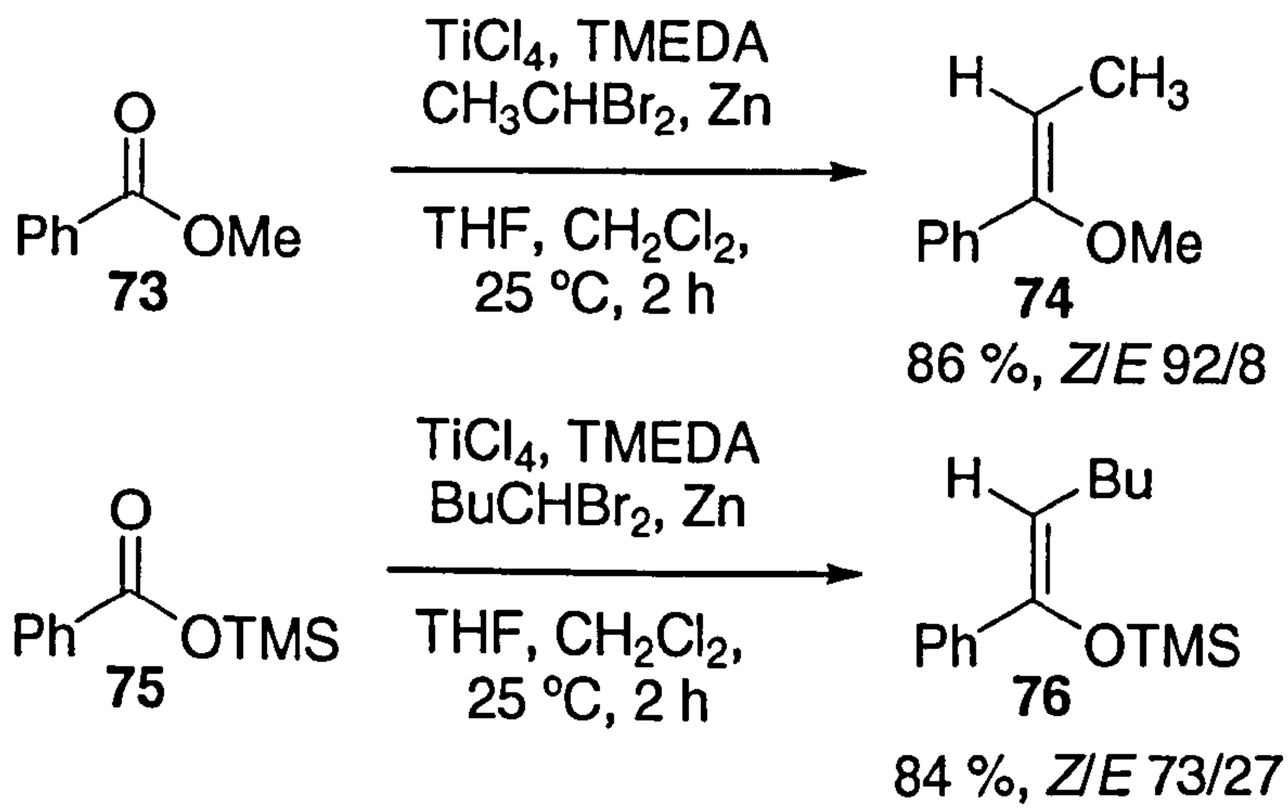
Scheme 22

Takai discovered that chemoselective methylenation of aldehydes such as **70** in the presence of ketones could be achieved by using titanium isopropoxide or trimethylaluminium as the Lewis acid (as seen in the production of alkene **71**).[70] By pre-complexing the aldehyde with titanium(IV) diethylamide and using titanium tetrachloride as the Lewis acid, the complementary chemoselective methylenation of the ketone was accomplished to give alkene **72** (Scheme 23).[70]



Scheme 23

Takai extended the scope of the reaction to encompass the alkylidenation of many carboxylic acid derivatives such as esters **73**,[71,72] silyl esters **75**,[73] thioesters **77**,[74] and amides **79**[74] to give the corresponding enol ethers **74**, silyl enol ethers **76**, vinyl sulfides **78** and enamines **80**. He achieved this by using a reagent prepared from titanium tetrachloride, TMEDA, zinc and a 1,1-dihaloalkane. He showed that esters, thioesters and silyl esters reacted with high levels of *Z*-stereoselectivity, whereas amides reacted to give *E*-enamines. The reaction could also be used to form β-hetero-substituted alkenylsilanes,[75] e.g. **81** (Scheme 24).

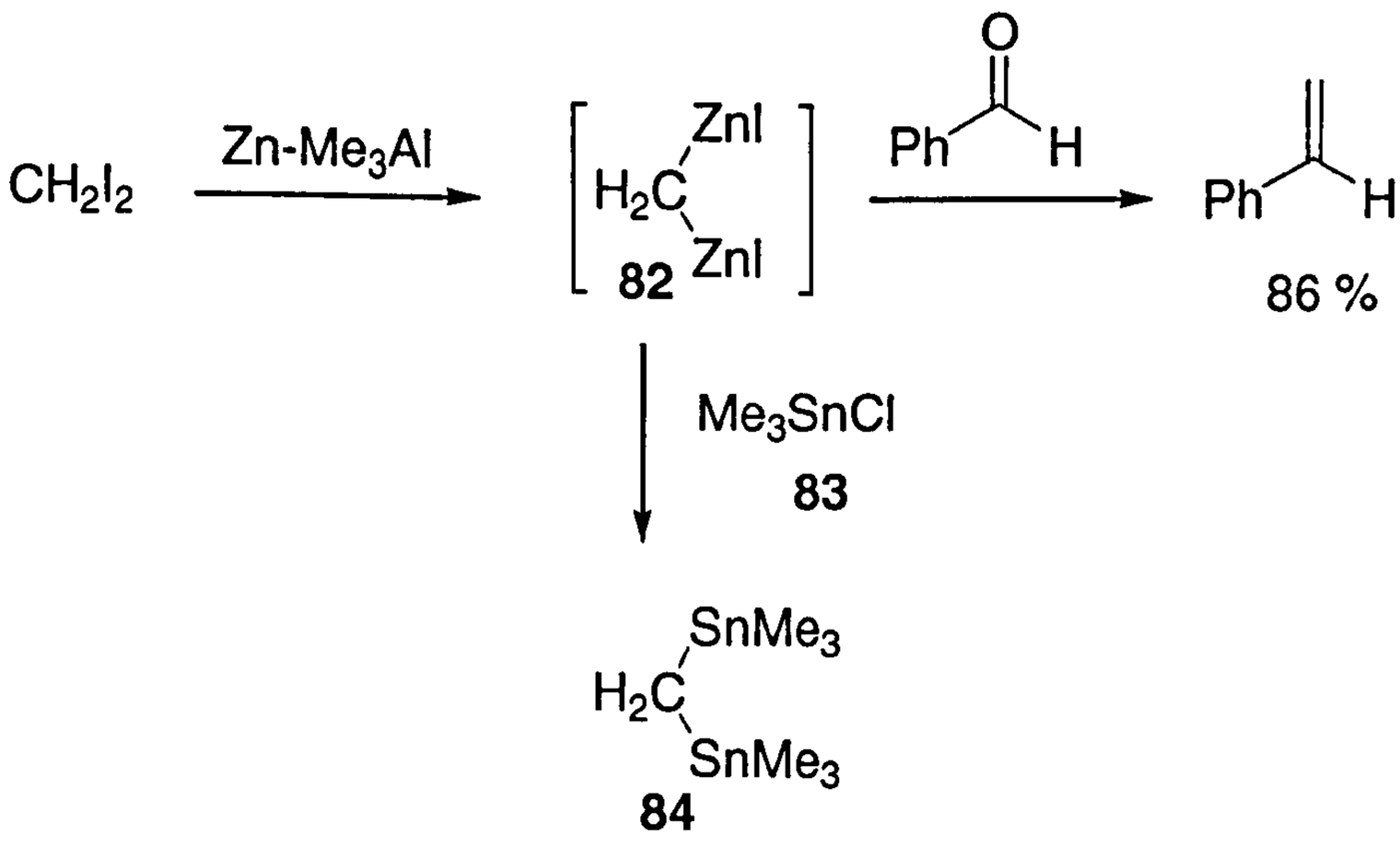


Scheme 24

1.3.4.2 Mechanism

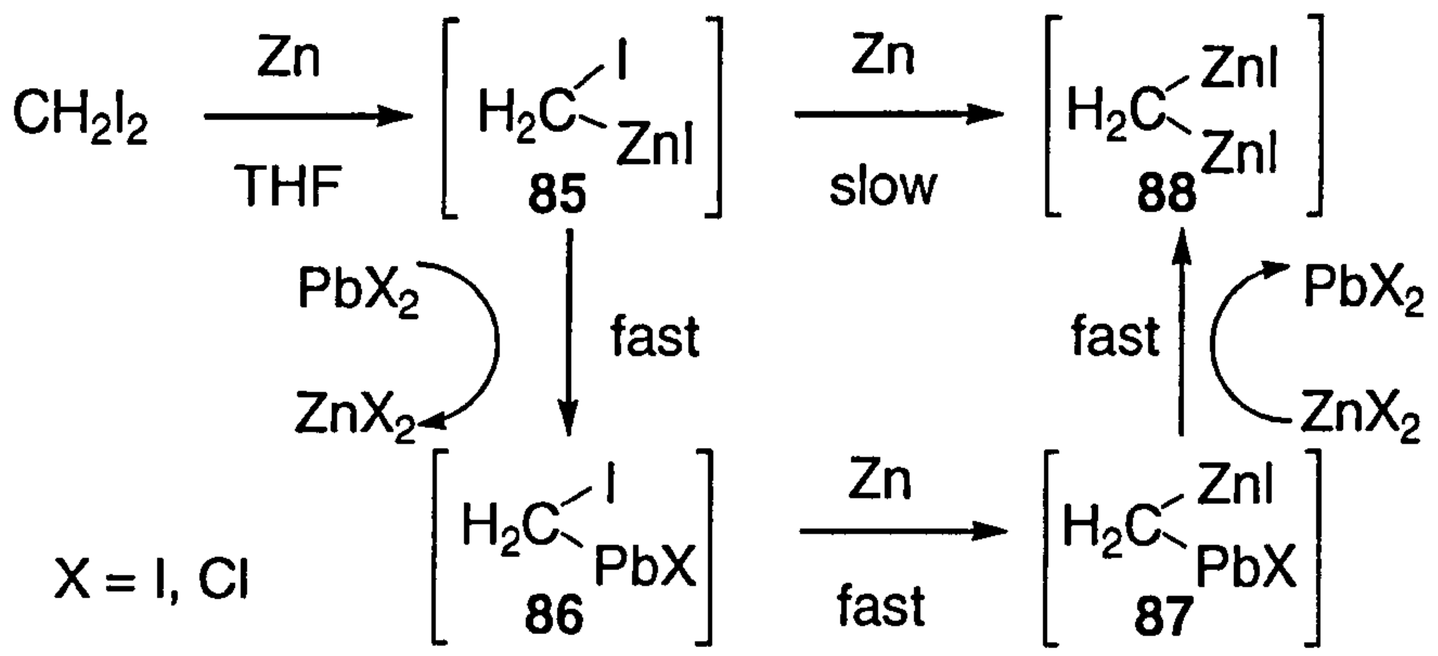
The reactive species in the Takai alkylidenation has not yet been identified and the mechanism therefore remains poorly understood. In his original methylenation reaction, Oshima[68] had suggested that a geminal dizinc compound **82** was a key reaction intermediate (Scheme 25). He showed that upon reaction with trimethyltinchloride **83**, $CH_2(SnMe_3)_2$ **84** was exclusively produced, and referred to the work of Hashimoto[76] who had previously methylenated benzaldehyde using only zinc and a 1,1-dihaloalkane, albeit in moderate to poor yield. However, Oshima was unable to explain the role of the Lewis acid in his reaction.

More recently Yamashita has shown that methylenation of aldehydes could occur with zinc and diiodomethane using ultrasound irradiation.[77]



Scheme 25

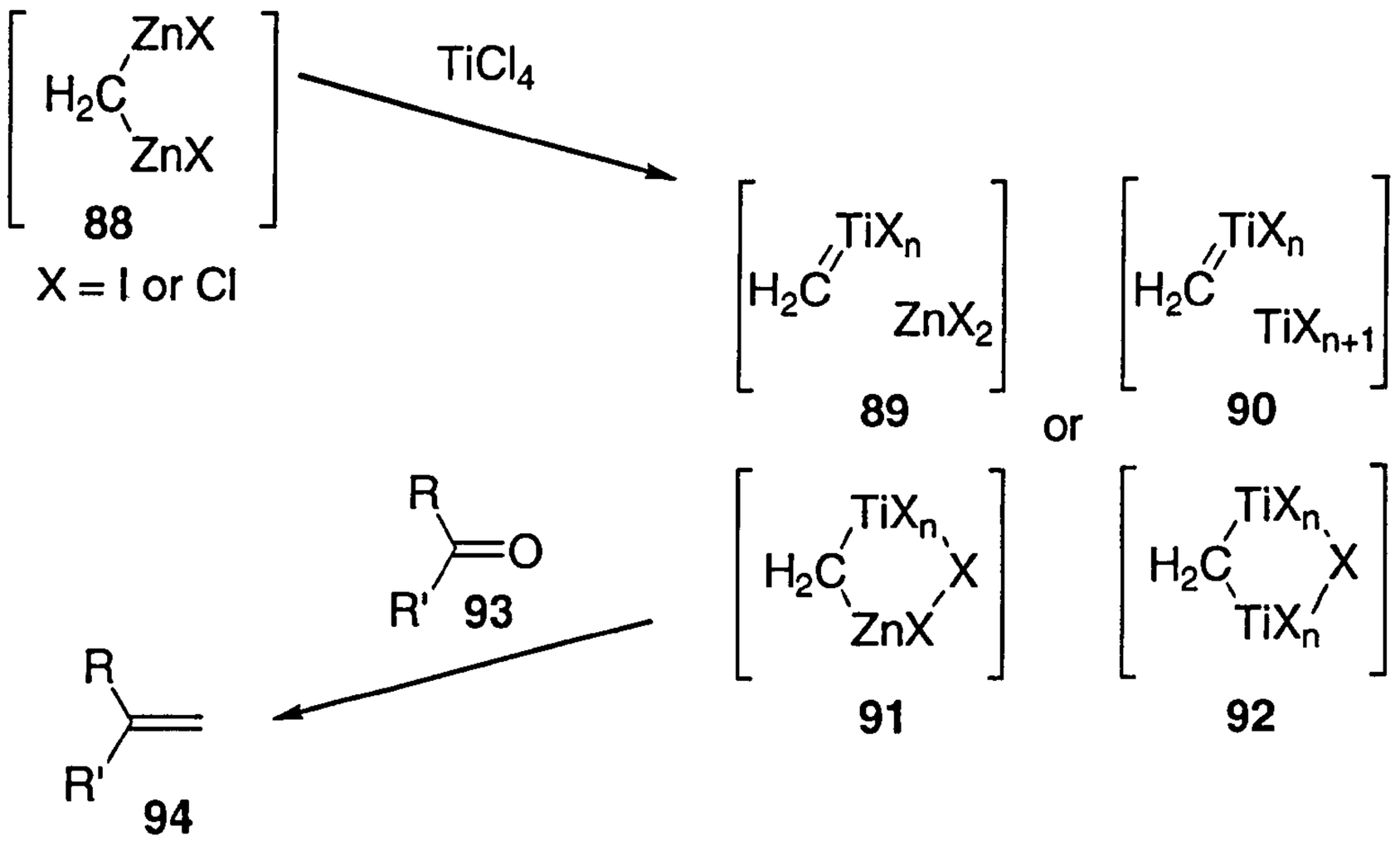
In 1994, Takai reported that the carbonyl methylenation could be accelerated by the addition of catalytic $PbCl_2$, particularly when using the $CH_2I_2/Zn/TiCl_4$ system.[78] He suggested the lead aided the formation of the geminal dizinc compound as shown in Scheme 26.



Scheme 26

Transmetallation of zinc-carbenoid **85** with lead(II) gives lead-carbenoid **86**. This is easily reduced by zinc to give the lead-zinc species **87**. Transmetallation from lead to zinc produces the desired geminal dizinc compound **88**.

Takai suggested that the geminal dizinc compound **88** then reacted with titanium tetrachloride forming one of the Tebbe-type (titanium alkylidene) complex e.g. **89** and **90** or a titanium-containing geminal dimetallic reagent (**91** or **92**) which reacted with the carbonyl compound **93** forming the desired alkene **94** (Scheme 27).

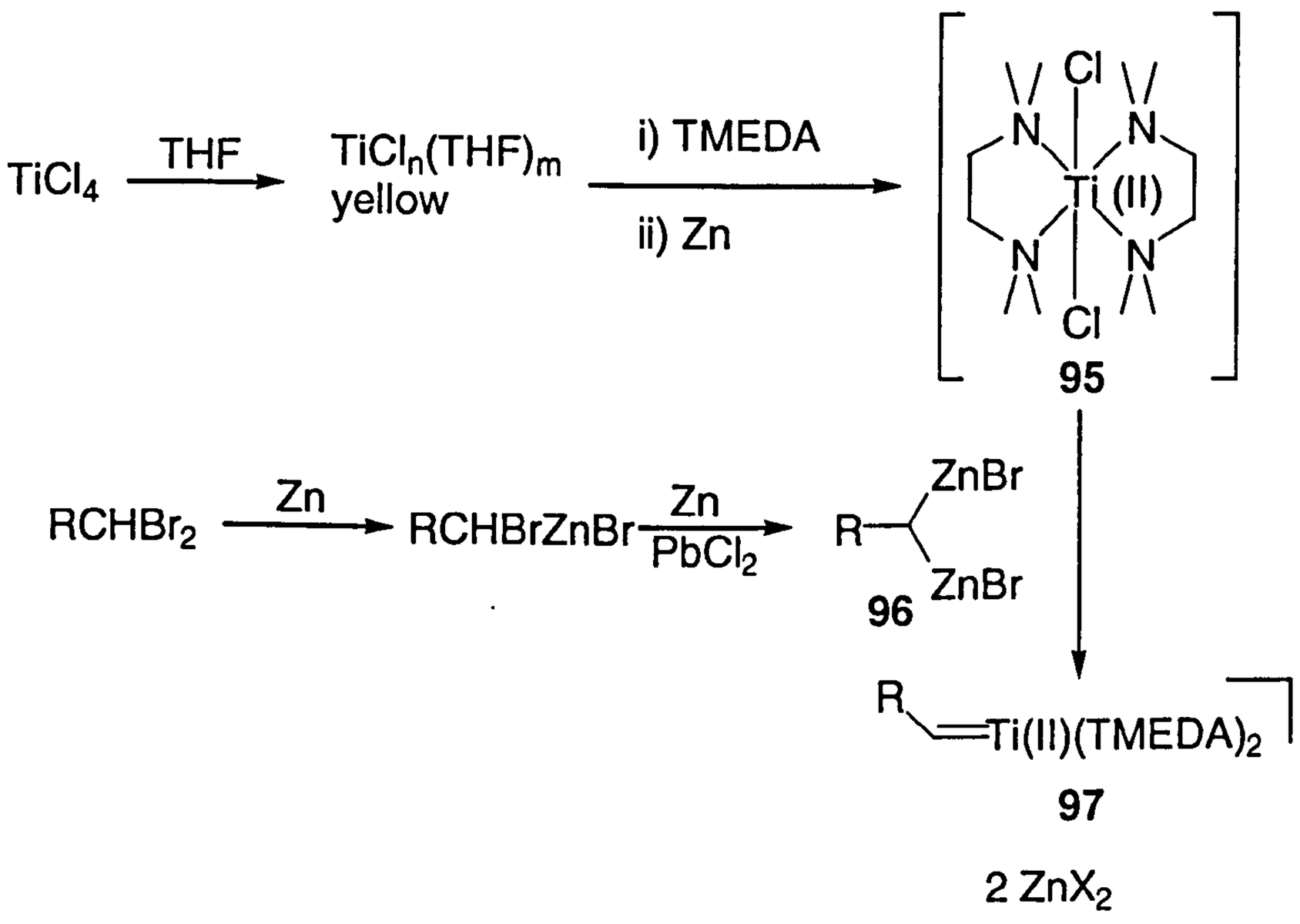


Scheme 27

We have always had a problem with this mechanism, particularly when considering the role of zinc in the $TiCl_4$/TMEDA/CH_2Br_2/Zn system. Empirical evidence does suggest that the presence of lead accelerates the reaction and therefore Takai's theory of the geminal dizinc formation seems probable. However, one only has to look at the equivalents used in the reaction [$TiCl_4$ (4 eq.), TMEDA (8 eq.), zinc (9 eq.) and CH_2Br_2 (2.2 eq.)] to consider the possibility that the zinc has a dual role in the reaction. This is also suggested by the order of addition of the reagents and colour changes in the reaction: titanium tetrachloride is stirred in THF giving a bright yellow complex, then TMEDA is added to give an orange/brown adduct. At this point zinc (together with catalytic lead) is added giving a blue/green mixture, followed by the addition of the 1,1-dihaloalkane and the ester, at which point the mixture turns black.

We propose that the zinc not only forms the digeminal complex, but also has a role in reducing the Ti(IV) to Ti(II), which would explain the colour change which occurs upon addition of the zinc to the reaction mixture. Our alternative mechanism is therefore as follows - the titanium tetrachloride/THF complex reacts with 2 equivalents of TMEDA and 2 equivalents of zinc to give a Ti(II) complex **95** (a crystal structure of such a complex has been published).[79] This complex then reacts with the digeminal zinc complex **96** (which forms *via* Takai's suggested method) giving the active alkylidenating species **97** (Scheme 28).

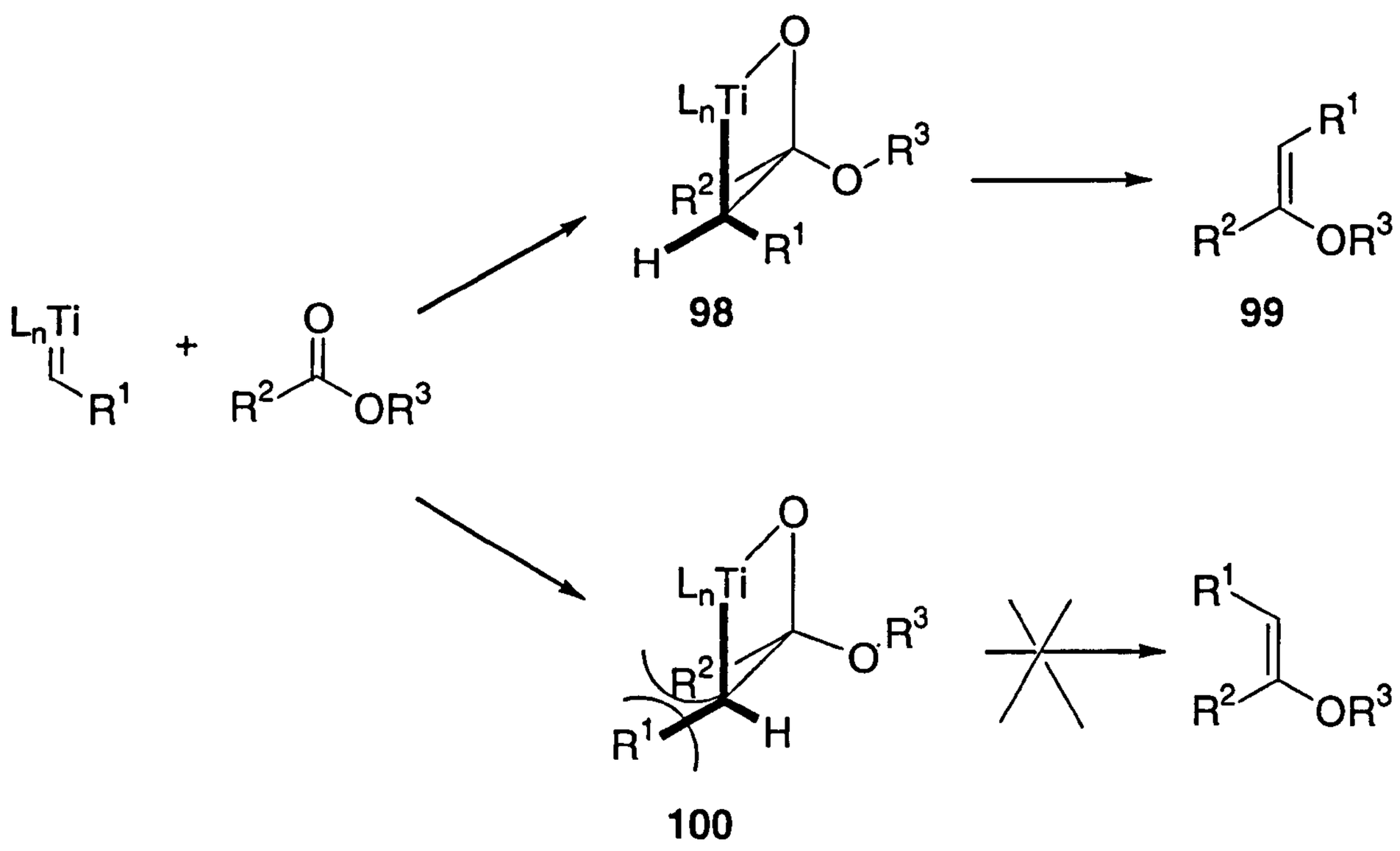
Thus, the alkylidenating agent could be a titanium(II) rather than a titanium(IV) alkylidene.



Scheme 28

Once formed, the titanium alkylidene **97** may react with an ester to give either oxatitanacyclobutane **98** or **100** (Scheme 29).

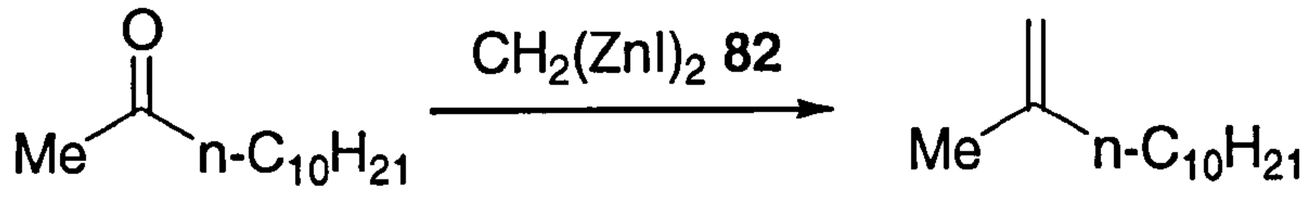
Due to the developing steric crowding between R^1 and R^2 in the transition state leading to oxatitanacyclobutane **100**, the transition state is higher in energy. The enol ether **99** will therefore form *via* oxatitanacyclobutane **98**. The fact that stereoselectivity improves as R^2 increases in size agrees with this model, as does the *E*-selectivity experienced in the alkylidenation of the cyclic amides in Scheme 24.



100

Scheme 29

Recent work by Takai's co-worker Utimoto lends weight to our proposed mechanism. He has recently published a series of papers where methylenation reactions have been carried out using a pre-formed geminal dizinc reagent **82** and a Lewis acid (Scheme 30).[80]

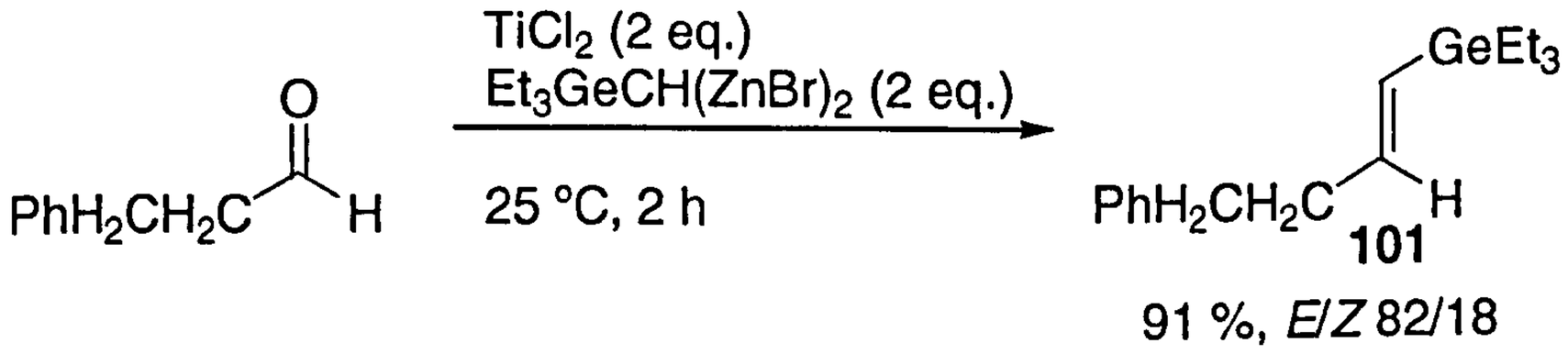


1) stoichiometric **82**, sluggish reaction, no yield reported
2) stoichoimetric **82**,stoichoimetric $TiCl_4$, 26 %
3) 2 equivalents **82**, stoichoimetric $TiCl_4$, 79 %
4) stoichoimetric **82**, stoichoimetric $TiCl_2$, 83 %

Scheme 30

When stoichiometric titanium tetrachloride is used as the Lewis acid, the alkene is formed in 26 %. Increasing the number of equivalents of the geminal dizinc reagent **82** to two results in an increase yield (79 %). Using stoichiometric titanium dichloride gives the alkene in 83 %. Utimoto suggests that Ti(II) mediates the reaction and that in example 3 (Scheme 30) case the geminal dizinc reagent reduces the Ti(IV) to Ti(II).

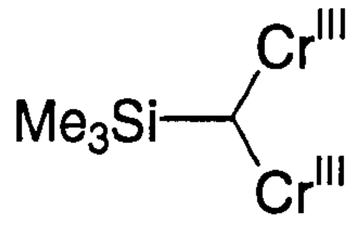
Utimoto and co-workers have since used similar methodology to form alkenylgermanes **101**,[81] and has used a related $CH_2(ZnI)_2/TiCl_2$ system to form alkenyl germane compounds from aldehydes (Scheme 31).[82]



Scheme 31

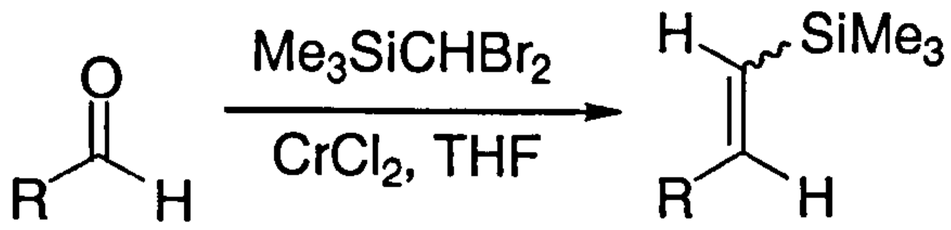
1.3.4.3 Related reactions - Chromium chemistry

Takai and Utimoto have also developed a related reaction where a *gem*-dichromium reagent **102** (Figure 12) is used to form *E*-alkenylsilanes **103** from aldehydes (Scheme 32).[83]



102

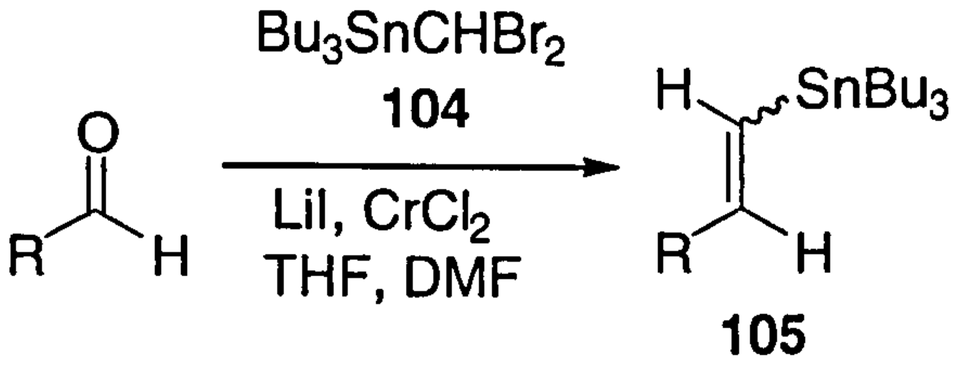
Figure 12



103

Scheme 32

Hodgson and co-workers have employed this methodology to make alkenyltins **105** from aldehydes using tributyl(dibromomethyl)tin **104** (Scheme 33).[84-86]



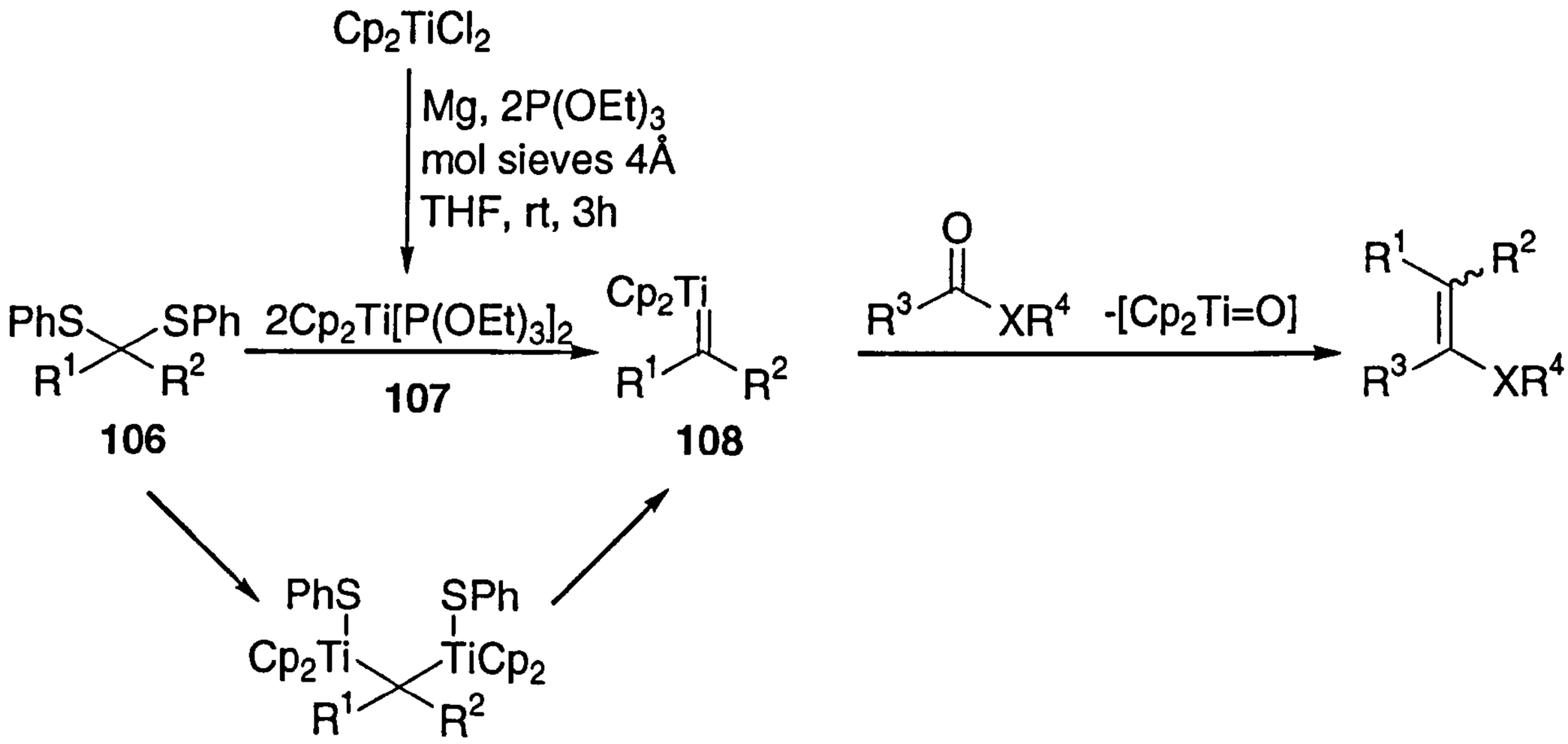
105

Scheme 33

During the course of my research, Hodgson published improved results using tributyl(diiodomethyl)tin as an alternative to the dibromo reagent.[87]

1.3.5 The Takeda alkylidenation

The Takeda reaction is a more recent addition to the titanium-based alkylidenation reactions in the literature.[88] The alkylidenation reagent **108** is formed from a dithioacetal **106** and a titanium(II) complex **107** generated *in situ* (Scheme 34).

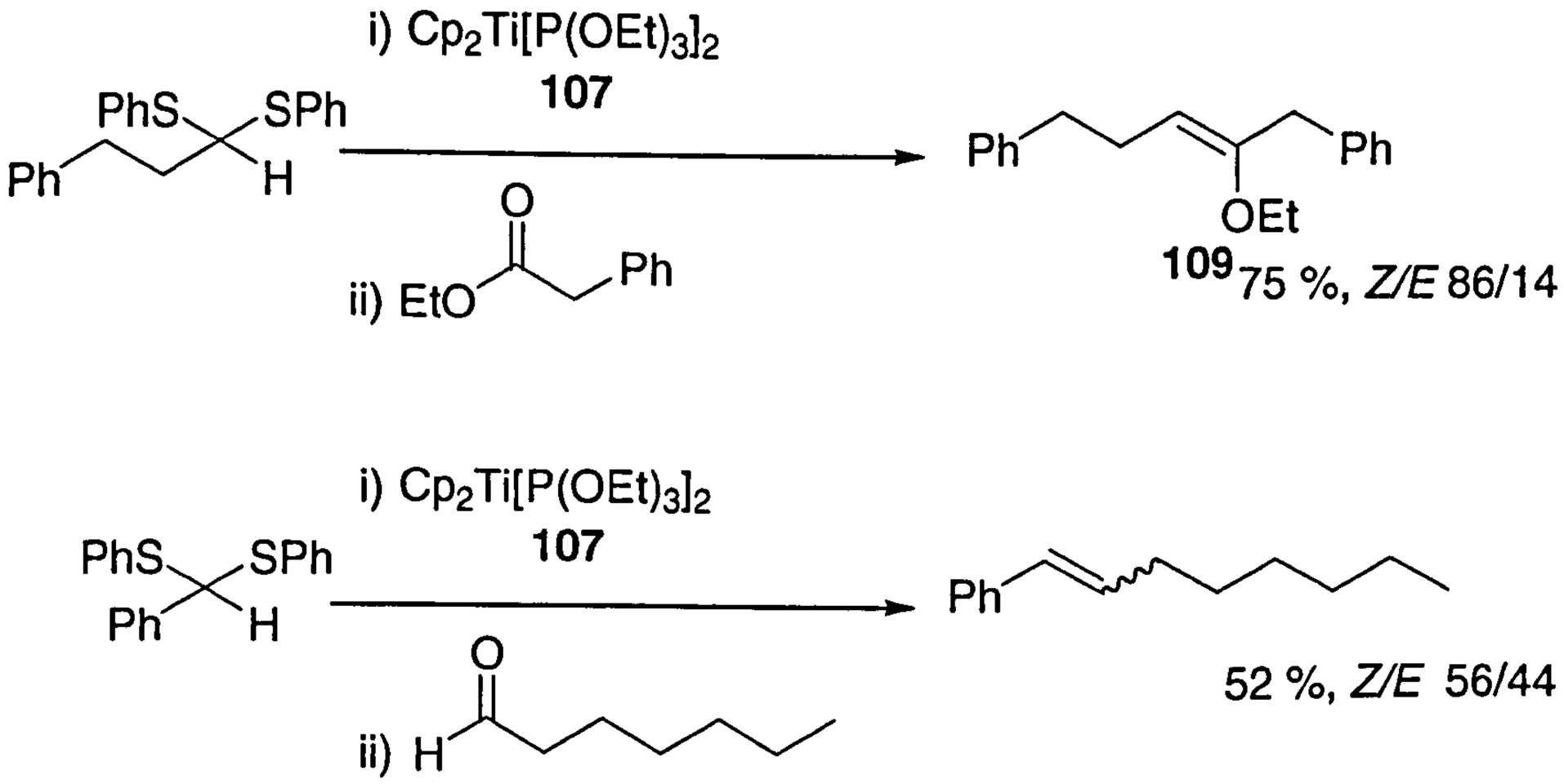


Scheme 34

The mechanism is assumed to proceed *via* desulfurisation of dithioacetal **106** by the titanium complex **107** to give a titanium alkylidene reagent **108**.[89]

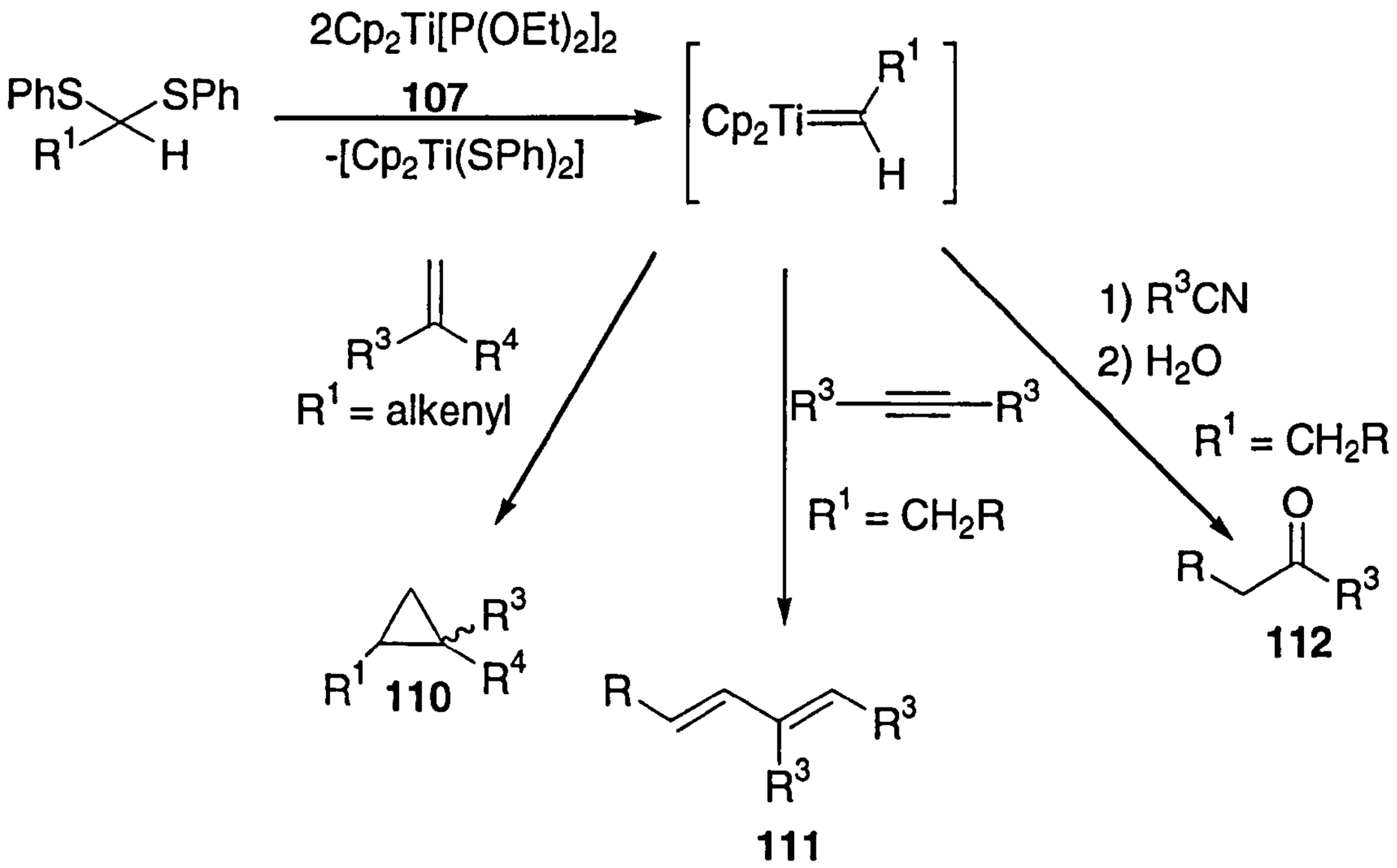
The Takeda reaction shows clear advantages over both the Takai and Petasis alkylidenations. The dithioacetals **106** used are easily accessible from carbonyl compounds, whereas the synthesis of the 1,1-dihaloalkanes required for Takai alkylidenations has been a continuing problem.[88] The *in situ* production of the titanium complex also makes the Takeda reaction particularly attractive. Additionally the conditions employed are very mild, with the reaction carried out completely at room temperature (*c.f.* the reflux conditions of the Petasis reaction) and in the absence of strongly Lewis acidic materials such as $TiCl_4$.

The reaction proceeds smoothly with aldehydes, ketones, esters, thioesters and lactones and no limitations with respect to the structure of the dithioacetal has yet been discovered prior to our work.[88] When esters and lactones are alkylidenated the reaction shows high stereoselectivity, giving predominantly *Z*-enol ethers such as **109**. However the stereoselectivity in alkylidenations of aldehydes and ketones is poor (Scheme 35).[88]



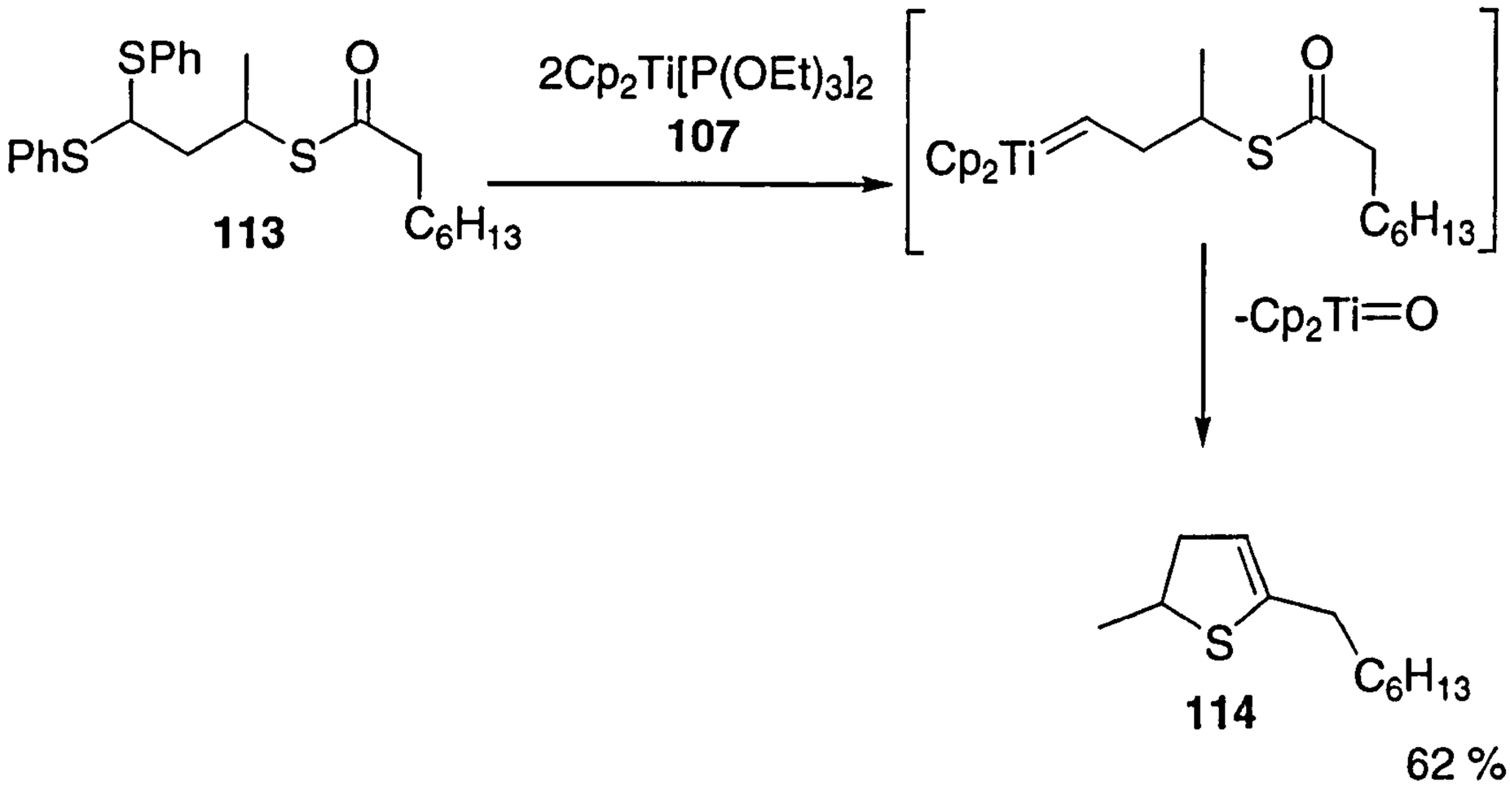
Scheme 35

Takeda has shown that the use of the titanium reagent **107** is not limited to carbonyl alkylidenation. When titanium alkylidenes are prepared using this reagent in the presence of alkenes, cyclopropanation[90] products **110** have been observed, while reaction with alkynes yields conjugated dienes **111**[91] Reaction with nitriles gives α-substituted ketones **112** (Scheme 36).[92]



Scheme 36

Ring-closing metathesis reactions have also been carried out using low valent titanium complex **107**.[93,94] While these reactions have been successful, attempts to produce a general intramolecular alkylidenation reaction using Takeda's method have been more variable. Reactions on thioesters (e.g. **113**) containing a thioacetal moiety have worked well to give 2,3-dihydrothiophenes **114** (Scheme 37),[95] but reactions with the corresponding esters have been poor yielding.[96] A discussion of intramolecular Takeda reactions attempted by myself appears later (Chapter 3).

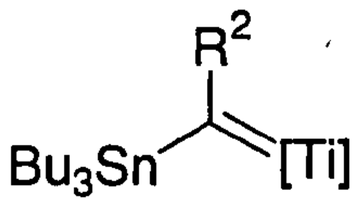


Scheme 37

1.4 Tin chemistry

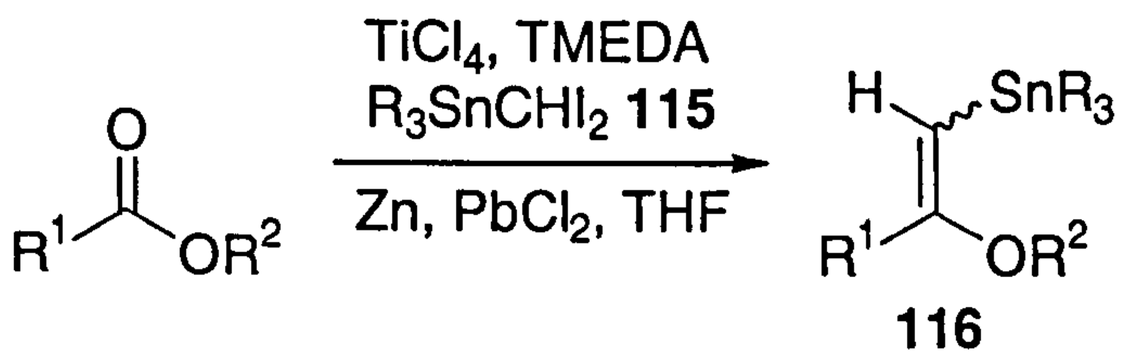
1.4.1 Background

Our first suggested route to benzofurans (**Route A**, p 2) involved a novel tin-containing alkylidene reagent (Figure 13) being formed from a trialkyl(dihalomethyl)tin **115** under Takai's conditions. Reagent **4** would be formed as an intermediate in the alkylidenation reaction and used to make alkenyltin products **116** (Scheme 38).



4

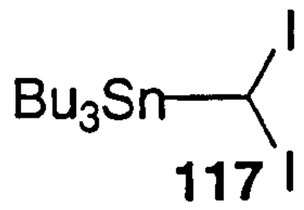
Figure 13



116

Scheme 38

The main concern in using such an organotin reagent in the Takai reaction would be that the zinc present could reduce the tin-carbon bond.[97] Diiodoalkanes react more quickly than the corresponding dibromo reagents under Takai's conditions. We therefore decided to synthesise diiodide **117** (Figure 14) with the hope that zinc would insert more readily into a C-I bond than a C-Sn bond. A tributyltin reagent was chosen over a trimethyl or triethyl equivalent due to the high toxicity of the more volatile organotin compounds.



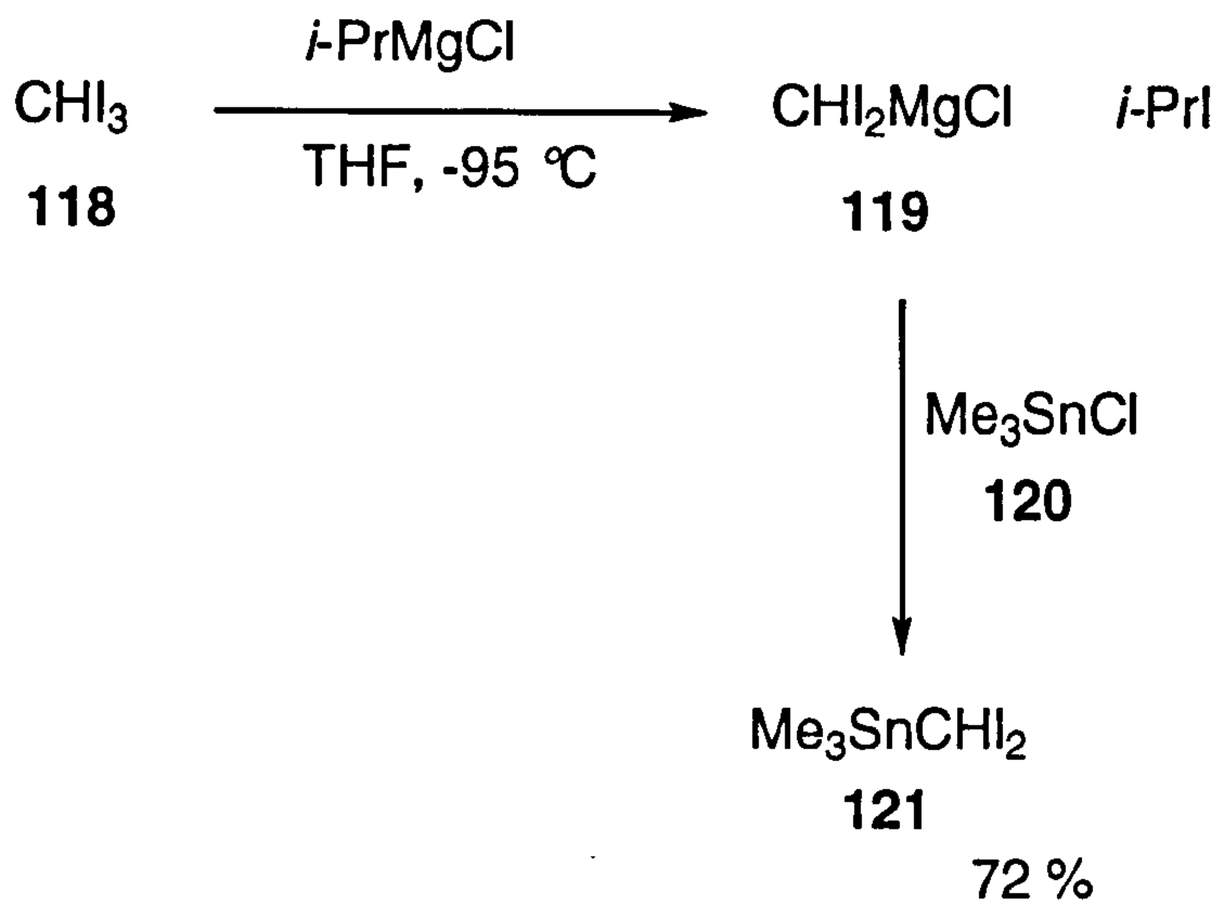
117

Figure 14

This section looks at the different literature syntheses of dihalides **115**.

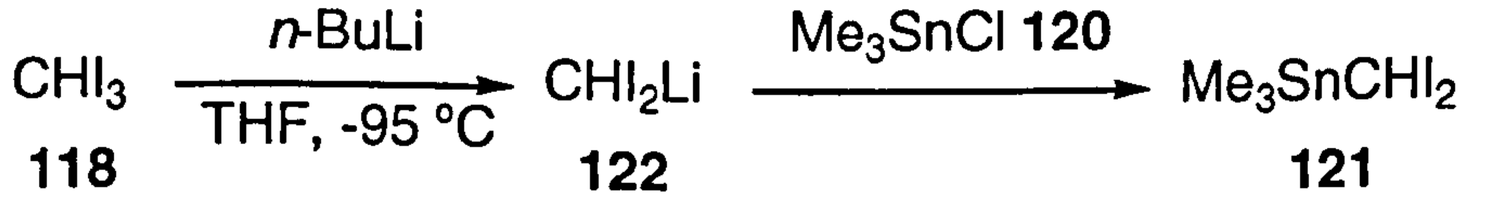
1.4.2 Syntheses of trialkyl(dihalomethyl)tins

There are several methods of synthesising trialkyl(dihalomethyl)tins **115** that avoid many of the problems associated with the analogous monohalide compounds (namely many side products and the inability to perform the reactions on large scales). However the dihalides have been shown to be less stable than their monohalide equivalents[98] and so care must be taken in their handling. Seyferth *et al.* synthesised trimethyl(diiodomethyl)tin **121**[99] by preparing the diiodomethylmagnesium chloride **119** from iodoform **118** using the procedure of Normant and Villeras.[100] Treatment of the Grignard reagent **119** with trimethyltin chloride **120** gave the diiodide in 72 % yield (Scheme 39).



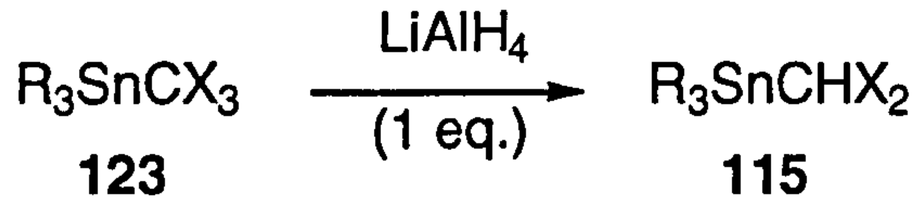
Scheme 39

The same compound was made in 66 % yield from the analogous lithium reagent **122**, (Scheme 40).[101]



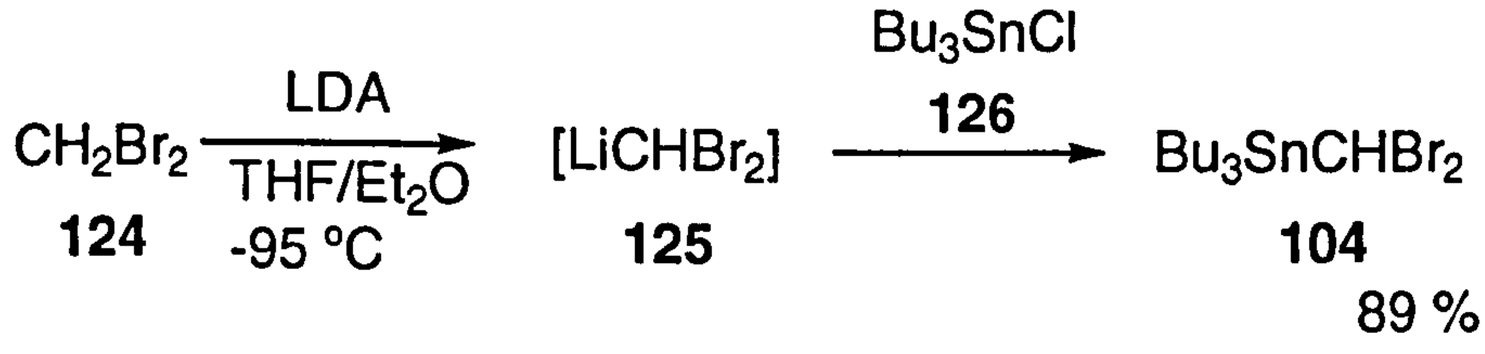
Scheme 40

Dihalide **115** can also be prepared by reduction of the trihalide **123** using one equivalent of lithium aluminium hydride (Scheme 41).[102]



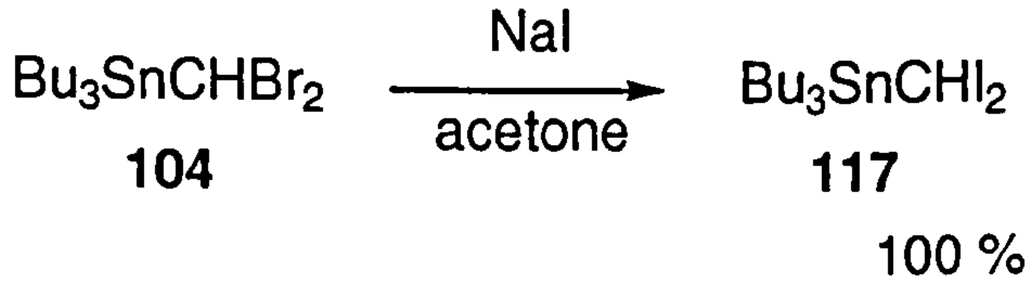
Scheme 41

Hodgson *et al.* used dibromide **104** to form *E*-alkenyltin compounds using low-valent chromium chemistry (see Scheme 33).[84-86] The reagent was formed by treatment of dibromomethane **124** with LDA and the intermediate species **125** then reacted with tributyltin chloride **126** to give the dibromide in 89 % yield (Scheme 42).[86]



Scheme 42

During the course of my research Hodgson also generated his chromium reagent from diiodide **117**[87] which he formed by carrying out a Finkelstein reaction[103] on dibromide **104** (Scheme 43).



Scheme 43

As can be seen by the above, there are a number of approaches to the key diiodo reagent **117**. A discussion on the synthetic strategy chosen by myself appears in Chapter 2.

The following section in this chapter gives a background to solid-phase synthesis.

1.5 Solid support chemistry

1.5.1 Background

The techniques for solid-phase synthesis (SPS) are based on the work of Merrifield,[104] who in 1963 described the use of solid-phase for peptide synthesis. Since that time the use of SPS has grown to encompass the synthesis of small organic molecules and many different organic reactions have been carried out on solid-phase. The growth of SPS has been mirrored by that of combinatorial chemistry, a technique that now proves invaluable to the modern industrial chemist. The section does not dwell on the topic of combinatorial chemistry,[105] but looks at standard organic reactions in SPS, particularly alkylidenations. Different types of linker are discussed, along with ways of cleaving products from the resin.

One of the main attractions of SPS to the organic chemist is in the ease of product isolation. Assuming that complete conversion from resin-bound starting material to product occurs, purification merely requires the washing away of reagents and side products, thus avoiding the need for costly chromatography. Most SPS reactions are therefore driven to completion by use of excess reagents, although this obviously reduces the atom-economy of such procedures. However it must be noted that not all reactions can be moved seamlessly from solution to solid-phase and it often requires time to develop the optimal conditions for solid-phase procedures. In addition, the introduction of two extra steps in linking compounds to and cleaving compounds from the resin must be taken into account, and these procedures are often not trivial. In these steps the choice of linker (the moiety which attaches the molecule to the resin) can be of vital importance.

The next section looks at a number of linkers that have been developed and the methods by which they are cleaved.

1.5.2 Linkers/Cleavage methods

1.5.2.1 Introduction

The criteria used when assessing which type of linker to employ in a solid-phase reaction should be much the same as when making a choice of protecting group. Indeed a linker could be described as a bifunctional protecting group, in that it is attached to the molecule being synthesised through a bond labile to the cleavage conditions and attached to the resin through a more stable bond (Figure 15).

Protecting Group-/-Functional Group-Molecule

↓ Deprotection

Functional Group-Molecule

Polymer-Spacer-Linker-/-Functional Group-Molecule

↓ Cleavage

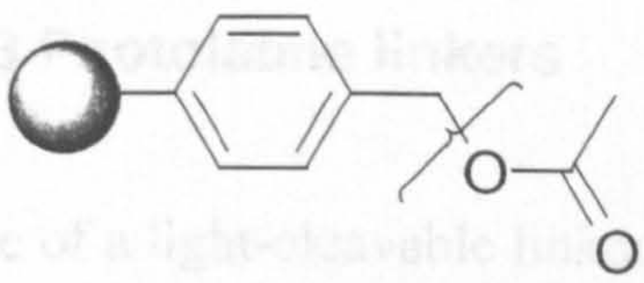
Functional Group-Molecule

Figure 15

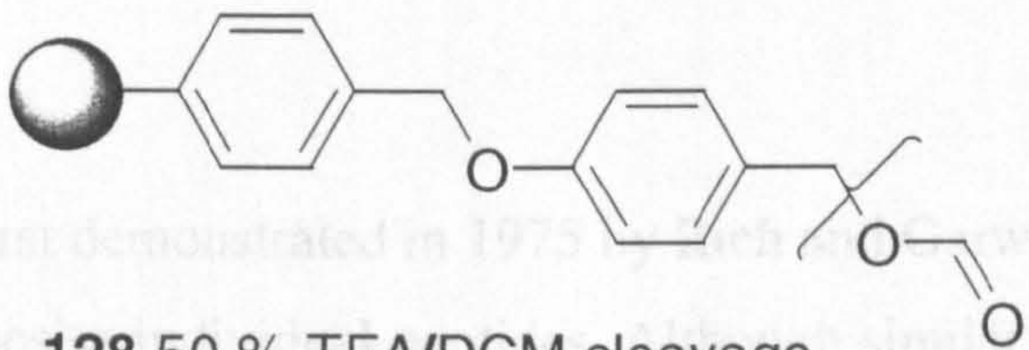
An ideal linker would be cheap, its attachment to the starting material would be facile and high yielding, it would withstand the chemistry carried out on the attached molecule and would be cleavable under conditions that would not affect the final product. Most importantly it must be possible to cleave the final product from the resin under conditions that would not destroy it. Not all of these conditions are always readily achievable. In particular the cleavage step can be problematic, particularly with traditional peptide linkers, which tend to require harsh conditions for cleavage (e.g. HF or TFA). However, the peptide linkers have found a role in the SPS of small molecules, alongside a new generation of linkers developed especially for the task.

1.5.2.2 Acid-Labile linkers

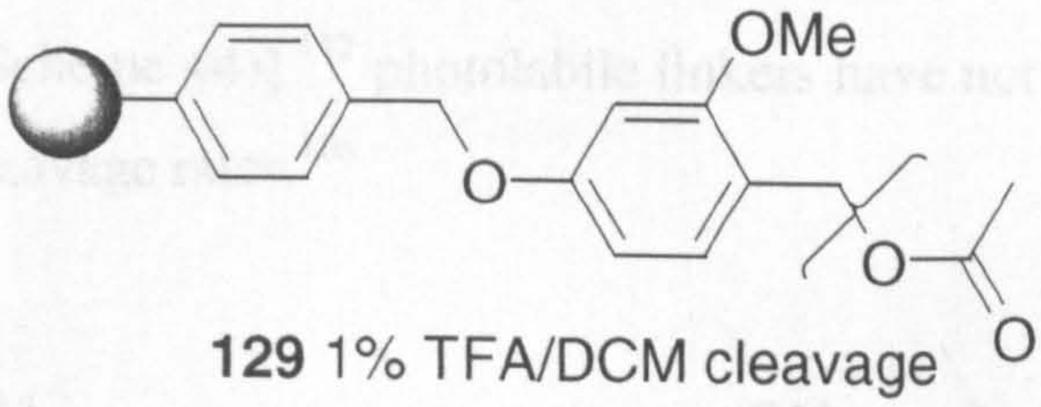
Merrifield gave his name to the original linker used in peptide synthesis.[104] Merrifield resin **127** comprises cross-linked polystyrene functionalised with a chloromethyl group. Carboxylic acids are attached by means of reaction with the acid's cesium salt and cleavage of the functionalised resin occurs when the resin is treated with HF (Figure 16). In 1973 Wang developed a second-major class of resin linker **128** for carboxylic acids (Figure 16).[106] This linker comprises an activated benzyl alcohol design and is also known as HMP (hydroxmethylphenoxy resin). Although originally designed for the synthesis of peptides using the Fmoc-protection strategy, it has found great use in mainstream organic synthesis. [107] It is more acid labile than the Merrifield linker, and so cleavage can occur under milder conditions (50 % TFA/DCM).[108] A linker that is even more sensitive to acid was developed by Mergler *et al.*[109] in 1988. The SASRIN (Super Acid Sensitive Resin) resin **129** has a similar structure to that of Wang's, but contains an additional methoxy group (Figure 16). This group stabilises the carbocation formed during acid-cleavage and it has been shown that successful cleavage can occur with only 0.5-1 % TFA in DCM.[108]



127 HF cleavage



128 50 % TFA/DCM cleavage



129 1% TFA/DCM cleavage

Figure 16

A similar pattern in cleavage reactivity can be seen in carboxyamide linkers where the benzhydral linker **130** requires harsher conditions (HF) to cleave than the related rink-amide linker **131** (TFA). This linker **131** has now become the method of choice for generating resin-bound carboxyamides (Figure 17).[110]

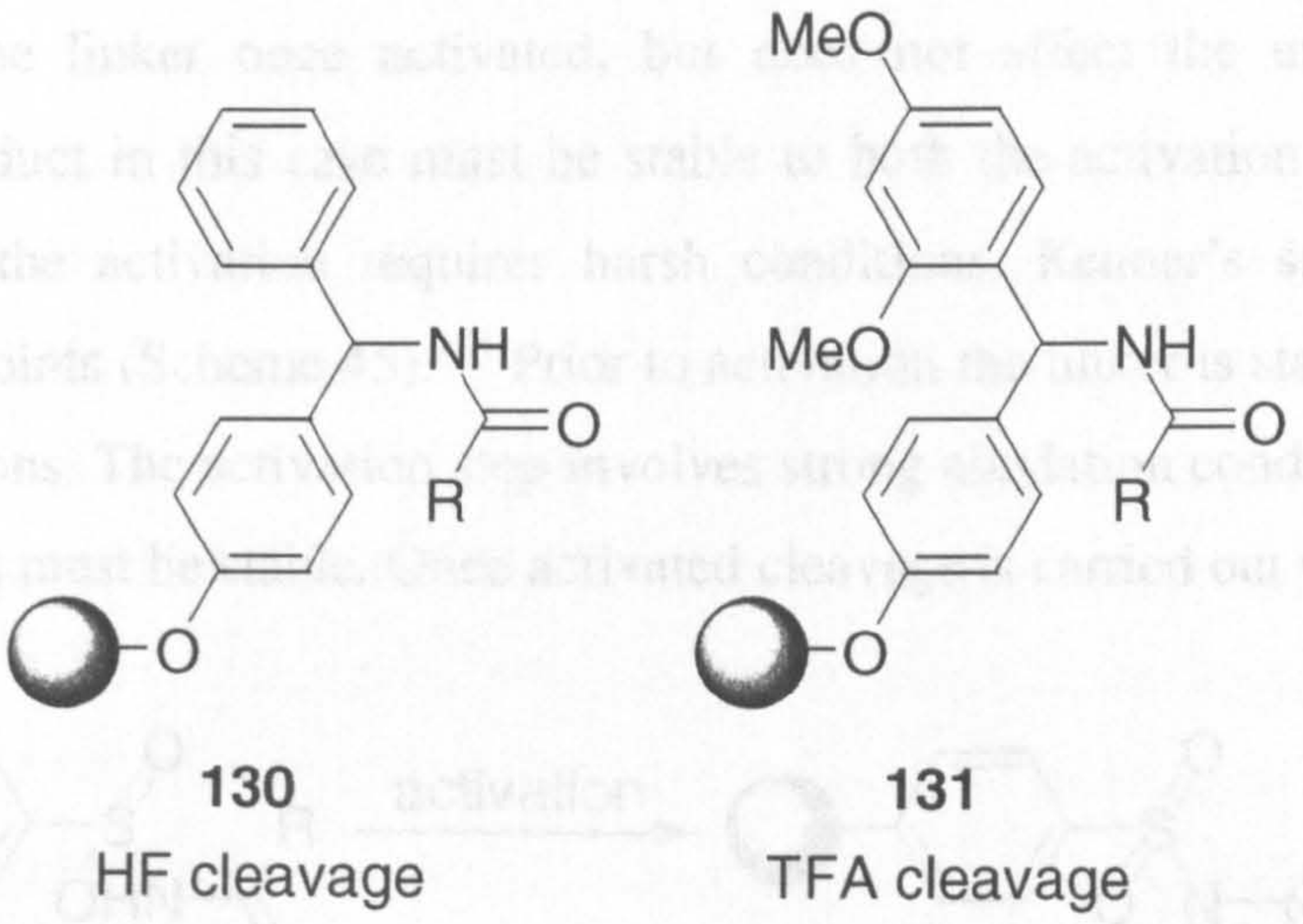
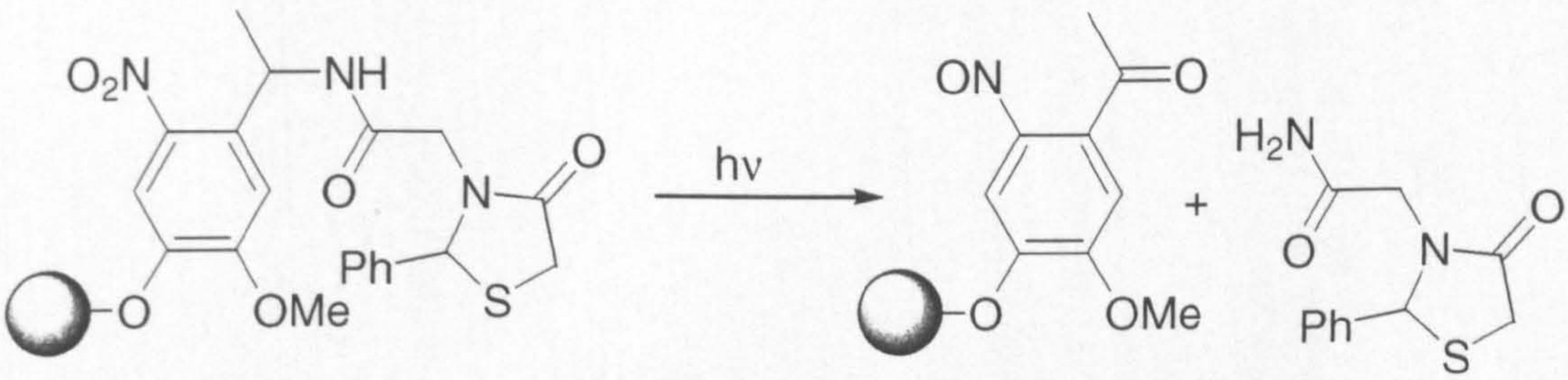


Figure 17

1.5.2.3 Photolabile linkers

The use of a light-cleavable linker was first demonstrated in 1975 by Rich and Gurwara,[111] who employed nitrobenzyl resin to synthesise individual peptides. Although similar resins have been developed, [most notably by Holmes and Jones for the synthesis of thiazolidinones **132** (Scheme 44)],[112] photolabile linkers have not been widely used due to problems with slow cleavage rates.[108]

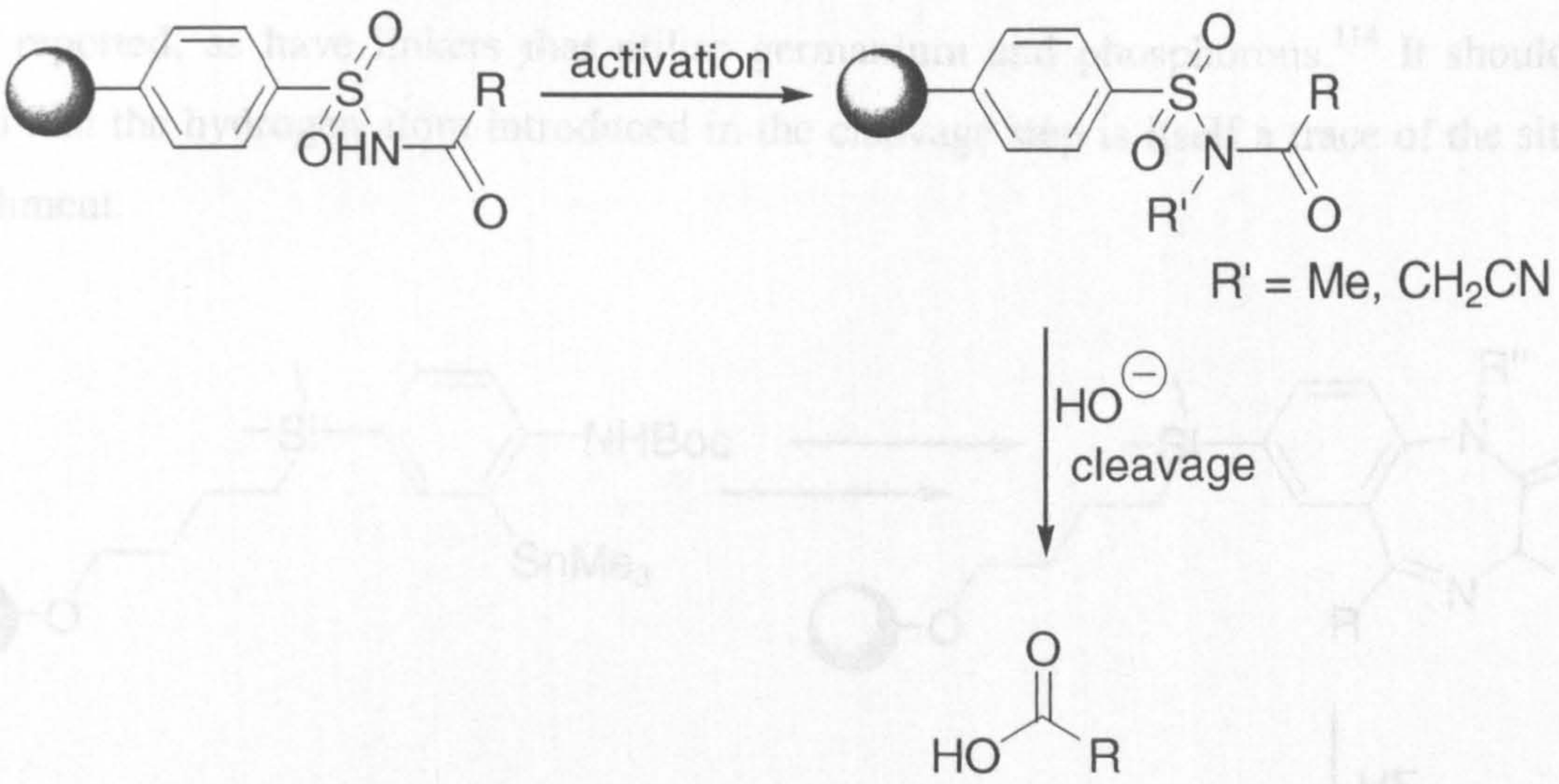


132

Scheme 44

1.5.2.4 Safety-Catch Linkers

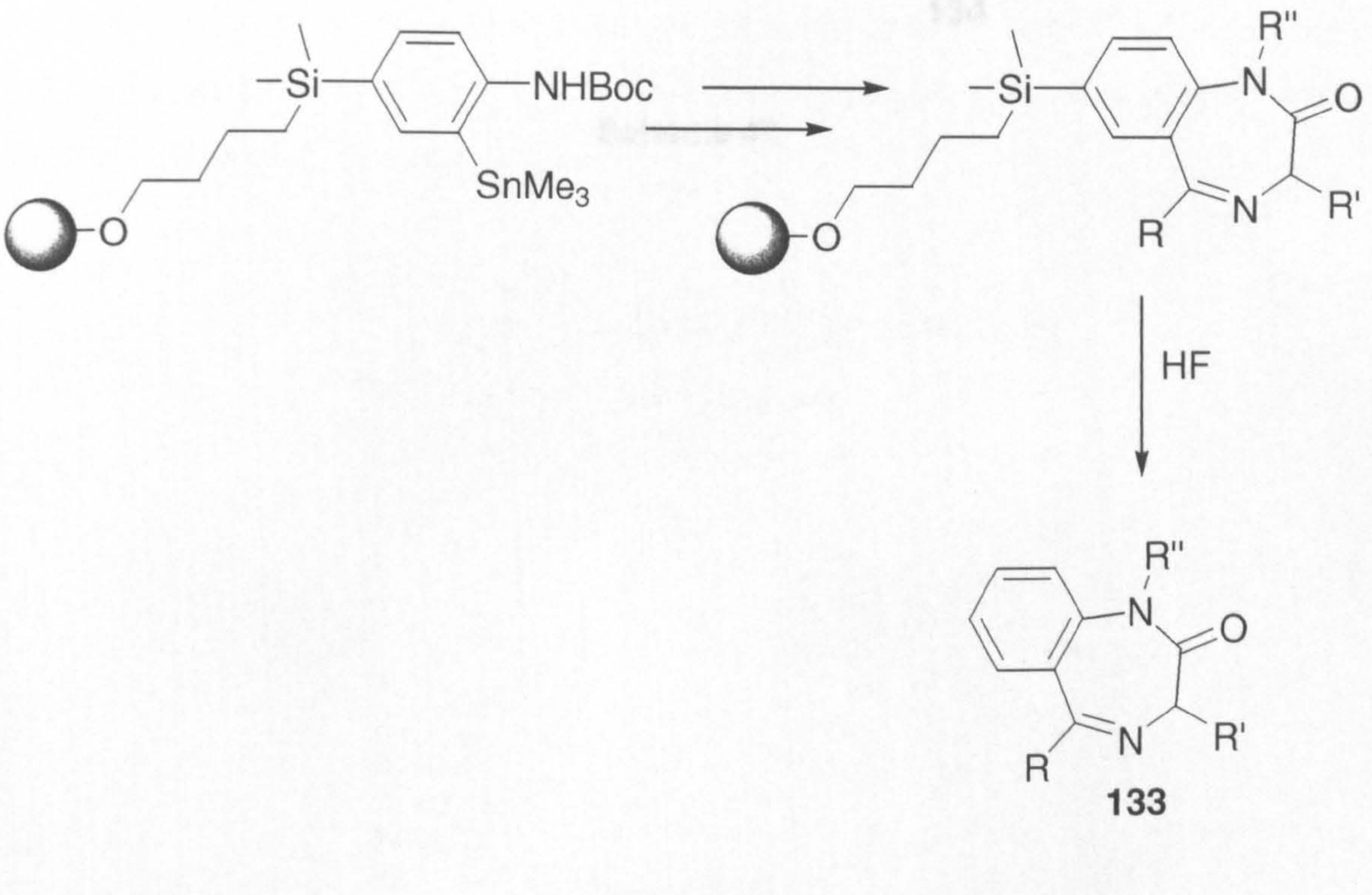
The safety-catch linker relies on a two-step cleavage process. A stable linker is first activated, ensuring that the following cleavage step occurs under mild conditions. This can prove advantageous if there is a step in the synthesis that requires conditions that would usually cleave the linker once activated, but does not affect the unactivated linker. However the product in this case must be stable to both the activation and the cleavage steps and often the activation requires harsh conditions. Kenner's safety-catch linker illustrates these points (Scheme 45).[113] Prior to activation the linker is stable to both acidic and basic conditions. The activation step involves strong alkylation conditions however, to which the product must be stable. Once activated cleavage is carried out with base.



Scheme 45

1.5.2.5 Traceless linkers

Cleavage of the product from a resin generally leaves functionality at the site of where it was attached to the linker, e.g. a carboxylic acid or alcohol. While this is acceptable if the functionality is a desired part of the product, (e.g. the carboxylic acid in peptide synthesis), this is not always the case, and unwanted functionality may affect structure-activity relationships for products used in pharmaceutical or agrochemical research. Consequently *traceless linkers*, where there is no obvious sign of the site of attachment to the linker following cleavage, have been developed. Most examples in this area involve aryl silicon linkers, which cleave under strongly acidic conditions, forming a new carbon-hydrogen bond (e.g. synthesis of **133,** Scheme 46). Such harsh cleavage conditions obviously limits the scope of these linkers, although silicon linkers that cleave under milder conditions have been reported, as have linkers that utilise germanium and phosphorous.[114] It should be noted that the hydrogen atom introduced in the cleavage step is itself a trace of the site of attachment.



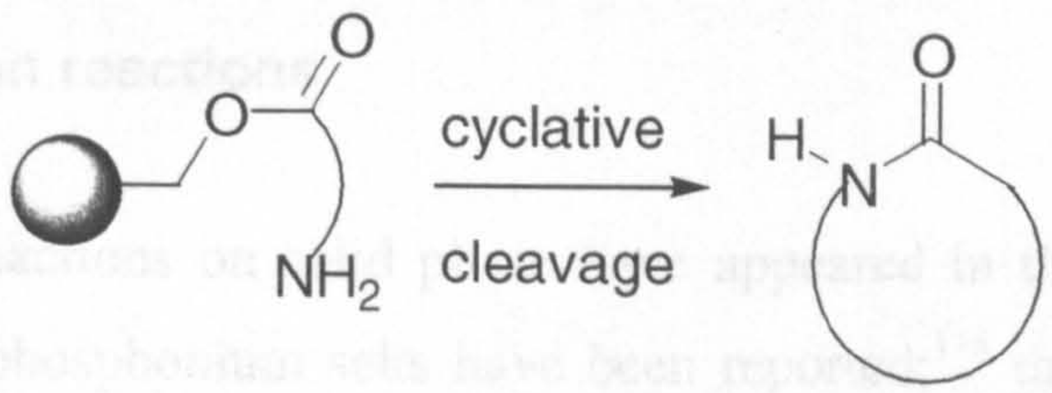
Scheme 46

Our method for the SPS of benzofurans, described in Chapter 4, is truly *traceless* since it leaves no trace of the site of attachment, not even a hydrogen atom.

1.5.2.6 Cyclative cleavage

In certain cases cyclisation and cleavage can occur in a single step. This is the case if the bond being broken in an intramolecular reaction is involved in attaching the molecule to the resin (i.e. it is part of the linker); an example is the release of lactam **133** shown below (Scheme 47). Cyclative cleavage is attractive because target molecules are produced in high purity, the reason being that only compounds with the internal nucleophile can cleave. However, problems with yields may occur due to differing rates of cyclisation, which can vary depending on the side chain present.[108]

Cyclative cleavage *via* ruthenium catalysed metathesis has also been demonstrated.[115]



134

Scheme 47

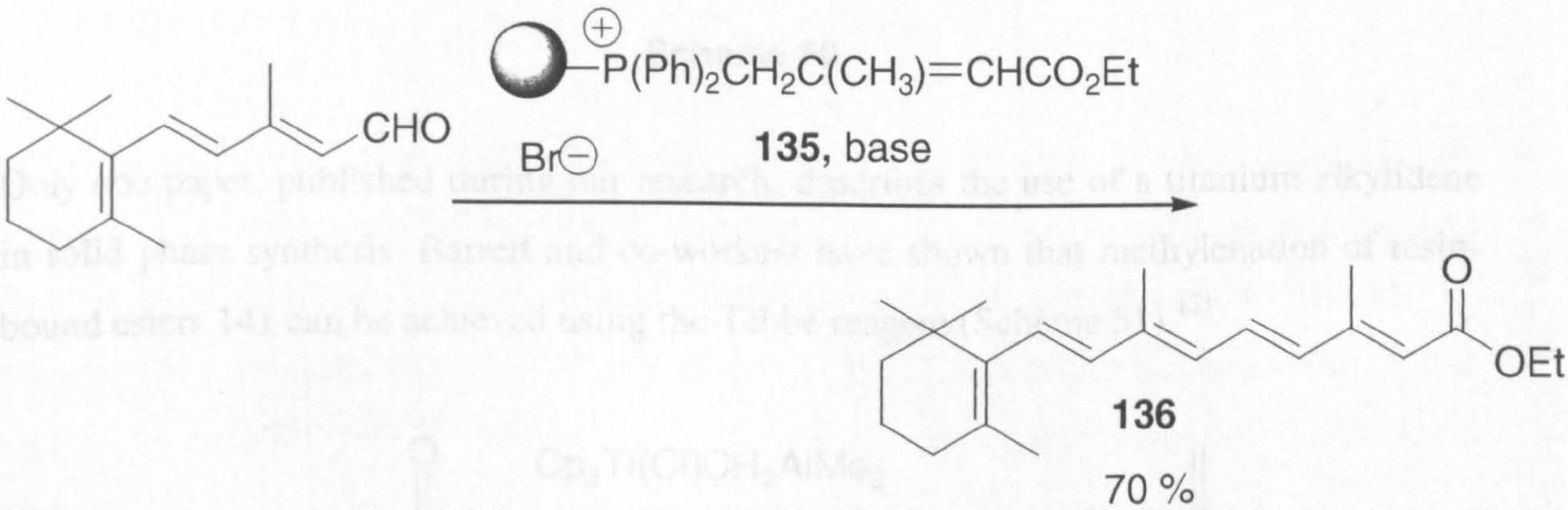
1.5.3 Organic reactions on Solid-Phase

1.5.3.1 Introduction

As previously stated, a large number of SPS papers have shown that many of the key organic reactions can now be carried on solid phase. Foremost among these have been carbon-carbon bond forming reactions[116] with Stille and Suzuki couplings, Heck reactions and cycloadditions being carried out routinely. Heterocycles appear to be key targets in many solid phase syntheses; many of these syntheses are described by Corbett[117] in a recent review. Most pertinent to this project is the use alkylidenation reactions in SPS and benzofuran syntheses by SPS. A number of these syntheses are described below.

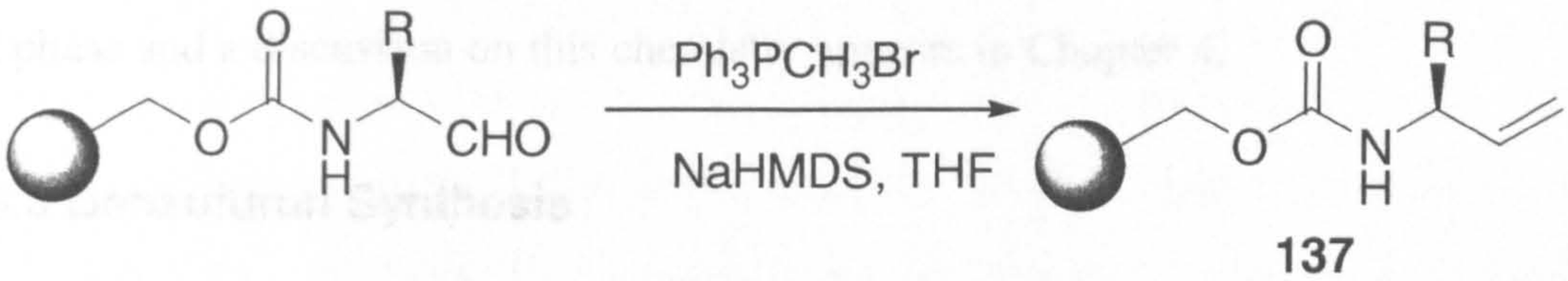
1.5.3.2 Alkylidenation reactions

A number of Wittig reactions on solid phase have appeared in the literature. Examples using polymer-bound phosphonium salts have been reported;[118] these reactions have the advantage that the usual by-product of phosphine oxide remains resin-bound. An example of this is Ford and co-workers' synthesis of ethyl retinoate **136** using polymer-bound phosphonium salt **135** (Scheme 48).[119]



Scheme 48

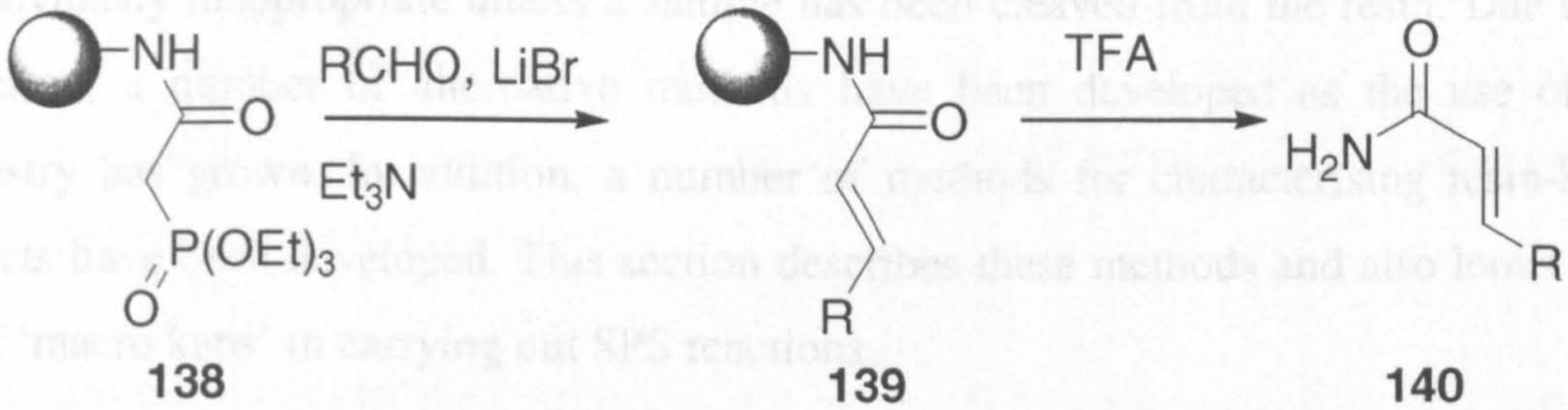
Wittig reagents have also been applied to resin-bound aldehydes and ketones (e.g. Kurth and Lorbach's formation of alkene **137**), (Scheme 49).[116]



137

Scheme 49

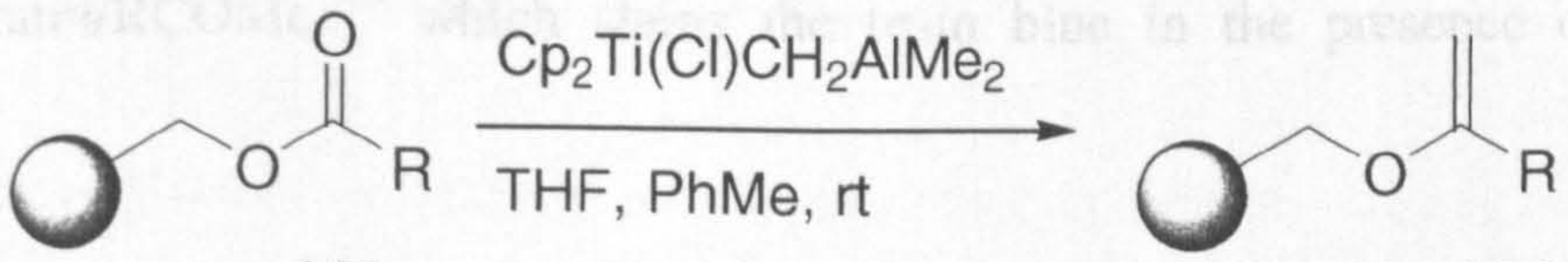
Unsurprisingly, HWE reactions have also been carried out on solid phase. For example, a polymer-bound diethylphosphonacetamide **138** was used in an HWE reaction that effectively synthesised primary amides **140** after cleavage of the resin-bound product **139** (Scheme 50).[120]



138 **139** **140**

Scheme 50

Only one paper, published during our research, describes the use of a titanium alkylidene in solid phase synthesis. Barrett and co-workers have shown that methylenation of resin-bound esters **141** can be achieved using the Tebbe reagent (Scheme 51).[121]



141 **41 - 92 %**

Scheme 51

Petasis has also mentioned the possibility of carrying out alkylidenations on polymer-supported peptides using his reagent,[122] but has yet to publish any details.

As one of the main challenges in titanium-based alkylidenation reactions is in the purification of the products, the idea of carrying out the reactions on polymer-supported substrates is an attractive one. I have successfully carried out the Takeda alkylidenation on solid phase and a discussion on this chemistry appears in Chapter 4.

1.5.3.3 Benzofuran Synthesis

A number of syntheses of benzofurans that employ SPS chemistry have been discussed in section 1.2.2.3.

1.5.4 Reaction Monitoring/Product characterisation

One of the main challenges in using SPS chemistry is monitoring the progress of the reactions. While thin-layer chromatography is traditionally used for this purpose, with SPS it is obviously inappropriate unless a sample has been cleaved from the resin. Due to this restriction, a number of alternative methods have been developed as the use of SPS chemistry has grown. In addition, a number of methods for characterising resin-bound products have been developed. This section describes these methods and also looks at the use of 'macro kans' in carrying out SPS reactions.

1.5.4.1 Colourimetric Analysis

A number of colour tests were developed alongside the growth in solid phase peptide synthesis. Such tests are concerned with detecting amine functionality. The most famous of these is the Kaiser test - a sensitive assay that uses ninhydrin, a blue stain, to indicate the presence of a primary amine[123]. Other reagents include 2,4,6-trinitrobenzenesulfonic acid and *p*-chloranil/RCOMe,[123] which stains the resin blue in the presence of secondary amines.

1.5.4.2 Infra Red Spectroscopy

Although not used for quantitative analysis, IR spectroscopy proves a useful non-destructive method for the qualitative analysis of certain functional groups on solid phase. Dried polystyrene resin can be used to prepare KBr discs that provide adequate spectra.[124] Newer pieces of equipment such as the Golden Gate (used to analyse the resin-bound products in this thesis) mean that the resin can be analysed with no further manipulation.

1.5.4.3 Nuclear Magnetic Resonance Spectroscopy

Gel phase NMR spectra can be obtained but suffer from significant line broadening due to chemical-shift anisotropy and dipolar coupling.[123] For this reason, only nuclei with a strong chemical shift dispersion such as ^{13}C, ^{15}N, ^{19}F and ^{31}P give useful spectra, while ^{1}H NMR spectra remain poorly resolved. However the development of magic angle spinning (MAS) has addressed this problem. This technique was developed particularly for resin-bound compounds. Well-resolved spectra including high quality ^{1}H NMR spectra can be produced.

1.5.4.4 Use of 'kans'

The use of IRORI 'kans' has proved very useful to our group in carrying out SPS reactions. These reaction vessels are best described as 'plastic tea bags' as the resin remains within the reactor while the reaction mixture can flow in and out through the plastic mesh. A number of sizes of kan exist, the 'macro kan' used by our group is the largest and holds approximately 0.3 mmol of resin-bound material. The advantages of using these vessels are numerous -

- By weighing precisely the correct amount of preloaded resin into each kan it is possible to tell if the reaction has gone to completion by calculating the theoretical weight gain and weighing the dried resin within the kan after reaction work-up.

- A number of different resin-bound products can be produced in one pot by reacting different starting materials in different kans. Kans are used in industry in combinatorial synthesis, where a radio-labelled tag is present in each kan and allows the 'split and mix' procedure to be effectively carried out.

- Kans are very useful in heterogeneous reactions (such as the Takeda reaction which uses powdered molecular sieves). When using loose resin it proves difficult to separate the resin from the heterogenous reagent; the use of kans eliminates this problem.

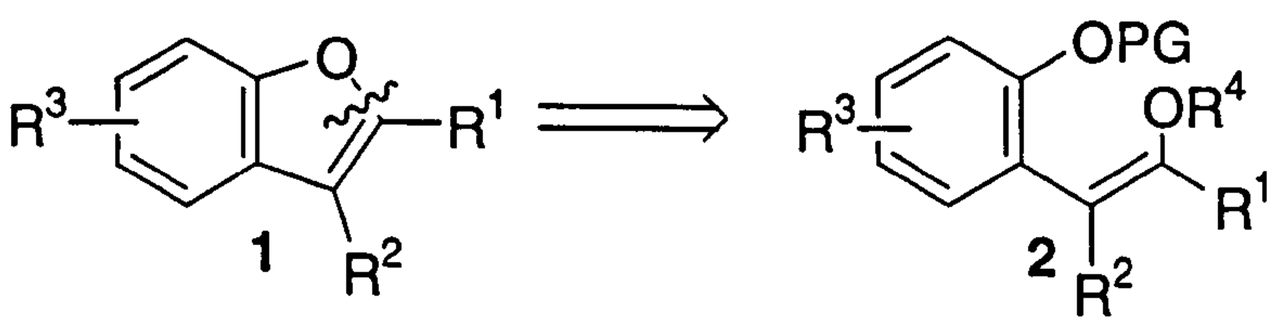
I have used IRORI macro kans in all my SPS reactions. Further details are contained in the experimental section.

Chapter 2 - Route A

Tin-containing alkylidenes - benzofurans

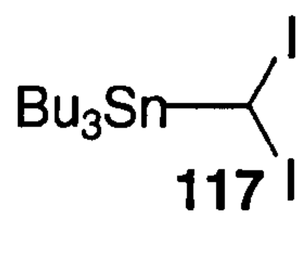
2.1 Introduction

It was proposed in the previous chapter that a novel tin-containing alkylidene reagent **4** could be used as part of a route to give substituted benzofurans **1** (Scheme 52, see also Route A, Scheme 1). The key step in this route was to be a Takai alkylidenation reaction giving β-alkoxyvinylstannanes **3**. This reaction would be novel, as although Takai has formed β-alkoxyvinylsilanes from esters, he has yet to report the formation of the corresponding tin compound using his methodology (see section 1.3.4).



Scheme 52

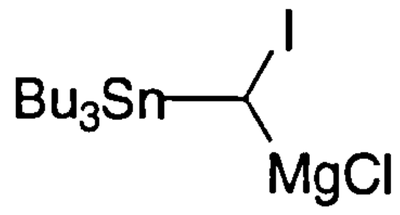
This chapter describes my attempts to synthesise benzofurans using **Route A** and concentrates on the synthesis of diiodide **117** and its use in the Takai alkylidenation. The reasons for choosing this particular reagent are described in section 1.4.1 and are based on the lower toxicity of the tributyltin reagents in comparison to more volatile trialkyl equivalents and also the higher reactivity of diodoalkanes in Takai's reaction as compared to the corresponding dibromo compounds.



117

Figure 18

In the course of investigating this reaction it was realised that diiodide **117** could be monode-iodinated using a Grignard reagent. Reactions with the dimetallic compound **142** (Figure 19) that formed were investigated and are described later in this chapter.



142

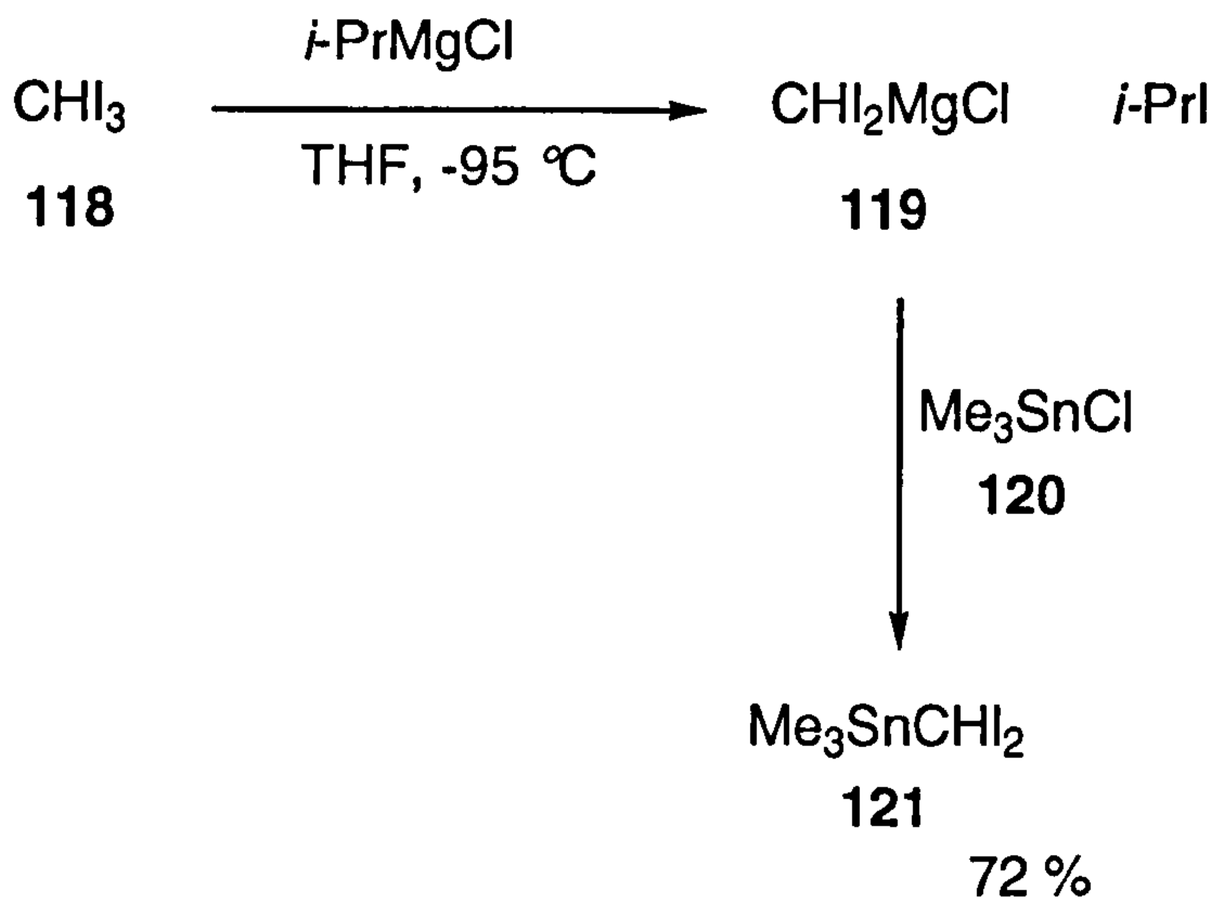
Figure 19

The chapter is therefore split into 4 main sections -

- the synthesis of Bu_3SnCHI_2 **117**
- the alkylidenation reactions performed
- the synthesis of the reagent $Bu_3SnCHIMgCl$ **142** and a discussion of its potential uses
- a section on the synthesis of GC standards

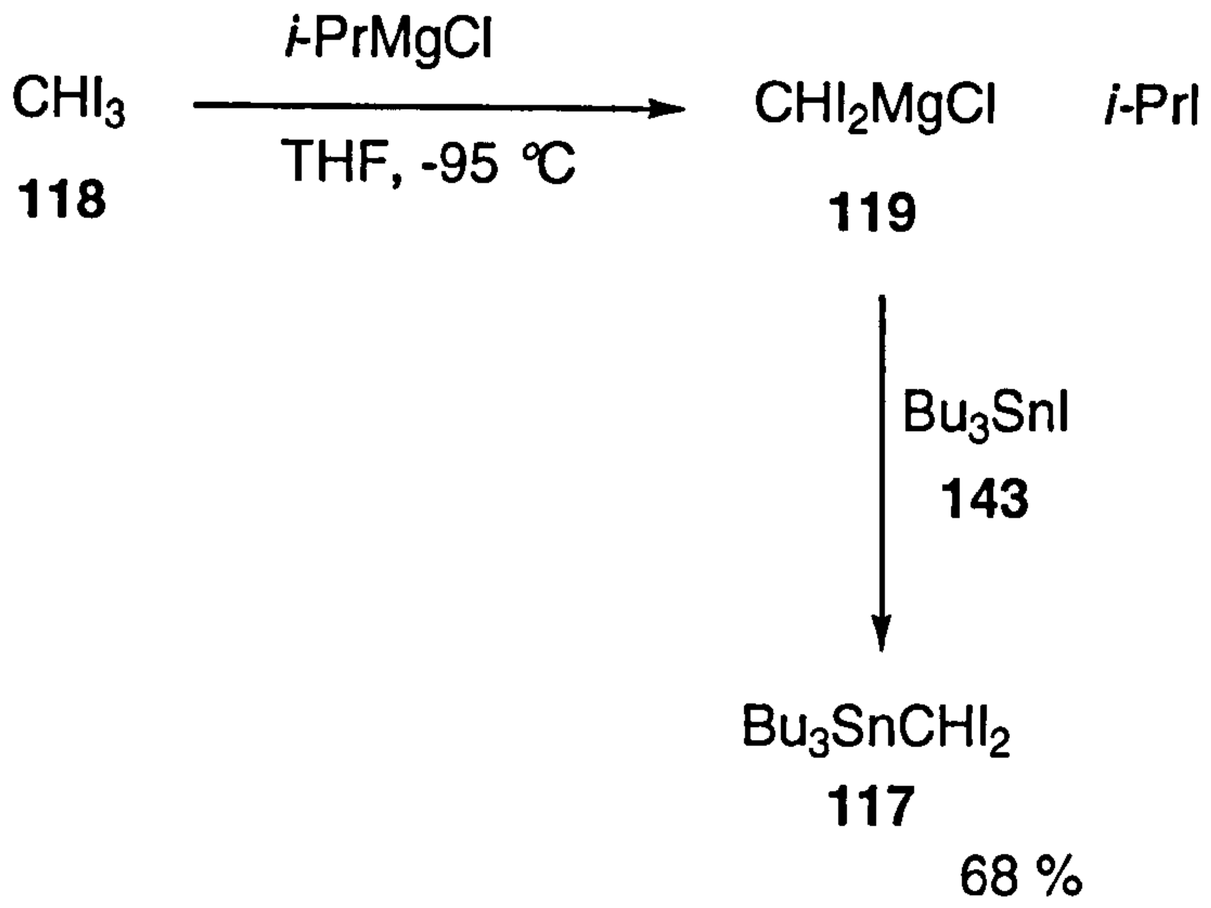
2.2 Synthesis of Bu_3SnCHI_2

There are a number of ways to synthesise trialkyl(dihalomethyl)tin compounds and these have been discussed in section 1.4.2. The method chosen by myself was based on that of Seyferth and Lambert[99] who synthesised diiodomethylmagnesium chloride **119** from iodoform **118** using the procedure of Normant and Villieras.[100] Treatment of the Grignard reagent with trimethyltin chloride **120** gave the diiodide **121** in 72 % yield (Scheme 53, see also section 1.4.2).



Scheme 53

I carried out the equivalent reaction using tributyltin chloride to form tributyl(diiodomethyl)tin **117**. Initial yields were disappointingly low (18 – 33 %) and so to test my experimental technique I formed trimethyl(diiodomethyl)tin **121** in 46 % yield using the procedure of Seyferth.[99] The yield of the tributyl compound **117** was increased to 68 % by changing the procedure somewhat; the more reactive tributyltin iodide **143** was used in place of the chloride, purification was carried out by chromatography with alumina in place of silica (as used by Seyferth) and distillation was avoided (Scheme 54). These changes in purification were employed due to the sensitivity of this class of compounds to decomposition,[99] and avoiding distillation contributed to the higher product yield. The results are summarised in Table 1.



Scheme 54

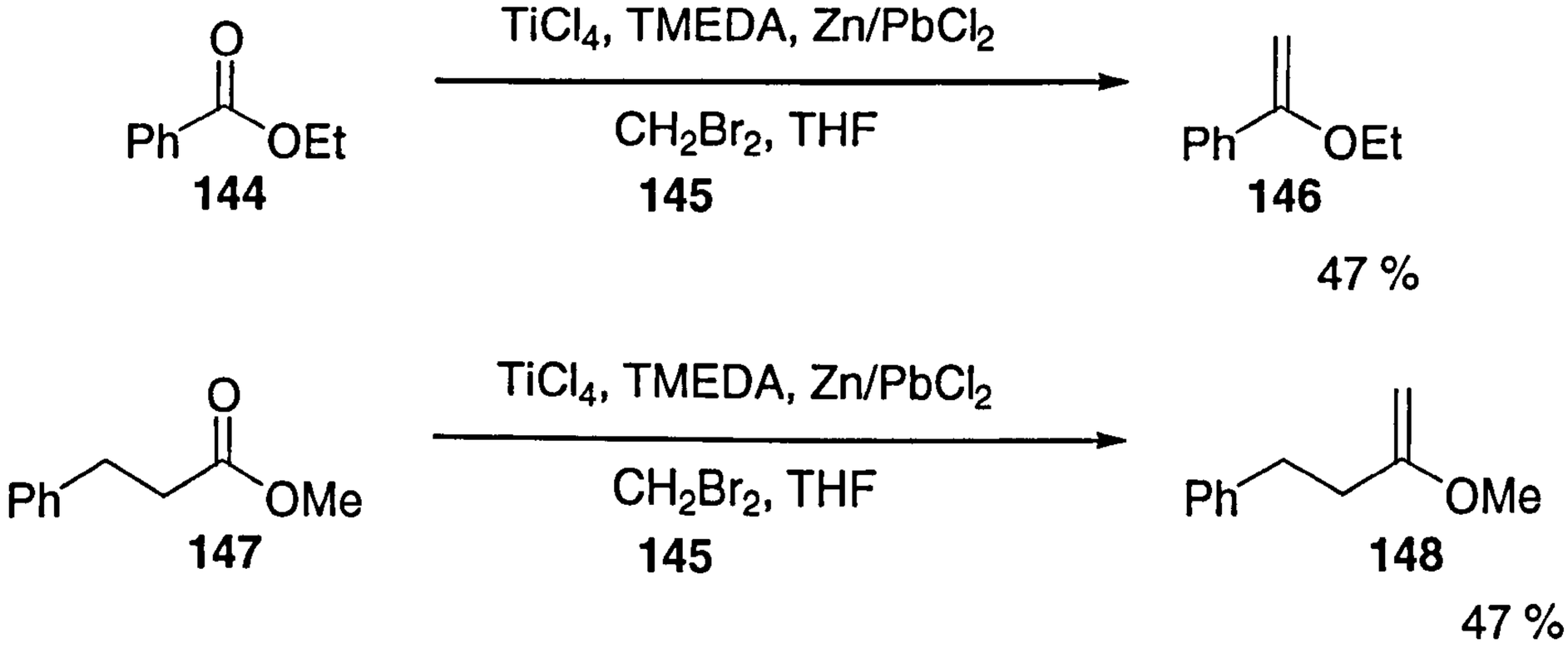
Reaction Conditions	Purification	Product	Yield
CHI_3, *i*-PrMgCl, Bu_3SnCl	alumina chromatography	Bu_3SnCHI_2 **117**	33 %
CHI_3, *i*-PrMgCl, Me_3SnCl	silica chromatography	Me_3SnCHI_2 **121**	46 %
CHI_3, *i*-PrMgCl, Bu_3SnI	alumina chromatography	Bu_3SnCHI_2 **117**	68 %

Table 1

2.3 Alkylidenation reactions

2.3.1 Standard alkylidenations

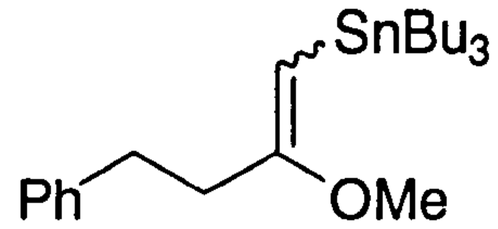
Before carrying out the Takai reaction using the tributyl(diiodomethyl)tin **117**, I carried out a number of 'standard' reactions to check that Takai's methodology worked in my hands. Two commercially available esters **144** and **147** were alkylidenated using dibromomethane **145** to give the corresponding enol ethers **146** and **148**, both in 47 % yield (Scheme 55).



Scheme 55

2.3.2 Alkylidenation to give β-alkoxyvinylstannanes

The key alkylidenation reaction was then carried out as above using tributyl(diiodomethyl)tin **117**. Ester **147** was again used as the substrate and it was hoped that the β-methoxyvinylstannane **149** would form (Figure 20).

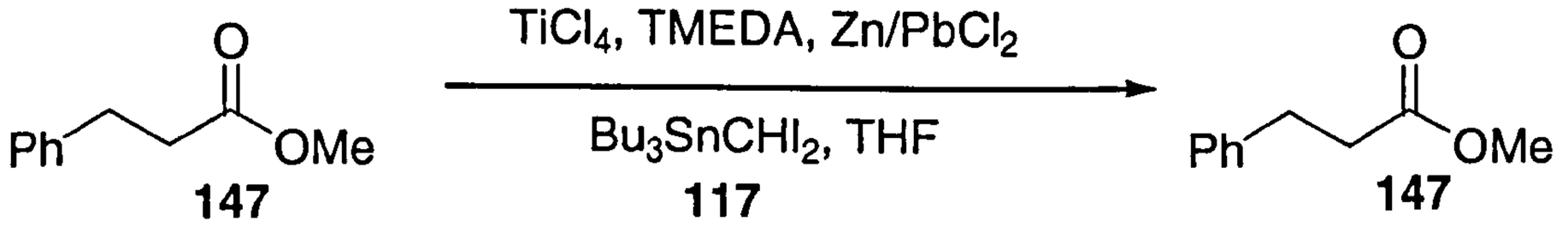


149

Figure 20

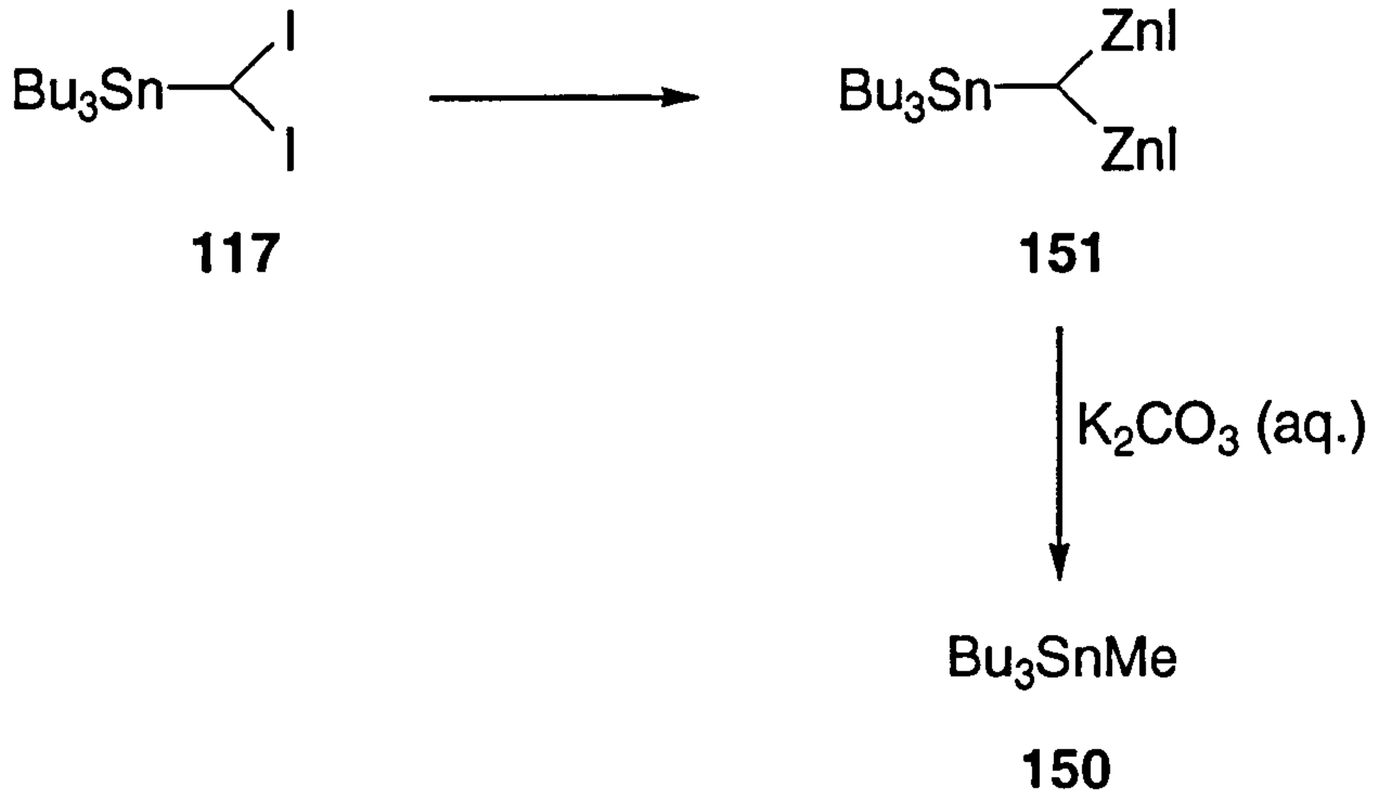
As discussed in section 1.4.2, the main concern in this reaction was that the zinc in the reaction mixture would insert into the carbon-tin bonds of the diiodide **117**.[97] This turned out not to be the case, the tin-carbon bond remained intact and in this and further reactions it became apparent that these bonds were far more stable than we had previously thought.

However alkylidenation did not occur in the reaction and when the reaction was quenched after 1.5 h the products were found to be tributylmethyltin **150** and unreacted ester **147** (Scheme 56, entry 1 Table 2).



Scheme 56

The clean formation of tributylmethyltin **150** suggested that zinc had rapidly inserted into the carbon-iodine bonds of the diiodide, producing a geminal dizinc compound **148** (Scheme 57). However, this trimetallic reagent appeared insufficiently reactive to alkylidenate the ester.



Scheme 57

While it was interesting to see that a geminal dizinc intermediate appeared to have formed (see section 1.3.4.2 on Takai mechanism) it was disappointing that alkylidenation had not taken place. Various reactions were performed to see under which conditions the zinc insertion occurred; the mixtures following work-up were analysed by ^{1}H NMR to determine the products formed (Table 2; n.b. 'standard reaction' relates to the general procedure 1 given in the experimental section).

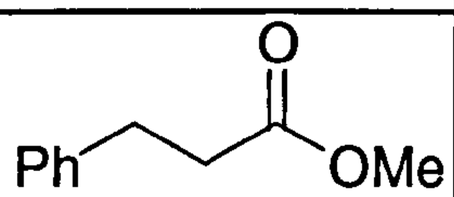
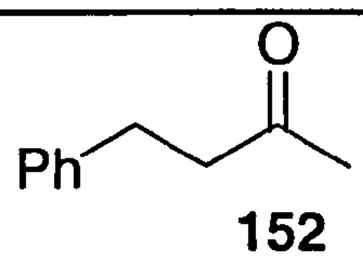
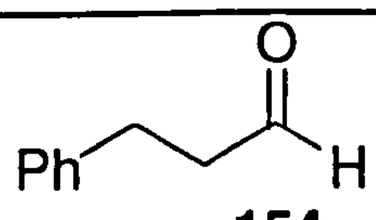
Entry	Substrate	Reaction Conditions	Product
1	 **147**	$TiCl_4$, TMEDA, $Zn/PbCl_2$ Bu_3SnCHI_2 **117**, THF standard reaction, 1.5 h	methyl 3-phenyl propionate **147** and Bu_3SnMe **150**
2	none	$Zn/PbCl_2$, Bu_3SnCHI_2, THF O°C ⇒ room temperature, 5.5 h	Bu_3SnCHI_2 **117**
3	none	$Zn/PbCl_2$, Bu_3SnCHI_2, THF sonication, 5.5 h	Bu_3SnCHI_2 **117**
4	none	$TiCl_4$, TMEDA, $Zn/PbCl_2$ Bu_3SnCHI_2 **117**, THF standard reaction, 4 h	Bu_3SnMe **150** and minor impurities
5	 **152**	$TiCl_4$, TMEDA, $Zn/PbCl_2$ CH_3CHBr_2, THF standard reaction	McMurry coupling products
6	none	$TiCl_4$, $Zn/PbCl_2$, Bu_3SnCHI_2 **117**, THF standard ketone alkylidenation reaction[125]	mixture of Bu_3SnMe **150**, Bu_3SnCH_2I **153** and unidentified tin products
7	none	$Ti(Oi\text{-}Pr)_4$, $Zn/PbCl_2$ Bu_3SnCHI_2 **117**, THF standard aldehyde alkylidenation reaction[126]	mixture of Bu_3SnMe **150** and Bu_3SnCH_2I **153** (1:1.6)
8	 **154**	$Ti(Oi\text{-}Pr)_4$, $Zn/PbCl_2$ Bu_3SnCHI_2 **117**, THF standard aldehyde alkylidenation reaction[126] 2.5 h	3-phenyl propionaldehyde **154** and mixture of Bu_3SnMe **150** and Bu_3SnCH_2I **153**

Table 2

It was noted that when only zinc/lead dichloride and diiodide **117** were present, no metal insertion occurred, even when the reaction was performed under sonication (ultrasound has been shown to accelerate organometallic reactions including those involving zinc)[77] (entries 2 and 3).

It therefore appears that in this case that the titanium tetrachloride and TMEDA in the reaction mixture mediate the zinc insertion (*c.f.* examples in the Takai mechanism discussion section 1.3.4.2). The Takai reagent generation was also carried out for a longer time in the absence of the ester, and although the conversion to tributylmethyltin **150** was not as clean, it remained the major product (entry 4).

Takai had carried out alkylidenation reactions on ketones and aldehydes instead of esters,[125, 126] and as they are more reactive, it was decided to investigate these reactions using diiodide **117**. However, Takai had only ever alkylidenated ketones and aldehydes in the absence of TMEDA and a concern was that this reaction system would be too acidic for the tin compounds to survive.

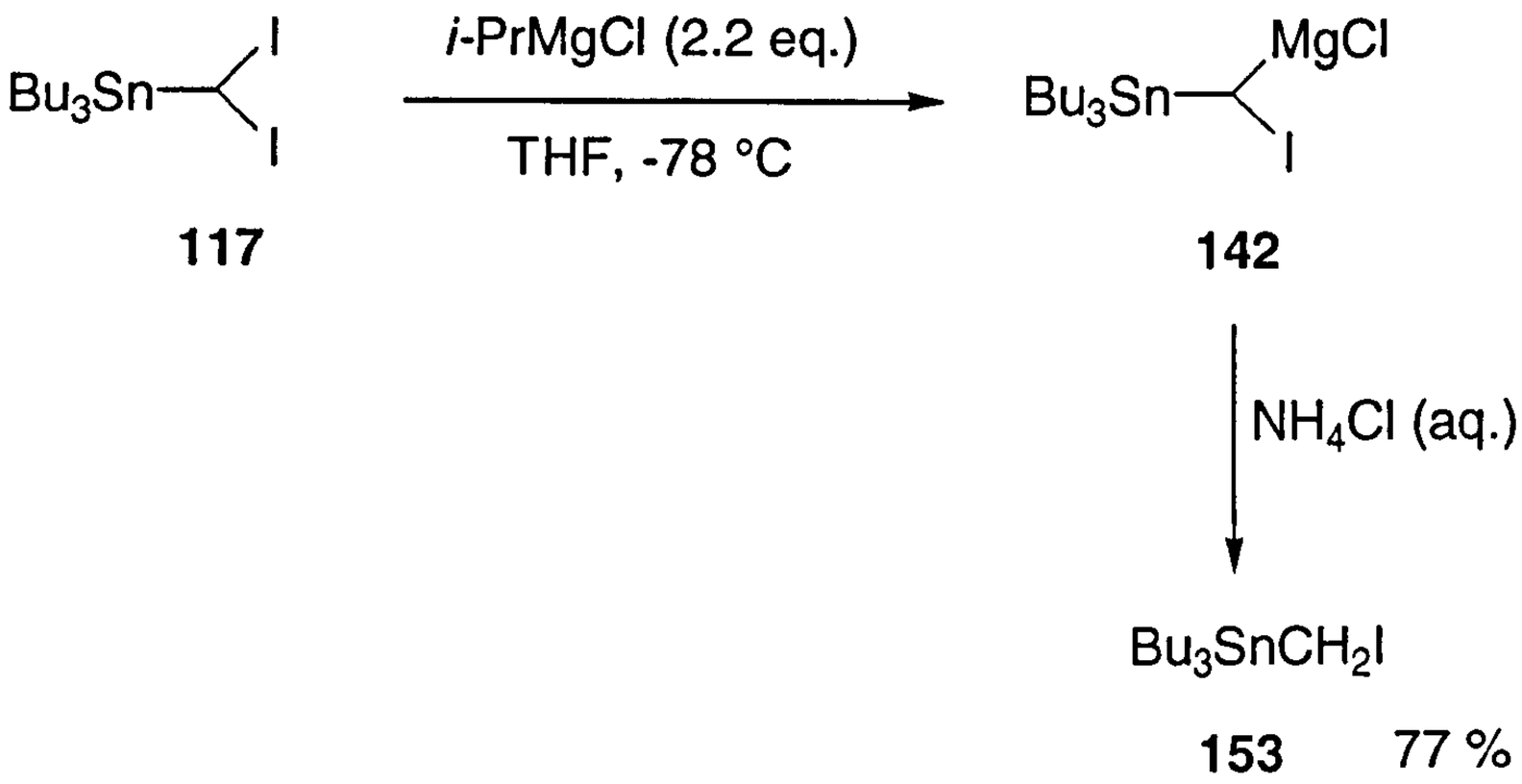
To determine whether a ketone could be alkylidenated in the presence of TMEDA, a standard reaction was carried out on 4-phenylbutan-2-one **152** using dibromomethane (entry 5). However, the desired product was not formed under these conditions, instead it appeared that a McMurry coupling reaction had occurred, giving various alkene-coupling products. To determine whether diiodide **117** would survive the acidic conditions mentioned, it was reacted with titanium tetrachloride, zinc and lead dichloride following Takai's protocol for ketone alkylidenation (entry 6).[125] No ketone was added. After quenching, the crude product mixture was found to contain tributylmethyltin **150**, tributyl(iodomethyl)tin **153** and various unidentified tin compounds. It therefore appeared that the tin-carbon bond was not completely stable under these conditions.

Takai had used other milder Lewis acids in his aldehyde alkylidenations than titanium tetrachloride including titanium tetraisopropoxide.[126] To determine whether the tin species would survive under these milder conditions, diiodide **117** was reacted with titanium tetraisopropoxide, zinc and lead dichloride (entry 7). This time no tin side products were obtained, only tributylmethyltin **150** and tributyl(iodomethyl)tin **153**. This result was promising and so the reaction was repeated in the presence of 3-phenylpropionaldehyde **154** (entry 8). Unfortunately no alkylidenation was witnessed.

In my hands it proved very difficult to form a vinylstannane using Takai's methodology. Due to time constraints it was decided to abandon **Route A** and proceed with a second route to benzofurans that is discussed in the following chapters. However, the next section of this chapter looks at an interesting result that was obtained while investigating the activity of diiodide **117**.

2.4 $Bu_3SnCHIMgCl$

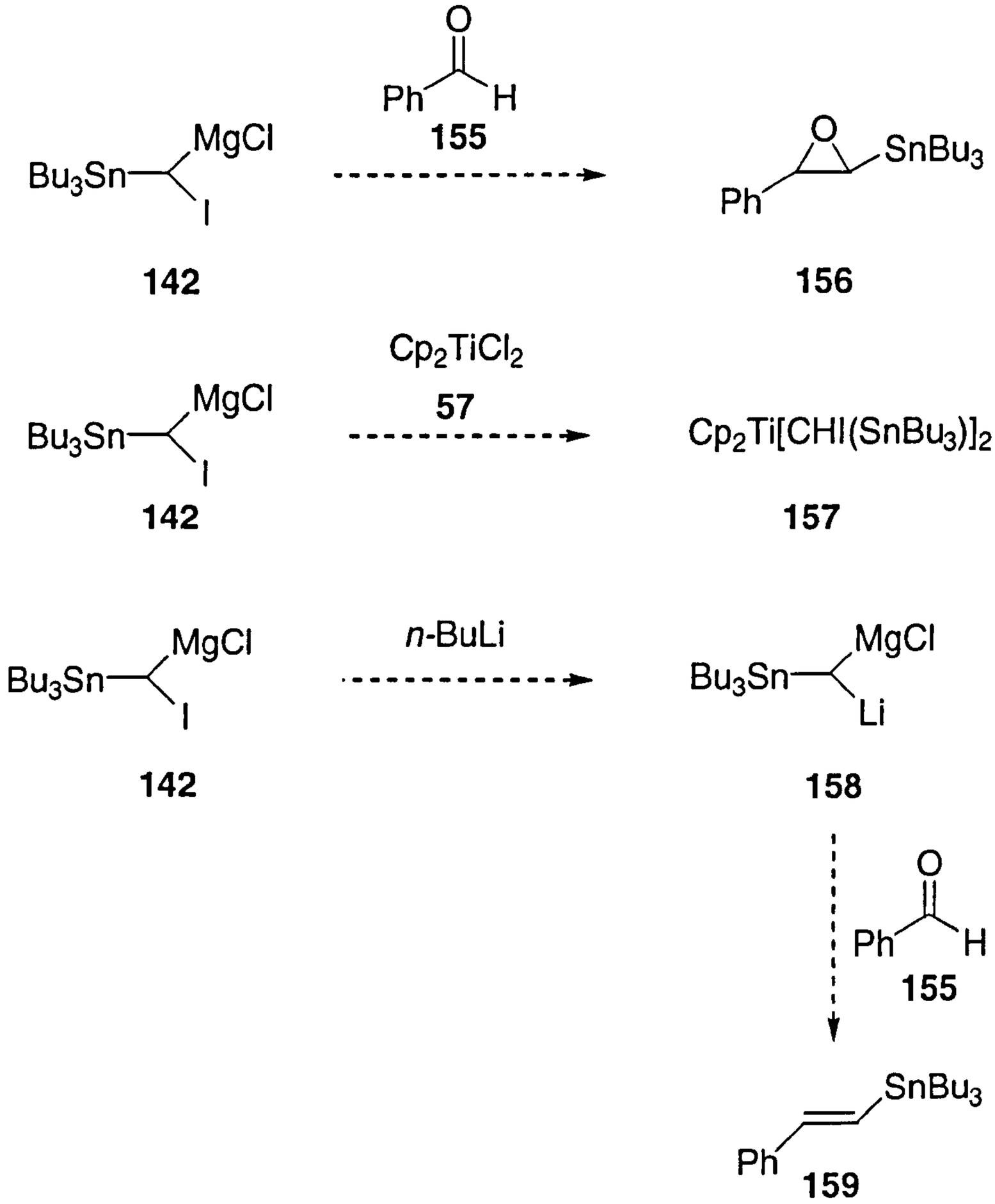
It appeared obvious that the dizinc species **151** was very stable and therefore it was decided to try using a more reactive metal to form the alkylidenating species. Therefore, diiodide **117** was reacted with isopropylmagnesium chloride in a similar manner to the deiodination of iodoform previously described.[99,100] It was expected that the tin compound would be doubly deiodinated because in excess of two equivalents of the Grignard reagent was used. However, on quenching the reaction after one hour it was observed that clean conversion to tributyl(iodomethyl)tin **153** had occurred. This suggested that only mono insertion had occurred giving the intermediate **142** (Scheme 58).



117 **142** **153** 77 %

Scheme 58

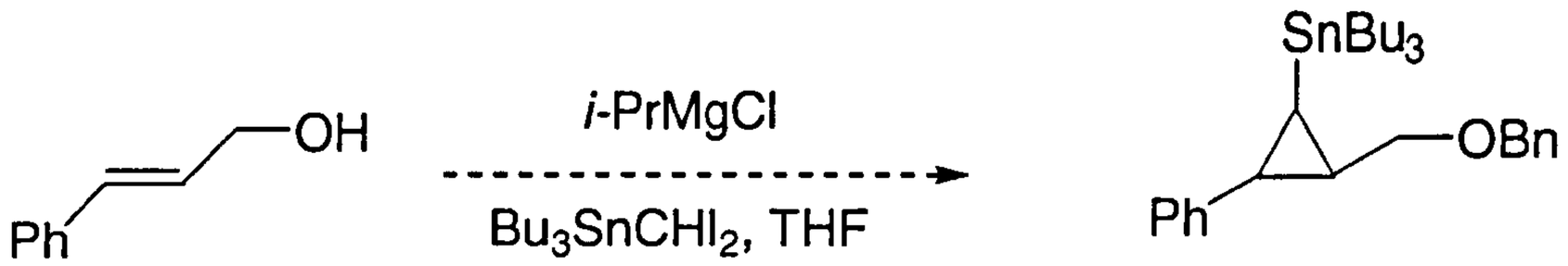
Although this was not the result anticipated and the reagent is not useful as an alkylidenating agent, this dimetallic species **142** could have many uses (Scheme 59).



Scheme 59

One could imagine formation of epoxide **156** occurring upon reaction of organomagnesium reagent **142** with benzaldehyde **155**. Compound **142** could also be reacted with titanocene dichloride **57** to form a tin Petasis-style reagent **157** that itself could undergo alkylidenation reactions (see section 1.3.3). Another possibility was to attempt to lithiate the species, producing a trimetallic compound **158**. The reactivity of such a compound would be such that it certainly should alkylidenate aldehydes such as **155**, providing a simpler alternative to Hodgson's method of synthesising alkenyl tin products such as **159** (see section 1.3.4.3).[84-87]

Another possible use for **142** could be as a cyclopropanating agent. Recently a cyclopropanation reaction was reported where a Grignard was employed in place of the more commonly used diethylzinc.[127] It seemed possible that organomagnesium reagent **142** could be used in such a reaction, giving a cyclopropane with a useful tin handle such as **160** (Scheme 60).



117 **160**

Scheme 60

A number of these reactions were attempted and the results summarised in Table 3. As with the alkylidenations described previously, GC was used to follow the reactions. Unfortunately it appeared more difficult to exploit the organomagnesium reagent than had been imagined. Reaction with *n*-butyllithium (entry 2) gave a mixture of products including an intermediate with a molecular weight corresponding to Bu_3SnCH_2Bu. This suggested that butyl insertion, instead of the desired lithium-halogen exchange had occurred. In an attempt to prevent this, *sec*-butyllithium was employed instead (entry 3), but a mixture of compounds was again produced. A mixture of tin products was also produced upon reaction with benzaldehyde **155** (entry 4) and no epoxide formation was observed. A similar disappointing result occurred in the attempted cyclopropanation of 3-hydroxy-2-phenylprop-1-ene (entry 5). In a further set of reactions the reactivity of the reagent was tested; it appeared unreactive in the presence of trimethylsilyl chloride (entry 6). The only successful reaction occurred upon quenching with deuterium oxide (entry 7), here the deuterated product **161** formed cleanly in 85 %.

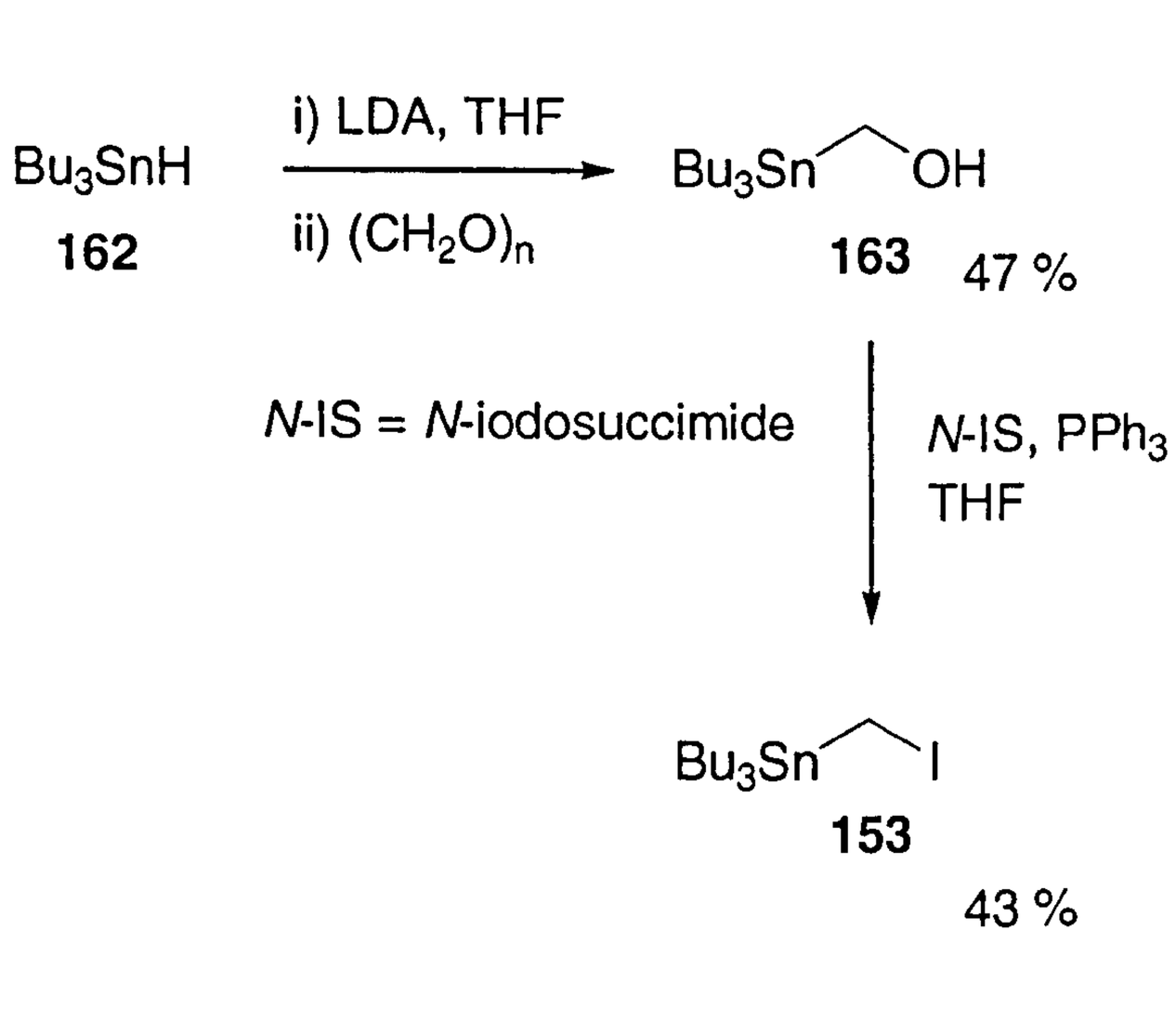
Entry	Attempted reaction	Reaction conditions	Isolated product	Yield
1		Bu_3SnCHI_2 **117**, *i*PrMgCl, THF,-78 °C,1 h	Bu_3SnCH_2I **153**	77 %
2	lithiation	Bu_3SnCHI_2 **117**, *i*-PrMgCl, then *n*-BuLi THF, -78 °C 1 h	mixture of products including Bu_3SnMe **150**, Bu_3SnCH_2Bu and Bu_3SnCH_2I **153**	n/a
3	lithiation	Bu_3SnCHI_2 **117**, *i*-PrMgCl, then *sec*-BuLi, THF, -78 °C 1 h	Mixture of products including Bu_3SnMe **150**, Bu_3SnCH_2Bu, Bu_3SnCH_2I **153** and high molecular weight tin compounds	n/a
4	epoxide formation	Bu_3SnCHI_2 **117**, *i*-PrMgCl, then PhCHO**155**, THF, -78 °C 1 h	Unidentified tin compounds (no epoxide formation) and unreacted aldehyde	n/a
5	cyclo-propanantion	Bu_3SnCHI_2 **117**, *i*-PrMgCl, then $PhC{=}CCH_2OH$, THF, -78 °C 72 h	Unidentified tin compounds (no cyclopropane formation)	n/a
6	TMS quench	Bu_3SnCHI_2 **117**, *i*-PrMgCl, then TMSCl THF, -78 °C, 1 h	Bu_3SnCH_2I **153**	n/a
7	deuterium quench	Bu_3SnCHI_2 **117**, *i*-PrMgCl, THF, -78 °C, 1 h, quench D_2O	$Bu_3SnCHID$ **161**	85 %

Table 3

Although the magnesium species has yet to live up to its early promise we still believe it to be a reagent with great potential and work on it continues within our group.[128] However, at this point I began work on a second route. This route also employed titanium-based alkylidenation chemistry and again showed the potential to form highly substituted heterocycles. The difference was that this second **Route B** employed chemistry based on the work of Takeda and co-workers. A discussion on this work and the results obtained appears in the following two chapters.

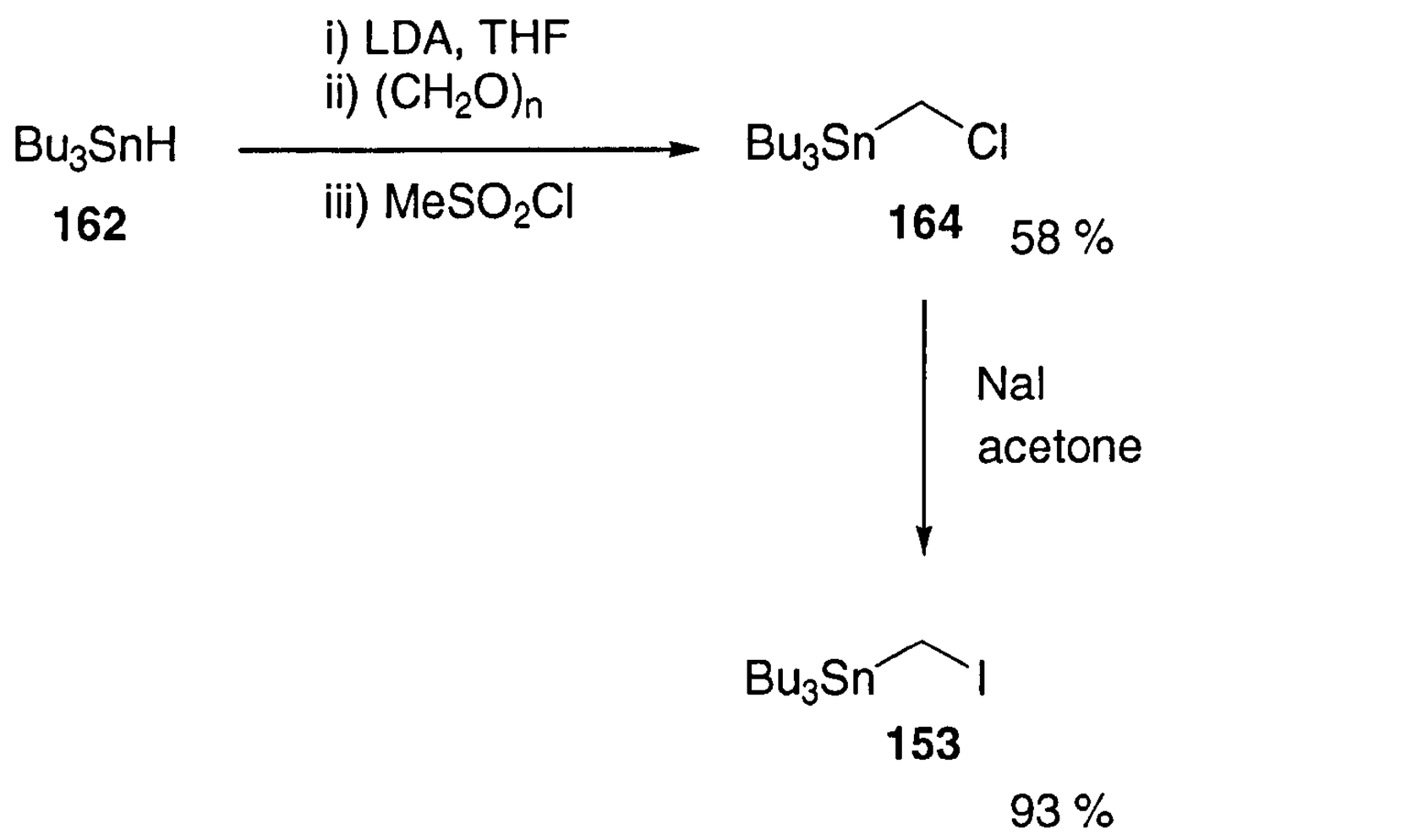
2.5 Synthesis of GC standards

In the investigation of the properties of the magnesium-tin reagent **142**, reactions were followed by gas chromatography. Reactions were monitored for the presence of Bu_3SnCHI_2 **117**, Bu_3SnCH_2I **153** and Bu_3SnMe **150** and standards of these three compounds were synthesised for comparison. Tributyl(iodomethyl)tin **153** was synthesised in two different ways. The first method followed that of Åhman and Somfai[129] who synthesised the iodide from the corresponding alcohol **163**, which itself was synthesised from tributyltin hydride **162** (Scheme 61). In my hands the iodide was formed in 20 % over two steps



Scheme 61

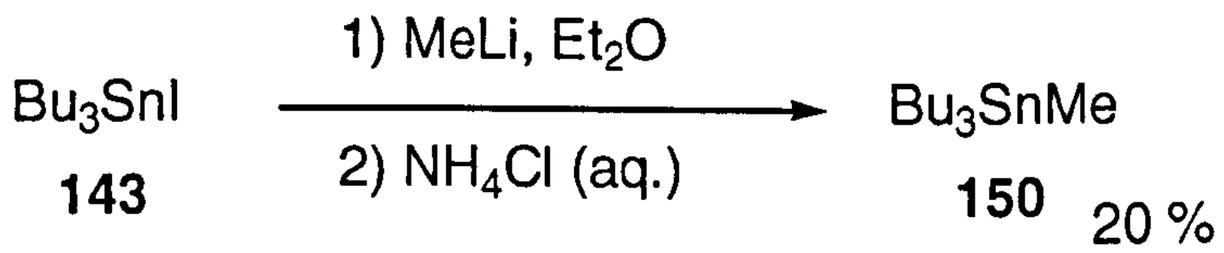
A second, higher yielding approach was based on the method of Seitz and co-workers.[130] Here the chloride **164** was formed from tributyltin hydride **162** as above and then converted to the desired iodide **153** using Finkelstein[103] methodology (Scheme 62). In my hands the iodide was formed in 62 % over two steps.



(or 62 % over two steps when **164** is not purified)

Scheme 62

Methyltributyltin **150** was formed in 20 % by treating tributyltin iodide **143** with methyl lithium and quenching with ammonium chloride (Scheme 63).



Scheme 63

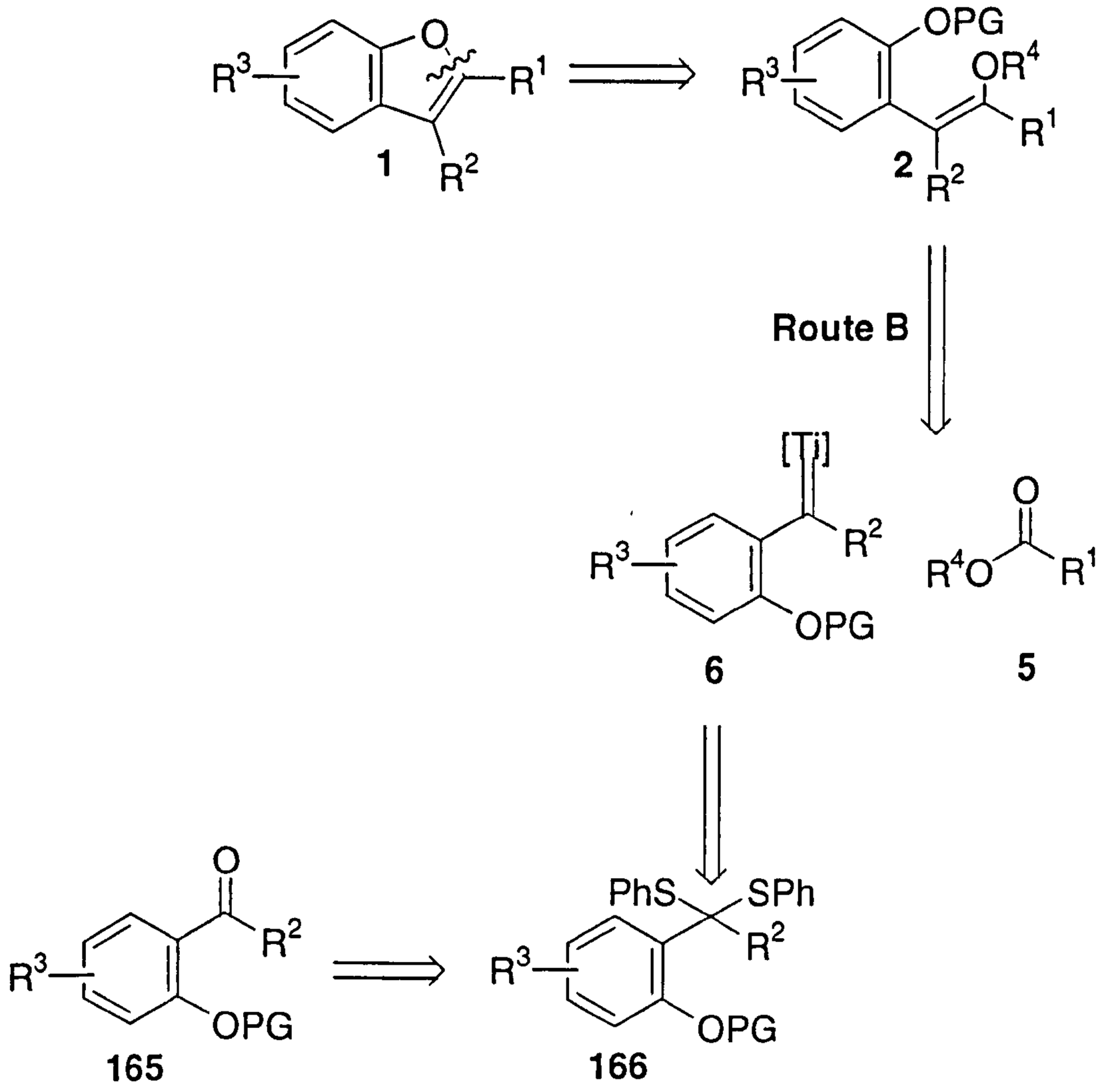
Bu_3SnCHI_2 **117** was synthesised in the method described in Scheme 54.

Chapter 3 - Route B

Benzofuran synthesis - Solution Phase

3.1 Introduction

Route B, introduced in chapter 1 employs the Takeda reaction (see section 1.3.5)[88] in the synthesis of functionalised benzofurans **1**. Retrosynthetic Scheme 64 shows that benzofurans **1** are formed from enol ethers **2** by acid-induced cyclisation.[2] Enol ethers **2** are in turn made from reaction between esters **5** and novel titanium alkylidenes **6**. Novel alkylidene reagents **6** are produced by reaction of Takeda's titanium reagent $Cp_2Ti[P(OEt)_3]_2$ with thioacetals **166** which themselves are formed from aldehydes or ketones **165**.



Scheme 64

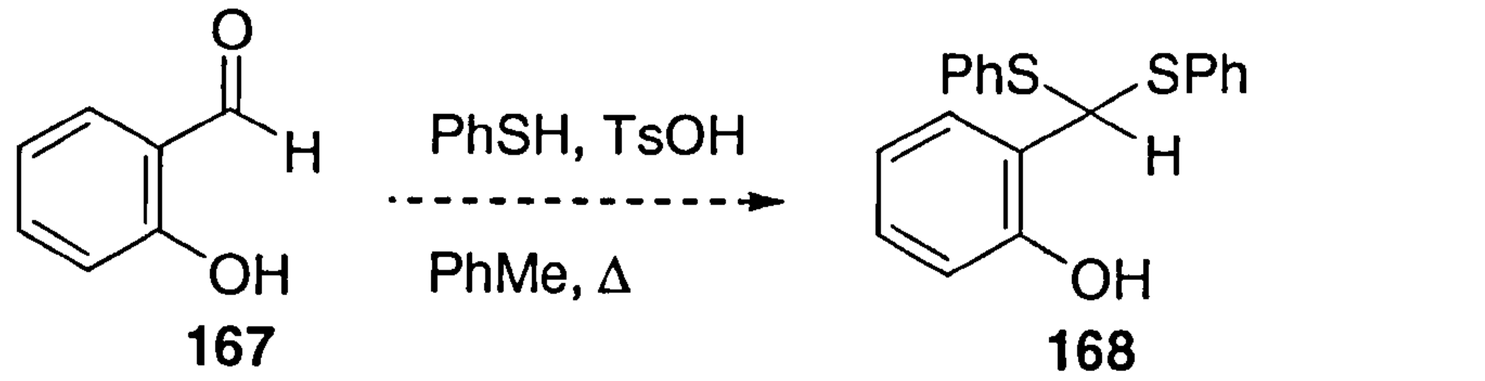
This chapter discusses the work carried out on **Route B** and summarises the results. The synthesis of carbocycles using intramolecular Takeda reactions was also investigated and is discussed at the end of the chapter.

The chapter is therefore divided into 3 main sections -

- the synthesis of the thioacetals
- the alkylidenation reaction and formation of benzofurans from the resulting enol ethers
- attempted intramolecular Takeda reactions

3.2 Synthesis of Thioacetals

The thioacetals used in the Takeda reaction were formed from aldehyde **167** and derivatives thereof. Formation of 2-hydroxybenzaldehyde diphenyldithioacetal **168** was first attempted using Ager's Dean and Stark based method.[131] Unfortunately the reaction was unsuccessful. The only product was a red solid (not characterised) that proved to be insoluble in acetone, diethyl ether, ethyl acetate and water (Scheme 65).

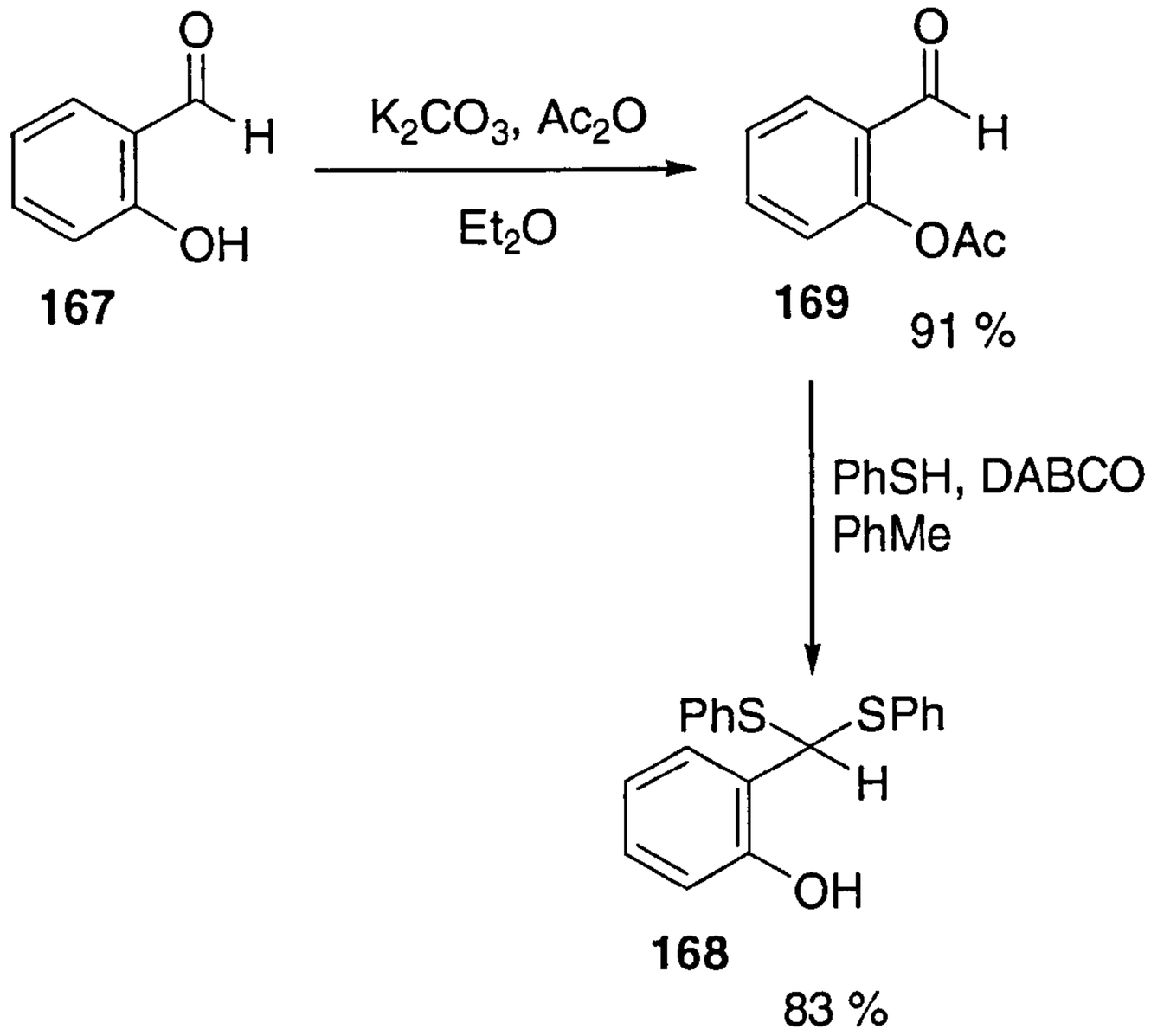


167 **168**

no product formation

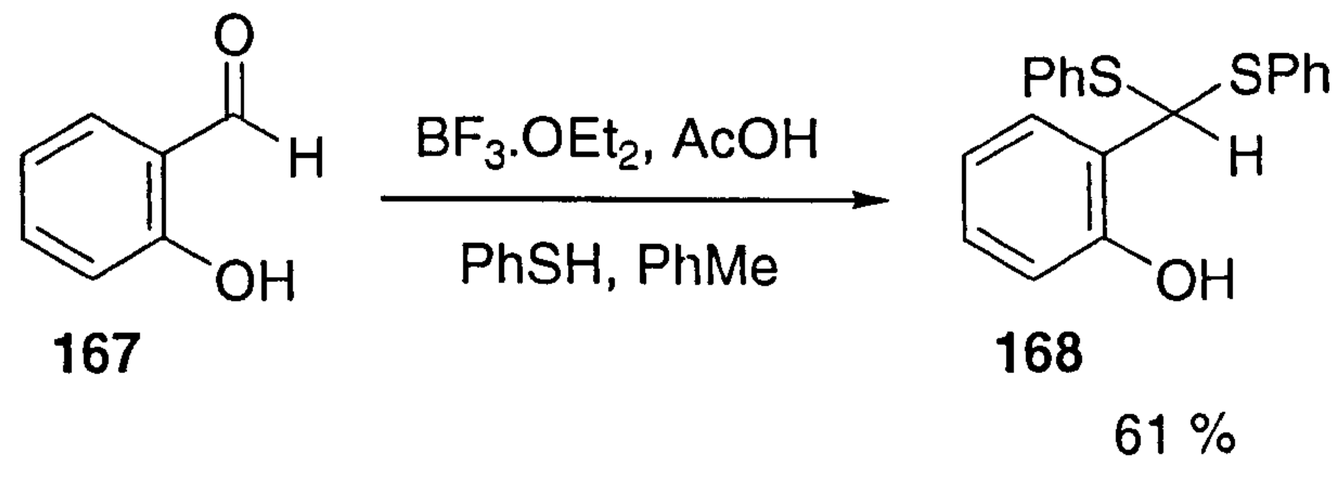
Scheme 65

Liepa and Morton[132] have discussed the difficulties involved in forming an acetal in the presence of a free phenol, and although a few examples exist in the literature,[133,134] none involve the Dean-Stark method. I decided to use the approach of Liepa and Morton[132] in which thioacetal formation is performed on an acetate protected phenol in the presence of an amine base. During the reaction an intramolecular acyl shift occurs giving the product as a free phenol. Aldehyde **167** was therefore acetylated using standard methods and the resulting aldehyde **169** was treated under Liepa and Morton's conditions to give the desired thioacetal **168** in 76 % over the two steps (Scheme 66).



Scheme 66

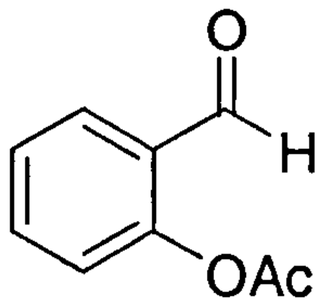
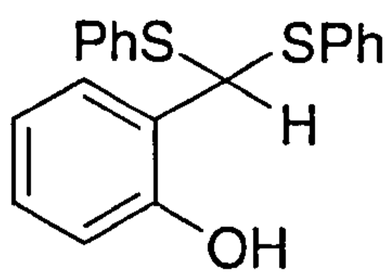
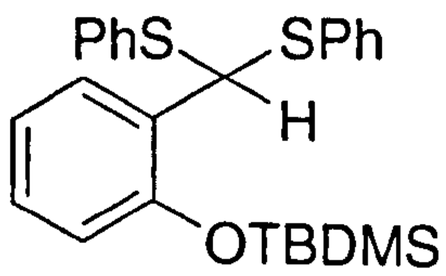
Although their reaction was successful in my hands, Liepa and Morton's method uses a large excess of thiophenol (>23 equivalents) and this proved to be a problem when the reaction was scaled-up. Therefore another method was chosen, this one based on work published by Barton and co-workers. In this approach the thioacetal was formed in the presence of acetic acid and boron trifluoride diethyletherate (Scheme 67).[133]

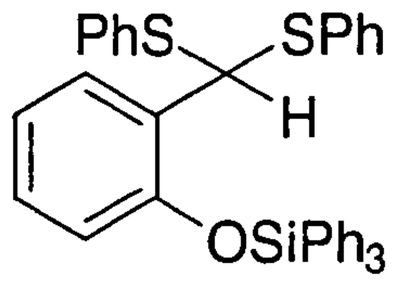
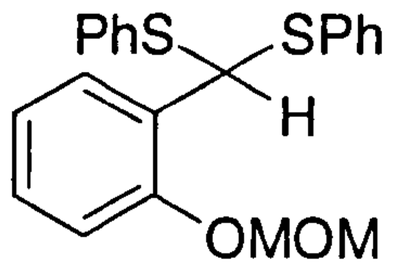
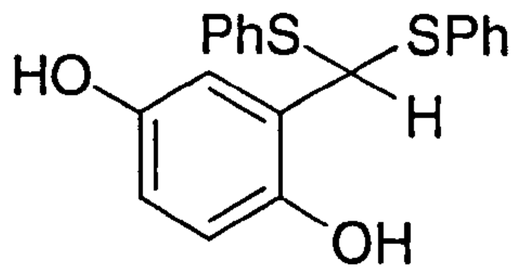
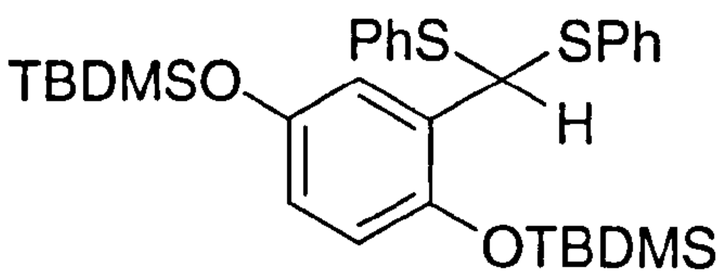
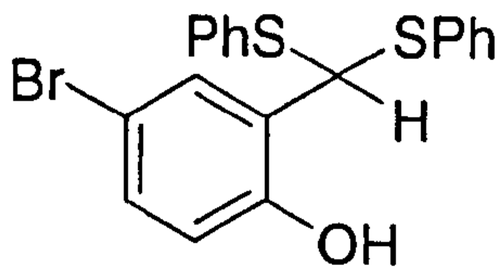
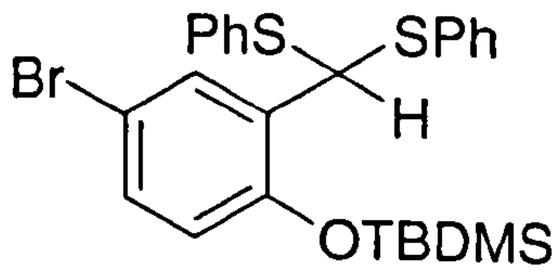


Scheme 67

Barton also used a large excess of thiophenol in his paper but I found that the reaction could be performed successfully using only a slight excess of the thiol. This modified one-step procedure ('General procedure 2' in the experimental section) was used for the synthesis of all the thioacetals as summarised in Table 4.

While only a small number of the thioacetals reported here were used in the solution-phase Takeda reaction, the others were employed in the solid-phase version of the reaction, which is discussed in the next chapter. Silyl and MOM protection of the phenols was achieved using standard methods and these are described in greater detail in the experimental section (TBDMS protection is described in 'General procedure 3' in the experimental section of this thesis).

Entry	Thioacetal	Method of Synthesis	Yield
1	 **169**	Liepa and Morton[132]	91 %
2	 **168**	Liepa and Morton[132]	83 % (76 % over two steps from **167**)
		General procedure 2	99 %
3	 **170**	General procedure 3	86 %

4	 **171**	See experimental section	81 %
5	 **172**	See experimental section	71 %
6	 **173**	General procedure 2	50 %
7	 **174**	General procedure 3	100 %
8	 **175**	General procedure 2	86 %
9	 **176**	General procedure 3	67 %

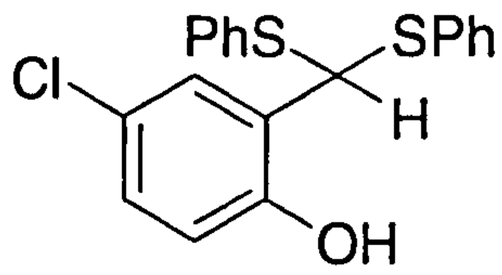
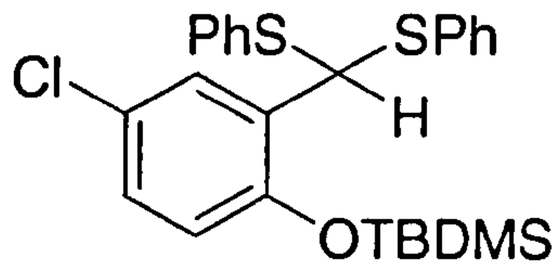
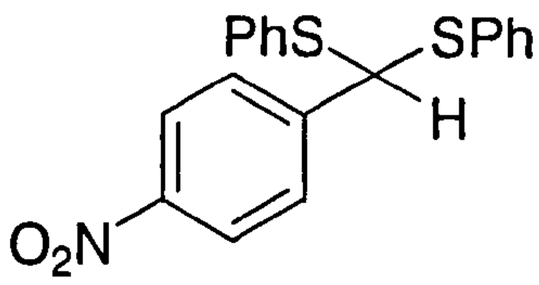
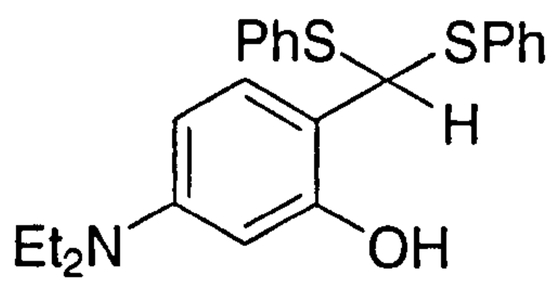
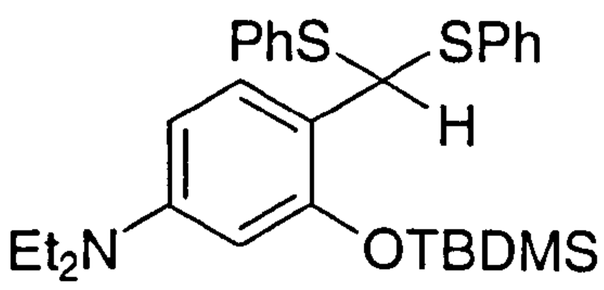
10	 **177**	General procedure 2	85 %
11	 **178**	General procedure 3	94 %
12	 **179**	General procedure 2	93 %
13	 **180**	See experimental section	25 %
14	 **181**	General procedure 3	59 %

Table 4

The only problem in forming the thioacetals occurred when an electron-donating substituent laid *para* to the aldehyde. Having such a substituent made the thioacetal particularly susceptible to acid-induced cleavage as shown in Figure 21.

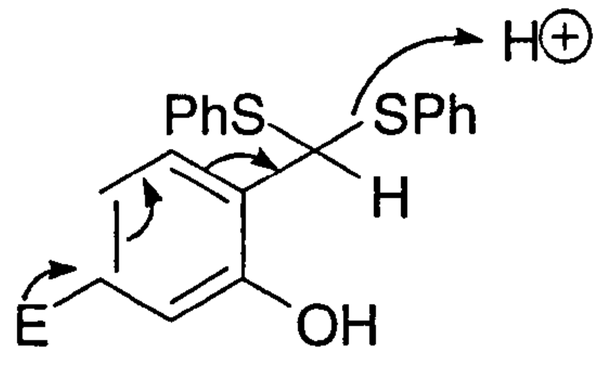


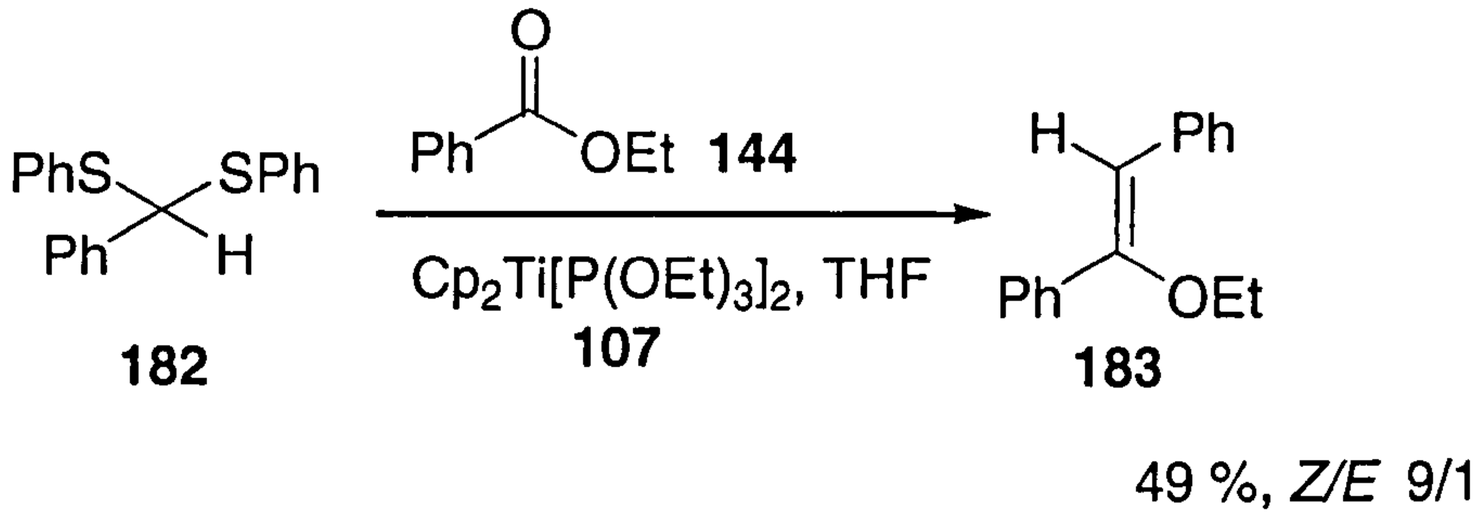
Figure 21

The effect of having such a substituent is demonstrated by the poor yields of thioacetals **180** and **181** (entries 13 and 14). The synthesis of 4-diethylamino-2-hydroxybenzaldehyde diphenyldithioacetal **180** was attempted in the absence of acetic acid but this resulted in solubility problems. The reaction was therefore carried out under acidic conditions using THF instead of toluene as a solvent. Complete product formation did not occur under these conditions and so the reaction was quenched while starting material was still present. Purification was then achieved using chromatography on neutral alumina rather than on silica.

Many of the thioacetals appeared to be unstable at elevated temperatures and it was not always possible to obtain their mass spectra and/or microanalysis. Crystal structures were obtained for a number of the thioacetals and these appear in the Appendix at the end of the thesis.

3.3 Alkylidenation/Synthesis of Benzofuran

Once the thioacetals were synthesised, the key alkylidenation step was carried out (Scheme 68). The first reaction synthesised enol ether **183** from the unfunctionalised thioacetal **182** and ethyl benzoate **144**.



Scheme 68

This reaction was successful but low yielding. As with many organometallic reactions, a main challenge lay in the purification of the final product. In Takeda's reaction a number of side products have to be removed. In his procedure the crude reaction mixture was filtered through celite and then concentrated and purified using alumina chromatography. In my hands this method proved ineffective at removing all of the impurities, particularly the triethylphosphite.

I therefore employed an alternative reaction work-up and purification procedure that was carried out as followed. The celite step was omitted; instead the crude reaction mixture with treated with pentane. This caused most of the cyclopentadienyl titanium impurities to precipitate and these were then removed by filtration. The filtrate was concentrated and distilled using a kugelrohr to remove the triethylphosphite. Finally chromatography on alumina was employed giving the desired enol ether. The results of alkylidenations using ethyl benzoate are summarised in Table 5, and as can be seen the yields remain low. I believe that low yields are mainly due to problems with purification. The steps taken to address these problems are discussed in the next chapter.

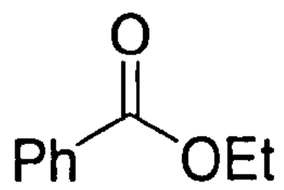
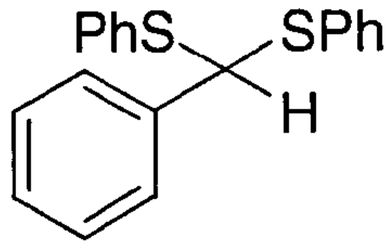
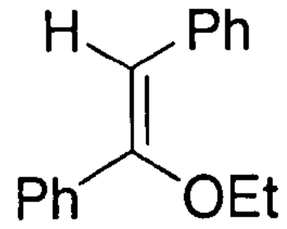
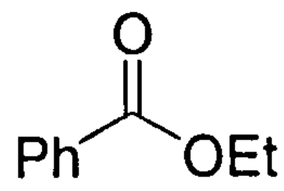
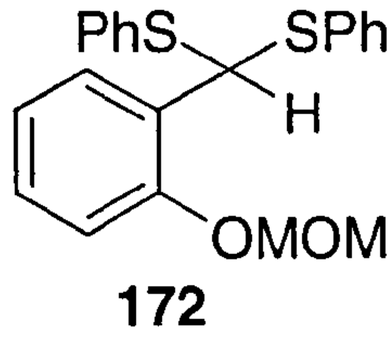
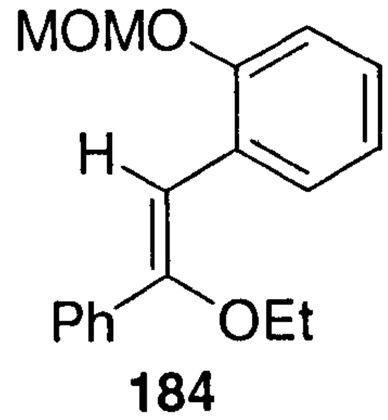
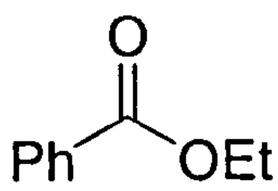
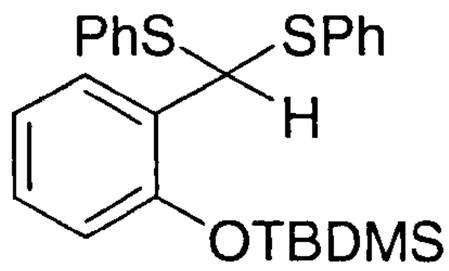
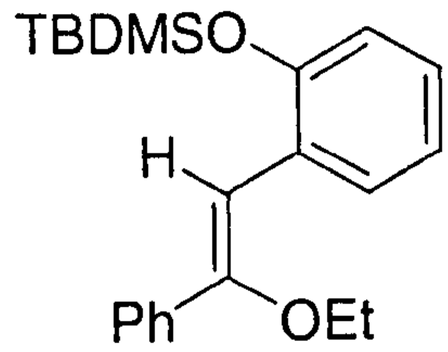
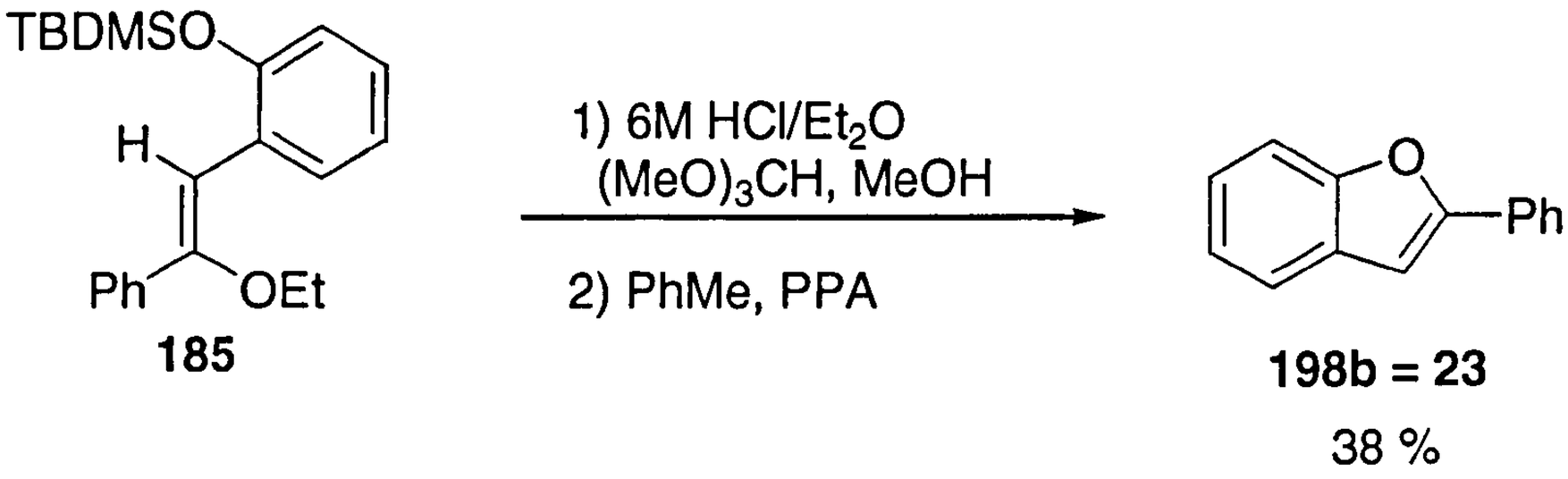
Entry	Ester	Thioacetal	Enol ether	Yield
1	 **144**	 **182**	 **183**	49 % (*Z*:*E* 9:1)
2	 **144**	 **172**	 **184**	35 % (*Z*:*E* 9.3:1)
3	 **144**	 **170**	 **185**	22% (*Z*:*E* 12:1)

Table 5

Cyclisation of the TBDMS-protected enol ether **185** was then carried out using the deprotection-cyclisation strategy of Kato and Miyaura[18] giving 2-phenyl benzofuran **198b (23)** in 38 %. (Scheme 69).



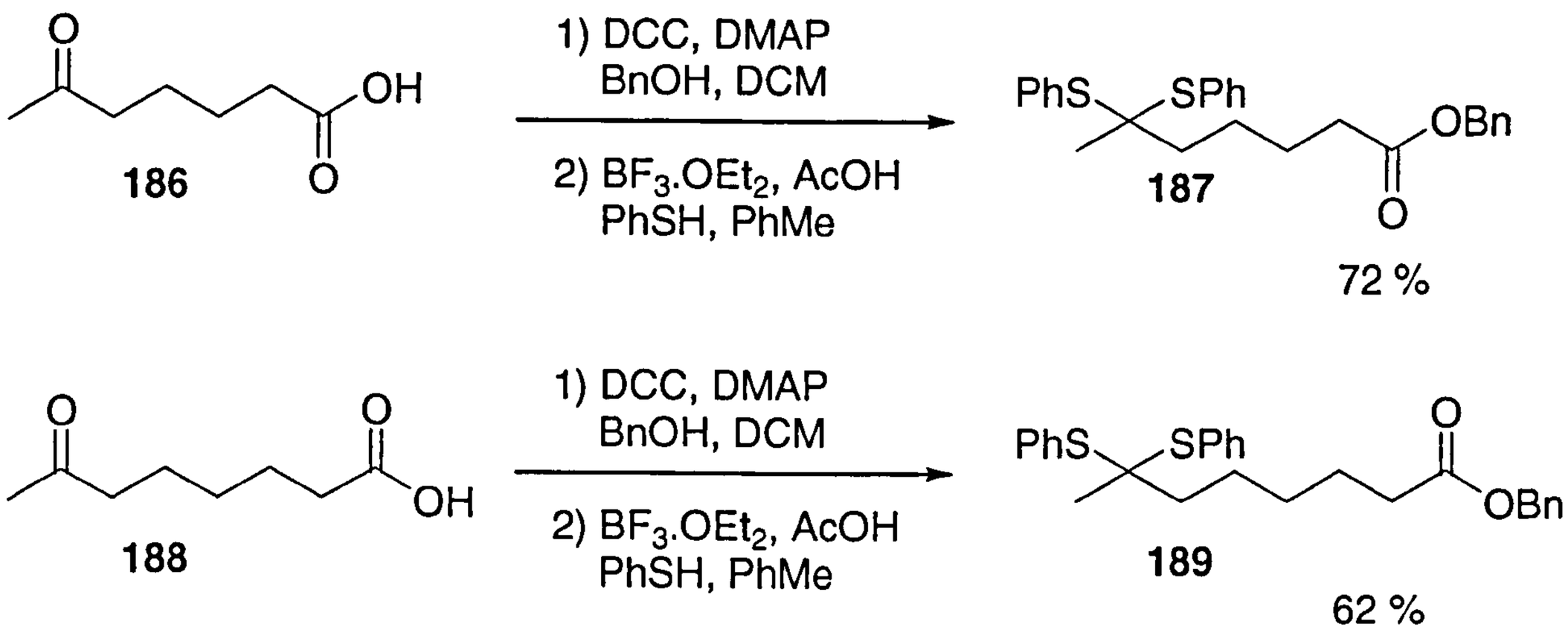
Scheme 69

This yield was also rather low, and using polyphosphoric acid (PPA) proved to be a very messy procedure. Work in the next chapter will show that it is possible to form a benzofuran under far milder and user-friendly conditions.

Route B was successful with 2-phenylbenzo[*b*] **198b (23)** being formed as had been hoped in four steps. However the alkylidenation step was problematic (particularly in terms of purification) and the yields of the enol ethers disappointing. The deprotection-cyclisation step proved to be a difficult and again low yielding procedure. Because of these problems no other benzofurans were synthesised *via* this route. The next chapter describes the same route carried out using solid phase synthesis. As will be seen a number of the problems that arose with the solution phase chemistry are addressed by switching to solid phase.

3.4 Intramolecular reactions

Before the solid phase chemistry was carried out a number of intramolecular Takeda reactions were attempted. I envisaged that the Takeda reaction could be used as a mild method for constructing medium-sized carbocycles. This would be achieved by carrying out intramolecular alkylidenation reactions on thioacetals **187** and **189** derived from long chain oxo-esters **186** and **188**. To this end 6-oxo-heptanoic acid **186** and 7-oxo-octanoic acid **188** were esterified using the DCC coupling procedure and thioacetal formation was then carried out using the modified Barton synthesis[133] (Scheme 70).



Scheme 70

The alkylidenation reaction was attempted but unfortunately the desired carbocycles were not formed.

Takeda himself has recently reported similar difficulties with intramolecular alkylidenations of esters.[96] However, this year Hirama and co-workers have shown that this reaction is possible.[135] Intramolecular Takai alkylidenation has been found to be ineffective.[136]

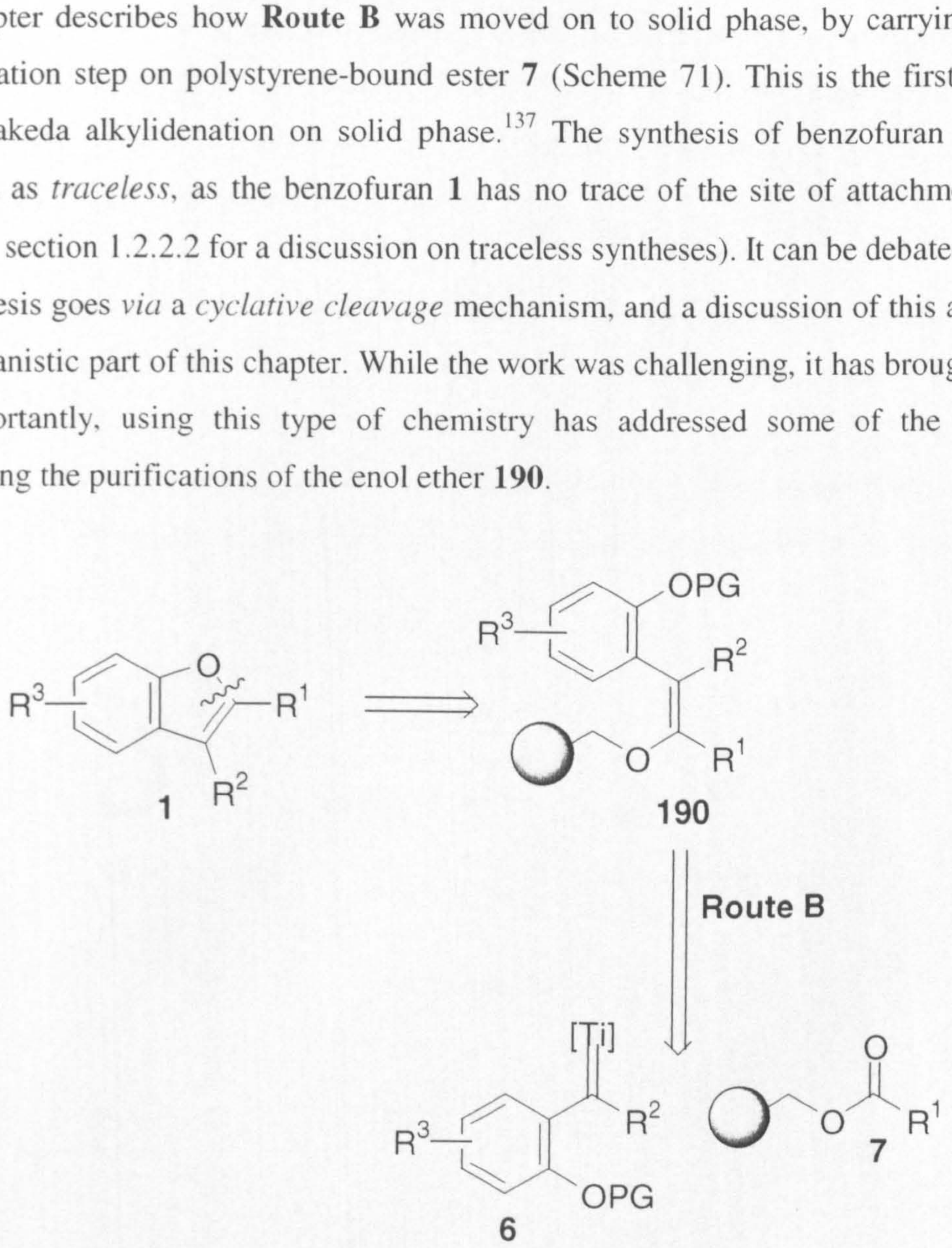
Chapter 4 Route B

Benzofuran synthesis - Solid phase

4.1 Introduction

As mentioned in the introduction to this thesis, one of the aims of this project was to form benzofurans using solid phase synthesis (SPS). The last chapter described the work on a synthesis of benzofurans using the Takeda alkylidenation. Some of the problems with this route were mentioned, particularly in the purification of the alkylidenation product.

This chapter describes how **Route B** was moved on to solid phase, by carrying out the alkylidenation step on polystyrene-bound ester **7** (Scheme 71). This is the first recorded use of Takeda alkylidenation on solid phase.[137] The synthesis of benzofuran **1** can be described as *traceless*, as the benzofuran **1** has no trace of the site of attachment to the resin (see section 1.2.2.2 for a discussion on traceless syntheses). It can be debated whether the synthesis goes *via* a *cyclative cleavage* mechanism, and a discussion of this appears in the mechanistic part of this chapter. While the work was challenging, it has brought results and importantly, using this type of chemistry has addressed some of the problems surrounding the purifications of the enol ether **190**.



Scheme 71

This chapter is divided into 5 sections –

- Synthesis of resin-bound esters
- SPS alkylidenation reactions
- Cleavage of the resin-bound enol ethers
- Mechanistic work
- Future work

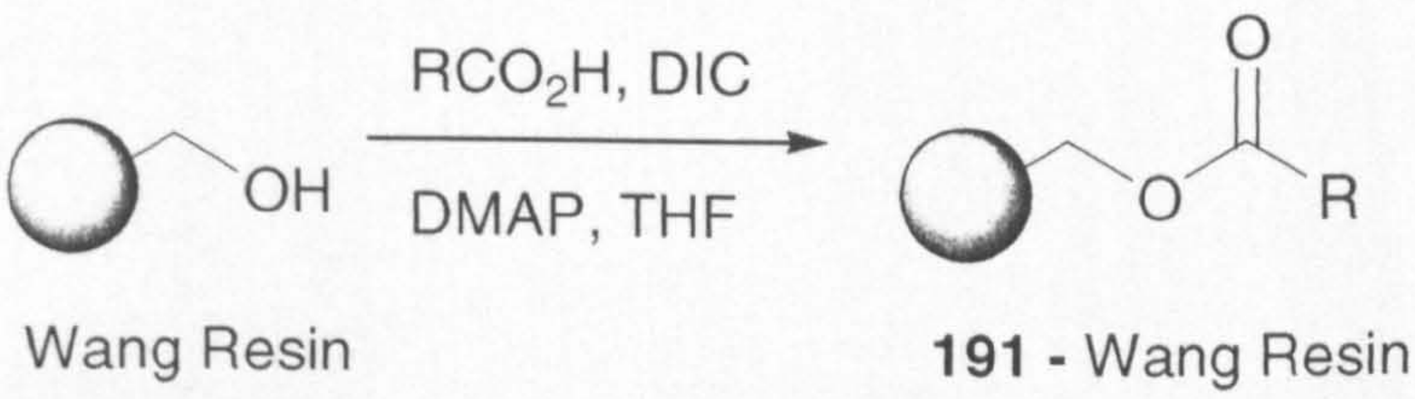
4.2 Synthesis of resin-bound esters

Esters were formed on Wang and Merrifield resin using standard methods. The differences between these types of resins have been discussed (see section 1.5.2.2) and the importance of their different reactivity under acidic conditions will be come apparent in later sections.

A number of resin-bound esters were formed (see Table 6). To examine whether steric factors affected the success of the alkylidenation reaction, a benzoate ester **191b** was synthesised. As a comparison, the much less sterically hindered acetate **191a** was made, as well as esters with an increasing path length between the carbonyl group and the benzene ring (**191c**, **191d** and **192a**).

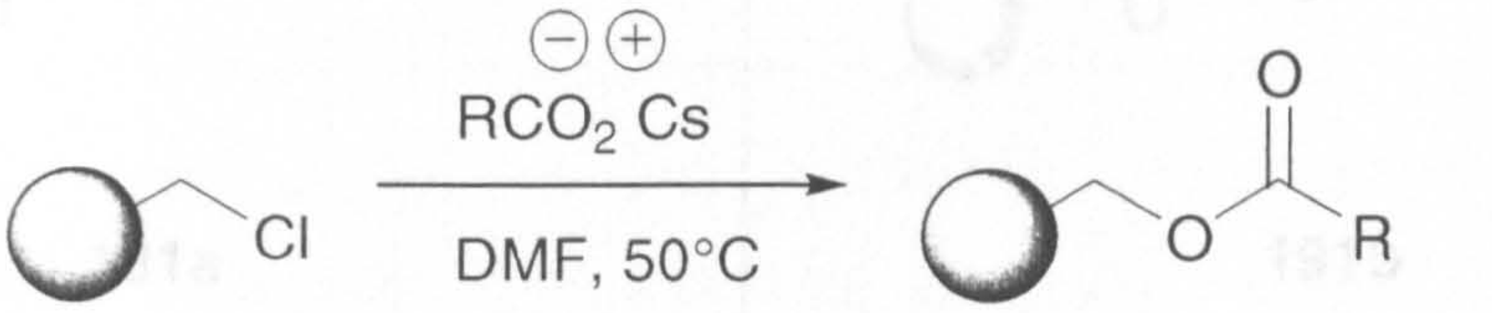
The biological activity of benzofurans that contain a heterocycle substituent has been discussed in Section 1.2. With this in mind, and also as a means of testing the scope of the reaction, esters containing heterocycles were synthesised including ones with a furan **192b**, a pyridine **192c** and a thiophene **192d**.

The formation of esters **191** on Wang resin was achieved by reacting swollen resin in THF with the corresponding carboxylic acid and the coupling agent DIC (1,3-diisopropylcarbodiimide), along with a catalytic amount of DMAP (4-dimethylaminopyridine) (Scheme 72). DIC was employed instead of the more commonly used DCC (1,3-diisopropylcarbodiimide) due to the greater solubility of its by-product in organic solvents.[138]



Scheme 72

For Merrifield-bound esters **192**, the swollen resin was reacted in DMF with the cesium salt of the appropriate acid at 50 °C (Scheme 73). The cesium salt has a larger cation than the equivalent lithium or sodium salt. This results in a greater dissociation between the ion pair, particularly when using a polar solvent such as DMF. The resulting naked carboxylate anions give a higher rate of ester formation than that achieved with other metal counterions.[139]

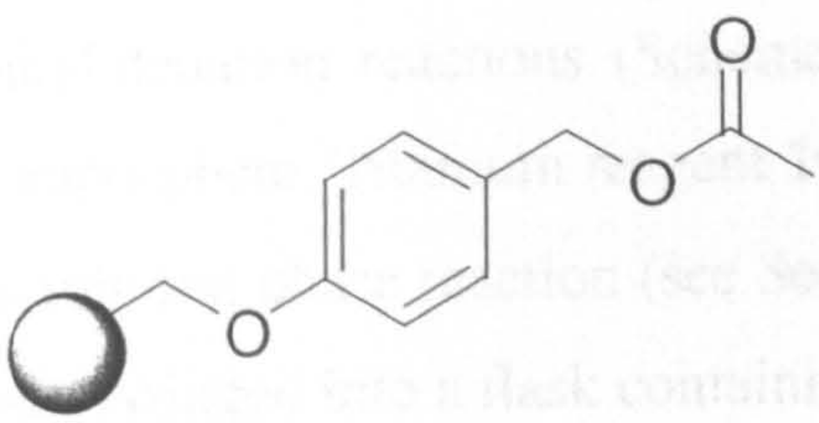


Merrifield resin **192 -** Merrifield resin

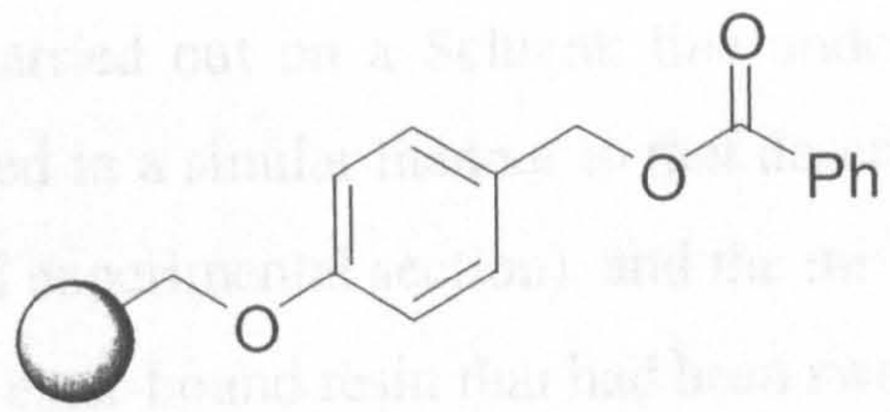
Scheme 73

As is normal in SPS reactions, a large excess of the other reagents was employed to force the reaction to completion (6 times the amounts generally used in solution-phase used). IRORI macro kans were employed (see Section 1.5.4.4) with 6-12 kans used per reaction. Table 6 shows the esters that were synthesised.

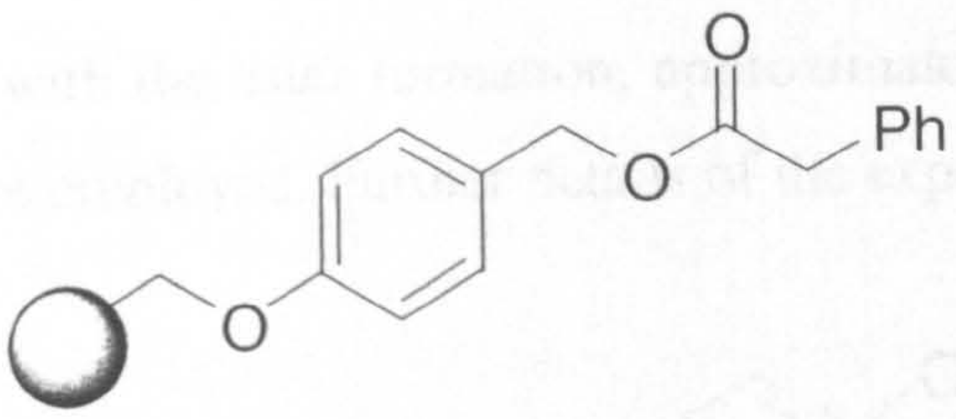
Wang-Bound Esters Synthesised



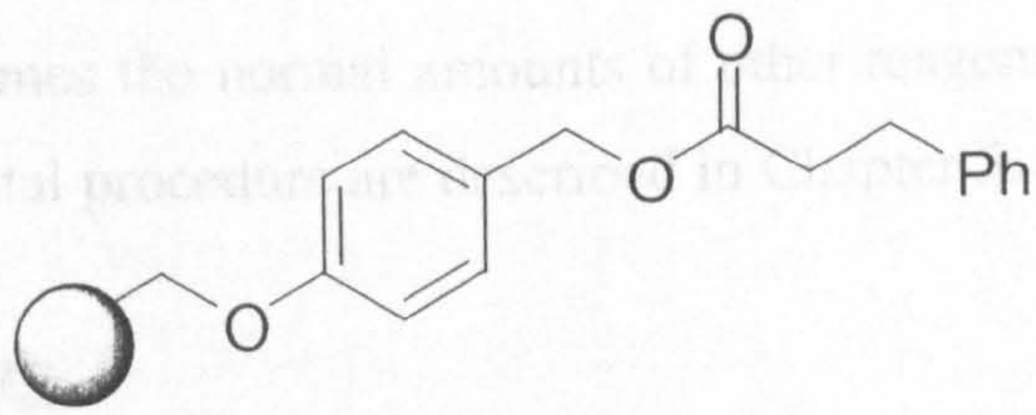
191a



191b

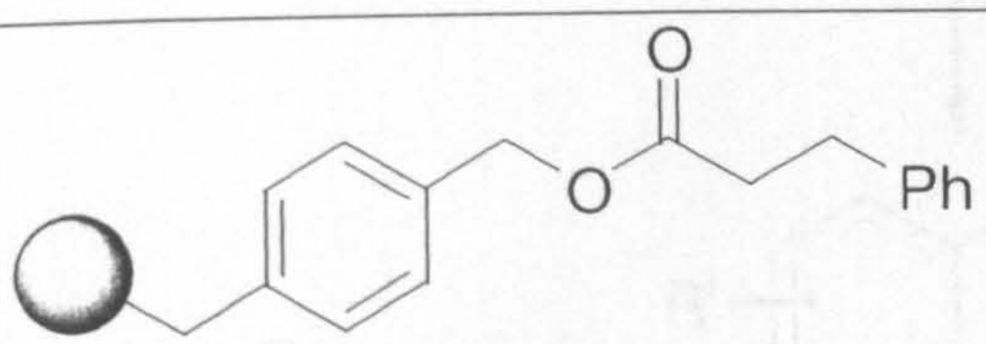


191c

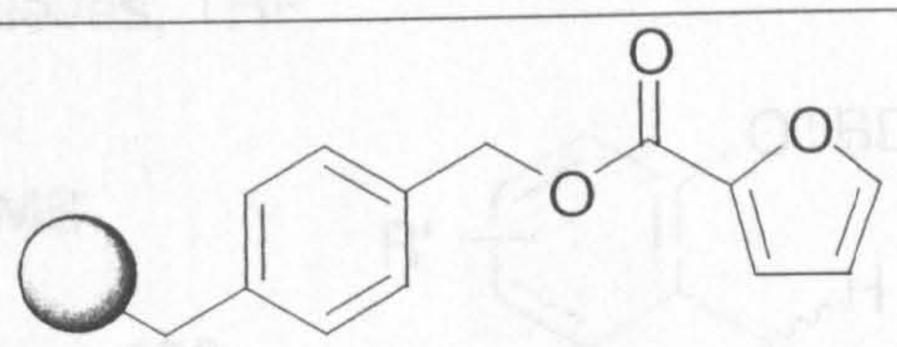


191d

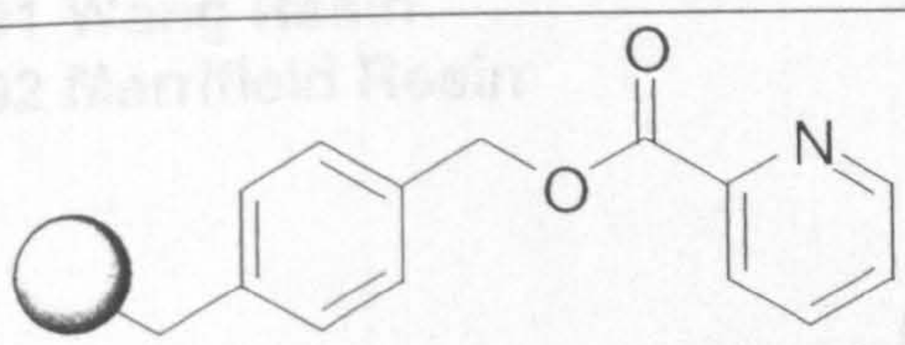
Merrifield-Bound Esters Synthesised



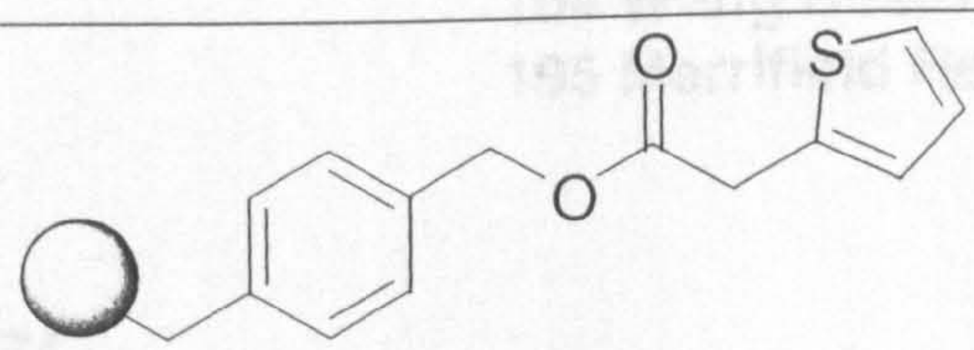
192a



192b



192c



192d

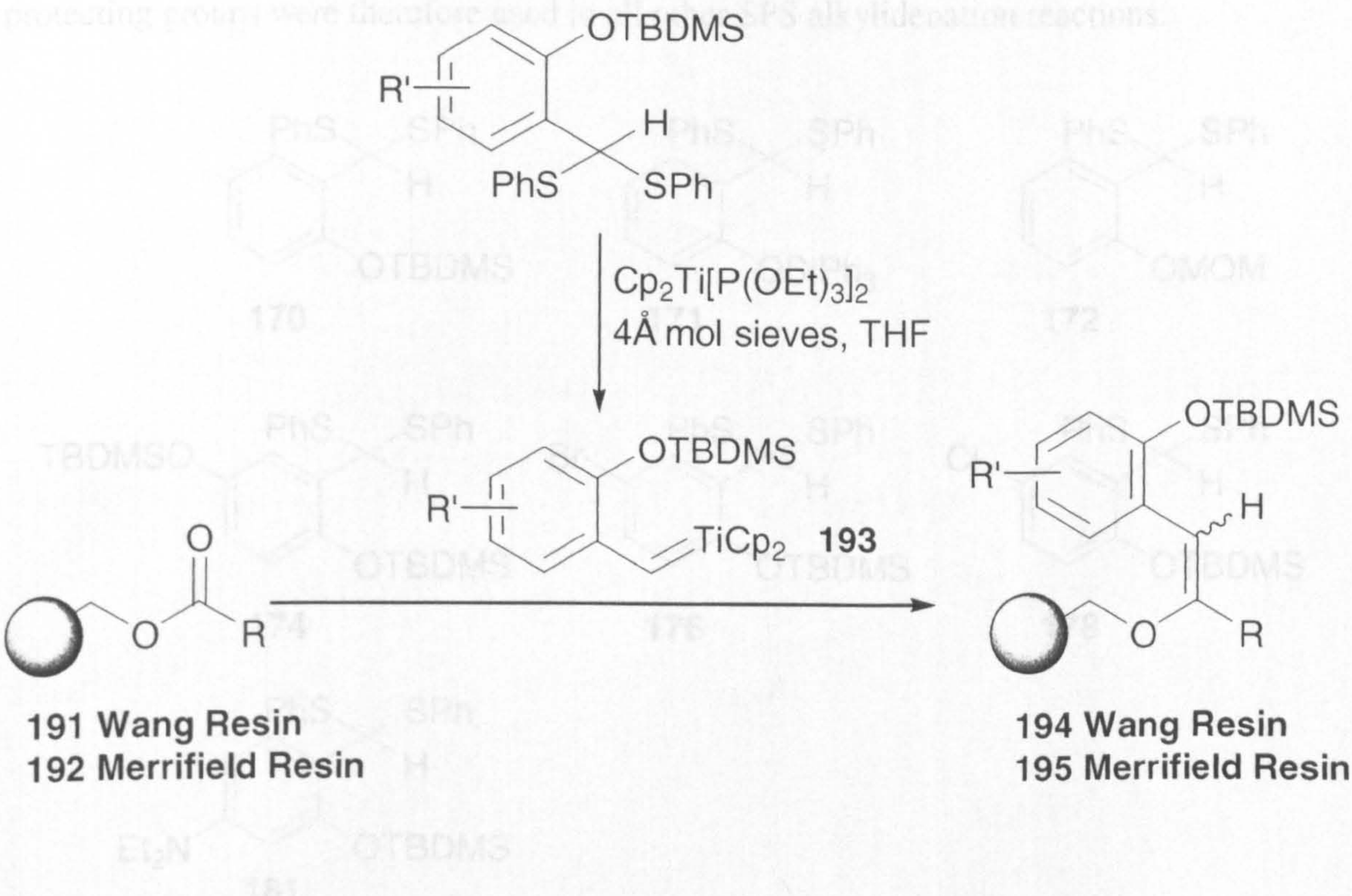
Table 6

4.3 Alkylidenation Reactions

4.3.1 SPS Alkylidenation Reactions

The alkylidenation reactions (Scheme 74) were carried out on a Schlenk line under an argon atmosphere. Titanium reagent **193** was formed in a similar manner to that described for the solution phase reaction (see Section 3.3 and experimental section), and the mixture was then syringed into a flask containing 3 kans of ester-bound resin that had been swollen in THF. The reaction mixture was left to stir overnight at room temperature and the kans were then washed, firstly with THF and then alternately with dichloromethane and methanol to remove the reaction by-products. The desired resin-bound enol ether was dried under vacuum.

As with the ester formation, approximately 6 times the normal amounts of other reagents were employed. Further details of the experimental procedure are described in Chapter 5.



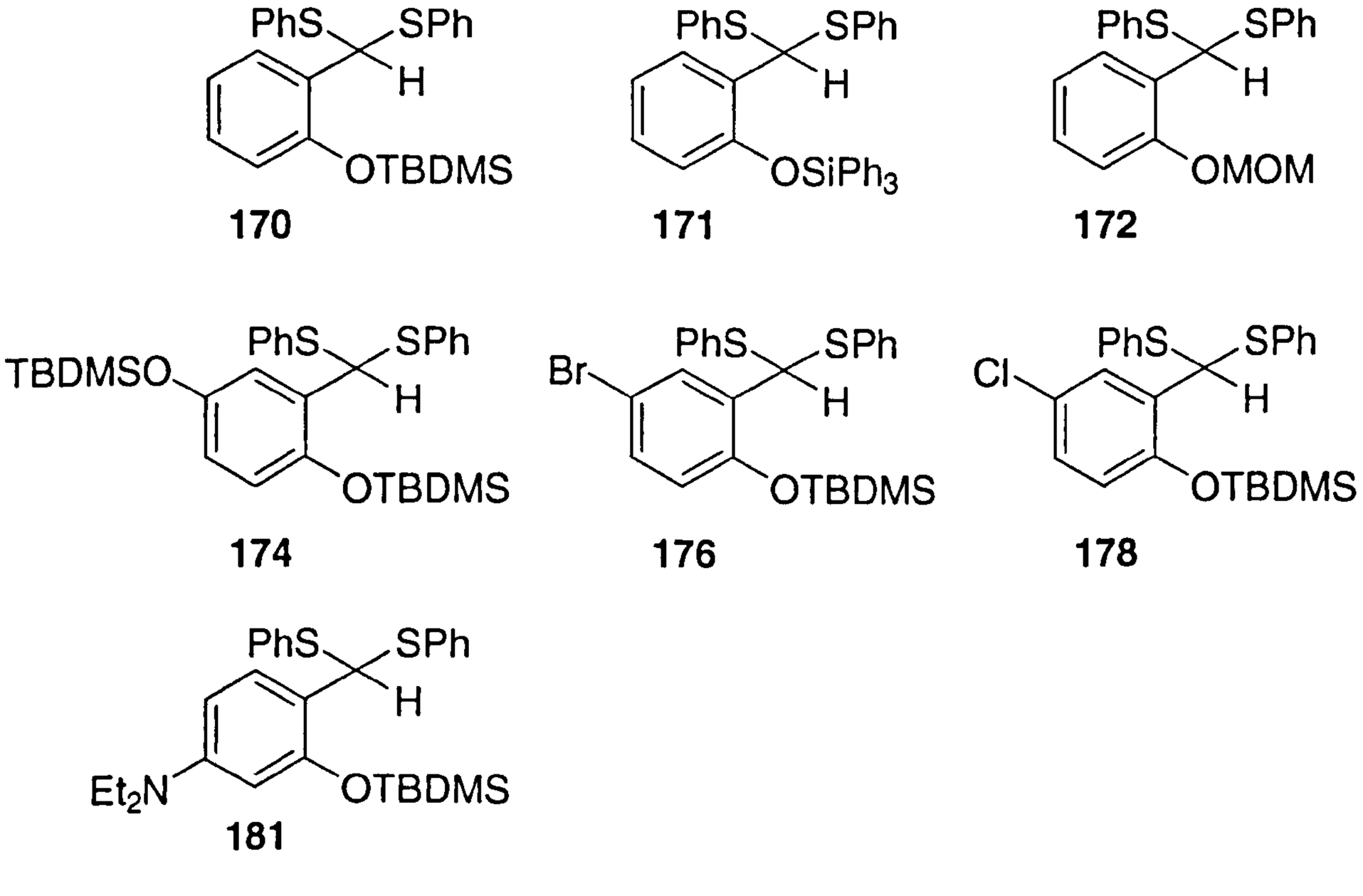
Scheme 74

4.3.2 Thioacetals

As with the solution phase Takeda reactions described in Chapter 3, the thioacetals used were the salicylaldehyde derivatives whose synthesis was described in Section 3.2.

The choice of thioacetal used was based on two criteria: firstly, a range of functionality was chosen to demonstrate the range of functionality that could be tolerated in the alkylindenating reagent and under the conditions used to generate it; secondly, the salicylaldehyde derivatives should be commercially available. Reactions using thioacetals with free hydroxyls were not attempted, as it was not thought that this functional group would survive.

Thioacetal **172** with a MOM-protected hydroxy was used in a trial alkylidenation reaction. However, upon cleavage from the resin a mixture of products was formed. More pleasingly, a trial alkylidenation reaction using a thioacetal with a TBDMS-protected hydroxyl **170** (Figure 22) gave clean products upon cleavage from the resin. Silyl protecting groups were therefore used in all other SPS alkylidenation reactions.



170 **171** **172**

174 **176** **178**

181

Figure 22

The resin-bound enol ethers that have been formed and characterised are shown in Tables 7 and 8.

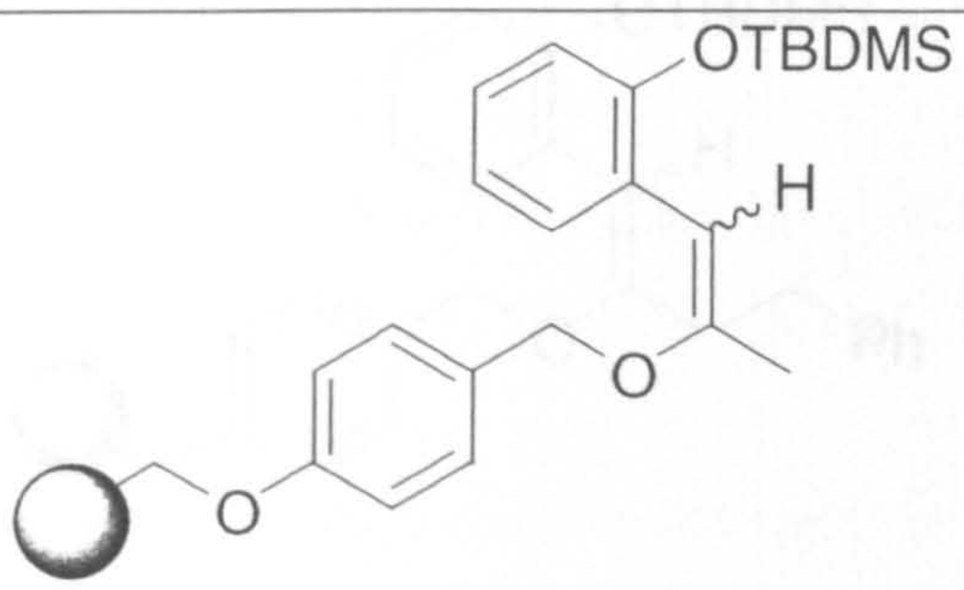
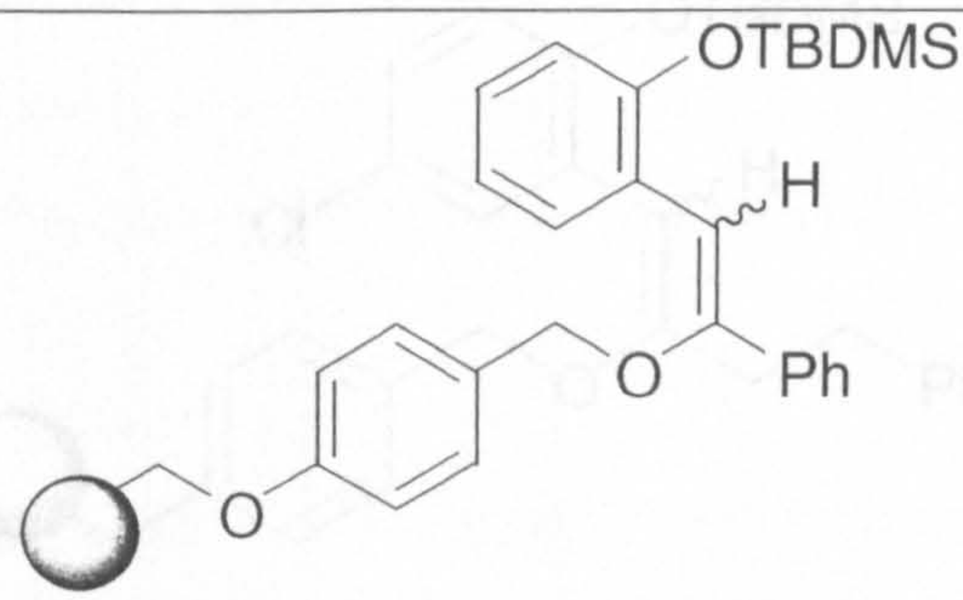
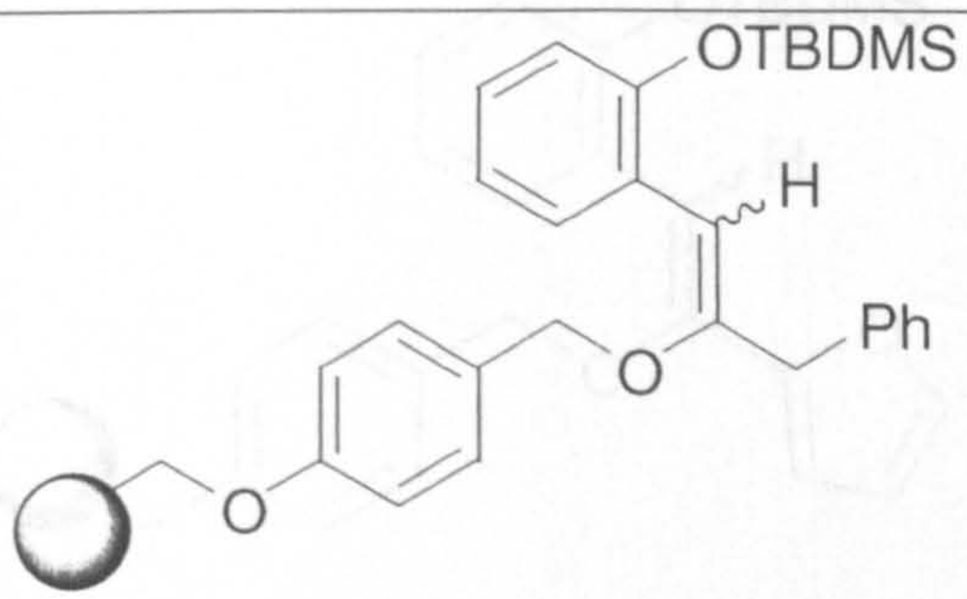
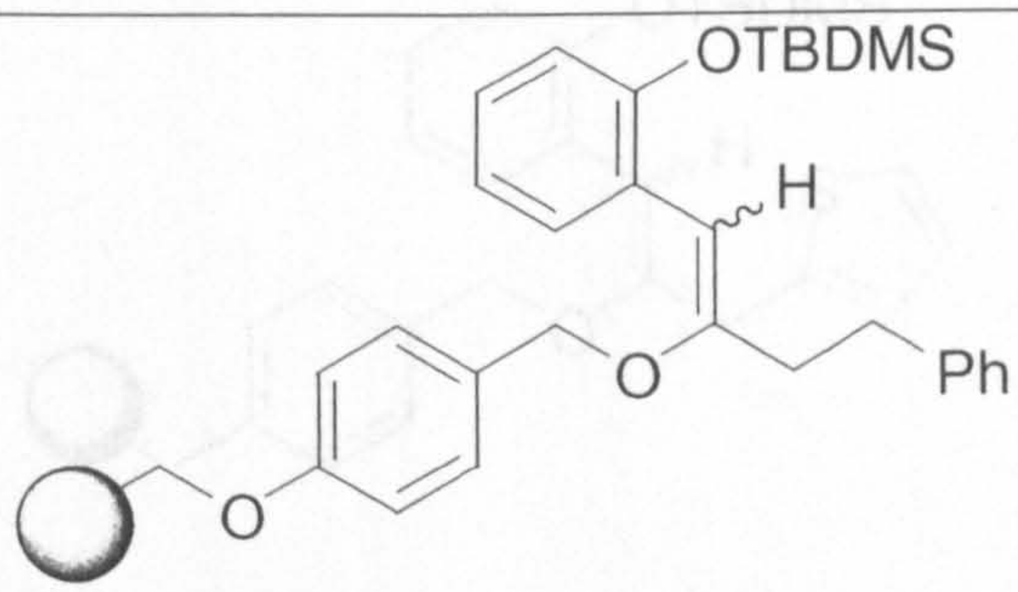
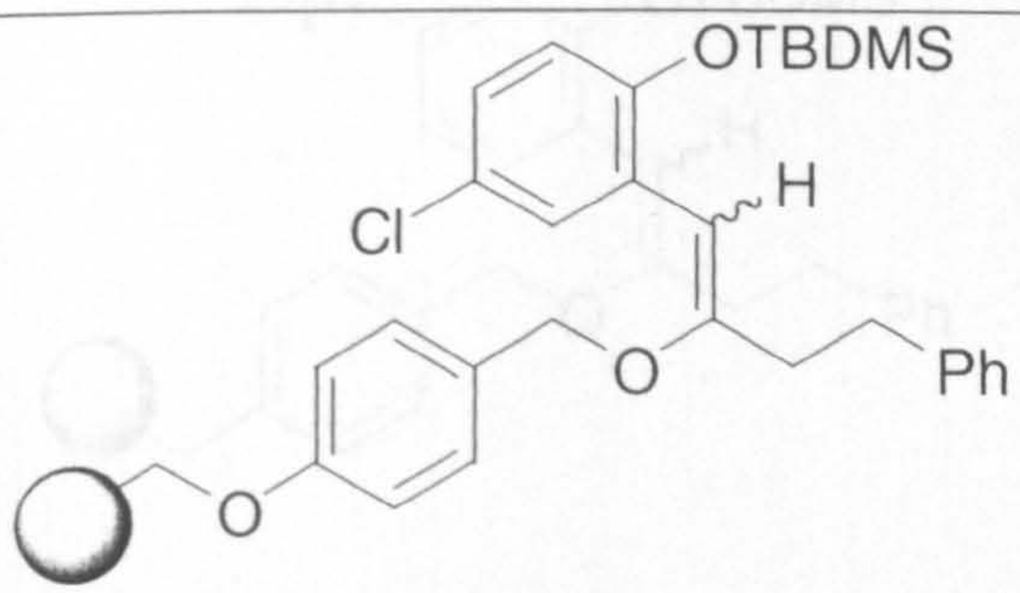
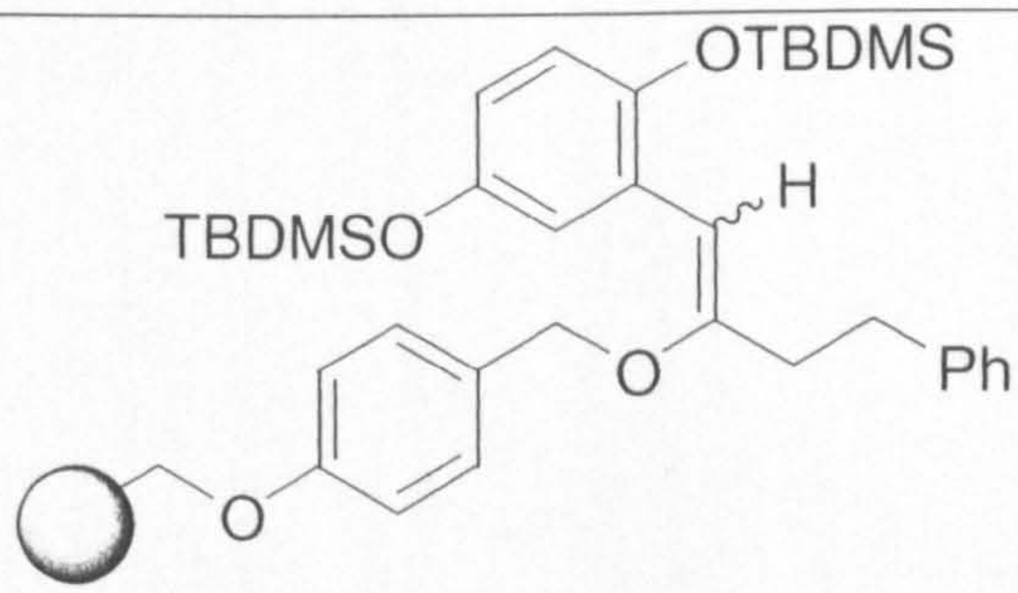
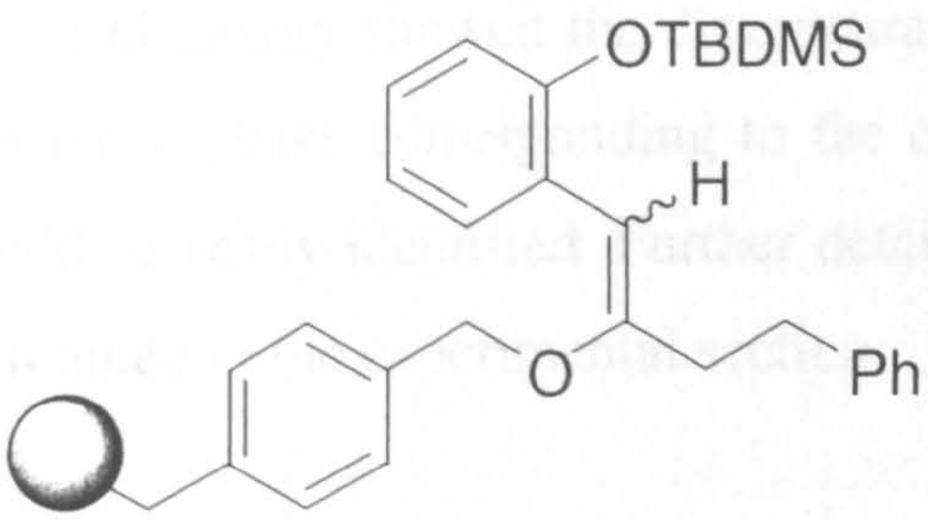
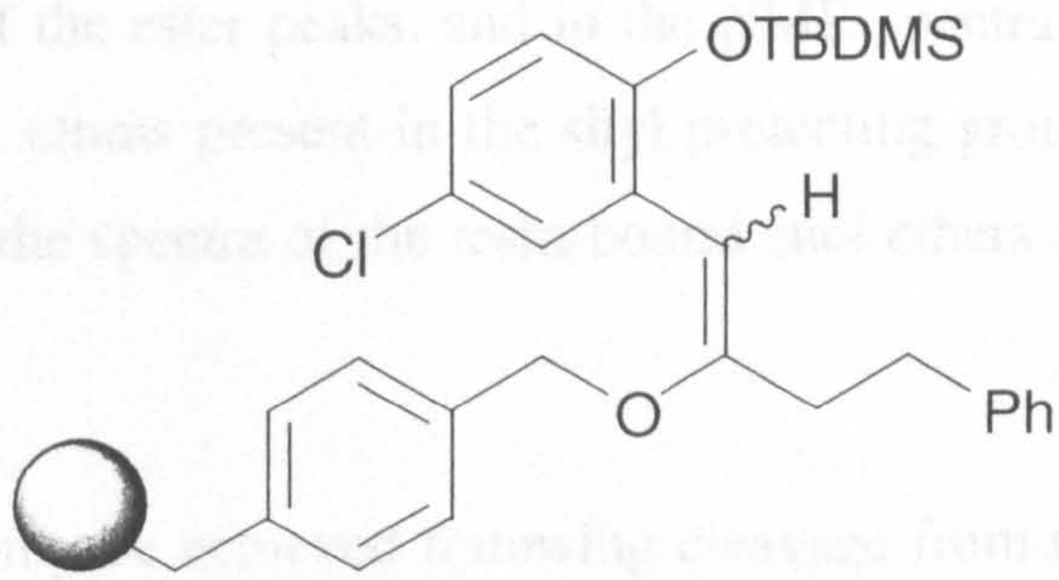
Wang-Bound Enol Ethers Synthesised	
 **194a**	 **194b**
 **194c**	 **194d**
 **194e**	 **194f**

Table 7

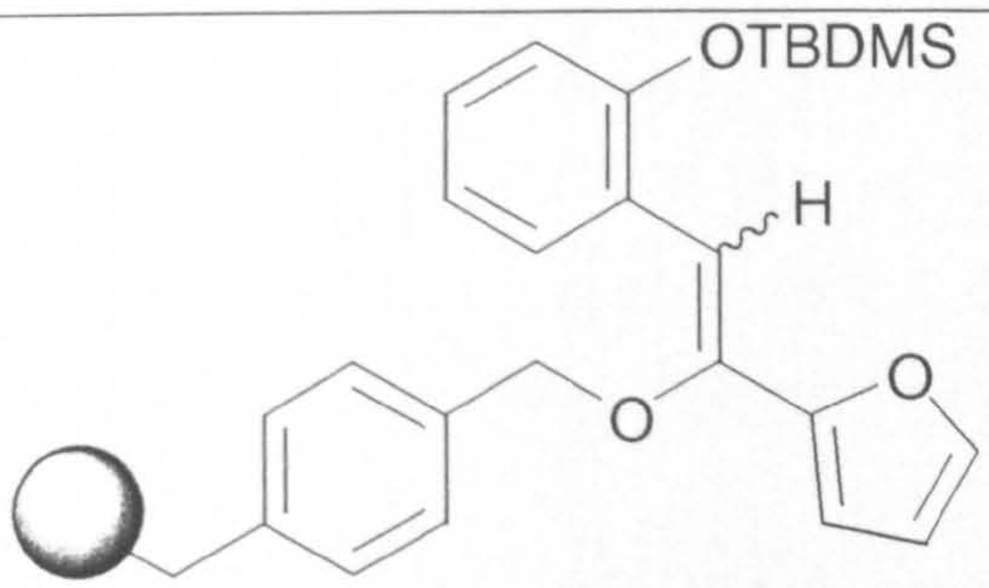
Merrifield-Bound Enol Ethers Synthesised



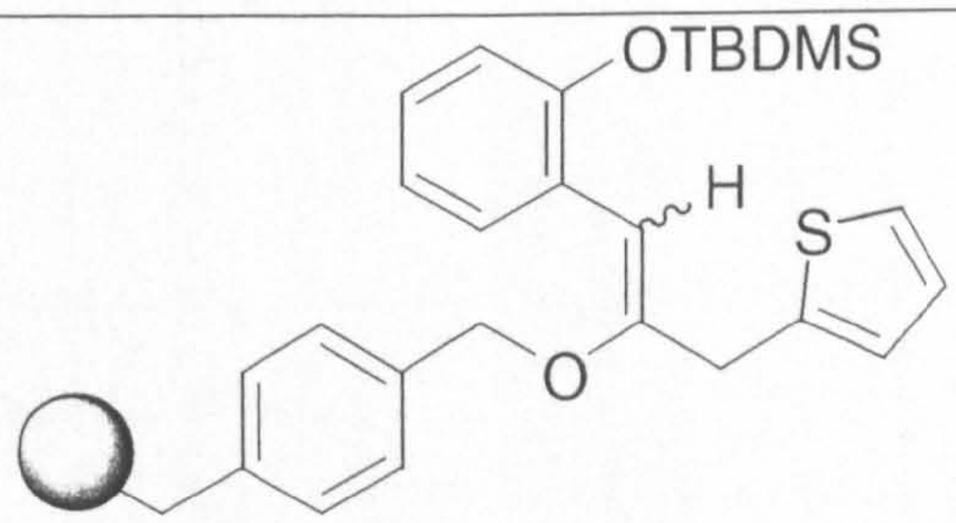
195a



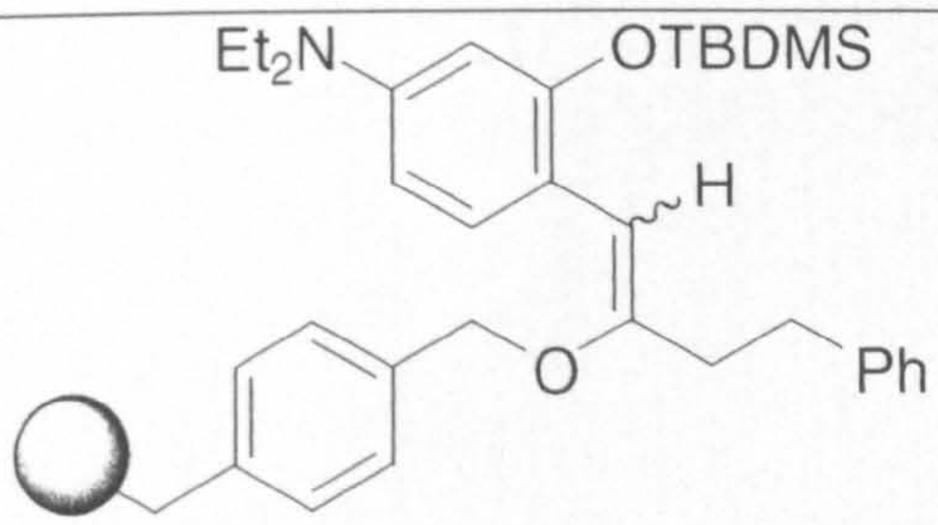
195b



195c



195d



195e

Table 8

4.3.3 Product Determination

Formation of the enol ether was determined qualitatively using IR and ^{13}C NMR spectroscopy. With one exception (**194b**), the IR spectra of the resin-bound enol ethers **194** and **195** clearly showed the disappearance of the ester peaks, and in the NMR spectra of the resin, peaks corresponding to the carbon atoms present in the silyl protecting groups could be easily identified. Further details of the spectra of the resin-bound enol ethers are contained in the experimental section.

Quantitative analysis of the reaction could only be achieved following cleavage from the resin. Cleavage was initially carried out by treatment of the resin-bound enol ethers **194** and **195** with acid to give the corresponding ketone (Schemes 76 and 77). This procedure is described in the following section.

4.4 Cleavage of resin-bound enol ethers.

4.4.1 Cleavage to Ketones

4.4.1.1 Wang cleavage to ketones

Wang-bound enol ethers **194** were cleaved using 50 % aqueous trifluroacetic acid (TFA) in dichloromethane.[140] The kan was shaken in this mixture for 30 minutes and the resulting solution was then dried and concentrated to give ketones **196** (Scheme 75, overleaf). It was later realised that cleavage to ketones could be successfully achieved using only 1 % TFA in dichloromethane. This removed the need for the drying step required when using the aqueous mixture.

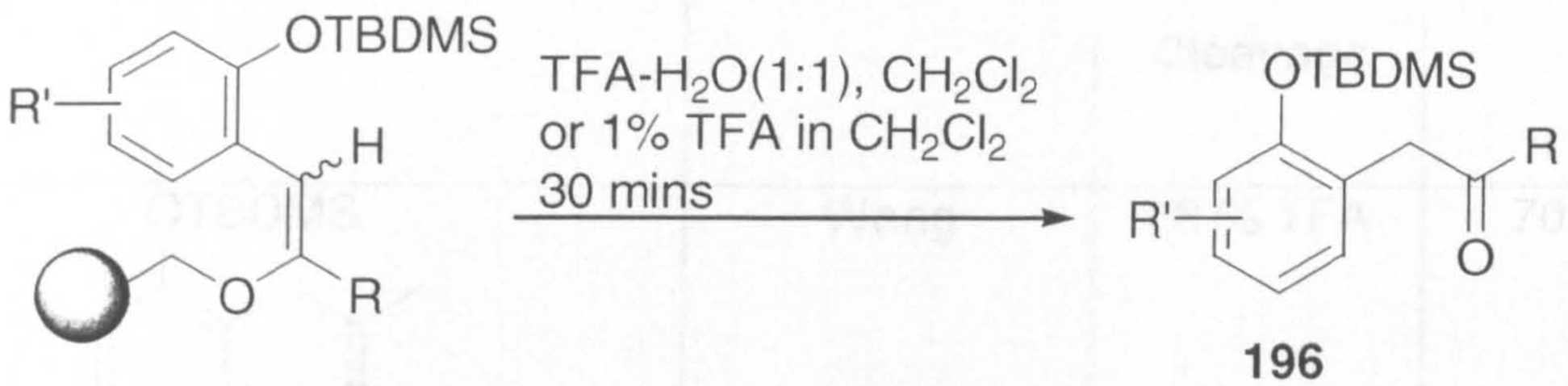
With the exception of examples in Section 4.4.1.4, all the ketones were formed cleanly. 50 % aqueous TFA would have cleaved any unreacted resin-bound ester from Wang resin, giving the corresponding carboxylic acid. As no acid was observed it can be deduced that all the ester had reacted to give the corresponding enol ether.

The IR of enol ether **194b** did show a peak corresponding to an unreacted ester group. However upon cleavage no carboxylic acid was identified, also no carbonyl peak was observed in the ^{13}C of the enol ether. It may be in this case that the reaction did not go to completion, however it must be remembered that IR cannot be used as a quantitative measurement and it may be that the unreacted ester was a very minor component.

4.4.1.2 Merrifield cleavage to ketones

Ketones **196** were released from Merrifield resin using 1 % TFA in dichloromethane. Resin-bound esters **192** would not cleave under such mild conditions.

Although the work on Wang resin cleavage suggested that the alkylidenation reactions had gone to completion, the use of Merrifield and 1 % TFA cleavage ensures that even if there were unreacted ester present, the ketone could still be formed cleanly.



194 Wang Resin
195 Merrifeld Resin

196

TFA = trifluroacetic acid
TBDMS = *tert*butyldimethylsilyl

Scheme 75

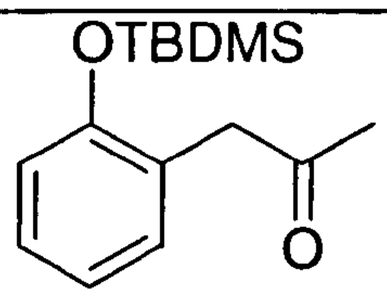
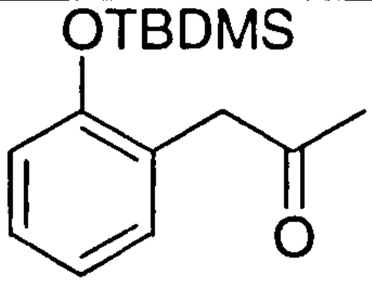
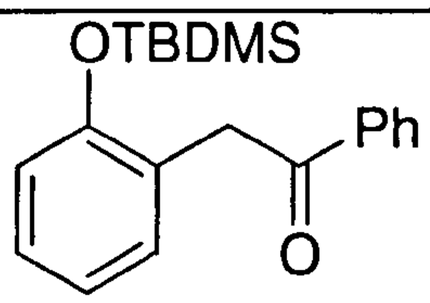
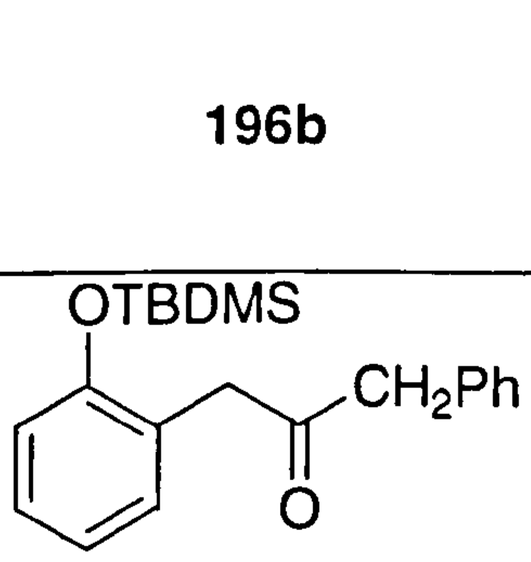
The results of the cleavage to ketone reactions are summarised below (Table 9).

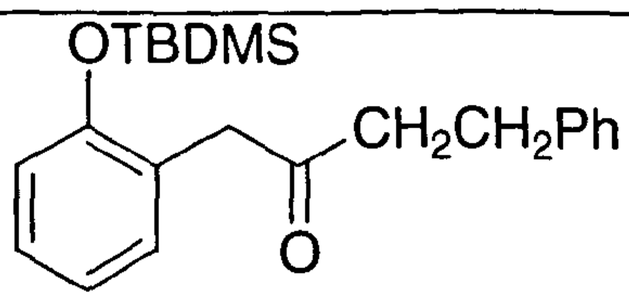
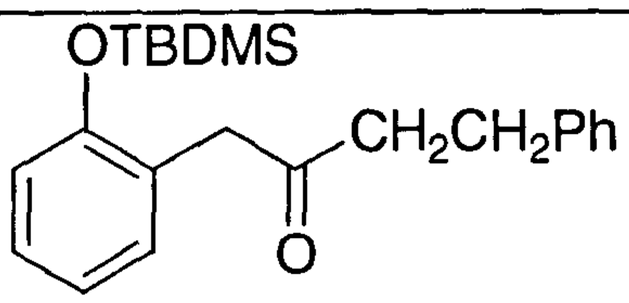
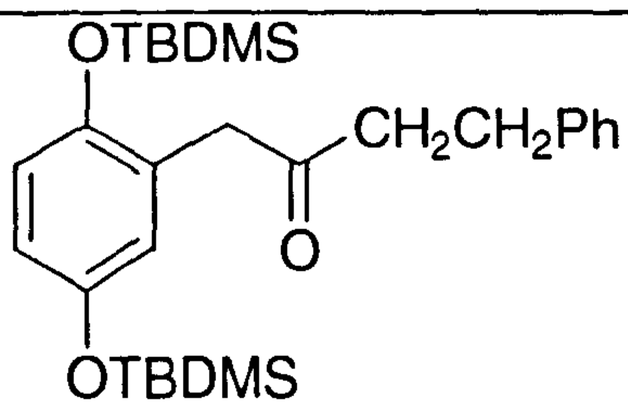
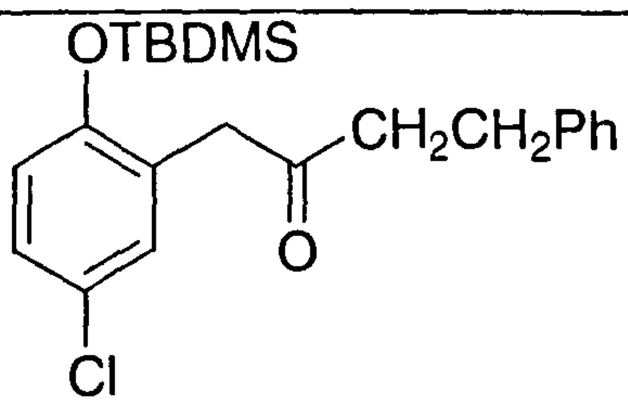
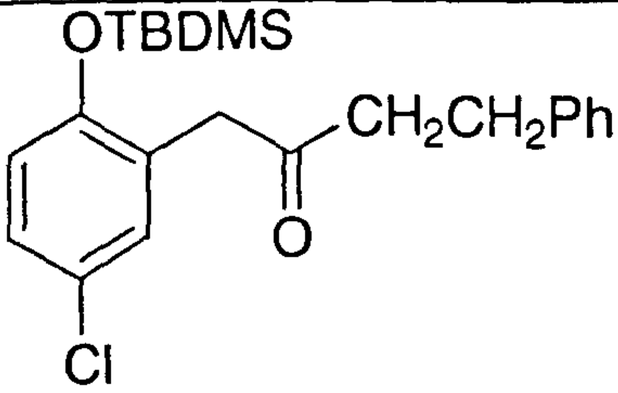
Resin Type	Compound Type	Cleavage conditions	Product Cleaved
Wang	Enol ether	50 % aqueous TFA	Ketone
Wang	Enol ether	1 % TFA	Ketone
Merrifield	Enol ether	1 % TFA	Ketone

Table 9

4.4.1.3 Results

The table below shows the ketones **196** formed *via* cleavage of the resin-bound enol ethers **194** and **195** and their yields (Table 10). All the ketones below were formed cleanly and no further purification was necessary.

Ketones synthesised			
Ketone	**Resin**	**Method of Cleavage**	**Yield**
 **196a**	Wang	50 % TFA	70 %
 **196a**	Wang	1 % TFA	77 %
 **196b**	Wang	50 % TFA	63 %
 **196c**	Wang	50 % TFA	77 %

 **196d**	Wang	50 % TFA	82 %
 **196d**	Merrifield	1 % TFA	56 %
 **196e**	Wang	1 % TFA	73 %
 **196f**	Wang	1 % TFA	42 %
 **196f**	Merrifield	1 % TFA	30 %

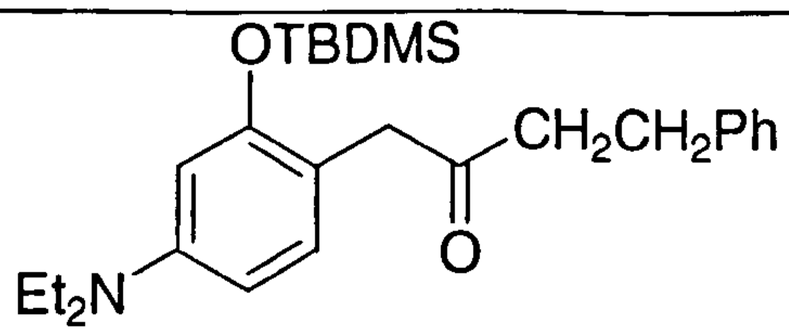
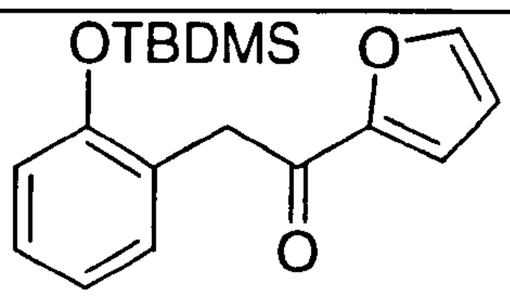
 **196g**	Merrifield	1 % TFA	41 %
 **196h**	Merrifield	1 % TFA	66 %

Table 10

4.4.1.4 Failed Reactions

Although the majority of the ketones **196** formed cleanly (see Table 10), a number of the cleavage reactions did not give the clean product as planned (Table 11). These results are summarised below.

Cleavage to Ketone

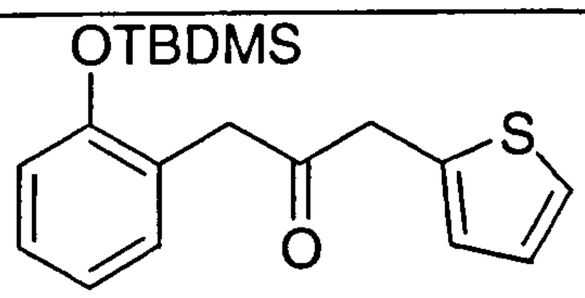
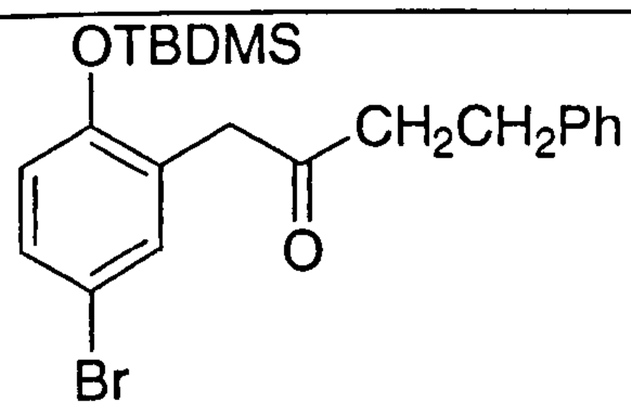
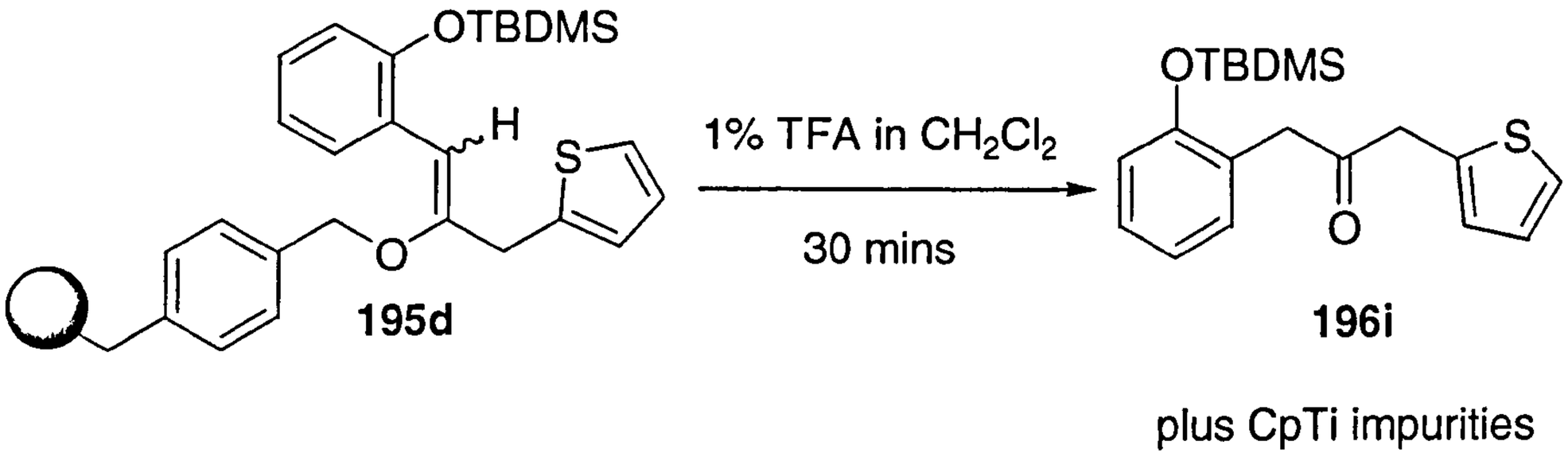
Ketone	Resin	Method of Cleavage	Actual Products formed	Yield
 **196i**	Merrifield	1 % TFA	Ketone plus titanium impurities	13 % (after column chroma-tography)
197	Merrifield	1 % TFA	Titanium impurities	n/a
 **196j**	Merrifield	1 % TFA	Clean formation of ketone **196d** (no bromine present)	60 %

Table 11

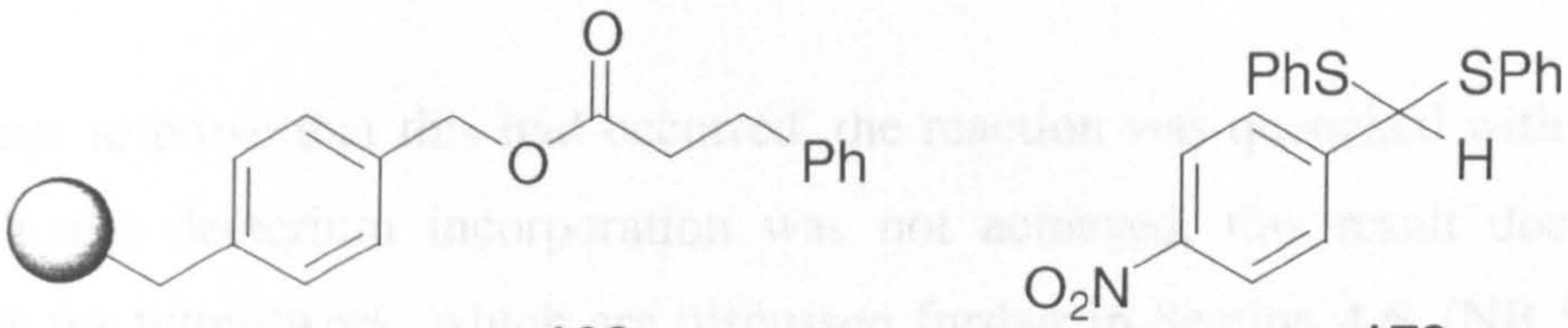
The thiophene **196i** was one of the few ketones that did not form cleanly. Upon cleavage of the resin-bound enol ether **195d**, a number of cyclopentadienyl titanium groups were evident in the ^{1}H NMR spectrum of the ketone (Scheme 76). This suggests that the washing procedure was ineffective at removing all of the titanium residues after the alkylidenation reaction. As this occurrence was not observed with any of the other resin-bound enol ethers **194** and **195** (N.B. see the nitro-functionalised thioacetal result below), it seems that the thiophene ring is preventing the titanium residues from being removed, perhaps by chelation of the sulfur to the titanium atom.



Scheme 76

The poor yield of the ketone **196i** (13 %) could be explained by the fact that complete purification *via* column chromatography was difficult to achieve and some of the impure product remained on the column.

An alkylidenation reaction was carried out using a nitro-functionalised thioacetal **179** and Merrifield-bound ester **192a** (Figure 23). This was a trial reaction to observe whether the nitro group survived the low valent titanium reagent used to generate the titanium alkylidene - no hydroxyl group was present on the thioacetal and hence no benzofuran could be formed from this reaction.



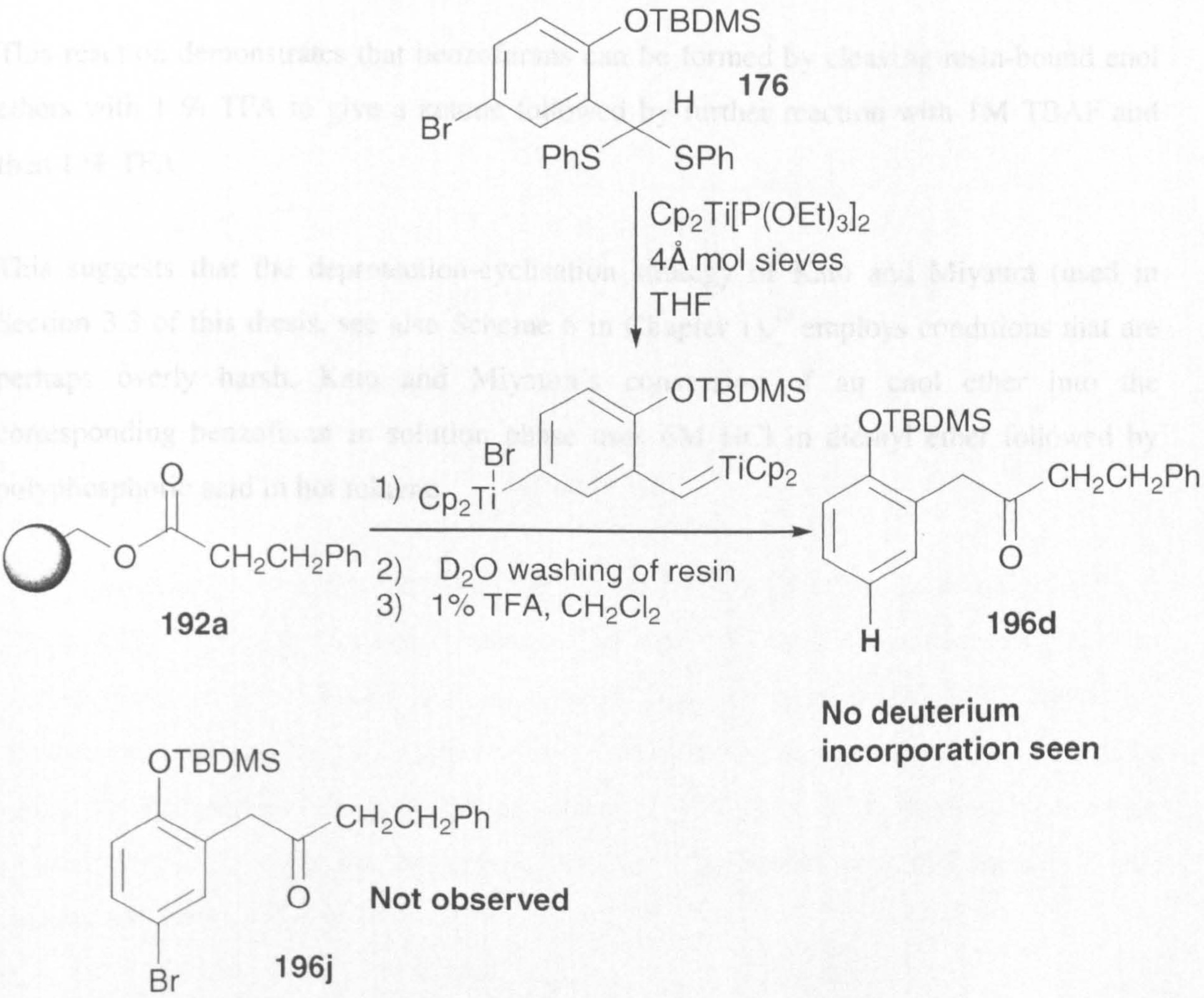
192a **179**

Figure 23

The results of cleavage from the resin suggested that the nitro group is incompatible with the alkylidenation reaction conditions. The IR and ^{13}C data of the resin-bound product did not suggest that any alkylidenation had occurred, with the IR still showing the presence of the carbonyl group. It also proved very difficult to remove all of the titanium residues - this was witnessed by the fact that when the resin was washed the washings consistently came through purple (suggesting the presence of Cp_2Ti groups). Despite the fact the resin was washed far more than was usual, upon treatment with acid more titanium residues were observed.

An interesting result was obtained when an alkylidenation reaction was carried out using a bromine functionalised thioacetal **173** (Scheme 79). After cleavage, instead of the expected bromine-functionalised ketone **196j**, an unfunctionalised ketone **196d** was formed cleanly. The result suggests that the titanium had inserted into the carbon-bromine bond of thioacetal **176**. The formation of ketone **196d** may occur as a result of traces of moisture entering the reaction during the long stirring time.

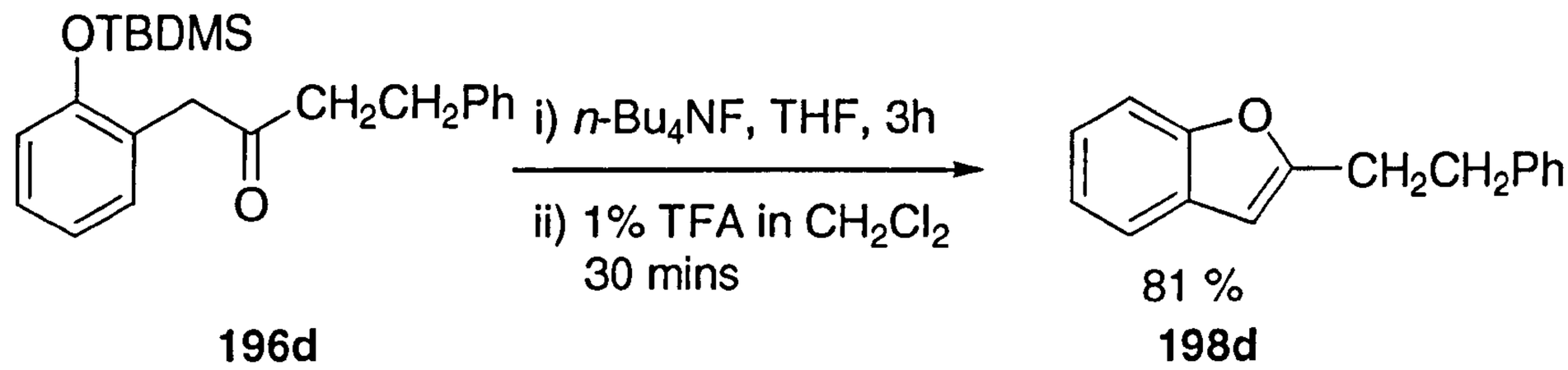
In an attempt to prove that this had occurred, the reaction was quenched with deuterium oxide. Although deuterium incorporation was not achieved, this result does generate possibilities for future work, which are discussed further in Section 4.6. (NB Scheme 77 shows an example where D_2O quenching was carried out, however **196d** formed whether D_2O quenching was carried out or not).



Scheme 77

4.4.1.5 Conversion of Ketones to Benzofurans

The cleaved ketones can be converted into the desired benzofurans by deprotection of the hydroxyl group followed by acid-induced cyclisation, e.g. ketone **196d** was converted cleanly into benzofuran **198d** in 81 % yield (Scheme 78).



196d **198d**

Scheme 78

This reaction demonstrates that benzofurans can be formed by cleaving resin-bound enol ethers with 1 % TFA to give a ketone followed by further reaction with 1M TBAF and then 1 % TFA.

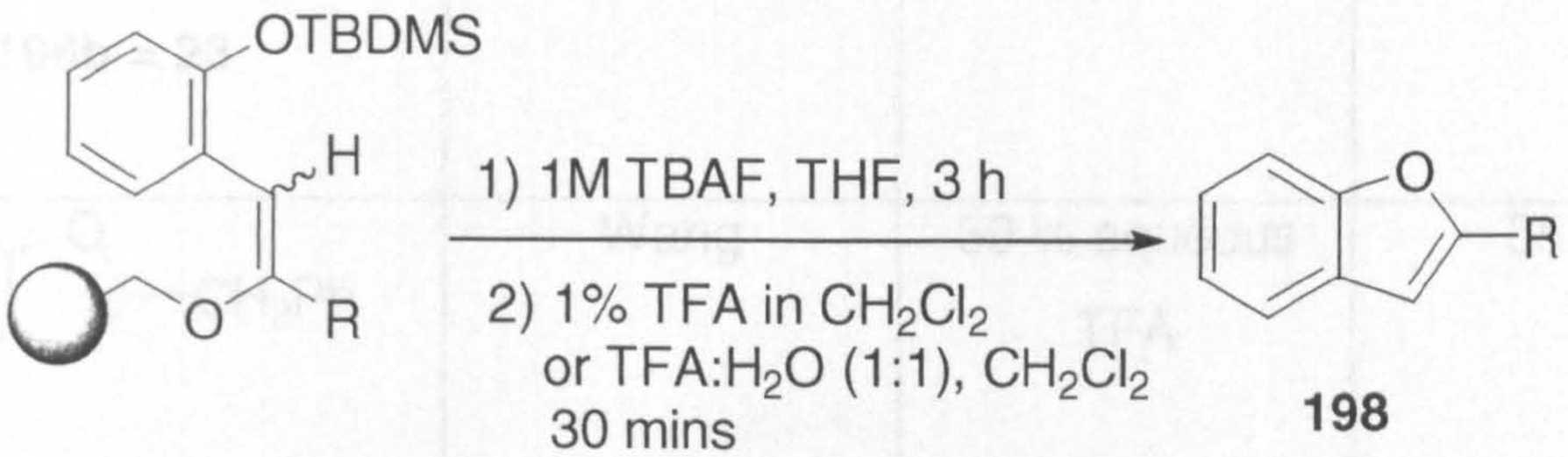
This suggests that the deprotection-cyclisation strategy of Kato and Miyaura (used in Section 3.3 of this thesis, see also Scheme 6 in Chapter 1),[18] employs conditions that are perhaps overly harsh. Kato and Miyaura's conversion of an enol ether into the corresponding benzofuran in solution phase uses 6M HCl in diethyl ether followed by polyphosphoric acid in hot toluene.

4.4.2 Cleavage to benzofurans

4.4.2.1 Results

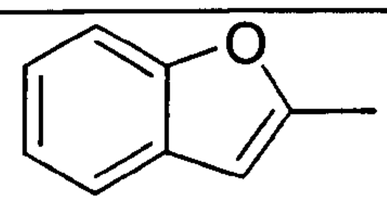
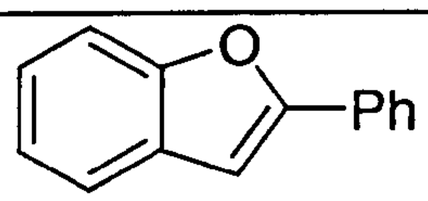
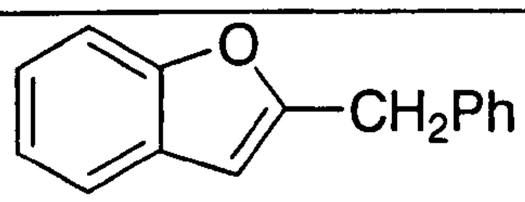
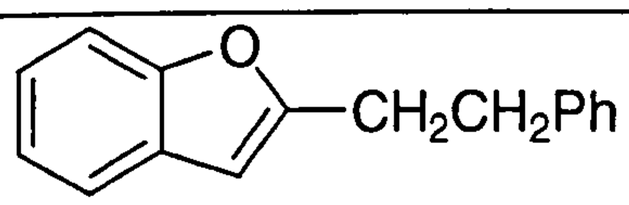
I had now demonstrated that benzofurans could be formed *via* solid phase alkylidenation, followed by a 3-step cleavage deprotection/cyclisation method. I also wished to investigate the possibility of forming the target benzofuran directly upon cleavage from the resin, which would remove the need for the extra solution phase steps at the end.

Direct cleavage to benzofurans **198** could be achieved by deprotecting the silyl group while the enol ether **194,195** was still attached to the resin, and then treating with acid (Scheme 79). The following sections look at the formation of benzofurans using this method.



Scheme 79

The deprotection/cleavage strategy was carried out on a number of resin-bound enol ethers **194** and **195**. The enol ether was swollen in THF and 1M TBAF was added. The resin was shaken under an argon atmosphere for 3 hours and then washed with THF, alternating dichloromethane and methanol and finally diethyl ether. Cleavage was carried out using either 50 % aqueous TFA in dichloromethane or 1 % TFA in dichloromethane in the manner described as for the cleavage to ketones. The benzofurans **198** formed in this manner are shown in Table 12.

Benzofurans synthesised direct from resin cleavage			
Benzofuran	**Resin**	**Method of Cleavage**	**Yield**
 **198a**	Wang	50 % aqueous TFA	38 %
 **198b = 23**	Wang	50 % aqueous TFA	69 %
 **198c**	Wang	50 % aqueous TFA	38 %
 **198d**	Wang	50 % aqueous TFA	84 %

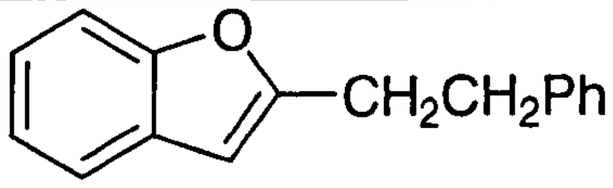
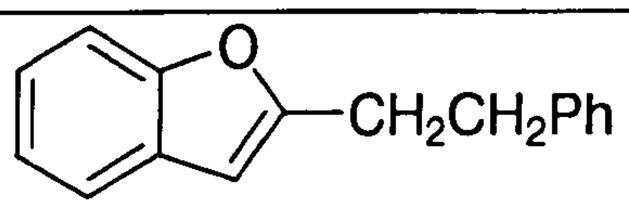
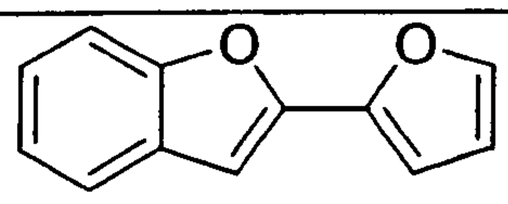
 **198d**	Wang	1 % TFA	60 %
 **198d**	Merrifield	1% TFA	25 %
 **198e**	Merrifield	1 % TFA	34 %

Table 12

4.4.2.2 Purification - removal ammonium salt

The benzofurans **198** in the above table formed cleanly in as much as they were the only products to come off the resin, no ketones **196** or carboxylic acids were observed and hence no chromatography was required. However, a problem lay in the removal of the ammonium salt from the TBAF used to deprotect the silyl group. Upon cleavage residues of the salt often remained and proved somewhat difficult to remove from the benzofuran products **198**.

The best way found to remove all of the salt was to take up the benzofuran/salt mixture in diethyl ether and wash the solution with copious amounts of water. The salt dissolved in the aqueous layer, leaving the pure benzofuran in the ether. The organic layer was then dried and concentrated. This method had its limitations in that it was impossible to tell whether all the salt had been removed until the organic layer had been concentrated, and if any remained the above process had to be repeated.

We suspect that the deprotected resin-bound enol ether is stabilised by the formation of the salt **200** (Figure 24). Perhaps the free phenol **199** spontaneously cleaves from the resin. This would explain the lower yields of benzofurans **198** compared to the corresponding ketones **196**. When ketone **196d** was deprotected in solution phase, the product was washed with water before reaction with 1 % TFA so no tetrabutylammonium contaminants remained.

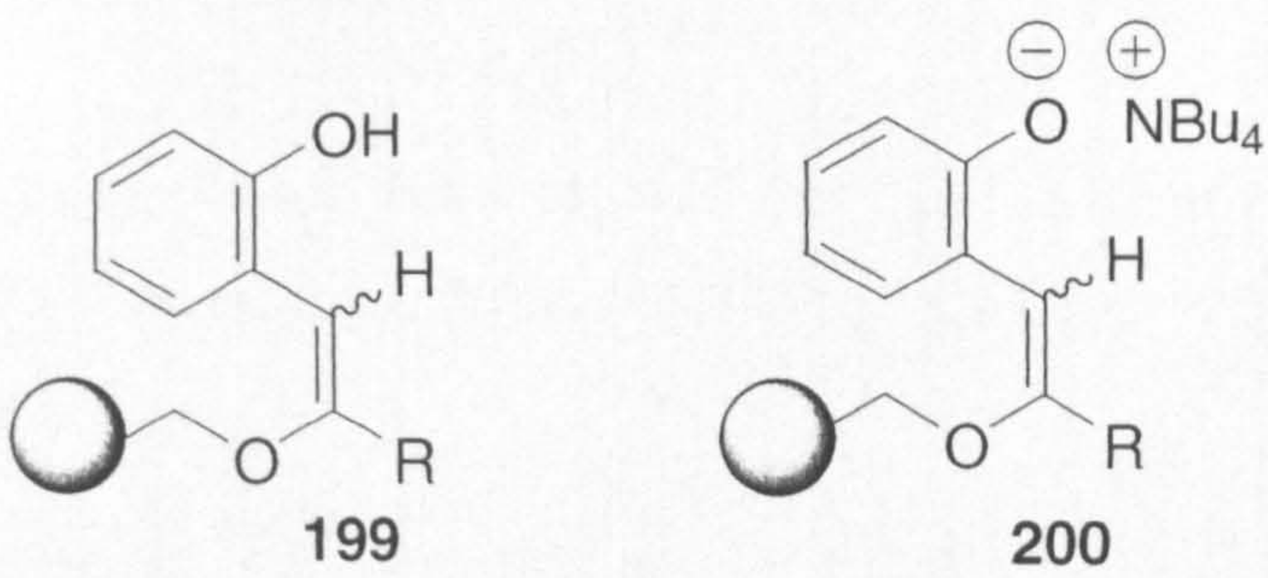


Figure 24

A way of avoiding this problem could be to use an alternative protecting group. This possibility is discussed in the Future Work section of this chapter (Section 4.6).

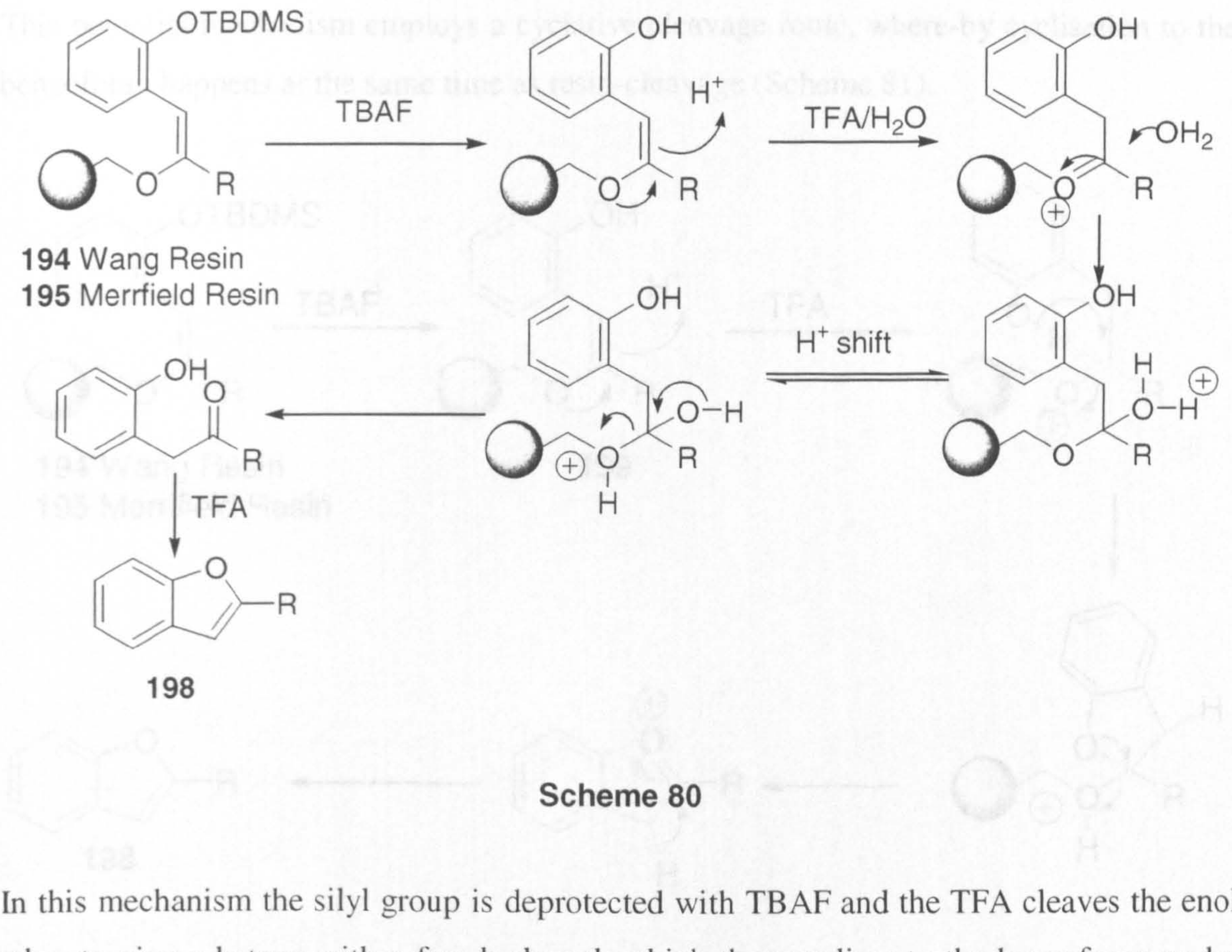
4.5 Mechanistic Work

The previous section describes how the resin-bound enol ethers **194** and **195** can be treated with TBAF and then TFA to give (ammonium salt impurities aside) pure benzofurans **198**. There are a number of potential mechanisms *via* which the benzofurans could form and three possibilities are discussed below (Scheme 82-84).

To recap – the resin-bound enol ether (Merrifield or Wang) was treated with 1M TBAF in THF under argon for 3 hours, after which the resin was washed with THF, alternating dichloromethane and methanol and finally diethyl ether. Resin-cleavage was then carried out by treatment with either 50 % aqueous TFA in dichloromethane or 1% TFA in dichloromethane for 30 mins. This produced clean benzofuran although in most cases some ammonium salt had to be removed.

It should be noted that the TFA used was not rigorously dried and some moisture may be required for the reaction to be successful.

4.5.1 Mechanism 1 - Deprotection then cleavage to ketone followed by cyclisation to benzofuran



Scheme 80

In this mechanism the silyl group is deprotected with TBAF and the TFA cleaves the enol ether to give a ketone with a free hydroxyl, which then cyclises to the benzofuran under acidic conditions (Scheme 80).

Evidence in favour of this mechanism:

- Results from Section 4.4.1.5 which showed that cyclisation of deprotected hydroxy ketone **196d** to benzofurans **198d** could be achieved using 1 % TFA in dichloromethane.

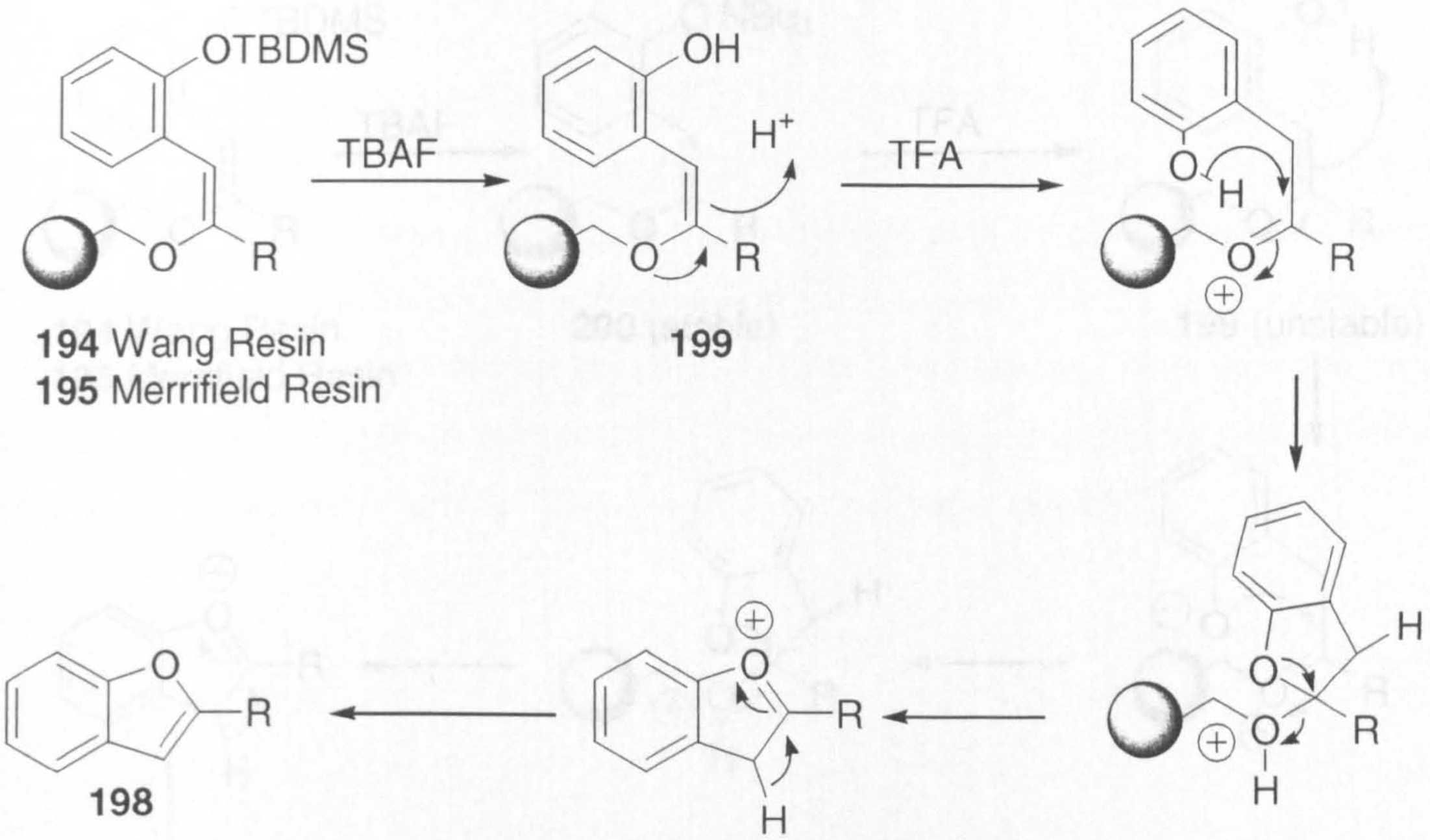
- Ketones **196** are released from the resin in acid when no internal nucleophile is available.

However:

- The free hydroxyl in resin-bound enol ether must be very reactive and the possibility of a cyclative cleavage reaction occurring (see Mechanism 2) cannot be discounted.

4.5.2 Mechanism 2 - Cyclative cleavage to benzofuran involving internal nucleophile

This potential mechanism employs a cyclative cleavage route, where-by cyclisation to the benzofuran happens at the same time as resin-cleavage (Scheme 81).



194 Wang Resin
195 Merrifield Resin

199

198

Scheme 81

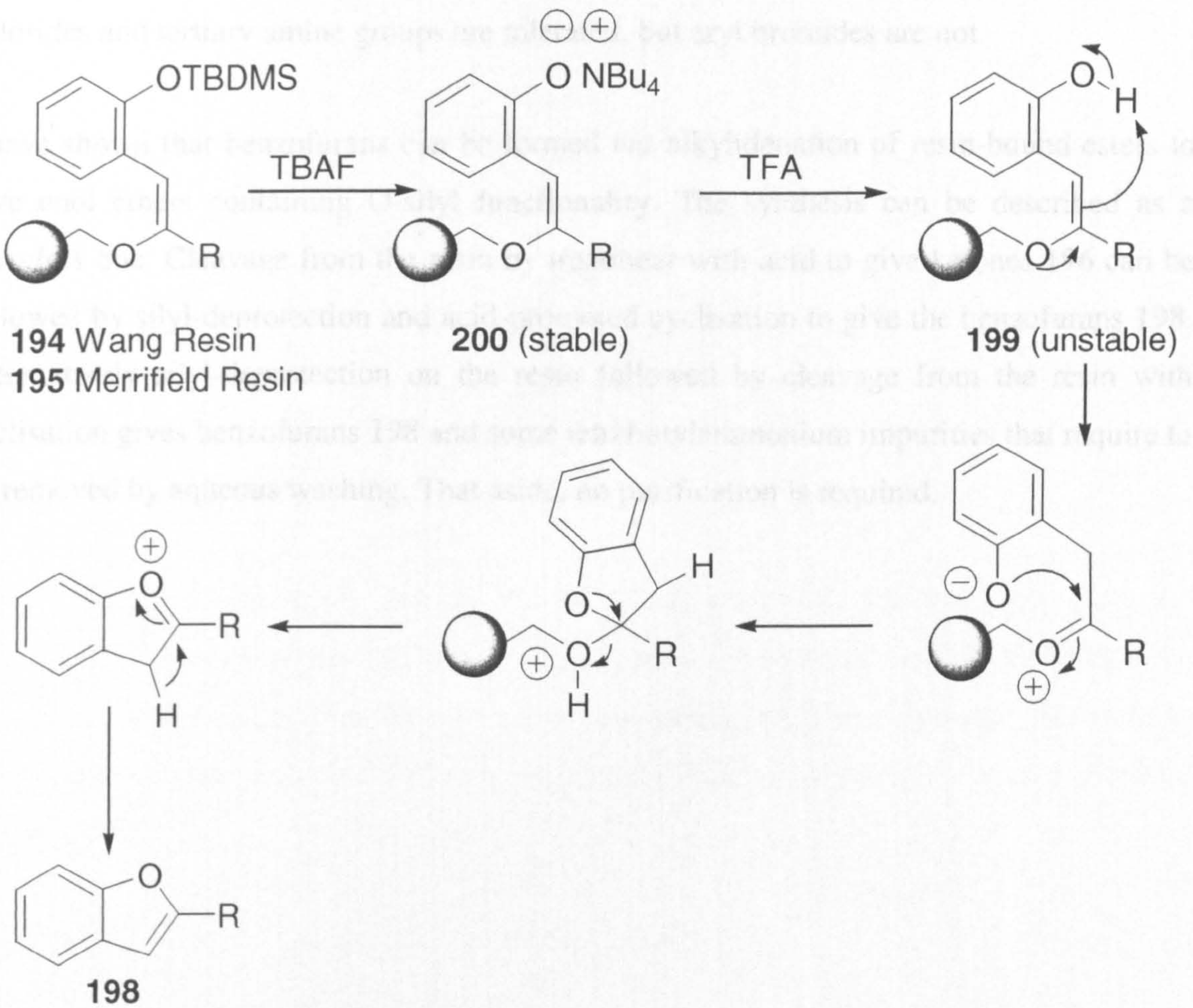
In this mechanism cleavage occurs *via* attack from an internal nucleophile.

In its favour:

- Reaction of the internal nucleophile involves a favoured 5-exo-trig process.

An adaptation of this mechanism (Mechanism 3) could explain the problems in removing the ammonium salt. It is possible that the salt **200** is the product of deprotection and that phenol **199** is generated when the TFA is added and spontaneously decomposes to the benzofuran **198** as shown overleaf (Scheme 82).

Mechanism 3 - Cyclative cleavage to benzofuran involving internal nucleophile (adaptation)



Scheme 82

However:

- It cannot be stated conclusively whether the reaction goes *via* Mechanism 1, 2 or 3, or by a combination of the three.

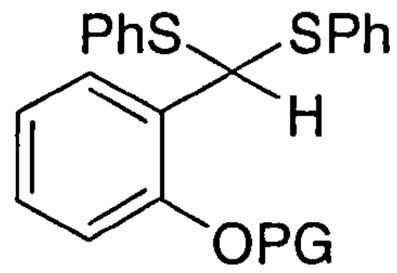
4.6 Summary & Future Work

In this chapter I have demonstrated that Takeda alkylidenation is more effective on solid-phase than in solution-phase as the product is more easily purified. I have shown that functional titanium alkylidene reagents can be generated. In particular TBS ethers, aryl chlorides and tertiary amine groups are tolerated, but aryl bromides are not.

I have shown that benzofurans can be formed *via* alkylidenation of resin-bound esters to give enol ethers containing O-silyl functionality. The synthesis can be described as a *traceless* one. Cleavage from the resin by treatment with acid to give ketones **196** can be followed by silyl-deprotection and acid-promoted cyclisation to give the benzofurans **198**. Alternatively silyl-deprotection on the resin followed by cleavage from the resin with cyclisation gives benzofurans **198** and some tetrabutylammonium impurities that require to be removed by aqueous washing. That aside, no purification is required.

4.6.1 Protecting group

One way to avoid the removal of the ammonium salt could be to use a different protecting group on the thioacetal (**201**, Figure 25).



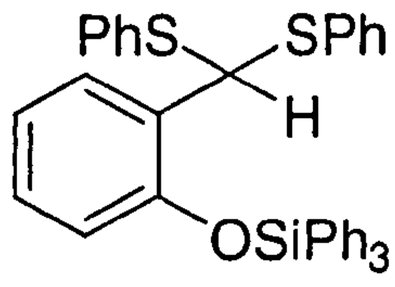
PG = protecting group

201

Figure 25

4.6.1.1 TPS Protecting Group

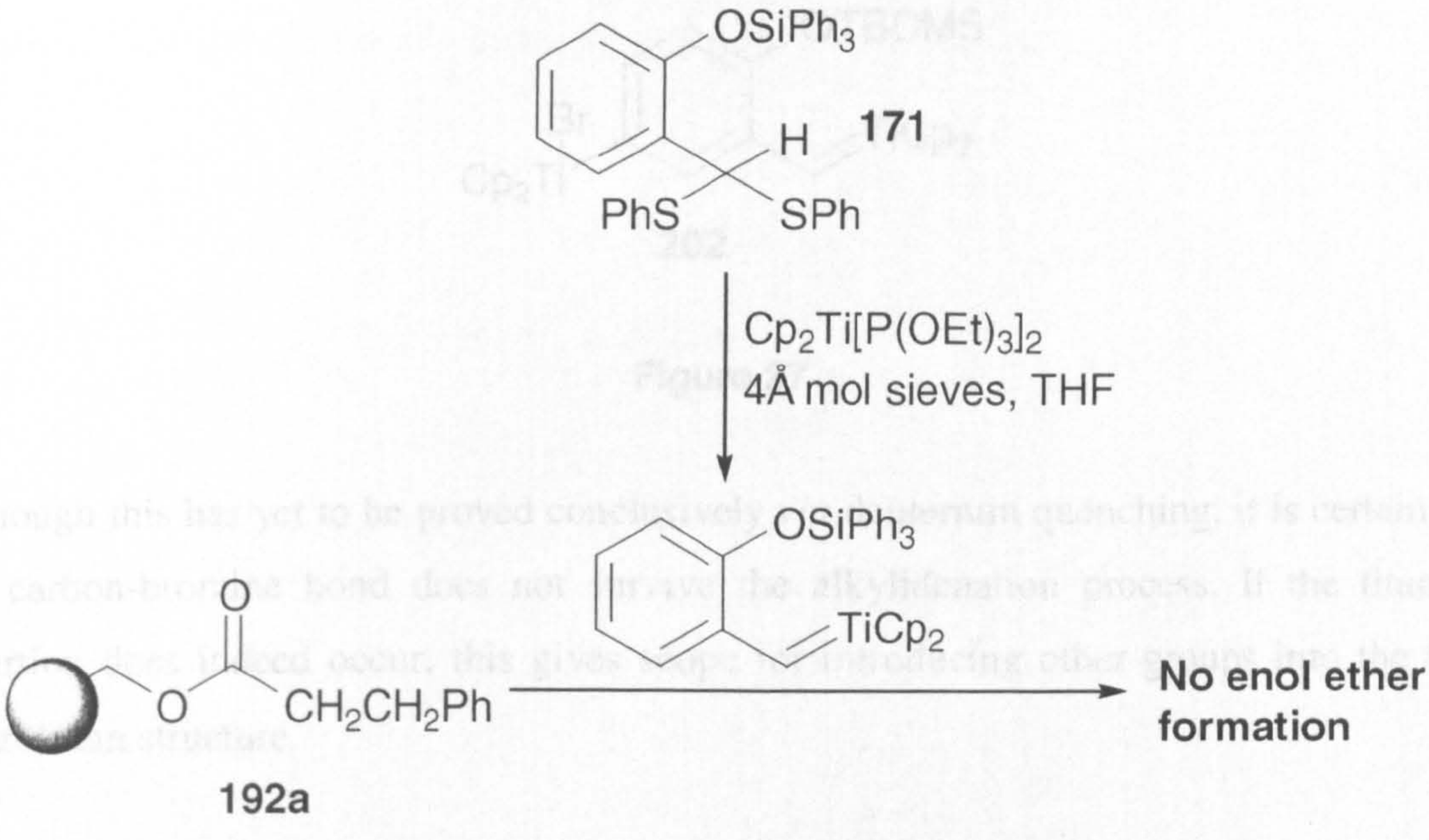
As stated in Section 4.3.2, use of the MOM protecting group was attempted and discounted. However, as the TBDMS group has been shown to survive the alkylidenation conditions, it is possible another silyl protecting group could be employed. With this in mind a thioacetal containing a TPS (triphenylsilyl) protected hydroxyl **171** was synthesised (Figure 26).



171

Figure 26

It was thought that deprotection of the enol ether could be achieved by reacting the resin with sodium methanoate to give a sodium phenoxide. The sodium trifluoroacetate that would be produced following treatment with acid would be more easily removed than tetrabutylammonium salts. An alkylidenation reaction was attempted using the thioacetal **171** and Merrifield-bound ester **192a** (Scheme 83).



Scheme 83

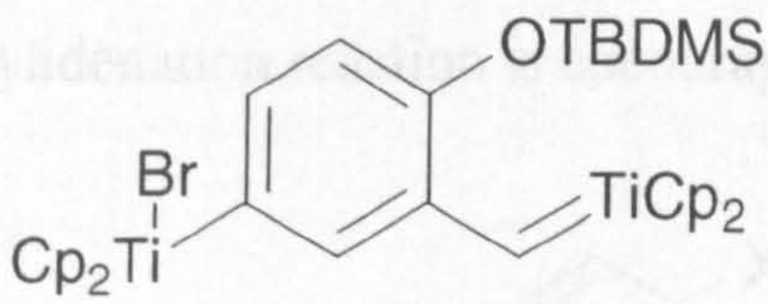
Unfortunately the alkylidenation reaction was unsuccessful. The resin product was treated with NaOMe and washed with methanol as described above. Cleavage was carried out using 1 % TFA in dichloromethane as described previously. A mixture of unidentified products was formed upon cleavage from the resin. A ^{13}C NMR spectrum of the resin product showed unreacted ester, suggesting that no alkylidenation had taken place. This suggests that TPS is too bulky and prevents alkylidenation from occurring.

4.6.1.2 TMS Protecting Group

It is possible that the TMS (trimethylsilyl) group would be a better choice for the alkylidenation reaction – given that it is far less bulky than the TPS group. The use of thioacetals with TMS–protected hydroxyls in SPS alkylidenations were not attempted here but work on investigating this possibility continues within our research group.

4.6.2 Bromine work

The result of alkylidenation using bromine functionalised thioacetals was described in Section 4.4.1.4. It would appear that a titanocene group inserts into the carbon-bromine bond during the alkylidenation process (**202**, Figure 27).

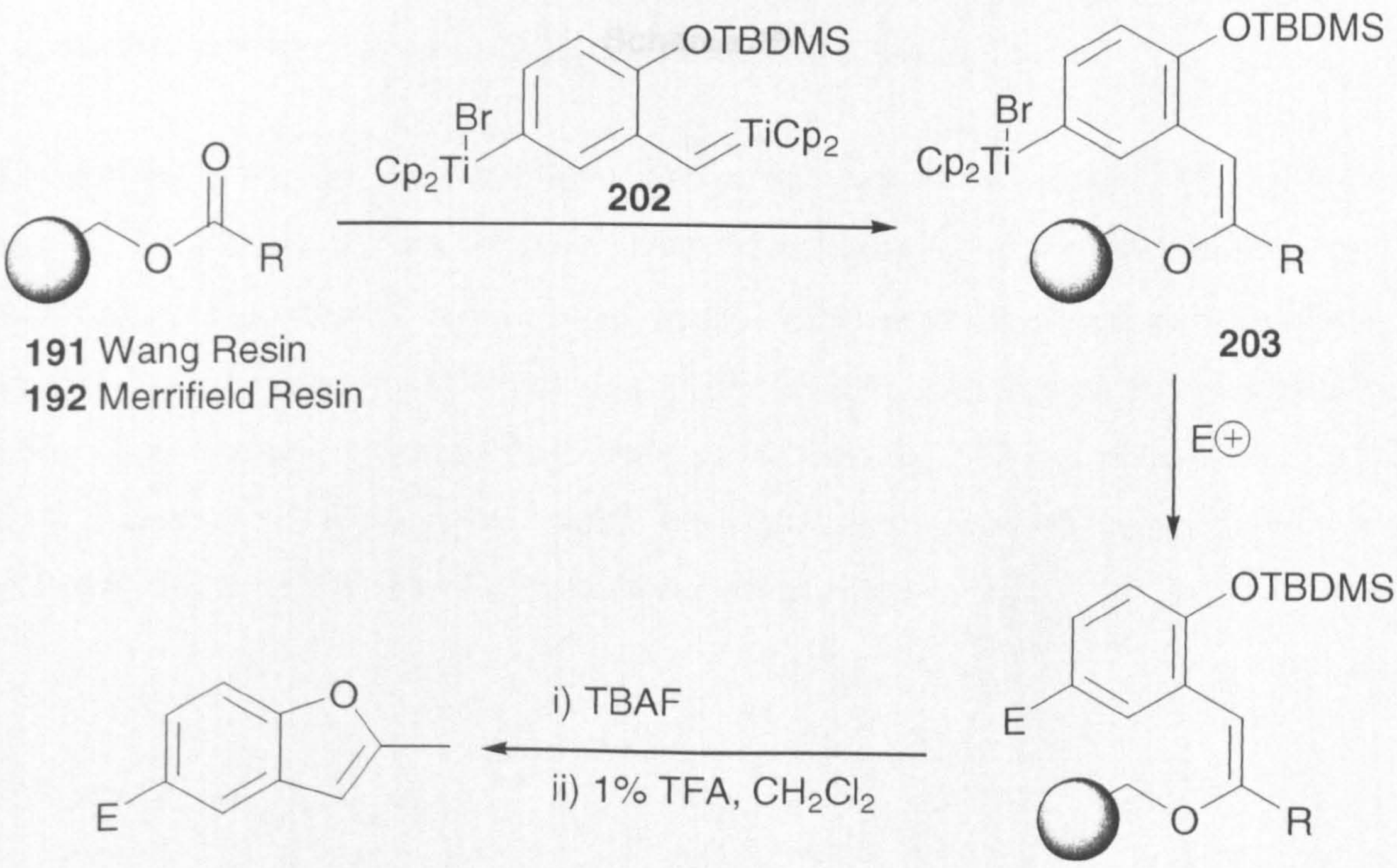


202

Figure 27

Although this has yet to be proved conclusively *via* deuterium quenching, it is certain that the carbon-bromine bond does not survive the alkylidenation process. If the titanium insertion does indeed occur, this gives scope for introducing other groups into the final benzofuran structure.

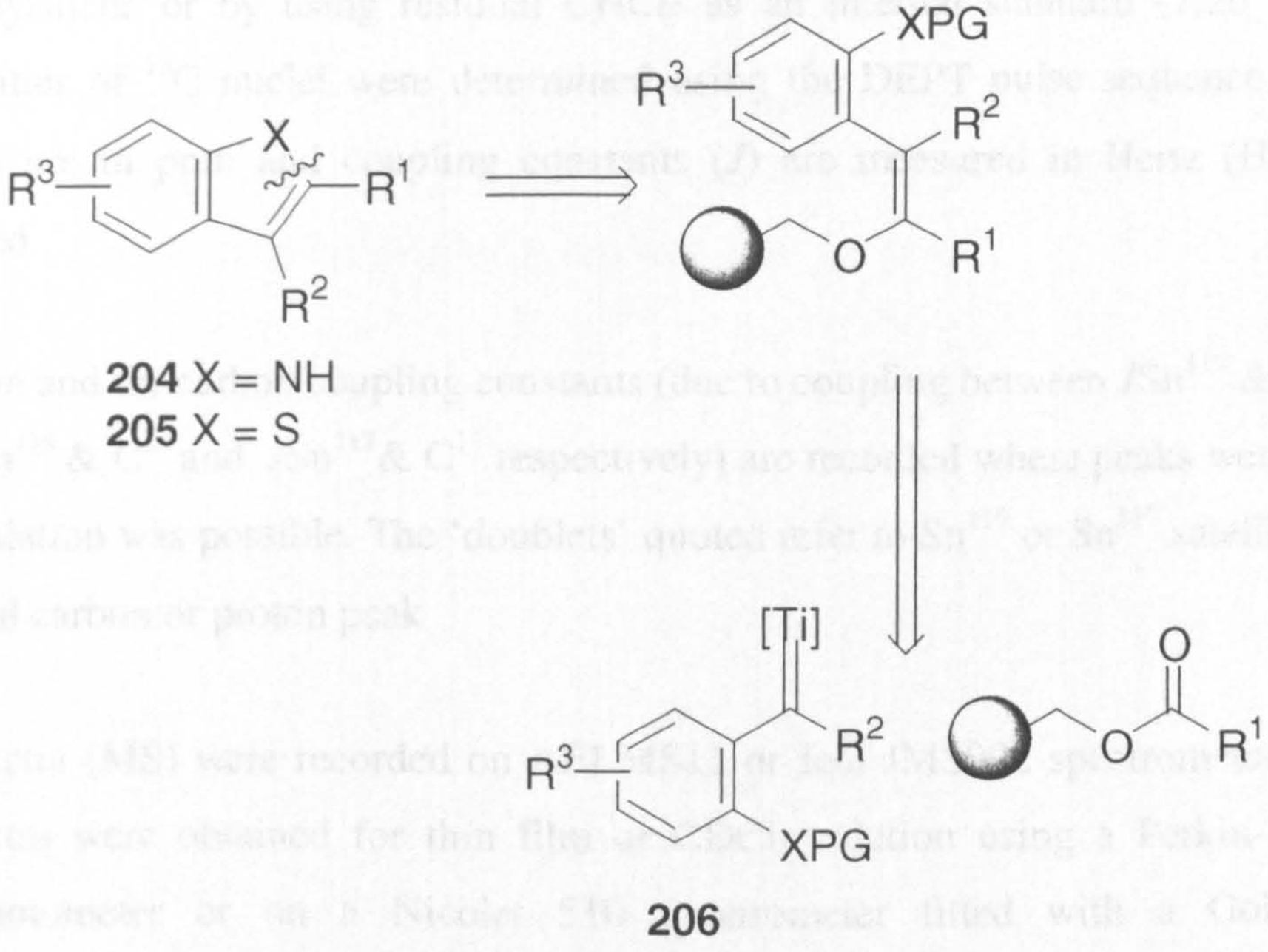
Thus alkylidenation of resin-bound esters **191,192** with reagent **202** should give enol ethers **203** which may be reacted with electrophiles before cleaving from the resin under standard conditions (Scheme 84). Work in the area continues within the research group.



Scheme 84

4.6.3 Other heterocycles

Having shown that benzofurans can be formed *via* SPS alkylidenation of resin-bound esters with thioacetals, an obvious path would be to investigate the synthesis of other heterocycles, such as indoles **204** and benzothiophenes **205** (Scheme 85). This could be achieved by using the corresponding titanium alkylidene **206**. The fact that tertiary amino groups are tolerated in the alkylidenation reaction is encouraging.



Scheme 85

Chapter 5 - Experimental

General

^{1}H and ^{13}C NMR spectra were obtained on either a Bruker AM-200SY, WP-200SY or on a DPX-400 spectrometer operating at 200 MHz or 400 MHz for ^{1}H NMR spectra and at 50 MHz or 100 MHz for ^{13}C NMR spectra respectively. Chemical shifts are given relative to tetramethylsilane or by using residual $CHCl_3$ as an internal standard (7.26 ppm). The multiplicities of ^{13}C nuclei were determined using the DEPT pulse sequence. Chemical shifts (δ) are in ppm and coupling constants (J) are measured in Hertz (Hz) and are unadjusted.

Tin-proton and tin-carbon coupling constants (due to coupling between JSn^{119} & H^{1}, JSn^{117} & H^{1}, JSn^{119} & C^{13} and JSn^{117}& C^{13} respectively) are recorded where peaks were observed and calculation was possible. The 'doublets' quoted refer to Sn^{119} or Sn^{117} satellites around the central carbon or proton peak

Mass spectra (MS) were recorded on AEI MS12 or Jeol JMS902 spectrometers. Infrared (IR) spectra were obtained for thin film or $CDCl_3$ solution using a Perkin-Elmer 983 spectrophotometer or on a Nicolet 510 spectrometer fitted with a Golden Gate. Combustion analysis was carried out using a Carlo-Erba 1106 elemental analyser. Gas chromatography was carried out using a Shimadzu GC-14A.

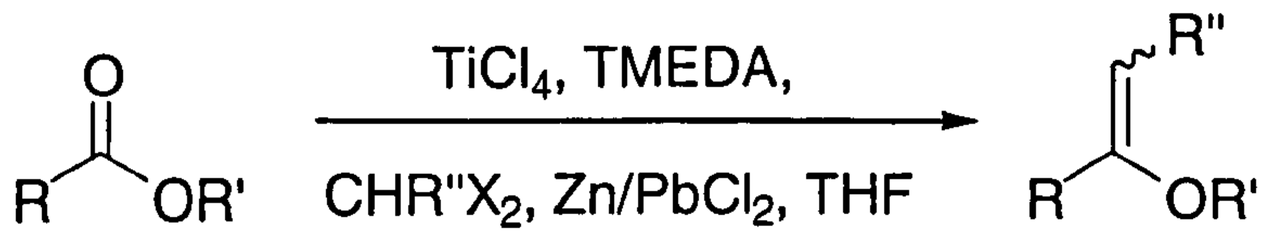
Purification by column chromatography was carried using Fisher Matrix™ silica gel, mesh size 35-70 μm, Fluka basic alumina Brockmann grade III or Aldrich neutral alumina Brockmann grade III mesh size ~150 μm as the stationary phase. Reactions were followed by thin-layer chromatography where appropriate using Merck silica gel 60 F_{254} foil-backed plates (0.25 mm layer thickness) or Merck aluminium oxide 60 F_{254} neutral (type E) foil-backed plates (0.2 mm layer thickness). The plates were visualised by illumination with UV light, iodine vapour, vanillin solution or permanganate solution.

All solutions were added *via* syringe unless otherwise stated. When reactions were carried out under a nitrogen or argon atmosphere, oven-dried glassware and dried solvents were employed. Tetrahydrofuran and diethyl ether were distilled under a nitrogen atmosphere from sodium and benzophenone. *N*,*N*,*N*',*N*'-Tetramethylethylenediamine (TMEDA) and DCM were distilled from calcium hydride. Acetone was distilled from potassium carbonate immediately prior to use. Methyl 3-phenylpropionoate and ethyl benzoate were distilled. Zinc powder was activated by washing with dilute HCl, water and diethyl ether and stored under a nitrogen atmosphere. Iodoform was recrystallised from methanol.

A general procedures section is included with the experimental so as to avoid replication. Approximate molarities are given here; the specific volumes of solvent used in the synthesis of a particular compound are given with that compound.

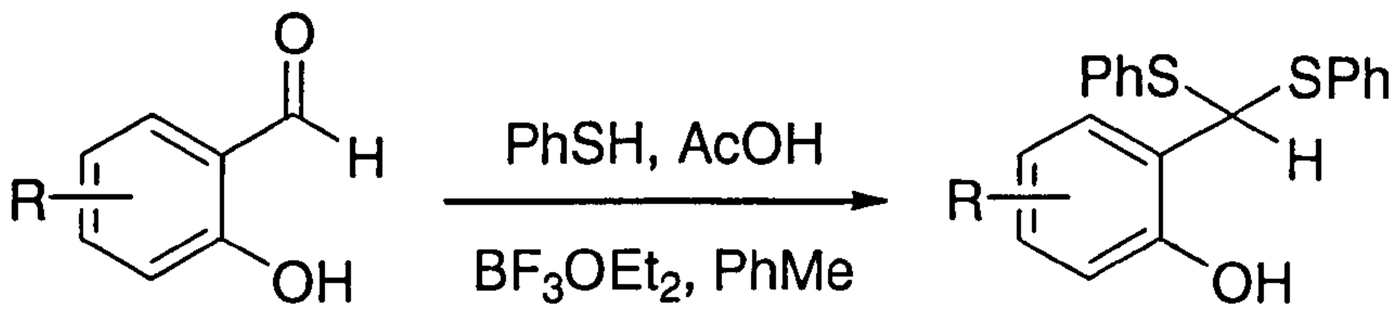
General Procedures

General method (1) - Modified Takai alkylidenation



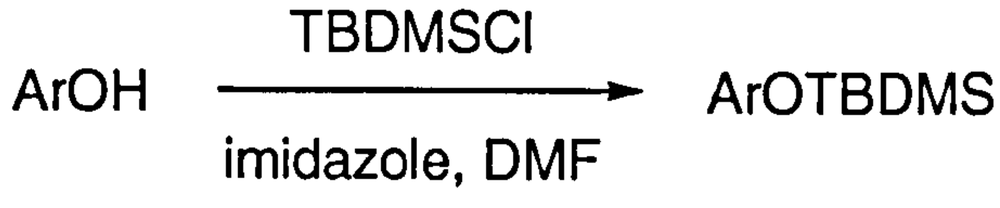
The alkylidenation was carried out using a modified version of Takai's method.[71,72] To titanium tetrachloride (4.00 eq.) in THF (concentration *ca* 1.1. mol L^{-1} with respect to titanium tetrachloride) was added TMEDA (8.00 eq.) and the solution stirred for 20 mins at 0 °C under a nitrogen atmosphere to give an orange/brown suspension. Zinc (9.00 eq.) and lead dichloride (catalytic amount, *ca* 0.002 eq.) were added at 0 °C and the mixture warmed to room temperature and stirred for 1 h. During this addition an exotherm occurred and the mixture turned from blue/grey to dark green as it warmed to room temperature. The reaction mixture was cooled to 0 °C and a THF solution (concentration *ca* 1.2. mol L^{-1} with respect to the 1,1-dihalo compound) of the 1,1-dihalo compound (2.20 eq.) and ester (1.00 eq.) was added. The reaction mixture was warmed to room temperature and stirred under a nitrogen atmosphere, turning a dark brown/black colour after *ca* 30 mins. The reaction was quenched by the addition *via* syringe of saturated aqueous potassium carbonate (*ca* 25 cm^3) at 0 °C. The mixture was stirred for 15 mins as a black precipitate formed. The black residue was washed with diethyl ether until it turned a pale green/white colour. The organic washings were combined then dried (magnesium sulfate) and the solvent removed under reduced pressure to give a solid/oil mixture. Removal of the solid by filtration gave the crude enol ether as an oil.

General method (2) - Thioacetal Formation



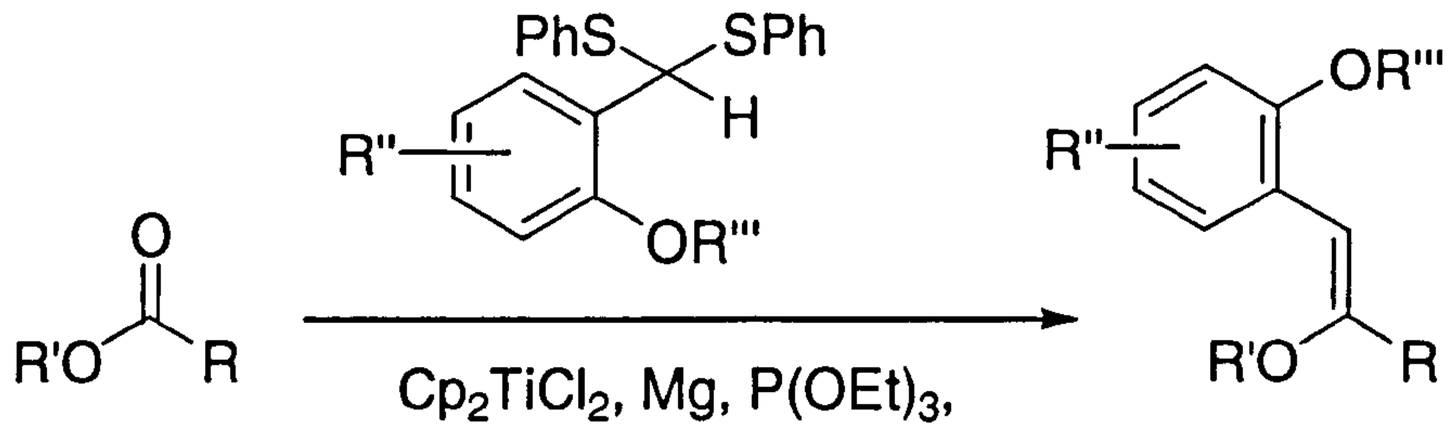
The diphenyldithioacetals were formed using a modified version of Barton's method.[133] To a solution of the aldehyde (1.00 eq.) in toluene (concentration *ca* 1.0. mol L^{-1} with respect to the aldehyde) at room temperature was added thiophenol (2.20 eq.), boron trifluoride diethyl etherate (0.84 eq.) and acetic acid. The reaction was quenched by the addition of water and the mixture extracted with diethyl ether. The combined organic extracts were washed with saturated aqueous sodium bicarbonate until neutral then dried and the solvent removed under reduced pressure to give the crude thioacetal.

General method (3) - TBDMS protection



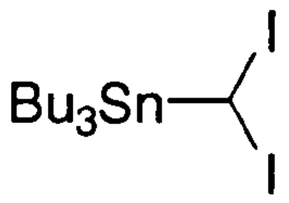
The *tert*-butyldimethylsilyl ethers were formed using a modified version of Kendall's method.[141] To a solution of the phenol (1.00 eq.) in DMF (concentration *ca* 1.0. mol L^{-1} with respect to the phenol) was added *tert*-butyldimethylsilyl chloride (1.20 eq.) and imidazole (2.60 eq.) and the solution stirred at room temperature. The reaction was quenched by the addition of saturated aqueous sodium bicarbonate and the mixture extracted with hexane. The combined organic extracts were washed with water then dried and the solvent removed under reduced pressure to give the silyl ether.

General method (4) - Modified Takeda alkylidenation - solution-phase



The alkylidenation was carried out using a modified version of Takeda's method.[89] Titanocene dichloride (4.00 eq.), magnesium (4.50 eq.) and 4Å molecular sieves (*ca* 400 mg/mmol of ester) were stirred at room temperature under an argon atmosphere. The reagents were heated briefly under vacuum after which triethylphosphite (8.00 eq.) and THF (concentration *ca* 0.5. mol L^{-1} with respect to titanocene dichloride) were added. Heat was evolved and the reaction mixture turned from red to green to black. After stirring for 3.5 h, a THF solution (concentration *ca* 0.6. mol L^{-1} with respect to the thioacetal) of the thioacetal (1.10 eq.) was added and the mixture stirred for a further 15 mins. A THF solution of the ester (1.00 eq., concentration *ca* 0.7 mol L^{-1} with respect to the ester) was added and the reaction mixture stirred under an argon atmosphere overnight. The solvent was removed under reduced pressure and the residue taken up in *n*-pentane and stirred at room temperature for 20 mins. Any undissolved material was filtered off leaving the crude enol ether.

Tributyl(diiodomethyl)tin 117



Iodoform, (3.42 g, 8.69 mmol, 1.14 eq.) was stirred in THF (20 cm^3) at -95 °C under a nitrogen atmosphere. Isopropylmagnesium chloride (2.0 M in THF, 4.80 cm^3, 9.60 mmol, 1.26 eq.) was added and the solution stirred for 25 mins. Tributyltin iodide (3.18 g, 7.62 mmol) was added and the solution warmed to room temperature over 2 h. The reaction was quenched by the addition of a saturated solution of ammonium chloride (10 cm^3) and the mixture extracted with diethyl ether (3 × 10 cm^3). The organic washings were combined then dried (magnesium sulfate) and the solvent removed under reduced pressure to give a yellow oil. The crude product was purified using column chromatography [neutral alumina, light petroleum b.p. 40-60 °C : diethyl ether (9:1)] to give the diiodide **117** as a yellow oil (2.87 g, 5.15 mmol, **68 %**).

R_F [alumina, hexane : diethyl ether (4:1)] : 0.68

δ_H(400 MHz, $CDCl_3$): 0.92 (9 H, t, *J* 7.3, CH_3), 1.08-1.12 (6H, m, CH_2), 1.27-1.33 (6H, m, CH_2), 1.49-1.56 (6H, m, CH_2), 4.25 (1H, s, CH)

δ_C(100 MHz; $CDCl_3$): -53.55 (CH), 12.90 [CH_2, (d, $^1J_{SnC}$ 324.2, d, $^1J_{SnC}$ 339.4)], 13.68 (CH_3), 27.30 [CH_2, (d, $^3J_{SnC}$ 59.6)], 28.46 [CH_2, (d, $^2J_{SnC}$ 20.0)]

ν_{max} (thin film)/cm^{-1}: 2870 (CH stretch), 2851 (CH stretch), 598 (SnC asymmetric stretch)

m/z (EI^+): 558 (0.1 %, ^{120}Sn $M^{+\bullet}$), 556 (0.1, ^{118}Sn $M^{+\bullet}$), 501 (1.2, ^{120}Sn, $M^{+\bullet}$-$C_4H_9^{\bullet}$), 499 (0.9, ^{118}Sn, $M^{+\bullet}$-$C_4H_9^{\bullet}$), 445 (30, ^{120}Sn, $M^{+\bullet}$-$C_4H_9^{\bullet}$ and C_4H_8), 443 (25, ^{118}Sn, $M^{+\bullet}$-$C_4H_9^{\bullet}$ and C_4H_8)

Accurate mass:

$C_{13}H_{28}{}^{116}SnI_2$ requires 553.9298, actual 553.9319

$C_{13}H_{28}{}^{118}SnI_2$ requires 555.9297, actual 555.9294

$C_{13}H_{28}{}^{119}SnI_2$ requires 556.9314, actual 556.9300

$C_{13}H_{28}{}^{120}SnI_2$ requires 557.9303, actual 557.9301

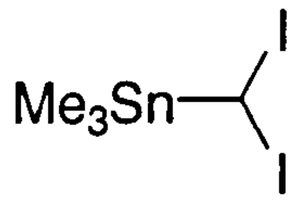
$C_{13}H_{28}{}^{122}SnI_2$ requires 559.9315, actual 559.9295

$C_{13}H_{28}{}^{124}SnI_2$ requires 561.9312, actual 561.9323

Literature:[87]

δ_H ($CDCl_3$): 0.94 (9 H, t, *J* 7), 1.08-1.16 (6H, m), 1.33 (6H, sextet, J 7), 1.55-1.71 (6H, m), 4.27 (1H, s); δ_C (125 MHz; $CDCl_3$): 12.9, 13.7, 16.4, 27.3 ($^3J_{SnC}$ 60), 28.4; ν_{max} (neat)/cm^{-1} : 2956, 2926, 2851, 1463, 1375, 1071, 875.

Trimethyl(diiodomethyl)tin 121



Following the method of Seyferth and Lambert,[99] trimethyl(diiodomethyl)tin **121** was produced using iodoform, (2.53 g, 6.43 mmol, 1.00 eq.), isopropylmagnesium chloride (2.0 M in THF, 3.50 cm^3, 7.00 mmol, 1.09 eq.) and trimethyltin chloride (1.0 M in THF, 6.40 cm^3, 6.40 mmol) in THF (20 cm^3) (reaction time 1 h). The crude product was purified using column chromatography [silica, light petroleum b.p. 40-60 °C : diethyl ether (1:1)] to give the diiodide **121** as a yellow oil (1.27 g, 2.96 mmol, **46 %**).

R_F [silica, light petroleum b.p. 40-60°C : diethyl ether (1:1)] : 0.65

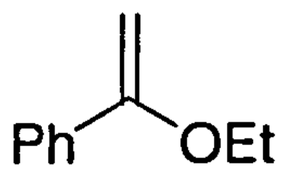
δ_H(400 MHz, $CDCl_3$): 0.31 [9H, s, CH_3 (d, $^2J_{SnH}$ 53.6, d, $^2J_{SnH}$ 55.6)], 4.25 (1H, s CH)

δ_C(100 MHz; $CDCl_3$): -52.05 [CH, (d, $^1J_{SnC}$ 197.0)],
6.84 [CH_3, (d, $^1J_{SnC}$ 344.6, d, $^1J_{SnC}$ 358.6)]

ν_{max} (thin film)/cm^{-1}: 2982 (CH stretch), 2911 (CH stretch),
602 (SnC asymmetric stretch), 510 (CI)

Literature:[99] δ_H ($CDCl_3$): 0.33 [9H, s, (d, $^2J_{SnH}$ 48, d, $^2J_{SnH}$ 50)], 4.20 (1H, s).

1-Ethoxy-1-phenylethene 146



Following *general method (1)*, 1-ethoxy-1-phenylethene **146** was formed using titanium tetrachloride (9.5 cm^3, 86.6 mmol, 4.0 eq.), TMEDA (26.0 cm^3, 172 mmol, 8.0 eq.), zinc (12.78 g, 195.4 mmol, 9.09.) and lead dichloride (0.009 g, 0.03 mmol, 0.0001 eq.) in THF (80 cm^3) and 1,1-dibromomethane (3.30 cm^3, 46.4 mmol) and ethyl benzoate (3.23 g, 21.5 mmol) in THF (40 cm^3) (reaction time 17 h). The crude enol ether was distilled under reduced pressure (kugelrohr, *ca* 1 mmHg, oven temperature 94-104 °C) to give the enol ether **146** as an oil (approximately 90 % pure) (1.51 g, 10.2 mmol, ***ca* 47 %**).

R_F [alumina, light petroleum b.p. 40-60 °C : diethyl ether (1:1)] : 0.76

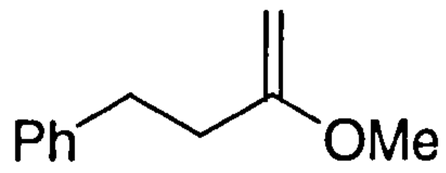
δ_H(400 MHz, $CDCl_3$): 1.42 (3H, t, *J* 7.0, CH_3), 3.92 (2H, q, *J* 7.0, CH_2), 4.19 (1H, d, *J* 2.6, C=CH), 4.63 (1H, d, *J* 2.6, C=CH), 7.25-7.35 (3H, m, ArH), 7.59-7.64 (2H, m, ArH)

δ_C(100 MHz; $CDCl_3$): 14.51 (CH_3), 63.27 (CH_2), 82.13 (CH_2), 125.36 (CH), 128.05 (CH), 128.33 (CH), 136.68 (C), 159.97 (C)

ν_{max} (thin film)/cm^{-1}: 3085 (C=CH_2), 3026 (ArH stretch), 1599 (aromatic ring), 1494 (aromatic ring), 1457 (aromatic ring), 768 (mono-substituted aromatic ring), 689 (mono-substituted aromatic ring)

Literature:[142] δ_H ($CDCl_3$): 1.4 (3H, t, *J* 7.2), 3.9 (2H, q, *J* 7.2), 4.2, (1H, d, *J* 2.5), 4.6 (1H, d, *J* 2.5), 7.15-7.35 (3H, m), 7.5-7.7 (2H, m); δ_C ($CDCl_3$): 14.5, 63.3, 82.2, 125.5, 128.1, 128.4, 136.8, 160.1.

2-Methoxy-4-phenyl-but-1-ene 148



Following *general method (1)*, 2-methoxy-4-phenyl-but-1-ene **148** was formed using titanium tetrachloride (9.7 cm^3, 88 mmol, 4.2 eq.), TMEDA (25.2 cm^3, 169 mmol, 8.1 eq.), zinc (12.36 g, 189.0 mmol, 9.05 eq.) and lead dichloride (0.02 g, 0.07 mmol, 0.003 eq.) in THF (80 cm^3) and 1,1-dibromomethane (3.3 cm^3, 46 mmol, 1.5 eq.) and methyl 3-phenyl propionate (3.43 g, 20.9 mmol.) in THF (40 cm^3). The crude product was purified *via* distillation under reduced pressure (kugelrohr, *ca* 1 mmHg, oven temperature 114-116 °C) to give the enol ether **148** as an oil (1.59 g, 9.80 mmol, **47 %**).

R_F [alumina, light petroleum b.p. 40-60 °C : diethyl ether (1:1)] : 0.77

δ_H(400 MHz, $CDCl_3$): 2.39 (2H, t, *J* 8.0, CH_2), 2.81 (2H, t, *J* 8.0, CH_2), 3.55 (3H, s, OCH_3), 3.85 (2H, s, $C=CH_2$), 7.19-7.16 (3H, m, ArH), 7.26-7.29 (2H, m, ArH)

δ_C(100 MHz; $CDCl_3$): 33.77 (CH_2), 36.84 (CH_2), 54.70 (CH_3), 80.74 (CH_2), 125.80 (CH), 128.24 (CH), 128.37 (CH), 141.74 (C), 163.38 (C)

ν_{max} (thin film)/cm^{-1}: 3085 (CH stretch of $C=CH_2$), 3027 (ArH stretch), 1604 (aromatic ring), 1496 (aromatic ring), 747 (mono-substituted aromatic ring), 699 (mono-substituted aromatic ring)

m/z (EI^+): 162 (65 %, $M^{+\bullet}$), 147 (60, $M^{+\bullet}$-$CH_3^\bullet$), 91 (100, $PhCH_2^+$)

Accurate mass: $C_{11}H_{14}O$ requires 162.1044, actual 162.1042

Literature:[143] δ_H ($CDCl_3$): 2.48-2.54 (2H, m), 2.9-2.95 (2H, m), 3.97 (2H, s), 7.25-7.40 (5H, m); δ_C ($CDCl_3$): 30.7, 48.1, 54.1, 80.7, 126.8, 128.3 (2C), 128.5 (2C), 141.8. (Literature data is not in agreement with my data).

Tributylmethyl tin 150

Bu_3SnMe

To tributyltin iodide (0.50 g, 1.20 mmol) in THF (10 cm^3) at -78 °C under a nitrogen atmosphere was added methyllithium (1.6 M in diethyl ether, 0.75 cm^3, 1.20 mmol, 1.0 eq.) drop-wise and the solution stirred for 1 h. The solution was warmed to room temperature over 1 h and stirred for a further hour. The reaction was quenched by the addition of saturated aqueous ammonium chloride (10 cm^3). The aqueous layer was extracted with diethyl ether (3 × 30 cm^3) and the organic washings combined and dried (magnesium sulfate). The solvent was removed under reduced pressure to give the product as a yellow oil. This oil was distilled under reduced pressure (kugelrohr, 0.6 mmHg, oven temperature 118 °C) to give the methyltin **150** as an oil (0.076 g, 0.25 mmol, **20 %**).

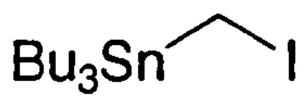
R_F [silica, light petroleum b.p. 40-60 °C : diethyl ether (1:1)] : 0.55

δ_H(400 MHz, $CDCl_3$): -0.04 [3 H, s, CH_3 (d, $^2J_{SnH}$ 46.4, d, $^2J_{SnH}$ 48.8)], 0.79-0.84 (6H, m, CH_2), 0.90 (9H, t, *J* 7.2, CH_3), 1.28-1.38 (6H, m, CH_2), 1.46-1.54 (6H, m, CH_2)

δ_C(100 MHz; $CDCl_3$): -12.78 (CH_3), 9.47 (CH_2), 13.71 (CH_3), 27.25 (CH_2), 29.16 [CH_2 (d, $^2J_{SnC}$ 20.2)]

Literature:[144] δ_H ($CDCl_3$): -0.04 [3 H, s, (d, $^2J_{119SnH}$ 51)], 0.80 (6H, m), 0.84 (9H, m), 1.28 (6H, m), 1.47 (6H, m,); δ_C ($CDCl_3$): -12.75 (d, J_{SnC} 315), 9.56 (d, J_{SnC} 315), 13.9, 27.34 (d, J_{SnC} 51), 29.33 (d, $^2J_{SnC}$ 20), m/z: 207, 192, 177, 165, 151, 135, 121.

Tributyl(iodomethyl)tin 153



Method 1

Following the method of Åhman and Somfai,[129] tributyl(iodomethyl)tin **153** was produced using tributylstannylmethanol **163**, (2.59 g, 8.12 mmol), *N*-iodosuccinimide (2.76 g, 12.27 mmol, 1.51 eq.) and triphenylphosphine (3.18 g, 12.14 mmol, 1.49 eq.) in THF (50 cm^3) (reaction time 19 h). The crude product was purified using column chromatography [silica, hexane : diethyl ether (5:1)] to give the iodide **153** as an oil (1.51 g, 3.52 mmol, **43 %**).

Method 2

Following the method of Seitz *et al.*,[130] tributyl(iodomethyl)tin **153** was produced using tributyl(chloromethyl)tin **164** (1.47 g, 4.35 mmol) and sodium iodide (1.32 g, 8.81 mmol, 2.02 eq.) in acetone (100 cm^3) (reaction time 16 h). The crude product was purified using distillation (b.p. 136-148 °C, 1 mmHg)(Lit.[130] b.p. 106 °C, 0.05 mmHg) to give the iodide **153** as a colourless oil (1.73 g, 4.03 mmol, **93 %**).

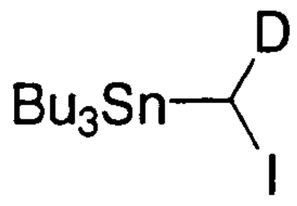
Method 3 - Magnesium De-iodination

To tributyl(diiodomethyl)tin **117** (1.02 g, 1.8 mmol) in THF (10 cm^3) at -78 °C under a nitrogen atmosphere was added isopropylmagnesium chloride (2.0 M in THF, 2.00 cm^3, 4.00 mmol, 2.22 eq.) drop-wise and the solution was stirred for 1 h. The reaction was quenched at -78 °C by the addition of saturated aqueous ammonium chloride (10 cm^3). The mixture was warmed to room temperature and the aqueous layer extracted with diethyl ether (3 × 50 cm^3). The organic washings were combined, dried (magnesium sulfate) and the solvent removed under reduced pressure to give a yellow oil, which was found to be tributyl(iodomethyl)tin **153** (0.60 g, 1.39 mmol, **77 %**).

R_F [light petroleum b.p. 40-60 °C : diethyl ether (1:1)] : 0.71

δ_H(400 MHz, $CDCl_3$):	0.91 (9 H, t, *J* 7.2, CH_3), 0.98 (6H, t, *J* 8.0, CH_2), 1.32 (6H, m, CH_2), 1.49-1.56 (6H, m, CH_2), 1.94 [2H, s, CH_2I, (d, $^2J_{SnH}$ 18.0)]
δ_C(100 MHz; $CDCl_3$):	-26.91 (CH_2I), 10.70 [CH_2, (d, $^1J_{SnC}$ 326.7, d, $^1J_{SnC}$ 341.8)], 13.71 (CH_3), 27.28 [CH_2, (d, $^3J_{SnC}$ 56.5)], 28.83 [CH_2, (d, $^2J_{SnC}$ 21.0)]
ν_{max}(thin film)/cm^{-1}:	2924 (CH stretch), 428 (SnC asymmetric stretch)
m/z (EI^+):	431 (<1 %, ^{119}Sn, $M^{+\bullet}$), 375 (100, ^{120}Sn, $M^{+\bullet}$-$C_4H_9^\bullet$), 373 (75, ^{118}Sn, $M^{+\bullet}$-$C_4H_9^\bullet$), 319 (22, ^{120}Sn, $M^{+\bullet}$-$C_4H_9^\bullet$ and $C_4H_8^\bullet$), 317 (18, ^{118}Sn, $M^{+\bullet}$-$C_4H_9^\bullet$ and C_4H_8)
Accurate mass:	$C_9H_{20}{}^{116}SnI$, $(M-C_4H_9)^+$ requires 370.9628, actual 370.9630 $C_9H_{20}{}^{118}SnI$, $(M-C_4H_9)^+$ requires 372.9626, actual 372.9630 $C_9H_{20}{}^{120}SnI$, $(M-C_4H_9)^+$ requires 374.9632, actual 374.9634
Literature:[129]	b.p. 106 °C/0.05 torr; no other data available

Tributyl(iododeuteromethyl)tin 161



Tributyl(diiodomethyl)tin **161** (0.19 g, 0.34 mmol) was stirred in THF (10.5 cm^3) at room temperature under a nitrogen atmosphere. The solution was cooled to -78 °C and a THF solution of isopropylmagnesium chloride (2.0 M in THF, 0.40 cm^3, 0.80 mmol, 2.35 eq.) added over 5 mins. After stirring for a further 45 mins the reaction was quenched by the addition of D_2O (7.5 cm^3) and the solution allowed to warm to room temperature. The aqueous layer was extracted with diethyl ether (3 × 5 cm^3) and the organic washings combined and dried (magnesium sulfate). Removal of the solvent under reduced pressure gave the *deuterated iodide* **161** as a yellow oil (0.12 g, 0.29 mmol, **85 %**).

R_F [light petroleum b.p. 40-60 °C : diethyl ether (1:1)] : 0.70

δ_H(400 MHz, $CDCl_3$): 0.89 (9 H, t, *J* 7.2, CH_3), 0.97 (6H, t, *J* 8.2, CH_2), 1.27-1.36 (6H, m, CH_2), 1.45-1.52 (6H, m, CH_2), 1.91 (1H, m, CHD)

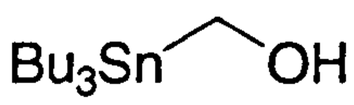
δ_C(100 MHz; $CDCl_3$): -26.91 (CH_2), -27.01 (CDH, t, *J* 21.8) , 10.63 [CH_2, (d, $^1J_{SnC}$ 326.7, d, $^1J_{SnC}$ 342.0)], 13.66 (CH_3), 27.51 [CH_2, (d, $^3J_{SnC}$ 55.9)], 28.78 [CH_2, (d, $^2J_{SnC}$ 20.7)]

ν_{max}(thin film)/cm^{-1}: 2926 (CH stretch), 2852 (CH stretch), 1458 (CH deformation)

m/z (EI$^+$): 376 (100,^{120}Sn, $M^{+\bullet}$-$C_4H_9^\bullet$), 374 (80,^{118}Sn, $M^{+\bullet}$-$C_4H_9^\bullet$), 320 (22,^{120}Sn, $M^{+\bullet}$-$C_4H_9^\bullet$ and C_4H_8), 318 (18,^{118}Sn, $M^{+\bullet}$-$C_4H_9^\bullet$ and C_4H_8)

Accurate mass: $C_9H_{19}D^{116}SnI$, $(M-C_4H_9)^+$ requires 371.9690, actual 371.9677
$C_9H_{19}D^{118}SnI$, $(M-C_4H_9)^+$ requires 373.9688, actual 373.9691
$C_9H_{19}D^{120}SnI$, $(M-C_4H_9)^+$ requires 375.9695, actual 375.9695.

Tributylstannylmethanol 163



Following the method of Åhman and Somfai,[129] tributylstannylmethanol **163** was produced using tributyltin hydride (4.00 g, 13.7 mmol), paraformaldehyde (0.57 g, 19.0 mmol, 1.38 eq.), *n*-butyllithium (1.6 M, 9.4 cm^3, 15.0 mmol, 1.1 eq.) and diisopropylamine (2.20 cm^3, 15.8 mmol, 1.14 eq.) in THF (35 cm^3) (reaction time 22 h). The crude product was purified using column chromatography [silica, light petroleum b.p. 40-60 °C : diethyl ether (3:1)] to give the alcohol **163** as an oil (2.07 g, 6.49 mmol, ***ca* 47 %**). The product contained minor impurities and was used without further purification.

R_F [silica, light petroleum b.p. 40-60 °C : diethyl ether (1:1)] : 0.54

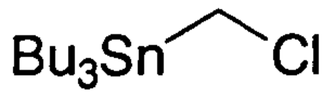
δ_H(400 MHz, $CDCl_3$): 0.86-0.94 (15 H, m, CH_2 and CH_3), 1.26-1.36 (6H, m, CH_2), 1.48-1.59 (6H, m, CH_2), 4.01 [2H, s, CH_2, (d, $^2J_{SnH}$ 13.3)]

δ_C(100 MHz; $CDCl_3$): 8.62 [CH_2, (d, $^1J_{SnC}$ 304.4, d, $^1J_{SnC}$ 318.6)], 13.72 (CH_3), 27.37 [CH_2, (d, $^3J_{SnC}$ 51.5)], 29.13 (CH_2), 53.63 (CH_2)

Literature:[145] δ_H ($CDCl_3$): 3.9 (2H) (only peak mentioned)

Literature:[146] δ_H (300 MHz $CDCl_3$): 0.8-1.1 (15H, m), 1.2-1.7 (13H, m), 4.02 (2H, d, *J* 4.5).

Tributyl(chloromethyl)tin 164



Following the method of Seitz *et al.*,[130] tributyl(chloromethyl)tin **164** was produced using tributyltin hydride (7.08 g, 24.33 mmol), *n*-butyllithium (1.6 M, 17.5 cm^3, 28.0 mmol, 1.1 eq.), diisopropylamine (3.90 cm^3, 27.83 mmol, 1.14 eq.), paraformaldehyde (0.76 g, 25.33 mmol, 1.04 eq.) and methanesulfonyl chloride (2.60 cm^3, 33.59 mmol, 1.38 eq.) in THF (60 cm^3) (reaction time 3 h). The crude product was purified using column chromatography [silica, hexane : diethyl ether (5:1)] and distillation (b.p. 118-130 °C, 1 mmHg)(Lit.,[130] b.p. 84 °C, 0.5 mmHg) to give the chloride **164** as an oil (4.79 g, 14.2 mmol, **58 %**).

R_F [silica, light petroleum b.p. 40-60 °C : diethyl ether (1:1)] : 0.58

δ_H(400 MHz, $CDCl_3$): 1.07 (9 H, t, *J* 7.7, CH_3), 1.20 (6H, t, *J* 8.0, CH_2),
1.32 (6H, m, CH_2), 1.46 (6H, m, CH_2),
3.07 [2H, s, CH_2Cl, (d, $^2J_{SnH}$ 16.0)]

δ_C(100 MHz; $CDCl_3$): 9.52 (CH_2, [d, $^1J_{SnC}$ 338.4, d, $^1J_{SnC}$ 323.6)], 13.69 (CH_3),
24.39 (CH_2), 27.30 [CH_2, (d, $^3J_{SnC}$ 55.6)],
28.92, [CH_2, (d, $^2J_{SnC}$ 10.6)]

ν_{max}(thin film)/cm^{-1}: 2957 (CH stretch), 2853 (CH stretch), 1464 (CH deformation),
1377 (CH deformation), 596 (SnC asymmetrical stretch)

m/z (EI$^+$): 291 (100 %, ^{120}Sn, $M^{+\bullet}$-$C_4H_9^\bullet$), 289 (85, ^{118}Sn, $M^{+\bullet}$-$C_4H_9^\bullet$),

283 (80, ^{112}Sn, $M^{+\bullet}$-$C_4H_9^\bullet$),

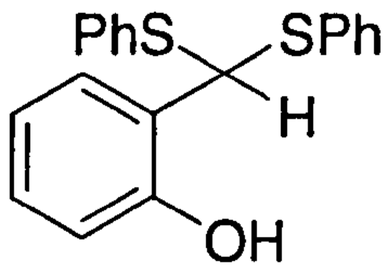
235 (85, ^{120}Sn, $M^{+\bullet}$-$C_4H_9^\bullet$ and C_4H_8),

233 (65, ^{118}Sn, $M^{+\bullet}$-$C_4H_9^\bullet$ and C_4H_8),

227 (75, ^{112}Sn, $M^{+\bullet}$-$C_4H_9^\bullet$ and C_4H_8), (M^+ peak unobtainable)

Literature:[102] δ_H ($CDCl_3$): 3.09 (2H, $J_{119Sn-C}$ 17.0).

2-Hydroxybenzaldehyde diphenyldithioacetal 168



Method 1

Following the method of Liepa and Morton,[132] 2-hydroxybenzaldehyde diphenyldithioacetal **168** was produced using thiophenol (13.1 cm^3, 127.8 mmol, 23.2 eq.), DABCO (0.32 g, 2.85 mmol, 0.51 eq.) and 2-acetoxybenzaldehyde (0.91 g, 5.55 mmol) in toluene (3 cm^3) (reaction time 42 h). The crude product was produced as an oil that was purified using column chromatography [silica, light petroleum b.p. 60-80 °C : diethyl ether (9:1) then (1:1)] to give the *thioacetal* **168** as a viscous oil (1.49 g, 4.60 mmol, **83 %**).

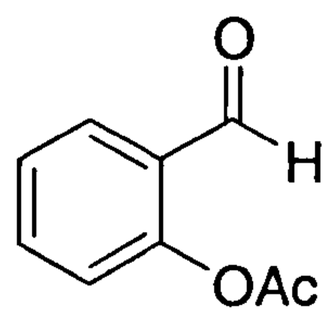
Method 2

Following *general method (2)*, 2-hydroxybenzaldehyde diphenyldithioacetal **168** was produced using thiophenol (7.50 cm^3, 73.04 mmol, 2.42 eq.), boron trifluoride diethyl etherate (3.20 cm^3, 25.25 mmol, 0.84 eq.), acetic acid (20 cm^3) and salicylaldehyde (3.20 cm^3, 30.06 mmol) in toluene (40 cm^3) (reaction time 22 h). The crude product was purified using column chromatography [silica, light petroleum b.p. 60-80 °C : diethyl ether (9:1), then diethyl ether] to give the *thioacetal* **168** as a viscous oil (9.62 g, 29.69 mmol, **99 %**).

R_F [silica, light petroleum b.p. 40-60 °C : diethyl ether (1:1)] : 0.67

δ_H(400 MHz, $CDCl_3$):	5.71 (1H, s, CH), 6.32 (1H, bs, OH), 6.76 (1H, dt, *J* 1.1 and 7.5, H-5), 6.83 (1H, dd, *J* 1.0 and 8.0, H-3), 7.11 (1H, dt, *J* 1.5 and 7.8, H-4), 7.15 (1H, dd, *J* 1.4 and 7.7, H-6), 7.18-7.27 (6H, m, SArH), 7.36-7.43 (4H, m, SArH)
δ_C(100 MHz; $CDCl_3$):	56.15 (CH), 116.92 (CH), 120.64 (CH), 124.27 (C), 127.99 (CH), 128.88 (CH), 129.53 (CH), 129.61 (CH), 132.51 (CH), 133.82, (C), 153.71 (C)
ν_{max}(thin film)/cm^{-1}:	3412 (OH), 2976 (CH stretch), 2923 (CH stretch), 2873 (CH stretch), 1596 (aromatic ring), 1582 (aromatic ring), 1270 (OH bend), 752 (*o*-disubstituted aromatic ring)
m/z (FAB^+):	347 [10 %, $(M+Na)^+$], 215 [100, $(M+H)^+$-PhSH]
Accurate mass:	$C_{19}H_{16}ONaS_2$, requires 347.0532, actual 347.0536.

2-Acetoxybenzaldehyde 169

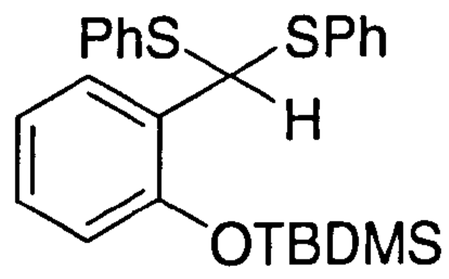


Potassium carbonate (48.20 g, 344.29 mmol, 2.02 eq.) was stirred in dry diethyl ether (100 cm^3) at room temperature under a nitrogen atmosphere. Salicylaldehyde (18.1 cm^3, 170.0 mmol) was added whereupon the solution was cooled to 0 °C. Acetic anhydride (32 cm^3, 340 mmol, 2.0 eq.) was added and the resulting solution stirred for 2 h. The reaction mixture was filtered and the residue washed with diethyl ether (100 cm^3). The organic washings were combined, washed with 1 M HCl (2 × 30 cm^3), 1 M NaOH, (2 × 30 cm^3), brine (30 cm^3) and dried (magnesium sulfate). The solvent was removed under reduced pressure. Trituration with hexane gave the acetate **169** as white needles, which were further washed with hexane and dried *in vacuo*. (23.0 g,155.4 mmol, **91 %**).

R_F [silica, light petroleum b.p. 40-60 °C : diethyl ether (1:1)] : 0.44; m.p. 34-36 °C

δ_H (400 MHz, $CDCl_3$):	2.38 (3H, s, CH_3), 7.18 (1H, dd, *J* 0.8 and 8.2, H-3), 7.39 (1H, dt, *J* 0.7 and 7.5, H-5), 7.62 (1H, dt, *J* 1.7 and 7.7, H-4), 7.87 (1H, dd, *J* 1.7 and 7.7, H-6), 10.10 (1H, s, CHO)
δ_C (100 MHz; $CDCl_3$):	20.84 (CH_3), 123.51(CH), 126.45 (CH), 128.06 (C), 131.30 (CH), 135.32 (CH), 151.50 (C), 169.26 (C), 188.79 (CHO)
ν_{max} ($CDCl_3$ sol^n)/cm^{-1}:	2743 (CH stretch), 1765 (C=O), 1706 (C=O), 1604 (aromatic ring), 752 (*o*-disubstituted aromatic ring)
m/z (EI$^+$):	164 (5 %, $M^{+\bullet}$), 122 (100, $M^{+\bullet}$-CH_2CO)
Accurate mass:	$C_9H_8O_3$ requires 164.0474, actual 164.0474
Literature:[147]	m.p. 37-38 °C; δ_H ($CDCl_3$): 10.02 (1H, s); δ_C ($CDCl_3$): 20.53, 169.03, 188.64.

2-*tert*-Butyldimethylsilyloxybenzaldehyde diphenyldithioacetal 170



Following *general method (3)*, 2-*tert*-butyldimethylsilyloxybenzaldehyde diphenyldithioacetal **170** was prepared using 2-hydroxybenzaldehyde diphenyldithioacetal **168** (3.14 g, 9.69 mmol), *tert*-butyldimethylsilyl chloride (1.79 g, 11.87 mmol, 1.22 eq.) and imidazole (1.60 g, 23.50 mmol, 2.42 eq.) in DMF (20 cm^3) (reaction time 3 h). The crude product was purified using column chromatography [silica, light petroleum b.p. 40-60 °C : diethyl ether (9:1)] to give the *silyl ether* **168** as an oil (3.39 g, 7.74 mmol, **80 %**).

R_F [silica, light petroleum b.p. 40-60 °C : diethyl ether (1:1)] : 0.89

δ_H (400 MHz, $CDCl_3$): 0.17 (6H, s, $SiCH_3$), 0.92 (9H, s, *t*-Bu), 6.04 (1H, s, CH), 6.72 (1H, d, *J* 8.4, H-3), 6.89 (1H, t, *J* 7.6, H-5), 7.08 (1H, dt, *J* 1.2 and 8.2, H-4), 7.15-7.22 (6H, m, SArH), 7.29-7.33 (4H, m, SArH), 7.56 (1H, dd, *J* 1.4 and 7.8, H-6)

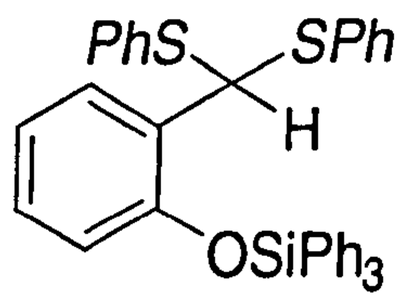
δ_C (100 MHz; $CDCl_3$): -4.20 (CH_3), 18.17 (C), 25.74 (CH_3), 51.98 (CH), 117.93 (CH), 121.30 (CH), 128.21 (CH), 128.65 (CH), 128.76 (CH), 129.53 (CH), 129.92 (C), 135.10 (C), 131.59 (CH), 151.91 (C)

ν_{max} (Golden gate)/cm^{-1}: 3059 (ArH stretch), 2954 (CH stretch), 2927 (CH stretch), 2858 (CH stretch), 1597 (aromatic ring), 1581 (aromatic ring), 1481 (CH deformation),1454 (CH deformation), 1361 (CH deformation), 1254 (SiMe), 833 (SiMe)

m/z (CI^+): 439 [0.55 %, $(M+H)^+$], 423 [0.5, $(M+H)^+$-CH_4], 381 [0.9, $(M+H)^+$-*t*-BuH], 329 [100, $(M+H)^+$-PhSH]

Accurate mass: $C_{25}H_{30}OSiS_2$, $(M+H)^+$ requires 439.1586, actual 439.1589.

2-Triphenylsilyloxybenzaldehyde diphenyldithioacetal 171



To 2-hydroxybenzaldehyde diphenyldithioacetal **168** (5.53g, 17.07 mmol) in pyridine (50 cm^3) was added triphenylsilyl chloride (5.53 g, 17.07 mmol, 1.10 eq.) and the solution stirred at room temperature for 24 h. The reaction was quenched by the addition of water (20 cm^3) and the product extracted into ethyl acetate (3 × 25 cm^3). The organic washings were combined, washed with 1 M HCl (5 × 25 cm^3), dried (magnesium sulfate) and the solvent removed under reduced pressure. Trituration with diethyl ether gave the *silyl ether* **171** as a solid (8.05 g, 13.83 mmol, **81 %**). A small sample was re-crystallised from ethanol to give plates that were used to determine the melting point.

R_F [silica, light petroleum b.p. 40-60 °C : diethyl ether (1:1)] : 0.48; m.p. 84-86 °C

δ_H(400 MHz, $CDCl_3$): 6.30 (1H, s, CH), 6.61-6.66 (1H, m, ArH), 6.83-6.89 (2H, m, ArH), 7.70-7.19 (6H, m, SArH), 7.23 (4H, dd, *J* 1.6 and 6.4, SArH, H-2' and H-6'), 7.32 (6H, t, *J* 7.2, OSiArH, H-3''and H-5''), 7.42 (3H, tt, *J* 1.6 and 7.4, OSiArH, H-4''), 7.60 (6H, dd, *J* 1.2 and 8.0, OSiArH, H-2''and H-6''), 7.63-7.64 (1H, m, ArH)

δ_C(100 MHz; $CDCl_3$): 52.68 (CH), 118.59 (CH), 121.72 (CH), 127.16 (CH), 128.04 (CH), 128.62 (CH), 128.69 (CH), 129.30 (CH), 129.59 (C), 130.38 (CH), 131.62 (CH), 133.05 (C), 135.06 (C), 135.38 (CH), 151.52 (C)

ν_{max}($CDCl_3$ sol^n)/cm^{-1}: 3022 (ArH stretch), 2980 (CH stretch), 2890 (CH stretch), 1593 (aromatic ring), 1257 (SiPh)

m/z (FAB^+): 605.3 [10 %, $(M+Na)^+$], 473.3 [100, $(M+H)^+$-PhSH)]

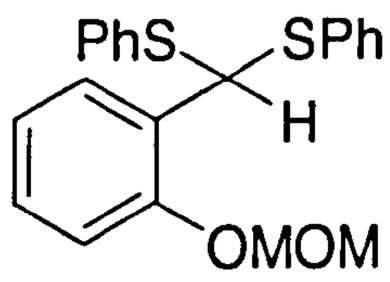
Accurate mass: $C_{37}H_{30}ONaSiS_2$, $(M+Na)^+$ requires 605.1405, actual 605.1407

Microanalysis: $C_{37}H_{30}OSiS_2$

C – theory 76.25 %, actual 76.19 %

H – theory 5.19 %, actual 5.25 %.

2-Methoxymethylbenzaldehyde diphenyldithioacetal 172



To 2-hydroxybenzaldehyde diphenyldithioacetal **168** (5.27 g, 16.26 mmol) in dry DCM (20 cm^3) at 0 °C under a nitrogen atmosphere was added diisopropylethylamine (3.00 cm^3, 17.20 mmol, 1.10 eq.). Methoxymethyl chloride (3.00 cm^3, 32.35 mmol, 1.98 eq.) was added drop-wise and the solution slowly warmed to room temperature. After 20 h the reaction mixture was poured into a 1:1 solution of saturated aqueous sodium bicarbonate : diethyl ether (70 cm^3). The aqueous layer was extracted with diethyl ether (3 × 30 cm^3) and the organic washings combined and washed with 1 M HCl (30 cm^3), 1 M NaOH (30 cm^3) and brine (30 cm^3). The solution was dried (magnesium sulfate) and the solvent removed under reduced pressure. The crude product was purified using column chromatography [neutral alumina, light petroleum b.p. 60-80 °C : diethyl ether (9:1), then (1:1)] giving the *thioacetal* **172** as prisms (4.32 g, 11.47 mmol, **71 %**).

R_F [alumina, diethyl ether : hexane (4:1)] : 0.62; m.p. 44-46 °C

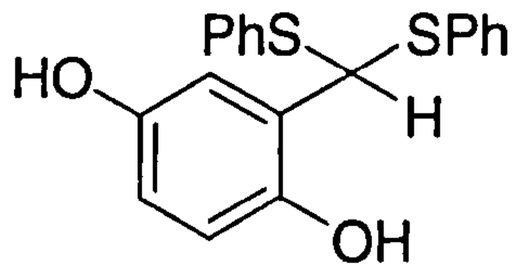
δ_H(400 MHz, $CDCl_3$): 3.39 (3H, s, OCH_3), 5.10 (2H, s, OCH_2O), 6.05 (1H, s, CH), 6.94 (1H, t, *J* 7.5, H-5), 7.03 (1H, d, *J* 8.2, H-3), 7.15-7.24 [7H, m, SArH (6H), and H-4], 7.32-7.36 (4H, m, SArH), 7.56 (1H, dd, *J* 1.5 and 7.6, H-6)

δ_C(100 MHz; $CDCl_3$): 52.81 (CH), 56.07 (CH_3), 94.43 (CH_2), 113.98 (CH), 121.94 (CH), 127.41 (CH), 128.55 (C), 128.71 (CH), 129.07 (CH), 129.09 (CH), 132.05 (CH), 135.04 (C), 53.38 (C)

ν_{max} ($CDCl_3$ sol^n)/cm^{-1}: 3059 (ArH stretch), 2956 (CH stretch), 2949 (CH stretch), 1599 (aromatic ring), 1583 (aromatic ring), 1478 (CH deformation), 1439 (CH deformation), 1150 (COC stretch), 756 (mono-substituted aromatic ring), 689 (mono-substituted aromatic ring)

m/z (CI^+):	386 [5 %, $(M+NH_4)^+$], 259 [100, $(M+H)^+$- PhSH)]
Accurate mass:	$C_{21}H_{24}O_2NS_2$, $(M+NH_4)$ requires 386.1248, actual 386.1246
Microanalysis:	$C_{21}H_{20}O_2S_2$ C – theory 68.44 %, actual 68.32 % H – theory 5.47 %, actual 5.52 %.

2,5-Dihydroxybenzaldehyde diphenyldithioacetal 173



Following *general method (2)*, 2,5-dihydroxybenzaldehyde diphenyldithioacetal **173** was produced using thiophenol (3.10 cm^3, 30.2 mmol, 2.28 eq.), boron trifluoride diethyl etherate (1.40 cm^3, 11.05 mmol, 0.83 eq.), acetic acid (20 cm^3) and 5-hydroxysalicylaldehyde (1.83 g, 13.26 mmol) in toluene (50 cm^3) (reaction time 53 h). The crude product was purified using column chromatography [silica, light petroleum b.p. 40-60 °C : diethyl ether (9:1) then (1:1), then diethyl ether] to give the *thioacetal* **173** as a viscous oil (2.26 g, 6.65 mmol, **50 %**).

R_F [silica, light petroleum b.p. 40-60 °C : diethyl ether (1:1)] : 0.17

δ_H(400 MHz, $CDCl_3$): 5.73 (1H, s, CH), 6.62 (1H, dd, *J* 2.8 and 8.8, H-4), 6.71 (1H, d, *J* 8.8, H-3), 6.78 (1H, d, *J* 2.8, H-6), 7.21-7.24 (6H, m, SArH), 7.35-7.38 (4H, m, SArH)

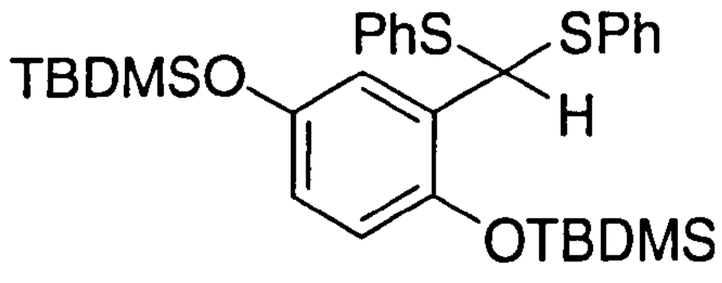
δ_C(100 MHz; $CDCl_3$): 55.39 (CH), 115.86 (CH), 116.38 (CH), 117.78 (CH), 125.60 (C), 127.87 (CH), 128.85 (CH), 132.24 (CH), 133.91 (C), 147.12, (C), 149.43 (C)

ν_{max} (thin film)/cm^{-1}: 3374 (OH), 2938 (CH stretch),1577 (aromatic ring), 1451 (aromatic ring), 1220 (OH bend), 767 (*o*-disubstituted aromatic ring)

m/z (CI^+) 231 [95 %, $(M+H)^+$-PhSH], 138 (100), (M^+ peak unobtainable)

Accurate mass: Unobtainable, SPh lost on probe

2,5-di*tert*-Butyldimethylsilyloxybenzaldehyde diphenyldithioacetal 174



Following *general method (3)*, 2,5-di*tert*-butyldimethylsilyloxybenzaldehyde diphenyldithioacetal **174** was prepared using 2,5-dihydroxybenzaldehyde diphenyldithioacetal **173** (2.26 g, 6.65 mmol), *tert*-butyldimethylsilyl chloride (2.54 g, 16.85 mmol, 2.53 eq.) and imidazole (1.25 g, 18.36 mmol, 2.76 eq.) in DMF (20 cm^3) (reaction time 18 h). The *silyl ether* **174** was isolated as an oil (3.78 g, 6.64 mmol, ***ca* 100** *%*).

R_F [silica, light petroleum b.p. 40-60 °C : diethyl ether (1:1)] : 0.60

δ_H(400 MHz, $CDCl_3$): 0.16 (12 H, s, $SiCH_3$), 0.94 (9H, s, *t*-Bu), 0.98 (9H, s, *t*-Bu), 6.00 (1H, s, CH), 6.60-6.61 (2H, m, H-3, H-4), 6.95 (1H, bs, H-5), 7.18-7.25 (6H, m, SArH), 7.35-7.38 (4H, m, SArH)

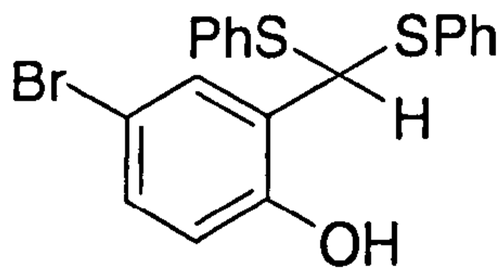
δ_C(100 MHz; $CDCl_3$): -4.47 (CH_3), -4.23 (CH_3), 18.14 (C), 18.17 (C), 25.74 (CH_3), 51.85 (CH), 118.45 (CH), 120.20 (CH), 120.55 (CH), 127.19 (CH), 128.64 (CH), 130.40 (C), 131.56 (CH), 135.12 (C), 146.29 (C), 149.57 (C)

ν_{max} (thin film)/cm^{-1}: 2968 (CH stretch), 2843 (CH stretch), 1582 (aromatic ring), 1456 (CH deformation), 1272 (SiMe)

m/z (CI^+): 569 [0.8 %, $(M+H)^+$], 553 [1.6, $(M+H)^+$-CH_4], 511 [1.6, $(M+H)^+$- *t*-BuH], 459 [100, $(M+H)^+$-PhSH]

Accurate mass: $C_{31}H_{45}O_2Si_2S_2$, $(M+H)^+$ requires 569.2399, actual 569.2387.

5-Bromo-2-hydroxybenzaldehyde diphenyldithioacetal 175



Following *general method (2)*, 5-bromo-2-hydroxybenzaldehyde diphenyldithioacetal **172** was produced using thiophenol (7.70 cm^3, 75.0 mmol, 2.47 eq.), boron trifluoride diethyl etherate (3.20 cm^3, 25.9 mmol, 0.85 eq.), acetic acid (20 cm^3) and 5-bromosalicyaldehyde (6.08 g, 30.4 mmol) in toluene (30 cm^3) (reaction time 21 h). Upon solvent removal a solid was obtained. This was washed with light petroleum b.p. 40-60 °C to remove the excess thiophenol and give the *thioacetal* **175** as a solid (10.55 g, 26.24 mmol, **86 %**). A small sample was crystallised from $CDCl_3$ to give needles, which were used for characterisation.

R_F [silica, light petroleum b.p. 40-60 °C : diethyl ether (1:1)] : 0.23; m.p. 128-130 °C

δ_H(400 MHz, $CDCl_3$): 5.59 (1H, s, CH), 6.39 (1H, bs, OH),
6.72 (1H, dd, *J* 2.2 and 7.0, H-4),
7.21-7.23 (1H, m, H-3 and H-6), 7.23 (1H, d, *J* 2.4, H-6),
7.25-7.28 (6H, m, SArH), 7.37-7.40 (4H, m, SArH)

δ_C(100 MHz; $CDCl_3$): 56.36 (CH), 112.60 (C), 118.90 (CH), 126.18 (C), 124.48 (CH),
129.05 (CH), 132.13 (CH), 132.36 (CH), 132.91 (CH),
132.97 (C), 152.95 (C)

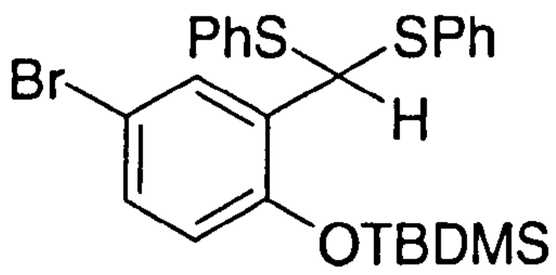
ν_{max} ($CDCl_3$ sol^n)/cm^{-1}: 3327 (OH stretch), 3148 (ArH stretch), 2896 (CH stretch),
1645 (aromatic ring), 1482 (aromatic ring),
1377 (CH deformation)

m/z (FAB^+): 426.9 [32 %, ^{81}Br,$(M+Na)^+$], 424.9 [32, ^{79}Br,$(M+Na)^+$],
316.9 [72, ^{81}Br,$(M+Na)^+$-PhSH],
314.9 [70,^{79}Br,$(M+Na)^+$-PhSH],
294.9 [98, ^{81}Br, $(M+H)^+$-PhSH],
292.9 [100, ^{79}Br, $(M+H)^+$-PhSH]

Accurate mass: $C_{19}H_{15}{}^{79}BrNaOS_2$,$(M+Na)^+$ requires 424.9645, actual 424.9643
$C_{19}H_{15}{}^{81}BrNaOS_2$,$(M+Na)^+$ requires 426.9625, actual 424.9628

Microanalysis: $C_{19}H_{15}OBrS_2$
C – theory 56.59 %, actual 56.54 %
H – theory 3.83 %, actual 3.72 %.

5-Bromo2-*tert*-butyldimethylsilyloxybenzaldehyde diphenyldithioacetal 176



Following *general method (3)*, 5-bromo-2-*tert*-butyldimethylsilyloxybenzaldehyde diphenyldithioacetal **176** was prepared using 5-bromo 2-hydroxy-benzaldehyde diphenyldithioacetal **175** (2.71 g, 6.72 mmol), *tert*-butyldimethylsilyl chloride (1.20 g, 8.13 mmol, 1.21 eq.) and imidazole (1.17 g, 16.8 mmol, 2.50 eq.) in DMF (50 cm^3) (reaction time 24 h). The *silyl ether* **176** was isolated as a colourless oil, which crystallised as plates overnight (1.98 g, 4.52 mmol, **67 %**).

R_F [silica, light petroleum b.p. 40-60 °C : diethyl ether (1:1)] : 0.65; m.p. 126 °C

δ_H(400 MHz, $CDCl_3$): 0.16 (6H, s, $SiCH_3$), 0.92 (9H, s, *t*-Bu), 5.93 (1H, s, CH), 6.60 (1H, d, *J* 8.4, H-3), 7.01 (1H, dd, *J* 2.4 and 8.8, H-4), 7.20-7.24 (6H, m, SArH), 7.30-7.34 (4H, m, SArH), 7.60 (1H, d, *J* 2.4, H-6)

δ_C(100 MHz; $CDCl_3$): -4.26 (CH_3), 18.14 (C), 25.68 (CH_3), 51.75 (CH), 113.43 (C), 119.54 (CH), 127.62 (CH), 128.74 (CH), 131.49 (CH), 132.05 (CH), 132.29 (C), 132.35 (CH), 134.37 (C), 151.06 (C)

ν_{max} ($CDCl_3$ sol^n)/cm^{-1}: 3149 (ArH stretch), 2949 (CH stretch), 2860 (CH stretch), 1656 (aromatic ring), 1588 (aromatic ring), 1393 (CH deformation), 1262 (SiMe), 1052 (SiO), 868 (SiMe)

m/z (FAB^+): 541 [8 %, ^{81}Br,$(M+Na)^+$], 539 [9.5, ^{79}Br,$(M+Na)^+$], 409 [100, ^{81}Br,$(M+H)^+$-PhSH], 407 [95 %, ^{79}Br,$(M+H)^+$-PhSH]

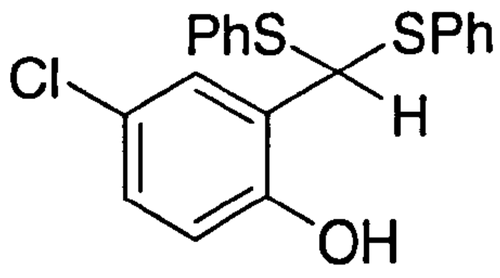
Accurate mass: $C_{25}H_{29}{}^{79}BrNaOS_2$, $(M+Na)^+$ requires 539.0511, actual 539.0521
$C_{25}H_{15}{}^{81}BrNaOS_2$, $(M+Na)^+$ requires 541.0490, actual 541.0484

Microanalysis: $C_{25}H_{15}BrOS_2$

C – theory 58.01 %, actual 58.07 %

H – theory 5.65 %, actual 5.66 %.

5-Chloro-2-hydroxybenzaldehyde diphenyldithioacetal 177



Following *general method (2)*, 5-chloro-2-hydroxybenzaldehyde diphenyldithioacetal **177** was produced using thiophenol (2.50 cm^3, 24.4 mmol, 2.44 eq.), boron trifluoride diethyl etherate (1.10 cm^3, 8.91 mmol, 0.86 eq.), acetic acid (10 cm^3) and 5-chlorosalicylaldehyde (1.63 g, 10.4 mmol) in toluene (10 cm^3) (reaction time 11 h). Upon solvent removal a pale pink solid was obtained. This was washed with light petroleum b.p. 40-60 °C to remove the excess thiophenol and give the *thioacetal* **177** as a pale pink solid (3.17 g, 8.84 mmol, **85 %**). A small sample was crystallised from $CDCl_3$ to give needles, which were used for characterisation.

R_F [silica, light petroleum b.p. 40-60 °C : diethyl ether (1:1)] : 0.23; m.p. 118 °C

δ_H(400 MHz, $CDCl_3$): 5.61 (1H, s, CH), 6.37 (1H, bs, OH), 6.75 (1H, d, *J* 8.4, H-3), 7.06 (1H, d, *J* 2.4, H-6), 7.09 (1H, m, H-4), 7.24-7.28 (6H, m, SArH), 7.35-7.40 (4H, m, SArH)

δ_C(100 MHz; $CDCl_3$): 56.32 (CH), 118.42 (CH), 125.43 (C), 125.78 (C), 128.44 (CH), 129.05 (CH), 129.24 (CH), 129.42 (CH), 132.85 (CH), 133.01 (C), 152.37 (C)

ν_{max} ($CDCl_3$ sol^n)/cm^{-1}: 3327 (OH stretch), 3159 (ArH stretch), 3069 (CH stretch), 2985 (CH stretch), 2896 (CH stretch), 1635 (aromatic ring), 1577 (aromatic ring), 1377 (CH deformation)

m/z (EI^+): 358 (0.1 %, ^{35}Cl, $M^{+\bullet}$), 248 (65, ^{35}Cl, $M^{+\bullet}$-PhSH), 110 (100, $PhSH^{+\bullet}$)

Accurate mass: $C_{19}H_{15}{}^{35}ClOS_2$ requires 358.0253, actual 358.0251

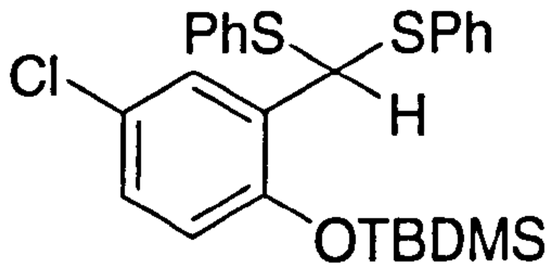
$C_{19}H_{15}{}^{37}ClOS_2$ requires 360.0223, actual 360.0180

Microanalysis: $C_{19}H_{15}ClOS_2$

C – theory 63.60 %, actual 63.63 %

H – theory 4.18 %, actual 4.22 %.

5-Chloro-2-*tert*-butyldimethylsilyloxybenzaldehyde diphenyldithioacetal 178



Following *general method (3)*, 5-chloro-2-*tert*-butyldimethylsilyloxybenzaldehyde diphenyldithioacetal **178** was prepared using 5-chloro-2-hydroxybenzaldehyde diphenyldithioacetal **177** (3.10 g, 8.65 mmol), *tert*-butyldimethylsilyl chloride (1.48 g, 9.82 mmol, 1.13 eq.) and imidazole (1.48 g, 21.7 mmol, 2.51 eq.) in DMF (10 cm^3) (reaction time 24 h). The *silyl ether* **178** was isolated as an oil, which crystallised into plates overnight (3.84 g, 8.13 mmol, **94 %**).

R_F [silica, light petroleum b.p. 40-60 °C : diethyl ether (1:1)] : 0.57; m.p. 40 °C

δ_H(400 MHz, $CDCl_3$): -0.16 (6H, s, $SiCH_3$), 0.91 (9H, s, *t*-Bu), 5.69 (1H, s, CH), 6.64 (1H, d, *J* 8.8, H-3), 7.03 (1H, dd, *J* 2.8 and 8.8, H-4), 7.19-7.24 (6H, m, SArH), 7.30-7.33 (4H, m, SArH), 7.47 (1H, t, *J* 2.8, H-6)

δ_C(100 MHz; $CDCl_3$): -4.23 (CH_3), 18.14 (C), 25.69 (CH_3), 51.81 (CH), 119.07 (CH), 126.17 (C), 127.60 (CH), 128.57 (CH), 128.75 (CH), 129.42 (CH), 131.82 (C), 132.01 (CH), 134.45, (C), 150.57 (C)

ν_{max} ($CDCl_3$ sol^n)/cm^{-1}: 3159 (ArH stretch), 2953 (CH stretch), 2859 (CH stretch), 1582 (aromatic ring), 1272 (SiMe), 925 (SiMe)

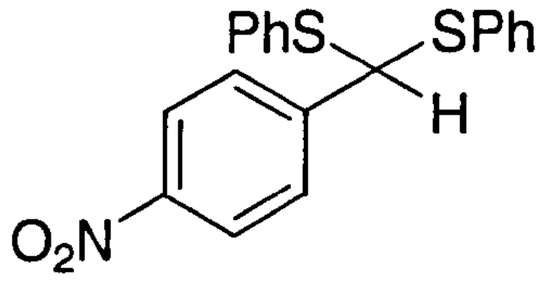
m/z/Accurate mass: Unobtainable

Microanalysis: $C_{25}H_{29}ClOSiS_2$

C – theory 63.49 %, actual 63.31 %

H – theory 6.14 %, actual 6.04 %.

4-Nitrobenzaldehyde diphenyldithioacetal 179



Following *general method (2)*, 4-nitrobenzaldehyde diphenyldithioacetal **179** was produced using thiophenol (3.10 cm^3, 30.2 mmol, 2.91 eq.), boron trifluoride diethyl etherate (1.10 cm^3, 8.76 mmol, 0.84 eq.), acetic acid (10 cm^3) and 4-nitrobenzaldehyde (1.57 g, 10.4 mmol) in toluene (10 cm^3) (reaction time 22 h). Upon solvent removal a yellow solid was obtained. This was washed with light petroleum b.p. 40-60 °C to remove the excess thiophenol and give the thioacetal **179** as a yellow solid (3.42 g, 9.69 mmol, **93** %). A small sample was crystallised from ethanol to give yellow plates, which were used for characterisation.

R_F [silica, light petroleum b.p. 40-60 °C : diethyl ether (1:1)] : 0.51; m.p. 99 °C

δ_H(400 MHz, $CDCl_3$): 5.43 (1H, s, CH), 7.23-7.28 (6H, m, SArH),
7.30-7.37 (4H, m, SArH),
7.44 (2H, d, 8.8, H-2 and H-6), 8.09 (2H, d, 8.8, H-3 and H-5)

δ_C(100 MHz; $CDCl_3$): 59.79 (CH), 123.64 (CH), 128.55 (CH), 128.72 (CH),
129.09 (CH), 133.08 (C), 133.21 (CH), 147.09 (C), 147.26 (C)

ν_{max} ($CDCl_3$ sol^n)/cm^{-1}: 3153 (CH), 3075 (CH), 2980 (CH stretch), 2906 (CH stretch),
2854 (CH stretch), 1598 (aromatic ring), 1500 (CNO),
1335 (CNO)

m/z (EI^+): 353 (2 %, $M^{+\bullet}$), 244 (100, $M^{+\bullet}$-$PhS^\bullet$),
197 (15, $M^{+\bullet}$-$PhS^\bullet$ and HNO_2)

Accurate mass: $C_{19}H_{15}O_2NS_2$ requires 353.0543, actual 353.0545

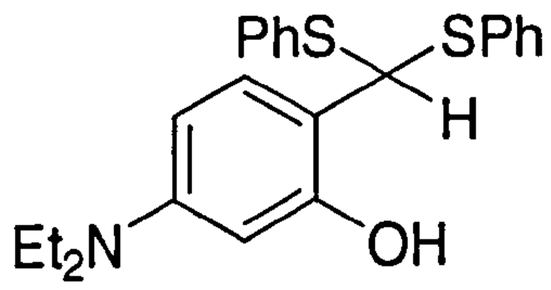
Microanalysis: C – theory 64.56 %, actual 64.34 %

H – theory 4.28 %, actual 4.29 %

N – theory 3.96 %, actual 3.89 %

Literature:[148] m.p. 98-99 °C (EtOH); δ_H ($CDCl_3$): 5.43 (1H, s, CH), 7.26-7.36 (10H, m), 7.45 (2H, d, *J* 8.5), 8.10 (2H, d, *J* 8.8).

4-Diethylamino-2-hydroxybenzaldehyde diphenyldithioacetal 180



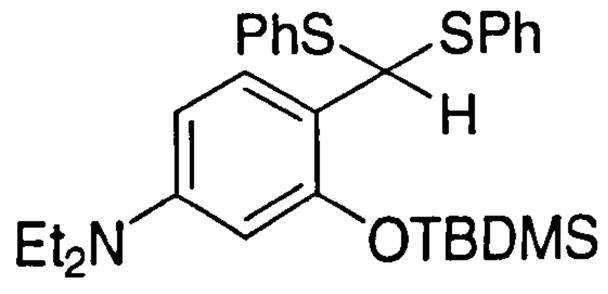
4-Diethylaminosalicylaldehyde (11.44 g, 59.3 mmol) was dissolved in THF (50 cm^3) and stirred at room temperature. Thiophenol (15.4 cm^3, 150 mmol, 2.53 eq.) and boron trifluoride diethyl etherate (6.4 cm^3, 51.9 mmol, 0.87 eq.) were added and the mixture stirred for 24 h. Ethyl acetate (20 cm^3) was added to give a solution that was washed with saturated aqueous sodium bicarbonate (5 × 20 cm^3). The organic solution was dried (magnesium sulfate) and the solvent removed under reduced pressure to give the crude thioacetal as a viscous red oil. Purification was carried using column chromatography [neutral alumina, light petroleum b.p. 40-60 °C : diethyl ether (9:1) then (1:1), then diethyl ether] to give the *thioacetal* **180** as a viscous red oil (5.97 g, 15.1 mmol, ***ca* 25 %**). The compound was contaminated with diethyl ether that proved difficult to remove. The thioacetal was used in the next step without further purification.

R_F [alumina, light petroleum b.p. 40-60 °C : diethyl ether (1:1)] : 0.39

δ_H(400 MHz, $CDCl_3$): 1.12 (6H, t, *J* 7.0, CH_2CH_3), 3.28 (4H, q, *J* 7.1, CH_2CH_3), 5.65 (1H, s, CH), 6.10 (1H, dd, *J* 2.4 and 8.4, H-5), 6.17 (1H, bs, H-3), 6.55 (1H, bs, OH), 6.94 (1H, d, *J* 8.4, H-6), 7.13-7.30 (6H, m, SArH), 7.37-7.41 (4H, m, SArH)

δ_C (100 MHz; $CDCl_3$): 12.57 (CH_2CH_3), 57.05 (CH), 44.40 (CH_2CH_3), 127.70 (CH), 128.82 (CH), 129.08 (C), 129.43 (C), 130.47 (CH), 132.22 (CH), 134.39 (C), 155.34 (C)

4-Diethylamino-2-*tert*-butyldimethylsilyloxy benzaldehyde diphenyldithioacetal 181



Following *general method (3)*, 4-diethylamino-2-*tert*-butyldimethylsilyloxybenzaldehdye diphenyldithioacetal **181** was prepared 4-diethylamino-2-hydroxybenzaldehyde diphenyldithioacetal **180** (6.00 g, 15.19 mmol), *tert*-butyldimethylsilyl chloride (2.71 g, 18.0 mmol, 1.18 eq.) and imidazole (2.77 g, 40.7 mmol, 2.68 eq.) in DMF (20 cm^3) (reaction time 18 h). The crude product was isolated as a red crystalline solid that was purified using column chromatography [alumina, light petroleum b.p. 40–60 °C : diethyl ether (3:1)] to give the *silyl ether* as a white solid. The product contained minor aromatic impurities (thought to be due to thiophenol) that proved very difficult to remove (re-crystallisation from ethanol was attempted but did not remove the impurities). The silyl ether was therefore used in the alkylidenation step without further purification. Yield crude thioacetal **181** (3.55 g, 8.99 mmol, ***ca* 59 %**). ^{1}H NMR showed 89:11 molar ration of target compound : diphenol disulfide. The impure sample was used in further alkylidenation reactions with no further purification.

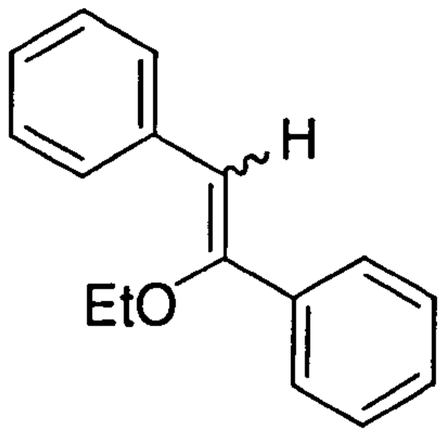
For characterisation purposes Gordon McKiernan dissolved a sample of the impure material in dichloromethane. This was reacted with 1 equivalent (relative to the disulfide impurity) of lithium aluminium hydride and stirred for 30 mins. The reaction was quenched by the addition of water and the pure thioacetal extracted and concentrated to give the pure thioacetal **181** as a yellow solid.

R_F [silica, light petroleum b.p. 40-60 °C : diethyl ether (1:1)] : 0.63

mp 71-72 °C

δ_H(400 MHz, $CDCl_3$):	0.20 (6H, s, $SiCH_3$), 0.94 (9H, s, CH_3),
	1.14 (6H, t, *J* 6.9, CH_2CH_3), 3.29 (4H, q, *J* 7.0, CH_2CH_3),
	5.99 (1H, s, CH), 6.03 (1H, d, *J* 2.4, H-3),
	6.27 (1H, dd *J* 2.6 and 8.8, H-5), 7.13-7.22 (6H, m, SArH),
	7.31-7.34 (4H, m, SArH), 7.41 (1H, d, *J* 8.7, H-6)
δ_C (100 MHz; $CDCl_3$):	-3.64, 13.05, 18.62, 26.22, 44.86, 52.27, 101.68, 105.92,
	116.61, 127.07, 128.97, 130.36, 131.31, 136.53, 148.93, 153.37
ν_{max} (KBr)/cm^{-1}:	3057 (ArH stretch), 2960, 2927, 1103, 844
m/z (CI^+):	510 [5 %, $(M+H)^+$], 400 [75, $(M+H)^+$-PhS],
	292 [100, $(M+H)^+$-2(PhS)],
Accurate mass:	$C_{29}H_{40}OSiNS_2$ $(M+H)^+$ requires 510.2321, actual 510.2321
Microanalysis:	$C_{29}H_{40}OSiNS_2$
	C – theory 68.18 %, actual 67.98 %
	H – theory 7.89 %, actual 7.90 %
	N – theory 2.74 %, actual 2.67 %

1-Ethoxy-1,2-diphenylethene 183



Following *general method (4)*, 1-ethoxy-1,2-diphenylethene **183** was prepared using titanocene dichloride (1.01 g, 4.06 mmol, 4.06 eq.), magnesium (0.11g, 4.52 mmol, 4.52 eq.), 4Å molecular sieves (0.42 g), triethylphosphite (1.4 cm^3, 8.16 mmol, 8.16 eq.), ethyl benzoate (0.15 g in 2 cm^3 THF, 1.00 mmol) and benzaldehyde diphenyldithioacetal (0.34 g in 2 cm^3 THF, 1.10 mmol, 1.10 eq.) in THF (8 cm^3) (reaction time 16 h). The crude product was purified using column chromatography, [alumina, hexane : diethyl ether (9:1)] and finally placed on a kugelrohr (*ca* 1 mmHg, oven temperature 160 °C) to remove any phosphorous impurities to give the alkene **183** as an oil (0.11 g, 0.49 mmol, **49 %**, *Z:E* 9:1).

R_F [alumina, hexane : diethyl ether (9:1)] : 0.6

δ_H(400 MHz, $CDCl_3$): 1.35 (3H, t, *J* 7.0, *Z*, CH_3), 1.42 (3H, t, *J* 6.9, *E*, CH_3),
3.83 (2H, q, *J* 7.0, *Z*, CH_2), 4.00 (2H, q, *J* 6.93, *E*, CH_2),
5.83 (1H, s, *E*, C=CH), 6.09 (1H, s, Z, C=CH),
6.94 (2H, d, *J* 7.2, *E*, ArH), 7.02 (1H, t, *J* 7.2, *E*, ArH),
7.09 (2H, t, *J* 7.6, *E*, ArH),
7.18-7.41 (6H, *Z* and 5H, *E* m, ArH),
7.74 (2H, d, *J* 7.4, *Z*, ArH), 7.56 (2H, d, *J* 7.8, Z, ArH)

δ_C (100 MHz; $CDCl_3$): 14.77 (CH_3, *E*), 15.44 (CH_3, *Z*), 63.64 (CH_2, *E*), 65.91 (CH_2, *Z*),
102.42 (CH, *E*), 113.26 (CH, *Z*), 125.1 (C), 126.5 (CH),
126.59 (CH), 127.93 (CH), 128.17 (CH), 128.25 (CH),
128.31 (CH), 128.43 (CH), 128.48 (CH), 128.60 (CH),
128.86 (CH), 129.31 (CH), 136.14 (C), 138.11 (C), 155.19 (C)

ν_{max} ($CDCl_3$ sol^n)/cm^{-1}: 3055 (C=CH stretch), 2926 (CH stretch), 1655 (C=C-O), 1637 (C=C), 1491 (aromatic ring), 765 (mono-substituted aromatic ring), 694 (mono-substituted aromatic ring)

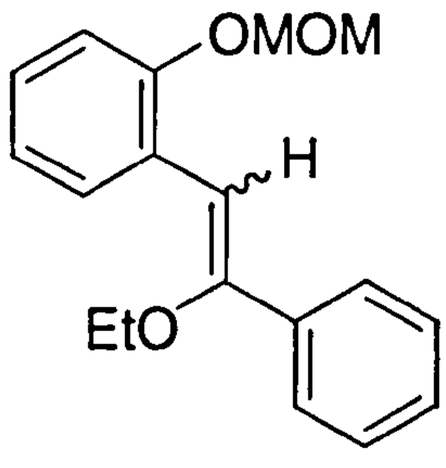
m/z (EI$^+$): 224 (100 %, $M^{+\bullet}$), 196 (40, $M^{+\bullet}$-CH_2=CH_2), 178 (20, $M^{+\bullet}$-EtOH), 167 (70, $M^{+\bullet}$-CH_2=CH_2 and $^\bullet$CHO)

Accurate mass: $C_{16}H_{16}O$ requires 224.1201, actual 224.1200

Literature:[149] δ_H(60 MHz, $CDCl_3$): 1.24 (3H, t, *J* 6.5, *E*), 3.76 (2H, q, *J* 6.5, *E*), 6.03 (1H, s, *E*), 7.03-7.40 (10H, m, *E*); ν_{max} (film, *E*)/cm^{-1}: 1685, 1630, 1590, 1215, 1055

δ_H (60 MHz, $CDCl_3$): 1.27 (3H, t, *J* 6.5, *Z*), 3.81 (2H, q, *J* 6.5, *Z*), 5.75 (1H, s, *Z*), 7.05-7.75 (10H, m, *Z*); ν_{max} (film, *Z*)/cm^{-1}: 1680, 1640, 1605, 1205, 1060.

1-Ethoxy-1-phenyl-2-(2'-methoxymethyloxyphenyl)ethene 184



Following *general method (4)*, 1-ethoxy-1-phenyl-2-(2'-methoxymethyloxyphenyl)ethene **184** was prepared using titanocene dichloride (1.02 g, 4.10 mmol, 4.36 eq.), magnesium (0.14g, 6.0 mmol, 6.36 eq.), 4Å molecular sieves (0.13 g), triethylphosphite (1.3 cm^3, 7.60 mmol, 8.08 eq.), ethyl benzoate (0.14 g in 2 cm^3 THF, 0.94 mmol) and 2-methoxymethylbenzaldehyde diphenyldithioacetal (**172**, 0.37 g in 2 cm^3 THF, 1.0 mmol, 1.06 eq.) in THF (7 cm^3) (reaction time 14 h). The crude product was purified by column chromatography, [alumina, light petroleum b.p. 40-60 °C : diethyl ether (9:1)] and placed on a kugelrohr (1 mmHg, oven temperature 100 °C) to remove any phosphorous impurities and give the alkene **184** as an oil (0.093 g, 0.33 mmol, **35 %**, *Z*:*E* 9.3:1).

R_F [alumina, light petroleum b.p. 40-60 °C : diethyl ether (1:1)] : 0.72

δ_H(400 MHz, $CDCl_3$): 1.32 (3H, t, *J* 7.0, *Z*, CH_3), 1.43 (3H, t, *J* 7.0, *E*, CH_3),
3.48 (3H, *Z* and 3H *E*, CH_3O), 3.82 (2H, q, *J* 7.1, *Z*, OCH_2),
4.04 (2H, q, *J* 6.9, *E*, OCH_2), 5.16 (2H, s, *E*, OCH_2O),
5.21 (2H, s, *Z*, OCH_2O), 5.93 (1H, s, *E*, C=CH),
6.54 (1H, s, *Z*, C=CH), 6.66 (1H, dt, *J* 2.40 and 6.70, *E*, H-5'),
6.76 (1H, d, *J* 7.2, *E*, H-3'),
7.03 (1H, dt, *J* 2.4 and 6.7, *Z*, H-5'),
7.10 (1H, dd, *J* 1.2 and 8.0, *Z*, H-3'),
7.16 (1H, dt, *J* 1.5 and 7.6, *Z*, H-4'),
7.20-7.30 (1H *Z* and 7 H *E*, m, ArH),
7.38 (2H, m, *Z*, ArH), 7.59 (2H, d, *J* 7.2, *Z*, ArH),
8.19 (1H, dd, *J* 1.5 and 7.8, *Z*, H-6')

δ_C (100 MHz; $CDCl_3$): 14.74 (CH_3, *E*), 15.40 (CH_3, *Z*), 56.09 (CH_3), 63.63 (CH_2, *E*), 66.05 (CH_2, *Z*), 94.89 (CH_2), 106.32 (CH), 114.54 (CH, *Z*), 114.79 (CH, *E*), 121.48 (CH, *E*), 121.79 (CH, *Z*), 125.82 (CH), 126.53 (CH), 127.53 (CH), 127.94 (CH), 128.09 (CH), 128.34 (CH), 129.14 (CH), 130.84 (CH), 137.35 (C), 138.08 (C), 154.26 (C), 155.13 (C)

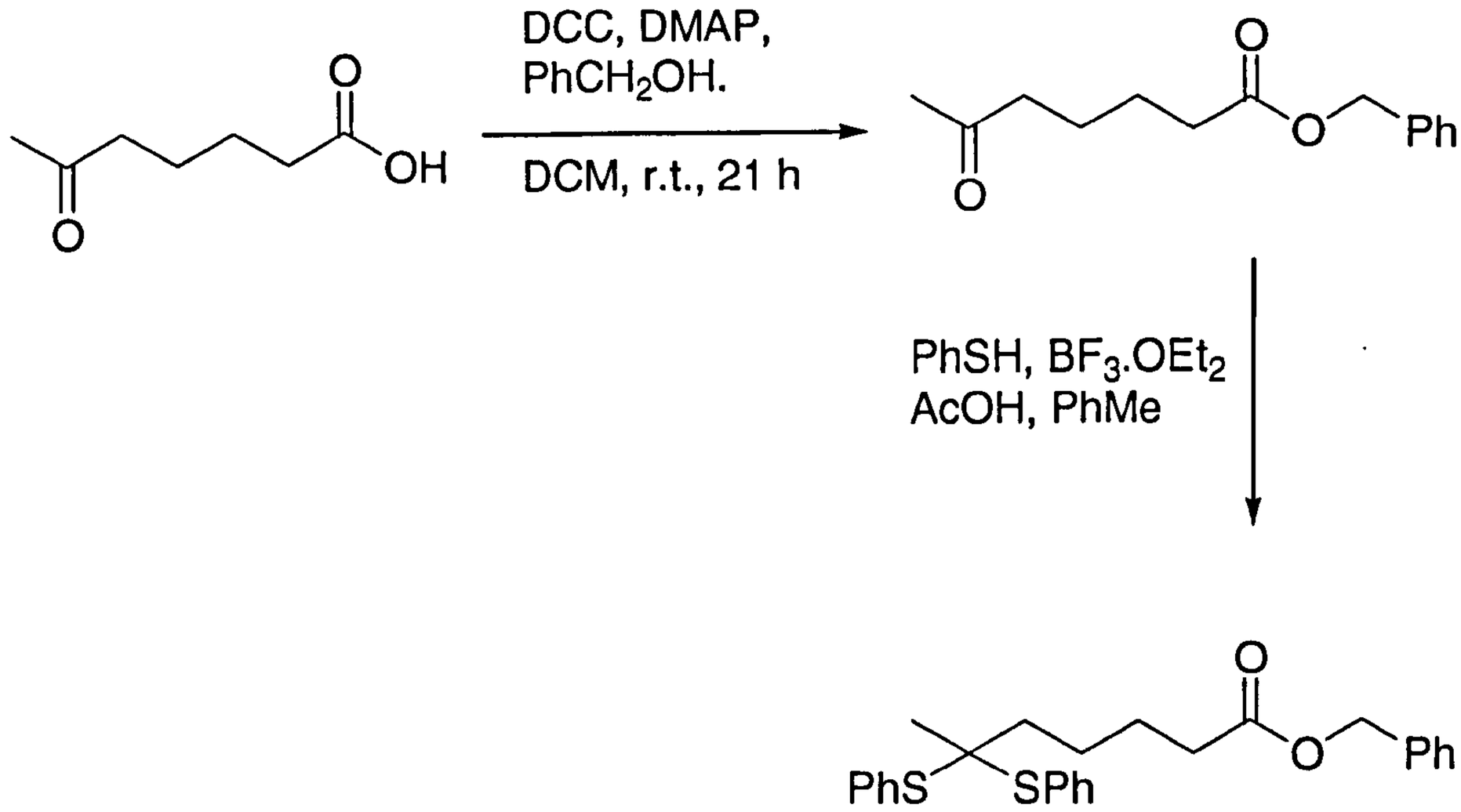
ν_{max} ($CDCl_3$ sol^n)/cm^{-1}: 3030 (ArH stretch), 2958 (CH stretch), 2923 (CH stretch), 2825 (OCH_3), 2788 (OCH_2O), 1689 (C=C-O), 1632 (aromatic ring), 1597 (aromatic ring), 1574 (aromatic ring), 765 (mono-substituted aromatic ring), 699 (mono-substituted aromatic ring)

m/z (EI$^+$): 284 (60 %, $M^{+\bullet}$), 252 (10, $M^{+\bullet}$-MeOH), 105 (100)

Accurate mass: $C_{18}H_{20}O_3$ requires 284.1412, actual 284.1411

Literature:[18] δ_H (275 MHz, $CDCl_3$): 1.43 (3H, t, *J* 6.93, *E*), 3.49 (2H, s, *E*), 4.04 (2H, q, *J* 6.93, *E*), 5.16 (2H, s, *E*), 5.93 (1H, s, *E*), 7.0-7.4 (9H, m, *E*); ν_{max} (neat, *E*)/cm^{-1}: 1690, 1600, 1580, 775, 755, 700.

Benzyl 6,6-*bis*(phenylthio)heptanoate 187



Step one

Benzyl 6-oxo-heptanoate was formed thus: 6-oxo-heptanoic acid (1.00 g, 6.94 mmol, 1.00 eq.), DCC (1.54 g, 7.46 mmol, 1.10 eq.), DMAP (0.15 g, 1.23 mmol, 0.18 eq.) and benzyl alcohol (0.70 cm^3, 6.76 mmol) were stirred in DCM (8 cm^3) at room temperature under a nitrogen atmosphere for 21 h. The undissolved solids were filtered from the reaction mixture, washing with diethyl ether. The combined organic washings and filtrate were washed with water (3 × 20 cm^3), acetic acid (1.5 % solution, 3 × 20 cm^3) and again with water (3 × 20 cm^3). After drying (magnesium sulfate), the solvent was removed under reduced pressure to give the crude ester as a yellow oil (1.63 g, 6.96 mmol, ***ca* 100 %**). Minor impurities were present but the ester was used without further purification.

R_F [silica, light petroleum b.p. 40-60 °C : diethyl ether (1:1)] : 0.56

Literature:[150] no spectral data given

Step two

1.30 g (*ca* 5.56 mmol) of the crude benzyl 6-oxo-heptanoate was used to form benzyl 6,6-*bis*(phenylthio)heptanoate **187**. Following *general method (2)* thiophenol (1.70 cm^3, 16.68 mmol, 3.00 eq.), boron trifluoride diethyl etherate (0.55 cm^3, 4.62 mmol, 0.83 eq.), acetic acid (5 cm^3) and benzyl 6-oxo-heptanoate (1.30 g, *ca* 5.56 mmol) were stirred in toluene (6 cm^3) for 74 h. The crude product was purified using column chromatography [silica, light petroleum b.p. 60-80°C : diethyl ether (9:1), then diethyl ether] to give the *thioacetal* **187** as an oil (1.75 g, 4.01 mmol, **72 %** from 6-oxo-heptanoic acid).

R_F [silica, light petroleum b.p. 40-60 °C : diethyl ether (1:1)] : 0.56

δ_H(400 MHz, $CDCl_3$): 1.36 [3H, s, $CH_3C(PhS)_2$], 1.51-1.71 [6H, m, ($3 \times CH_2$)], 2.34 (2H, t, *J* 7.40, CH_2), 5.10 (2H, s, CH_2O), 7.27-7.38 (11H, m, ArH), 7.58-7.63 (4H, m, ArH)

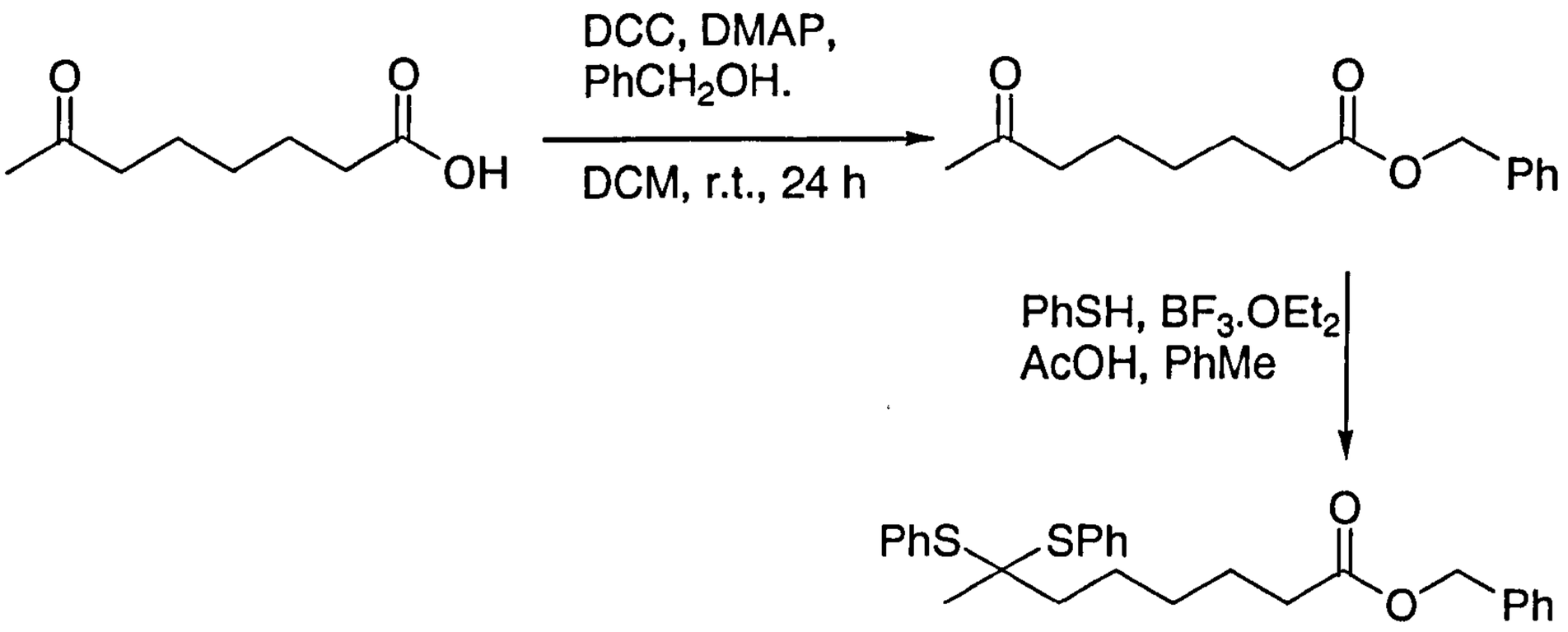
δ_C (100 MHz; $CDCl_3$): 24.41 (CH_2), 24.78 (CH_2), 28.07 (CH_3), 34.07 (CH_2), 40.98 (CH_2), 63.72 (C), 66.06 (CH_2), 128.11 (CH), 128.48 (CH), 128.97 (CH), 131.82 (C), 135.95 (C), 136.85 (CH), 173.20 (C)

ν_{max} ($CDCl_3$ sol^n)/cm^{-1}: 3033 (ArH stretch), 2944 (CH stretch), 2866 (CH stretch), 1736 (C=O), 1582 (aromatic ring), 1572 (aromatic ring), 1497 (aromatic ring), 1455 (CH deformation), 1438 (CH deformation), 751 (mono-substituted aromatic ring), 694 (mono-substituted aromatic ring)

m/z (CI^+): 454 [6 %, $(M+NH_4)^+$], 344 [100, $(M+NH_4)^+$-PhSH], 327 [6, $(M+H)^+$-PhSH)]

Accurate mass: $C_{26}H_{32}O_2NS_2$ $(M+NH_4)^+$requires 454.1874, actual 454.1883.

Benzyl 7,7-*bis*(phenylthio)octanoate 189



Step one

Benzyl 7-oxo-octanoate was formed thus: 7-oxo-octanoic acid (1.04 g, 6.58 mmol, 1.15 eq.), DCC (1.47 g, 7.12 mmol, 1.24 eq.), DMAP (0.15 g, 1.23 mmol, 0.21 eq.) and benzyl alcohol (0.6 cm^3, 5.74 mmol) were stirred in DCM (6 cm^3) at room temperature under a nitrogen atmosphere for 24 h. The undissolved solids were filtered from the reaction mixture, washing with diethyl ether. The combined organic washings and filtrate were washed with water (3 × 20 cm^3), acetic acid (1.5 % solution, 3 × 20 cm^3) and again with water (3 × 20 cm^3). After drying (magnesium sulfate), the solvent was removed under reduced pressure to give the crude ester as a yellow oil. The crude product was washed through a short column of silica [ethyl acetate: hexane (3:2)] to give the ester as a yellow oil (1.47 g, 5.92 mmol, ***ca* 94 %**). Minor impurities were present but the ester was used without further purification.

R_F [silica, light petroleum b.p. 40-60 °C : diethyl ether (1:1)] : 0.58

δ_H (400 MHz, $CDCl_3$): 1.18-1.24 (2H, m, CH_2), 1.42-1.61 (4H, m, CH_2), 2.00 (3H, s, CH_3), 2.25 (2H, t, *J* 7.4, CH_2CO), 2.30 (2H, t, *J* 7.6, CH_2CO), 5.00 (2H, s, CH_2O), 7.12-7.20 (5H, m, ArH)

Literature:[151] δ_H ($CDCl_3$): 2.00 (3H, s), 2.00-2.48 (4H, m), 4.99 (2H, s), 7.24 (5H, s).

Step two

1.43 g, (*ca* 5.76 mmol) of benzyl 7-oxo-octanoate was used to form benzyl 7-*bis*(phenylthio)octanoate **189**. Following *general method (2)* thiophenol (1.90 cm^3, 18.5 mmol, 3.22 eq.), boron trifluoride diethyl etherate (0.60 cm^3, 5.04 mmol, 0.87 eq.), acetic acid (5 cm^3) and benzyl 7-oxo-octanoate (1.43 g, *ca* 5.76 mmol) were stirred in toluene (7 cm^3) for 2.3 h. The crude product was purified using column chromatography [silica, light petroleum b.p. 60-80°C : diethyl ether (9:1), then diethyl ether] to give the *thioacetal* **189** as an oil (1.78 g, 3.96 mmol, **62 %** from 7-oxo-octanoic acid).

R_F [silica, light petroleum b.p. 40-60 °C : diethyl ether (1:1)] : 0.56

δ_H (400 MHz, $CDCl_3$): 1.36 [3H, s, $CH_3C(PhS)_2$], 1.20-1.31 (2H, m, CH_2), 1.55-1.70 [6H, m, $(CH_2)_3$], 2.34 (2H, t, *J* 7.4, CH_2), 5.11 (2H, s, CH_2O), 7.22-7.38 (11H, m, ArH), 7.58-7.64 (4H, m, ArH)

δ_C (100 MHz; $CDCl_3$): 25.36 (CH_2), 25.65 (CH_2), 28.99 (CH_3), 29.88 (CH_2), 35.03 (CH_2), 42.11 (CH_2), 65.83 (C), 65.93 (CH_2), 129.00 (CH), 129.35 (CH), 129.83 (CH), 132.84 (C), 136.90 (C), 137.72 (CH), 174.28 (C)

ν_{max} ($CDCl_3$ sol^n)/cm^{-1}: 3033 (ArH stretch), 2862 (CH_3/CH_2 stretch), 2939 (CH_3/CH_2 stretch), 1736 (C=O), 1583 (aromatic ring), 1572 (aromatic ring), 1498 (aromatic ring), 1455 (CH_3/CH_2 deformation), 1438 (CH_3/CH_2 deformation), 751 (mono-substituted aromatic ring), 694 (mono-substituted aromatic ring)

m/z (CI^+): 468 [10 %, $(M+NH_4)^+$], 358 [10, $(M+NH_4)^+$ -PhSH], 341 [100, $(M+H)^+$-PhSH]

Accurate mass: $C_{27}H_{34}O_2NS_2$ $(M+NH_4)^+$requires 468.2031, actual 468.2028.

SPS Chemistry General

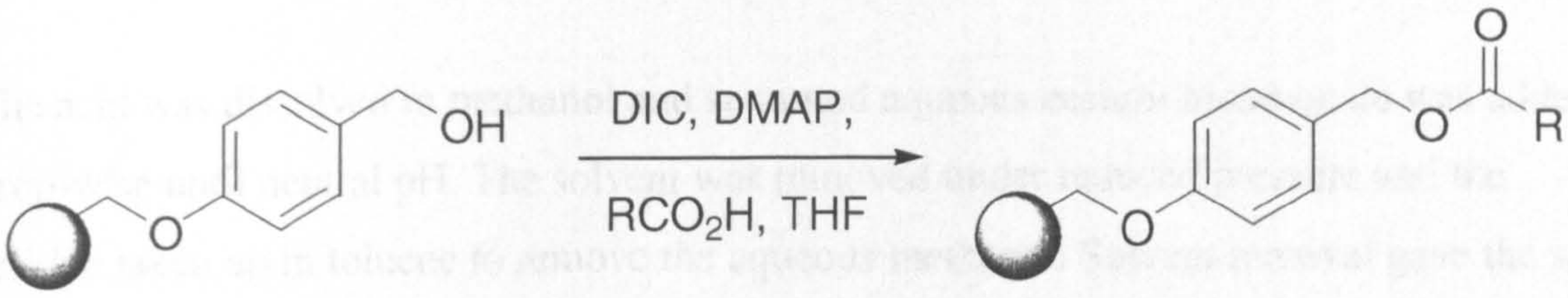
The loading of the resin used is described in terms of mmol/gram, as used by Nova Biochem.[152] This terminology refers to the number of mmols of the key functional group per gram of resin and can also be described as milli-equivalents/gram (meq.).

The resin types used in the solid phase reactions were PL-Wang size 150-300 μm with loading of 1.7 mmol/g and PL-CMS (Merrifield) with a loading of 1.7 mmol/g or 4.0 mmol/g. IRORI macrokans were employed with 168 mg/0.286 mmol (loading 1.7 mmol/g) or 168 mg/0.672 mmol (loading 4.0 mmol/g) of resin weighed into each kan. A large excess of the other reagents (*ca* 6 times the amount used in the corresponding solution phase reactions) was used so as to force the reaction to completion. The yields of the final cleaved products were based on the 168 mg of resin weighed. After ester formation one kan was opened and the contents weighed. If the requisite weight gain had not been obtained the resin was retreated. In the following alkylidenation reactions three kans were typically reacted together; the contents of the previously opened kan were used for characterisation, the second kan was cleaved under conditions to give the ketone and the third cleaved under conditions to give the benzo[*b*]furan. Following all the SPS reactions the kans containing the resin were cleaned by washing with the reaction solvent and then alternately with methanol and DCM. This action caused the resin to shrink and swell respectively and so force out any molecules not bound to the resin.

^{13}C NMR spectra for resin-bound samples were obtained on a Bruker AM-360 spectrometer operating at 90 MHz with the resin swollen in $CDCl_3$ to create a gel. Peak assignments for these spectra are recorded where possible and peaks referring to the Wang or Merrifield resin part are noted where possible. No DEPTS were run and any multiplicities of ^{13}C nuclei that are noted are suggestions by myself. Infrared (IR) spectra for resin-bound samples were obtained using a Nicolet 510 spectrometer fitted with a Golden Gate.

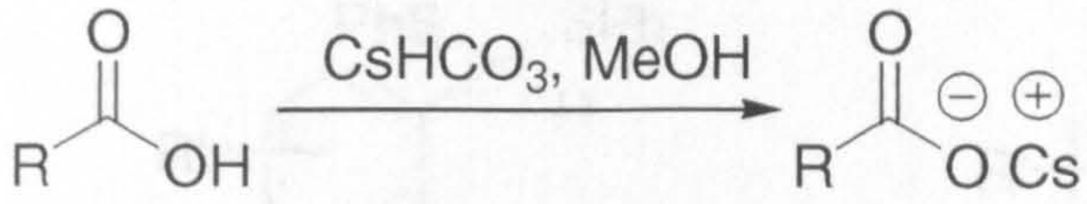
General Procedures – SPS chemistry

General method (5) - Formation of esters - Wang resin



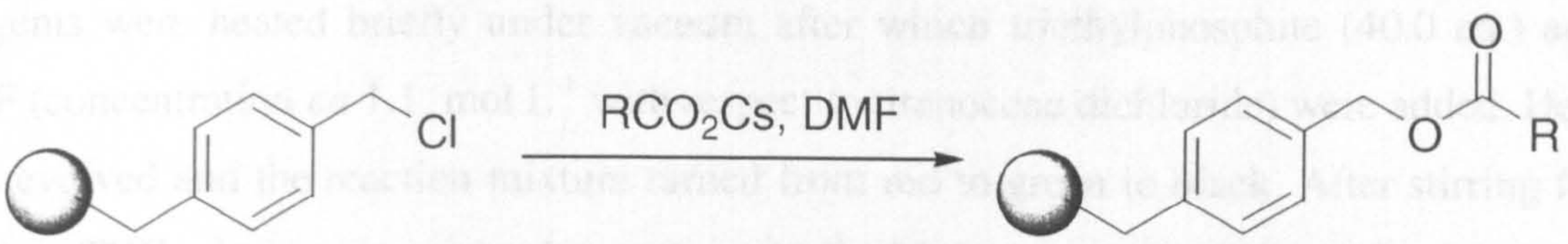
To Wang resin (1 eq., weighed in kans) swollen in THF (concentration *ca* 0.02. mol L^{-1} with respect to the resin) was added the appropriate acid (5.00 eq.) and DMAP (0.90 eq.) and the mixture stirred at room temperature. DIC (5.00 eq.) was added drop-wise and the mixture stirred overnight. The THF was removed and the kans washed with THF, alternating methanol then DCM (5×30 cm^3 of each), methanol (30 cm^3) and finally diethyl ether (30 cm^3). The resin was dried under vacuum and retreated as above using the acid, DMAP and DIC. Washing and drying of the resin as before yielded the desired ester on resin. Product formation was confirmed by weight gain of the resin, IR and ^{13}C NMR.

General method (6) - Cesium Salt formation



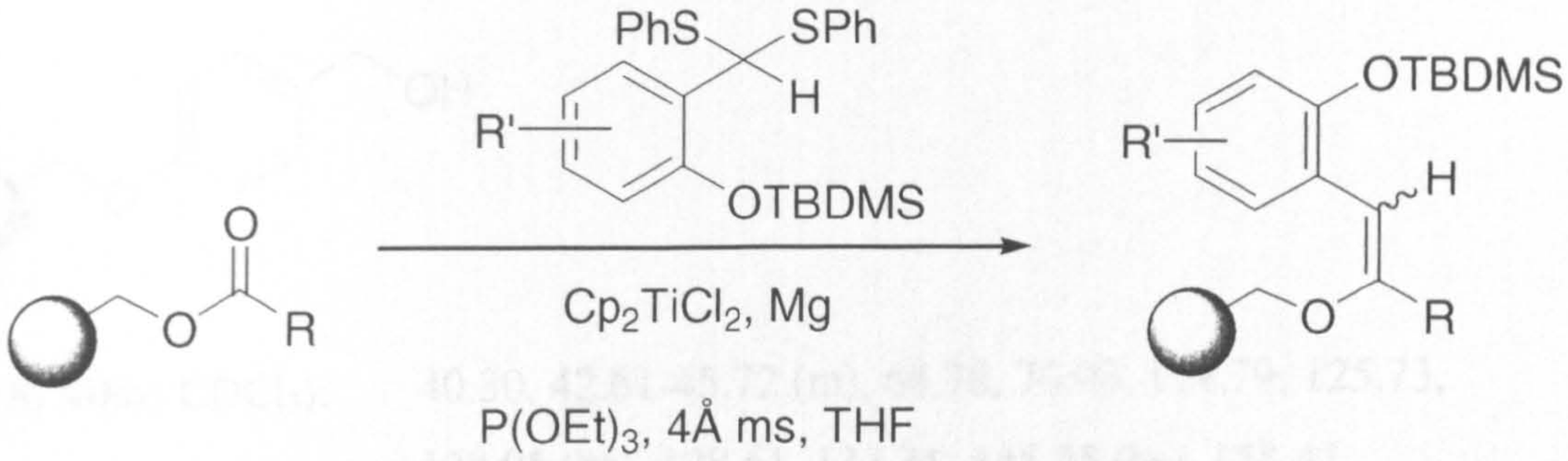
The acid was dissolved in methanol and saturated aqueous cesium bicarbonate was added drop-wise until neutral pH. The solvent was removed under reduced pressure and the residue taken up in toluene to remove the aqueous methanol. Solvent removal gave the salt as a solid that was dried in a dessicator over P_2O_5.

General method (7) - Formation of esters - Merrifield resin



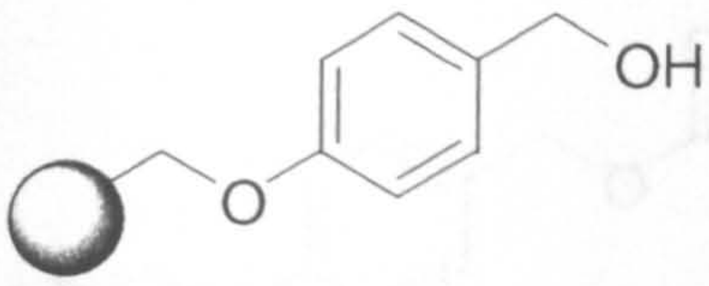
To Merrifield resin (1 eq., weighed in kans) swollen in DMF (concentration *ca* 0.02. mol L^{-1} with respect to the resin) at 50 °C was added the cesium salt of the appropriate acid (1.55 eq.) and the mixture stirred overnight. The DMF was removed and the kans washed with DMF (2×30 cm^3), water (30 cm^3), alternating methanol then DCM (5×30 cm^3 of each) and finally diethyl ether (30 cm^3). The resin was dried under vacuum. Product formation was confirmed by weight gain of the resin and IR and ^{13}C NMR.

General method (8) - Modified Takeda alkylidenation - solid-phase



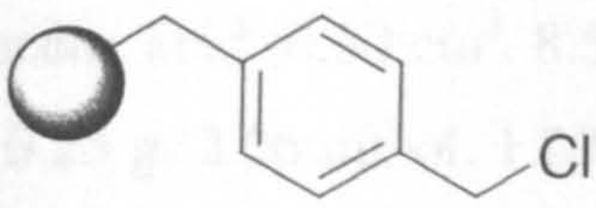
The alkylidenation was carried out on solid phase using a modified version of Takeda's method.[89] Titanocene dichloride (22.0 eq.), magnesium (29.0 eq.) and 4Å molecular sieves (2 g/mmol of ester) were stirred at room temperature under an argon atmosphere. The reagents were heated briefly under vacuum after which triethylphosphite (40.0 eq.) and THF (concentration *ca* 1.1. mol L^{-1} with respect to titanocene dichloride) were added. Heat was evolved and the reaction mixture turned from red to green to black. After stirring for 3.5 h, a THF solution (concentration *ca* 1. mol L^{-1} with respect to the thioacetal) of the *tert*-butyldimethylsilyloxybenzaldehyde diphenyldithioacetal (5.00 eq.) was added and mixture stirred for a further 15 mins. The reaction mixture was syringed into a flask containing the resin-bound ester (1.0 eq., swollen in THF; concentration *ca* 0.15 mol L^{-1} with respect to titanocene dichloride) in kans and stirred under an argon atmosphere overnight. The THF was removed and the kans washed with THF, alternating methanol then DCM (5×30 cm^3 of each), methanol (30 cm^3) and finally diethyl ether (30 cm^3). The resin was dried under vacuum to give the resin-bound enol ether on resin. Product formation was confirmed by IR and ^{13}C NMR.

Wang Resin



δ_C (90 MHz; $CDCl_3$): 40.30, 42.61-45.72 (m), 64.78, 70.03, 114.79, 125.73, 128.05 (bs), 128.61, 133.31, 145.75 (bs), 158.42.

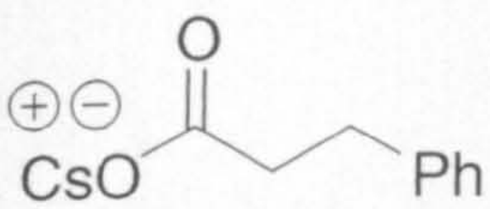
Merrifield Resin



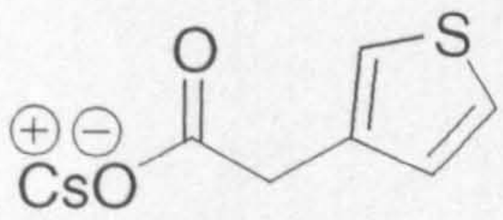
δ_C (90 MHz; $CDCl_3$): 40.32 (bs), 42.42 (bs), 43.81 (bs), 67.91, 125.69 (bs), 127.99 (bs), 145.86 (bs).

Cesium Salts

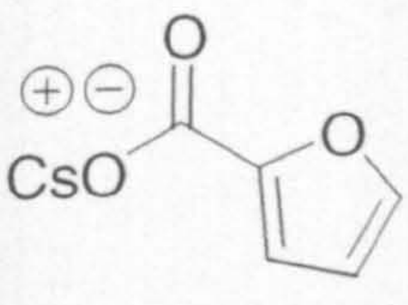
The cesium salts were formed using *general method (6)*.



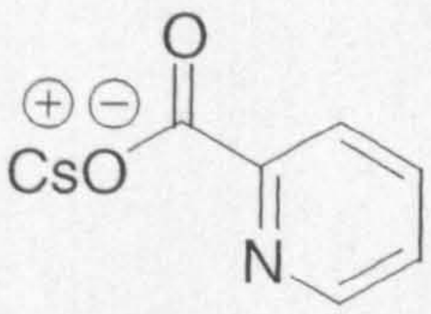
m.p. >280 °C



m.p. 117-119 °C

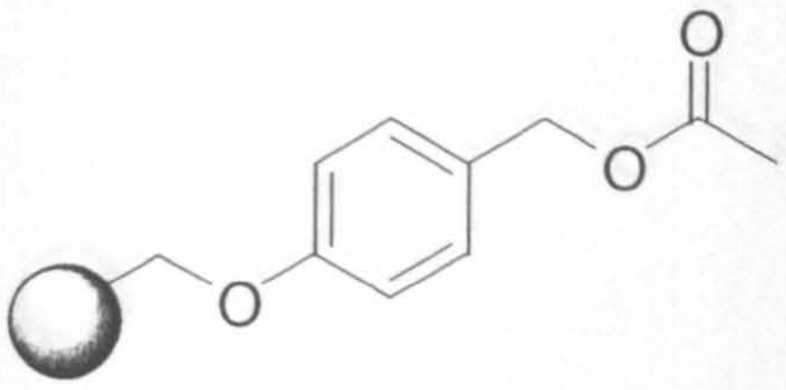


m.p. 96-100 °C



m.p. 118-122 °C

Wang-bound acetic acid 191a

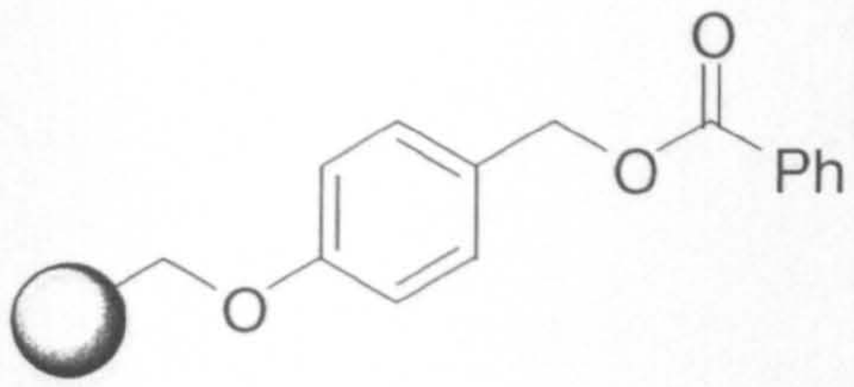


Following *general method (5)*, **191a** was prepared using Wang resin (6 kans, each containing 168 mg resin, loading 1.7 mmol/g, 0.29 mmol/kan, 1.71 mmol), acetic acid (0.50 cm^3, 8.5mmol, 5.0 eq.), DIC (1.30 cm^3, 8.30 mmol, 4.84 eq.) and DMAP (0.26 g, 2.13 mmol 1.24 eq.) in THF (100 cm^3) (reaction time 20 h). The kans were retreated using acetic acid (0.50 cm^3, 8.5 mmol, 5.0 eq.), DIC (1.30 cm^3, 8.30 mmol, 4.84 eq.) and DMAP (0.25 g, 2.06 mmol, 1.20 eq.) in THF (100 cm^3) (reaction time 19 h). Washing and drying of the kans yielded the resin-bound ester **191a.**

δ_C (90 MHz; $CDCl_3$): 20.91 (CH_3), 40.17 (Wang), 42.27-43.28 (m, Wang), 65.93 (CH_2O), 69.87 (Wang), 114.63 (Wang), 125.56, 127.90 (bs), 129.97 (bs), 145.28 (bs), 159, 170.66 (C=O)

ν_{max} (Golden gate)/cm^{-1}: 1736 (C=O), 1219 (CH_2O).

Wang-bound benzoic acid 191b

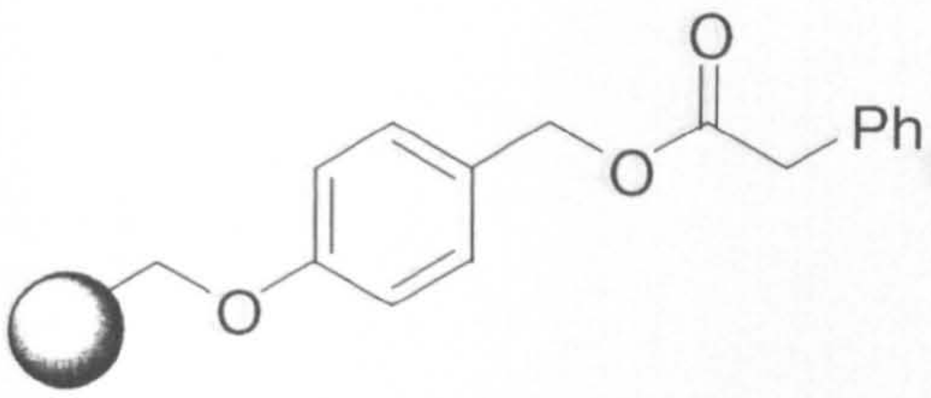


Following *general method (5)*, **191b** was prepared using Wang resin (3 kans, each containing 168 mg resin, loading 1.7 mmol/g, 0.29 mmol/kan, 0.86 mmol), benzoic acid (0.64 g, 5.2 mmol, 6.12 eq.), DIC (0.70 cm^3, 4.4 mmol, 5.1 eq.) and DMAP (0.12 g, 0.96 mmol, 1.12 eq.) in THF (50 cm^3) (reaction time 5 h). The kans were retreated using benzoic acid (0.69 g, 5.7 mmol, 6.6 eq.), DIC (0.70 cm^3, 4.4 mmol, 5.1 eq.) and DMAP (0.13 g, 1.2 mmol, 1.4 eq.) in THF (50 cm^3) (reaction time 15 h). Washing and drying of the kans yielded the resin-bound ester **191b**.

δ_C (90 MHz; $CDCl_3$): 40.65 (Wang), 42.81-46.17 (m, Wang), 66.76 (CH_2O), 70.22 (Wang), 115.05 (Wang), 125.94, 128.58 (bs), 129.95 (bs), 130.30 (bs), 132.18 (bs), 145.66 (bs), 159.19, 166.72 (C=O)

ν_{max} (Golden gate)/cm^{-1}: 1716 (C=O).

Wang-bound phenylacetic acid 191c

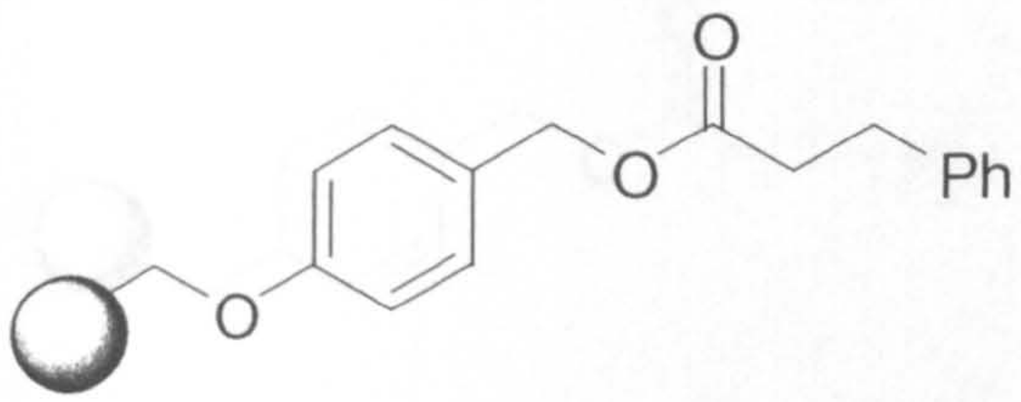


Following *general method (5)*, **191c** was prepared using Wang resin (4 kans, each containing 168 mg resin, loading 1.7 mmol/g, 0.29 mmol/kan, 1.14 mmol), phenylacetic acid 1.20 g, 8.82 mmol, 7.60 eq.), DIC (0.90 cm^3, 5.8 mmol, 5.1 eq.) and DMAP (0.16 g, 1.3 mmol, 1.2 eq.) in THF (50 cm^3) (reaction time 19 h). The kans were retreated using phenylacetic acid (1.17 g, 8.60 mmol, 7.5 eq.), DIC (0.90 cm^3, 5.8 mmol, 5.1 eq.) and DMAP (0.15 g, 1.23mmol, 1.08 eq.) in THF (50 cm^3) (reaction time 15 h). Washing and drying of the kans yielded the resin-bound ester **191c**.

δ_C (90 MHz; $CDCl_3$): 40.35 (Wang), 41.33 (CH_2), 42.37-45.87 (m, Wang), 66.43 (CH_2O), 70.00 (Wang), 114.75 (Wang), 127.08, 128.09 (bs), 128.55 (bs), 129.29, 130.03, 133.95, 145.39 (bs), 158.96, 171.44 (C=O)

ν_{max} (Golden gate)/cm^{-1}: 1732 (C=O), 1215 (CH_2O).

Wang-bound hydrocinnamic acid 191d

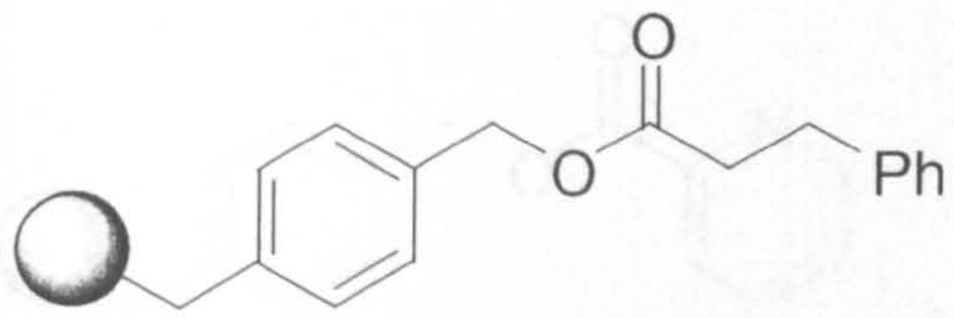


Following *general method (5)*, **191d** was prepared using Wang resin (12 kans, each containing 168 mg resin, loading 1.7 mmol/g, 0.29 mmol/kan, 3.43 mmol), hydrocinnamic acid (3.29 g, 21.9 mmol, 6.93 eq.), DIC (2.70 cm^3, 17.2 mmol, 5.03 eq.) and DMAP (0.47 g, 3.85 mmol, 1.12 eq.) in THF (100 cm^3) (reaction time 24 h). The kans were retreated using hydrocinnamic acid (3.23 g, 21.5 mmol, 6.28 eq.), DIC (2.70 cm^3, 17.2 mmol, 5.03 eq.) and DMAP (0.48 g, 3.93 mmol, 1.14 eq.) in THF (100 cm^3) (reaction time 18 h). Washing and drying of the kans yielded the resin-bound ester **191d**.

δ_C (90 MHz; $CDCl_3$): 30.90 (CH_2), 35.88 (CH_2), 40.38 (Wang), 41.70-44.25 (m,Wang), 66.05 (CH_2O), 69.99 (Wang), 114.71 (Wang), 126.23, 128.28 (bs), 128.46, 130.06, 140.38, 145.49-146.03 (m), 158.95, 172.6 (C=O)

ν_{max} (Golden gate)/cm^{-1}: 1732 (C=O), 1219 (CH_2O).

Merrifield-bound hydrocinnamic acid 192a

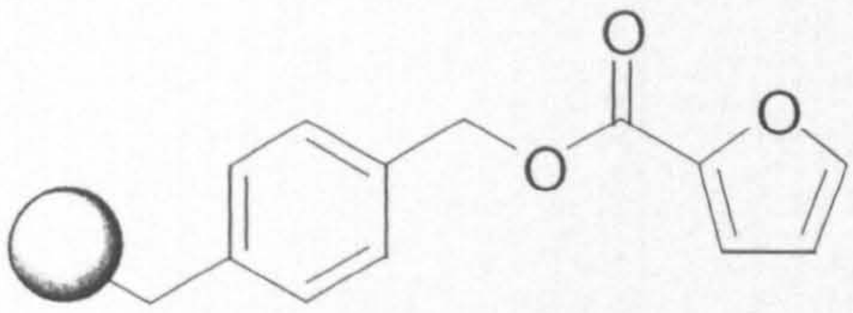


Following *general method (7)*, **192a** was prepared using Merrifield resin (3 kans, each containing 168 mg resin, loading 1.7 mmol/g, 0.29 mmol/kan, 0.86 mmol) and cesium hydrocinnamate (0.44 g, 1.3 mmol, 1.57 eq.) in DMF (50 cm^3) (reaction time 18 h). Washing and drying of the kans yielded the resin-bound ester **192a**.

δ_C (90 MHz; $CDCl_3$): 30.89 (CH_2), 35.84 (CH_2), 40.30 (Merrifield), 42.23-43.61 (m Merrifield), 66.24 (CH_2O), 126.24, 128.27-128.48 (m), 140.37, 145.18, 172.58 (C=O)

ν_{max} (Golden gate)/cm^{-1}: 1732 (C=O).

Merrifield-bound 2-furoic acid 192b

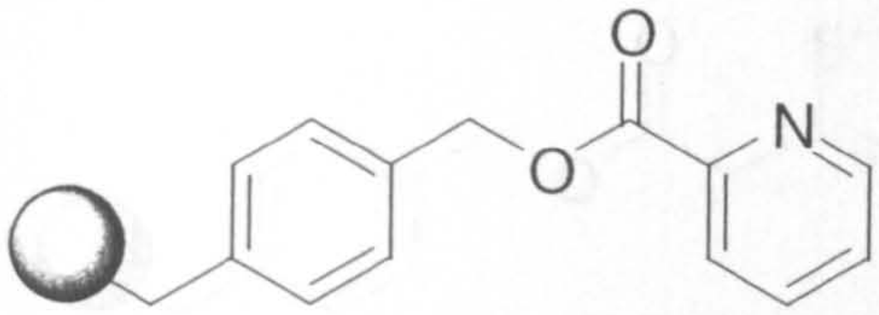


Following *general method (7)*, **192b** was prepared using Merrifield resin (3 kans, each containing 168 mg resin, loading 1.7 mmol/g, 0.29 mmol/kan, 0.86 mmol) and cesium 2-furoate (0.60 g, 2.5 mmol, 2.9 eq.) in DMF (50 cm^3) (reaction time 17 h). Washing and drying of the kans yielded the resin-bound ester **192b**.

δ_C (90 MHz; $CDCl_3$): 40.33 (Merrifield), 42.15-46.32 (m, Merrifield), 66.42 (CH_2O), 111.83, 118.05, 125.70, 128.02 (bs), 144.59-145.76 (m), 146.37, 158.56 (C=O)

ν_{max} (Golden gate)/cm^{-1}: 1716 (C=O), 1290 (=C-O-C stretch), 1111 (=C-O-C stretch).

Merrifield-bound picolinic acid 192c

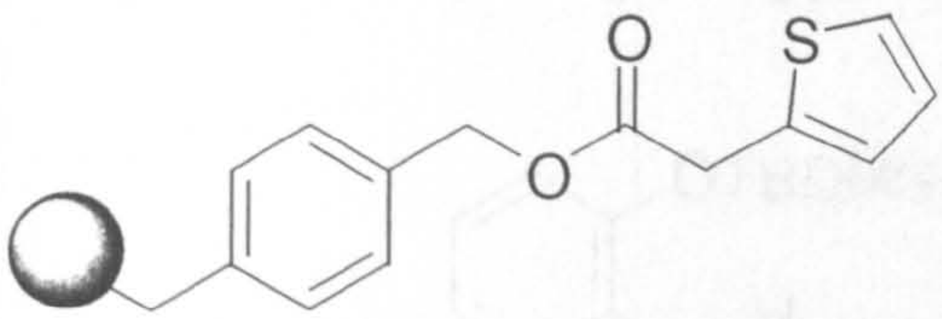


Following *general method (7)*, **192c** was prepared using Merrifield resin (3 kans, each containing 168 mg resin, loading 1.7 mmol/g, 0.29 mmol/kan, 0.86 mmol) and cesium 2-picolinate (0.40 g, 1.6 mmol, 5.5eq.) in DMF (50 cm^3) (reaction time 25 h). Washing and drying of the kans yielded the resin-bound ester **192c**.

δ_C (90 MHz; $CDCl_3$): 40.34 (Merrifield), 42.45-43.91 (m, Merrifield), 46.33 (Merrifield), 67.39 (CH_2O) 125.14, 125.67, 127.90, 136.90, 145.20-145.64 (m), 149.89 ,(no carbonyl peak was discernible)

ν_{max} (Golden gate)/cm^{-1}: 1722 (C=O), 1678 (C=N).

Merrifield-bound 2-thiophenacetic acid 192d

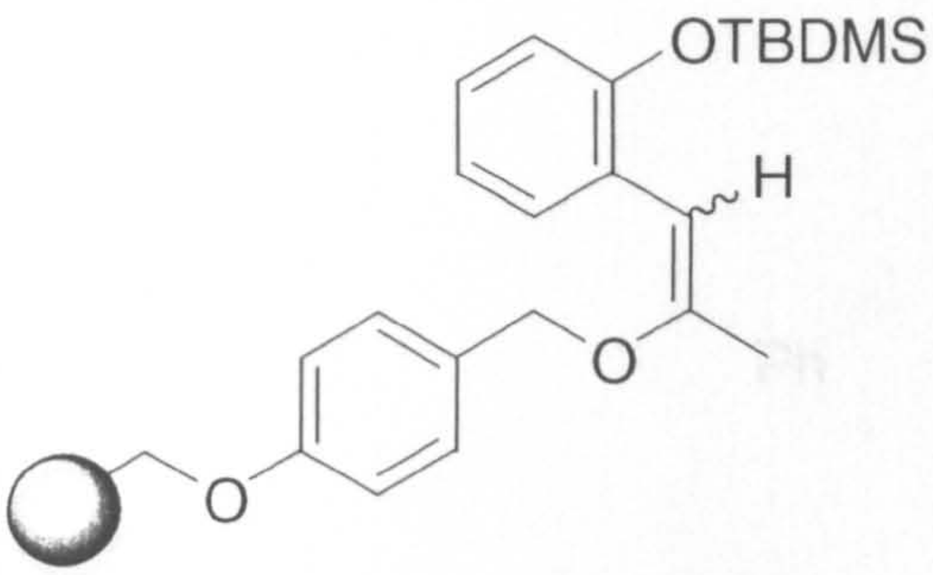


Following *general method (7)*, **192d** was prepared using Merrifield resin (3 kans, each containing 168 mg resin, loading 1.7 mmol/g, 0.29 mmol/kan, 0.86 mmol) and cesium 2-thiopheneacetate (0.39 g, 1.43 mmol, 1.67 eq.) in DMF (50 cm^3) (reaction time 18 h). Washing and drying of the kans yielded the resin-bound ester **192d**.

δ_C (90 MHz; $CDCl_3$): 35.16 (CH_2), 40.34 (Merrifield), 41.90-46.28 (m, Merrifield), 66.86 (CH_2O),125.06-132.78 (m), 145.18-146.91 (m), 170.26 (C=O)

ν_{max} (Golden gate)/cm^{-1}: 1738 (C=O).

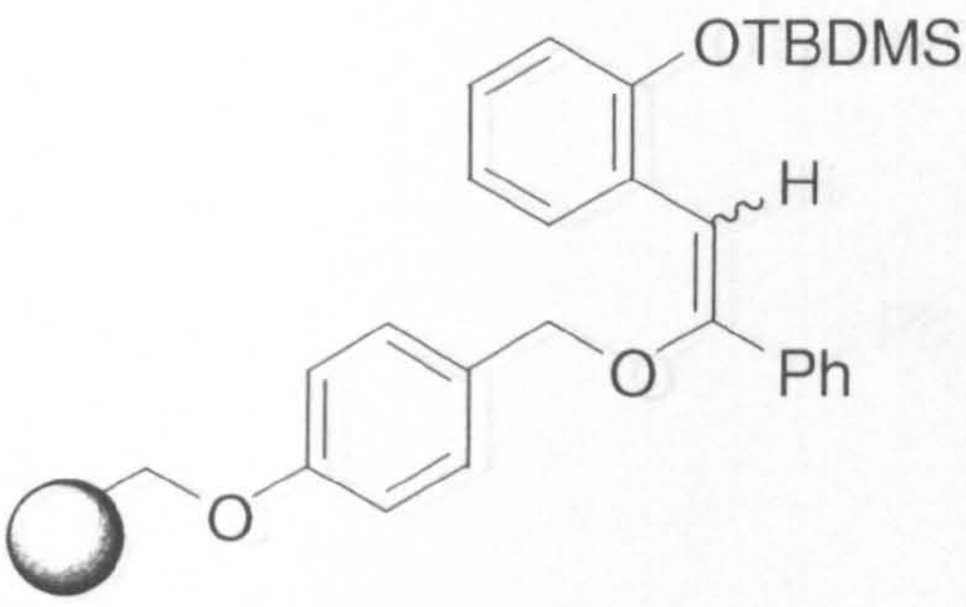
1-Wang-oxy-1-methyl-2-[2'-(*tert*-butyldimethylsilyloxy)phenyl]propene 194a



Following *general method (8)*, **194a** was prepared using 2-*tert*-butyldimethylsilyloxybenzaldehyde diphenyldithioacetal (**170**, 1.40 g, 3.20 mmol, 5.60 eq. in 4 cm^3 THF) that was added to a mixture of titanocene dichloride (2.84 g, 11.4 mmol, 20.0 eq.), magnesium (0.42 g, 17.3 mmol, 30.3 eq.), 4Å molecular sieves (1.10 g) and triethylphosphite (4.0 cm^3, 23 mmol, 41 eq.) in THF (10 cm^3). The mixture was added to the resin-bound ester (**191a**, Wang resin, 2 kans, each containing 0.29 mmol/kan, 0.571 mmol in 4 cm^3 THF) and stirred under an argon atmosphere (reaction time 20 h). Washing and drying of the kans yielded the resin-bound enol ether **194a**.

δ_C (90 MHz; $CDCl_3$):	-4.19 (CH_3), 18.35 (C of *t*-Bu), 19.92 (CH_3), 25.89 (CH_3 of *t*-Bu), 40.40 (bs, Wang), 64.91 (CH_2O), 69.40 (Wang), 114.75 (Wang), 118.92, 121.16, 126.09, 127.95, 128.61, 128.76, 129.63, 145.33
ν_{max} (Golden gate)/cm^{-1}:	1651 (C=C), 1246 (SiMe), 914 (SiO).

1-Wang-oxy-1-phenyl-2-[2'-(*tert*-butyldimethylsilyloxy)phenyl]ethene 194b

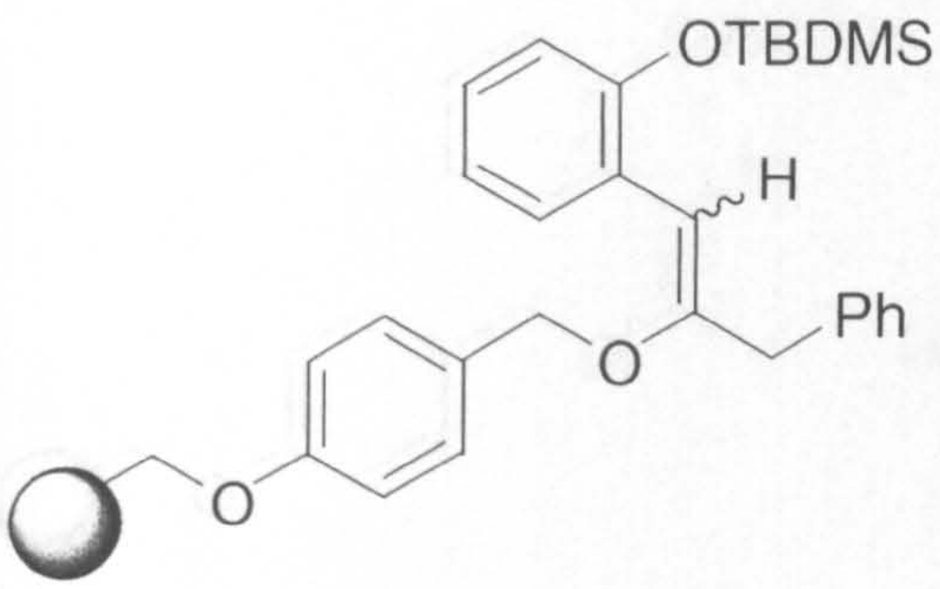


Following *general method (8)*, **194b** was prepared using *tert*-butyldimethylsilyloxybenzaldehyde diphenyldithioacetal (**170**, 1.97 g, 4.50 mmol, 5.25 eq. in 5 cm^3 THF) that was added to a mixture of titanocene dichloride (4.28 g, 17.2mmol, 20.1 eq.), magnesium (0.66 g, 27 mmol, 32 eq.), 4Å molecular sieves (1.83 g) and triethylphosphite (6.0 cm^3, 35 mmol, 41 eq.) in THF (15 cm^3). The mixture was added to the resin-bound ester (**191b**, Wang resin, 3 kans, each containing 0.29 mmol/kan, 0.86 mmol in 5 cm^3 THF) and stirred under an argon atmosphere (reaction time 24 h). Washing and drying of the kans yielded the resin-bound enol ether **194b**. (The IR suggested that a residual amount of ester remained attached to the resin)

δ_C (90 MHz; $CDCl_3$): -4.19 (CH_3), 18.27 (C of *t*-Bu), 25.83 (CH_3 of *t*-Bu), 40.39 (Wang), 66.53, 69.98 (Wang), 71.82 (CH_2O), 114.79 (Wang), 119.03, 121.23, 126.23, 128.31, 129.65, 130.04, 132.91, 134.54, 135.40, 137.17, 128.53 (bs), 128.49 (bs)

ν_{max} (Golden gate)/cm^{-1}: 1716 (C=O), 1246 (SiMe), 918 (SiO).

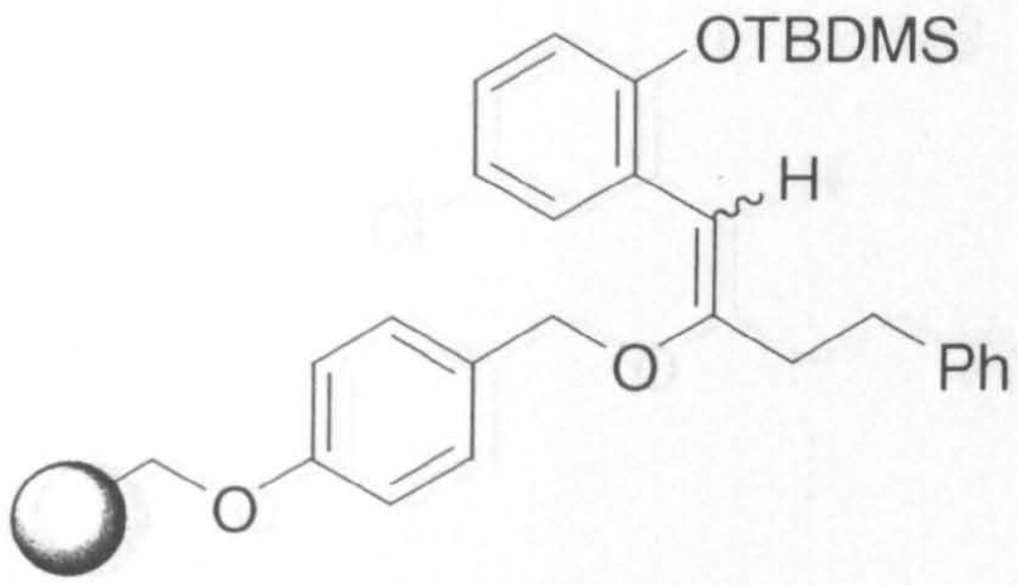
1-Wang-oxy-1-benzyl-2-[2'-(*tert*-butyldimethylsilyloxy)phenyl]ethene 194c



Following *general method (8)*, **194c** was prepared using 2-*tert*-butyldimethylsilyloxybenzaldehyde diphenyldithioacetal (**170**, 1.90 g, 4.34 mmol, 5.06 eq. in 2 cm^3 THF) that was added to titanocene dichloride (4.43 g, 17.79 mmol, 20.76 eq.), magnesium (0.66 g, 27 mmol, 32 eq.), 4Å molecular sieves (1.79 g) and triethylphosphite (6.0 cm^3, 35 mmol, 41 eq.) in THF (15 cm^3). The mixture was added to the resin-bound ester (**191c**, Wang resin, 3 kans, each containing 0.29 mmol/kan, 0.86 mmol in 4 cm^3 THF) and stirred under an argon atmosphere (reaction time 23 h). Washing and drying of the kans yielded the resin-bound enol ether **194c**.

δ_C (90 MHz; $CDCl_3$):	-4.21 (CH_3), 18.22 (C of *t*-Bu), 25.81 (CH_3 of *t*-Bu), 40.59 (Wang), 41.26 (CH_2), 64.78 (CH_2O), 70.00 (Wang), 114.72 (Wang), 118.82, 128.53 (bs), 128.49 (bs)
ν_{max} (Golden gate)/cm^{-1}:	1651 (C=C), 1246 (SiMe), 918 (SiO).

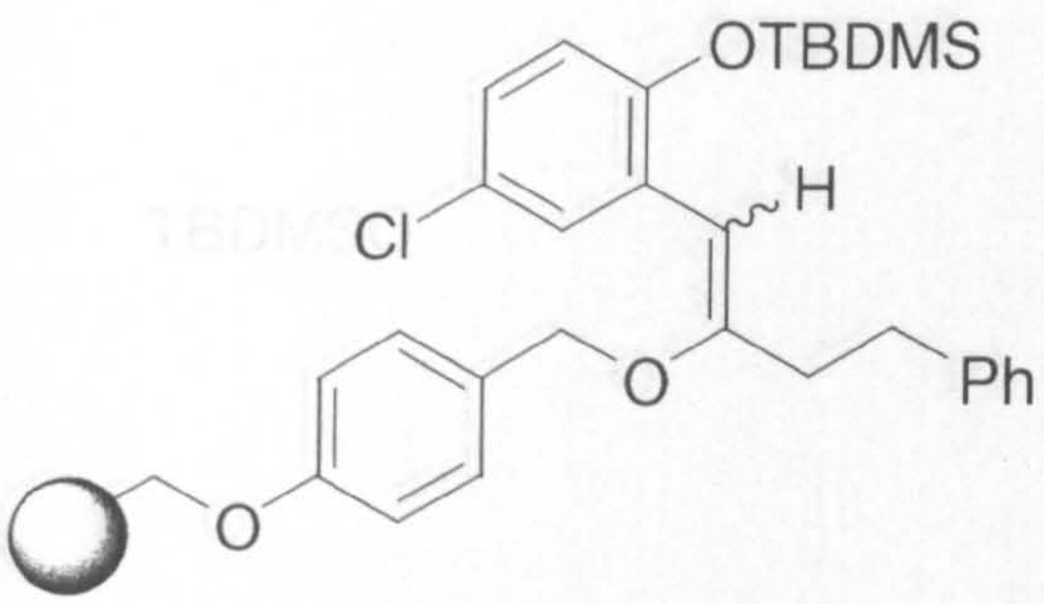
1-Wang-oxy-1-(2'-phenyl)ethane-2-[2''-(*tert*-butyldimethylsilyloxy)phenyl]ethene 194d



Following *general method (8)*, **194d** was prepared using 2-*tert*-butyldimethylsilyloxybenzaldehyde diphenyldithioacetal (**170**, 1.95 g, 4.45 mmol, 5.19 eq. in 4 cm^3 THF) that was added to titanocene dichloride (4.33 g, 17.39 mmol, 20.29 eq.), magnesium (0.65 g, 26.75 mmol, 31.21 eq.), 4Å molecular sieves (1.84 g) and triethylphosphite (6.0 cm^3, 35 mmol, 41 eq.) in THF (15 cm^3). The mixture was added to the resin-bound ester (**191d**, Wang resin, 3 kans, each containing 0.29 mmol/kan, 0.86 mmol in 6 cm^3 THF) and stirred under an argon atmosphere (reaction time 19 h). Washing and drying of the kans yielded the resin-bound enol ether **194d**.

δ_C (90 MHz; $CDCl_3$):	-4.20 (CH_3), 18.25 (C of *t*-Bu), 25.82 (CH_3 of *t*-Bu), 30.87 (CH_2), 35.88 (CH_2), 40.32 (Wang), 66.04 (CH_2O), 70.00 (Wang), 114.68 (Wang), 118.91, 121.09, 126.18, 126.63, 128.30, 128.38, 129.16, 130.03
ν_{max} (Golden gate)/cm^{-1}:	1651 (C=C), 1246 (SiMe), 918 (SiO).

1-Wang-oxy-1-(2'-phenyl)ethane-2-[2''-(*tert*-butyldimethylsilyloxy)-5''chlorophenyl]ethene 194e

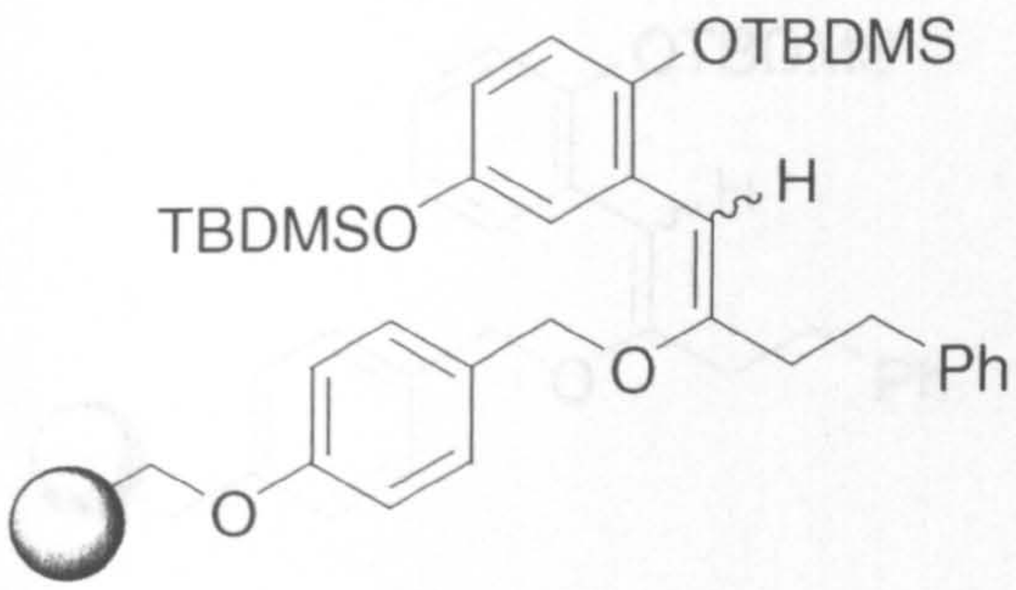


Following *general method (8)*, **194e** was prepared using 2-*tert*-butyldimethylsilyloxy-5-chlorobenzaldehyde diphenyldithioacetal (**178**, 2.15 g, 4.55 mmol, 5.31 eq. in 6 cm^3 THF) that was added to titanocene dichloride (4.36 g, 17.5 mmol, 20.4 eq.), magnesium (0.60 g, 25 mmol, 29 eq.), 4Å molecular sieves (1.66 g) and triethylphosphite (6.0 cm^3, 35 mmol, 41 eq.) in THF (15 cm^3). The mixture was added to the resin-bound ester (**191d**, Wang resin, 3 kans, each containing 0.29 mmol/kan, 0.86 mmol in 6 cm^3 THF) and stirred under an argon atmosphere (reaction time 25 h). Washing and drying of the kans yielded the resin-bound enol ether **194e**.

δ_C (90 MHz; $CDCl_3$): -4.30 (CH_3), 18.23 (C of *t*-Bu), 25.76 (CH_3 of *t*-Bu), 34.15 (CH_2), 35.53 (CH_2), 40.35 (bs, Wang), 44.24 (Wang), 64.82 (CH_2O), 70.00 (Wang), 114.76 (Wang), 119.89, 126.12, 126.65, 128.33 (bs), 129.41, 133.41

ν_{max} (Golden gate)/cm^{-1}: 1242 (SiMe), 900 (SiO).

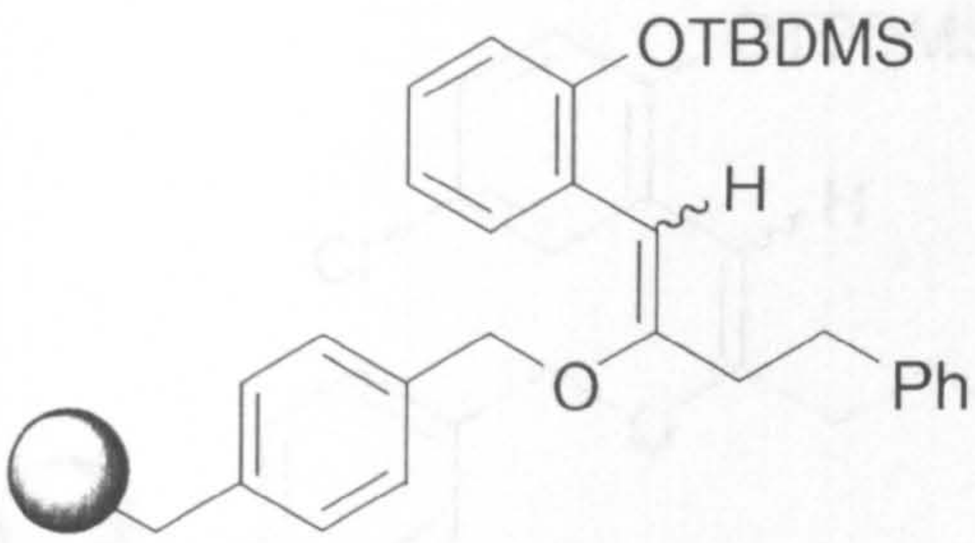
1-Wang-oxy-1-(2'-phenyl)ethane-2-[2'',5''(di*tert*-butyldimethylsilyloxy)phenyl]ethene 194f



Following *general method (8)*, **194f** was prepared using 2,5-di*tert*-butyldimethylsilyloxybenzaldehyde diphenyldithioacetal (**174**, 2.56 g, 4.51 mmol, 5.26 eq. in 5 cm^3 THF) that was added to titanocene dichloride (4.36 g, 17.5 mmol, 20.4 eq.), magnesium (0.66 g, 27 mmol, 32 eq.), 4Å molecular sieves (1.88 g) and triethylphosphite (6.0 cm^3, 35 mmol, 41 eq.) in THF (15 cm^3). The mixture was added to the resin-bound ester (**191d**, Wang resin, 3 kans, each containing 0.29 mmol/kan, 0.86 mmol in 7 cm^3 THF) and stirred under an argon atmosphere (reaction time 16 h). Washing and drying of the kans yielded the resin-bound enol ether **194f**.

δ_C (90 MHz; $CDCl_3$):	-4.53 (CH_3), -4.27 (CH_3), 18.11 (C of *t*-Bu), 18.23 (C of *t*-Bu), 25.75 (CH_3 of *t*-Bu), 25.85 (CH_3 of *t*-Bu), 34.29 (CH_2), 35.86 (CH_2), 40.34 (bs, Wang), 64.88 (CH_2O), 69.83 (Wang), 114.64 (Wang), 119.14, 120.61, 128.33, 128.40, 129.16
ν_{max} (Golden gate)/cm^{-1}:	1647 (C=C), 1252 (SiMe), 910 (SiO).

1-Merrifield-oxy-1-(2'-phenyl)ethane-2-[2''-(*tert*-butyldimethylsilyloxy)phenyl]ethene 195a

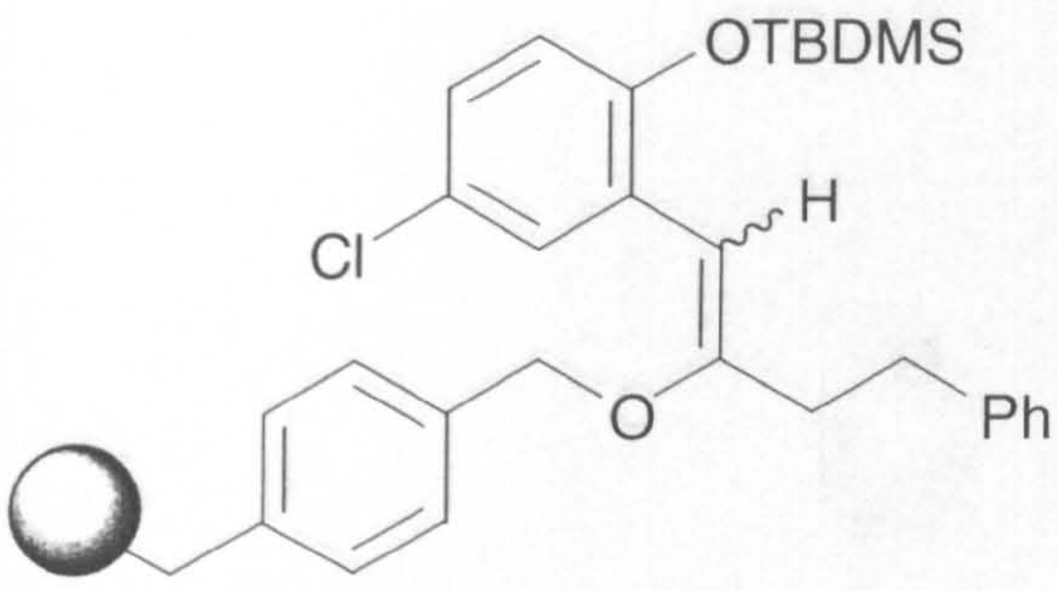


Following *general method (8)*, **195a** was prepared using *tert*-butyldimethylsilyloxybenzaldehyde diphenyldithioacetal (**170**, 1.92 g, 4.38 mmol, 5.11 eq. in 5 cm^3 THF) that was added to a mixture of titanocene dichloride (4.32 g, 17.3 mmol, 20.2 eq.), magnesium (0.72 g, 30 mmol, 35 eq.), 4Å molecular sieves (1.89 g) and triethylphosphite (6.0 cm^3, 35 mmol, 41 eq.) in THF (15 cm^3). The mixture was added to the resin-bound ester (**192a**, Merrifield resin, 3 kans, each containing 0.29 mmol/kan, 0.86 mmol in 5 cm^3 THF) and stirred under an argon atmosphere (reaction time 31 h). Washing and drying of the kans yielded the resin-bound enol ether **195a**.

δ_C (90 MHz; $CDCl_3$): -4.18 (CH_3), 18.27 (C of *t*-Bu), 25.85 (CH_3 of *t*-Bu), 34.27 (CH_2), 35.84 (CH_2), 40.32 (Merrifield), 42.55-45.88 (bs, Merrifield), 65.19 (CH_2O), 70.28, 118.90, 121.10, 126.00, 126.63, 128.32, 129.89

ν_{max} (Golden gate)/cm^{-1}: 1651 (C=C), 1250 (SiMe).

1-Merrifield-oxy-1-(2'-phenyl)ethane-2-[2''-(*tert*-butyldimethylsilyloxy)-5''chlorophenyl]ethene 195b

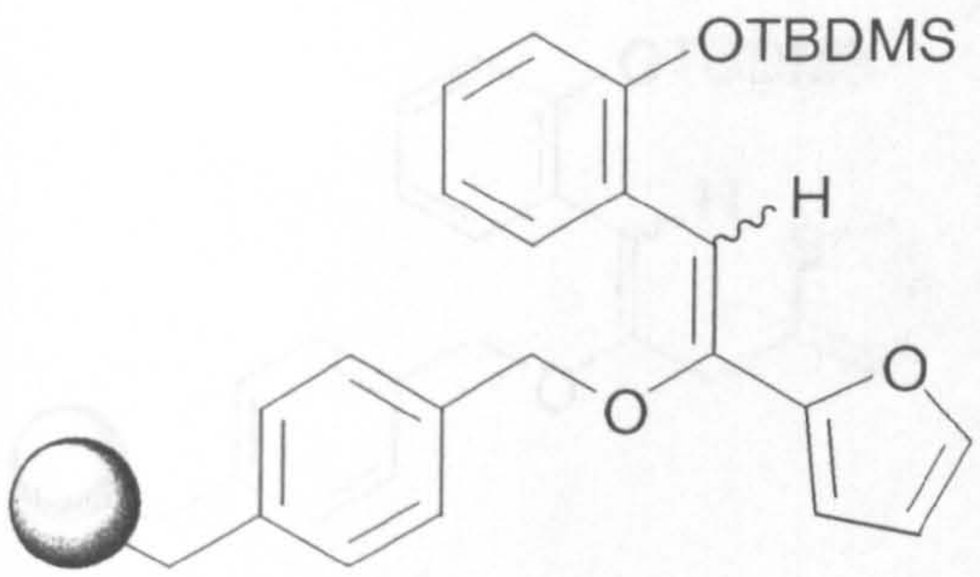


Following *general method (8)*, **195b** was prepared using 5-chloro-2-*tert*-butyldimethylsilyloxybenzaldehyde diphenyldithioacetal (**178**, 1.93 g, 4.08 mmol, 4.26 eq. in 5 cm^3 THF) that was added to titanocene dichloride (5.16 g, 20.7 mmol, 21.6 eq.), magnesium (0.84 g, 34 mmol, 36 eq.), 4Å molecular sieves (1.70 g) and triethylphosphite (6.0 cm^3, 35 mmol, 36 eq.) in THF (10 cm^3). The mixture was added to the resin-bound ester (**192a**, Merrifield resin, 2 kans, one containing 0.29 mmol/kan and the other containing 0.67 mmol/kan, 0.96 mmol in 5 cm^3 THF) and stirred under an argon atmosphere (reaction time 22 h). Washing and drying of the kans yielded the resin-bound enol ether **195b**.

δ_C (90 MHz; $CDCl_3$): -4.28 (CH_3), 18.22 (C of *t*-Bu), 25.77 (CH_3 of *t*-Bu), 34.19 (CH_2), 35.49 (CH_2), 40.31 (bs, Merrifield), 41.57-45.61 (m, Merrifield), 65.10 (CH_2O), 119.99, 126.11, 128.28 (bs)

ν_{max} (Golden gate)/cm^{-1}: *ca* 1630 (C=C)

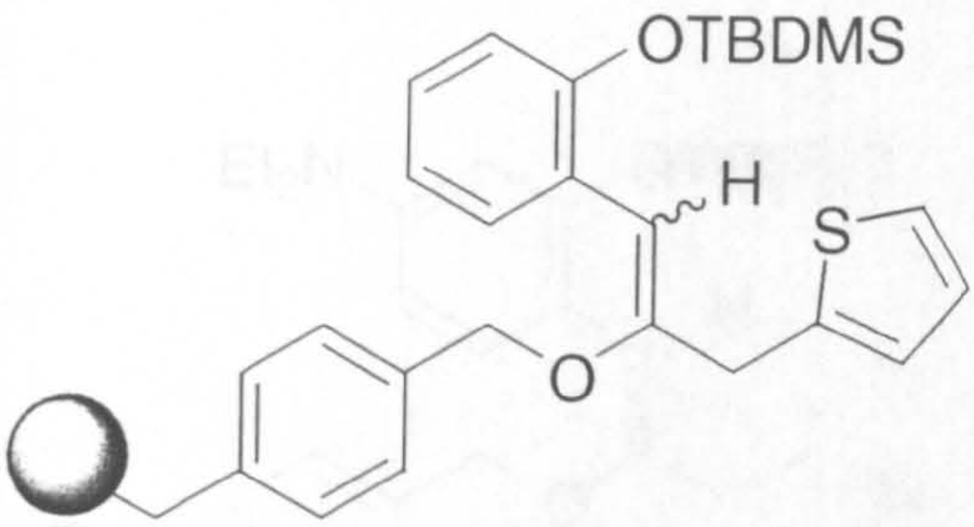
1-Merrifield-oxy-1-(2'-furoyl)ethane-2-[2''-(*tert*-butyldimethylsilyloxy)phenyl]ethene 195c



Following *general method (8)*, **195c** was prepared using *tert*-butyldimethylsilyloxybenzaldehyde diphenyldithioacetal (**170**, 2.04 g, 4.66 mmol, 5.44 eq. in 5 cm^3 THF) which was added to a mixture of titanocene dichloride (4.28 g, 17.2 mmol, 20.1 eq.), magnesium (0.60 g, 25 mmol, 29 eq.), 4Å molecular sieves (1.91 g) and triethylphosphite (6.0 cm^3, 35 mmol, 41 eq. in THF (10 cm^3). The mixture was added to the resin-bound ester (**192b**, Merrifield resin, 3 kans, each containing 0.29 mmol/kan, 0.86 mmol in 5 cm^3 THF) and stirred under an argon atmosphere (reaction time 16 h). Washing and drying of the kans yielded the resin-bound enol ether **195c**.

δ_C (90 MHz; $CDCl_3$):	-4.22 (CH_3), 18.28 (C of *t*-Bu), 25.83 (CH_3 of *t*-Bu), 40.29 (Merrifield), 41.56-55.57 (bs, Merrifield), 66.45 (CH_2), 73.40 (CH_2), 111.35, 111.77, 117.97, 128.25 (bs), 149.11
ν_{max} (Golden gate)/cm^{-1}:	1252 (SiMe), 908 (SiO).

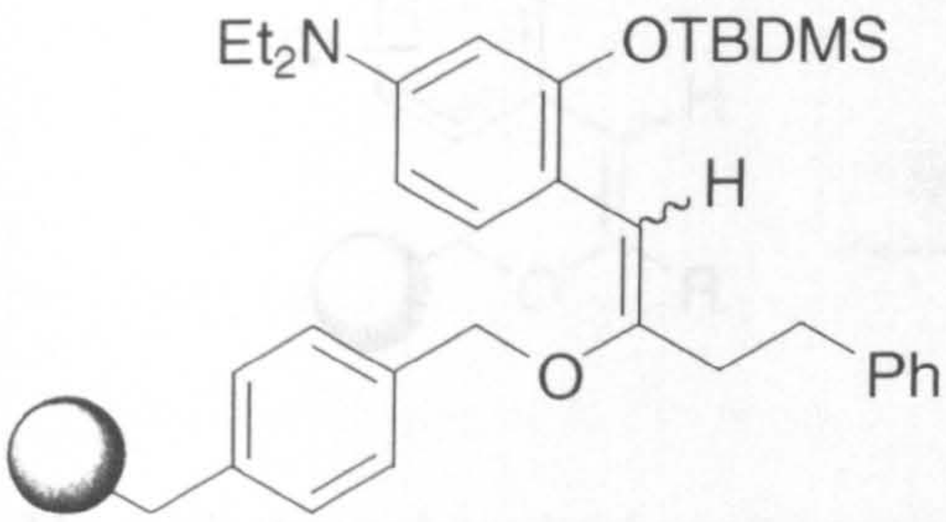
1-Merrifield-oxy-1-(2'-thiopheneacetyl)ethane-2-[2''-(*tert*-butyldimethylsilyloxy)phenyl]ethene 195d



Following *general method (8)*, **195d** was prepared using *tert*-butyldimethylsilyloxybenzaldehyde diphenyldithioacetal (**170**, 2.01 g, 4.59 mmol, 5.36 eq. in 5 cm^3 THF) that was added to a mixture of titanocene dichloride (4.38 g, 17.6 mmol, 20.5 eq.), magnesium (0.67 g, 28 mmol, 32 eq.), 4Å molecular sieves (1.84 g) and triethylphosphite (6.0 cm^3, 35 mmol, 41 eq.) in THF (10 cm^3). The mixture was added to the resin-bound ester (**192d**, Merrifield resin, 3 kans, each containing 0.29 mmol/kan, 0.86 mmol in 5 cm^3 THF) and stirred under an argon atmosphere (reaction time 20 h). Washing and drying of the kans yielded the resin-bound enol ether **195d**. (The sample contained titanium impurities – see **196i**).

δ_C (90 MHz; $CDCl_3$):	-4.09 (CH_3), 18.32 (C of *t*-Bu), 25.93 (CH_3 of *t*-Bu), 33.52 (CH_2), 40.17 (Merrifield), 127.00-137.42
ν_{max} (Golden gate)/cm^{-1}:	1635 (C=C), 920 (SiO).

1-Merrifield-oxy-1-(2'-phenyl)ethane-2-[2''-(*tert*-butyldimethylsilyloxy)-4''(diethylamino)phenyl]ethene 195e



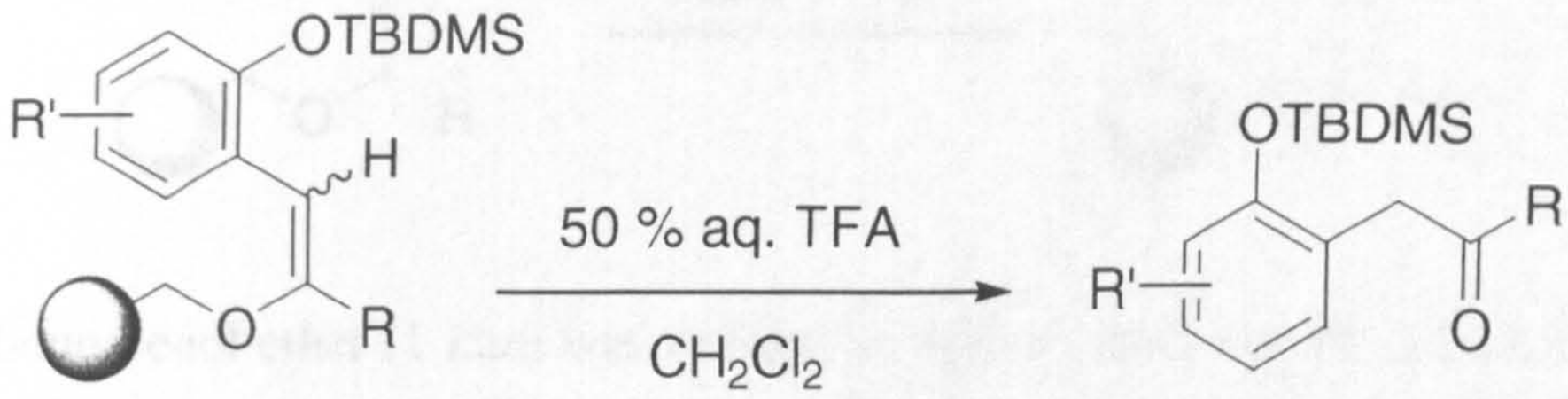
Following *general method (8)*, **195e** was prepared using 2-*tert*-butyldimethylsilyloxy-4-diethylaminobenzaldehyde diphenyldithioacetal (**181**, 2.21 g, 4.34 mmol, 5.06 eq. in 5 cm^3 THF) that was added to a mixture of titanocene dichloride (4.54 g, 18.2 mmol, 21.3 eq.), magnesium (0.67 g, 28 mmol, 32 eq.), 4Å molecular sieves (1.85 g) and triethylphosphite (6.0 cm^3, 35 mmol, 41 eq.) in THF (15 cm^3). The mixture was added to the resin-bound ester (**192a**, Merrifield resin, 3 kans, each containing 0.29 mmol/kan, 0.86 mmol in 5 cm^3 THF) and stirred under an argon atmosphere (reaction time 20 h). Washing and drying of the kans yielded the resin-bound enol ether **195e**.

δ_C (90 MHz; $CDCl_3$): -4.27 (CH_3), 12.71 (NCH_2CH_3), 18.30 (C of *t*-Bu), 25.90 (CH_3 of *t*-Bu), 34.34 (CH_2), 36.13 (CH_2), 40.30 (Merrifield), 41.67-42.34 (bs, Merrifield), 44.36 (NCH_2CH_3), 70.10 (CH_2O), 105.53, 125.82, 128.34, 141.86, 147.03, 152.38, 153.28

ν_{max} (Golden gate)/cm^{-1}: 1604 (C=C), 1209 (SiMe), 980 (SiO).

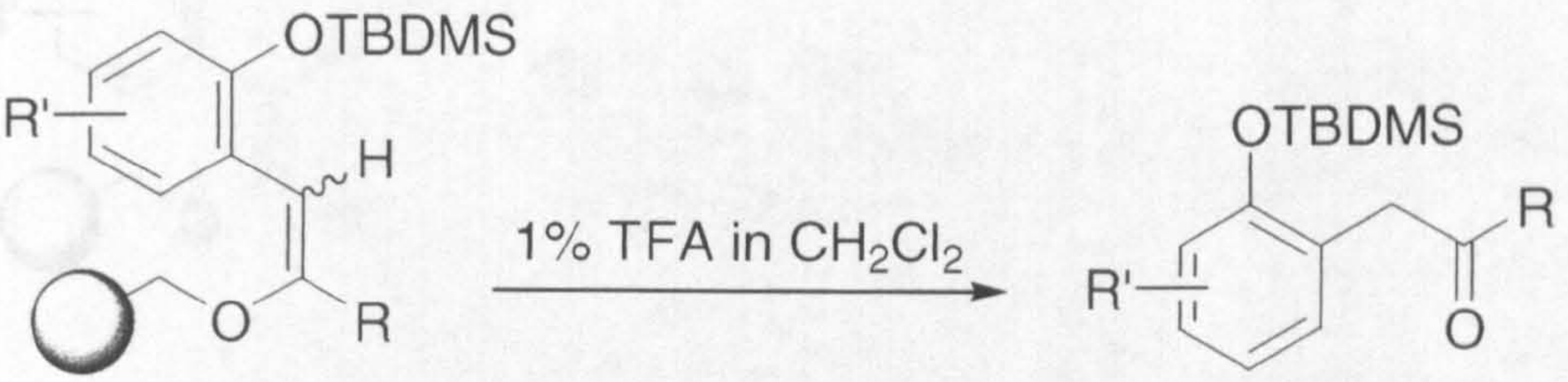
General Procedures - resin cleavage

General Method (9) - Cleavage from resin giving ketones (I)



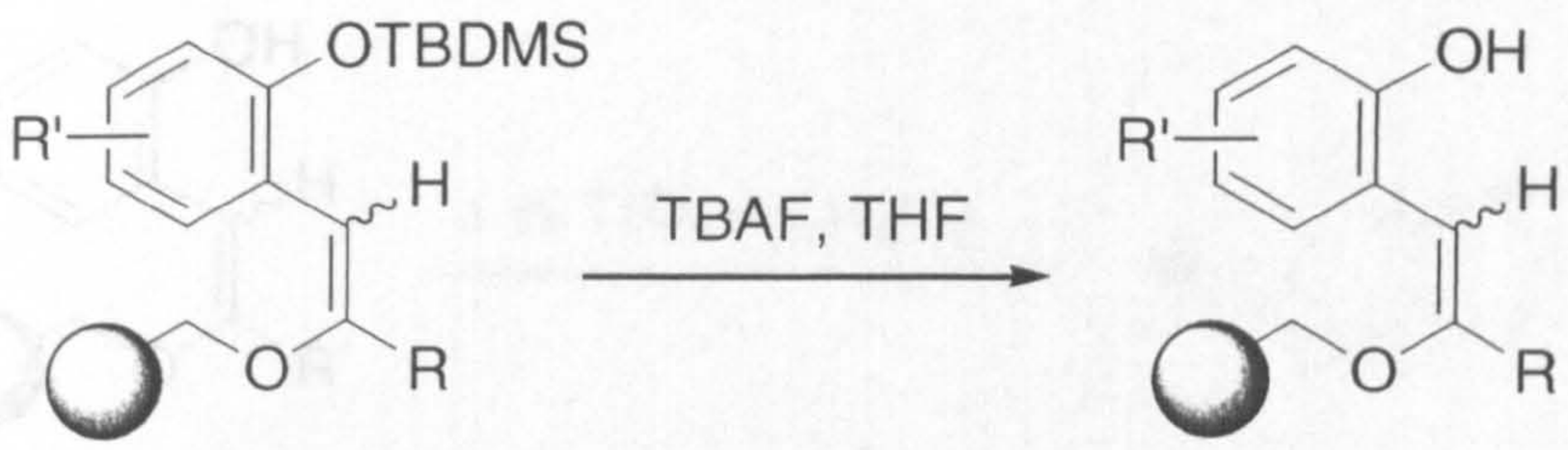
The resin-bound enol ether (1 kan) swollen in DCM (3.5 cm^3) was treated with TFA (2.5 cm^3, 50 % aqueous solution) and shaken for 30 mins. The kan was washed with DCM (3 × 30 cm^3) and the organic washings combined and dried (magnesium sulfate). Solvent removal under reduced pressure gave the ketone.

General method (10) - Cleavage from resin giving ketones (II)



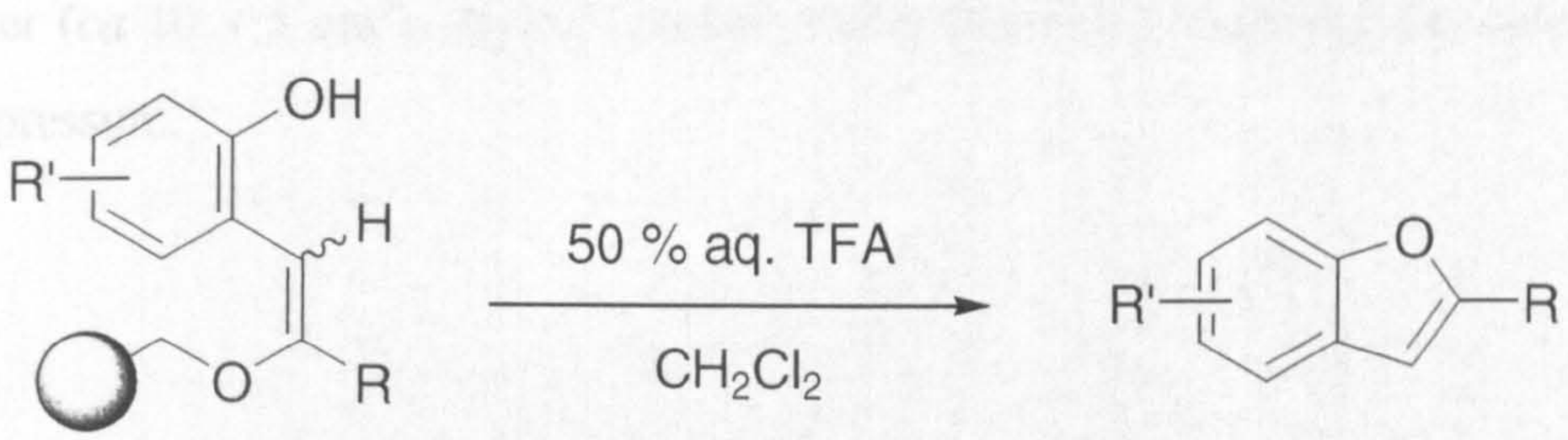
The resin-bound enol ether (1 kan) was swollen in a solution of 1 % TFA in DCM (5 cm^3) and shaken for 30 mins under an argon atmosphere. The kan was washed with DCM (3 × 30 cm^3) and the organic washings combined. Solvent removal under reduced pressure gave the ketone.

General method (11) - Silyl deprotection



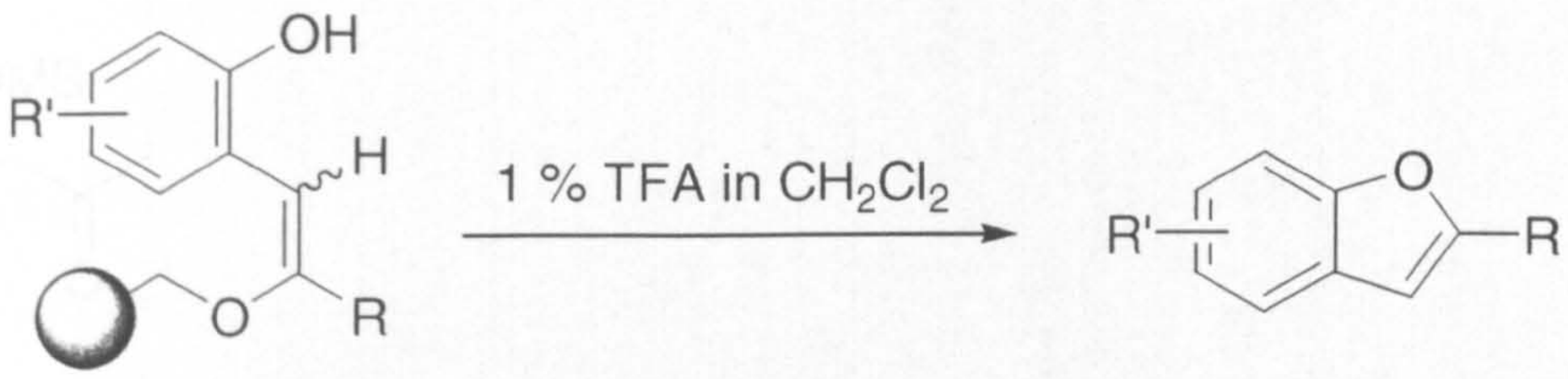
The resin-bound enol ether (1 kan) was swollen in THF (5 cm^3) and placed on a shaker at room temperature under an argon atmosphere. TBAF (1.0 M in THF, 1.00 cm^3, 1.00 mmol) was added and the kan shaken as before for 3 h. The kan was washed with THF (3 × 30 cm^3), alternating methanol then DCM (6 × 30 cm^3 of each), methanol (30 cm^3) and finally diethyl ether (30 cm^3), after which it was dried in a dessicator.

General method (12) - Cleavage from resin giving benzofurans (I)



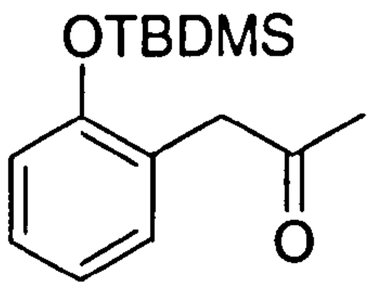
Following silyl deprotection, the resin-bound enol ether (1 kan) was swollen in DCM (4 cm^3) and treated with TFA (2.5 cm^3, 50 % aqueous solution) for 30 mins. The kan was washed with DCM (3 × 30 cm^3) and the organic washings combined and dried (magnesium sulfate). After solvent removal the residue was taken up in diethyl ether and the solution washed with water (10 × 30 cm^3) to remove traces of tetrabutylammonium salts. Drying (magnesium sulfate) followed by solvent removal under reduced pressure gave the benzofuran. Where required, remaining ammonium salt impurities were removed by taking the benzofuran up in diethyl ether (5 cm^3), washing with water (*ca* 10 × 5 cm^3), drying (magnesium sulfate) and removing the solvent under reduced pressure.

General method (13) - Cleavage from resin giving benzofurans (II)



Following silyl deprotection, the resin-bound enol ether (1 kan) was swollen in a solution of 1 % TFA in DCM (5 cm^3) and shaken for 30 mins under an argon atmosphere. The kan was washed with DCM (3 × 30 cm^3) and the organic washings combined. After solvent removal the residue was taken up in diethyl ether and the solution washed with water (10 × 30 cm^3) to remove traces of TBAF. After drying (magnesium sulfate), solvent removal under reduced pressure gave the benzofuran. Where required, remaining ammonium salt impurities were removed by taking the benzofuran up in diethyl ether (5 cm^3), washing with water (*ca* 10 × 5 cm^3), drying (magnesium sulfate) and removing the solvent under reduced pressure.

1-(2'-*tert*-Butyldimethylsilyloxyphenyl)propanone 196a



Method 1

Cleavage of resin-bound enol ether **194a** (Wang resin, 0.29 mmol) was carried out using *general method (9)* to give the *ketone* **196a** as an oil (0.053 g, 0.20 mmol, **70 %**).

Method 2

Cleavage of resin-bound enol ether **194a** (Wang resin, 0.29 mmol) was carried out using *general method (10)* to give the *ketone* **196a** as an oil (0.057 g, 0.22 mmol, **77 %**).

R_F [silica, light petroleum b.p. 40-60 °C : diethyl ether (1:1)] : 0.30

δ_H(400 MHz, $CDCl_3$): 0.24 (6H, s, $SiCH_3$), 0.99 (9H, s, *t*-Bu), 2.15 (3H, s, CH_3), 3.70 (2H, s, CH_2), 6.84 (1H, dd, *J* 0.8 and 8.1, H-3'), 6.92 (1H, dt, *J* 1.0 and 7.4, H-5'), 7.11 (1H, dd, *J* 1.7 and 7.5, H-6'), 7.17 (1H, dt, *J* 1.8 and 7.7, H-4')

δ_C (100 MHz; $CDCl_3$): -4.41 (CH_3), 18.19 (C), 25.69 (CH_3), 28.99 (CH_3), 45.96 (CH_2), 118.38 (CH), 121.29 (CH), 125.12 (C), 128.55 (CH), 131.26 (CH), 153.76 (C), 209.86 (C)

ν_{max} ($CDCl_3$ sol^n-Golden Gate)/cm^{-1}: 1709 (C=O), 1601 (aromatic ring), 1581 (aromatic ring), 1254 (SiMe), 922 (SiO),

m/z (CI^+): 265 [100 %, $(M+H)^+$], 207 [40, $(M+H)^+$-CH_3COCH_3]

Accurate mass: $C_{15}H_{24}O_2Si$, $(M+H)^+$ requires 265.1624, actual 265.1626

2'-(2''*tert*-Butyldimethylsilyloxyphenyl)acetophenone 196b

Cleavage of resin-bound enol ether **194b** (Wang resin, 0.29 mmol) was carried out using *general method (9)* to give the *ketone* **196b** as an oil (0.060 g, 0.18 mmol, **63 %**).

R_F [silica, light petroleum b.p. 40-60 °C : diethyl ether (1:1)] : 0.53

δ_H (400 MHz, $CDCl_3$): 0.22 (6H, s, $SiCH_3$), 0.93 (9H, s, *t*-Bu), 4.28 (2H, s, CH_2),
6.85 (1H, dd, *J* 1.2 and 8.4, H-3''),
6.90 (1H, dt, *J* 1.2 and 7.4, H-5''),
7.13-7.16 (2H, m, H-4'' and H-6''),
7.44 (2H, t, *J* 7.2, H-3 and H-5),
7.55 (1H, dt, *J* 1.2 and 7.1, H-4),
8.03 (2H, dd, *J* 1.2 and 7.8, H-2 and H-6)

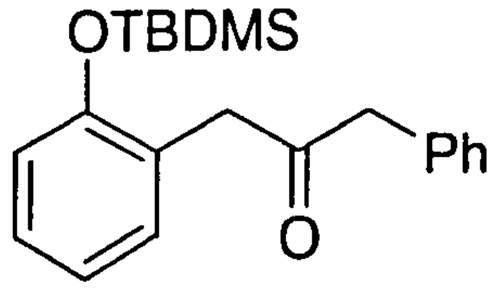
δ_C (100 MHz; $CDCl_3$): -4.18 (CH_3), 18.20 (C), 25.74 (CH_3), 40.36 (CH_2), 118.50 (CH),
121.23 (CH), 125.56 (C), 128.20 (CH), 128.53 (CH),
128.57 (CH), 131.15 (CH), 132.91 (CH), 136.65 (C),
153.45 (C), 198.52 (C)

ν_{max} (thin film)/cm^{-1}: 1686 (C=O), 1599 (aromatic ring), 1582 (aromatic ring),
1265 (SiMe), 928 (SiO)

m/z (CI^+): 327 [100 %, $(M+H)^+$], 269 [20, $(M+H)^+$-$SiMe_2$]

Accurate mass: $C_{20}H_{27}O_2Si$, $(M+H)^+$ requires 327.1780, actual 327.1779.

3-Phenyl-1-(2'-*tert*-butyldimethylsilyloxyphenyl) propanone 196c



Cleavage of resin-bound enol ether **194c** (Wang resin, 0.29 mmol) was carried out using *general method (9)* to give the *ketone* **196c** as a pale yellow oil (0.075 g, 0.22 mmol, **77** *%*).

R_F [silica, light petroleum b.p. 40-60 °C : diethyl ether (1:1)] : 0.28

δ_H(400 MHz, $CDCl_3$): 0.18 (6H, s, $SiCH_3$), 0.96 (9H, s, *t*-Bu), 3.70 (2H, s, CH_2), 3.72 (2H, s, CH_2), 6.83 (1H, dd, *J* 0.8 and 8.0, H-3'), 6.90 (1H, dt, *J* 1.0 and 7.6, H-5'), 7.05 (1H, dd, *J* 1.6 and 7.6, H-6'), 7.10 (2H, dd, *J* 1.6 and 7.6, H-2''and H-6''), 7.16 (1H, dt, *J* 1.6 and 7.7, H-4'), 7.21-7.30 (3H, m, H-3'', H-4''and H-5'')

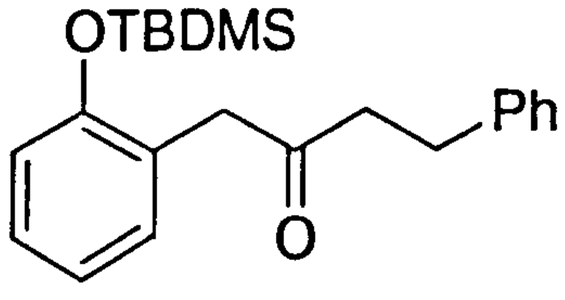
δ_C (100 MHz; $CDCl_3$): -4.18 (CH_3), 18.22 (C), 25.76 (CH_3), 44.47 (CH_2), 48.69 (CH_2), 118.47 (CH), 121.22 (CH), 125.21 (C), 126.84 (CH), 128.33 (CH), 128.52 (CH), 129.51 (CH), 131.46 (CH), 134.17 (C), 153.84 (C), 206.12 (C)

ν_{max} (thin film)/cm^{-1}: 1720 (C=O), 1600 (aromatic ring), 1584 (aromatic ring), 1263 (SiMe), 924 (SiO)

m/z (CI^+): 341 [95 %, $(M+H)^+$], 283 [25, $(M+H)^+$-$SiMe_2$]

Accurate mass: $C_{21}H_{29}O_2Si$, $(M+H)^+$ requires 341.1936, actual 341.1938.

4-Phenyl-1-(2'-*tert*-butyldimethylsilyloxyphenyl) butan-2-one 196d



Method 1

Cleavage of resin-bound enol ether **194d** (Wang resin, 0.29 mmol) was carried out using *general method (9)* to give the *ketone* **196d** as a pale yellow oil (0.083 g, 0.23 mmol, **82 %**).

Method 2

Cleavage of resin-bound enol ether **195a** (Merrifield resin, 0.67 mmol) was carried out using *general method (10)* to give the *ketone* **196d** as a pale yellow oil (0.083 g, 0.23 mmol, **56 %**).

Method 3

Following *general method (8)*, alkylidenation was carried out using 5-bromo2-*tert*-butyldimethylsilyloxybenzaldehyde diphenyldithioacetal (**176**, 1.80 g, 3.5 mmol, 5.22 eq. in 5 cm^3 THF) which was added to a mixture of titanocene dichloride (3.73 g, 15.0 mmol, 22.3 eq.), magnesium (0.62 g, 25.5 mmol, 38 eq.), 4Å molecular sieves (1.13 g) and triethylphosphite (6.0 cm^3, 35 mmol, 52 eq.) in THF (15 cm^3). The mixture was added to the resin-bound ester (**192a**, Merrifield resin, 1 kan, containing 0.67 mmol/kan 5 cm^3 THF) and stirred under an argon atmosphere (reaction time 19 h). The reaction was quenched with D_2O. Washing and drying of the kans yielded the resin-bound enol ether.

Cleavage of resin-bound enol ether (**195a**, Merrifield resin, 0.67 mmol) was carried out using *general method (10)* to give the *ketone* **196d** as a pale yellow oil (0.142 g, 0.40 mmol, **60 %**). None of the expected bromo (or deuterium)-functionalised ketone was observed.

R_F [silica, light petroleum b.p. 40-60 °C : diethyl ether (1:1)] : 0.61

δ_H(400 MHz, $CDCl_3$): 0.23 (6H, s, $SiCH_3$), 0.97 (9H, s, *t*-Bu),
2.74 (2H, t, *J* 7.5, CH_2), 2.85 (2H, t, *J* 7.6, CH_2),
3.65 (2H, s, CH_2), 6.82 (1H, dd, *J* 0.8 and 8.1, H-3'),
6.89 (1H, dt, *J* 1.1 and 7.4, H-5'),
7.07 (1H, dd, *J* 1.6 and 7.5, H-6'),
7.10 (2H, dd, *J* 1.1 and 7.6, H-2''and H-6''),
7.12-7.22 (2H, m, H-4'and H-4''),
7.24 (2H, dt, *J* 1.5 and 6.4, H-3''and H-5'')

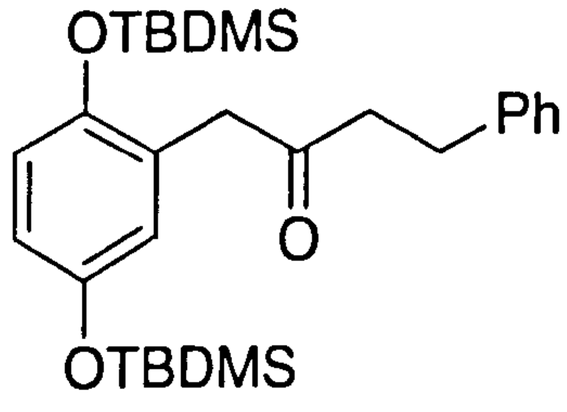
δ_C (100 MHz; $CDCl_3$): -4.19 (CH_3), 18.19 (C), 25.73 (CH_3), 29.71 (CH_2), 43.26 (CH_2),
45.29 (CH_2), 118.39 (CH), 121.25 (CH), 125.31 (C),
126.00 (CH), 128.28 (CH), 128.36 (CH), 129.41 (CH),
131.40 (CH), 141.00 (C), 153.74 (C), 208.71 (C)

ν_{max} (thin film)/cm^{-1}: 1714 (C=O), 1601 (aromatic ring), 1584 (aromatic ring),
1258 (SiMe), 925 (SiO)

m/z (CI^+): 355 [100 %, $(M+H)^+$], 297 [25, $(M+H)^+$-$SiMe_2$]

Accurate mass: $C_{22}H_{31}O_2Si$, $(M+H)^+$ requires 355.2093, actual 355.2092.

1-(2',5'di*tert*-Butyldimethylsilyloxyphenyl)-4-phenyl-butan-2-one 196e



Cleavage of resin-bound enol ether **194f** (Wang resin, 0.29 mmol) was carried out using *general method (10)* to give the *ketone* **196e** as a pale yellow oil (0.10 g, 0.21 mmol, **73** *%*).

R_F [silica, light petroleum b.p. 40-60 °C : diethyl ether (1:1)] : 0.54

δ_H(400 MHz, $CDCl_3$): 0.15 (6H, s, $SiCH_3$), 0.19 (6H, s, $SiCH_3$), 0.96 (9H, s, *t*-Bu), 0.96 (9H, s, *t*-Bu), 2.72 (2H, t, *J* 7.7, CH_2), 2.84 (2H, t, *J* 7.6, CH_2), 3.59 (2H, s, CH_2), 6.58 (1H, d, *J* 2.8, H-6'), 6.62 (1H, dd, *J* 2.8 and 8.8, H-4'), 6.68 (1H, d, *J* 8.8, H-3'), 7.10 (2H, d, *J* 7.2, H-2''and H-6''), 7.24 (1H, t, *J* 7.1, H-4''), 7.24 (2H, t, *J* 7.2, H-3''and H-5'')

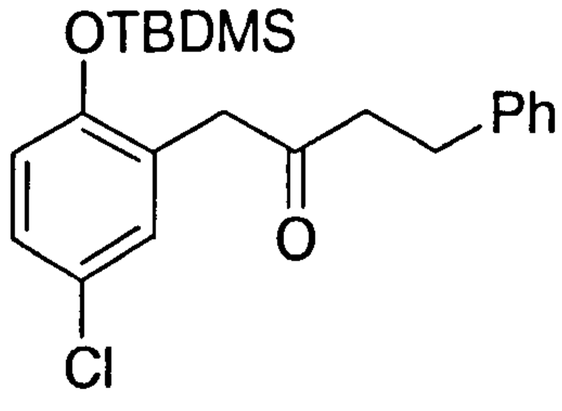
δ_C (100 MHz; $CDCl_3$): -4.52 (CH_3), -4.24 (CH_3), 18.14 (C), 18.17 (C), 25.67 (CH_3), 25.74 (CH_3), 29.72 (CH_2), 43.13 (CH_2), 45.37 (CH_2), 118.90 (CH), 119.41 (CH), 122.61 (CH), 126.04 (CH), 128.25 (CH), 128.43 (CH), 138.10 (C), 140.88 (C), 147.97 (C), 149.43 (C), 209.62 (C)

ν_{max} ($CDCl_3$ sol^n)/cm^{-1}: 1676 (C=O), 1592 (aromatic ring), 1271 (SiMe)

m/z (EI^+): 484 (20 %, $M^{+\bullet}$), 427 (40, $M^{+\bullet}$-$SiMe_2^{\bullet}$), 73 (100)

Accurate mass: $C_{28}H_{44}O_3Si_2$ requires 484.2829 actual 484.2829.

1-(5'-Chloro-2'-*tert*-butyldimethylsilyloxyphenyl) 4-phenybutan-2-one 196f



Method 1

Cleavage of resin-bound enol ether **194e** (Wang resin, 0.29 mmol) was carried out using *general method (10)* to give the *ketone* **196f** as an oil (0.048 g, 0.12 mmol, **42 %**).

Method 2

Cleavage of resin-bound enol ether **195b** (Merrifield resin, 0.29 mmol) was carried out using *general method (10)* to give the *ketone* **196f** as an oil (0.033 g, 0.08 mmol, **30 %**).

R_F [silica, light petroleum b.p. 40-60 °C : diethyl ether (1:1)] : 0.56

δ_H(400 MHz, $CDCl_3$): 0.22 (6H, s, $SiCH_3$), 0.96 (9H, s, *t*-Bu), 2.74 (2H, t, *J* 7.6, CH_2), 2.87 (2H, t, *J* 7.4, CH_2), 3.60 (2H, s, CH_2), 6.73 (1H, d, *J* 8.8, H-3'), 7.04 (1H, d, *J* 2.8, H-6'), 7.08-7.15 (3H, m, H-2'', H-6'' and H-4'), 7.20 (1H, t, *J* 7.0, H-4''), 7.26 (2H, t, *J* 7.2, H-3''and H-5'')

δ_C (100 MHz; $CDCl_3$): -4.22 (CH_3), 18.21 (C), 25.71 (CH_3), 29.72 (CH_2), 43.51 (CH_2), 44.97 (CH_2), 119.41 (CH), 125.93 (C), 126.15 (CH), 126.95 (C), 128.18 (CH), 128.31 (CH), 128.50 (CH), 131.16 (CH), 138.13 (C), 152.47 (C), 207.59 (C)

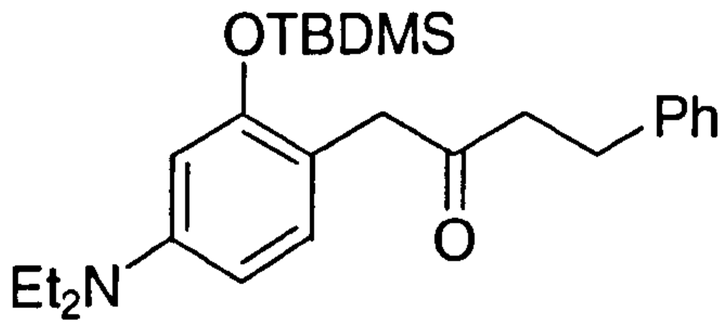
ν_{max} ($CDCl_3$ sol^n)/cm^{-1}: 1724 (C=O), 1262 (SiMe), 941 (SiO)

m/z (CI^+): 389 [100 %, $(M+H)^+$], 331 [20, $(M+H)^+$-$SiMe_2$]

Accurate mass: $C_{22}H_{30}O_2{}^{35}ClSi$ requires 389.1703, actual 389.1700

$C_{22}H_{30}O_2{}^{37}ClSi$ requires 391.1674, actual 391.1674.

1-(4'-Diethylamino-2'-*tert*-butyldimethylsilyloxyphenyl) 4-phenylbutan-2-one 196g



Cleavage of resin-bound enol ether **195e** (Merrifield resin, 0.67 mmol) was carried out using *general method (10)* to give the *ketone* **196g** as an oil (0.116 g, 0.27 mmol, **41 %**).

R_F [silica, light petroleum b.p. 40-60 °C : diethyl ether (1:1)] : 0.35

δ_H(400 MHz, $CDCl_3$): 0.26 (6H, s, $SiCH_3$), 0.97 (9H, s, *t*-Bu),
1.16 (6H, t, *J* 7.2, CH_2CH_3), 2.80 (2H, t, *J* 7.8, CH_2),
2.90 (2H, t, *J* 7.5, CH_2), 3.49-3.50 (4H, m, CH_2CH_3),
3.69 (2H, s, CH_2), 6.94 (1H, dd, *J* 2.2 and 8.2, H-5'),
7.13-7.19 (4H, m, ArH), 7.22 (1H, d, *J* 8.0, H-6'),
7.28 (2H, dd, *J* 1.6 and 7.2, H-2'' and H-6''),

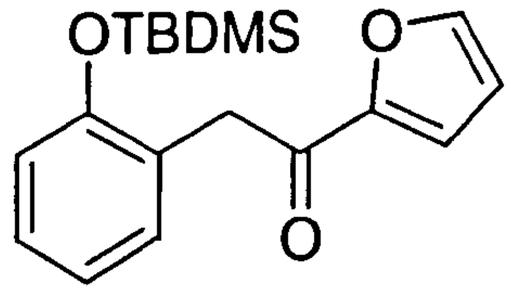
δ_C (100 MHz; $CDCl_3$): -4.50 (CH_3), 10.21 (CH_3), 18.26 (C), 25.63 (CH_3), 29.67 (CH_2),
43.97 (CH_2), 44.26 (CH_2), 53.51 (CH_2), 113.36 (CH),
113.76 (CH), 126.23 (CH), 127.77 (C), 128.31 (CH),
128.55 (CH), 133.16 (CH), 136.95 (C), 140.78 (C), 155.20 (C),
205.92 (C)

ν_{max} ($CDCl_3$ sol^n)/cm^{-1}: 3066 (ArH stretch), 3029 (ArH stretch), 2957 (CH stretch),
2900 (CH stretch), 2861 (NCH stretch), 1723 (C=O),
1505 (aromatic ring), 925 (SiO)

m/z (EI$^+$): 425 (10 %, $M^{+\bullet}$), 292 (40, $M^{+\bullet}$-$PhCH_2CH_2CO^{\bullet}$),
178 (25, $M^{+\bullet}$-$PHCH_2CH_2CO^{\bullet}$ and CH_2=SiMe*t*-Bu), 69 (100)

Accurate mass: $C_{26}H_{39}NO_2Si$ requires 425.2751, actual 425.2751.

1-(2'-Furyl)-
2-(2''-*tert*-butyldimethylsilyloxyphenyl)ethanone 196h



Cleavage of resin-bound enol ether **195c** (Merrifield resin, 0.29 mmol) was carried out using *general method (10)* to give the *ketone* **196h** as an oil (0.06 g, 0.19 mmol, **66 %**).

R_F [silica, light petroleum b.p. 40-60 °C : diethyl ether (1:1)] : 0.49

δ_H(400 MHz, $CDCl_3$): 0.22 (6H, s, $SiCH_3$), 0.94 (9H, s, *t*-Bu), 4.14 (2H, s, CH_2),
6.52 (1H, dd, *J* 1.8 and 3.4, H-4'),
6.83 (1H, dd, *J* 0.8 and 8.0, H-3''),
6.91 (1H, dt, *J* 1.2 and 7.6, H-5''),
7.13-7.20 (2H, m, H-4'' and H-6''),
7.21 (1H, d, *J* 0.8 and 3.6, H-3'),
7.58 (1H, dd, *J* 0.8 and 1.6, H-5')

δ_C (100 MHz; $CDCl_3$): -4.22 (CH_3), 18.19 (C), 25.76 (CH_3), 40.16 (CH_2), 112.31 (CH),
117.92 (CH), 118.39 (CH), 121.15 (CH), 125.05 (C),
128.33 (CH), 131.37 (CH), 146.55 (CH), 152.39 (C),
153.68 (C), 187.51 (C)

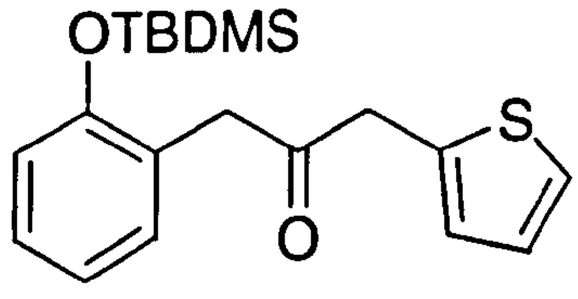
ν_{max} ($CDCl_3$ sol^n)/cm^{-1}: 1680 (C=O), 1600 (aromatic ring), 1584 (aromatic ring),
1257 (SiMe)

m/z (CI^+): 317 [100 %, $(M+H)^+$], 259 [40, $(M+H)^+$-$SiMe_2$],

Accurate mass: $C_{18}H_{25}O_3Si$, $(M+H)^+$ requires 317.1573, actual 317.1571.

1-(2'-Thiophenyl)-

3-(2''-*tert*-butyldimethylsilyloxyphenyl)propanone 196i



Cleavage of resin-bound enol ether **195d** (Merrifield resin, 0.29 mmol) was carried out using *general method (10)*. Solvent removal yielded a solid (0.033 g) that was found to contain the ketone and titanium impurities. The crude product was purified using column chromatography [silica, diethyl ether : light petroleum b.p. 40-60 °C (1:1) then (3:1)] giving the *ketone* **196i** as an oil (0.013 g, 0.04 mmol, **14 %**).

R_F [silica, light petroleum b.p. 40-60 °C : diethyl ether (1:1)] : 0.85

δ_H(400 MHz, $CDCl_3$): 0.24 (6H, s, $SiCH_3$), 0.98 (9H, s, *t*-Bu), 3.75 (2H, s, CH_2), 3.88 (2H, s, CH_2), 6.80 (1H, dd, *J* 0.8 and 3.6, H-3'), 6.84 (1H, dd, *J* 1.2 and 7.8, H-3''), 6.90-6.95 (2H, m, H-4' and H-5''), 7.10 (1H, dd, *J* 1.6 and 7.6, H-6''), 7.16 (1H, dd, *J* 1.6 and 7.6, H-4''), 7.19 (1H, dd, *J* 1.2 and 5.2, H-5')

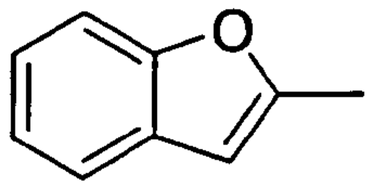
δ_C (100 MHz; $CDCl_3$): -4.13 (CH_3), 18.26 (C), 25.80 (CH_3), 42.25 (CH_2), 44.32 (CH_2), 118.49 (CH), 121.31 (CH), 124.96 (CH), 126.76 (CH), 126.82 (CH), 128.47 (CH), 131.48 (CH), 135.27 (C), 147.46 (C), 153.86 (C), 204.32 (C)

ν_{max} ($CDCl_3$ sol^n)/cm^{-1}: 1719 (C=O), 1600 (aromatic ring), 1257 (SiMe), 1097 (C-S)

m/z (CI^+): 347 [100 %, $(M+H)^+$], 289 [40, $(M+H)^+$-$SiMe_2$]

Accurate mass: $C_{19}H_{27}O_2SSi$, $(M+H)^+$ requires 347.1501, actual 347.1499.

2-Methylbenzo[*b*]furan 198a



Resin-bound enol ether **194a** (Wang resin, 0.29 mmol) was deprotected using the *general method (11)*. Cleavage was carried out using *general method (12)* to give the benzofuran **198a** as an oil (0.015 g, 0.11 mmol, **38 %**).

R_F [silica, light petroleum b.p. 40-60 °C : diethyl ether (1:1)] : 0.32

δ_H(400 MHz, $CDCl_3$): 2.45 (3H, s, CH_3), 6.36 (1H, s, H-3), 7.16-7.20 (2H, m, ArH), 7.39 (1H, brd, *J* 7.6, H-4 or H-7), 7.46 (1H, m, ArH)

δ_C (100 MHz; $CDCl_3$): 14.05 (CH_3), 102.55 (CH), 110.60 (CH), 120.04 (CH), 122.38 (CH), 123.01 (CH), 124.49 (C), 129.17 (C), 155.39 (C)

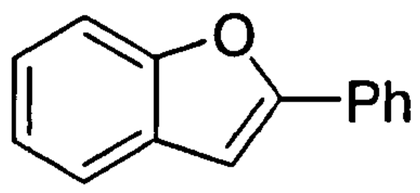
ν_{max} ($CDCl_3$ sol^n)/cm^{-1}: 3159 (ArH stretch), 2922 (CH stretch), 2854 (CH stretch), 1661 (C=C-O), 1466 (CH deformation)

m/z (EI$^+$): 132 (98 %, $M^{+\bullet}$), 131 (100, M^+-$H^\bullet$), 77 (50, C_6H_5)

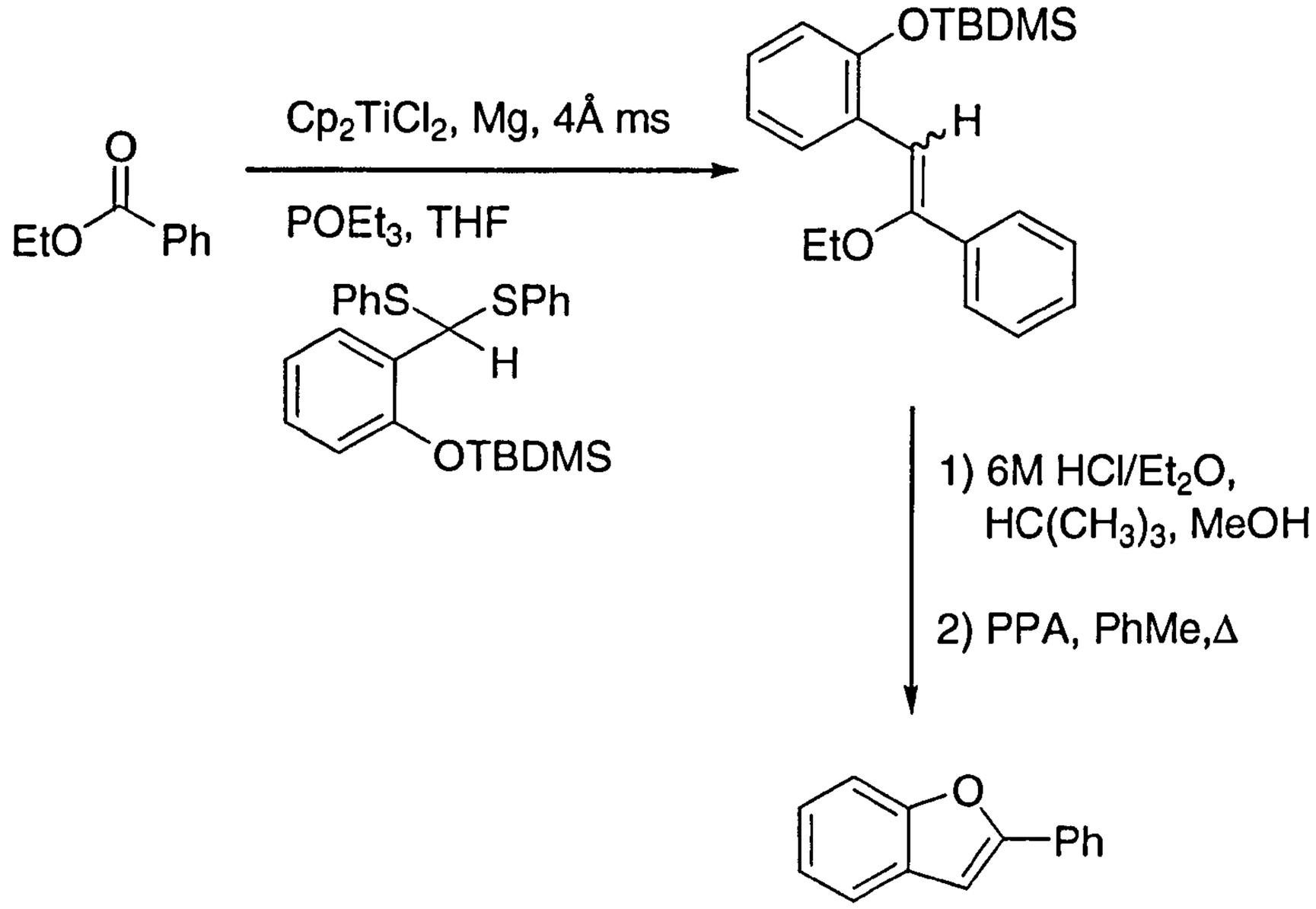
Accurate mass: C_9H_8O requires 132.0563, actual 132.0569

Literature:[153] δ_H ($CDCl_3$): 2.36 (1H, d, *J* 1), 6.02 (1H, m), 7.07 (4H, m); ν_{max}/cm^{-1}:1610, 1590, 1450, 1252, 1180, 1010. (Literature data is not in agreement with my data).

2-Phenylbenzo[*b*]furan 198b = 23



Method 1



Step 1

Following *general method (4)*, 1-ethoxy-1-phenyl-2-[2'-(*tert*butyldimethylsilyloxy)phenyl]ethene **185** was prepared using titanocene dichloride (2.04 g, 8.19 mmol, 3.81 eq.), magnesium (0.28g, 11.5 mmol, 5.36 eq.), 4Å molecular sieves (0.86 g), triethylphosphite (2.8 cm^3, 16 mmol, 7.59 eq.), ethyl benzoate (0.32 g in 3 cm^3 THF, 2.15 mmol) and 2-*tert*-butyldimethylsilyloxybenzaldehyde diphenyldithioacetal (**170**, 0.99 g in 3.5 cm^3 THF, 2.26 mmol, 1.05 eq.) in THF (7 cm^3) (reaction time 66 h). The crude product was placed on a kugelrohr (0.15 mmHg, oven temperature 100 °C) to remove any phosphorous impurities and then purified using column chromatography, [neutral alumina, light petroleum b.p. 40-60°C : diethyl ether (9:1)] to give the alkene as a yellow oil (0.17 g, 0.48 mmol, **22 %**, *Z*:*E* 12:1). Minor impurities remained and the enol ether **185** was used without further purification in the next step.

R_F [alumina, light petroleum b.p. 40-60 °C : diethyl ether (1:1)]: 0.98

Step 2

2-Phenylbenzo[*b*]furan **198b (= 23)** was synthesised by the method of Kato and Miyaura[18] using 1-ethoxy-1-phenyl-2-[2'-(*tert*-butyldimethylsilyloxy)phenyl]ethene (**185**, 0.14 g, 0.39 mmol), 6 M HCl in diethyl ether (0.75 cm^3, 4.50 mmol, 11.54 eq.), trimethylorthoformate (0.09 cm^3, 0.82 mmol, 2.10 eq.) in methanol (6 cm^3), then polyphosphoric acid (11 g, 114 mmol, 292 eq.) in toluene (6 cm^3) (reaction time 16 h). The crude product was extracted with toluene and purified using column chromatography [silica, light petroleum b.p. 40-60°C : diethyl ether (9:1)] to give the benzofuran **198b (= 23)** as a yellow solid [0.030 g, 0.15 mmol, **38 %**, (**8.7 %** from ethyl benzoate)].

Method 2

Resin-bound enol ether **194b** (Wang resin, 0.29 mmol) was deprotected using the *general method (11)*. Cleavage was carried out using *general method (12)* to give the benzofuran **198b (= 23)** as a yellow solid (0.038 g, 0.20 mmol, **69 %**).

R_F [silica, light petroleum b.p. 40-60 °C : diethyl ether (1:1)] : 0.62; m.p. 108-112 °C

δ_H(400 MHz, $CDCl_3$): 7.02 (1H, s, H-3), 7.21 (1H, dt, *J* 1.2 and 6.1, ArH), 7.28 (1H, dt, J 1.5 and 7.7, ArH), 7.35 (1H, tt, *J* 1.4 and 7.4, H-4'), 7.45 (2H, t, *J* 8.0, H-3' and H-5'), 7.52 (1H, d, *J* 8.0, ArH), 7.58 (1H, dd, *J* 0.8, 7.6, ArH), 7.88 (2H, d, *J* 7.8, H-2' and H-6', ArH)

δ_C (100 MHz; $CDCl_3$): 101.08 (CH), 110.97 (CH), 120.69 (CH), 122.71 (CH), 124.05 (CH), 124.73 (CH), 125.67 (C), 128.34 (CH), 128.58 (CH), 130.28 (C), 154.89 (C), 155.92 (C)

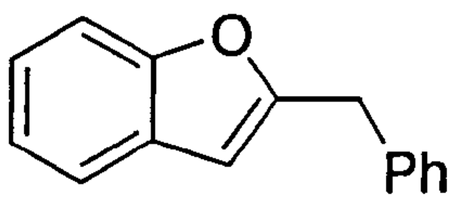
ν_{max} (Golden gate)/cm^{-1}: 3035 (ArH stretch), 2854 (CH stretch), 1604 (aromatic ring), 1562 (aromatic ring), 1072 (CO stretch), 741 (aromatic ring)

m/z (EI^+): 194 (100 %, $M^{+\bullet}$), 165 (40, $M^{+\bullet}$-$OHC^{\bullet}$)

Accurate mass: $C_{14}H_{10}O$ requires 194.0732, actual 194.0732

Literature: [147] m.p. 120-121 °C; δ_H (400 MHz, $CDCl_3$): 7.07 (1H, s), 7.29-7.65 (7H, m), 7.92 (2H, d); δ_C (75 MHz, $CDCl_3$): 156.18, 155.16, 130.8, 129.47, 128.98, 128.74, 125.18, 124.47, 123.14, 121.11, 111.38, 101.53; ν_{max}/cm^{-1}: 3054, 2926, 2855, 1605, 1562, 1455, 1038, 1020, 919, 806, 747, 703.

2-Benzylbenzo[*b*]furan 198c



Resin-bound enol ether **194c** (Wang resin, 0.29 mmol) was deprotected using the *general method (11)*. Cleavage was carried out using *general method (12)* to give the benzofuran **198c** as an oil (0.023 g, 0.11 mmol, **38 %**).

R_F [silica, light petroleum b.p. 40-60 °C : diethyl ether (1:1)] : 0.51

δ_H(400 MHz, $CDCl_3$): 4.10 (2H, s, CH_2), 6.37 (1H, s, H-3),
7.18 (2H, dt, *J* 1.4 and 7.9, H-3' and H-5'),
7.22-7.35 (5H, m, ArH), 7.40 (1H, d, *J* 8.0, H-4 or H-7),
7.46 (1H, d, *J* 7.2, H-4 or H-7)

δ_C (100 MHz; $CDCl_3$): 35.00 (CH_2), 103.36 (CH), 110.90 (CH),120.40 (CH),
122.51 (CH), 123.40 (CH), 126.76 (CH), 128.60 (CH),
128.80 (C), 128.91 (CH), 137.23 (C), 154.96 (C), 157.79 (C)

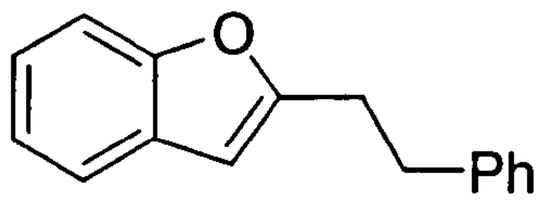
ν_{max} ($CDCl_3$ sol^n)/cm^{-1}: 3153 (ArH stretch), 2906 (CH stretch), 1592 (aromatic ring),
1255 (=C-O-C), 1093 (CO stretch), 772 (aromatic ring)

m/z (EI$^+$): 208 (100 %, $M^{+\bullet}$), 131 [40, ($M^{+\bullet}$-$Ph^{\bullet}$)]

Accurate mass: $C_{16}H_{14}O$ requires 208.0888, actual 208.0888

Literature:[20] δ_H (C_6D_6): 3.75 (2H, s), 6.05-6.06 (1H, m), 6.99-7.15 (7H, m),
7.28-7.34 (2H, m); δ_C (C_6D_6): 35.05, 103.69, 111.22, 120.71,
122.87, 123.82, 126.89, 128.78, 129.21, 129.29, 137.54,
155.55, 158.16; ν_{max} (neat)/cm^{-1}: 3013, 1600, 1252, 750, 704.

2-(2'-Phenylethyl)benzo[*b*]furan 198d



Method 1

Resin-bound enol ether **194d** (Wang resin, 0.29 mmol) was deprotected using the *general method (11)*. Cleavage was carried out using *general method (12)* to give the benzofuran **198d** as a solid (0.053 g, 0.24 mmol, **84 %**).

Method 2

Resin-bound enol ether **194d** (Wang resin, 0.29 mmol) was deprotected using the *general method (11)*. Cleavage was carried out using *general method (13)* to give the benzofuran **198d** as a solid (0.0383 g, 0.17 mmol, **60 %**).

Method 3

Resin-bound enol ether **195a** (Merrifield resin, 0.29 mmol) was deprotected using the *general method (11)*. Cleavage was carried out using *general method (13)* to give the benzofuran **198d** as a solid (0.016 g, 0.072 mmol, **25 %**).

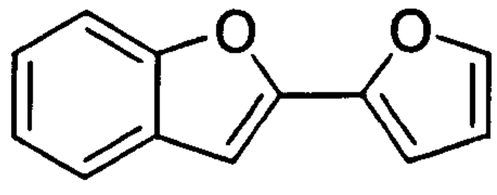
Method 4

4-Phenyl-1-(2'-*tert*-butyldimethylsilyloxyphenyl)-butan-2-one **196d** (0.135 g, 0.38 mmol) was dissolved in THF (5 cm^3) and stirred under an argon atmosphere. TBAF (1.0 M in THF, 1.00 cm^3, 1.00 mmol) was added and the solution stirred for 3 h at room temperature. The solvent was then removed under reduced pressure and the residue taken up in diethyl ether (10 cm^3) and washed with water (5 × 10 cm^3). After drying (magnesium sulfate) the solvent was removed under reduced pressure to give the deprotected ketone as an oil. The oil was dissolved in a solution of 1 % TFA in dichloromethane (5 cm^3) and stirred for 30 mins under an argon atmosphere at room temperature. Solvent removal under reduced pressure gave the benzofuran **198d** as a solid (0.068 g, 0.31 mmol, **81 %**).

R_F [silica, light petroleum b.p. 40-60 °C : diethyl ether (1:1)] : 0.58; m.p. 48-50 °C

δ_H(400 MHz, $CDCl_3$):	3.08 (4H, s, CH_2CH_2), 6.35 (1H, s, H-3), 7.15-7.23 (5H, m), 7.28 (2H, t, *J* 7.2, H-3'' and H-5''), 7.42 (1H, d, *J* 7.8, H-4 or H-7), 7.46 (1H, d, *J* 6.8, H-4 or H-7)
δ_C (100 MHz; $CDCl_3$):	30.35 (CH_2), 33.94 (CH_2), 102.32 (CH), 110.73 (CH), 120.30 (CH), 122.43 (CH), 123.22 (CH), 126.17 (CH), 128.34 (CH), 128.44 (CH), 128.86 (C), 140.88 (C), 154.63 (C), 158.42 (C)
ν_{max} ($CDCl_3$ sol^n)/cm^{-1}:	3154 (ArH stretch), 2943 (CH stretch), 1614 (aromatic ring), 1099 (CO stretch), 784 (aromatic ring), 642 (aromatic ring)
m/z (EI$^+$):	222 (40 %, $M^{+\bullet}$), 131 (100, $M^{+\bullet}$-$PhCH_2^{\bullet}$)
Accurate mass:	$C_{16}H_{14}O$ requires 222.1044, actual 222.1044
Microanalysis:	$C_{16}H_{14}O$ C – theory 86.49 %, actual 86.40 % H – theory 6.30 %, actual 6.48 %
Literature:[154]	δ_H: 2.92 (4H, s, CH_2CH_2), 6.16 (1H, s, H-3), 6.65-7.40 (9H, m); ν_{max} (thin layer): 3060, 3000, 2840, 1605, 1495, 1470, 1455, 1385, 1250, 765.

2-(Furan-2'-yl)benzo[*b*]furan 198e



Resin-bound enol ether **195c** (Merrifield resin, 0.29 mmol) was deprotected using the *general method (11).* Cleavage was carried out using *general method (13)* to give the benzofuran **198e** as a brown solid (0.018 g, 0.98 mmol, **34 %**).

R_F [silica, light petroleum b.p. 40-60 °C : diethyl ether (1:1)] : 0.65; m.p. 42-44 °C

δ_H(400 MHz, $CDCl_3$): 6.53 (1H, dd, *J* 1.8 and 3.4, H-4'),
6.80 (1H, d, *J* 3.6, H-3'), 6.91 (1H, s, H-3),
7.23 (1H, dt, *J* 1.2 and 7.6, H-5),
7.28 (1H, dt, *J* 1.6 and 7.6, H-6),
7.48-7.51 (2H, m, H-7 and H-5'),
7.87 (1H, dd, *J* 1.6 and 7.2, H-4)

δ_C (100 MHz; $CDCl_3$): 101.10 (CH), 107.64 (CH), 111.11 (CH), 111.69 (CH),
121.01 (CH), 123.15 (CH), 124.39 (CH), 128.73 (C),
138.13 (C), 143.02 (CH), 146.22 (C), 148.11 (C)

ν_{max} ($CDCl_3$ sol^n)/cm^{-1}: 3154 (ArH stretch), 2956 (CH stretch), 1644 (aromatic ring),
1602 (aromatic ring), 1561 (aromatic ring)

m/z (EI$^+$): 184 (100 %, $M^{+\bullet}$), 155 (25, $M^{+\bullet}$-$CHO^{\bullet}$)

Accurate mass: $C_{12}H_8O_2$ requires 184.0524, actual 184.0525

Literature: [155] m.p. 57-58 °C; δ_H: 6.6 (1H, m), 6.9 (1H, d, *J* 4), 7.03 (1H, s).

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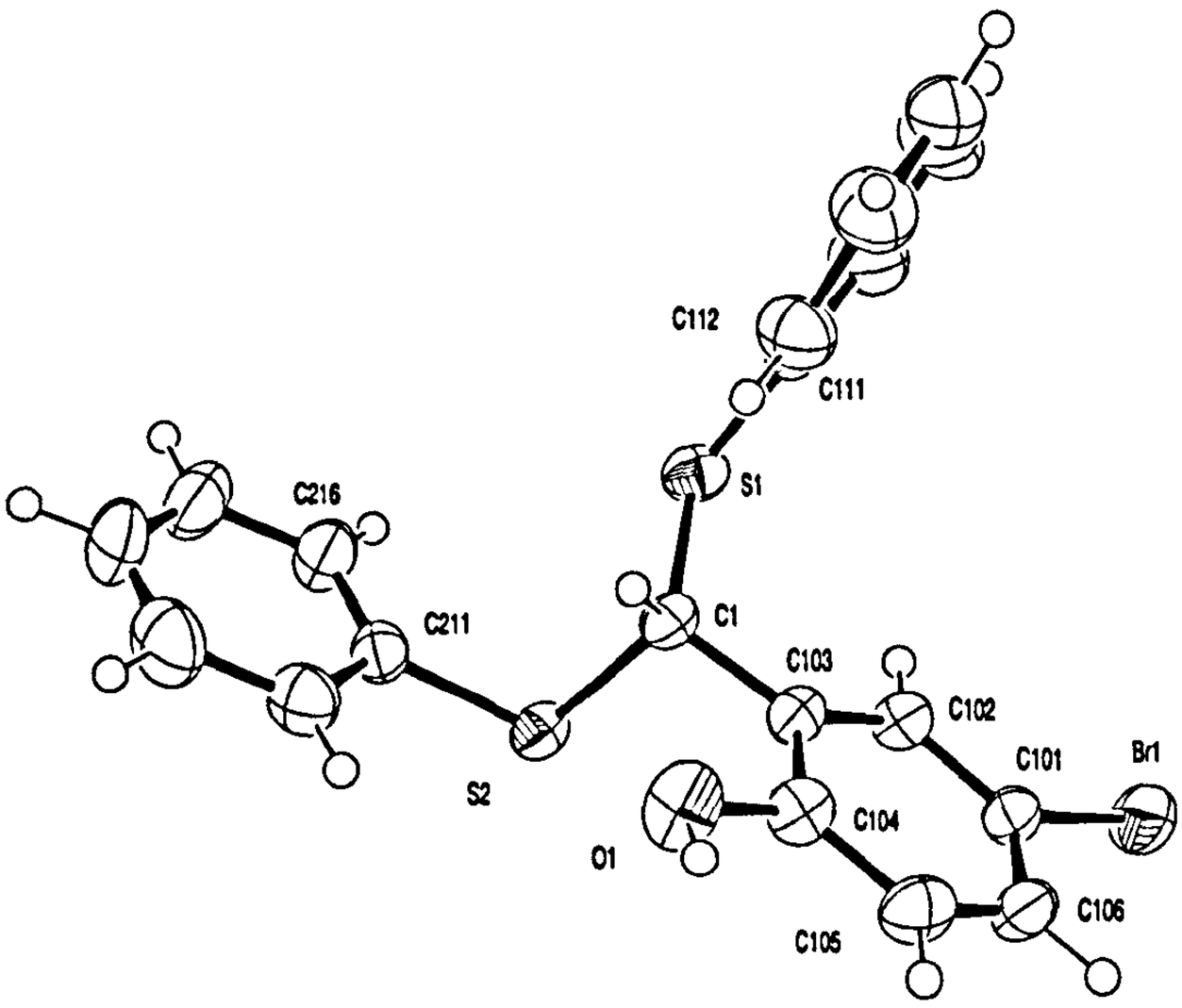
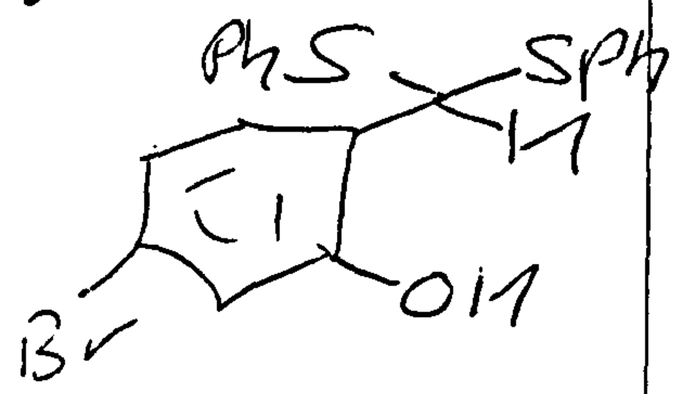
Appendix

Crystal structures of selected thioacetals

Glasgow-Strathclyde Joint Crystallographic Laboratory
CCD Structure Determination Report Synopsis



Structural diagram (ORTEP)

Chemical formula $C_{19}H_{15}BrOS_2$	Crystal morphology needle
Crystal color	Crystal size 0·5 0·15 0·1
Cell length a (Å) 6.4120(1)	alpha (°)
Cell length b (Å) 17.7776(4)	beta (°) 101·843(1)
Cell length c (Å) 15.6695(3)	gamma (°)
Temperature (K) 291	Volume (Å^3) 1748.14(6)
Crystal system monoclinic	Space group $P2_1/n$
R1 (obs) 0·0419	T(min) 0·515
Rw2 (all data) 0.1098	T(max) 0·621
Δρ eÅ^{-3} 0·589 −0·794	Abs correction type SORTAV
GOOF 1·018	
%age complete = 97·7 to theta$_{max}$ = 27	
Comments on data collection/reduction data collected originally in C-centred orthorhombic. Re-integrated using primitive monoclinic cell same as above but in $P2_1/c$. Transformed by 100, 0-10, 001 to match isomorphous LJF012	Comments on structure solution/refinement used coords of LJF012 no problems 
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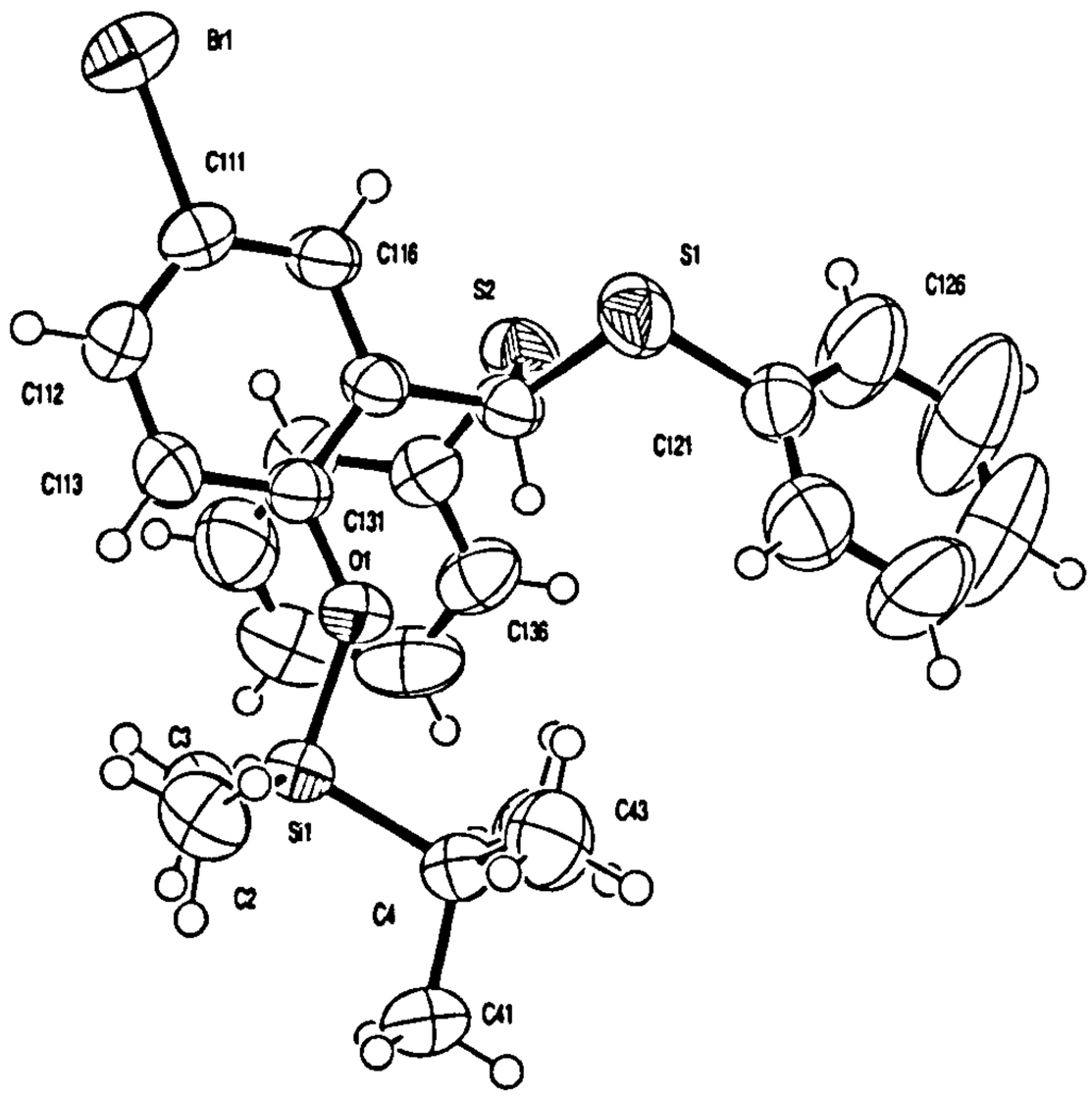
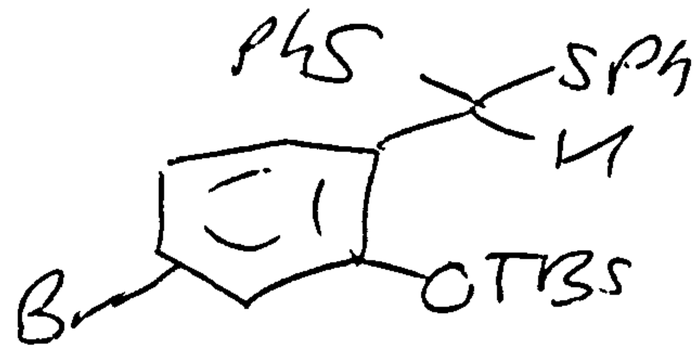
http://www.gla.ac.uk/~louis/d.d

Glasgow-Strathclyde Joint Crystallographic Laboratory
CCD Structure Determination Report Synopsis



Structural diagram (ORTEP)

Chemical formula $C_{25}H_{29}BrO_5S_2Si$	Crystal morphology large xtal
Crystal color colourless	Crystal size 0.43 0.33 0.32
Cell length a (Å) 8.9386(1)	alpha (°)
Cell length b (Å) 31.8060(4)	beta (°) 97.348(1)
Cell length c (Å) 9.2400(1)	gamma (°)
Temperature (K) 291	Volume (Å^3) 2605.37(5)
Crystal system monoclinic	Space group P2$_1$/c
R1 (obs) 0.0467	T(min) 0.667
Rw2 (all data) 0.1084	T(max) 0.690
Δρ eÅ^{-3} 0.50 − 0.564	Abs correction type SORTAV
GOOF 1.041	
%age complete = 95.5 to theta$_{max}$ = 27.5	
Comments on data collection/reduction sample cleaved from large crystal recollected because 1st data set incomplete.	Comments on structure solution/refinement no problems. large thermal ellipsoids for C121–126 ring possible disorder 
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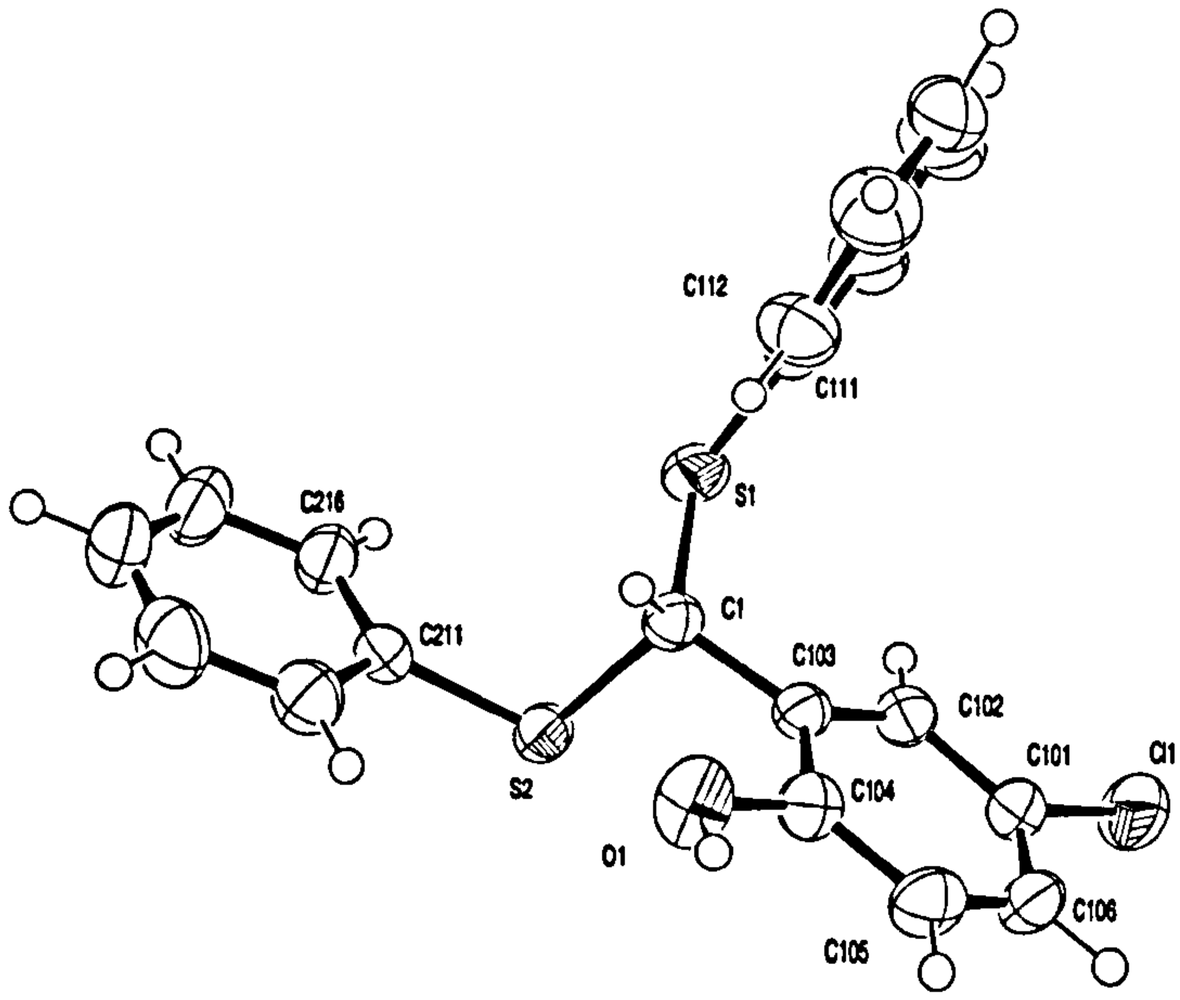
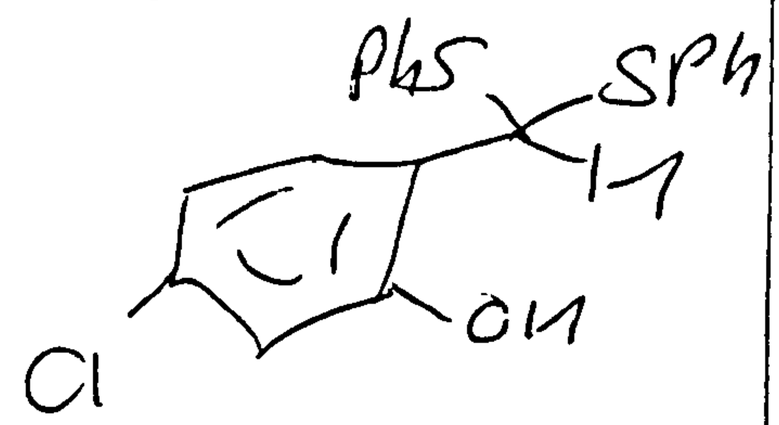
CCD Structure Determination Report Synopsis



Structural diagram (ORTEP)

Chemical formula $C_{19}H_{15}ClO_5S_2$	Crystal morphology needle
Crystal color colourless	Crystal size 0.4 0.15 0.1
Cell length a (Å) 6.4117 (1)	alpha (°)
Cell length b (Å) 17.6379 (4)	beta (°) 101.742 (1)
Cell length c (Å) 15.5537 (4)	gamma (°)
Temperature (K) 291	Volume (Å^3) 1722.14 (6)
Crystal system monoclinic	Space group P21/n
R1 (obs) 0.0405	T(min) 0.867
Rw2 (all data) 0.0939	T(max) 0.945
Δρ eÅ^{-3} 0.208 −0.303	Abs correction type SORTAV
GOOF 1.023	
%age complete = 99.6 to theta$_{max}$ = 27.47	
Comments on data collection/reduction recollection of LJF012 in correct monoclinic cell	Comments on structure solution/refinement ShelxS no problems 
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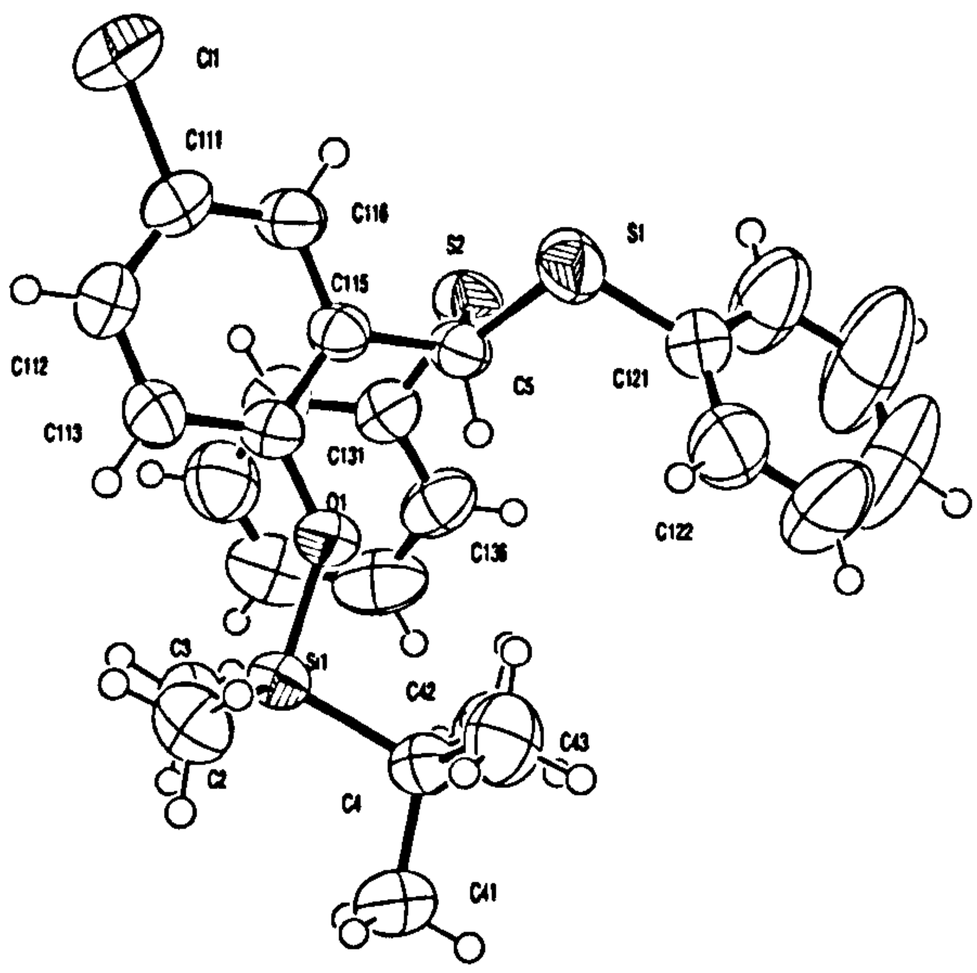
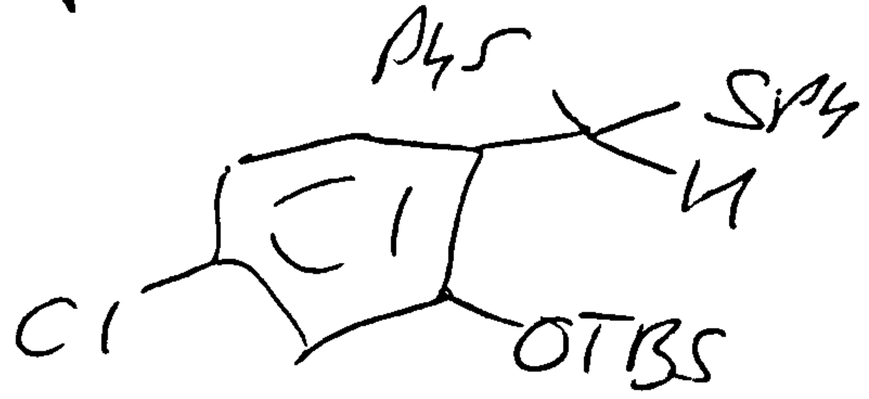
Glasgow-Strathclyde Joint Crystallographic Laboratory
CCD Structure Determination Report Synopsis



Structural diagram (ORTEP)

Chemical formula $C_{25}H_{29}ClO_2S_2Si$	Crystal morphology cleavel large xtal
Crystal color colourless	Crystal size 0.5 0.45 0.3
Cell length a (Å) 8.9218(1)	alpha (°)
Cell length b (Å) 31.7693(6)	beta (°) 96.530(1)
Cell length c (Å) 9.1931(2)	gamma (°)
Temperature (K) 293	Volume (Å^3) 2588.78(8)
Crystal system monoclinic	Space group $P2_1/a$
R1 (obs) 0.0478	T(min)
Rw2 (all data) 0.1511	T(max)
Δρ eÅ^{-3} 0.373 - 0.351	Abs correction type none
GOOF 1.009	
%age complete = 97.8 to theta$_{max}$ = 30	

Comments on data collection/reduction	Comments on structure solution/refinement
dx = 35 ∴ long axis	Shelx no problems 

CCDC deposit code 149309	SDET CODE LJF013